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Treatment with COLchicine in hospitalized patients affected by COVID-19: The COLVID-19 trial

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Abstract

Objective: To evaluate whether the addition of colchicine to standard of care (SOC) results in better outcomes in hospitalized patients with COVID-19.

Design: This interventional, multicenter, randomized, phase 2 study, evaluated colchicine 1.5 mg/day added to SOC in hospitalized COVID-19 patients (COLVID-19 trial) and 227 patients were recruited. The primary outcome was the rate of critical disease in 30 days defined as need of mechanical ventilation, intensive care unit (ICU), or death.

Results: 152 non-anti-SARS-CoV-2-vaccinated patients (colchicine vs controls: 77 vs 75, mean age 69.1 ± 13.1 vs 67.9 ± 15 years, 39% vs 33.3% females, respectively) were analyzed. There was no difference in co-primary end-points between patients treated with colchicine compared to controls (mechanical ventilation 5.2% vs 4%, ICU 1.3% vs 5.3%, death 9.1% vs 6.7%, overall 11 (14.3%) vs 10 (13.3%) patients, P = ns, respectively). Mean time to discharge was similar (colchicine vs controls 14.1 ± 10.4 vs 14.7 ± 8.1 days). Older age (>60 years, P = 0.025), P/F <275 mmHg (P = 0.005), AST >40 U/L (P < 0.001), pre-existent heart (P = 0.02), lung (P = 0.003), upper-gastrointestinal (P = 0.014), lower-gastrointestinal diseases (P = 0.009) and cancer (P = 0.008) were predictive of
1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) related disease (COVID-19) has caused one of the worst pandemics of modern times [1]. As of Sept 1st, 2022, the disease affected over 600,000,000 individuals and caused over 6,500,000 worldwide [2].

COVID-19 has gone through significant changes mainly due to the arise of virus variants, vaccination campaigns, and available treatments. The ancestral strain of SARS-CoV-2 usually provokes systemic and upper respiratory symptoms with dry cough, while lower respiratory and gastrointestinal symptoms less frequent and generally appear at the late stage of the disease [3]. Other symptoms include loss of sense of smell or taste, shortness of breath upon exertion, body aches and headache. In more severe cases, acute respiratory distress, thromboembolism, acute cardiac injury, and myocarditis can occur [4]. If not vaccinated, approximately 15% of infected adults may develop a severe pneumonia that requires supplemental oxygen and hospitalization [5].

So far, there is no consensus on disease treatment, especially in hospitalized cases. Despite initial enthusiasm on possible candidate drugs, currently few drugs have been approved by European Medicines Agency (EMA), including tixagevimab/cilgavimab, anakinra, paxlovid (PF-07321332/ritonavir), regdanvimab, tocilizumab, casirivimab/imdevimab, remdesivir and sotrovimab, while molnupiravir and baricitinib are currently under evaluation [6].

SARS-CoV-2 causes a release of pro-inflammatory cytokines and disease severity is associated with an increase in the amounts of plasma C-reactive protein (CRP), interleukin-6 (IL-6), and the chemokines CCL4 (macrophage inflammatory protein-1β), CCL2 (monocyte chemotractant protein 1) and CXCL9 (monokine induced by gamma interferon) [7], suggesting that a dysregulated activation and inflammatory activity of myeloid cells is one the main pathogenic events [8]. SARS-CoV-2 is also a potent activator of pro-IL-1β gene transcription and protein maturation and is able to activate the NLRP3 inflammasome [9].

Colchicine is a well-known potent inhibitor of the inflammasome and impedes the release of IL-1 into NETs by neutrophils [10]. Colchicine showed anti-viral properties against flaviviridae [11] and against the recombinant demyelinating strain of mouse hepatitis virus RSAS9 [12] and inhibits respiratory syncytial virus (RSV) replication by reducing IL-6 and TNF-α levels [13]. For these reasons, it was proposed as a treatment for SARS-CoV-2 infection [14,15].

Several case reports, small randomized non-controlled trials and retrospective cohort studies evaluated the effect of different doses and durations of colchicine treatment in hospitalized COVID-19 patients, showing conflicting results on clinical status, discharge rates, need of supplemental oxygen and deaths [16–31]. Large healthcare database analysis provided evidence that continuous colchicine treatment was not able to prevent the infection by SARS-CoV-2 [32]. Significant methodological limits, including small cohorts, open-label designs, differences in patient clinical features and concomitant COVID-19 treatments, hampers a proper interpretation of the results.

Herein, we present the results of an interventional, multicenter, randomized, open-label, phase 2 study, aimed to evaluate the effect of colchicine added to standard treatment in hospitalized patients with COVID-19 (COLVID-19 trial).

2. Methods

COLVID-19 is a multicentre, randomized, open-label clinical trial promoted by the Italian Society of Rheumatology (SIR), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Thoracic Society (ITS-AIPO). The participation of Italian Centers was approved by the Italian Drug Agency and National Ethics Committee at the Lazzaro Spallanzani Institute on April 11th, 2020. The study was coordinated through the web-based platform managed by the Centro Studi SIR.

2.1. Study design and population

This is a randomized Phase II, controlled and open-label clinical trial, comparing standard of care vs standard of care plus colchicine for 30 days in hospitalized adult COVID-19 patients with confirmed infection of SARS-CoV-2. The study has been registered on clinicaltrials.gov with registration number NCT04375202.

Patients admitted to hospital were eligible for the study if they had RT-PCR confirmed SARS-CoV2 infection, a clinical/instrumental diagnosis of pneumonia, an oxygen saturation at rest in ambient air ≤94% and a PaO2/FIO2 (P/F) ratio of 350 to 200 mmHg. The P/F ratio calculated from arterial blood gas analysis was used for the definition of acute respiratory distress syndrome (ARDS). A P/F ratio of 350 to 200 identifies mild ARDS, 200 to 100 moderate ARDS and a respiratory failure featuring a P/F less than 100 is suggestive for severe ARDS.

Exclusion criteria included: known hypersensitivity to colchicine or its excipients; severe diarrhea; impossibility to take oral therapy; pregnancy and breast-feeding; severe cardiac, renal disease (creatinine clearance (CCL) <30 mL/min); kidney or liver damage (AST or ALT > 5 times the normal limits in International Units (ULN)); concomitant therapy with CYP3A4 enzyme - P glycoprotein inhibitors; other clinical conditions that contraindicate colchicine and cannot be treated or solved; neutrophil count <1,000/µL; platelet count <50 × 10³/µL; diverticulitis or intestinal perforation; any condition requiring mechanical ventilation or treatment in the ICU; concomitant Tocilizumab treatment or being already enrolled in other clinical trials.

Patients meeting all the inclusion criteria and none of the exclusion ones were centrally randomized (1:1) to standard of care (SOC) plus colchicine (colchicine group) or SOC (control group) by an automated interactive web-based system (REDCap). Informed consent for participation in the study could be oral if a written consent was unfeasible.

The sample size was calculated aiming at verifying the hypothesis that colchicine may have produced a halving of the rate of entering the critical stage. This percentage was estimated in the early phase of the pandemic to be 25% [33], thus 308 patients were needed with an 80% power and a 5% bilateral alpha error.

Due to significant flattening of the pandemic curve and the beginning of the vaccination campaigns the trial was terminated when ~75% of the sample size was reached.

The primary outcome was the rate of critical disease at one month (any of the following):

a. respiratory failure requiring mechanical ventilation;

b. patients with other organ failure who needed ICU monitoring and treatment;

c. death.

The patient was considered as ended the study protocol once any of the primary outcomes was satisfied.

In case any of the above-mentioned conditions occurred, any rescue therapy could be adopted.
Secondary outcomes included:

1. White blood cell count (x10³ cells/µl)
2. "Sequential Organ failure Assessment" (SOFA) score
3. Levels of CK, ALT, ferritin
4. Comply with any of the followings:
   a) No fever, cough and other COVID-related symptoms;
   b) SpO₂ > 93% or P/F > 350mmHg without oxygen inhalation

1. Rate of adverse events codified by Common Terminology Criteria for Adverse Events (CTCAE) v5.0

*Sequential Organ Failure Assessment (SOFA) score* is a morbidity severity score and mortality estimation tool designed for evaluating organ dysfunction and morbidity. It evaluates 6 variables, each representing an organ system (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) scored from 0 (normal) to 4 (high degree of dysfunction/failure). The maximum score may range from 0 to 24. The tool can be used for estimating mortality risk.

*Comorbidities* were evaluated using the Modified Cumulative Illness Rating Scale (CIRS) which is a 0 (absent) to 4 (extremely severe) scale being: 0. No problem affecting that system, 1. Current mild problem or past significant problem, 2. Moderate disability or morbidity and/or requires first-line therapy, 3. Severe problem and/or constant and significant disability and/or hard-to-control chronic problems, 4. Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment [34].

### 2.2. Treatment

Patients randomized to the treatment arm received colchicine 0.5 mg three times a day if weight was less than 100 kg or 1 mg twice a day if weight was more than 100 kg for a maximum of 30 days or until hospital discharge. The colchicine dose could be reduced in case of gastrointestinal intolerance, at the investigator’s discretion. Such dose is the same approved by EULAR for the treatment of Gout and familiar Mediterranean fever [35,36]. There was no contraindication to concomitant treatments excluding tocilizumab, antiviral drugs interfering on CYP3A4 such as lopinavir, ritonavir, darunavir, cobicistat and any drug administered during another clinical trial. Both colchicine and control group patients received the SOC treatment. The SOC for COVID-19 was decided locally by each Hospital protocol. According to therapeutic recommendations, from October 2020 dexamethasone (6 mg once a day for 10 days) was considered a SOC in patients who required supplemental oxygen.

### 2.3. Statistical analysis

Descriptive analyses are presented with means and standard deviation for continuous variables, absolute and relative frequencies for categorical variables. Differences by group were estimated with Student’s t-test or Wilcoxon signed rank test for continuous variables and Chi-squared test or Fisher’s test for categorical ones, as appropriate. All descriptive, exploratory, and statistical analyses were performed with statistical software R 4.0, Foundation for statistical computing, Vienna, Austria.

### 3. Results

Between April 18th, 2020, and May 12th, 2021, 227 patients across 17 Italian Centers were recruited. Most of the patients were enrolled between October 2020 and January 2021 due to the flattening of the curve in Italy. Among the 227 recruited patients, data on 152 patients (77 allocated to the colchicine group and 75 to the control group) were analyzed, excluding 7 patients not meeting eligibility criteria, 7 patients which revoked their informed consent before starting colchicine, 3 patients with protocol violations, 28 patients enrolled after receiving vaccination against SARS-CoV-2 and 30 with incomplete or missing data (Fig. 1). The final population included 152 patients of which 77 were allocated to the colchicine group (mean age 69.1±13.1 years, 39% female) and 75 to the control group (mean age 67.9±15 years, 33.3% female). Baseline demographic characteristics were not different between groups. Twenty-four patients were excluded before randomization and sixty-two were not included in the analysis after randomization due to protocol violation, having received anti-SARS-CoV-2 vaccination, having received rescue tocilizumab therapy, or having incomplete/missing data. The clinical and laboratory features at inclusion of both groups are shown in Table 1. There were no significant differences in any of the clinical and laboratory features between groups at enrollment. In particular, parameters of respiratory functionality, including SpO₂, PaO₂ and P/F, were similar between the groups. Cough and dyspnoea were reported by the majority of patients while high-grade fever was registered at inclusion in less than one third of patients. The mean baseline SOFA score was 2.3 in both groups. Mean (SD) hospitalization duration in patients who recovered was 14.1±10.4 days in the colchicine group and 14.7±8.1 days in the control group (P>ns). No patients were lost to follow-up. Baseline comorbidities were similar between groups (supplementary table 1). Hypertension was the most frequent comorbidity in both colchicine (53.2%) and SOC (53.3%) groups with no significant differences. Mean colchicine dose at entry was 1.5±0.2 mg/die. A total of two patients received half-dose of colchicine (2.6%), according to pre-specified criteria.

Colchicine was administered concomitantly with multiple other treatments according to SOC during the study period. Use of concomitant treatment for COVID-19 was similar between groups (Table 2). All patients in both groups were treated with glucoctcorticoids and anti-viral drugs at baseline and almost all patients received low-weight molecular heparins as per hospital standard protocol. Hydroxychloroquine was used in those patients enrolled in the initial phase of the diseases and then no longer adopted. There was no difference in co-primary endpoints in terms of percentage of patients requiring mechanical ventilation for respiratory failure, ICU admission or death (Table 3). Overall, 11 (14.3%) patients in the colchicine group vs 10 (13.3%) in the control group entered the critical stage (P=ns, Table 3).

There were no significant differences also in any of the secondary endpoints between groups at baseline or at 6 days of follow-up, except for a higher mean level of AST (76.9±91.8 U/l in the colchicine group vs 33.5±20.7 in the SOC group; P=0.016, see paragraph adverse events). Thirty-nine patients (50.6%) in the colchicine group versus 47 (62.7%) in the SOC treatment group were discharged at home (Supplementary table 2).

Considering the entire treated population, 131 patients did not achieve the primary endpoint, 86 were discharged at home and 45 were still hospitalized at 30 days, while 21 patients worsened. Among the baseline clinical features, older age (>60 years), a P/F < 275 mmHg, AST > 40 U/L, pre-existent heart, lung disease, upper or lower gastrointestinal disease and concomitant neoplasia were predictive of achieving the any outcome of primary at 30 days (Table 4). The presence of upper gastrointestinal disease was more prevalent in patients who subsequently underwent ICU [4/5, 80% in ICU patients vs 19/147, 12.9% in non ICU patients, P<0.001]. Finally, patients who died were all above 73 years of age (12/12, 100% vs 40/140, P<0.001), had a higher prevalence of pre-existent heart disease (9/12, 75% vs 37/140, 26.4%, P<0.001), especially in severe forms (3/12, 25% vs 2/140, 1.4%, P<0.001), and lung disease (7/12, 58.3% vs 26/140, 18.6%, P=0.013) with higher frequency of moderate (3/12, 25% vs 10/140, 7.1%, P=0.038) and severe forms (3/12, 25%, 2/140, 1.4%<0.001).

Detailed clinical features of patients who subsequently died showed no significant difference among groups (supplementary table 3). Psychiatric diseases were apparently more prevalent in those patients who died in the colchicine group, while heart and lung diseases were more...
prevalent in the SOC group.

3.1. Safety and concomitant therapies

Twenty-one adverse events were reported in patients treated with colchicine (27.3%) compared with 9 in 9 patients treated with SOC (12%) (supplementary table 4). Seven patients suffered from diarrhea in the colchicine group vs none in the control group. Moreover, other GI manifestations (colitis, bloating, gastritis, nausea) were observed in 4 patients treated with colchicine. Other AEs included increased liver enzymes or hepatic necrosis in 8 patients in the colchicine group vs 1 in the SOC group. This was judged severe in 2 patients in the colchicine group in which colchicine treatment was quit. Also, the mean level of AST showed a greater increase in the first 6 days after treatment initiation in the colchicine treated group compared with controls (76.9 ± 91.8 U/l vs 33.5 ± 20.7 U/l, P = 0.016). Finally, other two severe adverse events were observed in the colchicine treated group (depressed level of consciousness and a thromboembolic event). Five severe adverse

Table 1
Clinical and laboratory features at baseline

| Baseline characteristics       | Colchicine (N=77) | SOC (N=75) | P-value |
|-------------------------------|------------------|------------|---------|
| Age, years [mean (SD)]        | 69.1 (12.1)      | 67.9 [15]  | 0.67    |
| Age >60 years, n (%)          | 58 / 77 (75.3%)  | 53 / 75 (70.7%) | 0.643   |
| Female – n (%)                | 30 / 77 (39%)    | 25 / 75 (33.3%) | 0.58    |
| Colchicine dose at entry (mg/die), [mean (SD)] | 1.5 (0.2) | —         |         |
| SpO2, % [mean (SD)]           | 93 [8]           | 92.6 (3.4) | 0.813   |
| PaO2, mmHg [mean (SD)]        | 75.5 (24.6)      | 73.3 (28.7) | 0.317   |
| P/F, mmHg [mean (SD)]         | 260.2 (56.4)     | 258.5 (60.1) | 0.947   |
| White blood cells, n/μl [mean (SD)] | 11,723.3 | 16,8578 | 0.554 |
| Platelets, n/μl [mean (SD)]   | 234.2 (96.3)     | 239.8 (84)  | 0.71    |
| Bilirubin mg/dl [mean (SD)]   | 0.7 (0.3)        | 0.7 (0.3)   | 0.623   |
| Creatinine, mg/dl [mean (SD)] | 0.9 (0.2)        | 0.9 (0.2)   | 0.965   |
| Creatinin kinase, U/l [mean (SD)] | 146.8 (149.4)  | 126.7 (126.3) | 0.472  |
| AST, U/l [mean (SD)]          | 40.3 (28.2)      | 41.5 (34.9)  | 0.722   |
| AST >40 U/l, n (%)            | 21 / 67 (31.3%)  | 21 / 62 (33.9%) | 0.906  |
| Mean arterial pressure, mmHg [mean (SD)] | 96.7 (19.1)    | 97.5 (12.6) | 0.798 |

Table 2
Concomitant treatments for COVID-19.

|                     | Colchicine | Control | P-value |
|---------------------|------------|---------|---------|
| Glucocorticoids, n (%) | 100%       | 100%    | 0.25    |
| Anticoagulants (enoxaparine or/and fundaparinux), n (%) | 65 | 61 | 0.25 |
| Anti-virals, n (%)     | 10 (13%)   | 13      | 0.45    |
| Hydroxychloroquine, n (%) | 13 (16.9%) | 15 (20%) | 0.62 |

Table 3
Primary end-points

|                     | Colchicine (N=77) | Control (N=75) |
|---------------------|------------------|----------------|
| Time from hospitalization to enrolment, days [mean (SD)] | 2 (6.3) | 2 (3.6) |
| Time to discharge, days [mean (SD)]                        | 14.1 (10.4) | 14.7 (8.1) |
| Mechanical ventilation, n (%)                              | 4 (5.2%) | 3 (4%) |
| Time to mechanical ventilation, days [mean (SD)]           | 5.5 (4.5) | 5 (1.7) |
| Intensive Care Unit (ICU), n (%)                           | 1 (1.3%) | 4 (5.3%) |
| Time to ICU, days [mean (SD)]                              | 5 (NA) | 4.2 (4.7) |
| Death, n (%)                                                | 7 (9.1%) | 5 (6.7%) |
| Time to death, days [mean (SD)]                            | 11.7 (4.1) | 14.2 (8) |
| Combined outcome: Mechanical Ventilation, ICU or death, n (%) | 11 (14.3%) | 10 (13.3%) |

manifestations (colitis, bloating, gastritis, nausea) were observed in 4 patients treated with colchicine. Other AEs included increased liver enzymes or hepatic necrosis in 8 patients in the colchicine group vs 1 in the SOC group. This was judged severe in 2 patients in the colchicine group in which colchicine treatment was quit. Also, the mean level of AST showed a greater increase in the first 6 days after treatment initiation in the colchicine treated group compared with controls (76.9 ± 91.8 U/l vs 33.5 ± 20.7 U/l, P = 0.016). Finally, other two severe adverse events were observed in the colchicine treated group (depressed level of consciousness and a thromboembolic event). Five severe adverse
events were observed in the control group (bacteremia, hematoma, cardiac arrest, myocardial infarction and respiratory failure).

### 4. Discussion

It is well recognized that hyperinflammation induced by SARS-CoV-2 is a major cause of disease severity and mortality in infected patients and many of the proposed treatments include agents currently used in rheumatologic clinical practice [37]. One critical question, however, is which anti-inflammatory drugs are most appropriate. Among the most traditional non-biological anti-inflammatory therapies, corticosteroids appear to provide some benefit in advanced stages of the disease [38], but concerns may arise from immunosuppression induced during viral replicative phase [39].

In this randomized, open-label trial we explored the potential benefit of colchicine in the setting of a population of hospitalized COVID-19 patients with moderate respiratory failure at hospitalization requiring non-invasive oxygen therapy. Administration of colchicine in association to SOC was not associated with significant difference in the co-primary end-points of the study (need of mechanical ventilation and 28-day mortality) [27]. Indeed, in these trials, administration of colchicine in association to standard therapy did not result in significant difference on several composite endpoints, including intubation for mechanical ventilation or 28-day mortality [24], change in WHO 7-point scale [26], and 28-days all-cause mortality [27]. As a consequence, current guidelines and a recent Cochrane meta-analysis do not support the use of colchicine in hospitalized patients with moderate to severe COVID-19 [40,41]. Few studies showed some promising results. In the GRECCO-19 trial, colchicine added to SOC improved time to clinical deterioration [18]. Lopes et al. showed that colchicine may reduce the median time of supplemental oxygen need and of hospitalization in a small cohort of hospitalized moderate-severe patients with SARS-CoV-2 pneumonia [24]. It is likely that including less severe patients, such those in the GRECCO-19, or younger, as in the trial conducted by Lopes et al., may explain these apparently conflicting results.

We have confirmed that older age represents a significant adverse prognostic factor in the disease course and on final outcomes both in patients treated with colchicine and in those treated with SOC [42]. We observed that age above 60 years was a significant predictor of not achieving hospital discharge at 30 days and that patients who died were all more than 73 years-old.

Colchicine administration was not associated with significant improvement of laboratory parameters. This is in line with the results of previous studies [18,26] not showing a significant effect of colchicine over SOC in reducing IL-6 and CRP levels, although Lopes et al. [24] observed a reduction in CRP levels already after 2 days in colchicine treated patients. Moreover, concomitant corticosteroid therapy at inclusion in all patients may have influenced CRP levels precluding a reliable data analysis.

Colchicine administration was associated with an acceptable safety profile. However, a higher frequency of increased liver enzymes was reported compared to SOC and in two patients colchicine treatment was interrupted. This requires consideration in a population of hospitalized COVID-19 patients with multiple comorbidities and receiving several concomitant drugs [43]. Other AEs were also overall more frequent in the colchicine group, these were mostly mild and expected, including diarrhoea and gastrointestinal complaints. The relatively small number of patients evaluated and the heterogeneity of the concomitant treatments suggest that these data need validation in larger cohorts.

We confirmed that older patients with comorbidities, especially pre-existent heart (excluding hypertension) and lung diseases, and with a lower respiratory function at baseline, were characterized by worse outcomes. Indeed, these patients were at higher risk of non-achieving hospital discharge at 30 days and at higher risk of death, as confirmed by literature data [44].

We acknowledge that the major limits of the study are the open-label design, the relatively low number of included patients and the lack of detailed information on several inflammatory parameters, such as IL-6 levels, and radiological features. A relevant percentage of patients (13.2%) was excluded from the analysis due to incomplete or missing data. Likely, the setting in which the trial was carried out, especially in the very first phases of the pandemic, in terms of severity of the disease and emergency conditions, may have hampered the collection of all the requested variables at all time points.

However, this is the first trial to employ a stable dose of colchicine along the hospitalization without loading dose or dose reduction during the study except in case of adverse events. To be noted that the disease has significantly evolved since the rise of the pandemic, considering that new variants have emerged with a different clinical outcome and the effects of the extensive vaccination campaigns. We excluded from the analysis those patients who were vaccinated in the early 2021 to have a homogeneous cohort not biased by the effect of the vaccines on disease outcome.

In conclusion, this randomized, open-label trial demonstrated that colchicine is not superior to SOC in reducing the risk of mortality, clinical worsening or mechanical ventilation in hospitalized patients with COVID-19 pneumonia. It is conceivable therefore that this drug is not able to positively act in the advanced phases of the disease.

### Data sharing statement

The datasets and statistical outputs generated during the current study are available from the corresponding author on reasonable request at any time.
Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the National Ethics Committee at the Lazzaro Spallanzani Institute.

Author contributions

The trial was promoted by the Italian Society of Rheumatology (SIR), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Thoracic Society (ITs-AIPO). All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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This paper is dedicated to the memory of Professor Roberto Perricone who put all his efforts into the development and realization of the trial.

Appendix





















































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































