Death by SARS-CoV 2 - a Romanian COVID-19 multi-centre comorbidity study

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Abstract

Evidence regarding the relation between SARS-CoV-2 mortality and the underlying medical condition is scarce. We conducted an observational, retrospective study based on Romanian official data about location, age, sex and comorbidities for COVID-19 fatalities.

Our findings indicate that males, hypertension, diabetes, obesity and chronic kidney disease were most frequent in the COVID-19 fatalities, that the burden of disease was low, and that the prognosis for 1-year survival probability was high in the sample. Evidence shows that age-dependent pairs of comorbidities could be a negative prognosis factor for the severity of disease for the SARS-CoV 2 infection.

Main

The rapid spread of the new type of coronavirus named novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) from Wuhan (China) in the world determined the World Health Organization (WHO) to declare novel coronavirus disease (2019 COVID-19 or nCOVID-19) a pandemic on March 11, 2020. [1],[2].

The first confirmed case in Romania was on February 26, 2020, and, by April 20 2020, 8936 confirmed case, 2017 healed cases and 520 deaths had been recorded,88 cases with missing data and 98.491 tests were done [3]. The case definitions, as well as the therapies applied by the Romanian physicians, were also used in Italy, Spain and France.[4-7] The diagnostic was established based on the clinical symptomatology like cough, temperature, breathing difficulty without a prescribed etiology, on patient's direct exposure to SARS-COV-2, and the corroboration by testing with the RT-PCR method.[8]

The Romanian government took strict measures to limit the outbreak, and a Coronavirus task force was set up to coordinate this effort under the direct supervision of the Ministry of Health (MS). Even though some cases of intra-hospital or community infection arose, they were isolated and contained with the help of special hygiene measures, social distancing and a very tight lockdown imposed by the authorities. However, a large number of deaths were confirmed among the adult population with no patient under 20 years of age dying because of COVID-19. Hence, issues regarding the COVID-19 mortality, especially the relationship with the comorbidities and the burden of disease are of great importance for the medical community.[8]

Several studies about the comorbidities of the patients infected with SARS-COV-2 indicate hypertension, diabetes, obesity, neoplasms, chronic kidney disease and chronic obstructive pulmonary disease (COPD) as leading risk factors for a lethal evolution of the disease. [9-11] Romania holds a top place in Europe for deaths caused by cardiovascular diseases with hypertension affecting over 45% of the adult population. Almost half of the population aged over 65 has at least one chronic disease, and 1 in 5 adults smokes daily (32% men as compared to 18% women).[12] Moreover, Romania has a record number of deaths due to preventable causes like ischemic cardiac disease, pulmonary cancer or alcoholism. [13]. The prevalence

of diabetes is approximately 11.6% and doubles for prediabetes as confirmed by Predatorr study [14] and Mentor study [15]. Therefore, it is expected that a high number of infections with SARS-CoV-2 in Romania to have a severe course of the disease or to end deadly.

To investigate the comorbidity profiles for SARS-CoV2 deaths, an observational retrospective study was conducted starting from the official public communications of Romanian Ministry of Internal Affairs (MAI) regarding the fatalities declared as COVID-19 deaths by the National Institute of Public Health (INSP). [4,8] Additionally, data from the National Center for Statistics and Informatics in Public Health were utilized to run a case-case study between the COVID-19 death population and the fatalities due to hospital pneumonia between March 22 and April 20 in the years 2016-2018 in Romania. As far as we know, this is the first study in Eastern Europe that investigates patterns of comorbidities for SARS-COV-2 fatalities.

Our principal research question is to generate hypothesis about comorbidity and burden of disease in the population deceased because of the COVID-19 virus and to investigate their association with sex and age. Additionally, the comparison between the fatalities due to COVID-19 and to pneumonia in terms of sex, age and comorbidity profiles allows us to characterize the specific medical pre-conditions of COVID-19 population.

Results

Population characteristics

Figure 1 illustrates the history of the SARS-CoV-2 pandemic in Romania from February 26 until April 20, including dates, number of fatalities and number of the missing subjects due to incomplete information. The Romanian COVID-19 mortality study has a sample size of 432 patients with complete data regarding sex, age and comorbidities. There are 282 (65.3%) men and 150 (34.7 %) women with a statistically significant difference between the size of these two groups (Table S1). The general mean age is 67, with an SD of 13.1, and the median value is 68 (Table S2).

Sources of infection with deaths due to COVID-19 virus were reported in 36 counties in Romania with significant case concentration in Suceava- 67 (15.51%), Arges - 44 (10.19%) and Hunedoara- 41 (9.49%). Details regarding the spatial distribution of the distinct diseases and aggregated groups of diseases are displayed in Table S6 and Table S7 in the supplementary material.

A total of 170 different conditions and 20 groups of diseases was identified in the study, with a broader diversity of 149 conditions for men over 107 conditions for women. The diseases with the highest prevalence in the sample are hypertension, obesity, diabetes and chronic kidney disease as well as diseases of the circulatory system and nutritional or metabolic disorders.

The sample size of the pneumonia study is equal to 874 persons with complete data as to sex, age and comorbidities. The sample includes 492 (56.3%) men and 382 (43.7%) women, the average age is 73.3,

with an SD of 13.5, and the median age is 76.

Association between sex or age and comorbidities

One-sample proportion test indicates a statistically significant difference in the relative frequency of males and females in the sample and in the subpopulations with hypertension, diabetes, diabetes mellitus type 2, chronic kidney diseases, dependence on renal dialysis, chronic obstructive pulmonary disease, acute ischaemic heart disease or respiratory failure as displayed in Table S1. This is also valid for the subpopulations without comorbidities and for those corresponding to the aggregated group of diseases with a relative frequency of more than 5% except for diseases of the nervous system. On the other hand, the variable sex is not significantly associated with single conditions or group of illnesses except for heart failure (see Table 1).

Because age is an established risk factor for mortality, we also performed an age-stratified analysis with the lifespan split in 10-year intervals starting with age 50. The chi-squared test of association between the sex and age factors is statistically significant, with the largest male relative frequency (81.16%) between 50 and 59 years. Moreover, the factor age is also significantly associated with most of the comorbidities, with hypertension and dependence on renal dialysis following also this trend but at a significance level of 10% (see Table 2).

Table 1. Association between sex and the distinct diseases or aggregated group of diseases, as absolute numbers and as percentage (by column). In bold the p-values for the differences in percentage that reached the statistical significance with respect to the chi-squared test.

Characteristics n,%		Male n=282	Female n=150	**p-value**
Diseases				
Hypertension		113 40.07%	49 32.67%	0.16
Obesity		32 11.35%	21 14.00%	0.52
Diabetes	105 37.23%	48 32.00%	48 32%	0.33
	40 14.18%	26 17.33%	26 17%	0.47
	56 19.86%	19 12.67%	19 13%	0.081
	9 3.19%	3 2.00%	3 2%	0.68
Diseases of the circulatory system, unspecified		41 14.54%	27 18.00%	0.42
Supraventricular tachyarrhythmia		16 5.67%	9 6.00%	1
Heart failure, unspecified		14 4.96%	16 10.67%	*0.043*
Cerebral ischaemic stroke		16	12	0.47

	5.67%	8%	
Chronic kidney disease	31 10.99%	13 8.67%	0.55
Kidney failure, unspecified	17 6.03%	9 6.00%	1
Dependence on renal dialysis	29 10.28%	14 9.33%	0.88
Chronic obstructive pulmonary disease	18 6.38%	7 4.67%	0.61
Acute ischaemic heart disease, unspecified	15 5.32%	4 2.67%	0.3
Respiratory failure	15 6.32%	4 2.67%	0.3
Aggregated group of diseases			
No comorbidities	11 3.90%	2 1.33%	0.23
Diseases of the circulatory system	168 59.57%	88 58.67%	0.94
Endocrine, nutritional or metabolic diseases	122 43.26%	63 42.00%	0.88
Diseases of the genitourinary system	54 19.15%	25 16.67%	0.61
Diseases of the respiratory system	47 16.67%	20 13.33%	0.44
Diseases of the nervous system	35 12.41%	26 17.33%	0.21
Diseases of the digestive system	30 10.64%	14 9.33%	0.79
Neoplasms	26 9.22%	14 9.33%	1
Mental, behavioural or neurodevelopmental disorders	25 8.87%	11 7.33%	0.71
Factors influencing health status or contact with health services	37 13.12%	17 11.33%	0.7
Symptoms, signs or clinical findings, not elsewhere classified	13 4.61%	11 7.33%	0.34
Certain infectious or parasitic diseases	15 5.32%	5 3.33%	0.49

Table 2. Association between the factor age and the distinct diseases or group of diseases, as absolute numbers and as percentage (by column). In bold the p-values for the differences in percentage that reached the statistical significance with respect to the chi-squared test

Characteristics n, %		<50 44 10.19%	50-59 69 15.97%	60-69 120 27.78%	70-79 128 29.93%	>=80 71 16.44%	p-value
Sex							
Male		29 66%	56 81.16%	73 60.83%	80 62.5%	44 61.97%	*0.05*
Female		15 34.09%	13 19.84%	47 39.17%	48 37.5%	27 38.03%	
Diseases							
Hypertension		12 27.28%	21 30.43%	49 40.83%	45 35.16%	35 49.30%	0.074
Obesity		13 29.55%	9 13.04%	20 16.67%	8 6.25%	3 4.23%	*0.000*
Diabetes	Total	14 31.82%	23 33.33%	53 44.17%	48 37.5%	16 22.53%	*0.045*
	Diabetes mellitus, unspecified	7 15.91%	8 11.59%	18 15.00%	24 18.75%	10 14.08%	0.74
	Diabetes mellitus type 2	7 15.91%	12 17.39%	31 25.83%	20 15.63%	5 7.04%	*0.021*
	Diabetes mellitus type 1	-	3 4.34%	4 3.33%	4 3.13%	1 1.40%	-
Diseases of the circulatory system, unspecified,		6 13.64%	7 10.14%	18 15.00%	23 17.97%	14 19.72%	0.53
Supraventricular tachyarrhythmia		1 2.27%	-	-	12 9.38%	10 14.08%	-
Heart failure, unspecified		-	5 7.25%	10 8.33% (	7 5.47%	8 11.27%	-
Cerebral ischaemic stroke		2 4.55%	1 1.49%	9 7.50%	9 7.03%	7 9.86%	0.31
Acute ischaemic heart disease, unspecified		-	2 2.90%	7 5.83%	4 3.13%	6 8.45%	-
Chronic kidney disease		4 9.09%	3 4.35%	14 11.67%	14 10.94%	9 12.67%	0.48
Dependence on renal dialysis		3 6.82%	13 13.04%	13 10.83%	15 11.72%	3 4.23%	0.072
Kidney failure, unspecified		3 6.82%	3 4.35%	9 7.50%	8 6.25%	3 4.23%	0.87
Respiratory failure		2 4.55%	4 5.80%)	3 2.50%	4 3.13%	6 8.45%	0.33
Chronic obstructive pulmonary disease		1 2.27%	-	12 10.00%	10 7.81%	2 2.82%	-

Aggregated group of diseases						
Diseases of the circulatory system	14 31.82%	33 47.83%	74 61.67%	82 64.06%	53 74.65%	*0.000*
Endocrine, nutritional or metabolic diseases	21 47.73%	30 43.48%	63 52.50%	53 41.41%	18 25.35%	*0.007*
Diseases of the genitourinary system	7 15.91%	7 10.14%	24 20.00%	29 22.66%	12 16.90%	0.27
Diseases of the respiratory system+	6 13.64%	10 14.49%	18 15.00%	20 15.63%	13 18.31%	0.96
Diseases of the nervous system	3 6.82%	2 2.90%	18 15.00%	19 14.84%	19 26.76%	*0.001*
Diseases of the digestive system	4 9.09%	8 11.59%	18 15.00%	10 7.81%	4 5.63%	0.23
Neoplasms	1 2.27%	7 10.14%	12 10.00%	16 12.50%	4 5.63%	0.25
Mental, behavioural or neurodevelopmental disorders	3 6.82%	2 2.90%	6 5.00%	15 11.72%	10 14.08%	*0.049*
Factors influencing health status or contact with health services	4 9.09%	10 14.49%	15 12.50%	19 14.84%	6 8.45%	0.66
Symptoms, signs or clinical findings, not elsewhere classified.	2 4.55%	3 4.35%	6 5.00%	11 8.59%	2 2.82%	0.46
Certain infectious or parasitic diseases	3 6.82%	2 2.90%	6 5.00%	4 3.13%	5 7.04%	0.63

Comparison between COVID-19 and pneumonia fatalities

The comparison with pneumonia fatalities yielded that the proportion of males in the COVID-19 death sample is also significantly higher than in the pneumonia death sample as illustrated in Table 3. The age structure and the relative frequency of essential hypertension, diseases of the circulatory system, obesity, dependence of renal dialysis, and chronic kidney failure are also different between the COVID-19 and pneumonia groups. Additionally, the odds to die of COVID- 19 versus hospital pneumonia are 150% greater for men over women with similar comorbidities (see Table 4). Moreover, the adjusted odds to die of COVID-19 compared to pneumonia are 22 times higher for persons with the chronic kidney failure, doubled for persons with hypertension, and are almost equal for patients with type 2 diabetes.

Table 3. Comparison between the characteristics of the COVID-19 and pneumonia groups. In bold the p-values for the differences in the relative frequency between groups that reached the statistical significance with respect to the chi-squared test.

Characteristics	COVID-19	Pneumonia	p-value
Sample size n, %	432 100%	711 100%	
Sex n, %			*0.000*
Female	150 35%	320 45%	
Male	282 65%	391 54.99%	
Age, mean (sd), median	66.97 (13.07) 68	73.14 (13.68) 78	
Age group **n, %**			*0.000*
<50	44 10.19%	49 6.89%	
50-59	69 15.97%	51 7.17%	
60-69	120 27.78%	141 19.83%	
70-79	128 29.63%	199 27.99%	
>=80	71 16.44%	271 38.12%	
Comorbidities			
Hypertension	162 37.50%	181 25.46%	*0.000*
Obesity	56 12.96%	63 8.86%	*0.03*
Diabetes mellitus type I	12 2.78%	5 0.70%	*0.01*

Diabetes mellitus type II	75 17.36%	145 20.39%	0.21
Dialysis	43 9.95%	4 0.56%	*0.000*
Chronic kidney disease	43 9.95%	88 12.38%	0.21
Supraventricular tachyarrhythmia	25 5.79%	201 28.27%	*0.000*
Congestive heart failure	12 2.78%	204 28.69%	*0.000*
COPD	24 5.56%	72 10.13%	*0.01*
Heart failure	29 6.71%	27 3.80%	*0.03*
Kidney failure	26 6.02%	4 0.56%	*0.000*
Respiratory failure	19 4.40%	88 12.38%	*0.000*
Cerebral ischaemic stroke	28 6.48%	- 	*0.000*

Table 4: Logistic regression for the comparison between COVID-19 and Pneumonia death groups. In bold the p-values for the covariates that reached the statistical significance

Covariates	**Coefficient** β	**OR** (COVID-19 vs. Pneumonia)	**95% CI**	**p-value**
Age	-0.022	0.978	[0.968-0.988]	*0.000*
Sex (0=female)	0.414	1.513	[1.145-2.000]	*0.01*
Hypertension	0.740	2.096	[1.560-2.818]	*0.000*
Obesity	0.266	1.305	[0.843-2.019]	0.23
Diabetes type 2	-0.355	0.701	[0.494-0.996]	*0.05*
Dialysis	3.104	22.290	[7.244-68.590]	*0.000*

Chronic kidney disease	-0.522	0.593	[0.369-0.955]	*0.03*
Heart failure	1.095	2.990	[1.612-5.546]	*0.000*
COPD	-0.730	0.482	[0.284-0.817]	*0.01*
Supraventricular tachyarrhythmia	-1.687	0.185	[0.116-0.295]	*0.000*
Respiratory failure	-1.045	0.352	[0.203-0.609]	*0.000*
Intercept	0.884	2.420		*0.02*

The burden of disease and survival probability

In the next step, we extended the analysis to the coexistence of multiple health conditions, and we focused on the multimorbidity. This has a mean value of 2.109, an SD of 1.66 and a median value of 2 in our study. The multimorbidity factor with levels 0,1,2,3,4 or more than 5 for single or aggregated comorbidities is significantly associated with the factor age but not with sex, confirming the pattern displayed at the level of single conditions and group of diseases (Table S3 and Table S4).

CCI had a mean of 1.324, SD of 0.95 and median of one indicating that the severity of the underlying medical condition in the study was mainly mild. This was confirmed by the high relative frequency of 91.20% for the mild level for the factor CCI. There were no significant differences between males and females or among age groups with respect to CCI (Table S3 and Table S4). Moreover, 1-year survival probability averaged out at 81%, and 50% of the study individuals had a prognosis for it of 85%.

Co-occurrence patterns

The co-occurrence of the diseases is of great importance since the mean multimorbidity of 2.109 indicates that not single but pair of diseases are pre-conditions in our mortality study. Pearson's phi coefficient is a robust measure of the comorbidity association, and its values for diseases in general and separated for men and women are displayed in the Table S5. Different co-occurrence patterns emerge between men and women with the striking lack of the correlation between pneumonia or respiratory failure, respectively stroke and dissociative neurological symptom disorder in the female profile. The largest value of the parameter phi of 0.47 respectively 0.40 for female and 0.59 for male corresponds to kidney failure and dependence to dialysis, while the latter is also correlated with chronic kidney disease as the correlation lies by 0.30 in general and

0.38 in men. They are followed by pneumonia or respiratory failure with phi equal to 0.45 in general and to 0.55 in male and by stroke and dissociative neurological symptom disorder with a correlation coefficient of 0.41 in the whole study and of 0.49 in men. Diabetes mellitus type 2 is correlated with hypertension not only for the whole study (phi = 0.11) but also in the male (phi=0.10) and female subsample (phi=0.11). Hypertension appears mainly together with stroke with phi equal to 0.15, 0.16 respectively 0.14 for the whole study, men and women.

Finally, a comorbidity network analysis rounded off our exploratory investigation. This identified 11 clusters in the general study, 8 clusters in male, and 6 clusters in female subgroups, each including two or three diseases reinforcing the previous results about pair of diseases as pre- condition for COVID-19 fatalities (see Figure 2).

Discussion

The high relative frequency of men in the whole study (65.3% males vs 34.7% females, p-value <0.001) and in all subpopulations with distinct diseases and aggregated group of diseases shows that an important risk factor for death by COVID-19 is being male. This is in concordance with other studies about predictors for severity and mortality due to infection with SARS-CoV 2. [9,16]

Comorbidities with the highest prevalence in our study like hypertension (37.5%), diabetes (35.4%), obesity (12.27%) and chronic kidney disease (10.19%) as well as diseases of the circulatory system (59.26%) and nutritional or metabolic disorders (42.82%) and their relative frequencies are similar to those reported in Chinese or American studies.[9,17,18] These percentages are closed to surveys made China by Li et al., where the most persons deceased in hospital (N=128) were men (73%), and hypertension (47%) and diabetes (13%) had the highest prevalence for death by COVID-19 and by Zhou et al. where, from N=54 fatalities, 62% were male, and hypertension (30%), diabetes (19%) and coronary heart disease (8%) had the highest frequency. [19,20] These diseases display significant differences in the relative frequency of men over women in our study: 74.67% male vs 25.33% female for diabetes mellitus type 2, 69.75% male vs 30.25% female for hypertension, 70.45% male vs 29.55% female for chronic kidney disease, as well as 65.62% vs 34.38% respectively 65.95% vs 34.95% for diseases of the circulatory system and for nutritional or metabolic disorders. Almost all comorbidities in our studies are not associated with sex but with the factor age as reported before. [21,22]

The highest number of deceased in this study was in the age group between 70-79 (N=128,29.63%), followed by 60-69 (N=120,27.78%) and the majority were men (62.5% male versus 37.5% female). The Romanian age-specific mortality statistics are similar to the estimates of crude-case fatality from Italy, Spain or Germany at the beginning of April in contrast to the United Kingdom, where the death count was higher in 65+years population cluster with a relative frequency of 44% for persons aged 65-79 and 46% for the 80+ age group. [4-8,23] The Romanian age structure of the COVID-10 fatalities is similar to the Chinese and lower than the Italian group. [9,22] People younger than 50 are less susceptible to die by COVID-19 with a relative frequency of 10% as it was reported in other articles, and people over 70 are almost half of the study participants (46%).[24] In the survey of Du et al. it was found that the people who died by SARS- CoV-2 infection were older than 65, and the main comorbidities related with the death were hypertension and CVD.[25] On the other side, in ten European countries and Canada, fatalities due to COVID-19 for individuals younger than 65 years represented 4.8-9.3% of all. Only 13.0% of the COVID-19 fatalities in the UK and 7.8-23.9% in the USA were younger than 65 years. On the other hand, the prevalence of the persons older than 80 was 54-69% in Europe, 67% in Canada and 36-63% in US.[24] Another important meta-analyze made by Verity et al. showed that the SARS-CoV-2 killed 13.4% persons older than 80 with more than one

comorbidity and the estimated case fatality rate was 1.38% for 38 countries. [26] In the Spanish study by Perez-Tanoira et al. men older than 85 represented 27% of the sample (N=108), the most prevalent comorbidity was coronary heart disease and the crude mortality rate was 19%.[27]

Statistics displayed in Table S1 and Table 3 show that sex and age are decisive factors for the COVID-19 mortality. This is of great importance in the personalized medicine, where treatment management needs to be adapted to patients' characteristics, and in the epidemiology, where population stratification is the key to the identification of the high risk groups.

In the whole world, the incidence of COVID-19 and its mortality rate was higher for people with diabetes and/or obesity. The real mechanism of SARS-CoV-2 infection is not precisely known, but two theories suggest that this is due to the chronic inflammatory state and/or insulin- resistance.[28] In our study, diabetes mellitus was classified in type 1, type 2 and unspecified. The unspecified diabetes is most probably of type 2 because most of the deceased people are between 50 and 79 years old and the incidence of the diabetes mellitus of type 2 in Romania is higher than of type 1 as it was shown in the Predatorr study [14]. Hence, we can assume that the relative frequency of the diabetes mellitus of type was higher than of the hypertension for the three clusters of age 50-59, 60-69 and 70-79 years.

The association between the age and different comorbidities suggest the existence of age- stratified positive and negative markers for the COVID-19 mortality. Generally, obesity correlates positively with diabetes [29,30], but this is confirmed here only in the lowest group age lower with a prevalence of 29.55%. Hence, we can interpret obesity as a negative marker for the severity of COVID-19 infection in combination with age under 50. Negative marker for the age group 50-59 is diabetes mellitus (33.33%), for 60-69 is diabetes mellitus (44.17%) and hypertension (35.16%), for 70-79 is diabetes mellitus (44.17%), hypertension (35.16%) and chronic kidney diseases (17.87%) and for the age group over 80 are hypertension (49%), diabetes (22.53%) and the diseases of the circulatory system (19.72%). At the level of the aggregated groups of diseases, main risk factors for death by patients infected with SARS-CoV-2 are: for persons under 50, the endocrine diseases (diabetes, obesity) with a prevalence of 47.73% and in all other age groups, diseases of the circulatory system with a prevalence between 47.83% and 74.65%.

The prevalence of respiratory failure and chronic pulmonary diseases in our study was almost the lowest compared to the rest of the comorbidities but it was similar with the statistics reported elsewhere.[19,20] Diseases of the respiratory system were more frequent in the age group over 80 (18.31 %) and had higher prevalence in men (16.67%) versus women (13.33%). This is surprising because pneumonia had a higher prevalence in the Romanian population in the last three years. Usually, the patients with comorbidities from this group of diseases are more vulnerable to viral respiratory infections.[31] Moreover, it is known that a symptom for the infection with SARS-CoV 2 is an atypical pneumonia with a variable degree of severity[32]. Because the pneumonia could be a negative prognostic factor for COVID-19 patients [33], we investigated the relation between the comorbidities of the two diseases. The results show significant differences between them as you can see in the Table 3. The hypothesis about the diseases of the respiratory system and the neoplasms as prognosis factors for the mortality through COVID-19 is not confirmed in our study. Therefore, it is probable that the patients died because of the impact and virulence

of the SARS-CoV-2 infection over comorbidities like hypertension, diabetes mellitus or obesity, in combination with age and sex [34].

Surprisingly, the average multimorbidity for the COVID-19 fatalities is low but confirms previous results about infected populations or groups with a severe form of the disease. [17]

The high relative frequency of the mild CCI corroborates this conclusion about people with a low burden of disease, also. Our prognosis regarding the survival probability confirms other results about the estimated year's life lost by the COVID-19 fatalities being "considerably more than the "1–2 years"" as presented in [35].

This is the first paper where the co-occurrence profiles are investigated with the help of Pearson's co-occurrence coefficient and where co-occurrence patterns are explicitly described through clustering. The cluster membership offers no medical surprises since diabetes appears mainly with cardiovascular diseases, and kidney diseases with dialysis. The sparsity of respiratory diseases especially in the female subgroup should be further investigated.

In conclusion, our study characterizes comorbidities of the COVID-19 fatalities in Romania and their association with sex and age. Most of our results are in concordance with the previous studies, and the main differences lie in the lower average age of the deceased patients, on their small multimorbidity count and their high 1-year survival probability. In addition, the comparison with the pneumonia group offers a new perspective on the medical pre-conditions of SARS-CoV 2.

Fortunately, we registered a low incidence of COVID-19 deaths in Romania, and future studies are needed to determine precisely the pathogenic mechanism that affected these patients, especially males with hypertension, diabetes, chronic kidney disease or obesity and potential protective conditions.

Methods

Study design.

1. The Cohort

The Romanian COVID-19 mortality sub-study was conducted between March 22 and April 20, 2020, with the aim to explore the comorbidity patterns in the patients who died because of this new virus. A multiple-case, the multiple-center design was chosen to answer this research question with data collected from the official public notifications of MAI concerning the COVID- 19 deaths registered by the INSP.[3,4,8]

Initially, 451 COVID-19 deaths were reported by INSP from the beginning of the epidemic until April 20. (Figure 1).

The list was completed afterwards with 69 additional cases due to the delay in the reporting process from some centres of COVID-19 infection. The official report included information about sex, age, county of residence, history of hospitalization and diagnostics, and/ or comorbidities. Only cases with information

about sex, age and comorbidities were included in the study due to the main focus of the research. [36] Eventually, 432 patients who fulfilled these criteria were kept in the Romanian COVID-19 mortality sub-study. Since we aim at an analytic and not statistical generalization of the results regarding the comorbidity patterns, statistical testing was just serving exploratory purposes. [36] Hence, the complete-case analysis is justified in this case both by purpose and by the state of things.

2. Case-case study

Additionally, we run a case-case study utilizing data regarding the deaths due to hospital pneumonia between March 22 and April 20 in the years 2016-2018 extracted from the administrative database of the INSP.

The study was carried out with the approval of the Local Bioethics Council of the INSP (number 6342/04 MAY 2020) and with the permission of the Local Bioethics Council of the "Carol Davila "University of Medicine, Bucharest Romania (9984/11 MAY 2020).

3. Statistical analysis.

An exploratory data analysis was applied to identify general, spatial-, sex- or age-specific comorbidity patterns in our study. In a first step, the various conditions were sorted according to the standard diagnosis tool ICD-11 (The International Classification of the Diseases) as it was recommended for the mortality and morbidity statistics by the WHO. [37] The ICD-11 taxonomy includes categories of single diseases or the aggregated groups of diseases. We investigated the comorbidities at both levels of aggregation because the stud< included a large number of distinct conditions with low prevalence. The statistical analysis was done with the help of the statistical software R version 3.6.2.

Continuous variables were expressed as mean, standard deviation (SD) and median. We focused in this paper on comparing the individual crude relative frequencies of the single and aggregated comorbidities between different sex and age groups. Since age is a significant risk factor for mortality, we investigated the frequency of the comorbidities stratified on ten-year intervals starting with the 50+ age groups. Categorical variables were tabulated in frequency (n) and relative frequency (%). A binomial and a chi-squared test for one proportion (only the last was reported) and a chi-squared test for equal proportions were applied when it was appropriate at the 5% level of significance.

The post-hoc tests were not corrected for multiple comparisons since the focus of our study was on generating hypotheses for single diseases or group of diseases and not on an experiment-wise approach. The spatial distribution of the COVID-19 mortality corresponded to the country- specific administrative units– counties and was illustrated by single or aggregated disease frequency and relative frequency (%).

The association between different comorbidities and the odds ratio between COVID-19 and pneumonia deaths was investigated with the help of the logistic regression, and the results were reported as coefficients β, as point estimates for odds ratio and their 95% confidence intervals.

Multimorbidity was computed for each person in the sample since this is a good indicator of the burden of disease [39] and transformed it in a multimorbidity factor with levels 0, 1, 2, 3, 4, or more the 5 for single or aggregated comorbidities.

A controversial issue regarding the epidemic of COVID-19 is the burden of disease in the deceased population and the hypothetical survival probability in the case that these people would not have been infected with this virus. A simplified version of the Charlson Comorbidity Index (CCI) was calculated on a scale from 0- 8, as indicated in [21] for an assessment of the individual disease severity. We introduced the CCI factor with two levels (mild for CCI< 3 and severe for CCI >=3), and we tested its differences between sex and age groups by a chi-squared test.

Following the same paper [21], we adapted their statistical model for the individual prognosis of the death risk based on the reported hazard ratio for the age levels and for the CCI in multiple European studies as explained in the section 8 of the supplementary material. This gave us a prognosis for the mean, the standard deviation and the median of the crude 1-year death risk and survival probability.

The next step in the analysis of the COVID-19 comorbidities concerns the co-occurrence of the diseases. This was explored with the help of the Pearson's phi coefficient as defined and investigated, e.g. in [38] and computed for each pair of single or aggregated diseases with an incidence of at least 4. A value of 1 means a "perfect match", 0 means no co-occurrence and negative values up to -1 means "inverse occurrence".

A comorbidity network approach was considered to investigate the relationships between diseases. We computed the dissimilarity between the conditions studied in the previous step as one minus the Pearson's phi. Hence, a value of 1 corresponds to "no association" and values larger than 1 to "inverse association". The hierarchical classification was performed through an agglomerative clustering algorithm with the Ward method since this proved to have the largest agglomeration coefficient. Furthermore, the dendrogram was cut at nodes corresponding to branch length of 1 based both on a visual inspection and on predefined length of the branch.

†This study has several limitations. We considered only the deaths up to April 20 when the peak of the pandemic was reached in Romania. Moreover, total case design was used because of the missing data in official public communications.

Declarations

Author contribution: **APS, MPJ, AP** conceived the research question. **APS, MPJ, AP, BVI, MR, AC, RS** and **VJ** designed the study and analysis plan. **APS,MPJ,AP,RS,MG,MR,AC,SP,CN,RH,AIS,DC,LM** and **CP** prepared the data. **MPJ** did the statistical analysis. **APS,MPJ,AP,BT,AT,CS,AA,AC,MR,** and **VJ** drafted the initial and final versions of the manuscript. All authors critically reviewed early and approved final versions of the manuscript.

***AP**, **RS, MR, AC** equally contributed to the paper.

Conflict of interest: **APS, MR, AC** have given talks, attended conferences, and participated in advisory boards and clinical trials sponsored by various pharmaceutical companies; yet, no financial or professional help was received for the preparation of this manuscript. **APS** is currently Vice-President, National Diabetes Commission, Ministry of Health, Romania.MR is currently Director, Clinical Medical & Regulatory Department, Novo Nordisk Europe East and South. The rest of the authors do not have a conflict of interests to declare for this article.

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Figures

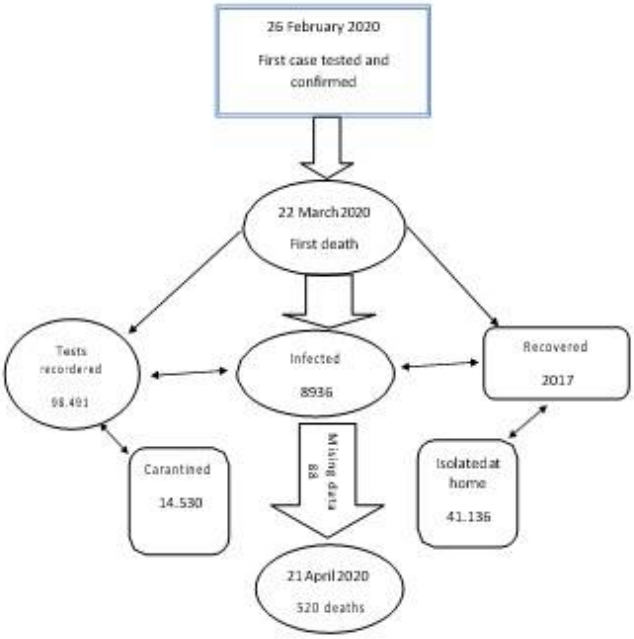

Figure 1

History of SARS-CoV-2 pandemic in Romania up to April 20

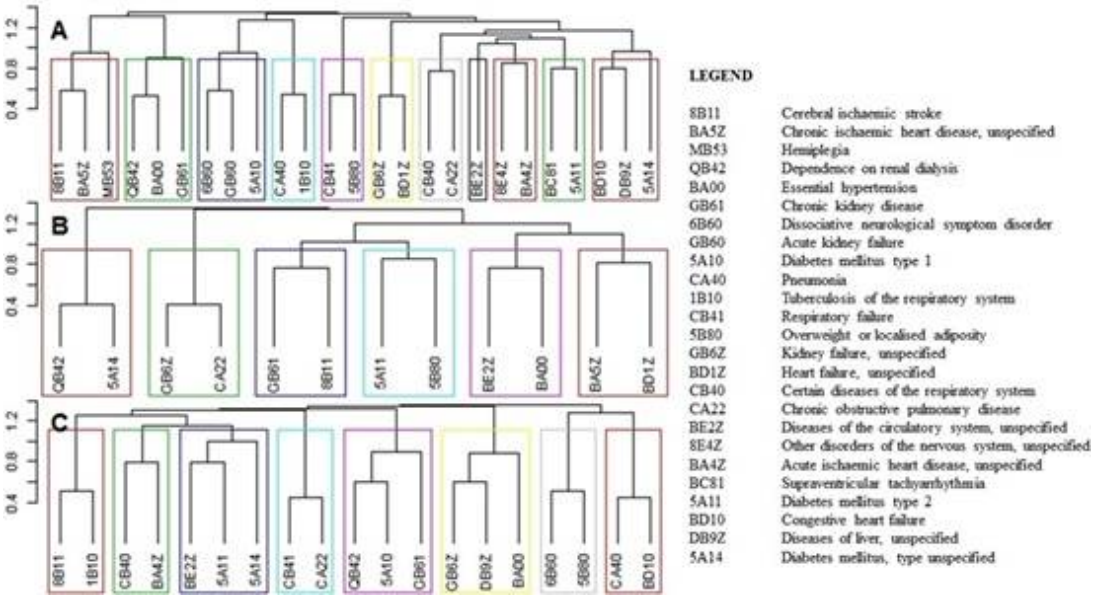

Figure 2

Co-occurrence clusters for general (A), female (B) and male (C) groups

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PanteaStoianetalDeathbySARSCoV2aRomanianCOVID19comorbiditystudySupplementaryMaterial.pdf