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Common Comorbidities and Complications in COVID-19 Deaths: An Analysis from Italian Data in Comparison with Influenza

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Abstract: Multiple cause data refer to all conditions reported on death certificates. Compared to the single underlying cause of death, these data provide additional information concerning the presence of comorbidities and complications leading to death. The objective of the study is to use a novel multiple cause approach for identifying comorbidities and complications of COVID-19. We analysed certificates referring to deaths that occurred in Italy in 2020–2021. With a double step chi squared test, we identified the conditions associated with COVID-19 and whether such conditions were reported as 'cause of' (comorbidities) or 'due to' (complications) COVID-19. For comparison, we adopted the same procedure for influenza deaths that occurred in Italy in 2016–2019. Pneumonia, respiratory failure and adult respiratory distress syndrome are the most frequent complications of COVID-19 and are also associated with it. These diseases have the same role for influenza, nevertheless this latter is strongly associated also with heart failure reported as a complication. Comorbidities are similar for COVID-19 and influenza: diabetes mellitus, chronic obstructive pulmonary disease (COPD) and obesity are the most frequent, with obesity much more frequent in COVID-19 cases. Hypertension is strongly associated with COVID-19 and is more frequent than in influenza cases. This approach is also suitable for other target diseases.

Keywords: COVID-19; influenza; multiple causes of death; comorbidities; complications

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1. Introduction

Since January 2020, SARS-CoV-2 has progressively moved across the world, leaving almost no country untouched and resulting in an unprecedented global health challenge [1]. In Italy, COVID-19 has become one of the leading causes of death [2,3]. In contrast, seasonal influenza, a recurring respiratory viral infection, has been a perennial public health concern, albeit with comparatively less impact on public health [4,5].

Understanding the differential impact of COVID-19 and seasonal influenza on public health, the demographic characteristics of deaths, and geographical distributions is crucial for guiding public health interventions and resource allocation strategies. While both diseases share similarities in transmission routes and clinical manifestations, notable differences exist in terms of severity, case fatality rates, and population susceptibility.

Severe outcome of COVID-19 is associated with old age, male gender and comorbidities such as obesity, diabetes, hypertension, cardiovascular disease and multimorbidity in general, while pneumonia and other respiratory conditions are its most frequent complications [5–10]. In contrast, influenza tends to affect younger patients more than COVID-19; indeed, children under 14 years old are more susceptible to influenza than to COVID-19 [11]. Comorbidities for both influenza and COVID-19 are malignancy, chronic lung disease, renal failure, and heart failure [6,12,13].

Cause-of-death statistics are a primary source of information on the health of a population. These data derive from death certificates, on which the physician reports the complete sequence of conditions leading to death and the other relevant conditions associated with it. Usually, national statistics provide only information on the cause that initiated the sequence of morbid events leading to death, the so-called underlying cause (UC). Nevertheless, the analysis of all conditions reported on death certificates, referred to as multiple cause analysis, can shed light on conditions associated with the underlying causes as well as on the sequences leading to death [14].

The present study aims to compare complications leading to death and comorbidities associated with influenza and COVID-19 mortality. For this purpose, death certificates were analysed, using all of the information about causes reported on them.

2. Materials and Methods

Analyses were carried out on the Italian National Cause of Death Register (https://www.istat.it/it/archivio/4216, accessed on 13 November 2024), managed by the Italian National Institute of Statistics (ISTAT). Causes of death are provided by physicians, who report the sequence of causes directly leading to death and the other relevant morbid conditions contributing to death on a death certificate. In the sequence, each reported condition is caused by the preceding one. For each year, all death certificates referring to deaths that occurred on Italian territory are collected by ISTAT and coded with the International Classification of Diseases (ICD-10). Multiple causes of death are coded and the UC is selected [15]. The coding and the selection of the UC are performed with the aid of the Iris 5.8.1 (www.iris-institute.org) software, which is used around the world. All coded data are stored in the Italian National Cause of Death Register.

For the present study, all certificates referring to deaths that occurred in the years 2016–2021 were considered. All death certificates from the years 2020–2021 were used for the analysis of COVID-19, while all 2016–2019 death certificates were used for influenza, in order to avoid the confounding effect of possible misclassification of COVID-19 and influenza cases during the pandemic period.

Numbers of deaths and rates have been calculated taking both only the UC and multiple causes of death into consideration. Age standardized rates were calculated with the direct method using 5-year age groups (except for 0 years, 1–4 and 95+) and using the European standard population for weighting the specific rates [16]. European population was used to ensure better comparability with other European countries and with national standardized rates for other causes of death, which are calculated using this standard [17].

The analysis of comorbidities and complications was focused only on people aged 65 and over, as the associations between diseases can vary by age, and it is therefore necessary to calculate them by age groups to avoid confounding. These associations were therefore calculated only for the 65 and over age group, due to the low number of cases in the other age groups.

The methods for the analysis of comorbidities and complications are described in detail in a previous paper [10]. For the analysis, conditions were grouped according to the list provided in Supplementary Table S1. A two-step evaluation was performed. In the first step, we evaluated the association of a given condition with the reference cause, COVID-19 or influenza. A certain condition X is considered to be associated with the reference cause if the frequency of certificates mentioning both the reference cause and X is higher than expected (probability of chi-squared test higher than 95%).

In the second step, we evaluated whether a condition X is reported by certifying physicians as a complication or comorbidity of the reference cause. For this purpose, we used certificates in which the condition X and the reference cause are both reported in the sequence of causes directly leading to death, and one is reported as caused by the other. We defined X as being reported as a complication of the reference cause if the frequency of certificates with X reported as caused by the reference cause is higher than expected. We defined X as being reported as a comorbidity of the reference cause if the frequency of

certificates with the reference cause reported as caused by X is higher than expected. The expected frequencies were calculated using the hypothesis of equal probability of the two configurations: half of the certificates should report X caused by the reference cause and half the opposite. The difference with the expected distribution was evaluated with the chi squared test, with 95% probability.

At the end of the two steps, each group of diseases can be included in one of the following categories according to its relation to the reference cause: associated with and complication of; not associated with and complication of; associated with and comorbidity of; not associated with and comorbidity of; associated with without a specific relation (neither complication nor comorbidity); and not associated with without a specific relation (neither complication nor comorbidity). The category can be the same for the two reference causes or not, highlighting the similarities and differences between COVID-19 and influenza in relation to other diseases.

In addition, for each cause, the two proportions of certificates that mention it among certificates with influenza and COVID-19 were compared using the chi-squared test, with a threshold of $p <= 0.05$. Results are shown in Supplementary Table S1.

3. Results

Table 1 shows the number of deaths and the mortality rates for influenza in the period 2016–2019 and for COVID-19 in 2020–2021.

Table 1. Mortality for influenza and COVID-19 by sex and age groups. Absolute numbers and standardized mortality rates (per 100,000 inhabitants). Years 2016–2021.

Age Group (Years)	Multiple Causes						UC					
	Influenza			COVID-19			Influenza			COVID-19		
	2016–2019			2020–2021			2016–2019			2020–2021		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
	Deaths											
0–64	256	160	416	10,260	4140	14,400	197	124	321	9042	3471	12,513
65 and over	1056	1500	2556	80,390	70,000	150,390	840	1246	2086	71,231	58,843	130,074
All ages	1312	1660	2972	90,650	74,140	164,790	1037	1370	2407	80,273	62,314	142,587
	Standardized mortality rates											
0–64	0.3	0.2	0.2	19.2	7.4	13.2	0.2	0.1	0.2	17.0	6.2	11.5
65 and over	5.0	3.8	4.3	667.4	356.8	486.6	4.0	3.1	3.5	590.7	301.0	421.8
All ages	1.2	0.9	1.0	145.6	75.5	105.5	0.9	0.7	0.8	128.9	63.7	91.5

During 2020 and 2021 there were 164,790 deaths with mention of COVID-19, 87% of which (142,587) had COVID-19 as the UC. The corresponding standardized mortality rate, considering all deaths mentioning COVID-19, was 105.5 deaths per 100,000 (91.5 when considering only the UC). Influenza-related deaths in the period 2016–2019 were 2972 and the corresponding rate was 1.0 deaths per 100,000. The percentage of influenza related deaths in which influenza is also the UC was 81%, slightly smaller than the value found for COVID-19. In 2020–2021 deaths for influenza were 880 (see Supplementary Information, Table S2), with an average yearly number of 440, a smaller value compared to 743 average yearly deaths observed in 2016–2019.

For both influenza and COVID-19, deaths occurred primarily among individuals over 65 years of age (87% for influenza and 91% for COVID-19). For influenza, only 10% of total deaths involve younger people (less than 65); nevertheless, this percentage varies across geographical areas and reaches 32% in the Centre for men only (see Supplementary Information, Table S2). Mortality rates for both causes are higher in men than women and this is more pronounced for COVID-19 in the younger age group. As a result, the mortality

rate ratios for men vs. women are 1.6 for influenza and 2.7 for COVID-19 in the 0–64 age group and 1.3 and 2.0, respectively, in the 65+ age group.

The influenza and COVID-19 standardized mortality rates differ by approximately two orders of magnitude: this difference is higher in the older age group where the COVID-19 vs. influenza mortality rate ratio is 121.

The number of causes reported (three digit codes level of the ICD) on the death certificates of people who died from influenza or COVID-19 are 5.0 and 5.3, respectively (Supporting Information, Table S3). Focusing on deaths of people aged 65 and over, Figure 1 shows the causes reported together with COVID-19 and influenza, whether they are associated with the reference cause and whether they are reported as complications or comorbidities.

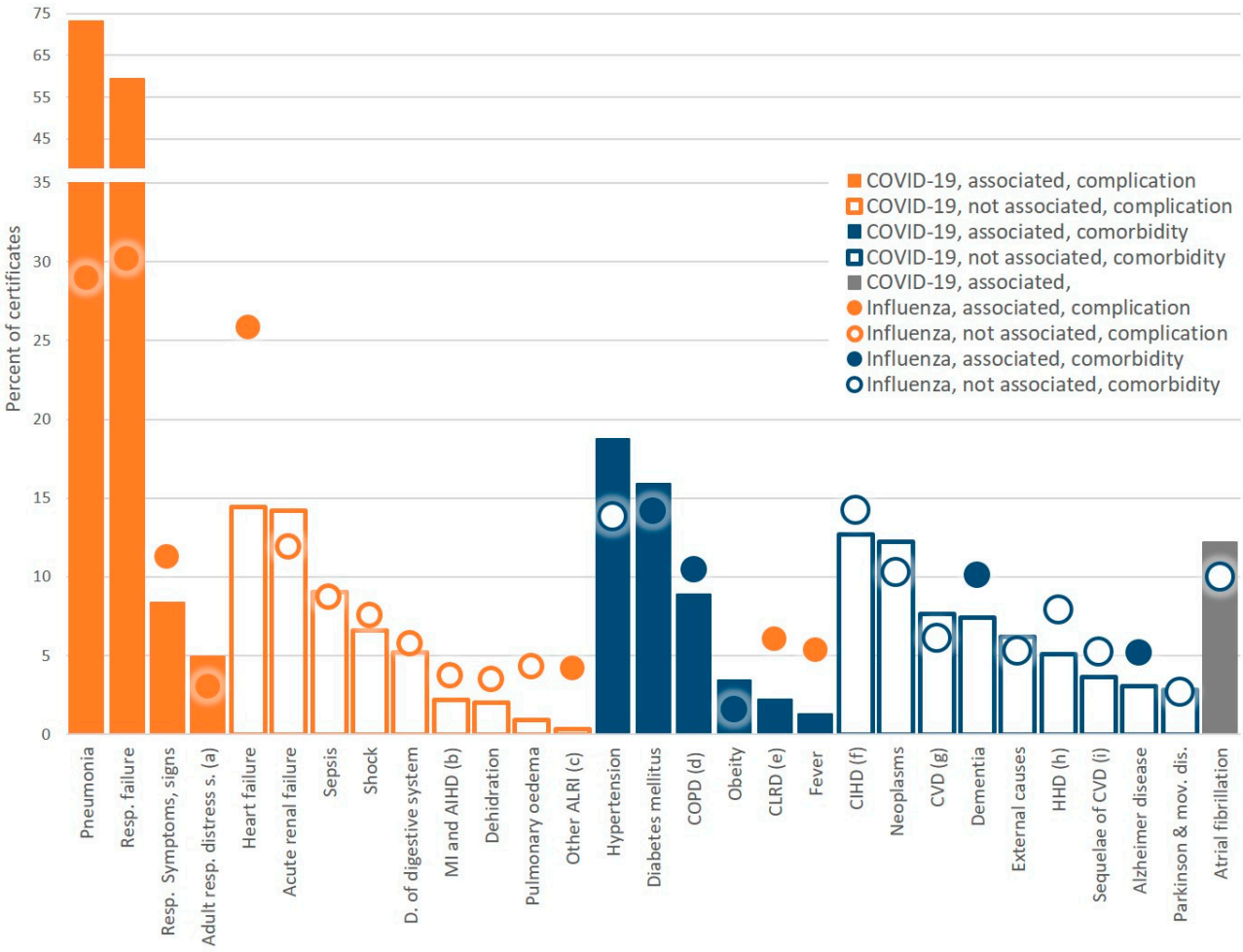

Figure 1. Conditions reported together with COVID-19 and influenza. The height of the bars represents the percentage of certificates reporting the cause and COVID-19 out of the total number of certificates reporting COVID-19. The position of the bullets represents the percentage of certificates reporting the cause and influenza out of the total number of certificates reporting influenza. Causes with low frequencies and those referring to residual categories of the ICD10 (causes including heterogeneous and unspecific ICD10 codes) are not shown, but the additional table reports the complete list of multiple cause analyzed. (a) Adult respiratory distress syndrome; (b) Acute myocardial infarction (MI) and other acute ischemic heart diseases (AIHD), (c) Other acute lower respiratory infections (ALRI) (other than pneumonia); (d) Chronic obstructive pulmonary diseases (COPD), unspecified; (e) Chronic lower respiratory diseases (CLRD); (f) Chronic ischemic heart diseases (CHD); (g) Cerebrovascular diseases (CVD); (h) Hypertensive heart diseases (HHD).

Conditions reported as complications and associated with COVID-19 involve mainly the respiratory system: pneumonia, respiratory failure, respiratory symptoms and signs and adult respiratory distress syndrome. These conditions are also associated with and are complications for influenza. Pneumonia and respiratory failure are the causes most frequently reported with both influenza and COVID-19. Furthermore, while they are reported in the majority of certificates reporting COVID-19 (73% pneumonia and 59% respiratory failure), this does not happen for influenza: both are reported on about 30% of influenza certificates. Adult respiratory distress syndrome is also reported more frequently with COVID-19 (5% vs. 3%), while respiratory symptoms and signs are reported more frequently with influenza (11% vs. 8%).

Conditions reported as complications of COVID-19, but not associated with it, are heart failure, acute renal failure, sepsis, shock, diseases of the digestive system, acute myocardial infarction and other acute ischemic heart diseases, dehydration, pulmonary oedema and other acute lower respiratory infections. All of these are reported as complications of influenza; heart failure and other acute lower respiratory infections are also associated with it. The majority of these complications are reported more frequently with influenza. In particular, heart failure is the third-most frequently reported condition with influenza (26% of certificates also reporting influenza), while the percentage is 14% for COVID-19. Acute renal failure is reported more frequently with COVID-19 (14% vs. 12%); sepsis is reported in the same percentage (9%) of certificates reporting COVID-19 and influenza.

Hypertension, diabetes mellitus, COPD, obesity, chronic lower respiratory diseases and fever are reported as comorbidities of and associated with COVID-19. Among these, hypertension, diabetes mellitus, COPD and obesity are also reported as comorbidities of influenza, while hypertension is not associated with it. Hypertension and diabetes mellitus are reported more frequently with COVID-19 and COPD is reported more frequently with influenza, while there is no statistically significant difference between the percentages of certificates reporting obesity with influenza and COVID-19. Hypertension is the most frequent comorbidity reported with COVID-19, being reported on 19% of COVID-19 certificates, while this percentage is 14% for influenza. On the other hand, chronic lower respiratory diseases and fever are more frequent in influenza deaths (6% vs. 2% and 5% vs. 1%, respectively) and are both associated with it and are reported as complications.

Chronic ischemic heart diseases, neoplasms, cerebrovascular diseases, dementia, external causes, hypertensive heart diseases, sequelae of cerebrovascular diseases, Alzheimer's disease, Parkinson's disease and movement disorders are reported as comorbidities of both COVID-19 and influenza. However, while none of these conditions is associated with COVID-19, dementia and Alzheimer's disease are associated with influenza and more frequently reported with it (10% vs. 7% and 5% vs. 3%, respectively). Chronic ischemic heart diseases, hypertensive heart disease and sequelae of cerebrovascular diseases are also more frequently reported with influenza. For external-cause and movement disorders there is no statistically significant difference between the percentages of certificates reporting them with influenza and COVID-19. The other comorbidities are more frequently reported with COVID-19.

Finally, atrial fibrillation is reported as a comorbidity of influenza, while it is associated and more frequently reported with COVID-19 (12% vs. 10%), with no specific role, whether complication or comorbidity.

Senility is associated with both influenza and COVID-19, but it is not identified as a complication or a comorbidity; it is more often reported with influenza. The residual group of the other heart diseases is associated with influenza (see Supplementary Information, Table S1).

4. Discussion

COVID-19 standardized mortality rates are much higher compared to influenza, highlighting the bigger impact of COVID-19 on public health in 2020–2021, data in line with those of Global Burden Disease [18,19]. COVID-19 and influenza are the UC in 86%

and 81%, respectively, of certificates reporting these causes, but they are generally reported in association with a higher number of other conditions compared to deaths from other causes, indicating that individuals who die from these causes often have numerous other comorbidities or complications.

The analysis of comorbidities and complications shows that pneumonia, respiratory failure and adult respiratory distress syndrome are the most frequent conditions complicating COVID-19. All these conditions are associated with COVID-19; i.e., they are significantly more frequent in COVID-19 cases than in general mortality. Other complications, such as heart or renal failure, are also frequent but do not show a specific association with COVID-19. The comparison with influenza shows that influenza and COVID-19 have similar complications, but heart failure seems to be more typical in influenza deaths. In some cases, diseases that are classified as complications in the analysis may actually not be real complications from a medical point of view, but rather symptoms or signs occurring due to the disease. An example is fever, which is not a complication of COVID-19, but rather a symptom of it.

Also, looking at comorbidities, COVID-19 and influenza share a similar pattern with diabetes mellitus, COPD and obesity associated with both diseases. A difference is represented by hypertension, which is strongly associated with COVID-19 and more frequently reported with it.

The findings are consistent with the literature, which links increased susceptibility to COVID-19 hospitalization and mortality to comorbidities such as diabetes, hypertension, cardiovascular diseases and obesity [20], as well as to the well-known respiratory and non-respiratory complications [21]. Specific studies comparing seasonal influenza and COVID-19 are scarce, but our results suggest very similar comorbidity profiles for both diseases. In addition, for some comorbidities, such as COPD, chronic ischemic heart disease, hypertensive heart diseases, Alzheimer's and other dementias, we found a higher association with influenza. This seems consistent with the findings of Brehm et al. [22] who found that COVID-19 patients had fewer baseline comorbidities than seasonal influenza patients.

The main limitation of the study concerns the fact that the approach analyses death certificates, the quality of which is not always high, as data reported by physicians are sometimes incomplete and unspecific. Cause-of-death statistics may also be affected by under-reporting of some causes. Although clear data are lacking, it is likely that influenza is under-reported in cause-of-death statistics, so some unreported influenza deaths are not included in our analysis. Another limitation of the study is that we based our analysis on influenza deaths that occurred during the four years prior to the COVID-19 pandemic. We cannot rule out that some undiagnosed COVID-19 deaths may have occurred in 2019 and may have been mistaken for influenza, as COVID-19 was still unknown and the symptoms of the two conditions are often similar. Nevertheless, the influenza mortality trend in 2019 does not show peaks compared to previous years and the number of influenza cases is consistent with prior years. Evidence suggests that potential COVID-19 cases in Italy in 2019 were few in number and localized only in some northern cities [23]. Therefore, for these reasons, even if there are some misdiagnoses, the number is very low and does not statistically affect the results. Among the strengths of our study, there is the use of a nationwide data source, which includes all the deaths that occurred in the country. As a consequence, there is no sampling or selection bias.

Our method is a simple approach, but it adds a novel component to the analysis of multiple causes of death data, an area of increasing interest. In fact, multiple causes analysis is currently mainly focused on providing a better estimate of the mortality burden for low-lethality conditions, such as chronic diseases, and on studying the association between causes [24], but little attention has been given to studying the sequences reported by physicians. Our method is an attempt to contribute to this gap. In addition, the method can be replicated in other settings where multiple cause of death statistics are available.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid4110126/s1, Table S1: Conditions reported together with COVID-19 and influenza by presence of association and role; Table S2: Deaths and standardized mortality rates for influenza and COVID-19 by sex and geographical areas. Years 2020–2021; Table S3: Annual average number of diseases reported in death certificates with mention of COVID-19, influenza or other causes of death, according to sex and geographical areas.

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