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MORTALITY OF HOSPITALIZED PATIENTS WITH SARS-COV-2 INFECTION IN UNIVERSITY TERTIARY CARE OF ITALY

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ABSTRACT

This study on the mortality trends in hospitalized patients at the University tertiary care Hospital "P. Giaccone" in Palermo (Italy) affected by the SARS-CoV-2 analyses clinical information from necroscopy medical record and death certificates in order to: 1) discern patients who died due to COVID-19 (understood as the immediate cause of death, reported in death certificates, the course of the disease documented within a causal chain (immediate and underlying cause) and patients who died of other diseases with SARS-CoV-2 infection as a comorbidity; 2)evaluate the pre-existing conditions of SARS-CoV-2 positive patients and their influence on the mortality rate with reference to the Charlson Comorbidity Index; 3)compare variables concerning patients who died at the University Hospital of Palermo, with data from the National Institute of Health during the analyzed period, in order to strengthen or refute the hypotheses of other studies or to bring in new findings. The results of this retrospective study confirm, in public health terms, the importance of proper certification of cause of death, complete with indications of comorbidities and complications, as it is of fundamental value from both an epidemiological and medico-legal point of view.

1. Introduction

Coronaviruses are known to be viral agents causing several syndromes in both humans and animals, including the well-known Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (isolated for the first time in 2002) and the Middle East Respiratory Syndrome caused by MERS-CoV (isolated in 2012). On December 31st, 2019, the Wuhan Municipal Health Commission (China) reported a cluster of unusual pneumonia cases, subsequently ascribed to a novel coronavirus, to date known as SARS-CoV-2, whose rapid spread led the WHO to declare a state of pandemic on March 2020 [1, 2]. Sars-Cov2 has a transmission capacity which meant that by November 1st, 2020, 45,678,440 cases of the disease had been reported [1]. However, Sars-Cov2appears to be less lethal than SARS-CoV or MERS-CoV [3]. Human CoVs are mainly transmitted via respiratory droplets (>v5µm), but also via aerosols, direct contact with contaminated surfaces and fecal-oral transmission.

Finally, there are a few cases of infants of positive mothers carrying SARS-CoV2 nucleic acid, which would indicate the possibility of vertical transmission [4]. The analysis of transmission patterns was essential for the adoption of the correct control measures, such as the use of masks, physical isolation and contact tracing [3, 5] although the high transmission of SARS-CoV-2 may be linked to its peculiar virological characteristics [6]. Clinical manifestations vary in individuals depending on factors such as age, comorbidities, and gender. Approximately half of the infected individuals remain asymptomatic, many others present only flu-like symptoms, while 10-15% of the infected, without early treatment, develop a severe illness that can result in death [7].

In this context, vaccination appears to reduce hospital admissions and serious manifestations of infection, representing a necessary tool to protect the world population's right to health.[8-12]. To date, over 6.566.610 cases of death have been confirmed worldwide.

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Analysis of mortality due to covid-19 disease, through death certification, is useful in assessing the extent and progression of the disease and consequently in implementing pandemic control strategies [13-14].

The death certificate (DC) is a document typically completed by the attending physician, containing the underlying disease and any contributing comorbidities. By its nature, the DC is a useful tool for monitoring mortality and improving and planning for public health and safety [15]. The death certificate also has a direct implication in civil and criminal legal proceedings; in fact, it provides causes and manner of death, which may be required to settle estates, property disputes, insurance claims and other survivor benefits. [16]. However, inappropriate completion of death certification may compromise the legal implications and accurate counting of deaths due to COVID-19, and have a negative effect on prevention and mitigation strategies [13].

Death certificate data are tool used to control mortality trends, and improve public health and public safety. Accurate death certification related to coronavirus disease 2019 (COVID-19) is vital to understand the extent and progression of the pandemic.

Death certificate data can inform the public and policy makers on the progress of the COVID-19 pandemic and provide important information about who is dying, where they are from, and what their associated medical conditions were. In order to ensure proper compilation, the Italian National Center for Health Statistics has published guidelines for the proper certification of deaths by Covid-19, in accordance with WHO (Medical certification, ICD mortality coding, and reporting mortality associated with COVID-19 Technical note 7 June 2020), clarifying that deaths should be categorized into 2 groups: those in which the person died from direct complications of laboratory-confirmed SARS-CoV-2 infection and those with a compelling clinical history of SARS-CoV-2 infection but who did not undergo COVID-19 testing or whose test was negative.

The death certificate thus becomes essential to differentiate between deaths with Covid-19 and deaths due to Covid-19. The need for this differential diagnosis has several implications in terms of criminal liability, considering the importance of the concept of causality and causal chain of natural death in forensic medicine [17]. It is worth noting that last December 20th, 2022 the Chinese National Health Commission revised its guidelines to "scientifically and objectively reflect deaths caused by the coronavirus pandemic", classifying only fatalities caused by pneumonia and respiratory failure in patients who had the virus as Covid deaths. By these criteria, China's new method of classifying Covid deaths that excludes underlying diseases would make it difficult to compare fatalities with other countries, thereby hindering control of the pandemic. The present work aims to estimate the comorbidities and the causes of death of SARS-CoV2 positive patients with laboratory-confirmed infection (death due to Covid-19).

For the present analysis, we referred to data from Italian High Institute of Health (ISS) and compared these with clinical information obtained from necroscopy medical records and the death certificates of patients hospitalized in University Hospital, Palermo.

2. Methods

The authors analyzed the clinical information from death certificate records of SARS-CoV-2-positive patients hospitalized at the University Hospital Palermo between March 2020 and April 2022.

The purposes of the study are 1) to discern patients who died due to COVID-19 (understood as the cause first reported in the death certificates) and patients who died of other diseases but who had SARS-CoV-2 infection as comorbidity; 2) to evaluate the preexisting conditions of SARS-CoV-2 positive patients and their influence on the disease; 3)compare the variables concerning the patients who died at the University Hospital, with national data, to strengthen or refute the hypotheses of other studies or to bring new pathological findings; 4) discuss the emerging data and highlight the importance of death certification and the related medico-legal issues.

The collected data were organized using the Excel 2018 program from Microsoft Office.

Specifically, each case was categorized according to sex, age, inpatient diagnosis, cause of death, preexisting conditions, symptoms, complications, secondary admission to the Covid ward, therapies administered, vaccinations, frailty scale and Charlson index.

The data obtained were analyzed using percentages, mean values, and standard deviation. In addition, the authors used the Chi-square test to compare two variables (cause of death and symptoms leading to hospitalization), finding a statistically significant association (p-value=0.002).

Finally, the Kaplan-Meier estimator was used to estimate the survival index in the patients in our sample, considering age, gender, preexisting conditions, and the Charlson Comorbidity index.

3. Results

The analysis is based on a sample of 156 SARS-CoV-2-positive patients hospitalized at the University Hospital "Paolo Giaccone" in Palermo between March 2020 and April 2022. Positivity to SARS-CoV-2 was confirmed by a positive molecular test. According to the 156 patients recruited in the study, 73 were female, and 83 were male. The average age is 77.67 ± 11.93. The vast majority of subjects were aged 50 years or older (96.8%), and this is slightly more evident in males (98.8%) than in females (94.5%).

In the analysis of the 156 patients, 23 (14.7%) had had the Covid-19 vaccine, of which 63.9% had received at least two doses.

Most patients, 133 (85.3%), were not vaccinated. However, these results are inconclusive because we do not know the period between the vaccine dose and death; specifically, a time of fewer than 14 days would rule out immunization. The authors studied the hospitalization diagnosis of all 156 SARS-CoV-2 positive patients admitted to University Hospital "Paolo Giaccone".

Results shown demonstrate that the majority of subjects are admitted with a diagnosis of Covid infection 101 (68.2%) followed by other diagnoses 13 (8.8%) and diagnoses of cardiovascular disease 12 (8.1%).

Considering the 26 unavailable values, the majority of subjects were directly admitted to the COVID ward (54.5%), while 45.5% were admitted to another hospital and subsequently transferred to the University Hospital, with the diagnosis of COVID infection. Unfortunately, it is not possible to assess with certainty whether SARS-CoV-2 positivity occurred before admission (i.e. at home) or during hospitalization.

Therefore, among the 59 patients transferred to the University Hospital, it is not possible to define the COVID-19 infection as nosocomial. Investigating the immediate causes of death, most individuals died from Covid infection (67.9%), followed by cardiovascular disease (11.5%). Metabolic and neurological diseases are the least frequent causes of death, respectively 1.3% and 0.6%.

The median time from hospitalization to death was 7 days. Analyzing the joint distribution of the subjects by cause of death and symptoms leading to hospitalization (Table 1), it can be seen that the majority (77.1%) of the subjects who died from SARS-CoV-2 infection had the typical symptoms of COVID-19, whereas of the patients who did not die of the infection, but who did have it, 45.2% had the common symptoms of the disease.

With regard to the severity of Covid-related symptoms, it is observed that most of the common symptoms in COVID-19 are mild (55.6%). Mild symptoms include fever, rhinorrhea, headache, myalgia, asthenia, and diarrhea; severe symptoms include dyspnea and desaturation. Only two patients showed signs of over-infection, such as a productive cough. As for complications, most of these are pneumological disorders (50.7%), such as pneumonia, pleural effusion, thromboembolism and respiratory failure, followed by cardiovascular disorders (16.1%), including arrhythmias, heart failure and atrial fibrillation.

	Symptoms		
	Covid symptoms	Other symptoms	Total
Covid Infection	64 (77.1 %)	19 (22.9 %)	83 (72.8 %)
Other causes of death	14 (45.5 %)	17 (54.8 %)	31 (27.2 %)
Total	78 (68.4 %)	36 (31.6%)	114 (100%)

Table 1. Distribution of subjects by cause of death and determinant symptoms for hospitalization. Of the total (156 subjects), 42 values not available.

	1	2	3	4	5	≥6	Total
Very fit	0 (0.0 %)	2 (66.7%)	0 (0.0%)	0 (0.0 %)	0 (0.0%)	1 (33.3%)	3 (2.5%)
Fit	0 (0.0 %)	0 (0.0 %)	0 (0.0%)	0 (0.0 %)	0 (0.0%)	0 (0.0 %)	0 (0.0 %)
Very Mild frailty	1 (6.3 %)	7 (43.8 %)	3 (18.8 %)	1 (6.3 %)	2 (12.5 %)	2 (12.5 %)	16 (13.2 %)
Mild frailty	3 (18.8 %)	3 (18.8 %)	6 (37.5 %)	4 (25 %)	0 (0.0%)	0 (0.0 %)	16 (13.2 %)
Moderate frailty	2 (6.7 %)	8 (26.7 %)	7 (23.3 %)	2 (6.7 %)	3 (10 %)	8 (26.7 %)	30 (24.8 %)
Severe frailty	1 (100 %)	0 (0.0 %	0 (0.0%)	0 (0.0 %)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Very severe frailty	1 (2.3 %)	0 (0.23 %)	5 (11.6 %)	10 (23.3 %)	11 (25.6 %)	16 (37.2 %)	43 (35.5 %)
Terminal ill	0 (0.0 %)	0 (0.0 %)	0 (0.0%)	3 (25.0 %)	5 (41.7 %)	4 (33.3%)	12 (9.9 %)
Total	8 (6.6 %)	20 (16.5 %)	21 (17.4 %)	20 (16.5 %)	21 (17.4 %)	31 (25.6 %)	121 (100 %)

Table 2. Distribution of people by frailty scale and number of pathologies (1 to ≥6). Of the total (156 subjects), 35 values not available.

The Charlson Comorbidity Index [18] [19] is a score that predicts the life expectancy of a patient with a wide range of coexisting disease conditions. The Charlson Comorbidity Index is a simple and reliable method for measuring comorbidity, and the produced values correlate well with mortality, morbidity, and health resource. The index is based on the presence of diseases in the individual patient, each of which contributes a score between 1 and 6; the sum of scores from coexisting conditions is then weighted by age.

The range of the Charlson age-adjusted Index' is from 0 to 43 points; however, despite the 'width of the spectrum, a Charlson score of 5 or higher is generally an expression of severe clinical engagement. Most subjects (56.4%) have a Charlson Comorbidity index ≥6; while 43,5% of subjects have a Charlson Index <6. Consumption data: our results demonstrate that most subjects (56,4% with index ≥6) present comorbidity and severe clinical engagement.

Specifically, at the time of hospitalization, the most common pre-existing diseases within the sample are cardiovascular diseases (34.6%) followed by metabolic diseases (19.5%), such as diabetes, severe obesity, or liver cirrhosis. In this sample, respiratory diseases such as asthma, COPD, or pulmonary emphysema account for 6.3% of the total, a distribution similar to renal diseases (8.2%) and neurological diseases (9.3%).

In the analysis of the distribution of therapies before hospitalization, it can be seen that the most frequently used drugs are antihypertensives (34.2%), followed by drugs such as (14.2%) anti-platelets and anticoagulants (12.0%).

In contrast, oxygen therapy is the least frequently used (0.8%).

This result confirms that cardiovascular diseases are among most frequent pre-existing conditions in deceased individuals. In relation to the frailty scale, 35.5% of the patients belong to the very severe frailty group, followed by the moderate frailty patients (24.8%). Analyzing the joint distribution between the frailty scale and the number of pathologies (1 to ≥6), it was found that as the degree of frailty increases, the number of pathologies present in the subject increases (Table 2). Overall, an average of 4.30 ± 2.31 pre-existing conditions was observed.

In medical research, survival curves calculated using the Kaplan-Meier estimator are very useful.

This is an estimator used to approximate he survival function of lifespan data. In our analysis, it was used to calculate the survival index of the patients in our sample, considering age, gender, pre-existing conditions, and the Charlson Comorbidity index. In relation to gender and age, there was little difference in terms of the probability of dying between males and females (Figure 1) and between those under 65 and over 65 (Figure 2).

With regard to overall survival, after about ten days, 50% of patients died, and after 20 days, more than 80% (Figure 3).

Considering the Charlson index, the probability of survival is highest for patients with an index less than 6. After 20 days, about 85% of patients with an index greater than or equal to 6 died (Figure 4).

Finally, considering the cause of death (Figure 5), in relation to duration of hospitalization, until about the first 10 days, the probability of survival is similar for patients whose death was directly attributed to Covid infection compared to those with other causes of death. Then, the survival probability becomes higher for patients with Covid disease: after 20 days, nearly 90% of patients died from a reason other than Covid, while 75% died from Covid infection.

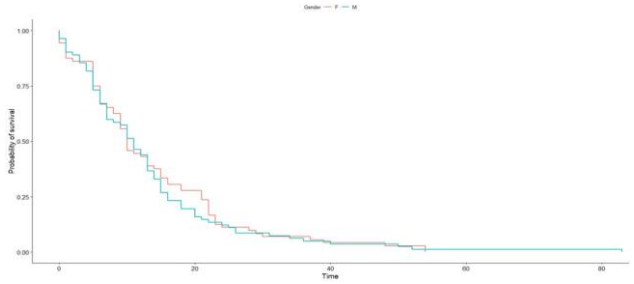

Figure 1. Survival curves by gender (F in red).

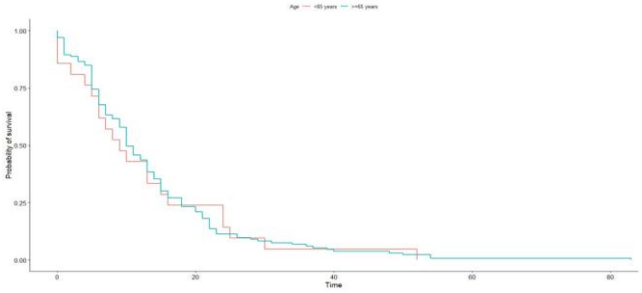

Figure 2. Survival curves by age (<65 y.o. in red).

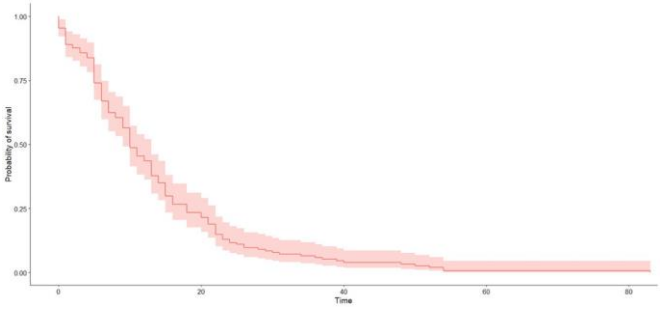

Figure 3. Overall survival curve.

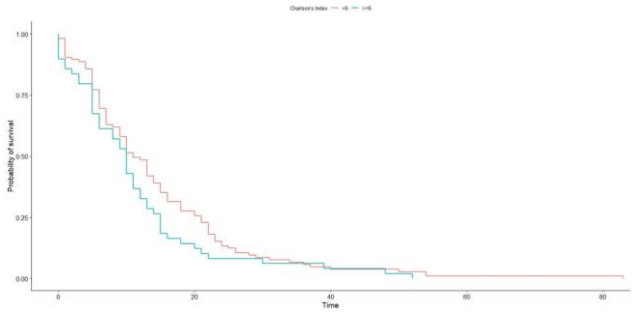

Figure 4. Survival curves by Charlson index (<6 in red).

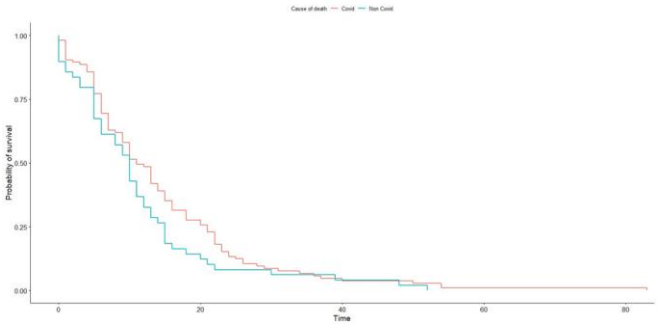

Figure 5. Survival curves by causes of death (covid in red).

4. Discussion

The current work analyzed clinical information from death certificates of 156 SARS-CoV-2 positive patients hospitalized at the University Hospital in Palermo between March 2020 and April 2022.

Considering the study's first objective, correct death certification is essential, as death certificate data for COVID-19 during the pandemic emergency significantly influenced regional and national health interventions for control of disease transmission, disease surveillance and quarantine measures [20].

Our analysis is based on the analysis of necroscopy medical records and death certification data of 156 patients with Sars-Cov2 infection confirmed with laboratory tests (death due to Covid); among them, the investigation of the causes of death reported on the death certificate showed that the majority died as a consequence ofCOVID-19 (67.9%),this was followed by cardiovascular diseases (11.5%), such as heart failure, ischemic heart disease and ischemic stroke.

Analyzing the distribution of the subjects by cause of death and symptoms leading to hospitalization (Table 1), it can be seen that the majority (77.1%) of the patients who died from SARS-CoV-2 infection had the classic symptoms of COVID-19, while of the patients who died of other causes, (45.2%) had the common symptoms of the disease.

If we look the distribution of subjects by cause of death and the distribution of subjects by hospitalization diagnosis, we can state that the percentages of patients who died from COVID-19 according to the death certificate and the rates of patients hospitalized for SARS-CoV-2 infection are very similar to each other and are close to the result obtained from the joint distribution analysis, with a difference of about 10%. This is an important finding because, as mentioned above, the correct compilation of death certificates significantly influences local and national responses regarding optimizing medical resources and disease surveillance.

With regard to the pre-existing conditions of SARS-CoV-2 positive patients, our results show that the most common pre-existing diseases within the sample are cardiovascular diseases (34.6%) followed by metabolic diseases (19.5%), such as diabetes, severe obesity, or liver cirrhosis. These data coincide with what is reported in the scientific literature; according to reports from China, up to 40% of infected hospitalized patients had cardiovascular disease [21]. The prevalence of cardiovascular disease was estimated at 8.3% and hypertension at 13.3% in 3,470 COVID-19 patients from a systematic review of 72 studies from different countries [22].

In addition, our analysis demonstrates that 56,4 % of patients have a Charlson Comorbidity index ≥6, predicting severe clinical engagement. 35.5% of the patients belong to the very severe frailty group, followed by

the moderate frailty patients (24.8%). Finally, analyzing the joint distribution between the frailty scale and several pathologies, it is observed that as the degree of frailty increases, the number of pathologies present in the subject increases.

A study by C.A. Martellucci et al. [7] showed that most patients presented only flu-like symptoms. At the same time, 10-15% developed severe disease and could die, especially if untreated or associated with pre-existing illnesses. Since all 156 patients inour analysis died after a worsening of the clinical condition, including patients with mild symptoms, we could argue that these patients are also part of the 10-15% of patients who develop severe disease, but this would be explicable if we assumed that SARS-CoV-2 was not the direct cause of death, but that it amplified the severity of the underlying diseases.

The third goal was to compare our results with the data from the Italian High Institute of Health report (ISS). Firstly, data from the ISS shows that from the beginning of the pandemic until May 4th, 2022, 16,582,636 SARS-CoV-2 positive patients had been registered in Italy, 161,576 of whom died; in the second week of May, the 7-day incidence rate was between 250 and 1000 cases per 100,000 inhabitants in all age groups [23]. Up to January 10th, 2022, according to the ISS report, the median age of deceased patients was 80 years; 60,201 (43.6%) of the deceased were women, the number of male deaths was higher than the number of female deaths, in accordance with our results.

However, while in the ISS data, the women who died positive for the infection were older than men (median age: women 85 years - men 80 years), in our data the median age at death for women was 66.5 years and men 70.5 years.

The medical records analyzed by ISS during that period showed that the most common comorbidities diagnosed in a sample of SARS- CoV-2 positive deceased patients are acute respiratory distress syndrome (93.3% of cases), followed by acute renal failure (25.4%); superinfection was observed in 21.0% of patients and acute cardiac injury in 10.4% of cases; in our sample, respiratory diseases, among the comorbidities account for 6.3% of the total, a distribution similar to that of renal diseases (8.2%) and neurological diseases (9.3%).

In addition, looking at ISS data, most patients (67.8%) have three or more complications. The results of men and women are similar: 71.1% of women and 65.6% of men have three or more comorbidities. These results also again coincide with what was found in our analysis, where most 124/156 patients (79.4%) have three or more complications, three people have no complications, precisely 78% of women (57/73) and 79.6% (66/83) of men have three or more complications.

Accurate death certification and mortality statistics are crucial for epidemiological and malpractice purposes [24, 25].

Death certificates are a significant information source for public health with a beneficial influence on local and National responses to mitigation of disease transmission, especially during the Covid-19 pandemic [26]. Inaccuracies in death certification are frequent, and in our work, a deep analysis of errors and discrepancies between clinical data and certificates is missing. A deep study of medical records, as well as clinical autopsy findings, could be helpful in this regard to highlight discrepancies between clinical and pathological data and death certification [17]. At the same time, accuracy of death certification is critical in medical care responsibility to evaluate the casualty of death. As we mentioned before, several medico-legal issues in the death certification of Covid-19 should be the object of further research. Our data confirm the literature by demonstrating that Covid-19 patients frequently have comorbidities and die from several underlying diseases [27]. However, further research should focus on patient characteristics and the severity of their comorbidities by evaluating medical and autopsy records in depth for a reliable estimation of death mechanisms and a proper death certification.

5. Conclusions

In conclusion, our hospital analysis partially agree with the literature and national data regarding male gender prevalence and comorbidity.

In addition, this retrospective study confirms, in public health terms, the importance of proper certification of cause of death, complete with indications of comorbidities and complications, as it is of fundamental value from both an epidemiological and medico-legal point of view.

Correctly certifying the death of a patient makes it possible to estimate the impact of SARS-CoV-2 and optimize healthcare resources to guarantee a service worthy of trust to all users.

Further research should focus on methodologies to establish the reliability of death certification and its correlation with clinical and autopsy diagnosis to determine possible changes in patient management and the effects of COVID-19. Indeed, a standardized methodology is needed for Covid-19 death certificates, both for public health and medico-legal issues.

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