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¹) Baker, Morya. "1,500 scientists lift the lid on reproducibility." Nature, no. 533 (May 26, 2016): 452-54. doi:10.1038/533452a.

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The role of teicoplanin in the treatment of SARS-CoV-2 infection: A retrospective study in critically ill COVID-19 patients (Tei-COVID study)

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Abstract

Teicoplanin has a potential antiviral activity expressed against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was suggested as a complementary option to treat coronavirus disease 2019 (COVID-19) patients. In this multicentric, retrospective, observational research the aim was to evaluate the impact of teicoplanin on the course of COVID-19 in critically ill patients. Fifty-five patients with severe COVID-19, hospitalized in the intensive care units (ICUs) and treated with best available therapy were retrospectively analysed. Among them 34 patients were also treated with teicoplanin (Tei-COVID group), while 21 without teicoplanin (control group). Crude in-hospital Day-30 mortality was lower in Tei-COVID group (35.2%) than in control group (42.8%), however not reaching statistical significance ($p = .654$). No statistically significant differences in length of stay in the ICU were observed between Tei-COVID group and control group ($p = .248$). On Day 14 from the ICU hospitalization, viral clearance was achieved in 64.7% patients of Tei-COVID group and 57.1% of control group, without statistical difference. Serum C-reactive protein level was significantly reduced in Tei-COVID group compared to control group, but not other biochemical parameters. Finally, Gram-positive were the causative pathogens for 25% of BSIs in Tei-COVID group and for 70.6% in controls. No side effects related to teicoplanin use were observed. Despite several limitations require further research, in this study the use of teicoplanin is not associated with a significant improvement in outcomes analysed. The antiviral activity of teicoplanin against SARS-CoV-2, previously documented, is probably more effective at early clinical stages.

KEYWORDS

COVID-19, glycopeptide, ICU, intensive care unit, pneumonia, SARS-CoV-2, Teicoplanin

1 | INTRODUCTION

One of the main problems in the management of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is the current unavailability of drugs specifically active in the management of coronavirus disease 2019 (COVID-19).¹ For this reason, the search for therapeutic resources represents the main target of research, pending the availability of an effective vaccine.

Evidence from the scientific literature highlighted that a number of glycopeptide antibiotics and their chemical derivatives have a potential antiviral activity expressed against SARS-CoV, Middle East respiratory syndrome coronavirus Ebola virus, influenza A and B viruses and feline infectious peritonitis virus.²⁻⁵

SARS-CoV-2 infection, similarly to SARS-CoV, is a multistep process including cathepsin L proteolysis of the S protein; teicoplanin was found to specifically inhibit the cathepsin L activity and to play a potential role in blocking cell entry of the cathepsin L-dependent viruses.⁶⁻⁸

Based on the aforementioned, teicoplanin was suggested as an alternative complementary option to treat also SARS-CoV-2 infected patients.⁹⁻¹¹ Moreover, teicoplanin is a possible choice for treatment of *Staphylococcus aureus* superinfection, a major complication of respiratory viral infections.¹²

Here we present the first retrospective analysis of a real-life cohort of critically ill patients with COVID-19 complementary treated with teicoplanin, used with a double purpose: as empiric treatment of possible *S. aureus* superinfection and as antiviral agent for SARS-CoV-2. Comparable severe COVID-19 cases untreated with teicoplanin were used as control group. The aim of the study was to evaluate the impact of teicoplanin on the course of COVID-19 in critically ill patients.

2 | METHODS

This was a multicentric, retrospective, observational research, formally named "Tei-COVID Study." The primary outcome was comparison of crude Day-30 mortality rate in two groups; the secondary outcomes were length of in-intensive care unit (ICU) stay (LOS). Other parameters evaluated were changes in (1) kidney and liver function, (2) inflammatory markers, (3) day 6-12 viral clearance rate, (4) bacterial and fungal superinfection.

We retrospectively analyzed a multicentric cohort of 55 patients with severe COVID-19 related lung involvement, progressively hospitalized in the ICUs of three teaching hospital in Lazio administrative Region (Italy), between March 9th and April 30th, 2020.

Only adult patients (>18 years) who underwent invasive mechanical ventilation due to COVID-19 related severe acute hypoxemia were included in this analysis.

Diagnosis of SARS-CoV-2 infection was defined as one positive oropharyngeal and nasopharyngeal swab performed in duplicate for SARS-CoV-2 E and S gene by a reverse transcriptase polymerase chain reaction.¹³

All patients involved in the analysis were treated with ad interim best available combination therapy as suggested by the provisional

guidelines published by Italian Society of Infectious and Tropical Diseases¹⁴: hydroxychloroquine (200 mg twice daily) plus azithromycin (500 mg daily) and tocilizumab (8 mg/kg, up to a maximum of 800 mg/dose, twice) were administered. All patients, treated with lopinavir/ritonavir or darunavir/cobicistat, discontinued antivirals without viral clearance previously with respect to ICU admission. Steroids (dexamethasone) and unfractionated heparin were also prescribed in all patients.

Patients enrolled in one ICU received teicoplanin 6 mg/kg every 24 h (loading dose every 12 h for three doses) as a "pre-emptive" therapeutic strategy for possible *S. aureus* superinfection (Tei-COVID group). In other ICUs teicoplanin was not used (control group).

The source for patient data was medical records stored in the Electronic Information System of ICUs involved. The variables considered for the study included: (1) anamnestic data, (2) past clinical history (comorbidities), (3) current clinical history (including LOS and in-hospital death) and laboratory data, (4) bacterial and fungal superinfection data.

Reporting of the study conforms to broad EQUATOR guidelines.¹⁵ Ethical approval was obtained from Ethics Committee of Policlinico Umberto I - Sapienza University of Rome, Italy (approval number/ID Prot. 109/2020).

2.1 | Statistical analysis

The statistical analyses were performed with Statistical package for social science software, version 22. The data were presented as median and interquartile range ([IQR]: 25th-75th) and the presence of statistically significant differences between groups were assessed by the Mann-Whitney *U* test (or Student *t* test). The categorical variables were described as simple frequencies, proportion, or percentages (%) and then compared by the χ^2 test (or Fisher's exact test for small cells) for the two groups, since some continuous variables exhibited skewed distributions on visual inspection, and the Kolmogorov-Smirnov test indicated non-normal distributions. Unstandardized mean difference (USMD) and their 95% CIs were analyzed between the COVID-19 and the control groups.^{16,17} USMD has been computed as the difference between the COVID-19 measured and control group, divided by the whole population variance. We have done a standard survival analysis, tracing participants from entry into the clinic to the discharge or death at 30 days. The event-free survival in follow-up was depicted graphically by Kaplan-Meier's survivor curve, using Cox regression analysis, including the confounding factors with fixed baseline covariates. A two-sided *p* value test of less than .05 was considered statistically significant.

3 | RESULTS

All 55 patients included in the analysis were Caucasian subjects intubated for mechanical ventilation support and admitted to the ICUs for severe respiratory complications after a median of 6 days (range: 2-10 days) from COVID-19 symptom onset. Their demographic and baseline clinical characteristics were reported in Table 1. Tei-COVID group enclosed 34 subjects, while control group 21. The characteristics of the two

TABLE 1 Baseline characteristics of all patients included in the study, of the Tei-COVID group and control group

Parameters	Total population (N° 55)				Control group (N° 21)				Tei-COVID group (N° 34)				p Value Tei-COVID group versu control group	USMD (95% CI)						
	Median	IQR	25%	75%	Number	N%	Median	IQR	25%	75%	Number	N%			Median	IQR	25%	75%	Number	N%
Sex (male)	-	-	-	-	43	78%	-	-	-	-	14	67%	-	-	-	-	29	85%	0.123	0.22 (0.18 to 0.32)
Age (years)	70.0	59.0	76.0	76.0	-	-	69.0	59.0	73.0	73.0	-	-	70.5	59.3	76.0	76.0	-	-	0.971	0.01 (-0.34 to 0.4)
CCI	1	1	3	3	-	-	1	1	3	3	-	-	1	1	3	3	-	-	1.000	-0.01(-0.42 to 0.15)
SAPS II	40	34	47	47	-	-	39	34	45	45	-	-	41.0	34.3	47.0	47.0	-	-	0.998	-0.01(-0.15 to 0.2)
WBC	8.5	6.2	12.3	12.3	-	-	11.8	6.2	13.2	13.2	-	-	7.6	5.8	10.0	10.0	-	-	0.123	-0.48 (-0.9 to -0.04)
Lymphocytes	1.2	0.6	6.4	6.4	-	-	8.7	0.6	17.9	17.9	-	-	0.8	0.5	1.2	1.2	-	-	0.161	0.35 (-0.25 to 0)
Creatinine	1.1	0.8	1.6	1.6	-	-	0.9	0.8	1.3	1.3	-	-	1.2	0.9	1.8	1.8	-	-	0.625	-0.17 (-0.52 to 0.33)
ALT	28.0	22.0	45.5	45.5	-	-	27.0	22.0	46.0	46.0	-	-	28.5	22.3	42.0	42.0	-	-	0.860	-0.05 (-0.48 to 0.38)
AST	36.0	25.0	57.0	57.0	-	-	38.0	25.0	51.0	51.0	-	-	34.5	25.5	61.0	61.0	-	-	0.166	0.34 (-0.04 to 0.82)
PCT	0.3	0.1	1.3	1.3	-	-	0.4	0.1	1.4	1.4	-	-	0.3	0.1	1.1	1.1	-	-	0.274	0.08 (-0.35 to 0.51)
CRP	15	11	27	27	-	-	12.3	17.1	18.7	18.7	-	-	18.0	4.5	34.3	34.3	-	-	0.078	-0.37 (-0.75 to 0.11)
D-Dimer	1816	858	3468	3468	-	-	1741	793	2900	2900	-	-	1891	922	4036	4036	-	-	0.858	0.06 (-0.36 to 0.49)
P/F ratio	208.5	148.5	333.3	333.3	-	-	197.0	148.5	334.0	334.0	-	-	225.0	164.0	324.5	324.5	-	-	0.557	0.17 (-0.25 to 0.6)

Abbreviations: ALT, aminoalanine transferase; AST, aspartate aminotransferase; CCI, Charlson comorbidity index; CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; SAPS II, simplified acute physiology score; USMD, unstandardized mean difference; WBC, white blood cells.

groups are shown in Table 1. No statistically significant differences in the characteristics between groups were observed at baseline. The median time of teicoplanin administration was 8 days (range: 6–12 days) in Tei-COVID group.

3.1 | Teicoplanin did not significantly reduce crude in-hospital Day 30 mortality for critically ill patients

Crude in-hospital Day-30 mortality was lower in Tei-COVID group (35.2%) than in control group (42.8%), however not reaching statistical significance ($p = .654$). Kaplan–Meier survival curve was showed in Figure 1; log-rank test cut-off was greater than 0.05 at Day 14 and 30 for mortality.

3.2 | Teicoplanin did not significantly reduce length of in-ICU stay

Regarding the length of stay in the ICU, no statistically significant differences were observed between Tei-COVID group and control group (median 14.5 days [IQR: 5.3–21.8] vs. 13 days [IQR: 9–16]; $p = .248$). The overall median length of in-ICU hospitalization was 14 days (IQR: 9–20).

3.3 | Teicoplanin treated group showed a more effective reduction of inflammatory markers

Serum C-reactive protein level was significantly reduced in Tei-COVID group compared to control group (Figure 2). No statistically significant differences were observed for white blood cells and

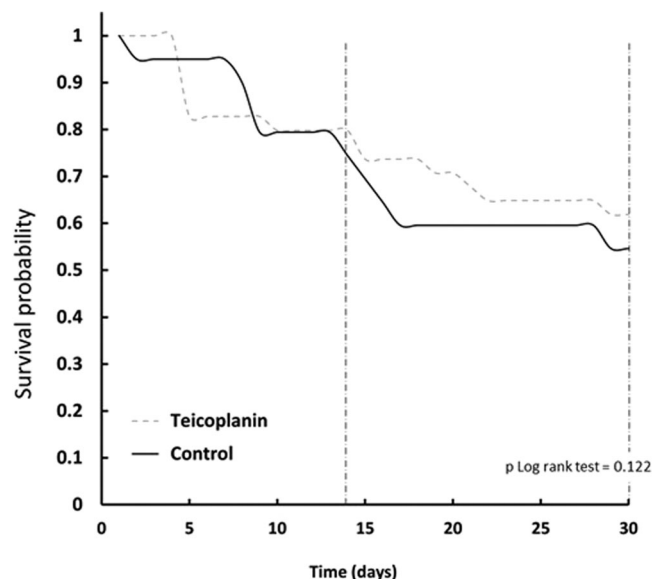


FIGURE 1 Kaplan–Meier survival curve in Tei-COVID e control groups. COVID, coronavirus disease

lymphocytes counts, kidney and liver function, PO_2/FiO_2 and weaning from mechanical ventilation between the two groups at day 8 (median time of teicoplanin administration). On Day 14 from the ICU hospitalization, 22 out of 34 (64.7%) patients of Tei-COVID group achieved viral clearance and 12 out of 21 (57.1%) of control group, without statistical difference.

3.4 | Bloodstream superinfections were less frequent in Teicoplanin treated group

Overall, 33 episodes of BSI were observed. Bacterial bloodstream superinfections were reported in 35% (12/34) of patients included in Tei-COVID group (were due to) and in 57% (12/21) of controls as reported in Table 2. Gram-positive were the causative pathogens for 25% of BSIs in Tei-COVID group and for 70.6% in controls. A total of two cases of candidemia were observed without statistical differences between the two groups; no cases of aspergillosis were reported.

3.5 | Safety

No side effects related to teicoplanin administration were observed in Tei-COVID group.

4 | DISCUSSION

We previously described the first report of in vivo use of teicoplanin as an antiviral agent for COVID-19.¹⁰ Here we reported an update, analyzing a retrospective multicentric cohort composed of mechanical ventilated SARS-CoV-2 infected patients complementary treated and untreated with teicoplanin. Our data showed that teicoplanin does not impact on the crude mortality in critically ill COVID-19 patients: the primary outcome of the study failed due to lack of statistical significance despite mortality being lower in the Tei-COVID group than in the control group (35.2% vs. 42.8%). In the same way, LOS was not reduced by teicoplanin administration. Commonly, the antiviral activity of a drug is considered more effective at the onset of disease when viral replication and direct viral damage are still significant. As the disease progresses, the damage is progressively sustained by pathogenic mechanisms not directly correlated with the presence of the virus, thus reducing the potential therapeutic role of antivirals at this stage.¹⁸ In particular, in critically ill patients, a massive chemokine and cytokine release has been described associated with an uncontrolled and aberrant response from the host immune system which results in multiorgan dysfunction and acute respiratory distress syndrome, the leading cause of mortality in SARS-CoV-2 infected patients.^{19–21} In our case, the patients enrolled were in an advanced stage of the disease, chronologically distant from the onset of symptoms: therefore, the potential antiviral role of teicoplanin may not be adequately observed in this setting.

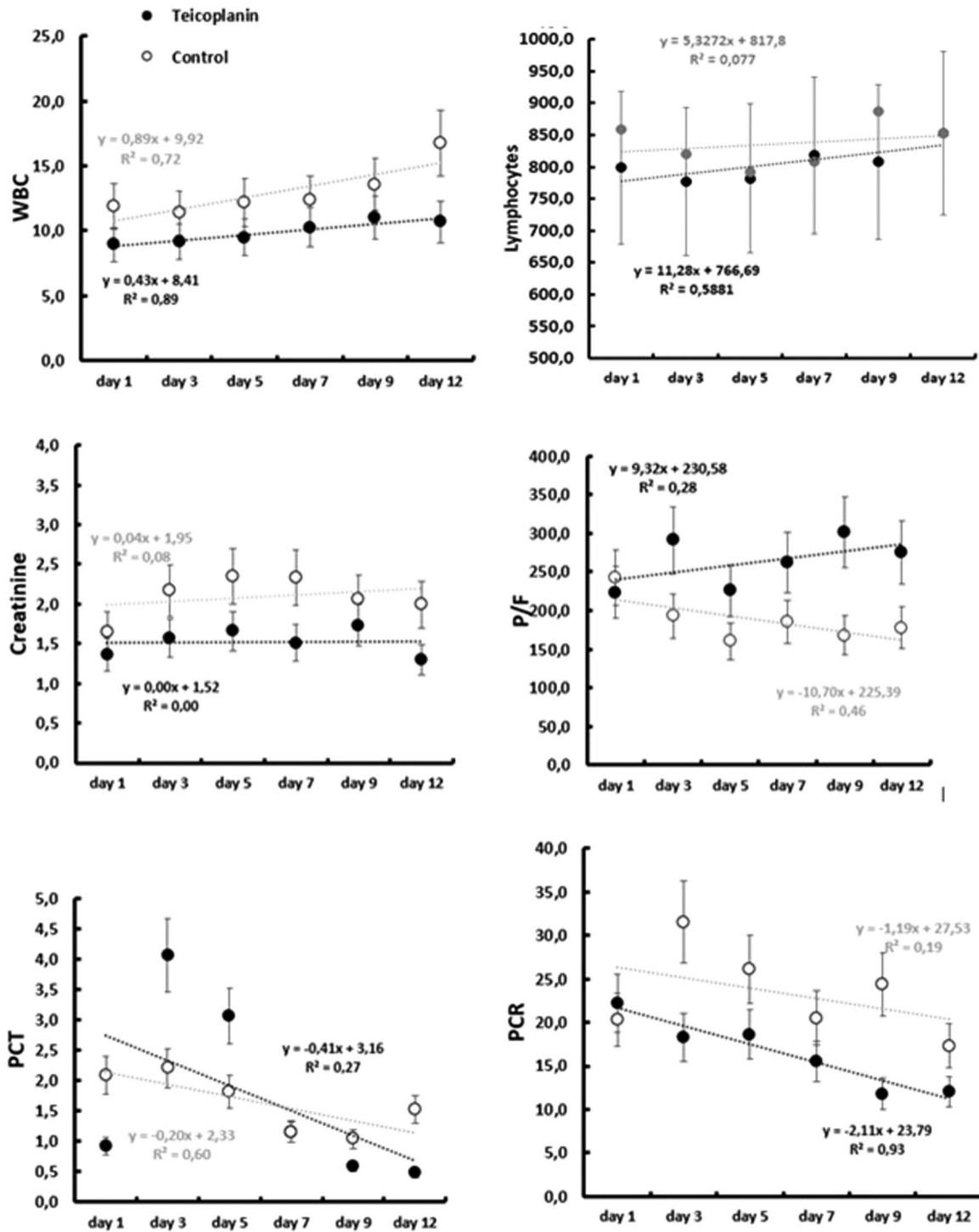


FIGURE 2 Chronological modifications of clinical and laboratory markers in the two groups

Furthermore, the sample size of the analyzed cohort may not be adequate to highlight statistically significant differences in terms of mortality and ability to achieve viral clearance: as a matter of fact, both the percentage of survivors and percentage of subjects achieving SARS-CoV-2 clearance was higher in Tei-COVID group than in the controls, although not reaching a $p < .05$. Further and larger clinical investigations would be necessary to verify the

antiviral role of teicoplanin, if any, as complementary therapy of COVID-19, at least in critically patients. Finally, the teicoplanin doses adopted in this cohort might be considered as potentially adequate to express antiviral activity against SARS-CoV-2: in fact, a previous study reported that teicoplanin potently prevents the entrance of SARS-CoV-2 into the cytoplasm with an IC_{50} of 1.66 μ M. Despite therapeutic drug monitoring (TDM) was not available in our setting,

BSI (33 episodes in 55 patients)	Tei-COVID group (16 episodes in 12/34 patients)	Gram-positive (25%)	- MSSA (25%) - MRSA (25%) - <i>Enterococcus spp</i> (50%)
		Gram negative (62.5%)	- <i>Klebsiella pneumoniae</i> (30%) - <i>Acinetobacter baumannii</i> (30%) - <i>Pseudomonas aeruginosa</i> (10%) - Others (30%)
		Fungal (12.5%)	- <i>Candida spp</i> (100%)
	Control group (17 episodes in 12/21 patients)	Gram-positive (70.6%)	- MRSA (17%) - CONS (50%) - <i>Enterococcus spp</i> (33%)
		Gram negative (29.4%)	- <i>Klebsiella pneumoniae</i> (40%) - <i>Acinetobacter baumannii</i> (40%) - Others (20%)

TABLE 2 BSI superinfection in the two groups

Abbreviations: BSI, bloodstream infections; COVID, coronavirus disease.

teicoplanin was administered at a dosage of 6–8 mg/kg/day, that usually results in a serum drug concentration approximately 7–8 μ M, adequate for both antiviral activity and treatment of bacterial infections.^{7,22}

Notwithstanding its potential complementary role as an antiviral agent, teicoplanin was primarily used in this cohort as antibiotic drug for either empiric treatment or prevention of potential Gram-positive superinfections. To this end it is worthy of mention our observation of a lower incidence of these infections compared to other published studies.^{23,24} As previously published, the proportionately greater number of gram-negative infections could be related with the changes in the abundance of aerobic bacteria in the gut microbiota that can be expected with teicoplanin administration and SARS-CoV-2 infection.^{10,25,26} Moreover, the number of Gram-negative superinfections observed in Tei-COVID group could be also influenced by a longer median follow up time than that of the other previously published studies.^{23,24} Data suggest that teicoplanin could represent a contributing factor in the reduction of Gram-positive superinfections, anyway further investigations are needed to clarify the possible impact of the drug on host microbiome in critically ill COVID-19 patients.

This study has a number of limitations, including in particular the retrospective observational nature and the small sample size. This may have limited the statistical power of the study considering that the Tei-COVID group showed better trends than controls on a number of parameters examined (i.e., Day-14 viral clearance and crude in-hospital Day-30 mortality), although not reaching statistical significance. Not less important, our observations were limited to critically ill patients requiring mechanical ventilation and the patients enrolled were in an advanced stage of the disease, chronologically distant from the onset of symptoms. Moreover, TDM for teicoplanin was not available in our setting. Finally, the impossibility of discriminating specific effects of the different drugs administered reduced the accuracy of the analysis.

5 | CONCLUSION

Currently at the best of our knowledge, this is the first real-life study on the use of teicoplanin in the setting of critically ill COVID-19 patients. In our patient population, use of this drug provided no significant antiviral effect but it was associated with a promising low incidence of Gram-positive infection. This latter favorable observation, in addition to study limitations, is worthy of further study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

CONSENT

Consent to publish was given by all participants and authors. Patients signed consent to participate.

AUTHOR CONTRIBUTIONS

Giancarlo Ceccarelli wrote manuscript and have made substantial contributions to conception, design, and interpretation of data. Francesco Alessandri, Alessandra Oliva, and Cristian Borrazzo have made contributions to analysis and interpretation of data. Serena Dell' Isola, Anna Ialungo, Elena Rastrelli, Massimiliano Pelli, Ombretta Turriziani, Giammarco Raponi, Franco Ruberto, and Monica Rocco have made substantial contributions to acquisition of data. Francesco Pugliese, Alessandro Russo, Gabriella d'Ettorre, and Mario Venditti have been involved in drafting the manuscript or revising it critically for important intellectual content and have given final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. All data are available in the manuscript. Database is available writing to the corresponding author.

ETHICS STATEMENT

Ethical approval was obtained from the Ethics Committee of Policlinico Umberto I—Sapienza University (Rome, Italy) [approval no./ID Prot. 109/2020].

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