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Article

Effectiveness and Tolerability of Early Treatment with Monoclonal Antibodies against SARS-Cov-2: Results from A Real-Life Study before Omicron Surge

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Abstract: Despite the lightning-fast advances in the management of SARS-CoV after 2 years of pandemic, COVID-19 continues to pose a challenge for fragile patients, who could benefit from early administration of monoclonal antibodies (mAbs) to reduce the risk of severe disease progression. We conducted a prospective study to evaluate effectiveness of mAbs against SARS-CoV-2 among patients at risk for severe disease progression, namely elderly and those with comorbidities, before the omicron variant surge. Patients were treated with either casirivimab/imdevimab, sotrovimab, and bamlanivimab/etesevimab. The rates and risk factos for clinical worsening, hospitalization, ICU admission and death (unfavourable outcomes) were evaluated. A stratified analysis according to the presence of SARS-CoV-2 IgG was also performed. Among 185 included patients, we showed low rates of unfavorable outcomes (9.2%), which were more frequent in patients with chronic kidney disease (aOR: 10.44, 95CI: 1.73-63.03; $p<0.05$) and basal D-dimer serum concentrations >600 ng/ml (aOR 21.74, 95CI: 1.18-397.70; $p<0.05$). Patients with negative SARS-CoV-2 serology at baseline showed higher C-reactive protein values compared with patients with positive serology ($p<0.05$) and showed a trend toward a higher admission rate to SICU and ICU compared with patients with positive serology. Our results thus showed, in a real-life setting, the efficacy of mAbs against SARS-CoV-2 before Omicron surge when the available mabs become not effective.

Keywords: Mabs; VoC; COVID-19; real-life

1. Introduction

Since the beginning of COVID-19 pandemic in 2020, plenty of efforts have been spent in the race for a cure against SARS-CoV-2. During the first months of emergency, the clinicians involved in the management of patients with COVID-19 were used to administer drugs that, later, showed no clinical efficacy, such as hydroxychloroquine, azithromycin, and lopinavir/ritonavir (1-3). The availability of several evidence-based treatments (such as corticosteroids, low-molecular-weight heparin, remdesivir and tocilizumab) changed

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the scenario in the management of severe COVID-19 (4-7). Moreover, thanks to an unprecedent sprint in the research, several vaccines were approved for the prevention of COVID-19, including both mRNA and viral vector vaccines. These vaccines showed excellent efficacy and safety profiles (8-10) and they significantly contributed in reducing the impact of the pandemic in terms of severe disease incidence, deaths and hospitalizations (11, 12). Despite the unquestionable usefulness of SARS-CoV-2 vaccination, fragile categories of patients may show a sub-optimal response to vaccines. Older patients and those with primary or secondary immunodeficiencies showed indeed an impaired antibody-mediated response after SARS-CoV-2 vaccination, remaining at high risk for severe COVID-19 (13-16). The optimal clinical management of SARS-CoV-2 infection in these patients is represented by early diagnosis and treatment with medication able to minimize the risk of progression towards severe disease. Monoclonal antibodies (mAbs) literally revolutionized the treatment of several human diseases and their use have been recently implemented in the context of SARS-CoV-2 infection, in particular for the early treatment of frail patients (17). In Italy, their use is indeed approved for patients with risk factors for severe COVID-19 (including older patients, patients with immunodeficiencies and those with chronic comorbidities) in whom a diagnosis of COVID-19 was made in the previous ten days (18). Monoclonal antibodies, and their associations, currently administrable in Italy are: casirivimab/imdevimab, bamlanivimab/etesevimab and sotrovimab. According to a recent meta-analysis, administration of mAbs may reduce the risk of hospitalization, oxygen requirement, invasive mechanical ventilation, and death (19). Nevertheless, the authors of the meta-analysis concluded that the certainty in the evidence of mAbs efficacy is low, especially among non-hospitalised individuals, and that further studies and long-term data are needed to confirm the efficacy of mAbs among patients with COVID-19. In this scenario, real-world data from patients treated with mAbs in tertiary medical centres may provide crucial data in supporting the use of these medications in frail patients with SARS-CoV-2 infection. Thus, we conducted a retrospective, observational real-life study to assess efficacy and safety of mAbs in patients with early mild/moderate disease with the presence of risk factors for progression to severe COVID-19, according to the indication provided by the Italian Drug Agency (AIFA, *Agenzia Italiana del Farmaco)*.

2. Methods

This real-life study was conducted among all inpatients and outpatients referring to the Unit of Infectious Diseases, University of Naples Federico II, Campania Region, Italy, between 1st of February 2021 to 6th of December 2021 with a diagnosis of SARS-CoV-2 infection who were treated with anti-SARS-COV-2 mAbs. The enrolment was stopped on the 6th of December 2021 when the first case of Omicron variant of concern (VoC) of SARS-CoV-2 was confirmed in Italy. No inclusion or exclusion criteria were set, in order to provide real-life results not influenced by selection criteria. However, in Italy the administration of mAbs for COVID-19 is regulated by strict indications provided by AIFA (18). Namely, only adult non-hospitalized patients (or patients hospitalized for reasons different from COVID-19) who received early treatment with mAbs were included. Early-treatment can be administered within 10 days from the diagnosis of SARS-CoV-2 infection among patients who do not require oxygen supplementation and who are at high risk for severe COVID-19 due to older age (> 60 years) or comorbidities (e.g., obesity, chronic kidney disease, cardiovascular disease, chronic pulmonary disease, immunodeficiency). These patients were treated with either casirivimab/imdevimab 600 mg + 600 mg, sotrovimab 500 mg, and bamlanivimab/etesevimab 700 mg + 1400 mg. All the enrolled patients had to provide a positive molecular oro-rhyno-pharyngeal (ORP) swab for SARS-CoV-2 (by RT-PCR) performed in the previous 10 days and were asked to sign an informed consent form on the day of mAbs administration (T0). At T0, before treatment infusion, all the enrolled patients were asked to perform blood sampling for routinary blood tests (including blood cells count, white cells count, C-reactive protein [CRP], procalcitonin [PCT], lactate dehydrogenases [LDH]) and SARS-CoV-2 IgG dosing, as well as arterial blood gas

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(ABG) analysis. Patients' refusal to perform blood sampling and ABG was not considered an exclusion criterion to reflect the real-life nature of the study. For outpatients who received early-treatment, treatment was chosen by the medical staff according to local availability of the three different mAbs associations. Since the use of mAbs in patients with SARS-CoV-2 infection was authorized as emergency treatment by AIFA and before the final approval of local and international regulatory agencies, the sorting and distribution of limited stocks of mAbs were indeed governed by the regional crisis unit. . All inpatients and outpatients also performed a follow-up visit at 7 days after mAbs administration (T1). At T1, patients underwent clinical examination, blood test analysis and ABG and they were asked for the occurrence of adverse drug reactions (ADRs). Only ADRs related to mAbs administration, as judged by the medical staff, were recorded. Outpatients were asked to contact the medical staff in case of worsening of symptoms or occurrence of ADRs. Worsening of symptoms and the occurrence of ADRs were recorded daily in inpatients, and they were asked to contact the medical staff in case of worsening of ADR after discharge. Outpatients who showed a worsening in clinical conditions were admitted as inpatients and continued the study, regularly performing the T1 follow-up visit 7 days after mAbs administration. The prevalence of occurrence of the following outcomes was collected: hospitalization (among outpatients), increase of oxygen supplementation, admission in sub-intensive care unit (SICU), admission in intensive-care unit (ICU), and death. Increase in oxygen supplementation was defined as the occurrence of desaturation requiring oxygen therapy in patients who showed valid oxygen saturation percentages at T0, or as the occurrence of desaturation in patients already in oxygen therapy at T0, which required an increase in fraction of inspired oxygen (FiO_2) or in oxygen flux. Admission to SICU, ICU and death were defined as "unfavorable outcomes". This study was conducted according to the world medical association declaration of Helsinki on ethical principles for medical research involving human subjects. The study protocol was approved by the local ethical committee (Prot. N. 88/2022 ID: N.1032)

2.1 Statistical analysis

All the variables were tested for parametric/non-parametric distribution with the Kolmogorov-Smirnov test. Comparisons between categorical dichotomous variables were performed with the χ^2 test (or with Fischer's exact test when applicable), while comparisons between quantitative variables were conducted with the T-student test (parametric variables) or the Mann-Whitney's U test (non-parametric variables). Descriptive statistical analysis was conducted on clinical and laboratory variables collected at both T0 and T1. For continuous variables, the difference between T1 and T0 were calculated and reported as "delta" (Δ). A stratified comparative analysis between T1 and T0 was conducted according to pre-infusion (at T0) serum SARS-CoV-2 IgG status (positive or negative serology). Outcomes rates and prevalence of ADRs were reported among the whole study sample and stratified according to baseline serum SARS-CoV-2 IgG status. Finally, univariate and multivariate logistic regression analysis were conducted to perform the risk analysis for the occurrence of at least one unfavorable outcome. Variables associated with at least one unfavorable outcome at the univariate analysis with p-value < 0.2 were included in the multivariate adjusted model. For all the tests, a p-value < 0.05 was considered significant. IBM SPSS© version 27 was used for statistical analysis.

3. Results

According to the AIFA criteria for monoclonal antibodies administration, 185 patients were included in the study (110 outpatients, 75 inpatients). Most patients were female 60.0%), while the median age was 57 years (IQR: 37-72) (Table 1). Most patients (115, 62.2%) had at least one comorbidity among the following: chronic kidney disease, diabetes, immunodeficiency, cardiovascular disease, chronic liver disease, chronic pulmonary disease, neurodegenerative disease, obesity, haemoglobinopathy. In detail, 58 patients

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(31.4%) had one comorbidity, 31 patients (16.8%) had 2 comorbidities, and 26 patients (14.0%) had ≥ 3 comorbidities. The most common comorbidities were obesity (22.2%), cardiovascular disease (19.5%) and immunodeficiency (13.0%). Despite the high frequency of comorbidities in the study population, only 55.7% had received SARS-CoV-2 vaccination and only 45.9% of the enrolled patients who performed serum SARS-CoV-2 IgG dosing (163, 88.1.% of the total sample) showed a positive result. The most commonly administered mAbs combination was casirivimab/imdevimab (70.3%). At the enrollment (T0), most patients (151, 81.6%) did not require oxygen supplementation and had a median P/F ratio of 462 (IQR: 452-467). At T1 the percentage of patients who required oxygen supplementation therapy decreased to 7.6%, while no clinically significant differences were observed in the laboratory parameters at T1, compared with T0 (Supplementary Table 1). Globally, enrolled patients showed almost favorable outcomes, with low rate of increase oxygen supplementation (9.7%), SICU admission (4.9%), ICU admission (1.1%) and exitus (4.9%) (Figure 1). Seventeen patients (9.2%) showed at least one unfavorable outcome, while 4 among 110 outpatients (3.6%) needed hospitalization. ADRs occurred in 34 (18.4%) patients. Fever was almost the only ADR reported (33 out of 34 patients 97%), while only one patient had vomiting. In most cases fever resolved after 24-36 hours from its occurrence, with or without the aid of antipyretic drugs. At the univariate outcome analysis, age > 60 years, CKD, diabetes mellitus, chronic liver disease, chronic pulmonary disease, neurodegenerative disease, obesity and Charlson comorbidity index > 2, showed to be associated with an unfavorable outcome (at least one among SICU, ICU and death) (Table 2), while plasmatic D-dimer > 600 ng/ml was tendentially associated with unfavorable outcome At the multivariate analysis, patients with CKD (aOR: 10.44, 95CI: 1.73-63.03; p<0.05) and basal D-dimer serum concentrations > 600 ng/ml (aOR 21.74, 95CI: 1.18-397.70; p<0.05) were found to be independent risk factors for unfavorable outcome. In particular, 28.6% and 50% of patients who needed SICU/ICU admission and died, respectively had CKD. Moreover, 77.8% and 87.5% of patients who needed SICU/ICU and died, respectively had serum D-dimer concentrations > 600 ng/ml at admission, needed SICU/ICU admission and died, respectively. Interestingly, CRP values, negative SARS-CoV-2 serology at admission and incomplete SARS-CoV-2 vaccination were not associated with an increased risk of unfavorable outcome. At the stratified comparison analysis between clinical and laboratory parameters at T1 and T0, patients with negative SARS-CoV-2 serology at baseline showed a significant reduction in serum CRP compared with patients with positive serology (median Δ -16.5 [IQR: -49.2 to -0.4] vs -1.7 [IQR: -20.0 to +0.4], p <0.05). No other significant differences in clinical and laboratory parameters between T1 and T0 were recorded at the stratified comparison analysis (Table 3). Moreover, patients with a negative SARS-CoV-2 serology showed a trend toward a higher admission rate to SICU and ICU compared with patients with positive serology (6.5% vs 1.2%, p=0.084), as well as a higher rate of ADRs (28.6% vs 7.1%, p<0.001). No differences in the hospitalization rate, increase in oxygen supplementation or death were recorded at the stratified analysis (Table 4). Both the median time of negativization (15 days [IQR: 10-20] vs 14 days [IQR: 9-18; p=0.308]) and the median time between positive SARS-CoV-2 RNA on ORP swab and mAbs infusion (3 [IQR: 1-5] vs 3 [IQR: 1-4]; p=0.717) were similar in patients with negative serology compared with patients with positive SARS-CoV-2 IgG.

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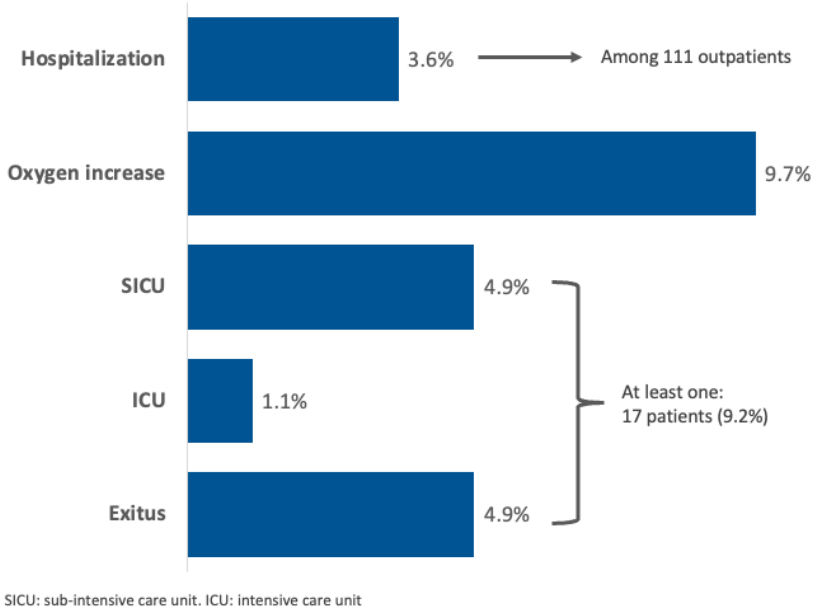

Figure 1. Unfavorable outcomes among enrolled patients (n=182).

Table 1. Demographic and clinical characteristics of the enrolled patients (n=185).

Age (median, IQR)	**57 (37-72)**
Age > 65 years (n, %)	64 (34.6)
Sex (male; n, %)	74 (40.0)
Hospitalization regimen (n, %)	
- Outpatients	110 (59.5)
- Inpatients	75 (40.5)
Comorbidities	
- Chronic kidney disease[#]	17 (9.2)
- Diabetes	13 (7.0)
- Immunodeficiency	24 (13.0)
- Cardiovascular disease	36 (19.5)
- Chronic liver disease	6 (3.2)
- Chronic pulmonary disease	20 (10.8)
- Neurodegenerative disease	6 (3.2)
- Obesity	41 (22.2)
Body mass index (median, IQR)	26 (25-30)
Charlson comorbidity index (median, IQR)	2 (0-4)
MASS Score* (median, IQR)	2 (0-4)
SARS-CoV-2 vaccination received (n, %)	103 (55.7)
- Among these, all doses received[§]	68 (66.0)
SARS-CoV-2 IgG (n, %)	
- Positive	85 (45.9)
- Negative	77 (41.6)
- Not Available	23 (12.4)
Monoclonal antibodies received (n, %)	
- Casirivimab-imdevimab	130 (70.3)
- Sotrovimab	16 (8.6)
- Bamlanivimab-etesevimab	39 (21.1)
Time between positive TNF and mAbs infusion (days; median, IQR)	2(1-4)

[#]Stage 3 to 5 according to KDIGO

*MASS score was calculated according to the US Food and Drug Administration (FDA) Emergency Use Authorization eligibility criteria, as follow: age ≥65 (2 points), BMI ≥ 35 (1

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point), diabetes (2 points), chronic kidney disease (3 points), cardiovascular disease in a patient ≥ 55 years (2 points), chronic respiratory disease in a patient ≥ 55 years (2 points), hypertension in a patient ≥ 55 years (1 point) and immunocompromised status (3 points)
§ second dose or booster dose during the previous 4 months

Table 2. Univariate and multivariate logistic regression analysis for unfavorable outcome.

	Univariate analysis			Multivariate analysis		
	OR	**95CI**	**p-value**	aOR	95CI	p-value
Male Sex	1.78	0.65-4.85	0.258	-	-	-
Age > 60 years	**6.09**	**1.69-22.00**	**<0.01**	0.63	0.01-106.11	0.858
Comorbidities						
- CKD*	**10.64**	**3.13-36.11**	**<0.001**	**10.44**	**1.73-63.03**	**<0.05**
- Diabetes	**4.38**	**1.03-17.85**	**<0.05**	4.78	0.49-46.57	0.178
- Immunodeficiency	1.90	0.49-7.36	0.355	-	-	-
- Cardiovascular disease	1.69	0.50-5.73	0.401	-	-	-
- Chronic liver disease	**6.79**	**1.13-40.90**	**<0.05**	0.70	0.01-33.48	0.855
- Chronic pulmonary disease	**5.63**	**1.67-19.98**	**<0.01**	4.17	0.65-28.83	0.133
- Neurodegenerative disease	**2.49**	**0.27-22.95**	0.420	-	-	-
- Obesity	**4.45**	**1.32-14-92**	**<0.05**	4.62	0.89-23.89	0.068
Charlson comorbidity index > 2	**3.20**	**1.08-9.49**	**<0.05**	3.81	0.02-707.71	0.615
Incomplete SARS-CoV-2 vaccination schedule	1.14	0.21-6.33	0.876	-	-	-
Negative SARS-CoV-2 IgG	1.35	0.37-4.62	0.630	-	-	-
Laboratory parameters at admission						
- Lymphocyte count < 1000 cell/µL	2.25	0.82-6.15	0.114	2.42	0.49-12.17	0.280
- D-dimer > 600 ng/ml	3.50	0.96-12.75	0.058	**21.74**	**1.18-397.97**	**<0.05**
- CRP > 60 mg/l	1.53	0.51-4.62	0.453	-	-	-
- LDH > 300 U/l	1.71	0.56-5-18	0.347	-	-	-
Time between positive ORP swab and mAbs infusion > 5 days	0.81	0.18-3.90	0.817	-	-	-

*Stage 3 to 5 according to KDIGO
OR: odds ratio; 95CI: 95% confidence interval; CKD: chronic kidney disease; CRP: c-reactive protein; LDH: lactate dehydrogenase; ORP: oro-rhino-pharyngeal

Table 3. Stratified comparison analysis between T1 and T0 according to baseline SARS-CoV-2 serology.

	Positive SARS-CoV-2 IgG (n=85)			*Negative SARS-CoV-2 IgG (n=78)*			
	T0	**T1**	**Δ (median, IQR)**	T0	T1	Δ (median, IQR)	p-value
Oxygen supplementation needed (n, %)	8 (9.8)	4 (6.1)	-	25 (32.5)	10 (16.4)	-	-
P/F ratio (median, IQR)	462 (457-463)	467 (462-471)	+5 (0, +10)	457 (277-467)	462 (453-467)	+0 (+0, +9)	0.140
WBC (cell/µL; median, IQR)	6560 (4890-8485)	8000 (6545-10450)	+1150 (-22, +2537)	6260 (4065-8585)	7890 (5870-10020)	+1370 (-670, +3425)	0.686
Lymphocyte count (cell/µL, median, IQR)	1420 (1020-1980)	1850 (1320-2720)	+410 (0, +787)	1070 (725-1615)	1470 (985-2170)	+240 (-145, +77)	0.601
Fibrinogen (mg/dl; median, IQR)	371 (298-461)	336 (268-439)	-22 (-73, +30)	396 (343-502)	370 (293-440)	-24 (-110, +33)	0.527
D-dimer (ng/ml; median, IQR)	542 (322-1195)	668 (364-1246)	+22 (-97, +188)	1051 (482-1621)	983 (550-1502)	-60 (-475, +199)	0.104
CRP (mg/l; median, IQR)	**10.6 (2.8-30.3)**	**4.8 (2.2-15.5)**	**-1.7 (-20.0, +0.4)**	**29.7 (11.3-62.4)**	**6.7 (3.3-26.3)**	**-16.5 (-49.2, -0.4)**	**<0.05**
LDH (U/l; median, IQR)	204 (187-257)	201 (181-237)	-1 (-25, +16)	227 (183-305)	229 (186-297)	-11 (-55, +30)	0.432

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P/F: perfusion/fraction of inspired oxygen. WBC: white blood count; CRP: c-reactive protein; LDH: lactate dehydrogenase; Δ: delta value between T1 and T0

Table 4. Stratified outcomes analysis according to baseline SARS-CoV-2 serology (n=162).

	Positive SARS-CoV-2 IgG (n=85)	Negative SARS-CoV-2 IgG (n=77)	p-value
Hospitalization needed (n, %) [#]	3 (4.6)	1 (3.0)	0.586
Increase in oxygen therapy (n, %)	8 (9.4)	9 (11.7)	0.637
Exitus (n, %)	4 (4.7)	2 (2.6)	0.389
SICU/ICU (n, %)	1 (1.2)	5 (6.5)	0.084
Time of negativization (days; median, IQR)	14 (9-18)	15 (10-20)	0.308
ADRs (n, %)	**6 (7.1)**	**22 (28.6)**	**<0.001**

[#]Among 110 outpatients

SICU: sub-intensive care unit. ICU: intensive care unit. ADRs: adverse drug reactions

4. Discussion

In our study we showed real-life data about SARS-CoV-2 treatment with monoclonal antibodies in a tertiary care center of Southern Italy. The study was conducted when alpha e delta VoCs of SARS-CoV-2 were prevalent in Italy and was stopped when the first Omicron VoC case was detected in the country. In this setting, the activity of all these mAbs combinations was high beyond any doubt (20). It is noteworthy that the characteristics of patients included in this study are quite different from those enrolled in phase 2/3 clinical trials on mAbs for SARS-CoV-2 infection, especially considering the risk factors for severe COVID-19. In fact, only a minority of the patients enrolled in clinical trials evaluating effectiveness of mAbs for SARS-CoV-2 infection had CKD or immunodeficiencies (21-23), which were relatively common in our study population (Immunodeficiency: 12.8%, CKD: 9.1%). For instance, in the phase 3 study by Weinreich DM et al., only 1.3% and 3.2% of patients treated with casirivimab/imdevimab (which was the most administered mAbs combination in our cohort) had CKD and immunodeficiencies, respectively. Moreover, we showed a poor acceptance of vaccination program, despite the frailty of our study population. In fact, only 55% of the included patients received SARS-CoV-2 vaccination. In this setting the early treatment with monoclonal antibodies is crucial also considering that we showed an IgG positivity to anti Spike protein only in 45% of tested patients. Given the frailty of the included patients the outcome of the disease was generally good. First, we showed an overall improvement of patients' characteristics at T1 compared to T0, with a lower rate of patients requiring oxygen supplementation (8.0% vs. 19.3%) and lower median CRP values (5.7 mg/l vs. 22.4 mg/l). This is significant since, according to the SARS-CoV-2 infection pathogenesis, an impairment in clinical condition and systemic inflammation is expected after 7-10 days from the diagnosis (24). Moreover, we showed relatively low rates of hospitalization, SICU/ICU admission and death. It is plausible that the presence of CKD in about 10% of included patients biased these results. In fact, a significant percentage of patients who required hospitalization (20%) or ICU/SICU (22.2%) had CKD, while an even higher percentage (40%) of patients who died had CKD. We indeed showed that the presence of CKD and high D-Dimer values (> 600 ng/ml) at admission were the two factors associated with unfavorable outcome at multivariate analysis. In detail, patients with CKD showed a ten-fold risk of unfavorable outcome compared with patients without CKD (aOR: 10.44; 95CI: 1.73-63.03, $p<0.05$). No results reporting low efficacy of monoclonal antibodies in CKD patients are available in literature. In fact, CKD is one of the main indications for early treatment of COVID-19. Since the first wave of COVID-19 it has been indeed demonstrated that CKD patients had a three-fold risk of developing severe COVID-19 compared with patients without CKD (25), while patients with CKD stages 3 to 5 according to KDIGO had a significant increase in mortality rate,

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compared with those without kidney disease (11.1% vs. 4%)(26). Surprisingly, in the RECOVERY trial, in which efficacy of Casirivimab/Imdevimab in outpatients with severe COVID-19 was evaluated, no data about CKD patients were available (27). Similarly, in Sotrovimab registration trial no data about efficacy of monoclonal antibodies in CKD patients were reported as only one enrolled patient was affected by CKD (23). In one of the first real-life study by Savoldi et al. comparing efficacy of different mAbs combinations only 1.7% of patients were on dialysis for end stage renal disease, and they did not show impaired efficacy in this category of patients. It must however be said that all included patients were on dialysis an no patients with other stages of CKD were enrolled (28).

It is known that D-Dimer values are associated with worse outcome. In 2021, Poudel et al. indeed showed in a cohort of 182 patients that a D-Dimer value higher than 1.5 μg/mL was an accurate biomarker for mortality, with a sensitivity of 70.6% and a specificity of 78.4% (29). Our study confirmed the association between high D-dimer values and poor outcome, also in a cohort of patients during their first phase of the disease and with high risk of developing severe COVID-19. In fact, previous data came from patients already hospitalized for COVID-19.

Treatment with mAbs was well tolerated. A treatment-related ADR was showed in 18.4 % of patients, with fever being the most common ADR. Even though fever was considered a mAbs-related ADR, it must be stressed that it could be difficult to discriminate an actual ADRs from of COVID-19 symptoms, as all patients were treated in the first days of the disease and may not have already showed fever as COVID-related symptom. This consideration may be the reason for the higher rate of ADRs in seronegative patients, as it is well-known that vaccinated subjects tend to be milder symptoms if get infected.

We finally conducted a stratified analysis according to serum anti-spike IgG, as patients with a negative SARS-CoV-2 serology (either unvaccinated or non-responders to vaccination) were considered at higher risk of clinical worsening. We showed that patients with baseline negative SARS-CoV-2 serology had a significant reduction in serum CRP at T1compared to patients with baseline positive serology (median Δ -16.9 [IQR: -51.6 to -0.4] vs -1.7 [IQR: -20.0 to +0.4], $p < 0.01$). Although we cannot state conclusive messages due to the absence of a control group, we can postulate that mAbs administration may have a high clinical burden in patients with negative anti-spike serology as it is noteworthy that an increase in CRP and in other pro-inflammatory markers at baseline was widely associated with worse outcome in patients with COVID-19 (30-32). However, mAbs directly act binding SARS-CoV-2 spike domain and leading to inhibition of virus replication and to subsequent blockage of the cytokinin cascade mediated by the virus and reduction in CRP values (33).

Despite monoclonal antibodies administration, we showed that patients with negative serology had a higher risk of SICU/ICU admission rather than patients with positive serology. Again, we cannot draw final conclusions, but we can hypothesize that patients with negative serum SARS-CoV-2 spike IgG were those at higher risk of severe progression of COVID-19 and that mAbs administration could have reduced the rate of unfavorable outcome. Unfortunately, the lack of a control group did not allow to evaluate the real efficacy of mAbs drugs in this setting. However, negative serology at admission was not associated with unfavorable outcome (at least one between SICU/ICU admission or death) at univariate and multivariate analysis, and this result may vicariously support our abovementioned hypothesis.

5. Conclusions

In conclusion, this is one of the first prospective study showing efficacy of monoclonal antibodies in a real-life setting. In cohort of frail patients, including those with immunosuppression and CKD, we showed a low rate of hospitalization, ICU/SICU admission and death. . The lack of a control group is surely a major limitation of our study and did not allow us to directly confirm efficacy of this therapeutic approach in such a population. However, we believe that results from this work are relevant since they shed light on a

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class of drug that should be the cornerstone of early treatment of SARS CoV-2 also in the next future.

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