Real-world effectiveness and factors associated with increased mortality in non-critically ill patients with COVID-19 pneumonia receiving remdesivir

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ABSTRACT

Objectives Evidence on the effectiveness of remdesivir when used in real-life clinical practice is controversial. This study aims to analyse its effectiveness and the factors associated with increased mortality in non-critically ill patients with COVID-19 pneumonia who require supplemental low-flow oxygen and received remdesivir.

Methods A retrospective cohort study was conducted at Ramón y Cajal University Hospital (Madrid, Spain) which included all patients treated with remdesivir in our institution during the second pandemic breakout in Spain, from August to November 2020. Treatment with remdesivir was limited to non-critically ill patients with COVID-19 pneumonia requiring low-flow supplemental oxygen, with a treatment duration of 5 days.

Results A total of 1757 patients were admitted with COVID-19 pneumonia during the study period, of which 281 non-critically ill patients were treated with remdesivir and included in the analysis. Mortality at 28 days after initiation of treatment was 17.1%. The median (IQR) time to recovery was 9 days (6–15). 104 (37.0%) patients had complications during hospitalisation, with renal failure being the most frequent (31 patients; 36.5%). After adjustment for confounding factors, high-flow oxygen therapy was associated with increased 28-day mortality (HR 2.77; 95% CI 1.39 to 5.53; p=0.004) and decreased 28-day clinical improvement (HR 0.54; 95% CI 0.35 to 0.85; p=0.008). A significant difference in survival and clinical improvement was identified between patients treated with high and low-flow oxygen.

Conclusion The 28-day mortality rate in patients treated with remdesivir needing low-flow oxygen therapy was higher than that published in clinical trials. Age and increased oxygen therapy needed after the beginning of treatment were the main risk factors associated with mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Remdesivir was the first drug approved for the treatment of COVID-19 pneumonia. Although its benefit is controversial, it appears to have a greater effect in patients with low-flow oxygen requirements.

WHAT THIS STUDY ADDS

⇒ This retrospective cohort study analyses the real-life benefit on 28-day mortality and time to recovery, and factors associated with increased mortality. We found a 28-day mortality rate of 17.1%, and high-flow oxygen therapy was associated with increased 28-day mortality and decreased 28-day clinical improvement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results are in line with current recommendations for the use of remdesivir in patients who require low-flow supplemental oxygen. Further research is needed to evaluate the effect of remdesivir in a similar population in terms of oxygen requirements but who have been previously vaccinated or who are infected with other variants.

INTRODUCTION

Over the last 3 years, the coronavirus disease 2019 (COVID-19) pandemic has become a major global health crisis. By June 2022, more than 500 million confirmed cases and more than 6 million deaths had been reached worldwide.[1] Multiple drugs have been investigated to manage this disease including remdesivir, the first antiviral approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Evidence on the effectiveness of remdesivir when used in real-life clinical practice is controversial. In the controlled setting of clinical trials, remdesivir was associated with a reduction in days until symptom resolution but did not achieve significant differences compared with placebo in terms of mortality.[2 3] Several systematic reviews have analysed the efficacy and safety of remdesivir and other drugs for the treatment of COVID-19, with conflicting findings.[4–6]

In July 2020 the EMA granted conditional marketing authorisation for remdesivir for the treatment of COVID-19 in adults and adolescents with pneumonia who required supplemental oxygen. As in other EU countries, the Spanish Agency for Medicines and Medical Devices (AEMPS) favoured remdesivir treatment for non-critically ill patients with COVID-19 pneumonia requiring low-flow supplemental oxygen, and recommended a specified duration of treatment of 5 days. This was justified by the shortage of supply and the uncertainty

Table 1 Demographic and clinical characteristics of the patients at baseline by 28-day mortality

	Total	Alive	Death		
	n=281	n=237	n=44	P value	N
Age (years)	68.0 (56.0–81.0)	64.0 (54.0–79.0)	81.0 (73.8–84.2)	<0.001	281
Men (%)	168 (59.8%)	141 (59.5%)	27 (61.4%)	0.948	281
Weight (kg)	78.0 (69.0–88.0)	77.0 (70.0–90.0)	80.0 (67.0–84.0)	0.559	157
Charlson Index score	1.00 (1.00–2.00)	1.00 (1.00–2.00)	2.00 (1.00–5.00)	<0.001	281
CURB-65 score:				<0.001	275
0–1 (low risk)	150 (54.5%)	141 (60.8%)	9 (20.9%)		
2 (moderate risk)	80 (29.1%)	58 (25.0%)	22 (51.2%)		
3–5 (high risk)	45 (16.4%)	33 (14.2%)	12 (27.9%)		
Low SaO_2 (age adjusted)*	107 (39.3%)	88 (38.4%)	19 (44.2%)	0.590	272
Laboratory parameters					
LDH (U/L)	385 (314–439)	374 (311–430)	402 (384–489)	0.002	268
CRP (mg/L)	93.8 (52.8–142)	91.3 (50.2–144)	96.8 (69.8–133)	0.370	278
Procalcitonin (ng/mL)	0.09 (0.05–0.19)	0.09 (0.05–0.21)	0.09 (0.07–0.14)	0.915	188
D-dimer (ng/mL)	649 (396–1020)	648 (382–1020)	709 (490–1012)	0.492	155
Serum interleukin-6 (pg/mL)	24.0 (9.60–53.3)	22.4 (8.65–49.3)	31.1 (13.9–69.3)	0.203	134
Serum ferritin (ng/mL)	922 (409–1866)	987 (436–1946)	604 (256–1118)	0.173	77
Serum creatinine (mg/dL)	0.80 (0.70–1.00)	0.80 (0.70–1.00)	0.90 (0.70–1.10)	0.188	281
eGFR CKD EPI (mL/min/1.73 m^2)	81.1 (64.3–94.5)	82.3 (66.6–96.1)	73.8 (52.7–83.4)	0.001	281
AST (U/L)	36.0 (26.2;51–0)	35.0 (27.0–49.0)	40.5 (26.0–60.0)	0.323	278
ALT (U/L)	28.0 (19.2–48.0)	29.0 (20.0–49.0)	24.5 (17.0–38.2)	0.091	278
GGT (U/L)	47.0 (30.0–102)	48.5 (31.0–104)	44.5 (27.0–72.8)	0.285	266
Serum albumin (g/dL)	3.20 (2.80–3.50)	3.20 (2.90–3.50)	3.00 (2.50–3.45)	0.122	188
Leukocytes (10^3/µL)	6.70 (4.63–9.55)	6.78 (4.65–9.56)	6.47 (4.30–9.13)	0.432	279
Neutrophils (10^3/µL)	5.34 (3.38–7.80)	5.37 (3.44–7.81)	5.07 (2.91–7.77)	0.714	279
Lymphocytes (10^3/µL)	0.83 (0.58–1.23)	0.86 (0.60–1.27)	0.72 (0.53–0.93)	0.026	279
Haemoglobin (g/dL)	13.8 (12.5–14.9)	14.0 (12.6–15.1)	13.0 (12.0–13.8)	0.001	279
Platelets (×10^9/L)	185 (136–239)	189 (141–249)	152 (126–192)	0.007	279
Serum creatine kinase (U/L)	93.0 (49.0–206)	94.0 (49.0–203)	93.0 (49.5–208)	0.817	175

*≤90% for patients aged >50 years and ≤93% for patients aged ≤50 years.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; SaO_2, saturation of oxygen.

of clinical evidence, selecting the population group with the most robust results in clinical trials.

In this context, this study aims to analyse the real-world effectiveness of remdesivir and the factors associated with increased mortality in non-critically ill patients with COVID-19 pneumonia who require supplemental low-flow oxygen and who received remdesivir.

METHODS

We conducted a retrospective single-centre longitudinal observational study at Ramón y Cajal University Hospital (Madrid, Spain), covering the dates of the second pandemic breakout in Spain from August to November 2020. According to the WHO panel for SARS-CoV-2 variants, at that point the alpha variant (B.1.1.7) was the most widespread in our geographical area.[7]

According to AEMPS criteria, treatment with remdesivir was limited to non-critically ill patients with COVID-19 pneumonia requiring low-flow supplemental oxygen (defined as nasal cannula 1–6 L/min) with a treatment duration up to 5 days. In addition, following the manufacturer's labelling, patients with aspartate aminotransferase/alanine aminotransferase levels more than five times the upper limit of normal or with severe renal impairment (glomerular filtration rate <30 mL/min) or on haemodialysis or peritoneal dialysis did not receive treatment with remdesivir.

For study purposes, all adult patients consecutively admitted with COVID-19 infection and treated with remdesivir between 1 August and 30 November 2020 were included, excluding those who participated in any clinical trial of remdesivir and who did not complete an entire course of 5 days of treatment. COVID-19 infection was confirmed by PCR testing.

The primary outcome was 28-day all-cause mortality after remdesivir initiation. The secondary outcome was time to clinical improvement, defined as the first day during the 28 days after the start of remdesivir on which a patient met the criteria for category 1, 2, or 3 on the eight-category World Health Organization disease severity score.[8] Death and failure of clinical improvement were censored at 28 days.

Additional variables included as potential risk factors associated with higher mortality rate were patient age, sex, Charlson Comorbidity Index (CCI) score, CURB-65 pneumonia severity score, days since symptom onset, supplemental oxygen therapy, intensive care unit (ICU) admission, and laboratory values, vital signs and inpatient COVID-19 medication. For analysis purposes, laboratory values and vital signs were collected as baseline variables as close to the start of remdesivir treatment as registered. We considered initial oxygen therapy as the type of supplemental oxygen administered 24 hours after the onset of remdesivir.

Table 2 Patient characteristics during hospitalisation by 28-day mortality

	Total	Alive	Death	
	n=281	n=237	n=44	P value
Days from symptom onset to initiation of remdesivir	6.00 (5.00–7.00)	6.00 (5.00–7.00)	6.00 (5.00–7.00)	0.644
Days from admission to initiation of remdesivir	2.00 (1.00–3.00)	1.00 (1.00–3.00)	2.00 (1.00–4.00)	0.051
Other medication				
Tocilizumab	58 (20.6%)	40 (16.9%)	18 (40.9%)	0.001
Systemic corticosteroids	273 (97.2%)	229 (96.6%)	44 (100%)	0.615
Azithromycin	23 (8.19%)	19 (8.02%)	4 (9.09%)	0.767
Other antibiotic	214 (76.2%)	172 (72.6%)	42 (95.5%)	0.002
Hydroxychloroquine	1 (0.36%)	1 (0.42%)	0 (0.00%)	1.000
Low molecular weight heparin	275 (97.9%)	233 (98.3%)	42 (95.5%)	0.238
Oxygen therapy				
High-flow	39 (13.9%)	25 (10.5%)	14 (31.8%)	<0.001
Low-flow	224 (79.7%)	196 (82.7%)	28 (63.6%)	0.007
NIV	7 (2.49%)	5 (2.11%)	2 (4.55%)	0.302
MV	4 (1.42%)	4 (1.69%)	0 (0.00%)	1.000
None	7 (2.49%)	7 (2.95%)	0 (0.00%)	0.601
ICU admission	42 (14.9%)	32 (13.5%)	10 (22.7%)	0.178
ICU stay (days)	17.0 (9.50–32.0)	17.5 (10.0–33.5)	11.0 (6.50–17.5)	0.323
Orotracheal intubation	37 (13.2%)	28 (11.8%)	9 (20.5%)	0.189
Complications during hospitalisation	104 (37.0%)	74 (31.2%)	30 (68.2%)	<0.001
Renal failure	31 (11.0%)	21 (8.86%)	10 (22.7%)	0.015
Respiratory distress syndrome	57 (20.3%)	37 (15.6%)	20 (45.5%)	<0.001
Nosocomial infection	34 (12.1%)	23 (9.70%)	11 (25.0%)	0.009
Sepsis	18 (6.41%)	11 (4.64%)	7 (15.9%)	0.012
Septic shock	13 (4.63%)	6 (2.53%)	7 (15.9%)	0.001
Thrombosis	7 (2.49%)	5 (2.11%)	2 (4.55%)	0.302
Hepatic failure	2 (0.71%)	1 (0.42%)	1 (2.27%)	0.289
Acute bleeding	8 (2.85%)	4 (1.69%)	4 (9.09%)	0.023
Limitation of treatment	29 (10.3%)	3 (1.27%)	26 (59.1%)	<0.001
Grade 3–4 toxicity during remdesivir treatment	32 (11.4%)	23 (9.70%)	9 (20.5%)	0.071
Days from symptom onset to initiation of remdesivir	6.00 (5.00–7.00)	6.00 (5.00–7.00)	6.00 (5.00–7.00)	0.644

ICU, intensive care unit; MV, mechanical ventilation; NIV, non-invasive ventilation.

Patient-level data were collected using the information available in the hospital's electronic medical record until the resolution of admission (death or discharge) or up to 28 days after the start of treatment in case of early discharge. Only the first episode that met the inclusion criteria was considered in patients with multiple admissions during the study period. Post-discharge follow-up was completed through the electronic medical record, integrated with outpatient follow-up.

Additionally, data on all the patients admitted for COVID-19 infection during the study were obtained through the hospital's admission database. For this secondary analysis, only in-hospital mortality could be taken into account.

All participants for whom the variables of interest were available were included in the final analysis, and no assumptions were made for missing data. Non-normally distributed variables were compared by the Mann–Whitney U test and categorical data were analysed with the Fisher's exact test. A Kaplan–Meier curve was used to analyse 28-day survival and clinical improvement. Survival curves were stratified by oxygen therapy and compared using the log-rank test. Two-sided significance was tested with p values <0.05 considered significant.

A multivariate Cox proportional hazards regression model was developed to identify factors associated with increased mortality, including factors with a significant association in the univariate

Table 3 Cox regression analysis for 28-day mortality and clinical improvement

	Mortality			Clinical improvement		
Characteristic	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.06	1.03 to 1.09	<0.001	0.99	0.98 to 1.00	0.031
Charlson Index score	1.15	1.04 to 1.28	0.009	0.905	0.841 to 0.974	0.008
LDH (U/L)	1.01	1.00 to 1.01	<0.001	1.00	1.00 to 1.00	<0.001
Haemoglobin (g/dL)	0.79	0.66 to 0.96	0.015			
High-flow oxygen therapy	2.77	1.39 to 5.53	0.004	0.54	0.35 to 0.85	0.008
Platelets ($\times 10^9$/L)				1.00	1.00 to 1.00	0.013

HR, hazard ratio; LDH, lactate dehydrogenase.

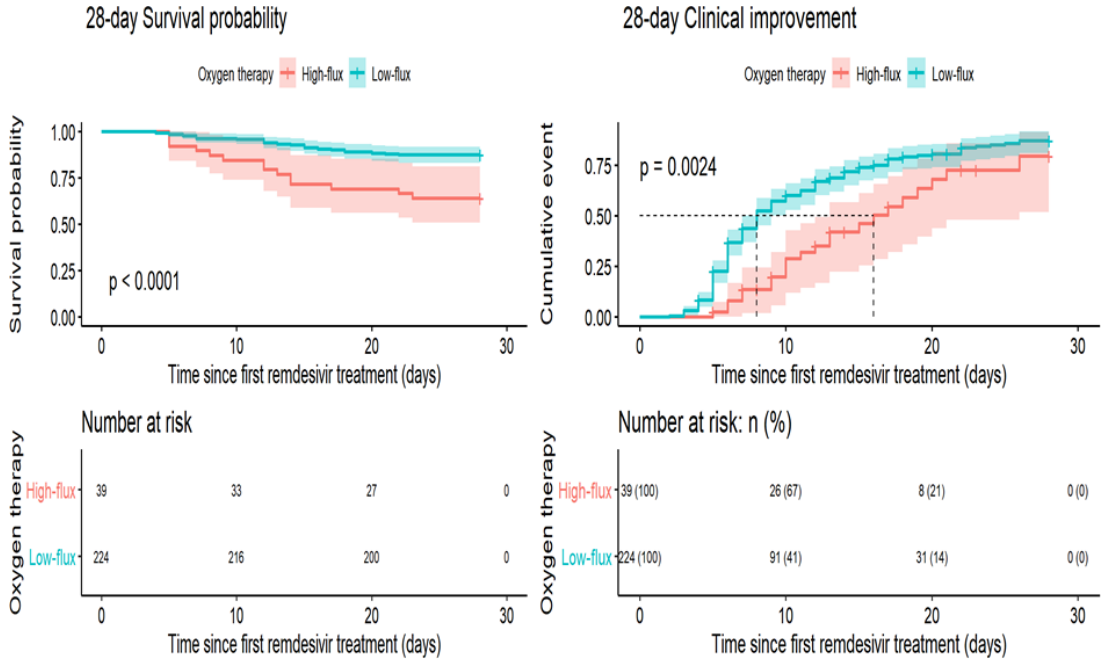

Figure 1 28-day survival and clinical improvement according to oxygen therapy.

analysis. A stepwise procedure was used to select the final model according to the Akaike Information Criteria. Potential multicollinearity between predictors was analysed by the variance inflation factor. Study data were collected and managed with Research Electronic Database Capture (REDCap versión 9.9.1). Analysis was performed with the R statistical package version 4.0.0 (R Foundation for Statistical Computing).

RESULTS

During the study period, 1757 patients were admitted with COVID-19 pneumonia to our institution, of which 318 non-critical patients received treatment with remdesivir. For the study, 37 patients were excluded because they did not complete 5 days of treatment with remdesivir. The main reasons for discontinuation were toxicity (4%), death (0.6%), early discharge (6.3%) or limitation of therapeutic effort (2.8%).

The baseline characteristics of the patients included are shown in table 1. Median (IQR) age was 68.0 (56.0–81.0) years and 54.5% were classified as low risk at admission according to the CURB-65 score. Although before the start of treatment all patients required low-flow oxygen, in the following 24 hours 39 (13.9%) required high-flow oxygen, seven (2.5%) required non-invasive ventilation, four (1.4%) mechanical ventilation and seven (2.5%) did not require any supplemental oxygen. According to the local COVID-19 protocol, 58 (20.7%) patients were treated with tocilizumab and 273 (97.2%) with systemic corticosteroids. The median (IQR) number of days from symptom onset to initiation of remdesivir was 6 (5–7) and from admission to initiation of remdesivir was 2 (1–3).

In this cohort of non-critically ill patients treated with remdesivir, 28-day mortality was 17.1%. The median (IQR) time to recovery was 9 (6–15) days and 42 (14.9%) patients were admitted to the ICU. A total of 104 (37.0%) patients had complications during hospitalisation, of which renal failure was the most frequent (31 patients; 36.5%). During remdesivir treatment, 32 (11.4%) patients experienced grade 3–4 toxicity.

In the univariate analysis (tables 1 and 2), factors associated with higher 28-day mortality were age, Charlson Index score, higher pneumonia severity according to the CURB-65 score, increased lactate dehydrogenase and decreased baseline estimated glomerular filtration rate, lymphocytes, platelets and haemoglobin. Table 3 shows the variables included in the final multivariate Cox regression model. After adjustment for confounding factors, high-flow oxygen therapy was associated with increased 28-day mortality (HR 2.77; 95% CI 1.39 to 5.53; p=0.004) and decreased 28-day clinical improvement (HR 0.54; 95% CI 0.35 to 0.85; p=0.008).

Using the log-rank test, the Kaplan–Meier method found a significantly inferior survival and clinical improvement among patients who required high-flow versus low-flow oxygen (p=0.0001 and p=0.0024, respectively) (figure 1).

During the same period, inpatient mortality in all patients admitted with COVID-19 (n=1750) was 15.9%. Although it was not the study's main objective, the impact of remdesivir on patient mortality was analysed globally through the hospital's admission database. Remdesivir had no significant effect on in-hospital mortality either independently (OR 1.08; 95% CI 0.76 to 1.51, p=0.7) or adjusted for sex, age and Charlson Index score at admission (OR 1.17; 95% CI 0.79 to 1.71, p=0.4).

DISCUSSION

Our study evaluated clinical results (time to recovery and mortality) within a retrospective cohort of non-critically ill patients treated with remdesivir during the second pandemic breakout in Spain. Median age was near 70 years and most patients had comorbidities and pneumonia associated with a low-to-moderate risk according to the CURB-65 index, which required low-flow oxygen therapy at admission.

The mortality rate at 28 days from the beginning of treatment was 17.1% in our cohort, higher than that reported by Wang *et al* (14.0%),[9] Beigel *et al* (11.4%)[2] and the SOLIDARITY trial (11.0%),[10] none of which could link the use of remdesivir to a reduction in mortality. When analysing mortality in the subgroup of hospitalised patients requiring oxygen therapy, Beigel *et al* found a rate of 4.0%. This difference is especially striking since all our patients were included in that category, and could be explained by

the older median age of our population and variations in oxygen therapy requirements within the first 24 hours of treatment in our cohort. Furthermore, mortality in our study was significantly associated with high-flow oxygen therapy needs. This result matches those obtained in the ACTT-1 study, in which a more significant benefit of remdesivir treatment was observed in those patients who only required low-flow oxygen therapy.[2]

In our cohort, mortality was also higher than in other real-life studies carried out in our country. García-Vidal *et al*[11] and Murgadella-Sancho *et al*[12] published results of two cohorts of 123 and 111 patients, observing mortality rates of 4.1% and 6.3%, respectively. Baseline characteristics were similar to our population in terms of days from the beginning of symptoms to the start of remdesivir treatment (6 and 7 days vs 6 days, respectively) and comorbidities. However, the median age was lower (58.0 and 56.8 years, respectively). Finally, Hidalgo-Tenorio *et al* found a 10.3% mortality in their cohort.[13] Even though baseline characteristics in this cohort were similar to our study, in the subgroup analysis a difference in the median age of deceased patients can be observed (68.2 vs 81.0 years).

An association between 28-day mortality and the following factors was found in our study: advanced age, Charlson Comorbidity Index, severe pneumonia according to CURB, high lactate dehydrogenase, lymphopenia, anaemia and oxygen need increasing after the beginning of remdesivir treatment. These prognostic factors are similar to those identified in other studies.[2 3 13 14] Interleukin-6 levels could not be taken into account in this analysis due to the large proportion of missing data.

The median time to recovery in our cohort was 9 days, which is comparable to that of Beigel *et al*,[2] although slightly higher than that seen in the low-flow oxygen subgroup (7 days median). These results support the hypothesis of the greater severity of the disease suffered by our patients.

Our findings are in line with the recommendations of international clinical guidelines on the treatment of COVID-19 pneumonia. European and American clinical guidelines suggest using remdesivir only in patients with COVID-19 pneumonia requiring low-flow supplemental oxygen, while they advise against its use in those requiring high-flow oxygen, non-invasive ventilation or mechanical invasion.[15 16]

The large sample size and the fact that all patients were treated according to a unified protocol are strengths of our study. In addition, being a real-life study allowed us to register changes in oxygen therapy needs in the first 24–48 hours following treatment onset, which is significantly different from clinical studies. Moreover, given that the AEMPS defined the criteria for access to remdesivir, this study shows the real-world effectiveness of remdesivir in a homogeneous population that, theoretically, obtained better results in the initial clinical trials.

The main limitations include its retrospective and single-centre nature. Furthermore, since the study was conducted before COVID-19 vaccines were available, its extrapolation to vaccinated populations may be limited. Even so, we consider that this study is of interest when assessing the effectiveness of treatment in unvaccinated patients or in the face of possible vaccine escapes.

CONCLUSION

The 28-day mortality in patients treated with remdesivir needing low-flow oxygen therapy in our practice was higher than that published in clinical trials. Age and increased oxygen therapy needed after the beginning of treatment were the main mortality risk factors.

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Contributors LQM, JF-F and JSdlF contributed to the study conception and design. LQM, JF-F, HM-B, MSC, MMR, MRPR, CQR-N, AMA-D and JSdlF performed material preparation, data collection and analysis. LQM wrote the first draft of the manuscript and JF-F, HM-B, MSC, MMR, MRPR, CQR-N, AMA-D and JSdlF commented on early versions of the manuscript. LQM, JF-F, HM-B, MSC, MMR, MRPR, CQR-N, AMA-D and JSdlF read and approved the final manuscript. HM-B is acting as a guarantor

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Patient consent for publication Not applicable.

Ethics approval Ramón y Cajal University Hospital Institutional review boards approved this study (ID008-21) as minimal risk and waived informed consent requirements. No compensation was offered or received for participating.

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