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Impact of the Main Pharmacological Option and Risk Factors for COVID-19 Disease Progression in Hospitalized Patients in Northern Italy: A Single-Center Retrospective Study

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Impact of the Main Pharmacological Option and Risk Factors for COVID-19 Disease Progression in Hospitalized Patients in Northern Italy: A Single-Center Retrospective Study

Cesare Bolla [1,*,†], Serena Penpa [2], Eleonora Sarchi [1], Andrea Schimmenti [1], Giorgia Piceni [2], Marinella Bertolotti [2], Simona Panzacchi [3], Daniele Mandrioli [3], Guido Chichino [1] and Antonio Maconi [2]

[1] Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo - Alessandria (Italy),
[2] Research Training Innovation Infrastructure, Research and Innovation Department, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo – Alessandria (Italy),
[3] Cesare Maltoni Cancer Research Center Ramazzini Institute - Bologna (Italy)
* Correspondence:
† These authors contributed equally to this work.

Abstract: Severe Acute Respiratory Disease Syndrome Coronavirus 2 has caused a global pandemic. Monoclonal antibodies, antiviral therapy (Remdesivir) and immunomodulatory agents represent one of the most promising therapies to prevent disease progression and reduce the relative risk of severe COVID-19. The aim of this study was to evaluate the impact on the disease progression of the main pharmacological options approved for the patients admitted in hospital with acute COVID-19 infection, according to their vaccination status. We conducted a study including adult patients with confirmed COVID-19 admitted to the Infectious Diseases Unit of Alessandria's Hospital in Italy, from October 2021 to March 2022. 102 patients were included in the analysis. The mean age was 69.2 ±15.4 years, 66.7% were males. According to the internal hospital's guidelines, 47.06% patients with mild to moderate disease were treated with mAbs, 45.10% were treated with Remdesivir, of which 10.78% received combination therapy with mAbs. The most frequently complications were pneumonia (18.63%), respiratory failure (15.68%) and acute respiratory distress syndrome (13.72%). The mean length of hospitalization was 13.42 (±10.90) days and the mortality rate was 11.76%. The treatment with mAbs and immunomodulatory therapy for mild to moderate COVID-19 infection seem to be effective to improve the outcome reducing disease progression and mortality. C-reactive protein (CRP) and ferritin could be considered a good inflammatory marker of disease progression.

Keywords: COVID-19; disease progression; vaccination; antiviral agents; therapeutics

1. Introduction

Since December 2019, Coronavirus disease 2019 (COVID-19) has caused a pandemic with over 6 million deaths and millions of infections worldwide (1).

COVID-19 is an infection caused by the virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family. In humans, coronavirus infections may be asymptomatic or accompanied by fever, cough, shortness of breath and gastrointestinal irritation. In certain cases, such as in elderly and immunocompromised individuals, coronavirus infections may lead to severe pneumonia and

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subsequently, the death of the patient (2). COVID-19 symptoms are observed approximately 5 days after incubation(7). The median time of symptom onset from COVID-19 incubation is 5.1 days, and those infected display symptoms for an average of 11.5 days (3).

The dominant route of transmission of SARS-CoV-2 is respiratory. Particularly through droplets (generated by coughing, sneezing or even talking) andthrough aerosols (4). Infection through contact with contaminated surfaces and/or objects is infrequent (in the range of about 1:10,000) (5, 6).

The pathogenesis of COVID-19 is associated with two primary processes: the replication of SARS-CoV-2 and the dysregulated immune response to the infection (7). Consequently, the newly released treatments for COVID-19 have two targets: the virus itself (anti-viral drugs) and the immune system (immune-modulators).

In response to this unprecedented situation, a global effort has been made to develop new vaccines and effective treatments within a remarkably short timeframe (8).

The standard of care (SOC), according to the recent World Health Organization (WHO) guidelines, released at the beginning of 2023, for mild symptomatic patients includes antipyretics, adequate nutrition and appropriate rehydration; for those with severe symptoms, guidelines recommend administration of supplemental oxygen therapy (1).

The antiviral therapy available today, recommended in hospitalized patients, is Remdesivir. Regarding efficacy, Remdesivir has been evaluated for both severe and non-severe COVID-19 in hospitalized patients (9).

Moreover, Remdesivir is an anti-viral drug that inhibits the enzyme polymerase nsp12 which is crucial for SARS-CoV-2 replication. The early beginning (within 7-10 days, in the first stage of the disease when viral replication is predominant) of Remdesivir in people with SARS-CoV-2 pneumoniae requiring low oxygen flow showed the reduction of disease progression (need for high oxygen flow and/or intubation) in addition to reducing the duration of hospitalization. Nowadays, Remdesivir is the only anti-viral drug that has proven effective in patients whit SARS-CoV-2 pneumoniae and it is indicated in all guidelines (WHO, NIH (1, 9). The duration of treatment should be at least 5 days and should not exceed 10 days (10, 11).

Furthermore, in patients with SARS-CoV-2 pneumoniae requiring oxygen supplementation (regardless if low or high flow) has been demonstrated the efficacy of corticosteroid treatment. The RECOVERY trial showed a reduction of mortality in patient hospitalized with SARS-CoV-2 pneumoniae requiring oxygen supplementation in treatment with desametasone 6 mg/die for 10 days versus patients in treatment with the standard of care. No benefit was observed in patient without oxygen supplementation. Therefore, desametasone 6 mg/die is recommended in all patients with SARS-CoV-2 pneumoniae requiring oxygen supplementation, regardless the stage of infection and if low or high flow of oxygen (12).

For patients with mild to moderate symptoms, who do not require supplemental oxygen but are at high risk for clinical progression, neutralizing monoclonal antibodies (mAbs) to SARS-CoV-2 are available option in addition to standard treatment. These antibodies specifically target the spike protein of SARS-CoV-2. However, their effectiveness can vary significantly depending on the variants and sub-variants of the virus, and they are not recommended when a known resistant variant is predominant in a geographic area. Monoclonal antibodies available for the treatment are bamlanivimab in combination with etesevimab. In vitro experiments revealed that etesevimab binds to an epitope other than bamlanivimab and neutralizes resistant variants with mutations in the epitope bound by bamlanivimab. In phase 2 of the BLAZE-1 study, the bamlanivimab/etesevimab combination demonstrated a significant reduction in viral load SARS-CoV-2 compared with placebo (13). According to Cochrane Systematic reviews, for pre exposure prophylaxis (PrEP), there is a decrease in development of clinical COVID-19 symptoms, infection with SARS-CoV-2 and admission to hospital (low certainty) with tixagevimab/cilgavimab. There is low certainty of a decrease in infection with SARS-CoV-2 and development of clinical COVID-19 symptoms with casirivimab/imdevimab. For post exposure prophylaxis (PEP), there is high certainty of a decrease in infection with SARS-CoV-2,

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development of clinical COVID-19 symptoms with casirivimab/imdevimab. Although there is high to moderate certainty evidence for some outcomes, it is insufficient to draw meaningful conclusions. These findings only apply to people unvaccinated against COVID-19. They are only applicable to the variants prevailing during the study and not to other variants (e.g. Omicron) (14).

Conversely, for hospitalized COVID-19 patients who require increasing oxygen supplementation, immunomodulatory agents such as tocilizumab and baricitinib are recommended in addition to standard care, for better patient recovery. Tocilizumab is an antagonist of the interleukin-6 (IL-6) receptor, a recombinant monoclonal antibody with a high affinity with IL-6, which in turn prevents its binding to its original receptor, reducing the inflammatory response (15). Baricitinib, a Janus Kinase (JAK) inhibitor, was tested in combination with remdesivir in the Adaptive Covid-19 Treatment Trial-2 (ACTT-2) and was shown to improve time to recovery compared with remdesivir alone (16). Both medications ultimately modulate the immune response during COVID-19 disease. Several trials have investigated their efficacy in patients requiring oxygen supplementation, particularly those with increasing oxygen flow, either with or without corticosteroids. However, none of them have clearly demonstrated their benefits in terms of positive outcomes in a specific subgroup of patients.

Some RCTs have reported that tocilizumab was not effective in preventing intubation or death in moderately ill hospitalized patients with COVID-19 (17-20). However, several studies have found that tocilizumab may be a safe and promising therapeutic option for use in combination with standard care to prevent disease progression in hospitalized patients with moderate COVID-19 and hyperinflammation (21-25). In a recent systematic review and meta-analysis (26) about efficacy of baricitinib, it was found around up to 94% probability that baricitinib is non inferior to tocilizumab.

Several systematic reviews of COVID-19 efficacy and effectiveness studies have been published, but none of them have evaluated the duration of protection of COVID-19 vaccines (27-32). Recently, a systematic review and meta-regression showed that COVID-19 vaccine efficacy or effectiveness against severe disease remained high, although it did decrease somewhat by 6 months after full vaccination. By contrast, vaccine efficacy or effectiveness against infection and symptomatic disease decreased approximately 20–30 percentage points by 6 months. The decrease in vaccine efficacy or effectiveness is likely caused by, at least in part, waning immunity, although an effect of bias cannot be ruled out (33)

The purpose of our study was to evaluate the impact on the disease progression of the main pharmacological options approved for the patients admitted in hospital with acute COVID-19 infection, according to their vaccination status. Furthermore, we aimed to contribute to the existing knowledge about the clinical features of SARS-CoV-2 infection by investigating the correlation between risk factors of clinical evolution and treatment outcome.

2. Materials and Methods

2.1. Design and Participants

We conducted a retrospective, single centre observational study including adult patients with laboratory-confirmed SARS-CoV-2 infection admitted to the Infectious Diseases Unit of the "SS Antonio e Biagio e Cesare Arrigo" Alessandria's Hospital in the Piedmont Region in northern Italy, from October 2021 to March 2022.

The inclusion criteria were as follow: hospitalized adult male or female subjects, aged ≥ 18 years old, positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and treatment with monoclonal antibodies, approved for the circulating covid variants up to September 2023 (Bamlanivimab / Etesevimab, Casirivimab / Imdevimab, Sotrovimab), Remdesivir or immunomodulator agents (Tocilizumab, Baricitinib). The exclusion criteria were COVID-19

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positivity greater than 10 days and acute kidney injury and chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30 ml/min.

All data of hospitalized patients was obtained from the electronic medical records system (TrackCare) as well as paper-based medical records and collected using an electronic case report form (eCRF). The electronic case report form (eCRF) was developed using the Research Electronic Data Capture (REDCap) platform, a user-friendly web interface that enables the rapid design, construction and deployment of databases for structured data collection. All data was anonymized in accordance with data protection regulations. The information collected included: demographic data, comorbidities, COVID-19 signs and symptoms, clinical presentation on admission, vaccination status, treatment received, need for supplemental oxygen therapy (including noninvasive or invasive ventilation), hospitalization related complications and patient outcomes (discharge or mortality). For each patient, a score on the World Health Organization (WHO) ordinal scale was assigned to assess the disease severity of patients with COVID-19 on admission. This ordinal scale classifies patients into eight categories, ranging from Category 0 (no clinical or virological evidence of infection) to Category 8 (death). The intermediate categories reflect different levels of disease severity, the categories 0 to 2 refer specifically to ambulatory patients, while categories 3 to 7 related to hospitalized patients with moderate and severe symptoms. In detail, category 3 indicates patients who don't require oxygen therapy, category 4 requires the use of supplemental oxygen, such as an oxygen mask or nasal cannula. Category 5 presents a progressive deterioration of respiratory that include non-invasive mechanical ventilation (NIMV) or high flow nasal cannula (HFNC). Category 6 involves intubation and invasive mechanical ventilation (IMV). Category 7 requires IMV along with additional support, such as pressors or extracardiac membranous oxygenation (ECMO), category 8 represents patient death.

The operational methods applied to take charge of the patient with COVID-19 and to intercept and initiate patients eligible for monoclonal antibody treatment in a timely manner follow the internal guidelines DVA 115 (Document of Corporate Validity).This study population was divided into 4 groups: patients treated with monoclonal antibodies monotherapy, patients treated with remdesivir monotherapy, patients treated with immunomodulatory antibody therapy and patients treated with monoclonal antibodies in combination with remdesivir. This last association includes drugs that have demonstrated their efficacy in the early stage of the disease and it speed viral elimination. In particular, the rate of virological response was higher in patients treated with a combination including mAbs and antiviral drugs, especially in immunosuppressed patients (34).

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the local Ethical Committee of "SS Antonio e Biagio e Cesare Arrigo" Alessandria's Hospital, protocol n° ASO.MInf.22.02.

2.2. Statistical Analysis

Descriptive statistics were produced for the demographic and clinical characteristics of the patients, using the mean and standard deviation for continuous variables and numbers and percentages for categorical variables. A comparison, of the different variables, between patients who had a progression (understood as a transition from 0-3 to 4-5 WHO category or a further worsening to 6-8 WHO category that it means intubation and admission to an intensive care unit (ICU)) up to death and those who did not, was performed for continuous variables and using The Pearson's test (Fisher's exact test where appropriate) or the t test for evaluate differences of means for continuous variables.

The logistic regression model, a non-linear regression model used when the dependent variable is of a dichotomous type (pre-processed or not) was used to separately evaluate the different types of variables, so as to establish the probability with which the observation can generate one or the other value of the dependent variable. In detail, we performed a Logit Model considering disease progression as a dependent and dichotomous study variable (Y). Disease progression was entered as a dichotomous variable yes or no (according to the parameters chosen). The other variables (or regressors) entered into the model were of various magnitudes (dichotomous or continuous). When

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the coefficient of the explanatory variable (or regressor) is positive then the Odds Ratio (OR) is >1 and it can be considered a risk factor (there is more probability of our event); if the coefficient of the explanatory variable (or regressor) is negative then OR will be <1 and that variable can be considered as protective for our variable. If the coefficient is very close to zero the variable can be neglected.

The significance value was set at $p<0.05$. The statistical analysis was conducted using Stata18/BE software (StataCorp LLC, Texas 77845 USA).

3. Results

3.1. Demographic and Global Characteristics of the Study Population

Between October 1st 2021 to March 31th, 2022, a total of 102 hospitalized COVID-19 patients with laboratory confirmed SARS-CoV-2 infection were included in this study. The mean age was 69.2 ± 15.4 years (minimum 19, maximum 98 years), 68 (66.7%) were male and 34 (33.7%) were woman. The most common comorbidities were arterial hypertension, [42 (41.2%)], cardiovascular disease [16 (15.7%)], diabetes mellitus [20 (19.6%)], tumor [17 (16.7%)], chronic renal insufficiency [11 (10.8%)], dyslipidemia [8 (7.8%)] and 13 (12.7%) of hospitalized patients had no underlying conditions. At the time of admission to the hospital, the most frequent signs and symptoms were fever [49 (48.04%)], dyspnea [42 (41.18%)], asthenia [20 (19.61%)], dry cough [12 (11.76%)] and muscle pain [10 (9.80%)].

Table 1. Demographic and global characteristics of the study population.

Variable	n = 102
Epidemiological data	
Female, n° (%)	34 (33.3%)
Male, n° (%)	68 (66.67%)
Age (years), mean ± SD	69.2 (±15.4)
Risk factors and comorbidities, n (%)	
None	13 (12.8%)
Arterial hypertension	42 (41.2%)
Cardiovascular disease	16 (15.7%)
Diabetes mellitus	20 (19.6%)
Tumor	17 (16.7%)
Chronic obstructive pulmonary disease (COPD)	5 (4.9%)
Obesity	5 (4.9%)
Dyslipidemia	8 (7.8%)
Dementia	4 (3.9%)
HIV infection	1 (1%)
Chronic renal insufficiency	11 (10.8%)
Vaccination status, n(%)	
One dose of anti-SARC-CoV2 vaccine	9 (8,82%)
Two doses of anti-SARC-CoV2 vaccine	19 (18,6%)
Fully vaccinated (Three doses of anti-SARC-CoV2 vaccine)	14 (13,7%)
No dose of anti-SARC-CoV2 vaccine	60 (58.8%)

3.2. Clinical, Analytical and Pharmacological Aspects of the Acute Infection

As reported in Table 2, 35 (34.31%) patients had an eight-category ordinal scale of 3; 66 (64.71%) had a score of 4 and one patient had a score of 5. 58.8% of the patients was unvaccinated (n=60), 13.72% (n=14) received a full vaccination with three doses of anti-SARC-CoV2 vaccine, 18,63% (n=19) received a double dose and 8.8% (n=9) received a single dose.

According to the internal hospital's guidelines on the management of covid 19 infection, in addition to standard of care including steroids in case of radiologically confirmed pneumonia in hospitalized patients requiring oxygen supplementation and prophylactic dose of heparin, 48

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(47.06%) patients with mild to moderate disease were treated with mAbs [8 (16.67%) with Bamlanivimab / Etesevimab, 29 (60.42%) with Casirivimab / Imdevimab and 11 (22.78%) with Sotrovimab], 46 (45.10%) were treated with Remdesivir, of which 11 (10.78%) received combination therapy with mAbs.

Always according to the aforementioned guidelines, the patients who were receiving dexamethasone and who had rapidly increasing oxygen needs and systemic inflammation were treated with immunomodulatory agents, overall, 29 (28.43%). Moreover, 7 (24.14%) were treated with Tocilizumab and 22 (75.86%) with Baricitinib. Among aforementioned 29 patients, 19 (18.62%) with severe SARS-CoV-2 infection at admission were treated only with immunomodulatory agents [5 (26.32%) with Tocilizumab and 14 (73.68%) with Baricitinib].

Table 2. Clinical, analytical and pharmacological aspects of the acute infection.

Variable	n = 102
Asymptomatic	1 (0.98%)
Fever	49 (48.04%)
Chills	4 (3.92%)
Dry cough	12 (11.76%)
Cough with mucus (phlegm)	3 (2.94%)
Rhinorrhea	3 (2.94%)
Headache	3 (2.94%)
Muscle pain	10 (9.80%)
Asthenia	20 (19.61%)
Nausea	4 (3.92%)
Vomiting	2 (1.96%)
Diarrhea	4 (3.92%)
Dyspnea	42 (41.18%)
Ageusia	1 (0.98%)
Anosmia	2 (1.96%)
Chest pain	3 (2.94%)
Pharyngodynia	6 (5.88%)
WHO Ordinal Scale at hospitalization, n (%)	
WHO ordinal scale 3	35 (34.31)
WHO ordinal scale 4	66 (64.71)
WHO ordinal scale 5	1 (0.98%)
Treated with monoclonal antibody, n (%)	48 (47.06%)
Bamlanivimab / Etesevimab	8 (16.67 %)
Casirivimab / Imdevimab	29 (60.42%)
Sotrovimab	11 (22.92%)
Treated with remdesivir, n (%)	46 (45.10%)
Combination therapy (mAbs plus Remdesivir), n (%)	11 (10.78%)
Immunomodulatory agent, n (%)	29 (28.43%)
Tocilizumab	7 (24.14%)
Baricitinib	22 (75.86%)
Treatment included in standard of care, n (%)	
Corticosteroids	73 (71.57%)
Low molecular weight heparin/other anticoagulants	77 (75.49%)
Respiratory therapy	
Low-flow oxygen therapy - nasal cannula and Venturi mask, n(%)	77 (75.49%)
Low-flow oxygen therapy - nasal cannula and Venturi mask - days mean ± SD	5.62 (±4.26)
High-flow therapy - high-flow nasal cannula and CPAP, n(%)	42 (41.18%)

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High-flow therapy - high-flow nasal cannula and CPAP - days, mean ± SD	11.14 (±7.50)

3.3. Outcome

During the hospitalization 11 patients with mild to moderate infection developed disease progression, necessitating the utilization of immunomodulatory agents, HFNC oxygen therapy and in 3 cases the endotracheal intubation.

The most frequently complications were pneumonia in 19 patients (18.63%), followed by respiratory failure in 16 patients (15.68%) and acute respiratory distress syndrome in 14 patients (13.72%).

The mean length of hospitalization was 13.42 (± 10.90) days and the in-hospital mortality rate was 11.76%, whereas, the three-month post-discharge mortality rate was 5.88%.

Table 3. Outcome.

Variable	n = 102
Septic shock	0
Acute respiratory distress syndrome (ARDS)	14 (13.73%)
Acute kidney injury	3 (2.94%)
Hemorrhage	0
Rhabdomyolysis	0
Pneumonia	19 (18.63%)
Heart failure	2 (1.96%)
Respiratory failure	16 (15.69%)
Hypoalbuminemia	1 (0.98%)
Acidosis	0
Sepsis	4 (3.92%)
Acute cardiac injury	1 (0.98%)
Pulmonary embolism	2 (1.96%)
Deep vein thrombosis	2 (1.96%)
Cachexia	5 (4.9%)
None	54 (52.94%)
Access to the Intensive Care Unit (ICU)—n (%)	3 (2.94 %)
In-hospital mortality—n (%)	12 (11.76%)
Three-month post-discharge mortality—n (%)	6 (5.88 %)
Length of hospital stay—days, mean ± SD	13.42 (±10.90)

To multivariate analysis, age has a coefficient of 0.034 and therefore positive although very close to 0, so it is relatively negligible. Sex, on the other hand, was not considered as a regressor of interest after an initial analysis because it was not significant with either univariate or multivariate analysis.

Since the regressors are very many and very different from each other, both biologically and numerically, different models were run for 'categories' of regressors namely: clinical data, symptoms, risk factor, WHO score, complications during hospitalization, treatments, and indices of inflammation. Univariate and multivariate analysis evidenced that cardiovascular disease is the only comorbidity that affects progression (respectively, p=0.038 and p=0.012). Out of a total of 56 patients with evidence of progression, only 5 are affected by cardiovascular disease, in fact the logistic regression coefficient is negative.

No statistically significant differences were evidenced in patients with a WHO score admission of 3 (35 cases) compared to a WHO score admission of 66 cases or a WHO score admission of 5 (only 1 case). Additionally, 42 of the 56 patients with progression were not treated with mAbs, while 14 of 56 have received mAbs treatment; thus in our case series, those who received monoclonal antibody treatment as monotherapy progressed less. Univariate analysis showed a clear statistically significant (P=0.009) modulation of progression with or without monoclonal antibody treatment; this result is

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confirmed by logistic regression where the coefficient is negative (-0.668), underlining the negative association between progression and antibody treatment or in other words a protective effect of this particular treatment.

The analysis also shows that 75% of progression cases (42 of 56) didn't have acute respiratory distress syndrome (ARDS), while the remaining 25% (14 of 56) got it; but among those who do not have progression (total cases 46), none have ARDS, thus 100% of cases. Similar results were obtained considering respiratory failure, where 41 of 56 patients with progression (73%) had no respiratory failure while 12 of 56 (27%) did, but among the patients who did not experience progression only one also showed respiratory failure (2%).

The laboratory biomarkers were analyzed both considering a threshold for each parameter with a logistic regression model and also with a general mixed regression model, without threshold, due to the lack of observations in some of the analyzed biomarkers (no observations or 1 per some parameters with respect to the main output or the progression).

Only the univariate analysis shows that ferritin and c-reactive protein can be considered as predictors of progression since the patients who had progression had higher mean ferritin (835.63 vs 313.27 – 24 cases) and a higher mean c-reactive protein (8.23 vs 5.19 – 50 cases) values. Considering a limit of 500 ng/ml for ferritin, the number of patients with ferritin above this threshold, out of the 24 with progression, is 14. Considering a limit of 10 mg/dl for pcr the number of patients with pcr above this threshold, out of the 50 with progression, is 18. Procalcitonin: only 1 case of very high value (threshold 0.5 ng/ml) of procalcitonin was observed above the 20 cases with progression. Both univariate and multivariate analysis showed that the treatment with immunomodulatory agents for mild to moderate COVID-19 infection can be a protective factor since in the Table 2 the coefficient of the regression in the multivariate analysis is 2.718, which is positive and much greater than 1.

Table 4. Predictors of COVID-19 progression.

	Univariate Analysis	**Multivariate Analysis**		
	p-Value	**coefficient**	**95% CI**	**p-Value**
Age	0.238	**0.034**	**(0.003 - 0.066)**	**0.033**
Sex	0.143	0.890	(-0.064 - 1.844)	0.067
Risk factors and comorbidities				
Arterial hypertension	0.981	-0.276	(-1.306 - 0.754)	0.599
Cardiovascular disease	**0.038**	**-1.776**	**(-3.156 - 0.395)**	**0.012**
Diabetes mellitus	0.992	-0.224	(-1.354 – 0.906)	0.697
Tumor	0.859	-0.341	(-1.584 – 0.0902)	0.591
Chronic obstructive pulmonary disease (COPD)	1.000	0.242	(-2.029 - 2.514)	0.834
Obesity	0.375	0.905	(-1.394 - 3.203)	0.441
Dyslipidemia	0.727	1.160	(-0.686 - 3.006)	0.218
Dementia	1.000	-0.060	(-2.260 - 2.141)	0.958
HIV infection	1.000	-	-	-
Chronic renal insufficiency	0.337	1.286	(-0.351 - 2.922)	0.124
Vaccination Status				
No dose of anti-SARC-CoV2 vaccine	-	-	-	-
At least one dose of anti-SARC-CoV2 vaccine	0.981	1.689	(-0.499 - 3.878)	0.130
WHO score admission				
WHO SCORE 3	0.455	0.284	(-0.547 - 1.115)	0.503
WHO SCORE 4	0.607	-	-	-
WHO SCORE 5	0.268	-	-	-
Treatment				
Monoclonal antibody monotherapy	**0.009**	- 0.668	(-1.608 - 0.272)	0.164
Remdesivir monotherapy	1.000	-	-	-

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Combination Monoclonal antibody plus remdesivir	0.505	- 0.354	(-1.715 - 1.006)	0.610
Immunomodulatory agent	**<0.001**	**2.718**	**(0.598 - 4.839)**	**0.012**
Infections	0.099	-	-	-
Laboratory biomarkers				
C-reactive protein (CRP)	**0.015**	0.0029483	(-0.0378228 - 0.0437194)	0.887
Procalcitonin (PCT)	0.330	0.2984671	(-0.247066 - 0.8440001)	0.284
D-dimer	0.999	0.0001413	(0.0115953 0.8362068)	0.044
LDH (Lactate Dehydrogenase)	0.061	0.423901	(-0.0006764 - 0.0009591)	0.735
Ferritin	**0.001**	**0.0005859**	(0.0002128 - 0.0009591)	**0.002**
WBC (White Blood Cells)	0.278	-0.0000103	(-0.0000821 - 0.0000616)	0.779
Lymphocytes	0.267	-0.0190189	(-0.0474709 - 0.009433)	0.190

4. Discussion

Several therapeutical options are available both for patients with non-severe and for those ones with life threatening COVID-19 infection. The choice depends on the severity of disease, patients comorbidities and co-medication, risk of disease progression and time from onset of symptoms (35). Pharmacological treatment options range from steroids if severe and / or critical infection is diagnosed, targeted antiviral drugs (first of all remdesivir) in case of mild symptoms in patients at high risk of hospitalization and / or progression to severe disease, up to baricitinib, Janus kinase inhibitors, and tocilizumab, IL-6 receptor blockers, if severe and critical infection is diagnosed (36). Remdesivir inhibits the enzyme polymerase nsp12 and consequently impedes SARS-CoV-2 replication, this is very important in the first stage of infection, the "viral response phase", as reducing viral burden. This is the reason why you need to start the treatment early, before the host inflammatory response is established, to reduce the risk of disease progression. The use of Janus kinase inhibitors (baricitinib) and IL-6 receptor blockers (tocilizumab) is crucial in the late stage of infection, the "hyperinflammation phase", to reduce the host inflammatory response and the consequent damages due to cytokine storm (37(39), 38(40)).

Regarding to neutralizing monoclonal antibodies, they are projected to recognize a specific part of spike protein of SARS-CoV-2. This protein is used by the virus to enter the human cell and then replicate. So, the neutralizing monoclonal antibodies bind to this protein and prevent the entry into the host cells of the virus. As remdesivir also this therapeutic strategy is important in the first stage of infection (39(41)). Despite the initial recommendation for patients with non-severe COVID-19 infection, now are not considered as treatment option anymore due to the recent data showing little or not in vitro neutralization activity at all with currently circulating SARS-CoV-2 variants and sub variants (35, 40(42)).

The global campaign of vaccination, since 2021, drastically decreased the spread of infection and mortality, especially among frail patients. Most vaccines reduce, or likely reduce, the proportion of people with confirmed symptomatic COVID-19 and, for some, there is high-certainty evidence that they reduce severe or critical disease (41).

In our study, patients with mild symptoms and early treated with mAbs or mAbs in combination with remdesivir, had a lower mortality rate despite their risk factors as age, cardiovascular disease, respiratory disease, metabolic disease or cancer and a low rate of progression to severe disease.

Only 7% had such a worsening of their symptoms as to require additional treatment with baricitinib or tocilizumab. In particular, those-ones treated with remdesivir had better outcome than those treated with mAbs and required less oxygen supplementation, confirming the effectiveness of the drug if given very early, and highlighting the little or no efficacy of mAbs on new viral variants.

Moreover Pepera et al., in their review show that preexisting cardiovascular disease (CVD) is associated with worse outcomes and increased risk of mortality in patients with COVID-19 (42); this result is in line with what we observed in our study too.

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Even in patients without cardiovascular disease at diagnosis there is a possibility of developing myocardial damage by three main mechanisms: 1. Myocardial dysfunction given by direct viral action on cardiomyocytes mediated by ACE2; 2. The excessive inflammatory response and 3. Hypoxia and oxidative stress resulting in the need for increased oxygen resulting in myocardial necrosis. This leads to arrhythmias, principally atrial fibrillation (AF), increased QTc, myocardial ischemia to uninjured coronary arteries. In addition, patients admitted to the intensive care unit have higher incidence of lethal cardiac events. Apparently increasing in patients with severe COVID-19 is the incidence of stress related cardiac myopathies such as Takotsubo syndrome (37). Given the reported data in the hospitalized patient with severe COVID-19 and inflammation, attention to cardiac manifestations should be kept high, and collaboration with cardiology colleagues would be optimal. However, any extrapulmonary manifestations caused by SARS-CoV-2 should be considered.

As reflected in the literature, antivirals, monoclonal antibody such as Bamlanivimab, Etesevimab, Casirivimab, Imdevimab, for a few variants, and immunomodulatory agents appears to have positive effects on the treatment of COVID-19 patients but, in general, no solid conclusion has been obtained from the results of the clinical trials and subsequent randomized studies are needed to warrant the determination of their usefulness (24). In our study, mAb monotherapy and immunomodulatory agents can be considered as protective factors since the univariate analysis showed that patient who received the treatment progress less. Conversely, patients who received high flows oxygen therapy are more likely to die, probably because of their more severe disease.

Concerning laboratory values, only univariate analysis showed that higher levels of c-reactive protein (p=0.015) and ferritin (p=0.001) significantly affect disease progression; this is probably because of the few cases considered in the study.

When we analysed the difference between vaccinated and not-vaccinated individuals in the group of patients with mild symptoms, We didn't had a significant difference in mortality. In our case series, the correlation between the vaccination status and clinical course and outcome of the disease was not statistically significant. There was no difference according to the type of vaccine as well.

Our Study Has Some Limitations

First of all, the monocentric design of the study and the small sample size which may make it difficult the interpretation of the results and which may have limited our conclusions and contributed to the exploratory nature of this study. The single-center nature of the study is partially justified by the fact that the Hospital SS. Antonio and Biagio and Cesare Arrigo of Alessandria is a HUB center deputed to the storage and administration of the drugs analyzed in this paper. In addition, the Infectious Diseases Unit and the Pharmacy of this hospital are the referral facilities for territorial health agencies without an infectious diseases department. Moreover, the Alessandria's hospital was chosen because the authors work there, and it was thus possible to select patients who were also being followed clinically by the authors themselves. In addition, many patients with Sars-CoV-2 infection were hospitalized during the period described in the study, and therefore it was possible to select a cohort using the criteria listed below.

Secondly, the results are based on retrospective study which has important limitations in the quality and quantity of data available for analysis, but which assess outcomes in regular clinical practice, thereby reflecting real adherence to treatment/intervention.

Another important limitation of our research is the absence of control group. We were in the midst of a pandemic, an emergency situation caused by a new potentially lethal virus, against which we had so few weapons. So, it was not ethically possible to have a control group.

In addition, we included only the patients admitted in the Infectious Diseases department where the staff was well trained in COVID-19 management.

However, our research described a real-life situation, reporting clinical characteristics and risk factors related to progression disease in a cohort of patients hospitalized for COVID-19. that could contribute to future evaluation of these drugs.

It is imperative to underscore the ever-evolving nature of our understanding of COVID-19. As newer strains emerge and the global community continues to adapt, the therapeutic landscape will also likely undergo transformations. The effectiveness of the treatments discussed in this study is, to a certain extent, contingent on the predominant strains circulating during the study period. Thus, continuous monitoring and updating of treatment protocols are paramount as the virus evolves.

Another dimension worth considering is the long-term effects, or "long COVID," experienced by a subset of patients. While our study primarily focused on immediate outcomes and disease progression, future research should delve deeper into the prolonged effects of the infection and how our therapeutic interventions might influence these outcomes.

In conclusion, we observed that the treatment with mAbs and immunomodulatory therapy for mild to moderate COVID-19 infection seem to be effective to improve the outcome reducing disease progression and mortality. Moreover, the analysis of our data proves that CRP and ferritin could be considered a good inflammatory marker of disease progression.

Further multicentric studies with a bigger sample size and a more heterogeneous population are needed to confirm and generalize our results.

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Institutional Review Board Statement: This study was conducted according to the principles of good clinical practice and the Declaration of Helsinki. It is approved by the Ethics Committee of Azienda Ospedaliera Nazionale SS Antonio e Biagio e Cesare Arrigo, protocol number ASO.MInf.22.02). This is an observational retrospective study. According to Local Ethics Committee recommendations, patients provided a signed consent form for retrospective studies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets analysed during the current study are not publicly available due to privacy protection reasons but are available from the corresponding author on reasonable request.

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