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Research Article

COVID-19 IN A NORTHEAST SPANISH COMMUNITY HOSPITAL Using the ISARIC WHO Clinical Characterisation Protocol

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Submitted: 09 August 2023

Accepted: 29 August 2023

Published: 01 September 2023

Keywords

- Covid-19
- Community Hospital
- ISARIC
- Outcomes
- Spain

Abstract

PURPOSE: To characterize the clinical and demographic features of adult patients admitted to HRS hospital with Covid-19

METHODS: Retrospective observational study of all adult patients admitted to this community hospital in Tudela, Spain, between 8 March 2020 and 31 December 2021s, using the ISARIC Clinical Characterization Protocol (CCP) core case report form to collect data.

RESULTS: 1143 adult patients with laboratory-confirmed diagnosis. The median age was 65.7 years (interquartile range 27.7, RANGE 84). More men than women (men 54.9%, N=628, women 45.1%, N=515). 76.2% had comorbidities (median 2, IQR 2): hypertension (47.6%), obesity (31.1%), chronic cardiac disease (22.5%), diabetes (21.3%), dementia (11.6%), neurological diseases (11.5%), and chronic pulmonary disease (7.3%). Overall, 20.1%, needed ventilatory support (12.6% non-invasive, 7.5% invasive), 11.8% were admitted to critical care, and 17% died (48% of those admitted to critical care during 2020, 25% along 2021). 82.1% were discharged alive, 22.2% were prescribed oxygen on discharge. Increasing age, some comorbidities, and male sex, were associated with in-hospital mortality. 78.6% received glucocorticoids, 16.8% tocilizumab, 6.3% remdesivir, 63.7% antibiotics, and 96.5% were on some form of anticoagulation.

CONCLUSIONS: We have retrospectively described the clinical and demographic characteristics of 1143 adult patients admitted to our hospital along the first two years of the pandemic, using a well-validated protocol. Our findings can be compared with similar series from other hospitals and describe the impact of Covid-19 on our area.

ABBREVIATIONS

MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; SSRIs: Selective Serotonin Reuptake Inhibitors

INTRODUCTION

During the past three years, SARS-CoV-2 has spread globally, causing a devastating pandemic. Covid-19, the disease caused by this virus, has led to substantial morbidity and mortality, and it is the most significant medical and public health challenge that our society has encountered in the last 100 years, with short and long term effects [1].

As of 3rd of June 2023, 776 million people have been diagnosed with infection by this new coronavirus, and 6.8 million have died; a total of 13.7 million infections have been reported from Spain, with an estimated 121,213 Covid-19 related deaths [2]. However, the full impact of the pandemic is probably much greater than what is indicated by reported deaths and number of cases [3,4]. In our country, the ratio between excess mortality rate and reported Covid-19 mortality rate is 1.64, with 114.1 (per 100,000) Covid-19 reported mortality rate and 186.7 estimated excess mortality rate (per 100,000); in Navarre, a Spanish region in the northeast of the country, this ratio is 1.74 (from 108.0 to 188.3, per 100,000) [4]. Aside from human losses, the economic burden inflicted by the disease is enormous, in Spain and elsewhere [5]. Furthermore, the Covid-19 pandemic is far from over, with new variants arising, in general with increasing transmissibility, although so far they do not cause more severe disease [6,7].

Several tools have been used to characterize and disseminate scientific information, with timely data sharing being critical to generate a body of knowledge and tackle the novel disease [8,9]. During this process, the utilization of established methods of data collection has been widely recommended [10]. One of these tools is the ISARIC Clinical Characterization Protocol, which has demonstrated its usefulness in several scenarios [11-15]. In this respect, an analysis of detailed information based on the ISARIC standardized form and collected in a community hospital, regarding their experience during Covid-19 pandemic, could yield valuable insights into the clinical presentation, potential risk factors, and disease progression within a particular population. Moreover, the parameters and estimates obtained in the study can be used in future meta-analyses and global-scale studies, facilitating the comparison of findings across diverse regions, and contribute to the understanding of COVID-19 and its management.

In this article, we aim to describe the demographic characteristics, clinical manifestations, clinical management, potential mortality risk factors, and disease progression in adult patients admitted to our hospital with laboratory-confirmed Covid-19 along the first two years of the pandemic, using the ISARIC standardized protocol.

MATERIALS AND METHODS

Setting

Hospital Reina Sofía (HRS) is a 190-bed community hospital located in Tudela, Spain (a town with around 37,000 inhabitants), with a reference area ("La Ribera county") of almost 100,000 inhabitants, grouped in small villages where agriculture is the main source of income. It has a 6-bed Critical Care Unit. Adult medical patients are admitted to the general internal medicine ward, which includes home-care hospitalization.

Study design and population

Retrospective study of all adult patients (17 years and older) admitted to HRS with a diagnosis of Covid-19, since the first case was diagnosed (8th march 2020) to 31st December 2021. Diagnosis was done using reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs, either performed at hospital laboratory or at another laboratory facility in the main town of the county, following standard methods. Our study is limited to laboratory-confirmed cases. No adult patient was excluded if their RT-PCR on admission was positive. Genomic analysis was not generally available and it has not been included in our study.

Written consent was not required because we report routinely collected clinical data, which have been analyzed retrospectively once, anonymized. The Research Ethics Committee in Navarra, Spain (reference 0001-3318-2021-000061) gave ethical approval.

Data collection

Data were collected according to a detailed protocol (based on ISARIC CCP core form) by members of the staff and residents (HRS collaborative group). A standardized electronic case report form to enter the data was created and stored within a secure research electronic database. All data were encrypted (a comprehensive list of all the included variables can be found in appendix A).

Patient demographic characteristics included age, sex at birth, ethnicity, and country of origin. Clinical characteristics included physiological parameters at presentation, signs and symptoms, and presence of comorbidities. Laboratory parameters and findings of radiologic images were also collected, as well as treatments received at any moment during hospital stay (pharmacological, type of respiratory support, critical care procedures). In-hospital complications were also studied (organ-specific diagnoses alone or together with any characteristic of Covid-19 illness). All complications were determined from routine clinical records, and microbiological confirmation was required for sepsis (positive blood cultures) and bacterial pneumonia (sputum sample). Acute kidney injury and acute liver injury were defined according to international grading criteria [14].

Main outcomes

The primary outcome was death or survival, with the patient being discharged from hospital at the end of hospital stay. Other secondary outcomes were presence or absence of complications and need of critical care, with or without invasive respiratory support; finally, functional outcomes on discharge were also assessed (discharged home/health facility, able to look after oneself/unable, health status as previous to illness/different), as well as admission to home-care hospitalization.

Statistical analysis

Baseline characteristics of the total sample and by sex were summarized using descriptive measures such as frequencies with percentages for categorical variables and mean with standard deviations or median with interquartile range (IQR) for quantitative variables depending on their distribution. The weekly incidence of infections during the study period was represented for both sexes. The incidence of outcomes (ICU admission, invasive mechanical ventilation –IMV-, non- invasive mechanical ventilation –NIMV-, mortality, oxygen at discharge and readmissions) were presented as pyramid plots stratifying by sex and age group. To evaluate the association of symptoms and comorbidities with mortality, multivariate Cox regression models were constructed for each symptom/comorbidity considering death/alive as outcome and adjusting by age group and sex. The adjusted hazard ratios (HR) with their 95% CI were graphically presented. No imputation of data was made. All analyses were performed in R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS AND DISCUSSION

Demographic and clinical characteristics; radiologic and laboratory findings

Between8th March 2020 and 31st December 2021, 1,143 adult patients were admitted with laboratory-diagnosed Covid-19 and were included in our study. There were more men (628, 54.9%) than women, and more patients were admitted during 2020 (764, 66.8%), than 2021. Their demographic characteristics (sex, age, distribution by decades, ethnicity), and comorbidities are shown in Table 1 (those with higher numbers and statistically significant variables are included; and complete tables with all the variables studied are offered as supplementary material). Most patients (81%) were white. Median age was 66.6 years (interquartile range –IQR- 27.7). Admission incidence by week and sex appears at Figure 1.

Regarding comorbidities, 76.2% had some comorbidity, hypertension being the most frequent, followed by obesity, cardiac diseases and diabetes. Neurological conditions (dementia, other diseases) were also prevalent (23.1% taken together), as well as pulmonary diseases (chronic obstructive pulmonary disease –COPD- and asthma, 12%). 24 patients were pregnant on admission (mean 35 weeks, SD 7.8), and 21 children were delivered alive, with 1 fetus dead and 2 women discharged before delivery date. 61.9% of the newborns were Covid-19+.

Clinical characteristics (symptoms and signs), are also shown in Table 1. Fever (73.2%), cough (68.5%), dyspnea (66%) and fatigue (57%) were the most prevalent presenting complaints. Patients were tachypneic on admission (mean respiratory rate 24, SD 6) and presented low-grade fever (mean axillary temperature 37.3ºC, SD 1.1) and low S02 (mean 93% breathing room air, IQR 5).

Radiologic and laboratory findings on admission are shown in Table 1 as well. Plain chest X-ray was performed in 97.8%, with abnormal findings described in 92.6%. Patchy, predominantly peripheral infiltrates was the most common pattern. CT-scan was performed in 112 patients (9.8%), with abnormal findings in 93.5%.

CRP, LDH, D-dimer, fibrinogen and ferritin were the laboratory parameters more commonly elevated. Liver enzymes (ALT, AST), bilirubin, renal parameters (urea, creatinine), ions (Na^+, K^+), PCT, lactate, and cardiac enzymes (CK, troponin) were usually in the normal range. Regarding hematological parameters, there was anemia in 29.3% (women more than men), leukopenia in 10%, lymphocytopenia in 45.2% (men more than women), and thrombopenia in 27.8%.

Treatments

Pharmacological treatments and level of respiratory support are summarized in table 2. Regarding drugs, 78.6% (848) received corticosteroids (most of them intravenous dexamethasone at a dose of 6mg/day), 63.7% (727) were treated with antibiotics (mainly ceftriaxone, started at the emergency department), 18.7% received an antiviral and 16.8% received an immunomodulator (tocilizumab). Finally, 14.3% were treated with hydro chloroquine, 1.1% with interferon-β, and 0.3%

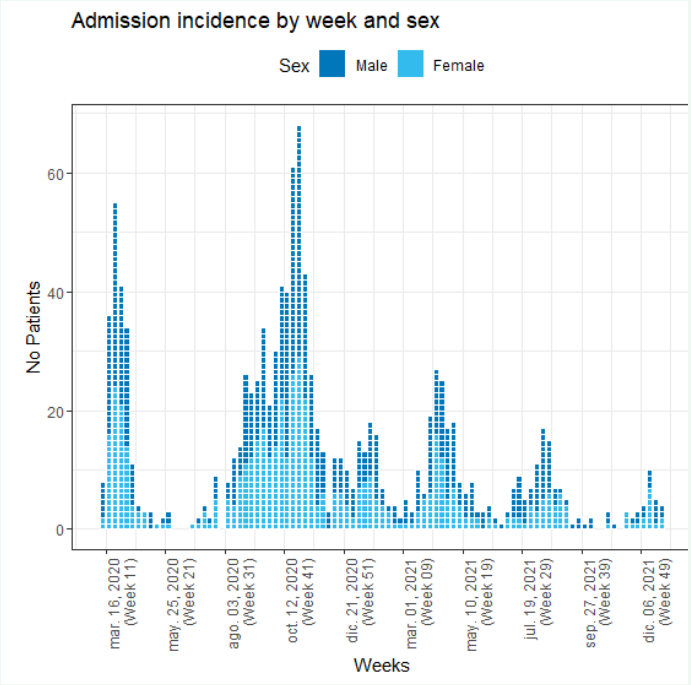

Figure 1: Admission incidence by week and sex.

Table 1: Patient demographic and clinical characteristics on admission

Variable	Male	Female	Total	p
Total N (%)	628 (54.9)	515 (45.1)	1143(100)	
Demographics				
Age[&]	64.3 (25.3)	70.0 (31.2)	66.6 (27.7)	0.028
Age group				<0.001
0-19	1 (0.2)	5 (1.0)	6 (0.5)	
20-29	11 (1.8)	10 (1.9)	21 (1.8)	
30-39	41 (6.5)	43 (8.3)	84 (7.3)	
40-49	69 (11.0)	58 (11.3)	127 (11.1)	
50-59	127 (20.2)	67 (13.0)	194 (17.0)	
60-69	116 (18.5)	75 (14.6)	191 (16.7)	
70-79	130 (20.7)	95 (18.4)	225 (19.7)	
80-89	104 (16.6)	112 (21.7)	216 (18.9)	
90+	29 (4.6)	50 (9.7)	79 (6.9)	
Ethnicity				0.451
African	5 (0.8)	2 (0.4)	7 (0.6)	
Arabic	50 (8.0)	41 (8.0)	91 (8.0)	
Asian	1 (0.2)	1 (0.2)	2 (0.2)	
Caucasian	517 (82.3)	409 (79.4)	926 (81.0)	
Latin	47 (7.5)	56 (10.9)	103 (9.0)	
Unknown	8 (1.3)	6 (1.2)	14 (1.2)	
Comorbidities				
Chronic cardiac disease	153 (24.4)	104 (20.2)	257 (22.5)	0.108
Hypertension	298 (47.5)	246 (47.8)	544 (47.6)	0.963
Chronic respiratory disease	66 (10.5)	17 (3.3)	83 (7.3)	<0.001
Obesity	180 (29.6)	164 (32.9)	344 (31.1)	0.271
Clinical characteristics, signs, symptoms				
Temperature[$]	37.4 (1.1)	37.1 (1.1)	37.3 (1.1)	<0.001
Heart rate[$]	87.5 (17.7)	88.1 (18.4)	87.8 (18.0)	0.571
Respiratory rate[$]	24.3 (6.3)	24.6 (6.8)	24.4 (6.6)	0.606
Systolic blood pressure[$]	130.2 (22.1)	128.7 (22.1)	129.5 (22.1)	0.259
Diastolic blood pressure[$]	76.2 (12.1)	73.1 (13.5)	74.8 (12.8)	<0.001
Oxygen saturation[&]	93.0 (5.0)	93.0 (6.0)	93.0 (5.0)	0.849
Fever (≥ 37.5ºC)	477 (76.6)	354 (69.0)	831 (73.2)	0.005
Cough	435 (69.4)	347 (67.5)	782 (68.5)	0.540
Dyspnea	400 (63.7)	358 (69.5)	758 (66.3)	0.045
Radiologic and laboratory findings				
Dx_ pneumonia	584 (93.1)	457 (88.9)	1041 (91.2)	0.016
Chest X-ray	617 (98.4)	499 (97.1)	1116 (97.8)	0.188
Abnormal findings	584 (94.2)	457 (90.7)	1041 (92.6)	0.033
Chest CT-scan	73 (11.6)	39 (7.6)	112 (9.8)	0.028
Abnormal findings	65 (92.9)	35 (94.6)	100 (93.5)	1.000
CRP (mg/L)[&]	87.2 (112.7)	70.1 (93.7)	78.6 (104.5)	<0.001
Ferritin (µg/L)[&]	604.5 (912.5)	306.0 (448.5)	460.0 (691.0)	<0.001
Fibrinogen (mg/dl)[&]	618.0 (156.2)	590.0 (152.8)	604.0 (154.0)	<0.001
Hemoglobin (<13g/dL)	120 (19.1)	215 (41.7)	335 (29.3)	<0.001
WBCs (<4x109/L)	57 (9.1)	55 (10.7)	112 (9.8)	0.420
Lymphocytes (<1x10^9/L)	312 (49.7)	205 (39.8)	517 (45.2)	0.001
Platelets (<150x109/L)	207 (33.0)	111 (21.6)	318 (27.8)	<0.001

[$]Mean (SD); [&]Median (IQR).
Dx: diagnosis; WBCs: white blood cells; CRP: C-reactive protein

with convalescent plasma. Concerning anticoagulation, 96.5% received some sort of anticoagulation, largely low molecular weight heparin –lmwh- (either enoxaparin or bemiparin), in the context of different strategies (Table 2).

Clinical outcomes and in-hospital complications (Table 2, Figure 2)

Acute kidney injury (AKI) was the most frequent in-hospital complication (16.7%), followed by respiratory distress (15.2%), anemia (13%), and bacterial pneumonia (9.1%, including co-infection and secondary infection). Other reported complications of Covid-19 were relatively rare in our series (pulmonary embolism –PE- 1.7%; deep venous thrombosis –DVT- and myocarditis, both 1.1%).

Overall mortality of our series was 17%; 11.8% (135 patients) were admitted to the ICU and 7.5% needed invasive respiratory support (invasive mechanical ventilation –IMV-). Additionally, 12.6% needed non-invasive ventilatory support (NIVS, either continuous positive airway pressure –CPAP-/Bilevel positive airway pressure –BiPAP- or high-flow nasal cannula –HFNC-). Mortality rate (MR) of patients admitted to the ICU was 48% during 2020 and 25% during 2021.

Hospitalized patients had an average stay duration of 9.4 days (median 7, IQR 7). Most (76.6%) were discharged alive; 5.3% were taken to another hospital, and 0.3% were admitted to palliative care. Concerning the need of oxygen, 22.2% were discharged on supplemental oxygen. Readmission rate in the first three months was 7.4%. Regarding functional outcomes, 68.7% were functionally worse than before the infection and 32.9% needed some form of care. Finally, 11% were admitted to home-care hospitalization after their stay on the medical ward. Clinical and functional outcomes and in-hospital complications are also described in table 2. Additionally, the number of cases for some of these functional outcomes have been graphically represented in pyramid plots, according to sex and age group (Figure 2).

Mortality risk factors

The analysis of potential mortality risk factors showed that patients with cardiac disease, pulmonary disease, or dementia, had a significantly higher risk of mortality with adjusted HRs equal to 1.40 (95% CI: 1.03-1.89), 1.63 (95% CI: 1.11-2.39), and 2.14 (95% CI: 1.53-3.01), respectively. Regarding symptoms, the analysis of potential mortality risk factors showed that labored breathing, audible wheezes and a depressed level of consciousness were significantly associated with mortality with adjusted HRs equal to 1.84 (95% CI: 1.30-2.61), 1.69 (95% CI: 1.09-2.61), and 1.44 (95% CI: 1.04-2.01),respectively. These results are graphically represented in Figure 3.

DISCUSSION

General Discussion

Our series describes the impact of Covid-19 on our hospital and its reference area during the first two years of the pandemic.

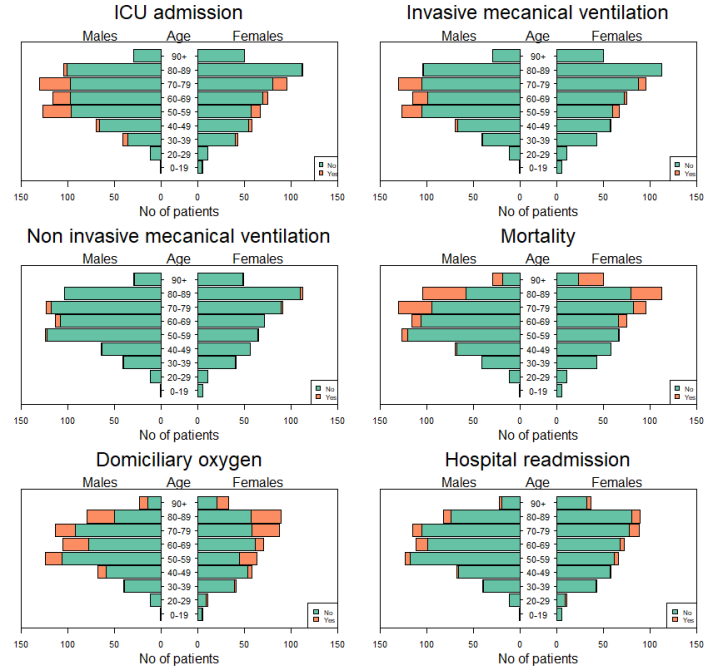

Figure 2: Outcomes.

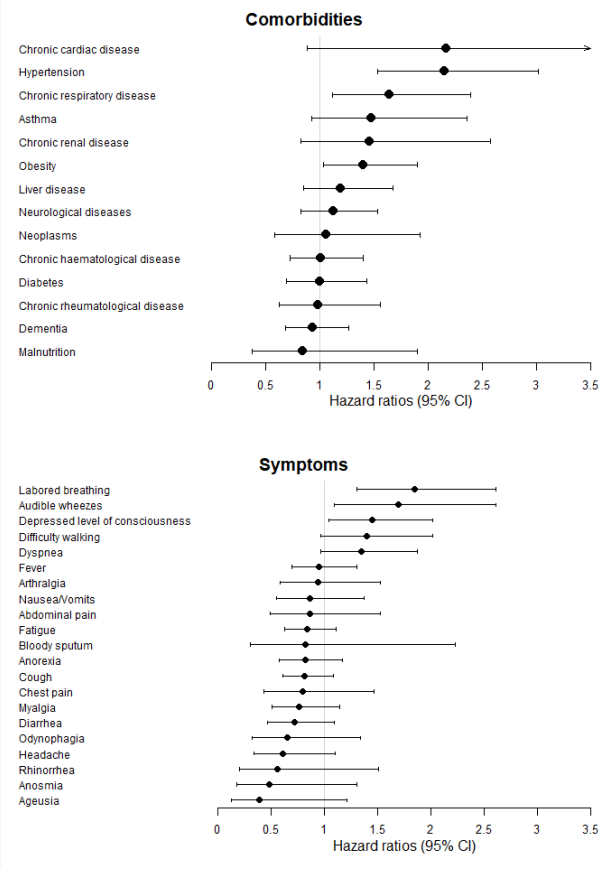

Figure 3: Mortality risk factors.

Table 2. Patient management and outcomes

Variable	Male	Female	Total	p
Total N (%)	628 (54.9)	515 (45.1)	1143 (100)	
Pharmacological treatments				
Antibiotics (any)	421 (67.1)	313 (60.8)	734 (64.3)	0.030
Antiviral (any)	216 (34.4)	140 (27.2)	356 (31.1)	0.011
Lopinavir/ritonavir	72 (11.6)	63 (12.3)	135 (11.9)	0.768
Remdesivir	48 (7.6)	24 (4.7)	72 (6.3)	0.052
HCLQ	93 (14.8)	70 (13.6)	163 (14.3)	0.617
Tocilizumab	131 (20.9)	61 (11.8)	192 (16.8)	<0.001
Anticoagulants	609 (97.1)	492 (95.7)	1101 (96.5)	0.260
Anticoagulant indication				0.003
Conventional	390 (63.6)	364 (73.8)	754 (68.2)	
Extended	115 (18.8)	73 (14.8)	188 (17.0)	
Therapeutic	108 (17.6)	56 (11.3)	164 (14.8)	
Corticosteroids	495 (83.5)	358 (72.9)	853 (78.7)	<0.001
Dexamethasone	464 (83.3)	348 (82.1)	812 (82.8)	0.675
Other corticosteroids	145 (27.0)	75 (17.5)	220 (22.8)	0.001
Level of respiratory support				
Supplementary oxygen	557 (88.8)	438 (85.0)	995 (87.1)	0.070
Days oxygen[&]	7.0 (7.0)	6.0 (6.0)	6.0 (6.0)	0.008
Maximum oxygen flow				<0.001
<2 L/min	80 (14.4)	69 (15.8)	149 (15.0)	
2-5 L/min	225 (40.4)	194 (44.4)	419 (42.2)	
6-10 L/min	50 (9.0)	47 (10.8)	97 (9.8)	
11-15 L/min	65 (11.7)	70 (16.0)	135 (13.6)	
>15 L/min	137 (24.6)	57 (13.0)	194 (19.5)	
NMIV	15 (2.5)	7 (1.4)	22 (2.0)	0.295
IMV	67 (10.7)	19 (3.7)	86 (7.5)	<0.001
High-flow oxygen	81 (12.9)	40 (7.8)	121 (10.6)	0.007
In-hospital complications				
Bacterial pneumonia*	64 (10.3)	39 (7.6)	103 (9.1)	0.156
ARDS	108 (17.2)	66 (12.8)	174 (15.2)	0.049
Arrythmia	42 (6.7)	19 (3.7)	61 (5.4)	0.033
Myocarditis/Pericarditis	13 (2.1)	6 (1.2)	19 (1.7)	0.336
CHF	28 (4.5)	32 (6.2)	60 (5.3)	0.236
Bacteriemia	14 (2.2)	6 (1.2)	20 (1.8)	0.252
PE	13 (2.1)	6 (1.2)	19 (1.7)	0.331
DVT	8 (1.3)	4 (0.8)	12 (1.1)	0.586
Anemia	70 (11.2)	78 (15.1)	148 (13.0)	0.058
AKI	111 (17.7)	80 (15.5)	191 (16.7)	0.363
Liver failure	21 (3.3)	13 (2.5)	34 (3.0)	0.521
Hyperglycemia	150 (23.9)	91 (17.7)	241 (21.1)	0.013
Admission to ICU	95 (15.1)	40 (7.8)	135 (11.8)	<0.001
Inotropes	56 (8.9)	20 (3.9)	76 (6.7)	0.001
Tracheostomy	18 (2.9)	5 (1.0)	23 (2.0)	0.039
Outcomes				
Overall mortality	111 (17.7)	83 (16.1)	194 (17.0)	0.536
Outcome				0.491
Transfer to palliative care	2 (0.3)	1 (0.2)	3 (0.3)	
Discharged alive	475 (75.6)	400 (77.7)	875 (76.6)	
Hospital	8 (1.3)	2 (0.4)	10 (0.9)	
Death	111 (17.7)	83 (16.1)	194 (17.0)	
Transfer to another center	32 (5.1)	29 (5.6)	61 (5.3)	
Hospital-at-home transferred	48 (7.8)	36 (7.2)	84 (7.5)	0.774
Hospital-at-home admission	24 (3.9)	15 (3.0)	39 (3.5)	0.503
Discharged with oxygen	115 (20.4)	111 (24.3)	226 (22.2)	0.151
In need of care (covid)	173 (31.3)	153 (34.8)	326 (32.9)	0.282
In need of care (other)	91 (17.1)	85 (19.6)	176 (18.2)	0.356
Worse than before				0.519
No	294 (46.8)	225 (43.7)	519 (45.4)	
Unknown	79 (12.6)	73 (14.2)	152 (13.3)	
Yes	255 (40.6)	217 (42.1)	472 (41.3)	
Readmission	41 (7.2)	36 (7.7)	77 (7.4)	0.826

HCLQ: hydroxychloroquine; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation

*Includes co-infection and secondary infection. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; PE, pulmonary embolism; DVT, deep venous thrombosis;

[&]Median (IQR).

Data collection based on ISARIC case report form allows comparison with other series reported from other countries and levels of care. Relatively large differences in outcomes have been reported along the pandemic (see below) [16-20]. In general, our findings do coincide with the data previously published.

Thus, clinical symptoms and signs on presentation of Covid-19 patients from this part of Spain are in agreement with previous reports, with fever, cough, dyspnea and fatigue as the more frequently reported [15,20]. Other symptoms such as myalgias, gastrointestinal complaints, headache, sore throat, dysgeusia and anosmia, have been reported with varying frequency in the different series. Main symptoms and signs point to the fact that, even though Covid-19 is a multisystem disease, pulmonary involvement is characteristic, with its pathophysiology being progressively elucidated.

Our series also confirms the association between some comorbidities and presence of complications and outcomes, as it has been widely described [21,22]. Advanced age, presence of previous cardiac or pulmonary disease, and dementia, have been statistically associated with mortality in our study. Other widely described risk factors, such as obesity, have been highly prevalent but without showing a statistical association.

Concerning in-hospital complications, which have been widely reported in the medical literature with variable frequencies [14], AKI and respiratory distress were the most frequent in our series, as elsewhere [23,24]. Bacterial infection in the context of Covid-19 in hospitalized patients has been reported as 4.9% for co-infections (8.4% of ICU patients, pooled data from different studies) and 8.4% for secondary infections (39.9% of ICU patients,

Table 3: Comparison of outcomes with other series, according to date of elaboration

Author, reference	Dates of elaboration	Type of study, setting	N of cases	Country	MR (%)	IMV (%)	NIMV (%)	Other data
Docherty-ISARIC4C [15]	02-04/2020	Prospective cohort study, 208 acute care hospitals	20,133	UK	26	10	NR	(1)
Posso et al. [22]	02-05/2020	Retrospective, single centre (university hospital)	834	Spain	23.5	NR	NR	
Giesen et al. [34]	02-06/2020	Retrospective, single centre (secondary hospital)	1,169	Spain	14.6	NR	10	(2)
Drake-ISARIC4C [14]	01-08/2020	Prospective cohort, 302 health-care facilities	80,388	UK	31.5	NR	NR	(3)
Lim et al [35]	01-07/2020	Meta-analysis	57,420	International (23 countries)	45	NR	NR	(4)
WHO Solidarity Trial Consortium [29]	03/2020-01/2021	RCT (PT)	10,480	International (35 countries)	12.5/14.1	NR	NR	(5)
Annane et al. [36]	05/2020-01/2021	RCT (PT) ICUs	202	International (5 countries)	38/41	80/84	15/18	(6)
Matsunaga et al. [20]	03/2020-03/2021	Retrospective, 553 health-care facilities	33,554	Japan	5	4.3	NR	(7)
REMAP-CAP [37, 28]	03/2020-06/2021	RCT (PT)	4,869	International (14 countries)	27/36	NR	NR	(8)
Ozonoff et al. IMPACC study [17]	05/2020-03/2021	Prospective cohort study, 20 hospitals	1,164	USA	14	20	NR	
Jassat et al. [38]	06/2020-09/2021	Retrospective, national database	335,219	South Africa	21.5/28.8/26.4	NR	NR	(9)
Thygesen et al. [19]	12/2020-11/2021	Retrospective cohort study, NHS datasets	7M	England	2.2	5.6	15	(10)
ACTT-4 Study Group [39]	12/2020-04/2021	RCT (PT)	1,010	International (5 countries)	2.9/4.7	10/11	16/21	(11)
Teran-Tinedo et al. [32]	07-09/2021	Prospective cohort study, single monographic hospital	1,888	Spain	0.7	6	18	
Frat-SOHO-COVID [30]	01-12/2021	RCT (type of respiratory support, ICUs)	711	France	10/11	50	NR	(12)

Abbreviations: ICU(s): intensive care unit(s); IMV: invasive mechanical ventilation; M, million; MR: mortality rate; NHS, national health service; NIMV: non-invasive mechanical ventilation; NR: not reported; PT, pharmacological treatment; UK, United Kingdom (England, Scotland and Wales in this study)

(1) 17% admission rate to ICU/high dependency unit; if IMV, MR 37%
(2) 6.7% admitted to ICU
(3) Overall rate of in-hospital complications 49.7%; 26.6% of survivors with worse ability to self-care
(4) Meta-analysis of 69 studies. MR depends on the age, <50% for <40 years, to 84% if >80 years
(5) MR depending on treatment; 42% for patients on IMV
(6) Phase 3 multicentric trial of ravulizumab in mechanically ventilated patients, MR did not differ statistically between treatment groups
(7) 7.2% admission rate to ICU; 17% over 65 years worse self-care on discharge, 4.1% transferred to long-term care facility; 11.5% required oxygen
(8) MR depends on the treatment group; overall, 27% at 28 days, 36.9% at 180 days
(9) MR on first three waves, before omicron variant
(10) 10.6% were admitted to ICU; MR of those with ventilatory support outside the ICU during the first wave was 50.7%
(11) MR Depending on study group
MR 10% in the high-flow nasal cannula (HFNC) group, 11% standard oxygen group

also pooled data from different studies) [25], figures which do not differ from our own data. Thromboembolic complications and cardiac involvement have been relatively uncommon in our patients, which concurs with data from other publications. Thus, prevalence of myocarditis in our study is slightly higher than in the series of Ammirati et al (prevalence of 0.2 –diagnosis definite/probable- to 0.4% -including possible diagnosis) [26]. Prevalence of PE and DVT is also slightly higher than reported in the large series of Matsunaga et al from Japan [20], diagnosed in 0.2% and 0.7% of the patients, respectively. Neurologic and gastrointestinal or liver complications have also been reported, but with lesser frequency [27]

Regarding the medical treatments provided, we can describe –as elsewhere- relative successes and setbacks. During the early months of the Covid-19 pandemic, based on studies, which were badly conducted or had few patients, some drugs were repurposed and had widespread use; some of them were later demonstrated to be ineffective in better-designed randomized clinical trials.

Thus, antibiotics are an ineffective treatment for viral syndromes, including Covid-19, but they have however been extensively used in these patients [25]. Another drug which was subsequently demonstrated ineffective was chloroquine, as well as an antiviral such as lopinavir-ritonavir, also used in our patients during the first months of the pandemic. This approach was similar in other hospitals in Spain [28] (in this series of 100 patients, 60% receive antibiotics, 65% lopinavir-ritonavir, and 42% hydroxychloroquine) and elsewhere [29]. As more robust

data were published and included in the different guidelines, we used antivirals such as remdesivir, corticosteroids, and inmunomodulators such as tocilizumab. Convalescent plasma was seldom used in our setting (in just 4 cases). Respiratory support, the other cornerstone of the treatment of Covid-19, is far from a solved topic [23,30], and every health facility has supported its patients according to the available means at any given moment and its clinical expertise.

Clinical and functional outcomes have been broadly reported and show a wide range. Furthermore, outcomes have been changing as new therapies were incorporated and vaccines became available [31]. That Covid-19 displayed a wide range of disease severity was known from the initial series published from China [16].Overall mortality in our series has been 17%, although much higher in patients admitted to critical care (48% along 2020, diminishing to 25% during 2021). Our figures relate to a hospital of our size and complexity. Other series from other settings and periods of the pandemic show different results regarding admissions to ICU, deaths, and functional outcomes. Comparison in outcomes between several series are summarized in table 3, following a chronological order (date of elaboration [14,15,17,19,20,29,30,33-39]). They have been published during different stages and waves of the pandemic, and come from diverse types of studies (descriptive like ours, randomized clinical trials) and different types of hospitals (in general university and reference centers and middle-sized hospitals). This wide heterogeneity is reflected in parameters such as admission rates to hospital wards and intensive care (which ranged from 5% to 32%); Furthermore, the published studies use heterogeneous reporting criteria and outcomes; hence, results cannot be extrapolated and are difficult to interpret. They are the picture of the pandemic at a given place and time.

The burden to society from all this mortality (including excess all-cause mortality, a metric needed to understand the real effects of Covid-19), has been enormous. In Navarre, the part of Spain where the study has been performed, life expectancy at birth was 1.4 years and 1.0 years lower for men and women, respectively, in 2020; excess mortality was 19.3%, and concentrated in individuals >75 years (87% of deaths because of Covid-19 took place in this age group) [40].

Our study pertains to a specific period of the pandemic [6,7]. Nowadays, situation may be very different: clinical trials and emerging real world data have shown that vaccines are effective at preventing symptomatic disease; they reduce intensity of symptoms in infected individuals, hospital admissions and mortality [41,42]. They also reduce infectiousness (decreasing infectivity duration and viral load) [43]. Immunity afforded by vaccines compounds with immunity from infection, and large numbers of individuals enjoy hybrid immunity. However, vaccines do not completely control transmission [43]. Furthermore, all beneficial effects decline progressively and re-vaccination with booster doses becomes unavoidable [41]. Moreover, vaccination coverage varies within countries and continents; there remain unvaccinated layers of population, mainly in low and middle-income countries. In summary, for many people, SARS-CoV-2 infection no longer carries the same risks of adverse outcomes as it did at the beginning of the pandemic, and the clinical picture may be different from that described in our series. However, and as the recent increase in transmission rates demonstrates, the problem is far from over [6].

LIMITATIONS AND STRENGTHS OF OUR STUDY

We are aware of some limitations. It is a purely retrospective study, with all the limitations of this type of study. Our investigation describes a period of time, which may well be regarded of historical interest: nowadays, amidst a population with high levels of vaccine-acquired or hybrid immunity, the disease usually behaves differently. Our report would have been more timely and would have contributed to the body of knowledge about Covid-19 should it have been published earlier, but that was incompatible with daily clinical care. We are however convinced that to contribute with our data will be worthwhile for future meta-analysis that can generate quality data about this period of the pandemic.

Another limitation concerns the timing of some of the variables studied: clinical, radiologic and laboratory parameters were collected on admission, representing just the initial picture of the disease. ISARIC CRF allows data collection in as many moments of hospital stay as desired, but we decided to include just admission values for most variables.

Our study has strengths. For instance, we consider that reporting data using a validated protocol adds value to our results, which can be compared with other series reported from hospitals elsewhere. It portrays an accurate description of the full impact that Covid-19 had on our area during the first waves, and it will add on to other studies from different locations, drawing a more detailed picture of the consequences of the pandemic in Europe. Results from large university hospitals, have been widely reported, but we are not aware of any study with comprehensive data from a community hospital using ISARIC CCP.

CONCLUSION

As anywhere else in the world, in 2020 and 2021 Covid-19 put enormous pressure on our hospital. This paper tries to contribute to understand what Covid-19 meant to our community, and it may help to increase the knowledge about this disease, which still poses a threat to our societies.

ACKNOWLEDGMENTS

This paper intends to be our homage to our patients and their relatives, who went through the ordeal described in this paper; many of whom have not still fully recovered; some will never do. We also thank all members of the health care staff (nurses, nursing assistants, porters, pharmacists, technicians, physiotherapists, administrative personnel), and non-clinical staff (cleaners, cooks, waitresses), without their support the hospital could not have cared for wave after wave of Covid-19 patients.

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