Comorbidities and autopsy findings of COVID-19 deaths and their association with time to death: a systematic review and meta-analysis.

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Word Count: 5167

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Objective: Examination of postmortem findings can help establish effective therapeutic strategies to reduce mortality. The aim of this study was therefore to review complete autopsy cases and their postmortem findings and comorbidities associated with death caused by COVID-19, in order to establish a profile of the deceased and the likelihood of time to death. Methods: A systematic review was carried out following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and meets Cochrane criteria recommendations (PROSPERO registration number CRD 42020209649). An electronic search in the databases Pubmed, Scopus, Web of Science, Wiley Online Library and Scientific Electronic Library Online (SciELO) was performed. Results: The search strategy yielded a total of 25 articles where 140 cases of complete autopsies were reported. The most prevalent comorbidity was vascular diseases. Patients with vascular disease, heart disease and diabetes died significantly in a shorter period of time. Autopsies mainly focused on the lungs. The proliferative phase of Diffuse Alveolar Damage (DAD) was the most reported in the microscopic postmortem findings, and these patients died in a shorter period of time. However, individuals aged over eighty years significantly presented fibrotic phase of DAD at the time of death. The kidney was the second most affected organ with thrombosis and tubular damage, followed by the liver with congestion and necrosis. Conclusion: Given that accurate information of complete autopsies findings is still scarce, it is necessary to perform complete autopsies by examining organs other than the lungs in order to provide information to improve new treatment strategies in patients with a high risk of mortality.

Keywords: COVID-19; SARS-CoV-2; autopsy; comorbidities, mortality, forensic medicine.

Introduction

COVID-19 was the third leading cause of death for most of 2020 and the first months of 2021. With the rapid adoption of vaccines, deaths from COVID-19 have been drastically reduced in developed countries. However, with the more infectious Delta and Omicron variants of COVID-19 and insufficient vaccination rates in some areas of the world, COVID-19 cases, hospitalisations and deaths are on the rise again. Moreover, the new variant Omicron, first identified in Botswana and South Africa, is spreading rapidly around the world, often in settings where the Delta variant was dominant. This may compromise vaccine effectiveness and lead to reinfections [1].

The virus has caused over 413 million infected cases and over 5.83 million confirmed deaths to date. Mortality linked to COVID-19 seems to be associated with underlying conditions such as obesity, heart and vascular diseases, diabetes, advancing age and chronic lung diseases [2–5]. Coronary heart disease is associated with a poor prognosis for COVID-19, with higher mortality and a higher likelihood of admission to the Intensive Care Unit (ICU). In addition, it has been observed that the association between coronary heart disease and poor prognosis of COVID-19 is influenced by hypertension [6]. Moreover, individuals with diabetes mellitus and severe obesity are more likely to be infected with and die from COVID-19 [7]. Based on experience with other respiratory viruses, a higher proportion of hospitalised patients with lung diseases could be expected [8]. However, studies conducted in China, Italy and Spain show that cases of COVID-19 of patients with asthma and chronic obstructive pulmonary disease were below expectations [9–12]. In contrast, its frequency is much higher in the New York area and the United Kingdom [3,13]. The discrepancy between these studies is of great interest in the scientific community and has not yet been resolved. Trained immunity and vaccines based on trained immunity may explain these discrepancies

between countries. In this regard, it has been shown that the number of cases and deaths per population during the COVID-19 pandemic appears to be lower in countries with Bacille Calmette-Guerin (BCG) vaccination programmes than in those without, which could be attributed to the possible effects of trained immunity induced by BCG vaccination [14,15]. However, further research and clinical trials are needed to demonstrate whether new vaccines based on trained immunity could represent a suitable strategy for the prevention and treatment of SARS-CoV-2 infection [16].

Some studies have shown that male patients with COVID-19 were associated with significantly increased risk of mortality compared to female patients [17,18]. Likewise, other studies have found that patients older than 50 years had a higher likelihood of mortality in cases confirmed by COVID-19 [12,17,19]. However, there is still no consensus, meaning the associated risk factors need more in-depth study, as a patient suffering from these underlying diseases can suffer a fatal outcome.

The autopsy and its findings determine the cause of death, allow us to know the physiopathology of death, and can help establish effective therapeutic strategies to reduce mortality. Autopsies can instruct us about the disease, its prevention and the treatment received, and optimise clinical management [20]. They can also provide information on the spread of the virus through the body, the involvement of systems and organs, or the late effects of the disease [21]. Autopsies should therefore be a key element in understanding this phenomenon. However, autopsies are not being carried out and the autopsy findings and comorbidities associated with COVID-19 are not being sufficiently studied.

The aim of this systematic review was threefold: (1) to identify complete autopsy cases of SARS-CoV-2 deceased, (2) to identify their comorbidities and

postmortem findings, and (3) to establish a profile of COVID-19 deceased and the likelihood of time to death

Material and Methods

This systematic review was carried out following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22], and meets Cochrane criteria. The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD 42020209649).

Search strategy and selection criteria

Bibliographic searches were performed in the databases Pubmed, Scopus, Web of Science, Wiley Online Library and Scientific Electronic Library Online (SciELO) to identify studies available up to August 2020. The search terms were: "coronavirus disease" OR "COVID-19" OR "SARS-coV-2" AND "autopsy" OR “biopsy "OR "forensic biopsy" OR “pathological findings" OR "postmortem findings". All studies on autopsies in patients who died due to COVID-19 were included. In order to collect all autopsy cases with COVID-19, studies with individuals who were SARS-CoV-2 positive but the cause of death was not a consequence of it were also included. We did not apply language restrictions in the search or in the selection process. Exclusion criteria were: biopsies in animals, in vivo biopsies, biopsies in death, partial or minimal invasive autopsies, COVID-19 autopsy guidelines or COVID-19 diagnostic test protocols.

Quality assessment

Studies with incomplete descriptions, duplicate cases, incidental diagnosis of COVID-19 during autopsies or polymerase chain reaction (PCR) sampling protocols in COVID-19 autopsies were excluded.

Data extraction

Two reviewers (JMM and LR) independently reviewed the titles and abstracts identified in the search and retrieved articles to determine eligibility and to extract study data. Disagreements around eligibility between both authors were resolved by consensus after reading the full text together. If the discrepancy was not resolved, a third reviewer (SMH) decided whether to proceed with inclusion.

For each eligible study, we retrieved information based on the following categories: age, body mass index (BMI), comorbidities, symptoms, hospitalisation time, ICU time, organ COVID-19 diagnostic test, cause of death, postmortem interval and autopsy findings.

Statistical analysis

GraphPad Prism 7.05 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Kappa index was performed to assess the degree of concordance in the inclusion and exclusion of studies based on two reviewers (JMM and LORL). A descriptive analysis based on percentages was performed on the autopsy findings found. All data are represented as the mean ± standard deviation (SD). Groups were compared using the Student's t-test or one-way ANOVA and Bonferroni post hoc test for multiple comparisons ($p < 0.05$ was considered significant) when appropriate. To obtain model and Pearson-r correlation analysis, only the cases where age and BMI were defined

were chosen. Mortality curves (likelihood of death) were developed to analyse time of hospitalisation until death, comorbidities and autopsy findings, and a Chi-square analysis was carried out.

Results

Figure 1 shows the flowchart process applied in the systematic review. The search strategy yielded 1282 articles. After removing duplicate items, 1034 were reviewed titles and abstracts. 958 articles were discarded following exclusion criteria. The remaining 76 were potentially eligible full-text articles for this study (Figure 1). Concordance between reviewers was 84.2% (κ= 0.64, 95% CI 0.45-0.82, $p<0.05$), corresponding to "good concordance" [23]. Applying the quality assessment yields an exclusion of 51 studies (Figure 1). A total of 25 articles were included for qualitative and quantitative synthesis in the present study. One hundred and forty cases were reported (92 men and 48 women) (Table 1).

Figure 1. Flow diagram for the systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Guidelines).

Table 1. Summary of articles identified in the systematic literature review.

Mean age was 70.7 ± 14.7 years, ranging from 27 to 96 years. Female mean age was 72 ± 15.4 years (ranged 31 to 94 years), and male mean age was 70 ± 14.3 years, (ranged 27 to 96 years). No significant differences were found between men and women ($p=0.544$)

The BMI was categorised according to the World Health Organization (WHO) indices as underweight (<18.5), normal (18.5-24.9), pre-obese (25.0 - 29.9), obesity class 1 (30.0 - 34.9), obesity class 2 (35.0 - 39.9), and obesity class 3 (≥40). BMI was reported in 66 cases (45 men and 21 women). The mean BMI was 31.9 ± 9, ranging from 15.4 to 61.5. Male mean BMI was 31.9 ± 8.6, ranging from 20.7 to 59 and female mean BMI was 31.8 ± 10, ranging from 15.4 to 61.5. There were no significant differences between genders (p=0.756).

The symptoms were reported in 90 cases. The most common symptoms were: fever (67.7%), dyspnoea (61.1%), cough (54.4%), weakness (25.5%), and digestive symptoms (15.5%).

Time of hospitalisation was reported in 103 cases, the mean being 12.2±12.8 days (ranging from 1 to 71 days). Time on mechanical ventilation was reported in 25 cases (mean= 5.7±6.6 days; ranging from 1 to 45 days) and time of stay in ICU in 7 cases (mean=12.45±12.79 days, ranging from 4 hours to 35 days).

Comorbidity was reported in 114 cases (77 men and 37 women). The most prevalent comorbidity in men and women was vascular diseases (59.6%), followed by heart disease (42.9%) (especially high arterial blood pressure), diabetes (38.5%) and respiratory diseases (27.1%) (emphysema and chronic obstructive pulmonary diseases) (Table 2). Prevalence of comorbidities by gender is shown in Table 2. No statistically significant differences were found between genders.

Table 2. Prevalence of comorbidities of COVID-19 deceased by gender.

Mortality curves showed different behaviour between comorbidities. Patients with vascular or heart diseases or diabetes significantly died in a shorter time ($p<0.0001$) compared to those without these diseases (Figure 2).

Figure 2. Likelihood of death and comorbidities.

Autopsy findings

One hundred and ten cases reported the sample organ to COVID-19 PCR test. The most sampled organ was lungs (78.2%), followed by heart (50%) and brain (45.5%).

Postmortem interval was reported in 40 cases. The mean was 2.7 ± 2.5 days, ranging from 1 hour to 41 days. The cause of death reported was COVID-19 except in 5 cases, in which the death was with SARS-CoV-2 but not as a consequence of it.

The macroscopic and microscopic autopsy findings were reported in 140 cases, mainly focused on the lungs. The macroscopic finding most reported in the lung was general damage (81.4%), followed by oedema, congestion and patchy areas of condensation (Table 3). Lung combined weight was reported in 32 cases, mostly between 1000-2000 grams (26 cases) (Table 3).

Table 3. Macroscopic and microscopic lung autopsy findings of Covid-19 deceased.

The main microscopic pathological finding of the lung was Diffuse Alveolar Damage (DAD) in its different phases. The proliferative phase was the most reported among autopsy findings (48.5%), followed by exudative (31.4%) and fibrotic phases (14.2%). Bronchopneumonia and pneumonia were also reported in a high percentage

(46.4 and 25%, respectively), followed by thrombosis in the lung parenchyma (14.2%) (Table 3).

We found that individuals with no pulmonary thrombosis died in a shorter time ($p=0.0142$) (Figure 3).

Figure 3. Likelihood of death with no pulmonary thrombosis vs. pulmonary thrombosis.

A more in-depth statistical analysis of the DAD phases showed that older individuals significantly presented fibrotic phase of DAD at the time of death compared to the other DAD phases ($p <0.01$) (Figure 4A). In addition, individuals that experienced more days of hospitalisation significantly presented proliferative and fibrotic DAD phases ($p=0.0064$) in the autopsies (Figure 4B).

Figure 4. Age and days of hospitalisation (at the time of death of the patients). 4A: DAD phases and age (in years). 4B: DAD phases and days of hospitalisation until death. ## $p < 0.01$ vs. Fibrotic phase, ** $p < 0.01$ vs. Exudative phase.

The study of mortality curves showed that individuals with proliferative phase significantly died in a shorter time ($p=0.016$) (Figure 5).

Figure 5. Likelihood of death with exudative, proliferative, or fibrotic phase.

Macroscopic and microscopic findings in other organs different from lungs showed that the kidney was the most affected organ, especially with thrombosis and tubular damage, followed by the liver with congestion and necrosis (Table 4).

Table 4. Macroscopic and microscopic autopsy findings in other organs other than lungs of Covid-19 deceased.

Discussion

In this systematic review, we have analysed 140 complete autopsy cases, their findings (both macroscopic and microscopic) and comorbidities associated with death caused by infection with the SARS-CoV-2 virus, in order to establish a profile of the deceased by COVID-19 and the likelihood of time to death. To date, few research studies have shown results of complete autopsy findings performed on patients who died from SARS-CoV-2 [49].

In line with other research work [50,51], we also found that the deceased were mostly men, with a ratio of 92 compared to 48 women. Moreover, we observed that the mean age of the subjects was 70.7 years, in accordance with studies that affirm that there is a greater risk of death after 60 years of age [5,52].

Given the related mortality of COVID-19, it is important to identify the profile of vulnerable patients that are more likely to die. In our systematic review, we identified that vascular disease, heart disease and diabetes are the most prevalent comorbidities, followed by respiratory and kidney diseases. Several studies have analysed the presence of comorbidities and risk factors in patients with COVID-19. In this sense, most of the deceased had pre-existing health conditions such as diabetes and cardiovascular

diseases [53–56]. Other studies have also associated chronic kidney disease and chronic lung diseases with an excessive risk of mortality [57,58]. As a novelty, our results show that patients with vascular or heart diseases or diabetes significantly died in a shorter period of time.

Obesity is also considered a risk factor to be infected with and die from COVID-19. It might be caused by the underlying inflammation in obese subjects, but the exact mechanisms underlying are not fully elucidated [2,59]. In this study, BMI was reported in 66 cases, most of them were categorised as obesity classes 1 and 2 (< 40 kg/m2) and, in contrast, no significant differences between BMI and likelihood of death were found (p=0.5468). It seems that severe obesity with BMI ≥ 40 kg/m2 is the one that apparently shows a higher risk of complications and death from COVID-19 [7].

The majority of the autopsies described deep lung damage. From our results, patients who died from COVID-19 mostly presented the proliferative phase of DAD in the lungs. Those patients significantly experienced a shorter time to death. On the other hand, fibrotic phase was the least observed, probably due to the short duration of the disease [60]. However, patients older than 80 years are more likely to present fibrotic phase of DAD in the lung examination versus the youngest patients who showed exudative and proliferative phases. Thrombotic complications are also frequent in COVID-19 and contribute significantly to mortality [61]. In our study, we found thrombosis in lungs and kidneys, showing that individuals with no pulmonary thrombosis in the autopsy examination died in a shorter time. Despite the few complete autopsies performed during the pandemic, some studies have observed frequent macrovascular and microvascular fibrinous thrombi in the lungs and occasionally within other organs [34,61,62].

SARS-CoV-2 infection causes multisystem disease and significant pathology in most organs in patients with and without comorbidities [63]. In this systematic review, the kidney was the second most affected organ in the autopsies, in particular presenting thrombosis and tubular damage. Indeed, acute kidney injury (AKI) has been associated with COVID-19 with a reported prevalence of up to 46% [64], although it is still not clearly known how SARS-CoV-2 damages the kidney. In general, data on macroscopic and histopathological changes in organs other than the lungs are still scarce.

One limitation of this study is that the publications on COVID-19 have increased in a short time, so others have been published while analysing these articles. However, the number of cases that have been analysed support the results obtained. The lack of standardisation among studies may also be a limitation to extract data not only in our research but also in any future studies. In this sense, an international postmortem protocol tool is crucial to ensure the consistency of data extraction of autopsy findings to assist health care programmes.

We have followed the quality criteria for reviews, the PRISMA recommendations and Cochrane criteria to identify the major findings at autopsy from patients diagnosed with SARS-CoV-2. Moreover, only cases of complete autopsy have been analysed in this study in order to improve the data comparisons. As far as we know, it is the only study that associates autopsy findings with comorbidities and mortality through mortality curves.

Conclusion

A profile of the deceased by COVID-19 was established through analysis of 140 cases of complete autopsies. The lung was the organ most affected and examined in the autopsies. In the lung examination, the patients who died from COVID-19 mostly

presented the proliferative phase of DAD and experienced a shorter time to death, although fibrotic phase was more frequent in patients older than 80 years. The kidney was the second most affected organ, presenting thrombosis and tubular damage. The comorbidities most prevalent were vascular disease, heart disease and diabetes and patients suffering these conditions died in a shorter period of time. Most of the individuals were categorised as obesity classes 1 and 2, and no significant association was found between BMI and time to death. This systematic review highlights the need to provide information from postmortem complete autopsies and comorbidities associated with death caused by infection with the SARS-CoV-2 virus, in order to improve new treatment strategies in patients with a high risk of mortality. Further complete autopsies including macroscopic and microscopic findings in the lungs and other organs are recommended to better elucidate the pathophysiology of SARS-CoV-2 infection in order to reduce mortality.

Declaration of Funding

No funding was available for this research.

Author Contribution

J.M.M: conception and design, interpretation data, drafting the paper, revising critically and final approval.

F.M.C: conception and design, interpretation data, revising critically and final approval.

J.S: conception and design, drafting the paper, revising critically and final approval.

L.R: conception and design, interpretation data, drafting the paper, revising critically and final approval.

S.M.D.L.H: conception and design, drafting the paper, revising critically and final approval.

Statement of Ethics

This study is exempt from Ethical Committee approval since it is a systematic review and meta-analysis.

Conflict of Interest:

None

References

[1] Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature. 2021; 1-11. DOI: 10.1038/s41586-021-04387-1

[2] Banerjee M, Gupta S, Sharma P, et al. Obesity and COVID-19: A Fatal Alliance. Indian J Clin Biochem. 2020;35(4):1–8.

[3] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323:2052–2059.

[4] Sidhu G, Samson R, Nedunchezian SH, et al. COVID 19 in-hospital mortality, body mass index and obesity related conditions. J Diabetes Complications. 2021;35(12):108054.

[5] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.

[6] Liang C, Zhang W, Li S, et al. Coronary heart disease and COVID-19: A meta-analysis. Med Clin (Barc). 2021;156:547–554.

[7] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318:E736–E741.

[8] Jha A, Dunning J, Tunstall T, et al. Patterns of systemic and local inflammation in patients with asthma hospitalised with influenza. Eur Respir J. 2019;54:1900949.

[9] Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201:1380–1388.

[10] García-Pachón E, Zamora-Molina L, Soler-Sempere MJ, et al. Asthma and COPD in Hospitalized COVID-19 Patients. Arch Bronconeumol (Engl Ed). 2020;56:604–606.

[11] Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–95.

[12] Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730–1741.

[13] Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.

[14] Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? Allergy. 2020;75:1815–1819.

[15] Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination affecting the spread and severity of COVID-19? Allergy. 2020;75:1824–1827.

[16] Sokolowska M, Lukasik ZM, Agache I, et al. Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives-A report of the European Academy of Allergy and Clinical Immunology (EAACI). Allergy. 2020;75:2445–2476.

[17] Biswas M, Rahaman S, Biswas TK, et al. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. Intervirology. 2020;9: 1-12.

[18] Posso M, Comas M, Román M, et al. Comorbidities and Mortality in Patients With COVID-19 Aged 60 Years and Older in a University Hospital in Spain. Arch Bronconeumol. 2020;56:756–758.

[19] Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81:e16–e25.

[20] Pomara C, Li Volti G, Cappello F. COVID-19 Deaths: Are We Sure It Is Pneumonia? Please, Autopsy, Autopsy, Autopsy! J Clin Med. 2020;9(5):1259.

[21] Sperhake J-P. Autopsies of COVID-19 deceased? Absolutely! Leg Med (Tokyo). 2020;47:101769.

[22] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–784.

[23] Abraira V, Vargas AP de. Generalization of the kappa coefficient for ordinal categorical data, multiple observers and incomplete designs. Qüestiió: quaderns d'estadística i investigació operativa. 1999;23(3):561–571.

[24] Adachi T, Chong J-M, Nakajima N, et al. Clinicopathologic and Immunohistochemical Findings from Autopsy of Patient with COVID-19, Japan. Emerging Infect Dis. 2020;26:2157–2161.

[25] Aguiar D, Lobrinus JA, Schibler M, et al. Inside the lungs of COVID-19 disease. Int J Legal Med. 2020;134:1271–1274.

[26] Barton LM, Duval EJ, Stroberg E, et al. COVID-19 Autopsies, Oklahoma, USA. Am J Clin Pathol. 2020;153:725–733.

[27] Beigmohammadi MT, Jahanbin B, Safaei M, et al. Pathological Findings of Postmortem Biopsies From Lung, Heart, and Liver of 7 Deceased COVID-19 Patients. Int J Surg Pathol. 2021;29(2):135–145.

[28] Bösmüller H, Traxler S, Bitzer M, et al. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch. 2020;477:(3)349–357.

[29] Buja LM, Wolf DA, Zhao B, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol. 2020;48:107233.

[30] Ducloyer M, Gaborit B, Toquet C, et al. Complete post-mortem data in a fatal case of COVID-19: clinical, radiological and pathological correlations. Int J Legal Med. 2020;134(6):2209–2214.

[31] Fitzek A, Sperhake J, Edler C, et al. Evidence for systematic autopsies in COVID-19 positive deceased. Rechtsmedizin (Berl). 2020;30(3):184–189.

[32] Grosse C, Grosse A, Salzer HJF, et al. Analysis of cardiopulmonary findings in COVID-19 fatalities: High incidence of pulmonary artery thrombi and acute suppurative bronchopneumonia. Cardiovascular Pathology. 2020;49:107263.

[33] Konopka KE, Nguyen T, Jentzen JM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD. Histopathology. 2020;77(4):570–578.

[34] Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology. 2020;77(2):198–209.

[35] Navarro Conde P, Alemany Monraval P, Medina Medina C, et al. Autopsy findings from the first known death from Severe Acute Respiratory Syndrome SARS-CoV-2 in Spain. Rev Esp Patol. 2020;53:188–192.

[36] Okudela K, Hayashi H, Yoshimura Y, et al. A Japanese case of COVID-19: An autopsy report. Pathology International. 202;70(10):820–824.

[37] Oprinca G-C, Muja L-A. Postmortem examination of three SARS-CoV-2-positive autopsies including histopathologic and immunohistochemical analysis. Int J Legal Med. 2021;135:329–339.

[38] Hospital Universitario Ramón y Cajal. The first COVID-19 autopsy in Spain performed during the early stages of the pandemic. Rev Esp Patol. 2020;53:182–187.

[39] Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. EClinicalMedicine. 2020;24:100434.

[40] Remmelink M, De Mendonça R, D'Haene N, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Crit Care. 2020;24:495.

[41] Santana MF, Pivoto G, Alexandre MAA, et al. Confirmed Invasive Pulmonary Aspergillosis and COVID-19: the value of postmortem findings to support antemortem management. Rev Soc Bras Med Trop. 2020;53:e20200401.

[42] Skok K, Stelzl E, Trauner M, et al. Post-mortem viral dynamics and tropism in COVID-19 patients in correlation with organ damage. Virchows Arch. 2020;478(2):343–353.

[43] Stone JR, Tran KM, Conklin J, et al. Case 23-2020: A 76-Year-Old Woman Who Died from Covid-19. N Engl J Med. 2020;383:380–387.

[44] Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol. 2020;33:1007–1014.

[45] Tombolini A, Scendoni R. SARS-CoV-2-related deaths in routine forensic autopsy practice: histopathological patterns. Int J Legal Med. 2020;134:2205–2208.

[46] Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020;173:268–277.

[47] Yan L, Mir M, Sanchez P, et al. COVID-19 in a Hispanic Woman. Arch Pathol Lab Med. 2020;144:1041–1047.

[48] Youd E, Moore L. COVID-19 autopsy in people who died in community settings: the first series. J Clin Pathol. 2020;73:840–844.

[49] Barth RF, Xu X, Buja LM. A Call to Action: The Need for Autopsies to Determine the Full Extent of Organ Involvement Associated With COVID-19. Chest. 2020;158:43–44.

[50] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–513.

[51] Li L-Q, Huang T, Wang Y-Q, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92:577–583.

[52] Shahid Z, Kalayanamitra R, McClafferty B, et al. COVID-19 and Older Adults: What We Know. J Am Geriatr Soc. 2020;68:926–929.

[53] Fitzek A, Schädler J, Dietz E, et al. Prospective postmortem evaluation of 735 consecutive SARS-CoV-2-associated death cases. Sci Rep. 2021;11:19342.

[54] Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

[55] Guan W-J, Liang W-H, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547.

[56] Sun K, Chen J, Viboud C. Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. Lancet Digit Health. 2020;2:e201–e208.

[57] Lana RM, Freitas LP, Codeço CT, et al. Identification of priority groups for COVID-19 vaccination in Brazil. Cad Saude Publica. 2021;37:e00049821.

[58] Marques F, Gameiro J, Oliveira J, et al. Acute Kidney Disease and Mortality in Acute Kidney Injury Patients with COVID-19. J Clin Med. 2021;10:4599.

[59] Soeroto AY, Soetedjo NN, Purwiga A, et al. Effect of increased BMI and obesity on the outcome of COVID-19 adult patients: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14:1897–1904.

[60] Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135–1140.

[61] Hanff TC, Mohareb AM, Giri J, et al. Thrombosis in COVID-19. Am J Hematol. 2020;95:1578–1589.

[62] Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1–13.

[63] Falasca L, Nardacci R, Colombo D, et al. Postmortem Findings in Italian Patients With COVID-19: A Descriptive Full Autopsy Study of Cases With and Without Comorbidities. J Infect Dis. 2020;222:1807–1815.

[64] Farouk SS, Fiaccadori E, Cravedi P, et al. COVID-19 and the kidney: what we think we know so far and what we don't. J Nephrol. 2020;33:1213–1218.