

RESEARCH ARTICLE

The link between the fatal cases with SARS-CoV-2 infection and multimorbidity: Our single institution experience

Laura Chinezu^{1,2*}, George Radu³, Paula-Roxana Adi², Rareș Chinezu⁴, Timur Hogeza^{2,5}

1. Department of Histology, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

2. Institute of Forensic Medicine, Targu Mures, Romania

3. Pathology Department, Mures Clinical County Hospital, Targu Mures, Romania

4. Department of Neurosurgery, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

5. Department of Forensic Medicine, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

Objective: During the pandemic, the SARS-CoV-2 infection with its different variants had determined high morbidity and mortality. As the clinical autopsies were reduced in our country, complete forensic autopsies had provided important valuable information regarding the pathological changes and pathophysiological mechanisms associated with SARS-CoV-2 infection. Our aim was to focus on different variants of SARS-CoV-2, trying to determine the contribution of SARS-CoV-2 infection to the lethal outcome and to establish the cause of death.

Methods: Complete autopsies were performed on cases confirmed by polymerase chain reaction for SARS-CoV-2 infection. All autopsies findings and the patient's comorbidities were analyzed.

Results: Forty-nine cases were studied. Twenty were female (41%), and 29 were male (59%). The median age at death was 63 years (range 26-93 years), with an upward trend during the four variants of SARS-CoV-2. The age of the cases that died due to their comorbidities and were associated with SARS-Cov-2 infection was higher compared to the age of the cases that died due to SARS-CoV-2 infection. Two thirds of cases died at hospital, most of them with less than one week of hospitalization and one third of them were found dead at home. Most cases without significant health conditions died at home.

Conclusions: The immediate cause of death for many of our cases was of respiratory origin and most of them died of diffuse alveolar damage. The cases without evident comorbidities were less represented, that highlight the importance of multimorbidity in the development of critical illness.

Keywords: SARS-CoV-2 infection, forensic autopsies, comorbidities

Received 12 December 2024 / Accepted 24 December 2024

Introduction

The illness caused by the coronavirus first identified in December 2019 in Wuhan, China, is called COVID-19 (Coronavirus Disease 2019). The virus responsible for this disease is known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) [1]. The risk of developing a critical illness or death from SARS-CoV-2 depends on age and previous comorbidities, but a clear correlation in between existing comorbidities and higher risk of death is not clear [2,3].

Since the outbreak numerous studies have investigated this disease, focusing primarily on clinical aspects, but also covering histopathological, immunohistochemical, molecular, electron microscopy, and other multidisciplinary approaches.

Even so, there are not many autopsy studies, most of them being on hospitalized patients [4–6]. This was mainly because, in many countries [7], medical autopsies to confirm or clarify death diagnoses of COVID-19 were deemed not necessary and were avoided to reduce the risk of disease transmission.

Nevertheless, combined with epidemiological, clinical, and laboratory data, medical autopsies were a very useful tool for improving knowledge about the pathophysiology of COVID-19 infections, and complete autopsies were still regarded as the “gold standard” [8].

Forensic autopsies, conducted in legally required cases, including cases with COVID-19 infection, were still performed. Therefore, forensic autopsies were in many places the only method to add new and essential information related to the pathological changes and pathophysiological mechanisms associated with COVID-19 infection [9,10].

Our study presents the causes of death and comorbidities for all the cases positive for SARS-CoV-2, for which a full autopsy was performed in our institution. We focused on different variants of SARS-CoV-2 and we highlighted the differences between the cases that died at home in comparison to cases that died after a period of hospitalization. We try also to determine the contribution of SARS-CoV-2 infection to the lethal outcome and to establish the cause of death.

* Correspondence to: Laura Chinezu
E-mail:laura.chinezu@umfst.ro

Methods

Study design, organizational structure

This is a retrospective study, analyzing the autopsies performed at the Institute of Forensic Medicine Targu Mures, Romania, between 04 April 2020 and 11 September 2023.

Only the cases that tested positive ante- and/or post-mortem for SARS-CoV-2 infection and confirmed by polymerase chain reaction (PCR) were included.

Four variants of SARS-Cov-2 were described in Romania and our cases were classified according to date of death/the date of admission in the hospital in one of these categories: original, alpha, delta, or omicron type. Each of the cases was included in the specific wave of COVID-19 infections described in our country [11–14].

Demographic and medical data, macroscopic and microscopic characteristics were collected from the autopsy files. Age, gender, place of death, relevant health conditions and comorbidities were noted. If the death occurred while the patient was admitted to a hospital, the survival time starting from the admission to the institution was included.

No data were available regarding the vaccination profile of our cases.

Institutional review board approval from the ethics committee of the Institute of Forensic Medicine Targu Mures was obtained. Informed consent was obtained from a legal representative.

Evaluation methods: autopsy procedure and interpretation

Prior to the autopsy careful examination of all the medical records, laboratory results, patient history were performed to determine the most likely cause of cause of death.

For all the cases a full complete conventional autopsy was performed, and all the three body cavities were opened, using standard forensic medicine autopsy protocol. Safety precautions were undertaken for infection control. For the personnel involved in autopsy, FFP2-masks, protective suits, and cut resistant gloves were mandatory to use.

The histopathological examination was performed for all cases included in our study. Representative tissue samples were taken from brain, heart, lungs, liver, and/or kidney. All the samples were processed via standard procedure and all the slides were stained with haematoxylin-eosin (H&E).

In each case the contribution of SARS-CoV-2 infection to lethal outcome was interpreted considering all autopsies findings and the patient's comorbidities. In accordance with WHO guidelines [15], the underlying cause, condition leading to cause of death, and immediate cause of death were assessed for each of the case. For each of the cases, the severity of all findings was evaluated, and their causal chains were assessed. Following prior published classifications [9,16], we classified the cases based on the presence of COVID-19 and of the comorbidities.

Microscopically, we considered a positive COVID-19 case, if the pulmonary tissue consisted of inflammation

suggestive for pneumonia and/or criteria for diffuse alveolar damage (DAD). Severe COVID-19 was considered if the pulmonary changes were consistent and started the sequence of events leading to death. We considered a mild COVID-19 if the pulmonary changes were focal, and the immediate cause of death was determined by the pre-existing comorbidities.

Based on all the acquired information, the cases were classified in three main categories: cases that died of severe COVID-19 without evident comorbidities (group A), cases that died of severe COVID-19 with evident and significant comorbidities (group B), and cases that died of comorbidities with SARS-CoV-2 infection and/or mild or absent COVID-19 (group C). For the last category, we considered the pre-existing illness as the major cause of death.

Statistical analysis

Descriptive statistics was used to characterize the population groups. All data collected in the study were labelled as categorical variables (sex, covid variant, place of death, type of death, comorbidities) or quantitative variables (age, year, hospitalisation period). Qualitative variables were summarized as counts and frequencies. All statistical analyses were conducted using Epi Info version 7.2.0.1. To compare parametric data, the Fisher exact test was used. T test was applied for comparing the means of different groups regarding type of death. The level of statistical significance was set at $p < 0.05$.

Results

Clinical presentation

For all cases that were confirmed prior to necropsy or were suspected and confirmed post-mortem with SARS-CoV-2 infection, a full autopsy was performed. Forty-nine cases were included in our study. Of the deceased, 20 (41%) were female and 29 (59%) were male (Table 1). During all described variants, there were more men than women, except omicron variant.

The median age at death was 63 years (range 26-93 years), with an upward trend during the four variants of SARS-CoV-2 (Table 2).

Two thirds of cases (31 cases) died at hospital, most of them with less than one week of hospitalization and one third of them were found deceased at home. Regarding the place of death, the distribution of the cases during the different variants of SARS-CoV-2 was uniform. There were more cases that died during hospitalization than cases that died at home.

The median period of hospitalization was 8 days (range 0-45 days), also with an upward/ascending trend during the four variants of SARS-CoV-2 (Table 2).

The distribution of our cases during Covid-19 pandemic period was in accordance with the numbers of the reported deaths and the different waves described in our country

Table I. The most important characteristics of the cases.

Characteristics	Total(n=49)	Percent (%)	p
Gender			0.840
Men	29	59.2%	
Women	20	40.8%	
Age			0.174
<45 years	6	12.2%	
46-59 years	14	28.6%	
>=60 years	29	59.2%	
Comorbidities			
Cardiovascular disease	38		0.024
Chronic neurologic disease	12		0.708
Obesity	11		0.246
Chronic liver disease	9		0.220
Type II diabetes mellitus	5		0.598
Malignancy	3		1
Chronic renal disease	2		0.464
Chronic respiratory disease	2		0.464
Comorbidities No.			0.747
0	10	20,4%	
1	12	24,5%	
>=2	27	55.1%	

Table II. The characteristic of the cases based on different variants of SARS-CoV-2.

	ORIGINAL (n=11)	ALFA (n=9)	DELTA (n=19)	OMICRON (n=10)
Gender (no., %)				
Women	5 (45,5%)	3 (33,3%)	6 (31,6%)	6 (60%)
Men	6 (54,5%)	6 (66,7%)	13 (68,4%)	4 (40%)
Age (median, range)	57,09 (26-85)	64,33 (36-93)	64,47 (33-88)	67,7 (41-89)
Comorbidities (no.)				
Cardiovascular disease	8	7	15	8
Chronic neurologic disease	3	3	4	2
Obesity	3	1	7	0
Chronic liver disease	2	3	3	1
Type II diabetes mellitus	1	0	1	3
Malignancy	0	0	3	0
Chronic renal disease	1	1	0	0
Chronic respiratory disease	1	1	0	0
Place of death (no., %)				
Home	4 (36,4%)	3 (33,3%)	8 (42,1%)	3 (30%)
Hospital	7 (63,6%)	6 (66,7%)	11 (57,9%)	7 (70%)
Mean time of hospitalization (days, range)*	2 days (0-7)	5 days (0-16)	5,89 days (0-45)	9,1 days (0-23)
Cause of death (no., %)				
Group A (severe Covid-19)	2 (18,2%)	2 (22,2%)	4 (21,1%)	2 (20%)
Group B (severe Covid-19 +Comorbidities)	7 (63,6%)	1 (11,1%)	14 (73,7%)	4 (40%)
Group C (Comorbidities + mild or absent Covid-19 and SARS-CoV2 infection)	2 (18,2%)	6 (66,7%)	1 (5,3%)	4 (40%)

*cases that died at home were excluded

(Figure 1). Most of our cases were included in the second and fourth waves of SARS-CoV-2 infection.

Comorbidities

Relevant health conditions and known chronic comorbidities were noted for each of the case (Table 3). In our study, most of the cases were included in group A and B, and died of severe COVID-19 (73,46%, 36 cases) and among these the majority were part of the group B, being associated with comorbidities (72,22%, 26 cases).

The distribution of cases during the four variants described was uniform, except for alfa period, in which more of the cases were part of the group C. From all cases included in the study, most of them (55,11%, 27 cases) had

at least two comorbidities (Table 1). The most accounted comorbidities were cardiovascular (77,55%, 38 cases) and neurological (24,48%, 12 cases) diseases. Obesity was identified in 11 cases (22,44%), especially in cases that died during the delta wave period. The median age at death was significantly higher (72,3 vs. 60,25, $p < 0,05$) in the group C compared with the group of cases that died of COVID-19 (group A and B).

Causes of death determined at autopsies

After the evaluation of autopsy findings including the histopathological data, the immediate causes of death, the conditions leading to the cause of death, and the underlying causes were established (Appendix).

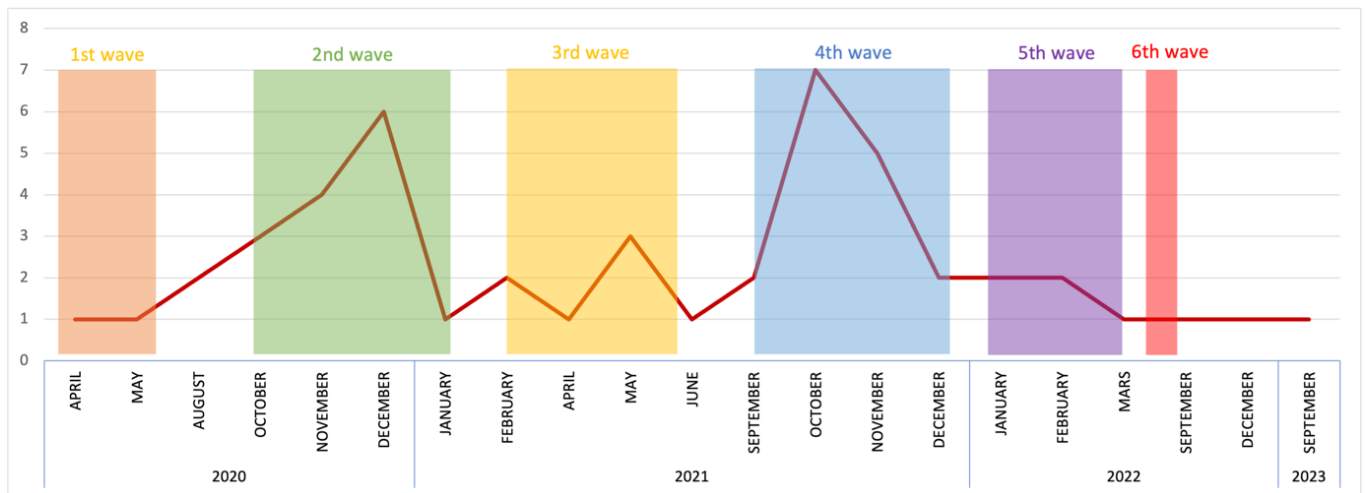


Fig. 1. The distribution of our cases based on different waves of COVID-19 disease described in our country.

The most common causes of immediate death were represented by DAD in 26 cases (53,1%), followed by respiratory failure in 9 cases (18,4%). In 5 cases (10,2%), the septic shock was considered the immediate cause of death and three cases presented with central cardio-respiratory failure. Only one case with acute myocardial infarction and one case with cardiogenic shock were described.

When we considered the condition leading to the cause of death, pneumonia was the most common cause and was seen in 25 cases (51,0%), being associated with pulmonary embolism in 6 cases. Acute pulmonary edema was seen in 9 cases (18,4%), acute subdural hematoma and cerebral contusion in three cases (6,1%).

We found individual cases with invasive aspergillosis, diffuse alveolar damage, myocarditis, acute myocardial infarction, and pulmonary embolism (2% each). In 7 cases (14,3%), the condition leading to the cause of death was impossible to establish.

The most frequent underlying cause of death was SARS-CoV-2 infection in 34 cases (69,4%), followed by trauma in 8 cases (16,3%): craniocerebral in four cases (8,2%), polytrauma in two cases (4,1%), and individual cases with femoral neck and pertrochanteric fractures (2% each). Coronary atherosclerosis was described in 4 cases as the underlying cause of death (8,2%). Two cases with decompensated liver cirrhosis (4,1%) and one case with alcohol induced cardiomyopathy were also noted (2%).

Histopathology

The microscopic description was mainly focused on the lung tissue, which was the most affected organ in our cases. DAD was described in many of the reports (57,1%), and among these cases 57,1% were associated with pneumonia. DAD was classified into acute/exudative or organizing phase based on the specific alveolar, epithelial and vascular changes. Compared to acute phase of DAD, the organizing phase of DAD was less seen in our reports, being in the same percentage when we compared the cases with and without pneumonia (around 25%). The presence of the

(micro)thrombi was reported in 32 cases. In all of them, (micro)thrombi were found in lung tissue, and in few cases, they were found in heart and renal tissue (Figure 2).

Discussion

Our study highlights, that respiratory complications, mainly DAD, were the most encountered immediate causes of death (71,4%) in cases that died with SARS-CoV-2 infection.

We found that men have presented a higher mortality. Whilst the factors that lead to this are not clear in our study, the results can be seen in accordance with other studies [17], that highlight the differences in immunologic reaction between men and female and the lack of protective effect of estrogen signaling seen in females [18,19], and that likely men presented higher risk severe COVID-19 sequelae.

Age over 60 has been associated with increased risk of death, this was previously described, as older patients have a tendency towards severe symptoms and lower recovery rates than patients under 60 years of age [9]. In our study, the majority of the cases older than 60 years had comorbidities, being part of the group B and C (96,6%). The age of the cases that were part of the group C was significantly higher ($<0,05$), compared with the age of the cases that died due to severe COVID-19 (group A and B), which is in accordance with other studies [17,20].

The majority of our cases were associated with prior comorbidities (79,6%). Presence of at least one known comorbidity has been proven to associate with higher risk of death [21,22]. There is still uncertainty if there is a proper correlation between some types of comorbidities and higher risk of death. Our study has shown that most often identified comorbidities were cardiovascular disease and chronic neurologic disease, whereas other authors have shown in their series higher prevalence of type II diabetes mellitus, chronic lung disease and cardiovascular disease [23]. Petrili et al has found that age, heart failure, male sex, chronic kidney disease, and obesity were associated

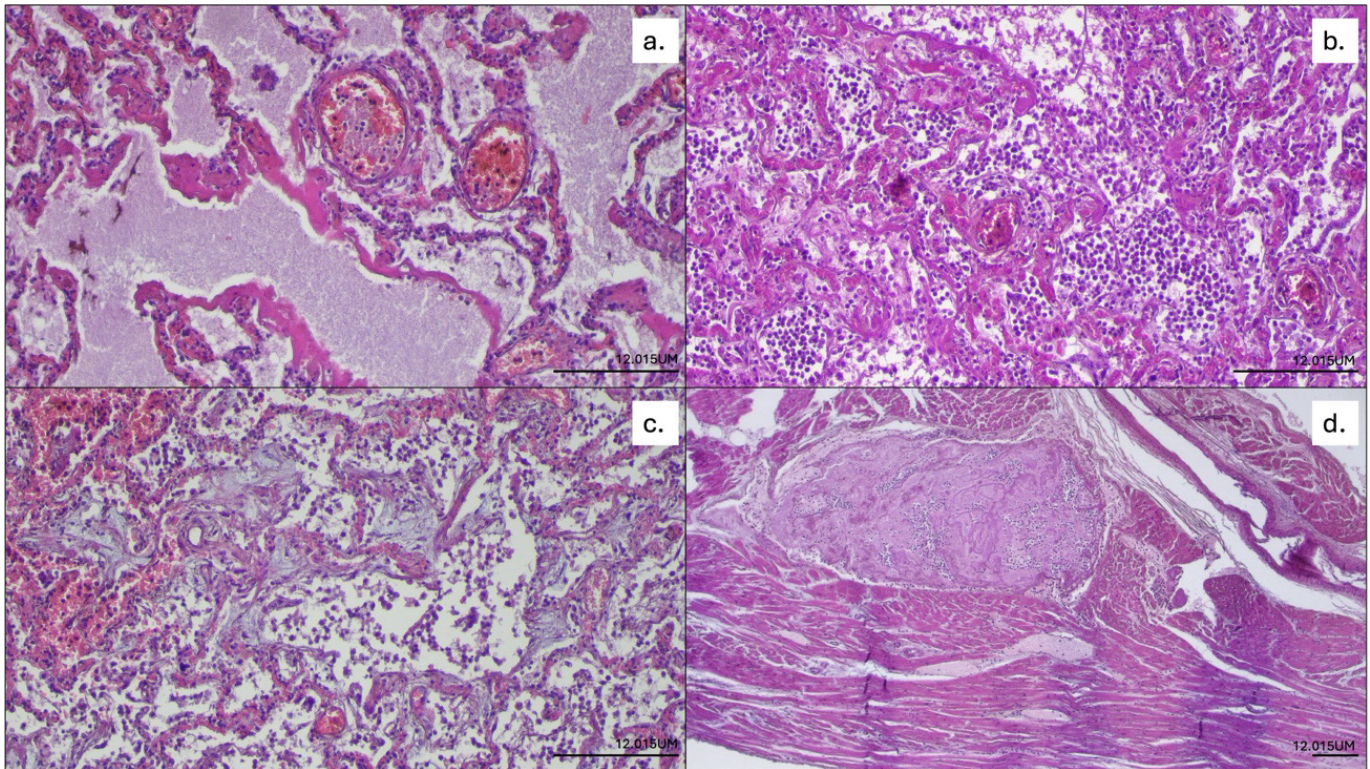


Fig. 2. Histopathological changes: a. DAD, exudative phase (lungs, H&E stain, 10x objective); b. DAD, exudative phase associated with acute inflammatory foci (lungs, H&E stain, 10x objective); c. DAD, organizing phase (lungs, H&E stain, 10x objective); d. the identification of the thrombi into the heart tissue (myocardium, HE stain, 4x objective).

with development of critical illness [24]. We have seen that obesity was identified in 22,4% of cases, and as obesity is considered a pro-inflammatory condition, it was strongly associated with high risk of critical illness [24]. It could be tentatively to hypothesize that there might be not a single comorbidity factor, but rather the severity or extent of the prior disease that is associated with higher risk of death.

Other studies concluded that not only chronic health disease, but also lifestyle risk factors were increased the risk for fatal outcome of COVID-19 [25]. In our study, the evaluation of lifestyle risk factors, such as alcohol consumption and nicotine abuse, was difficult to assess for all the patients, alcohol consumption being documented only in two cases.

In our country three highest peaks were described in: April 2020, October 2020, and November 2021 [26]. Many of our cases died during the second wave and fourth wave of SARS-CoV-2 infection, which is in accordance with available WHO data and with the second and third peaks described in our country. The absence of the first peak in our study, it could be partially explained by the lower number of tested cases in that period. The higher peak in our series of cases had also corresponded to the pandemic period with most of the reported deaths.

The literature is scarce with studies comparing the effect of the different SARS-Cov-2 variants and associated mortality. Most the literature being focused are on hospitalized COVID-19 cases alone [4–6]. Schwab et al. being one of the few that have described the effect of different variants of SARS-CoV-2 on fatal outcomes [27] and they conclude

that omicron variant affected the lungs less frequently with a less severe lung disease. In our study, there were no evident differences on histologic appearance of the lungs, but instead we observed an ascending trend of the mean age of the cases and an increase of mean time of hospitalization during the four variants described. The ascending trend of the mean age could be related to the decrease of aggressiveness of SARS-CoV-2 variants in cases with more significant comorbidities. The period of hospitalization increased from one variant of SARS-CoV-2 to another was also seen in other studies and could be at least partially explained by the improvement of COVID-19 therapies, some results of the vaccination campaign, and likely to the decrease of aggressiveness with each subsequent variant of SARS-CoV-2 [9,12,28].

We have seen a higher incidence in cases that deceased at home (36%) than other authors (28.5%). Even more interestingly most of these patients that didn't have any known comorbidities (group A) died at home (80%). A possible reason for this could be the presence of minor or non-specific symptoms of disease or unfortunately a lack of medical education leading to severe symptoms being disregarded, or unwillingness to visit medical facilities. This finding is not solitary, other authors have suggested that people avoided visiting healthcare facilities during pandemic, as diverse sociodemographic groups may differ in their ability to successfully navigate a healthcare system under pressure [29].

There is a clear association in between COVID-19 infection and thrombosis. We found that almost two-thirds

of the cases had either microthrombosis or thrombosis present in the lung tissue. While earlier studies suggested a significant risk of pulmonary embolism in COVID-19 patients [30] and underscored hypercoagulability as a major fatal factor [30–32], the role of pulmonary embolism as a direct cause of death remains less clear. Notably, pulmonary embolism was present in 14,3% of our cases and it was deemed a condition leading to death in most of the cases. Other investigations also identified pulmonary embolism as an immediate cause or a condition contributing to death, hinting at the potential efficacy of anticoagulant therapies. These findings emphasize the nuanced role of thrombotic complications in COVID-19 and underscore the importance of targeted therapeutic strategies.

Conclusion

As expected, the immediate cause of death in many of the cases with SARS-CoV-2 infection was of respiratory origin and was represented by diffuse alveolar distress.

The ascending mean age of death, seen during the subsequent variants of SARS-CoV-2 could be related to the decrease of aggressiveness of SARS-CoV-2 variants, affecting towards the end of the pandemic only the very elderly and patients with severe comorbidities.

Improvement in the treatment therapies of COVID-19, and possible decrease of aggressiveness with each variant of SARS-CoV-2 could be related to the increased period of hospitalization prior to death seen from one variant of SARS-CoV-2 to another.

Forensic autopsies represented an important tool to add new and essential information related to the pathological changes and pathophysiological mechanisms associated with SARS-CoV-2 infection.

Authors' contribution:

LC (Conceptualization; Funding acquisition; Investigation; Writing – original draft; Writing – review & editing)
GR (Methodology; Software; Validation)

PRA (Data curation; Formal analysis; Investigation; Visualization)

RC (Formal analysis; Methodology; Supervision; Visualization; Writing – review & editing)

TH (Supervision; Investigation; Visualization)

Acknowledgements

This work was supported by the University of Medicine, Pharmacy, Science and Technology „George Emil Palade“ of Târgu Mureș Research Grant number 510/2 / 17.01.2022

Conflict of interest

None to declare.

References

- Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Vol. 395, *The Lancet*. Lancet Publishing Group; 2020. p. 1014–5.

- Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Vol. 29, *Nature Medicine*. Nature Research; 2023. p. 334–43.
- Marc MS, Rosca D, Bratosin F, Fira-Mladinescu O, Oancea C, Pescaru CC, et al. The Effect of Comorbidities and Complications on COVID-19 Mortality: A Detailed Retrospective Study in Western Romania. *J Pers Med*. 2023 Nov 1;13(11).
- Iftimie S, López-Azcona AF, Lozano-Olmo MJ, Hernández-Aguilera A, Sarrà-Moretó S, Joven J, et al. Characteristics of hospitalized patients with SARS-CoV-2 infection during successive waves of the COVID-19 pandemic in a reference hospital in Spain. *Sci Rep*. 2022 Dec 1;12(1).
- Iftimie S, López-Azcona AF, Vicente-Miralles M, Descarrega-Reina R, Hernández-Aguilera A, Riu F, et al. Risk factors associated with mortality in hospitalized patients with SARS-CoV-2 infection. A prospective, longitudinal, unicenter study in Reus, Spain. *PLoS One*. 2020 Sep 1;15(9 September 2020).
- Iftimie S, Lopez-Azcona AF, Vallverdu I, Hernandez-Flix S, De Febrer G, Parra S, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. *PLoS One*. 2021 Mar 1;16(3 March 2021).
- Mele F, Santoro V, Sablone S, Logrado D, Berterame C, Calvano M, et al. Prevention of COVID-19 transmission from deceased subject: A critical point of view. *J Glob Health*. 2022;12.
- Monteiro RA de A, Duarte-Neto AN, da Silva LFF, de Oliveira EP, Filho JT, Dos Santos GAB, et al. Ultrasound-guided minimally invasive autopsies: A protocol for the study of pulmonary and systemic involvement of COVID-19. Vol. 75, *Clinics*. Universidade de Sao Paulo; 2020. p. 1–2.
- Fitzek A, Schädler J, Dietz E, Ron A, Gerling M, Kammal AL, et al. Prospective postmortem evaluation of 735 consecutive SARS-CoV-2-associated death cases. *Sci Rep*. 2021 Dec 1;11(1).
- Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, et al. Dying with SARS-CoV-2 infection—an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med*. 2020 Jul 1;134(4):1275–84.
- Zoran MA, Savastru RS, Savastru DM, Tautan MN. Impacts of exposure to air pollution, radon and climate drivers on the COVID-19 pandemic in Bucharest, Romania: A time series study. *Environ Res*. 2022 Sep 1;212.
- Túri G, Kassay J, Virág A, Dózsa C, Horváth K, Lorenzovici L. Riding the Pandemic Waves—Lessons to Be Learned from the COVID-19 Crisis Management in Romania. *Trop Med Infect Dis*. 2022 Jul 1;7(7).
- Dascalu S, Geambasu O, Valentin Raiu C, Azoicai D, Damian Popovici E, Apetrei C. COVID-19 in Romania: What Went Wrong? *Front Public Health*. 2021 Dec 17;9.
- Number of COVID-19 cases reported to WHO (cumulative total) [Internet]. Available from: <https://data.who.int/dashboards/covid19/cases?m49=642&n=c>
- Cause of death.
- Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, et al. Dying with SARS-CoV-2 infection—an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med*. 2020 Jul 1;134(4):1275–84.
- Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. Vol. 64, *Intervirology*. S. Karger AG; 2021. p. 36–47.
- Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *The Journal of Immunology*. 2017 May 15;198(10):4046–53.
- Djharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. *Gac Sanit*. 2021 Jan 1;35:S530–2.
- Kang SJ, Jung SI. Age-Related Morbidity and Mortality among Patients with COVID-19. *Infect Chemother*. 2020 Jun 1;52(2):154–64.
- Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *New England Journal of Medicine*. 2020 Jun 18;382(25).
- Pighi L, Lippi G, Mattiuzzi C. The incremental impact of comorbidities in COVID-19-related deaths compared to patients dying from cancer or cardiovascular disease. *Egypt J Intern Med*. 2024 Aug 5;36(1).
- Health Ontario P. One-minute summary [Internet]. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm?s_cid=mm6913e2_w
- Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. *The BMJ*. 2020 May 22;369.

25. Elezurtaj S, Greuel S, Ihlow J, Michaelis EG, Bischoff P, Kunze CA, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep.* 2021 Dec 1;11(1).
26. Tudora A, Lungeanu D, Pop-Moldovan A, Puschita M, Lala RI. Successive Waves of the COVID-19 Pandemic Had an Increasing Impact on Chronic Cardiovascular Patients in a Western Region of Romania. *Healthcare (Switzerland).* 2023 Apr 1;11(8).
27. Schwab C, Merle U, Schirmacher P, Longerich T. Lethality of SARS-CoV-2 infection—a comparative autopsy study focusing on COVID-19 development and virus variants. *Histopathology.* 2023 Aug 1;83(2):242–51.
28. Bauer W, Diehl-Wiesenecker E, Ulke J, Galtung N, Havelka A, Hegel JK, et al. Outcome prediction by serum calprotectin in patients with COVID-19 in the emergency department. Vol. 82, *Journal of Infection.* W.B. Saunders Ltd; 2021. p. 84–123.
29. Frey A, Tilstra AM, Verhagen MD. Inequalities in healthcare use during the COVID-19 pandemic. *Nat Commun.* 2024 Dec 1;15(1).
30. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. *Ann Intern Med.* 2020 Aug 18;173(4):268–77.
31. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020 Jun 1;46(6):1089–98.
32. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020 Jul 1;191:145–7.

Appendix

nr crt	Gender	Age (years)	Group	Immediate cause of death (I)	Condition leading to cause of death (II)	Underlying cause (III)	Comorbidities (IV)
1	M	52	C	Central cardiorespiratory failure	Cerebral contusion	Polytrauma	SARS-CoV2 infection, MF, pneumonia
2	F	85	C	Cardiorespiratory failure	Acute pulmonary edema, myocardial ischemia	Coronary atherosclerosis	Multinodular goiter, LVH, MF, nephrosclerosis, chronic interstitial nephritis, SARS-CoV2 infection
3	M	66	B	DAD		SARS-CoV2 infection	MF, LVH, steatohepatitis, nephrosclerosis, chronic interstitial nephritis
4	M	65	B	DAD		SARS-CoV2 infection	MF, LVH, liver cirrosis, nephrosclerosis, chronic interstitial nephritis, chronic renal insufficiency stage IV with dialysis, COPD, CPHD, type II diabetes mellitus
5	F	57	A	DAD	Pneumonia	SARS-CoV2 infection	
6	M	52	B	Respiratory failure	Pneumonia	SARS-CoV2 infection	Old cerebral infarction, MF
7	F	53	B	DAD	PE, Pneumonia	SARS-CoV2 infection	DCM, LVH, MF, nephrosclerosis, chronic interstitial nephritis, obesity
8	M	48	B	Respiratory failure	Pneumonia	Polytrauma	SARS-CoV2 infection
9	F	70	B	DAD		SARS-CoV2 infection	MF, LVH, DCM, CHD, coronary atherosclerosis, aortic atherosclerosis, obesity
10	M	54	B	DAD		SARS-CoV2 infection	Obesity, DCM, lipomatosis of right heart ventricle, MF, coronary and aortic atherosclerosis
11	F	26	A	Respiratory failure	Acute pulmonary edema	SARS-CoV2 infection	coronary atherosclerosis
12	M	62	B	DAD	PE, Pneumonia	SARS-CoV2 infection	MF, old myocardial infarction
13	F	76	C	Central cardiorespiratory failure	Cerebral contusion	Cranio-cerebral trauma	SARS-CoV2 infection, pneumonia
14	M	66	C	Cardiorespiratory failure	Acute pulmonary edema	Alcohol-induced dilated cardiomyopathy	MF, nephrosclerosis, SARS-CoV2 infection
15	F	93	C	Central cardiorespiratory failure	Acute subdural hematoma and minimal subarachnoid hemorrhage	Cranio-cerebral trauma	SARS-CoV2 infection, hypertensive cardiomyopathy, high blood pressure, aortic insufficiency, atrial fibrillation, NYHA class 2 heart failure, stage IV chronic renal diseases, nephrosclerosis, renal tumor (2014), kidney stones, sistemic atherosclerosis
16	M	86	C	AMI	Acute pulmonary edema	Cranio-cerebral trauma	DAD, SARS-CoV2 infection
17	M	62	C	Respiratory failure	Pneumonia	Cranio-cerebral trauma	DCM, LVH, MF, coronary atherosclerosis, hepatosplenomegalia, steatohepatitis, obesity, closed thoracic trauma, SARS-CoV-2 infection
18	F	36	A	DAD		SARS-CoV2 infection	MF
19	M	41	A	Respiratory failure	Pneumonia	SARS-CoV2 infection	MF, LVH, steatohepatitis
20	M	57	C	Respiratory failure	Acute pulmonary edema	Decompensated liver cirrhosis	SARS-CoV2 infection, MF, pneumonia
21	F	69	B	DAD	PE, Pneumonia	SARS-CoV2 infection	clear cell renal cell carcinoma, colic adenocarcinoma, type II diabetes mellitus, obesity
22	M	43	B	DAD	Pneumonia	SARS-CoV2 infection	DCM, old cerebral infarction, MF, LVH, NFS, NITC, obesity
23	M	63	B	DAD	Pneumonia	SARS-CoV2 infection	MF, LVH, CHD; lipomatosis of right heart ventricle, miocarditis
24	M	75	B	DAD	Pneumonia	SARS-CoV2 infection	Old myocardial infarction, MF, LVH, coronary, aortic and vertebral atherosclerosis, old cerebral infarction

25	M	58	B	Septic shock	Pneumonia, acut fibrinous pleuritis, bedsores	SARS-CoV2 infection	MF, LVH, myocardial necrosis, liver cirrosis, splenic infarction
26	M	33	A	DAD	Acute pulmonary edema	SARS-CoV2 infection	MF, LVH
27	M	74	A	DAD	Acute pulmonary edema	SARS-CoV2 infection	MF, LVH
28	M	77	C	Cardiorespiratory failure	Acute pulmonary edema, myocardial ischemia	Coronary atherosclerosis	Pulmonary tumor, MF, SARS-CoV2 infection, old renal infarction
29	M	51	A	DAD	Pneumonia	SARS-CoV2 infection	MF
30	M	61	B	Respiratory failure	PE, Pneumonia	SARS-CoV2 infection	submandibular gland carcinoma, DCM, MF, sistemic atherosclerosis
31	M	88	B	DAD	Pneumonia	Femoral neck fracture	SARS-CoV2 infection, MF, LVH, myocardial necrosis, nephrosclerosis, chronic interstitial nephritis
32	F	55	B	DAD	Acute pulmonary edema	SARS-CoV2 infection	myocardial lipomatosis, MF, coronary and aortic atherosclerosis, obesity
33	M	78	B	DAD	Pneumonia	SARS-CoV2 infection	Obesity, MF, LVH, nephrosclerosis, chronic interstitial nephritis, coronary atherosclerosis
34	M	54	B	DAD	PE, Pneumonia	SARS-CoV2 infection	MF, nephrosclerosis
35	F	71	B	DAD	PE, Pneumonia	SARS-CoV2 infection	MF, nephrosclerosis, chronic interstitial nephritis, steatohepatitis, obesity
36	M	51	A	Septic shock	Pneumonia	SARS-CoV2 infection	MF, steatohepatitis
37	F	72	B	DAD	Pulmonary Aspergillosis	SARS-CoV2 infection	MF, obesity, steatohepatitis
38	F	72	B	DAD		SARS-CoV2 infection	MF, LVH, pneumonia
39	F	80	B	DAD		SARS-CoV2 infection	Obesity, aortică atherosclerosis, MF
40	F	75	B	DAD	Pneumonia	SARS-CoV2 infection	nephrosclerosis, chronic interstitial nephritis, acute pyelonephritis, MF
41	M	62	B	DAD	Pneumonia	SARS-CoV2 infection	Gastric ulcer, MF, LVH, nephrosclerosis, chronic interstitial nephritis, acute fibrinous pleuritis, acute pielonephritis, skin infection
42	M	82	C	Respiratory failure	PE	SARS-CoV2 infection	hear failure, high blood pressure, colic adenocarcinoma (2012), nephrectomy (1987)
43	F	41	A	Septic shock	Pneumonia	SARS-CoV2 infection	MF, LVH, acute kidney injury
44	M	53	A	Septic shock	Miocarditis	SARS-CoV2 infection	MF, LVH, CHD, nephrosclerosis, acute kidney and liver injury
45	F	83	C	Cardiorespiratory failure	Myocardial ischemia	Coronary atherosclerosis	MF, LVH, pneumonia, SARS-CoV2 infection
46	F	67	C	Cardiogenic shock	AMI	Coronary atherosclerosis	SARS-CoV2 infection, pyonephrosis, coronary angioplasty, CHD, old myocardial infarction, MF, LVH, persistent atrial fibrillation, high blood pressure, type II diabetes mellitus, purulent acute bronchitis, nephrosclerosis, chronic interstitial nephritis, acute kidney and liver injury
47	F	71	B	DAD	Pneumonia	Petrochanteric fracture	Type II diabetes mellitus, LVH, old myocardial infarction, MF, coronary atherosclerosis, SARS-CoV-2 infection
48	F	89	B	Septic shock	Pneumonia	SARS-CoV2 infection	MF, LVH, CHD, old cerebral infarction, dementia, high blood pressure, atrial fibrillation, congestive hepatopathy, nephrosclerosis, chronic interstitial nephritis, acute kidney injury
49	M	54	C	Respiratory failure	Pneumonia	Decompensated liver cirrhosis	Type II diabetes mellitus, MF, LVH, CHD, cerebral and coronary ATS, nephrosclerosis, SARS-CoV-2 infection, DAD