Whether COVID-19 Affected Hospital Death Rate in Split - Dalmatia County, Croatia

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ABSTRACT

The main aim of this study was to examine whether the COVID-19 pandemic affected hospital death rate. A cross-sectional comparative study using two different periods, pre-COVID-19 (March 2019 to February 2020) and the COVID-19 era (March 2020 to February 2021) was employed to explore the possibilities of COVID-19 influencing hospital death rate in Split and Dalmatian County, Croatia. Data from the National Public Health Information System was used in this research. The indicators were statistically analyzed. The study showed that in the COVID-19 era, there was a significantly higher hospital death rate in comparison to the pre-COVID-19 era ($z=-14.084$; $p<0.001$), mainly due to the significant increase in hospital death rate from respiratory diseases. The Intensive Care Unit and the Infectious Diseases Department showed a significantly higher hospital death rate among hospital department. Among deaths with confirmed COVID-19, deaths from respiratory diseases were significantly more positive ($z=23.975$, $p<0.001$). The results of the study showed that COVID-19 had an impact on hospital death rate in Split-Dalmatia County. Given that the study analysed the first year of the pandemic, additional research will be needed over a wider period to get a more detailed insight of the impact of COVID-19 on hospital death rate in Croatia, as well as in other regions.

1. Introduction

In China in December 2019 the first case of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified. After the virus has spread worldwide and on March 11, 2020, the World Health Organization declared Coronavirus COVID–19 a pandemic [1]. In Croatia the first case of COVID–19 was reported in February 2020, and the first one in Split and Dalmatian County in March 2020 [2].

Rapid spread of COVID-19 pandemic put under pressure healthcare systems all around the world. Croatia took many extreme measures to contain the spread of the disease. such as locking down communities. The Croatian response to pandemic was fast and mostly followed measures adopted by other European countries such as locking down communities, closing borders, limiting social contacts, and creating COVID-19 isolation wards within hospitals and other suitable facilities [3].

In addition to a large number of patients, the increasing mortality rate has been associated with SARS-CoV-2. In different countries the mortality rates vary from less than 1% to over 10% [4] with the large number of factors influencing it [5].

In addition, in tackling public health problems, and thus this pandemic, it is important to collect data on the incidence and spread of the disease to inform and decide about epidemic control strategies. There is a need to focus on disease outcomes, especially deaths, given the growing burden of mortality. In public health crisis, mortality tracking gives important information about population-level disease advancement. It also guides the development of public health policies, interventions and estimation of their success. The analysis of mortality data enables authorities to shares critical information to general public and key stakeholders of the health system. Moreover, monitoring and analysis of hospital mortality data allow insight that can provide the evaluation of the response of the hospital system to a pandemic, which depends on several factors like increased patient influx, work organization, and available resources.

Objectives

This study aimed to understand the potential influence of COVID-19 epidemic on hospital death rates in Split and Dalmatian County, Croatia in the first pandemic year. Focus of the study was to detect the existence of differences in hospital-based death rates by comparing two periods, pre-COVID-19 (March 2019 to February 2020) and the COVID-19 era (March 2020 to February 2021).

2. Methodology

Study Design

In the conducted research, we made a comparative cross-sectional study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [6] using two different periods, pre-COVID-19 (March 2019 to February 2020) and the COVID-19 era (March 2020 to February 2021). The study examined data from the Clinical Hospital Centre Split, the University Hospital (UH) of Split, and tertiary-level hospitals. UH Split is the largest hospital center in Dalmatia. It is the central health institution of Split and Dalmatian County and the entire southern part of Croatia. About 1,000,000 citizens of the Republic of Croatia gravitate to this regional hospital.

Data Sources and Statistics

The source of data was the National Information Health System at the Croatian Institute of Public Health, in which all inpatient health institutions submit electronically individual data on persons hospitalized for treatment or rehabilitation under the Health Statistics of the Republic of Croatia. The data from Daily Hospital were excluded. The analysed data related to those receptions that resulted in a fatal outcome. They were analysed by age and sex, year and month, the main discharge diagnosis coded according to the 10th edition of the International Classification of Diseases (ICD-10) [7], and the Department where the death occurred. Additionally, 2020 data were analysed about COVID-19-related hospitalizations. According to WHO guidelines, association with COVID-19 is considered if a person has had a positive result of polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), which is coded according to ICD-10 with code U07.1 - a virus identified in either major or other diagnoses [8]. To compare the mean length of stay in these two periods we calculated the variances of the data, and then used two samples for means Z-test on two populations. It was used for the whole population, for the male group, and female group. Further, data were divided into four groups according to age, namely: 0-15 years, 16-50 years, 51-70 years, and 70 and more. For the 0–15-year age group, we employed a nonparametric two-tailed Mann-Whitney U test. For other age groups, we used two samples for means Z-test on two populations. Two samples for means Z-test were also used to calculate differences between individual months in these observed two periods. We employed the Two-tailed Mann Whitney U test calculator [9], and Microsoft Office Standard 2013 Excel software package for the Z-test. A p-value of less than 0.05 was accepted as indicating the statistical significance.

3. Results and Discussion

Overall, there were more deaths in hospitals in the pandemic (COVID-19) than in the non-pandemic (pre-COVID-19) era ($z=-14.084$; $p<0.001$) (Table 1) that occurred in males ($z=-2.599$; $p=0.009$) (Table 2). There was no statistical difference in mortality rates between 2019 and 2020 by age (Table 2).

Table 1. Admissions and deaths data in the study period

	Pre COVID-19 era		COVID-19 era			
	Admissions	**Deaths: n (%)**	**Admissions**	**Deaths: n (%)**	**Z value**	**95% P-value**
March	4071	138 (8.2)	3050	125 (6.1)	-1.569	0.116
April	3779	125 (7.5)	2160	155 (7.5)	-	< 0.001

					6.766	
May	4101	143 (8.5)	2440	99 (4.8)	-1.182	0.238
June	3927	103 (6.2)	3355	136 (6.6)	-3.416	0.001
July	4176	150 (9.0)	3537	140 (6.8)	-0.842	0.401
August	3641	153 (9.1)	3282	199 (9.7)	-3.52	0.001
September	4183	146 (8.7)	3590	152 (7.4)	-1.702	0.089
October	4342	146 (8.7)	3642	149 (7.2)	-1.719	0.085
November	4043	123 (7.3)	3289	208 (10.1)	-6.732	< 0.001
December	3863	152 (9.1)	3179	287 (13.9)	-8.797	< 0.001
January	4268	157 (9.4)	3239	231 (11.2)	-6.694	< 0.001
February	3979	138 (8.2)	3232	180 (8.7)	-4.322	< 0.001
Total	48373	1674 (100)	37995	2061 (100)	-14.084	< 0.001

*Statistical difference between periods (P<0.05 is significant).

Table 2. Demographic characteristics

Variable	Overall n (%)	Pre COVID-19 era n (%)	COVID-19 era n (%)	Z value	95% *P*-value
Sex					
Male	2131 (57.1)	916 (54.7)	1215 (58.9)	-2.599	0.009*
Female	1604 (42.9)	758 (45.3)	846 (41.1)		
Age					
Up to 15 years old	53 (1.4)	30 (1.8)	23 (1.1)	1.738	0.082
16 to 50 years old	141 (3.8)	61 (3.6)	80 (3.9)	-0.379	0.704
51 to 70 years old	952 (25.5)	413 (24.7)	539 (26.1)	-1.033	0.303
Older than 70 years	2589 (69.3)	1170 (69.9)	1419 (68.9)	0.687	0.490

*Statistical difference between periods (P<0.05 is significant

Statistical differences in mortality rates between the COVID-19 vs the pre-COVID-19 era are shown in Table 1. A statistically significant difference was found in the months of April, June, August, November, December, January, and February. Variations in mortality rates by month's rates between the pandemic (COVID-19) vs the non-pandemic (pre-COVID-19) era are shown in Figure 1.

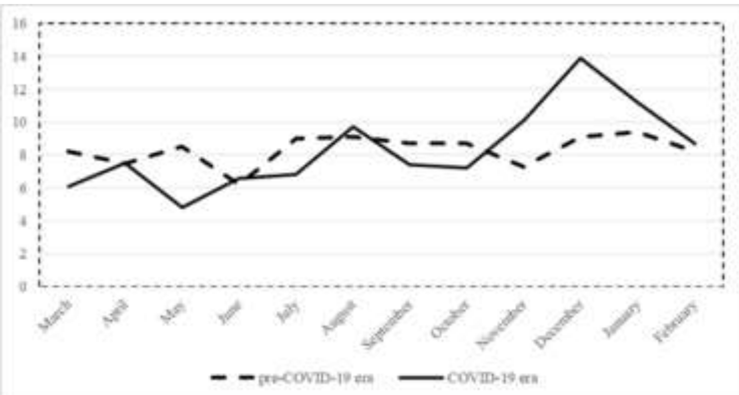

Figure 1. In hospital-based mortality rates between the pandemic (COVID-19) vs the non-pandemic

(pre-COVID-19) era

Regarding death as a diagnosis of discharge, there was a statistical difference in deaths in the X category (Respiratory disease), showing a much higher rate in 2020 compared to 2019, while in the II category (Neoplasms), V category (Mental and behavior disorders), XI category (Diseases of the digestive tract) and XIV category (Diseases of the genitourinary system) mortality rate was higher in 2019 compared to 2020 (Table 3). The remaining categories have no significant statistical differences between 2019 and 2020.

Table 3. Deaths according to disease or condition group (ICD-X)

Variable	Overall n (%)	Pre COVID-19 era n (%)	COVID-19 era n (%)	Z value	95% *P*-value
ICD-X†					
I	462 (12.4)	225 (13.4)	237 (11.5)	1.792	0.073
II	546 (14.6)	281 (16.8)	265 (12.9)	3.379	0.001*
III	22 (0.6)	9 (0.5)	13 (0.6)	-0.367	0.711
IV	36 (1.0)	19 (1.1)	17 (0.8)	0.965	0.337
V	4 (0.1)	4 (0.2)	0 (0)	2.220	0.026*
VI	25 (0.7)	13 (0.8)	12 (0.6)	0.724	0.472
IX	989 (26.5)	465 (27.8)	524 (25.4)	1.621	0.105
X	968 (25.9)	294 (17.6)	674 (32.7)	-10.501	< 0.001*
XI	194 (5.2)	109 (6.5)	85 (4.1)	3.270	0.001*
XII	1 (0.0)	1 (0.1)	0 (0)	1.110	0.267
XIII	6 (0.2)	2 (0.1)	4 (0.2)	-0.566	0.569
XIV	135 (3.6)	77 (4.6)	58 (2.8)	2.908	0.004*
XV	1 (0.0)	0 (0)	1 (0.1)	-0.901	0.368
XVI	38 (1.0)	22 (1.3)	16 (0.8)	1.629	0.103
XVII	2 (0.1)	1 (0.1)	1 (0.1)	0.147	0.881
XVIII	156 (4.2)	73 (4.4)	83 (4.0)	0.507	0.610
XIX	126 (3.4)	68 (4.1)	58 (2.1)	2.101	0.036*
XXI	19 (0.5)	11 (0.7)	8 (0.4)	1.149	0.250
XXII	5 (0.1)	0 (0)	5 (0.2)	-2.017	0.043*

*Statistical difference between periods (P<0.05 is significant).
†ICD-X:
I Certain infectious and parasitic diseases (A00-B99)
II Neoplasms (C00-D48)
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50—D89)
IV Endocrine, nutritional and metabolic diseases (E00-E90)
V Mental and behavioural disorders (F00-F99)
VI Diseases of the nervous system (G00-G99)
IX Diseases of the circulatory system (I00-I99)
X Diseases of the respiratory system (J00-J99)
XI Diseases of the digestive system (K00-K93)
XII Diseases of the skin and subcutaneous tissue (L00-L99)
XIII Diseases of the musculoskeletal system and connective tissue (M00-M99)
XIV Diseases of the genitourinary system (N00-N99)
XV Pregnancy, childbirth and the puerperium (O00-O99)
XVI Certain conditions originating in the perinatal period (P00-P96)
XVII Congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)
XIX Injury, poisoning, and certain other consequences of external causes (SOO-T98)
XXI Factors influencing health status and contact with health services (Z00-Z99)
XXII Codes for special purposes (U00-U99)

Within hospital wards, a statistical difference was recorded in the Intensive Care Unit (ICU) and the

Department of Infectious Diseases in 2020 compared to 2019 (Table 4). As for the deaths that occurred in 2020, almost a quarter had a positive PCR test results for SARS-Cov-2. Mortality with a positive test was statistically more significant with males and all persons over 70 years of age treated for respiratory diseases in the ICU and Department of Pulmonary Disease (Table 4).

Table 4. Some characteristics in hospital-based death rates in relationship with positive COVID-19 cases

Variable	**Overall n (%)**	**Pre COVID-19 era n (%)**	**COVID-19 era n (%)**	**Z value**	**95% *P*-value**
Sex					
Male	1215 (58.9)	321	894	3.060	0.002*
Female	846 (41.1)	174	672	-3.060	0.002*
Age					
Up to 15 years old	23 (1.1)	0	23	-2.712	0.007*
16-50 years old	80 (3.9)	10	70	-2.460	0.014*
51-70 years old	539 (26.1)	121	418	-0.992	0.322
Older than 70 years	1419 (68.9)	364	1055	2.582	0.001*
ICD-X†					
I	237 (11.5)	29	208	-4.513	< 0.001*
II	265 (12.9)	8	257	-8.572	< 0.001*
IV	17 (0.8)	1	16	-1.758	0.490
IX	524 (25.4)	46	478	-9.456	< 0.001*
X	674 (32.7)	380	294	23.975	< 0.00001*
XI	85 (4.1)	10	75	-2.701	0.007*
XVIII	83 (4.0)	7	76	-3.393	0.001*
XIX	58 (2.8)	3	55	-3.408	0.001*
Department					
Internal	202	27	175	-3.731	0.001*
Pulmonology	237	15	222	-6.776	< 0.001*
Infectious	342	254	88	23.820	< 0.001*
Intensive care	269	175	94	16.897	< 0.001*

*Statistical difference between periods ($P<0.05$ is significant).
†ICD-X:
I Certain infectious and parasitic diseases (A00-B99)
II Neoplasms (C00-D48)
IV Endocrine, nutritional and metabolic diseases (E00-E90)
IX Diseases of the circulatory system (I00-I99)
X Diseases of the respiratory system (J00-J99)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)
XIX Injury, poisoning, and certain other consequences of external causes (SOO-T98)

The mean length of stay for the hospitalizations that ended in death between pre-COVID-19 (mean=9.6 days) and the COVID-19 era (mean=10.4 days) shows no significant difference (z=-1.770, p=0.077). The mean length of stay for female patients is 8.6 days in the non-pandemic (pre-COVID-19) and 9.8 days in the pandemic (COVID-19) era, and it shows no statistically significant difference (z=-1.790, p=0.074). For male patients, the mean length of stay in the pre-COVID-19 era was 10.5 days, and in the COVID-19 era 10.9 days. There is no statistically significant difference in the mean length of stay for the male patients in these two periods (z=-0.649, p=0.517).

For the 0-15, 16-50, and 51-70 age years group, there was no difference in length of stay between pre-COVID-19 and COVID-19 era. In the oldest age group, 71+, there was a significant difference in the length of stay in the pre-COVID-19 (mean=8.2 days) and COVID-19 (mean=9.5 days) era (z=-3.255, p=0.001).

We checked the differences in the length of stay between individual months in these two periods. There is a statistically significant difference only in one pair of months, namely between December 2019 (mean=4.1 days) from the pre-COVID-19 era and December 2020 (mean=5.6 days) from the COVID-19 era (z=-2.592, p=0.001).

Discussion

The study was focused on investigation whether the COVID-19 pandemic affected hospital death rates in Split-Dalmatia County, Croatia. Regarding hospital mortality rates, evidence shows that the disease caused an increase in hospital death rates over the previous year, as in most countries around the world [10,11]. Mortality was particularly pronounced in those months when the intensity of the pandemic was at its peak [12]. Significantly higher mortality was recorded in the ICU and the Lung Department in the respiratory diseases category (ICD-X). The data is not surprising, the negative consequence associated with infection and death with SARS-CoV-2 are acute respiratory distress syndrome, disseminated intravascular coagulation and sepsis [13].

European Centre for Disease Prevention and Control (ECDC) records starting from April 2020, roughly calculated that 32% of COVID-19 cases in the European Union (EU) require hospital care and 2.4% require intensive care [14]. There are significant differences between European countries in the number of available intensive care beds, ranging in Portugal from 4.2 beds per 100,000 people to 29.2 in Germany (EU average: 11.5) [15]. It is not surprising, among other things, that from the very beginning, the response to the pandemic was different in various world's countries. According to research done by Bauer end associates, it is precisely the low availability of intensive care beds the main cause of a higher COVID-19 mortality rate [16]. This is confirmed by Džupova and associates considering that the decisive factor in the management of the COVID-19 epidemic is a sufficient number of intensive care beds, organ support equipment, and well-trained staff, as shown by the experience in dealing with the COVID-19 epidemic around the world [17].

The year 2020 was like no other one considering the utilization of intensive care due to the COVID-19 pandemic. In the first halh of the year many countries across the world were faced with unprecedented request for emergency care resources, with slight summer respite, rising again before the end of the year [18]. This was the case in Croatia as well [19] including Split and Dalmatian County, where the number of positive cases of COVID-19 was the most pronounced.

The ICU is a demanding environment that relies on well-trained people, and experienced medical personnel who can safely use specific technologies and care for patients. The pandemic has atrociously shown that the resources of the ICU can quickly become overloaded. The lack of access to the ICU and the high prevalence of COVID-19, in turn, creates an excess demand for other hospital services and is associated with lower treatment outcomes [16,20,21]. Outcomes with COVID-19 patients admitted to the ICU in countries or regions with higher ICU capacity or lower demand, through more effective community controls on COVID-19, were generally better.

Furthermore, in the UK, the ICNARC group reported a decline in mortality in the periods before and after the peak of the first wave of the pandemic [10]. This report is significant because it shows that mortality increased during the peak period. In addition, the characteristics of the patients admitted during this period varied, the patients were, on average, younger and in worse condition. This work suggests both, improved outcomes over time and worse outcomes when health systems are under stress. Changes in outcomes during and after periods of health system stress, comparing care between multiple locations with different resources and different levels of health stress, have implications for defining an adequate health resource [10].

Pandemics globally, as well as this one, test health systems in many ways. There are periods when the need for health care is far greater than the ability of the health system to respond to them. So, the health system is put to a great test because it is necessary to ensure universal access to diagnosis and treatment during such a situation. If the health system is overburdened, then it cannot be avoided that patients die due to a lack of adequate medical care. Therefore, the health system must be adequately prepared. In some countries, health systems can cope with the increased healthcare needs, implementing the necessary actions to respond, while in other countries health system capability is a major problem [22].

An important aspect that affects the effectiveness of the national response is the ability to supply the health system with the important resources on time in order to adequately respond to the population demands [16].

To face the upcoming problems, a reorganization was carried out in Croatia. Most large hospitals, including UH Split, have established isolated wards for COVID-19, and 13% of hospital beds have been designated as beds for COVID-19. In times of epidemic waves, health workers have a special shift mode to provide sufficient staff for the potential replacement of infected and COVID-19-positive staff [19]. However, the reorientation of hospital care provision and prioritization of needs toward COVID-19 has resulted in a general delay in other disease admission procedures and treatments. Thus, this study shows that the admission rate (other than COVID-19) is significantly lower in 2020 compared to the previous period, which is no exception since numerous countries also noticed a obvious decrease in normal hospital tasks due to the pandemic development [19,23]. All this raises great concerns about how the current situation will affect health outcomes in the future. One research from UK projected that delaying early detection and treatment of cancer for the next 5 years would increase the cancer mortality rate in the following categories: breast (9%), colon (16%), lung (5%)), and oesophagus (6%) [24]. Future studies will certainly confirm the congruence of these and other projections.

An additional risk factor considering increased mortality relates to gender. In this study, and many others, women appear to be less affected than men with severe/fatal COVID-19 infection, regardless of their age. It remains unclear whether this is due to biological factors and/or comorbid, occupational, behavioural, or institutional factors. Several potential factors, underlying these differences in pathogenic mechanisms, have been identified at the molecular level [25]. However, attributing differences in disease susceptibility, course, and outcome solely to sex can be extremely complex and, regarding COVID-19 even premature.

Age is significant risk factor associated with increased death rate from COVID-19, which was also considered in this study. The study confirmed higher mortality in older hospitalized patients. Older people are at higher risk of infection; they often have other diseases. With them, the virus encounters much less resistance than in healthy individuals. Immunity also declines with age. The immune system does not function as well as in younger people. Therefore, the elderly belong to health risk groups when it comes to infectious diseases. As Rudan explained, at the beginning of every epidemic of a new virus, the virus must "jump" from animals to humans, and then from humans to humans. This process can be quite challenging. Therefore, the virus is more likely to successfully infect those with a weakened immune system, which will make it harder to reject it. Because of that, the first patients are often people who are either older or already have some basic diseases, which makes them more vulnerable. They end up in a hospital, where at the time no one doubts that the pneumonia they have may have epidemic potential. It then infects other hospital patients and some medical staff. The latter can then spread the disease to other patients in the hospital - mostly those who are most vulnerable, such as the sick or immunocompromised, treated for serious illnesses, or the elderly. This is the reason why the mortality rate among all COVID-19 patients was initially very high in Wuhan and later in Italy. Many people died of COVID-19 infection in hospitals and these were mostly very old and sick people [26].

Numerous studies have sought to clarify which treatments are most effective in the COVID-19 treatment. The use of steroids (especially dexamethasone), which have shown improvement in the survival of patients who are dependent on oxygen or receiving mechanical respiratory support [27], has been considered, while other drugs including chloroquine, azithromycin, lopinavir/ritonavir have not shown clear benefit [28]. Certainly, during dealing with COVID-19 the treatment will evolve in approaches to appropriate therapies. The circumstances across the pandemic are changing rapidly, and our response must be equally dynamic and responsible if we are to counter the spread of new dangerous pathogens, with the ability to rapidly reshape health systems, making them crucial for the population's survival in the context of health crises.

The importance of this research is that it reports on basic information related to the outcomes of hospital treatment and provides the mortality causes analysis, which is important for the response of the health system in the situation to changing epidemiological circumstances.

The study has several limitations. First, we used routine medical data with a limited number of indicators, whose primary intent is not specific to the research conducted. Second, the contribution of SARS-CoV-2 infection to related deaths is a major issue. It is difficult to distinguish death caused by SARS-CoV-2 infection from death caused by other diseases where SARS-CoV-2 infection only contributed to the inability to perform an autopsy. While autopsy findings are an ideal gold standard for assessing the cause of death, this approach is overly expensive and rarely applied. It would not be practical to perform autopsies for all deaths that have occurred in a country - or even for all deaths in a single. This forces us to interpret result of our study with caution, as exploratory and descriptive. The protocol should include an unambiguous definition of death from COVID-19 and guidelines for reporting COVID-19 infection within a causal sequence or as a contributing cause [29].

In conclusion, our data show that COVID-19 contributed to hospital mortality in the pandemic's first year. Respiratory diseases were the main cause for the significant increase in mortality. Within the hospital departments, mortality was significantly higher in the ICU and the Infectious Diseases Unit. Among those who died in 2020 with confirmed COVID-19, mortality from respiratory diseases was significantly higher. The highest mortality was recorded in the period when the health system was under the greatest load, which implies the search for the optimal models related to the most effective outcomes.

Given that the study analyzed the first year of the pandemic, additional research will be needed over a wider period to get a more comprehensive and detailed picture of the pandemic's impact on hospital death rate in Split-Dalmatia County, as well as in other regions and countries.

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