UDC 616.98:578.834COV]-091/-092-036.88-07»2020»
DOI: 10.14739/2310-1237.2021.3.242247

Clinical and pathomorphological analysis of deaths from COVID-19 in 2020

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of the work – to conduct clinical and pathomorphological analysis of deaths from COVID-19 in 2020.

Materials and methods. We analyzed 41 case histories and results of pathological-anatomical examination of patients who were died of COVID-19 during 2020.

Results. The lethal outcome of COVID-19 disease was recorded at day 22 (16; 27) of the disease. Among the dead, there is a high percentage of men (73.2 %), early old age and middle old age patients (75.6 %) with comorbid pathology (92.7 %). Early lung damage with COVID-19 in the deceased was determined by pronounced interstitial and interstitial-alveolar edema, the presence of erythrocyte stasis in the pulmonary microvessels, blood clots and hypoperfusion leukocyte stasis, as well as the presence of erythrocytes in the alveoli. Bilateral polysegmental subtotal viral pneumonia in 90.2 % of dead patients was characterized by significant edema and thickening of the alveolar walls with their moderate infiltration by lymphocytes, focal peribronchial and perivascular inflammatory polymorphonuclear infiltration, multiple and small exfoliated alveolar epithelium (87.8 %), as well as metaplasia of a few alveolocytes preserved on the luminal surface of the alveoli (82.9 %). Every tenth person who died of COVID-19 had signs of secondary bacterial microflora. In 85.4 % of patients who died on day 22–27 of the disease focal or sublobar pneumofibrosis was diagnosed. In those who died due to COVID-19, multiorgan failure was characterized by focal necrosis of the renal tubular epithelium (73.2 %), focal lymphocytic-leukocyte infiltration (12.2 %) and renal microvascular thrombosis (17.1 %), focal centro-lobular necrosis (90.2 %) and focal lymphocytic-leukocyte infiltration of lobes (7.3 %) of the liver. Thrombotic complications were confirmed in 22.0 % of deceased patients: ischemic cerebral infarction, transmural myocardial infarction, pulmonary embolism, deep vein thrombosis of the lower extremities under the pathology. These thrombotic complications were not diagnosed during life in all patients. The majority of deaths due to COVID-19 had morphological signs of chronic cardiovascular pathology. Ischemic heart disease and hypertension during the life of patients were not diagnosed in all cases.

Conclusions. Early lung damage in COVID-19 in the deceased was determined by pronounced interstitial-alveolar edema, blood clots and leukocyte stasis in microvessels, less often – the presence of "hyaline membranes". In 90.2 % of the dead patients bilateral polysegmental subtotal pneumonia with edema and lymphocytic infiltration of the pulmonary interstitium, inflammatory peribronchial and perivascular focal polymorphonuclear infiltrates, foci of atelectasis and dyscryphaseses was found. In 9.7 % of patients bilateral subtotal viral-bacterial fibrinous-purulent bronchopneumonia developed. In those who died on the 22nd–27th day of the disease focal pneumofibrosis was determined. Pathomorphologically, thrombotic complications, which were not diagnosed in all patients during their lifetime, were confirmed in 22.0 % of deceased patients. Most deaths from COVID-19 had morphological signs of chronic cardiovascular disease.

Key words: coronavirus disease, COVID-19, pathology.

Pathologia 2021; 18 (3), 269-277

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Клініко-патоморфологічний аналіз летальних випадків внаслідок COVID-19 у 2020 році

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Мета роботи – здійснити клініко-патоморфологічний аналіз летальних випадків від коронавірусної хвороби (COVID-19) у 2020 році.

Матеріали та методи. Проаналізували 41 історію хвороби та результати патологоанатомічного дослідження пацієнтів, які померли внаслідок COVID-19 протягом 2020 року.

Результати. Летальний наслідок від COVID-19 зафіксований на 22 (16; 27) добу захворювання із переважанням серед померлих чоловіків (73,2 %), пацієнтів похилого та старечого віку (75,6 %) із наявністю коморбідної патології (92,7 %). Раннє ураження легень при COVID-19 у померлих визначали як виразний інтерстиційний та інтерстиційно-альвеолярний набряк, наявність у легеневих мікросудинах стазу еритроцитів, мікрозгустків крові та гіпоперфузійних лейкоцитарних стазів, а також наявність в альвеолах еритроцитів, рідше – «гіалінових мембран». Двобічна полісегментарна субтотальна вірусна пневмонія в 90,2 % померлих хворих виявлялася як суттєвий набряк і потовщення стінок альвеол із помірною інфільтрацією лімфоцитами, вогнищевою перибронхіальною та периваскулярною запальною поліморфноклітинною інфільтрацією, множинними дрібними вогнищами ателектазів і дислектазів, наявністю в альвеолах скупчень еритроцитів, гемосидерофагів і макрофагів, злущеного альвеолярного епітелію (87,8 %), а також метаплазії нечисленних альвеолоцитів, що збереглися на люмінальній поверхні альвеол (82,9 %).

У кожного десятого померлого від COVID-19 зафіксували ознаки приєднання вторинної бактеріальної мікрофлори. У 85,4 % померлих на 22–27 добу хвороби встановили великовогнищевий або сублобарний пневмофіброз. У померлих

Ключові слова: коронавірусна хвороба COVID-19, патологія.

Патологія. 2021. Т. 18, № 3(53). С. 269-277

унаслідок COVID-19 поліорганна недостатність характеризувалася вогнищевим некрозом епітелію канальців нирок (73,2 %), вогнищевою лімфоцитарно-лейкоцитарною інфільтрацією (12,2 %), тромбозом мікросудин (17,1 %) нирок, вогнищевими центролобулярними некрозами (90,2 %) та вогнищевою лімфоцитарно-лейкоцитарною інфільтрацією часток (7,3 %) печінки. Тромботичні ускладнення патоморфологічно підтверджені у 22,0 % померлих: ішемічний інфаркт головного мозку, трансмуральний інфаркт міокарда, інфаркт міокарда, що ускладнився вогнищевою інфаркт-пневмонією через ТЕЛА дрібних гілок легеневої артерії, рецидивна ТЕЛА дрібних гілок легеневої артерії з формуванням множинних інфарктів легень різної давнини, тромбоз глибоких вен верхньої кінцівки.

У більшості померлих унаслідок COVID-19 виявляли морфологічні ознаки хронічної серцево-судинної патології. Ішемічна хвороба серця та гіпертонічна хвороба в деяких випадках не були діагностовані за життя пацієнтів.

Висновки. Раннє ураження легень при COVID-19 у померлих визначали за виразним інтерстиційно-альвеолярним набряком, мікрозгустками крові та лейкоцитарними стазами в мікросудинах, рідше – за наявністю «гіалінових мембран». У 90,2 % померлих виявлена двобічна полісегментарна субтотальна пневмонія з набряком і лімфоцитарною інфільтрацією легеневого інтерстицію, запальними перибронхіальними та периваскулярними вогнищевими поліморфноклітинними інфільтратами, вогнищами ателектазів і дислектазів, наявністю в альвеолах еритроцитів, гемосидерофагів, макрофагів, диспластично зміненого та злущеного альвеолярного епітелію. У 9,7 % хворих виникла двобічна субтотальна вірусно-бактерійна фібринозно-гнійна бронхопневмонія. У померлих на 22–27 добу хвороби реєстрували великовогнищевий пневмофіброз. Патоморфологічно тромботичні ускладнення підтверджені у 22,0 % померлих, які за життя вдалося діагностувати не в усіх пацієнтів. У більшості померлих унаслідок COVID-19 виявляли морфологічні ознаки хронічної серцево-судинної патології.

Ключевые слова: коронавирусная болезнь COVID-19, патология.

Патология. 2021. Т. 18, № 3(53). С. 269-277

Клинико-патоморфологический анализ летальных случаев вследствие COVID-19 в 2020 году

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Цель работы – провести клинико-патоморфологический анализ летальных случаев от коронавирусной болезни (COVID-19) в 2020 году.

Материалы и методы. Проанализировали 41 историю болезни и результаты патологоанатомического исследования пациентов, умерших вследствие COVID-19 в 2020 году.

Результаты. Летальный исход вследствие COVID-19 зафиксирован на 22 (16; 27) сутки болезни с преобладанием среди заболевших мужчин (73,2 %), пациентов пожилого и старческого возраста (75,6 %) с наличием коморбидной патологии (92,7 %). Раннее поражение лёгких при COVID-19 у умерших проявлялось выраженным интерстициальным и интерстициально-альвеолярным отёком, наличием в микрососудах лёгких стаза эритроцитов, микросгустков крови и гипоперфузионных лейкоцитарных стазов, а также наличием в альвеолах эритроцитов, реже – «гиалиновых мембран». Двусторонняя полисегментарная субтотальная вирусная пневмония у 90,2 % умерших пациентов проявлялась значительным отёком и утолщением стенок альвеол с умеренной инфильтрацией лимфоцитами, очаговой перибронхиальной и периваскулярной воспалительной инфильтрацией, множественными мелкими очагами ателектазов и дислектазов, наличием в альвеолах скоплений эритроцитов, гемосидерофагов и макрофагов, слущенного альвеолярного эпителия (87,2 %), а также метаплазии немногочисленных альвеоцитов, которые сохранились на люминальной поверхности альвеол (82,9 %).

У каждого десятого умершего от COVID-19 отмечены признаки присоединения вторичной бактериальной микрофлоры. У 85,4 % умерших на 22–27 сутки болезни пациентов фиксировали крупноочаговый или сублобарный пневмофиброз. У умерших от COVID-19 полиорганная недостаточность характеризовалась очаговым некрозом эпителия канальцев почек (73,2 %), очаговой лимфоцитарно-лейкоцитарной инфильтрацией (12,2 %), тромбозом микрососудов (17,1 %) почек, очаговыми центролобулярными некрозами (90,2 %) и очаговой лимфоцитарно-лейкоцитарной инфильтрацией долек (7,3 %) печени.

Тромботические осложнения патоморфологически подтверждены у 22,0 % умерших пациентов: ишемический инфаркт головного мозга, трансмуральный инфаркт миокарда, инфаркт миокарда, осложнившийся очаговой инфаркт-пневмонией из-за ТЭЛА мелких ветвей лёгочной артерии, рецидивирующая ТЭЛА мелких ветвей лёгочной артерии с формированием множественных инфарктов лёгких разной давности, тромбоз глубоких вен верхней конечности. У большинства умерших вследствие COVID-19 отмечены морфологические признаки хронической сердечно-сосудистой патологии. Ишемическая болезнь сердца и гипертоническая болезнь при жизни пациентов диагностированы не во всех случаях.

Выводы. Раннее поражение лёгких при COVID-19 у умерших определялось выраженным интерстициально-альвеолярным отёком, микросгустками крови и лейкоцитарными стазами в микрососудах, реже – наличием «гиалиновых мембран». У 90,2 % умерших пациентов зафиксирована двусторонняя полисегментарная субтотальная пневмония с отёком и лимфолейкоцитарной инфильтрацией лёгочного интерстиция, воспалительными перибронхиальными и периваскулярными очаговыми полиморфноклеточными инфильтратами, очагами ателектазов и дислектазов, наличием в альвеолах эритроцитов, гемосидерофагов, макрофагов, диспластически измененного и слущенного альвеолярного эпителия. У 9,7 % больных возникла двусторонняя субтотальная вирусно-бактериальная фибринозно-гнойная бронхопневмония. У умерших на 22–27 сутки болезни регистрировали крупноочаговый пневмофиброз. Патоморфологически тромботические осложнения подтверждены у 22,0 % умерших, которые при жизни удалось диагностировать не у всех пациентов. У большинства умерших вследствие COVID-19 установлены морфологические признаки хронической сердечно-сосудистой патологии.

Under the conditions of pandemic spread of coronavirus SARS-CoV-2, every fifth patient develops a severe course of the disease with a high risk of death [1]. Even in the presence of modern diagnostic tests, pathomorphological examination of deaths during the pandemic of the new coronavirus COVID-19 is of particular importance and can significantly affect the understanding of the disease pathogenesis. The data obtained may have an impact on the therapeutic strategy for the treatment of a new infection [2].

It is known that ACE2 is a receptor that uses SARS-CoV and SARS-CoV-2 to penetrate the target cell [3,4]. At the tissue level, ACE2-receptors are highly expressed in the lungs, kidneys, heart, and vascular endothelium, which may explain the presence of multiorgan lesions in patients with SARS-CoV and SARS-CoV-2 coronavirus [5,6]. The appearance of multiorgan lesions can be explained by the development of "cytokine storm" in conditions of severe and critical course of the disease. "Cytokine storm" can be a manifestation of a hyperimmune response with hyperproduction of proinflammatory cytokines and chemokines by immune cells and the development of systemic endotheliitis with hypercoagulation [7,8]. Despite the fact that in the pandemic of highly contagious COVID-19 pathomorphological studies are somewhat limited, the accumulation of results of these studies continues [9–12]. At the same time, the clinical and pathomorphological analysis of the obtained results is of special importance.

Aim

The aim of the work – to conduct clinical and pathomorphological analysis of deaths from COVID-19 in 2020.

Materials and methods

We analyzed 41 case histories and results of pathoanatomical examination of patients who were treated in the intensive care unit of the Municipal Non-Profit Enterprise "Regional infectious diseases clinical hospital" of Zaporizhzhia Regional Council and died of coronavirus COVID-19 during 2020. Pathoanatomical examination was performed in Municipal Institution "Zaporizhzhia Regional Bureau of Forensic Medical Examination" of Zaporizhzhia Regional Council.

Age of the dead was from 48 to 85 years. There were 30 men and 11 women. The diagnosis of COVID-19 in all cases was confirmed by the isolation of SARS-CoV-2 RNA in nasopharyngeal mucus or sputum. All patients were examined and treated in accordance with current regulations: Order of the Ministry of Health (MOH) of Ukraine dated 28.03.2020, No. 722 "Organization of medical care for patients with coronavirus disease (COVID-19)" (as amended by the order of the MOH of Ukraine dated 17.09.2020, No. 2122 "On amendments to the Standards of medical care of "Coronavirus disease (COVID-19)"); Order of the MOH of Ukraine No. 10 dated 07.01.2021 "On approval of Amendments to the Standards of medical care of "Coronavirus disease (COVID-19)"; Order of the MOH of Ukraine dated April 6, 2021 No. 638 "Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19)".

Statistical data processing was performed in the program Statistica for Windows 13 (StatSoft Inc., license number JPZ804I382130ARCN10-J).

Results

According to the results of the analysis, it was found that men predominated among those who died as a result of COVID-19 (n = 30, 73.2 %). More than half of the patients were early old aged (n = 23, 56.1 %), every fourth patient was middle adulthood (n = 10, 24.4 %), and every fifth was middle old aged (n = 8, 19.5 %).

Patients were hospitalized in an infectious hospital at day 9.0 [7.0; 12.0] of illness, and after deterioration – by day 8.5 [6.0; 11.0] of treatment in an outpatient setting. Deterioration was expressed by febrile (n = 26, 63.4 %) or subfebrile (n = 13, 31.7 %) fever, shortness of breath with a respiratory rate of 28.0 [28.0; 32.0] per minute, hemoptysis (n = 4, 9.8 %), reducing oxygen saturation to 82.0 [75.0; 86.0] %, short-term diarrheal syndrome (n = 5, 12.2 %). At hospitalization, all patients had auscultatory signs (respiratory failure, crepitation) of bilateral pneumonia, which was confirmed radiologically, by computed tomography or lungs ultrasound with a lesion of 56.0 [51.0; 62.5] % of the lungs. The development of acute respiratory failure was accompanied by the appearance of acrocyanosis (n = 27, 65.9 %), and 2 (4.9 %) patients were taken to the intensive care unit (ICU) from other hospitals on artificial ventilation of the lungs (AVL).

Patients showed the following laboratory changes that characterized the severity of immune inflammation and hypercoagulation: leukocytosis in 29 (70.7 %) patients, the median of this indicator was 11.1 [7.9; 13.7] × 10^9/l; band neutrophils shift in 16 (39.0 %) with the presence of metamyelocytes in 2 (4.9 %) patients; development of absolute lymphopenia from 1.00 to 0.39 with a median of 0.8 [0.6; 1.1] × 10^9/l in the vast majority of patients (n = 35, 85.4 %); acceleration of ESR to 38.0 [25.0; 47.0] mm/h; increase in C-reactive protein in all patients to 150.5 [101.5; 235.5] ng/ml; increasing the level of interleukin-6 to 60.1 [25.0; 81.4] ng/ml; hyperfibrinogenemia from 4.8 to 8.4 g/l in 32 (78.0 %) patients with a median of this indicator of 5.1 [4.3; 6.4] g/l; increasing the level of D-dimer to 1.4 [0.9; 9.4] mg/l and ferritin to 760.0 [482.0; 1148.0] ng/ml.

The duration of patients treatment in the ICU was from 2 to 38 days, the median was 11.0 [7.0; 18.0] days. During this period, patients received treatment according to the protocol of the MOH of Ukraine, every fifth patient (n = 8, 19.5 %) received tocilizumab. Despite the ongoing treatment, these patients progressed to respiratory failure, which required the transfer of patients to non-invasive ventilation or AVL. The median duration of AVL was 2.0 [1.0; 6.0] days. The dynamics increased the proportion of patients with signs of leukocytosis (n = 39, 95.1 %) with a median of this indicator of 16.2 [12.5; 24.2] × 10^9/l. It should be noted that every fourth patient (n = 11, 26.8 %) has hyperleukocytosis in the range from 20.3 to 54.4 × 10^9/l. The increase in endogenous intoxication and immune inflammation with hypercoagulation was evidenced by the preservation of absolute lymphopenia

Table 1. Pathomorphological changes in the lungs of patients who died of COVID-19, abs (%)

Pathomorphological sign	Detection frequency (n = 41)
Interstitial-alveolar pulmonary edema with the presence of erythrocyte stasis and blood clots in microvessels	41 (100 %)
Bilateral polysegmental subtotal viral pneumonia:	37 (90.2 %)
– edema and thickening of the alveoli walls with moderate lymphocytic-leukocyte infiltration;	37 (90.2 %)
– focal peribronchial and perivascular inflammatory polymorphonuclear infiltration;	37 (90.2 %)
– multiple small foci of atelectases and dyslectases;	37 (90.2 %)
– the presence of erythrocytes, hemosiderophages, macrophages, squamous alveolar epithelium in the alveoli;	36 (87.8 %)
– metaplasia of small alveolocytes on the luminal surface of the alveoli;	34 (82.9 %)
– presence of fibrin in some parietal layers alveoli – "hyaline membranes";	15 (36.6 %)
– hypoperfusion leukocyte stasis in microvessels.	11 (26.8 %)
Interoveolar fibrosis, perivascular and peribronchial fibrosis	35 (85.4 %)
Big-focal or sublobar pneumosclerosis	35 (85.4 %)
Bilateral hydrothorax	9 (21.9 %)
Fibrinous-purulent tracheobronchitis and bilateral subtotal viral-bacterial fibrinous-purulent bronchopneumonia	4 (9.7 %)
Bilateral fibrinous-purulent pleuritis	3 (7.3 %)

(n = 24, 58.5 %), band neutrophils shift (n = 10, 24.4 %), an increase in the proportion of patients with metamyelocytes (n = 17, 41.5 %), an increase of median D-dimer level up to 5.5 [1.6; 21.1] mg/l. Despite treatment, hyperfibrinogenemia persisted (n = 28, 68.3 %), increasing the level of C-reactive protein to 127.0 [42.0; 221.0] mg/l and ferritin to 511.0 [360.0; 1314.0] ng/ml.

Fatal outcome of COVID-19 disease was recorded at day 22.0 [16.0; 27.0] of the disease. Pathomorphological signs of early lung damage in COVID-19 in the deceased were determined by pronounced interstitial and interstitial-alveolar edema, the presence in the pulmonary microvessels of erythrocytes stasis and blood clots and hypoperfusion leukocyte stasis, and erythrocytes in alveoli (*Fig. 1, 2*). The presence of fibrin in the alveoli of the parietal layers, the so-called "hyaline membranes" occurred in 36.6 % of deceased patients (*Table 1*).

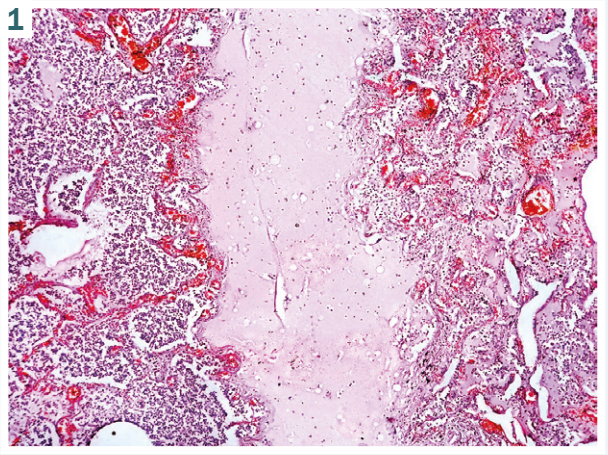
The vast majority of patients (90.2 %) subsequently developed bilateral polysegmental subtotal viral pneumonia. According to pathomorphological data (*Fig. 2, 3, 4*), it was characterized by significant edema and thickening of the alveolar walls with their moderate predominantly lymphocytic infiltration (90.2 %), focal peribronchial and perivascular inflammatory polymorphonuclear infiltration (90.2 %), multiple small atelectases and dyslectases (90.2 %), the presence of erythrocytes clusters, hemosiderophages and macrophages, squamous alveolar epithelium in the alveoli (87.8 %), and metaplasia of a few alveolocytes preserved on the luminal surface of the alveoli (82.9 %). Bilateral subtotal viral-bacterial fibrinous-purulent bronchopneumonia (9.7 %) was detected in 4 deceased men during the pathomorphological examination of the lungs (*Table 1*). In these cases, treatment in the ICU lasted from 17 to 24 days. Patients received sequential oxygen therapy in a mask mode, then non-invasive lung ventilation and only during the last 1–2 days were transferred to ALV. In 35 (85.4 %) patients, who died on day 22–27 of the disease, there were fibrosis of the interalveolar septa, perivascular and peribronchial fibrosis (*Fig. 5*), big-focal or sublobar pneumosclerosis (*Fig. 6*).

One 54-year-old patient treated with a protocol using immunotropic drugs (including tocilizumab, for the correction of clinical and laboratory manifestations of "cytokine storm"), antibacterial drugs and low molecular weight heparins, was diagnosed in the second week of the disease with sepsis (progression of respiratory failure, multiorgan failure syndrome, bacteriologically isolated from the blood *Klebsiella pneumonia*). The lethal outcome was recorded after three weeks of treatment. At pathoanatomical examination in the lung tissue, along with the presence of bilateral polysegmental subtotal hemorrhagic viral pneumonia signs, there was fibrinous-purulent pleurisy with pronounced inflammatory polymorphic-cellular infiltration of the layers of the parietal and visceral pleura, fibrinous-purulent tracheobronchitis. Foci of leukocyte-lymphocytic infiltration, as well as tubular necrosis of the kidneys and centrolobular necrosis of the liver were found in the tissue of the kidneys and liver. Morphological manifestations of sepsis were characterized by the presence of septic spleen: foci of red pulp myelosis, plasma-leukocyte infiltration, hemolysis of erythrocytes, hemosiderin sedimentation, foci of necrosis.

It should be noted that the unfavorable course of COVID-19 was facilitated by comorbid pathology, which was diagnosed in life in 38 (92.7 %) patients who died from COVID-19. Thus, the vast majority had cardiovascular comorbidities, namely coronary heart disease (80.5 %) with arrhythmias in the form of permanent atrial fibrillation (29.3 %) and hypertension (75.6 %). The presence of type 2 diabetes mellitus in almost half of patients (46.3 %) and grade II–III obesity in every third patient (31.7 %) is noteworthy. It should be noted that more than half of the COVID-19 patients who died had a combination of three or more comorbid conditions (*Fig. 7*).

Pathomorphological changes in other organs of those who died due to COVID-19 reflect multiorgan failure, which arose due to acute respiratory failure of III degree and endogenous intoxication. On the other hand, pathomorphological changes indicate the presence of a number of comorbid states. It should be noted that pathomorphological signs of comorbid cardiovascular pathology were found somewhat more often than was diagnosed in life. There was high frequency of pathomorphological signs detection of necrotic changes in the kidneys (73.2 %), liver (90.2 %), selective neuronal necrosis in the brain (19.5 %) (*Table 2*).

According to the results of pathoanatomical examination, 9 (22.0 %) deaths due to COVID-19 developed



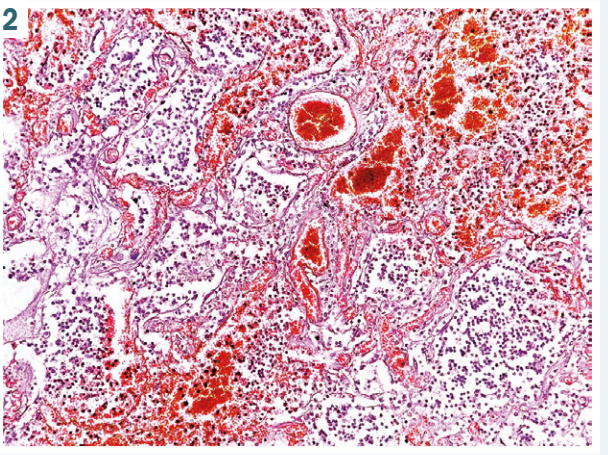
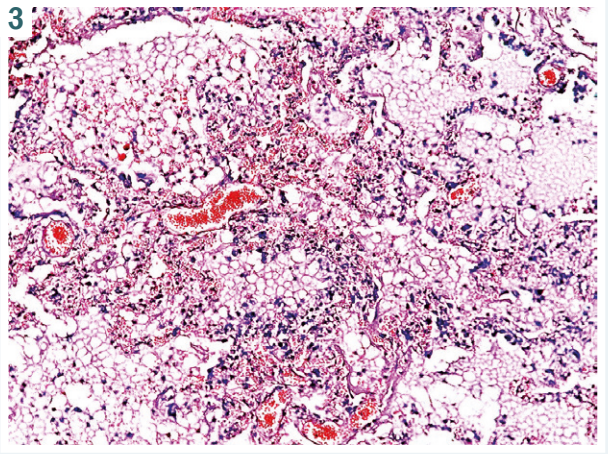


Fig. 1. Bilateral polysegmental pneumonia in COVID-19: significant swelling of the interlobular interstitium, lymphocyte-leukocyte exudate in the alveoli. Hematoxylin and eosin staining. Magnification: ×100.

Fig. 2. Bilateral polysegmental pneumonia in COVID-19: microvascular hyperemia and edema of the interalveolar septa, blood clots in the arterioles and venules, lymphocyte-leukocyte exudate and erythrocytes in the alveoli. Hematoxylin and eosin staining. Magnification: ×400.



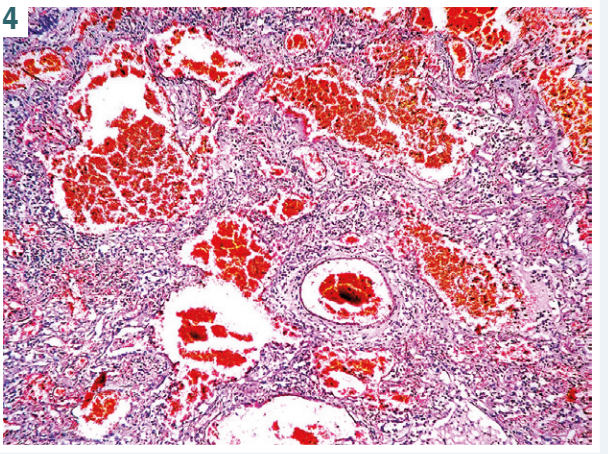
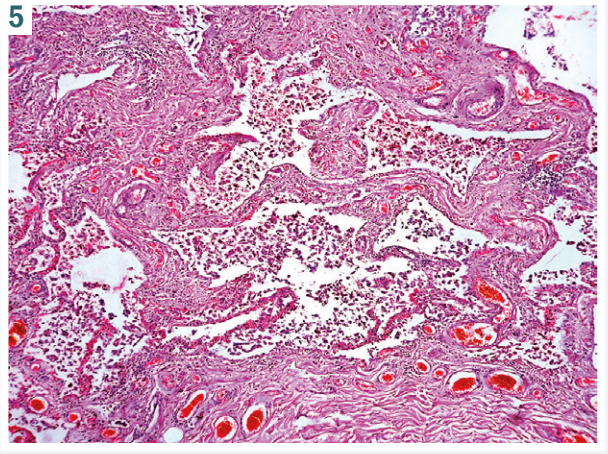


Fig. 3. Bilateral polysegmental pneumonia with COVID-19: predominantly alveolar edema, alveolocyte metaplasia. Hematoxylin and eosin staining. Magnifiation: ×400.

Fig. 4. Bilateral polysegmental pneumonia in COVID-19: mainly lymphocytic infiltration of thickened interalveolar septa, desquamation of alveolocytes, erythrocytes in alveoli. Hematoxylin and eosin staining. Magnification: ×300.



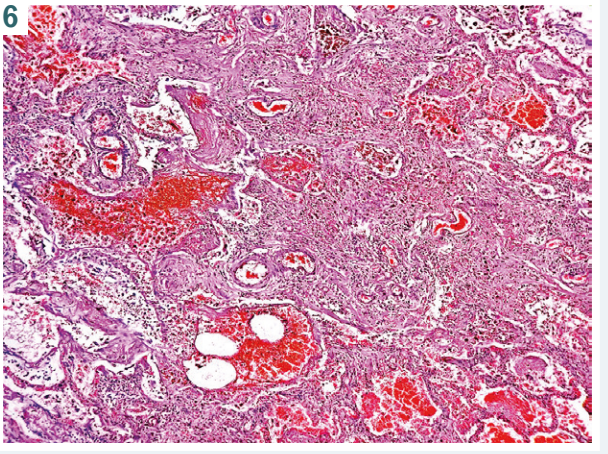


Fig. 5. Interalveolar membranes fibrosis, desquamated alveolocytes and macrophages in alveoli in bilateral polysegmental COVID-19 pneumonia. Hematoxylin and eosin staining. Magnification: ×200.

Fig. 6. Focal pneumosclerosis; erythrocytes, desquamated alveolocytes, macrophages and hemosiderophages in the alveoli in bilateral polysegmental COVID-19 pneumonia. Hematoxylin and eosin staining. Magnification: ×200.

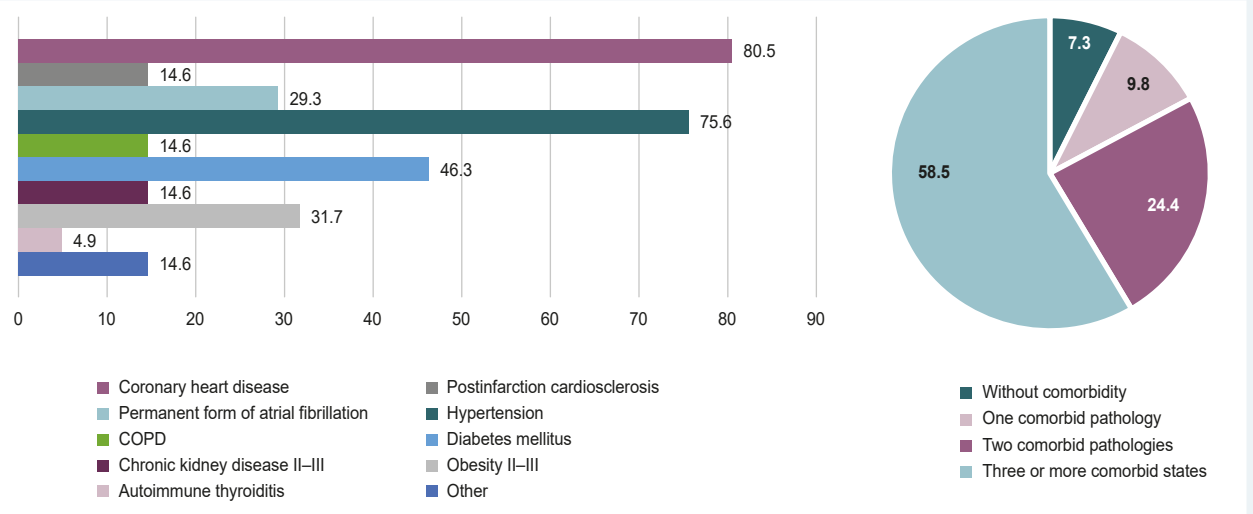


Fig. 7. The spectrum of comorbidity (A) and the combination of the frequency of comorbid conditions (B) of those who died as a result of COVID-19 (%).

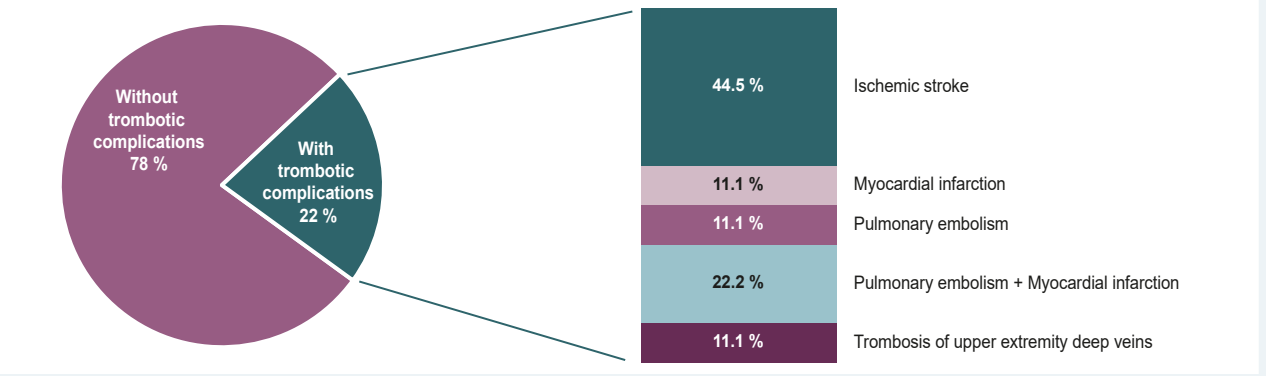


Fig. 8. Frequency and spectrum of pathological-anatomical signs detection of thrombotic complications in patients who died due to COVID-19 (%).

Table 2. Pathomorphological changes in other organs of patients who died of COVID-19, abs (%)

Pathomorphological sign	Detection frequency (n = 41)
Heart	
Atherosclerosis of coronary arteries in the stage of atheromatosis and calcification, stenosis of coronary arteries from 50 % to 75 %;	36 (87.8 %)
Diffuse interstitial cardiosclerosis;	37 (90.2 %)
Big-focal postinfarction cardiosclerosis;	3 (7.3 %)
Concentric or eccentric myocardial hypertrophy	32 (78.0 %)
Kidneys	
Acute tubular necrosis	30 (73.2 %)
Focal leuko-lymphocytic infiltration	5 (12.2 %)
Micro blood clots in blood vessels	7 (17.1 %)
Focal arterionephrosclerosis	25 (61.0 %)
Liver	
Focal centro-lobular necrosis	37 (90.2 %)
Foci of leuko-lymphocytic infiltration of the interstitial	3 (7.3 %)
Brain	
Ischemic stroke	4 (9.8 %)
Cerebral edema	25 (61.0 %)
Focal selective-neuronal complete and incomplete necrosis	8 (19.5 %)
Pancreas	
Liposclerosis and lipomatosis of the interparticle spaces with atrophy of the islet apparatus	12 (29.3 %)
Islet atrophy with amyloid accumulation and vascular hyalinosis	4 (9.8 %)

thrombotic complications. They led to the development of ischemic heart attack (4 patients); transmural myocardial infarction (1 patient); myocardial infarction complicated by focal infarction-pneumonia due to pulmonary embolism of small vessels of the pulmonary artery (2 patients); recurrent pulmonary embolism of small vessels of the pulmonary artery with the formation of multiple pulmonary infarctions of different statutes of limitations (1 patient); deep vein thrombosis of the upper extremity (1 patient) (*Fig. 8*). Thrombotic complications were not diagnosed during life in all patients: ischemic cerebral infarction was diagnosed in life in 3 patients on the basis of relevant clinical symptoms, transmural myocardial infarction – in 2 patients by electrocardiographic changes and elevated serum troponin I. Pulmonary embolism has not been diagnosed in a lifetime (*Fig. 2*).

Discussion

In the first publications of Chinese researchers, male gender and older age of patients with COVID-19 were identified as risk factors for adverse disease [13]. It was demonstrated that among patients in need of intensive care, death was observed mainly in patients older than 60 years. Each increase in age by 10 years was associ-

ated with a 58 % additional risk of adverse effects [14]. According to our data, 75.6 % of deaths due to COVID-19 are elderly and senile. However, the data presented in the literature on the effects of COVID-19 on the sex of the patient, show some contradictions. Thus, the authors [14] did not find differences in the survival of patients with severe COVID-19 depending on gender, but other researchers [15] showed a predominance of male patients (67 %) among those who died. According to the results of our study, men significantly predominated among those who died as a result of COVID-19 (73.2 %). It is assumed that one of the explanations for the higher percentage of severe COVID-19 and, accordingly, lethal outcome in men is a more pronounced expression of ACE2 than in women, but this statement still needs further study [16].

It is believed that the most common pathological sign in lethal cases of COVID-19 is diffuse alveolar damage [11,12]. In COVID-19, the acute stage is characterized by the presence of "hyaline membranes", and the phase of organization – varying degrees of fibroblasts and myofibroblasts proliferation [11,12]. Signs of diffuse alveolar damage have been described even in the absence of pulmonary ventilation, which was an additional confirmation of the viral nature of the changes found, excluding the effects of ventilation and oxygen [11,17]. Pathomorphological manifestations of diffuse alveolar damage in COVID-19 in 8 of 12 correspond to early acute respiratory distress syndrome [10]. The predominant findings are protein-enriched interstitial edema, "hyaline membranes", activated pneumocytes, microvascular thromboembolism, blood stasis in capillaries [10], as well as the presence of inflammation signs with lymphocytic infiltration [17]. Alveolar septa are unevenly dilated due to infiltrates of varying severity. They consist mainly of $CD4^+$ and $CD8^+$ T lymphocytes [11,17].

According to the results of our study, the early and dominant in the subsequent course of COVID-19 signs of lung damage in all deaths due to COVID-19 were significant interstitial-alveolar pulmonary edema with the presence of erythrocyte stasis and blood clots in microvessels. Bilateral polysegmental subtotal viral pneumonia in 90.2 % of deceased patients was manifested by significant edema and thickening of the alveoli walls with their moderate infiltration by lymphocytes, focal peribronchial and perivascular inflammatory polymorphonuclear infiltration, multiple small atelectases and dislectases. In the majority (87.8 %) of deaths from COVID-19, the presence of erythrocytes clusters, hemosiderophages and macrophages, squamous alveolar epithelium, as well as metaplasia of a few alveolocytes on the luminal surface of the alveoli (82.9 % of deaths) was determined. It was combined with the presence of absolute lymphopenia in the peripheral blood of 75.6 % patients. In patients with COVID-19, peripheral blood lymphopenia correlated with lymphocytic infiltration of the lungs. It was found during morphological examination of the lungs in the deceased, as reported by other researchers [14]. In their opinion, this coincides with the pathogenetic mechanism of viral infection.

Zinserling et al. [18] pay attention to the lesions that indicate a direct effect of the COVID-19: desquamation of the ciliated epithelial cells, the appearance of viral inclusions in the cells of the alveolar epithelium [18]. The role of the virus in the formation of these pathomorphological changes confirms the positive result of PCR on RNA SARS-CoV-2 in the study of lung tissue of deceased patients (9 of 12) in the range from 1.2×10^4 to 9.0×10^9 copies/ml [10]. Under conditions of viral infection, there is a significant cellular immune response. This is evidenced by mononuclear infiltration of lung tissue with the largest number of CD3+ T lymphocytes. Among them, CD2+, CD5+, CD8+ and the formation of small peribronchial clusters (CD20+) by B-lymphocytes are most often detected [18]. According to D. Wichmann et al. [10] epithelial metaplasia occurs at later stages of COVID-19.

The appearance of neutrophils in the lungs in diffuse alveolar damage is explained by the addition of secondary bacterial microflora [11,12]. The addition of secondary bacterial microflora in our study was pathomorphologically confirmed by the development of fibrinous-purulent tracheobronchitis and bilateral subtotal fibrinous-purulent bronchopneumonia in 4 patients, as well as bilateral fibrinous-purulent pleurisy in 3 (7.3 %) patients. Big-focal or sublobar pneumofibrosis was detected by us in 35 (85.4 %) patients who died on day 22–27 of the disease.

Particular attention is drawn to acute kidney damage, despite the fact that the respiratory system is the main target in COVID-19. It can also have a significant impact on the prognosis. Today, data on morphological changes that occur in the kidneys in patients with a critical course of this infection are accumulating. Thus, H. Su et al. [9] analyzed the pathological changes in the kidney tissue of 26 deaths due to the progression of respiratory failure and multiorgan failure syndrome in COVID-19. In 34.6 % of patients, there were laboratory signs in vivo of renal impairment in the form of increased serum creatinine and/or proteinuria, which occurred for the first time [9]. Pathomorphological signs of kidney damage according to the results of light microscopy were represented by diffuse damage to the proximal tubules with loss of border and even foci of necrosis. According to the results of electron microscopic examination, the researchers found accumulations of coronavirus-like particles in the tubular epithelium and in the podocytes of the glomeruli. The main targets for SARS-CoV-2 are tubular and glomerular visceral renal epithelial cells [9]. According to the results of our study, a lifetime increasing in creatinine levels in most patients (75.6 %) with a critical course of the disease was found. It revealed the pathomorphological examination in COVID-19 patients: acute tubular necrosis signs (73.2 %), focal leukocyte infiltration (12.2 %) and microthrombosis (17.1 %). Literature data suggest that renal cells absorb factors including systemic hypoxia, abnormal coagulation, and possibly rhabdomyolysis, which is associated with drug or hyperventilation [9]. Also immune inflammation was found. It was confirmed by immunohistochemical infiltration of T-lymphocytes (CD3+, CD8+) tissues of many organs, including the intestines, kidneys, adrenal glands [18].

In the modern literature in many studies, the authors draw attention to the significant frequency of thrombotic complications that occur in severe and critical course of COVID-19, and the complexity of their lifelong diagnosis [10,17]. This feature in COVID-19 is explained by the high

expression of ACE2 in the vascular endothelium. This to some extent explains both the presence of multiorgan lesions and the high risk of thrombosis [6]. The study of pathomorphological signs of thrombosis in patients with COVID-19 allowed researchers to use the term "pulmonary vasculopathy" [19,20]. Autopsy revealed deep vein thrombosis in 58 % of patients in whom venous thromboembolism was not suspected in life [10]. Pulmonary artery thromboembolism was the direct cause of death in one in three deaths due to COVID-19, while microthrombi were regularly detected in small arteries [10]. In our study, more than one in five deaths (22.0 %) due to COVID-19 was pathomorphologically diagnosed with signs of thrombotic complications, the presence of which in almost half of the cases was not established during life. Other researchers report the absence of clinical symptoms of thrombotic complications, including pulmonary embolism [17]. Researchers report clear macroscopic signs of pulmonary embolism in a pathoanatomical study in one of three deaths due to COVID-19 [11]. In addition, researchers have documented several cases not only of pulmonary embolism but also of prostate vein thrombosis, the presence of blood clots in the glomerular capillaries of the kidneys and alveolar capillaries [11].

When analyzing the results of pathomorphological changes, one should pay attention to the high frequency of morphological features in different organs. These changes indicate the presence of chronic comorbidities and a slightly lower level of lifelong diagnosis of these conditions. The vast majority of deaths due to COVID-19 had morphological signs of chronic cardiovascular pathology in the form of diffuse interstitial cardiosclerosis (90.2 %), big-focal postinfarction cardiosclerosis (7.3 %), atherosclerosis of coronary arteries with 50–75 % stenosis (87.8 %), myocardial hypertrophy (78.0 %), focal arteriosclerosis (61.0 %). It should be noted that lifelong coronary heart disease was diagnosed in 80.5 % and hypertension in 75.6 % of patients. Literature data also indicate that pre-existing chronic diseases can be identified in all deaths due to COVID-19 [10] with a predominance of the cardiovascular system chronic pathology in most cases, including high-grade coronary artery sclerosis; myocardial scarring, which indicates coronary heart disease, and congestive cardiomyopathy [10]. In the study [17], authors reported the detection of myocardial hypertrophy signs, atherosclerosis of the coronary artery with microscopic acute ischemia signs. Our previous studies on the prognostic role of comorbid pathology in COVID-19 demonstrated a statistically significant effect of the presence of chronic cardiovascular pathology and chronic kidney disease [21].

Conclusions

1. The lethal outcome of COVID-19 disease was recorded at day 22.0 [16.0; 27.0] of the disease. Among the dead, there is high percentage of early old age and middle old age patients (75.6 %), men (73.2 %), patients with comorbid pathology (92.7 %).

2. Early lung damage with COVID-19 in the deceased was determined by pronounced interstitial and interstitial-alveolar edema, the presence of erythrocyte stasis, blood clots and hypoperfusion leukocyte stasis in the pulmonary microvessels, as well as the presence in the alveoli of erythrocytes.

3. Bilateral polysegmental subtotal viral pneumonia in 90.2 % of dead patients was characterized by significant edema and thickening of the alveolar walls with their moderate infiltration by lymphocytes, focal peribronchial and perivascular inflammatory polymorphonuclear infiltration, multiple and small exfoliated alveolar epithelium (87.8 %), as well as metaplasia of a few alveolocytes preserved on the luminal surface of the alveoli (82.9 %).

4. One of ten deaths from COVID-19 showed signs of secondary bacterial microflora in the form of fibrinous-purulent tracheobronchitis and bilateral subtotal fibrinous-purulent bronchopneumonia, as well as bilateral fibrinous-purulent pleurisy (7.3 %) and sepsis. In 85.4 % of patients who died on day 22–27 of the disease focal or sublobar pneumofibrosis is determined.

5. In those who died as a result of COVID-19, multiorgan failure is characterized by focal necrosis of the renal tubular epithelium (73.2 %), focal lymphocytic-leukocyte infiltration (12.2 %) and renal microvascular thrombosis (17.1 %), focal centro-lobular necrosis 90.2 %) and focal lymphocytic-leukocyte infiltration of lobes (7.3 %) of the liver. Lifetime laboratory signs of renal failure were found in 75.6 % of patients, and hepatic failure – in 68.3 % of patients.

6. Pathomorphologically confirmed thrombotic complications occurred in 22.0 % of deceased patients: ischemic cerebral infarction (4 patients); transmural myocardial infarction (1 patient); myocardial infarction complicated by focal infarction pneumonia due to pulmonary embolism of pulmonary artery small vessels (2 patients); recurrent pulmonary embolism of pulmonary artery small vessels with the formation of multiple pulmonary infarctions of different ages (1 patient); deep vein thrombosis of the upper extremity (1 patient).

7. Morphological signs of chronic coronary heart disease and hypertension were identified in most deaths due to COVID-19: atherosclerosis and 50–75 % coronary artery stenosis (87.8 %), diffuse interstitial cardiosclerosis (90.2 %), focal postinfarction cardiomyocardial infarction (7.3 %), myocardial hypertrophy (78.0 %), focal arteriosclerosis (61.0 %). At the same time during the life of patients ischemic heart disease was diagnosed in 80.5 % of cases, hypertension – in 75.6 % of cases.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшло до редакції / Received: 09.10.2021
Після доопрацювання / Revised: 13.10.2021
Прийнято до друку / Accepted: 01.11.2021

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