Analysing complications of COVID-19 from death certificates: which ones kill most?

Chiara Orsi [1], Daniele De Rocchi [2], Simona Cinque [1], Roberta Crialesi [1], Vincenzo Della Mea [3], Luisa Frova [1], Enrico Grande [1], Stefano Marchetti [1], Simone Navarra [1], Marilena Pappagallo [1], Silvia Simeoni [1], Francesco Grippo [1]

Abstract

Death certificates compiled by physicians are the basis for cause-of-death statistics and contain the whole sequence of diseases leading to death. This information is useful for understanding pathways from disease to death. Several complications are associated to COVID-19, nevertheless limited data are available on the frequency of these conditions leading to death. For identifying complications of COVID-19, a method was developed and applied to deaths occurred in Italy in March-April 2020. In order to test the method on other causes, analyses have been carried-out also for pneumonia and diabetes related deaths occurred in 2018. Pneumonia is the most frequent complication of COVID-19 together with some other respiratory conditions; besides those, some other conditions were identified as linked to COVID-19 related deaths such as cardiac complications, shock and infections. The method proves to be powerful in distinguishing complications and causes of diseases.

Keywords: COVID-19, comorbidity, causes of death, death certificates.

1 Italian National Institute of Statistics - Istat.
2 National Research Council - Institute for Research on Population and Social Policies (CNR - IRPPS).
3 Università degli Studi di Udine, Italy.

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1. Introduction[4]

COVID-19 is characterised by a high rate of lethality. In patients infected by SARS-CoV-2, death can occur as the consequence of various complications, especially pneumonia and other respiratory system conditions. In addition, the presence of comorbidities, as hypertension, diabetes, cardiovascular diseases, and chronic respiratory conditions, can increase vulnerability to the development of these complications (Zheng *et al.*, 2020; Palmieri *et al.*, 2020).

Death certificates are considered the most reliable source of information for comparing cause-specific mortality across different populations and countries. However, limited data are available on the complications and comorbidities reported on death certificates of patients who presented COVID-19. The UK Office of National Statistic conducted some analyses of conditions existing prior to contracting COVID-19 (ONS, 2020), but the complications of COVID-19 on death certificates are less explored.

Cause-of-death (CoD) data are based on the information reported by physicians on a standardised death form recommended by the World Health Organization (WHO international format of death certificate). Data collected with the death certificates are coded according to provisions of the International Classification of Diseases, 10th revision (ICD10) (WHO, 2019): the corresponding ICD10 code is assigned to each condition reported on the certificate. Despite certificates generally report several causes, CoD statistics are traditionally based on the concept of underlying cause (UC), *i.e.* the disease or condition that initiated the train of events leading to death (WHO,

4 The method described was developed in the frame of a project aimed at evaluating the effort needed for the implementation of the International Classification of Diseases, 11th revision (ICD11) in the automated coding systems Iris (www.Iris-institute.org).

Chiara Orsi and Francesco Grippo prepared the draft and contributed to the analysis of data and results interpretation. Francesco Grippo, Daniele De Rocchi and Chiara Orsi conceived the method and contributed to its development. Daniele De Rocchi and Francesco Grippo developed the SAS programme; Simona Cinque, Enrico Grande, Francesco Grippo, Simone Navarra, Chiara Orsi and Silvia Simeoni contributed to ICD10 data coding of 2020 mortality data. All authors contributed to the revision of the text and agreed to this published version of the manuscript.

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2019). Since several years, in Italy, as in other countries, automated coding systems are in use for CoD coding and selecting the UC. In Italy the software Iris is used, which is the most widely used. This software follows rules and provisions established by ICD10.

Death certificates consist of two parts: in part 1 the certifier reports the sequence of diseases or events leading directly to death, in part 2 he lists other significant conditions contributing to death. Part 1 of the death certificate includes four different lines: conditions reported on each line are due to what is reported on the line below. The condition that initiated the sequence leading to death should be reported in the lowest used line. Therefore, filling the death certificates, certifiers provide information on causal relations among the conditions leading to death.

1.1 Objectives

This paper presents a method to individuate causal relations among conditions reported on death certificates. In particular, the method allows identifying, for a given condition, which are its complications or its antecedent causes in the death certificate. The paper describes the procedure in detail and shows the results of its application to identify the complications of COVID-19 as well as to provide a measure of the frequency of such complications in deaths occurred in Italy during the first wave of the pandemic (March-April 2020). To show the potential general applicability to other conditions, we also performed analyses on two selected causes of death: pneumonia and diabetes.

2. Methods

The method presented is an advancement of a procedure developed as part of a project for the new version of ICD (ICD11) implementation in automated coding systems (www.iris-institute.org; Orsi *et al.*, 2020).

2.1 Causal relations in death certificates

Figure 2.1 shows an example of filled international death certificate. The person died for a cardiac arrest due to a congestive heath failure due to an ischemic heart disease, and was affected by diabetes and hypertension. These latter conditions both contributed to death, but were not part of the sequence leading directly to death; for this reason, the certifier reported them in part 2. UC is the ischemic heart disease, which is the condition that initiated the train of events leading to death.

In general, given a condition, which we will hereafter name *A*, all conditions reported in lines above (we will name other conditions *S*) can be considered due to *A*. On the other hand, *A* can be considered due to conditions reported below. In example 1 of figure 2.2[5], with regard to the causal relations of congestive heart failure (condition A corresponding to the ICD10 code I500), cardiac arrest (condition S_1, I469) is due to congestive heart failure, while congestive heart failure is due to ischemic heart disease (S_2, I259).

However, it should be taken into account that sometimes the order reported on death certificates does not correspond to a real causal connection between diseases. For instance, in example 2 of figure 2.2, the certifier misplaced liver metastasis (ICD10 code C787) on a row that indicates this condition as due to pneumonia (J189) but this is an incorrect causal sequence.

Provided that the death certificates could contain two given conditions reported in both directions (*A due to S* as well as *S due to A*), we developed a method for the identification of recurrent causal patterns in multiple cause-of-death data.

5 For the examples shown in figure 1.2, to each condition is given a corresponding ICD10 code, so in this document, the terms condition and code are used with the same meaning.

Figure 2.1 - Example of filled international death certificate

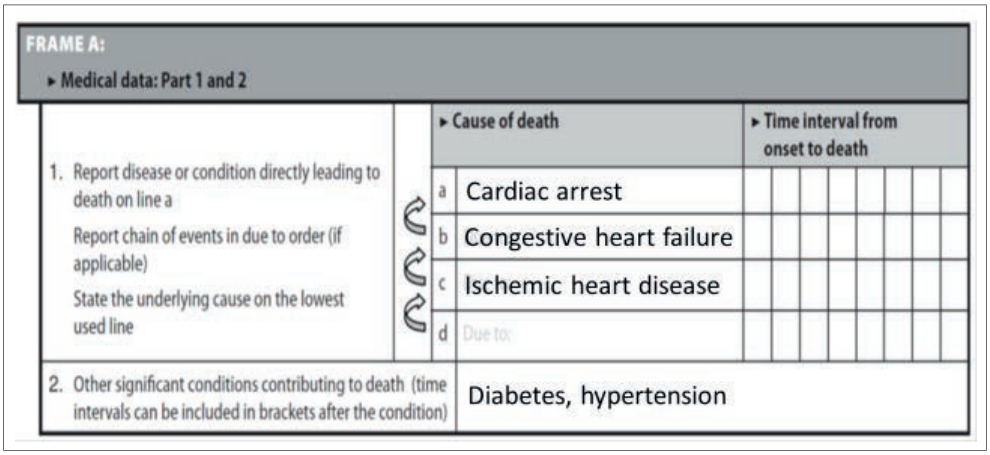


Figure 2.2 - Examples of filled death certificates

Example 1		ICD10 codes
Part 1	a. Cardiac arrest	I469
	b. Congestive heart failure	I501
	c. Chronic ischemic heart disease	I259
	d.	
	e.	
Part 2	Diabetes, hypertension	E149 I10
*Iris multiple cause string: I469 I501/I259*E149 I10*		

Example 2		ICD10 codes
Part 1	a. Liver metastasis	C787
	b. Pneumonia	J189
	c.	
	d.	
	e.	
Part 2	Lung cancer	C349
*Iris multiple cause string: C787/J189*C349*		

Example 3		ICD10 codes
Part 1	a. Acute respiratory failure	J960
	b. Interstitial pneumonia, congestive heart failure	J849 I500
	c. Covid-19	U071
	d. Ischemic heart disease	I259
Part 2		
Iris multiple cause string: J960/J849 I500/U071/I259		

Example 4		ICD10 codes
Part 1	a. ARDS	J80
	b. Covid-19 pneumonia	U071 J189
	c.	
	d.	
	e.	
Part 2	Hypertensive heart disease	I119
*Iris multiple cause string: J80/U071 J189*I119*		

Example 5		ICD10 codes
Part 1	a. Sepsis	A419
	b. Pneumonia	J189
	c.	
	d.	
	e.	
Part 2	Covid19	U071
*Iris multiple cause string: A419/J189*U071*		

Example 6		ICD10 codes
Part 1	a. Covid19	U071
	b.	
	c.	
	d.	
	e.	
Part 2	Pneumonia and respiratory failure	J189 J969
*Iris multiple cause string: U071*J189 J969*		

2.2 Overview of the method

The input data is the multiple cause string produced by the automated coding system Iris (shown in figure 1.2 below each certificate). This string consists of ICD10 codes and separators representing all conditions reported on the death certificate and their relative position.

The method focusses only on part 1 of certificates and, in summary, involves two steps:

1. causal relations: analysis of causal relations reported in part 1; a chi-square test is carried out in order to identify the preferred causal order between two conditions;
2. associations between conditions: analysis of associations between conditions in part 1; a second chi-square test identifies if two conditions are reported together in part 1 more frequently than expected. This step is used as a confirmation of the first.

The following paragraphs describe the two steps in detail.

2.3 Causal relations

This step is aimed at identifying the preferred causal order between two conditions reported by certifiers: given two conditions, *A* and *S*, a test is performed to verify if the pattern *A due to S* is significantly more frequent than *S due to A*.

For each pair of codes (*A* and *S*), certificates jointly mentioning the two codes in different lines of part 1 were selected, excluding those in which they are reported on the same line. The frequencies of certificates reporting the pattern *A due to S* and *S due to A* were calculated. Afterwards, these observed frequencies were compared with the expected ones calculated under the null hypothesis of equal probability for the two patterns, assuming that 50% of total certificates would have the pattern *A due to S* and 50% *S due to A* (table 2.1). The null hypothesis was tested by means of chi-square test (double tailed with 1 degree of freedom). Based on the results, we can distinguish the following cases.

- *A due to S* (positive due to relation between the two codes): the frequency of certificates reporting *A due to S* is significantly ($p<0.05$) higher than expected.
- *S due to A* (negative due to relation between the two codes): the frequency of certificates reporting *A due to S* is significantly ($p<0.05$) lower than expected.
- No due to relation between *A* and *S*: there is not a significant difference between observed and expected frequencies ($p>=0.05$).

Table 2.1 - Observed and expected frequencies of certificates for the analysis of causal relations between conditions (a)

Pattern of disposition of *A* and *S*	Observed	Expected
A due to S	$N_{AduetoS}$	$N^{exp}_{AduetoS} = \frac{1}{2} N^{*}_{AS}$
S due to A	$N_{SduetoA}$	$N^{exp}_{SduetoA} = \frac{1}{2} N^{*}_{AS}$
Total	N^{*}_{AS}	N^{*}_{AS}

(a) Subscripts $AduetoS$ and $SduetoA$ indicate respectively the presence of *A due to S* and *S due to A* on the death certificate.
N^{*}_{AS} indicates the number of certificates reporting *A* and *S* on different lines.

2.4 Association between conditions

This step serves as a confirmation of the previous one and it is aimed at verifying if two codes are associated, *i.e.* reported in part 1 more frequently than expected under the hypothesis that the two codes are reported independently from each other. Certificates are cross-tabulated by presence/absence of the codes under analysis (*A* and *S*) as shown in table 2.2. Observed and expected distributions are compared by a chi-square test (double tailed with 1 degree of freedom). For each possible pair of codes we define that there is association between the two conditions when the pair is mentioned significantly more than expected: the frequency of certificates reporting both the codes is higher than expected and the chi-square test highlights a statistically significant ($p<0.05$) association.

In the other possible cases, when either the pair is mentioned on certificates significantly ($p<0.05$) less than expected or the chi-square is not significant ($p>=0.05$), the two conditions are not considered associated.

The method was developed using the software SAS Studio (Release: 3.6 Enterprise edition).

Table 2.2 - Observed and expected frequencies of certificates for the analysis of association between conditions (a)

Observed frequencies

		Code *S*		
		Mentioned	Not mentioned	Total
Code *A*	Mentioned	$N_{A\bar{S}}$	$N_{A\bar{S}}$	N_A
	Not mentioned	$N_{\bar{A}S}$	$N_{\bar{A}\bar{S}}$	$N_{\bar{A}}$
	Total	N_S	$N_{\bar{S}}$	N

Expected frequencies

		Code *S*		
		Mentioned	Not mentioned	Total
Code *A*	Mentioned	$\mathrm{N}_{\mathrm{AS}}^{\mathrm{exp}} = \mathrm{N}_{\mathrm{A}} * \mathrm{N}_{\mathrm{S}}/\mathrm{N}$	$\mathrm{N}_{\mathrm{A\bar{S}}}^{\mathrm{exp}} = \mathrm{N}_{\mathrm{A}} * \mathrm{N}_{\bar{\mathrm{S}}}/\mathrm{N}$	N_{A}
	Not mentioned	$\mathrm{N}_{\mathrm{\bar{A}S}}^{\mathrm{exp}} = \mathrm{N}_{\bar{\mathrm{A}}} * \mathrm{N}_{\mathrm{S}}/\mathrm{N}$	$\mathrm{N}_{\mathrm{\bar{A}\bar{S}}}^{\mathrm{exp}} = \mathrm{N}_{\bar{\mathrm{A}}} * \mathrm{N}_{\bar{\mathrm{S}}}/\mathrm{N}$	$\mathrm{N}_{\bar{\mathrm{A}}}$
	Total	N_{S}	$\mathrm{N}_{\bar{\mathrm{S}}}$	N

(a) N indicates absolute frequencies.
Subscripts A and $\bar{A}$ indicate respectively the presence or the absence of the condition *A* on the death certificate. Subscripts S and $\bar{S}$ indicate respectively the presence or the absence of the condition *S* on the death certificate. N_{AS} indicates the number of certificates reporting both *A* and *S*, where $N_{AS} \leq N_{AS}$ used in table 1.2, since N_{AS} refers only to certificates that have the condition *A* and *S* in different lines of part 1, excluding cases where these two conditions are on the same line.

2.5 Definitions of precipitating and antecedent conditions, complications and causes

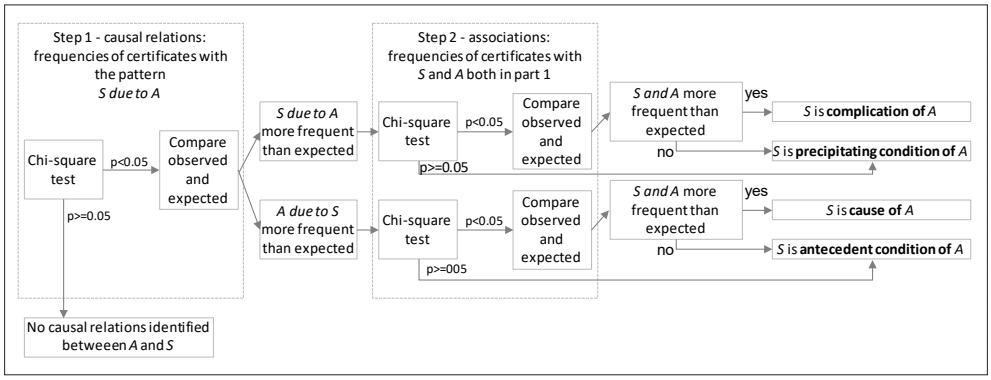
Based on the results of the first step, we define a condition *S* precipitating condition of *A* if *S due to A* is significantly more frequent than expected; we define *S* antecedent condition of *A* if *A due to S* is significantly more frequent than expected.

Based on the results of the second step, we define i) complication of *A* a precipitating condition *S* associated with *A* and ii) cause of *A* an antecedent condition *S* associated with *A*.

Conditions *S* not associated with *A* in the analysis of causal relations (first step), *i.e.* conditions that are not complications nor causes nor precipitating causes nor antecedent conditions of *A*, were not considered and therefore not shown in the results.

Figure 2.1 represents the process of the method.

Figure 2.2 - Representation of the method's process



2.6 Analysis performed on mortality data

We applied this method to data from the national CoD register, managed by the Italian National Institute of Statistics - Istat and referring to all deaths occurred in Italy among people aged 1 year and above. Provisional data of March-April 2020 were used in order to identify the most relevant complications and precipitating conditions (corresponding to the conditions *S* mentioned in the methods Section) of COVID-19 (ICD10 codes U071-U072, corresponding to the condition *A*). To show the potential general applicability of the method to other conditions, we applied it to Italian CoD data for the year 2018 by evaluating the causal relations of pneumonia (ICD10 codes J12-J18, condition *A*) and diabetes (ICD10 codes E10-E14, condition *A*) with other diseases (conditions *S*). Data were processed with Iris according to ICD10 provisions and the rejects of Iris (about 20% of total deaths) were revised by expert nosologists. Pneumonia and diabetes were chosen, as they are both common conditions on death certificates. On the other hand, they have different characteristics: pneumonia is a complication of many diseases, while diabetes is a disease whose onset does not generally result as a complication of other conditions. Moreover, these diseases are both related to COVID-19, but in different ways. Pneumonia is a common manifestation of COVID-19, while diabetes increase frailty of individuals and consequently the risk of dying for COVID-19.

We first carried out an explorative analysis using all ICD10 codes (third digit level). Successively, we grouped codes with similar behaviour in the explorative analysis, taking also into account the nosological similarity in ICD10. Groups studied are shown in table 2.3. Final analysis was performed on these groups instead of single ICD10 codes. In case of duplications of code-group on the same certificate, only the one on the lowest line of part 1 has been retained.

For the analysis of COVID-19 the method was applied on the whole sample of certificates, as well as by age groups to evaluate if the pattern of COVID-19 complications could depend on the age at death. We carried out the analysis on four age groups (1-49, 50-64, 65-79, 80 and more) but we did not observe differences between 0-49 year old and 50-64 and between 65-79 and 80 and more. For this reason, we focus only on two age groups: 1-64 years and 65 years and more.

Table 2.3 - Groups of diseases used for the analyses

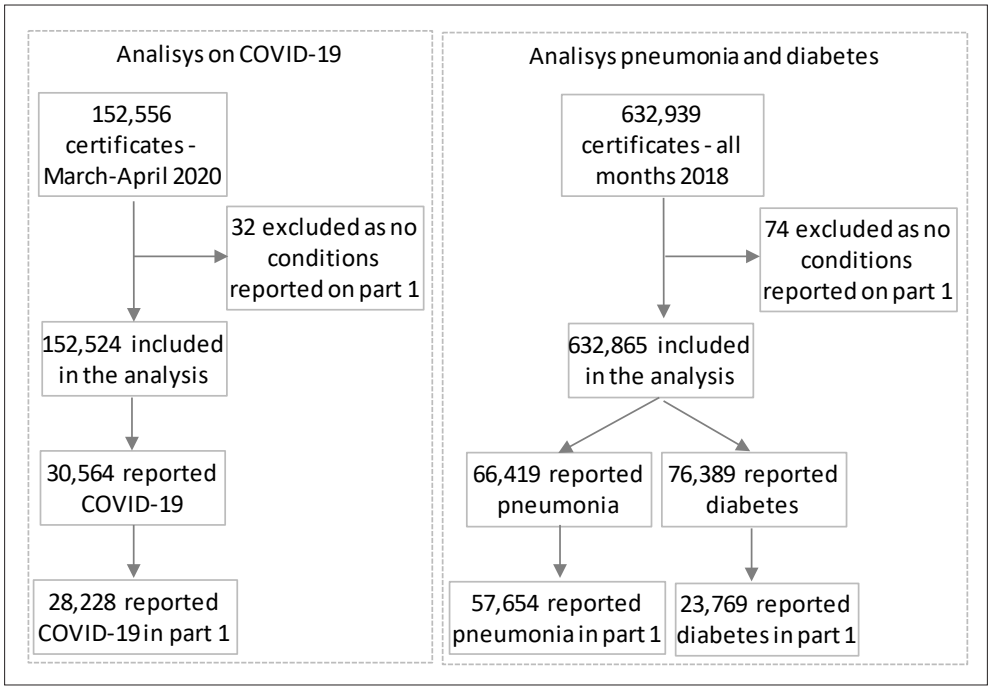
ICD10 codes	Description
A40-A41, B37, B49, B99	Sepsis and infections of unspecified site
Other codes in A00-B99	Other infectious and parasitic diseases
C00-D48	Neoplasms
D60-D64	Aplastic and other anaemias
D84-D87	Specified disorders of the immune mechanism
D89	Unspecified disorders of the immune mechanism
E10-E14	Diabetes mellitus
E86-E87	Volume depletion and other fluid disorders
Other codes in E00-E99	Other metabolic and endocrine diseases
F00-F03	Dementia
Other codes in F00-F99	Other mental and behavioural disorders
G00-G09, G93	Inflammatory d. of the central nervous system
G20, G22-G26	Extrapyramidal and movement disorders
G30-G31	Alzheimer disease
G61-G64	Other neuropathies
Other codes in G00-G99, H60-H99	Other disorders of nervous system
H00-H59	Diseases of the eye and adnexa
I10-I13	Hypertensive heart disease
I15	Secondary hypertension
I20-I24	Acute ischemic heart diseases
I25	Chronic ischemic heart disease
I26	Pulmonary embolism
I27-I28	Pulmonary heart disease and diseases
I48	Atrial fibrillation
I50-I51	Heart failure and other cardiac diseases
I00-I09, I30-I45, I47	Other heart diseases
I60-I66, I670, I672-I679	Cerebrovascular accident
I671, I69	Sequela of cerebrovascular diseases
I70	Atherosclerosis
I73-I79	Other peripheral vascular diseases
I00-I09, I90-I99	Other circulatory diseases
J12-J18, J849	Pneumonia (including interstitial pulmonary disease)
J40-J47	Chronic lower respiratory diseases
J80	Adult respiratory distress syndrome (ARDS)
J81	Pulmonary oedema
J960, J969	Respiratory failure
J961	Acute respiratory failure
J00-J11, J30-J39, J60-J70, J82-J848, J85-J99	Other diseases of the respiratory system
Other codes in K00-K99	Other diseases of the digestive system
Other codes in L00-L99	Other diseases of the skin
L89	Pressure ulcer
M00-M99	Diseases of the musculoskeletal s. and connective
N17, N19	Renal failure, acute and unspecified
N18	Chronic renal failure
Codes in N00-N29 (excluding N17-N19)	Other renal diseases
Q00-Q99	Congenital anomalies and chromosomal defects
R04-R09	Symptoms and signs involving the respiratory systems
R570-R571, R573-R579	Shock
R65	Systemic inflammatory response syndrome (SIRS)
U071-U072	COVID-19
V00-Y39, S00-T79	External causes

3. Results

At the time of this paper was drafted, 152,556 death certificates were collected and coded for March-April 2020, referring to deaths of people aged above 1 year. The analysis was performed on 152,524, since 32 had no conditions reported on part 1. COVID-19 was mentioned on 30,564 death certificates and in 28,228 (92.4%) was reported in part 1 (Figure 3.1).

Data used for pneumonia and diabetes, referring to all months of 2018, contained 632,939 death certificates and 632,865 had part 1 completed. Pneumonia was reported in 66,419 death certificates and was in part 1 in 57,654 cases (86.8%), while diabetes was found in 76,389 certificates of which in 23,769 in part 1 (31.1%) (Figure 3.1).

Figure 3.1 - Data analysed



3.1 COVID-19

Table 3.1 shows the results for COVID-19. The analysis allowed to distinguish conditions found associated in the first step of the analysis into complications, precipitating conditions, causes, and antecedent conditions of COVID-19.

Pneumonia, respiratory failure, respiratory symptoms, ARDS (adult respiratory distress syndrome), and SIRS (systemic inflammatory response syndrome) were complications of COVID-19. Overall, pneumonia was reported in part 1 in 40,580 certificates, of which 56% together with Covid-19. ARDS was together with COVID-19 more than 85% of the times it was mentioned (1,823 out of 2,133). Several other conditions, mainly non-respiratory, were precipitating conditions of COVID-19. Among these, the most frequent were heart failure, sepsis, shock, and renal failure.

Neoplasms, chronic lower respiratory diseases, cerebrovascular accident, hypertensive heart disease, and dementia resulted antecedent conditions of COVID-19. Nevertheless, none of them was cause of COVID-19, since none of them showed a significant association with it. Actually, all these conditions represent pre-existing diseases placed by certifiers in a lower line compared to COVID-19.

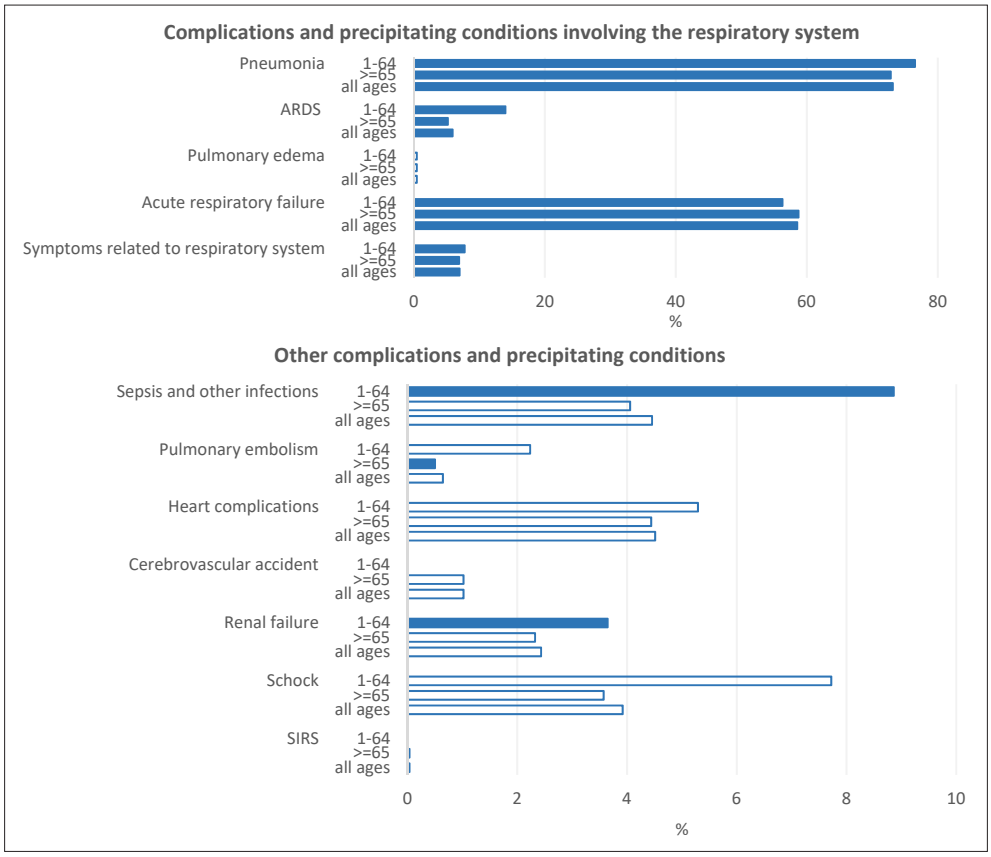
Figure 3.1 shows the results of the analysis by age group. Only complications and precipitating conditions of COVID-19 are shown, represented by blue and white bars respectively. Several respiratory conditions were found to be complications of COVID-19 in all age groups, except pulmonary oedema, which was a precipitating condition.

Non-respiratory conditions were mainly precipitating conditions of COVID-19, except for SIRS, which was a complication. However, we could highlight different patterns for the different age groups. Sepsis and renal failure were complications of COVID-19 for the age group 1-64 years, while they were precipitating conditions in the older age group. Pulmonary embolism was a complication of COVID-19for the age group 65+, while it was a precipitating condition in the younger age group.

The length of the bars in figure 3.2 represents, for each condition, the proportion of certificates reporting the condition due to or on the same line of

COVID-19 among certificates with mention of COVID-19, *i.e.* the proportion of cases where we cannot rule out that COVID-19 played a role in causing the condition. Overall, respiratory conditions were far more frequent than non-respiratory ones, with pneumonia reaching about 73% of COVID-19 related deaths and respiratory failure 58%. ARDS, overall reported in 6% of COVID-19 related deaths, was more frequent in 1-64 years old. Among non-respiratory conditions, some differences among age groups were observed. Sepsis, pulmonary embolism, heart complications, renal failure, and shock were more common among younger people. Cerebrovascular accidents and SIRS were observed only among older people.

Figure 3.2 - Complications (blue bars) and precipitating conditions (white bars) of COVID-19 by age group (a)



Source: Istat, National register of cause of death
(a) Precipitating conditions are represented only if the frequency is above 1%.

Table 3.1 - Conditions in a causal relation with COVID-19

Condition (a)	Certificates with both Covid-19 and *S* in part 1							Expected certificates with COVID-19 and *S*	Certificates with *S* (with or without COVID-19) in part 1
	COVID-19 *due to S*		*S due to* COVID-19		COVID-19 and *S* on the same line		Total (observed certificates with COVID-19 and *S*)		
S	N	%	N	%	N	%	N	N	N
Complication of COVID-19									
Pneumonia	659	2.9	9,348	40.6	13,003	56.5	23,010	7,510	40,580
Respiratory failure	767	4.1	17,395	93.2	496	2.7	18,658	7,771	41,989
Symptoms and signs involving the respiratory sys.	206	8.8	2,072	88.6	60	2.6	2,338	1,898	10,255
Adult respiratory distress syndrome (ARDS)	10	0.5	1,735	95.2	78	4.3	1,823	395	2,133
Systemic inflammatory response syndrome (SIRS)	0	0.0	10	90.9	1	9.1	11	5	26
Precipitating conditions of COVID-19									
Heart failure and other cardiac diseases	449	24.6	1,341	73.4	38	2.1	1,828	5,192	28,053
Sepsis and infections of unspecified site	147	9.7	1,303	86.3	59	3.9	1,509	1,846	9,977
Shock	29	2.4	1,189	96.9	9	0.7	1,227	2,093	11,308
Renal failure, acute and unspecified	144	16.2	739	83.2	5	0.6	888	1,581	8,544
Other diseases of the respiratory system	126	38.1	173	52.3	32	9.7	331	780	4,212
Volume depletion and other fluid disorders	42	16.6	201	79.4	10	4.0	253	489	2,641
Acute ischemic heart diseases	50	21.6	176	76.2	5	2.2	231	1,005	5,429
Pulmonary embolism	29	12.8	194	85.8	3	1.3	226	257	1,388
Other infectious and parasitic diseases	62	32.3	118	61.5	12	6.3	192	248	1,342
Other circulatory diseases	46	26.9	123	71.9	2	1.2	171	395	2,132
Pulmonary oedema	18	11.3	136	85.0	6	3.8	160	782	4,223
Antecedent conditions of COVID-19									
Neoplasms	578	88.8	62	9.5	11	1.7	651	5,312	28,703
Chronic lower respiratory diseases	472	82.2	78	13.6	24	4.2	574	1,218	6,580
Cerebrovascular accident	366	66.8	176	32.1	6	1.1	548	2,214	11,963
Hypertensive heart disease	407	85.9	64	13.5	3	0.6	474	2,627	14,197
Dementia	411	91.7	34	7.6	3	0.7	448	1,212	6,550
Chronic ischemic heart disease	356	81.1	80	18.2	3	0.7	439	2,008	10,851
Diabetes mellitus	271	77.0	78	22.2	3	0.9	352	1,074	5,805
Atrial fibrillation	186	59.6	123	39.4	3	1.0	312	1,134	6,126
Alzheimer disease	206	91.2	19	8.4	1	0.4	226	654	3,533
Chronic renal failure	135	63.4	76	35.7	2	0.9	213	702	3.791

Source: Istat, National register of cause of death
(a) Precipitating and antecedent conditions with less than 150 cases are not represented.

3.2 Pneumonia

Table 3.2 shows the results of the analysis on pneumonia. Conditions more frequently reported with pneumonia were respiratory failure (24,882 certificates), sepsis and infections of unspecified site (12,197 certificates), heart failure and other cardiac diseases (10,469 certificates). Generally, conditions were reported on the same line of pneumonia in a small percentage of cases; other diseases of the respiratory system were instead reported in the same line of pneumonia in 27.1% of certificates.

Complications of pneumonia are mainly diseases related to respiratory system (respiratory failure, symptoms and signs involving the respiratory systems, other diseases of the respiratory system, acute respiratory failure, pulmonary heart disease, ARDS), but include also sepsis and volume depletion and other fluid disorders. Precipitating conditions were mainly disease of circulatory system, but include also shock, renal failure, and pulmonary oedema. The following conditions were causes of pneumonia: chronic lower respiratory diseases, extrapyramidal and movement disorders, specified and unspecified disorders of the immune mechanism. Several conditions were found to be antecedent, mainly involving the circulatory system.

3.3 Diabetes

Table 3.3 shows the results for diabetes. Conditions more frequently reported with diabetes were hypertensive heart disease (6,829 certificates), heart failure and other cardiac diseases (5,545 certificates), chronic ischemic heart disease (4,924 certificates). Hypertensive heart disease and chronic lower respiratory diseases were frequently reported on the same line of diabetes (more than 31% of cases), followed by other metabolic and endocrine diseases, other mental and behavioural disorders, diseases of the eye and adnexa, and other neuropathies (between 21 and 26% of cases).

A large number of conditions were complications of diabetes, mainly diseases of circulatory system, followed by diseases of the genitourinary system. Other complications include dementia and other mental and behavioural disorders, volume depletion and other fluid disorders and other metabolic and endocrine diseases, diseases of the musculoskeletal system and

connective tissue, pressure ulcer and other diseases of the skin, diseases of the eye and adnexa, and other neuropathies. The most frequent precipitating conditions were neoplasms and shock. Congenital anomalies and chromosomal defects were antecedent conditions of diabetes, while causes of diabetes were not found.

Table 3.2 - Conditions in a causal relation with pneumonia

Condition (a)	Certificates with both pneumonia and *S* in part 1							Expected certificates with pneumonia and *S*
	Pneumonia *due to S*		*S due to* pneumonia		Pneumonia and *S* on the same line		Total (observed certificates with pneumonia and *S*)	
S	N	%	N	%	N	%	N	N
Complications of pneumonia								
Respiratory failure	1,557	6.3	22,385	90.0	940	3.8	24,882	8,898
Sepsis and infections of unspecified site	836	6.9	10,860	89.0	501	4.1	12,197	5,008
Symptoms and signs involving the respiratory systems	343	6.4	4,769	89.6	209	3.9	5,321	4,020
Other diseases of the respiratory system	974	30.9	1,322	42.0	852	27.1	3,148	1,976
Acute respiratory failure	459	25.9	1,247	70.4	66	3.7	1,772	657
Volume depletion and other fluid disorders	238	14.7	1,289	79.6	93	5.7	1,620	1,321
Pulmonary heart disease and diseases	154	26.9	388	67.8	30	5.2	572	360
Adult respiratory distress syndrome (ARDS)	12	3.0	354	89.8	28	7.1	394	89
Precipitating conditions of pneumonia								
Heart failure and other cardiac diseases	2,415	23.1	7,263	69.4	791	7.6	10,469	11,563
Shock	89	2.1	4,156	97.4	20	0.5	4,265	5,495
Renal failure, acute and unspecified	566	17.3	2,541	77.8	158	4.8	3,265	3,835
Pulmonary oedema	130	7.4	1,547	88.0	81	4.6	1,758	2,296
Causes of pneumonia								
Chronic lower respiratory diseases	3,163	72.6	781	17.9	413	9.5	4,357	2,483
Extrapyramidal and movement disorders	789	92.4	46	5.4	19	2.2	854	725
Specified disorders of the immune mechanism	172	90.1	16	8.4	3	1.6	191	50
Unspecified disorders of the immune mechanism	11	91.7	1	8.3	0	0.0	12	7
Antecedent conditions of pneumonia								
Neoplasms	6,264	90.7	457	6.6	182	2.6	6,903	16,269
Cerebrovascular accident	2,599	82.7	474	15.1	70	2.2	3,143	5,526
Dementia	1,971	92.5	130	6.1	30	1.4	2,131	2,360
Chronic ischemic heart disease	1,423	75.1	373	19.7	98	5.2	1,894	4,782
Hypertensive heart disease	1,339	76.9	293	16.8	109	6.3	1,741	5,544
Other heart diseases	882	51.4	770	44.9	64	3.7	1,716	3,172
Atrial fibrillation	824	51.7	693	43.5	76	4.8	1,593	2,417
External causes	1,144	87.8	111	8.5	48	3.7	1,303	2,214
Other diseases of the digestive system	766	58.9	398	30.6	136	10.5	1,300	2,690
Alzheimer disease	1,097	92.9	68	5.8	16	1.4	1,181	1,371

Source: Istat, National register of cause of death
(a) Precipitating and antecedent conditions with less than 1,500 cases are not represented.

Table 3.3 - Conditions in a causal relation with diabetes

Condition (a)	Certificates with both diabetes and *S* in part 1							
	Diabetes *due to S*		*S due to* diabetes		Diabetes and *S* on the same line		Total (observed certificates with diabetes and *S*)	Expected certificates with diabetes and *S*
S	N	%	N	%	N	%	N	N
Complications of diabetes								
Hypertensive heart disease	2,102	30.8	2,592	38.0	2,135	31.3	6,829	2,286
Heart failure and other cardiac diseases	641	11.6	4,441	80.1	463	8.3	5,545	4,767
Chronic ischemic heart disease	1,149	23.3	3,196	64.9	579	11.8	4,924	1,972
Cerebrovascular accident	445	15.5	2,236	77.9	189	6.6	2,870	2,278
Renal failure, acute and unspecified	259	9.3	2,367	84.9	161	5.8	2,787	1,581
Chronic renal failure	255	11.1	1,705	74.5	330	14.4	2,290	666
Acute ischemic heart diseases	136	6.6	1,907	91.9	33	1.6	2,076	1,135
Sequela of cerebrovascular diseases	313	21.0	1,080	72.4	99	6.6	1,492	825
Chronic lower respiratory diseases	305	22.2	638	46.5	428	31.2	1,371	1,024
Atrial fibrillation	291	23.1	772	61.3	196	15.6	1,259	997
Other circulatory diseases	67	5.7	963	82.1	143	12.2	1,173	406
Other peripheral vascular diseases	65	6.1	917	85.6	89	8.3	1,071	243
Dementia	210	20.3	698	67.4	128	12.4	1,036	973
Other metabolic and endocrine diseases	78	10.9	476	66.6	161	22.5	715	244
Atherosclerosis	51	7.3	588	84.4	58	8.3	697	288
Volume depletion and other fluid disorders	79	13.0	486	80.1	42	6.9	607	545
Diseases of the musculoskeletal s. and connective	65	24.3	155	58.1	47	17.6	267	207
Other mental and behavioural disorders	88	33.2	120	45.3	57	21.5	265	193
Pressure ulcer	16	6.5	215	87.4	15	6.1	246	169
Other diseases of the skin	20	8.2	196	80.0	29	11.8	245	78
Other renal diseases	27	14.7	128	69.6	29	15.8	184	113
Diseases of the eye and adnexa	7	8.0	58	66.7	22	25.3	87	14
Other neuropathies	6	7.8	54	70.1	17	22.1	77	15
Secondary hypertension	7	11.7	46	76.7	7	11.7	60	11
Precipitating conditions of diabetes								
Neoplasms	823	37.9	1,087	50.0	262	12.1	2,172	6,707
Shock	58	2.8	2,044	97.0	5	0.2	2,107	2,266
Antecedent conditions of diabetes								
Congenital anomalies and chromosomal defects	12	70.6	3	17.6	2	11.8	17	50

Source: Istat, National register of cause of death
(a) Precipitating conditions with less than 1,500 cases are not represented.

4. Discussion and concluding remarks

The present analysis used the complete information provided by physicians on death certificates, widely considered the most reliable source of information to compare cause-specific mortality across populations. The described method, based on the simple application of chi-square tests, is able to identify causal relations between diseases leading to death. This is an important information for public health, since it provides data on the major complications to be tackled for specific diseases.

In the first step of the method, causal pattern are taken into account, while the second step confirms the results. This latter step verifies if there is an association between conditions within causal sequences, *i.e.* if the two conditions under exam are found in causal sequences more frequently than expected. If this association is not found, it cannot be concluded that one condition is a cause or a complication of the other even if a causal pattern is found in the first step.

With the introduction of automated coding systems, several countries have been able to produce statistics on all causes reported on certificates. This kind of data, referred to as multiple causes of death, have been used to recalculate mortality levels attributed to a given condition, and to determine the most frequent associations of causes involving such condition (Desesquelles *et al.*, 2012). From the analysis of multiple causes reported in the sequence of part 1, additional information can be withdrawn concerning pathways of diseases, for instance which are the most frequent complications of underlying conditions. Our study fits into this context. However, it investigates an aspect, that of causes and complications in the process leading to death, which has not been studied so far.

Results of the first step on COVID-19 deaths show that respiratory conditions are the most common complications leading to death. Non-respiratory conditions, for instance cardiac complications, are generally precipitating conditions of COVID-19 but they cannot be considered direct complications of it. This could mean that, although these conditions are reported due to COVID-19, the causal relation might be not direct, but mediated by other conditions associated to COVID-19. An example of this scenario is shown in example 3 of figure 1.2, where congestive heart failure is reported due to both COVID-19 and ischemic heath disease.

Some conditions are antecedent of COVID-19, but none of them is a cause of COVID-19, meaning that they are actually underlying conditions that increase the risk of death but cannot be seen as direct causes of COVID-19. Nevertheless, certifiers wrongly place them in a causal relation with COVID-19 as shown in example 3 of figure 1.2. The second step of the procedure seems to be essential for the interpretation of the results.

Results on antecedent conditions confirm the knowledge on risk factors for critically ill COVID-19 as well as the role of SIRS as a complication of this disease. Our results on the precipitating conditions also confirm the indirect role of cardiovascular complications described in literature and linked to the pre-existing health status of the patients. Nevertheless, some rare complications such as kidney injury, coagulation disorders, thromboembolism, and vascular inflammation appear in our results only as precipitating conditions (Gao *et al.*, 2021; Zheng *et al.*, 2020; Chang *et al.*, 2021). This could be due to the rarity of these complications but also to the lack of quality in cause-of-death reporting.

Different patterns of non-respiratory conditions by age were found, especially for sepsis, renal failure, and pulmonary embolism. The first two conditions are complications of COVID-19 in younger subjects (<65 years), while they are precipitating conditions in older (>=65 years). Pulmonary embolism is a complication of COVID-19 in older deaths and a precipitating condition in younger deaths. Since these conditions do not have a common pattern for all age groups, the presence of them as complications of COVID-19 might reflect the presence of different underlying conditions across the different age groups. These patterns should be further analysed.

The first step of this method was used for measuring the frequencies of complications of deaths of SARS-CoV-2 infected patients (Grippo *et al.*, 2020). Changes of these frequencies in different periods of the pandemic waves have also been analysed, showing an increase of non-respiratory complications in the transition phase (May-September 2020), when COVID-19 mortality was lower (Grippo *et al.*, 2021). Results of the current paper are consistent with those of previous ones. In the previous researches the second step of the analysis was not performed, therefore the method described here represents an improvement of the previous work.

In order to validate the method, we carried out the analysis on pneumonia, a common manifestation of COVID-19 and a complication of many diseases, and on diabetes, a completely unrelated disease whose onset does not generally result as a complication of other conditions. We chose to run the analysis on 2018 data since 2020 data would have been affected by the presence of COVID-19, especially for pneumonia.

Findings on pneumonia confirm the strength of the method. Complications found for pneumonia are very similar to those of COVID-19 but, differently from COVID-19, pneumonia is a complication of some conditions: chronic lower respiratory diseases, extrapyramidal and movement disorders, specified disorders of the immune mechanism and unspecified disorders of the immune mechanism. On the other hand, diabetes is not a complication of any disease. It has only one group of antecedent conditions: congenital malformations and chromosomal anomalies. Several conditions were found to be complications of diabetes, especially cardiovascular complications known to be the leading cause of morbidity and mortality in diabetic patients (Zheng *et al.*, 2018). The analysis on pneumonia and diabetes allows to highlight the potentialities of the method. Some conditions, for instance pneumonia and sepsis, can be due one to each other. Both the causal relations are plausible on a medical point of view. The method allows identifying the pattern of the causal relation on death certificates: in the context of deaths, sepsis is a complication of pneumonia, and not vice-versa.

In summary, the method succeeds in highlighting patterns between conditions and it is useful to document complications of diseases as well as causative conditions. Moreover, it has been proven helpful for describing characteristics of COVID-19 related deaths. For its simplicity, it can be applied to all settings where multiple causes of death are available providing comparable results, since cause-of-death data are highly comparable.

Nevertheless, the patterns identified by the method include only relations between two conditions at the time, without taking into account more complex relations involving multiple conditions. As a matter of fact, with the aging population, multimorbidity at death is common and complications of conditions directly leading to death may depend on the presence of different comorbidities. The method does not allow to take into account the presence of such comorbidities reported on the death certificate.

Our study highlights some differences in complications for different age groups, further analysis by smaller age groups and gender should be performed.

Moreover, the method presented does not take into account part 2 of the death certificate. It could be interesting to take into account also this part in order to better characterise antecedent and precipitating conditions, distinguishing conditions for which there is an association on the whole death certificate from those completely not associated, when the complete year of data will be available.

Some limits linked to the nature of data used should also be taken into account. The method relies on cause-of-death reporting and the quality of the information reported by the certifying physicians may vary greatly: both under and over-reporting may occur and only in rare cases the causes are confirmed by autopsy or other pathological findings (Anderson, 2011). However, findings from previous research support the accuracy of COVID-19 mortality surveillance using official death certificates (Gundlapalli *et al.*, 2021). Moreover, causal sequences are sometimes misreported by certifiers, who, instead of reporting conditions in causal order, report them by chronological or importance order. Nevertheless, the second step of the method provides additional hints on the association between conditions.

Overall, the results show that the proposed method is reliable and can be of great utility to understand the role of a condition in the morbid process and to reduce its lethality; strategies for preventing deaths should focus not only on the condition itself but also on the complications which lead to death.

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