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The main causes of death in patients with COVID-19

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Abstract. – By March 21, 2022, 6.1 million deaths from COVID-19 were reported, most of them in the United States, Brazil, and India. Between January 1, 2020, and December 31, 2021, the global estimated mortality due to the COVID-19 pandemic was 120.3 deaths (113.1–129.3) per 100,000 of the population for all ages. So far many of the potentially fatal mechanisms of COVID-19 have been reported. In this manuscript, we analyzed the available data on the causes of deaths from COVID-19. This analysis suggests that the primary attributable cause of death from COVID-19 is multiple organ failure resulting from numerous pathological mechanisms including genetic predisposition to the severe inflammatory response. Increased inflammatory response affects the lungs locally as well as systemic thrombotic microangiopathy. It seems that many comorbidities associated with an increased mortality rate among patients with COVID-19 per se predispose them to an increased risk of thrombotic changes. Furthermore, the role of inflammation in the lungs and the changes that lead to hypoxia cannot be overlooked. However, the thrombotic changes in microcirculation seem to be the most dominant.

Key Words:
Cause of death, COVID-19 pandemic, Mortality, SARS-CoV-2 infection.

Introduction

The first case of a novel coronavirus infection leading to the respiratory failure was reported in Wuhan in December 2019, and this disease was named Coronavirus disease 2019 (COVID-19)[1,2]. By March 21, 2022, 6.1 million deaths from COVID-19 were reported[3], most of them in the United States, Brazil, and India. Between January 1, 2020, and December 31, 2021, the global estimated mortality due to the COVID-19 pandemic was 120.3 deaths (113.1-129.3) per 100,000 population for all ages. The rate differs significantly between countries, as indicated by the highest rate among Bolivian residents [734.9 deaths (95% UI 594.1-879.2)] per 100,000 population. However, it is believed that the full scale of the COVID-19 pandemic in 2020 and 2021 was much greater than indicated by reported[4] deaths. An additional problem is a fact that 22-25% of excess all-cause mortality during the pandemic by September 2020 in the United States was due to an unknown cause. It seems that psychiatric or injurious causes are the frequent causes because the onset of unexplained mortality coincided with previously reported[5] increases in psychotropic drug use. The World Health Organization (WHO) recommended coding COVID-19 as a cause of death independent of pre-existing conditions that are suspected of triggering a severe course of COVID-19 and that COVID-19 deaths should not be considered as due to anything else[6]. However, it should be noted that the number of deaths due to COVID-19 is difficult to determine due to the ambiguous reporting in different countries, the choice of a cause of death in reports, and the coexistence of myriad events and comorbidities[7]. Data[8] from 14 countries on COVID-19 deaths indicate an age-related relationship between deaths and that age dependency is stronger for COVID-19 mortality than for all-cause mortality.

We aimed to summarize the current reports on deaths during severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection and its possible causes.

Autopsies and Pathomorphological Reports at the Initial Stage of the Pandemic

The first series of autopsies of the first 12 consecutive COVID-19-positive deceased patients

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[median age 73 years (range between 52 and 87 years), 75% male] were performed at the German Academic Medical Center, including postmortem computed tomography (CT), and histopathologic and virologic analysis which showed deep venous thrombosis in more than half of patients (58%), and pulmonary embolism in 33% of patients as a direct cause of death. Thus, it has been suggested[9] that thromboembolic events may play an important role in the pathogenesis of COVID-19-related deaths.

Another German study[10] describing autopsies of 26 bodies of patients [median age 70 years (IQR 61.8-78.3, range 30-92 years), 65% male] who died during SARS-CoV-2 infection showed that the majority of the causes of death were directly related to COVID-19 and not a direct result of the presence of comorbidities. The most common mechanisms of death were septic shock and/or multiple organ failure (30.8%) and purulent pneumonia (19.2%) with subsequent respiratory failure, and COVID-19-related right ventricular failure[10]. Similar results were reported in another study[11] from Germany describing 80 autopsies [median age 82.4 years (range 52-96 years), 62% male]. This study has shown that the main cause of death was pneumonia, with or without sepsis. Furthermore, in 40% of patients (46% male and 32% female) thromboembolic events were reported. Moreover, 21% of fatal fulminant and/or peripheral pulmonary artery embolism was found. Whereas different German reports[12] described 735 autopsies of patients with SARS-CoV-2 associated deaths using conventional autopsy, ultrasound-guided minimally invasive autopsy, postmortem computed tomography, and medical records. 84.1% of deaths were classified as COVID-19 deaths [median age 83.0 years; 54.4% male], 6.4% as non-COVID-19 deaths, and 9.5% remained unclear. In the autopsy group (n=283), 73.6% died of pneumonia and/or diffuse alveolar damage (DAD), 39.2% of thromboses, and 22.1% of pulmonary embolisms were found. Similar results[13] were reported in a report from Russia including 102 consecutive forensic (58.8%) and clinical (41.2%) autopsies with positive post-mortem SARS-CoV-2 PCR in the lungs (mean age 73 years, 50% male). Based on medical records and histological reports of 71% of cases of clinical and 83% of forensic autopsies, the cause of death was DAD and 81% had thrombotic phenomena in the lungs. DAD is the histological sign of the acute phase of acute respiratory distress syndrome (ARDS) and consists of oedema, inflammation, and hyaline membranes, with the second, organizing phase comprising type II pneumocyte hyperplasia and fibrosis[14]. It has been shown[15] that DAD during COVID-19 is similar to the development of ARDS with other causes.

The above data confirmed the results of a recently published systematic review and meta-analysis[16] of 25 articles that described 140 complete autopsies and showed that the most affected organ during SARS-CoV-2 infection was the lungs. In 81.4% of cases the macroscopic pathological findings such as oedema, congestion, and patchy areas of condensation, in 48.5% of postmortem cases, microscopic examination of DAD in the different phases (48.5% proliferative phase, 31.4% exudative phase, 14.2% fibrotic phase), in 46.4% bronchopneumonia, in 25% pneumonia and 14.2% thrombosis in the lung parenchyma were found. In addition, a significant positive association between the proliferative phase of DAD and the short period of death was observed. The second most affected organ was the kidney including thrombosis (10%), tubular damage (7.8%), necrosis (7.8%), and glomerular damage (9.4%); then the liver including congestion (15%), necrosis (10.7%), and acute inflammation (7.1%), followed by heart necrosis (4.2%), myocarditis (1.2%), and spleen damage [congestion (4.2%) and acute splenitis (1.4%)][16]. In addition, comprehensive data[17] from 135 deceased patients showed a high prevalence of DAD in autopsy findings (75% acute and 47% organizing). It should be noted that Konopka et al[15] assessed the utility of a Center for Disease Control and Prevention (CDC) guidelines-based Coronavirus disease 2019 (COVID-19) screening checklist for postmortem severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surveillance and revealed that DAD in autopsy studies is underestimated[15].

Mukerji et al[18] analyzed data reporting brain findings at the autopsy of patients who died due to COVID-19 (n=142) and showed that 65% of them reported either no significant findings or no acute abnormalities. While in 35% multiple changes were described, the most common hemorrhage (petechial bleedings and punctate subarachnoid hemorrhages, large cerebral/cerebellar hemorrhages, hemorrhagic conversion of middle cerebral artery stroke, and a recently drained subdural hematoma), was followed by large acute and/or subacute, lacunar infarcts/microinfarcts and watershed infarcts, severe oedema resulting in herniation and mild to moderate oedema without

herniation. Whereas, in microscopic findings, the most frequent abnormality was mild to moderate acute hypoxic injury, followed by focal microhemorrhage or hemorrhagic suffusion. Additionally, mild focal perivascular, parenchymal, and leptomeningeal T-cell predominant lymphocytic infiltrates were often observed.

Interestingly, myocarditis was rarely observed in most of the studies[17,19-21]. In the multi-center study[17], myocarditis was present only in 6% of the deceased and 1/4 of adolescents presented the multisystem inflammatory syndrome. Most pathological findings in the heart such as hypertrophy were reported in 77% of patients, fibrosis and/or old infarction in 58%, and coronary artery disease in 25% and were mainly sequelae of preexisting comorbidities[17]. The rare occurrence of myocarditis was also reported in meta-analyses[19-21].

Infection-Related Mechanisms of Death

Severe COVID-19 immunopathology is related to overactivated inflammatory, innate immune response, and impaired protective, adaptive immune response. SARS-CoV-2 enters the host cells by the angiotensin-converting enzyme 2 (ACE2) receptor. The innate immune system response is related to the detection of the virus by pattern recognition receptors and the identification of molecular patterns. It activates the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase pathways, the production of inflammatory cytokines, and the expression of type 1 interferon (IFN). It is considered[22] that SARS-CoV-2, like severe acute respiratory syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome Coronavirus, interfere with these signaling pathways, which correlates with the severity of infection.

Life-threatening COVID-19 pneumonia may be a result of a deficiency of regulatory factor 7 (IRF7) or autosomal-recessive IRF7 or IFN-α/β subunit 1 receptor. In addition, in 10% of patients with critical COVID-19, immunoglobulin G autoantibodies (auto-Abs) neutralizing high amounts of IFN-α 2 and IFN-Ω were found. Interestingly, it has also been shown[23] that in the patients with autoimmune polyglandular syndrome type-1, infected with SARS-CoV-2, the presence of auto-Abs against IFN was associated with a higher frequency of hospitalization for COVID-19 pneumonia. It should be noted[23] that the prevalence of auto-Abs increases with age, which may explain the severe course of SARS-CoV-2 infection in some older individuals. Moreover, SARS-CoV-2 infection is related to lymphopenia caused by the direct infection of T cells by the ACE2 receptor expressed on T cells, the accelerated depletion of T cells by cytokines, and the destruction of secondary lymphoid tissues of the spleen and lymph nodes[24]. Furthermore, Zhou et al[25] have shown that lymphopenia, especially CD4+ T cells, was an indicator of the severity of COVID-19 and the need for hospitalization. Moreover, a CD4+ T cell count below 200 cells/μL was associated with the critical course of COVID-19. It has also been found[25] that cytokine storm, especially related to IL-6, leads to the death of activated lymphocytes.

Furthermore, the mechanism of severe COVID-19 development is an overactive and deregulated neutrophil response since SARS-CoV-2 infection changes the number, phenotype, and functionality of these cells[26]. It should be noted that activation of neutrophils is associated with endothelial damage, platelet aggregation, and thrombus formation[27]. In addition, the association between lung fibrosis and neutrophil extracellular traps (NET) was shown[28]. NET resembles a web consisting of chromatin with proteases (myeloperoxidase, human neutrophils elastase) released from neutrophils to restrain the tissue spread of microorganisms[29]. In certain conditions, NET may be responsible for tissue damage[30] and ARDS development[31]. Lung tissue damage is also associated with the hyperactivation of pulmonary macrophages, a pro-inflammatory cytokine release, and the recruitment of cytotoxic effector cells[32].

The presence of microvascular thrombosis in the lung is reported[33] as one of the fatal factors of the course of COVID-19. Additionally, it is considered that thrombosis is related to severe hypoxia in some patients with well-preserved lung mechanics. Numerous postmortem data[33,34] confirmed the presence of microangiopathic thrombosis in the lungs of patients with COVID-19. The mechanisms of thrombosis development include direct viral infection, NET, pro-inflammatory cytokines action, hypoxemic injury, and complement cascade[33]. A case report of a deceased 65-year-old man with COVID-19 showed a postmortem microvascular thrombosis and DAD in both lungs despite the use of prophylactic anticoagulation. Both acute exudative and chronic proliferative phases of DAD were found[34].

Moreover, an important aspect of COVID-19 is the coagulopathy caused by the excessive production of proinflammatory cytokines, increased levels of damage-associated patterns, the stimulation of cell-death mechanisms, and endothelial damage. A characteristic change in the course of the disease includes the predominant increase of D-dimer and fibrin degradation products, prothrombin time prolongation, and thrombocytopenia[35]. It is considered[36] that the combination of low-grade disseminated intravascular coagulation (DIC) and pulmonary thrombotic microangiopathy (coagulopathy associated with COVID-19) is believed to affect organ function in patients with severe COVID-19. The development of ARDS may be caused by the deposition of fibrin and thrombin in pulmonary microcirculation. Changes in microcirculation may also be associated with sepsis-induced coagulopathy[36].

The Role of Cytokine Pathway in Deaths Due to COVID-19

The systemic inflammatory response associated with cytokine release syndrome is one of the causes of mortality due to COVID-19. During SARS-CoV-2 infection, major inflammatory pathways are activated including interleukin (IL)-6/Janus Kinase (JAK)/signal transducer and the activator of transcription signaling pathways, interferon cell signaling pathway, tumor necrosis factor-α (TNF-α)-NF-κB pathway, toll-like receptor pathway, and T-cell receptor pathway. It has been shown[37] that in COVID-19 patients, the activation of these inflammatory pathways is associated with severity, pathological progression, and organ damage. In addition, SARS-CoV-2 infection activates disintegrin and metalloproteinase-17 and increases the levels of angiotensin II (Ang-II) and TNF-α. A synergistic increase of Ang-II and TNF-α levels induces the expression and activity of matrix metallopeptidase 9. These mechanisms participate in the development of a cytokine storm and the severity of destructive inflammation[38].

Cytokine storm is a fast-developing, life-threatening, clinical condition, closely related to severe complications and poor prognosis[24]. It is associated with the infiltration of macrophages and neutrophils into lung tissue due to the pro-inflammatory immune responses of pathogenic Th1 cells secreting granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6. GM-CSF activates the production of large quantities of IL-6, tumor necrosis factor-α (TNF-α), and other cytokines by CD14+ CD16+ monocytes[39].

The dysregulation of the immune system may be a cause of the hyperinflammatory stage of COVID-19, considered to be the foremost reason for mortality. The increase of inflammatory cells and cytokines in the blood increases the permeability of blood vessels, which, in turn, leads to systemic capillary shunt. Leakage of blood plasma into neighboring cells may be a cause of the formation of an intravascular blood clot and associated thrombosis, which result in hypoxia and multi-organ failure. Additionally, impaired anticoagulant mechanisms contribute to the occurrence of DIC and multiple organ damage. A cytokine storm also damages the follicular cells and participates in the development of ARDS[40].

Hypersensitivity and COVID-19 Deaths

Mast cell degranulation is the result of immunoglobulin E (IgE)-mediated cross-linking of the IgE receptor, FcεRI, and is a cause of the dilation and increased permeability of capillaries. A retrospective case-control study[41] showed a relationship between the presence of specific anti-SARS-CoV-2-IgE antibodies in COVID-19 patients and the development of hypoxemic respiratory failure by the mechanism of type I hypersensitivity. The link between the severity of COVID-19 on admission to the hospital and the levels of specific IgE has also been shown. A positive correlation between specific IgE and the total lung damage severity scores and a negative with the PaO/FiO_2 ratio was found[41]. Moreover, histological examinations showed[41] nucleocapsid protein and positive staining with activated mast cells (CD63+) bound with IgE, in respiratory and intestinal tissues. Furthermore, airway hyperresponsiveness in the early recovery from COVID-19 was observed. In addition, the association between IgE and COVID-19 may confirm a good response in patients infected with SARS-CoV-2 to omalizumab and glucocorticosteroids[41].

Genetic Factors in the Fatal Course of SARS-CoV-2 Infection

The genome-wide association studies[42,43] showed that the region of chromosome 3p21.31 has the strongest association with susceptibility

to severe SARS-CoV-2 infection (twofold increased risk of respiratory failure). However, it should be noted that in other studies[44,45], this locus was more strongly associated with susceptibility to infection than its severity.

Interestingly, Downes et al[46] showed that the probable causative variant is the A allele of a single-nucleotide polymorphism, rs17713054G>A. The rs17713054-affected enhancer upregulates the interacting gene, leucine zipper transcription factor-like 1 (*LZTFL1*), which plays a key role as a regulator in a viral response pathway associated with epithelial-mesenchymal transition (EMT), rather than immune cells[46]. EMT is a reversible process of the trans-differentiation program of epithelial cells into mesenchymal cells and is crucial in the innate immune response. It is a consequence of lung inflammation and is involved in both the development and resolution of pneumonia[47,48]. SARS-CoV-2 infection of nasal and bronchial epithelium induces metabolic and transcriptional changes causing an intensification of EMT. Ultimately, this process shifts infects cells into an increasingly mesenchymal state, and losses of tight junction components favor the development of acute respiratory distress syndrome[49]. Moreover, in CRISPRi studies[50], it was found that a region near rs11385942 at chromosome 3p21.31 significantly influenced the expression of *LZTFL1*, an airway cilia regulator, and may play an important role in weakened airway viral clearance in a patient with COVID-19.

Concomitant Diseases and COVID-19 Mortality

Numerous studies[51,52] have shown that patients with multiple comorbidities are more prone to the fatal course of COVID-19. It has been shown[51] that 70% of patients with comorbidities required hospitalization in the Intensive Care Unit (ICU). Obesity, diabetes, hypertension, and cardiovascular disease increased the risk of mortality during the course of COVID-19[51,52]. The meta-analysis[53] of 12 studies including 34,390 patients showed that obesity was a risk factor for copositive poor outcomes and COVID-19 severity. Moreover, the risk increases with BMI and the association becomes more potent with higher values of BMI. Furthermore, in an autopsy study[11] of the first consecutive 80 cases in Hamburg, 38% of the patients were overweight and obese.

A series of 72,314 cases from China reported[54] a higher rate of mortality among patients with comorbidities (10.5% with cardiovascular disease, 7.3% with diabetes, 6.3% with chronic respiratory disease, 6.0% with hypertension, and 5.6% with cancers) than overall (2.3%).

As was mentioned above, autopsy studies[11] also showed that most patients who died directly from SARS-CoV-2 infection had multiple comorbidities. In a prospective postmortem evaluation[12] involving more than 700 deaths associated with COVID-19 infection, the most common comorbidities were cardiovascular diseases (89.0%). Moreover, in the autopsy group[12], patients who died from COVID-19 had an average of 2.9 comorbidities. Similar results revealed the meta-analysis[16] of 25 studies including 140 autopsies. This meta-analysis showed that 81.42% (114/140) of the deceased had at least one comorbidity, most often vascular diseases, followed by heart disease, diabetes, and respiratory diseases. It should be noted that among the patients with cardiovascular diseases or diabetes, a significantly shorter time of survival was observed[16]. The high rate of comorbidities among patients who died from COVID-19 was also reported in a study[17] performed in 19 medical centers or forensic institutions in the United States and Brazil. This study showed an average of 8.89 pathological conditions in autopsy in patients dying of or with COVID-19 including a combination of prior chronic diseases and acute conditions acquired during hospitalization. All of the 135 deceased undergoing autopsies had more than 1 preexisting condition and the average was 2.88. The clinical conditions developed during terminal hospitalization predominantly included the acute failure of multiple organ systems and/or impaired coagulation[17].

In the UK Biobank population cohort study[55] which included 470,034 participants, 438 died of COVID-19. The results revealed an exponential and independent association between age and COVID-19 mortality. Patients aged 75 years and over had a 13-fold (95% CI 9.13-17.85) higher risk of death than those below 65 years. Moreover, in patients aged 75 years and over without comorbidities, the risk was 4-fold higher than in those below 65 years (95% CI 1.57-9.96, p=0.004).

Conclusions

In summary, the data shown above suggests that the main direct cause of death from COVID-19 is multiple organ failure resulting from numerous pathological mechanisms including genetic pre-

disposition to a severe inflammatory response. Increased inflammatory response predisposes the lungs locally and systemic thrombotic microangiopathy. It seems that advanced age and many comorbidities, which are associated with an increased mortality rate among patients with COVID-19 *per se*, predispose to an increased risk of thrombotic changes. Furthermore, the role of inflammation in the lungs and the changes that lead to hypoxia cannot be overlooked. However, the thrombotic changes in microcirculation seem to be the most dominant.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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References

1) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si H, Zhu Y, Huang C, Chen H, Chen J. Addendum: A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
2) WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020
3) Number of coronavirus (COVID-19) cases worldwide as of February 3, 2023, by country or territory. Available at: https://www.statista.com/statistics/1043366/novel-coronavirus-2019ncov-cases-worldwide-by-country/
4) Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, Aravkin A, Bisignano C, Barber R, Alam T, Fuller J, May E, Jones D, Frisch M, Abbafati C, COVID-10 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. Lancet 2022; 399:1513-1536.
5) Fairman KA, Goodlet KJ, Rucker JD, Zawadzki RS. Unexplained mortality during the US COVID-19 pandemic: retrospective analysis of death certificate data and critical assessment of excess death calculations. BMJ Open 2021; 11: e050361.
6) Lindahl BIB. COVID-19 and the selection problem in national cause-of-death statistics. Hist Philos Life Sci 2021; 43: 72.
7) Armstrong D. The COVID-19 pandemic and cause of death. Sociol Health Illn 2021; 43: 1614-1626.
8) Bauer P, Brugger J, König F, Posch M. An international comparison of age and sex dependency of COVID-19 deaths in 2020: a descriptive analysis. Sci Rep 2021; 11: 19143.
9) Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schroder A, Burdelski C, de Heer G, Nierhaus A. Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. Ann Intern Med 2020; 173: 268-277.
10) Elezkurtaj S, Greuel S, Ihlow J, Michhaelis E, Bischoff P, Kunze C, Sinn B, Gerhold M, Hauptmann K, Ingold-Heppner B, Miller F, Herbst H, Corman V, Martin H, Radbruch H, Heppner F, Horst D. Causes of death and comorbidities in hospitalized patients with COVID-19. Sci Rep 2021; 11: 4263.
11) Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, Klen A, Langenwalder F, Lutgehetmann M, Meisner K, Puschel K, Schadler J, Steurer S, Mushumba H, Sperhake J. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med 2020; 134: 1275-1284.
12) Fitzek A, Schädler J, Dietz E, Ron A, Gerling M, Kammal A, Lohner L, Falck C, Mobius D, Goebels H, Gerberding A, Schreder A, Sperhake J, Klein A, Frob D, Mushumba H, Wilmes S, Anders S, Kniep I, Heinrich F, Langewalder F, Meissner K, Lange P, Zapf A, Puschel K, Heinemann A, Glatzel M, Matschke J, Aepfelbacher M, Lutgehetmann M, Steurer S, Thorns C, Edler C, Ondruschka B. Prospective postmortem evaluation of 735 consecutive SARS-CoV-2-associated death cases. Sci Rep 2021; 11: 19342.
13) Romanova ES, Vasilyev VV, Startseva G, Karev V, Rybakova MG, Platonov PG. Cause of death based on systematic post-mortem studies in patients with positive SARS-CoV-2 tissue PCR during the COVID-19 pandemic. J Intern Med 2021; 290: 655-665.

14) Cardinal-Fernández P, Lorente JA, Ballén-Barragán A, Matute-Bello G. Acute respiratory distress syndrome and diffuse alveolar damage. New Insights on a Complex Relationship. Ann Am Thorac Soc 2017; 14: 844-850.

15) Konopka KE, Nguyen T, Hlavaty L, Rayes O, Schmidt C, Dahl J, Myers J. Utility of CDC screening guidelines and autopsy findings in identifying decedents who die of SARS-CoV-2 infection. Am J Forensic Med Pathol 2021; 42: 118-120.

16) Martín-Martín J, Martín-Cazorla F, Suárez J, Rubio L, Martín-de-Las-Heras S. Comorbidities and autopsy findings of COVID-19 deaths and their association with time to death: a systematic review and meta-analysis. Curr Med Res Opin 2022; 38: 785-792.

17) Hooper JE, Padera RF, Dolhnikoff M, da SLiva L, Duarte-Neto A, Kapp M, Lacy M, Mauad T, Saldiva P, Rapkiewicz A, Wolf D, Felix J, Benson P, Shanes E, Gawelek K, Marshall D, McDonald M, Muller W, Priemer D, Solomon I, ZakT, Bhattacharjee M, Fu L, Gillbert A, Harper H, Litovsky S, Lomasney J, Mount S, Reilly S, Sekulic M, Steffensen T, Threlkeld K, Zhao B, Williamson A. A postmortem portrait of the coronavirus disease 2019 (COVID-19) pandemic: A large multi-institutional autopsy survey study. Arch Pathol Lab Med 2021; 145: 529-535.

18) Mukerji SS, Solomon IH. What can we learn from brain autopsies in COVID-19? Neurosci Lett 2021; 742: 135528.

19) Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, Hernandez-Montfort J, Islam A. Systematic review of COVID-19 related myocarditis: insights on management and outcome. Cardiovasc Revasc Med 2021; 23: 107-113.

20) Ho JS, Sia CH, Chan MY, Lin W, Wong RC. Coronavirus-induced myocarditis: A meta-summary of cases. Heart Lung 2020; 49: 681-685.

21) Roshdy A, Zaher S, Fayed H, Coghlan JG. COVID-19 and the heart: A systematic review of cardiac autopsies. Front Cardiovasc Med 2021; 7: 626975.

22) Farahani M, Niknam Z, Amirabad LM, Amiri-Dashatan N, Koushki M, Nemati M, Pouya F, Rezaei-Tavirani M, Rasmi Y, Tayebi L. Molecular pathways involved in COVID-19 and potential pathway-based therapeutic targets, Biomed Pharmacother 2022; 145: 112420.

23) Bastard P. Why do people die from COVID-19? Science 2022; 375: 829-830.

24) Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Signal Transduct Target Ther 2021; 6: 326.

25) Zhou X, Ye G, Lv Y, Guo Y, Pan X, Li Y, Shen G, He Y, Lei P. IL-6 drives T cell death to participate in lymphopenia in COVID-19. Int Immunopharmacol 2022; 111: 109132.

26) Reusch N, De Domenico E, Bonaguro L, Schulte-Schrepping J, Bassler K, Schultze J, Aschenbrenner A. Neutrophils in COVID-19. Front Immunol 2021; 12: 652470.

27) Iliadi V, Konstantinidou I, Aftzoglou K, Iliadis S, Konstantinidis TG, Tsigalou C. The emerging role of neutrophils in the pathogenesis of thrombosis in COVID-19. Int J Mol Sci 2021; 22: 5368.

28) Pandolfi L, Bozzini S, Frangipane V, Percivalle E, Luigi A, Violatto M, Lopez G, Gabanti E, Carsana L, D'Amato M, Morosini M, De Amici M, Nebuloni M, Fossali T, Colombo R, Saracino L, Codullo V, Gnecchi M, Bigni P, Baldanti F, Lilleri D, Meloni F. Neutrophil extracellular traps induce the epithelial-mesenchymal transition: implications in post-COVID-19 fibrosis. Front Immunol 2021; 12: 663303.

29) de Bont CM, Boelens WC, Pruijn GJM. NETosis, complement, and coagulation: a triangular relationship. Cell Mol Immunol 2019; 16: 19-27.

30) Narasaraju T, Tang BM, Herrmann M, Muller S, Chow VTK, Radic M. Neutrophilia and NETopathy as key pathologic drivers of progressive lung impairment in patients with COVID-19. Front Pharmacol 2020; 11: 870.

31) Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison J, Blair C, Weber A, Barnes B, Egeblad M, Woods R, Kanthi Y, Knight J. Neutrophil extracellular traps in COVID-19. JCI Insight 2020; 5: e138999.

32) Knoll R, Schultze JL, Schulte-Schrepping J. Monocytes, and macrophages in COVID-19. Front Immunol 2021; 12: 720109.

33) Campbell C, Kahwash R. Microvascular Thrombi in COVID-19. ACC 2021. Available at: https://www.acc.org/latest-in cardiology/articles/2021/01/25/14/28/microvascular-thrombi-in-covid-19.

34) Carvalho LVS, da Silva Souza C, Fontes JLM, Cardoso L, Salomar M, Duarte-Neto-A, Figueira C, Brito R, Mesquita B, de Freitas L, Olivira G, dos-Santos W. COVID-19 beyond DAD: Persisting microcirculation thrombosis, hidden infections, and early pulmonary fibrosis as remaining challenges of the disease. Hum Pathol Rep 2022; 27: 300607.

35) Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost 2020; 18: 2103-2109.

36) Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martin AJ. Thrombosis and Coagulopathy in COVID-19. Curr Probl Cardiol 2021; 46: 100742.

37) Yarmohammadi A, Yarmohammadi M, Fakhri S, Khan H. Targeting pivotal inflammatory pathways in COVID-19: A mechanistic review. Eur J Pharmacol 2021; 890: 173620.

38) Ben Moftah M, Eswayah A. Intricate relationship between SARS-CoV-2-induced shedding and cytokine storm generation: A signaling inflammatory pathway augmenting COVID-19. Health Sci Rev (Oxf) 2022; 2: 100011.

39) Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021; 93: 250-256.

40) Choudhary S, Sharma K, Silakari O. The interplay between inflammatory pathways and COVID-19: A critical review on pathogenesis and therapeutic options. Microb Pathog 2021; 150: 104673.

41) Tan C, Zheng X, Sun F, He J, Shi H, Chen M, Tu C, Huang Y, Wang Z, Liang Y, Wu J, Liu Y, Liu J, Huang J. Hypersensitivity may be involved in severe COVID-19. Clin Exp Allergy 2022; 52: 324-333.

42) Severe Covid-19 GWAS Group. Genomewide association study of severe COVID-19 with respiratory failure. N Engl J Med 2020; 383: 1522-1534.

43) Pairo-Castineira E, Clohisey S, Klaric L, Bretherick A, Rawlik K, Pasko D, Walker S, Parkinson N, Fourman M, Russel C, Furniss J, Richmond A, Gountouna E, Wrobel N. Genetic mechanisms of critical illness in COVID-19. Nature 2021; 591: 92-98.

44) COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature 2021; 600: 472-477.

45) Roberts GHL, Park DS, Coignet MV, McCurdy S, Knight S, Partha R, Rhead B, Zhang Z, Berkowitz N, Baltzell A, Guturu H, Girshick A, Rand K, Hong E, Ball C. AncestryDNA COVID-19 host genetic study identifies three novel loci. MedRxiv 2020. Pre-print: doi: 10.1101/2020.10.06.20205864.

46) Downes DJ, Cross AR, Hua P, Roberts N, Schwessinger R, Cutler A, Munis A, Brown J, Mielczarek O, Andrea C, Melero I, Gill D, Hyde S, Knight J, Todd J, Sansom S, Issa F, Davies J, Hughes J. Identification of LZTFL1 as a candidate effector gene at a COVID-19 risk locus. Nat Genet 2021; 53: 1606-1615.

47) Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 2014; 15: 178-196.

48) Yang J, Antin P, Berx G, Banpain C, Brabletz T, Bronner M, Campbell K, Cano A, Casanova J, Christofori G, Dedhar M, Derynck K, Ford H, Fuxe J, de Herrerors A. Guidelines and definitions for research on epithelial-mesenchymal transition [published correction appears in Nat Rev Mol Cell Biol 2021; 22: 834]. Nat Rev Mol Cell Biol 2020; 21: 341-352.

49) Stewart CA, Gay CM, Ramkumar K, Cargill K, Cardinell R, Nilsson M, Heeke S, Park E, Kundu S, Diao L, Wang Q, Shen L, Xi Y, Zhang B, Corte C, Fan Y, Kundu K, Gao B, Avila K, Pickering C, Johnson F, Zhang J, Kadara H, Minna J, Gibbons D, Wang J, Heymach J, Byers L. Lung cancer models reveal severe acute respiratory syndrome coronavirus 2-induced epithelial-to-mesenchymal transition contributes to Coronavirus Disease 2019 Pathophysiology. J Thorac Oncol 2021; 16: 1821-1839.

50) Fink-Baldauf IM, Stuart WD, Brewington JJ, Guo M, Maeda Y. CRISPRi links COVID-19 GWAS loci to LZTFL1 and RAVER1. EBioMedicine 2022; 75: 103806.

51) Gasmi A, Peana M, Pivina L, Srinath S, Benahmed A, Semenova Y, Menzel A, Dadar M, Bjorklund G. Interrelations between COVID-19 and other disorders. Clin Immunol 2021; 224: 108651.

52) Liang C, Zhang W, Li S, Qin G. Coronary heart disease and COVID-19: A meta-analysis. Med Clin (Barc) 2021; 156: 547-554.

53) Pranata R, Lim MA, Yonas E, Vania R, Lukito A, Siswanto B, Meyer M. Body mass index and outcome in patients with COVID-19: A dose-response meta-analysis. Diabetes Metab 2021; 47: 101178.

54) Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-1242.

55) Ho F, Petermann-Rocha F, Gray S, Jani B, Katikireddi S, Niedzwiedz C, Foster H, Hastie C, Mackay D, Gill J, O'Donnel C, Welsh P, Mair F, Sattar N, Celis-Morales C, Pell J. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PLoS One 202; 15: e0241824.