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REVIEW

Autopsy findings of COVID-19 in children: a systematic review and meta-analysis

Anju Khairwa[1] · **Kana Ram Jat**[2]

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Abstract

Clinical features of COVID-19 range from mild respiratory symptoms to fatal outcomes. Autopsy findings are important for understanding COVID-19-related pathophysiology and clinical manifestations. This systematic study aims to evaluate autopsy findings in paediatric cases. We searched PubMed, EMBASE, and Cochrane Database Reviews. We included studies that reported autopsy findings in children with COVID-19. A total of 11 studies (24 subjects) were included. The mean age of patients was 5.9 ± 5.7 years. Grossly, there was pericardial and pleural effusion, hepatosplenomegaly, cardiomegaly, heavy soft lung, enlarged kidney, and enlarged brain. The autopsy findings of the lungs were diffuse alveolar damage (78.3%), fibrin thrombi (43.5%), haemorrhage (30.4%), pneumonia (26%), congestion and oedema (26%), angiomatoid pattern (17.4%), and alveolar megakaryocytes (17.4%). The heart showed interstitial oedema (80%), myocardial foci of band necrosis (60%), fibrin microthrombi (60%), interstitial and perivascular inflammation (40%), and pancarditis (30%). The liver showed centrilobular congestion (60%), micro/macrovesicular steatosis (30%), and arterial/venous thrombi (20%). The kidney showed acute tubular necrosis (75%), congestion (62.5%), fibrin thrombi in glomerular capillaries (37.5%), and nephrocalcinosis, mesangial cell hyperplasia, tubular hyaline/granular casts (25% each). The spleen showed splenitis (71.4%), haemorrhage (71.4%), lymphoid hypoplasia (57.1%), and haemophagocytosis (28.6%). The brain revealed oedema (87.5%), congestion (75%), reactive microglia (62.5%), neuronal ischaemic necrosis (62.5%), meningoencephalitis (37.5%), and fibrin thrombi (25%). SARS-CoV-2 and CD68 were positive by immunohistochemistry in 85.7% and 33.3% cases, respectively. Autopsy findings of COVID-19 in children are variable in all important organs. It may help in better understanding the pathogenesis of SARS-CoV-2.

Keywords SARS-CoV-2 · Autopsy · Pathophysiology · Correlation · Children

Introduction

SARS-CoV-1 caused severe acute respiratory syndrome (SARS) in 2002, MERS-related coronavirus (MERS-CoV) caused Middle East respiratory syndrome (MERS) in 2012, and now SARS-CoV-2 is causing COVID-19 disease since December 2019 that started from Wuhan city of China [1, 2]. This has affected most of the countries in the world [2]. SARS-CoV-2 is an RNA virus and belongs to a family of beta coronaviruses such as SARS-CoV-1 and MERS-CoV [3]. There are minor differences in the spike protein of SARS-CoV-2, which increases the transmission rate of this virus [3]. The SARS-CoV-2 has affected all age groups but caused severe disease in persons with comorbidity [4]. Clinical features of SARAS-CoV-2 range from mild respiratory symptoms to severe and fatal outcomes, including acute respiratory distress syndrome, multiorgan failure, and death [5]. COVID-19 is associated with many complications like cardiovascular, including thrombosis and neurological manifestations [6, 7]. To understand COVID-19-related clinical manifestations, complications, and pathogenesis, it is required to investigate cellular targets of SARS-CoV-2 tropism, replication, and mechanism of viral dissemination [8]. Autopsy studies may provide deeper insight into the underlying pathophysiology and pathogenesis of SARS-CoV-2 [9]. But there are a limited number of autopsies for evaluating COVID-19-related pathogenesis and pathophysiology,

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✉ Anju Khairwa
anjukhairwa@gmail.com

[1] Department of Pathology, University College of Medical Sciences, Delhi, India

[2] Department of Pediatrics, All India Institute of Medical Sciences, Delhi, India

especially in children. Restricted autopsies may be due to the recommendations to suspend post-mortems on patients with suspected/confirmed COVID-19 infection [10]. Performing the autopsy of COVID-19 patients is very risky due to its highly contagious tissue material, and it requires an autopsy facility with appropriate biosafety measurements [11]. There is a need to review the autopsy findings of COVID-19 to understand the COVID-related pathology in children.

This systematic review aims to describe the autopsy findings in children due to COVID-19.

Method and material

It is a systematic review where we included studies where autopsies were performed in COVID-19-positive children who died. We searched PubMed (inception to 30th June 2021), EMBASE (inception to 30th June 2021), Google Scholar (inception to 30th June 2021), and Cochrane Database Reviews (30th June 2021). Search strategy for PubMed included "Autopsy in children COVID" OR "Autopsy COVID-19 children". We searched EMBASE with keywords/exp "Autopsy COVID-19 children" AND "Autopsy COVID-19 Child". The keywords for Google Scholar were "Autopsy COVID-19 children", and for Cochrane Database Reviews, were "Autopsy COVID-19 children". References of included studies were hand searched for additional studies. The authors initially selected studies through title and abstract and reviewed the full text if required. We extracted data from included studies in a pre-defined form. We used the Appraisal tool for Cross-Sectional Studies (AXIS [12]) to assess the methodological quality of included studies.

Inclusion criteria

The studies performed an autopsy on children (< 18 years) who were positive for COVID-19. We also included the studies that reported autopsy of children and adults and collected data for paediatric (< 18 years) patients from such studies.

Exclusion criteria

Randomised controlled trial (RCT) studies and an autopsy performed only on adult patients.

Statistical methods

We presented the continuous outcome data as mean ± SD and categorical data as percentages. We used STATA 12 for descriptive statistics. Meta-analysis was performed using Cochrane RevMan 5.1. Meta-analysis was performed only on studies of similar design and outcome measures.

Results

The study selection flow diagram is shown in Fig. 1. By electronic database search, we found a total of 8564 records. After excluding duplicates and irrelevant studies by screening titles and abstracts, 42 potentially eligible studies were identified to review the full text (Fig. 1). After reviewing full texts, 31 articles were further excluded, and 11 studies were included for qualitative synthesis and meta-analysis (Fig. 1). There were 26 patients in the included studies. The critical appraisal of included studies is shown in Table 1.

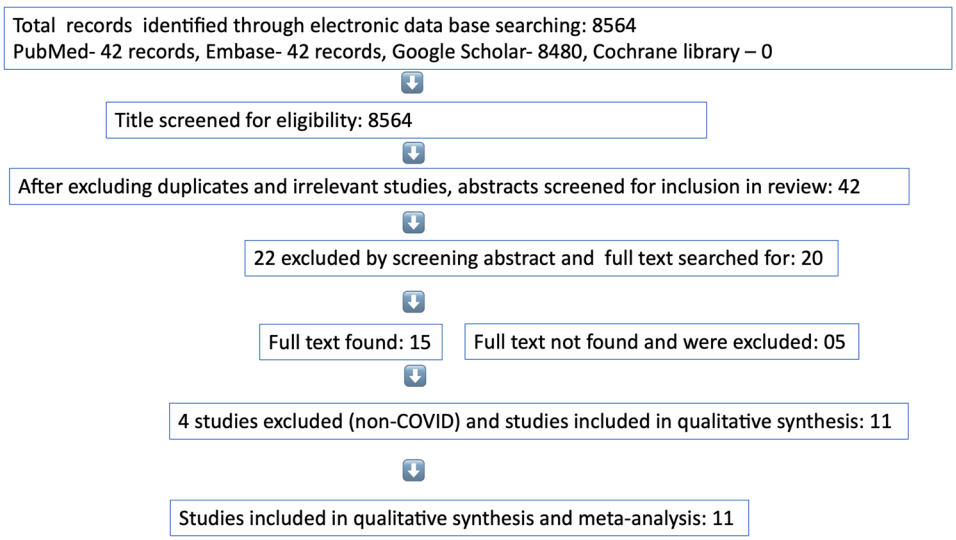

Fig. 1 Study selection flow diagram

Table 1 Critical appraisal of included studies

S.N	Question*	Studies										
		Duarte-Neto et al. [15]	Craver et al. [16]	Mulale et al. [17]	Bhatnagar et al. [8]	Ninan et al. [18]	Matuck et al. [19]	Konopka et al. [20]	Dolhnikoff et al. [21]	Imam et al. [22]	Matuck et al. (SG) [23]	Monteiro et al. [24]
1	Were there clear criteria for inclusion in the case series?	Yes	NA	NA	No	NA	No	Yes	NA	No	No	Yes
2	Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
3	Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
4	Did the case series have consecutive inclusion of participants?	Yes	NA	NA	No	NA	No	Yes	NA	Yes	No	No
5	Did the case series have complete inclusion of participants?	Yes	NA	NA	No	NA	No	No	NA	No	No	No
6	Was there clear reporting of the demographics of the participants included in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Were the outcomes or follow-up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Was there clear reporting of the presenting sites'/clinics' demographic information?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was statistical analysis appropriate?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes

NA not applicable

*JBI's tool for assessing case series: each questions is answered yes, no, unclear or not application, and any "no" answer negatively impacts the quality

Table 2 Demographical and radiological parameters of included patients

S.N	Studies	Type of autopsy	No of subjects/ sex	Age (Y)	SARS-CoV-2 positive	Test for SARS-CoV-2	Underlying disease	BMI	CT/MRI X-ray	Duration of disease (days)	Hospital stay (days)
1	Duarte-Neto et al. [15]	PA	5 (M-1, F-4)	6.85 (0.58 to 15)	Positive	RT-PCR (ante-mortem) RT-PCR, IHC and EM post-mortem	1-Adrenal carcinoma, 1-Edwards syndrome 3-Previously healthy	21.14 ± 2	B/L pleural effusion (CT)	16.4	9.4
2	Craver et al. [16]	CA	1 (F)	17	Positive	RT-PCR in NP, post-mortem	Previously healthy	–	–	2	–
3	Mulale et al. [17]	CA	1 (M)	0.25	Positive	RT-PCR in NP, ante-mortem	Disseminated TB	4.5 ± 3	B/L pleural effusion (CT)	14	5
4	Bhatnagar et al. [8]	PA	10 (5 M, 5 F)	6 (0.08 to17)	Positive	RT-PCR in respi sample, ante-mortem	No separate data for children	–	–	6	1.5
5	Ninan et al. [18]	PA	1 (F)	8	Positive	RT-PCR in NP, ante-mortem	Previously healthy	-	(MR) brain-sulcal loss suggesting global oedema	4	3
6	Matuck et al. [19]	PA	1 (F)	8	Positive	RT-PCR in NP, ante-mortem	Previously healthy	–	–	10	6
7	Konopka et al. [20]	PA	1 (F)	0.25	Positive	RT-PCR in NP, post-mortem	No separate data for children	–	–	–	–
8	Dolhnikoff et al. [21]	CA	1 (M)	11	Positive	RT-PCR in NP, post-mortem	Previously healthy	–	Multiple ground-glass pulmonary opacities, with thickening of interlobular septa (CT)	7	1
9	Imam et al. [22]	PA	3 (M)	0.42 (0.41–0.82)	Positive	Probable COVID-19, test not reported	Post-liver transplant		Diffuse infiltrate B/L lung (X-ray)	–	–
10	Matuck et al. (SG) [23]	PA	1 (F)	8	Positive	RT-PCR in NP, ante-mortem	No separate data for children	–	–	21.12	–
11	Monteiro et al. [24]	PA	1 (F)	0.58	Positive	RT-PCR in NP, ante-mortem	No separate data for children	–	–	–	–
Pooling result		4 CA 11 PA	26 (15 F, 11 M)	5.9 ± 5.7	All positive	RT-PCR	TB, malignancy, healthy	3.8 ± 2.5		– 12.6 ± 10.7	7.8 ± 10.6

CA complete autopsy, *PA* partially autopsy, *TB* tuberculosis, *M* male, *F* female, *BMI* body mass index, *NP* nasopharyngeal sample, *IHC* immunohistochemistry, *EM* electron microscopy

Table 3 Autopsy finding (gross and histopathological)

Organs	Duarte-Neto et al. [15]	Craver et al. [16] Gross and microscopy		Mulale et al. [17]	Bhatnagar et al. [8]	Ninan et al. [18]	Matuck et al. [19]
Lung	Congestion and oedema = 80% Foci of haemorrhagic exudative = 80% DAD = 100% Thrombi in arterial vessels, septal capillaries = 80% Angiomatoid pattern = 80% Many megakaryocytes = 80%	Heavy and congested right and left 1030, 900 g	Congestion, oedema = 100% Focal acute haemorrhage = 100%	Disseminated TB, with numerous necrotising granulomatous inflammation = 100%, diffuse platelet–fibrin microthrombi = 100%	DAD = 100% Fibrin thrombi = 30% Pulmonary haemorrhage = 20% Interstitial pneumonitis = 20%	–	–
Heart	Interstitial oedema = 100% Pericarditis, myocarditis, endocarditis = 40% Myocardial necrosis and foci of band necrosis = 80%	500 g, soft and rubbery, mottled pale 80 ml of pericardial fluid	Diffuse inflammatory infiltrates of lymphocytes, macrophages prominent eosinophils = 100% Multiple foci of myocyte necrosis = 100%	Diffuse platelet–fibrin microthrombi = 100% interstitial oedema = 100% mononuclear inflammatory = 100%		–	–
Liver	Congestion = 100% Centrilobular necrosis and ischaemic necrosis = 80% Arterial thrombi = 40% Micro/macrovesicular steatosis = 20%	Centrilobular congestion = 100% Minimal steatosis = 100%		Macrovesicular steatosis = 100%	–	–	–
Kidneys	ATN = 100% Congestion = 100% Nephrocalcinosis and mesangial cell hyperplasia = 20% Fibrin thrombi in glomerular capillaries = 40% Tubular hyaline and granular casts = 40%	–		Disseminated TB, with numerous necrotising granulomatous = 100%		–	–
Spleen	Splenitis = 100% Haemorrhages = 100% Lymphoid hypoplasia with reactive cells = 80% Haemophagocytosis = 40% Fibrin thrombi = 20%	–		Disseminated TB, with numerous necrotising granulomatous = 100%	–	–	-

Table 3 (continued)

Organs	Duarte-Neto et al. [15]	Craver et al. [16] Gross and microscopy		Mulale et al. [17]	Bhatnagar et al. [8]	Ninan et al. [18]	Matuck et al. [19]
Lung	Congestion and oedema = 80% Foci of haemorrhagic exudative = 80% DAD = 100% Thrombi in arterial vessels, septal capillaries = 80% Angiomatoid pattern = 80% Many megakaryocytes = 80%	Heavy and congested right and left 1030, 900 g	Congestion, oedema = 100% Focal acute haemorrhage = 100%	Disseminated TB, with numerous necrotising granulomatous inflammation = 100%, diffuse platelet–fibrin microthrombi = 100%	DAD = 100% Fibrin thrombi = 30% Pulmonary haemorrhage = 20% Interstitial pneumonitis = 20%	–	–
Brain	Reactive microglia = 100% Neuronal ischaemia = 100% Congestion = 100% Oedema = 40% Capillary fibrin thrombi = 40%	–		–	–	Global brain oedema = 100% Transtentorial herniation = 100% Ischaemic neuronal necrosis = 100% Chronic inflammatory cells in leptomeninges intraparenchymal blood vessels = 100%	-
Bone marrow	Hypercellular = 20% Haemophagocytosis = 20% Emperipolesis by megakaryocytes = 20%, normocellular = 20%	–		–		–	–
Colon	Oedema = 20% Colitis with dense inflammation cell infiltration = 40% Arteriolar microthrombi = 20% Peritonitis appendicitis with peritonitis = 20%	–		–		–	–
Skin	Superficial perivascular mononuclear infiltrate = 60%	–		–		–	–
Muscle	Myolysis = 80% Necrotic fibres = 80%	–		–		–	–

Table 3 (continued)

Organs	Duarte-Neto et al. [15]	Craver et al. [16] Gross and microscopy		Mulale et al. [17]	Bhatnagar et al. [8]	Ninan et al. [18]	Matuck et al. [19]
Lung	Congestion and oedema = 80% Foci of haemorrhagic exudative = 80% DAD = 100% Thrombi in arterial vessels, septal capillaries = 80% Angiomatoid pattern = 80% Many megakaryocytes = 80%	Heavy and congested right and left 1030, 900 g	Congestion, oedema = 100% Focal acute haemorrhage = 100%	Disseminated TB, with numerous necrotising granulomatous inflammation = 100%, diffuse platelet–fibrin microthrombi = 100%	DAD = 100% Fibrin thrombi = 30% Pulmonary haemorrhage = 20% Interstitial pneumonitis = 20%	–	–
Other	Adrenal carcinoma with intense necrosis = 20%, parotiditis = 40%, lymphoid hypoplasia and haemophagocytosis = 20%	–		–		Chronic lymphocytic thyroiditis = 100% Parotid cysts = 100%	SARS-CoV-2 genetic material was present in mostly periodontal tissue samples, altered keratinocytes, vacuolisation of cytoplasm and nucleus

Table 4 Autopsy finding (gross and histopathological)

Organs	Dolhnikoff et al. [21]	Imam et al. [22]	Matuck et al. [23]	Konopka et al. [20]
Lung	Microthrombi in pulmonary arterioles = 100% Pneumonia = 100% Patchy exudative changes in alveolar space = 100% Pneumocyte hyperplasia = 100%	Interstitial oedema = 50% Focal inflammatory infiltration = 100% Many microvascular thrombi = 100% DAD = 50% Intra-alveolar fibrin exudates = 50%	DAD = 100% Fibrin thrombi = 100%	–
Heart	Myocarditis, pericarditis, endocarditis = 100% Inflammation was mainly interstitial and perivascular = 100% Cardiomyocyte necrosis = 100% Myocardial stunning or oedema = 100%	–	–	–
Liver	Hepatic centrilobular necrosis = 100%	Inflammatory cell infiltrates = 100%	–	
Kidneys	Microthrombi renal glomerular capillaries = 100% Acute tubular necrosis = 100%		–	
Spleen	–	–	–	–
Brain			–	
BMR				–
Colon				–
Skin				–
Muscle				–
Other			Cytoplasmic and nuclear vacuolisation as well as nuclear pleomorphism in acinar cells and ductal epithelial cells of SG = 100%	–

DAD diffuse alveolar damage, *B/L* bilateral, *SG* salivary gland

Autopsy procedure

In the COVID-19 pandemic, there are some recommendations for autopsy performance. There should be at least a biosafety level-2 autopsy facility [11]. In this pandemic, a complete autopsy (ideal) may not be possible because SARS-CoV-2 is highly contagious to autopsy staff; there are alternative autopsy methods like in situ sampling or minimally invasive techniques of puncture/core biopsy autopsies [13, 14]. This systematic review found that three studies partially performed the complete autopsy, and eight partially performed autopsies (Table 2). Table 2 shows the clinical parameters of included patients. The mean age of patients was 5.9 ± 5.7 years who got infected by COVID-19. The review had 15 (57.7%) girls and 11 (42.3%) boys, with a ratio of 1.36. The mean total duration of the disease (10 studies) was 12.6 ± 10.7 days and the mean duration of hospital stay (8 studies) was 7.8 ± 10.6 days. Children's mean body mass index (three studies) was 3.8 ± 2.5. Out of 11 studies, four reported CT findings were bilateral pleural effusion and multiple ground-glass pulmonary opacities with thickening interlobular septa. One study reported X-ray findings of diffuse infiltration. One study reported MRI findings as brain-sulcal loss, suggesting global oedema (Table 2).

The histopathological findings of individual studies are described in Tables 3 and 4. The proportion of studies reporting autopsy findings in different organs was as follows: lung 81.8%, heart 54.5%, liver 54.5%, brain 36.4%, kidney 36.4%, spleen 27.3%, periodontal 18.2%, and bone marrow, colon, skin, muscles, salivary gland, adrenal gland, and vessels, 9.1% of each.

The gross findings were reported in three studies, and histology was reported in 10, as shown in Tables 3 and 4. The gross findings were pericardial and pleural effusion, hepatomegaly, splenomegaly, cardiomegaly, heavy soft lung, enlarged kidney, and enlarged brain.

The pooled results of the autopsy findings of all 11 studies are summarised in Table 5.

Table 6 depicts immunohistochemistry and molecular markers in included studies. All studies reported positive SARS-CoV-2 by RT-PCR, and it was reported by IHC (immunohistochemistry) also in 85.7%. The CD68 was positive in 33.3% of cases by IHC. The electron microscopic findings were reported in 33.3%, showing SARS-CoV-2 as a spherical viral particle with spikes in different organs'

Table 5 Pooling the results autopsy findings of various studies

Studies	Organs						
	Lung	Heart	Liver	Kidney	Spleen	Brain	Salivary gland
Duarte-Neto et al. [15]	DAD = 100% Congestion and oedema = 80% Haemorrhagic exudative = 80% Thrombi in arterial vessels = 80% Angiomatoid pattern = 80% Alveolar megakaryocytes = 80%	Interstitial oedema = 100% Myocarditis, pericarditis, endocarditis = 40% Myocardial and foci of band necrosis = 80%	Congestion = 100% Centrilobular necrosis and ischaemic necrosis = 80% Arterial thrombi = 40% Micro/macrovesicular steatosis = 20%	ATN = 100% Congestion = 100% Nephrocalcinosis and mesangial cell hyperplasia = 20% Fibrin thrombi in glomerular capillaries = 40% Tubular hyaline and granular casts = 40%	Splenitis = 100% Haemorrhages = 100% Lymphoid hypoplasia = 80% Haemophagocytosis = 40% Fibrin thrombi = 20%	Reactive microglia = 100% Neuronal ischaemia = 100% Congestion = 100% Oedema = 40% Fibrin thrombi = 40%	Parotiditis = 40%
Bhatnagar et al. [8]	DAD = 100% Fibrin thrombi = 30% Pulmonary haemorrhage = 20% Interstitial pneumonitis = 20%	–	–				
Imam et al. [22]	DAD = 50% Pneumonitis = 100% Microvascular thrombi = 100% Intra-alveolar fibrin exudates = 50% Interstitial oedema = 50%	–	Inflammatory cell infiltrates = 100%				
Dolhnikoff et al. [21]	Microthrombi in arterioles = 100% Pneumonia = 100% Patchy exudative changes in alveolar space = 100% Pneumocyte hyperplasia = 100%	Myocarditis, pericarditis, endocarditis = 100% Stunning or oedema = 100% Cardiomyocyte necrosis = 100% Interstitial and perivascular inflammation = 100%	Centrilobular necrosis = 100%	Microthrombi renal glomerular capillaries = 100% ATN = 100%			
Matuck et al. [23]	–	–	–	–	–	–	Cytoplasmic and nuclear vacuolisation, nuclear pleomorphism in acinar cells and ductal epithelial cells of SG = 100%

Table 5 (continued)

Studies	Organs						
	Lung	Heart	Liver	Kidney	Spleen	Brain	Salivary gland
Mulale et al. [17]	Tubercular necrotising granulomatous inflammation = 100% Platelet–fibrin microthrombi = 100%	Diffuse fibrin microthrombi = 100% Interstitial oedema = 100% Mononuclear inflammatory infiltrate = 100%	Macrovesicular steatosis = 100%	Tubercular necrotising granulomas = 100%	Disseminated TB, with necrotising granulomas = 100%		
Konopka et al. [20]	DAD = 100% Fibrin thrombi = 100%	–					
Craver et al. [16]	Congestion and oedema = 100% Haemorrhage = 100%	Myocarditis = 100% Myocytes—necrosis = 100%	Centrilobular congestion = 100% Minimal steatosis = 100%				
Ninan et al. [18]						Brain oedema = 100% Transtentorial herniation = 100% Ischaemic neuronal necrosis = 100% Chronic inflammatory cells in leptomeninges and intraparenchymal blood vessels = 100%	Parotid cysts = 100%

Table 5 (continued)

Studies	Organs						
	Lung	Heart	Liver	Kidney	Spleen	Brain	Salivary gland
Pooling the results of autopsy findings	DAD = 78.3% Congestion and oedema = 26% Fibrin thrombi = 43.5% Haemorrhage = 30.4% Intra-alveolar fibrin exudates = 8.7% Pneumonia = 26% Angiomatoid pattern = 17.4% Alveolar megakaryocytes = 17.4% Tubercular necrotising granulomas = 4.3%	Interstitial oedema = 80% Myocarditis, pericarditis, endocarditis = 30% Myocardial and foci of band necrosis = 60% Fibrin microthrombi = 60% Aneurysm formation = 10% Interstitial and perivascular inflammation = 40% Myocardial infarction = 10%	Centrilobular congestion = 60% Centrilobular necrosis and ischaemic necrosis = 10% Arterial/venous thrombi = 20% Micro/macrovesicular steatosis = 30% Centrilobular vesicular degeneration = 10% Inflammatory cell infiltrates = 10%	ATN = 75% Congestion = 62.5% Fibrin thrombi in glomerular capillaries = 37.5% Nephrocalcinosis and mesangial cell hyperplasia = 25% Tubular hyaline or granular casts = 25% Tubercular necrotising granulomas = 12.5% Interstitial nephritis = 12.5%	Splenitis = 71.4% Haemorrhage = 71.4% Lymphoid hypoplasia with reactive cells = 57.1% Haemophagocytosis = 28.6% Fibrin thrombi = 14.2% Tubercular necrotising granuloma = 14.2% Hyperplasia of white pulp = 14.2%	Oedema = 87.5% Reactive microglia = 62.5% Neuronal ischaemic necrosis = 62.5% Congestion = 75% Fibrin thrombi = 25% Transtentorial herniation = 12.5% Meningoencephalitis = 37.5% Hydrocephalus of lateral and third ventricles = 12.5% Reduction in deep cerebral white matter = 12.5% Reduced thickness of brain parenchyma = 12.5%	Parotiditis = 50% Cytoplasmic and nuclear vacuolisation, nuclear pleomorphism in acinar cells and ductal epithelial cells = 25% Parotid cysts = 25%

DAD diffuse alveolar damage

Table 6 Immuno-histological, molecular marker related to COVID-19 and ultra-structure by electron microscopy

Molecular marker	Dolhnikoff et al. [21]	Matuck et al. in SG [23]	Duarte-Neto et al. [15]	Bhatnagar et al. [8]	Ninan et al. [18]	Matuck et al. [19]	**Pooled result**
CK-AE1/AE3	–						4.7%
CD68	+		+				**33.3%**
IgA	–						4.7%
WT1	–						4.7%
CD3	–						4.7%
CD45	+						4.7%
ACE2		+					4.7%
TMPRSS		+					4.7%
SARS-CoV-2		+	+	+	+	+	**85.7%**
HCoV-OC43 RNA							4.7%
EM		70–100-nm spherical viral particle in ducal epi, acinar cell and duct lumen	Viral particles in heart, lungs, intestine, brain				**33.3%** spherical viral particle with spikes in different organs' epithelium

Bold values indicate pooled results from more than one study

epithelium. The pooled results of laboratory findings of various studies are described in Table 7. Most studies showed that the D-dimers (8954.5 DDU) and fibrinogen (414.5 mg/dl) were significantly high. In most studies, laboratory tests were done before death.

Discussion

The SARS-CoV-2 caused the COVID-19 pandemic that started in December 2019. COVID-19 has variable clinical presentations ranging from a mild symptomatic respiratory illness to fulminant ARDS (acute respiratory syndrome), multiorgan failure, and even death. The index study is one of the largest systematic reviews and meta-analysis of post-mortem findings in paediatric patients with SARS-CoV-2. In this review, we found that the lungs were mostly affected by COVID-19, which corroborated with several other studies [8, 15–17]. In lung pathology, DAD (diffuse alveolar damage) was found in 78.3% of paediatric autopsy cases, similar to adult lung autopsy findings [25]. Histopathology findings of DAD due to COVID-19 were similar to other causes of DAD [26]. CDC (centre for disease control) provided COVID-19 testing criteria (checklist positive) for detection of DAD [27].

The fibrin thrombi were a consistent finding of COVID-19, and it was reported in almost all organs of paediatric autopsies in several studies [8, 15, 16, 18]. Other findings like congestion, oedema, and haemorrhage in different organs were reported by various studies [15, 16, 21]. After

Table 7 Laboratory parameters of autopsy patients

Laboratory findings	Ninan et al. [18]	Mulale et al. [17]	Duarte-Neto et al. [15]	Dolhnikoff et al. [21]	Pooled result
TLC (10^9/l)	6.9	–	12	35	7.7
HB (g/dl)	10.6	11.5	10	11	5.4
Plat (10^9/l)	183	93	160	160	74.6
BUN (mg/dl)	12	–	60.5	75	23.4
Creatinine (mg/dl)	0.39	–	0.93	2.19	0.48
ESR (mm/h)	19	–	–	–	19
CRP (mg/l)	19.1	–	129.6	309	59.0
D-dimer (DDU)	3493	–	5036	54,153	8954.5
Fibrinogen (mg/dl)	316	–	–	513	414.5
PT (sec)	14.4	–	–	–	14.4
APTT (sec)	36.1	–	34	–	11.7
LDH (U/l)	742	–	1400	35	311
Troponin, ng/dl	–	–	–	0.290	0.290

Table 8 Difference of autopsy findings of paediatric and adult patients of COVID-19

S.N	Autopsy findings of organ	Paediatric	Adult	Studies
1	Lung	DAD in 78.3%	DAD 80%	Ref. 21, 25
2	Heart	Foci of band necrosis in myocardium 60%, myocarditis, pericarditis, endocarditis 30%	Myocardial necrosis 8%, lymphocytic myocarditis 3%	Ref. 15, 21, 25
3	Kidney	Acute tubular necrosis 75%, fibrin thrombi in glomerular capillaries 37.5%	Acute tubular damage 51.3%, fibrin thrombi 6.4%	Ref. 8, 15, 21, 25
4	Brain	Oedema 87%, congestion 75%, reactive microglial and ischaemic necrosis 62.5%, fibrin thrombi 25%, meningoencephalitis 37.5%	Focal punctate haemorrhages in subarachnoid and brain stem, focal hypoxic changes, no inflammation or necrosis, one study reported thrombi in small vessels, microhaemorrhages, acute infarction	Ref. 15, 18, 21, 25, 28
5	Liver	Centrilobular congestion 60% Centrilobular necrosis and ischaemic necrosis 10%, arterial/venous thrombi 20%, micro/macrovesicular steatosis 30%	Hepatocyte necrosis 18.6%, portal inflammation 15.9%, thrombi 18.3%	Ref. 22, 21, 25, 28
6	Spleen	Splenitis 71.4%, haemorrhage 71.4%, lymphoid hypoplasia with reactive cells 57.1%, haemophagocytosis 28.6%, fibrin thrombi 14.2%, arterial/venous thrombi 20%	Splenitis 19.2%, white pulp depletion 22.2%, necrosis 6.2%, thrombi 0%	Ref. 15, 23, 29

DAD diffuse alveolar damage

pooling the results, foci of band necrosis in the myocardium were found in 60% of cases, which concord with another study [15]. In adult patients, myocardial necrosis was reported at 8%, significantly less than a paediatric autopsy [21]. Acute tubular necrosis (ATN) of the kidney was found in 75% of cases which was correlated with findings of other studies [8, 15]. In the brain, the most common autopsy findings were oedema (87%) and reactive microglial (62%), which were similar to with Duarte-Neto et al., Ninan et al., and Kasereka et al. studies [15, 18]. In most of the studies of the adult autopsy, the brain showed foci of punctate haemorrhage, minimal inflammation and no myelin loss, no necrosis and microglial reaction [21, 28].

In autopsy series of 5 paediatric cases by Duarte-Neto et al., two children had the severe pre-existing disease (adrenal carcinoma and Edwards syndrome), and three patients had MIS-C (multisystemic inflammatory syndrome) with myocarditis, colitis, and meningoencephalitis [15]. Similarly, Dolhnikoff et al. reported the cause of death as COVID-19-related MIS-C in their case [21]. There was underlying disseminated TB in one case [15], and one was a post-liver transplant patient [19]. The remaining cases were premorbid healthy, and death can be attributed to COVID-19 (Table 2). It is difficult to attribute the death to COVID-19 if a patient has an underlying disease.

The typical laboratory findings of COVID-19 in various studies were anaemia and thrombocytopenia [17, 18]. Most of the studies reported an elevated level of D-dimer (DDU) and fibrinogen (mg/dl) levels in COVID-19 patients in children [18, 21]. The similarities and differences between paediatric and adult autopsy findings are described in Table 8.

There are some limitations of this review. Firstly, the number of patients is small as most studies are case reports. Secondly, it is challenging to attribute autopsy findings to COVID-19 in patients with underlying diseases. Finally, many studies only did a partial autopsy, not a complete one.

Conclusion

The lung was the most commonly affected organ due to COVID-19. We suggest that autopsies are the best way to understand the pathophysiology of COVID-19 diseases and their correlation with clinical findings. To the best of our knowledge, this is one of the most extensive systematic reviews and meta-analysis of paediatric autopsy findings.

Key points

- The key points to assess the methodological quality of cross-sectional studies include inclusion criteria, methods to identify the condition, and clearly defined and reported outcome measures.

Declarations

Conflict of interest The authors declare no competing interests.

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