Article

A Population-Based Registry Analysis on Hospitalized COVID-19 Patients with Previous Cardiovascular Disease: Clinical Profile, Treatment, and Predictors of Death

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Abstract: A high percentage of patients with COVID-19 (coronavirus disease 2019) have previous cardiovascular disease (CVD). The findings presented here came from an epidemiological population-based registry study (real-world data) that enrolled all in-hospital COVID-19 patients with previous CVD from 1 March to 31 May 2020. Death, other comorbidities, hospital stay variables, ventilation type, and main clinical outcomes were evaluated. In Castile and Leon, 35.83% of the 7307 in-hospital COVID-19 patients who participated in this study had previous CVD, particularly arrhythmias (48.97%), cerebrovascular disease (25.02%), ischemic heart disease (22.8%), and chronic heart failure (20.82%). Of the patients, 21.36% were men and more than 90% were over 65 years of age, and the mortality rate achieved 32.93%. The most used medicines were antibiotics (91.41%), antimalarials (73.3%), steroids (46.64%), and antivirals (43.16%). The main predictors of death were age over 65 years (OR: 5), ventilation needs (OR: 2.81), treatment with anti-SIRS (systemic inflammatory response syndrome) medicines (OR: 1.97), antivirals (OR: 1.74) or steroids (OR: 1.68), SIRS (OR: 5.75), SARS (severe acute respiratory syndrome) (OR: 2.44), or AKI (acute kidney injury) (OR: 1.63) occurrence. Chronic heart failure and cerebrovascular disease were associated with a worse clinical course of COVID-19, especially in men older than 65 years with diabetes who developed SIRS, SARS, or AKI.

Keywords: SARS-CoV-2; COVID-19; cardiovascular diseases; heart failure; cerebrovascular diseases; clinical characteristics; treatment; mortality

1. Introduction

Since the beginning of the COVID-19 (coronavirus disease 2019) pandemic in China in December 2019, a significant prevalence of previous cardiovascular diseases (CVDs) among SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infected patients has been observed [1–5]. In addition, these patients with underlying CVD have shown a worse

disease prognosis with an increasing mortality [1,6–9], especially in elderly people [3], and due to the presence of several factors such as low cardiovascular reserve, increased metabolic demand, procoagulant activity, and dysregulated immunity and inflammation due to the underlying CVD [10,11].

The respiratory symptoms produced by COVID-19 are more severe in patients with previous CVD, which has been related to higher secretion of angiotensin converting enzyme 2 (ACE2) in such patients compared to healthy subjects [3]. ACE2 is an aminopeptidase involved in heart function, which has been proposed as the entry site for SARS-CoV-2 [12], via receptor-mediated endocytosis [13]. Approximately 7.5% of myocardial cells show positive ACE2 activity, which may explain the virus' entry into cardiomyocytes and the underlying cardiotoxicity [14]. According to some authors, ACE2 is related to a worse outcome in males with COVID-19 compared to females. First, the ACE2 gene is located on the X chromosome; thus, the expression of ACE2 will be higher in males than in females. Second, hypertension and heart failure are associated with an elevated serum ACE2 level in males [15]. Furthermore, ACE2 inhibition has been related to cytokine storm, which together with increased metabolic demand and procoagulant activity explains, to some extent, the worse clinical outcomes in COVID-19 patients with previous CVD [16–18].

Cytokine storm, characterized by the overproduction of pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-α, IL-1β, and IL-6, can result in vascular inflammation, plaque instability, myocardial inflammation, hypercoagulability, and direct myocardial suppression [19–21] and, as a consequence, in serious cardiovascular damages such as tachycardia, hypotension, and left ventricular dysfunction [22]. In the same sense, cardiac injury can be influenced by other systemic consequences of COVID-19 infection, such as sepsis and disseminated intravascular coagulation (DIC) [23], characterized by increased D-dimer levels, which is observed in 71.4% of deceased patients [24].

One should be aware of medicine related heart damage during COVID-19 treatment [3], except for remdesevir [25], that are used in an off-label manner with relevant side effects and cardiovascular toxicity [26]. Antivirals can cause heart failure, arrhythmia, and other cardiovascular disorders [3], anti-inflammatory agents, such as hydrochloroquine and chloroquine, are associated with a cardiotoxicity risk, and corticosteroids, such as methylprednisolone, can cause water retention and consequent ionic imbalance [27].

This study was carried out in Castile and Leon, the largest region in Spain with a population of 2,323,770 inhabitants. The public healthcare system has 7141 beds spread over 14 hospitals, of which five are first-level referral hospitals, six are general hospitals, and three are regional hospitals. As in the rest of the world, at the beginning of the COVID-19 pandemic, the health system "collapsed", and rapid therapeutic decisions had to be made based on poor existing scientific evidence. In this sense, each hospital developed its own pharmacological protocol based on national standards [28,29]. On the assumption that in patients with previous CVD, the clinical course of COVID-19 is associated with a worse prognosis, the main aim of this study was to provide real-world data on the influence of previous CVD on the hospital death of patients with COVID-19 as well as discerning what type of CVD has the most marked influence on a possible fatal outcome. In this way, the prevalence of in-hospital COVID-19 patients affected by previous CVD in Castile and Leon, taking gender into consideration, is described. In addition, the pattern of pharmacological treatment, mortality rate, and the main predictors of mortality were analyzed.

2. Materials and Methods

2.1. Real-World Study Details

The findings presented here came from an epidemiological population-based registry study (real-world data). The study was carried out following the main standards established for observational studies, the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) [30] recommendations, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [31] standards.

This study was approved by the East Valladolid Area Ethics Committee on 11 June 2020 (reference: PI 20-1863).

The study period covered from 1 March 2020 to 31 May 2020, and all in-hospital COVID-19 patients with previous CVD were included. The Castile and Leon public hospital network includes 14 hospitals with a total capacity of 7141 beds to cover a population of 2,323,770 inhabitants. To facilitate analysis, biweekly periods were established.

Previous CVDs were established using the International Classification of Diseases, 10th revision (ICD-10). The following categories were considered: aneurysms, arrhythmias, atherosclerosis, heart dysfunction, cerebrovascular disease, ischemic heart disease, chronic heart failure, cardiomyopathy, and thrombosis–thrombophlebitis. In addition, other comorbidities, such as hypertension, diabetes, obesity (BMI $\geq$ 30 kg/m^2), chronic kidney diseases, chronic respiratory disease, neoplasia, and autoimmune disease were considered.

Data were obtained from different healthcare databases: Jimena and Medora (https://www.saludcastillayleon.es/sanidad/cm, accessed on 6 May 2021), electronic medical records from hospitals and primary healthcare centers, respectively; Pestadístico (https://pestadistico.inteligenciadegestion.mscbs.es/publicoSNS/N/rae-cmbd/rae-cmbd, accessed on 6 May 2021), hospital discharges information in Castile and Leon; CONCYLIA pharmaceutical care information system (http://www.saludcastillayleon.es/portalmedicamento/es/indicadoresinformes/concylia, accessed on 6 May 2021), hospital medicine dispensing.

2.2. Variables

The main study outcome was in-hospital patient death. Hospital stay variables were considered such as hospitalization period (in days) and length of stay in the intensive care unit (ICU) (in days). Furthermore, ventilation type data were obtained: oxygenation, non-invasive positive pressure ventilation (NIPPV), and invasive ventilation (IV). Finally, the following clinical outcomes were evaluated: severe acute respiratory syndrome (SARS), acute kidney injury (AKI), systemic inflammatory response syndrome (SIRS), acute heart failure, bacterial and fungal superinfection, and DIC.

For medicine selections, the national recommendations [28,29] were followed and grouped according to the Anatomical Therapeutic Chemical Code (ATC): antibiotics, antimalarials, steroids, antivirals, tocilizumab, and other anti-SIRS medicines (Supplementary Materials Table S1).

2.3. Statistical Analysis

For all analyses, the gender and age distribution of the population were considered, establishing two groups with a cut-off age of 65 years. The findings related to the prevalence of previous CVD, comorbidities, pharmacological treatment, and clinical outcomes are expressed in frequencies (percentage) with their corresponding 95% confidence intervals (95% CI) and as means accompanied by their standard deviations (SDs) or as medians accompanied by their interquartile range (IQR).

For comparisons between groups, the Student's *t*-test or the Mann–Whitney U test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables were used, as appropriate. The normal data distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

To identify the predictors of in-hospital patients' death with previous CVD, a multivariate logistic regression with a forward selection approach was performed. The results are expressed in terms of adjusted odds ratio (OR) and 95% CI, and the following variables were included in the model: age ($\geq$65), gender, ventilation, type of previous CVD (aneurysms, arrhythmias, atherosclerosis, heart dysfunction, cerebrovascular disease, ischemic heart disease, chronic heart failure, cardiomyopathy, and thrombosis–thrombophlebitis), other comorbidities (hypertension, diabetes, chronic kidney diseases, obesity, chronic respiratory disease, neoplasia, and autoimmune disease), obesity, medication use (antibiotics, anti-

malarials, steroids, antivirals, tocilizumab, and anti-SIRS), and clinical outcomes (SARS, SIRS, DIC, acute heart failure, and bacterial and fungal superinfections).

The level of significance was set at $p \leq 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 24.0., SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical Findings

In Castile and Leon, 7307 patients were hospitalized for COVID-19 between 1 March 2020 and 31 May 2020, 2618 (35.83%) of whom had previous CVD. Among patients with COVID-19 and previous CVD, more male than female (59.63% vs. 40.37%; $p = 0.001$) and approximately 90% of the patients were older than 65 years with a mortality rate of 32.93%. With respect to previous CVD, arrhythmias (48.97%), cerebrovascular disease (25.02%), ischemic heart disease (22.8%), and chronic heart failure (20.82%) were observed. Regarding the rest of the comorbidities, the following were representative: hypertension (66%), diabetes mellitus (29.56%), chronic respiratory disease (19.86%), neoplasia (14.21%), and chronic kidney disease (12.03%). SARS (15.51%), AKI (14.86%), and SIRS (4.05%) occurred among the participants (Table 1). The percentage of obesity was higher in patients with previous CVD (25.62% vs. 15.14%; $p = 0.001$), being higher in female than in male (27.82% vs. 24.08%; $p = 0.001$).

Medians for hospitalization and ICU length of stay were 10 (6–16) days and 14 (7–30) days, respectively. The most used ventilation mode was IV (3.13%), being almost four times higher in male than in female (4.61% vs. 0.95%; $p = 0.001$). On the other hand, the most used medicines were antibiotics (91.41%), antimalarials (73.3%), steroids (46.64%), and antivirals (43.16%) (Table 1).

The mortality rate has decreased from 1 March 2020 and 15 March 2020, (69.05%) to 15 May 2020 and 31 May 2020 (16.55%). The hospital and ICU length of stay also decreased throughout the study period, from a median of 19.5 to 9 days and 26.5 to 8 days, respectively (Figure 1).
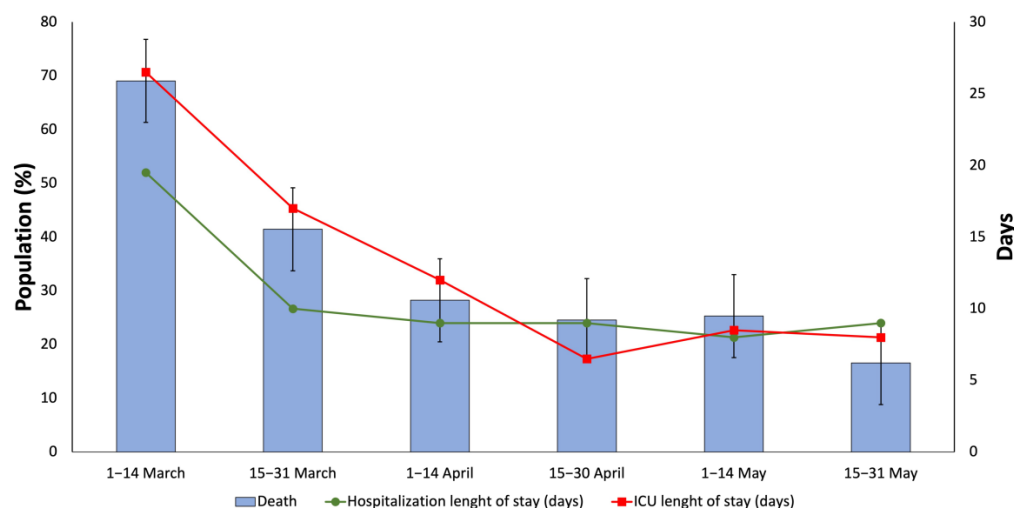

Figure 1. Biweekly clinical baselines in hospitalized COVID-19 patients with previous cardiovascular disease (1 March 2020–31 May 2020).

Table 1. Baseline characteristics and clinical outcomes of hospitalized COVID-19 patients with previous cardiovascular disease (1 March 2020–31 May 2020).

	TOTAL	MALE	FEMALE	*p*
N	2618	1561	1057	0.001
Age (median and IQR)	83 (73–88)	80 (71–86)	85 (76–90)	0.001
Age < 65 (95% CI)	12.18 (10.93–13.44)	13 (11.34–14.67)	10.97 (9.09–12.86)	0.013
Age >= 65 (95% CI)	87.82 (86.56–89.07)	87 (85.33–88.66)	89.03 (87.14–90.91)	0.013
Chronic diseases (95% CI)				
Hypertension	66 (64.19–67.82)	62.97 (60.58–65.37)	70.48 (67.73–73.23)	0.001
Diabetes	29.56 (27.82–31.31)	30.62 (28.33–32.91)	28 (25.3–30.71)	0.162
Chronic respiratory diseases	19.86 (18.33–21.39)	22.87 (20.79–24.95)	15.42 (13.24–17.6)	0.001
Neoplasia	14.21 (12.87–15.55)	16.27 (14.44–18.1)	11.16 (9.27–13.06)	0.001
Chronic kidney disease	12.03 (10.79–13.28)	12.11 (10.49–13.73)	11.92 (9.97–13.87)	0.903
Autoimmune disease	8.21 (7.16–9.26)	8.58 (7.19–9.97)	7.66 (6.06–9.27)	0.425
Previous cardiovascular disease (95% CI)				
Arrhythmias	48.97 (47.05–50.88)	48.11 (45.63–50.59)	50.24 (47.22–53.25)	0.286
Cerebrovascular disease	25.02 (23.36–26.68)	23.77 (21.66–25.88)	26.87 (24.2–29.54)	0.072
Ischemic heart disease	22.8 (21.2–24.41)	27.48 (25.27–29.7)	15.89 (13.69–18.1)	0.001
Chronic heart failure	20.82 (19.26–22.37)	17.55 (15.67–19.44)	25.64 (23.01–28.27)	0.001
Thrombosis–thrombophlebitis	16.73 (15.3–18.16)	14.29 (12.55–16.02)	20.34 (17.91–22.77)	0.001
Atherosclerosis	10.73 (9.55–11.92)	12.3 (10.67–13.93)	8.42 (6.75–10.09)	0.02
Aneurysms	8.79 (7.7–9.87)	12.36 (10.73–14)	3.5 (2.39–4.61)	0.001
Cardiomyopathy	1.99 (1.45–2.52)	2.63 (1.83–3.42)	1.04 (0.43–1.65)	0.004
Heart dysfunction	1.3 (0.87–1.73)	1.22 (0.67–1.76)	1.42 (0.71–2.13)	0.654
Treatment				
Oxygen delivery and ventilation (95% CI)				
IV	3.13 (2.46–3.8)	4.61 (3.57–5.65)	0.95 (0.36–1.53)	0.001
Oxygen delivery	2.94 (2.29–3.59)	3.33 (2.44–4.22)	2.37 (1.45–3.28)	0.159
NIPPV	2.06 (1.52–2.61)	2.63 (1.83–3.42)	1.23 (0.57–1.89)	0.014
Medicines (95% CI)				
Antibiotics	91.41 (90.33–92.48)	91.1 (89.68–92.51)	91.86 (90.22–93.51)	0.491
Antimalarials	73.3 (71.61–74.99)	75.98 (73.86–78.1)	69.35 (66.57–72.13)	0.001
Steroids	46.64 (44.73–48.55)	49.84 (47.36–52.32)	41.91 (38.94–44.89)	0.001
Antivirals	43.16 (41.27–45.06)	47.28 (44.8–49.75)	37.09 (34.17–40)	0.001
Tocilizumab	8.33 (7.27–9.39)	11.08 (9.53–12.64)	4.26 (3.04–5.47)	0.001
Other anti-SIRS *	8.21 (7.16–9.26)	10.95 (9.41–12.5)	4.16 (2.96–5.37)	0.001
Clinical Outcomes				
Hospital LoS (median and IQR)	10 (6–16)	10 (6–17)	9 (6–16)	0.111
ICU LoS (median and IQR)	14 (7–30)	14 (7–29)	13.5 (6–30)	0.969
N (Number of patients admitted to the ICU)	159	133	26	
Death (95% CI)	32.93 (31.13–34.73)	35.81 (33.43–38.19)	28.67 (25.94–31.39)	0.001
SARS (95% CI)	15.51 (14.12–16.89)	18 (16.1–19.91)	11.83 (9.88–13.77)	0.001
AKI (95% CI)	14.86 (13.5–16.22)	15.44 (13.65–17.23)	14 (11.91–16.09)	0.311
SIRS (95% CI)	4.05 (3.29–4.8)	4.23 (3.23–5.23)	3.78 (2.63–4.93)	0.543
Bacterial superinfection (95% CI)	3.4 (2.71–4.09)	3.72 (2.78–4.65)	2.93 (1.92–3.95)	0.278
Fungal superinfection (95% CI)	2.29 (1.72–2.87)	2.05 (1.35–2.75)	2.65 (1.68–3.62)	0.315
Acute heart failure (95% CI)	2.1 (1.55–2.65)	2.88 (2.05–3.71)	0.95 (0.36–1.53)	0.001
DIC (95% CI)	0.19 (0.02–0.36)	0.32 (0.04–0.6)	0 (0–0)	0.066

* Anakinra, baricitinib, interferon, ruxolitinib, and siltuximab. 95% CI, confidence interval; IQR, interquartile range; IV, invasive ventilation; NIPPV, non-invasive positive pressure ventilation; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; LoS, length of stay; SARS, severe acute respiratory syndrome; AKI, acute kidney injury; DIC, disseminated intravascular coagulation.

3.2. Pharmacological Treatment

Table 2 shows the most used medicines grouped by type: ceftriaxone (70.24%) and azithromycin (67.49%) (antibiotics), hydroxychloroquine (69.14%) (antimalarials), methyl-prednisolone (43.32%) (steroids), lopinavir–ritonavir (43.12%) (antivirals), and interferon beta (6.38%) (other anti-SIRS). Among non-deceased patients, antimalarials were used more frequently, specifically hydroxychloroquine (*p* = 0.005), while among deceased patients,

steroids, such as methylprednisolone (p = 0.001), and other anti-SIRS (p = 0.001) were used more frequently (Table 2).

Table 2. Pharmacological treatment in hospitalized COVID-19 patients with previous cardiovascular disease (1 March 2020–31 May 2020).

Medicines	TOTAL (95% CI) N = 2618	No Death (95% CI) N = 1756	Death (95% CI) N = 862	*p*
Antibiotics	**91.41 (90.33–92.48)**	**91.69 (90.32–93.06)**	**90.84 (89.1–92.57)**	**0.466**
Ceftriaxone	70.24 (68.49–72)	69.93 (67.66–72.21)	70.88 (68.14–73.62)	0.617
Azithromycin	67.49 (65.7–69.29)	69.36 (67.08–71.65)	63.69 (60.79–66.59)	0.004
Levofloxacin	16.31 (14.89–17.73)	14.69 (12.94–16.45)	19.61 (17.21–22)	0.001
Cefditoren	2.52 (1.92–3.12)	3.25 (2.37–4.13)	1.04 (0.43–1.66)	0.001
Teicoplanin	1.57 (1.09–2.04)	1.14 (0.61–1.67)	2.44 (1.51–3.37)	0.012
Clarithromycin	0.42 (0.17–0.67)	0.4 (0.09–0.71)	0.46 (0.05–0.87)	0.808
Moxifloxacin	0.19 (0.02–0.36)	0.11 (0.02–0.33)	0.35 (0.01–0.72)	0.197
Cefotaxime	0.19 (0.02–0.36)	0.23 (0.01–0.48)	0.12 (0.01–0.23)	0.538
Ceftaroline	0.11 (0.01–0.27)	0.17 (0.03–0.44)	0 (0–0)	0.225
Antimalarials	**73.3 (71.61–74.99)**	**74.54 (72.38–76.71)**	**70.77 (68.02–73.51)**	**0.041**
Hydroxychloroquine	69.14 (67.37–70.91)	70.9 (68.65–73.15)	65.55 (62.68–68.41)	0.005
Chloroquine	5.5 (4.63–6.37)	4.78 (3.72–5.84)	6.96 (5.43–8.49)	0.022
Steroids	**46.64 (44.73–48.55)**	**44.25 (41.78–46.71)**	**51.51 (48.5–54.52)**	**0.001**
Methylprednisolone	43.32 (41.42–45.21)	40.26 (37.83–42.69)	49.54 (46.52–52.55)	0.001
Prednisone	10.66 (9.48–11.84)	12.41 (10.78–14.05)	7.08 (5.53–8.62)	0.001
Antivirals	**43.16 (41.27–45.06)**	**42.26 (39.8–44.71)**	**45.01 (42.01–48.01)**	**0.181**
Lopinavir-Ritonavir	43.12 (41.23–45.02)	42.2 (39.75–44.65)	45.01 (42.01–48.01)	0.172
Remdesevir	0.08 (0.01–0.22)	0.11 (0.02–0.33)	0 (0–0)	0.322
Tocilizumab	**8.33 (7.27–9.39)**	**8.83 (7.42–10.23)**	**7.31 (5.74–8.88)**	**0.186**
Others anti SIRS	**8.21 (7.16–9.26)**	**7 (5.74–8.27)**	**10.67 (8.81–12.53)**	**0.001**
Interferon Beta	6.38 (5.44–7.32)	5.3 (4.19–6.41)	8.58 (6.9–10.27)	0.001
Anakinra	1.45 (0.99–1.91)	1.37 (0.79–1.94)	1.62 (0.86–2.39)	0.605
Baricitinib	0.38 (0.15–0.62)	0.46 (0.12–0.79)	0.23 (0.02–0.55)	0.384
Ruxolitinib	0.11 (0.01–0.27)	0.11 (0.02–0.33)	0.12 (0.01–0.23)	0.988
Siltuximab	0.08 (0.01–0.22)	0 (0–0)	0.23 (0.02–0.55)	0.043

95% CI, confidence interval; SIRS, systemic inflammatory response syndrome.

Between 1 March 2020 and 31 May 2020, the use of antibiotics and steroids remained stable. On the other hand, a decrease in the use of antimalarials (61.9–25.9%), antivirals (50–9.35%), tocilizumab (9.52–1.44%), and other anti-SIRS, especially interferon beta (26.19–1.44%) was observed (Supplementary Materials Table S2 and Figure 2).

3.3. Risk Factor for Clinical Outcomes and Medication Prescribed

The multiple logistic regression analysis for all in-hospital COVID-19 patients showed that previous CVD impact on death (OR: 1.57; 95% CI: 1.39–1.79). Furthermore, in patients with previous CVD, the presence of comorbidities, such as diabetes mellitus, was associated with a higher probability of death compared to those patients with previous CVD without comorbidities (OR: 1.27, 1.05–1.55). In patients with previous CVD, it was observed that patients with chronic heart failure (OR: 1.27, 1.02–1.58) and with cerebrovascular disease (OR: 1.35, 1.09–1.66) were most likely to die than those who had other types of previous CVD.

In addition, among in-hospital COVID-19 patients, death was more likely to occur in those over 65 years of age (OR: 5, 3.32–7.52), in males (OR: 1.36, 1.12–1.65), in those needing ventilation (OR: 2.81, 1.97–4), in those treated with anti-SIRS drugs (OR: 1.97, 1.39–2.81), antivirals (OR: 1.74, 1.39–2.17), and steroids (OR: 1.68, 1.39–2.02), and in those who developed SIRS (OR: 5.75, 2.53–13.07), SARS (OR: 2.44, 1.91–3.12), or AKI (OR: 1.63, 1.27–2.11).
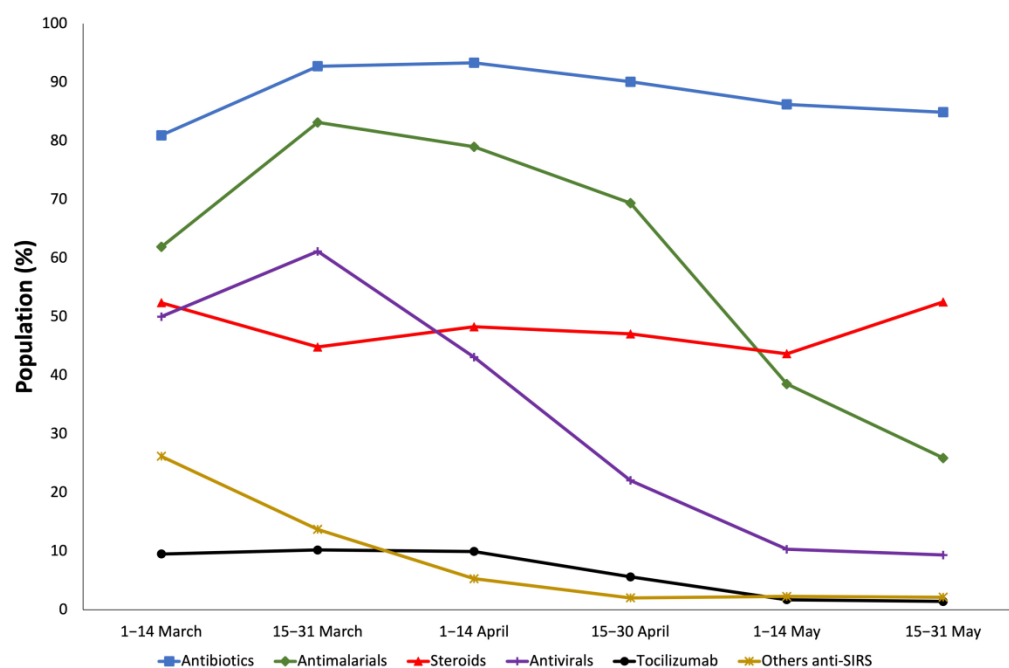
Figure 2. Therapy evolution in hospitalized COVID-19 patients with previous cardiovascular disease (1 March 2020–31 May 2020).

4. Discussion

Approximately one out of three in-hospital COVID-19 patients had previous CVD, mainly arrhythmias, cerebrovascular disease, ischemic heart disease, and chronic heart failure. The mortality rate of these patients was the third highest, after those who developed AKI (46.1%) and SARS (42.53%). As in other studies conducted by our team [32,33], the use of antibiotics and steroids remained stable, while the use of antimalarials, antivirals, tocilizumab, and other anti-SIRS decreased between 1 March 2020 and 31 May 2020. Our results show that males with previous CVD, especially chronic heart failure or cerebrovascular diseases, older than 65 years, who needed some type of ventilation, and who developed SIRS, SARS, and AKI had a higher risk of death. In addition, the use of anti-SIRS medicines, antivirals, and steroids was related to a worse prognosis of the disease.

At this point, it is convenient to clarify the dual role of ACE2. First, COVID-19 symptoms were more severe in patients with CVD, which might be associated with increased secretion of ACE2 in these patients compared with healthy individuals [3]. Second, the inhibition of ACE2 may be another factor of lung injury as well as the cause of the systemic inflammation following cytokine release, which can result in acute respiratory distress syndrome (ARDS) and multiorgan dysfunction [16–18].

The prevalence of in-hospital COVID-19 patients with previous CVD is higher than other Spanish [34,35], European [36], and Chinese [1] cohorts, while it is lower compared to another US cohort [37]. This finding is possible in relation to the predominance of the elderly in Castile and Leon, which is demonstrated by the elevated median age observed (83 years). As in other national [34,35] and international cohorts [38–41], our findings showed a higher prevalence in males than in females. A meta-analysis carried out by Ortolan et al. [42] showed that males are 61% more likely to die from COVID-19 infection than females. This higher predisposition in males appears to be related to differences in innate immunity, steroid hormones, and factors related to sex chromosomes. In this sense, the double copy of the X chromosome in females is essential against viral infections. However, it is observed that female are at a higher risk of COVID-19 clinical manifestations in the long term than males [43].

Surprisingly, in our cohort, hospital death was not influenced by the obesity factor as was the case in other studies [44,45]. One possible explanation is that the obesity rate of our patients was lower than in other cohorts [46].

Although primarily a respiratory disease, COVID-19 also causes important systemic effects, especially on the cardiovascular and immune systems. For this reason, in patients with previous CVD, mortality rates of 5–10 times higher are observed [8]. Our findings showed that the increase in mortality was not so pronounced among patients without previous CVD (19.68%) compared to patients with previous CVD (32.93%).

As in other published studies [38,40,41,47–49], hypertension and diabetes were the most observed comorbidities, followed by chronic respiratory disease and some type of neoplasia, increasing the thrombotic event risk, which is associated with a mortality increase [50].

The pharmacological treatments used for COVID-19 have significant cardiovascular toxicities and side effects. However, data on side effects come from chronic treatments for other clinical conditions such as autoimmune diseases (hydroxychloroquine, chloroquine, and tocilizumab), hepatitis (interferon), or HIV (lopinavir–ritonavir) [26].

Azithromycin was consumed mainly by patients who did not die (69.36%), although it is known that this antibiotic in combination with hydroxychloroquine prolongs the QT interval [51].

Antimalarial drugs (i.e., hydroxychloroquine and chloroquine) were used in three out of four patients. It is known that these drugs at high doses mainly cause cardiac conduction disorders, in addition to ventricular hypertrophy, hypokinesia, heart failure, pulmonary arterial hypertension, and valve dysfunction [52].

Steroids were used in half of deceased patients (51.51%) and a positive OR was observed (1.68). This may be since in the case of methylprednisolone, which was the most frequently used steroid, it has been associated with electrolyte derangements, fluid retention, and hypertension [53].

The percentage of patients treated with antivirals (43.16%) was lower than in other studies [54], but it has been related to a higher probability of death (OR: 1.74). The combination of lopinavir–ritonavir must be used with caution, since it can interact with cardiovascular medicines metabolized by cytochrome P450-3A4 such as antiarrhythmics, antiplatelets, and anticoagulants [55], in addition to causing QT and PR segment prolongation [56]. In the case of remdesevir, no associated cardiovascular adverse effects have been reported [25].

The use of tocilizumab (8.33%) has demonstrated cardiovascular safety in patients with rheumatoid arthritis, although it is not currently confirmed in patients with previous CVD [57].

The anti-SIRS medicines are associated with a greater probability of death (OR: 1.97), probably because the patients are in a more advanced and more severe phase of the disease; therefore, the probability of death is higher.

Regarding thromboprophylaxis strategies, according to different studies [58,59], initial treatment with heparin improves the prognosis of COVID-19 by increasing survival until hospital discharge compared to routine thromboprophylaxis, especially in non-critical patients.

Lastly, this study has several limitations that must be mentioned. Occasionally, the diagnosis of COVID-19 was made according to clinical and radiological criteria without microbiological confirmation. Another possible limitation was the unavailability of other variables, such as earlier lifestyle factors, physical activity level, or sleep, which can influence the results of the logistic regression model regarding the prediction of hospital death in patients with previous CVD. Regarding pharmacological treatment, only the Spanish guidelines [28,29] indicators were considered, and other possible treatments used may have been ignored. On the other hand, cardiovascular pharmacological treatments during patient admission were not available, which may be a limitation.

5. Conclusions

Almost one out of three in-hospital COVID-19 patients had a previous CVD, of which half had arrhythmias history. In addition, these patients had a worse disease prognosis with higher mortality than the global patient average [32].

According to our findings, men older than 65 years with diabetes who developed SIRS, SARS, or AKI had a higher probability of hospital death. Among previous CVDs, chronic heart failure and cerebrovascular disease were associated with a worse clinical course of the disease, and a greater probability of associated death was observed.

Regarding pharmacological treatment, antivirals and antimalarials, especially, have shown long-term cardiovascular toxicity, but it is too early to analyze their short-term effects. The medicines used for COVID-19 treatment were modified throughout the study period according to the availability and the national guideline recommendations [28,29].

Definitely, previous CVDs are related to a worse prognosis of COVID-19; therefore, "special attention" to these patients must be paid, especially after steroid, antiviral, and anti-SIRS administration, which are associated with a higher probability of death.

References

1. Li, B.; Yang, J.; Zhao, F.; Zhi, L.; Wang, X.; Liu, L.; Bi, Z.; Zhao, Y. Prevalence and Impact of Cardiovascular Metabolic Diseases on COVID-19 in China. *Clin. Res. Cardiol.* **2020**, *109*, 531–538. [CrossRef]
2. Asokan, I.; Rabadia, S.V.; Yang, E.H. The COVID-19 Pandemic and Its Impact on the Cardio-Oncology Population. *Curr. Oncol. Rep.* **2020**, *22*, 60. [CrossRef]
3. Zheng, Y.-Y.; Ma, Y.-T.; Zhang, J.-Y.; Xie, X. COVID-19 and the Cardiovascular System. *Nat. Rev. Cardiol.* **2020**, *17*, 259–260. [CrossRef]
4. Nishiga, M.; Wang, D.W.; Han, Y.; Lewis, D.B.; Wu, J.C. COVID-19 and Cardiovascular Disease: From Basic Mechanisms to Clinical Perspectives. *Nat. Rev. Cardiol.* **2020**, *17*, 543–558. [CrossRef] [PubMed]

5. Lang, J.P.; Wang, X.; Moura, F.A.; Siddiqi, H.K.; Morrow, D.A.; Bohula, E.A. A Current Review of COVID-19 for the Cardiovascular Specialist. *Am. Heart J.* **2020**, *226*, 29–44. [CrossRef] [PubMed]

6. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]

7. Ruan, Q.; Yang, K.; Wang, W.; Jiang, L.; Song, J. Clinical Predictors of Mortality Due to COVID-19 Based on an Analysis of Data of 150 Patients from Wuhan, China. *Intensive Care Med.* **2020**, *46*, 846–848. [CrossRef]

8. Liu, P.P.; Blet, A.; Smyth, D.; Li, H. The Science Underlying COVID-19: Implications for the Cardiovascular System. *Circulation* **2020**, *142*, 68–78. [CrossRef] [PubMed]

9. Castagna, F.; Kataria, R.; Madan, S.; Ali, S.Z.; Diab, K.; Leyton, C.; Arfaras-Melainis, A.; Kim, P.; Giorgi, F.M.; Vukelic, S.; et al. A History of Heart Failure Is an Independent Risk Factor for Death in Patients Admitted with Coronavirus 19 Disease. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 77. [CrossRef] [PubMed]

10. Petrie, J.R.; Guzik, T.J.; Touyz, R.M. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can. J. Cardiol.* **2018**, *34*, 575–584. [CrossRef] [PubMed]

11. Long, B.; Brady, W.J.; Koyfman, A.; Gottlieb, M. Cardiovascular Complications in COVID-19. *Am. J. Emerg. Med.* **2020**, *38*, 1504–1507. [CrossRef] [PubMed]

12. Hamming, I.; Timens, W.; Bulthuis, M.L.C.; Lely, A.T.; Navis, G.J.; van Goor, H. Tissue Distribution of ACE2 Protein, the Functional Receptor for SARS Coronavirus. A First Step in Understanding SARS Pathogenesis. *J. Pathol.* **2004**, *203*, 631–637. [CrossRef] [PubMed]

13. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–280. [CrossRef]

14. Zou, X.; Chen, K.; Zou, J.; Han, P.; Hao, J.; Han, Z. Single-Cell RNA-Seq Data Analysis on the Receptor ACE2 Expression Reveals the Potential Risk of Different Human Organs Vulnerable to 2019-NCoV Infection. *Front. Med.* **2020**, *14*, 185–192. [CrossRef] [PubMed]

15. Salah, H.M.; Mehta, J.L. Hypothesis: Sex-Related Differences in ACE2 Activity May Contribute to Higher Mortality in Men Versus Women With COVID-19. *J. Cardiovasc. Pharmacol. Ther.* **2021**, *26*, 114–118. [CrossRef]

16. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; et al. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature* **2020**, *579*, 270–273. [CrossRef]

17. Ge, X.-Y.; Li, J.-L.; Yang, X.-L.; Chmura, A.A.; Zhu, G.; Epstein, J.H.; Mazet, J.K.; Hu, B.; Zhang, W.; Peng, C.; et al. Isolation and Characterization of a Bat SARS-like Coronavirus That Uses the ACE2 Receptor. *Nature* **2013**, *503*, 535–538. [CrossRef]

18. Zhang, H.; Penninger, J.M.; Li, Y.; Zhong, N.; Slutsky, A.S. Angiotensin-Converting Enzyme 2 (ACE2) as a SARS-CoV-2 Receptor: Molecular Mechanisms and Potential Therapeutic Target. *Intensive Care Med.* **2020**, *46*, 586–590. [CrossRef]

19. Tay, M.Z.; Poh, C.M.; Rénia, L.; MacAry, P.A.; Ng, L.F.P. The Trinity of COVID-19: Immunity, Inflammation and Intervention. *Nat. Rev. Immunol.* **2020**, *20*, 363–374. [CrossRef] [PubMed]

20. Prabhu, S.D. Cytokine-Induced Modulation of Cardiac Function. *Circ. Res.* **2004**, *95*, 1140–1153. [CrossRef]

21. Levi, M.; van der Poll, T.; Büller, H.R. Bidirectional Relation between Inflammation and Coagulation. *Circulation* **2004**, *109*, 2698–2704. [CrossRef]

22. Jamal, F.A.; Khaled, S.K. The Cardiovascular Complications of Chimeric Antigen Receptor T Cell Therapy. *Curr. Hematol. Malig. Rep.* **2020**, *15*, 130–132. [CrossRef]

23. Kang, Y.; Chen, T.; Mui, D.; Ferrari, V.; Jagasia, D.; Scherrer-Crosbie, M.; Chen, Y.; Han, Y. Cardiovascular Manifestations and Treatment Considerations in COVID-19. *Heart* **2020**, *106*, 1132–1141. [CrossRef] [PubMed]

24. Danzi, G.B.; Loffi, M.; Galeazzi, G.; Gherbesi, E. Acute Pulmonary Embolism and COVID-19 Pneumonia: A Random Association? *Eur. Heart J.* **2020**, *41*, 1858. [CrossRef]

25. Lamb, Y.N. Remdesivir: First Approval. *Drugs* **2020**, *80*, 1355–1363. [CrossRef] [PubMed]

26. Guzik, T.J.; Mohiddin, S.A.; Dimarco, A.; Patel, V.; Savvatis, K.; Marelli-Berg, F.M.; Madhur, M.S.; Tomaszewski, M.; Maffia, P.; D'Acquisto, F.; et al. COVID-19 and the Cardiovascular System: Implications for Risk Assessment, Diagnosis, and Treatment Options. *Cardiovasc. Res.* **2020**, *116*, 1666–1687. [CrossRef] [PubMed]

27. Driggin, E.; Madhavan, M.V.; Bikdeli, B.; Chuich, T.; Laracy, J.; Biondi-Zoccai, G.; Brown, T.S.; Der Nigoghossian, C.; Zidar, D.A.; Haythe, J.; et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J. Am. Coll. Cardiol.* **2020**, *75*, 2352–2371. [CrossRef]

28. Spanish Ministry of Health Clinical Management of COVID-19. Available online: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf (accessed on 6 May 2021).

29. Spanish Agency for Medicine and Health Products Available Treatments for the Management of Respiratory Infection by SARS-CoV-2. Available online: https://www.aemps.gob.es/laAEMPS/docs/medicamentos-disponibles-SARS-CoV-2-22-5-2020.pdf?x57200 (accessed on 6 May 2021).

30. Benchimol, E.I.; Smeeth, L.; Guttmann, A.; Harron, K.; Moher, D.; Petersen, I.; Sørensen, H.T.; von Elm, E.; Langan, S.M.; RECORD Working Committee. The REporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement. *PLoS Med.* **2015**, *12*, e1001885. [CrossRef]

31. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P.; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *J. Clin. Epidemiol.* **2008**, *61*, 344–349. [CrossRef] [PubMed]

32. Gutiérrez-Abejón, E.; Tamayo, E.; Martín-García, D.; Álvarez, F.J.; Herrera-Gómez, F. Clinical Profile, Treatment and Predictors during the First COVID-19 Wave: A Population-Based Registry Analysis from Castile and Leon Hospitals. *Int. J. Environ. Res. Public Health* **2020**, *17*, 9360. [CrossRef]

33. Gutiérrez-Abejón, E.; Martín-García, D.; Tamayo, E.; Álvarez, F.J.; Herrera-Gómez, F. Clinical Profile, Pharmacological Treatment, and Predictors of Death Among Hospitalized COVID-19 Patients With Acute Kidney Injury: A Population-Based Registry Analysis. *Front. Med.* **2021**, *8*, 657977. [CrossRef] [PubMed]

34. Casas-Rojo, J.M.; Antón-Santos, J.M.; Millán-Núñez-Cortés, J.; Lumbreras-Bermejo, C.; Ramos-Rincón, J.M.; Roy-Vallejo, E.; Artero-Mora, A.; Arnalich-Fernández, F.; García-Bruñén, J.M.; Vargas-Núñez, J.A.; et al. Clinical Characteristics of Patients Hospitalized with COVID-19 in Spain: Results from the SEMI-COVID-19 Registry. *Rev. Clin. Esp.* **2020**, *220*, 480–494. [CrossRef]

35. Berenguer, J.; Ryan, P.; Rodríguez-Baño, J.; Jarrín, I.; Carratalà, J.; Pachón, J.; Yllescas, M.; Arriba, J.R.; COVID-19@Spain Study Group; Fundación SEIMC-GESIDA; et al. Characteristics and Predictors of Death among 4035 Consecutively Hospitalized Patients with COVID-19 in Spain. *Clin. Microbiol. Infect.* **2020**, *26*, 1525–1536. [CrossRef] [PubMed]

36. Solano-López, J.; Zamorano, J.L.; Pardo Sanz, A.; Amat-Santos, I.; Sarnago, F.; Gutiérrez Ibañes, E.; Sanchis, J.; Rey Blas, J.R.; Gómez-Hospital, J.A.; Santos Martínez, S.; et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. *Rev. Esp. Cardiol.* **2020**, *73*, 985–993. [CrossRef]

37. McMichael, T.M.; Currie, D.W.; Clark, S.; Pogosjans, S.; Kay, M.; Schwartz, N.G.; Lewis, J.; Baer, A.; Kawakami, V.; Lukoff, M.D.; et al. Epidemiology of COVID-19 in a Long-Term Care Facility in King County, Washington. *N. Engl. J. Med.* **2020**, *382*, 2005–2011. [CrossRef]

38. Guan, W.-J.; Ni, Z.-Y.; Hu, Y.; Liang, W.-H.; Ou, C.-Q.; He, J.-X.; Liu, L.; Shan, H.; Lei, C.-L.; Hui, D.S.C.; et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720. [CrossRef] [PubMed]

39. Chen, T.; Wu, D.; Chen, H.; Yan, W.; Yang, D.; Chen, G.; Ma, K.; Xu, D.; Yu, H.; Wang, H.; et al. Clinical Characteristics of 113 Deceased Patients with Coronavirus Disease 2019: Retrospective Study. *BMJ* **2020**, *368*, m1091. [CrossRef]

40. Docherty, A.B.; Harrison, E.M.; Green, C.A.; Hardwick, H.E.; Pius, R.; Norman, L.; Holden, K.A.; Read, J.M.; Dondelinger, F.; Carson, G.; et al. Features of 20 133 UK Patients in Hospital with COVID-19 Using the ISARIC WHO Clinical Characterisation Protocol: Prospective Observational Cohort Study. *BMJ* **2020**, *369*, m1985. [CrossRef] [PubMed]

41. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W.; the Northwell COVID-19 Research Consortium; Barnaby, D.P.; Becker, L.B.; Chelico, J.D.; et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* **2020**, *323*, 2052–2059. [CrossRef] [PubMed]

42. Ortolan, A.; Lorenzin, M.; Felicetti, M.; Doria, A.; Ramonda, R. Does Gender Influence Clinical Expression and Disease Outcomes in COVID-19? A Systematic Review and Meta-Analysis. *Int. J. Infect. Dis.* **2020**, *99*, 496–504. [CrossRef]

43. Ya'qoub, L.; Elgendy, I.Y.; Pepine, C.J. Sex and Gender Differences in COVID-19: More to Be Learned! *Am. Heart J. Plus* **2021**, *3*, 100011. [CrossRef]

44. Simpson, A.H.R.; Simpson, C.J.; Frost, H.; Welburn, S.C. COVID-19: Obesity, Deprivation and Death. *J. Glob. Health* **2020**, *10*, 020389. [CrossRef] [PubMed]

45. Rottoli, M.; Bernante, P.; Belvedere, A.; Balsamo, F.; Garelli, S.; Giannella, M.; Cascavilla, A.; Tedeschi, S.; Ianniruberto, S.; Rosselli Del Turco, E.; et al. How Important Is Obesity as a Risk Factor for Respiratory Failure, Intensive Care Admission and Death in Hospitalised COVID-19 Patients? Results from a Single Italian Centre. *Eur. J. Endocrinol.* **2020**, *183*, 389–397. [CrossRef] [PubMed]

46. Petrilli, C.M.; Jones, S.A.; Yang, J.; Rajagopalan, H.; O'Donnell, L.; Chernyak, Y.; Tobin, K.A.; Cerfolio, R.J.; Francois, F.; Horwitz, L.I. Factors Associated with Hospital Admission and Critical Illness among 5279 People with Coronavirus Disease 2019 in New York City: Prospective Cohort Study. *BMJ* **2020**, *369*, m1966. [CrossRef] [PubMed]

47. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]

48. Onder, G.; Rezza, G.; Brusaferro, S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* **2020**, *323*, 1775–1776. [CrossRef] [PubMed]

49. Borobia, A.M.; Carcas, A.J.; Arnalich, F.; Álvarez-Sala, R.; Monserrat-Villatoro, J.; Quintana, M.; Figueira, J.C.; Torres Santos-Olmo, R.M.; García-Rodríguez, J.; Martín-Vega, A.; et al. A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe. *J. Clin. Med.* **2020**, *9*, 1733. [CrossRef]

50. Tang, N.; Li, D.; Wang, X.; Sun, Z. Abnormal Coagulation Parameters Are Associated with Poor Prognosis in Patients with Novel Coronavirus Pneumonia. *J. Thromb. Haemost.* **2020**, *18*, 844–847. [CrossRef] [PubMed]

51. Hancox, J.C.; Hasnain, M.; Vieweg, W.V.R.; Crouse, E.L.B.; Baranchuk, A. Azithromycin, Cardiovascular Risks, QTc Interval Prolongation, Torsade de Pointes, and Regulatory Issues: A Narrative Review Based on the Study of Case Reports. *Ther. Adv. Infect. Dis.* **2013**, *1*, 155–165. [CrossRef]

52. Chatre, C.; Roubille, F.; Vernhet, H.; Jorgensen, C.; Pers, Y.-M. Cardiac Complications Attributed to Chloroquine and Hydroxy-chloroquine: A Systematic Review of the Literature. *Drug Saf.* **2018**, *41*, 919–931. [CrossRef]

53. Liu, Y.; Yang, Y.; Zhang, C.; Huang, F.; Wang, F.; Yuan, J.; Wang, Z.; Li, J.; Li, J.; Feng, C.; et al. Clinical and Biochemical Indexes from 2019-NCoV Infected Patients Linked to Viral Loads and Lung Injury. *Sci. China Life Sci.* **2020**, *63*, 364–374. [CrossRef] [PubMed]

54. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061–1069. [CrossRef]

55. Stockman, L.J.; Bellamy, R.; Garner, P. SARS: Systematic Review of Treatment Effects. *PLoS Med.* **2006**, *3*, e343. [CrossRef]

56. KALETRA(R) Oral Film Coated Tablets, Oral Solution, Lopinavir Ritonavir Oral Film Coated Tablets, Oral Solution. Product Insert. North Chicago, IL: AbbVie Inc. (per FDA). 2013. Available online: https://books.google.com.cu/books?hl=es&lr=&id=E Tv2DQAAQBAJ&oi=fnd&pg=PA75&dq=KALETRA(R)+oral+film+coated+tablets,+oral+solution,+lopinavir+ritonavir+oral+ film+coated+tablets,+oral+solution.+Product+Insert.+AbbVie+Inc.+(per+FDA),+North+Chicago,+IL,+2013.+66.+34.+&ots= A4xd8b9QG9&sig=yPH3vqbA74Tv69vJ7GjsiDj8CIo&redir_esc=y#v=onepage&q&f=false (accessed on 10 April 2020).

57. Giles, J.T.; Sattar, N.; Gabriel, S.; Ridker, P.M.; Gay, S.; Warne, C.; Musselman, D.; Brockwell, L.; Shittu, E.; Klearman, M.; et al. Cardiovascular Safety of Tocilizumab Versus Etanercept in Rheumatoid Arthritis: A Randomized Controlled Trial. *Arthritis Rheumatol.* **2020**, *72*, 31–40. [CrossRef] [PubMed]

58. Bertoletti, L.; Bikdeli, B.; Zuily, S.; Blondon, M.; Mismetti, P. Thromboprophylaxis Strategies to Improve the Prognosis of COVID-19. *Vascul. Pharmacol.* **2021**, *139*, 106883. [CrossRef] [PubMed]

59. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler, P.R.; Goligher, E.C.; Berger, J.S.; Neal, M.D.; McVerry, B.J.; Nicolau, J.C.; Gong, M.N.; et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with COVID-19. *N. Engl. J. Med.* **2021**, *385*, 790–802. [CrossRef]