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Does early combination vs. Monotherapy improve clinical outcomes of clinically extremely vulnerable patients with COVID-19? Results from a retrospective propensity-weighted analysis

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Abstract

Background The potential efficacy of early combination therapy, based on an antiviral plus a monoclonal antibody, for COVID-19 in severely immunocompromised patients is matter of debate.

Objectives Our aim was to describe the impact on clinical outcomes of COVID-19 treatments in severely immunocompromised individuals, evaluating differences between a combination and a monotherapy.

Methods We included severely immunocompromised outpatients with mild-to-moderate COVID-19 who received an early treatment (either monotherapy with nirmatrelvir/ritonavir or remdesivir or the combination of an antiviral plus sotrovimab). We then assessed differences between the two treatment strategies on three main outcomes (30-day mortality, access to emergency department, hospitalization), separately and as a composite by using a propensity score weighted (PSW) approach.

Results Eighty one severely immunocompromised patients were included, 39 receiving early combination therapy and 42 receiving monotherapy. No significant difference was observed in the 30-day mortality rate and hospitalization rate between subjects in the two groups, while access to the emergency department following treatment administration was significantly higher in people who received a combination therapy. After applying the PSW, it was observed that combination therapy impacted favourably on the composite outcome, in a statistically significant fashion. In addition, PSW approach for mortality showed that age was the only significant factor influencing the death as stand-alone outcome.

Conclusions Early combination therapy showed a favourable impact on a composite outcome (including mortality, hospitalizations and access to emergency department) in severely immunocompromised hosts who were all vaccinated. However, further studies are needed to support our results.

Keywords SARS-CoV-2, Early treatment, Severe immunocompromised patients, Combined treatment, Monotherapy

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Introduction

The COVID-19 pandemic continues to challenge global healthcare systems, particularly concerning vulnerable populations [1, 2]. Among these, individuals with severe immunosuppression represent a particularly high-risk group due to their compromised ability to mount an effective immune response against viral pathogens. As a result, they have a higher risk of developing a complicated clinical course and adverse outcomes [3, 4]. After the first year period in which several and different treatments were employed trying to find an effective treatment with different results, early intervention strategies, including the use of antiretrovirals and monoclonal antibodies, have emerged as promising approaches to mitigate the severity of COVID-19 in fragile individuals and prevent disease progression, even in recent time with less aggressive SARS-CoV-2 variants [5–10].

The rationale for early intervention in this population stems from the observation that individuals with compromised immune systems often experience prolonged viral shedding, increased viral replication, and greater susceptibility to severe complications from COVID-19 [11]. Initiating an antiviral therapy in the early phase of the SARS-CoV-2 infection can reduce the viral burden, preventing disease progression and improving clinical outcomes in severely immunocompromised patients [12]. Early evidence supporting the use of antivirals in COVID-19 management comes from both observational studies and randomized controlled trials [13, 14].

Remdesivir was the first clinically effective antiviral to be introduced into clinical practice for COVID-19 as early as 2020 [15]. Remdesivir is currently the only antiviral recommended for both outpatients and hospitalized patients with COVID-19, with or without a supplemental oxygen requirement [16]. Notably, its efficacy was tested in randomized clinical trial (RCTs) mainly in the pre-vaccine era. Remdesivir is widely used in immunocompromised patients based on extrapolations from findings of RCTs, in which these patients were underrepresented [13]. In addition, observational, retrospective data, has demonstrated significant survival benefit across all variant waves, including prior to the emergence of the Omicron variant, when the therapy is promptly initiated [17, 18].

Nirmatrelvir/ritonavir also originated from trials conducted before the introduction of vaccines. As an oral drug, it is primarily used in the outpatient setting [13]. It has been successfully used in immunocompromised patients but large use in that population has been limited by the potential for drug–drug interactions between ritonavir and many immunosuppressive medications [19].

Previous study showed conflicting results about performance of antivirals and their impact on major clinical outcomes; indeed, some showed no differences between remdesivir and nirmatrelvir/ritonavir, while others showed that the oral one may be more effective [20, 21].

In addition to antivirals, monoclonal antibodies have emerged as a promising therapeutic option for COVID-19. Monoclonal antibodies are designed to mimic the body's natural immune response by targeting specific epitopes on the viral surface, thereby preventing viral attachment and entry into host cells. Early clinical trials evaluating the efficacy of monoclonal antibodies in COVID-19 have shown promising results, particularly when administered early in the course of infection [13]. A phase 3 trial by Gottlieb et al. demonstrated that a combination of bamlanivimab and etesevimab significantly reduced the risk of hospitalization or death in high-risk patients with mild-to-moderate COVID-19 [22]. Similarly, the REGEN-COV antibody cocktail, comprising casirivimab and imdevimab, showed efficacy in reducing viral load and accelerating symptom resolution in non-hospitalized patients with COVID-19 [23]. The problem for monoclonal antibodies is that ongoing alteration in the spike glycoprotein has ensued in antibody evasion making these agents ineffective [24].

Recently, observational studies have been published about the use of a combination treatment in patients with different level of immunosuppression and at high level of diseases progression [25]. However, to date, no studies have directly compared monotherapy with combination therapy in a homogenous group of extremely vulnerable patients.

Therefore, our aim was to describe the clinical outcome of COVID-19 treatment in severely immunocompromised individuals, and to evaluate whether a combination therapy has a different impact on clinical outcomes (considering both the 30-day mortality and a composite outcome including access to emergency department, hospitalization, and 30-day mortality) compared to monotherapy, by using a propensity score-weighted approach.

Materials and methods

This study was conducted and coordinated by the Infectious and Tropical Diseases Unit of Padua University Hospital, in accordance with the Declaration of Helsinki and Principles of Good Clinical Practice. Each patient was requested to sign written informed consent for participation. Study protocol was approved by Local Ethic Committee (n. AOP 0002323, January 1rst, 2022). In this retrospective series, we included all severely immunocompromised hosts who received an early treatment for mild-to-moderate COVID-19 at Padua University Hospital from January 1rst, 2022 to December 31rst, 2023. We included patients who were severely immunocompromised, with the highest risk of severe outcome related

to COVID-19 and all belonging to group 1 of the Clinically Extremely Vulnerable (CEV) classification system [26]. This system includes three categories: CEV 1, CEV 2, and CEV 3. CEV 1 includes individuals with severe primary immunodeficiencies, haematological malignancies undergoing active treatment, solid organ transplant recipients, bone marrow or stem cell transplant recipients, those receiving anti-CD-20 agents, and individuals undergoing b-depleting therapies. CEV 2 includes individuals with moderate primary immunodeficiencies, those undergoing cancer treatment for solid tumours, individuals using immunosuppressive agents not included in CEV 1, individuals with advanced untreated HIV or AIDS with CD4+ count < 200, individuals on dialysis, and individuals with severe kidney diseases. CEV 3 includes individuals with respiratory diseases, blood and metabolic disorders, diabetes treated with insulin, significant developmental disabilities, neurological impairments, and pregnant individuals with serious health conditions [27].

Treatment was classified as monotherapy (patients who received an antiviral agent, either nirmatrelvir/ritonavir or remdesivir) and combination therapy (patients who received an antiviral agent, either nirmatrelvir/ritonavir or remdesivir plus sotrovimab).

Antiviral therapy was administered according to international guidelines for outpatients: 3 days as to remdesivir (200 mg the first day, 100 mg on day 2 and on day 3), 5 days as to nirmatrelvir/ritonavir (three tablets twice daily for the planned course) [28].

For each patient we recorded time from symptom onset to treatment, number and type of symptoms, comorbidities, number of comedications, 30-day mortality, access to emergency department, hospital admission, kidney and liver function tests, vaccination status and SARS-CoV-2 serology. Time to SARS-CoV-2 negativization, by means of nasopharyngeal swab, was also recorded. The primary outcome was all-cause 30-day mortality. Outcome status was evaluated according to the patient's clinical records on day 30 from the diagnosis COVID-19 in case of hospital admission or through patient telephone contact otherwise. The secondary outcome was a composite endpoint including death, hospital admission and emergency department encounter.

Continuous variables were described using median and interquartile ranges, and categorical variables using frequencies and percentages. Wilcoxon rank-sum test was used to compare continuous variables and Pearson's χ^2 test was applied for categorical variables. A p value lower than 0.05 was used to consider differences statistically significant. Since these comparisons were potentially impacted by small sample sizes, standardized mean differences (SMD) were computed by dividing the difference between the groups by the pooled standard deviation of the two groups. A standardized difference lower than 0.1 was interpreted as a not meaningful difference. An inverse probability of treatment weighting (IPTW) approach based on propensity score (PS) was used to minimize baseline differences between the two groups of interest: patients receiving combination therapy (antiviral, either remdesivir or nirmatrelvir/ritonavir, plus the monoclonal antibody sotrovimab) versus patients receiving monotherapy (only antiviral). The PS method was chosen in addition to the conventional regression model in the light of its better performance when the number of events is low and there are multiple confounders [29]. IPTW uses the PS to balance baseline patient characteristics in the two by weighting each individual by the inverse probability of receiving his/her actual treatment [30]. In this case, the weights correspond to the inverse of the conditional PS of receiving combination therapy. In other words, a patient who was treated with the association of antiviral and sotrovimab was weighted by the inverse of the probability that they would be treated with the combination, and a patient who received antiviral alone was weighted by the inverse of the probability that they would receive only the antiviral, equivalent to 1 minus their PS. The PS was estimated using a generalized boosted model, namely a flexible, nonparametric estimation technique that can regress the treatment variable onto a large number of confounding covariates [31]. To favour the convergence of the algorithm, 5000 iterations were run; the stop method. To avoid misspecification, the PS model was constructed by subject matter knowledge [32] resorting to variables hypothesized to be associated with both treatment and outcome in a non-parsimonious fashion [33]. Specifically, the following covariates were factored in: age, gender, dyspnoea on presentation, tachypnoea on presentation, serology (presence or absence of anti-SARS-CoV-2 antibodies), viral variant, clinically extremely vulnerable (CEV) status according to a classification provided elsewhere [27], solid organ transplantation, leukaemia, lymphoma, myeloma, advanced human immunodeficiency virus infection, autoimmune disorder, necessity of oxygen therapy at baseline (independently of COVID-19), diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular or cerebrovascular disease, obesity, haemoglobin disease, altered kidney function, altered liver function, use of remdesivir or nirmatrelvir/ritonavir as antiviral, serum creatinine levels, estimated glomerular filtration rate (eGFR) measured by CKD-EPI, days from symptoms onset to diagnosis, days from symptoms onset to therapy, number of concurrent drugs, number of comorbidities, level of oxygen saturation at baseline. The quality of the IPTW was assessed by the means of

graphics and balance tables (see Appendix). Crude and propensity-weighted univariable and multivariable logistic regression models were performed to gauge factors independently associated with the outcomes. A logistic regression strategy was implemented considering the availability of complete follow-up information about the outcome status and the absence of missing data. In the multivariable models all the factors potentially associated with outcomes in univariable models ($p < 0.20$) were entered. Covariates were further selected for the final model using a stepwise backward procedure based on the lowest Akaike Information Criterion value. Combination therapy was forced in each multivariable model. Stabilized weights were used to compute the treatment effect that corresponded to the average treatment effect (ATE).

Statistical analyses were performed with R software v.4.3.2 and RStudio 31/12/202312.31 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. The following packages were used: 'twang', 'gtsummary', 'broom', 'tidyverse', 'dplyr'.

Results

During the study period 81 severely immunocompromised patients were included, with 39 receiving an early combination therapy and 42 receiving monotherapy. Full baseline characteristics, overall and by study group are reported in Table 1.

According to CEV1 conditions, we included: 50 patients on active treatment for haematological malignancies (21 leukaemia, 15 lymphoma and 14 myeloma), three patients with advanced HIV diseases with < 200 CD4+ and concomitant lymphoma (1 case) and visceral Kaposi sarcoma (2 case), and 21 patients had immunological disorders for which they were receiving anti-CD20 drugs plus steroids. No statistically significant difference was detected at the baseline between the two groups in terms of age, gender, time from symptoms to diagnosis and treatment, distribution of symptoms and comorbidities. The only difference we detected was in the eGFR value, which was significantly lower in the group receiving combination therapy than in the group receiving monotherapy (80 ml/min vs. 94.5 ml/min, $p = 0.008$). In the monotherapy group 71.4% (30/42) were treated with nirmatrelvir/ritonavir, while 28.6% (12/42) received a 3-day course of intravenous remdesivir. Conversely, subjects who received a combination therapy with sotrovimab were given a three-day course of intravenous remdesivir in 74% of cases, and nirmatrelvir/ritonavir in 25.6% (10/39) of cases. As previously stated, antivirals were used in association with sotrovimab for individuals receiving combination therapy.

Considering the study outcomes presented in Table 2, there was no significant difference observed in the 30-day mortality rate between subjects who received combination therapy and those who received monotherapy. (3/39, 7.7% vs. 4/42, 9.5%, $p = 1$).

Access to the emergency department following treatment administration was significantly higher in people who received a combination therapy compared to those who received a monotherapy (4/39, 10.3% vs. 4/42, 9.5%, $p = 0.025$), while no significant differences ($p = 0.918$) were observed in hospitalization rate between the two groups. Time to detection of first negative swab was significantly shorter in people who received monotherapy compared to those who received combination therapy (5 days vs. 7 days, $p = 0.044$). Based on the analysis of the composite outcome which includes mortality, emergency department access and hospitalization, no statistically significant difference was observed between the two groups.

After applying the PSW approach as shown in Table 3, it was observed that combination therapy, and both altered liver and kidney function were significantly associated with the composite outcome, in a favourable and unfavourable manner, respectively. In addition, PSW approach for mortality showed that age was the only relevant factor influencing the outcome.

Discussion

In this study, we assessed differences in major outcomes in the early treatment of SARS-CoV-2 infection between combined treatment (antiviral plus monoclonal antibody) or monotherapy (antiviral alone) in a cohort of severely vulnerable and immunocompromised people. The unique characteristic of this study was the selection of patients belonging to the CEV-1 group, according to the above-mentioned classification [27]. To date, information concerning the early treatments of COVID-19 using either single or combined therapies has been limited. Literature data include individuals with different degrees of immunosuppression, a small sample size, different time when combination therapy was started, making it difficult to draw definitive conclusions [12, 25, 34]. Moreover, some of them focused only on viral clearance effect, and not on major clinical outcomes [25].

In fact, as underlined in guidelines, high-quality data for combination treatment exploiting antivirals and neutralizing antibodies do not exist in the outpatient setting [35], especially in severe immunocompromised individuals. Nevertheless, several studies have attempted to investigate the effect of this approach and although these are often observational studies without control groups, generally no severe adverse reactions from the combination therapy have been reported [34, 36]. As early as 2022,

Table 1 Features of the CEV-1 study population, overall and by treatment group

Characteristics	Combination therapy, $n=39$	Monotherapy, $n=42$	*p*-value
Age, years, median (IQR)	65 (46.50–77.5)	60.5 (49–68.75)	0.202
Age > 65 years, *n* (%)	21 (53.8)	16 (38.1)	0.231
Gender, male, *n* (%)	21 (53.8)	20 (47.6)	0.736
Nirmatrelvir/ritonavir, *n* (%)	10 (25.6)	30 (71.4)	< 0.001
Remdesivir, *n* (%)	29 (74.4)	12 (28.6)	< 0.001
Days from symptoms onset to diagnosis, median (IQR)	1 (0–2)	1 (0–2)	0.582
Days from symptoms to therapy, median (IQR)	2 (1–4)	2 (2–4)	0.845
Symptoms, *n* (%)			
Fever	31 (79.5)	35 (83.3)	0.874
Coryza	10 (25.6)	19 (45.2)	0.108
Cough	23 (59.0)	32 (76.2)	0.156
Asthenia	13 (33.3)	18 (42.9)	0.514
Ageusia/dysgeusia	4 (10.3)	1 (2.4)	0.313
Anosmia	1 (2.6)	1 (2.4)	1.000
Sore throat	17 (43.6)	18 (42.9)	1.000
Myalgia	10 (25.6)	14 (33.3)	0.607
Headache	9 (23.1)	12 (28.6)	0.756
GI symptoms	5 (12.8)	4 (9.5)	0.906
Dyspnoea	3 (7.7)	1 (2.4)	0.556
Tachypnoea	1 (2.6)	1 (2.4)	1.000
Number of symptoms, median (IQR)	3 (2–3.5)	3 (3–4.75)	0.038
SpO_2, %, median (IQR)	97 (95–98)	97.5 (96–98)	0.057
SARS-CoV-2 positive serology status, *n* (%)	12 (30.8)	11 (26.2)	0.834
Variant, *n* (%)			0.006
BA.2 Omicron	28 (71.8)	31 (73.8)	
Omicron BQ.1.1	1 (2.6)	1 (2.4)	
Omicron BQ.1.X	1 (2.6)	0 (0.0)	
Omicron XBB	9 (23.1)	10 (23.8)	
Vaccination status, yes, *n* (%)	39 (100.0)	42 (100.0)	NA
Comorbidities/disease for treatment indication, *n* (%)			
Advanced HIV disease + lymphoma or KS	1 (2.6)	2 (4.8)	1.000
Autoimmune disorder under anti-CD 20 drugs	8 (20.5)	13 (31.0)	0.414
Cardio/cerebrovascular disease	11 (28.2)	5 (11.9)	0.118
Chronic obstructive pulmonary disease	7 (17.9)	4 (9.5)	0.435
Chronic kidney disease	24 (61.5)	18 (42.9)	0.145
Diabetes	4 (10.3)	6 (14.3)	0.831
Leukaemia	9 (23.1)	12 (28.6)	0.756
Lymphoma	7 (17.9)	7 (16.7)	1.000
Myeloma	7 (17.9)	8 (19.0)	1.000
Obesity	1 (2.6)	3 (7.1)	0.662
Solid organ transplant	7 (17.9)	1 (2.4)	0.048
O_2 therapy at baseline	2 (5.1)	0 (0.0)	0.442
Number comorbidities/patient other than immunodeficiency median (IQR)	1 (0–1.5)	1 (0–1)	0.778
Number concurrent drugs, median (IQR)	8 (6–10)	6 (5–7)	0.005
Altered liver function tests, n (%)	6 (15.4)	6 (14.3)	1.000
eGFR, mL/minute, median (IQR)	80 (52–95)	94.5 (80.5–101)	0.008
Serum creatinine, mmol/L, median (IQR)	78 (63.5–95)	70 (60.75–90)	0.091
AST, IU/mL, median (IQR)	20 (16.5–27.5)	24.5 (20–30.75)	0.055
ALT, IU/mL, median (IQR)	22 (16–27)	19.5 (16.25–28.5)	0.906

Table 1 (continued)

n number, % percentage, *IQR* interquartile range, *eGFR* estimated glomerular filtration rate, *IU* international unit

Table 2 Study outcomes by treatment group

Outcome	Combination therapy, $n=39$	Monotherapy, $n=42$	Standardized mean difference	*p*-value
30-day mortality, yes, *n* (%)	3 (7.7)	4 (9.5)	0.065	1
Access to the emergency department, *n* (%)	4 (10.3)	4 (9.5)	0.025	1
Hospitalization, *n* (%)	4 (10.3)	3 (7.1)	0.111	0.918
Composite outcome, *n* (%)	6 (15.4)	8 (19)	0.097	0.887
Time to negative swab, days, median (IQR)	7 (4–11)	5 (4–7)	0.508	0.044

n number, % percentage, *IQR* interquartile range

Table 3 Results of propensity score-weighted analysis for composite outcome and mortality

Variables	Estimate (odds ratio)	Standard error	*p*-value	Conf. low	Conf. high
Composite outcome					
Age	1.04	0.03	0.11	0.99	1.11
Gender (male)	0.38	0.59	0.11	0.11	1.19
Combination therapy	0.23	0.69	0.03	0.05	0.83
Number of comorbidities	0.52	0.38	0.08	0.23	1.02
T achypnoea	0.77	1.46	0.86	0.03	16.48
eGFR	0.96	0.02	0.02	0.93	0.99
Altered liver function tests	5.32	0.76	0.03	1.2	25.07
Number Comorbidities*combination	0.99	0.69	0.99	0.26	4.08
Number Comorbidities*monotherapy	1.01	0.69	0.99	0.25	3.84
30-day death					
Age	1.1	0.04	0.02	1.03	1.22
Combination therapy	0.28	0.89	0.15	0.04	1.42
Tachypnoea	11.93	1.71	0.15	0.39	419.59
Altered liver function tests	4.05	0.8	0.08	0.77	19.74

In some instances, an interaction term was introduced. Age, number of comorbidities and eGFR were modelled as continuous variables, the remaining ones as binary. In both cases the final model after backward selection was showed

Scaglione et al. described a cohort of 288 vulnerable subjects due to different conditions (unvaccinated, elderly, immunosuppressed patients), of which 8% (23/288) received the association of antiviral and monoclonal antibodies and none experienced a bad outcome, although against the backdrop of a very low rate of progression in the overall population [36]. From the same research group came a retrospective study specifically focused on severely immunocompromised outpatients (due to haematological malignancy, transplantation or treatment with anti-CD20 monoclonal antibodies) with asymptomatic-to-mild COVID-19: all individuals received a combination therapy within a median of 2 days from diagnosis and time-to-first negative swab was of just 11 days, also showing a good outcome profile in a very long follow-up [37]. That study was non-comparative, similar to another intriguing yet small study from Italy. Gentile et al. described the early combination (defined as within 10 days from symptoms onset) of two antivirals plus a neutralizing antibody in 7 immunocompromised patients ensuing in no deaths and viral clearance for all within 30 days. However, it is important to note that the study was conducted on hospitalized patients with mild-to-severe COVID-19 [12].

Initially, our study's analysis did not reveal any significant difference between monotherapy and combination therapy in the early treatment of SARS-CoV-2. Nevertheless, upon employing a statistical method aiming at

mitigating any differences at the baseline between the two treatment groups, it was observed that combination therapy, along with liver and kidney function, showed a significant association with the composite outcome. These findings highlight the continued significant impact of the SARS-CoV-2 pandemic on immunocompromised individuals, even in the Omicron era and within a fully vaccinated population. This impact is evident in terms of hospitalizations, admissions to intensive care units, and mortality rates [38]. As a result, it is crucial to prioritize the investigation of poor COVID-19 outcomes in this specific population, increase awareness among stakeholders and implement targeted preventive and treatment strategies. Moreover, what is notable is the imbalance in the impact of COVID-19 on vulnerable populations and their participation in regulatory studies, as these individuals were significantly underrepresented in clinical trials for vaccines, monoclonal antibodies, and small molecule antivirals [39].

Recently, the focus has been shifted to the management of persistent infection by SARS-CoV-2 [40]. Indeed, the development of "persistent COVID-19" in patients with weakened immune system, especially but not exclusively the ones with B-cell depletion, is a well-known complication [41], although the exact timing to define persistence is still matter of debate [42].

Even more elusive is the proper management of this novel entity, that can fuel the continuing circulation of new variants emerging from the within-host evolution of the virus in subjects who result infected for very long periods, from month to years sometimes [40]. When persistent infection develops, to maximize the chances of viral eradication a combination of different therapeutic approaches has been proposed, specifically the association between antivirals and passive immunotherapies [43]. The difficulties in treating patients with persistent COVID-19 fall within the logic of "*closing the stable door after the horse has bolted*", therefore it is crucial to try to strike a decisive blow against the virus in the early course of infection, to improve short-term outcomes and, at once, prevent in survivors the harsh consequences of lingering infection. As matter of fact, in the acute infection the window of opportunity for effective antiviral therapy is quite narrow and it is usually open in the earlier phases [44] when the viral load reaches its peak [45]. Indeed, in our study, we observed a rapid clearance of SARS-CoV-2 from nasopharyngeal swabs, with no lingering COVID-19 presence. We attribute this favourable outcome to the prompt initiation of treatment, with a median of two days between symptom onset and therapy administration.

Our study presents some limitations. First, the overall sample size is quite low, although large experiences enrolling an elevated number of profoundly immunosuppressed subjects to compare different therapeutic strategies anti-SARS-CoV-2 are lacking. Second, the limited sample size might have prevented the detection of significant differences in clinically important outcomes between groups. Furthermore, investigating a fully vaccinated population might have rendered even more difficult spotting a difference of relevant magnitude as far as hard outcomes such as mortality are concerned. Third, the study relied on the use of a monoclonal antibody such as sotrovimab whose use currently (mid-2024) is strongly discouraged owing to the lack of binding to newer variants [46]. Nevertheless, the principle to combine passive immunotherapy and antivirals can still hold, and the results related to novel long-acting neutralizing monoclonal antibodies are eagerly awaited. Moreover, observational data seemed to show an effect even during omicron era, especially in elderly people [47]. Another aspect not addressed by the present study is the possibility to extend the schedule of antivirals beyond the standard indications, for instance a prolonged course of remdesivir [16]. Fourth, the use of PS methods can attenuate but not undo biases in observational studies, since weighting relies only on observed variables, thereby unmeasured confounding cannot be ruled out. Lastly, this study was conceived to assess short-term outcomes, although of utmost importance, first and foremost mortality. Our study did not contemplate a sufficiently long follow-up to capture potential viral rebound, defined as recurrence of signs or symptoms or a new positive viral test result after initial recovery from COVID-19 [48], or viral persistence. In our study SARS-CoV-2 negativization was assessed through either molecular or antigenic tests, and we acknowledge that the latter show lower sensitivity, with suboptimal negative predictive values in immunocompromised subjects within the first weeks of positivity [49].

In conclusion, early combination of antiviral and monoclonal antibody may reduce the risk of progression of severely immunocompromised people with SARS-CoV-2. Properly conducted randomized controlled trials are eagerly awaited to highlight the optimal strategies to prevent short-term and long-term negative outcomes in these patients. It is crucial for all stakeholders to remember the lessons learned from COVID-19 and persist in addressing the challenges while supporting research to tailor intervention strategies efficiently for these particular populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02062-5.

Supplementary Material 1

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Author contributions
M.M. conceived the study. A.M. performed statistical analysis. M.M. and A.M wrote the draft of the manuscript. C.C., M.B., L.S., A.F, V.S., N.B. and E.V. curated and collected the data. A.M.C. supervised the project. All authors reviewed, approved the final version of the manuscript, and by having access to all the data had final responsibility for the decision to submit this paper for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Study protocol was approved by Local Ethic Committee (n. AOP 0002323, January 1rst, 2022). Each patient was requested to sign written informed consent for participation.

Competing interests
M.M. and A.C. received a research grant from Gilead Sciences, speakers' honoraria from ViiV Healthcare, Gilead Sciences, and Merck Sharp & Dohme, and advisory board fees from ViiV Healthcare. V.S. received speakers' honoraria from Angelini. All the other authors do not have any conflicts of interest to disclose. The authors declare no competing interests.

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