

Peculiarities of in-Stent Thrombosis and Restenosis in Coronary Arteries Post-COVID-19: A Systematic Review of Clinical Cases and Case Series

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Background: One of the most serious complications of coronary artery stenting is restenosis and in-stent thrombosis; their prevalence can reach 20–25%. Stent thrombosis can be acute (up to 24 hours), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (> 1 year after previous stenting). In the patients with COVID-19 in intensive care units, the proportion of those with elevated troponin levels reached 25%.

Objective: Evaluation of the association between COVID-19 and the development of in-stent thrombosis and restenosis of the coronary arteries based on the analysis of clinical cases and case series.

Materials and Methods: We searched the PubMed and Scopus databases for relevant case reports and case series of stent restenosis and in-stent thrombosis associated with coronavirus infection (CVI) published between 2020 and the present. Thirty-eight full-text publications were screened and manually checked for analysis. We found 10 publications describing cases of thrombosis and restenosis of stents associated with coronavirus infection, of which only 2 were case series. In total, we analyzed 22 cases.

Results: In the structure of in-stent restenosis and thrombosis, 59.1% were very late, 9.1% were late; 18.2% were considered subacute events, and 13.6% were acute events. All cases were angiographically confirmed. The main location of restenosis or thrombosis was the left coronary artery (LAD) (51.1%), thrombosis of the right coronary artery (RCA) occurred in 27.3%, and location in circumflex artery was in 22.7%. All patients had COVID-19 confirmed by a PCR test or the presence of immunoglobulins G and M. In fourteen patients (54.5%), an X-ray examination showed the presence of bilateral polysegmental infiltration.

Conclusion: Analysis of publications demonstrates the association between restenosis and in-stent thrombosis in patients with coronary arteries disease (CAD) and coronavirus infection.

Keywords: restenosis, in-stent thrombosis, stenting, COVID-19, coronary artery disease, case report, case series

Introduction

Percutaneous coronary interventions (PCI) are currently the most common invasive method of medical care for acute coronary syndrome. More than five million such interventions were performed worldwide in 2019.¹ One of the most dangerous complications of coronary stenting is restenosis and in-stent thrombosis; their prevalence reaches 20–25%.² This is a major challenge to healthcare systems around the world, as it leads to an increase in mortality rates from myocardial infarction.³

The introduction of drug-eluting stents reduced the incidence of thrombotic complications and coronary restenosis up to 2–10% of cases of percutaneous coronary intervention. In the case of stent restenosis, even reimplantation with a drug-eluting stent can lead to its complete occlusion in 15% of cases during the first year.^{4,5}

Complete or partial in-stent occlusion of the coronary artery in the long term can be caused by thrombosis, restenosis, and newly developed atherosclerosis. Restenosis that develops up to one year is associated with the proliferation and migration of vascular smooth muscle cells, leading to the formation of neointimal hyperplasia. The development of neoatherosclerosis in the stent walls is considered as the main factor responsible for the development of both restenosis and thrombosis for more than a one year after stent implantation.⁶

One of the important factors influencing the formation of restenosis and thrombosis is systemic or infectious inflammation, which can damage the endothelium of the vessel, the plaques and trigger hypercoagulation mechanisms with development of prothrombotic effect. In recent years, the situation has become largely complicated due to the coronavirus pandemic.

COVID-19 is characterized by the ability to cause acute myocardial damage, endothelial dysfunction and thrombus formation.⁷ Despite the fact that the WHO officially announced the end of the pandemic in May 2023, this problem has not lost its relevance, since even in December 2023; peaks in the incidence of COVID-19 of more than 300 thousand cases per day were observed worldwide.⁸ Epidemiological data suggest the emergence of new SARS-CoV-2 variants, which are impacting disease transmission and severity. COVID-19 is characterized by prolonged symptomatic illness (shortness of breath, fatigue, and muscle weakness) lasting several months after initial infection (long COVID). The appearance of new variants may also have a detrimental impact on long COVID-19, with additional associated morbidity and mortality.⁹ In 2024, according to the Infectious Diseases Society of America (IDSA), cases of new variants have increased sharply in the United Kingdom, South Korea, and New Zealand, raising concerns about a new wave of COVID-19.¹⁰ This demonstrates the dynamic nature of the COVID-19 pandemic and emphasizes the importance of ongoing monitoring and research.

The aim of the systematic review is to evaluate the association between COVID-19 and in-stent thrombosis and restenosis of the coronary arteries in patients with CAD based on the analysis of clinical cases and case series.

Current Concepts of Stent Thrombosis

According to the Academic Research Consortium classification (2006), stent thrombosis is divided into acute (up to 24 hours after previous stenting), subacute (more than 24 hours to 30 days), late (more than 30 days to 1 year), and very late (more than 1 year after previous stenting).^{11,12} According to the clinical course, the following types are distinguished: 1) definite (angiographically confirmed) stent thrombosis, when the symptoms correspond to acute coronary syndrome (ACS); 2) probable stent thrombosis, when sudden cardiac death or myocardial infarction is observed in the territory of the stented vessel within 30 days after stenting without angiographic confirmation; 3) possible stent thrombosis, when unexplained death occurs a month or more after stent implantation.¹²

The incidence of stent thrombosis in recent years has tended to decrease due to the use of more effective double and triple antiplatelet therapy;¹³ their frequency ranges from 1 to 4% of all cases of coronary artery stenting.¹⁴ However, despite the rarity of this complication, stent thrombosis is often a catastrophic event associated with complete occlusion of the lumen and the need for a rapid decision on repeated revascularization.¹⁵⁻¹⁷ In the case of multivascular lesions, stent thrombosis rates reached 3%.¹⁸ Almost all cases of stent thrombosis occur within the first month after stenting.¹⁹

Pathogenetic Mechanisms of Restenosis of Coronary Arteries

In-stent restenosis is a decrease in vessel lumen after percutaneous coronary intervention, angiographically defined as a decrease in stent patency by 50% or more.²⁰⁻²² One of the well-studied risk factors for in-stent restenosis is chronic kidney disease (CKD). The main pathogenetic mechanism is vascular calcification due to the transdifferentiation of arterial smooth muscle cells.^{23,24} It leads to increased stiffness, which makes it difficult to deploy the stent and inflate the balloon. Incomplete deployment of the stent causes disruption of blood flow associated with an inflammatory reaction, accumulation of cytokines and growth factors, thrombus formation and adhesion of leukocytes, expression of endothelial genes, which can subsequently cause neointimal growth.²⁵ Violation of the integrity of the stent structure is also caused by the increased rigidity of the vascular wall. Trauma to a vessel by such a stent is accompanied by local inflammation, subintimal hemorrhages, exposure of the endothelium, release of the drug from the stent coating, activation of vascular smooth muscle cells through excessive proliferation and migration, and, ultimately, hyperplasia of neointimal tissue.

Stent fractures occur in 2.6–2.9% of all stenting cases; in such situation, restenosis develops up to 50%.^{26–28} In the case of bare-metal stenting, a predictor of stent restenosis can be an increased level of C-reactive peptide, as well as matrix metalloproteinase (MMP) and plasminogen activator inhibitor (PAI-1).^{29,30}

Vitamin D deficiency may increase the expression of endothelin, tissue factor, and epidermal growth factor by smooth muscle cells, which is accompanied by increased smooth muscle cell migration and accelerated atherosclerotic plaque growth.³¹

All risk factors for coronary artery stent thrombosis can be divided:¹⁴

related to the patient: diabetes, previous MI with ST elevation, smoking, thrombocytosis, anemia for early thrombosis (OR<5); for late and very late thrombosis it can be CKD, low ejection fraction, African-American ethnicity, older age (OR<5); for malignancies, peripheral arterial disease OR=5-10; for dual antiplatelet therapy disorders and genetic polymorphisms OR >10;

related to coronary artery injury: location in the left anterior descending coronary artery, small vessels, ulcerated or aneurysmal lesion, prolonged lesion or multiple implanted stents, lesion at the arterial bifurcation, baseline TIMI flow grade 0–1, saphenous vein graft CABG (OR<5); restenosis within the drug-eluting stent, geographic miss, bifurcation, or type C lesion (OR=5-10 for all risk factors); post-procedural TIMI flux <3 (OR>10).

related to stents: strut thickness and stent base area, incomplete endothelialization, inflammatory reactions (OR<5); small diameter stent (OR= 5–10).

related to the stenting procedure: no use of clopidogrel; no use of heparin before surgery; damage to several vessels; use of multiple stents; use of glycoprotein IIb/IIIa inhibitors; overlapping stent implantation; residual stenosis with drug-eluting stents (OR<5); use of low doses of bivalirudin (OR 5–10); insufficient stent size or incorrect placement; vessel dissection; residual stenosis or incomplete dilatation of the vessel or stent (OR>10).¹⁴

The Role of Coronavirus Infection in the Development of in-Stent Thrombosis and Restenosis

The coronavirus pandemic has contributed to our understanding of the risk factors for in-stent thrombosis and restenosis.^{32,33} Studies by Chinese scientists demonstrate that acute inflammatory myocardial damage is typical for 17–19.7% cases of COVID-19. Acute myocardial damage during COVID-19 is not always accompanied by ischemic manifestations; however, the level of cardiac markers was increased in all cases.^{34–36} Among people with COVID-19 being treated in intensive care units, the proportion of patients with elevated troponin levels reached 25%.³⁷

Despite a pronounced decrease in rates of myocardial revascularization during the pandemic,³⁸ the rate of in-stent thrombus formation even increased to 8.1–21%.³⁹ In the UK in 2018–2019, myocardial revascularization rates were consistently between 7000 and 8000 per month. In March 2020, during the first peak of COVID-19, the PCI rate dropped to 4,400 cases. In 2021–2022 there was an increase in cases of emergency medical care with a delay of more than 150 minutes - only 55% of patients received care on time.⁴⁰ These data correspond with the results of another study, which showed that hospitalization of patients with MI in 2020–2021 decreased by more than 20%. There was an increase in mortality after PCI during the coronavirus pandemic by 10%.⁴¹ During the COVID-19 pandemic, 2.2% of patients had a preoperative diagnosis of coronavirus infection (CVI).⁴² The patients had an increased risk of postoperative mortality compared to patients without CVI⁴³ because CVI can cause direct damage to the heart muscle.^{44,45}

In the countries and regions with high population density, where there were problems with transporting patients, the strategy of primary thrombolysis was preferred.⁴⁶ However, professional societies have recommended PCI as the primary treatment option even during the COVID-19 pandemic.⁴⁷ Elective surgery should be postponed until complete recovery and compensation of concomitant diseases, since the risks of postoperative complications persist for up to 8 weeks.⁴⁸ Interventions should be delayed for at least 7 weeks after COVID-19 in patients who have not received vaccination.⁴⁹

Pathogenesis of Thrombosis Associated with Coronavirus Infection

The basis for increased thrombus formation during coronavirus infection is an acute systemic inflammatory response, characterized by increased synthesis of inflammatory mediators because of an imbalance in T-cell activation with dysregulation of the release of interleukin (IL)-6, IL-17 and other cytokines. Activation of platelets after inflammatory damage to the vascular endothelium leads to increased synthesis of thromboxane A, thrombin and adenosine diphosphate (ADP), followed by calcium-dependent activation of the process of platelet aggregation and their adhesion to the endothelium of the damaged vessel and among themselves. These processes enhance the prothrombotic environment and increase the risk of thrombosis. An increase in the level of tissue thromboplastin leads to an increase in the level of thrombin and fibrin synthesis with the possible development of disseminated intravascular coagulation syndrome.^{50,51} Inflammatory process can lead to plaque rupture, thrombus formation, and risk of local microthromboembolism with subsequent impairment of perfusion or reperfusion in the case of coronary artery stenting.^{52,53} The mechanisms of thrombus formation during coronavirus infection are shown schematically in [Figure 1](#).

Materials and Methods

Protocol and Registration

The protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)⁵⁴ and registered in PROSPERO (ID: CRD42024506976).

Information Sources and Search Strategy

We performed a comprehensive literature search for relevant publications describing cases and case series of restenosis and stent thrombosis associated with coronavirus infection in the PubMed/MEDLINE, EMBASE, Cochrane databases, Scopus, Web of Science, and Google Scholar databases, including case reports published during the period from 2020 to present. Medical Subject Headings (MeSH) were used, including the following keywords: “COVID-19” OR “coronavirus 2019” OR “in-stent thrombosis” OR “in-stent restenosis” OR “thrombosis of coronary stents” AND “case reports” OR “case series”. Additionally, a manual search of reference lists from retrieved articles and relevant journals was performed.

We have selected publications in English that are available in full text. Brief reports and newspaper publications will be excluded. For inclusion, we will independently screen titles and abstracts of publications, and any discrepancies will be resolved by consensus.

Based on the detailed search strategy, the specific research question for this systematic review was “How does COVID-19 impact on formation of in-stent thrombosis and restenosis of coronary artery in the patients with coronary artery disease?”

Eligibility Criteria

Inclusion Criteria

Studies needed to be available as full-text articles and only in the English language. The target studies were case reports and case series included adult patients with in-stent thrombosis or restenosis associated with COVID-19.

Exclusion Criteria

Exclusion criteria: non-English articles, non-original articles, duplicate publications (risk of bias), articles without complete demographic information of each patient, editorial letters, review articles, and case reports and case series included patients with stenosis and thrombosis of the coronary arteries but not in-stent thrombosis or restenosis associated with COVID-19.

Data Extraction

The screening process involved the independent evaluation of titles and/or abstracts retrieved through the designated search strategy and additional sources. Data extracted included authors and year of publication, studied peoples, age, gender and study design; methods of PCI. Two review authors meticulously assessed these documents to identify studies potentially meeting the predefined inclusion criteria. Subsequently, the full texts of these potentially eligible studies were

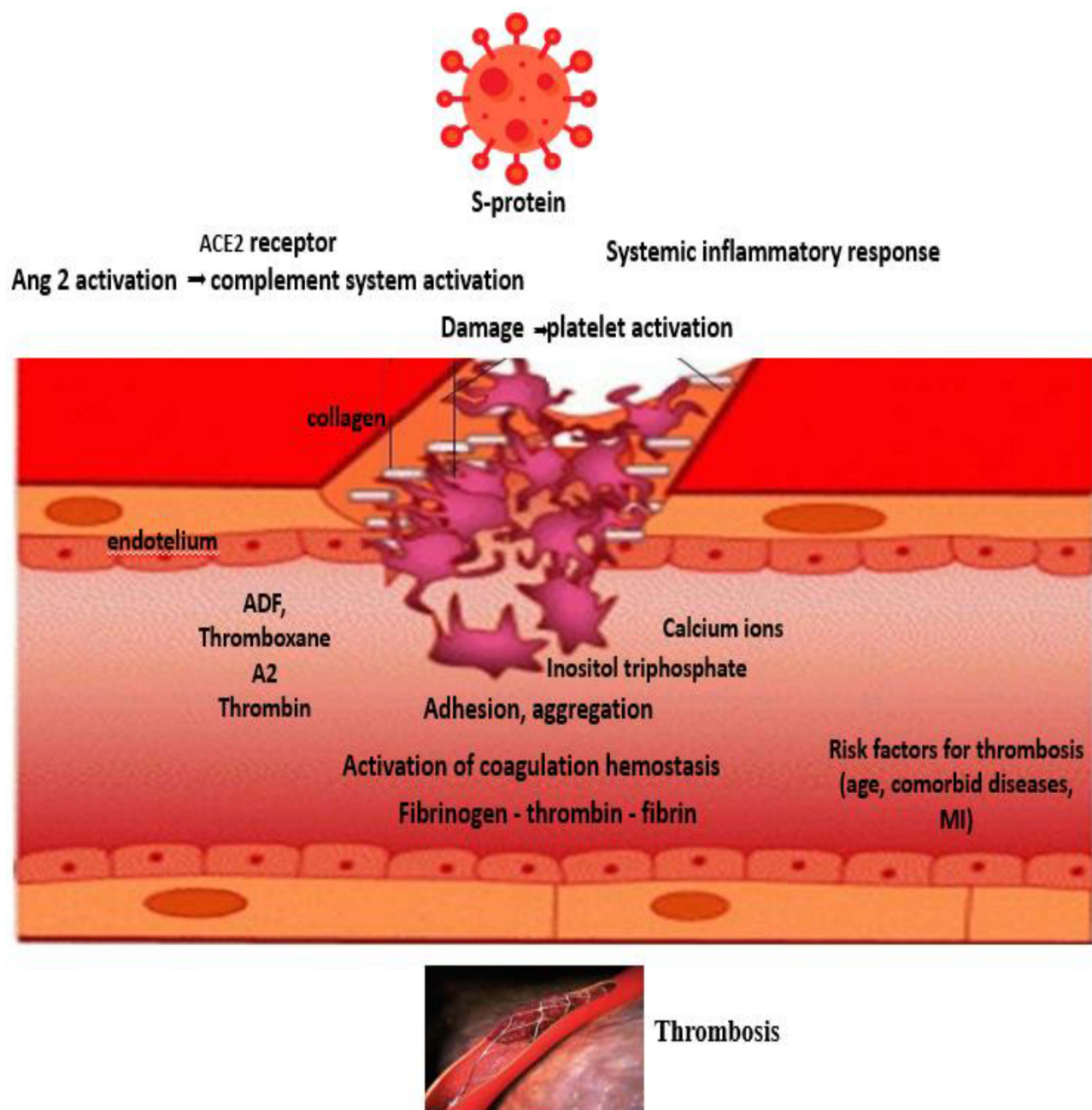


Figure 1 Pathogenesis of in-stent thrombus formation associated with COVID-19.

obtained and independently scrutinized for eligibility by two members of the review team. Any disagreements regarding the eligibility of specific studies were resolved through discussion involving a third reviewer. In instances of missing data, efforts were made to obtain the necessary information from the other study authors.

Methodological Assessment of Study Quality

The recommended Newcastle Ottawa Scale modification⁵⁵ checklist was used to assess the quality in all identified and collected full-text articles included in this study. The quality of the included studies was assessed independently by two authors (L.P. and G.B). The scale consists of eight items categorized into four domains: selection, assurance, causality and reporting. Given that Q5 and Q6 are related to the effects of drugs, we excluded them from the analysis of study quality. We rated the case report studies as high quality if there were six positive characteristics (7 studies), five studies

were rated as moderate in quality (4 positive characteristics), and three studies were rated as low quality (3 to 1 positive characteristics) (Table 1). To assess the quality of case series studies, we applied the same scale. We rated two of the three studies as high quality and one study as moderate quality (Table 2).

Risk of Bias Assessments

Studies that met the inclusion criteria were assessed using The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systemic Reviews Checklist for Case Reports and Checklist for Case Series.^{73,74} The tool focuses on method selection, sufficient demographics, presentation, diagnosis, and proper intervention. The Case Report Studies scoring from six to eight were considered as a “high quality” (eight studies), scoring from four to five were a “moderate quality” (four studies), and scores of ≤ 3 were estimated as a “low quality” (three studies) (Table 3). When assessing the risk of bias in Case Series Studies, we classified two studies as high-quality (9–10 positive answers out of 10 questions) and one study as low-quality (4 positive answers) (Table 4).

Data Analysis

We used tabulation and analysis, which reflected the characteristics of the included studies (age and sex, data about COVID-19, Chest X-Ray, SpO₂, previous revascularization, current revascularization, coronary angiography, EhoCG (EF), ECG, risk factors, outcomes).

Statistical tests to assess heterogeneity, including the χ^2 -test and the I^2 statistic, demonstrated a high degree of heterogeneity among the publications included in the studies. This fact did not allow us to conduct a qualitative meta-analysis of the results.

Results

Search of Literature

We used the “The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)” checklist to write the systematic review. A total of 38 full-text publications were found in the databases, which were manually screened to select relevant publications and further analyze them (Figure 2).

Twenty publications were excluded from the analysis because they related to thrombosis of non-coronary arteries (5 cases), or they did not contain information about COVID-19 (1 case) or the patients did not have prior revascularization before the current in-stent thrombosis or restenosis (12 cases) or stent thrombosis was associated with vaccination against coronavirus infection (2 cases). After screening, a total of 18 publications remained for further analysis. As a result of assessing the quality of publications and the risk of bias, we selected 10 high-quality publications (8 cases and 2 case series) for further synthesis.

Characteristics of Cases of in-Stents Thrombosis and Restenosis Associated with Coronavirus Infection

After assessing the quality of publications and the risk of errors, we selected 10 articles from scientific literature describing cases of thrombosis and restenosis of stents in individuals with coronavirus infection, of which only 2 publications were case series (from 4 to 10 cases) (Tables 5 and 6). 31.8% of people included in the study were aged from 40 to 59 years, 68.2% were over 60 years old. All patients were admitted to emergency departments with clinical signs of ACS or MI (typical chest pain, hemodynamic instability, shortness of breath). Most of the cases presented were thrombotic lesions of coronary stents due to the current coronavirus infection; only in seven cases, we encountered restenosis of previously implanted stents.

In the structure of restenosis and thrombosis, 59.1% (13 cases) were very late (more than one year from previous revascularization), 9.1% (2 cases) were late (from one month to one year from revascularization); 18.2% (4 cases) were considered as subacute events (from one day to one month) and 13.6% (3 cases) as acute events (within 24 hours from previous revascularization). All cases presented in this article were classified as definite because they were angiographically confirmed.

Table 1 Quality Assessment of Included Cases of in-Stent Thrombosis and Stenosis of Coronary Arteries Associated with COVID-19

Reference	Selection	Ascertainment		Causality				Reporting	Quality of the Case Report
	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	
Hinterseer M, 2020 ⁵⁶	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Kunal S, 2021 ⁵⁷	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Joshi D, 2022 ⁵⁸	No	Yes	Yes	No	N/a	N/a	Yes	No	Low
Zaher N, 2020 ⁵⁹	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Shinkai W, 2022 ⁶⁰	Yes	Yes	Yes	No	N/a	N/a	Yes	No	Moderate
Yildirim U, 2022 ⁶¹	No	Yes	Yes	No	N/a	N/a	No	No	Low
Hauguel-Moreau M, 2022 ⁶²	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Karic A, 2022 ⁶³	No	No	Yes	No	N/a	N/a	No	No	Low
Liebenberg J, 2022 ⁶⁴	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Elkholy, K, 2021 ⁶⁵	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Ayan M, 2020 ⁶⁶	Yes	Yes	Yes	No	N/a	N/a	No	Yes	Moderate
Sidhu N, 2022 ⁶⁷	Yes	Yes	Yes	Yes	N/a	N/a	Yes	Yes	High
Sonsoz M, 2022 ⁶⁸	yes	Yes	Yes	No	N/a	N/a	No	Yes	Moderate
Lacour T, 2021 ⁶⁹	No	Yes	Yes	Yes	N/a	N/a	Yes	No	Moderate
Antuña P, 2020 ⁷⁰	Yes	Yes	Yes	Yes	N/a	N/a	No	No	Moderate

Notes: Q1 - Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? Q2 - Was the exposure adequately ascertained? Q3 - Was the outcome adequately ascertained? Q4 - Were other alternative causes that may explain the observation ruled out? Q5 - Was there a challenge/rechallenge phenomenon? Q6 - Was there a dose-response effect? Q7 - Was follow-up long enough for outcomes to occur? Q8 - Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

Table 2 Quality Assessment of Included Case Series of in-Stent Thrombosis and Stenosis of Coronary Arteries Associated with COVID-19

Reference	Selection	Ascertainment		Causality				Reporting	Quality of the Case Report
	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	
Prieto-Lobato A, 2020 ⁷¹	Yes	Yes	Yes	No	N/a	N/a	No	Yes	High
Montaseri M, 2022 ⁷²	No	Yes	Yes	No	N/a	N/a	No	No	Moderate
Batenova G, 2023 ³³	Yes	Yes	Yes	No	N/a	N/a	No	Yes	High

Notes: Q1 - Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? Q2 - Was the exposure adequately ascertained? Q3 - Was the outcome adequately ascertained? Q4 - Were other alternative causes that may explain the observation ruled out? Q5 - Was there a challenge/rechallenge phenomenon? Q6 - Was there a dose-response effect? Q7 - Was follow-up long enough for outcomes to occur? Q8 - Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

In one patient, a previous case of revascularization had undergone CABG, and given the bypass occlusion, LAD stenting was performed. In another case, stenting was previously performed, and now, due to the multivessel disease of the coronary arteries, emergency CABG was performed. In the remaining cases, repeated stenting of the affected vessel was observed, followed by balloon dilation and thrombus aspiration in case of arterial thrombosis.

The main localization of restenosis or thrombosis was the left coronary artery (13 cases or 51.1%), thrombosis of the right coronary artery occurred in six cases (27.3%), thrombosis of the circumflex artery - in five cases (22.7%). The left marginal artery had thrombotic lesions in only one case (4.5%).

Table 3 Risk of Bias Assessment for Included Case Reports for in-Stent Thrombosis and Stenosis of Coronary Arteries Associated with COVID-19

Reference	Were Patient's Demographic Characteristics Clearly Described?	Was the Patient's History Clearly Described and Presented as a Timeline?	Was the Current Clinical Condition of the Patient on Presentation Clearly Described?	Were Diagnostic Tests or Assessment Methods and the Results Clearly Described?	Was the Intervention(s) or Treatment Procedure(s) Clearly Described?	Was the post-Intervention Clinical Condition Clearly Described?	Were adverse Events or Unanticipated Events Identified and Described?	Does the case Report Provide Takeaway Lessons?
Hinterseer M, 2020 ⁵⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kunal S, 2021 ⁵⁷	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Joshi D, 2022 ⁵⁸	Yes	Yes	Yes	Unclear	Unclear	Unclear	No	Yes
Zaher N, 2020 ⁵⁹	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes
Shinkai W, 2022 ⁶⁰	Yes	Yes	No	Yes	Yes	No	N/a	Yes
Yildirim U, 2022 ⁶¹	Yes	Yes	Unclear	Yes	Yes	Unclear	N/a	Yes
Hauguel-Moreau M, 2022 ⁶²	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Karic A, 2022 ⁶³	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Liebenberg J, 2022 ⁶⁴	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Elkholy, K, 2021 ⁶⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ayan M, 2020 ⁶⁶	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Sidhu N, 2022 ⁶⁷	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Sonsoz M, 2022 ⁶⁸	Yes	Yes	No	Unclear	Yes	No	No	No
Lacour T, 2021 ⁶⁹	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Antuña P, 2020 ⁷⁰	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear

Notes: Adapted from Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E, Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evidence Synthesis*. 2020;18(10):2127-2133.⁷⁴

All patients had a current or previous COVID-19, confirmed by PCR test or the immunoglobulins G and M. In 12 patients (54.5%), an X-ray examination showed bilateral polysegmental infiltration, corresponding to imagine of COVID-19 associated pneumonia; in other cases, the patients were asymptomatic or had mild symptoms of coronavirus infection.

Most patients had a significant decrease in left ventricular ejection fraction (18 cases or 81.8%). In addition to angiography, acute coronary syndrome or MI were confirmed by ECG data. Additional risk factors for in-stent restenosis and thrombosis of the coronary arteries were arterial hypertension (72.7%), type 2 diabetes mellitus (45.5%), hyperlipidemia (13.6%), hypothyroidism (4.5%), chronic kidney disease (18 0.2%), and previous strokes (13.6%).

Table 4 Risk of Bias Assessment for Included Case Series of in-Stent Thrombosis and Stenosis of Coronary Arteries Associated with COVID-19

Reference	Were there Clear Criteria for Inclusion in the Case Series?	Was the Condition Measured in a Standard, Reliable Way for All Participants Included in the Case Series?	Were valid Methods Used for Identification of the Condition for All Participants Included in the Case Series?	Did the Case Series Have Consecutive Inclusion of Participants?	Did the Case Series have Complete Inclusion of Participants?	Was there Clear Reporting of the Demographics of the Participants in the Study?	Was there Clear Reporting of Clinical Information of the Participants?	Were the Outcomes or Follow up Results of Cases Clearly Reported?	Was there Clear Reporting of the Presenting Site (s)/Clinic(s) Demographic Information?	Was Statistical Analysis Appropriate?
Prieto-Lobato A, 2020 ⁷¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/a
Montaseri M, 2022 ⁷²	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	N/a
Batenova G, 2023 ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Notes: Adapted from Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E, Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evidence Synthesis*. 2020;18(10):2127-2133.⁷⁴

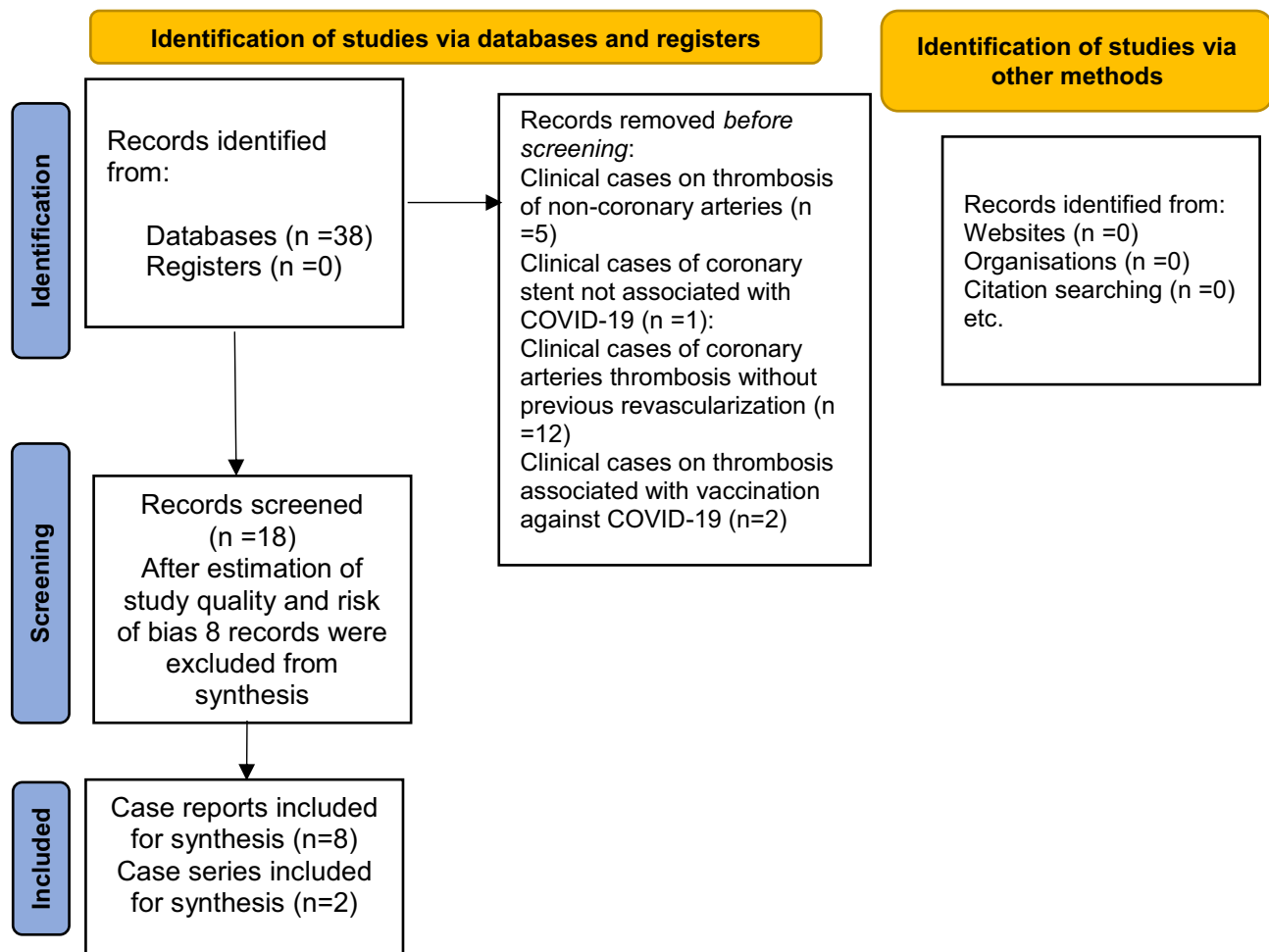


Figure 2 PRISMA flow diagram.

Considering the cases of deceased patients (5 cases), it can be noted that two of them were aged 48–51 years. Four patients had diabetes mellitus as risk factors, and all patients suffered from hypertension. Four patients had symptoms of severe COVID-19 infection with bilateral polysegmental pneumonia and signs of acute respiratory distress syndrome characterized by low oxygen saturation; two of them developed sepsis with acute kidney injury due to bacterial superinfection. The remaining patients did not have pronounced symptoms of coronavirus infection, but a positive PCR result gave grounds to conclude that coronavirus infection could act as a trigger factor for launching the coagulation cascade, leading to acute or subacute stent thrombosis. All patients experienced severe hemodynamic disturbances with the development of cardiogenic shock and fatal arrhythmias leading to death. In three out of five cases, acute or subacute stent thrombosis was observed.

Discussion

Research data indicate that the main risk factors for late and very late thrombosis of coronary artery stents are diabetes mellitus, multivessel disease requiring implantation of more than two stents, acute myocardial infarction, CKD, implantation of a sirolimus-eluting stent, impaired dilation after PCI, as well as bad adherence to antiplatelet therapy.⁷⁵

Analysis of the cases that we reviewed allows us to consider systemic infectious inflammation with the release of inflammatory mediators, such as cytokines (interleukin 6, tumor necrosis factor), as a factor that can cause endothelial damage and trigger the coagulation cascade. One of the key biochemical processes in COVID-19 is the interaction between the viral spike protein and the ACE2 receptor on host cells. This interaction allows the virus to enter host cells and replicate, leading to virus spread and disease progression. In addition, the virus causes a pro-inflammatory response

Table 5 Characteristics of Included Case Report Studies

Reference	Age and sex	Data about COVID-19	Chest X-Ray	SpO2	Previous revascularisation	Current revascularisation	Coronary angiography	EhoCG (EF)	ECG	Risk factors	Outcome
Hinterseer M, 2020 ⁵⁶	65-year-old male	Positive RT-PCR	Bilateral pulmonary infiltrates	78%	Stenting of marginal artery and LAD four years ago; in-stent thrombosis 2 years ago	Thrombus aspiration, stenting	Thrombus in in stent thrombosis in LAD	EF of 35%	ST-segment elevation in aVR, complete RBBB	DM, HTN, hyperlipidemia	Died
Kunal S, 2021 ⁵⁷	40-year-old male	Positive RT-PCR	Bilateral pulmonary consolidations	95%	Stenting in LAD two years ago due to STEMI	Balloon angioplasty and thrombus aspiration	Non-occlusive thrombus in the LAD stent	EF of 35%	ST-segment elevation in V1-V6	N/A	Survived
Zaher N, 2020 ⁵⁹	51-year-old man	Positive RT-PCR	Pulmonary vascular congestion	91%	Previous myocardial infarction with DES placed in the LAD.	LCX angioplasty with overlapping DES. Acute rethrombosis minutes later. Balloon angioplasty	100% occlusion of LCX with diffuse disease in the LAD	Dilated left ventricle with low EF	ST elevations in III, aVF, V5, and V6	CAD, HTN, DM	Died
Hauguel-Moreau M, 2022 ⁶²	65-year-old man	Positive RT-PCR	COVID-19 interstitial pneumonia	N/A	10 years before 2 DES were implanted PDA due to STEMI. 2 years ago a DES was implanted in mid-LAD.	Two DES implanted in mid-LAD and PDA	Acute dual thrombotic occlusion in the LAD and PAD DES	EF of 25%	Anterior and inferior ST-segment elevation with Q waves	Psoriatic arthritis, HNT, CAD	Survived
Liebenberg J, 2022 ⁶⁴	71-year-old man	Positive RT-PCR	No findings	88%	Forty-six hours before two DES stents were placed to LCX and RCA	Balloon inflations and thrombus aspiration. Intracoronary injection of metalyse	Subacute stent thrombosis of both the LCx and RCA stents	EF of 40–45%	Posterior ST-elevation MI	HNT	Died
Elkholy, K, 2021 ⁶⁵	48-year-old male	Positive RT-PCR	Bilateral interstitial lung infiltrates	N/A	3 days before thrombectomy and placement of a DES was performed to LAD	Angioplasty and thrombectomy of the lesion in the mid-RCA	100% occlusion of the stent, and novel 100% occlusion in the RCA	EF of 40–50%	ST elevation in II, III, aVL, aVF, and V2-V5; AV block	DM, HNT, hyperlipidemia, and smoking	Died
Ayan M, 2020 ⁶⁶	64-year-old black man	Positive RT-PCR	Bilateral lung infiltrates, ARDS	83%	100% thrombotic occlusion of the second obtuse marginal artery 3 days ago, PCI with DES	Balloon angioplasty and new Resolute Onyx stent	Complete thrombotic occlusion of the second obtuse marginal artery	EF of 45–50%	ST segment depressions in lateral leads.	Chronic hepatitis C, HNT, and tuberculosis	Survived
Sidhu N, 2022 ⁶⁷	56-year-old man	Positive RT-PCR	No findings	Norm	Implantation of 2 everolimus-eluting stents to LAD 8 days ago.	DAPT and dabigatran 110 mg after five days of enoxaparin	Dual stent thrombosis of LAD (30% and 75%)	EF of 45%.	Lateral wall ST elevation MI	Dislipidemia	Survived

Abbreviations: CAD, coronary arteries disease; CKD, chronic kidney disease; DES, drug-eluting stent; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; LAD, left anterior descending artery; LCX, left circumflex artery; LVD, left ventricle dysfunction; MI, myocardial infarction; N/A, not available; PAD, peripheral artery disease; PDA, posterior descending artery; RCA, right coronary artery; RT-PCR, reverse transcription polymerase chain reaction.

Table 6 Characteristics of Included Case Series Studies

Reference	Age and Sex	Data about COVID-19	Chest X-Ray	SpO2	Previous Revascularisation	Current Revascularisation	Coronary Angiography	EhoCG (EF)	ECG	Risk Factors	Outcome
Prieto-Lobato A, 2020 ⁷¹	49-year-old man	IgG was positive for COVID-19	Bilateral lung infiltrates	90%	Balloon angioplasty and stenting of LCX with 2 overlapped stents 30 min ago	Intracoronary tirofiban and proximal overexpansion of stent	Acute LCX stent thrombosis	EF of 45%	Lateral ST-elevation MI	DM, LVD	Survived
	71-year-old man	Positive RT-PCR	Bilateral lung infiltrates	96%	Inferior STEMI seven years ago treated with RCA DES	Thrombectomy, tirofiban, and 2 DES restored flow	Very late RCA stent thrombosis	EF of 55%	ST-elevation in the precordial leads	CKD	Survived
	85-year-old man	Positive IgM serological testing	No findings	95%	PCI with LAD artery DES implantation 15 years ago	Balloon angioplasty, thrombectomy, and tirofiban	Very late LAD artery stent thrombosis, and neoatherosclerosis	EF of 30%	Anterior ST-elevation with Q waves	LVD, age	Survived
	86-year-old man	Positive RT-PCR	No findings	95%	LAD artery DES due to MI two years ago	A new DES was implanted to LAD	LAD stent thrombosis	EF of 45%	Anterior ST-elevation	DM, CKD, PAD, age	Survived
Batenova G, 2023 ³³	65-year-old man	Positive RT-PCR	Bilateral pneumonia	97%	DES stenting RCA five months ago	Balloon angioplasty and DES implantation	RCA in-stent restenosis	EF of 25%	ST-depression in precordial leads	HNT, DM	Survived
	69-year-old man	Positive RT-PCR	No findings	95%	DES stenting to RCA 7 years ago	Balloon angioplasty and DES implantation	RCA in-stent restenosis	EF of 35%	ST-depression in precordial leads	HNT	Survived
	66-year-old woman	Positive RT-PCR	No findings	87%	DES stenting to LAD 8 years ago	Balloon angioplasty and DES implantation	LAD in-stent thrombosis	EF of 55%	ST-elevation in V5-V6	HNT, DM	Survived
	80-year-old man	Positive RT-PCR	Bilateral pneumonia	78%	DES stenting to LAD 4 years ago	Balloon angioplasty and DES implantation	LAD in-stent thrombosis	EF of 26%	ST-elevation in aVL, V3-V6	HNT, stroke, DM, AF	Died
	66-year-old man	Positive RT-PCR	No findings	92%	DES stenting to LCX 8 years ago	Balloon angioplasty and DES implantation	LCX in-stent restenosis	EF of 34%	ST-elevation and Q VI-V3	HNT, DM, CKD	Survived
	59-year-old man	Positive RT-PCR	No findings	95%	DES stenting to LCX 8 years ago	Balloon angioplasty and DES implantation	LAD in-stent thrombosis	EF of 41%	ST-elevation VI-V6	HNT	Survived
	71-year-old woman	Positive RT-PCR	Bilateral pneumonia	95%	DES stenting to LAD 11 months ago	Balloon angioplasty and DES implantation	LAD in-stent restenosis	EF of 44%	A new LBBB	HNT, stroke, CKD	Survived
	46-year-old man	Positive RT-PCR	Bilateral pneumonia	97%	DES stenting to LAD 5 years ago	Balloon angioplasty and DES implantation	LAD in-stent restenosis	EF of 52%	ST-depression in V5-V6	HNT	Survived
	70-year-old woman	Positive RT-PCR	No findings	98%	Stent implantation to LCX 14 years ago	Balloon angioplasty and DES implantation	LCX in-stent restenosis	EF of 56%	Lateral ST-elevation	HNT, stroke, hypothyreosis	Survived
	65-year-old man	Positive RT-PCR	No findings	97%	CABG in LAD and RCA 13 years ago	DES implantation to LAD	Thrombosis of LAD and RCA	EF of 48%	Lateral ST-elevation	HNT, DM	Survived

Abbreviations: CKD, chronic kidney disease; DES, drug-eluting stent; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; LAD, left anterior descending artery; LCX, left circumflex artery; LVD, left ventricle dysfunction; MI, myocardial infarction; N/A, not available; RCA, right coronary artery; RT-PCR, reverse transcription polymerase chain reaction.

through the activation of various immune cells, which leads to the release of cytokines and tissue damage.^{76,77} A study conducted by Chinese scientists showed that in people hospitalized due to COVID-19 associated pneumonia, coagulopathies occurred in 19%, heart failure in 23%, and acute cardiac injury in 17%. Among the deceased, coagulopathies were found in 50%, heart failure - in 52% of cases, acute cardiac injury - in 59%. The main risk factors for mortality in these patients were diabetes mellitus (OR=2.85), arterial hypertension (OR=3.05) and smoking (OR=2.23).³⁵

All of the described patients had a coronary history before CVI, they were all prescribed dual antiplatelet therapy (aspirin and a P2Y12 receptor inhibitor), and they demonstrated good adherence to treatment. However, against the background of a viral infection, despite correctly prescribed antiplatelet therapy and additional prescription of anticoagulants (heparin, unfractionated and low molecular weight heparins) progression of the thrombus formation process was noted. This progression can also be explained by the development of heparin resistance, which some authors discussed previously.^{78,79} On the other hand, concomitant use of antiviral drugs with direct oral anticoagulants may increase the risk of bleeding. This effect is caused by the inhibition of cytochrome isoenzymes by antiviral drugs, which disrupts the metabolism of anticoagulants and increases their concentrations in the blood.^{80,81}

A limitation of our study is the lack of information about anamnestic data, as well as laboratory parameters indicating both the severity of systemic inflammation and the lipid spectrum, coagulation activity, bacterial superinfection, and the state of immunity in patients in the cases we examined. This shortage can be explained by the limited time and resources during the initial period of the coronavirus pandemic, which caused a slowdown in hospitalization and medical care in catheterization laboratories, as well as the urgency of the situation in patients with ACS or MI. In the current literature, we could only find case study designs and case series. These studies were characterized by a high degree of heterogeneity, making statistical analysis and meta-analysis of the results impossible.

Conclusion

In the structure of restenosis and thrombosis, 75% of cases were late and very late events, only 6.25% occurred within 24 hours of the previous revascularization. The main localization of restenosis or thrombosis was the left coronary artery (71.9%). Risk factors for restenosis and thrombosis of the coronary arteries were arterial hypertension (56.25%), type 2 diabetes mellitus (37.5%), smoking (12.5%), hyperlipidemia (9.4%), hypothyroidism (6.25%), chronic kidney disease (12.5%), severe obesity (6.25%), and previous strokes (9.4%). Analysis of cases allows us to consider systemic infectious inflammation as a factor capable of causing endothelial damage and triggering the coagulation cascade. Considering that COVID-19 continues to infect the residents of all countries up to present time, special attention should be paid to persons suffering from coronary heart disease who have undergone revascularization. Since this category of patients has an increased risk of complications, in case of COVID-19 infection they should be provided with access to the fastest possible examination of the cardiovascular system (ECG, EchoCG, laboratory tests), coronary angiography and confirmation of coronavirus infection (PCR test, study of immunoglobulins G and M). It is necessary to monitor the adherence of such patients to antiplatelet therapy and inform them about the risks associated with COVID-19. To more accurately determine the relationship between coronavirus infection and restenosis and stent thrombosis, it is necessary to continue clinical studies on large groups of patients using thematic registers and databases.

Data Sharing Statement

The datasets generated for this study are available on request to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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