

## Hisotopathological Changes of Lung , Renal System and Liver in Covid 19 (Review of Articles)

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### ABSTRACT

Corona-virus disease "COVID-19" is a greatly contagious disease that affect the public healthiness. It affects the respiratory and many other organs. This study reviews the pathological finding obtained from biopsies and autopsies of "Covid- 19" infected patients. Different articles and researchers which had been published till July 2022 had been reviewed. Overall, 60 articles were identified as full articles and included in this study. Diffuse alveolar destruction, vascular damage with thrombosis, inflammatory changes in tissues were the chief pathological findings in this review. These differences in the pathological features among patients indicate various mechanisms of organs injuries caused by the virus which may affect the prognosis and the treatment protocol.

**Keywords:** corona virus, biopsy, pathological finding

### التغيرات النسيجية في الرئة والكلى والكبد في كوفيد - ١٩ (مقالة استعراضية)

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#### الخلاصة

مرض كورونا هو مرض شديد العدوى يؤثر على الصحة العامة. إنه يؤثر على الجهاز التنفسي والعديد الاعضاء الأخرى. تستعرض هذه الدراسة الاكتشافات المرضية التي تم الحصول عليها من الخزعات للمريض المصاب. تمت مراجعة المقالات والأبحاث المختلفة التي تم نشرها حتى يوليو ٢٠٢٢. بشكل عام ، تم تحديد ٦٠ مقالة كمقالات كاملة وتضمينها في هذه الدراسة. كان الضرر الحويصلي المنتشر ، إصابة الأوعية الدموية مع تجلط الدم ، التغيرات الالتهابية في الأنسجة هي النتائج المرضية الرئيسية في هذه المراجعة. تشير هذه الاختلافات في السمة المرضية بين المرضى إلى آليات مختلفة لإصابات الأعضاء الناجمة عن الفيروس والتي قد تؤثر على تأثير المرض وعلى الية العلاج.

**الكلمات المفتاحية :** فيروس كورونا ، الخزعة ، الاكتشافات المرضية

### INTRODUCTION

Corona-virus disease "COVID-19" is a contagious disease, caused by a group of viruses that is officially referred as severe acute respiratory syndrome coronavirus 2 "SARS-Cov-2". In human, the virus incline to infect respiratory tract causing symptoms ranging from mild influenza to sever and may be lethal respiratory distress

syndrome<sup>1</sup>. Covid-19 affects different people in different ways, about 10-20% of affected people had been died. It mostly enters the human body through the "angiotensin-converting enzyme 2" (ACE2) and "trans-membrane serine protease 2" receptors and nasal cavity cells of the respiratory system and then gradually moves towards the lung to initiate infection<sup>2</sup>. Even though "Covid-19" is a

disease that predominantly affect the lungs, it also hurt other body tissues, as the liver, kidneys, cerebrum and heart. organ damage may result in long-term health problems post-covid<sup>3</sup>. The infection with covid 19 induces systemic inflammatory response with evidence of micro-thrombi and micro-angiopathic disease in the most organs<sup>4</sup>. A previous study revealed that 29% of patients with covid 19 had renal injury and protein urea<sup>5</sup>. The renal involvement may be due to ischemia induced by pulmonary dysfunction or direct infection of renal tissues with corona virus however, high level of inflammatory protein cytokines in circulation may responsible for renal dysfunction<sup>6</sup>. Other researcher found that 44% of patients with "covid19" had unusual liver function test which means liver injury, they showed that these abnormalities were correlated to the severity of pulmonary infection<sup>7,8</sup>.

The aim of this work is to systemically review current data of pulmonary, liver and renal tissue pathology to understand organs involvement in "SARSCV-2" infected patients and detect the prognosis relationship with Covid-19 patients.

## METHOD

In this study, review of different articles and researches which had been published till July 2022 was performed. Authors searched on Scopus articles, Pub-Med, Embase electronic databases, biomedical, Google scholar and other medical lines. The following search terms were used: "corona-virus, renal biopsy, liver and lung histopathological abnormalities, covid 19, autopsy. All related subject reviewed with exclusion / inclusion criteria and the collected data then were reported and analysis.

### Inclusion And Exclusion Criteria

All pupillages that studied the pathological alterations either as biopsy or autopsy from liver, lung and kidney in "covid 19" proven patients from 2019 till July 2022 were involved in this review. While others without structural assessment or those with Incomplete data were excepted.

## RESULT AND DISCUSSION

The authors reviewed a full text publication of lung, liver and kidney pathology in covid 19. About 60 articles met inclusion criteria and were involved in this review.

## Histopathological Assessment of Lung Tissue

Covid -19 is frequently disturbing the lung producing lung injury. Lung fibrosis is a common reason of death in covid. The severity of lung injury depends on the severity of covid contagion, age of the patient as older age has low lung elasticity and low immunity, the existing respiratory problem, hypertensive, diabetes and on an accurateness of the treatment<sup>9-11</sup>. Depending on biopsy and autopsy, most patients with severe covid19 infection developed lung pathology<sup>12-28</sup> as shown in table 1. The lung impairment is diverse in different persons. Most frequent histological finding of lung tissue of postmortem autopsy in all person with covid-19 was extensive parenchymal lung destruction, including damage of endothelial cells, smooth muscles, and pneumocyte, along with the aggravated fibroblast productin<sup>21</sup>. Pulmonary sequelae were varying considerably depending on the duration of the disease<sup>29</sup>. During the first weak post infection, lung histopathology characterized by edema in an intra and extra alveolar (exudative phase), little inflammation, hyaline membrane either focal or diffuse and thrombi may be found (figure 1). After the first week the histological findings characterized by diffuse alveolitis, necrosis, squamous pneumocyte dysplasia, septal cells hyperplasia, hyaline membrane incorporated into alveolar septa. In addition cellular atypia of alveolar cells may be developed in this phase which recognized as organizing stage. The incidence of Interstitial fibrosis was increased over time and may be regard as end point<sup>17,21</sup>. 68 autopsies from Italy and USA patients whose positively confirmed as "covid 19" showed inflammatory changes of airway alveoli with hyperplasia of pneumocytes type 2 and alveolar hyaline membrane, while those with lung duration of disease presented mainly with interstitial fibrosis and septal cells hyperplasia. Thus, 87% of patient had feature of diffuse alveolar damage with hyaline membrane and atypical, giant, multinucleated pneumocyte type 2 hyperplasia. While in those had long duration of disease, 43% had squamous cells metaplasia and 34% had feature of organizing pneumonia, 42% of autopsy had focal or diffuse vessels thrombi<sup>13</sup>. Borczuk reported that organized pneumonia and proliferation with metaplasia could be seen with oxidative phase of DAD which indicate heterogenic pattern of lung injury in some cases of covid -19<sup>13</sup>. Viral particles in the endothelial cells of blood capillary with swelling of their cytoplasm and vacuolaziation of basement membrane were observed by electron microscope<sup>13</sup>. The criobiopsy of lung tissue from mild- moderate "covid 19" infected patient showed alveolar small blood vessels dilatation, focal septal cells hyperplasia and perivenular infiltration with

lymphocytic cells, neither alveolar collapse nor hyaline membrane were observed<sup>30,31</sup>. Many novel blood vessels were observed in the inter alveolar space of lung autopsy from covid infected patient suffered from pneumonia<sup>32</sup>.

These differences in the pathological features among patients indicate various mechanism of lung injury caused by the virus<sup>23,33</sup>. Valdebenit suggested three mechanisms for pathogenesis of lung damage in covid-19 these are, exhausted immunity, direct destructive effect of the virus and vascular damage with enhanced coagulation<sup>23</sup>.

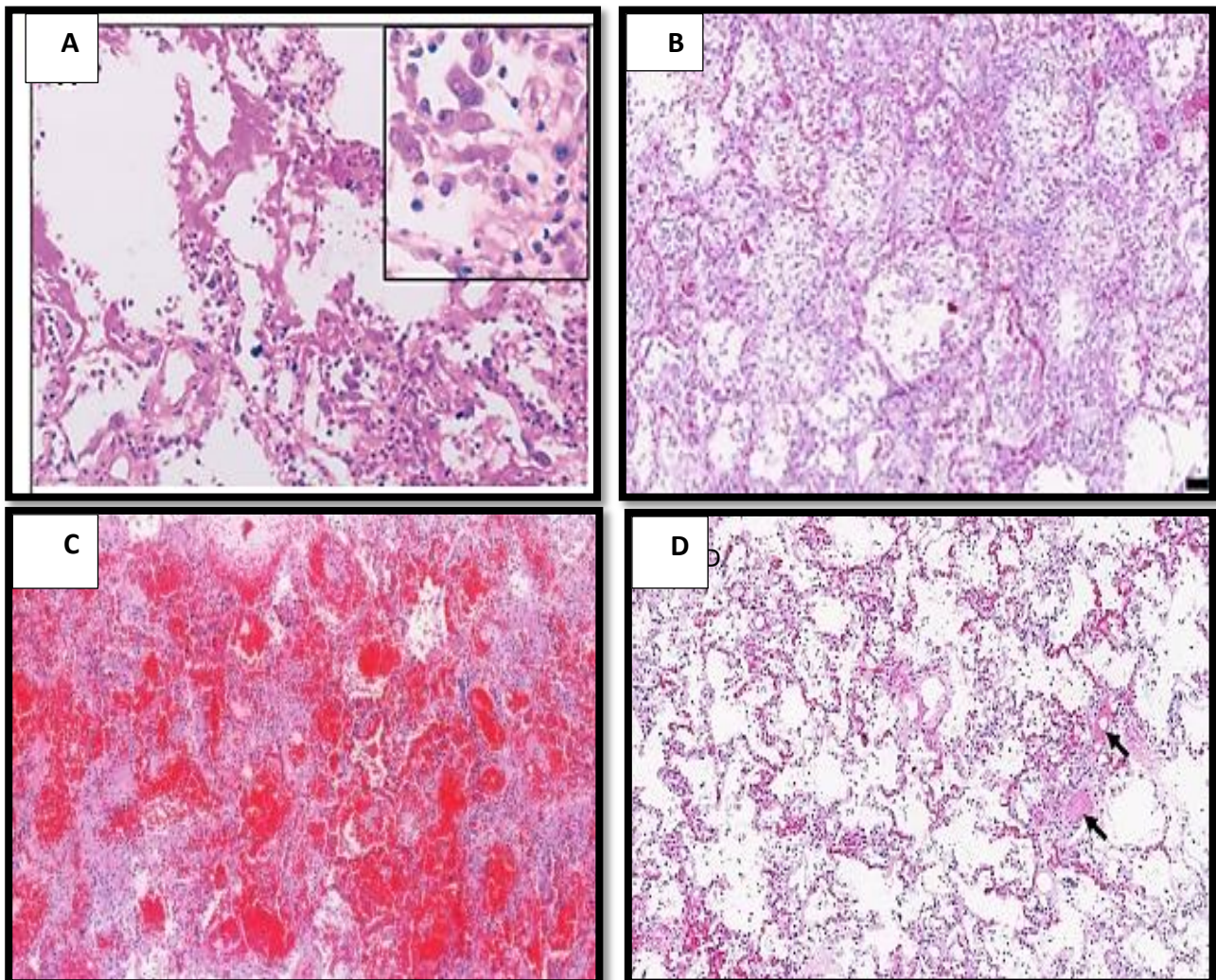


Figure 1. Pathology of lung tissue in covid 19 .A : alveolitis with many inflammatory cells infiltrate the wall of alveoli H&E, X 200. B: diffuse alveolar destruction with fibroproliferation and hyaline membrane H&E, X 200.C: Hemorrhage and edema in the alveolar space H&E, X 200.D: thrombosis in the alveolar blood vessels H&E, X 200.

Table 1 : pulmonary pathology in "covid 19" as desecibed by different study

Author ( year)	No. of cases		Pathological finding
	Autopsy	Biopsy	
Xu Z eta al ( 2020) <sup>12</sup>		1	bilateral alveolar destruction , lymphocytic infiltration , abnormal giant pneumocyte with intraluminal exudates
Borczuk eta al (2020) <sup>13</sup>	68		Trachio-bronchitis , alveolar injury, and vascular / thrombotic
Bradley eta al (2020) <sup>14</sup>	14		diffuse alveolar destruction, virus particles observed in the pneumocyte and epithelium of trachea
Wu JH (2020) <sup>15</sup>	10		Brochiolitis with accumulation of secretion fibrous , acute alveolitis with intraluminal exudate , hyperplasia of septal pneumocyte with hyaline membrane formation. Intra-capillary micro-thrombus
Fox eta al (2020) <sup>16</sup>	10		Micro-angiopathy in capillaries and small blood vessels with hemorrhage, diffuse alveolitis with hyaline membranes.
Menter et al (2020) <sup>17</sup>	10		Vasculitis , thrombosis , diffuse alveolar injury
Copin eta al (2020) <sup>18</sup>	6		intra –alveolar fibrin with connective tissue and acute alveolar injury
Lacy et al ( 2020) <sup>19</sup>	1		Necrosis of pneumocyte alveolar edema with hemorrhage and accumulation of macrophage and fibrin
Grimes eta al ( 2020) <sup>20</sup>			Pneumocyte necrosis, fibrin accumulation in capillary corse electron dense areas of cytoplasmic fibrin deposition.
Konopka eta al ( 2020) <sup>21</sup>	4		Diffuse alveolar damage
Stoyanov eta al ( 2021) <sup>22</sup>	27		Diffuse alveolar damage, degeneration of vascular epithelium, fibrin deposition and micro thrombus
Valdebenito eta al ( 2021) <sup>23</sup>			Hyperplasia of Alveolar wall ,alveolar fibrin with clot in blood -vessels
Bösmüller eta al (2021) <sup>24</sup>	4		Alveolar cells metaplasia, intra alveolar fibroblast proliferation, organized pneumonia
Mauad eta al (2021) <sup>25</sup>	41		Diffuse alveolar destruction with hyaline membranes formation,fibrosis
Rendeiro eta al (2021) <sup>26</sup>	8		Alveolar damage and fibrosis
Pannone eta al (2021) <sup>27</sup>			Alveolitis , fibrosis, interstitial edema , pneumocyte hyperplasia, vascular micro thrombus
Merdji eta al (2022) <sup>28</sup>	22		Proliferative and fibrotic changes

### Histopathological Assessment of Renal System

Though The main targets of corona virus are respiratory and immune system, renal injury in covid -19 had been reported. Several studies explained the histopathological evidence in renal autopsy of patient with SARS-covid infection<sup>34</sup> (table 2) . So the main pathological features (figure 2) were observed in proximal renal tubule in which the lining epithelium loss its brush border

and most of the cells degenerated and the lumen was dilated and filled with cellular debris, the lumen of capillaries congested with blood with sign of vasculitis , inflammatory cells were observed in the interstitial space . Moreover, virus particles was seen by electron microscope in the tubular epithelium and in the inner layer of bowman membrane<sup>36</sup>. Volbeda eta al studied renal autopsies from 6 adult diagnosed with corona virus

by molecular test they found that acute tubular necrosis was the main structural finding in all biopsy. Additionally, thrombi and micro-thrombi were observed in peritubular vessels while the endothelial activation and inflammation of renal tissue were absent<sup>45</sup>. Many risk factors may associated with the development of renal injury among patients with covid- 19 these include, old age, sex, black-race and pre- exciting disease as diabetes, hypertension. Shetty eta al mention that acute renal injury characterized by glomerulosclerosis with glomerular tuft collapse , hypertrophy of parietal cells, podocyte and capillaries obliteration<sup>46</sup>. Renal injury occur in one-fifth of pediatric covid 19 infected patients with increase the mortality among that child<sup>47-49</sup>. Nomura eta al described the histological changes obtained from four renal biopsies and one autopsy from child with "covid19" associated with renal impairment they reported cortical necrosis, effacement of podocyte process vascular micro-angiopathy with thrombosis and vasculitis<sup>50</sup>.

Several animals could be infected with covid virus. Song eta al reported the renal histopathological findings of minks infected with "SARS-COV2" which include tubular epithelium necrosis and sloughing to the lumen, tubular lumen dilatation, interstitial inflammation, cortical glomeruli were contracted and bowman capsule expanded with increase mesangial volume<sup>51</sup> these findings approximately similar to those observed in human<sup>52</sup>. Many factor contributed to pathogenesis of renal disorder in patients with covid-19 , these include direct invasion of corona virus into renal tissue yet a few studies had been capable to establish the existence of viral elements in renal tissue , immune reactin , hypoxia which occur as a result of respiratory dysfunction , abnormalities in the coagulation which responsible for angiopathy, thrombosis and vessels obstruction and lastly the therapeutic agents for acute disorder as well as the systemic effect of covid-19 may predispose to renal damage<sup>53</sup>

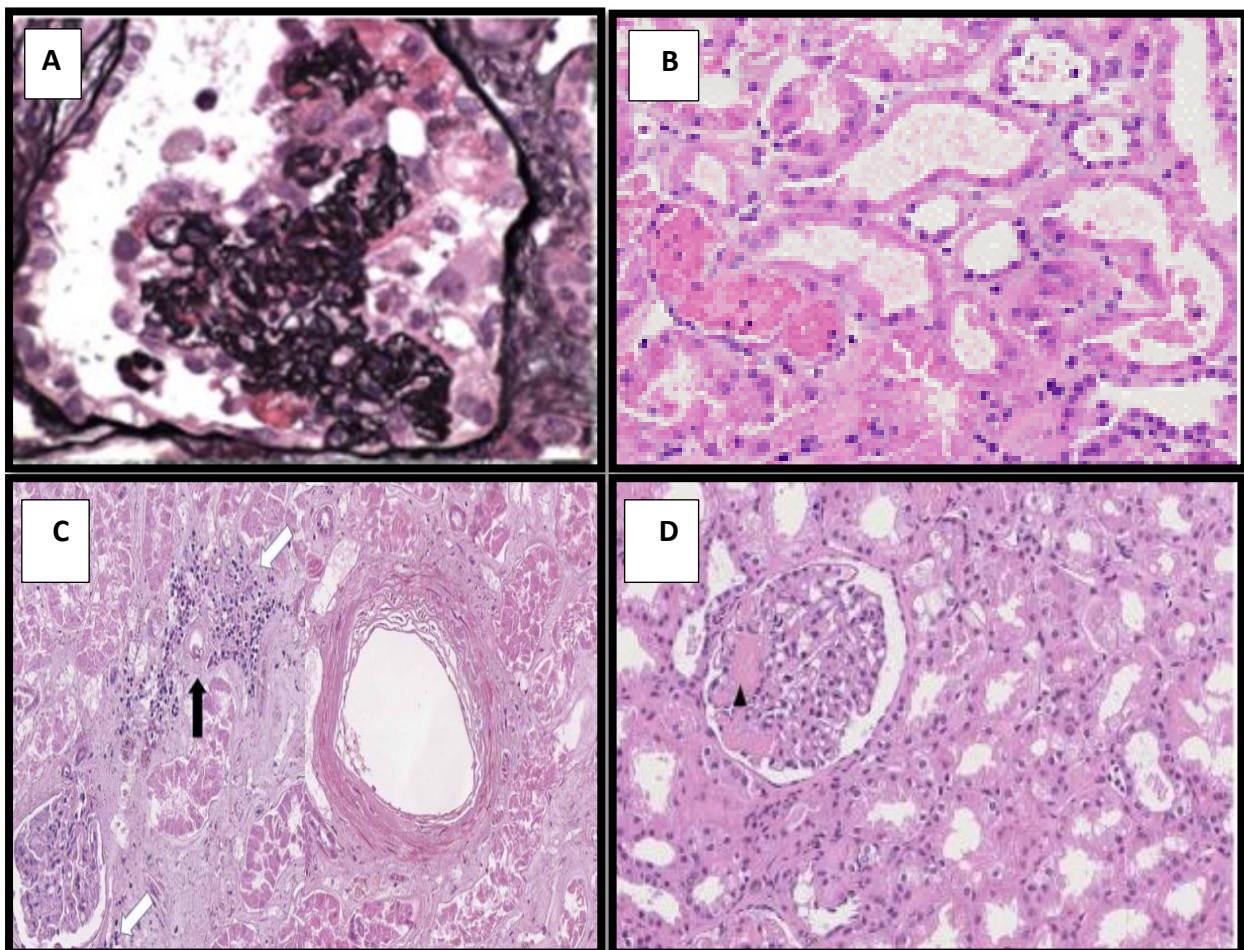


Figure 2: Renal pathology in covid 19 ( A) showing glomerular atrophy ( B) Tubular epithelial degeneration ( c) inflammatory cells nephritis ( D) segmental thrombi in glomerulus

Table 2 : Renal pathology in covid 19 as described by different study

Author ( year)	No. of cases		pathological finding
	Autopsy	Biopsy	
Kudose eta al (2020) <sup>34</sup>	14		Epithelial Hyperplasia of glomeruli, capillary collapse , tubular cells necrosis and shedding of degenerated cells to the lumen
Stoyanv eta al (2020) <sup>35</sup>	1		Tubular destruction, nephritis with infiltration of interstitium by lymphocytic cells, blood vessels thrombosis
Su H eta al (2020) <sup>36</sup>	26		Necrosis and degeneration of tubular epithelium, detachment of cells to the lumen, fibrin thrombi in the small blood vessels and capillaries with glmerulonephritis .
Wu eta al ( 2020) <sup>37</sup>	6		Interstitial infiltration of lymphocyte , tubular cells necrosis with infiltration of the wall by inflammatory cells
Ng eta al ( 2020) <sup>38</sup>	7		Endothelitis with dysfunction, degenerated tubular cells and nephritis
Santriello eta al (2020) <sup>39</sup>	42		Epithelial cells detachment from proximal tubule, destruction of glomerulous and distal tubule
Kapp eta al ( 2020) <sup>40</sup>	9		Renal tubular cells degeneration, interstitium nephritis
Sharma eta al (2021) <sup>41</sup>			Glomerular atrophy , vasculitis
Popov eta al (2022) <sup>42</sup>	10		Micro-angiopathy in capillaries with endothelitis , tubular destruction , podocyte hyperplasia , interstitial nephritis
Axenciuc eta al (2022) <sup>43</sup>	10		Damage and destruction of glomerular capillaries ,deformity of glomerulus , tubular cells degeneration
Gambella eta al (2022) <sup>44</sup>	9		Glomerular atrophy ,tubular cells injury, micro-angipathic , thrombosis

### Histopathological of Liver

Moderate to severe infection with covid- 19 was usually associated with liver injury. As ACE2 receptor has been expressed in hepatocytes and in cells of biliary system as like as that of alveolar cells so the liver regarded as anther common site for corona virus <sup>54</sup>. Many pathological findings were observed by different studies <sup>55-59</sup> (table 3, figure 3). Sonzogni *et al* examined liver autopsies from 48 covid infected patient they reported several vascular abnormality which include thrombosis of sinusoidal and phlebosclerosis of portal vein either focal or diffuse, endothelial cells damage, vascular wall thickening and increase periportal abnormal branches associated with mild inflammation. Thus, they concluded that vascular damage might be considered as leading causes of liver dysfunction in covid 19 patient<sup>60</sup>. Chornenky and his companions studied 8 autopsies postmortem samples of liver from patients who diagnosed previously as covid positive by molecular tests and the virus was detected in lungs of all patients, they concluded that most of

covid -19 infected patients had some evidence of hepatitis which appear as periportal fibrosis with mild inflammation of lobular parenchyma and portal inflammation<sup>57</sup>. Other investigator study the structural abnormalities of liver autopsy obtained from tow covid -19 infected cases had been suffered from elevated liver enzyme they found apoptosis and bionuclear liver cells, steatosis, inflammatory cells infiltrate the liver lobule and portal tract. By electron- microscope, some hepatocytes appeared to have spike- shaped virus in their cytoplasm, expanded mitochondria, vague cisternae and abnormal canalicular damage<sup>61</sup>. These finding indicate that covid 19 related hepatic injury may occur as result of direct infection of hepatocyte with this virus. Additionally, respiratory distress and hypoxia ccur in sever covid-19 infection resulted in necrosis of hepatocytes and lobular inflammation <sup>62</sup>. Rapkiewicz eta al suggested that thrombosis which occur as a result hypercoagulable status of "SARS-COV-2" play a vital role in pathogenesis of liver injury in covid -19 infected person, the liver biopsy of seven patient

reveled that thrombosis and vascular damage were the main pathological features in all autopsies, sinusoidal micro- thrombus appeared in six cases while ischemic necrosis of hepatocyte are observed in tow cases<sup>63</sup>. Thus, the liver dysfunction in covid-19 appears to be multifactorial origin. Nuovo et al said that alcohol drinker persons have high risk for liver damage with corona virus they studied liver autopsies from person had pre-existing alcohol liver disorder who died by corona, the histological assessment showed centrilobular infiltration with inflammatory cells as neutrophils , mononuclear cells and Mallory bodies , macrosteatosis in mid and peripheral zones of liver lobule however cirrhosis present in one case, most of the cells

positive for spike virus protein<sup>64</sup>. The different studies mentioned that main pathological changes of liver in covid 19 were fatty liver, thrombosis, portal and centrilobular inflammation, kupffer cells hyperplasia and cholestasis <sup>65,66</sup>. These findings may be attributed to different factors which may be summaries as follow: A- direct influence of the virus on hepatocytes. B- reduction of hepatic flow by the virus C- disturbance of blood coagulation by effect of the SARS-COV-2<sup>66</sup> D- kupffer cells hyperplasia occur as response to inflammation. E- the virus provokes hepatic cholestatic enzymes that can induce ductal injury and increase cholangicellular growth factors<sup>67</sup>.

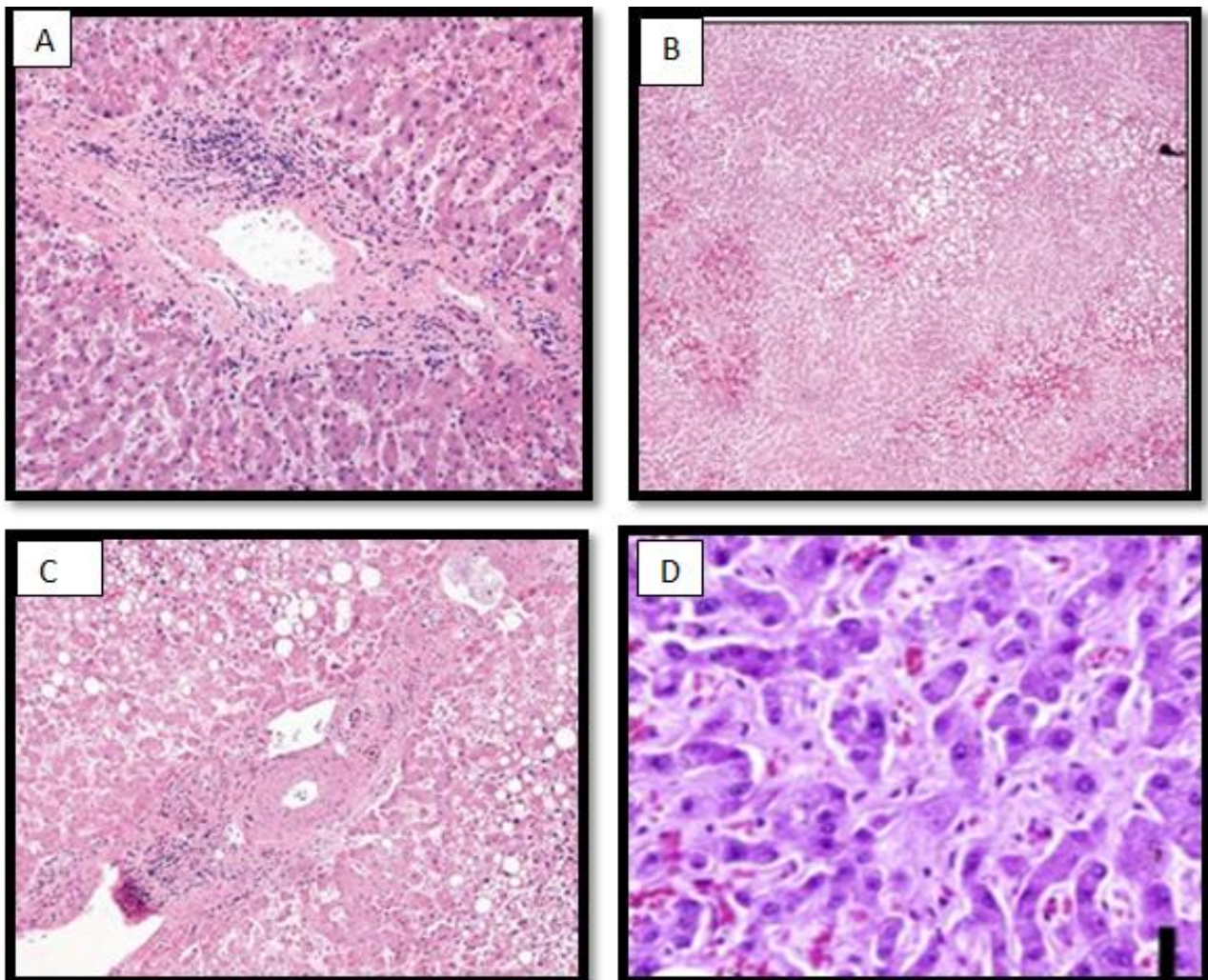


Figure 3: Liver pathology in covid -19 ( A) showing Portal area inflammation(B) sinusoidal congestion( C) steatosis(D) pericellular and sinusoidal fibrosis. H&E , X200

Table 3 : Liver pathology in covid -19 as described by different study

Author ( year)	No. of cases		Pathological finding
	Autopsy	biopsy	
Li Y eta al( 2020) <sup>55</sup>			Dilatation of hepatic sinasoid and infiltrated by inflammatory cells, focal necrosis of hepatocytes and steatosis
Lagana eta al (2020) <sup>56</sup>	40		Lipid drop in hepatocyte with inflammatory hepatitis and apoptotic cells mainly in the centrilobular area of the liver and in portal duct
Chornenkyy eta al (2021) <sup>57</sup>	4		Steatosis, Inflammatory changes of portal canal, vascular congestion , necrosis of cells of biliary duct and in some patient fibrosis of bile duct
Fassan eta al (2021) <sup>58</sup>	26		Sinasoidal congestion with thrombosis , steatosis with apoptosis, fibrosis of hepatic lobule
Chu eta al ( 2021) <sup>59</sup>	26		Hepatic cells degeneration with steatosis, lobular and portal inflammation , fibrosis, dilatation of sinusoid

### CONCLUSIONS

Despite the fact that COVID-19 is primarily affecting the lung , it can influence other parts of the body as kidney and liver particularly in severe cases . The present review help the physician and investigators to recognize the main histopathological changes of the affected organs aiding in correct management and in prevention of health deterioration

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