

ASSOCIATION OF PULMONARY AND CUTANEOUS CHANGES IN COVID-19-RELATED CONDITIONS

Gradil G.I¹, Torianyk I.P^{2,3}, Yurko K.V¹, Shiyan D.M⁴, Merkulova N.F¹, Mohylenets O.I¹, Tkachenko V.G¹, Karmazina I.S¹, Lantukh A.P⁵, Hryhorov Y.B⁶, Gargin V.V^{1,4,7}.

¹Kharkiv National Medical University, Kharkiv, Ukraine.

²National Academy of Physical Culture, Kharkiv, Ukraine.

³Private enterprise Polymed, Dnipro, Ukraine.

⁴Private Institution of Higher Education «Kharkiv International Medical University», Kharkiv, Ukraine.

⁵Private Institution of higher education "Kharkiv Institute of Medicine and Biomedical Sciences", Kharkiv, Ukraine.

⁶University of medicine and social sciences, Kharkiv, Ukraine.

⁷Karazin Kharkiv National University, Kharkiv, Ukraine.

Abstract.

Introduction: The study of skin manifestations in COVID-19 is relevant due to the possibility of their appearance before the onset of the typical pattern of respiratory lesions, and the typicality of this pattern has changed noticeably with the emergence of new strains of the virus (nosomorphosis), therefore skin manifestations have both early diagnostic and possible prognostic value.

Aim: The aim of our study was to identify the relationship between the course of SARS-CoV-2 and its specific features of skin manifestations during the COVID-19 pandemic.

Materials and methods: A retrospective study of data from patients with maculopapular lesions who had COVID-19 was conducted. Among all the skin manifestations of COVID, we selected maculopapular lesions for a more detailed study, as one of the most frequent dermatological pathological processes in this disease. Based on the assessment of the area of the lesion and symptoms (the nature of itching, dryness, pain or other accompanying discomfort that interferes with normal activity, sleep; skin peeling), the degree of the course was assessed as mild, moderate, severe. The severe form of the acute respiratory syndrome of the coronavirus 2 (SARS-CoV-2) was diagnosed based on a complex of clinical and laboratory data obtained from the medical histories of persons undergoing examination. Among the clinical and laboratory data, we selected C-reactive protein (CRP - a blood plasma protein belonging to the group of acute phase proteins, the concentration of which increases during inflammation), D-dimer (a protein fragment that is formed during the dissolution of a blood clot that occurs during blood clotting), procalcitonin (a precursor of calcitonin, which is involved in calcium metabolism and maintains its constant level in the blood) and blood oxygen saturation level.

Results: It has been established that moderate and severe SARS-CoV-2 is characterized by skin lesions in the form of maculopapular lesions. Typical are itching, dryness, painful or other accompanying discomfort, skin peeling. In most patients with rash (198 patients (65.8%)) it was a generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. The average duration of the rash was 10.4 ± 2.21 days.

Conclusions: Among the studied signs, a strong correlation was found between the area of alveolar cell desquamation in the

lungs and such changes as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$, respectively), which could be established in deceased individuals. A high dependence of the area of skin lesions on the level of D-dimer ($r=0.71$) and procalcitonin ($r=0.70$) was also found.

Key words. SARS-CoV-2, skin, COVID-19, morphology, nail plate, pathology, maculopapular skin eruptions, desquamation.

Introduction.

Infectious diseases occupy a significant place in the history of mankind, given their prevalence [1-4]. In particular, the SARS-CoV-2/COVID-19 pandemic raises the possibility of the emergence of the next threat, which may be caused by new strains of coronavirus, avian or pandemic influenza. In order to determine how the clinical and morphological features of coronavirus disease are related, a huge number of studies have been conducted in recent years [5,6]. Usually reported on clinicopathological autopsy studies in COVID-19, and indicate that most patients have significant pulmonary pathology, widespread microscopic thromboses, and characteristic findings in the liver and lymph nodes. Most patients showed both exudative and proliferative diffuse alveolar damage [7]. Also often indicate serious endothelial damage in COVID-19, associated with destruction of endothelial cell membranes [8]. In COVID-19, the SARS-CoV-2 virus can cause damage to the lung epithelium, leading to inflammation and destruction of alveolar structures.

Almost from the very beginning of the pandemic, there has been an increase in reports of skin manifestations accompanying infection with the SARS-CoV-2 virus [9], in particular, such as skin angitis caused by SARS-CoV-2 itself; papulovesicular rashes; lichen rosacea and papulosquamous rashes; crusted rash; toxicoderma; urticaria; artificial (trophic) changes in facial tissues. Their etiology and pathogenesis cannot yet be considered definitively proven. Dermatological manifestations in COVID-19 may be due to the binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE2) receptors present in skin blood vessels, epithelial cells of endocrine glands, and the basal layer of hair follicles [10]. It is also suggested that these rashes may be caused by a cytokine storm that occurs as a response of an overactive immune system to the virus [9]. Undoubtedly, the possibility of skin manifestations due to adverse reactions to drugs used to treat patients with COVID-19 cannot be ruled out. Finally, American authors in their review

(2024) stated that the mechanisms of the appearance of a rash in COVID-19 have not yet been clearly established [11], while stress related to the COVID-19 pandemic may exacerbate some chronic dermatological diseases [12,13]. The study of skin manifestations in COVID-19 is also relevant due to the possibility of their appearance before the onset of the typical pattern of respiratory lesions, and the typicality of this pattern has changed noticeably with the emergence of new strains of the virus (nosomorphosis), therefore skin manifestations have both early diagnostic and possible prognostic value.

The goal of our work was to identify the relationship between the course of SARS-CoV-2 and its specific features of skin manifestations during the COVID-19 pandemic.

Materials and Methods.

The study was performed in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical Principles of Medical Research Concerning Human Subjects" (2013) with written informed consent. A retrospective study of data from patients with maculopapular lesions who had COVID-19 (n=301) was conducted. An analysis of cases due to COVID-19 observed in 2020, 2021, and 2023 at the municipal non-profit enterprise of the Kharkiv Regional Council "Regional Clinical Infectious Diseases Hospital" is presented. Medical records and autopsy protocols (34 deceased) were studied. The diagnosis of COVID-19 in patients was confirmed by PCR with the detection of SARS-CoV-2 RNA, in some patients, JgM and JgG to AG SARS-CoV-2 were detected by immunochromatographic study. An in-depth study of micropreparations of 34 patients who died from COVID-19 was conducted by Professor of the Department of Pathological Anatomy of Kharkiv National Medical University G.I. Gubina-Vakulyk. Average age ($M \pm m$) 61.1 ± 4.5 years deterioration of the condition from the onset of the disease 8.0 ± 2.4 days; bed days on average 6.5 ± 1.3 days; day of illness during hospitalization 9.2 ± 2.4 days; life expectancy 14.8 ± 2.9 days. A more detailed analysis of clinical data is given in our work [14]. To study the morphological state of the lungs, microscopic examination of sections of lung tissue placed on slides stained with hematoxylin and eosin was used [15,16]. With an emphasis on the morphological state of the lungs, pathohistological features of the state of the endothelium of microvessels, hemorrhagic manifestations, thrombus formation, and changes in the interstitial tissue of the lungs were assessed. To obtain digital indicators, the area of desquamation of alveocytes was determined.

Any new cutaneous manifestation not attributable to a previous/pre-existing skin disease or alternative diagnosis was considered COVID-19-related. Among all the skin manifestations of COVID, we selected maculopapular lesions for a more detailed study, as one of the most frequent dermatological pathological processes in this disease [17]. Based on the assessment of the area of the lesion and symptoms (the nature of itching, dryness, pain or other accompanying discomfort that interferes with normal activity, sleep; skin peeling), the degree of the course was assessed as mild, moderate, severe on day of most pronounced changes.

The severe form of the acute respiratory syndrome of the coronavirus 2 (SARS-CoV-2) was diagnosed based on a

complex of clinical and laboratory data [18] obtained from the medical histories of persons undergoing examination on day of admitting in hospital. Among the clinical and laboratory data, we selected C-reactive protein (CRP - a blood plasma protein belonging to the group of acute phase proteins, the concentration of which increases during inflammation), D-dimer (a protein fragment that is formed during the dissolution of a blood clot that occurs during blood clotting), procalcitonin (a precursor of calcitonin, which is involved in calcium metabolism and maintains its constant level in the blood) and blood oxygen saturation level (Table 1). Area of alveocytes desquamation was selected as most important pulmonary findings detected during autopsy [7]. Male and female distribution was equally presented in both groups.

Statistical processing of the data was performed using the Statistica for Windows 8.0 software package. Methods of descriptive statistics (determination of numerical characteristics of variables - arithmetic mean (M), mean sampling error (m), determination of the reliability of differences (p), which were tested via the Student-Fisher t -test in representative samples) were used. Correlation between indicators was assessed using Spearman's correlation coefficient (r). The difference in values between comparative indicators was considered significant at $p < 0.05$.

Results.

Maculopapular-erythematous rashes are characterized by an erythematous skin rash, flat erythematous macules, and/or raised papules. In our study maculopapular lesions (maculopapular rash) was observed as skin rash consisting of a combination of flat spots (macules) and raised bumps (papules) above the skin surface. Majority of patients with maculopapular lesions described that rash began on lower extremities and had spread centrally to her abdomen and upper extremities as non-urticarial, painless, and spared the palms, feet and mucosal surfaces. Indistinct erythematous patches to coalescent maculopapules, some with a violaceous center, in one patient progressed into pustules and desquamation. Mean duration of rash 10.4 ± 2.21 days. In the majority of patients with rash (198 patients (65.8%)) it was generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. Among those patients who did not die, the rash elements tended to slowly disappear. Moreover, seven maculopapular patterns are identified: morbilliform, other maculopapular eruptions, purpuric, similar to erythema multiforme, pityriasis rosea, as persistent raised erythema, and perifollicular.

Microscopic examination of the lungs revealed the presence of massive thrombosis of blood clots parietally in the absence of vascular endothelium, mainly of the microcirculatory bed. There was mainly serous and hemorrhagic exudate in the alveoli, infiltration of their walls by macrophages in interstitial pneumonia, desquamation of alveolocyttes. The nature of changes in the lungs of those who died from SARS-CoV-2 is shown in Figure 1.

The relationship between indicators of SARS-CoV-2 severity and clinical manifestations of skin lesions is presented in Table 2.

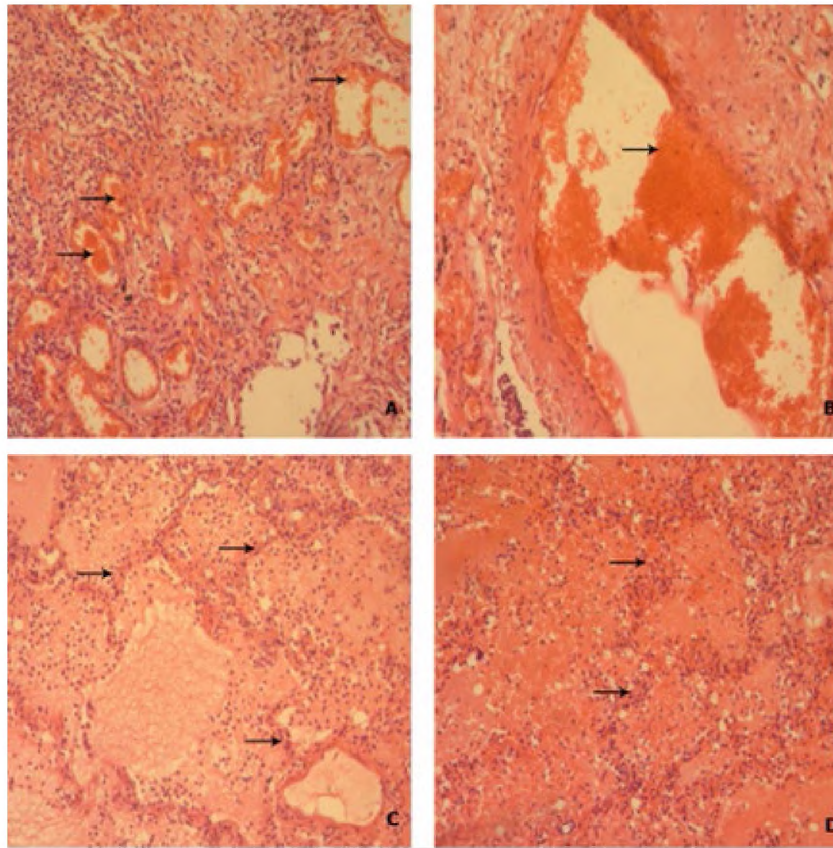


Figure 1. Morphological changes in the lungs of patients with a confirmed diagnosis of COVID-19. A. Several thrombi in the pulmonary vessels, including the parietal one (indicated by the arrow), complete absence of endothelium. Hematoxylin and eosin staining, magnification x200. B. Parietal thrombus growing into the lumen of the pulmonary vessel with the possibility of obstruction. Hematoxylin and eosin staining, magnification x200. C. Interstitial pneumonia. Serous and hemorrhagic exudate in the alveoli, infiltration of their walls by macrophages. Hematoxylin and eosin staining, magnification x200. D. Interstitial pneumonia, macrophages and lymphocytes in the alveolar walls (indicated by the arrows). Hematoxylin and eosin staining, magnification x200.

Table 1. Laboratory and microscopic findings in the COVID-19 patients.

Parameters and their values	
C-reactive protein, mg/l	98.63±9.17
D-dimer, ng/ml	769±32.82
Procalcitonin, ng/ml	0.64±0.13
Blood oxygen saturation level (%)	85.17±5.77
Area of desquamation of alveocytes (%)	74.13±7.02

Table 2. Relationship between SARS-CoV-2 severity indicators and clinical manifestations of skin lesions (*r*).

Severity index of SARS-CoV-2	Area of skin lesions	Severity of itching	Dry skin	Pain or other discomfort	Skin peeling
C-reactive protein	0.49	0.38	0.40	0.43	0.54
D-dimer	0.71	0.53	0.38	0.58	0.49
Procalcitonin	0.70	0.53	0.51	0.41	0.43
Oxygen saturation	0.36	0.47	0.67	0.51	0.45
Area of desquamation of alveocytes	0.73	0.63	0.66	0.64	0.74

Discussion.

Modern medicine is characterised by collaboration of specialists from variable fields [19-21]. The high level of contagiousness and asymptomatic transmission of the infection led to its rapid spread around the world and the development of a pandemic. Not only infectious disease specialists, but also general practitioners, outpatient clinics, anesthesiologists, intensive care physicians, neurologists, and dermatologists are faced with coronavirus infection. Skin manifestations of COVID-19 occur in approximately 20% of patients and sometimes appear before classic symptoms (cough, fever). They are caused by the immune system's response to the virus or microcirculation disorders, are most often self-limiting, and require mainly symptomatic treatment. Our study showed that patients with confirmed COVID-19 could display various cutaneous manifestations [22]. Maculopapular lesions (maculopapular rash) is a skin rash consisting of a combination of flat spots (macules) and raised bumps (papules) above the skin surface. It is not a separate diagnosis, but a symptom that can be a common skin manifestation of infection, mainly in adults. The hypothetical cause of the maculopapular rash could be a cytokine storm of the hyperinflammatory phase. It is generally accepted that such a rash could be an adverse reaction of the body to the drugs used to treat COVID-19, however, in some patients who were not treated pharmacologically, a maculopapular rash was found [23]. Vesicular "pox-like" lesions appeared predominantly on the trunk as monomorphic vesicles, occasionally with hemorrhagic contents, on an erythematous base, and resembled chickenpox. A potential pathophysiological mechanism for the appearance of vesicular lesions is a cytokine storm, which is the result of excessive reactivity of the immune system or direct effects of the coronavirus on the vascular endothelium [23,24]. It is suggested that the "morbilliform" erythematous lesions and skin lesions resembling erythema multiforme may not have been caused directly by SARS-CoV-2 infection.

Hyperactive immune responses in COVID-19 patients may contribute to the induction of a cytokine storm (particularly mediated by interleukin-6); these cytokines can infiltrate the skin, particularly dermal dendritic cells, lymphocytes, macrophages, mast cells, and neutrophils, and may contribute to the development of lesions such as maculopapular rash. This pattern of skin lesions has been previously described in diseases associated with hyperactive immune responses and excessive cytokine release (including systemic lupus erythematosus, adult-onset Still's disease, and antiphospholipid syndrome) [25]; cutaneous manifestations may be an early sign of immunological reactions in other parts of the body, similar to pulmonary infiltrates resulting from a cytokine storm.

From a histological point of view, several features of the maculopapular skin lesion in COVID-19 have been identified. Histological examination of the maculopapular lesions shows superficial perivascular dermatitis with lymphocytic infiltrate and dilated vessels in the papillary and mid-dermis with neutrophils, eosinophils and nuclear fragments. The epidermis shows scattered foci of hydropic changes accompanied by minimal acanthosis, subcorneal pustules, slight spongiosis, basal cell vacuolization, and foci of parakeratosis [17]. Similar

changes could be observed in other pathological processes also [26]. But it should be recognised with the detailing of pathogenetic links for adequate treatment [27-29].

A feature of our work was the identification of a possible relationship between the signs of the severity of the course SARS-CoV-2 and skin rashes. Among the studies conducted, a strong correlation between the area of alveolar cell desquamation in the lungs and changes such as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$ respectively), which could be established in deceased individuals. Also, a high dependence of the area of skin lesions on the level of D-dimer was found ($r=0.71$) and procalcitonin ($r=0.70$). Exactly detected correlations prove that described skin lesions are result of SARS-CoV-2 but not comorbidities, medication effects, and post-COVID conditions.

The above gives reason to assume that the mechanisms underlying desquamation in the lungs and skin lesions have similar links in pathogenesis, since the sequence of changes in the lungs and skin does not seem obvious.

A maculo-papular rash appears concomitantly with the other symptoms of infection and lasts for a short period (3–10 days), and itching is reported in most of the patients. It is often associated with severe disease in older patients [30]. Usually it's reported a prevalence of half patients. There is description of bed a perifollicular distribution in some cases and occasionally scaling. The erythematous rash may be particularly accentuated on the antecubital fossa and axillary folds. Skin biopsy shows some non-specific features of viral-related exanthema, such as slight spongiosis and mild perivascular lymphocytic infiltrate [30-32].

Potential reasons for this could be microthrombi formed due to activation of the complement system by immunoglobulins, increased concentrations of D-dimers and fibrin degradation products in the serum of patients with COVID-19, and prolonged prothrombin time.

There is a need to further diagnose the cutaneous manifestations of SARS-CoV-2 infection and to learn the detailed pathomechanism of their occurrence in order to better understand the essence of the disease and find an appropriate treatment method [12]. Using of digital medicine achievement should be implemented as way for obtaining faster diagnosis [33,34].

The study of skin manifestations of SARS-CoV-2 infection is important for the rapid identification of new patterns associated with the evolution of the virus, the adaptation of medical approaches to treatment and prevention, and is an important component of an effective strategy for responding to and preparing for pandemics [35,36]. The involvement of dermatovenereologists plays an important role in the response to the COVID-19 pandemic due to the possibility of early diagnosis of skin lesions indicative of SARS-CoV-2 infection, especially in asymptomatic cases, which will certainly contribute to improving the prognosis of the disease. Skin manifestations are significant for diagnosis, but they are difficult to recognize due to the impossibility of conducting routine dermatological consultations of such patients during the pandemic. Physicians' awareness of skin symptoms associated with COVID-19 infection is crucial to prevent misdiagnosis, as well as for the timely appointment of adequate treatment.

The skin, including mucous membranes, is an organ that frequently presents lesions caused by viral infections (e.g., dengue, Zika, measles, chickenpox, herpes zoster among others). These infections may be primarily localized in the skin or manifest at the cutaneous-mucosal level as part of the general symptomatology [37]. And maculopapular rashes could be pathophysiologically explained in SARS-CoV-2 by development of cytokine storm,

direct cytopathic effect of the moderate course SARS-CoV-2. The oral antihistamines, topical corticosteroids, systemic corticosteroids in more severe or generalized affections could be recommended for treatment [37].

Conclusion.

The maculopapular lesions is common manifestation of moderate and severe course of SARS-CoV-2. Typical are itching, dryness, painful or other accompanying discomfort, skin peeling. In most patients with rash (198 patients (65.8%)) it was a generalized process, more prominent on extremities. Bilateral jawline and periauricular area were affected in 234 (77.7%) patients. In 204 (67.8%) patients, rashes were observed on the abdomen. The average duration of the rash was 10.4 ± 2.21 days. Among the studied signs, a strong correlation was found between the area of alveolar cell desquamation in the lungs and such changes as the area of skin lesions, skin peeling ($r=0.73$ and $r=0.74$, respectively), which could be established in deceased individuals. A high dependence of the area of skin lesions on the level of D-dimer ($r=0.71$) and procalcitonin ($r=0.70$) was also found.

Acknowledgements.

The authors are sincerely grateful to Professor of the Department of Pathological Anatomy of Kharkiv National Medical University G.I. Gubina-Vakulyk for her assistance in interpreting microscopic slides.

Funding.

This research received no external funding.

Conflict of interest statement.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. Yakovlev S, Bazilevych K, Chumachenko D, et al. The concept of developing a decision support system for the epidemic morbidity control. *Ceur Workshop Proceedings*. 2020;2753:265-274.
2. Polyvianna Y, Chumachenko D, Chumachenko T. Computer aided system of time series analysis methods for forecasting the epidemics outbreaks. 2019 15th International Conference on the Experience of Designing and Application of CAD Systems. CADSM. 2019:1-4.
3. Savielieva N, Shelest M, Stoian O. Clinical features of generalized periodontitis of chronic course in patients with herpesvirus infection. *Kharkiv Dental Journal*. 2025;2:365-78.
4. Bondarenko AV, Pokhil SI, Lytvynenko MV, et al. Anaplasmosis: experimental immunodeficient state model. *Wiad Lek*. 2019;72:1761-1764.
5. Kamp JC, Neubert L, Ackermann M, et al. Time-Dependent Molecular Motifs of Pulmonary Fibrogenesis in COVID-19. *Int J Mol Sci*. 2022;23:1583.
6. Rzymiski P, Camargo CA Jr, Fal A, et al. COVID-19 Vaccine Boosters: The Good, the Bad, and the Ugly. *Vaccines (Basel)*. 2021;9:1299.
7. Elsoukkary SS, Mostyka M, Dillard A, et al. Autopsy Findings in 32 Patients with COVID-19: A Single-Institution Experience. *Pathobiology*. 2021;88:56-68.
8. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128.
9. Herrero-Moyano M, Capusan TM, Andreu-Barasoain M, et al. A clinicopathological study of eight patients with COVID-19 pneumonia and a late-onset exanthema. *J Eur Acad Dermatol Venereol*. 2020;34:e460-e464.
10. Abuelgasim E, Dona ACM, Sondh RS, et al. Management of urticaria in COVID-19 patients: A systematic review. *Dermatol Ther*. 2021;34:e14328.
11. Patel H, Tran L, Feldman SR. Overview of Dermatological Manifestations Associated with the COVID-19 Infection. *Skin Therapy Lett*. 2024;29:7-9.
12. Zaborska M, Chruszcz M, Sadowski J, et al. The most common skin symptoms in young adults and adults related to SARS-CoV-2 virus infection. *Arch Dermatol Res*. 2024;316:292.
13. Nikonov A, Shevchenko V, Shevchenko O, et al. Allergic and pseudoallergic reactions in dentistry. *Kharkiv Dental Journal*. 2026;3:181-202181-202.
14. Gradil G.I, Gubina-Vakulyk G.I, Yurko K.V, et al. COVID-19, pandemic influenza A (H1N1): clinical and pathoanatomical comparisons. *Infectious Diseases*. 2023;3:15-27.
15. Gargin V, Radutny R, Titova G, et al. Application of the computer vision system for evaluation of pathomorphological images. 2020 IEEE 40th International Conference on Electronics and Nanotechnology, ELNANO 2020 - Proceedings; 2020:469-473.
16. Krivenko S, Krylova O, Bataeva E, et al. Smart lossy compression of images based on distortion prediction. *Telecommunications and Radio Engineering (English translation of Elektrosvyaz and Radiotekhnika)*. 2018;77:1535-1554.
17. Shams S, Rathore SS, Anvekar P, et al. Maculopapular skin eruptions associated with Covid-19: A systematic review. *Dermatol Ther*. 2021;34:e14788.
18. Statsenko Y, Al Zahmi F, Habuza T, et al. Prediction of COVID-19 severity using laboratory findings on admission: informative values, thresholds, ML model performance. *BMJ Open*. 2021;11:e044500.
19. Shevchenko A, Shevchenko V, Pomogaybo K, et al. The system of risk factors for diseases in valeological disciplines. *Inter Collegas*. 2025;12:48-5.
20. Marakushyn D, Maslova N, Pandikidis N, et al. Modern methods of cognitive functions analysis (literature review, part 2). *Experimental and Clinical Medicine*. 2025;94.
21. Schenström A, Rönberg S, Bodlund O. Mindfulness-based cognitive attitude training for primary care staff: A pilot study. *Complement Health Pract Rev*. 2006;11:144-52.

22. Carrascosa JM, Morillas V, Bielsa I, et al. Cutaneous Manifestations in the Context of SARS-CoV-2 Infection (COVID-19). *Actas Dermosifiliogr (Engl Ed)*. 2020;111:734-742.
23. Türsen Ü, Türsen B, Lotti T. Cutaneous side-effects of the potential COVID-19 drugs. *Dermatol Ther*. 2020;33:e13476.
24. Genovese G, Moltrasio C, Berti E, et al. Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. *Dermatology*. 2021;237:1-12.
25. Novak N, Peng W, Naegeli MC, et al. SARS-CoV-2, COVID-19, skin and immunology - What do we know so far? *Allergy*. 2021;76:698-713.
26. Lytvynenko M, Bocharova T, Zhelezniakova N, et al. Cervical transformation in alcohol abuse patients. *Georgian Med News*. 2017;271:12-17.
27. Januzis G, Beleckas P, Statkevicius M, et al. Changes in the prevalence of antibiotic self-medication based on data from surveys conducted in 2014 and 2025. *Kharkiv Dental Journal*. 2026;3:75-87.
28. Rai M, Sinkar S, Kon K. Combining essential oils with antibiotics and other antimicrobial agents as a way of coping with multidrug resistant bacteria. in *Fighting Multidrug Resistance with Herbal Extracts, Essential Oils and Their Components (Second Edition)*, Academic Press. 2025:245-270.
29. Kon K, Rai M. Antibiotic Resistance: Mechanisms and New Antimicrobial Approaches. *Antibiotic Resistance: Mechanisms and New Antimicrobial Approaches*. 2016:1-413.
30. Gisondi P, Plaserico S, Bordin C, et al. Cutaneous manifestations of SARS-CoV-2 infection: a clinical update. *J Eur Acad Dermatol Venereol*. 2020;34:2499-2504.
31. Nyasulu PS, Tamuzi JL. Epidemiology, clinical profiles, and prognostic value of COVID-19-related cutaneous manifestations in African populations: a rapid narrative review. *Int J Dermatol*. 2024;63:10-22.
32. Martora F, Villani A, Fabbrocini G, et al. COVID-19 and cutaneous manifestations: A review of the published literature. *J Cosmet Dermatol*. 2023;22:4-10.
33. Alekseeva V, Nechyporenko A, Frohme M, et al. Intelligent Decision Support System for Differential Diagnosis of Chronic Odontogenic Rhinosinusitis Based on U-Net Segmentation. *Electronics (Switzerland)*. 2023;12.
34. Nechyporenko A, Frohme M, Strelchuk Y, et al. Galvanic Skin Response and Photoplethysmography for Stress Recognition Using Machine Learning and Wearable Sensors. *Applied Sciences*. 2024;14:11997.
35. Wong CSM, Hung IFN, Kwan MYW, et al. Cutaneous manifestations, viral load, and prognosis among hospitalised patients with COVID-19: a cohort study. *Hong Kong Med J*. 2023;29:421-431.
36. Momtazmanesh S, Ochs HD, Uddin LQ, et al. All together to Fight COVID-19. *Am J Trop Med Hyg*. 2020;102:1181-1183.
37. Fernández-Lázaro D, Garrosa M. Identification, Mechanism, and Treatment of Skin Lesions in COVID-19: A Review. *Viruses*. 2021;13:1916.