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ORIGINAL ARTICLE

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

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Abstract

Background: The 2019 Coronavirus disease is known to cause thromboembolic events. There is little information on the severe COVID-19 consequences in children.

Objectives: To determine whether elevated D-dimer levels in the pediatric population with COVID-19 are a risk marker for the development of thromboembolic events. If so, D-dimer levels could be used to determine prophylactic anticoagulation measures if needed.

Methods: This is a systematic review, performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The last database search update was on December 14, 2021, resulting in 79 documents for analysis. Data were taken from various databases and queried by topic, keyword, or abstract.

Results: Of the 79 articles found, only seven were selected for this analysis. Of these articles, only one had thromboembolic events. In the other articles, D-dimer levels were elevated but were considered controversial in terms of predicting events, with no clear association between the magnitude of D-dimer change and the magnitude of thrombosis risk.

Conclusion: Although used for adults, D-dimer was not a good parameter for assessing the risk of thromboembolic events in individuals younger than 21 years. The main shortcomings are the fact that D-dimer increases with any type of inflammation and is, therefore, not a specific marker, and that it is elevated in many patients even without the occurrence of thromboembolic events.

Keywords: COVID-19; Thromboembolism; Prognosis.

Introduction

The coronavirus disease 2019 (COVID-19) is an emerging viral disease that had its first detection in China in late 2019 and spread rapidly around the world, affecting healthcare systems and ways of life in several countries.[1,2] In Brazil, there are to date more than 34 million cases and more than 680,000 deaths. In Santa Catarina, there have been more than 1.8 million accumulated cases and more than 22 thousand deaths.[3]

The main symptoms of the disease include fever, cough, myalgia, fatigue, expectoration, and dyspnea. Symptoms such as headache, nausea, vomiting, and diarrhea have been reported less frequently. Lymphopenia, elevated C-reactive protein, and hemosedimentation rate levels, and decreased oxygen saturation were the main laboratory changes reported.[4,5] The common complications of the disease are acute respiratory distress syndrome (ARDS), shock, acute kidney injury, and acute heart injury.[6]

Moreover, an inappropriate increase in pro-inflammatory cytokines can be found in severe cases of the disease, called cytokine storm. It is pointed out as one of the main causes of ARDS and coagulation abnormalities since the endothelial damage it causes leads the body to a

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Central Illustration: Elevated D-Dimer as a Marker For Thromboembolic Events in Pediatric Patients With Covid-19: A Systematic Review

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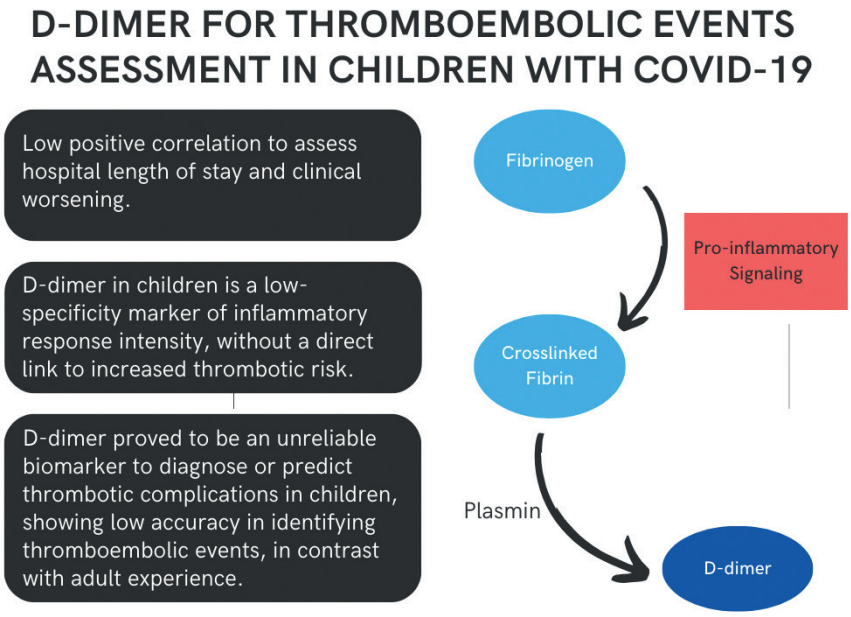

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state of hypercoagulation that generates thrombotic events.[7-9] These events include an increased risk of venous thromboembolism (VTE) and pulmonary embolism, as well as tissue necrosis, ischemic stroke, and death.[2,10,11]

D-dimers are protein products of fibrin degradation released into the circulation when a blood clot breaks down as a result of normal bodily processes or with the use of prescribed fibrinolytic medication. The measurement of D-dimer is used in cases of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) as a diagnostic marker since it tends to be elevated in cases of abnormal coagulation.[12,13] D-dimer tests are rapid, simple, and inexpensive, consequently decreasing the need to use more expensive and complex diagnostic tests.[14] Since abnormal coagulation has been demonstrated in the presence of COVID-19, mainly in the form of PTE and DVT, D-dimer proves to be an important diagnostic and prognostic marker and is also used to guide anticoagulant treatment management.[15,16]

Children under the age of 18 years tend to be less affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than adults, despite apparently having the same susceptibility to infection. Pediatric patients tend to have asymptomatic infections or mild symptoms, such as cough and fever.[17,18] Nevertheless, they may develop multisystem inflammatory syndrome in chidren (MIS-C) in severe cases, a still poorly described clinical condition characterized by cardiovascular changes, prolonged fever, skin manifestations, and coagulopathies.[19]

Since there is little information on severe COVID-19 and its thromboembolic consequences in children, this systematic review aimed to evaluate the applicability of D-dimer as a risk marker for thromboembolic events such as DVT and PTE in the pediatric population with COVID-19.

Methodology

This systematic review was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under CRD42022298330.

This present study used the PECO (population, exposure, comparison, outcome) framework to establish its research question. The population herein consists of people under 21 years old with COVID-19 diagnosis and measured D-dimer, the exposure is elevated D-dimer level, the comparison is normal D-dimer level, and the main outcome

is the risk of developing thromboembolism. Finally, the research question elaborated for this systematic review was: "Does increased D-dimer level increase the risk for the development of thromboembolic events in the pediatric population with COVID-19?"

Inclusion criteria

Studies that addressed the relationship between COVID-19 and thromboembolic events in the pediatric population (< 21 years) with data on D-dimer value were included.

The designs eligible for this review were randomized controlled trials, cohorts, case-control studies, case series, and observational studies. All articles in Portuguese, English, and Spanish were included. In addition, documents accessible in full text via the Coordination for the Improvement of Higher Education Personnel (CAPES), Google, or Google Scholar were also considered.

Exclusion criteria

Articles with focus on patients older than 21 years, pregnant women, and populations with comorbidities, such as coagulopathies or pulmonary diseases were excluded.

Systematic reviews, books, non-academic researches, reviews, abstracts, commentaries, policy statements, case reports, and contents in languages other than those listed in the inclusion criteria were also excluded, besides articles published before 2018.

Information sources

The database search was conducted on December 14, 2021 by two authors (JC and PC). Studies were chosen from five databases: PubMed (all fields; National Center for Biotechnology, Information, National Institutes of Health; Bethesda, Maryland, USA), Scopus (article title, abstract, keywords; Elsevier; Amsterdam, Netherlands), MEDLINE / Bireme (Virtual Health Library [VLH] title, abstract, subject; US National Library of Medicine, National Institutes of Health; Bethesda, Maryland, USA), Web of Science (article title, abstract, keywords; Thomson Reuters; New York, New York, USA), and Embase (article title, abstract, keywords; Elsevier; Amsterdam, Netherlands).

Study selection and data extraction

A total of 79 articles were found on the five chosen platforms using the search key detailed in Figure 1. The first step, in the process of selecting the study, was to organize the articles in a PRISMA flow diagram, shown in Figure 2. Secondly, two authors (JC and PC) initially checked for duplicate documents using the "find duplicates" tool of EndNote X9 software (Clarivate Analytics; Philadelphia, Pennsylvania USA; version for Windows). In this step, 20 texts were excluded. Thereafter, the duplicates that were not excluded by the platform tool were manually excluded, ruling out another 18 articles, and leaving 41 after these two steps.

In the third step, the authors read the titles and excluded those documents that did not fit the inclusion criteria cited above, totaling the exclusion of 16 more articles, being one with a focus on imaging tests, seven focused on other diseases, two were systematic reviews, one was not related to COVID-19, one had a focus on vaccination against COVID-19, and the others were case reports, reducing the number of documents to 25.

In the fourth step, the abstracts of the remaining articles were read and seven more, which did not meet the inclusion criteria, were eliminated, leaving 18 articles. Five were excluded because they focused on patients over 21 years of age, one was not on COVID-19, and one was a comparison between COVID-19 and Influenza patients regarding the need for extended extracorporeal membrane oxygenation (ECMO).

In the final procedure, these 18 texts were read in full and 12 more were eliminated: four because the focus was on the establishment of protocols, five for not focusing on the pediatric population, one was duplicated, and the last one, because it was not possible to find the complete content.

At the end of this process, we were left with six articles considered relevant to our research. Thereafter, a "citation tracking" was done in the bibliographical references of the selected papers, where one more pertinent article was found, totaling seven to be studied in the review.

The relevant data were added to the knowledge matrix, which was used to organize and systematize the relevant information, in a Microsoft Excel spreadsheet (Microsoft Corporation; Redmond, Washington, USA), version 7.0.25, for Windows 10.

Quality assessment

Articles were independently assessed by all authors (JC, PC, FC, and RM) for risk of bias. Any disagreement

was resolved through discussion among the group. The Joanna Briggs Institute (JBI) checklists for cohort studies, case series, and case-control studies were used.

These checklists have four possible answers: yes, no, unclear, and not applicable. When the answer was not applicable, the criterion was not considered in the evaluation, as recommended by the JBI guidelines. The bias assessment was calculated based on the amount of "yes" answers in the assessment instrument. Thus, it was possible to divide the articles into three groups: high (up to 49%), moderate (50 to 70%), and low risk (above 70%) of bias.

Synthesis of the results

Data considered relevant by the authors were extracted from the articles and added to the knowledge matrix elaborated using a spreadsheet from Microsoft Excel (Microsoft Corporation; Redmond, Washington, USA), version 7.0.25, for Windows 10.

The following information was extracted from each article: title, author(s), institution and country of the first author, year and journal of publication, the objective of the work, method, difficulties and limitations, age of the children in the study,

Databases used for the review	*Search Query*
PUBMED	*((("Wuhan coronavirus" OR "Wuhan virus" or "novel coronavirus" OR "'nCoV" OR "SARS-CoV-2" OR "SARS 2" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "coronavirus disease 2019 virus" or "2019-nCoV" or "2019 novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus" OR "coronaviruses") AND ("Fibrin Fibrinogen Degradation Products" OR "D-dimer fibrin" OR "D-dimer fragments" OR "fibrin fragment D-dimer")) AND ("Thromboembolism")) AND ("child" OR "Children" OR "infant" OR "newborn" OR "teen" OR "teenager" OR "youth")*
Web of Science	*ALL=(("Wuhan coronavirus" OR "Wuhan virus" or "novel coronavirus" OR "nCoV" OR "SARS-CoV-2" OR "SARS 2" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "coronavirus disease 2019 virus" or "2019 novel coronavirs" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus" OR "coronaviruses") AND ("Fibrin Fibrinogen Degradation Products" OR "D-dimer fibrin" OR "D-dimer fragments" OR "fibrin fragment D-dimer") AND ("Thromboembolism") AND ("child" OR "Children" OR "infant" OR "newborn" OR "teen" OR "teenager" OR "youth"))*
Embase(CAPES)	*('child' OR 'adolescent' OR 'newborn') AND 'thromboembolism' AND 'd dimer' AND 'coronavirus disease 2019' AND ('case report'/de OR 'case study'/de OR clinical article'/de OR 'cross sectional study'/de OR 'evidence based practice'/de OR 'human'/de OR 'human cell'/de OR 'human tissue'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'multicenter study'/de OR 'nonhuman'/de OR 'observational study'/de OR 'phase 2 clinical trial'de OR 'practice guideline'/de OR 'proportional hazards model'/de OR 'prospective study'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de OR 'transitional care'/de OR 'vignette'/de)*
Scopus	*TITLE-ABS-KEY ((("Wuhan coronavirus" OR "Wuhan virus" OR "novel coronavirus" OR "nCoV'" OR "SARS-CoV-2" OR "SARS 2" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR " coronavirus disease 2019 virus" OR "2019-nCoV" OR "2019 novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus" OR "coronaviruses") AND ("Fibrin Fibrinogen Degradation Products" OR "D-dimer fibrin" OR "D-dimer fragments" OR "fibrin fragment D1 dimer" OR "fibrin fragment DD" OR "D-dimer" OR "fibrin fragment D-dimer")) AND ("Thromboembolism") AND ("child" OR "Children" OR "infant" OR "newborn" OR "teen" OR "teenager" OR "youth")) AND (EXCLUDE (LANGUAGE, "French"))*
Medline EBSCO(CAPES)	*child and d-dimer and thromboembolism and covid-19*

Figure 1 – Databases used for the review and search queries.

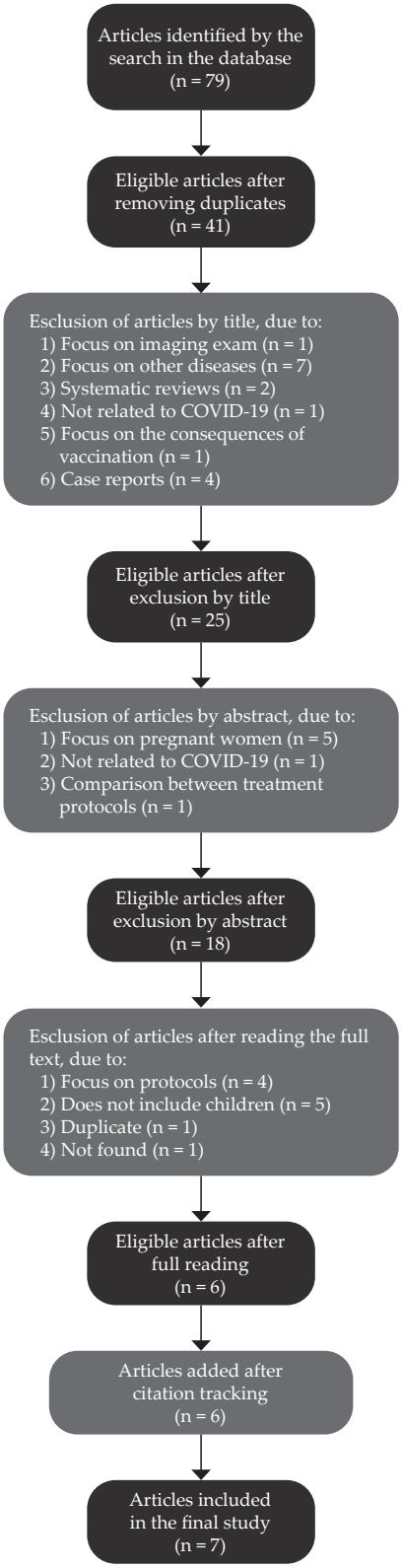

Figure 2 – PRISMA flowchart for study selection.

whether or not there was a change in D-dimer and if this influenced the prognosis, which were the pre-thrombotic events, and if the patients had symptoms before the development of PTE or DVT.

A narrative synthesis was chosen as an appropriate method to discuss the results of this review since multiple types of studies were evaluated. The data were assessed through the knowledge matrix (Table 1) which was used to discuss the key information drawn from the documents. A discussion on the impact of the methodological quality of the included articles, in addition to the main topics of the studies, was input into the matrix.

These data were used to interpret and describe the main information about the relationship between the D-dimer level and thrombotic events in COVID-19 pediatric population.

Results

Study selection

A total of seven articles were included since they met the inclusion criteria. All were evaluated with the JBI methodological assessment tools for cohorts, case series, and case-control studies, of which six demonstrated a low risk of bias and one demonstrated a moderate risk. Therefore, none of them were excluded for methodological failure.

Topics

Six topics were categorized for the presentation of this study results: 1) Characteristics of included studies, number of patients, and age of the children; 2) Occurrence of pre-thrombotic events; 3) Symptoms of PTE or DVT; 4) The use or not of prophylactic anticoagulation; 5) Whether the change in D-dimer worsened, improved, or had no influence on prognosis; and 6) Alleged difficulties and limitations.

Characteristics of the included studies

Three of the seven studies were conducted in the United States, one in Italy, one in Pakistan, one in Saudi Arabia, and one in China. Two of them were case series, with a mean number of eight patients, four were cohorts with a mean number of 43 patients, and one was a case-control study with 43 patients. The age ranged from less than one year to 21 years.

Table 1 – Main characteristics of the studies included in the review

Reference	Country	Year	Method	Number of Patients	Age Range	Presence of d-dimer alterations?	Did the change in D-dimer worsen, improve or not influence the prognosis?	Were there thromboembolic events among the patients	Was prophylatic anticoagulation done according to the adult protocol?	Did patients have symptoms of PTE or DVT?	Risk of Bias	Statistical Significance
Al-Ghafry, M. [20]	USA	2020	Case Series	8	2 years - 20 years	Yes	D-dimer was elevated in all intensive care unit patients, but there was no association with increased mortality and thromboembolic phenomena	No	Yes	No	Low	5%
Al-Ghafry, M. [21]	USA	2021	Cohort	66	4 months - 16 years	Yes	There was an association between D-dimer elevation, MIS-C severity and PICU admission	No	Yes	No	Moderate	5%
Del Borrello, G. [22]	Italy	2020	Cohort	36	10 days - 19 years	Yes	D-dimer did not discriminate severity of COVID-19, being elevated in mild cases and severe cases.	No	Yes	No	Low	5%
Mitchell, W. B. [23]	USA	2021	Cohort	27	2 months - 21 years	Yes	Elevated D-dimer has been observed in patients with VTE, but no association between the marker and prognosis has been made	DVT and PTE	Yes	Yes	Low	5%

Sadiq, M. [24]	*Pakistan*	*2020*	*Case Series*	*8*	*5 years - 15 years*	*Yes*	*D-dimer was used as a marker to justify therapeutic anticoagulation, but no association was made between the marker and prognosis*	*No*	*Yes*	*No*	*Low*	*5%*
Saleh, M. [25]	*Saudi Arabia*	*2021*	*Cohort*	*43*	*4 months - 13 years*	*Yes*	*There was an association between elevated D-dimer and PICU admission and lengh of hospital stay*	*No*	*Yes*	*No*	*Low*	*5%*
Wang, YL [26]	*China*	*2020*	*Control Case*	*43*	*1 year - 13 years*	*Yes*	*There was an association between elevated D-dimer and more severe cases*	*No*	*No*	*No*	*Low*	*5%*

PTE: Pulmonary Thromboembolism; DVT: Deep Venous Thrombosis; MIS-C: Multisystem inflammatory syndrome in children; PICU: Pediatric Intensive Care Unit; VTE: Venous thromboembolism

Number of patients

The number of patients in the studies was below 100 in all the papers evaluated, and below 10 for Al-Ghafry et al.[20] and Sadiq et al.,[21] as both were case series studies.

Age of the study children

The maximum age in the studies was variable with Al-Ghafry et al.,[20] Al-Ghafry et al.,[22] Del Borrello et al.,[23] and Mitchell et al.[24] considering the population under 21 years old. Sadiq et al.[21] considered the age under 15 years for the population of their study, Saleh et al.,[25] under 14 years, and Wang et al.,[26] under 18 years.

Prothrombotic events and symptoms of PTE and DVT

In most articles there were no reports of thromboembolic events, except for that of Mitchell et al.[24] Del Borrello et al.[23] stated that D-dimer is still controversial in predicting VTE because it tends to increase in all inflammatory conditions that are associated with an increase in thrombotic risk, with no clear association between the intensity of the change in D-dimer and the magnitude of thrombotic risk. However, in the cohort study by Mitchell et al.,[24] seven patients developed thrombotic events, two DVT and four PTE, one developed both DVT and PTE, and one of the later evolved to death.

Use of prophylactic anticoagulation

Prophylactic anticoagulation was widely used in the selected studies, which may have generated some degree of confusion about the correlation between increased D-dimer and thrombotic events.

Only the study by Wang et al.[26] did not use therapy in any of the patients. In the cases where it was used, prophylactic anticoagulation was applied according to the protocol for adults, due to the lack of a specific protocol for children.

The influence of D-dimer on prognosis

For Al-Ghafry et al.,[20] all patients in the case series admitted to the intensive care unit (ICU) had a three- to tenfold increase in D-dimer levels, but had no increase in mortality or thrombotic events. In the cohort of Al-Ghafry et al.,[22] there was a D-dimer value higher than 2,144 ng/mL, considered sensitive (82%) and specific (75%) to predict pediatric ICU (PICU) admission. This value was also used as a cutoff to correlate with MIS-C severity, based on higher rates of PICU admission and the need for supplemental oxygen. In the study by Wang et al.,[26] D-dimer was increased in 37.5% of patients with severe COVID-19.

For Del Borrello et al.,[23] the D-dimer values were not statistically different between COVID-19 patients and categories of disease severity. In the cohort, D-dimer levels increased slightly at the peak of clinical manifestations, returning to normal after disease resolution.

In the study by Saleh et al.,[25] D-dimer values were higher (above 0.5 μg/ml) in 55.8% of patients on admission. An association between high values and PICU admission has been noticed, as in the paper by Del Borrello. [23] Sadiq et al.[21] and Mitchell et al.[24] did not have D-dimer as the focus of their work but when measured in pediatric patients with COVID-19 it was also elevated.

Alleged difficulties and limitations

All authors in their case series claimed the low number of patients as one of the main difficulties in conducting the study, relating this to a possible lack of statistical relevance, except Al-Ghafry et al.[20]

Furthermore, Dal Borrello et al. stated that D-dimer assays in pediatrics are prone to pre-analytical confounding factors, such as blood drawing quality, which may limit their reliability. Al-Ghafry et al.[22] also claimed in their cutoff study that therapies administered for MIS-C simultaneously to the study may have confounded some results, and administration of aspirin or anticoagulation may have hindered the analysis of absolute pro-thrombotic status. Finally, platelet mapping was not possible due to the absence of some antithrombin III data and fibrinolysis parameters, rendering the study not as complete as the researchers would have hoped.

Discussion

D-dimer has been classified as a sensitive and important marker of the risk for thromboembolic events in adults with COVID-19.[27-28] It was therefore suspected that the same could be said for the pediatric population. However, the presentation of severe COVID-19 in children is uncommon within disease-infected populations[29] and thromboembolic events in this population are rare, about 0.07 to 0.14 per 10,000 children per year.[30] Despite this, hospitalized children

have this rate increased to 58 per 10,000,[31] an important risk to consider in COVID-19 pediatric patients, due to the unknown nature of the procoagulant state and the in-hospital interventions that increase the thrombotic risk, such as central venous access devices.[23,31]

Prophylactic anticoagulation is routinely performed in hospitalized patients and has an elevated D-dimer as one of the indication criteria. In adult patients with COVID-19, there is a higher risk of thromboembolic events and this treatment has been shown to be an important factor in reducing mortality.[10,32] In the pediatric population, on the other hand, it is plausible that children with MIS-C do not develop significant thrombosis, unlike adults infected with SARS-CoV-2, because they generally do not have smoking vasculopathy, atherosclerosis, diabetes, or hypertension, despite laboratory evidence of a hyperinflammatory and pro-thrombotic state.[22]

A D-dimer value above the upper limit proved to be a possible prognostic tool but of low positive correlation to assess hospital length of stay and clinical worsening, especially in worsening MIS-C. All values were normalized after disease resolution, with patients recovering without thrombotic sequelae. These observations support the view of D-dimer in children being a mere low-specificity marker of inflammatory response intensity, without a direct link to increased thrombotic risk. In contrast to the adult experience, D-dimer generally proved to be an unreliable biomarker to diagnose or predict thrombotic complications in children, showing low accuracy in identifying pulmonary embolism, predicting venous thrombosis recurrence, and as an indicator to initiate prophylaxis with anticoagulants.

Among the studies, the main limitation cited was the low number of severe patients in the age group studied. There are still few publications on COVID-19 related to thromboembolism in the pediatric population. Some of the selected studies had D-dimer quantification and analysis, but the focus was on the effects of MIS-C. In addition, most studies claimed the sample space small to make any association. Prophylactic anticoagulation treatment, done in children following the adult protocol, may have been a confounding factor for coagulation markers.

Conclusion

This article aimed to identify whether the increased D-dimer level in the pediatric population with COVID-19 increased the risk of developing thromboembolic events. Despite being a subject of great importance due to the early tenor of 2019 coronavirus disease, not a significant number of studies on the population under 21 years of age were found.

We can conclude from the analysis of the existing articles that D-dimer is not a good parameter to assess the risk of thromboembolic events in the pediatric range. The main limitations are that D-dimer increases in any type of inflammation and is therefore not a specific marker and that it is increased even without the occurrence of thromboembolic events.

Although it has been possible to build an overview of the subject, more studies focusing on the pediatric population are still needed to give us a clearer idea of how COVID-19 and D-dimer relate to thrombotic events in patients under 21 years of age. These studies will be important in creating treatment and prevention protocols unique to the pediatric population that can be used to save lives.

Author Contributions

Conception and design of the research: Costa JZ, Casagrande PP, Cola M, Martins RP; acquisition of data: Costa JZ, Casagrande PP; analysis and interpretation of the data: Costa JZ, Casagrande PP, Costa FV, Cola M, Martins RP; statistical analysis and writing of the manuscript: Costa JZ, Casagrande PP, Martins RP; critical revision of the manuscript for intellectual content: Costa JZ, Casagrande PP, Costa FV, Martins RP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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