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Evolution and consequences of moderate and severe SARS-CoV-2 pneumonia depending on comorbidities

PHD THESIS SUMMARY

PhD supervisor:

PROF. UNIV. DR. BOGDAN MIRON ALEXANDRU

PhD student:

SORA (căs. CRISTEA) ALEXANDRA-MARIA

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The fundamental problem

This PhD thesis started from the desire to study a completely new disease that the entire medical community has faced and which even at the time this paper was published does not benefit from a specific treatment.

From the first case of pneumonia of unknown cause that appeared in Wuhan province of China on 8th December 2019 [1], to the declaration of a pandemic by the World Health Organization on March 11, 2020 [2], the whole world and especially the medical community, watched terrified how a new virus named SARS-CoV-2 [3] produced severe pneumonia, initially in China, then in Europe, and later throughout the world.

The disease caused by it, COVID-19, is not fully understood even at this time, despite the efforts of the medical community. The development of a vaccine quickly became the main concern for disease prevention, and efforts led to the approval of the first messenger RNA vaccine on August 23, 2021 [4]. In addition to these, numerous therapies have been tried to treat the disease and its complications, some with good results, and in the case of other medications the recommendation was to eliminate them from the treatment protocols.

The WHO declared the end of the pandemic on May 5, 2023, with the mention that there is still a risk related to the new variants of the virus [5].

Although preventive measures have been taken, several vaccines have been developed, quarantine has been instituted, and the entire medical community has concentrated its physical and intellectual forces to fight this virus, on April 2024 there are over 767 million of confirmed cases and nearly 7 million deaths worldwide [6].

Research ipothesis

The hypothesis of this research was to determine if the evolution of patients with SARS-CoV-2 pneumonia is influenced by the associated pathology, especially if it is cardiovascular comorbidities or type 2 diabetes and if the therapy administrated had an influence on the outcomes. In addition to this, the purpose was to observe sequelae imaging or respiratory functional changes in patients cured of the disease of COVID-19.

The study objectives

The main objective of the study is to follow the evolution of hospitalized patients with a moderate or severe form of the disease, depending on demographic data, clinical manifestations, therapy administered, associated comorbidities or the need for admission to an Anesthesia and Intensive Care Unit.

Another objective was to study the complications developed by these patients in the short term (during hospitalization) and in the medium-long term (through a re-evaluation after discharge from the hospital).

Last but not least, another objective was to determine some risk factors that may lead to an unfavorable prognosis in the case of patients with SARS-CoV-2 pneumonia.

Research methodology

The study is retrospective observational, non-randomized, which included cases admitted to "Marius Nasta" Institute of Pneumology between March 2020 and August 2021, using the H3 Concept hospital program - Hippocrate medical system, from which the medical letters of these patients were extracted. The period includes hospitalized cases in the first three waves of the pandemic. All data were entered into the Microsoft Excel program version 2016, and the statistical analysis was performed using the R program, version 4.0.2.

From the total number of 2837 cases, those that met the criteria for inclusion in the study were selected, the final group including 1844 hospitalized patients with SARS-CoV-2 pneumonia, whose evolution was cured/deceased/transferred.

For the analysis of risk factors, transferred cases where the evolution could not be followed were excluded, the analysis being performed on a sample of 1813 cases, provided that the data are complete.

The inclusion criteria in the study are: age over 18 years; signing the informed consent at the time of admission; SARS-CoV-2 infection confirmed by one of the following tests: rt-PCR, rapid antigen test or IgG or IgM anti-SARS-CoV-2 antibodies; imaging lesions compatible with the diagnosis of SARS-CoV-2 viral pneumonia described in the literature: chest X-ray or computed tomography; detailed epicrisis, containing data about symptomatology or clinical examination (especially saturation at admission), associated comorbidities, complications

occurred during hospitalization and the patient's evolution; complete scheme of treatment administered during hospitalization (also verified during the epicrisis).

Exclusion criteria are: suspected cases, who had at least one negative PCR or rapid Ag test and who did not have any of these positive tests during hospitalization; the absence of imaging analysis such as chest X-ray or chest computed tomography or analysis present and within normal limits, on which no suggestive lesions are described to be compatible with the diagnosis of pneumonia; lack of informed consent.

Limitations of the study are as follows: (1) no data could be obtained on the type of virus strain with which the patients were infected; (2) only blood samples from admission could be analyzed, their subsequent evolution could not be followed; (3) the duration of the hospitalization could not be analyzed, because during the period that included the cases, hospitalization for at least 14 days was mandatory for each confirmed patient; (4) only the first 3 waves of the pandemic were included during the study period; (5) no data were available on patients' previous home treatment for SARS-CoV-2 infection, duration or type of medication used; (6) the chest computer tomography examination was performed in most cases only at admission; a reassessment would also have been useful, but this was not possible in many cases; (7) the percentage of damage in the chest CT scan was not available in all cases; (8) could not differentiate between type 1 or type 2 diabetes because there was only one case of type 1 diabetes; (9) glycosylated hemoglobin could not be assessed on admission to see glycemic control in the past 3 months and determine whether it is newly diagnosed, unbalanced diabetes or whether hyperglycemia is the acute consequence of viral infection; (10) body mass index was not available to see if there is a correlation between obesity and possibly its degree and infection with the SARS-CoV-2 virus; (11) in order to establish the "long COVID" impact, assessments were needed at set time intervals after discharge, for example 3, 6 and 12 months, at least two assessments to be able to obtain statistically significant data; (12) for reassessments, the 6-minute walk test and the mMrc dyspnea scale may be useful; (13) the smoker/non-smoker status was unknown.

The structure of the chapters

The thesis is structured in eight chapters, the general part includes Chapters 1 and 2, the special part includes Chapters 5, 6, 7 and Chapter 8 with the conclusions and personal contributions.

Chapter 1 presents general data about the SARS-CoV-2 virus. It belongs to the coronavirus family and is an enveloped virus with positive RNA polarity [7] whose viral reservoir is the bat [8]. It has four proteins in its structure, M, S, N and E, each of them having different structural and functional roles. Protein S constitutes the spicules that give the appearance of the crown of the virus and favors the penetration into the host cell, through the binding of the S1 subunit by the ACE 2 receptors on its surface [9,10]. The abundance of these receptors in the body makes the virus affect any organ, but having an increased tropism for the respiratory system [11,12]. The pathological processes that occur after infection are hyperinflammation, endothelitis and procoagulant status [13]. Symptomatology may be absent in approximately one third of infected cases [14], but when present, it consists of: fever, chills, disturbances of taste or smell, persistent cough, loss of appetite and myalgia [15]. Dyspnea can be present, but not perceived by the patient, in which case it is the consequence of a hypoxemia called˝silent hypoxemia˝ or ˝happy hypoxemia˝ [16]. The diagnosis of the infection is mainly made by a quantitative method of reverse transcription of the polymerase chain reaction (reverse transcription quantitative polymerase chain reaction or rt-PCR) [13]. Blood tests show some changes characteristic for the infection, and high-resolution chest CT examination is a sensitive diagnostic method, which can detect lesions from the early stages [17].

In Chapter 2, are presented data on the COVID-19 disease. This includes five clinical forms, defined according to symptomatology and clinical or laboratory changes and which guide the administered therapy [18]. From the point of view of comorbidities, the most common are type 2 diabetes and hypertension, which are also the main negative prognostic factors related to the associated pathology [19]. The increased tropism of the virus causes any organ to be affected, so that patients' comorbidities may suffer decompensations. At the same time, certain drugs used in chronic background treatment can worsen the evolution of patients, an example of this being metformin used first-line in the case of type 2 diabetes and which can cause lactic acidosis in the presence of hypoxia, requiring insulin replacement [20].

The therapy administered to patients with COVID-19 disease is still under research, with treatment guidelines being updated in real time, with some therapies being excluded from the recommendations. There are several ongoing studies, one of the largest being the RECOVERY study.

Another aspect related to the disease involves the complications that appear, both during hospitalization and at a distance from it, the sequelae changes being grouped under the name of″ long COVID″and can involve any organ.

Chapters 3 and 4 include research objectives, methodology, study inclusion and exclusion criteria, study limitations, and descriptive statistics data about the entire sample.

Chapter 5 includes the study of the therapy administered in the case of the entire sample including 1844 patients, medication administered according to the specific recommendations issued by Orders issued by the Ministry of Health. It was observed that in the case of certain therapies (corticosteroids, antibiotics, Remdesivir and Tocilizumab) mortality was higher, but this is most likely related to the severity of the form of the disease, this medication being recommended in the case of severe and critical forms. At the same time, in order to be able to issue pertinent conclusions with statistical significance, a placebo-controlled study would be necessary. Regarding the preference for a certain treatment in patients with diabetes or cardiovascular diseases, no statistical significance was identified for any drug.

Anticoagulant medication was administered in a percentage of over 90% each month, but 95 cases with thromboembolic events were identified, of which 94 benefited from anticoagulants. Administration of antibiotics is over 50% every month, but studies have shown that bacterial superinfection occurs in 3-10% of hospitalized patients, and even if over 50% received antibiotics, only 5% required this therapy [21]. Corticosteroids had a reduced administration in the first months, later exceeding 90%, the recommendation being in the case of those with respiratory insufficiency [22]. Of the specific antiviral medication, hydroxychloroquine and the lopinavir/ritonavir combination were administered only based on the recommendations, being discontinued when they changed. Tocilizumab had a reduced monthly administration, most likely based on availability and recommendations for critical forms. The main antivirals used were Remdesivir and Favipiravir.

Chapter 6 includes two studies: the identification of short-term complications, which occur during hospitalization and for the analysis of which the entire sample was included, and

the second study which is about medium-long-term complications and which was carried out on a sample of 402 cases, which they had mentioned the lesional percentage on the chest CT exam. Among the short-term complications, the most common are the respiratory and metabolic ones. Of the respiratory complications, approximately 98% represent respiratory failure and approximately 2% are represented by pneumomediastinum and pneumothorax. The latter have a low incidence of less than 1% [23], which can increase up to 15% in the case of those intubated and mechanically ventilated, secondary to the associated barotrauma [24]. However, this is a controversial theory, with some studies identifying pneumomediastinum as a complication of ARDS associated with severe forms of the disease [25].

Metabolic complications identified are the consequence of injury to the pancreas, liver or kidney. Hyperglycemia was identified in 805 cases, of which only 315 were known to have diabetes prior to admission. Renal injury was identified by GFR calcification and was identified in 787 cases, of which 62 had prior renal pathology. Liver injury was considered at higher values of liver transaminases, respectively at doubling the normal value and was identified in 235 cases, of which 77 had previous liver pathology.

The cardiovascular complications identified are thromboembolic events in 4.82% of the number of cases, with the main headquarters at the level of the pulmonary vessels and arrhythmias, the most frequent being atrial fibrillation. Enterocolitis was identified at a percentage below 2% as well as infectious complications, in the case of the latter the percentage is probably underestimated due to the lack of bacteriological tests, the main infection being enterocolitis with Cl. diff and lung-based infections. A percentage below 2% were also hemorrhagic complications, based most frequently at the level of the digestive tract, and neurological complications were identified at approximately 1.5%.

Medium-long-term complications were analyzed in a number of 100 cases from the sample of 402, those who came for evaluation after hospital discharge. A statistical analysis could not be performed, as a minimum of two evaluations at set time intervals were required, but some observations were made: of the 81 who had respiratory failure during hospitalization, 22 were discharged with long-term oxygen therapy at home, and at reassessment 7 had SpO2 lower than 90%; 47 stated dyspnea at the re-evaluation, out of the 70 who mentioned this symptom at the onset of the disease; out of 42 CT re-examinations, 1 shows sequelae changes, most of them with lesions in regression; the main change in respiratory tests is DVR, FEV1 is

decreased in 25 cases out of 87 evaluated, and DLCO is decreased in 44 cases out of 62 evaluated; 14 cases had known previous lung pathology.

Chapter 7 includes a study carried out on a sample of 1813 cases from the total number, whose evolution was towards healing or death. The aim was to identify risk factors by calculating the OR. Demographic data, symptomatology since the onset of the disease, comorbidities, laboratory investigations (parameters from blood tests), oxygen saturation at admission and the need for admission to an ATI department were analyzed. We identified male gender and advanced age as risk factors, a meta-analysis also identified these demographics as risk factors with OR=1.32 for male and OR=1.05 for each additional year of age [26]. Dyspnea is the main risk factor among symptoms at onset, with OR=2.72 in our study and a double OR in a meta-analysis that included 2091 patients [27]. Among the comorbidities, we identified as risk factors cardiovascular pathology, diabetes, chronic kidney disease and previous neurological pathology, and pulmonary and oncological diseases had no statistical significance.

Among the laboratory analyses, we identified the increased value above 554 ng/mL of D-dimers as a risk factor, with a mortality of 20%. A meta-analysis that included 40,614 patients showed that they are independent factors of mortality [28]. Other parameters identified as determining a negative prognosis are: high levels of neutrophils, leukocytosis, low lymphocytes, thrombocytopenia, neutrophil/lymphocyte ratio. Low saturation at admission is associated with a mortality of 24% for values <88%, and for admission to the ATI ward we identified mortality at approximately 60%.

The risk was also analyzed in the case of the association of age with diabetes or cardiovascular pathology, and it was identified that the influence of these diseases on mortality is greatly diminished in the case of patients under 51 years of age and those over 70 years of age.

Conclusions

1. Administered therapy was based on recommendations issued by some Ministry of Health Orders, updated according to real-time research results, but in the case of certain drugs (such as anticoagulants) the decision was made on the basis of medical judgment.

2. Some drugs have been associated with a higher risk of mortality, but this is most likely due to the fact that they were indicated more for severe and critical forms of the disease.

3. The most common complications identified are respiratory and metabolic, and among the respiratory complications, the most common is respiratory failure.

4. Pneumothorax and pneumomediastinum have a low incidence and do not appear to be associated with mechanical ventilation.

5. The most common nosocomial infection is enterocolitis with Clostridium difficile, but it is very possible that there is an underestimation of nosocomial infections, due to the lack of bacteriological confirmation.

6. Acute organ injury due to viral infection can be evidenced by biochemical changes such as hyperglycemia, increased liver transaminases and decreased glomerular filtration rate, in the conditions in which they occurred in patients without previously known pathology.

7. Among the cardiovascular complications, the most frequent were thromboembolic events, especially in the pulmonary vessels, and the most frequent arrhythmia is atrial fibrillation.

8. The main risk factors with the highest mortality are represented by respiratory failure and admission to the ATI ward.

9. From a paraclinical point of view, risk factors are: leukocytosis, lymphopenia, neutrophilia, thrombocytopenia, but especially high values of D-dimers and RNL.

10. From the point of view of symptoms, dyspnea is the only identified risk factor.

11. The comorbidities with the strongest impact on mortality are cardiovascular and type 2 diabetes, the presence of pre-existing pulmonary and oncological conditions not representing negative prognostic factors.

Personal contributions

1. I created an assemblage image regarding the therapeutic management of patients hospitalized in a first-line COVID center, starting with the onset of the pandemic and covering the first three waves of infection, a period when therapeutic guidelines and research were in their infancy.

2. I identified short-term complications that made the management of hospitalized patients difficult.

3. I identified the risk added by the existence of some comorbidities, but also the fact that certain diseases such as chronic pulmonary and oncological conditions are not risk factors for a negative prognosis in our study.

4. I briefly presented a hospitalized case in which embolic complications progressed despite anticoagulant treatment, and the changes given by the existence of pneumomediastinum improved even though the patient was intubated and mechanically ventilated, a situation that is controversial in the literature, mechanical ventilation being incriminated in development of pneumomediastinum.

5. I have identified negative prognostic factors that are easily obtained from demographic data, clinical parameters, or blood samples obtained since the admission of patients.

6. I analyzed the risk for different symptoms and identified a population that presents a maximum risk of an unfavorable prognosis, being represented by those who have dyspnea from the onset, but without cough, without fever and without anosmia.

Future possible research

The current study leaves room for much further research, leaving many unanswered questions related to SARS-CoV-2 virus infection or the pandemic:

- the impact of the infection from the point of view of symptoms and imaging changes depending on the smoking or non-smoking status of the individual;
- the differences between the infecting strain, respectively between the cases included in each wave;
- the impact of the virus in terms of type 2 diabetes, whether it is a pre-existing pathology or a consequence of the COVID disease;
- the framing of the long-term COVID as an independent pathology and possible therapeutic options for it - can residual lung changes be reversible?
- the effectiveness of vaccination against SARS-CoV-2 in Romania;
- are there laboratory changes in the blood samples in the dynamics, which can suggest the unfavorable evolution of a case?;
- are there individual protective factors that determine the evolution of the infection towards a mild or moderate form of the disease and the cure of pneumonia without sequelae?;
- identifying an effective and specific treatment against the SARS-CoV-2 virus.

Bibliography

1. 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*, 323(13):1239-1242, 2020

2. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation report – 51. https://www.who.int/docs/default-source/coronaviruse/situation-reports/2... , 2020

3. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*, 5(4):536-544, 2020

4. Padda IS, Parmar M. COVID (SARS-COV-2) Vaccine. [Updated 2023 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: ous (COVID-19) Dashboard, Global Situation, accesed on June 28Th 2023, https://covid19.who.int/. 2023

5. Statement of the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic, https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic, 2005

6. WHO Coronavirus (COVID-19) Dashboard, Global Situation, accesed on June 28Th 2023, https://covid19.who.int/, 2023

7. Drosten C, Preiser W, Günther S, Schmitz H, Doerr HW. Severe acute respiratory syndrome: identification of the etiological agent. *Trends Mol Med*, (8):325-7, 2003

8. Lau SKP, Luk HKH, Wong ACP, Li KSM, Zhu L, He Z, Fung J, Chan TTY, Fung KSC, Woo PCY. Possible Bat Origin of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg Infect Dis*, 26(7):1542-1547, 2020

9. Chilamakuri R, Agarwal S. COVID-19: Characteristics and Therapeutics. *Cells*, 10(2):206, 2021

10. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426(6965):450-4, 2003

11. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*, 12(1):8, 2020

12. Al-Tawfiq JA, Zumla A, Memish ZA. Travel implications of emerging coronaviruses: SARS and MERS-CoV. *Travel Med Infect Dis*, 12(5):422-8, 2014

13. Marik PE, Iglesias J, Varon J, Kory P. A scoping review of the pathophysiology of COVID-19. *Int J Immunopathol Pharmacol*, 35:20587384211048026, 2021

14. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review. *Ann Intern Med*, 174(5):655-662, 2021

15. Elliott J, Whitaker M, Bodinier B, Eales O, Riley S, Ward H, Cooke G, Darzi A, Chadeau-Hyam M, Elliott P. Predictive symptoms for COVID-19 in the community: REACT-1 study of over 1 million people. *PLoS Med*, 18(9):e1003777, 2021

16. Hentsch L, Cocetta S, Allali G, Santana I, Eason R, Adam E, Janssens JP. Breathlessness and COVID-19: A Call for Research. *Respiration*, 100(10):1016-1026, 2021

17. Shatri J, Tafilaj L, Turkaj A, Dedushi K, Shatri M, Bexheti S, Mucaj SK. The Role of Chest Computed Tomography in Asymptomatic Patients of Positive Coronavirus Disease 2019: A Case and Literature Review. *J Clin Imaging Sci*, 10:35, 2020

18. IDSA guidelines on the treatment and management of patients with COVID-19. Infectious Diseases Society of America. Updated June 29, 2022. Accessed July 21, 2022. www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-23. 2022

19. Al-Hussain OH. Complications and Comorbidities in COVID-19 Patients: A Comparative study. *Cureus*, 14(8):e28614, 2022

20. Liang Z, Yang M, Xu C, Zeng R, Dong L. Effects and safety of metformin in patients with concurrent diabetes mellitus and chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Endocr Connect*, 11(9):e220289, 2022

21. Vaughn VM, Gandhi TN, Petty LA, Patel PK, Prescott HC, Malani AN, Ratz D, McLaughlin E, Chopra V, Flanders SA. Empiric Antibacterial Therapy and Community-onset Bacterial Coinfection in Patients Hospitalized With Coronavirus Disease 2019 (COVID-19): A Multi-hospital Cohort Study. *Clin Infect Dis*, 72(10):e533-e541, 2021

22. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A,

Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*, 384(8):693-704, 2021

23. Melhorn J, Achaiah A, Conway FM, Thompson EMF, Skyllberg EW, Durrant J, Hasan NA, Madani Y, Naran P, Vijayakumar B, Tate MJ, Trevelyan GE, Zaki I, Doig CA, Lynch G, Warwick G, Aujayeb A, Jackson KA, Iftikhar H, Noble JH, Ng AYKC, Nugent M, Evans PJ, Hastings RA, Bellenberg HR, Lawrence H, Saville RL, Johl NT, Grey AN, Ellis HC, Chen C, Jones TL, Maddekar N, Khan SL, Muhammad AI, Ghani H, Myint YMM, Rafique C, Pippard BJ, Irving BRH, Ali F, Asimba VH, Azam A, Barton EC, Bhatnagar M, Blackburn MP, Millington KJ, Budhram NJ, Bunclark KL, Sapkal TP, Dixon G, Harries AJE, Ijaz M, Karunanithi V, Naik S, Khan MA, Savlani K, Kumar V, Gallego BL, Mahdi NA, Morgan C, Patel N, Rowlands EW, Steward MS, Thorley RS, Wollerton RL, Ullah S, Smith DM, Lason W, Rostron AJ, Rahman NM, Hallifax RJ. Pneumomediastinum in COVID-19: a phenotype of severe COVID-19 pneumonitis? The results of the United Kingdom (POETIC) survey. *Eur Respir J*, 60(3):2102522, 2022

24. McGuinness G, Zhan C, Rosenberg N, Azour L, Wickstrom M, Mason DM, Thomas KM, Moore WH. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. *Radiology*, 297(2):E252-E262, 2020

25. Chu CM, Leung YY, Hui JY, Hung IF, Chan VL, Leung WS, Law KI, Chan CS, Chan KS, Yuen KY. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. *Eur Respir J*, 23(6):802-4, 2004

26. Li Y, Ashcroft T, Chung A, Dighero I, Dozier M, Horne M, McSwiggan E, Shamsuddin A, Nair H. Risk factors for poor outcomes in hospitalised COVID-19 patients: A systematic review and meta-analysis. *J Glob Health*, 11:10001, 2021

27. Shi L, Wang Y, Wang Y, Duan G, Yang H. Dyspnea rather than fever is a risk factor for predicting mortality in patients with COVID-19. *J Infect*, 81(4):647-679, 2020

28. Li Y, Deng Y, Ye L, Sun H, Du S, Huang H, Zeng F, Chen X, Deng G. Clinical Significance of Plasma D-Dimer in COVID-19 Mortality. *Front Med (Lausanne),* 8:638097, 2021

List of published articles

1. Complications during hospitalization in patients with SARS-CoV-2 pneumonia in a Romanian pulmonary center

Alexandra Maria Cristea, Dragoş Cosmin Zaharia, Ştefan Leu, Miron Alexandru Bogdan

Published in Cureus, Volume 15, Number 1, 17 Jan 2023, BDI Pubmed

Link: https://pubmed.ncbi.nlm.nih.gov/36819389/

2. Pathological presence of free air in the thorax: pneumothorax and pneumomediastinum as a complication of COVID-19

Alexandra Maria Cristea, Dragoş Cosmin Zaharia, Ştefan Dumitrache-Rujinski, Alexandra Ţintea, Miron Alexandru Bogdan

Published in Cureus, Volume 15, Number 6, 26 Jun 2023, BDI Pubmed

Link: https://pubmed.ncbi.nlm.nih.gov/37503506/

3. Predictors of negative outcomes in hospitalized patients with SARS-CoV-2 pneumonia: A retrospective study

Alexandra-Maria Cristea, Dragoş-Cosmin Zaharia, Daniela Jipa-Dună, Ştefan Dumitrache-Rujinski, Oana Andreea Parlıţeanu, Alexandru Miron Bogdan, Claudia Lucia Toma

Published in Experimental and Therapeutic Medicine, Volume 26, Number 3, 31 Jul 2023, ISI, IF=2.7

Link: https://pubmed.ncbi.nlm.nih.gov/37614431/

4. Options of tratment in SARS-CoV-2 infections

Alexandra Maria Cristea, Dragoş Cosmin Zaharia, Miron Alexandru Bogdan

Published in Pneumologia, Volume 70, Number 2, 27 Sept 2022, Pages 60-67, BDI

Link: https://intapi.sciendo.com/pdf/10.2478/pneum-2022-0013