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

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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/macrovесicular 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 SARS-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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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.
### Table 1 Critical appraisal of included studies

| S.N | Question* | 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 | NA | 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 question is answered yes, no, unclear or not application, and any “no” answer negatively impacts the quality.
| 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) | 1-Adrenal carcinoma, 1-Edwards syndrome, 3-Previously healthy                      | 21.14 | 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 to 17)   | 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
| Organs | Duarte-Neto et al. [15] | Caver 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% | Heavy and congested right and left 1030, 900 g | Congestion, oedema = 100% | Disseminated TB, with numerous necrotising granulomatous inflammation = 100%, diffuse platelet–fibrin microthrombi = 100% | DAD = 100% | Pulmonary haemorrhage = 20% | Interstitial pneumonitis = 20% |
| Heart  | Interstitial oedema = 100% | 500 g, soft and rubbery, mottled pale 80 ml of pericardial fluid | Diffuse inflammatory infiltrates of lymphocytes, macrophages, prominent eosinophils = 100% | Diffuse platelet–fibrin microthrombi = 100% | – | – | – |
| Liver  | Congestion = 100% | Centrilobular congestion = 100% | Minimal steatosis = 100% | Macrovesicular steatosis = 100% | – | – | – |
| Kidneys| ATN = 100% | – | Disseminated TB, with numerous necrotising granulomatous = 100% | – | – | – | – |
| Spleen | Splenitis = 100% | – | Disseminated TB, with numerous necrotising granulomatous = 100% | – | – | – | – |
Table 3 (continued)

| Organs  | 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] |
|---------|------------------------|-------------------|-------------------|---------------------|-----------------|------------------|
| Lung    | Congestion and oedema = 80% | Foci of haemorrhagic exudative = 80% | DAD = 100% | Fibrin thrombi = 30% | Pulmonary haemorrhage = 20% | Interstitial pneumonitis = 20% |
|         | 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% | – |
|         | Thrombi in arterial vessels, septal capillaries = 80% | Angiomatoid pattern = 80% | Many megakaryocytes = 80% | – | – | – |
| Brain   | Reactive microglia = 100% | Neuronal ischaemia = 100% | Congestion = 100% | Oedema = 40% | Capillary fibrin thrombi = 40% | – |
|         | Hypercellular = 20% | Haemophagocytosis = 20% | Emperipolesis by megakaryocytes = 20%, normocellular = 20% | – | – | – |
| Bone marrow | Oedema = 20% | Colitis with dense inflammation cell infiltration = 40% | Arteriolar microthrombi = 20% | Peritonitis appendicitis with peritonitis = 20% | – | – |
| Colon   | Superficial perivascular mononuclear infiltrate = 60% | – | – | – | – | – |
| Skin    | Myolysis = 80% | Necrotic fibres = 80% | – | – | – | – |
| 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% |
| 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 | – | – | – |
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’

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**Table 4** Autopsy finding (gross and histopathological)

| Organs | Dolhinov et al. [21] | Imam et al. [22] | Matuck et al. [23] | Konopka et al. [20] |
|--------|----------------------|------------------|--------------------|---------------------|
| Lung   | Microthrombi in pulmonary arterioles = 100% | Interstitial oedema = 50% | DAD = 100% | – |
|        | Pneumonia = 100% | Focal inflammatory infiltration = 100% | Fibrin thrombi = 100% | – |
|        | Patchy exudative changes in alveolar space = 100% | Many microvascular thrombi = 100% | – | – |
|        | Pneumocyte hyperplasia = 100% | DAD = 50% | – | – |
| Heart  | Myocarditis, pericarditis, endocarditis = 100% | Inflammatory cell infiltrates = 100% | – | – |
|        | Inflammation was mainly interstitial and perivascular = 100% | – | – | – |
|        | Cardiomyocyte necrosis = 100% | – | – | – |
|        | Myocardial stunning or oedema = 100% | – | – | – |
| Liver  | Hepatic centrilobular necrosis = 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
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%                      | Interstitial oedema = 100%    | Congestion = 100%                    | Centrilobular necrosis and ischaemic necrosis = 80% | ATN = 100%                                | Splenitis = 100%                            | Reactive microglia = 100%                  | Parotiditis = 40%                        |
|                  | Congestion and oedema = 80%     | Myocarditis, endocarditis = 40% | Arterial thrombi = 40%               | Micro/macroversicular steatosis = 20%      | Congestion = 100%                           | Neuronal ischaemia = 100%                   |                                          |                                          |
|                  | Haemorrhagic exudative = 80%    | Myocardial and foci of band necrosis = 80% | Pneumonitis = 100%                  | Nephrocalcinosis                           | Haemorrhages = 100%                        | Congestion = 100%                            |                                          |                                          |
|                  | Thrombi in arterial vessels = 80% |                               | Patchy exudative changes in alveolar space = 100% | Hyperplasia = 20%                          | Lymphoid hyperplasia = 80%                 |                                          |                                          |                                          |
|                  | Angiomatoid pattern = 80%       |                               | Pneumocyte hyperplasia = 100%        | Cardiomyocyte necrosis = 100%              | Haemophagocytosis = 40%                    |                                          |                                          |                                          |
|                  | Alveolar megakaryocytes = 80%   |                               |                                      | Interstitial and perivascular inflammation = 100% | Tubular hyaline and granular casts = 40%    |                                          |                                          |                                          |
| Bhatnagar et al. [8] | DAD = 100%                      | –                             | –                                    | –                                          | –                                           |                                          |                                          |                                          |
|                  | Fibrin thrombi = 30%            |                               | –                                    | Inflammatory cell infiltrates = 100%       | –                                           |                                          |                                          |                                          |
|                  | Pulmonary haemorrhage = 20%     |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
|                  | Interstitial pneumonia = 20%    |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
| Imam et al. [22]  | DAD = 50%                       | –                             | –                                    | Inflammatory cell infiltrates = 100%       | –                                           |                                          |                                          |                                          |
|                  | Pneumonitis = 100%              |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
|                  | Microvascular thrombi = 100%    |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
|                  | Intra-alveolar fibrin exudates = 50% |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
|                  | Interstitial oedema = 50%       |                               | –                                    |                                            | –                                           |                                          |                                          |                                          |
| Dolhnikoff et al. [21] | Microthrombi in arterioles = 100% | Myocarditis, pericarditis, endocarditis = 100% | Centrilobular necrosis = 100%           | Microthrombi renal glomerular capillaries = 100% | ATN = 100%                                |                                          |                                          |                                          |
|                  | Pneumonia = 100%                |                               |                                      |                                            |                                            |                                          |                                          |                                          |
|                  | Patchy exudative changes in alveolar space = 100% |                                      |                                      |                                            |                                            |                                          |                                          |                                          |
|                  | Pneumocyte hyperplasia = 100%   |                               |                                      |                                            |                                            |                                          |                                          |                                          |
| Matuck et al. [23] | –                              | –                             | –                                    | –                                          | –                                           | –                                          | –                                         | Cytoplasmic and nuclear vacuolisation, nuclear pleomorphism in acinar cells and ductal epithelial cells of SG = 100% |
| Studies               | Organs                                      |
|----------------------|---------------------------------------------|
|                      | Lung                                        |
|                      | Heart                                       |
|                      | Liver                                       |
|                      | Kidney                                      |
|                      | Spleen                                      |
|                      | Brain                                       |
|                      | Salivary gland                              |
| Mulale et al. [17]   | Tubercular necrotising granulomatous inflam- |
|                      | nation = 100%                               |
|                      | Diffuse fibrin microthrombi = 100%          |
|                      | Interstitial oedema = 100%                 |
|                      | Mononuclear inflammatory infiltrate = 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%                        |
| Studies                                      | Lung                                      | Heart                                      | Liver                                      | Kidney                                      | Spleen                                      | Brain                                      | Salivary gland                                      |
|---------------------------------------------|-------------------------------------------|--------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|------------------------------------------------|
| Pooling the results of autopsy findings     | DAD = 78.3%                               | Interstitial oedema = 80%                  | Centrilobular congestion = 60%           | ATN = 75%                                  | Splenitis = 71.4%                          | Oedema = 87.5%                             | Parotiditis = 50%                                 |
| Congestion and oedema = 26%                 |                                           | Myocarditis, pericarditis, endocarditis = 30% | Centrilobular necrosis and ischaemic necrosis = 10% | Congestion = 62.5%                        | Lymphoid hyperplasia with reactive cells = 57.1% | Neuronal ischaemic necrosis = 62.5%          | Cytoplasmic and nuclear vacuolisation, nuclear pleomorphism in acinar cells and ductal epithelial cells = 25% |
| Fibrin thrombi = 43.5%                      |                                           | Myocardial and foci of band necrosis = 60% | Arterial/venous thrombi = 20%            | Fibrin thrombi in glomerular capillaries = 37.5% | Haemorrhage = 71.4%                        | Congestion = 75%                             |                                              |
| Haemorrhage = 30.4%                        |                                           | Fibrin microthrombi = 60%                  | Micro/macrosvesicular steatosis = 30%    | Nephrocalcinosis and mesangial cell hyperplasia = 25% | Fibrin thrombi = 25%                        | Fibrin thrombi = 14.2%                       |                                              |
| Intra-alveolar fibrin exudates = 8.7%       |                                           | Aneurysm formation = 10%                  | Centrilobular vesicular degeneration = 10% | Tubular hyaline or granular casts = 25%     | Tubular hyaline or granular casts = 25%     | Tubular necrotising granulomas = 14.2%      |                                              |
| Pneumonia = 26%                            |                                           | Interstitial and perivascular inflammation = 40% | Inflammatory cell infiltrates = 10%      | Tubercular necrotising granulomas = 12.5%  | Tubercular necrotising granuloma = 14.2%   | Hyperplasia of white pulp = 14.2%            |                                              |
| Angiomatoid pattern = 17.4%                 |                                           | Myocardial infarction = 10%               |                                          | Interstitial nephritis = 12.5%             |                                          |                                          |                                              |
| Alveolar megakaryocytes = 17.4%             |                                           |                                           |                                          |                                          |                                          |                                          |                                              |
| Tubercular necrotising granulomas = 4.3%    |                                           |                                           |                                          |                                          |                                          |                                          |                                              |

*DAD* diffuse alveolar damage
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 (check-list 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 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 ductal epi, acinar cell and duct lumen | Viral particles in heart, lungs, intestine, brain | **33.3%** spherical viral particle with spikes in different organs’ epithelium | 4.7% |

Bold values indicate pooled results from more than one study.

### Table 7  Laboratory parameters of autopsy patients

| Laboratory findings |  |  |  |  |  |  |  |
|---------------------|---|---|---|---|---|---|---|
| TLC (10⁹/l)          | 6.9 | – | 12 | 35 | 7.7 |
| HB (g/dl)            | 10.6 | 11.5 | 10 | 11 | 5.4 |
| Plat (10⁹/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 |
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%), congestion 75%, reactive microglial and ischaemic necrosis 62.5%, fibrin thrombi 25%, meningoencephalitis 37.5%.

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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