Sotrovimab in Severe COVID-19 anti-S Seronegative Immunocompromised Patients: Multicenter Retrospective Cohort

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Article

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Abstract

Purpose: Sotrovimab's effectiveness remains uncertain in severely immunocompromised inpatients with COVID-19, particularly amidst the emergence of Omicron subvariants. Our study aimed to evaluate the clinical progress and safety of severe COVID-19 at-risk inpatients treated with sotrovimab.

Methods: Retrospective multicentric cohort study (four teaching hospitals from Andalusian Health System) that included adult inpatients with inmunosupression with severe COVID-19 and negative anti-S serology who received sotrovimab from December 2021 to March 2023. Primary outcomes focused on respiratory progression (High-flow oxygen/Invasive and Non-invasive respiratory support and mortality at 28-day) while secondary variables encompassed hospital stay duration and readmission reasons.

Results: 79 patients were included, 58.2% were male, with a median age of 72 years (P_{25}-P_{75} 65-79). Significant immunosuppression factors included hematologic neoplasms in 51.9% of patients, solid organ transplants in 17.7%, and 13.9% with systemic autoimmune diseases. The median interval between symptom onset and sotrovimab infusion was 12 days (P_{25}-P_{75} 8-22), with a median hospital stay of 13 days (P_{25}-P_{75} 13-26). 36.7% of patients deceased, with 32.9% attributed directly to COVID-19. No adverse reactions to sotrovimab were reported. Univariate analysis linked age and severity at admission to COVID-19 clinical progression ($p<0.05$). Patients included in the study were distributed among dominant subvariants across five periods: BA.1 (15%), BA.2 (25%), BA.3 (31.3%), BQ.1 (16.3%), and XBB.1.5 (11.4%).

Conclusions The study underscores the need for further investigations to establish sotrovimab's efficacy in severe COVID-19 cases among immunocompromise. Early treatment initiation may be crucial considering potential limitations in its use for advanced clinical forms.

Purpose

Neutralizing monoclonal antibodies (nAbs) against SARS-CoV-2 infection target the S protein, both in epitopes located in the RBD (receptor binding-domain) region and outside of it, and can be used before or after infection to prevent and treat COVID-19 [1]. In ambulatory patients with risk factors for progression and mild-to-moderate COVID-19, nAbs have demonstrated efficacy in several clinical trials to prevent clinical worsening necessitating hospital admission or death [2–4]. Their utility in hospitalised patients with severe COVID-19 has been questioned, leading to the withdrawal of some nAbs from studies due to demonstrated clinical inefficacy [5,6]. Nevertheless, there is certainty of clinical benefit in severe patients without endogenous antibodies to SARS-CoV-2 [5,7,8]. Additionally, it is worth noting that these nAbs were designed for the early isolated variants of SARS-CoV-2, thus their neutralizing capacity is subject to the latest detected subvariants, such as omicron, whose in vitro efficacy varies [9]. Published evidence for this 'off-label' indication is limited, hence, the publication of clinical data from real-world use in treated patients with approved drugs for COVID-19 treatment is necessary, while continuing to monitor their efficacy [10].

The objective of our study is to assess the clinical progression and safety of high-risk patients with severe COVID-19 treated with sotrovimab with negative anti-S serology of SARS-CoV-2.

Methods

Study Design and Reference Population

A retrospective uncontrolled cohort study including patients hospitalized due to COVID-19 from December 2021 to March 2023 at the following public hospitals within the Andalusian Health System (Spain): University Hospital Jerez de la Frontera, University Hospital Puerto Real, University Hospital Puerta del Mar, Cadiz, and University Hospital Virgen de las Nieves, Granada.

Selection Criteria

Inclusion criteria encompassed adult patients over 18 years old with severe SARS-CoV-2 inpatients with infection confirmed microbiologically by rt-PCR, negative anti-S serology for SARS-CoV-2, and who received a 500 mg intravenous infusion of sotrovimab. Exclusion criteria included incomplete drug infusion, which, however, will be recorded for medication safety reporting, and the use of sotrovimab to prevent progression to severe forms of COVID-19.

Data Collection and Sources of Information

Patients were obtained through the Hospital Pharmacy registry, providing the medical record number to gather study variables via the electronic clinical record (Diraya®, Andalusia, Spain).

Definitions and Variables

Primary clinical progression variables were respiratory progression and mortality attributed to COVID-19 or other causes at 28-day. Secondary variables included hospital stay and hospital readmission due to COVID-19 or other causes.

Respiratory progression was defined based on the need for mechanical ventilation or life support in the intensive care unit and/or death during the follow-up period (obtained at admission and at 2, 5, 7, 14, and 28-day), serving as the primary outcome variable for the study (Score ≥ 5). It is an adaptation of the classification recommended by the World Health Organization (WHO) that proposes a common minimum in outcome measurement, based on the intensity of respiratory support [11]: 1. No need for oxygen therapy or no increase in requirements for patients with chronic home oxygen therapy; 2. Need for supplementary oxygen of 4 L/min or less via nasal cannula, or an increase in chronic home oxygen therapy requirements but ≤ 4 L/min; 3. Need for supplementary oxygen of more than 4 L/min with nasal cannula or using masks with Venturi effect; 4. Need for supplementary oxygen with reservoir mask; 5. Need for non-invasive ventilation or high-flow oxygen (i.e., high-flow nasal cannula); 6. Admission to the intensive care unit due to need for invasive ventilation, extracorporeal membrane oxygenation, hemodynamic support, or renal replacement therapy; and 7. Death.

Demographic variables, comorbidity, baseline immunosuppressive treatment, specific COVID-19 treatment, hospital stay, and clinical outcomes were collected.

To estimate dominant subvariants during the patient inclusion period, reports from the RELECOV Technical Committee (Annual Report of the SARS-CoV-2 Sequencing Laboratory Network) and the Coordinating Centre for Health Alerts and Emergencies of the spanish Ministry of Health were employed [12–14], enabling the identification of these periods:

- From week 51 of 2021 to week 8 of 2022: BA.1
- From week 9 to week 23 of 2022: BA.2
- From week 24 to week 44 of 2022: BA.5
- From week 45 of 2022 to week 4 of 2023: BQ.1
- From week 5 of 2023 to week 23: XBB.1

Analysis Strategy

Qualitative variables were described using frequencies and percentages, quantitative variables with median and 25th-75th percentile. Hypothesis testing was performed using Chi-square or Fisher's exact test for qualitative variables and the Mann-Whitney U test for quantitative variables between groups that did or did not show respiratory progression, with a p-value < 0.05 considered stadistically significant. Data analysis was conducted using SPSS version 25 (IBM, Armonk, NY, USA).

Ethical Aspects

The study was approved by the Research Ethics Committee of the Province of Cadiz, Spain (*Comité de Ética de la Investigación provincial de Cádiz*) under code 174.22. Due to the observational design, the need for informed consent was wained by the same committee. All methods in this paper were performed in accordance with the relevant guidelines and regulations. The data that support the findings of this study are available from Electronic Health Record by Andalusian Health System (Diraya®, Andalusia, Spain), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Results

A total of 79 patients were included, with 47 (58.8%) from H.U. Jerez de la Frontera, 15 (18.8%) from H.U. Puerto Real, 14 (17.5%) from H.U. Virgen de las Nieves (Granada), and 3 (3.8%) from H.U. Puerta del Mar (Cadiz). Of these, 46 patients (58.2%) were male, with a median age of 72 years (P_{25}-P_{75} 65–79). The median Charlson Comorbidity Index adjusted for age was 5 (P_{25}-P_{75} 4–7). Among these patients, the most significant immunosuppression factors were as follows: 41 patients (51.9%) had hematologic neoplasms, 14 underwent solid organ transplantation (17.7%; 10 renal, 1 renopancreatic, 2 lung, 1 hepatic), and 11 had systemic autoimmune disease (13.9%). The median number of days with symptoms before sotrovimab infusion was 12 days (P_{25}-P_{75} 8–22), with a median hospital stay until discharge or death of 13 days (P_{25}-P_{75} 13–26). Among the patients, 29 (36.7%) died, with direct attribution to COVID-19 in 26 cases (32.9%). No adverse reactions to the sotrovimab infusion were reported. The remaining variables of interest have been included in Table 1.

Table 1
Characteristics of severe COVID-19 inpatients with negative anti-S serology for SARS-CoV-2 treated with sotrovimab.

Variables	n = 79
Sex, n (%)	33(41.8)/46(58.2)
- Female/Male	
Age, median(P_{25}-P_{75})	72(65–79)
Comorbidity	5(4–7)
- Charlson Comorbidity Index age-adjusted, median(P_{25}-P_{75})	20(25.3)/39(49.4)/14(17.7)
- Diabetes, n(%)/Hypertension, n(%)/Obesity, n(%)	35(44.3)
- Hyperlipidemia, n(%)	22(27.8)
- Chronic kidney disease, n(%)	6(7.6)/41(51.9)
- Solid organ neoplasia, n(%)/Hemathologic neoplasia, n(%)	8(10.1)/4(5.1)
- COPD/Asthma, n(%)	2(2.5)
- Cirrhosis, n(%)	11(13.9)
- Autoinmune disease, n(%)	14(17.7)
- Organ solid transplant, n(%)	3(3.8)
- Primary inmunosupression, n(%)	24(30.4)
Inmunossupresive drug, n(%)	12(15.2)/2(2.5)
- Low-dose corticoesteroids (< 0.5 mg/kg)	16(20.3)/28(35.4)
- Calcineurin inhibitors/mTOR inhibitors	21(26.6)
- Myeloablative chemotherapy/antiCD20	
- Other	
SARS-CoV-2 vaccination, n(%)	9(11.4)
- Unvaccinated	23(29.1)/47(59.5)
- Standard dose/Booster dose	40(50.6)
- Last dose > 5 months	
Severity at admission, median(P_{25}-P_{75})	346(124–429)
- SpO2/FiO2	319(238–401)
- PaO2/FiO2 equivalence	
Lab values, median(P_{25}-P_{75})	119(67–162)
- C-reactive protein (mg/L; ref 0–5)	0.15(0.07–0.61)

Variables	n = 79
- Procalcitonin (ng/mL; ref < 0.1)	748(413–1537)
- Ferritin (ng/mL; ref 4.6–204)	335(236–451)
- LDH (UI/dL; ref 125–220)	657(234–1304)
- D-dimer (ng/mL; ref 0–500)	520(320–1230)
- Lymphocytes(cell/µL;1100–5000)	
SARS-CoV-2 treatment, n(%)	51(64.6)/21(26.6)
- Dexamethasone$^{6\ mg}$/Methylprednisolone$^{2mg/kg}$	23(29.1)/15(19)
- Baricitinib/Tocilizumab	2 (2.5)
- Convalescent plasma	40(50.6)
- Remdesivir	2(2.5)
- Nirmatrelvir/ritonavir	
Clinical classification*, median(P_{25}-P_{75})	2(1–3)/2(2–4)/2(2–5)
- Day 0/day 2/day 5	2(1–5)/1(1–5)/1(1–7)
- Day 7/day 14/Day 28	
Mortality, n(%); Covid-19/Other causes	26(32.9)/3(3.8)
Covid-19 readmission, n (%)/Other causes readmission, n (%)	3(3.8)/5(6.3)
Symptoms before admision days, median (P_{25}-P_{75})	9(5–15)
Hospital stay days, median(P_{25}-P_{75})	13(13–26)
Days from symptoms to sotrovimab infusion, median(P_{25}-P_{75})	12(8–22)

**No need for oxygen therapy or no increase in requirements in patients with home oxygen therapy (HOT); 2. Need for supplementary oxygen of 4 L/min or less via nasal cannula, or increased HOT requirements but less than or equal to 4 L/min; 3. Need for supplementary oxygen greater than 4 L/min with nasal cannula or use of Venturi masks; 4. Need for supplementary oxygen with non-rebreather mask; 5. Need for non-invasive ventilation or high-flow oxygen (i.e., high-flow nasal cannula); 6. Admission to intensive care unit due to need for invasive ventilation, extracorporeal membrane oxygenation, hemodynamic support, or renal replacement therapy; and 7. Death.*

Univariate analysis was conducted to determine variables associated with COVID-19 progression. Among others, age (71 vs 77; p = 0.04) and severity at admission, measured by the oxygen saturation ratio using pulse oximetry (SpO2) to fraction of inspired oxygen (FiO2) ratio (400 vs 239.5; p = 0.02), were linked to the primary outcome. The remaining analysis is presented in Table 2.

Regarding patients included according to the dominant subvariants in the established periods (Fig. 1): 12 patients (15%) were BA.1 (period 1), 20 (25%) BA.2 (period 2), 25 (31.3%) BA.3 (period 3), 13 (16.3%) BQ.1 (period 4), and 9 (11.4%) XBB.1.5 (period 5).

Table 2
Univariate analysis of severe COVID-19 inpatients with negative anti-S serology for SARS-CoV-2 who experience respiratory progression and/or decease.

Variable	No progression, n = 55	Progression, n = 24	p
Sex, n (%) - Female/Male	22(40)/33(60)	11 (45.8)/13(54.2)	0.62
Age, median (P_{25}-P_{75})	71(63.5–75)	77(65.2–80)	**0.04**
Comorbidity	5(4–7)	6(5–6,75)	0.37
- Charlson Comorbidity Index adjusted for age, median (P_{25}-P_{75})	11(20)/26(47.3)	9(37.5)/13(54.2)	0.1/0.57
- Diabetes, n(%)/Hypertension, n(%)	8(14.5)/24(68.6)	6(25)/11(31.4)	0.26/0.85
- Obesity, n(%)/Hyperlipidemia, n(%)	13(23.6)	9(37.5)	0.2
- Chronic kidney disease, n(%)	4(7.3)	2(8.3)	0.87
- Solid organ neoplasia, n(%)	30(54.5)	11(45.8)	0.47
- Hematologic neoplasia, n(%)	6(10.9)/3(5.5)	2(8,3)/1(4.2)	0.7/0.8
- COPD/asthma, n(%)	7(12.7)	4(16.7)	0.64
- Cirrhosis, n(%)	11(20)	3(12.5)	0.34
- Autoinmune disease, n(%)	10(71.4)	4(29.6)	0.57
- Solid organ transplant, n(%)	1(1.8)	2(8.3)	0.42
- Primary inmunodeficiency, n(%)			
Inmunossupresive drug, n(%)	19(34.5)	5(20.8)	0.22
- Low-dose corticoesteroids (< 0.5 mg/kg)	10(18.2)/1(1.8)	2(8.3)/1(4.2)	0.26/0.54
- Calcineurin inhibitors/mTOR inhibitors	14(25.5)	2(8.3)	0.08
- Myeloablative chemotherapy	21(38.2)	7(29.2)	0.44
- antiCD20	16(29.1)	5(20.8)	0.45
- Other			
SARS-CoV-2 vaccination, n(%)	7(12.7)	2(8.3)	0.71
- Unvaccinated	16(29.1)/28(50.9)	7(30.4)/15(62.5)	0.9/0.48
- Standard dose/Booster dose	28(56)	12(54.5)	0.9
- Last dose > 5 months			
Severity at admission, median (P_{25}-P_{75})	400(170–440)	239(118–387)	**0.02**
- SpO2/FiO2	336(291–410)	254(146–364)	**0.00**

Variable	No progression, n = 55	Progression, n = 24	p
- PaO2/FiO2 equivalence			
Lab values, median (P_{25}-P_{75})	114(65–80)	125(58–252)	**0.04**
- C-reactive protein (mg/L; ref 0–5)	0.11(0.06–0.35)	0.4(0.08–1.54)	**0.03**
- Procalcitonin (ng/mL; ref < 0.1)	854(428–1502)	681(297–2001)	0.69
- Ferritin (ng/mL; ref 4.6–204)	326(237–422)	372(236–487)	0.34
- LDH (UI/dL; ref 125–220)	451(101–1127)	1057(556–3388)	**0.04**
- D-dimer (ng/mL; ref 0–500)	670(365–1182)	425(170–1200)	0.67
- Lymphocytes(cell/µL;1100–5000)			
SARS-CoV-2 treatment, n (%)	39(70.9)	12(50)	0.74
- Dexamethasone$^{6\ mg}$	9(16.4)	12(50)	**0.02**
- Methylprednisolone$^{2mg/kg}$	17(30.9)/7(12.7)	6(25)/8(33.3)	0.59/0.05
- Baricitinib/Tocilizumab	1(1.8)	1(4.2)	0.51
- Convalescent plasma	30(54.5)	10(41.7)	0.29
- Remdesivir	2(3.6)	0(0)	1
- Nirmatrelvir/ritonavir			
Symptoms before admision days, median (P_{25}-P_{75})	9(5–16)	9.5(5–13)	0.8
Hospital stay days, median(P_{25}-P_{75})	13(8–30)	13(8–21)	0.76
Days from symptoms to sotrovimab infusion, median(P_{25}-P_{75})	11(7–25)	13.5(8–22)	0.7

Discussion

Use of nAbs in high-risk patients for disease progression and treatment necessity in severe cases in very high-risk patients

nAbs have garnered significant interest in the therapeutic arsenal against COVID-19 since the onset of the pandemic. Early administration has shown reduced progression to severe forms, including hospitalization and mortality, in patients with risk factors such as advanced age, diabetes, obesity, and cardiovascular disease, among others [15]. Regarding hospitalized patients with severe COVID-19, in the RECOVERY clinical trial, casirivimab/imdevimab demonstrated reduced mortality at 28 days in hospitalized COVID-19 patients with negative serology [16]. However, the ACTIV-3/TICO trial, involving hospitalized COVID-19 patients treated with

sotrovimab or BRII-196/BRII-198, did not show efficacy in clinical outcomes, although the latter might have benefited in sustained clinical improvement at 90 days in seronegative patients [5].

Patients considered 'very high risk', with high-level immunosuppression factors, have not been included in pivotal clinical trials [4,17] .It is known that the prognosis for oncohematological patients is worse than other patient populations, with in-hospital mortality associated with COVID-19 ranging between 21.3% and 36.5% [18,19]. However, observational studies support the early use of nAbs in these subpopulations to improve prognosis [20–23]. In the EPICOVIDEHA European cohort of 1548 oncohematological patients, a crude 30-day mortality decreased from 31.2% in the pre-vaccine era to 10.3% in the post-vaccine era (since January 2021) in COVID-19 patients (with a prevalence of 68.7% of omicron strains). In this study, the use of nAbs as monotherapy (HR 0.15; 95% CI 0.07–0.31) or in combination with antivirals (HR 0.4; 95% CI 0.2–0.8) were protective factors for crude 30-day mortality, irrespective of disease severity at diagnosis [24].

Regarding patients with solid organ transplantation and mild-to-moderate COVID-19, in a systematic review and meta-analysis, sotrovimab administration was associated with reduced hospitalization for all causes (OR 0.29; 95% CI 0.16–0.52) and mortality (OR 0.29; 95% CI 0.03–0.64) at 30 days [21].

Therefore, despite observational evidence supporting the early use of nAbs to prevent severe forms in very high-risk patients, clinical trials focused on hospitalized patients with severe COVID-19 are inconclusive as they do not include this specific population.

Subvariant Activity

The rapid emergence and spread of omicron subvariants during 2022 resulted in reduced *in vitro* activity levels of sotrovimab against subvariants BA.2, BA.5, BQ.1, and XBB.1.5. This, coupled with the virus's own characteristics of transmissibility, immune evasion, and virulence, has posed an additional challenge in comparing and interpreting clinical studies across different pandemic periods [10]. This situation has led us to continuously monitor the activity of nAbs [25], prompting the FDA (*Food and Drug Administration*) to restrict the use of sotrovimab in the United States in March 2022 [26].

Despite this demonstrated in vitro decrease, clinical efficacy seems to persist. In a meta-analysis (*rapid review*) of patients with mild-to-moderate COVID-19 treated with sotrovimab, encompassing periods of omicron variants, a reduction in mortality and hospitalization was observed, although efficacy in preventing disease progression and emergency department visits was not demonstrated [27].

Similar Studies and Results Analysis

The only study resembling ours, to our knowledge, is a retrospective, multicenter, uncontrolled cohort of 32 patients, comprising 46.9% solid organ transplant recipients and 37.5% actively treated oncohematological patients. In this study, sotrovimab was significantly associated with reduced clinical progression (12% vs 57.1%; p = 0.02) in patients who received the drug within the first 14 days of symptom onset and had a PaFiO2 at admission > 210. Consequently, the authors concluded that early treatment with sotrovimab in less severe patients might be beneficial [28]. Although the sample size is small and the included patients corresponded to delta and omicron BA.1 variants, where sotrovimab exhibited no reduction in *in vitro* activity.

In our cohort, there is a significant burden of patients with underlying diseases and causes of immunosuppression that increase their complexity and vulnerability. Additionally, factors such as advanced age, severity of hypoxemia at admission, and elevated inflammatory biomarkers (RCP, procalcitonin, and D-dimer) were associated with clinical progression, aligning with existing literature [29], and are crucial in predicting clinical evolution. We did not observe an association between the timing of sotrovimab infusion from COVID-19 symptom onset and improved prognosis. However, it's noteworthy that the median time from treatment initiation in both groups (progression *vs* no progression) exceeded 10 days, indicating a potential contribution of treatment delay with nAbs in these patients. Of interest was the association of methylprednisolone bolus use in patients with clinical progression, likely attributable to bias, where clinicians might have deemed it appropriate in more severe patients. This therapeutic option has fallen out of use since the RECOVERY trial compared high-dose dexamethasone (20 mg/day) *vs* standard doses (6 mg/day) in hypoxemic COVID-19 patients, demonstrating increased mortality (19% vs 12%; RR 1.59; 95% CI 1.20–2.10; p = 0.0012) [30]. Consequently, the standard therapy for severe COVID-19 patients remains low-dose dexamethasone.

Limitations

The limitations of our study include its observational nature, relatively small sample size, albeit larger than previously published in the literature, the variability of immunosuppression factors among included patients, and the presence of SARS-CoV-2 subvariants where sotrovimab's *in vitro* activity varies.

Conclusion

The use of sotrovimab in severe cases of COVID-19 among patients with immunosuppression factors and negative anti-S serology, while potentially having few adverse effects, warrants further investigations to substantiate its efficacy in clinical progression. Its utility may be limited in advanced disease stages, emphasising the importance of early intervention at the onset of COVID-19 symptoms.

Declarations

Author Contribution

R.L-C. conceived of the presented study, maked the statistical analysis and wrote the main manuscript. S.L-C revised the study and reviewed the statistical analysis and the manuscript. All authors reviewed the manuscript.

Data Availability

The data that support the findings of this study are available from Electronic Health Record by Andalusian Health System (Diraya®, Andalusia, Spain), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Andalusian Health System through the corresponding author who would be in charge of managing the authorizations.

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Figures

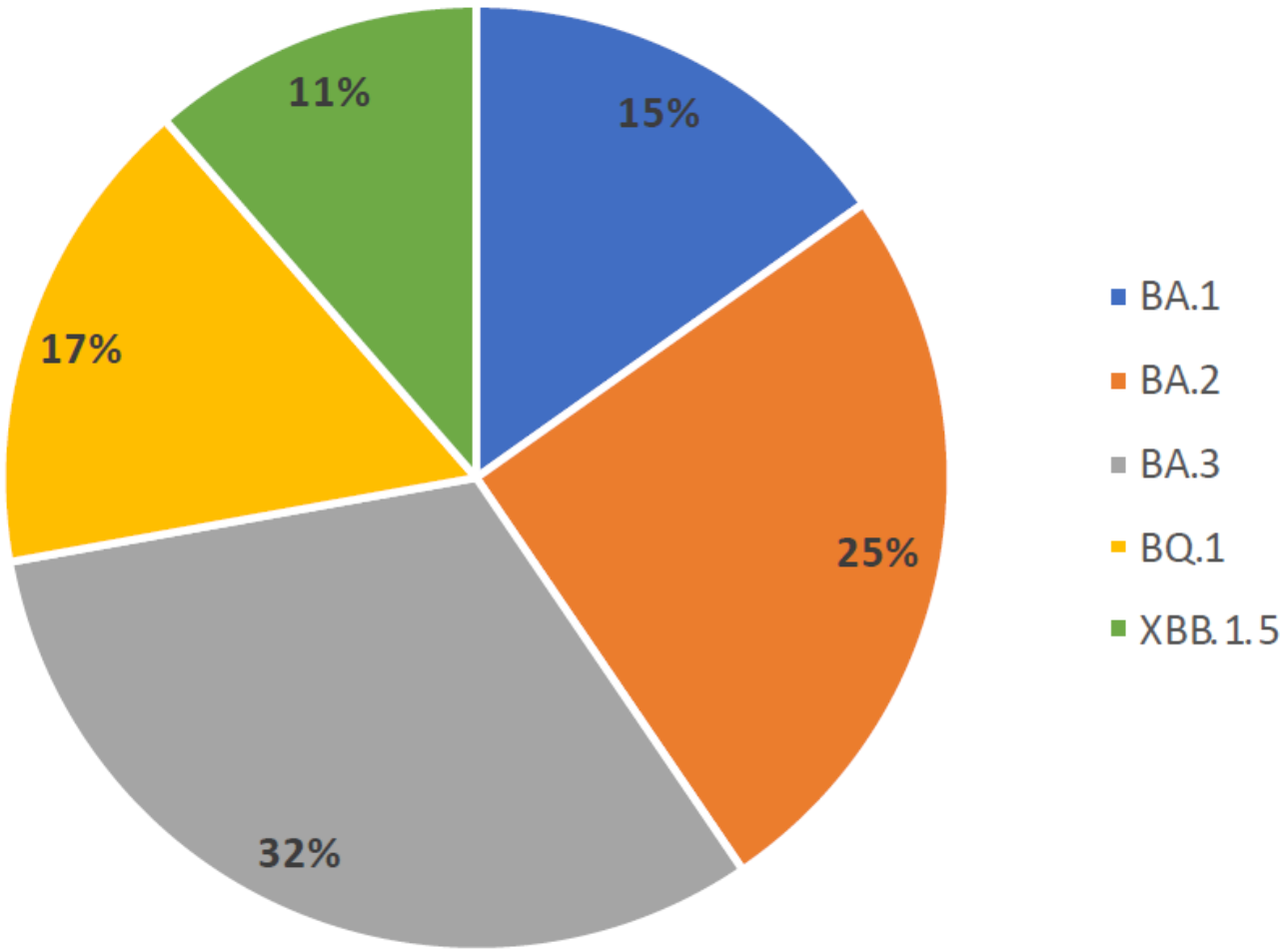

Figure 1

Temporal Prevalence of SARS-CoV-2 Subvariants in Spain among patients included according to reports from the RELECOV Technical Committee (Annual Report of the SARS-CoV-2 Sequencing Laboratory Network) and the Coordinating Centre for Health Alerts and Emergencies of the Ministry of Health.