

Histologic changes of COVID 19

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Mechanism of COVID infection

- The spike protein of the virus, through its receptor binding domain (RBD) gets attached to a human cell surface receptor protein Angiotensin Converting Enzyme -2 (ACE-2).

Acute lung injury

- Diffuse alveolar damage (DAD)
- Acute fibrinous and organizing pneumonia (AFOP)
- Organizing pneumonia (OP)

DAD (Diffuse alveolar damage)

Endothelial and alveolar lining cell injury which leads to fluid and cellular exudation

- Acute (exudative) phase
 - Subacute (organizing) phase
 - Chronic (fibrotic)
- Traditionally correlates to ARDS

AFOP(Acute fibrinous and organizing pneumonia)

- Formation of “fibrin balls” within the alveolar spaces, with organization resulting from fibroblast migration and secretion of young collagen within fibrin aggregates

OP (organizing pneumonia)

- Intraluminal tufts of plump fibroblasts and young/immature collagen tissue within alveolar ducts and distal airspaces
- Response to corticosteroids
- The previous name: BOOP

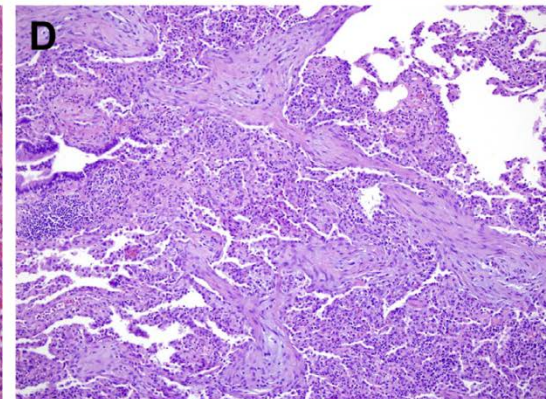
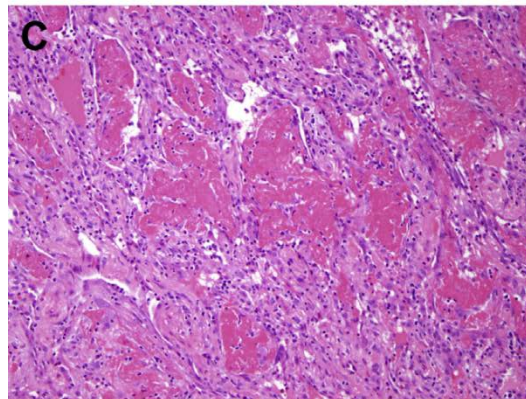
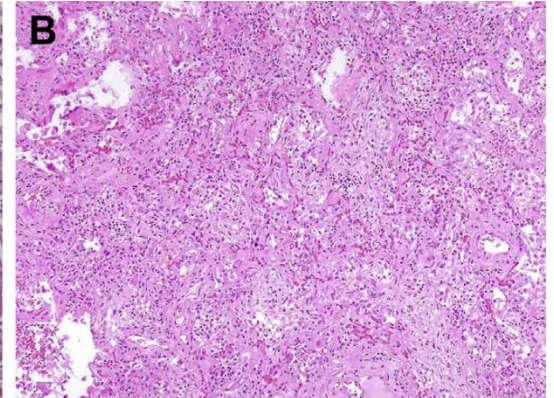
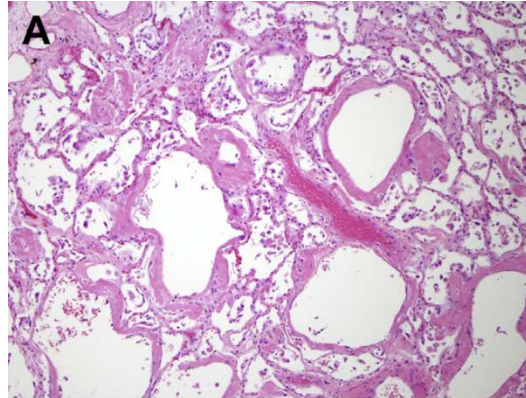
Histopathologic examples of acute lung injury pathology.

A, Acute exudative phase of diffuse alveolar damage (DAD).

B, Subacute organizing (or proliferative) phase of DAD.

C, Acute fibrinous and organizing pneumonia (AFOP).

D, Organizing pneumonia (OP).



Pulmonary changes comparison with H1N1 and SARS

- Acute phase DAD
- Transition to organizing phase of DAD
- Microthrombi

Gross description'of pulmonary changes

- From pulmonary edema to lung consolidation ([J Clin Pathol 2020;73:239](#))
- Increased lung weight
- Hemorrhagic changes ([Mod Pathol 2020;33:2128](#))
- Macroscopic pulmonary emboli ([Mod Pathol 2020;33:2128](#))
- Pleurisy (pleural inflammation) may be seen
- Purulent inflammation, if secondary infection superimposed

Microscopic (histologic) description

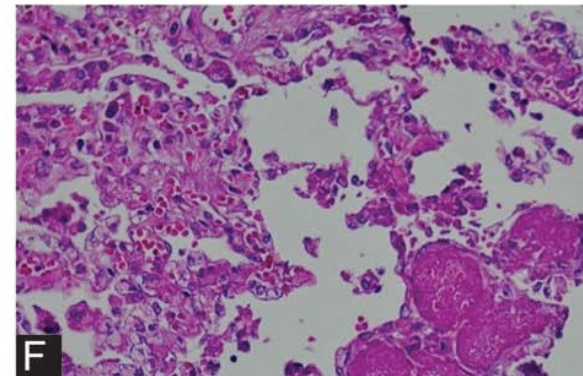
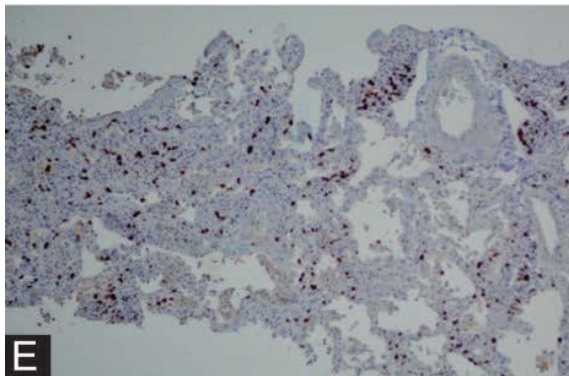
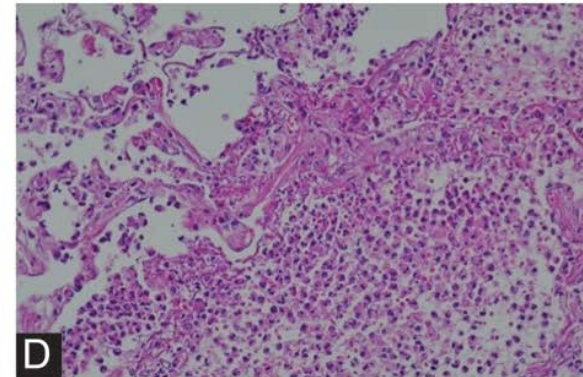
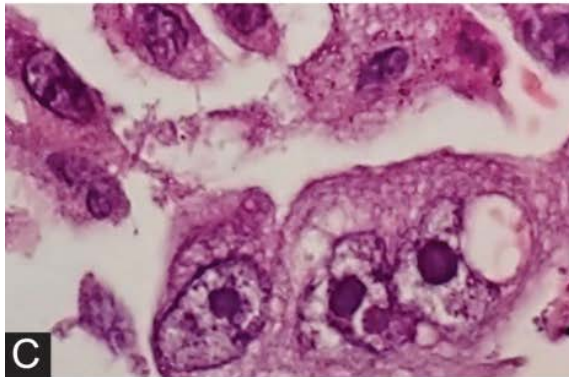
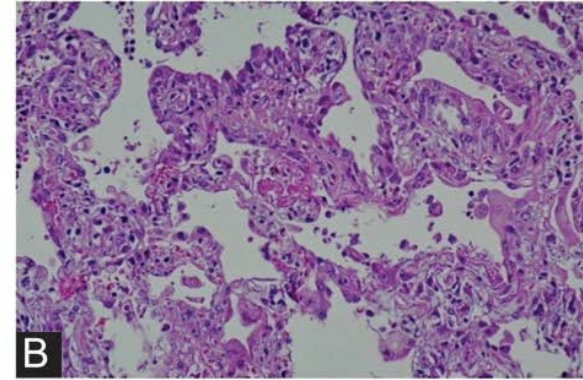
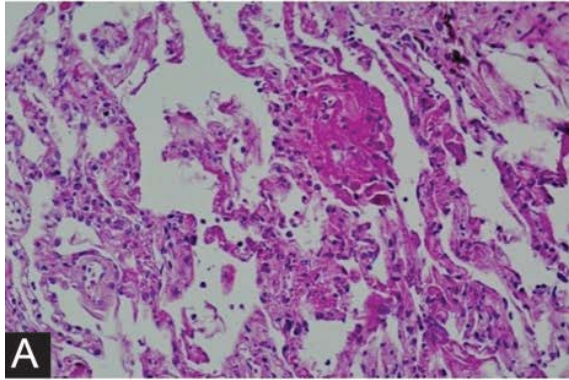
- Pulmonary changes are the most significant, although nonspecific ([Lancet Respir Med 2020;8:420](#), [J Thorac Oncol 2020;15:700](#), [Preprints 2020;2020030311](#))
Findings of [diffuse alveolar damage](#) (DAD) corresponding to the phase of disease:
 - Exudative phase: hyaline membrane formation, desquamation of pneumocytes, cellular or proteinaceous exudates, alveolar hemorrhage, fibrinoid necrosis of small vessels
 - Organizing phase: interstitial and intra-alveolar proliferation of fibroblasts, lymphocytic infiltration, type II pneumocyte hyperplasia, fibrin deposition
 - Fibrotic phase: dense collagenous fibrosis, architectural remodeling
- Lung injury patterns ([Mod Pathol 2020;33:2128](#), [Eur J Clin Invest 2020;50:e13259](#)):
 - Epithelial (85%): DAD with varying degrees of organization, denudation, hyperplasia of pneumocytes
 - Vascular (59%): diffuse intra-alveolar fibrin, microvascular damage, (micro) thrombi, acute fibrinous and organizing pneumonia
 - Fibrotic (22%): fibrotic DAD, interstitial fibrosis
- Viral infection changes:
 - Multinucleated enlarged pneumocytes with large nuclei, amphophilic cytoplasm and prominent nucleoli in alveolar spaces
 - Intranuclear inclusions
- Bacterial pneumonia may be superimposed

Respiratory system: Lung

Tian et al, Barton et al, Xu et al, Luo et al, Yao, Magroet al, Bradley et al

- ►► **Alveoli:** Damaged or atypical enlarged pneumocytes with large nuclei, type II pneumocyte hyperplasia, diffuse alveolar
- damage (DAD), focal sloughing, hyaline membrane formation, intra-alveolar
- haemorrhage, intra-alveolar
- neutrophil
- infiltration, amphophilic granular cytoplasm and prominent nucleoli characteristic of viral cytopathic-like
- changes.
- ►► **Vessels:** Oedematous and congested vessels, plug formation, fibrinoid necrosis of the small vasculature, hyaline thrombi in
- microvessels. Significant deposits of complements—C5b-9 (membrane attack complex), C4d, and
- (MBL)-associated
- serine protease (MASP)-2, in the microvasculature.
- ►► **Cellular components:** Presence of syncytial giant cells, focal infiltration of immune and inflammatory (lymphocytes and
- monocytes) and increased stromal cells.
- ►► **Ultrastructural changes:** Viral particles in bronchial mucosal epithelia and type II alveolar epithelia.

Lung tissue Reveals Alveolar Damage; Pneumocyte Necrosis, Desquamation and Hyperplasia with fibrin Deposition and Interstitial Inflammation H&E Stain, $\times 400$. (A) early interstitial fibrosis and presence of syncytial pneumocytes H&E stain, $\times 400$ (B), CMV-like cytopathic effect of pneumocytes; multinucleated giant cell with intranuclear inclusions and vacuolated cytoplasm H&E stain, $\times 1000$ (C), alveolar neutrophilic infiltration; bacterial superinfection H&E stain, $\times 400$ (D) CD4+ T lymphocytes infiltrating alveolar interstitium, IHC stain for CD4, $\times 30$



Extrapulmonary changes

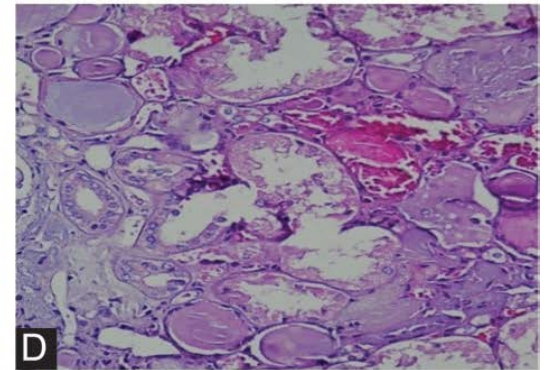
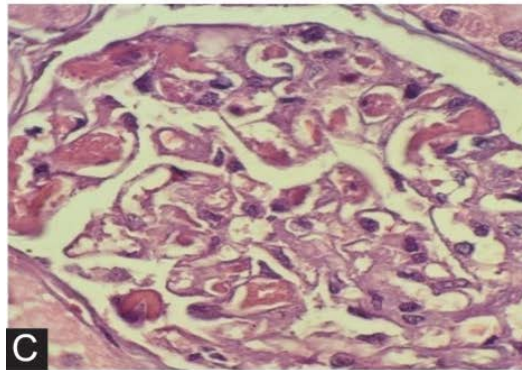
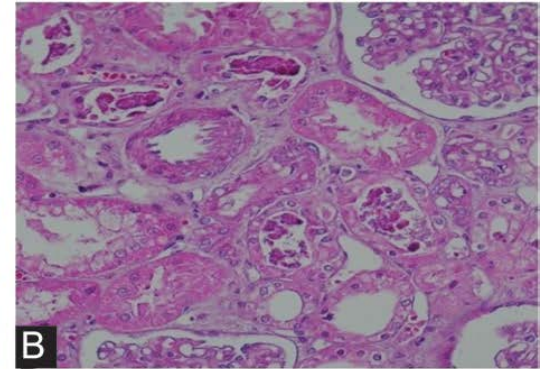
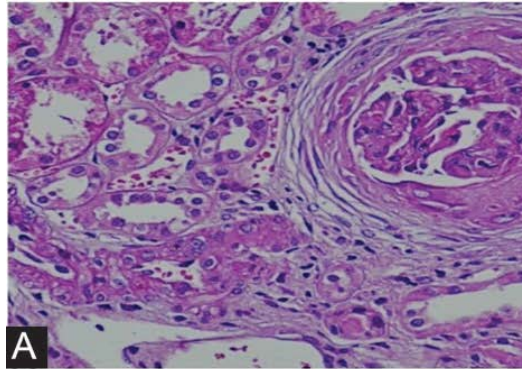
- Extrapulmonary changes ([Mod Pathol 2020;33:2128](#)): Cardiovascular: mild pericardial edema, some serosanguinous pericardial effusion, mild myocardial edema, low grade interstitial infiltration of mononuclear cells, endotheliitis
 - Widespread systemic vasculitis with associated thromboemboli is not as common as initially thought ([Lancet 2020;396:320](#))
- Hepatobiliary: hepatic congestion, mild steatosis, patchy hepatic necrosis, Kupffer cell hyperplasia, increased number of lymphocyte predominant inflammatory cells in the portal tracts and sinusoids, endotheliitis
- Renal: varying degrees of acute tubular injury, lymphocytic tubule interstitial infiltration, fibrin or hyaline thrombi in blood vessel, glomerular capillary dilatation, lymphocytic endotheliitis ([Kidney Int 2020;98:219](#))
- Gastrointestinal: epithelial damage, prominent endotheliitis, ischemic enterocolitis
- Spleen: reduced number of lymphocytes with necrosis, atrophy, congestion, hemorrhage, infarction
- Bone marrow: histiocytic hyperplasia, hemophagocytosis ([Mod Pathol 2020;33:2139](#))
- Other: cutaneous, prostatic manifestations, inflammation and clots in placenta with funisitis

Urinary system: Kidney

*Yao et al, Su et al, Tietavainen et al,
Grimes et al, Bradley et al*

- ►► **Glomerulus:** Ischaemic changes, podocyte vacuolation, focal segmental glomerulosclerosis, accumulation of plasma in Bowman's space.
- ►► **Renal tubules:** Loss of brush border in proximal tubule, non-isometric vacuolar degeneration, and necrosis, oedematous epithelial cells.
- ►► **Vessels:** Erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material with occasional hemosiderin granules and pigmented casts, hyalinosis of arteriole, arteriosclerosis of medium sized arteries, fibrin thrombus, shrinkage of capillary loops in glomeruli.
- ►► **Ultrastructural changes:** Clusters of viral particles with distinctive spikes in the tubular epithelium and podocytes.

Renal Tissue Exhibits Glomerular Crescent Formation, H&E Stain, $\times 400$. (A) acute tubular damage, H&E stain, $\times 400$, (B) frequent glomerular capillary thrombosis, H&E stain, $\times 1000$, and (C) renal thyroidization in addition to glomerular obsolescence, H&E stain, $\times 400$ (D).

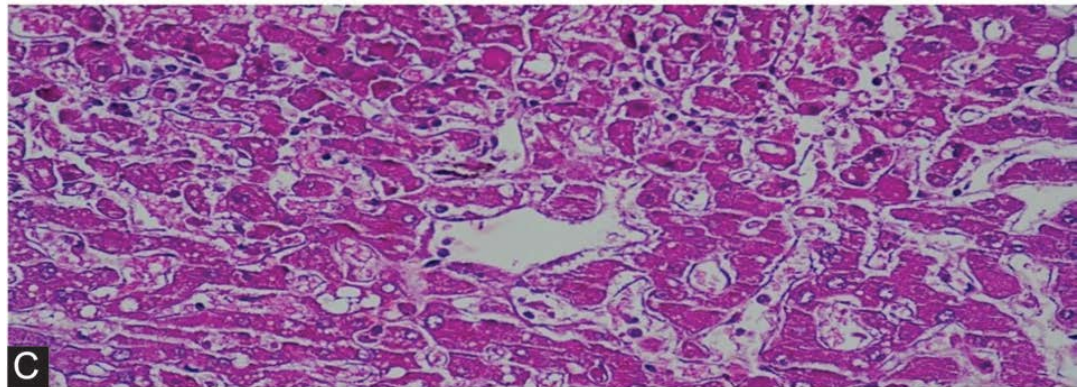
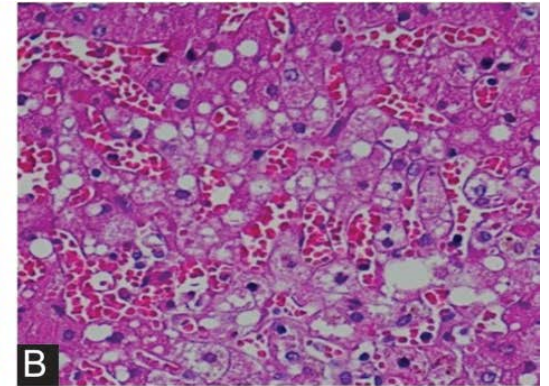
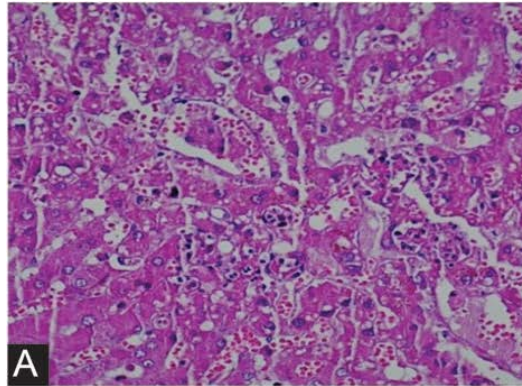


Gastrointestinal system

*Tian et al, Yao et al, Liu et al,
Xiao et al*

- ►► **Liver:** Focal macrovesicular steatosis, nuclear glycogen accumulation in hepatocytes, dense atypical small lymphocytes
- in portal tracts. Regenerative nodules and thick fibrous bands, mild zone 3 sinusoidal dilatation, mild lobular lymphocytic
- infiltration. Patchy hepatic necrosis in the periportal and centrilobular areas. Hepatic cell degeneration and focal necrosis,
- biliary plugs in the small bile duct.
- ►► **Oesophagus:** Occasional lymphocytic infiltration in the oesophageal squamous epithelium.
- ►► **Stomach:** Partial epithelial degeneration, necrosis and shedding of the gastric mucosa. Dilatation and congestion of small
- blood vessels and oedema of lamina propria and submucosa with infiltration of immune cells (as lymphocytes, monocytes
- and plasma cells).
- ►► **Intestine:** Stenosis of the small intestine and segmental dilatation. Numerous infiltrating plasma cells and lymphocytes with
- interstitial oedema in the lamina propria.
- ►► **Pancreas:** Degeneration of the cells of islets.

Liver Tissue Shows Lobular Neutrophilic Microabscess Formation and Sinusoidal Congestion (A), Micro-Vesicular Steatosis (B), Lobular Necrosis And Lymphocytic Infiltration (C). A,B,C: H&E stain, $\times 400$..

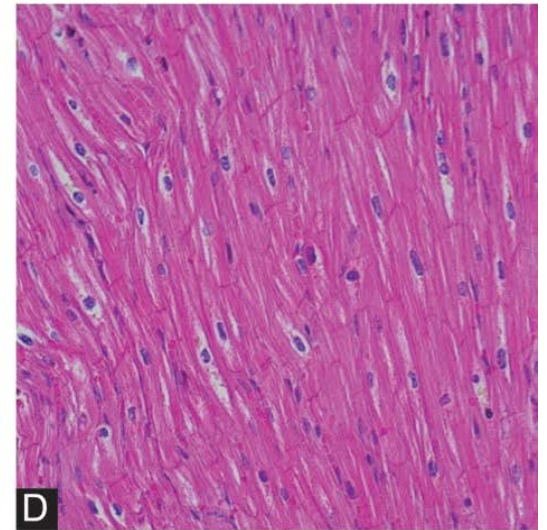
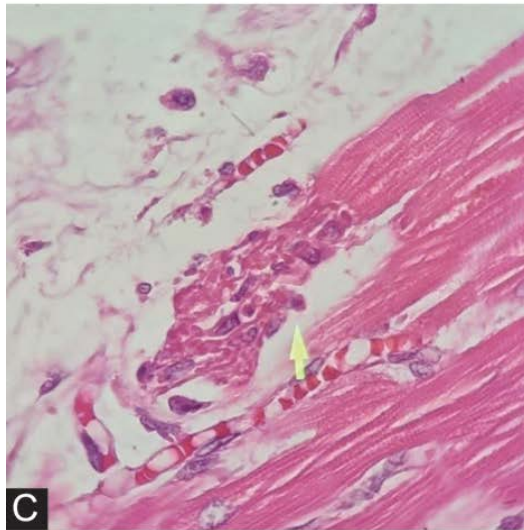
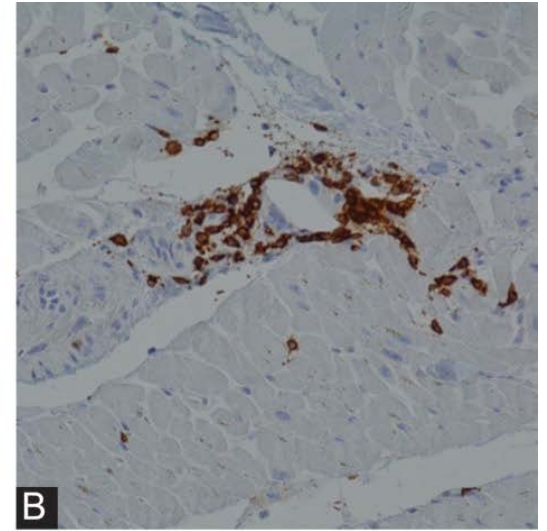
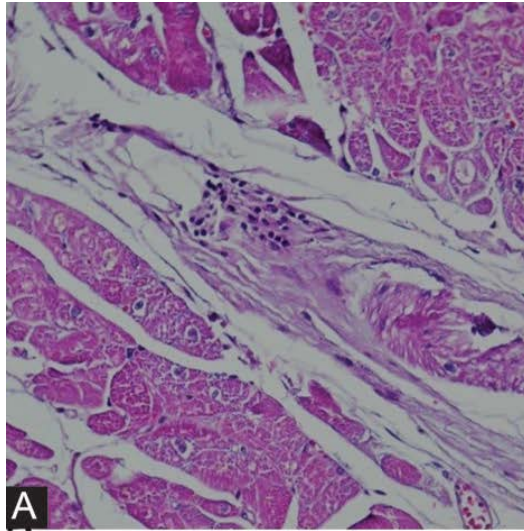


Cardiovascular system

Tian et al, Bradley et al, Wichmann et al, Tavazzi et al, Yao et al, Varga et al, Fox et al, Gianotti et al, Kolivras et al, Varga et al

- ► Foci of lymphocytic inflammation.
- ► Acute myocyte necrosis.
- ► Presence of inflammatory cells and apoptotic bodies.
- ► **Ultrastructural observation:** Viral inclusion bodies in vascular endothelial cells.
- ► **Immunohistochemistry:** Presence of CD61+ megakaryocytes in purpuric papulovesicular.

Myocardial Perivascular Inflammation, H&E Stain, $\times 400$ (A), CD8+ T lymphocytes infiltrating Small Vessels, IHC Stain for CD8, $\times 400$ (B), Scattered Single Cell Necrosis, H&E Stain, $\times 1000$ (C), Myocytes with Box-Car Nuclei, H&E Stain, $\times 400$ (D).



Reproductive system (testis)

Jian Xu et al, Chen et al

- ► Thickened basement membrane with peritubular fibrosis and vascular congestion.
- ► Leucocyte infiltration.
- ► Extensive germ cell destruction.
- ► **TUNEL assay**: Increased apoptotic spermatogonic cells.

Nervous system

*Solomon et al, Mahammedi et al,
Moriguchi et al*

- ►► Acute hypoxic ischaemic injury, hyperaemia, oedema and neuronal degeneration.
- ►► **CT, MRI:** Ischaemia and/or haemorrhage, and enhanced cortical/subcortical grey matter and fibre tracts.
- ►► SARS-CoV-2 RNA was detected in the brain tissue and cerebrospinal fluid in some patients.

Histopathological findings (skin)

*Hamming et al, Gianotti et al,
Kolivras et al*

- ► **Vessels:** Perivascular inflammatory cells, intraluminal thrombi.
- ► **Epidermis:** Parakeratosis, acanthosis, dyskeratotic keratinocytes, necrotic keratinocytes, acantholytic clefts, lymphocyte satellitosis and pseudoherpetic.
- ► **Immunohistochemistry:** ACE-2 positivity in basal layer of cells in hair follicle, sebaceous glands, smooth muscle cells.