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SYSTEMATIC REVIEW ARTICLE

Diagnostic importance of performing myocardial perfusion imaging in COVID-19 patients: A systematic review

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has posed a major challenge to the diagnosis and management of ischemic heart disease (IHD). Myocardial perfusion imaging (MPI) is a non-invasive technique that can assess myocardial ischemia and viability, as well as provide prognostic information for patients with IHD. However, the role of MPI in COVID-19 patients is not well established.
Methods: A comprehensive search of PubMed, Embase, Cochrane Library, and Web of Science was conducted to identify relevant studies published until Aprile 24th, 2024. The inclusion criteria were: (1) studies that performed MPI in COVID-19 patients; (2) studies that reported the results of MPI in terms of ischemia, infarction, or perfusion defects; and (3) studies that compared MPI with other diagnostic modalities or clinical outcomes. The quality of the studies was assessed using the QUADAS-2 tool for diagnostic accuracy studies or the ROBIS tool for systematic reviews. A narrative synthesis was performed to summarize the main findings and recommendations.
Results: A total of twenty-two studies met the inclusion criteria. The included study information was categorized into the following aspects: Change in the crude number of MPI scans performed, accidental and definite findings in MPI, and the prognostic outcome of COVID patients who underwent MPI.
Conclusion: During Covid-19 pandemic, a reduction in the number of MPI studies was seen. Individuals with a history of COVID-19 infection have higher likelihood of developing ischemic heart disease (IHD). SARS-CoV-2 is an independent risk factor for the development of IHD.

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INTRODUCTION

The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global health crisis. As of the latest available data in April 13, 2024, the COVID-19 virus has infected 704,753,890 people and claimed 7,010,681 lives worldwide [1]. While the primary impact of COVID-19 is on the respiratory system, it has also been observed to cause significant cardiovascular consequences, such as myocardial damage, arrhythmias, heart failure, and thromboembolic events [2]. The primary impact of COVID-19 is on the respiratory system; nonetheless, it has been observed to induce cardiovascular consequences, including myocardial damage, arrhythmias, heart failure, and thromboembolic events [3, 4]. These cardiovascular complications are strongly associated with unfavorable prognosis and increased mortality rates among COVID-19 patients [5]. The mechanisms underlying the cardiovascular implications of COVID-19 are complex and multifaceted, involving factors such as direct viral infiltration, systemic inflammation, cytokine storm, endothelial dysfunction, microvascular damage, coagulation abnormalities, and pre-existing comorbidities [6-8].

Gated myocardial perfusion imaging (MPI) is a non-invasive imaging modality used to assess myocardial perfusion and function [9]. MPI can be performed using single photon emission computed tomography (SPECT) or positron emission tomography (PET) techniques, which involve the administration of radioactive tracers into the bloodstream and the subsequent detection of their distribution throughout the myocardium [10]. This technique is used to identify myocardial ischemia or infarction by comparing the uptake of the radiotracer under stress and rest conditions. In a healthy myocardium, the tracer uptake is uniform in both phases, whereas in an ischemic or infarcted myocardium, the tracer uptake is reduced or absent during stress and may or may not improve during rest [9, 10].

While MPI has been widely used to assess coronary artery disease (CAD), its role and significance in COVID-19 patients remain unclear (10). COVID-19 patients may have false-positive MPI results due to factors such as increased lung uptake of the tracer, reduced cardiac output, or increased sympathetic tone [11]. On the other hand, COVID-19 patients may also have true-positive MPI results due to pre-existing or newly developed CAD, myocarditis, or microvascular dysfunction. Therefore, it is crucial to understand the diagnostic value and clinical implications of MPI in COVID-19 patients [12].

Conversely, individuals afflicted with COVID-19 may exhibit accurate positive results in MPI because of preexisting or newly developed coronary artery disease (CAD), myocarditis, or microvascular dysfunction. Hence, it is imperative to comprehend the diagnostic significance and clinical ramifications of MPI in individuals afflicted with COVID-19 [13].

COVID-19 patients face a considerable risk of developing various cardiovascular complications, which can manifest during both the acute phase of the infection and the extended follow-up period. These complications include myocarditis, acute coronary syndromes (ACS), arrhythmias such as atrial fibrillation (AF), and pericarditis [14-17]. A study reported myocardial injury, evidenced by elevated troponin T levels, in 27.8% of hospitalized COVID-19 patients, which correlated with higher mortality rates [18]. The same study found a 10% incidence of ACS among COVID-19 patients, particularly those with pre-existing cardiovascular risk factors [18]. Furthermore, AF and other arrhythmias were reported in 3-17% of COVID-19 cases across multiple studies [17]. Pericarditis, presenting with chest pain and ST-segment elevation on electrocardiography (ECG), has also been documented in COVID-19 patients [16]. Notably, these complications may persist beyond the acute infection phase, necessitating long-term monitoring and management [19].

This systematic review aims to provide a comprehensive overview of the existing literature on the utilization and outcomes of MPI in COVID-19 patients. We conducted a thorough literature search to identify studies that have evaluated MPI findings in COVID-19 patients, including diagnostic accuracy metrics, clinical outcomes, and adverse events. The findings of this study are reported in accordance with the PRISMA criteria.

METHODS

Protocol

The present study was undertaken in accordance with the PRISMA Statement [20] to assess the diagnostic efficacy of MPI in individuals diagnosed with COVID-19.

Search strategy

The search was performed across multiple databases, including Scopus, Embase, PubMed, Medline, the Cochrane Library, Google Scholar, and the Web of Science, covering the entire period from the establishment of these databases to April 24, 2024. A distinct syntax, aligned with the search

rules of each individual database, was employed to conduct searches. Additionally, we were contemplating the manual exploration of gray literature sources such as conference abstracts, dissertations, and the Google search engine, utilizing the subsequent search strings:
(myocardial perfusion imaging OR Imaging, Myocardial Perfusion OR Perfusion Imaging, Myocardial OR Myocardial Scintigraphy OR Scintigraphy, Myocardial OR MPI) OR (CT Scan, Single-Photon Emission OR CT Scan, Single Photon Emission OR Radionuclide Tomography, Single-Photon Emission Computed OR Radionuclide Tomography, Single Photon Emission Computed OR Tomography, Single-Photon, Emission-Computed OR Single-Photon Emission Computerized Tomography OR Single Photon Emission Computerized Tomography OR Single-Photon Emission CT Scan OR Single Photon Emission CT Scan OR Single-Photon Emission-Computed Tomography OR Emission-Computed Tomography, Single-Photon OR Single Photon Emission Computed Tomography OR Tomography, Single-Photon Emission-Computed OR SPECT OR CAT Scan, Single-Photon Emission OR CAT Scan, Single Photon Emission OR Single-Photon Emission Computer-Assisted Tomography OR Single Photon Emission Computer Assisted Tomography) AND (COVID 19 OR 2019-nCoV Infection OR 2019 nCoV Infection OR 2019-nCoV Infections OR Infection, 2019-nCoV OR SARS-CoV-2 Infection OR Infection, SARS-CoV-2 OR SARS CoV 2 Infection OR SARS-CoV-2 Infections OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR COVID-19 Virus Infection OR COVID19 OR Coronavirus Disease 2019 OR Disease 2019, Coronavirus OR Coronavirus Disease-19 OR Coronavirus Disease 19 OR Severe Acute Respiratory Syndrome Coronavirus 2 Infection OR SARS Coronavirus 2 Infection OR 2019-nCoV Disease OR 2019 nCoV Disease OR 2019-nCoV Diseases OR Disease, 2019-nCoV)
Furthermore, we conducted a thorough examination of the references cited in the retrieved publications to identify any further pertinent studies. No language or other filters were applied to our search.

Eligibility criteria and study selection

We included studies that evaluated the use and outcomes of MPI in COVID-19 patients, regardless of their study design, participant characteristics, or MPI modality. We excluded abstracts, review articles, and animal studies. Our research question was: "What is the application of MPI during the COVID-10 pandemic as well as diagnostic value of MPI in COVID-19 patients?"
The titles and abstracts of the search results were separately reviewed by two reviewers, who identified studies that satisfied our qualifying criteria. The complete texts of the chosen studies were acquired and evaluated for potential inclusion. Disagreements amongst reviewers were settled by the intervention of a third party.

Data extraction and quality assessment

All the search results were imported to Endnote X8 citation manager and duplicate studies were removed. In addition, a preexisting Excel form was utilized to extract data from the whole texts of the papers that were included. The dataset comprised many elements, including the title, author, year of publication, country of origin, study design, criteria for inclusion and exclusion, sample size, and characteristics of the individuals, such as their mean age and severity of disease. Additionally, data pertaining to MPI findings, diagnostic accuracy metrics, clinical outcomes, and adverse events were retrieved. The authors of the research were contacted if clarification or more information was required. Missing or ambiguous data were addressed with imputation or exclusion, when deemed suitable.
The risk of bias or quality of each study was evaluated using either the QUADAS-2 tool for diagnostic accuracy studies or the ROBIS tool for systematic reviews. The domains or criteria were assessed and assigned ratings of low, high, or unclear risk of bias or quality. Any disagreements between reviewers were managed through discussion or by seeking input from a third party.

Data synthesis and analysis

The findings of the data extraction and quality assessment were presented through the utilization of tables, figures, and summary statements. The data was synthesized and analyzed using narrative synthesis, when deemed suitable.

RESULTS

Literature search results

The study selection process is depicted in Figure 1. An initial search yielded 11,200 studies, which were reduced to 332 after removing duplicates. The titles and abstracts of these studies were screened, and irrelevant studies, reviews, editorials, case reports, and case series were omitted. This left thirty-three studies for full-text assessment, of which twenty-two were deemed eligible for inclusion in our systematic review (Table 1).

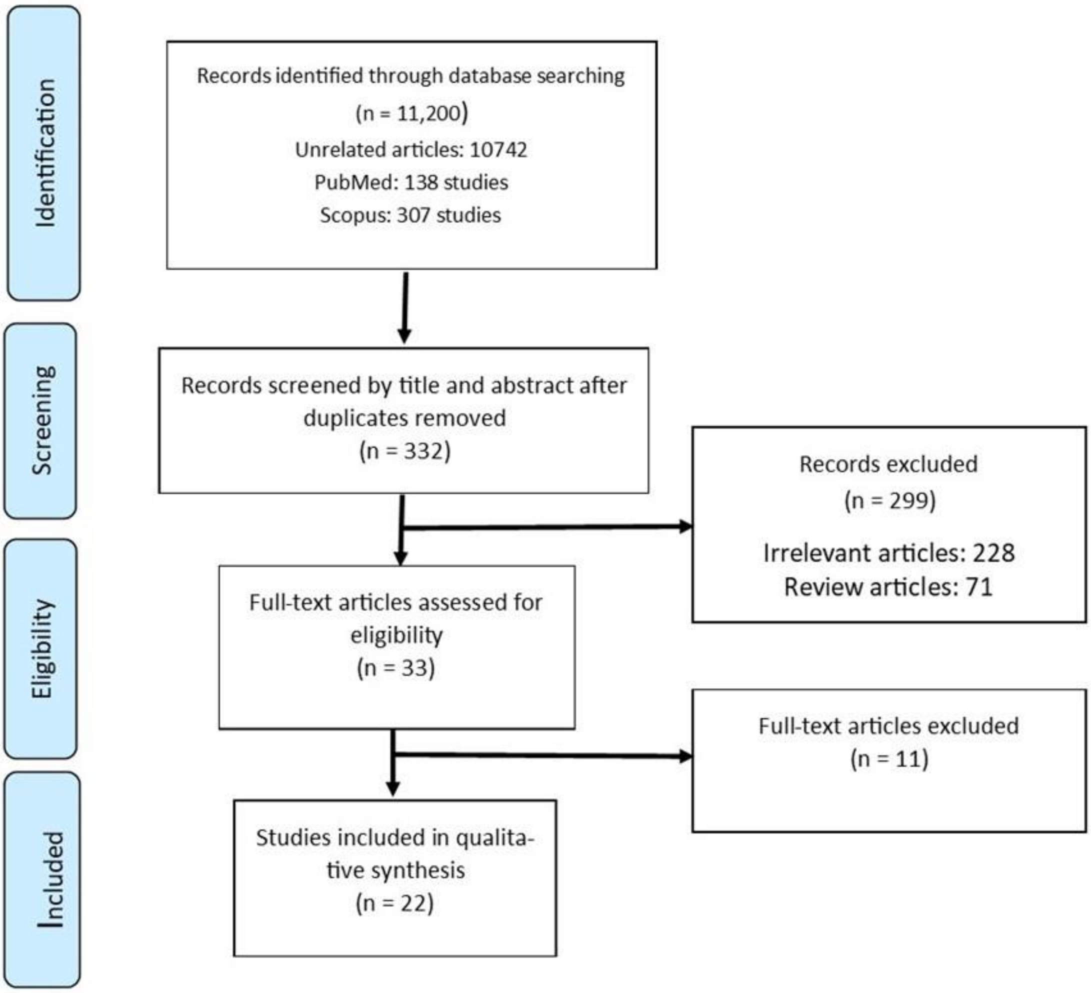

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Accidental findings in MPI

MPI is a non-invasive technique that uses radioactive tracers to assess the blood flow and function of the heart muscle. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel virus that causes Coronavirus Disease 2019 (COVID-19), a respiratory illness that can affect multiple organs, including the heart. Several studies have reported incidental findings of SARS-CoV-2 infection in patients who underwent MPI scans for cardiac evaluation. These studies suggest that MPI in term of myocardial perfusion SPECT or SPECT/CT may have a potential role in detecting pulmonary involvement of COVID-19, as well as assessing its impact on myocardial perfusion.

Delabie et al. [21] presented a case of a 50-year-old male patient who experienced exertional chest pain without any sign of COVID-19 and underwent gated Myocardial Perfusion SPECT/CT. The MPI showed normal myocardial perfusion, but the subsequent computed tomography (CT) scan revealed bilateral Ground-Glass Opacities (GGOs) and crazy-paving in subpleural region in the lower lobes of the lungs, in favor of COVID-19 pneumonia. The patient evaluated positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR). The authors proposed that increased tracer uptake in the lungs during MPI scans could be a marker of SARS-CoV-2 infection, as radiotracer binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are also used by SARS-CoV-2 to enter host cells.

Jochumsen et al. [22] reported a case of a 59-year-old male patient with a history of Ischemic Heart Disease (IHD) who underwent an $[^{15}O]H_2O$ myocardial perfusion positron emission tomography/computed tomography (PET/CT). The patient had a confirmed diagnosis of SARS-CoV-2 infection by RT-PCR 12 days before the scan. The scan revealed an inferior scar secondary to complete occlusion of the right coronary artery (RCA), and severe peri-infarction hypoperfusion throughout the entire RCA territory.

Table 1. Diagnostic information of MPI in COVID studies

Author(s)	Main Findings	Control group size (patients)	Study group size (patients)	Date of data collection	Type of Study
Araz et al. [28]	In the study group, ischemia was observed more frequently ($p < 0.001$) irrespective of the MPS. The need for invasive CAG examination and treatment was increased in the study group ($p = 0.006$ and $p = 0.015$). This was true for patients with abnormal MPS results ($p = 0.008$ and $p = 0.024$) but not those with ischemia ($p = 0.29$ and $p = 0.06$).	94	85	August 2020 to April 2021.	Retrospective cohort
Cap et al. [30]	After adjusting for clinical variables with Bayesian logistic regression, a substantial correlation between confirmed prior COVID-19 infection and aberrant MPI was discovered. (Posterior median odds ratio, 1.70 [95% CI, 1.20–2.40], risk difference, 9.6% [95% CI, 1.8%, 19.7%]).	1495	340	January 1st to June 30th, 2021.	Retrospective cohort
Assante et al. [34]	Abnormal MPS and COVID-19 infection are independent event predictors. There was no significant disparity in COVID-19 patients with or without abnormal MPS. Abnormal MPS increases the incident rate in individuals without COVID-19. In patients with normal and abnormal Total Perfusion Defect, infection increased the event rate.	960 individuals with confirmed or suspected CAD	-	January 2018 to June 2019.	Cohort
Hasnie et al. [39]	The quantity of SPECT-MPI experiments completed during the height of the pandemic's limits dropped significantly. The rate of abnormal results remained steady despite this constraint. A similar percentage of individuals in the cohorts of 2019 and 2020 had abnormal scans.	210	368	April 1st to May 31st, 2020.	Retrospective cohort
Hasnie et al. [26]	No serious adverse events were reported among the patients during or after the stress tests. However, one patient needed a reversal agent, aminophylline, for chest pain induced by Regadenoson. The stress tests took place approximately 65 days, with a range of 31 to 94 days, following their COVID-19 diagnosis.	N/A	15	March 2020 to July 2020	Retrospective observational study
Mills et al. [32]	Patients with COVID-19 showed a 27.9% higher in-hospital death rate for acute coronary syndrome than those without the virus (3.7%). During the initial stages of the pandemic, cardiac SPECT utilization rates decreased more than cardiac PET (74% vs. 51%).	N/A	N/A	N/A	Review
Nappi et al. [31]	The number of stress SPECT-MPI investigations done during the COVID-19 pandemic (n = 123) was substantially lower than in	1238	123	February to May of 2020, and	Retrospective cohort

	2017-2018-2019 (n = 413). The percentage of abnormal stress SPECT-MPI tests was similar (p = 0.65) during the pandemic (36%) compared to 2017-2019 (34%).			corresponding dates in 2017-2019	
Kirienko et al. [38]	In lieu of an exercise test, fast protocols and pharmacological stress evaluation were utilized.	N/A	N/A	Literature up to January 21st, 2021	Review
Bilge et al. [35]	The presence of pneumonia significantly enhanced the probability of ischemia in SPECT-MPI scans with an odds ratio of 2.90.	114	152	January 1st, 2021, to November 1st, 2021	Retrospective cohort
Freudenberg et al. [44]	113 full answers were registered. A reduction in nuclear medicine diagnostic procedures is reported by almost all participants (97%) in the study. Myocardium PET/CT scintigraphs had a mean decrease of -47.2%.	N/A	N/A	April 14th, 2020, to April 20th, 2020	Survey
Ananthasubramania et al. [6]	After attenuation correction, a mildly reversible anterior/anterolateral perfusion deficit becomes less noticeable.	N/A	N/A	April 8th, 2020	Case report
Chan et al. [27]*	Tl-avid localized uptake was seen incidentally over the left axillary region and improbable myocardial ischemia in MPI.	N/A	N/A	N/A	Case report
Delabie et al. [21]	An indication of asymptomatic COVID-19 infection might be high signal in the lungs on [^{99m}Tc]Tc-MIBI MPI, especially in individuals with a normal left ventricular ejection fraction.	N/A	N/A	N/A	Case report
Hindle-Kate et al. [23]	In a case presenting with chest tightness and exertional chest pain, MPI was normal, and the symptoms were attributed to COVID infection.	N/A	N/A	N/A	Case report
Kalantari et al. [24]	A 65-year-old female with atypical chest pain and dyspnea and a normal MPI scan implied that symptoms are a consequence of COVID infection.	N/A	N/A	N/A	Case report
Malek et al. [25]	A sign of pulmonary involvement of COVID-19 infection might be multifocal pulmonary uptake of [^{99m}Tc]Tc-MIBI.	N/A	N/A	N/A	Case report
Weber et al. [29]	MBFR abnormalities were detected in 44% of patients suffering from COVID-19. In more than half of the patients with abnormal stress myocardial perfusion, there were signs of obstructive CAD. A greater proportion of COVID-19 patients (44%) exhibited both abnormal maximal MBF and MBFR than did the control group (9.7%).	103	34	April 1, 2020, to July 1, 2021	Retrospective cohort

Verma et al. [36]	PASC-CVS patients exhibited a notably increased MBF (1.29 ± 0.27 vs. 1.08 ± 0.20 ml/g/min, p ≤ .024), though their MFR was lower than the control group (1.97 ± 0.54 vs. 2.27 ± 0.43, p ≤ .031). Furthermore, patients with PASC-CVS with pharmacologic vasodilation showed a significant reduction in longitudinal MBF during hyperemic MBF, a trend absent from the control group.	23	23	N/A	Retrospective cohort
Jochumsen et al. [22]	MPI revealed a complete blockage of the RCA, a scar in the inferior segment, and substantial hypoperfusion surrounding the entire RCA area. Additionally, the increased perfusion suggested the presence of sporadic, ground-glass-like peripheral lung infiltrates scattered throughout both lungs. Malignant and benign extracardiac coincidental findings with increased perfusion are readily visible and frequently seen on [^{15}O]H_2O PET MPI. Summed [^{15}O]H_2O PET images should be evaluated in addition to the low-dose CT attenuation images.	N/A	2963	January 2020 to June 2021	Case series
Thornton et al. [33]	Recovered COVID-19 patients with troponin elevation had a high prevalence of regional perfusion defects on CMR, suggesting ischemia rather than global blood flow reduction. These defects were associated with myocardial infarction and myocarditis-like scar, and that SARS-CoV-2 infection was an independent predictor of cardiovascular events.	27+90	90	June 2020 to March 2021	Case-control study
Scrima et al. [37]	A new ad hoc protocol for nuclear cardiology imaging during Covid-19 pandemic was safe and effective for both health providers and patients. The incidence of significant inducible ischemia increased when correct stratification of patients was performed.	N/A	46	April 7 to May 15, 2020	Observational study
Einstein, et al. [40]	COVID-19 led to a sharp decrease in cardiovascular diagnostic tests, particularly impacting poor regions. Countries classified as low-income and lower-middle-income experienced an additional 22% drop in cardiac procedures, coupled with less access to PPE and telehealth services.	909 centers in 108 countries	909 centers in 108 countries	March and April 2020	Web-based survey

*. Because this study was an incidental finding, we excluded it from the PRISMA analysis but used its data in the results section.

Additionally, increased perfusion was observed in patchy, ground-glass-like peripheral lung infiltrates distributed across both lungs, indicating active inflammation due to COVID-19. The authors demonstrated the utility of $[^{15}O]H_2O$ PET/CT for assessing both myocardial perfusion and pulmonary abnormalities in COVID-19 patients. They advised that the interpretation of $[^{15}O]H_2O$ PET/CT reports should include the analysis of summed $[^{15}O]H_2O$ images, as well as the parametric myocardial blood flow images generated by the cardiac software.

Hindle-Katel et al. [23] described a similar case of a 65-year-old female patient who presented with dyspnea and exertional chest tightness for two weeks. The patient underwent an MPI using $[^{99m}Tc]$Tc-sestamibi, which showed normal myocardial perfusion. However, the CT attenuation correction (CTAC) images showed no significant coronary calcification although patchy GGOs in both lungs, suggestive of COVID-19 pneumonia. The patient evaluated positive for SARS-CoV-2 by RT-PCR. The authors highlighted that CTAC images obtained during MPI SPECT/CT could be useful for detecting pulmonary manifestations of COVID-19, especially in asymptomatic or mildly symptomatic patients.

Kalantari et al. [24] reported a case of a 67-year-old female patient who presented with atypical chest pain and dyspnea for ten days. The patient underwent a stress/redistribution $[^{201}Tl]$Tl-chloride protocol for MPI. The MPI scan showed mild Tl-201 uptake in both lungs, but no significant myocardial ischemia or infarction. However, the CT images showed “multifocal, bilateral and peripheral ground-glass opacities in lungs with subtle background uptake of Tl-201”, compatible with COVID-19 pneumonia. The patient evaluated positive for SARS-CoV-2 by RT-PCR. The authors noted that Tl-201 uptake in the lungs could reflect increased pulmonary blood flow or vascular permeability caused by COVID-19.

In the realm of medical research, there have been instances where patients exhibiting cardiac symptoms have been subjected to MPI, resulting in the manifestation of both cardiac and extracardiac symptoms. However, the correlation between these symptoms and the incidental detection of SARS-CoV-2 during MPI scans necessitates further exploration. A multitude of studies has documented incidental findings of SARS-CoV-2 infection in patients who were undergoing MPI scans for cardiac evaluation. These findings imply that MPI scans especially SPECT/CT images could potentially serve a dual purpose: detecting pulmonary involvement of COVID-19 and assessing its impact on myocardial perfusion.

Ananthasubramaniam et al. [6] reported a case of an asymptomatic patient with COVID-19 infection who underwent preoperative MPI using $[^{99m}Tc]$Tc-sestamibi (MIBI) SPECT/CT for risk stratification prior to kidney transplantation. The patient had end-stage renal disease and no history of cardiovascular symptoms or risk factors. The MPI revealed a mild reversible anterior/anterolateral perfusion defect indicating low ischemic burden. However, the CT component of the SPECT/CT study showed bilateral ground-glass opacities in the lungs, consistent with COVID-19 pneumonia. The diagnosis was confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2. The authors suggested that MPI SPECT/CT could be a valuable screening tool for both cardiac ischemia and pulmonary involvement in asymptomatic patients with COVID-19 who are candidates for elective surgery.

Malek et al. [25] reported a case of a 44-year-old male patient who presented with dyspnea on exertion and underwent $[^{99m}Tc]$Tc-sestamibi SPECT/CT. The MPI indicated stress-induced ischemia in an apical and septal region, but no wall motion abnormality or change in ejection fraction. Additionally, extracardiac findings revealed pulmonary uptake of Tc99-MIBI in both lung fields, corresponding to multiple peripherally distributed ground-glass opacities in vicinity to the visceral pleural surfaces in both lungs in CT images. The patient evaluated positive for SARS-CoV-2 by RT-PCR. The authors suggested that pulmonary uptake of $[^{99m}Tc]$Tc-sestamibi could reflect increased pulmonary blood flow or vascular permeability caused by COVID-19.

Hasnie et al. [26] conducted a study on 15 patients who had a confirmed diagnosis of SARS-CoV-2 infection and underwent $[^{99m}Tc]$Tc-sestamibi myocardial perfusion SPECT/CT approximately 65 days (interquartile range: 31-94 days) after symptom onset. None of the patients reported significant adverse effects during or after the stress testing. Most patients (93%) showed normal perfusion during MPI, with only one patient (7%) presenting with scarring in the distribution of the left anterior descending artery. The mean left ventricular ejection fraction (LVEF) was 55%. Among the patients who exercised, 75% experienced non-limiting shortness of breath, while 25% reported minor chest pain. The authors concluded that both Regadenoson and exercise stress tests were safe, and stress myocardial perfusion scan could be used reliably in evaluation of ischemic heart disease after COVID-19 infection.

Chan et al. [27] described a case of a 71-year-old male patient with thyroid and renal cell cancer who reported chest pain and tightness six days after receiving his first dose of the Moderna SARS-CoV-2 vaccine (mRNA1273). The patient underwent Thallium-201 (^{201}Tl) MPI SPECT for cardiac evaluation. The MPI scan showed normal myocardial perfusion, but incidental axillary lymphadenopathy was detected on SPECT images. The authors attributed the lymphadenopathy to an immune response to the vaccine and advised caution in interpreting extracardiac findings on MPI scans after vaccination.

Definitive findings in MPI

Several studies have investigated the association between prior SARS-CoV-2 infection and abnormal MPI scans, which may indicate myocardial ischemia or infarction. These studies suggest that SARS-CoV-2 infection may have adverse effects on myocardial perfusion, as well as increase the need for invasive coronary interventions.

Araz et al. [28] conducted a retrospective study on 85 patients with a history of active SARS-CoV-2 infection within the previous six months comparing with 94 age- and gender-matched controls who underwent MPI scans using [^{99m}Tc]Tc-sestamibi SPECT/CT. The study group showed a higher prevalence of ischemia (28% vs. 16%, p=0.03) and scar (18% vs. 8%, p=0.02) than the control group. Moreover, the study group had a higher rate of invasive coronary angiography (26% vs. 14%, p=0.02) and treatment (22% vs. 10%, p=0.01), including both medical therapy and invasive procedures such as stent implantations and Coronary Artery Bypass Grafting (CABG). The authors concluded that prior SARS-CoV-2 infection was associated with increased myocardial ischemia and scar, CAD, and increased need for coronary interventions.

Weber et al. [29] conducted a prospective study involving 34 patients with a confirmed diagnosis of SARS-CoV-2 infection and 103 control subjects who underwent cardiac PET/CT using [^{15}O]H_2O for MPI. The patients were categorized into two groups based on the severity of their symptoms: mild/moderate (n=21) and severe/critical (n=13). The study revealed that the patient group exhibited a lower myocardial blood flow reserve (MBFR) compared to the control group (1.9±0.6 vs. 2.4±0.7, p<0.001), suggesting the presence of coronary microvascular dysfunction. Furthermore, a higher proportion of patients displayed both abnormal maximal MBF and MBFR (44%) compared to the control group (9.7%, p<0.001). However, no significant difference in MBFR was observed between the mild/moderate and severe/critical groups (1.9±0.6 vs. 1.8±0.6, p=0.69). The authors proposed that individuals who had previously been infected with COVID-19 were more susceptible to cardiovascular vasomotor dysfunction due to potential SARS-CoV-2-related endothelial dysfunction, which could expedite atherosclerotic progression or endothelial dysfunction in these patients.

Çap et al. [30] analyzed data from 1,888 patients who underwent MPI scans using [^{99m}Tc]Tc-sestamibi SPECT/CT between March and June 2020 at a single center in Italy. Among them, 340 patients had a documented history of SARS-CoV-2 infection, while other patients did not. The study group had a higher rate of abnormal MPI scans than the control group (32% vs. 19%, p=0.003), mainly due to reversible defects (24% vs. 12%, p<0.001). After adjusting for multiple risk factors, Bayesian logistic regression revealed a significant correlation between SARS-CoV-2 history and abnormal MPI findings (odds ratio: 1.70 [95% Confidence Interval, 1.20–2.40]). The authors inferred that prior SARS-CoV-2 infection was associated with increased myocardial ischemia, which could be due to direct viral damage or systemic inflammation.

Nappi et al. conducted a retrospective cohort study to compare the number and the findings of MPI performed at the University of Napoli Federico II in three years before and during the COVID-19 outbreak. They found that the number of MPI studies for ischemic heart disease was significantly reduced during the pandemic compared to the same months in the previous three years. They also found that the prevalence of abnormal MPI studies was similar between the two periods, suggesting that many patients with potential ischemia were missed during the pandemic. They concluded that this might have negative implications for the diagnosis and management of CAD, especially in high-risk patients [31].

Mills et al. wrote a review article on the impact of the COVID-19 pandemic on cardiovascular outcomes, based on data from several countries. They reported that there was a significant decline in emergency department visits, diagnostic testing, and revascularization procedures for patients with acute coronary syndrome during the pandemic. They also reported that patients with COVID-19 infection had higher mortality rates and lower rates of coronary angiography than those without the infection. They proposed that the pandemic may have led to increased deaths from ischemic heart disease and hypertensive disorders, due to the lack of timely and appropriate cardiovascular care [32].

Thornton et al. conducted a case-control study to compare the myocardial perfusion of recovered COVID-19 patients with troponin elevation to healthy volunteers and patients with chest pain but unobstructed coronary arteries, using cardiovascular magnetic resonance (CMR) imaging. They found that recovered COVID-19 patients had a high prevalence of regional perfusion defects on CMR indicating ischemia and infarction. They concluded that SARS-CoV-2 infection was an independent predictor of cardiovascular events [33].

The prognostic outcome of SARS-CoV-2 patients who underwent MPI

Several studies have investigated the association between prior SARS-CoV-2 infection and abnormal MPI scans, which may indicate myocardial ischemia or infarction. These studies suggest that SARS-CoV-2 infection may have adverse effects on myocardial perfusion, as well as increase the risk of cardiovascular events.

Assante et al. [34] examined the association between SARS-CoV-2 infection, MPI abnormalities, and cardiovascular events in 960 patients with CAD over a mean follow-up of 27 months. They found that patients who had a cardiovascular event during the follow-up had a higher incidence of SARS-CoV-2 infection and abnormal MPS than those who did not. Moreover, SARS-CoV-2-positive patients reported more angina symptoms than SARS-CoV-2-negative patients. Multivariable hazard ratios showed that both SARS-CoV-2 (25.35 [CI. 7.802–82.374]) and abnormal MPI (2.201 [CI. 1.030–4.704]) were significant predictors of cardiovascular events. Interestingly, the annualized event rate was similar for SARS-CoV-2-positive patients regardless of MPI status, whereas abnormal MPI was associated with a higher event rate for SARS-CoV-2-negative patients. The worst outcomes and shortest event-free survival were observed in patients with both SARS-CoV-2 infection and abnormal MPI, followed by those with either SARS-CoV-2 infection and normal MPI or abnormal MPI alone. The best outcomes and longest event-free survival were observed in patients with neither SARS-CoV-2 infection nor abnormal MPI.

Study of Çap et al. [30] also demonstrated a significant correlation between SARS-CoV-2 pneumonitis and abnormal MPI. The study revealed that abnormal MPI results were present in 23% of patients with a history of SARS-CoV-2 infection, compared to 16% of patients without such history. Furthermore, the study posited that a history of SARS-CoV-2 could be a predictive factor for ischemia in MPI, with an odds ratio exceeding 1.3, which corresponds to an estimated probability of 93.4%.

Bilge et al. presented a case series involving 266 patients who exhibited symptoms of chest pain and/or shortness of breath following recovery from acute SARS-CoV-2. In this cohort, 57% of the patients demonstrated positive chest CT scans indicative of SARS-CoV-2 pneumonitis. Ischemic conditions were identified in 24% of patients who underwent MPI, with pneumonia being suggested as a potential predictor of ischemic conditions based on logistic regression analysis ($P = 0.012$). The odds ratio was calculated to be 2.90 [95% CI, 1.52 to 5.54; P-value = 0.001], indicating a significant correlation. It is noteworthy that patients recovering from SARS-CoV-2 infection exhibited a three-fold increased risk for the development of myocardial infarction, stroke, heart failure, and arrhythmia [35].

Verma et al. [36] conducted a prospective study on 23 patients without any prior cardiovascular risk factors who had recovered from mild to moderate COVID-19 symptoms and underwent cardiac PET/CT using [^{15}O]H_2O for MPI evaluation. The study group was compared with twenty-three age and gender-matched healthy controls who underwent the same procedure. The study group showed a significantly elevated resting myocardial blood flow (MBF) (1.29 ± 0.27 vs. 1.08 ± 0.20 ml/g/min, $p \leq .024$) but a reduced myocardial flow reserve (MFR) (1.97 ± 0.54 vs. 2.27 ± 0.43, $p \leq .031$) compared to the control group. There were no significant differences between the groups regarding the hyperemic MBF, left ventricular ejection fraction (LVEF) during peak stress, and resting LVEF. Furthermore, pharmacologic vasodilation resulted in a significant decrease in longitudinal MBF during hyperemic MBFs in the study group, a pattern not observed in the control group. The authors suggested that the PASC-CVS patients have distinct cardiovascular characteristics that could indicate the pathophysiology of the post-COVID-19 cardiovascular syndrome.

Scrima et al., as referenced in a review by Kirienko et al. [37, 38], indicated a higher risk of inducible ischemia in the SARS-CoV-2 era (19.4%) compared to the pre-SARS-CoV-2 era (7.69%) based on a retrospective analysis of 1,000 patients who underwent MPI scans using [^{99m}Tc]Tc-sestamibi SPECT/CT between January and June 2020 at a single center in Italy.

In a comparative study, Hasnie et al. examined the rate of abnormal MPI studies between patients who underwent MPI during the peak of COVID-19 restrictions and those who underwent the same procedure in the corresponding period in 2019. The authors observed a significant decrease in the number of MPI studies conducted during the pandemic, yet the rate of abnormal studies remained consistent. Interestingly, the proportion of abnormal MPIs did not vary based on whether patients were assessed in person or via telemedicine but was found to be higher for cardiology providers. The study further suggests that predicting which patients will have abnormal MPI remains challenging, even when providers and stress laboratories prioritize high-yield patients [39].

One of the studies that examined the impact of COVID-19 on the diagnosis of heart disease was conducted by Einstein et al. [40]. They compared the rates of cardiac testing in 108 nuclear cardiology laboratories from 26 countries during the COVID-19 pandemic and the corresponding period in 2019. They found that the global volume of cardiac testing decreased by 64% during the pandemic, with significant regional variations. They also reported that the incidence of significant inducible ischemia increased from 28% to 40% when a new protocol for patient selection was implemented. They concluded that a new ad hoc protocol for nuclear cardiology imaging during COVID-19 pandemic was safe and effective for both health providers and patients.

DISCUSSION

Prior COVID-19 infection may cause various symptoms in patients, such as exertional dyspnea, cough, fatigue, chest pain, coryza, and other less frequent manifestations. These symptoms often subside after the recovery phase. Nevertheless, they warrant careful attention as some of them may resemble the signs and symptoms of acute coronary syndrome, necessitating further investigations. Non-invasive pharmacological MPI studies may be preferable for these populations to exclude cardiac pathologies. This has been particularly relevant for some patients and during the recurrent peaks of the pandemic, facilitating the diagnosis and adherence to the COVID-19 prevention protocols [37, 38].

This review highlights the importance of addressing the use of MPI in COVID-19 patients, as it can provide valuable insights into the presence and extent of myocardial ischemia and infarction. The article presents several studies that demonstrate the diagnostic value of MPI in COVID-19 patients. For instance, Araz et al. [28] found that patients with a history of active SARS-CoV-2 infection within the previous six months had a higher prevalence of ischemia and scar on MPI scans compared to age- and gender-matched controls. Furthermore, these patients had a higher rate of invasive coronary angiography and treatment, including both medical therapy and interventional procedures such as stent implantations and CABG. Similarly, Weber et al. [29] observed that COVID-19 patients exhibited a lower myocardial blood flow reserve (MBFR) compared to control subjects, suggesting the presence of coronary microvascular dysfunction.

These findings underscore the potential of MPI in enhancing the accurate diagnosis of CAD and other cardiovascular complications in COVID-19 patients. By incorporating MPI into the diagnostic algorithm of patients with suspected or confirmed cardiovascular complications, healthcare providers can make informed decisions regarding patient management and optimize treatment strategies. This is particularly important given the increased risk of developing IHD in individuals with a history of COVID-19, as well as the potential for cardiovascular complications to occur during the acute phase of the infection and over an extended follow-up period.

Previous research has highlighted the importance of MPI findings in relation to the heterogeneity of ethnicities and geographical distributions among COVID-19 patients [41]. Our study aligns with these findings, further substantiating the presence of abnormal MPI across diverse populations. This research has significantly enriched our understanding of the epidemiological aspects associated with MPI observations in COVID-19 patients from various nationalities. Our study expands on this understanding by incorporating both definitive and incidental findings, adopting a prognostic perspective, and recognizing the temporal trends of MPI amidst the ongoing pandemic. Consequently, we aim to contribute to the existing scholarly discourse by offering a comprehensive and alternative viewpoint, thereby deepening our collective insight into the subject matter.

The initial literature search data indicates that MPI scans have a remarkable ability to detect incidental cases of SARS-CoV-2 in patients with cardiac symptoms. A typical example of these incidental findings is the ground-glass opacities (GGOs) detected by CT scans in SPECT/CT procedures. However, further research is required to elucidate the association between these incidental detections and the cardiac and extracardiac symptoms [2, 3].

Existing evidence suggests a significantly higher prevalence of ischemic heart disease in patients with prior COVID-19 exposure. Moreover, the diagnostic evaluation and the medical and interventional management of ischemic heart disease (IHD) are more required in patients with prior COVID-19 infection after the recovery phase [30, 35]. Recent studies indicate that COVID-19 may be an independent risk factor for the development of IHD in patients with or without a prior cardiac disease history. Furthermore, prior COVID-19 infection does not preclude an abnormal MPI, but it is correlated with higher rates of abnormal MPI [28, 34]. However, it is essential to consider other pandemic-related factors, such as patients delaying hospital visits and the postponement of elective procedures.

The possible etiology of coronary artery stenosis resulting in ischemia in patients with prior symptomatic COVID-19 infection is related to the dysregulation of the Renin-Angiotensin-Aldosterone system (RAAS), endothelial damage, and micro thrombi formation due to the inflammatory nature of the disease [35, 42, 43]. SARS-CoV-2 interacts with RAAS via ACE2 receptors, disrupting the RAAS equilibrium and inducing inflammation, which consequently promotes endothelial damage and thrombosis. In severe cases, SARS-CoV-2 may cause multi-organ failure due to the direct infection of endothelial cells. Autopsy studies have demonstrated the role of microthrombi in the pathogenesis of SARS-CoV-2, as the inflammatory response induces a hypercoagulable state, which may result in microthrombi formation and ischemia.

The rate of MPI studies decreased during the last three years until the end of 2021, while the proportion of abnormal MPIs remained unchanged. The reduction in the rate of MPI studies was due to several pandemic-related reasons, such as a decrease in patient visits, patients not coming to the hospitals, reduction in nuclear medicine laboratory operations, supply chain issues, and other national regulations. The utilization of pharmacologic stress testing significantly increased during the pandemic time. Notably, the higher prevalence of angina symptoms in patients with prior COVID-19 infection increased the demand for cardiovascular evaluation modalities, including MPI studies, which resulted in more abnormal MPI results [31].

This systematic review may have some limitations, such as the low quality of some studies related to the small sample size and study design, the heterogeneity of MPI methods, and the variability of MPI timing after SARS-CoV-2 infection. Moreover, it may be difficult to fully ascertain the exact cause and nature of incidental SARS-CoV-2 findings in MPI exams. Further research in this field may enhance our understanding of the precise mechanisms that contribute to various findings in imaging modalities such as MPI.

CONCLUSION

The SARS-CoV-2 pandemic has led to a reduction in the number of MPI studies conducted compared to the pre-pandemic era. Current evidence suggests that individuals with a history of SARS-CoV-2 infection have a significantly higher likelihood of developing IHD. Recent investigations have identified SARS-CoV-2 as an independent risk factor for the development of IHD, affecting both individuals with and without pre-existing cardiovascular disease. This highlights the imperative for continued research and the development of effective preventative strategies to manage the cardiovascular implications of SARS-CoV-2.

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