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Journal homepage: https://www.achr.co.in/

Review Article

A systematic review of autopsy findings in COVID 19: The road ahead

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ARTICLE INFO

Article history:
Received 05-07-2021
Accepted 20-08-2021
Available online 16-09-2021

Keywords:
Autopsy COVID-19
Autopsy SARS-CoV-2
Postmortem findings COVID-19

ABSTRACT

Autopsy data on the COVID 19 is scarce and has left a gap in understanding the disease process. This study attempts to review the available data gleamed from the limited autopsies performed worldwide which would help in guiding future treatment protocols.

A literature search was undertaken using PubMed, Scopus, Embase and Google search engines for original and review articles. Studies that mentioned autopsy and COVID-19 were included. Findings from a total of 16 studies mentioning 139 autopsies in confirmed cases of COVID 19 were analysed. The most common features in fatal cases has been cough followed by progressive dyspnoea. Fatal cases show a predominance in the elderly age group, male gender and individuals with blood type A.

Autopsy findings in various organs have been described with the prominent feature being Diffuse alveolar damage and microthrombii formation in the lung. Massive pulmonary embolism and Deep vein thrombosis seem to be overlooked features in the fatal cases.

Complement mediated destruction is a potential pathogenetic mechanism suggested by C4d and C5b-9 deposition in the skin lesions and lung capillaries.

To conclude, Prophylactic dose of low molecular weight heparin, chest CT and serial D-dimer levels are recommended in all patients with suspected COVID 19 admitted to the hospital.

The demonstration of complement mediated injury to various tissues also suggest a role of anti-complement therapy to improve patient outcomes.

Detailed autopsy studies are required to evaluate the pathology of COVID 19 in various organs to understand the disease process better

1. Introduction

As the novel coronavirus now known as the Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) originated in Wuhan district of china and later spread to the entire world, it triggered a pandemic of Coronavirus disease 2019 (COVID 19) and has resulted in more than 3,00,000 deaths worldwide as on 16^{th} May 2020.

The family of coronavirus is known to cause many zoonotic disease outbreaks including the Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome Eastern (SARS) in the past.[1]

All the outbreaks originated from bats and infected secondary animal hosts like the dromedary camel (MERS) and the civet cat (SARS) before being transmitted to humans.[2]

The novelty of the SARS-CoV-2 virus combined with the higher infectivity than SARS-CoV and global hysteria has left a huge void in the understanding of the pathology of the disease with many medical governing bodies advising against autopsies in confirmed COVID 19 deaths.[3,4] The scarce post-mortem examination data needs to be examined

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https://doi.org/10.18231/j.achr.2021.036

to understand the course of the disease and determine future course of treatment protocols to improve patient outcomes.

2. Objective

This review aims to provide an overview of various autopsy findings in patients with COVID-19.

3. Materials and Methods

3.1. Data bases and search strategy

Our method protocol follows the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and is outlined in (Figure 1).[5] A literature search was conducted using PubMed / Medline, Scopus, Embase and Google search engines. The search terms used were: "Autopsy in COVID-19", "Post mortem in COVID-19", "Autopsy in SARS-CoV-2" and "Post mortem in SARS-CoV-2." The search was limited to articles published in 2020 and due to the large number of search results in grey literature, keyword search was limited only to the titles in the Google scholar search engine whereas no such restriction was placed on the other databases.

The literature search was concluded by May 16, 2020, and two independent researchers evaluated the search results.

3.2. Study selection

After removal of duplicate search entries, the initial search results were first screened by language, title and abstract. The full texts of relevant articles were examined for inclusion and exclusion criteria.

3.2.1. Inclusion criteria

1. Studies published till 16th May 2020.
2. English language.
3. Mentioning histopathology of any organ in partial or complete autopsies in confirmed cases of COVID 19.

3.3. Exclusion criteria

1. Studies published in other languages.
2. Studies not based on autopsy.
3. Studies mentioning only gross examination and no histopathological examination of the autopsy specimens.

3.4. Studies on non-human subjects

The selected studies were assessed for quality using the National Institutes of Health Quality Assessment Tool for Case Series Studies by two independent observers (Figure 2).[6]

3.5. Data collection process

After assessment and selection of the study, Information on the type of publication, country, year and date of publication, the number of reported cases, age, sex, comorbidities, clinical features, laboratory findings, and findings at autopsy were filled independently by two investigators.

A third researcher checked the article list and data extrapolation to ensure that relevant studies were included and that no duplicate data was entered erroneously.

3.6. Data anaysis

This data was analysed and recorded by two independent researchers. In case of discrepancy, the third researcher was consulted and consensus achieved. Data was analysed using Medcalc version 19.0.7 and descriptive statistics were used to compare findings.Meta-analysis to corelate age and ethnicity with pathological features could not be carried out due to limited data.

3.7. Guidelines for performing autopsy on confirmed/suspected covid 19 cases

Various regulatory health bodies like The Royal College of Pathologists (RCPath, UK), the Centre for Disease Control (CDC, USA) and the Ministry of Health and Family Welfare (MoHFW, India) have released guidance on post-mortem examination for mortuary workers in suspected/ confirmed COVID 9 cases.[4]

Adequate training and strict adherence to institutional SOPs in accordance with the guidelines should ensure minimal exposure of the mortuary staff.

4. Results

Findings from a total of 15 studies describing 139 autopsies in confirmed cases of COVID 19 by RT PCR were analysed. Additionally, histopathological findings were reported from the lung specimens of 2 patients who underwent lobectomy for lung carcinoma but were found to be positive for COVID 19 subsequently. Since these were technically not autopsies, the findings were not included in our data but have been discussed separately.[7–22]

The average age of all the deceased individuals was 62.5 years with an age range of 17 to 96 years. More than 75% of deaths were in males. Ethnicity was specified in only 8 cases amongst which 6 were African American and 2 were Hispanic.[9,18,21]

All the fatal cases had a history of one or more previous underlying disorders including diabetes mellitus, hypertension, obesity, CKD, COPD, malignancy, myotonic dystrophy, liver cirrhosis, hepatitis C with hypertension and obesity being the most common.

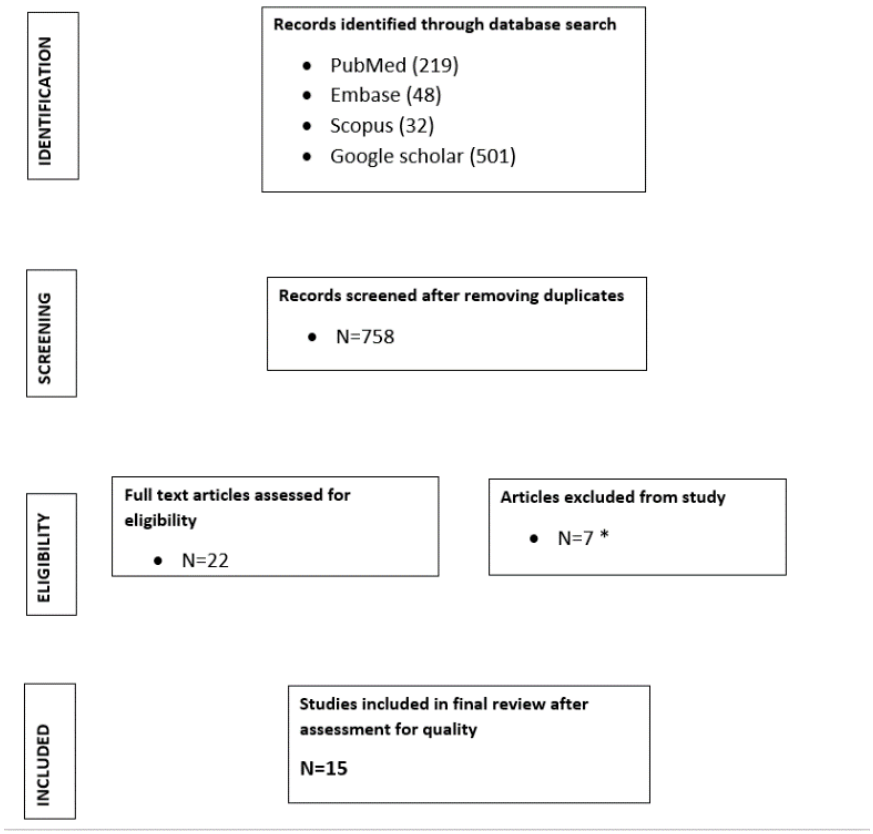

Fig. 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram outlining the study selection process. *3 studies were in Chinese language, 3 studies not based on autopsy and 1 study on non-human subjects

Reference Number→	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q3	CD	CD	Y	Y	CD	CD	NA	CD	Y	NA	CD	CD	CD	CD	NA
Q4	CD	CD	CD	CD	CD	CD	NA	CD	CD	NA	CD	CD	CD	CD	NA
Q5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q6	Y	Y	N	Y	Y	Y	NA	N	Y	NA	Y	Y	Y	Y	NA
Q7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Q8	Y	Y	CD	Y	Y	Y	NA	Y	Y	NA	NA	Y	Y	Y	NA
Q9	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y
Reviewer 1	Good	Good	Fair	Good	Good	Good	Fair	Poor	Good	Good	Fair	Good	Good	Good	Good
Reviewer 2	Good	Good	Poor	Good	Good	Good	Fair	Poor	Good	Good	Fair	Good	Good	Good	Good

Fig. 2: Quality ratings of included studies according to NIH Quality Assessment Tool for Case Series Studies Q1. Was the study question or objective clearly stated?
Q2. Was the study population clearly and fully described, including a case definition?
Q3. Were the cases consecutive?
Q4. Were the subjects comparable?
Q5. Was the intervention clearly described?
Q6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?
Q7. Was the length of follow-up adequate?
Q8. Were the statistical methods well-described?
Q9. Were the results well-described?

In the fatal cases studied, the predominant clinical feature was mentioned in 65 cases, which was cough (49%) followed by progressive dyspnoea (47%) and fever (43%). An initial presentation with Diarrhoea was reported in 2 cases. The youngest patient included in this study was a 17-year-old African American male who presented with headache, nausea and vomiting.[21]

Laboratory findings were available variably amongst the studies and elevated levels of LDH (96%), D-Dimer (100%) and Creatinine (81%) were seen in a majority of cases in which the reports were available.

Lymphocyte counts were available in 32 cases of which 29 showed lymphocytopenia. One autopsy series from Switzerland mentions lymphocytopenia as a prominent finding but individual patient data was not available.[20] Levels of Brain natriuretic peptide (4/4), serum ferritin (2/2) and CK MB (2/2) were elevated in all the recorded cases.

The demographic and laboratory data has been summarized in Table 1.

Autopsy findings were recorded from the lungs in 113 cases followed by heart (50), kidney (41), liver (23), spleen (12), Lymph nodes (9). bone marrow (5), brain (2) and skin (2). The findings have been summarised in Table 2.

Of the 113 cases in which pathological findings of the lung were recorded, the histological picture consisted of multiple features in every case. However, to facilitate enumeration of the most prominent changes, the features were individually recorded from the various studies.

The most common findings were features consistent with varying stages of Diffuse Alveolar Damage (DAD) including hyaline membrane formation, vascular congestion, pneumocyte injury with focal sloughing and intraalveolar haemorrhages.

57 of the 113 cases showed features of microthrombi formation in the pulmonary vessels with 39 cases showing presence of increased CD61 positive megakaryocytes in the alveolar capillaries.

Complement mediated Necrotising capillary injury was reported in the lungs of both cases studied by Magro et al.[10]

Amongst the 50 recorded findings from the heart, Cardiomegaly on gross examination and/or myocyte hypertrophy histologically were noted in 39 cases. Four studies recorded focal individual myocyte injury in a total of 11 cases. Senile amyloidosis was seen in 6 cases. Myocarditis was noted in 3 cases amongst which the heart tissue from the 17-year-old showed features of fulminant eosinophilic myocarditis.[21]

Histological findings from the Kidney were recorded in 42 cases of which 41 showed features of acute tubular injury with loss of brush border, vacuolar degeneration and occasional necrosis. Segmental fibrin thrombi and features of Disseminated intravascular coagulation were seen in 4 and 3 cases respectively. Electron microscopy was done in 23 cases of which 21 demonstrated spherical virus particles in the proximal tubular epithelium.

Liver was studied in 23 cases in which steatosis and sinusoidal dilation were the most common findings.

Findings from the spleens in 12 cases revealed diminished white pulp with loss of marginal zone in 6 and features of splenitis in 6. In addition to diminished white pulp, 3 cases also showed red pulp expansion with lymphoplasmacytic infiltrate.

Bone marrow was studied in 5 cases and 3 showed left shift corelating with neutrophilic leucocytosis whereas 2 showed infiltrates of Hematolymphoid malignancy.

Skin biopsies were available from 2 patients and showed complemented mediated vasculopathy.

Punctate haemorrhages were noted in the subarachnoid and brainstem in one case each Electron microscopy was used to demonstrate the viral particles in the pneumocytes in the studies conducted at Italy and New York whereas the series from Washington demonstrated the viral particles in the lung trachea, kidney and large intestine.[11,17,19]

Individual data was available from ultrastructural study of 23 kidney biopsies of which 21 showed the presence of viral particles.

Additionally PCR was used to determine the viral load in various tissues by Bradley et al. The highest concentrations were noted in lung, kidney, heart, liver, spleen, large intestines and lymph nodes. Viral RNA was not detected in the brain, bladder, esophagus or stomach.[19]

5. Discussion

Even though most guidelines advise against autopsy in known COVID 19 patients, many authors have called for increased autopsy studies to further the knowledge about the disease process and guide therapy.[23]

The mean age of patients who underwent autopsy in the studies reviewed by us was 62.5 and had one or more comorbidities with hypertension and obesity being the most common. This corelates with most of the demographic data available.[24]

Clinical studies have mentioned the most common manifestations of COVID 19 to include fever, dyspnoea, dry cough, headache, muscle pain, chest pain, diarrhoea, nausea and vomiting. A meta-analysis performed by Rodriguez Morales et al found fever, cough and dyspnea to be the most prevalent clinical manifestations with the frequency of fever being significantly higher in adults as compared to children. However, in the fatal cases included in our study, the most common clinical features were cough and dyspnoea. Amongst laboratory findings in clinical studies, indicators of acute inflammatory response like decreased albumin, high C-reactive protein, high lactate dehydrogenase, lymphopenia, and high erythrocyte sedimentation rate were most prevalent.[25] In our study, the laboratory findings in the fatal cases included high incidence of elevated D- dimer, LDH and serum creatinine

Table 1: Demographic and clinical data from 139 autopsies

Total autopsies	139	
Gender (134)	Male	102
	Female	33
	Not specified	04
Age	Average age	68.1*
	Youngest	17
	Oldest	96
Comorbidities (137)	Hypertension	65
	Obesity	43
	Diabetes Mellitus/Prediabetes	30
	Pre-existing heart disease	33
	Malignancy	15
	Pre-existing COPD	6
Clinical features	Fever	28
	Cough	32
	Dyspnea	31
	Diarrhoea	2
Laboratory findings	Increased LDH	24/25
	Increased D Dimer	38/38
	Lymphopenia	29/32 †
	Elevated creatinine	31/38 †
	Elevated BUN	13/22
	Elevated BNP	4/4
	Elevated CK MB	2/2
	Elevated ferritin	2/2

*Data not available from cases in New York. Both cases mentioned as middle aged.[17]
*Data not available from cases in New York. Both cases mentioned as middle aged.$
†Also seen in majority of cases from the Swiss study by Menter et al but individual data not available.$

accompanied by lymphocytopenia. This suggests infection related septic coagulopathy and/or organ dysfunction. Therefore elevated D-dimer and serum creatinine may be uses as an adverse prognostic marker in confirmed cases of COVID 19.

65% of the autopsy cases in the study by Menter et al had the blood type A which corelated with a population study in China suggesting that individuals with the blood type A were more susceptible to the thromboembolic sequelae of the disease.[26] Studies suggesting the effect of ABO alleles on the activity of Von Willebrand Factor(vWF) with the A1A1 subtype increasing vWF activity the most may explain this phenomenon.[27]

Earlier studies on the SARS coronavirus have suggested that the Viral S protein interacts with the A antigen to facilitate its entry into the cells which may be a shared characteristic with the SARS-CoV-2.[28]

The primary pathology in all the studies was noted in the lung and broadly composed of two patterns. Diffuse alveolar damage was the only striking feature in the 4 post-mortem samples studies by Tian et al in China and the single case reports from China and Iran whereas the autopsies

Table 2: Autopsy findings from various organs

Organ	Findings	Number
LUNG (data available from 113 cases)	Diffuse Alveolar Damage (exudative, proliferative or both)	102
	Thrombi in pulmonary vessels	57
	Pulmonary embolism	13
	Pulmonary edema (varying degrees)	48
	Pneumonia	38
	Tracheitis	16
	Emphysema	13
	Reactive pneumocytes, metaplasia and syncytial cells	61
	Prominent lymphoid infiltrate	42
	Necrotising capillary injury	2
	Pulmonary hemorrhage	41
	Amyloidosis of pulmonary vessels	3
	Vasculitis	1
	Increased CD 61 + Megakaryocytes in capillaries	39
	Viral particles by EM	2*
HEART (n=50)	Cardiomegaly/ Hypertrophy	39
	Senile amyloidosis	7
	Individual myocyte injury	11
	MI	2 †
	Myocarditis	3
	Pericarditis / epicarditis	3
SPLEEN (n=12)	No change	5
	White pulp diminished with loss of marginal zone	6
	Red pulp expansion with lymphoplasmacytic infiltrate	3
	Splenitis	6
KIDNEY (n=42)	Acute tubular injury	41/42
	Segmental fibrin thrombi	4
	Virus particles by EM	21/23
	DIC	3
	Hypertensive nephropathy	15
	Diabetic nephropathy	7
LIVER (n=23)	Sinusoidal dilatation	11
	Regenerative nodules	1
	Steatosis	20
	Shock necrosis	9
	Steatohepatitis/NASH	3
	Mild lobular lymphocytic infiltrate	6
Bone marrow (n=5)	Reactive left shift	3
	Infiltration by hematopoietic malignancy	2
Skin (n= 2)	Complement mediated vascular injury	2
Brain (n=2)	Punctate subarachnoid haemorrhages	1
	Punctate brainstem haemorrhages	1
Other	Thrombi in Para testicular veins	1
	Increased plasmablasts in lymph nodes	5/9

*Studies from Italy and Washington also reported viral particles in pneumocytes but did not mention exact number of cases.
†8 cases also showed signs of old myocardial infarction.

carried out in Brazil, Italy, New Orleans and Texas showed bilateral DAD with alveolar capillary thickening and fibrin thrombi with presence of atypical megakaryocytes in the capillary lumen. 2 cases studied by Magro et al showed predominant changes in the septal capillaries consistent with complement mediated destruction whereas alveolar damage was negligible.

The demonstration of deep vein thrombosis (58%) and massive pulmonary embolism (33.3%) in the autopsy series by Wichmann et al suggests that pulmonary embolism may be an overlooked clinical feature in cases of sudden death especially when CT chest is being avoided to minimize exposure of hospital staff.[15]

Amongst the pulmonary pathology of other coronavirus infections, varying degrees of exudative and proliferative phase of acute lung injury, along with vascular fibrin thrombi have been recorded in patients with SARS-CoV infection whereas the lungs of MERS patients only revealed DAD and no vascular thrombi. Therefore, some similarities exist in the pathogenesis and the mechanisms of tissue damage due to coronaviruses infections.[29–31] However DAD seems to strike early in SARS CoV-2 with patients succumbing after a brief history of the disease showing alveolar damage on autopsy whereas in SARS infection, DAD developed after longer duration of hospital stay.[32]

The different patterns of pathological presentations in the lung of COVID 19 patients warrant an investigation into the role of host factors including ethnicity, underlying comorbidity and immunity or the effect of different virus strains present in different geographical areas.

The therapeutic implications of understanding the primary pathology in the lung is that by starting anti coagulation therapy early in the course of the disease, perfusion can be maintained thereby improving patient outcomes. A Chinese single-centre retrospective study of 449 consecutive patients classified as having severe COVID-19 indicates that prophylactic anticoagulation therapy might be associated with improved survival in patients with sepsis induced coagulopathy.[33] Prophylactic low molecular weight heparin has been recommended by some authors in all patients admitted with suspected COVID 19 and has recently been included in the Ministry of Health and Family Welfare guidelines in the management of the disease.[34,35]

The demonstration of complement mediated destruction of the septal capillaries and the presence of vascular deposition of C5b-9 which is a feature of many microthrombotic syndromes like Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Uremic Syndrome points towards a possible role of anti-complement therapy like Eculizumab in such patients.[36,37] Similar findings in the skin biopsies suggest a systemic involvement rather than a local reaction.

Even though case reports have mentioned petechial rash and urticaria amongst the rarer manifestations of the disease, in a majority of them the severity of cutaneous lesions was unlikely to be or was not correlated with COVID-19 severity.[38]

Pathological changes in the heart were not characteristic as they may be sequelae of underlying comorbidities. However, scattered individual myocyte necrosis and myocarditis were noted in a few cases with one case showing extensive eosinophilic infiltrate. The elevated levels of BNP and CK MB noted in some patients accompanied by the demonstration of Viral RNA in the heart tissue support a study by Chen et al which suggests that pericytes may be infected by the virus and causes capillary endothelial cell dysfunction causing individual cell necrosis.[39]

Acute tubular injury was the most noted finding in the kidneys followed by changes suggestive of underlying diabetic or hypertensive disease. Few cases showing segmental fibrin thrombi suggest a thromboembolic component in the pathology in the kidney which also explains the rising serum creatinine levels in deteriorating cases.

The demonstration of coronavirus particles by electron microscopy in the various organs including Pneumocytes, Kidney, trachea, large intestine and spleen, a high viral RNA load detected by PCR in samples from Lung, pharyngeal tisue, kidney, heart, liver, spleen, large intestines and lymph nodes combined with the histological findings suggest direct invasion and cytopathic effect of the SARS Cov -2.[15,19]

Studies have suggested the entry of the virus into the cell via ACE 2 and CD 147 receptors.[40,41] The presence of ACE 2 receptors in the lungs and kidneys and the expression of CD 147 in the proximal tubular epithelial cells and the frequent demonstration of viral particles in these tissues provide merit to this hypothesis. The role of Cyclosporine A which downregulates the expression of CD147 needs to be investigated.[42–44]

It should also be noted that patients with hypertension, cardiac diseases, obesity related sleep apnea are frequently placed on angiotensin converting enzyme inhibitors or angiotensin receptor blockers which causes up-regulation of the ACE 2 receptors. This may contribute to the increased susceptibility of these patients to the virus.

The presence of high viral RNA load in various tissues and the presence of viral particles in the blood and stool suggest a simultaneous multiorgan involvement and raises apprehension in the fields such as transplant surgery and transfusion medicine as a negative nasopharyngeal test may not completely rule out the disease.[45,46]

6. Conclusion

The spectrum of pathological changes in the lung and other organs suggest a microvascular thrombotic

pathology in addition to DAD. Pulmonary embolism may be an overlooked clinical feature and prophylactic dose of low molecular weight heparin is recommended in all patients with suspected COVID 19 admitted to the hospital. In addition, chest CT and serial D-dimer levels are recommended for early detection of Pulmonary thromboinflammatory process and prognostic stratification. The demonstration of complement mediated injury to various tissues also suggest a role of anti-complement therapy to improve patient outcomes. The role of cyclosporine A as an inhibitor of CD147 which is suggested as an entry mechanism for the virus needs to be examined.

The increased susceptibility of individuals with blood group A needs to be investigated further by obtaining the available records of all fatalities of COVID 19.

Detailed autopsy studies are required to evaluate the pathology of COVID 19 in various organs to understand the disease process better.

7. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

8. Source of Funding

None.

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Cite this article: Faizal F, Kapoor U, Nambiar B. A systematic review of autopsy findings in COVID 19: The road ahead. *IP Arch Cytol Histopathology Res* 2021;6(3):145-152.