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Original Article

Multiorgan pathological findings of severe COVID-19 in deceased patients: a post-mortem study in the Indonesian population

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ABSTRACT

Since the WHO declared the COVID-19 epidemic on March 11, 2020, there has been a notable increase in morbidity and death on a global scale. Despite the growing number of cases, limited data exists on the pathological changes in deceased COVID-19 patients, particularly concerning the lungs, heart, and liver. This study aims to describe the histopathological results in the lungs, heart, and Indonesian COVID-19 patients' livers that have died, providing insights into the multiorgan impact of severe SARS-CoV-2 infection. A post-mortem study was conducted on 41 COVID-19 patients treated in a special isolation ward at Dr. Soetomo General Hospital, Surabaya, from July 1, 2020, to December 31, 2020. The heart, liver, and lungs were biopsied using core needles. Histopathological examinations were carried out, and findings were documented and analyzed. The study included 30 males (73.17%) and 11 females, with a mean age of 48.66 ± 12.93 years. In the lungs, the most common findings were interstitial and/or intra-alveolar inflammatory infiltrate (97.56%) and peri- or intravascular inflammatory infiltrate (87.80%). The liver exhibited mild to moderate lobular inflammation (87.80%) and portal inflammation (75.61%). The heart showed interstitial edema (95.12%) and mild myocardial hypertrophy (80.49%). This study revealed significant histopathological abnormalities in the lungs, liver, and heart of deceased COVID-19 patients, highlighting the disease's multiorgan impact. The findings underscore the need for careful monitoring of these organs in severe COVID-19 cases to stop further clinical decline.

Keywords: COVID-19, SARS-CoV-2, Lung, Heart, Liver, Pathology

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Introduction

The novel extreme acute respiration syndromes coronavirus 2 (SARS-CoV-2) is the cause of the terrible ailment referred to as COVID-19. The epidemic was initially reported in Wuhan, China, at the end of December 2019 and started as viral pneumonia brought on by an unknown microbiological

pathogen. It started with wild animals discovered in a South Chinese market [1]. It has spread worldwide and infected 440,318 people in 195 countries during its early wave [2, 3].

The prevalence of severe COVID-19 was reaching 18% of the world population (95% CI 12.6–23.5%), which further increased in hypertension to 44.5% (95% CI 27.0–61.9%) and diabetes mellitus to 41.7% (95% CI 26.4–56.9%) [4, 5]. The percentage of death among hospitalized coronavirus patients was high at approximately 17.62% (95% CI 14.26–21.57%) and even increasing in male [6]. Although the mortality and severity rate were seemingly high, the research regarding the subsequent histopathological changes was still limitedly available due to the fact that the research should be carried in post-mortem patients. Post-mortem core needle biopsies (PMCNB) histological examination might be used as a substitute technique to identify the pathophysiology of COVID-19 and the histopathological alterations that follow. The three most prevalent organs implicated in the seriousness and death of COVID-19 were the liver, heart, and lungs, based on published clinical and laboratory data on the virus [7, 8]. Therefore, more post-mortem biopsy studies are required to improve our understanding of this disease. Descriptive analysis of the histological abnormalities in the liver, heart, and lungs of post-mortem extreme coronavirus patients is the goal of this work.

Materials and Methods

Patients and data collection

Forty-one deceased COVID-19 patients were included in this post-mortem study from July 1, 2020 to December 31, 2020. All patients were confirmed with a positive ante-mortem SARS-CoV-2 infection through reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal and oropharyngeal swabs, which were performed by trained technicians according to existing guidelines. All patients have previously been treated in the special COVID-19 isolation ward at Dr. Soetomo General Hospital. The sex, age, number of days after COVID-19 onset, and comorbidities were obtained from the electronic medical records. This study was approved by the local ethics committee (0022/KEPK/VII/2020). The informed consents were all signed by the legal guardians of all included patients prior to post-mortem biopsy.

Histopathology

Post-mortem core needle biopsies were blindly performed on the lungs, heart, and liver of the post-mortem patients without the guidance of ultrasonography (USG). The puncture locations were determined according to the X-ray photo results. Those samples were taken in the intensive care unit (ICU) within 1–2 hours after the patients deceased by all trained authors other than the anatomical pathologists. As the hospital safety guidelines dictated, those who performed the biopsies should wear appropriate personal protective equipment. Each specimen was placed into an individual labeled specimen jar and macroscopically assessed for adequacy by a research team member. Those specimens were fixed in 10% buffered formalin and processed in the histopathology laboratory afterwards, including specimen slicing using Leica microtome, paraffin embedding in the Leica paraffin bath, and specimen staining using Hematoxylin & Eosin (H&E) according to the standard procedures. The stained sections were then observed using an *Olympus* binocular light microscope (*CX41RF*) with 10x and 40x magnifications, documented using *Olympus DP2-BSW* software, and interpreted by all anatomical pathologists to reduce the interpretation bias.

Descriptive analysis

We presented the basic characteristics of the samples in n (%) for categorical variables (sex and comorbidities) or mean ± standard deviation (SD) for continuous variables (age and number of days after COVID-19 onset). Descriptive analysis was then performed with Microsoft Excel.

Results and Discussion

Population characteristics

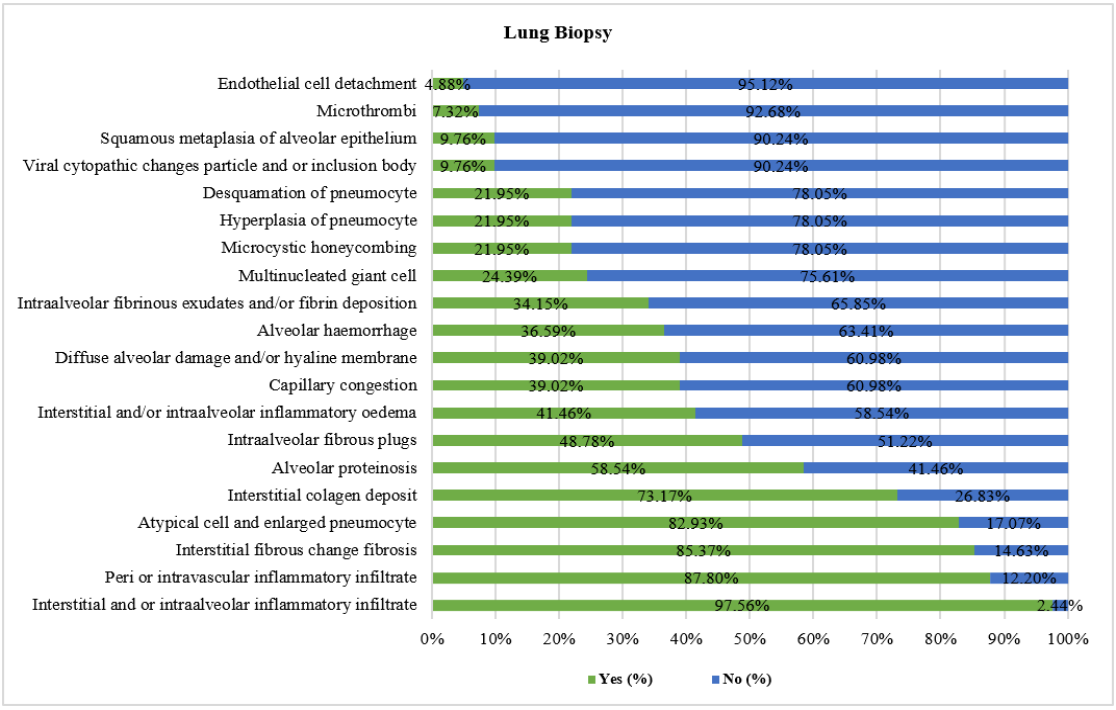
There were 41 post-mortem COVID-19 patients in our investigation **(Table 1)**. Of those, 73.17% (n = 30) of the samples was male. We obtained 41 adequate lung specimens, 41 adequate liver specimens, and 40 adequate heart specimens to be interpreted. The mean age was 48.66 ± 12.93 years (between 36 and 60 years old). The typical duration of hospitalization following the beginning of signs was 16.95 ± 6.89 days (with a range of 9 to 23 days). The most frequent comorbidity was type 2 diabetes mellitus in 77.55% of the samples (n = 38), while the least frequent was cardiovascular disease in only 12.24% of the samples (n = 6).

Table 1. The characteristics of study samples.

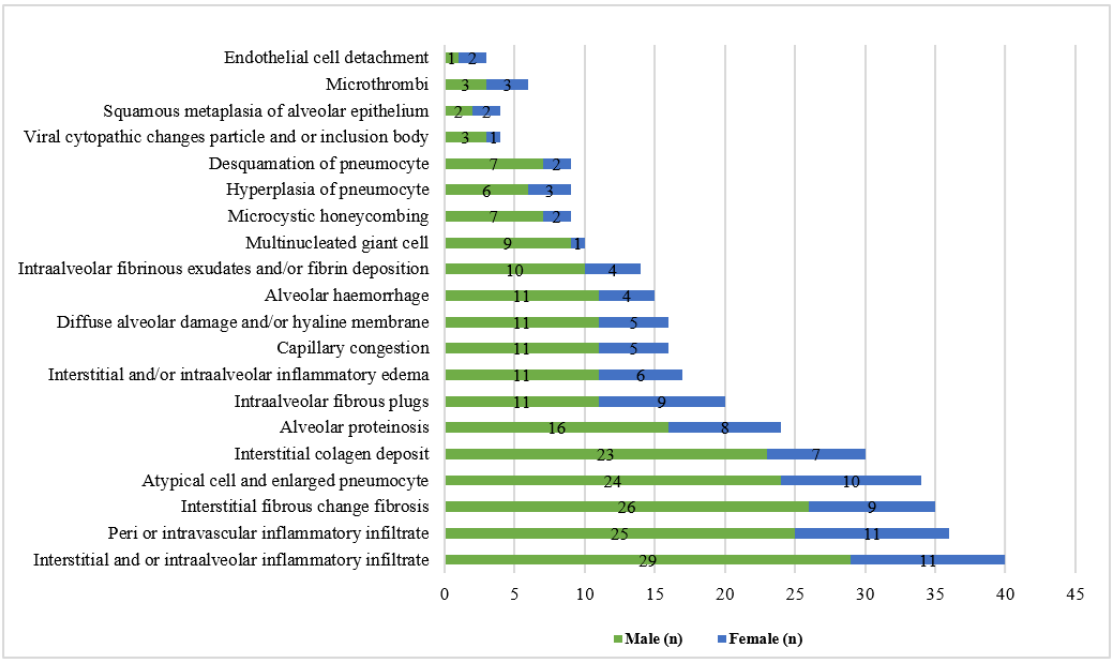
Variable	n (%) or mean ± SD
Sex	
Male	30 (73.17)
Female	11 (26.83)
Age (years)	48.66 ± 12.93
Male	50.67 ± 12.16
Female	43.18 ± 13.97
Days since onset (days)	16.95 ± 6.89
Male	16.53 ± 6.53
Female	18.09 ± 8.01
Comorbidities	
Type 2 diabetes mellitus	38 (77.55)
Hypertension	25 (51.02)
Obesity	17 (34.7)
Cardiovascular disease	6 (12.24)

Pathologic findings of lung tissue

A summary of lung biopsy findings from 41 adequate lung specimens was demonstrated in **Figure 1** along with their histopathologic images in **Figure 2** and their distributions in each patient in **S1 Table**. The five primary pathologic findings in our study **(Figure 1a)** were the interstitial and/or intra-alveolar inflammatory infiltrate (97.56%; n = 40), peri- or intravascular inflammatory infiltrate (87.80%; n = 36), interstitial fibrous change (85.37%; n = 35), atypical cell and enlarged pneumocyte (82.93%; n = 34), and interstitial collagen deposit (73.17%; n = 30). However, there were two least frequent findings in those specimens, including microthrombi (7.32%; n = 3) and endothelial cell detachment (4.88%; n = 2). Interestingly, almost all of the lung biopsy findings were found in male **(Figure 1b)**, except for squamous metaplasia of alveolar epithelium and endothelial cell detachment which showed 1:1 males-to-females ratio.



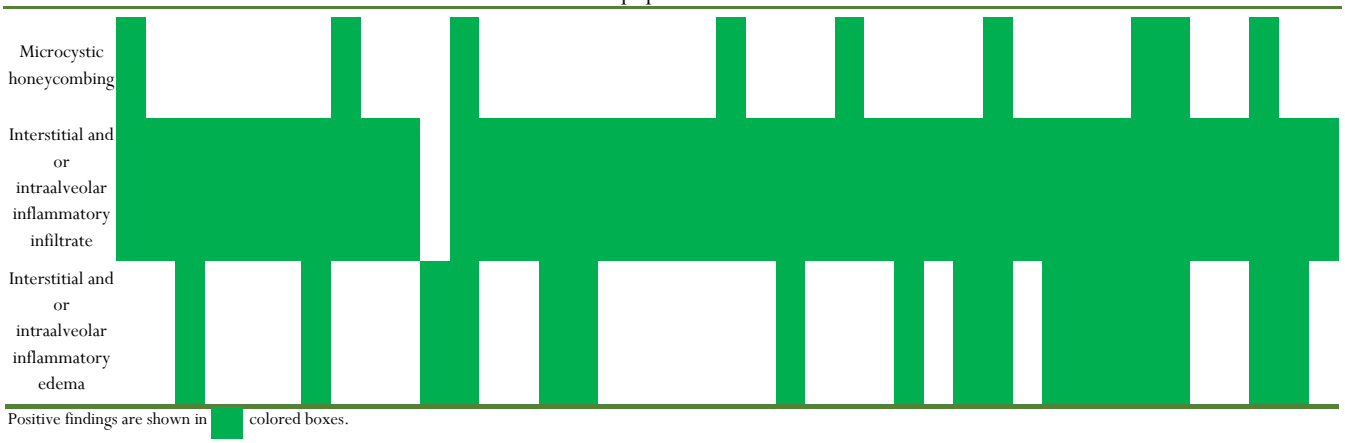
a)



b)

Figure 1. Lung biopsy characteristics in 41 post-mortem COVID-19 patients. a) Percentage distribut ions of positive and negative findings, b) Male and female distributions of each finding.

S1 Table. Distribution of lung histopathological findings in 41 postmortem COVID-19 patients.



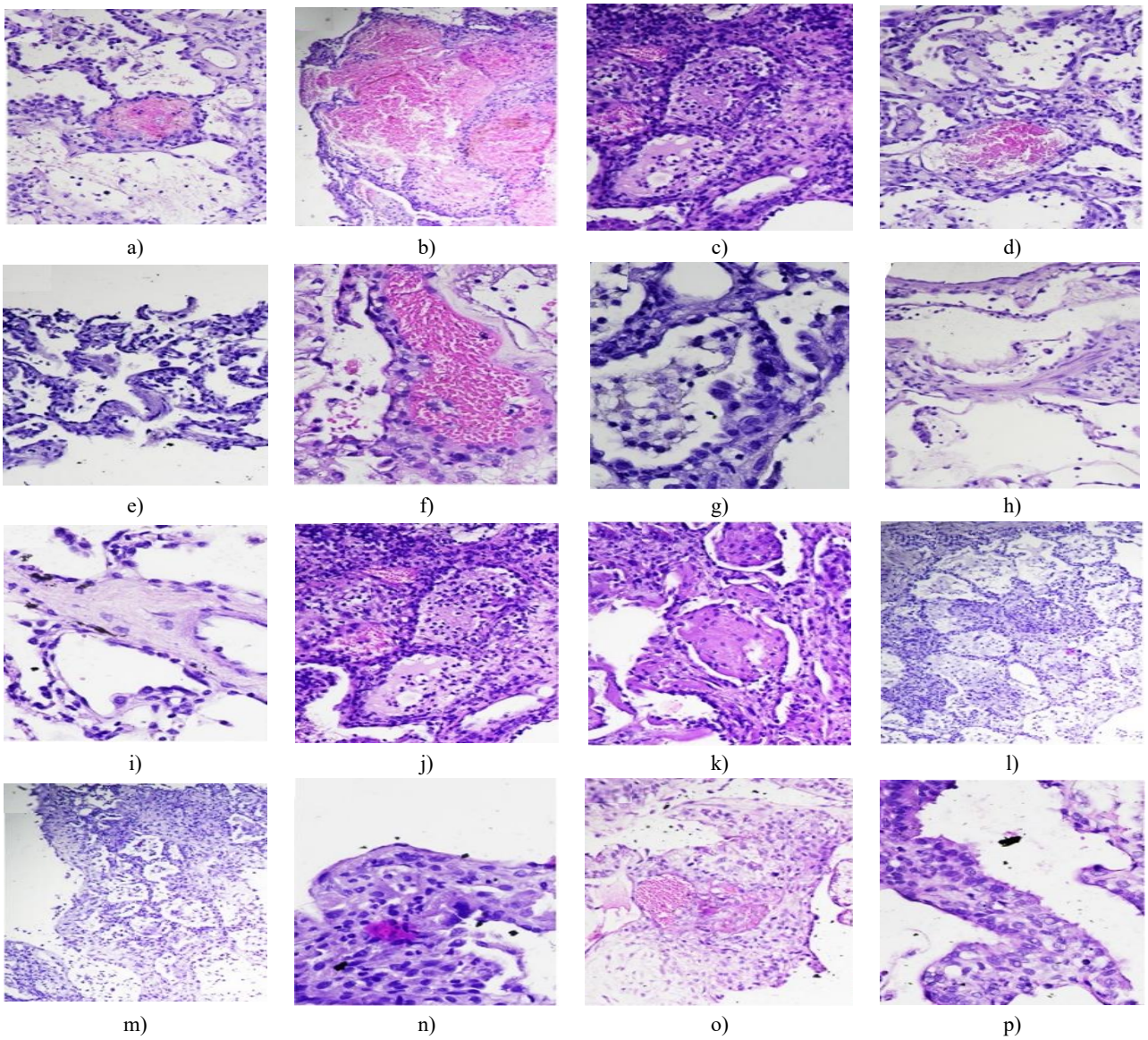
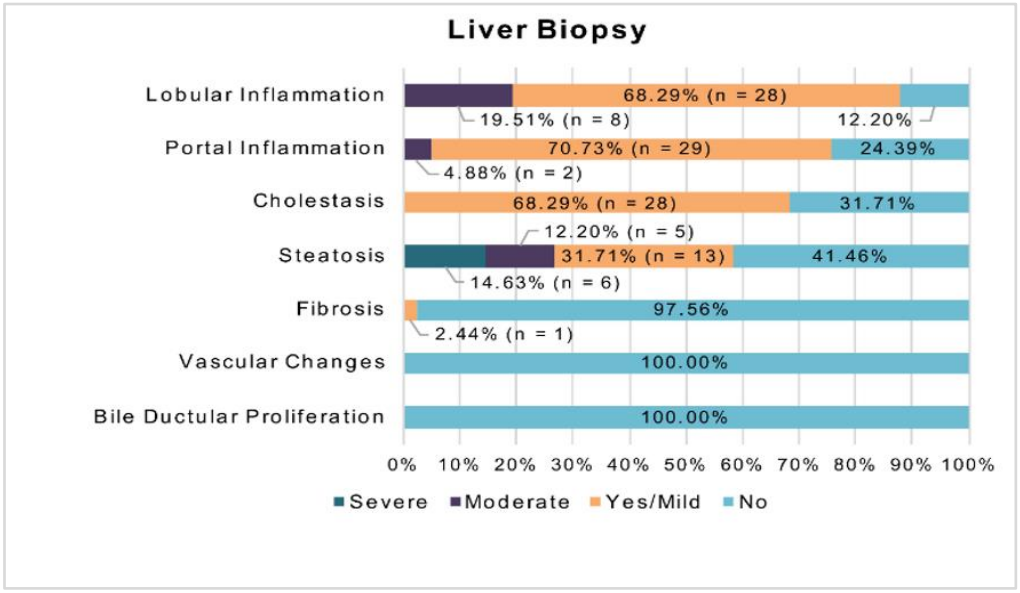


Figure 2. Histopathologic findings in the lung biopsy specimens. a) Microthrombi, b) Alveolar hemorrhage, c) Alveolar proteinosis, d) Capillary congestion, e) Desquamation of pneumocytes, f) Endothelial cell detachment, g) Pneumocyte hyperplasia, pneumocyte atypia, and inclusion bodies, h) Interstitial fibrosis, i) Interstitial collagen deposit, j) Intra-alveolar fibrinous exudate, k) Intra-alveolar fibrous plug, l, m) Microcystic honeycombs, n) Multinucleated giant cell, o) Perivascular infiltrate, p) Viral cytopathic changes (inclusion bodies).

Pathologic findings of liver tissue

We succeeded to obtained samples of liver tissue in 41 patients and summarized the findings in **Figure 3** along with their histopathologic images in **Figure 4** and their distributions in each patient in **S2 Table**. As shown in **Figure 2a**, the four most common pathologic findings of liver biopsy in our study were

mild to moderate lobular inflammation (87.80%; n = 36), mild to moderate portal inflammation (75.61%; n = 31), cholestasis (68.29% ; n = 28), and mild to severe steatosis (58.54%; n = 24). All of them were mostly found in male **(Figure 2b)**. Only one female patient (2.44%; n = 1) had liver fibrosis. No evidence of bile duct proliferation and vascular changes were observed in the liver tissue.



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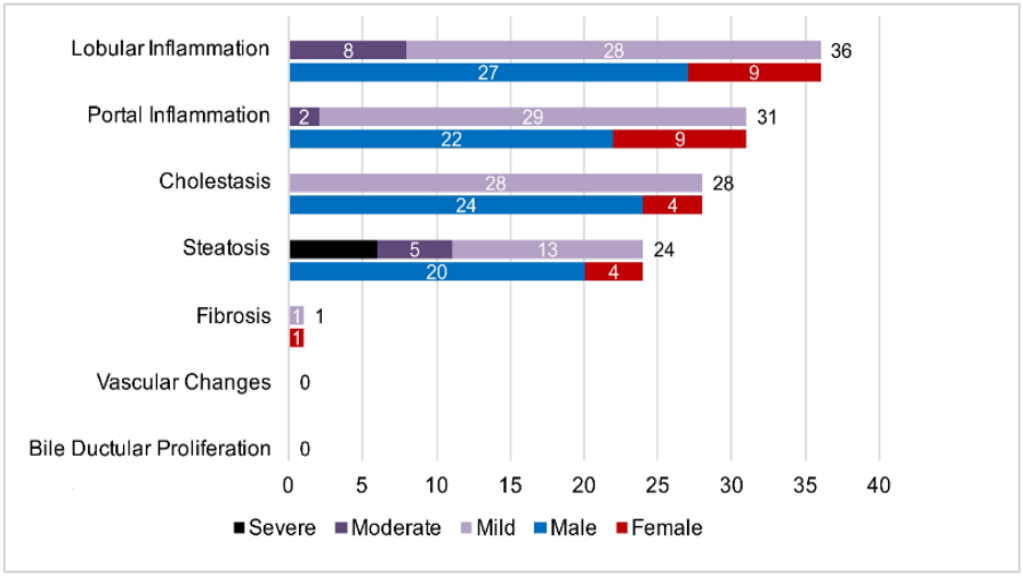
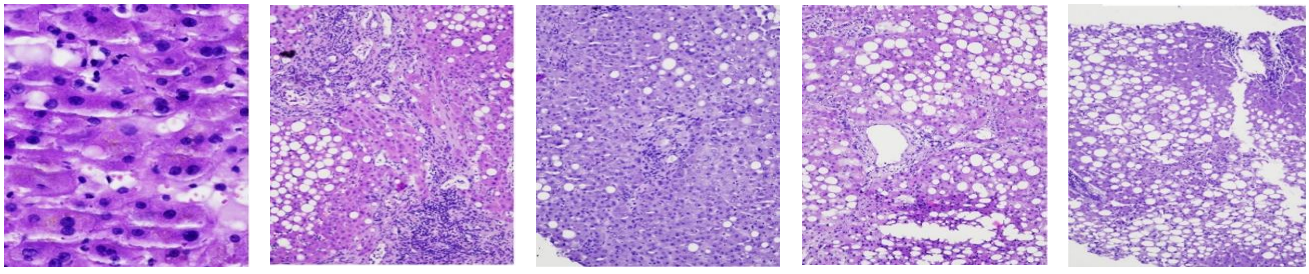


b)

Figure 3. Liver biopsy characteristics in 41 post-mortem COVID-19 patients. a) Percentage distributions of positive and negative findings, b) Severity and sex distributions of each finding.



a) b) c) d) e)

Figure 4. Histopathologic findings in liver biopsy specimens. a) Lobular cholestasis, b) Liver fibrosis or cirrhosis grade F2, c) Moderate lobular inflammation, d) Severe portal inflammation, e) Liver steatosis.

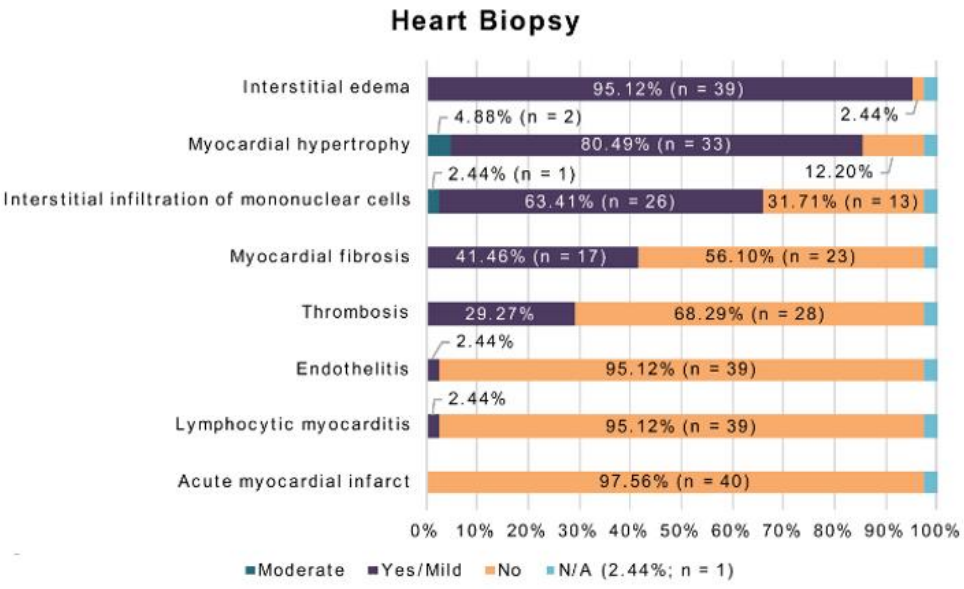
S2 Table. Distribution of liver histopathological findings in 41 postmortem COVID-19 patients.

Sample	N	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
	Sex	M	M	F	M	M	M	F	M	F	M	M	M	M	M	M	M	F	M	M	M	M	M	F	M	M	F	M	M	M	F	M	M	F	M	M	F	F	M	M	M	F
Liver Biopsy	Age	52	55	25	63	55	24	27	58	47	69	64	53	37	48	55	46	38	23	43	46	65	79	45	54	51	34	44	49	36	60	62	43	58	52	59	28	65	37	49	49	48
Steatosis																																											
Lobular Inflammation																																											
Portal Inflammation																																											
Fibrosis																																											
Bile Ductular Proliferation																																											
Cholestasis																																											
Vascular Changes																																											

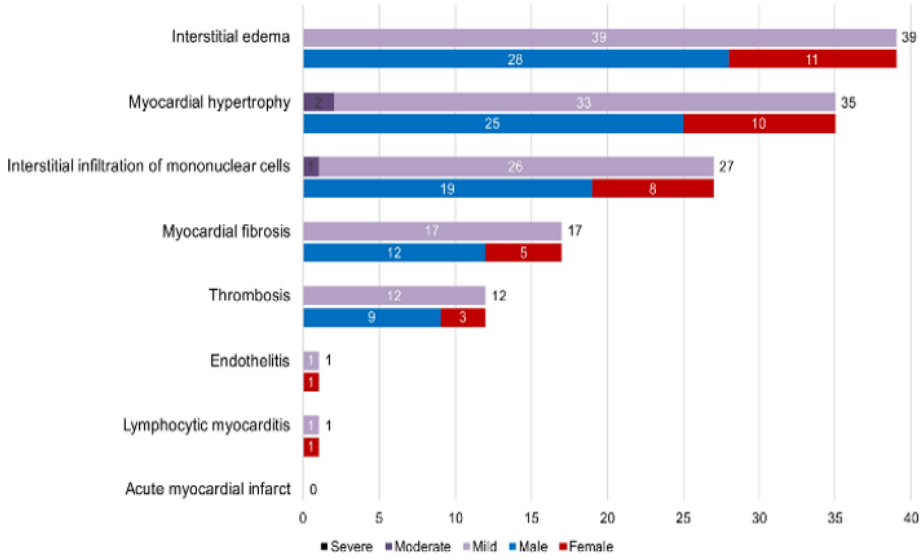
Positive severe findings are shown in colored boxes, positive moderate findings are shown in colored boxes, and positive mild findings are shown in colored boxes.

Pathologic findings of heart tissue

We succeeded to obtained heart tissue in 40 out of 41 patients and summarized the findings in **Figure 5** along with their histopathologic images in **Figure 6** and their distributions in each patient in **S3 Table**. As depicted in **Figure 5a**, the two most common pathologic findings in our study were interstitial edema (95.12%; n = 39) followed by myocardial hypertrophy (4.88% moderate [n = 2], 80.49% mild [n = 33]). The five histopathologic findings – interstitial edema, myocardial hypertrophy, interstitial infiltration of mononuclear cells, myocardial fibrosis, thrombosis – were all dominated by male **(Figure 5b)**. However, there was only one patient each with endothelitis (2.44%; n = 1) and lymphocytic myocarditis (2.44%; n = 1). Interestingly, both latter findings were only found in female. No evidence of acute myocardial infarction (AMI) was found in the current study.

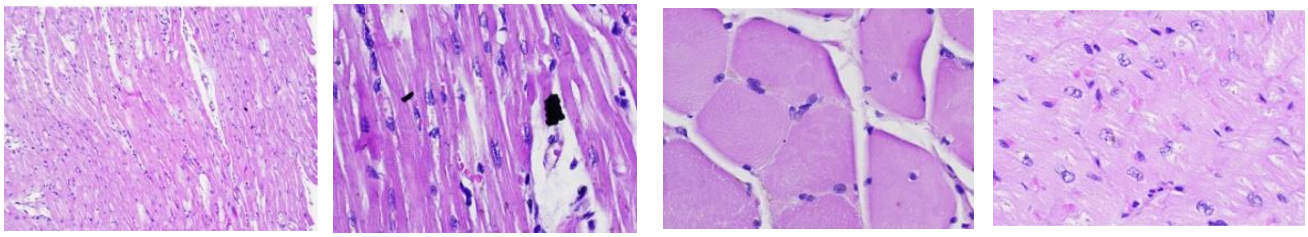


a)



b)

Figure 5. Heart biopsy characteristics in 40 post-mortem COVID-19 patients. a) Percentage distributions of positive and negative findings, b) Severity and sex distributions of each finding.



a) b) c) d)

Figure 6. Histopathologic findings in heart biopsy specimens. a) Interstitial infiltration of mononuclear cell, b) Lymphocytic myocarditis, c) Myocardial hypertrophy, d) thrombosis and myocardial fibrosis.

S3 Table. Distribution of heart histopathological findings in 40 postmortem COVID-19 patients.

Sample	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
Heart Biopsy	M	M	F	M	M	M	F	M	F	M	M	M	M	M	M	M	F	M	M	M	M	M	F	M	M	F	M	M	M	F	M	M	F	M	M	F	F	M	M	M	F
	52	55	25	63	55	24	27	58	47	69	64	53	37	48	55	46	38	23	43	46	65	79	45	54	51	34	44	49	36	60	62	43	58	52	59	28	65	37	49	49	48
Interstitial infiltration of mononuclear cells																																									
Lymphocytic myocarditis																																									
Endothelitis																																									
Thrombosis																																									
Acute myocardial infarct																																									
Myocardial Hypertrophy																																									
Myocardial fibrosis																																									

As far as we are aware, this study was the first to descriptively examine the histopathological results in the heart, liver, and lung tissues of post-mortem coronavirus patients in Indonesia. The majority of the patients' sex were men, while the two most typical comorbidities were t2dm and hypertension. As we know, most men in the world, not only in indonesia, have bad smoking habits. It might increase the danger of illness and fatality from coronavirus since male active smokers were established as the risk factor of COVID-19 [9]. Additionally, individuals who already had comorbid conditions, particularly metabolic conditions like diabetes mellitus, hypertension, chronic kidney disease (CKD), and other cardiovascular disorders, had more angiotensin-converting enzyme 2 (ACE2) receptors; as a result, those conditions may raise danger of illness and fatality from coronavirus [9]. Taken together, this study presented important facts that a population dominated by males, active smokers, and having metabolic comorbidities had a elevated likelihood of high coronavirus mortality cases. However, two other important factors – the heightened host defenses against the SARS-CoV-2 infection and the viral cytopathic ability to overpower its host immune system – also determined the coronavirus severity, mortality, and the degree of tissue damage [10]. Numerous proinflammatory mediators, including tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8, as well as hyperactivated CD4+ and CD8+ lymphocytes, were higher in instances of acute respiratory distress syndrome (ARDS) and deadly coronavirus, suggesting an overreaction of the immune system [11]. As the result of this immune response and several metabolic comorbidities, the covid-19 mortality cases might increase due to multiorgan dysfunction or end-organ injuries [12], including lung, liver, and heart.

Lung

The results of our studies indicated 22 findings in the lung biopsy specimens, including interstitial and/or intra-alveolar inflammatory infiltrate, peri- or intravascular inflammatory infiltrate, interstitial fibrous change, atypical cell and enlarged pneumocyte, and interstitial collagen deposit as the five most common findings. Those findings, not only the five most common, were generally similar to previous studies [13-18], which discovered thrombi fibrin, type 2 pneumocyte hyperplasia, organized pneumonia, distributed alveolar damage (DAD), squamous metaplasia of the alveolar epithelium, congestion, and superimposed acute bronchopneumonia. A systematic review including post-mortem studies with lung biopsy specimens revealed that 85% of the patients had epithelial patterns of injury and mononuclear cells, especially lymphocytes and/or plasma cells, were the most common sort of cells entering the interstitial space of the lungs [19]. One of the most common lung injury patterns in our study was atypical cell and enlarged pneumocytes. This finding was also found in a COVID-19 case report [13] and further confirmed by another COVID-19 post-mortem study [20], which showed atypical enlarged reactive pneumocytes in all lung tissue samples. Interestingly, the most kinds of histopathologic findings were found in the lung tissue. This might be due to the ACE2 receptors since 83% of pneumocytes expressing them, making these cells to be the perfect viral reservoirs [21]. SARS-CoV-2 was also found in 11 out of 17 lungs of COVID-19 patients (64.71%) through immunohistochemistry and rRT-PCR [19], further confirming that the respiratory tracts and lungs are the most susceptible organs to COVID-19.

Three types of histological lung damage have been identified in COVID-19: Type 2 pneumocyte hyperplasia, organization, desquamation, and viral cytopathic changes are among the variations of DAD, which is the most prevalent and early pattern. The second vascular pattern is intra-alveolar fibrin deposition and/or microvascular thrombi, and the third fibrotic pattern is fibrotic DAD and/or interstitial fibrosis [22-24]. In terms of vascular changes, our study showed capillary congestion, microthrombi, alveolar hemorrhage, alveolar proteinosis, intra-alveolar fibrinous exudate and/or fibrin deposition, and endothelial cell detachment. These changes were also found in a study by Polak *et al.* [19] that several vascular patterns of lung injury with main characteristics of vasculopathy were found in 76 out of 129 cases (59%), including microthrombi and proteinaceous and fibrinous exudates. We also observed interstitial collagen deposit, interstitial fibrous alterations, microcystic honeycombing, interstitial and/or intra-alveolar inflammatory infiltration, and interstitial and intra-alveolar inflammatory edema in relation to fibrotic changes. While some individuals experienced fibrosis early on, Polak *et al*. [19] report that fibrotic alterations, also known as interstitial fibrous changes, often manifested about three weeks following the beginning of symptoms. Since four of the patients had cancer before symptoms appeared and one had non-specific interstitial pneumonia, these were probably caused by pre-existing lung conditions [24, 25]. A high level of Krebs von den Lungen-6 (KL-6), which was revealed to be a chemoattractant to fibroblasts, may also be the source of this fibrotic process brought on by severe COVID-19 [26].

Liver

Although the precise mechanism of COVID-19-induced liver damage is yet unknown, systemic inflammatory response and drug toxicity have been proposed as potential causes [20]. According to our findings, the liver tissue obtained from COVID-19 patients who had passed away revealed four primary pathological characteristics: cholestasis, steatosis, portal inflammation, and lobular inflammation. Only one patient also had fibrosis.2 This finding was in line to previous post-mortem

COVID-19 studies, which also showed hepatic steatosis, lobular necroinflammation, portal inflammation, and cholestasis in the majority of the patients [20, 27]. Yet, according to Beigmohammadi *et al.* [20], those findings were stated as non-specific findings. Microvesicular steatosis along with portal, lobular, and sinusoidal inflammation in the post-mortem COVID-19 liver tissue were viewed as either a liver damage caused by a virus or a medication [13, 28]. It was suggested that the T cells overactivation might also be partially responsible for the immune system damage [13].

Our study also found no proof of bile duct proliferation and vascular change in the liver tissue, which were in line with a research by Lagana *et al*. [27], except for the allograft with a recent history of severe rejection, although some vascular abnormalities were histologically found. On the contrary, research has revealed that the bile duct epithelium has a very high density of ACE2 receptor expression [29]. This contradictory fact further proves that the liver injury mechanism during SARS-CoV-2 infection, whether the biliary system is involved or not, is still unclear. What we know so far in severe COVID-19, liver collapse may result from immune-mediated processes and hypotension, including cytokine storm. This process will be enhanced if the patients have prior chronic liver diseases, like hepatitis B, alcohol-induced hepatitis, and primary biliary cholangitis, may raise the possibility of liver damage when infected with SARS-CoV-2; therefore, liver enzymes and bilirubin levels should be carefully monitored [27, 28].

Heart

Although COVID-19 is believed to largely impact the lungs, it is becoming more well acknowledged that it affects other organs, including the heart [12]. Myocardial damage was common in COVID-19 patients admitted to an ICU [30-32]. A meta-analysis of 1,527 COVID-19 patients revealed that the prevalence of hypertension and heart disease as pre-existing conditions was 17.1% and 16.4%, respectively, and that these patients were more probable to suffer from serious conditions that required ICU treatment [33]. However, it is generally acknowledged that COVID-19 can potentially negatively impact cardiovascular health, resulting in or exacerbating heart damage, even in those who do not currently have a recognized cardiovascular illness [34]. Therefore, post-mortem studies on the heart may help improve our understanding on the disease. Most of the pathological findings in our study suggested the presence of interstitial edema, myocardial hypertrophy, interstitial infiltration of mononuclear cells, myocardial fibrosis, and thrombosis, without any evidence of AMI. However, only one patient had each lymphocytic myocarditis and endothelialitis. Our findings corresponded to the pathological findings in the previous studies, indicating that the most common patterns were interstitial edema [30, 35], right ventricular hypertrophy and dilation [15, 36, 37], mild interstitial mononuclear cells infiltration and lymphocytic myocarditis [19, 38], and lymphocytic endothelialitis [39]. In our study, myocardial fibrosis was found in 17 cases (41.46%). It may be brought on by a variety of acute or chronic processes, such as the activation of cardiac fibroblasts by several cytokines, and was documented in almost 25% of patients [40-42]. A number of documented comorbidities and aging were also closely linked to cardiac fibrosis. Interpreting the cardiac specimens, however, was challenging and contingent on several circumstances, which might indicate a de novo sub-acute or chronic condition [42]. Even with encouraging results, caution should be exercised in their interpretation since non-specific cardiac histopathological abnormalities may possibly be consistent with the patients' underlying heart conditions rather than COVID-19 [3, 21].

Even though one of the most common COVID-19-associated cardiovascular complications was AMI [43], no patients in our study had AMI. This finding was similar to the previous studies, demonstrating a reduction in AMI hospitalized patients [4] and stroke [44] while the epidemic was only being started. Many researches from the United States [45], Europe [46], and Hong Kong [8] have documented notable decreases ln AMI hospitalization and cardiology laboratory activation percentages since the start of the coronavirus epidemic in December 2019. Social constraints, a rise in telemedicine to stop serious illnesses from getting severe and necessitating hospital stays, and concerns about catching SARS-CoV-2 while in the hospital have all been blamed for these decreases [8, 46]. Conversely, in other research, there is a higher prevalence of AMI just after stressful events like earthquakes or terrorist acts [47, 48]. Either a genuine decline in the overall frequency of cardiovascular events as a result of lifestyle modifications made during the lockdown or a delay in seeking medical attention because of physical distance and fear of infection might account for this contradiction [49].

Limitations

Despite of those result, our research nonetheless contained significant restrictions. First, the population of present research was dominated by male approximately more than 50%; therefore, almost all of the histopathological findings were also male-dominant and should be interpreted carefully. Second, the post-mortem specimens were taken with the guidance of plain radiographs or X-rays, which might affect the precision of the sampling location. Furthermore, this sampling method and the histopathological interpretations might be influenced by the operator's experiences.

Conclusion

In severe COVID-19 infection, histopathological abnormalities existed in multiple organs, such as the lungs and other organs, including the liver and heart as investigated in our study. We found that the most histopathological abnormalities in the lung, liver, and heart were interstitial and/or intra-alveolar inflammatory infiltrate, mild to moderate lobular and portal inflammation, and interstitial edema and myocardial hypertrophy, respectively. Based on our findings, we suggested

that the lung, liver, and cardiac markers should be evaluated carefully during severe COVID_19 infection in order to search for any dysfunctions in those organs and to prevent further clinical deterioration.

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Conflict of interest: None

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Ethics statement: The study was approved by ethics committee of Health Research of Dr. Soetomo General Hospital Surabaya (code: 0022/KEPK/VII/2020, 6th July 2021).

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