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Aortic dissection and Covid-19; a comprehensive systematic review

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Abstract: Coronavirus disease 19 (Covid-19) has been declared as a pandemic disease since March 2020; causing wide array of signs and symptoms, many of which result in increased mortality rates worldwide. Although it was initially known as an acute respiratory disease, Covid-19 is accompanied with several extrapulmonary manifestations, of which the cardiovascular ones are of major importance. Among other cardiovascular complications of Covid-19, aortic dissection has been a significant yet underrated problem. The pathophysiology of aortic dissection consists of various inflammatory pathways, that could be influenced by Covid-19 infection. We herein have reviewed articles inclusive of aortic dissection concurrent with Covid-19 infection in a systematic manner, along with the probable similarities in pathophysiology of aortic dissection with Covid-19 infection. (Curr Probl Cardiol 2023;48:101129.)

Introduction

Since 11th March 2020, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) has been declared as a pandemic disease, causing numerous morbidities and mortalities

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worldwide.[1,2] Although Coronavirus disease 19 (Covid-19) had been Initially known as an acute respiratory distress syndrome, more recently it appeared to affect various organs and organ systems, including cardiovascular, gastrointestinal, renal, coagulation, and skin disorders; Most of which related to the hyper-inflammatory state in Covid-19.[3,4] Multiple findings imply that the inflammatory state in Covid-19 patients is similar to strong inflammatory syndrome; both of which showing abnormal platelet count, increase in D-dimer, increase in Von Willebrand Factor (VWF), endothelialitis, and pro-inflammatory cytokines activation.[3]

The Covid-19 is known to cause increased risk of several cardiovascular complications; including acute myocardial injury, arrhythmias, cardiogenic shock, acute coronary syndrome, and venous thromboembolism.[4] Among the cardiac complications, aortic dissection is an important yet underrated problem in Covid-19 patients. Even though few articles indicate that the rate of aortic dissection has been increased during the course of pandemic, no comprehensive studies have been conducted about the molecular basis and coincidence rate of Covid-19 and aortic dissection.[5]

We herein report a comprehensive systematic review of literature to cognize the patients with aortic dissection and concurrent or previous Covid-19. We have also discussed the similarities between the pathologic pathway of Covid-19 and aortic dissection.

Pathophysiology

Aortic dissection is the blood passage into the aortic media as a result of the rupture in intimal layer of the aortic wall.[6] Consequently, separation of the intimal layer from the outer layers occurs, and hence a false lumen appears in juxtaposition with the main aortic lumen. The ascending aorta is reported to be the most common site of aortic dissection, as 65% of the dissections originate in this region.[7]

Numerous major risk factors contribute to increased risk of aortic dissection, including hypertension and smoking, and genetic factors such as Marfan Syndrome (MFS) and Ehlers Danlos.[6] Vasculitis is also a notable factor that increases the risk of aortic dissection, as in Takayasu arteritis, Behcet's disease, and syphilis infection.[7] Interestingly, Numerous articles mentioned Covid-19 infection as a strong inflammatory syndrome.[3,8] Moreover, there are multiple cases of Covid-19 patients with hyper-inflammation who have had cardiac manifestations such as coronary microvascular dysfunction and peripheral artery thrombosis.[9,10]

There are several similarities between molecular pathways and markers of aortic dissection and Covid-19. For instance, the level of Von Willebrand Factor (VWF) Increases in Covid-19 patients, which is indicative of extensive endothelial cell activation.[3] Multiple molecular factors are known to be correlated in MFS and aortic dissection that are also elevated in Covid-19 patients. (Fig 1) The major factors include Transforming growth factor beta (TGF-β), total plasma homocysteine Y (tHCy), and Matrix metalloproteinases (MMPs).[11-13]

Several reports illustrated that excessive activation of TGF-β in MFS patients is correlated with aortic root dilation and predisposition to aortic dissection.[12] Ghazavi et al. indicated that in a study of 63 Covid-19 patients and their matched controls, the level of TGF-β increased in Covid-19 patients. Furthermore, TGF-β in this study was significantly higher in patients with severe form of Covid-19 compared to the patients with mild form. With these findings, one may assume that the Covid-19 can possibly increase the probability of aortic root dilation and henceforth aortic dissection. It is worthy to mention that in MFS patients, treatment with β-blockers decreases the TGF-β levels.

According to the literature, the tHCy is described as a marker of the level of aortic atherosclerosis. Moreover, in a study of one hundred and seven patients, Giusti et al. concluded that higher levels of tHCy in MFS patients is correlated with the incidence rate of aortic dissection and other cardiovascular complications.[12,14] In case of Covid-19, it has been shown that tHCy can be used as a predictive value for the severity of the disease, as the higher levels of tHCy corresponds to more severe pneumonia in imaging evaluations.

One of the major similarities between MFS patients with aortic dissection and Covid-19 patients, is the imbalance between MMP and Tissue inhibitor of metalloproteinase (TIMP).

Prior studies have demonstrated that macrophage infiltration in the media layer of aorta may result in excessive production of MMPs, specifically MMP-1, MMP-9 and MMP-12. As a result, collagen and elastin degeneration leads to aortic aneurysms and aortic dissections.[2]

One of the molecular characteristics of MFS is known to be increased expression of MMPs, that ensues an imbalance between MMP and TIMP levels.[12] Speaking of MMPs in Covid-19, several studies have reported an increase in MMPs expression. Shi et al. studied sixty-two cases of Covid-19 and their matched controls, and reported a significant rise in serum MMP3 levels in Covid-19. As mentioned in the article, MMP3 activates other MMPs, including MMP9.[15] Additionally, Neutrophils response to viral infection is followed by MMP9 release from neutrophil

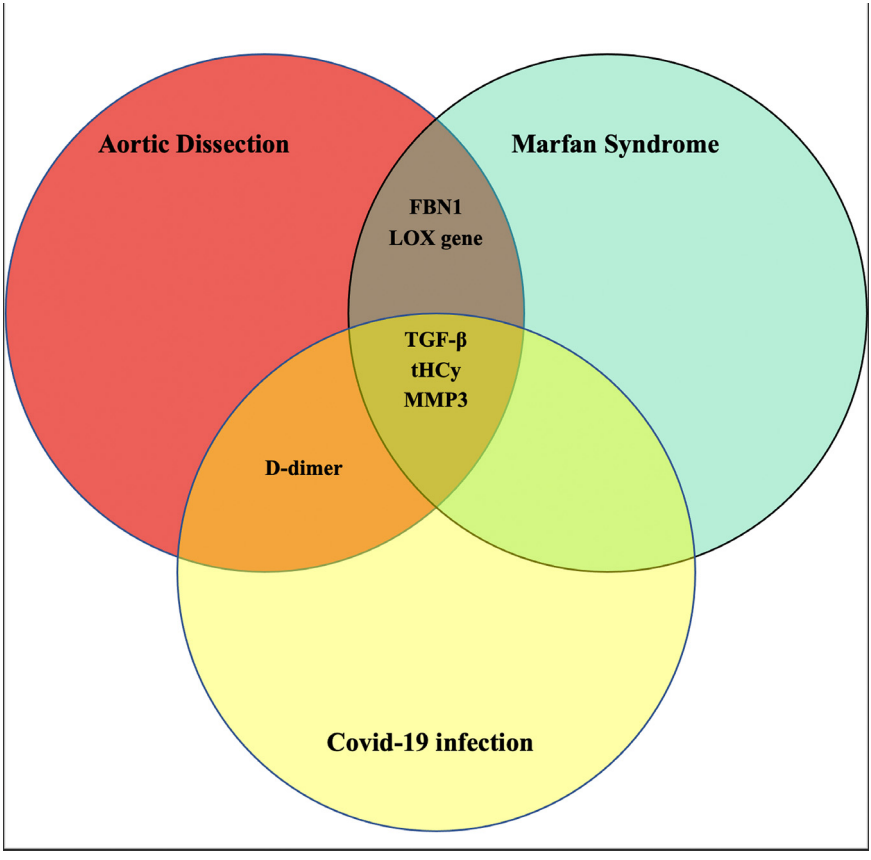


FIG 1. The similarities in molecular pathologic pathway of Covid-19 hyper-inflammatory state, aortic dissection, and Marfan syndrome. TGF- β, tHCy, and MMP3 are the major mutual pathways in Aortic dissection, Marfan syndrome, and Covid-19 infection. There are not enough data in literature approving the role of FBN1 and LOX gene in Covid-19 inflammation. FBN1, Fibrillin 1 gene; LOX, Lysyl oxidase; MMP3, matrix metalloproteinase-3; TGF- β, Transforming growth factor beta; tHCy, total plasma homocysteine Y.

granules. This process was previously known th contribute to lung damage in Covid-19 patients.[16]

Considering macrophage molecular pathway activation in Covid-19 patients, there are several other markers that are increased; including Ferritin, IL-15, IL-1β, IL-18. There has been a significant difference in Ferritin and IL-15 levels in Covid-19 patients with critically ill situations compared to other patients and healthy individuals.[17] These findings imply that there are several major pathway similarities between aortic dissection and the inflammation caused by Covid-19 infection.

For the LOX and FBN1 gene pathways, as two other factors that predispose MFS patients to aortic dissection, there is not enough evidence that Covid-19 has a similar pathway and hence is correlated. However, this idea may lead to further investigations in future publications.

Method

A comprehensive search was conducted on PubMed, Embase, Scopus, and Google scholar for the articles that have been published until January 2, 2022. Proper Boolean operators have been used for the subject headings "Covid-19" and "dissection" and any synonyms observed in literature. Multiple combinations of words have been used to ensure a comprehensive search. Indexing methods (e.g., Mesh terms, Emtree, etc.) were also utilized if available. The search was conducted by one reviewer and crosschecked by another. From the initial articles in the primary search, the duplicates and unrelated articles were excluded. After primary screening, suitable quality appraisal tool was utilized to assess the article before data extraction.[18,19] The exclusion criteria were 1) article written in languages other than English, 2) reviews and commentaries without any patients studied, 3) lack of demographic, clinical, imaging or laboratory evidences of Covid-19 infection, 4) insufficient details of the type of acute aortic syndrome (i.e., articles which did not differentiate dissection from aneurysm or other manifestations of acute aortic syndrome in the patients discussed). Due to unavailability of reverse transcription polymerase chain reaction test (RT-PCR) early in the course of the pandemic, we did not exclude patients who were diagnosed with Covid-19 based on clinical or imaging methods. Statistical analysis was conducted by using SPSS software (SPSS Inc, Chicago, Illinois, USA).

Results

Initially, 246 articles were obtained from the primary search. After comprehensive analysis of the articles according to Figure 2, 19 articles met the criteria for data extraction and qualitative synthesis (Table 1). Due to lack of eligible study types other than case reports, quantitative synthesis was considered inapplicable.

The overall quality of cases was good to moderate. Most cases have adequately mentioned demographic data, chief complaint, past medical history, history of Covid-19 detection, type of the aortic dissection, and the surgical method of choice (82.60%). Only 13 (56.52%) cases had the time interval between aortic dissection and the Covid-19 infection reported.

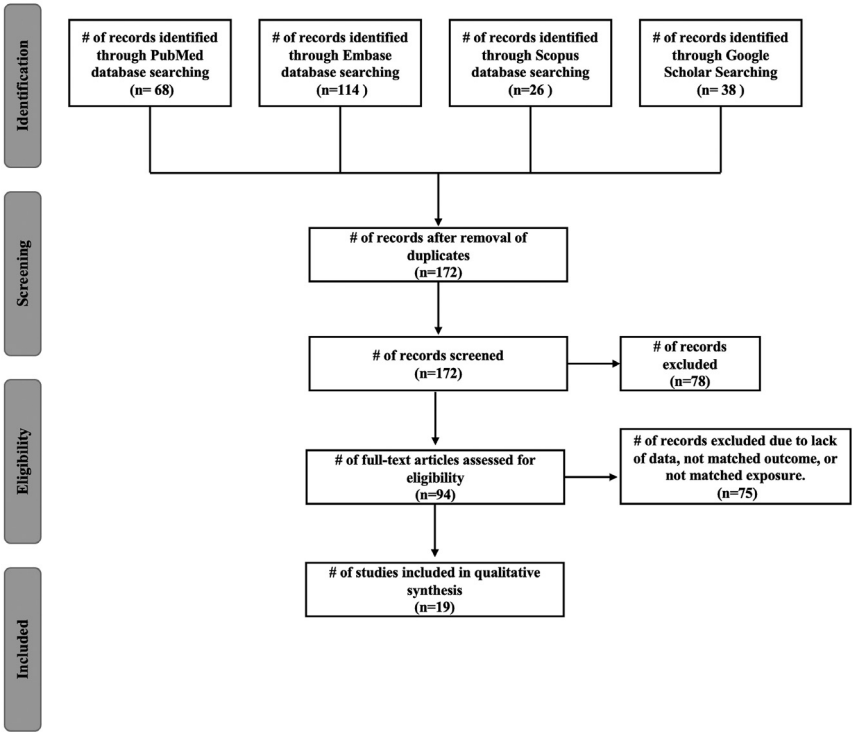


FIG 2. Flow diagram for the systematic review according to PRISMA Guidelines.

Total of 23 patients were included in this study; Of which 15 (65.22%) were men. The mean age of the patients was 52.61 years (Range:14-82; ± 17.84 SD). The majority of cases were reported from United States of America (n=6; 26.09%), China (n=5; 21.74%), and Iran (n=4; 17.40%). The most common clinical presentation was chest pain (68.42%), followed by cough and hypertension, both of which were seen in 26.32% of patients. The most prevalent Comorbidities found was a history of hypertension (26.09%).

The patients were proven to be infected by Covid-19 via either Reverse transcription polymerase chain reaction (RT-PCR) (n=12; 52.17%), pulmonary imaging (n=3; 13.04%), or on clinical basis (n=8; 34.78%). The mean time interval between occurrence of Covid-19 and the dissection was 9.69 days (Range: 0-25; ± 10.70 SD).10 patients (43.47%) did not have the time of Covid-19 diagnosis in their records.

The main diagnostic technique for aortic dissection was Computed tomography (CT; 44.44%), followed by CT-angiography (CTA; 33.33%) and Transesophageal Echocardiography (TEE; 11.11%). The least

Table 1. Review of literature of aortic dissection and Covid-19 infection.

	Country	Age	Sex	Clinical manifestation	Comorbidities	COVID-19	Timing of dissection	Dissection Diagnostic method	Dissection type (Stanford/DeBakey)	Extension of dissection	Surgical treatment
Basheer et al.[20]	USA	17	M	Acute-onset substernal chest pain;	COVID-19; Marfan-syndrome	Tested positive (test not specified)	14 days after covid test +	CTA	Stanford Type A; DeBakey type I	From sinotubular junction to proximal aortic arch	Single side branch graft (Gelweave-30 mm)
Engin et al.[21]	Turkey	62	M	Chest pain radiating to back;	COVID-19; AF; DM; lower extremity deep venous insufficiency	Tested positive (test not specified)	20 days after covid symptoms	CT	Stanford type A; DeBakey type I	from ascending aorta to iliac bifurcation	Aortotomy; poly-tetrafluoroethylene tube graft replacement (30 mm)
Fesharaki et al.[22]	Iran	43	M	Severe chest discomfort	COVID-19	RT-PCR Test Positive	21 days after covid symptoms and covid test +	CTA	Stanford type A; DeBakey type I	from right Valsalva sinus to ascending aorta, aortic arch, descending thoracic aorta, and renal arteries	Bental surgery with the repair of the right coronary artery
Fukuhara et al.[23]	USA	52	M	Chest pain; abdominal pain; low-grade fever	COVID-19	RT-PCR Test Positive	Same day as covid symptoms	CTA	Stanford type A; DeBakey type I	From sinotubular junction to the superior mesenteric and bilateral renal arteries	ascending and hemiarch aortic replacement
Jariwala et al.[24]	India	45	M	fever; cough and dyspnea	COVID-19	RT-PCR Test Positive	3 days after covid test+	CT	Stanford Type B; DeBakey type III	from below the origin of the left subclavian artery to origin of celiac trunk	Endo-vascular Aortic Repair (EVAR)
Martens et al.[25]	Belgium	64	M	acute onset chest pain; ischemia of the right leg.	COVID-19	RT-PCR Test Positive	Same day as covid symptoms	CT	Stanford type A; DeBakey type I	from sinotubular junction to iliac arteries	Surgical aortic substitution
Mori et al.[26]	USA	82	F	Sudden onset chest pain; facial	COVID-19; paroxysmal atrial fibrillation;	Clinically suspected	Same day as covid symptoms	TEE	Stanford type A; DeBakey type II	From ascending aorta to right, noncoronary,	Aortic valve resuspension;

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Table 1. (*continued*)

	Country	Age	Sex	Clinical manifestation	Comorbidities	COVID-19	Timing of dissection	Dissection Diagnostic method	Dissection type (Stanford/DeBakey)	Extension of dissection	Surgical treatment
				weakness; anuria; acute kidney injury	diastolic heart failure; COPD; pace maker for sick sinus syndrome; aortic valve insufficiency					and left coronary sinuses	coronary sinus reconstruction; ascending aorta and hemiarch replacement with Dacron Geaweave graft
Tabaghi et al.[27]	Iran	47	F	Dyspnea; dry cough; bloody diarrhea; chills	COVID-19; Severe; aortic valve insufficiency (post-COVID)	RT-PCR Test Positive	22 days after covid test+	TTE	Stanford type A; DeBakey type II	Ascending aorta	Non (the patient expired without intervention)
Volvovitch et al.[28]	Israel	73	F	Chest pain	COVID-19; Hyperlipidemia; impaired fasting glucose	RT-PCR Test Positive	Same day as covid test +	CTA	Stanford type A; DeBakey type I	From proximal side of brachiocephalic artery to aortic arch	bilateral pulmonary embolectomy; ascending aorta and hemiarch replacement with a Dacron Tube Graft 28 mm
Zheng et al.[29]	China	40	F	fever; coughing; expectoration; edema of the limbs	COVID-19; HTN; CKD; uremia; Hemodialysis; pulmonary embolism (post-COVID)	RT-PCR Test Positive	21 days after covid test+	CT, CTA	Stanford type A; DeBakey type I	from ascending aorta to left internal iliac artery and external iliac artery	Bentall's procedure; total arch replacement; "frozen" elephant trunk stent placemen
Akgul et al.[30]	Turkey	68	F	pulseless R. femoral artery; pulmonary rales at base of both lungs; hypertension (165/90)	COVID-19	Tested positive on admission (test not specified)	NR	CT	Stanford Type A; DeBakey type I	From ascending aorta extending through the right common iliac artery	Aortic transection above commissures + Dacron graft (28 mm)
Farkash et al.[31]	USA	53	M	NR	COVID-19; Obesity; Hyperlipidemia	RT-PCR Test Positive	Same day as covid test +	Angiography	Stanford type A; DeBakey type I		ascending and hemiarch aortic replacement

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Table 1. (*continued*)

	Country	Age	Sex	Clinical manifestation	Comorbidities	COVID-19	Timing of dissection	Dissection Diagnostic method	Dissection type (Stanford/DeBakey)	Extension of dissection	Surgical treatment
										From sinotubular junction to the iliac bifurcation	
Mamishi et al.[32]	Iran	14	M	High grade fever; weakness; myalgia; dry cough	COVID-19; William's syndrome	RT-PCR Test Positive	25 days after covid test+	Autopsy	Stanford type A	NR	Non (the patient expired without intervention)
Naderi et al.[33]	Iran	22	M	Compressive chest pain with radiation to back; dyspnea; sore throat; cough	COVID-19	Imaging and clinically suspected	NR	CTA	Stanford type A; DeBakey type I	from sinotubular junction to aortic arch, descending aorta and abdominal aorta	Patient was transferred to COVID hospital
Firstenberg et al.[34]	USA	77	M	Loss of consciousness	COVID-19; HTN	RT-PCR Test Positive	Same day as covid test +	TEE	Stanford type A	NR	NR
Katsiampoura et al.[35]	USA	46	M	Acute chest pain radiating to back and L. lower extremity	COVID-19	RT-PCR Test Positive	NR	CT	Stanford type A	NR	ascending aorta repair with tube graft
Lopez-Marco et al.[36]	UK	55	M	NR	COVID-19	Imaging and clinically suspected	NR	CT	Stanford type A; DeBakey type I	Aortic Root, ascending aorta and aortic arch	NR
Lopez-Marco et al.[36]	UK	53	F	NR	COVID-19	RT-PCR Test Positive	NR	CT	Stanford type A; DeBakey type I	Ascending aorta and hemiarch	NR
He et al.[37]	China	51	M	sudden on-set chest pain; low-grade fever; hypertension (205/112)	COVID-19; HTN	Clinically suspected	NR	NR	Stanford type A	NR	Surgical aortic substitution
He et al.[37]	China	51	M	sudden on-set chest pain; hypertension (171/73)	COVID-19; HTN	Clinically suspected	NR	NR	Stanford type A	NR	Surgical aortic substitution

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	Country	Age	Sex	Clinical manifestation	Comorbidities	COVID-19	Timing of dissection	Dissection Diagnostic method	Dissection type (Stanford/DeBakey)	Extension of dissection	Surgical treatment
He et al.[37]	China	62	M	sudden on-set chest pain; hypertension (149/60)	COVID-19;	Clinically suspected	NR	NR	Stanford type A	NR	Surgical aortic substitution
He et al.[37]	China	59	F	sudden on-set chest pain; fever; hypertension (159/76)	COVID-19; HTN	Clinically suspected	NR	NR	Stanford type A	NR	Surgical aortic substitution
Roman et al.[38]	UK	74	F	NR	COVID-19; Ex-smoker; HTN	Imaging and clinically suspected	NR	NR	Stanford type A; DeBakey type I	NR	no operation was done due to covid pandemics

frequent method of use was transthoracic echocardiography (TTE; 5.56%). The diagnostic method was not mentioned for 5 patients (21.74%). Considering the type of aortic dissection, 22 patient (95.65%) had Stanford type A aortic dissection, while 1 (4.35%) patient had Stanford type B. If categorized based on DeBakey classification, 20 patients (86.96%) were diagnosed with DeBakey type I, followed by 2 (8.70%) and 1 (4.35%) patient diagnosed by type II and III, respectively.

Discussion

Aortic dissection is a form of acute aortic syndrome that is more prevalent in men (2:1) and has a peak incidence in the sixth and seventh decades of life. It is known that the incidence of aortic dissection increases in cold seasons and places with lower climate temperature. Notably, in one study held in the United Kingdom in April 2020, the number of patients with Stanford type A acute aortic dissection was significantly higher than the same month in the last decade.[5] Although no signs of aortitis were found in evaluation of these patients, there should be a mutual factor between these patients that has increased this relatively rare manifestation. Similar studies have also demonstrated increase in the incidence of aortic dissection, along with other cardiovascular manifestations such as myocardial infarction and aortic aneurysms in the first wave of Covid-19.[39]

Among the risk factors, hypertension is one of the most prevalent causes of increased risk of aortic dissection. Some studies suggested that Covid-19 infection down-regulates angiotensin-converting enzyme 2 and activates renin−angiotensin−aldosterone system, causing the hypertensive state which may lead further towards aortic dissection.[40] these findings, along with other molecular findings discussed earlier, intensify the role of Covid-19 in predisposing patients to aortic dissection.

For diagnostic aspects of aortic dissection, several imaging modalities have been proposed; including plain chest radiography, CT, CTA, TEE, and TTE.[7] While TEE has overcome many of the constraints in other methods, the majority of patients in this study were diagnosed using CT. This may probably due to non-invasiveness and speed of CT while reducing the Covid-19 exposure for the medical staff compared to the TEE procedure. It is worthy to mention that high level protection is suggested for surgical procedures in patients with Covid-19, which further complicate any method of diagnosis other than noninvasive methods.[29]

In conclusion, aortic dissection may be a relatively rare but important complication in Covid-19 patients. Henceforth further research and

investigation is necessary for diagnosis, prevention, and treatment of this major problem.

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