Emerging Hot Topics - Review Article

Innovative diagnostic approach and investigation trends in COVID19-A systematic review

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Abstract

A highly contagious viral infection emerged in Wuhan city; China had increased mortality with uncertain pathogenesis spreads throughout the world to become a pandemic. It is reported to be caused by a member of β coronaviruses and named it as COVID-19 by the World Health Organization (WHO). The disease is caused by a mutant strain of coronavirus SARS-COV-2 that affects the respiratory tract causing mild to severe respiratory tract illness. The clinical manifestation ranges from mild, moderate, severe and very severe signs and symptoms result in death due to severe hypoxia or multi-organ dysfunction. Also, the affected persons were capable of infecting others through various modes of transmission through respiratory droplets (aerosol spread). A definite investigation protocol has followed to diagnose COVID 19 disease but mainly confirmed with reverse transcription polymerase chain reaction. Computerized tomography scan plays a significant role in the diagnosis and prognosis of affected individuals. The major problem with COVID-19 is due to its novelty and lack of vaccination or treatment. This review focuses on the mutation, pathogenesis, various diagnostic tests adopted and autopsy findings in patients affected with COVID-19.

Keywords: Angiotensin-converting enzyme type 2, coronavirus, COVID-19, reverse transcription polymerase chain reaction, serological antibodies

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INTRODUCTION

Tyrrell and Bynoe discovered human Coronavirus in 1965 from an adult with Common cold. Coronaviruses are a group of RNA viruses that belong to the Coronaviridae family in the Nidovirales order which is represented by crown-like spikes on their outer surface and thus the termed as "corona" and divided into four genera– α, β, α, δ. Initially, novel COVID-19 was emerged in the seafood market of Wuhan in December 2019, then spread across the state and throughout the World causing death and emerged as an Emergency Global crisis as declared by WHO. These viruses are found to be capable of adapting to the environment by mutation and recombination, like the novel COVID 19, which is a bat SARS-like coronavirus. The mortality rate associated with MERS and SARS was about 34.4% and 9.5% respectively, while the rate for COVID 19 is much lesser of about 2.4%.[1] Out of these SARS-CoV, and MERS-CoV caused an outbreak of fatal viral pneumonia and Severe Acute Respiratory Syndrome in 2002 and 2012, which became an epidemic with an 11% mortality rate.

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Aim

1. To collect all the literature evidence to understand study the strain variants, all possible modes of transmission, pathogenesis, and manifestations mentioned in predominant literature published during the pandemic
2. To estimate the sensitivity and specificity of the diagnostic test from the literature published during the pandemic.

MATERIALS AND METHODS

This systematic review conducted with Preferred Reporting Items for Systematic reviews and Meta-Analyses Statement Criteria.(Moher, Liberati, Tetzlaff, Altamn, and PRISMA Group, 2010) [Figure 1].

Inclusion criteria

All original research articles and observational studies such as cohort, case-control, retrospective studies on coronavirus since from December 2019 to August 2020.

Exclusion criteria

All the duplicates and abstract only articles excluded. The systematic review, meta-analysis, review articles and other language articles also excluded.

Sources, search strategy, and study selection: COCHRANE DATABASE OF SYSTEMATIC REVIEWS, MEDLINE, SCI-EXPANDED, PUBMED, PUBMED CENTRAL, SCOPUS, and GOOGLE SCHOLAR were searched to identify the records about this review [Table 1].

Search strategy

The eligibility of this study was individually assessed in an unblinded manner by three reviewers. In the first phase of the review, the entire database was screened by the title and abstract. The full article read by all the authors in the second phase. If any discrepancy found, another observer corrected it.

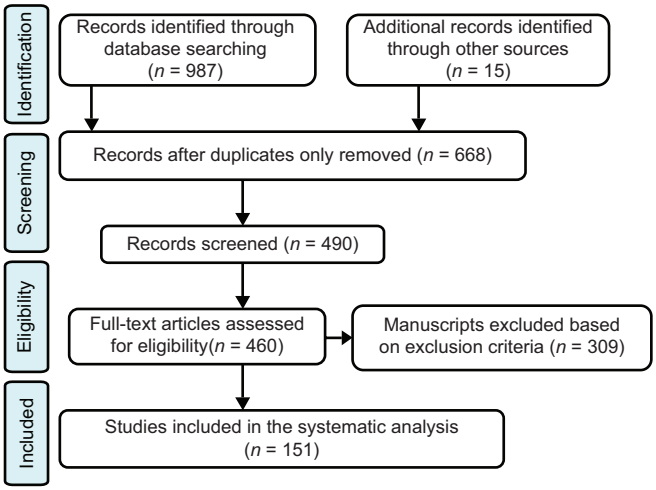

Figure 1: PRISMA 2009 flow chart for the systematic review

Data extraction and management

The data for this review such as origin, structure and genome, mutations of COVID19, along with their clinical features, pathophysiology, modes of transmission and various diagnostic tests were reviewed and checked by the authors. The data that was extracted, and tabulated were reviewed and analyzed by each author independently.

Risk of bias and quality assessment of studies: The quality and the nature of the paper were reviewed by the authors using a modified Ottawa scale. After completing the data extraction, the third author evaluated it.

RESULTS

In Table 2, the authors analyzed and tabulated the pathophysiology, modes of transmission, the samples used for diagnostic tests, biopsy, and autopsy findings. In Table 3, the inference for Table 2 is detailed.

DISCUSSION

In December 2019 an outbreak of pneumonia with an unknown aetiology emerged in Wuhan city, China. About 22% of the reviewed articles have documented that, it is Beta coronavirus with a positive sense, single-stranded RNA (25.5%). Though the initiation of SARS CoV2 infection is documented as a zoonotic one from the bats to human, the infection spreads from person to person. The mode of transmission is through aerosols and droplets expelled by the patients during coughing and sneezing. SARS-COV2 has a higher aerosol and surface stability leading to the widespread infection. Due to the airborne transmission of this infection, the World Health Organization is prescribing an interpersonal

Table 1: Systematic review search strategy for PubMed, EmBase, Google Scholar

Data base	Key word search
PubMed	Corona virus
Cochrane	Pathophysiology of Corona virus
Google scholar	Diagnostic test for corona virus
Scopus	Lab investigation for corona virus
	Corona virus
	Diagnosis of CoV
	COVID 19 clinical manifestation
	Covid 19 transmission
	Corona virus clinical features
	Mutant strains of Corona virus
	Autopsy in corona virus
	Covid virus genome
	Novel corona virus
	Covid19 autopsy

Table 2: Genome, modes of transmission and pathogenesis, diagnostic test, biopsy and autopsy of COVID-19

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
Robyn Ralph *et al.*[2]	RNA Open reading frame 1a, 1b, (S) (E), (M)		Angiotensin converting enzyme 2		Lymphocyte, platelet count serum creatinine, enzymes			
Fan Wu *et al.*[3]	"		"					
Na Zhu *et al.*[4]	Enveloped RNA, spherical			Computerized tomography				
Peng Zhou *et al.*[5]	S gene	Direct	"	X-ray	Antibodies		Cell lines RT-PCR NGS NAAT	Changes in Lung
PriyankaSaha *et al.*[6]	RNA S1, S2.		S-receptor					
Ryan J. Andrews *et al.*[7]	+ ss RNA ORF 1ab 16, Nsp1				Antibodies, enzyme, CRP, ESR		RT-PCR NGS	
Nidhan K. Biswas *et al.*[8]	+ssRNA S protein		ACE2					
Michael G Argenziano *et al.*[9]	Enveloped RNA				Antibodies, enzyme, CRP, ESR		RT-PCR	
Sheng-Qun Deng *et al.*[10]	+ssRNA S protein				Leukocytes, lymphocyte count, enzyme CRP, ESR, cytokine chemokine Antibodies		"	
BingkunJie *et al.*[11]	ss RNA	Direct		CT	Lymphocyte platelet count, CRP ESR, Enzyme, seroproteina, antibodies		"	
Jin-jin Zhang *et al.*[12]	Enveloped RNA	Genetic predisposition	"	CT X-ray	"		"	
Chaolin Huang *et al.*[11]		Zoonotic	"					
Guogang Xu *et al.*[13]	+ ssRNA	Droplets, direct, indirect contact, aerosol, ocular fecal-oral		"	"		"	
Jun Chen *et al.*[14]				"	"		"	
Rachele Cagliani *et al.*[15]	+ss RNA (ORFs), (S), (E), (M), (N), proteins		"					
Kelvin Kai-Wang *et al.*[16]	Nsp genome-ORF8, ORF3b, Sp genome, S mutation		"				NAAT RT-PCR Cell culture	
Ben Hu *et al.*[17]	ORF3a, 3b, ORF6, ORF7a, 7b, ORF8a, 8b, 9b recombination		"				RT-PCR Immunofluroscence	
Lucy van Dorp *et al.*[18]	RNAOrf1ab, Nsp11and13				Antibodies, enzymes, PT, PTT			
Leung *et al.*[19]	Enveloped+sense SS RNA						RT-PCR cell culture	Changes in lungs
Nan Hong *et al.*[20]			"				RT PCR	

Contd...

Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
Ting Liang *et al.*[21]	Enveloped+ssRNA.			CT	Lymphocyte count, ESR, CRP Chemokines, cytokines Enzyme Antibodies			
Michelle L. Holshue *et al.*[22]		Droplet			"	Viral RNA	RT-PCR NAAT NGS	
Pragya D. Yadav *et al.*[23]	Enveloped+SS RNA Spike protein-S1 and S2		"					
Aiping Wu *et al.*[24]	+ SS RNA. 14 ORF encoding 27 proteins. 8b, 3b protein substitutions		"					
Tai-Jay Changa *et al.*[25]	+ sense SS RNA, Enveloped. ORF1ab, E, S– S1, S2, M, N		"					
Roujian Lu *et al.*[26]	+ sense SS RNA		"				RT-PCR NAAT NGS	Changes in lungs
Rozhgar A. Khailany *et al.*[27]	orf1ab	Droplet	"					
Jasper Fuk-Woo Chan *et al.*[28]	Enveloped,+ sense RNA S1, S2		S1, S2-NTD RBD				RT-PCR	
Gianguglielmo *et al.*[29]	muTation S gene			"				
Yi-ChingHsieh *et al.*[30]	RNA, S, E, M, NC				Antibodies		Cell culture	
Manish Tiwaria *et al.*[31]	+ sense RNA ORFs, E, S, M, N				CBC			
Ali MohZaki *et al.*[32]	Enveloped+ss RNA ORF 1ab, S, E, M, N				Enzyme ESR, CRP			
Rajesh T. Gandhi *et al.*[33]				"	D dimer, ferritin Enzyme, ESR, CRP, PT, PTT, cytokines, chemokine, lymphocyte, CBC		RT-PCR	
Daniel K. W. Chu *et al.*[34]	ORF1b and N, nsp						"	
Wei Zhang *et al.*[35]	ORF encoding NSP-ORF a/b	Respiratory, fecal–oral, body fluid routes						
Xiaolu Tang *et al.*[36]	+ss RNA ORF8 and ORF10 mutations		"					
ZheXu *et al.*[37]	Enveloped+ssRNA			X-ray	Antibodies, chemokines cytokines		"	Changes in lungs
Suxin Wan *et al.*[38]	Enveloped+sense ss RNA	Direct contact, droplets	cytokine	CT X-ray	Lymphocyte count ESR, CRP, PT, PTT Chemokines, cytokines Enzyme, antibodies		"	
Chaomin W Xiaoyan *et al.*[39]	+ ss RNA		Chemokines cytokines.		"			

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Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
AnuHaveri *et al*.[40]	RNA				Antibodies Lymphocyte count		RT-PCR cells culture	Changes in lungs
Changtai Wang *et al*.[41]	RNA						RT-PCR	
Alexander E. *et al*.[42]	+ ss RNA Spike replication						"	
B. Coutarda *et al*.[43]	Enveloped+ss RNA S protein-furin-recognition pattern		S1/S2				"	
ShufaZheng *et al*.[44]					"	Viral load	"	
Paola Stefanelli *et al*.[45]	Enveloped RNA ORF1ab: ORF				"		"	
Ying-Hui Jin *et al*.[46]	Envelope, oval or polymorphic RNA	Droplet						
B. Cao *et al*.[47]	RNA	"		Xray	Lymphocyte count, ESR, CRP, PT, PTT Chemokines, cytokines Enzyme		"	
Rhian. Touyz *et al*.[48]	RBD		ACE2					
Leonardo Setti *et al*.[49]	RNA	Aerosol, droplets						
Weiqing Wang *et al*.[50]	S-protein		"					
Xun Ding *et al*.[51]			Cytokines chemokines					
Yang-kai LI *et al*.[52]					"			
Ritesh Gupta *et al*.[53]	ssRNA genome						"	
Xiaobo Yang *et al*.[54]					Hb, Serumcreatinine Enzymes Antibodies			
F. Zhen *et al*.[55]		Droplet	ACE 2					
W. Guan *et al*.[56]	Enveloped RNA	Gastrointestinal tract, saliva, and Urine						
Xin-Ying Zhao *et al*.[57]	ss RNA genome		"					
W. Guan *et al*.[58]			"					
Eu Suk Kim *et al*.[59]	RNA-envelope gene, E			CT	Antibodies			
Luwen Wang *et al*.[60]	RNA (ORF) 1ab gene		"					
Robinson Sabino-Silva *et al*.[61]		Droplets aerosols						
L. Meng *et al*.[62]		Zoonotic, direct contact, droplets			"		RT-PCR	
Heng Lia *et al*.[63]	+ss sense RNA.	Droplets, direct or indirect contact, aerosol	"				"	
Shukenie *et al*.[64]			"				"	

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Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
Muhammad Adnan *et al.*[65]	ss RNA, S protein		"					
DonatoGemmati *et al.*[66]	Spike (S) protein		"					
Yuanyuan Hana *et al.*[67]							"	
Wei-Kung Wang *et al.*[68]	RNA-ORF1ab	Droplets						
Yifei Chen *et al.*[69]			"					
Xi Jin *et al.*[69]	(S) protein substitutions and deletion				Antibodies		"	
Naveen Vankadari *et al.*[70]	Spike glycoprotein-S1 S2		"					
Changhai Lei *et al.*[71]	Spike (S) proteins- RBD		"					
Srirengalakshmi *et al.*[72]		Aerosol, contact						
Juan Simon Rico-Mesa *et al.*[73]	Spike s protein.		"					
Robert J. Mason *et al.*[74]	RNA genome				"		"	
Xiaolong *et al.*[75]	Spike protein-RBD		"					
Lei Huang X *et al.*[76]	RNA genome		cytokine-storm					
Bo Diao *et al.*[77]	Ssenveloped RNA spike protein RBD- mutation		"	X-rays CT	Lymphocyte count, cytokines, chemokines Antibodies		"	
Dabiao Chen *et al.*[78]	RNA		ACE2					
Yushun Wan *et al.*[79]	"		"					
SiukanLawa *et al.*[80]		Droplets, contact		CT	Lymphocyte, platelet count		"	
Vincent C. *et al.*[81]	Orf1ab, nsp.	Direct or indirect contact,	Degradation mRNA					
H. F. Rabenau *et al.*[82]		Direct, droplets, Feces						
Jun Lan *et al.*[83]	Spike (S) gene-S1, S2 subunit		ACE2.					
Mary Y. Y. Lai *et al.*[84]	RNA	Droplets, indirect contact						
Yan-RongGuo *et al.*[85]	Enveloped+sense RNA	Direct	"					
Roberto Lo Giudice *et al.*[86]	+ssRNA, spike glycoproteins	Droplets aerosol	"					
Yong Xionga *et al.*[87]			ACE2 cytokine storm				"	
XunLia *et al.*[88]					PCT, ESR, CRP, SAA Antibodies enzymes			
Chaolin Huang *et al.*[39]				"	CBC Enzymes PT. PTT antibodies	Virus isolation	NGS RT-PCR	
Chaomin Wu *et al.*[89]					"		RT-PCR	
Brian Hanley *et al.*[90]				X-ray				Changes in lungs, liver
Wei Xia *et al.*[63]				CT	"			
Yan Deng *et al.*[84]				"	"		"	

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Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
C J. Grein *et al.*[91]					"		"	
Soheil Kooraki *et al.*[92]				"	"			
Pavan K. Bhatraju *et al.*[93]				X-ray CT			"	
Mayla Gabriela *et al.*[94]					Hematological analysis Antibodies		"	
Temet M *et al.*[95]				CT			"	
Wei Tang *et al.*[96]				"	Lymphocyte count, ESR, CRP, PT, PTT chemokines, cytokines Enzyme		"	
Zixing Huang *et al.*[97]				"				
Chandrasekharan P *et al.*[98]					"		"	
Harmony R. Reynolds *et al.*[99]							"	
Luca Carsana *et al.*[100]					D dimer Antibodies		"	Changes in lungs, DIC
Jasper Fuk-Woo *et al.*[101]				X Ray			Cells cell culture RT-PCR NAAT NGS	
MandeepR. Mehra *et al.*[102]							RT-PCR	
Joshua Geleris *et al.*[103]				"			"	
Manish *et al.*[104]					Enzymes antibodies		"	
SaskiaMiddeldorp *et al.*[105]				CT	D– dimer		"	
Wei Li *et al.*[106]				"			"	
Wei Zhao *et al.*[107]				"			"	
Wei-jie Guan *et al.*[108]				X-ray CT	Blood urea nitrogen, leukocyteand platelet count antibodies		RT-PCR NGS	
Bo Diao *et al.*[109]				CT	Enzyme, lymphocyte count, ESR, CRP, PT, PTT cytokines, chemokine Antibodies		RT-PCR	
J. Zhang *et al.*[110]				"	"		"	
Shuchang Zhou *et al.*[111]				"	"		RT-PCR NAAT	
Kunhua Li *et al.*[112]					"		RT-PCR	
Rajab Mardani *et al.*[113]				X-ray CT	"		"	
Khan *et al.*[114]				"	Lymphocyte, platelet counts, CRP		"	
Liu D *et al.*[115]					Cytokine, CRP, ESR, ferritin, D dimer, LDH Antibodies			

Contd...

Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
Li J *et al.*[116]					CBC, platelet count, CRP, ESR, Enzyme level Antibodies		"	
Rozhgar A. *et al.*[27]							RT– PCR NGS	
Ali MohZaki *et al.*[117]				"	White cell count Antibodies		Cell culture RT-PCR	
Daniel K. W. *et al.*[32]							RT-PCR	
Maximilian Ackermann *et al.*[118]					Antibodies			Changes in lung, DIC, heart
T. Menter *et al.*[119]								Changes in lung, DIC, Heart, Kidney
Lisa M. Barton *et al.*[120]								Changes in lung, DIC, heart, liver
Anna Sapino *et al.*[121]								Changes in lung, DIC, heart
Liu Q *et al.*[122]								Changes in lung, DIC, heart, liver
Adachi T *et al.*[123]								Changes in lung, DIC, heart, liver, kidney
Megan Jenkins *et al.*[124]								Changes in lung, DIC, heart
SufangTian *et al.*[125]								Changes in lung
Kwok hongchu *et al.*[126]					Creatinine Enzyme			Changes in kidney
ShaoboSh *et al.*[127]				X ray	Enzyme			Changes in heart, DIC
Kochi AN *et al.*[128]					"			
Riccardo M. Inciardi *et al.*[129]					"			Changes in Heart
Micheal. F. Goldberg *et al.*[130]					D-dimer, serum ferritin, fibrinogen antibodies, enzymes			Changes in Lung, DIC, Heart
NereaLanda *et al.*[131]							RT-PCR	
A. Sharifi-Razavi *et al.*[132]				CT				
MuskaanSachdeva *et al.*[133]				"			"	
Chaoqun Han *et al.*[134]					D-dimer, serum ferritin, fibrinogen, antibodies, enzymes PT, PTT, Lymphocyte count	Viral RNA	"	
Julie Helms *et al.*[135]					"			DIC
Sharifi-Razavi *et al.*[136]					CRP			

Contd...

Table 2: Contd...

Authors	Structure	Mode of transmission	Pathogenesis	Imaging	Blood	Stool and urine	Sputum, transtracheal aspirates, or bronchoalveolar Lavage fluid	Autopsy and biopsy
Jiang Gu *et al.*[137]					Antibodies			Changes in lung, DIC, heart
Bridwell, R *et al.*[138]					"		"	
AmeenBiadsee *et al.*[139]					"		"	
Imagery, M. *et al.*[140]					Leucocyte, platelet count CRP, ESR Antibodies		"	
Acosta, B. V *et al.*[141]					Lactic dehydrogenase, ferritin, CRP, PCT			
Xiaoqiang Chai *et al.*[142]					ALT, AST			Changes in LIver DIC
CorradoLodigiani *et al.*[143]					Platelet count, D-dimer, PT, fibrinogen level			
Allesandro *et al.*[144]					Enzymes antibodies		"	
Zhenyu Fan *et al.*[145]					Enzymes		"	Changes in liver
Li Guo *et al.*[146]	Enveloped RNA			CT	Antibodies		RT-PCR	

CT: Computerized tomography, PT: Prothrombin time, PTT: Partial thromboplastin time, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RT-PCR: Reverse transcription-polymerase chain reaction, NGS: Next generation sequencing, NAAT: Nucleic acid amplification test, ACE²: Angiotensin-converting enzyme type II, LDH: Lactate dehydrogenase, DIC: Disseminated intravascular coagulation

distance of about 1.5-2 m/6 feet, to prevent the spread of viral particles which is dispersed through droplets from the nasal or oral cavity.[147] The incubation period of this disease is 1–14 days, of which the onset of symptoms is usually by the 3rd to 7th day after incubation. But the duration of viral shedding in COVID-19 can be up to 20 days in patients with severe illness and could be as long as 37 days. The alarming fact is that the infected person can remain asymptomatic and can still transmit the virus through direct or indirect contact, interfamilial transmission, ocular, faecal-oral transmission, and thereby acting as a super spreader.

The coronavirus, which is spherical to the pleomorphic virus, with a diameter of about 125 nm, has a phospholipid envelope with spike glycoproteins, which has an avital role in the pathogenesis of this infection. The SARS CoV2 binds to the angiotensin-converting enzyme type 2 receptors (ACE2) with the help of the S glycoprotein, with approximately 10–20-fold higher affinity than the former SARS CoV virus. ACE2 is a glycoprotein metalloprotease, a principle element in the protective arm of the renin-angiotensin system and it is responsible for conversion of Angiotensin II into Angiotensin, thereby regulating several physiological functions. On binding to the ACE2 receptors, the S protein undergoes furin cleavage to yield S1 and S2 subunits. The S1 subunit has a signal peptide, and receptor-binding domain (RBD), while the S2 subunit has conserved fusion peptide. This ACE-2 is widely distributed in the Type II pneumocytes, in the secretory cells of the intestine, to some extent in the cardiac muscles and also in salivary gland ducts, thus suggesting the possible presence of viral loads in human saliva as well.[148] Further, the expression of ACE-2 in the cardiac muscle is responsible for myocardial infarction in COVID-19 patients. And the presence of receptors in the cells lining the small intestine is the reason for diarrhoea in COVID-19 patients and transmission of this virus through the faecal route. Viral entry in to ACE2 receptor-expressing cells occurs by endocytosis following interaction of S1 (spike) glycoprotein with RBD of ACE receptors, followed by the release of the viral genome, synthesis of viral structural protein and genome, and assembly of mature virions in vesicles which are then released by exocytosis. The immune response following SARS-CoV-2 infection is responsible both for disease resolution as well as its pathogenesis.

Cytokine storm is an excessive inflammatory reaction in which large amounts of cytokine production is at a rapid rate, in response to microbial infection. Although beneficial inflammation is necessary for the local tissues to fight infection, exacerbated inflammatory responses in pneumonia patients infected with COVID-19 result in excessive release of pro-inflammatory cytokines known as cytokine storm leading to detrimental outcomes such as diffuse alveolar damage

Table 3: Inference for structure, modes of transmission and pathogenesis and number of articles studied

SARS CoV-2	Number of articles
Structure	
Enveloped	20
Spherical	2
Diameter	6
+Sense SS RNA	51
ORF	18
Structural proteins (E), (S), (M) (N)	
Envelope	8
Spike	28
Membrane	7
Nuclear	7
Non-structural proteins	20
Mutations	
Recombination in sp	2
Amino acid substitution	3
Point mutation	1
Insertion, deletion - nsp	7
Mode of transmission	
Zoonotic	2
Droplets	15
Direct	9
Indirect contact	4
Interfamilial	0
Aerosol	6
Ocular	1
Fecal-oral	3
Genetic predisposition	1
Pathogenesis	
ACE2	36
Spike (S) protein-receptor	
S1	3
S2	2
RBD	1
Cytokine storm	

ACE2: Angiotensin-converting enzyme type II, RBD: Receptor-binding domain

and fibrosis, progressive respiratory failure, and multi-organ dysfunction through disseminated intravascular coagulation. The most common and earliest symptoms are cough and sore throat, followed by fever, myalgia, headache, and nausea. Diarrhea is an uncommon symptom observed in a few cases. In patients with comorbidities like diabetes, the condition gets even worsened during infection as the coronavirus may destroy islets through its functional receptor ACE2 in islet and make the diabetic condition worsen. Also, ACE2 receptors are expressed more in diabetic patients leading to increased severity. Dysglycemia is known to down-regulate the key mediators of host innate immune response to pathogenesis. Metabolic disorders reduce macrophage and lymphocyte functions, rendering individuals susceptible to infectious disease complications.[149] Sepsis due to increased viral loads and disseminated intravascular coagulation caused by the formation of microthrombi pose a severe threat to the survival of patients with COVID-19. Cytokine storm causes activation of platelets leading to the microthrombi formation. There is increases platelet consumption during microthrombi formation and so decreases the number of circulating platelets. The accompanying multi-organ dysfunction results as a consequence of disseminated intravascular coagulation. Severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, and skin mottling are few of the various signs of organ failure. The respiratory tract samples of the individuals suspected for COVID-19 are preferred and collected up to 7 days post negative test. Virus (SARS-COV2 RNA) could be detected in blood and stool samples as well. The primary sample is from the upper respiratory specimen (nasopharyngeal and oropharyngeal swab) or lower respiratory specimen (sputum either-or endotracheal aspirate or bronchoalveolar lavage), and these samples are usually preferred.

From the blood and serum of the patient routine blood investigation and serological assays are carried out. The blood investigation includes total blood count, prothrombin time (PT), partial thromboplastin time, and the biochemical analysis are serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum creatine kinase, urea, cardiac troponin I, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, lactate dehydrogenase (LDH), D dimer, glucose as well as chemokine and cytokines. Higher levels of inflammatory mediators denote cytokine storm. Imaging of lungs by chest X-ray and computerized tomography (CT) scan in COVID-19 patients revealed ground-glass opacification. The serological assay, by flow cytometry, enzyme-linked immunosorbent assay (ELISA), and the chemiluminescent assay is used to detect viral antigen or antibody. On Serological analysis, the presence of antibodies was as early as 1 day after the onset of symptoms. Molecular nucleic acid analysis of the respiratory tract sample is by using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for the detection of viral antigen, considering it as the most reliable and standard diagnostic method till date. Sensitivity (%) is 82.7 (76.3–87.6) for IgM, 64.7 (57.4–71.5) for immunoglobulin G (IgG), and 86.9 (81.7–90.8) for combined IgG and IgM based serological tests. Thus the sensitivity is comparatively higher for combined IgG and IgM based serological tests. Positive antigen detection with RT-PCR and negative serological antibodies would indicate the severity of the disease. For the most accurate diagnosis, both antigen and antibody detection is essential.

The other test would be cell culture, urine and stool analysis, and various other molecular genetic tests like next generation sequencing. All the diagnostic tests employed in the previous studies are tabulated [Table 4].

Based on the analysis of the most commonly used diagnostic test employed are RT-PCR (34%) followed by lymphocyte count (28.6%) as well organ specific enzymes and then CT scan imaging (21.3%) [Table 5].

The result of blood investigation in patients affected with COVID-19, are Leukopenia, mild to moderate lymphopenia and thrombocytopenia. Higher PT, partial thromboplastin time (PTT) are associated with disseminated intravascular coagulation. The biochemical parameters will be raised LDH and normal ALT, AST, and enzymes. Any alteration or abnormalities of the enzyme test have been associated with organ comorbidities.

Biopsy of the tissue reveals cytopathic effect, viral inclusion bodies, inflammatory infiltrates and multinucleated giant cells through light and electron microscopic analysis. In those deceased, autopsy findings suggest that the virus was detected in many organs and the main cause of death was respiratory distress, which was due to diffuse alveolar damage. The gross findings of lungs were patchy to diffuse areas of consolidation with broncho-suppurative infiltrate; the heart showed myocardial hypertrophy and in kidney signs of shock were observed. Other common findings were pneumocyte Type II hyperplasia, single syncytial cells

Table 4: Inference for investigations and number of articles studied to understand diagnostic accuracy

Test	Number of articles
Diagnosis	
Imaging	
CT imaging	33
Chest X-ray	16
Blood	
Immunologic	
Antibodies (IgG, IgM, IgA)	52
Hematologic	
Lymphocyte (CD4, CD8) and platelet count	43
Biochemical	
Organ specific enzymes (AST, ALT, total protein albumin, creatinine , glucose, urea, BUN, LDL, LDH, cholinesterase, cardiac troponin I)	45
Infection related indices	
ESR and CRP	35
Inflammatory chemokines and cytokine	21
Ferritin	6
Coagulation	
PT, PTT	24
D - Dimers	8
Stool and urine	
Viral antigen isolation	4
Sputum, BAL	
RT-PCR	72
NAAT	5
NGS	7
Cell lines	9
Tissue	
Biopsy	
Inclusion bodies and multinucleated syntial cells	7
Inflammatory infiltrate	10
Type II pneumocyte hyperplasia	6
Autopsy	
Lung (DAD, frothy pulmonary edema hyaline membranes desquamation, squamous metaplasia, intralveolar hemorrhage)	9
Liver (microvascularsteatosis and mild lobular and portal injury, fatty degeneration and central lobular necrosis, fibrosis)	6
Kidney (renal shock, tubular impairment, glomerulonephritis, glomeruli microthrombi)	4
Heart (myocardial hypertrophy, necrosis of cardiomyocytes, artherosclerosis, right ventricular dilatation)	8
Duodenum (punctate hemorrhage)	1
DIC	6

CT: Computerized tomography, PT: Prothrombin time, PTT: Partial thromboplastin time, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RT-PCR: Reverse transcription-polymerase chain reaction, NGS: Next generation sequencing, NAAT: Nucleic acid amplification test, ACE2: Angiotensin-converting enzyme type II, LDH: Lactate dehydrogenase, DIC: Disseminated intravascular coagulation

Table 5: Percentage of each diagnostic test employed

Diagnostic test	Chest X-ray	CT imaging	Lymphocyte count	PT, PTT	CRP ESR	Inflammatory mediators	Organ specific enzyme analysis	Antibodies	RT-PCR	Autopsy
Total number of articles	20	32	43	24	35	21	45	52	72	10
Percentage	13.3	21.3	28.6	16	23	14	29.6	34.2	47.3	6

CT: Computerized tomography, PT: Prothrombin time, PTT: Partial thromboplastin time, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RT-PCR: Reverse transcription-polymerase chain reaction

and interstitial septal lymphoid infiltrates. Disseminated intravascular coagulation with small fibrin thrombi in glomerular capillaries along with interstitial edema with flattened and widened tubular epithelium of the kidney and focal necrosis of cardiomyocytes as a sequelae of shock were the other observed findings.[150]

Based on Literature survey, a wide range of recommended guidelines and standard protocols have been published so far and followed till now to provide utmost and elective dental care to suspected and confirmed COVID-19 patients and to prevent the wide spread of infection.

Current guidelines and protocols published so far,

- Interim Infection Prevention and Control Guidance for Dental Settings During the COVID-19 Response-Centers for Disease Control and Prevention (CDC) Guidance for Dental Settings[151]
- Interim Guidance for Management of Emergency and Urgent Dental Care, Summary of ADA Guidance During the COVID-19 Crisis, Guidance on dental emergency, nonemergency care-American Dental Association (ADA)[152]
- Interim guidance for the dental providers and Dental Healthcare Workers–Occupational Safety and Health Administration[153]
- Guidelines for Dental Professionals in COVID-19 pandemic situation– Ministry of health and Family Welfare India[154]
- Protocol for teledentistry during COVID-19 in Armed Forces dental establishments-Armed Forces Medical Services India[155]
- Indian Society of Oral Implantologists (ISOI) guidelines for dental practitioners during COVID-19 pandemic-ISOI.[156]
- Indian Dental Association's (IDA) Preventive Guidelines for Dental Professionals on the Corona virus Threat– IDA[157]
- Considerations for the provision of essential oral health services in the context of COVID-19 Interim guidance– WHO[158]
- FDI Council Statement on Dentistry and Oral Health during the COVID-19 Pandemic-FDI World Dental Federation.[159]

At present in dental practice, protocols for patient screening which includes, temperature assessment by a digital noncontact infrared thermometer and screening questionnaire with COVID-19 history proforma have become an Emerging trend in this pandemic period.

Similarly, various tests have also been implemented as clinical lab investigatory protocol during COVID era in dental practice.

Definitive test: Nucleic acid amplification test-RT-PCR.

Ancillary investigations

- Blood investigations: Total blood count (total lymphocyte count), PT, partial thromboplastin time, ESR
- Biochemical serum analysis– LDH, CRP, D-dimer
- Serological assays-flow cytometry, ELISA, and chemiluminescent assay.

CONCLUSION

The novel coronavirus, which is just another variation of the previously occurred SARS infection, is posing a great challenge to humankind. The higher affinity of the spike glycoprotein or the RBDs, the frequently mutated strains and easier mode of transmission which involves being in close proximity to the infected person during coughing, sneezing, shaking hands, even mere speaking or coming in contact with the surfaces contaminated by them, makes it more complicated to resolve. The expression of ACE2 receptors on the cells of vital organs like the cardiac, respiratory, intestinal and glandular tissues, further contributes to the severity of the disease. Despite the availability of effective diagnostic modalities like the RT-PCR, Serological antigen antibody assays, CT imaging and advanced molecular genetic tests, there are no definitive treatment protocol or prevention strategies for this COVID-19 infection, despite constant efforts from the researchers all over the world. Social distancing, hand hygiene practices, using masks, proper disinfection of surfaces which are more prone for contamination and avoiding social gatherings are the only known ways of by-passing the infection. As of now about 3% of the infected population, remain asymptomatic and even, those with symptoms could take an incubation period of 3–7 days to develop them. The risk of these patients acting as "super spreaders" is becoming the major threat of this hour. Elevating the number of people being subjected to diagnostic procedures and proper care of high risk individuals, can decrease mortalities.

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Conflicts of interest

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Dr.Adlin Saroja Rosaian. The first draft of the manuscript was written by Dr. Beryl Rachel. J, Dr. Divyna Daniel. T, Dr. B.S. Harishini Dr. N. Gururaj and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All the authors agree to be accountable for all aspects of the work in ensuring that question related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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