ORIGINAL PAPER

Vitamin D and disease severity in coronavirus disease 19 (COVID-19)

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SUMMARY

The role of 25-OH-vitamin D in the assessment of coronavirus disease 19 (COVID-19) has not been investigated. We sought to investigate the prevalence of 25-OH-vitamin D deficiency among COVID-19 patients, and to determine the associations between 25-OH-vitamin D status and the severity of the disease.

We have conducted a retrospective observational study of COVID-19 patients admitted to the University of Verona Hospital Trust. Demographic, clinical and biochemical parameters were collected at hospital admission, and serum 25-OH-vitamin D levels were measured. The following outcomes were assessed: arterial partial oxygen pressure (PaO_2); C-reactive protein (CRP); length of hospitalization; requirement of oxygen therapy; non-invasive ventilation (NIV); mechanical ventilation; and death.

Among 61 patients enrolled, 72.1% was 25-OH-vitamin D deficient (<20 ng/mL) and 57.4% had 25-OH-vitamin D <15 ng/mL. Patients with arterial PaO_2 <60 mmHg had significantly lower mean 25-OH-vitamin D levels compared to patients with PaO_2 ≥60 mmHg (13.3 ng/mL vs 20.4 ng/mL respectively, p=0.03). Vitamin D deficiency was associated with 3-fold higher risk of having arterial pO_2 <60 mmHg. 25-OH-vitamin D deficiency was associated with increased CRP and dyspnea.

25-OH-vitamin D deficiency was associated with more severe systemic inflammatory response and respiratory failure in COVID-19 patients.

Key words: COVID-19; vitamin D; SARS-CoV-2.

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INTRODUCTION

The coronavirus disease 19 (COVID-19), a novel acute respiratory disease caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has received worldwide attention. The clinical spectrum of COVID-19 ranges from asymptomatic infection to life-threatening disease due to acute respiratory distress syndrome (ARDS). In Italy, as of May 9, more than 200,000 cases had been recorded and up to 16% of the patients requiring hospitalization were admitted to intensive care units (ICUs) (1). SARS-CoV-2 is a β-coronavirus that causes interstitial pneumoniae by attaching to angiotensin-converting enzyme 2 (ACE2) receptors in the respiratory tract (2). There is growing evidence that the immune system and its response to SARS-CoV-2 infection plays a crucial role in the development of severe complications of the disease. Indeed, it has been increasingly recognized that the ARDS occurring in many severe cases of COVID-19 is due to an uncontrolled inflammatory response to the virus, which involves the production of high levels of pro-inflammatory cytokines such as interleukin-1 and interleukin-6 (3, 4).

Among the factors that influence our immune system, vitamin D and its metabolite 25-OH-vitamin D are known to have pleiotropic and multiple effects (5). Vitamin D deficiency (*i.e.*, 25-OH-vitamin D <20 ng/mL) is common among people of all ages

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all over Europe (6). Low 25-OH-vitamin D serum levels have been associated with increased production of pro-inflammatory cytokines, such as IL-6, and with more severe clinical manifestations in patients with pneumonia (*e.g.*, development of ARDS) (7). By acting on different pathways, vitamin D can modulate both the innate and adaptive systems thanks to its ubiquitously distributed receptors. Of particular interest is the hypothesized dual action of vitamin D on the mucosal defenses, indeed, vitamin D receptor (VDR) has been found on both resident immune cells and respiratory epithelial cells (8).

The aim of the present study is to describe the vitamin D status among hospitalized COVID-19 patients, and to define the relationship between 25-OH-D serum levels at hospital admission and COVID-19 disease severity.

MATERIALS AND METHODS

We conducted a retrospective analysis on patients admitted to the University of Verona hospital for COVID-19. We collected demographic, clinical, biochemical and radiological characteristics, as well as treatment and outcome data, from electronic medical records. We obtained complete medical histories, including underlying chronic diseases, symptoms (including dyspnea defined as difficult breathing or shortness of breath), clinical signs, laboratory findings, computed tomographic scans of the chest and/or standard radiography, and treatment (including antiviral therapy, antibiotics, corticosteroid therapy, and oxygen support) administered during the hospital admission. All the patients were tested at admission for serum 25-OH-vitamin D (LIAISON® 25 OH Vitamin D assay, DiaSorin, Italy, a direct competitive chemiluminescent immunoassay; the intra-assay variation coefficient was 8% and the inter-assay variation coefficient was 12%), blood gas analysis, complete blood count, liver and kidney function, creatine kinase, lactate dehydrogenase, ferritin, fibrinogen, C-reactive protein (CRP), procalcitonin (PCT) and d-dimer.

Continuous variables are presented as mean and standard deviation if normally distributed or median and interquartile range if they are not. Group comparisons were performed with *t*-student and Mann-Whitney U tests (for normally and non-normally distributed continuous variables, respectively). Associations between continuous variables were tested using Pearson correlation coefficients and multivariate linear regression. We compared proportions for categorical variables by using the χ^2 test. We used Fisher's exact test in the analysis of contingency tables when the sample sizes were small. All differences were considered significant when the p value was inferior or equal to 0.05. All analyses were performed with SPSS Version 26 (SPSS, Inc., Chicago, IL, USA). All patients provided informed consent and access to all clinical data was allowed as per study protocol (2598CESC), which was approved by the local ethics committee. All the analyses have been conducted in full accordance with the ethical standards of the qualified institutional and national committees on human subjects as well as with the Helsinki Declaration.

RESULTS

We consecutively enrolled 61 patients between March 8th and May 8th, 2020. Clinical and laboratory characteristics were collected for the whole sample. The mean age was 69.4 years with no gender differences in the study sample. Tables I and II show the demographic, clinical and laboratory characteristics of the population under analysis. We found a large prevalence of vitamin D deficiency, irrespective of the threshold adopted, with approximately 70% of the population having less than 20 ng/mL (Figure 1). Of note, the subjects younger than 50 years of age and 60 years of age (n=8 and n=19 respectively) had mean vitamin D serum levels of 9.5 ng/mL and 11.9 ng/mL respectively. We did not find any significant correlation between vitamin D serum levels and age or gender.

We found that patients with pO_2<60 mmHg had significantly lower levels of serum

25-OH-vitamin D compared to patients with pO_2 ≥60 mmHg (13.3 ng/mL *vs* 20.4 ng/mL respectively, p=0.03) (Figure 2). Among the 44 patients with vitamin D deficiency (<20 ng/mL, average 13.3 ng/mL), 56.8% had pO2 levels on admission lower than 60 mmHg whilst this was found in only 29.4% of patients with vitamin D ≥20 ng/mL (average 20.4 ng/mL) (χ^2 3.68, p=0.055). Patients with vitamin D serum <20 ng/mL were more prone to be dyspneic compared to non-deficient patients. Among dyspneic patients, 56.8% had vitamin D deficiency, this proportion was mar-

Table I - Clinical characteristics of the study population divided by vitamin D serum levels.

Characteristics	Complete cohort n=61	25-OH-vitamin D < 20 ng/mL n=44	25-OH-vitamin D ≥20 ng/mL n=17	p value
Demographic characteristics				
Age, years (SD)	69.4 (15.3)	67.7 (16.2)	74.0 (12.0)	NS
Sex, male (%)	32 (52.5)	25 (56.8)	7 (41.2)	NS
Weight, kg (SD)	73.1 (15.1)	73.4 (16.4)	72.4 (13.3)	NS
Height, cm (SD)	167 (9)	168 (8)	162 (9)	NS
Clinical characteristics on admission				
Time to first symptom, days (IQR)	5 (2.5-8-5)	6.5 (0.8-8.5)	5 (3.0-9.0)	NS
Temperature, °C (IQR)	37.9 (36.4-38.3)	37.7 (36.4-38.3)	38.0 (36.8-38.5)	NS
Distribution of temperature (%) <37.5 °C 37.5-38.0 °C 38.1-39.0°C >39°C	 24 (45.3) 11 (20.8) 15 (28.3) 3 (5.7)	 18 (47.4) 8 (21.1) 10 (26.3) 2 (5.3)	 6 (40.0) 3 (20.0) 5 (33.3) 1 (6.7)	NS
Systolic blood pressure, mmHg (SD)	129 (26)	131 (28)	122 (22)	NS
Diastolic blood pressure, mmHg (SD)	74 (12)	75 (13)	71 (11)	NS
Heart rate, bpm (SD)	86 (20)	86 (21)	87 (12)	NS
Respiratory rate (SD)	23 (5)	23 (5)	22 (4)	NS
Fever (Temperature >37.5°C) (%)	43 (70.5)	30 (68.2)	13 (76.5)	NS
Diarrhea (%)	6 (9.8)	4 (9.1)	2 (11.8)	NS
Sore throat (%)	2 (3.3)	2 (4.5)	0 (0)	NS
Anosmia or ageusia (%)	3 (4.9)	3 (6.8)	0 (0)	NS
Cough (%)	23 (37.7)	18 (40.9)	5 (29.4)	NS
Sputum production (%)	2 (3.3)	1 (2.3)	1 (5.9)	NS
Dyspnea (%)	30 (49.9)	25 (56.8)	5 (29.4)	0.055
Interstitial pneumonia on chest X-ray / HRCT (%)	52 (86.7)	39 (88.6)	13 (76.5)	NS
Treatment during hospitalization				
Hydroxychloroquine (%)	40 (65.6)	32 (72.7)	15 (88.2)	NS
Tocilizumab (%)	9 (14.8)	9 (20.5)	0 (0)	0.04
Lopinavir / Ritonavir (%)	40 (65.6)	28 (63.6)	12 (70.6)	NS
Intravenous methylprednisolone (%)	20 (32.8)	14 (31.8)	6 (35.3)	NS
Antibiotics (%) None Ceftriaxone Piperacillin/Tazobactam Azithromycin Others	 19 (31.1) 21 (34.4) 10 (16.4) 10 (16.4) 1 (1.6)	 11 (25.0) 18 (40.9) 7 (15.9) 7 (15.9) 1 (2.3)	 8 (47.1) 3 (17.6) 3 (17.6) 3 (17.6) 0 (0)	NS

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Characteristics	Complete cohort n=61	25-OH-vitamin D < 20 ng/mL n=44	25-OH-vitamin D ≥20 ng/mL n=17	p value
Demographic characteristics				
Cholecalciferol (%) None <1,000 IU/day ≥1,000 IU/day	 54 (88.5) 1 (1.6) 6 (9.9)	 44 (100) 0 (0) 0 (0)	 10 (58.8) 1 (5.9) 6 (35.3)	0.001
Outcomes during hospitalization				
Hospital stay length, days (IQR)*	17.0 (7.0-26.5)	17 (7.0-29.0)	14 (5.0-22.0)	NS
Required oxygen therapy (%) None Low-flow nasal cannulas High-flow nasal cannulas Venturi mask Non-rebreather mask	 26 (42.6) 9 (14.8) 3 (4.9) 10 (16.4) 12 (19.7)	 17 (38.6) 6 (13.6) 2 (4.5) 9 (20.5) 9 (20.5)	 9 (52.9) 3 (17.6) 1 (5.9) 1 (5.9) 3 (17.6)	NS
Required non-invasive ventilation (%)*	19 (55.9% of 34)	15 (78.9%)	4 (21.0%)	NS
Required mechanical ventilation (%)*	8 (23.5% of 34)	2 (33.3%)	6 (66.6%)	NS
Death (%)*	5 (14.7% of 34)	2 (40.0%)	3 (60.0%)	NS
Coexisting comorbidities				
Smoking history (%) Never Former Current	 40 (78.4) 1 (2.0) 10 (19.6)	 28 (63.6) 1 (2.3) 7 (15.9)	 12 (70.6) 0 (0) 3 (17.6)	 NS NS NS
Cardiovascular diseases (%)	17 (27.8)	12 (27.3)	5 (29.4)	NS
Type 2 diabetes (%)	11 (18.0)	9 (20.5)	2 (11.8)	NS
Hypertension (%)	36 (59.0)	27 (61.4)	9 (52.9)	NS
Cancer (%)	11 (18.0)	9 (20.5)	2 (11.8)	NS
Chronic kidney disease (%)	11 (18.0)	9 (20.5)	2 (11.8)	NS
Chronic obstructive pulmonary disease (%)	7 (11.5)	5 (11.4)	2 (11.8)	NS

*Data available in 34 patients.

ginally higher compared to 29.4% of patients with normal vitamin D serum levels (χ^2 3.68, p=0.055).

We found a significant relationship between vitamin D status (<15 ng/mL *vs* ≥15 ng/mL) and CRP levels (≤10 mg/L *vs* >10 mg/L). Indeed, patients with 25-OH-vitamin D below 15 ng/mL were more likely to show increased levels of CRP on admission (χ^2 4.78, p=0.02). We also found that patients with 25-OH-vitamin D below 20 ng/mL had a 3-fold higher risk of having CRP above 50 mg/L (n=28, 63.8%) compared to patients with normal vitamin D (n=6, 35.3%), χ^2 3.99, p=0.04.

During hospitalization, vitamin D deficient patients were treated more frequently with tocilizumab when compared with non-deficient individuals (20.5% *vs* 0% p=0.04). We found no association between vitamin D deficiency and other medications.

Not surprisingly, arterial pO_2 was strongly associated with duration of hospitalization, risk of non-invasive ventilation (NIV) and mechanical ventilation. We found that patients with arterial pO_2 <60 mmHg had a 10-times higher risk of receiving NIV (OR 10.3, 95% CI 2.5-41.7, p<0.0001) and approximately 4-times higher risk of being mechanically ventilated during the hospitalization (OR 3.8, 95% CI 1.1-13.9, p=0.04).

Among other laboratory markers tested on admission, we found that higher fibrinogen and higher CRP were associated with lower pO_2 on blood gas analysis. Fibrinogen levels were 6.3 g/L and 5.3 g/L for pO_2 lower than 60 mmHg and pO_2 greater than

Table II - Biochemical characteristics of the study population.

Biochemical parameter				
Distribution of laboratory findings	**All cohort n=61**	**25-OH-vitamin D <20 ng/mL n=44**	**25-OH-vitamin D ≥20 ng/mL n=17**	**OR (95% CI)**
25-OH-vitamin D, ng/mL <20 ng/mL 25-OH-vitamin D, ng/mL <15 ng/mL 25-OH-vitamin D, ng/mL <10 ng/mL 25-OH-vitamin D, ng/mL <5 ng/mL	44 (72.1) 35 (57.4) 19 (31.1) 8 (13.1)	NA	NA	NA
C-reactive protein >50 mg/L (%)	34 (55.7)	28 (63.6)	6 (35.3)	3.2 (1.0-10.3)
Procalcitonin >0.5 ng/mL (%)	11 (18.0)	7 (15.9)	4 (23.5)	0.6 (0.1-2.4)
Hemoglobin <10 g/dL (%)	6 (9.8)	5 (11.4)	1 (5.9)	2.0 (0.2-18.9)
Platelets <150.000/mm^3 (%)	8 (13.1)	7 (15.9)	1 (5.9)	3.0 (0.3-26.6)
Leukocytes <4,000/mm^3 (%)	8 (13.1)	6 (13.5)	2 (11.8)	2.0 (0.2-17.5)
Lymphocytes <1,200/mm^3 (%)	38 (62.3)	29 (65.9)	9 (52.9)	1.7 (0.5-5.3)
Neutrophils <1,800/mm^3 (%)	5 (8.2)	3 (6.8)	2 (11.8)	0.5 (0.1-3.6)
Fibrinogen >4.0 g/L (%) Fibrinogen >5.5 g/L (%)	46 (75.4) 34 (55.7)	33 (75.0) 25 (56.8)	13 (76.5) 9 (52.9)	0.9 (0.2-3.4) 1.2 (0.4-3.6)
D-dimer >500 ug/L (%)	50 (82.0)	37 (84.1)	13 (76.5)	1.6 (0.4-6.5)
Ferritin >300 ug/L (%)	48 (78.7)	37 (84.1)	11 (64.7)	2.9 (0.8-10.4)
Lactate dehydrogenase >250 IU/L (%)	42 (68.9)	31 (70.5)	11 (64.7)	1.3 (0.4-4.2)
Creatinine phosphokinase >200 IU/L (%)	11 (18.0)	9 (20.5)	2 (11.8)	1.9 (0.4-10.0)
Creatinine >1.0 mg/dL (%)	24 (39.3)	18 (40.9)	6 (35.3)	1.3 (0.4-4.0)
Peripheral oxygen saturation <93% (%)	17 (27.9)	13 (29.5)	4 (23.5)	1.4 (0.4-4.9)
Arterial pO2 on admission <60 mmHg (%)	30 (49.2)	25 (56.8)	5 (29.4)	3.2 (1.0-10.5)
Arterial pCO2 on admission >40 mmHg (%)	13 (21.3)	10 (22.7)	3 (17.6)	1.4 (0.3-5.7)
Worst P/F during hospitalization <200 (%)	22 (36.1)	17 (38.6)	5 (29.4)	1.5 (0.4-5.0)

60 mmHg respectively. Nonetheless, we found no association between fibrinogen levels and dyspnea. Among 34 patients with CRP above 50 mg/L, 21 had pO_2 lower than 60 mmHg (61.8%) compared to 9 (33.3%) patients with CRP below 50 mg/L (χ^2 4.87, OR 3.2, 95% CI 1.1-9.3, p=0.03). No association was found when the threshold was lowered to 10 mg/L or 5 mg/L.

DISCUSSION AND CONCLUSIONS

Herein we present a retrospective observational study on 25-OH-vitamin D serum levels in patients admitted to the inpatient ward for COVID-19. We found a large prevalence of vitamin D deficiency in our cohort, with approximately 70% of the pa-

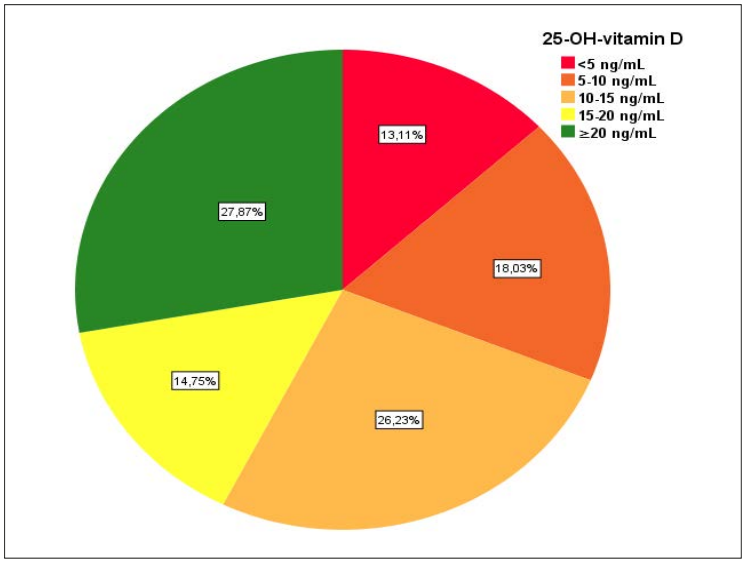

Figure 1 - Vitamin D serum levels in the study population.

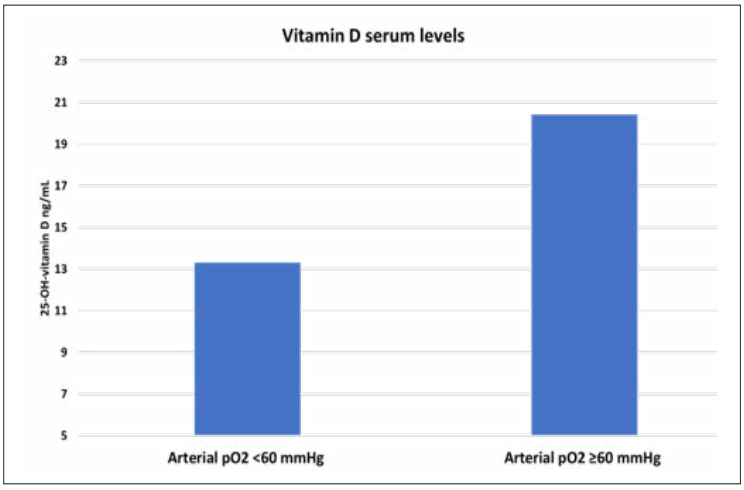

Figure 2 - Vitamin D serum levels and arterial pO_2 on admission, p=0.03.

tients with 25-OH-vitamin D <20 ng/mL, a threshold that is largely recognized as representing deficiency. More than half of the subjects had less than 15 ng/mL and approximately one out of ten had less than 5 ng/mL, corresponding to severe deficiency. Patients with lower (<60 mmHg) arterial pO_2 measured at admission had significantly lower vitamin D serum levels compared to patients with higher (≥60 mmHg) arterial pO_2. We also found an inverse relationship between vitamin D levels and CRP levels, a well-known marker of inflammation. Of note, we did not find an association between CRP above 10 mg/L or above 5 mg/L and arterial pO_2 on admission. Therefore, we can speculate that vitamin D can play a role as a marker of the inflammatory response, especially in patients without a dramatic increase in CRP (<10 mg/L). In addition, in our cohort, tocilizumab was prescribed only to vitamin D deficient patients, possibly in relation to the worse clinical presentation. Indeed, IL-6 hyperexpression has been associated with the cytokine release syndrome in COVID-19 patients and tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, showed promising results in severely ill COVID-19 patients (4, 9). In line with our results, vitamin D deficiency had been reported largely prevalent in severely ill patients admitted to Intensive Care Units (ICUs) (10) and had been associated with more severe ARDS and with worse clinical outcomes in patients admitted to ICU (11, 12). Moreover, in patients admitted to UTIs with ARDS, cholecalciferol administration has been associated with shorter hospitalization and decreased mortality, especially among vitamin D deficient patients (13), and vitamin D administration has been associated with fewer respiratory infections and decreased levels of serum IL-6 (14, 15). In this scenario, vitamin D serum levels might play an important role not only in the prognosis of COVID-19 patients but also in the pathogenesis of the inflammatory response (16). It has recently been speculated, mostly based on indirect evidence, that vitamin D might have a role in reducing the risk of COVID-19 and experts have advised to supplement COVID-19 patients with large doses of cholecalciferol (7, 17). At a population level, a negative correlation between vitamin D and the number of COVID-19 cases was observed (18). However, to date, direct evidence linking hypovitaminosis D and COVID-19 is missing and a causative role of vitamin D deficiency on COVID-19 susceptibility is yet to be determined. Large interventional placebo-controlled studies are needed to further determine the role of vitamin D in COVID-19.

Our study has strengths and limitations. We have enrolled a fairly homogenous sample for the analysis, and we have collected a large set of clinical and laboratory parameters. However, this is an observational study and no definitive assumptions on the causal role of vitamin D deficiency on COVID-19 severity can be drawn. No control group has been included in the study and a similar vitamin D deficiency may be expected in subjects with similar baseline characteristics or critically ill patients. Nevertheless, vitamin D could be considered at least a prognostic marker of disease severity in COVID-19 patients.

In conclusion, COVID-19 patients had a great prevalence of vitamin D deficiency, which is associated with a worse clinical presentation and worse arterial pO_2 at admission. Vitamin D can be a novel marker of disease severity in COVID-19 patients.

Further interventional placebo-controlled studies of vitamin D in COVID-19 patients are urgently needed to determine its role on disease severity.

Contributions
Conceptualization, Giovanni Adami, Alessandro Giollo, Maurizio Rossini; Data curation, Giovanni Adami, Alessandro Giollo, Eugenia Bertoldo; Formal analysis, Giovanni Adami; Investigation, Giovanni Adami, Alessandro Giollo, Angelo Fassio, Camilla Benini, Eugenia Bertoldo, Francesco Bertoldo, Giovanni Orsolini, Luca Idolazzi, Ombretta Viapiana, Sandro Giannini, Giovanni Passeri, Evelina Tacconelli, Claudio Micheletto, Davide Gatti, Maurizio Rossini; Project administration, Maurizio Rossini; Supervision, Maurizio Rossini; Validation, Giovanni Adami, Maurizio Rossini; Writing - original draft, Giovanni Adami, Alessandro Giollo; Writing - review & editing, Giovanni Adami, Alessandro Giollo, Angelo Fassio, Camilla Benini, Eugenia Bertoldo, Francesco Bertoldo, Giovanni Orsolini, Luca Idolazzi, Ombretta Viapiana, Sandro Giannini, Giovanni Passeri, Evelina Tacconelli, Claudio Micheletto, Davide Gatti, Maurizio Rossini.

Conflicts of interest
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no conflicts of interest.

Patient and Public Involvement statement
This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted in order to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethical approval
The institutional review board of the University of Verona approved this study (2598CESC).

Data sharing
No additional data available.

Transparency declaration
The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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