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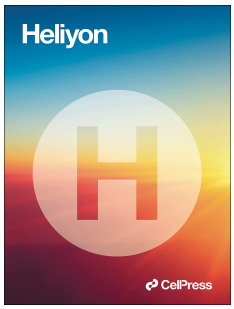

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Monoclonal antibodies against SARS-CoV-2 to prevent COVID-19 worsening in a large multicenter cohort

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Highlights

- Monoclonal antibodies (mAbs) reduces COVID-19 hospitalizations in people at risk
- Over a 2-year period, outpatients receiving mAbs in 17 centers were followed-up
- Among 1,534 subjects receiving mAbs, 28-day hospitalization rate was 5.6%
- Risk was higher for increasing age, immunodeficiency, pre-Omicron calendar period

Abstract

Objective

Monoclonal antibodies (mAbs) against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) reduced Coronavirus Disease 2019 (COVID-19) hospitalizations in people at risk of clinical worsening. Real-world descriptions are limited.

Methods

CONDIVIDIAMO, a two-year multicenter observational study, consecutively enrolled SARS-CoV-2 outpatients with ≥1 risk factor for COVID-19 progression receiving mAbs. Demographic data, underlying medical condition, type of mAbs combination received, duration of symptoms before mAbs administration, COVID-19 vaccination history, were collected upon enrolment and centrally recorded. Data on outcomes (hospitalizations, reasons of hospitalization, deaths) were prospectively collected. The primary endpoint was the rate of hospitalization or death in a 28-day follow-up, whichever occurred first; subjects were censored at the day of last follow-up or up to 28 days. The Kaplan-Meier method was used to estimate the incidence rate curve in time. The Cox regression model was used to assess potential risk factors for unfavorable outcome. Results were shown as hazard ratio (HR) along with the corresponding 95% Confidence Interval (95%CI).

Results

Among 1,534 subjects (median [interquartile range, IQR] age 66.5 [52.4-74.9] years, 693 [45.2%] women), 632 (41.2%) received bamlanivimab±etesevimab, 209 (13.6%) casirivimab/imdevimab, 586 (38.2%) sotrovimab, 107 (7.0%) tixagevimab/cilgavimab. After 28-day follow-up, 87/1,534 (5.6%, 95%CI: 4.4%-6.8%) met the primary outcome (85 hospitalizations, 2 deaths). Hospitalizations for COVID-19 (52, 3.4%) occurred earlier than for other reasons (33, 2.1%), after a median (IQR) of 3.5 (1-7) *versus* 8 (3-15) days (p=0.006) from mAbs administration.

In a multivariable Cox regression model, factors independently associated with increased hospitalization risk were age (hazard ratio [HR] 1.02, 95%CI 1.00-1.03, p=0.021), immunodeficiency (HR 1.78, 95%CI 1.11-2.85, p=0.017), pre-Omicron calendar period (HR 1.66, 95%CI 1.02-2.69, p=0.041).

Conclusions

MAbs real-world data over a 2-year changing pandemic landscape showed the feasibility of the intervention, although the hospitalization rate was not negligible. Immunosuppressed subjects remain more at risk of clinical worsening.

Keywords: monoclonal antibodies; COVID-19; SARS-CoV-2; hospitalization; Immunodeficiency; omicron variant

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally causing a serious threat to human health. COVID-19 ranges from mild to severe, and a high incidence of illness and death has been reported in a vulnerable subgroup of patients. The risk of death from COVID-19 is increased among older patients and among those with chronic medical conditions such as immunosuppression, cardiovascular disease, cancer, diabetes, lung disease, and obesity. Mild symptoms of COVID-19, which are typical of an upper airway respiratory syndrome, can progress to more serious complications, including viral pneumonia and the acute respiratory distress syndrome [1-2].

In the face of daunting absence of effective antiviral treatment during the initial year of Coronavirus Disease 2019 (COVID-19) pandemic, the advent of monoclonal antibodies (mAbs) targeting the spike protein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) marked a significant milestone, as it was the first proven intervention which reduced hospitalizations and deaths in non-vaccinated patients at risk of clinical worsening for underlying medical conditions, including old age [3-6]. Efficacy in clinical trials was confirmed by real world data [7-10]. However, scale up of mAbs use was tempered by several factors: i. logistical challenges in ensuring timely intravenous administration within controlled settings; ii. the concurrent expansion of vaccination coverage, raising questions about the potential redundancy of mAbs in fully vaccinated individuals; iii. the availability of more convenient oral antiviral treatment (namely nirmatrelvir/ritonavir [11]) for the same clinical scenario; iv. the evolving susceptibility of different SARS-CoV-2 variants and sub-variants to mAbs over time [12, 13]. Notwithstanding these limitations, mAbs have continued to be used, especially in more vulnerable patients, such as those who remained unvaccinated, the elderly, the immunosuppressed, and individuals burdened by multiple comorbidities.

Longitudinal information on mAbs use in different evolving clinical and epidemiological scenarios is lacking. Moreover, risk factors for mAbs failure have not been fully elucidated thus far.

Lombardy, in Northern Italy, was the first region in Western World to be heavily hit by the COVID-19 pandemic, especially in the first three waves, ranging from February 2020 to March 2021. When the first mAbs against SARS-CoV-2 were approved in Italy for emergency use in clinical practice in March 2021, Lombardy was still facing a great number of infections but a slow pace of vaccination campaign in the most vulnerable individuals. In these difficult conditions, without thorough knowledge of effectiveness in clinical practice, we started to deploy mAbs in our ambulatories.

Hence, we conducted a multicenter observational study since the beginning of mAbs use in clinical practice, to measure an unfavorable 28-day outcome (i.e. hospitalization or death without hospitalization) in mAbs recipients in a real-life setting. Here we describe the complete analysis focusing on temporal trends in mAbs use and risk factors for hospitalization.

Methods

Ethical declaration

The study was approved by the National Ethics Committee Lazzaro Spallanzani (Rome). All enrolled patients signed written informed consent. The study is registered in ClinicalTrials.gov (Identifier: NCT05268601).

Study population

CONDIVIDIAMO is a prospective multicenter observational study enrolling patients treated with mAbs in different infectious diseases and internal medicine centers in Lombardy, Northern Italy. All adult patients with a positive test result for SARS-CoV-2 (either antigenic or molecular) that were receiving mAbs according to Italian prescription rules as outpatients within 7 days from

symptoms' onset were included in the study and followed up for 28 days since mAbs administration. In summary, Italian prescription rules required that to be eligible to receive mAbs, patients with recent infection of SARS-CoV-2 (within 7 days from symptoms onset), and with mild symptoms not requiring hospitalization, should have at least one risk factor for clinical worsening, including age >65 years.

People receiving mAbs during hospitalization, either for treatment (casirivimab/imdevimab at higher dosage), or for prevention of clinical worsening in people already hospitalized for other reasons, were excluded.

Data collection

Demographic data (age, gender, height, weight, body mass index [BMI]), medical history (underlying medical condition), type of mAbs combination received, duration of symptoms before mAbs administration, COVID-19 vaccination history were collected upon enrolment and recorded on a web-based centralized case report form (REDCap Cloud, nPhase, Inc, version 1.7.3). Data on outcomes (hospitalizations, reasons of hospitalization, deaths) were prospectively collected integrating hospital charts with direct phone calls or queries on regional registry.

Statistical analysis

Median (interquartile range, IQR) were used for the description of continuous variables, while absolute and relative frequencies were used for qualitative variables. Between groups comparisons were performed by means of the Kruskall-Wallis, Mann-Whitney or the chi-squared test, as appropriate.

The primary endpoint was an unfavorable 28-day outcome calculated as the time between the day of mAbs administration and hospitalization for any reason (i.e. for COVID-19 or other reasons) or death, whichever occurred first; subjects were censored at the day of last follow-up or up to 28 days. The Kaplan-Meier method was used to estimate the incidence rate curve in time, while the

Cox regression model was used to assess potential risk factors. The final Cox model was the one that minimized the Akaike Information Criterium and the variables included were: gender, age, diabetes (absent/present), immunodeficiency (absent/present) and period of mAbs administration (period before/after Omicron variant, 21th December 2021). Since the last variable was highly correlated with the waves of COVID-19, the mAbs used and the cumulative vaccine doses, it indirectly incorporated into the model also the time-dependent information regarding the variants, the availability of mAbs in each hospital and the possibility of receiving a different number of doses of vaccine depending on the COVID waves.

The assumption of proportionality of the hazards in the Cox model was verified by graphical diagnostics based on the scaled Schoenfeld residuals and results were shown as hazard ratio (HR) along with the corresponding 95% Confidence Interval (95%CI).

Since we observed only two deaths, we focused only on hospitalizations and specifically on the reasons for hospitalization (i.e. COVID-19 or other reason). The Aalen-Johansen cumulative incidence curves were used to describe hospitalization for COVID-19, with hospitalization for other reasons as competing event. A cause specific hazard model was used to assess associations with potential specific risks factors for COVID-19 hospitalization, considering other reasons as competing risk. The model was adjusted for the same variables described before.

All the tests were two-sided at a nominal level of 5%. All analyses were conducted using R open-source software version 4.3.1 ("Beagle Scouts" http://www.R-project.org).

Results

Patients' characteristics and mAbs use

Between March 2021 and December 2022, in 17 referral centers in Lombardy (Figure S1), north of Italy, 1,735 subjects were screened for enrolment in CONDIVIDIAMO study. After excluding

patients who did not receive mAbs, and those who received mAbs while hospitalized (either for treatment of COVID-19 or for prevention of COVID-19 worsening while hospitalized for other causes) a total of 1,534 subjects were included in the analysis (Figure S2).

Median (interquartile range, IQR) age was 66.5 (52.4-74.9) years, 693 (45.2%) were women (Table 1). All patients had at least one risk factor for COVID-19 progression, the most common being age >65 years (672 [43.8%]), immunodeficiency (628 [40.9%]), cardiovascular disease (485 [31.6%]), obesity (275 [17.9%]), renal failure (241 [15.7%]), lung disease (194 [12.6%]). One hundred twenty-one patients (7.9%) had three or more risk factors simultaneously.

Six hundred thirty-two (41.2%) patients received bamlanivimab (of whom 616, 97.5%, in combination with etesevimab), 209 (13.6%) casirivimab/imdevimab, 586 (38.2%) sotrovimab, 107 (7.0%) tixagevimab/cilgavimab. The type of mAbs use varied over time, according to availability, prescription rules, and predicted activity against the circulating variant of SARS-CoV-2. In Figure S3 the cumulative use over calendar time of different types of mAbs is depicted.

Bamlanivimab/etesevimab and casirivimab/imdevimab were used in the first period, until approximately half of December 2021, when the Omicron variant superseded the others, thus only sotrovimab, and later tixagevimab/cilgavimab were used as they retained *in vitro* neutralizing activity against the virus.

At the day of mAbs administration, patients had received different number of doses of vaccine against COVID-19. Three-quarters of the cohort (1,140 patients, 75.8%) were fully vaccinated for COVID-19 before mAbs treatment, meaning that they had received at least 3 doses or 2 doses of which the last one within the previous 120 days. The median (IQR) time between the onset of symptoms and the administration of mAbs was 4 (3-6) days.

The description of population's characteristics according to the type of mAbs received is shown in Table 1. Differences in patient characteristics reflect the evolution of mAbs recipients over time.

Of note, the percentage of patients with immunodeficiency and renal failure increased over time, while the percentage of patients with obesity, diabetes, and cardiovascular disease decreased. The number of vaccinated persons was progressively higher from bamlanivimab/etesevimab to tixagevimab/cilgavimab recipients.

Outcome

A total of 87 (5.7%) patients presented unfavorable outcomes in the study period: 85 were hospitalized (5.5%), of whom 4 subsequently died in hospital during the 28-day follow-up window, and 2 died with no hospitalization. Among the 85 hospitalizations, 52 (61.2%) were due to COVID-19 progression, while 33 (38.8%) patients were admitted in hospital for other reasons; of note, 6 were hospitalized twice during the observation period: the first hospitalization was due to COVID-19 in two patients, and four were for other reasons (with one death occurring subsequently). Of the 6 deaths, occurred after a median of 14 days, 4 were due to COVID-19 (occurring during hospitalization for 3 of them), and 2 for other reasons (one during hospitalization). The cumulative incidence curve in time of the composite primary endpoint, i.e. hospitalization or death without hospitalization, is shown in Figure 1a and has an overall rate of 5.6% (95%CI 4.4%-6.8%).

Table 2 shows the characteristics of patients who have been hospitalized during the 28-day follow-up as compared to those who have not. Hospitalized patients were older and had more frequently three or more risk factors for clinical progression (mainly immunodeficiency, cardiovascular disease, diabetes) than those who were not hospitalized. Moreover, they were more frequently in the pre-Omicron period, and had a longer time to viral clearance.

The rate of hospitalization varied: it was 24/320 (7.5%) in the pre-Omicron period, and 61/1,212 (5%) during the Omicron wave (p=0.115), Figure S4.

In a multivariable Cox regression model (Figure 2a), the only factors independently associated with increased risk of hospitalization were age (HR 1.02, 95%CI 1.00-1.03, p=0.021), immunodeficiency

(HR 1.78, 95%CI 1.11-2.85, p=0.017) and the calendar time before Omicron (HR 1.66, 95%CI 1.02-2.69, p=0.041). Results were confirmed also when the analysis was done on the composite endpoint considering also death without hospitalization (Figure S5).

Regarding the reason of hospitalization, details of the 33 hospitalizations were listed in Table S1. No significant differences in terms of comorbidities were seen between the two groups (Table 3). The time to viral clearance in patients hospitalized for COVID-19 was significantly higher (median 24 *versus* 16 days, p=0.005). More importantly, the hospitalizations for worsening of COVID-19 occurred significantly earlier than those for other reasons as shown in the cumulative incidence curves in Figure 1b, with a median (IQR) of 3.5 (1-7) *versus* 8 (3-15) days (p=0.006) from mAbs administration, respectively.

In the cause specific hazard model on hospitalization for COVID-19 (Figure 2b), the calendar time before Omicron, age and diabetes were factors significantly associated with increased risk of hospitalization for COVID-19 (HR 1.97, 95%CI 1.09-3.58, p=0.025; HR 1.02, 95%CI 1.00-1.04, p=0.054; HR 2.17, 95%CI 1.02-4.61, p=0.045, respectively).

Discussion

The CONDIVIDIAMO study included more than 1,500 individuals who received mAbs as outpatients to prevent hospitalization over a period of 2 years. In this large multicenter observational setting, we showed that the hospitalization within 28 days of observation occurred in 5.6% of subjects. If we compare this percentage to what seen in randomized clinical trials, this rate aligns more closely with placebo arms rather than mAbs arms [3-6]. However, it should be emphasized that in our real-life cohort patients have more comorbidities and are older than those in clinical trials, potentially accounting for this disparity. Furthermore, when focusing solely on hospitalizations due to worsening of COVID-19 (which mAbs could potentially prevent), the

admission rate drops even further to 3.4%. The differentiation between reasons for hospitalization is consistent: people hospitalized for COVID-19 had a shorter time to admission than people hospitalized for other reasons, reflecting the natural history of COVID-19 progression, and a longer length of stay and time to viral clearance, in line with the main reason for hospitalization.

Considering the large number of subjects and the consistency over time of clinical characteristics of a frail population, these data show the feasibility of mAbs use in a real-world setting. This is not trivial, as the logistical effort to provide timely administration of intravenous drug in a controlled setting to contagious individuals during a pandemic with a huge strain on the hospital system, is all but easy. Moreover, the health offer of a complex medical intervention was homogenous throughout a wide regional territory.

The use of different types of mAbs varied over time. This was due to many factors: the different development and approval of the different molecules, change in availability because of shortage of production in periods of higher demand, but mostly because of change of viral variants (Figure S6), the passage from Delta to Omicron, which excluded the two mAbs pairs used up until then (bamlanivimab/etesevimab and casirivimab/imdevimab).

Following the different use of mAbs over time, we also observed different patients' characteristics between recipients of different mAbs combinations.

Differences reflect the changing pattern of patients over time, which mirrored the evolution of SARS-CoV-2 variants and the corresponding change in the type of mAbs used (Figure S3). Of note, the quote of vaccinated people was higher in sotrovimab and tixagevimab/cilgavimab recipients, as well as the percentage of patients with renal failure or immunodeficiency, probably because of the limitation on alternative options (antivirals were restricted for glomerular filtration rate >30 ml/min or could have drug interactions with immunosuppressive agents).

The long time of observation of our longitudinal study allowed us to assist to two big changes: the increasing number of people who get protected by COVID-19 vaccination, and the rapid viral shift from Delta to Omicron variant that occurred at the end of 2021. These facts determined a different clinical scenario in the second part of our observation, as the increasing number of vaccinated people posed them less at risk of clinical progression (also raising the question of possible futility of mAbs), compounded by Omicron's diminished pathogenicity [14-17]. The more favorable outcome in the second period of our observation was considered in our analysis, and it was protective of hospitalization even in the multivariable model. This is a strength of our work, since the long time span of observation allowed us to explore the interplay between the efficacy of a medical intervention and the calendar period of its application.

The other important point that emerged from our analysis is the detrimental effect of immunosuppression on COVID-19 outcome, as it was the only single comorbidity independently associated with an increased risk of hospitalization. Unfortunately, our data are not sufficiently detailed to differentiate between varying degrees of immunosuppression; for example, they could not distinguish between solid organ transplant recipients, hematopoietic stem cell transplant recipients, anti-CD20 monoclonal antibodies recipients, Bruton kinase inhibitors recipients, people with solid organ malignancies receiving standard chemotherapy, or people with rheumatologic diseases receiving steroids or other immunosuppressive agents. Thus, they could underestimate the effect of specific conditions which are known to be associated with a worse outcome, such as patients receiving rituximab or ibrutinib for hematological malignancies. Nevertheless, in a wide real-life cohort, this finding deserves attention, as it could identify patients more at risk of clinical progression (i.e., the most vulnerable people among vulnerable people).

The other factor associated with a worse outcome is age, with an increased independent 1% risk for each additional year of life. This aligns with the established literature indicating age as a key determinant of severe COVID-19 outcomes [18-21].

Limitations of the study

Our study has some limitations: first, as it is an observational study on a recommended medical intervention, it lacks a control group. Nonetheless, the aim of the present work was not to assess the efficacy of mAbs, rather to ascertain the effective deployment of mAbs use in real life and to identify, among patients receiving mAbs, risk factors for mAbs failure in preventing hospitalization. Second, as it is a large observational multicenter study based on common clinical data collection which are the eligibility criteria defined by Italian Agency of Medicines (AIFA), it could not provide more detailed insights on patient clinical characteristics, for instance it could not distinguish between low or high level of immunosuppression, the degree of cardiologic or pulmonary impairment and so on. By contrast, the homogeneity of the findings across a wide range of different centers and territories, corroborates the consistency of our results. Third, it could be argued that current clinical utility of this information is scarce, since mAbs are no longer in the guidelines of clinical management of outpatients with COVID-19 [22] due to the evolving scenario of SARS-CoV-2 variants and to the availability of alternative antiviral options. On this concern, some guidelines still recommend the use of specific mAbs in selected settings [23]. Moreover, our data could serve as a starting point in case of future availability of new mAbs targeting conserved regions of spike protein and thus not influenced by viral evolution. Fourth, systematic data on viral variants are missing. In this regard, the reduced susceptibility to current mAbs has become critical after mid-2022, when mAbs use was generally replaced by oral antivirals. Therefore, the partial information on viral variants, which is available only for a minority of patients, should not alter the consistency of our findings (Table S2).

Conclusions

In conclusion, our work shows that over a 2-year period, among 1,534 subjects receiving mAbs as outpatients in 17 centers, 28-day hospitalization rate was 5.6%, and risk was higher for increasing age, immunodeficiency, and pre-Omicron calendar period.

Monoclonal antibodies against the spike protein of SARS-CoV-2 have been the first etiological intervention for COVID-19 which proved successful in preventing severe outcome in most-at-risk patients. Its use has faded over time, as COVID-19 severity decreased with the Omicron variant and diffuse natural and/or induced by vaccination immunity has spread in the population (the current "omi-vax" scenario). Nonetheless, the use of mAbs could still have a role in selected patients, who are frail and remain at risk for COVID-19 progression, and for various reasons cannot access more convenient options. Thus, our data could provide some useful information on the characteristics of patients who remain at risk of hospitalization despite having received mAbs, in order to explore novel therapeutic strategies, such as concurrent antiviral treatment and/or a strict follow-up to ensure a safer outcome.

Data availability statement

Data will be made available on request.

Ethics statement

This study was reviewed and approved by Lazzaro Spallanzani Ethics Committee, Rome, with the approval number: 397/2020-2021 and 17/2022 (amendment). All participants (or their proxies/legal guardians) provided informed consent to participate in the study.

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Contributions:

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Figure legends

Figure 1. (a) Cumulative incidence of composite outcome (hospitalization or death) within 28 days since the receipt of monoclonal antibodies (mAbs). (b) Cumulative incidence of hospitalization according to the reason (COVID-19 or other) within 28 days in patients receiving mAbs: hospital admissions for worsening of COVID-19 (grey line) occurred significantly earlier than those for non-COVID-19 reasons (black line). 30 patients with missing data for follow-up.

Figure 2. Results from Cox regression model on hospitalization (a) and on hospitalization for COVID-19, considering other reasons as competing risk (b).

Legend: HR=Hazard Ratios; 95%CI=95% Confidence Intervals

Table 1. Comparison of characteristics between patients receiving different types of monoclonal antibodies (mAbs).

	Overall	**Monoclonal antibodies**				
Characteristics	**N=1534**	**BAM+ETE N=632 (41.2%)**	**CAS+IMD N=209 (13.6%)**	**Sotrovimab N=586 (38.2%)**	**TIX+CIL N=107 (7%)**	***P* Value**
Age, years, median (IQR)	66.5 (52.4-74.9)	66.6 (52.3-74.3)	66.4 (51.2-74.3)	65.8 52.4-75.4)	68.7 (56.8-78.4)	0.214
Female gender, n (%)	693 (45.2)	276 (43.7)	89 (42.6)	282 (48.1)	46 (43.0)	0.333
BMI, median (IQR)	25.7 (22.5, 29.3)	26.5 (22.9-30.4)	26.4 (23.1-32.1)	24.7 (22.1-28.1)	25.5 (22.1-28.6)	<0.001
Risk factors for severe COVID-19, n (%)						
BMI≥ 30	275 (17.9)	149 (23.6)	58 (27.8)	61 (10.4)	7 (6.5)	<0.001
Renal failure	241 (15.7)	47 (7.4)	10 (4.8)	132 (22.5)	52 (48.6)	<0.001
Diabetes	132 (8.6)	65 (10.3)	21 (10.0)	39 (6.7)	7 (6.5)	0.101
Immunodeficiency	629 (41.0)	190 (30.1)	55 (26.3)	334 (57.0)	49 (45.8)	<0.001
Age >65 years	672 (43.8)	275 (43.5)	79 (37.8)	261 (44.5)	57 (53.3)	0.069
Cardio-cerebro-vascular disease	485 (31.6)	230 (36.4)	76 (36.4)	151 (25.8)	28 (26.2)	<0.001
Chronic liver disease	40 (2.6)	16 (2.5)	3 (1.4)	18 (3.1)	3 (2.8)	0.646
Chronic lung disease	194 (12.6)	89 (14.1)	31 (14.8)	60 (10.2)	14 (13.1)	0.159
Haemoglobinopathy	13 (0.8)	2 (0.3)	1 (0.5)	8 (1.4)	2 (1.9)	0.129
Neurodegenerative diseases	57 (3.7)	19 (3.0)	5 (2.4)	31 (5.3)	2 (1.9)	0.072
≥3 risk factors for severe COVID-19, n (%)	121 (7.9)	45 (7.1)	13 (6.2)	50 (8.5)	13 (12.1)	0.229
Fully vaccinated[a], n (%)	1140 (75.8)	414 (66.2)	116 (57.7)	514 (89.1)	96 (95.0)	<0.001
Days from onset to mAbs, median (IQR)	4 (3-6)	4 (3-6)	5 (3-7)	4 (3-5)	3 (2-4)	<0.001

Abbreviations. IQR=interquartile range; BAM=bamlanivimab; ETE=etesevimab; CAS=casirivimab; IMD=imdevimab; TIX=tixagevimab; CIL=cilgavimab; BMI=Body Mass Index

[a]Fully vaccinated: has received at least 3 doses or 2 doses of which the last one within the previous 120 days

Table 2. Comparison of characteristics between patients who were hospitalized and those who were not during the follow-up after receiving monoclonal antibodies (mAbs).

	Not hospitalized N=1447	**Hospitalized N=85**	***P* Value**
Age, years, median (IQR)	66.4 (51.8-74.7)	68.7 (56.4-76.6)	0.066
Female gender, n (%)	658 (45.5)	35 (41.2)	0.508
BMI, median (IQR)	25.7 (22.5-29.3)	26.2 (22.9-29.1)	0.619
Risk factors for severe COVID-19			
BMI>=30	262 (18.1)	12 (14.1)	0.431
Renal failure	230 (15.9)	11 (12.9)	0.566
Diabetes	121 (8.4)	11 (12.9)	0.206
Immunodeficiency	588 (40.6)	40 (47.1)	0.297
Age >65 years	631 (43.5)	41 (48.2)	0.462
Cardiovascular disease	453 (31.3)	30 (35.3)	0.516
Chronic lung disease	182 (12.6)	11 (12.9)	1.000
>3 risk factors, n (%)	111 (7.7)	9 (10.6)	0.444
Fully vaccinated[a], n (%)	1073 (75.6)	66 (79.5)	0.500
Days from symptoms onset, median (IQR)	4 (3-6)	4 (3-5)	0.193
mAbs received, n (%)			
bamlanivimab+etesevimab	601 (41.5)	30 (35.3)	0.429
casirivimab+imdevimab	193 (13.3)	16 (18.8)	
sotrovimab	554 (38.3)	32 (37.6)	
tixagevimab+cilgavimab	99 (6.8)	7 (8.2)	
Calendar time (pre-Omicron[b]), n (%)	295 (20.5)	24 (28.2)	0.112
Time to viral clearance, days, median (IQR)	17 (13-22)	21.5 (16-30)	0.001

Abbreviations: BMI=Body Mass Index, IQR=interquartile range

[a]Fully vaccinated: has received at least 3 doses or 2 doses of which the last one within the previous 120 days

[b]pre-Omicron means before December 21, 2021

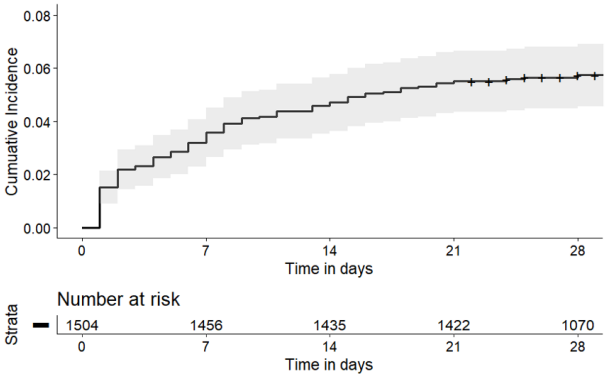
Table 3. Comparison of characteristics between patients hospitalized for COVID-19 progression and those admitted for other reasons.

	COVID-19 N=52	**Other reasons N=33**	***P* Value**
Age, years, median (IQR)	69.4 (57.7-77.7)	68.0 (56.4-76.2)	0.546
Female gender, n (%)	17 (32.7)	18 (54.5)	0.077
BMI, median (IQR)	26.9 (23.0-31.2)	24.7 (22.3-27.2)	0.136
Risk factors for severe COVID-19			
BMI>=30	9 (17.3)	3 (9.1)	0.459
Renal failure	7 (13.5)	4 (12.1)	1.000
Diabetes	9 (17.3)	2 (6.1)	0.240
Immunodeficiency	22 (42.3)	18 (54.5)	0.380
Age >65 years	26 (50.0)	15 (45.5)	0.852
Cardiovascular disease	19 (36.5)	11 (33.3)	0.945
Chronic liver disease	3 (5.8)	3 (9.1)	0.882
Chronic lung disease	7 (13.5)	4 (12.1)	1.000
Haemoglobinopathy	0 (0.0)	1 (3.0)	0.818
Neurodegenerative diseases	2 (3.8)	3 (9.1)	0.597
>3 risk factors, n (%)	6 (11.5)	3 (9.1)	1.000
Fully vaccinated[a], n (%)	38 (74.5)	28 (87.5)	0.251
mAbs received, n (%)			0.101
bamlanivimab+etesevimab	19 (36.5)	11 (33.3)	
casirivimab+imdevimab	13 (25.0)	3 (9.1)	
sotrovimab	18 (34.6)	14 (42.4)	
tixagevimab+cilgavimab	2 (3.8)	5 (15.2)	
Calendar time (pre-Omicron), n (%)	17 (32.7)	7 (21.2)	0.369
Time to hospitalization, days, median (IQR)	3.5 (1- 7)	8 (3- 15)	0.006
Length of stay, days, median (IQR)	8 (2-13)	5 (0.5-9)	0.049
Days from symptoms onset, median (IQR)	4 (3-5)	4 (3-5)	0.674
Time to viral clearance, days, median (IQR)	24 (19.5-32)	16 (14-28)	0.005

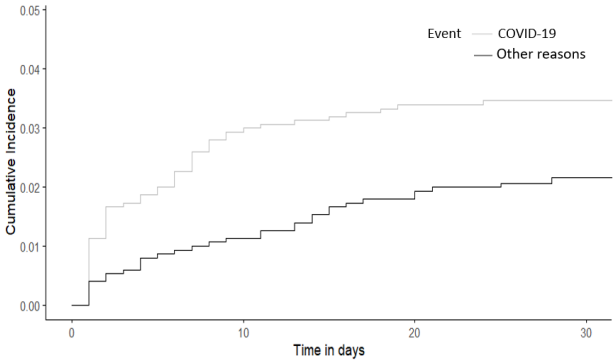
Abbreviations. BMI=Body Mass Index; IQR=interquartile range

[a]Fully vaccinated: has received at least 3 doses or 2 doses of which the last one within the previous 120 days

(a) Hospitalization or death

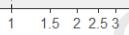


(b) Hospitalization



(a) Hospitalization

Variable		Events	N	HR (95%CI)	p
Time of mAbs administration	after 21.12.2021	61	1185	Ref	
	before 21.12.2021	24	318	1.66 (1.02, 2.69)	0.041
Gender	Female	35	682	Ref	
	Male	50	821	1.16 (0.75, 1.79)	0.497
Age (years)			1503	1.02 (1.00, 1.03)	0.021
Diabetes	Absent	74	1373	Ref	
	Present	11	130	1.67 (0.87, 3.24)	0.125
Immunodeficiency	Absent	45	885	Ref	
	Present	40	618	1.78 (1.11, 2.85)	0.017



(b) Hospitalization for COVID-19

Variable		Events	N	HR (95%CI)	p
Time of mAbs administration	after 21.12.2021	35	1185	Ref	
	before 21.12.2021	17	318	1.97 (1.09, 3.58)	0.025
Gender	Female	17	682	Ref	
	Male	35	821	1.64 (0.91, 2.93)	0.097
Age (years)			1503	1.02 (1.00, 1.04)	0.054
Diabetes	Absent	43	1373	Ref	
	Present	9	130	2.17 (1.02, 4.61)	0.045
Immunodeficiency	Absent	30	885	Ref	
	Present	22	618	1.64 (0.89, 3.03)	0.113