

Clinical features, laboratory findings and predictors of death in hospitalized patients with COVID-19 in Sardinia, Italy

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Abstract. – OBJECTIVE: Since December 2019, when the first SARS-CoV2 infections have been reported, the number of cases has increased exponentially. In our University Hospital Unit, the first patient with COVID-19 was admitted on the 8th of March 2020. We aimed to investigate the predictors of death among inpatients with COVID-19.

MATERIALS AND METHODS: We performed a retrospective, monocentric study, consecutively enrolling patients with SARS-CoV2 infection. Clinical, laboratory, and radiological data were collected from the 8th of March to the 8th of April 2020. We aimed to describe the most frequent clinical and laboratory features and predictors of death among patients admitted to our Unit.

RESULTS: 87 patients were enrolled, 56 (64.4%) were male, with a median age of 72 (IQR 62.5-83.5) years. The majority of our population had at least one comorbidity in their medical anamnesis. Hypertension and cardiovascular disease were the most frequent, followed by obesity. Eighty (92%) patients had at least one symptom, whereas 7 (8%) were asymptomatic. The most common symptoms were fever and dyspnoea. Overall, 53 patients had lung disease confirmed at CT scan (60.9%). Twenty-five (28.7%) deaths occurred. Statistically significant predictors of death at multivariate analysis were lymphocytes count <900 cells/mm³, moderate ARDS, and lack of compliance at baseline.

CONCLUSIONS: This is the first Italian experience available. Our results seem to be in line with international literature. As highlighted by our data, more studies are needed to investigate the role of lymphocytes subsets, CT scan values. Furthermore, therapy choice and timing in this challenging setting should be urgently investigated in randomized clinical trials.

Key Words:

COVID-19, SARS-CoV-2, CT scan, Pneumonia, Lymphocytes.

Introduction

At the end of December 2019, several cases of an unknown respiratory syndrome have been reported in Wuhan¹ (Hubei Province, China). On the 9th of January, Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-CoV2), the causative agent of the novel Chinese respiratory syndrome, was finally identified².

Until now, six Coronaviruses were known as pathogens in humans. 229E, HKU1, NL63, and OC43, cause the common seasonal cold. SARS-CoV (Severe Acute Respiratory Syndrome - Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome – Coronavirus) were associated with severe respiratory syndromes. Between 2002 and 2003, 8,237 cases of SARS-CoV were reported and caused 775 deaths (9% of mortality). The SARS-CoV outbreak started in Guangdong Province in China. MERS-CoV's outbreak originated from Jeddah in Saudi Arabia in 2012 and confirmed infections were 1621, with 584 deaths (36% of mortality)³.

Many studies have been conducted in the last two months to understand the origin of SARS-CoV2. Zhou et al⁴ were the first research team able to obtain the full-length virus genome sequences, which showed a 79.5% homology with SARS-CoV and 96% with a bat Coronavirus. To support the bat origin hypothesis, Lu et al⁵ confirmed the similarity between SARS-CoV2 and two bat Coronavirus (bat-SL-CoVZC45 and bat-SL-CoVZXC21). As for SARS-CoV and MERS-CoV, the SARS-CoV2 lineage is more complex, and probably another animal was an intermediate host between bats and humans.

SARS-CoV2 is primarily spread by droplets during coughing, sneezing, or talking by symptomatic patients, or mildly symptomatic and as-

ymptomatic people⁶. The incubation period is estimated from 2 to 14 days (median of 5.1 days)⁷. Typical clinical manifestations include fever, non-productive cough, dyspnoea, myalgia, fatigue, and less frequently gastrointestinal symptoms, such as vomiting or diarrhea⁸⁻¹¹. In some cases, SARS-CoV2 infection can cause a severe respiratory disease similar to SARS-CoV with radiological evidence of pneumonia, related to a high mortality rate.

Several risk factors, including older age, elevated SOFA score on admission, lymphopenia, and high levels of some blood markers (IL-6, cardiac troponin I, lactate dehydrogenase, serum ferritin, and d-dimer) have been associated with a worst outcome⁹ 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19).

Computed Tomography (CT) scan has an essential role in the diagnosis of SARS-CoV2-related pneumonia. Shi et al¹² found radiological abnormality also present in asymptomatic patients. The rapid evolution of the CT patterns from focal unilateral to diffuse bilateral ground-glass opacities and co-existed consolidations area occurred from 7 to 21 days since the onset of the symptoms.

Different approaches¹³⁻¹⁵, including monoclonal antibodies¹⁶⁻¹⁸, have been tried so far, but no definitive treatment is available for COVID-19.

We report our SARS-CoV2 infection experience during the first month of admissions in our ward.

Materials and Methods

Study Conduction

We performed a retrospective, monocentric study, consecutively enrolling all adult patients admitted to the Unit of Infectious Diseases of the University Hospital of Sassari (North-West Sardinia, Italy). We included patients admitted from the 8th of March to the 8th of April 2020, for SARS-CoV2 infection.

The diagnosis was based on Real Time-PCR on a nasopharyngeal swab. Anamnesis, clinical, and laboratory data were collected. Fever was defined as body temperature $> 37.3^{\circ}\text{C}$. Lymphopenia was defined as lymphocyte count under 900 cells/mm^3 . The increase of C-reactive protein (CRP) was defined as levels of more than 0.5 mg/dl . The instrumental diagnosis was based on a one-millimeter slices CT scan.

According to arterial blood gas evaluation, we classified patients without an acute respiratory distress syndrome (ARDS) if they had a $\text{PO}_2/\text{FiO}_2 > 300$, patients with a mild ARDS (PO_2/FiO_2 between 200 and 300), patients with a moderate ARDS (PO_2/FiO_2 between 100 and 200) and patients with severe ARDS if they had a $\text{PO}_2/\text{FiO}_2 < 100$.

Patients compliance was defined as the possibility of the patient to adhere to the medical advice about oral and intravenous treatment regimens, the respiratory exercise, and the use of medical devices.

During the study period, the Italian “red zone” was defined as North Italy (Lombardy, Veneto, Piemonte, Emilia-Romagna, Friuli Venezia Giulia, and Liguria).

SARS-CoV2 infection treatments consisted of lopinavir/ritonavir 400/100 mg twice a day (bid), hydroxychloroquine 200 mg bid, azithromycin 500 mg once a die (qd) for five days, and tocilizumab 8 mg/Kg, maximum 800 mg per dose, with an interval of 12 hours for the second dose. The treatment prescription was based on national guidelines according to the time of enrolment. Therapy was adjusted according to clinical features and drug-drug interactions with patients’ chronic therapy.

We aimed to describe the most frequent clinical and laboratory findings, as well as predictors of death among patients admitted during the first month of biocontainment activity in our Unit.

The research was conducted according to the Helsinki Declaration. All patients signed informed consent upon admission to the Hospital. The study was approved by the local Ethical Committee.

Statistical Analysis

Before performing the statistical analysis, data distribution was evaluated with the Kolmogorov-Smirnov test. Data were elaborated as numbers on total (percentages), means $\pm$ standard deviations, and median (IQR), as appropriate. Categorical variables were evaluated with univariate analysis for their influence on treatment outcome. Cox proportional-hazards model was used for multivariable logistic regression, including the independent variables with an of $p < 0.2$ at univariate analysis, considering death as the dependent variable. The significance level was defined as $p < 0.05$.

Results

General Information

Eighty-seven patients were included in our survey. Of them, 56 (64.4%) were male, with a median age of 72 (IQR 62.5-83.5) years. In most of the cases, they had the diagnosis in the hospital or retirement nursing houses (83.9%). Only 14 (16.1%) were diagnosed at home by the territorial services. With regards to the in-hospital diagnosis, 27 (31.1%) patients had it in the emergency department (ED), 12 (13.8%) patients in the coronary care unit (CCU) 4 (4.6%) in the dialysis department and 7 (8%) in a surgical ward.

The infection risk factor was unknown in nearly 50% of cases. Six (6.9%) had a recent history of travel in the “red zone”, 37 (42.5%) had contact with a confirmed SARS-CoV2-infected person.

The majority (81.6%) of patients had at least one comorbidity in their medical history. Hypertension and cardiovascular disease were the most frequent, followed by obesity, with a Body Mass Index > 30. The patients' demographic and clinical features have been summarized in Table I.

Clinical Features

At the ward admission, 80 (92%) patients had at least one symptom, and only seven (8%) were asymptomatic. Fever was present in 72 (82.8%) patients. Fifty-nine (67.8%) patients had dyspnoea and started O2 therapy during the admission.

Considering all hospitalizations period, 66 (75.9%) patients had respiratory failure. Thirty-two (36.8%) patients were included in Group A. On the contrary, 34 (39.1%) subjects were included in Group B. Among them, 14 (16.1%) used VM with more than 35% of FiO₂, in 11 (12.6%) the NIV with the helmet. Sixteen (18.4%) needed intubation.

Laboratory Findings and Imaging Examinations

Eighty-five (97.7%) patients performed blood tests at the moment of admission in our ward (Table II). Two (2.3%) patients died immediately after the admission, before taking the first blood sample. The 50% of patients had at baseline a lymphopenia. Only nine (10.3%) had a normal CRP, while 39 (44.8%) had a CRP value ten times higher than normal.

Besides, 79 (90.1%) performed the arterial blood gas test (ABG) at baseline. Based on these results, 29 (36.7%) patients did not have an AR-

DS, 40 (50.6%) had mild ARDS, and ten had (12.7%) moderate ARDS (PO₂/FiO₂ between 100 and 200). Furthermore, 50 (57.5%) had respiratory alkalosis, which was compensated by the decrease of the hydrogencarbonate in 20 cases (40%).

Regarding the instrumental diagnostics, 54 (62.1%) patients performed a radiologic examination with a CT scan (Table II). Fifty-three (98.1%) had pathologic findings, and in 49 (90.7%) cases, there was a bilateral involvement. Forty-seven (88.9%) patients had ground-glass opacities (GGO). In 25 (52.8%) cases, a consolidation was present, and six (11.1%) had pleural effusion.

Table I. Characteristic of 87 patients with COVID-19 admitted in our ward.

Variable	Total patients (No. = 87)
Sex (n, %)	
Male	56 (64.4)
Female	31 (35.6)
Age (years), median (IQR)	72 (62.5-83.5)
Place of diagnosis (n, %)	
ED	27 (31.1)
Other wards	17 (19.5)
Residence	14 (16.1)
Retirement nursing houses	19 (21.8)
Other Hospital	10 (11.5)
Risk factor (n, %)	
Travel in the “red zone”	6 (6.9)
Exposure to an infected person	37 (42.5)
Unknown	44 (50.6)
Smoking habits (n, %)	
No	56 (64.4)
Yes	13 (14.9)
Unknown	18 (20.7)
Comorbidities (n, %)	
At least one	71 (81.6)
At least three	48 (55.2)
At least five	18 (20.7)
BMI > 30	19 (21.8)
COPD	13 (14.9)
Diabetes	21 (24.1)
Hypertension	45 (51.7)
CVD	45 (51.7)
Liver disease	7 (8)
Cancer	9 (10.3)
Kidney disease	14 (16.1)
CNS disease	16 (18.4)
Immune deficiency	4 (4.6)
Other	47 (54)
Lack of compliance	36 (41.4)

IQR: interquartile range; ED: emergency department; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; CNS: central nervous system.

Table II. Laboratories, radiologic, and clinical finding ad baseline, in 87 patients with COVID-19.

Variable	Total patients (No. = 87)
Symptoms (n, %)	80 (92)
Asymptomatic	7 (8)
Fever	72 (82.8)
Cough	36 (41.4)
Dyspnoea	59 (64.4)
Time between the start of symptoms and admission in the hospital, days (median, IQR)	4 (2-7)
CT scan (n, %)	54 (62.1)
Pathologic findings	53 (98.1)
Bilateral involvements	49 (90.7)
GGO	47 (88.9)
Consolidation	25 (52.8)
Pleural effusion	6 (11.1)
Lung dysfunction at baseline, (n, %)	
Mild ARDS	40 (46)
Moderate ARDS	10 (11.5)
Severe ARDS	0
O2 therapy (n, %)	66 (75.9)
Nasal cannula	40 (60.6)
Venturi Mask	29 (43.9)
NIV	11 (16.7)
Intubation	16 (24.2)
Laboratories findings, (median, IQR)	
WBC (cells/mm ³)	6975 (5605-9212.5)
Neutrophil (cells/mm ³)	5300 (3875-7525)
Lymphocyte (cells/mm ³)	900 (600-1225)
CRP (mg/dl)	9.55 (3.15-13.4)
PCT (ng/ml)	0.2 (0.1-0.6)
LDH (mU/ml)	319 (240-443)
Creatinine (mg/dl)	0.96 (0.77-1.35)
Ferritin (ng/ml)	532 (273-1534)
AST (U/l)	35 (22-52.5)
ALT (U/l)	28 (19-45.25)
pH	7.45 (7.41-7.48)
Treatment (n, %)	59 (67.8)
Hydroxychloroquine + Lopinavir/ritonavir	26 (44)
Hydroxychloroquine + azithromycin	5 (8.5)
Hydroxychloroquine	21 (35.6)
Lopinavir/ritonavir	5 (8.5)
Lopinavir/ritonavir + azithromycin	1 (1.7)
Hydroxychloroquine + Lopinavir/ritonavir + Tocilizumab	1 (1.7)

IQR: interquartile range; CT: computerized tomography; GGO: ground-glass opacity; ARDS: acute respiratory distress syndrome; NIV: non-invasive ventilation; WBC: white blood count; CRP: C-reactive protein; PCT: procalcitonin; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Treatment Regimens

Fifty-eight (66.7%) started a treatment after admission to the Hospital. Concerning the other 29 (33.3%) patients, nine (10.3%) died before starting any treatment, 20 (23%) did not receive therapy because of drug-drug interactions, or due to their comorbidities.

Hydroxychloroquine was prescribed to 53 (60.9%) patients. In 21 cases, it was given alone, whereas in 26 cases, it was used in combination with lopinavir/ritonavir, and in five cases with azithromycin. Lopinavir/ritonavir was used

alone in 5 patients because of G6PDH deficiency. One patient, a 29 years old female, developed a moderate ARDS and was treated with hydroxychloroquine, lopinavir/ritonavir, and tocilizumab in combination. Although eligible, four more patients clinically improved without tocilizumab administration.

Outcomes

On the 8th of April 31 (35.6%) patients have been discharged, and 31 (35.6%) patients were still in the ward. Of these, 15 (48.4%) were clin-

ically healed but still had a positive nasopharyngeal swab. Sixteen (51.6%) still needed medical treatment. About the discharged patients, the median time between the first positive and the first negative swab was 12 (IQR 10-17) days, while the median time between the starts of symptoms and the first negative swab was 17 (IQR 12-22) days.

Twenty-five (28.7%) patients died. Sixteen (64%) were male, with a median age of 84 (IQR 77-87; range 46-93) years. The median time between the admission in the ward and death was 5 (IQR 2-7) days.

At the univariate analysis, the factors associated with death were age < 72 years, COPD, hypertension, having more than 3 and 5 comorbidities, a lack of compliance, a moderate ARDS, and lymphocytes counted $\leq 900/\text{mm}^3$ and showed a $p\text{-value} \leq 0.2$. For this reason, they were all included in the Cox proportional-hazards model (Table III). Only the lack of compliance, having a moderate ARDS, and having a number of lymphocyte $\leq 900/\text{mm}^3$, were confirmed as statistically significant predictors of death risk ($p\text{-value} < 0.05$).

Discussion

To our knowledge, this report is one of the largest studies, including hospitalized COVID-19 patients in Italy. On the 8th of April, 2020, the total number of SARS-CoV2 infected people in Italy was 139,442, with 17,669 deaths¹⁹. The number of infected people in Sardinia was 975, with 59 deaths²⁰.

In our cohort, the most common clinical symptoms were fever, cough, and dyspnoea. Headache, nausea, abdominal pain, diarrhea, and sore throat were less frequent. In a previous study²¹, we tested a part of our patients to evaluate the presence

of anosmia and dysgeusia, and a high percentage (-75%) of them reported an alteration of the sense of smell and taste.

About the radiological findings, several studies have been conducted and showed how the most typical findings are the peripheral GGO, followed by consolidation. Pleural effusion, thoracic lymphadenopathy, and cavitation have been rarely found^{12,22,24}. In our cohort, only one patient was negative to instrumental findings. This confirms the high value of CT scan in the diagnostic workup and the approach to treatment. Although it is a preliminary data, and only one patient had negative radiological findings, we can argue about the utility of CT scan in predicting the time of hospitalization and SARS-CoV-2 first negativity at nasopharyngeal swab. In fact, the only one patient without lung disease had his first negativity after only eleven days from symptoms onset.

In previous cohort studies, the mortality rate was quite variable. Chen et al²⁵ declared that among 1099 subjects, the mortality rate was 1.4%, and it raised to 8.1% in severe patients. Similar mortality has been shown by Liu et al²⁶ in their cohort, where the deaths were 16/137 (11.6%). Zhou et al²⁰¹⁹, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19 argued about higher rates of mortality. In particular, in their study, the mortality (28.8%) was similar to our cohort (28.7%). The high percentage of mortality in our Unit could be explained by the fact that many patients have been previously admitted in the CCU (12 patients, 13.8%) or dialysis department (4 patients, 4.6%), and 19 (21.8%) were elderly patients host of a nursing home. Besides, the median age in our cohort was significantly older than the previous studies, and it also could explain the higher mortality. Although a recent study suggests that the severity of the clinical course and the mortal-

Table III. Predictors of mortality in patients with SARS-CoV2 infection (Cox proportional hazard model) in our cohort.

Variable	Odds ratio	CI	p-value
Age > 72 years	0.71	0.165-3.056	0.646
COPD	0.669	0.183-2.441	0.543
Hypertension	0.468	0.11-1.996	0.305
> 3 comorbidities	1.376	0.391-4.84	0.619
> 5 comorbidities	3.898	0.92-16.519	0.065
Not compliance patients	53.961	9.273-313.994	< 0.001
Moderate ARDS	9.793	2.262-42.388	0.002
Lymphocyte $\leq 900/\text{mm}^3$	4.235	1.371-13.085	0.012

COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome.

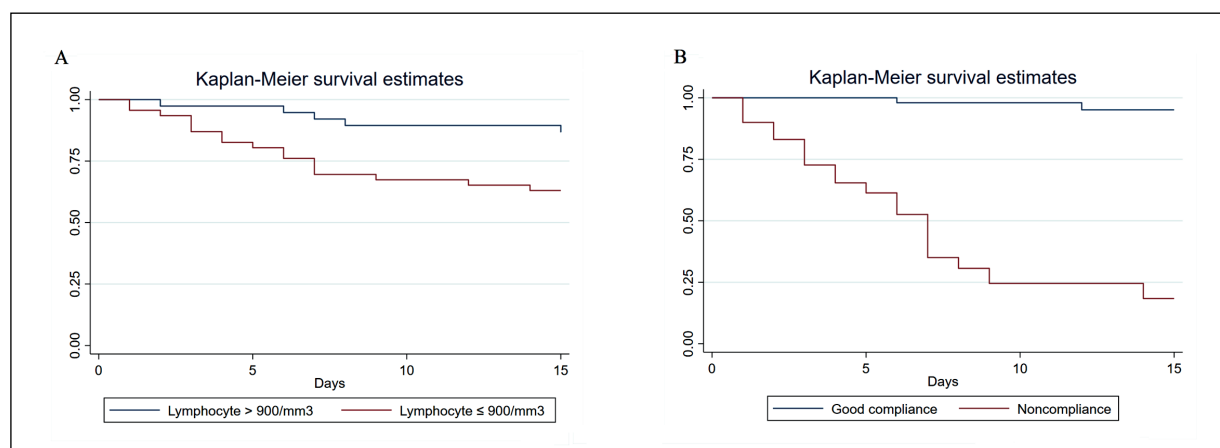


Figure 1. A, Survival estimates for lymphocyte count with Kaplan-Meier ($p = 0.0126$, calculated with Log-Rank test). B, survival estimates by patients' compliance with Kaplan-Meier ($p < 0.001$ calculated with Log-Rank test).

ity caused by COVID-19 could be alleviated by the early antiviral treatment²⁷, many patients were hospitalized after a long time since the symptoms start. Therefore, our results suggest that more efforts need to be made to avoid delays in therapy starts. A comprehensive intervention should include home care-based testing for SARS-CoV-2, prompt initiation of antiviral, supportive therapy, and close monitoring of respiratory function. This approach could reduce the progression of COVID-19, avoid unnecessary hospitalizations, and identify the patients who could benefit from early inpatient management.

Regarding laboratory findings, He et al²⁸ and Chu et al²⁹ showed that in SARS and MERS, lymphopenia was common and correlated with a severe outcome (Figure 1A). They suggested the capacity by the two viruses to infect the T-cells and cause apoptosis with the activation of both the extrinsic and intrinsic pathways. Chen et al²⁵ showed how even in SARS-CoV-2, the virus could affect lymphocytes, particularly CD4+ and CD8+ T cells, resulting in lymphopenia.

According to the previous studies^{9,25,28,29}, lymphopenia was correlated with a high risk of death in our cohort, especially in the first 15 days after admission. Further studies are needed to clarify the lymphocytes' role in COVID-19 pathogenesis, paying particular attention to the different subpopulations' involvement.

Another interesting predictor of death highlighted by our results has been patients' compliance. People with better compliance showed higher rates of survival, compared with patients with lower ones. Kaplan-Meier's estimates on

the probability of survival by compliance status, showed how non-compliant patients had a significant early death risk (Figure 1B). Probably, given the particularities of the isolation setting characterized by programmed room accesses by the health-care providers, and the high number of patients admitted, the patient/nurse-doctor communication could represent a fundamental bridge for better care in such a challenging setting.

Remote monitoring, including close-circuit video cameras in all patients' rooms, may be of great help in such critical conditions.

Conclusions

Our results are, in part, confirmatory and, in part, original. Moreover, our study represents the first real-life Italian experience. We showed how a lymphocytes count <900 cells/mm³ and moderate ARDS were risk factors for a negative outcome. Furthermore, we showed that non-compliant patients had an early increased risk of death. More efforts are needed to adequately care for these patients in a so complicated setting as COVID-19 management. Undoubtedly, further investigations are needed to identify the correct treatment timing and drug choice based on symptoms onset and clinical features.

Conflict of Interest

Andrea De Vito, Nicholas Geremia, Vito Fiore, Elija Princic, Sergio Babudieri, and Giordano Madeddu declared that there were no competing interests.

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