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SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients

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ABSTRACT

Background: Whether patients with autoimmune rheumatic diseases (ARD) have a higher risk for SARS-CoV-2 infection (COVID-19) and how SARS-CoV-2 pandemic impacts on adherence to therapy has not been fully elucidated. We assessed the rate and clinical presentation of COVID-19, and adherence to therapy in a large cohort of patients with ARD followed-up in a tertiary University-Hospital in Northeast Italy.

Methods: Between April 9th and April 25th, 2020, after SARS-CoV-2 infection peak, a telephone survey investigating the impact of COVID-19 on patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), ANCA-associated vasculitis (AAV), and idiopathic inflammatory myopathies (IIM) was administered. Demographics, disease activity status, therapy, occupational exposure, and adherence to social distancing advise were also collected.

Results: 916 patients (397 SLE, 182 AAV, 176 SSc, 111 RA, 50 IIM) completed the survey. 148 patients developed at least one symptom compatible with COVID-19 (cough 96, sore throat 64, fever 64, arthromyalgias 59, diarrhea 26, conjunctivitis 18, ageusia/hyposmia, 18). Among the 916 patients, 65 (7.1%) underwent SARS-CoV-2 nasopharyngeal swab (18 symptomatic and 47 asymptomatic), 2 (0.21%) tested positive, a proportion similar to that observed in the general population of the Veneto region. No deaths occurred. 31 patients (3.4%) withdrew ≥1 medication, mainly immunosuppressants or biologics. Adoption of social distancing was observed by 860 patients (93.9%), including 335 (36.6%) who adopted it before official lockdown.

Conclusions: COVID-19 incidence seems to be similar in our cohort compared to the general population. Adherence to therapy and to social distancing advise was high.

1. Introduction

The recent outbreak of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) has raised concerns about patients affected with autoimmune rheumatic diseases (ARD) [1].

Indeed, patients with ARD are considered at higher risk of bacterial, viral and opportunistic infections compared to the general population, owing to the underlying condition and the use of immunosuppressive drugs [2,3].

According to recommendations from EULAR, ACR, BSR and SIR (Italian Society for Rheumatology), the maintenance of immunomodulating and immunosuppressive therapies was suggested during the COVID-19 pandemic [4–7]. This suggestion aims at avoiding disease relapses, which could occur with abrupt therapy withdrawal.

A few papers dealing with the management of ARD during COVID-19 pandemic have been published to date [8–10], but whether these patients are at higher risk for SARS-CoV-2 infection (including symptomatic and asymptomatic forms), or whether they present a higher probability of developing severe COVID-19 is still unknown [11]. Notably, these publications report data collected at the beginning of the pandemic, before the infection peak incidence [12,13]. Moreover, little data is available on the adherence to therapy of patients with ARD during the SARS-CoV-2 pandemic.

The aim of our study was to assess the rate and clinical presentation of SARS-CoV-2 infection and adherence to therapy for the background autoimmune condition in patients affected with ARD followed in a tertiary University-Hospital in Northeast Italy.

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2. Patients and methods

Between April 9th and April 25th 2020– starting 28 days after the declaration of general lockdown by the Italian Prime Minister on March 12th, 48 days after the first confirmed COVID-19 case in the Veneto Region, and 19 days after March 21st, date of peak incidence in Italy [14]– a telephone structured survey (Supplementary Table S1) investigating the impact of COVID-19 on ARD was administered by trained rheumatologists to patients affected with systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV), systemic sclerosis (SSc), rheumatoid arthritis (RA) and idiopathic inflammatory myopathy (IIM) followed-up at the Rheumatology Unit of Padua University Hospital.

Exclusion criteria were: failure to acquire informed consent, insufficient proficiency in both Italian and English to thoroughly understand the questions, invalid contact details.

All SLE patients followed in Padua cohort were considered for inclusion. In addition, we sampled patients affected with AAV, SSc, AR, and IIM, considering for enrollment all the consecutive patients that we were able to contact by phone between April 9th and April 25th. Patients were sampled in alphabetical order, making sure that a similar number of patients for each alphabetical letter was represented. Briefly, anonymized data were collected on patient demographics, disease activity at last follow-up, current therapeutic regimen including glucocorticoids > 7.5 mg/day, antimalarials, immunosuppressants, conventional/synthetic/biological disease modifying anti-rheumatic drugs (DMARDs), occupational exposure, close contacts with SARS-CoV-2 nasopharyngeal swab-confirmed cases, adherence to and date of adoption of social distancing measures. Occupational exposure was defined as either healthcare professional, non-healthcare professional with exposure to the public, none of the above, or pensioner. Whether patients adopted social distancing measures even before the official lockdown in Italy was also evaluated.

Data on treatment discontinuation specifically due to concerns about COVID-19 was collected.

Respiratory symptoms (cough, sore throat) that had developed between February 1st and the date of the structured survey were registered; additionally, new-onset fever > 37.5 °C, arthromyalgias, diarrhea, conjunctivitis, ageusia/hyposmia were registered.

We performed descriptive analyses and applied chi-square test or *t*-test for comparison of categorical and continuous variables as appropriate.

As reference for comparisons to the general population, publicly available data from the Civil Protection Department were used [14,15]. The Italian Civil Protection department disseminated data daily on total swabs performed each day, divided by Region. Every single swab performed for any reason since the first confirmed cases – i.e. 21st February 2020 -, was counted in the reports. These included swabs made for screening purposes on asymptomatic individuals, in-hospital or at-home swabs on symptomatic patients, work-related screening, testing of close contacts of confirmed cases. All analyses were performed using SPSS Software for Windows, Version 25.0, Chicago, IL.

Padua University-Hospital Ethics committee approved the study.

3. Results

One-thousand fifty-six patients were considered for inclusion. Among them, 916 patients (397 SLE, 182 AAV, 176 SSc, 111 RA, 50 IIM) completed the survey. Clinical and demographic characteristics and SARS-CoV-2 related variables are reported in Table 1.

A total of 140 patients were excluded; reasons for exclusion are detailed in Supplementary Fig. 1.One-hundred-forty-eight patients (16.2%) developed at least one symptom from February1st onwards; 23 (2.5%) had a reasonably suspect symptom complex (fever plus cough plus at least one more symptom)(Table 2).

Testing for SARS-CoV-2 infection via nasopharyngeal swab RT-PCR was performed in 65 (7.1%) patients from February onwards. Patient groups did not significantly differ in testing rates. Tested patients included 18 symptomatic and 47 asymptomatic subjects; among the latter, 1 patient underwent the test due to admission to the hospital for scheduled procedures, 3 due to SARS-CoV-2 positive swab among cohabitants, 24 for work-related reasons (15 healthcare professionals, 9 with job involving contact with the public), 19 due to other reasons (e.g. voluntary screening, contact of a confirmed COVID-19 case non-cohabitant).

Two patients resulted positive (3.1% of tested patients, 0.21% of the entire cohort) and were admitted to the hospital: one asymptomatic remitted pregnant SLE patient on hydroxychloroquine was discharged after negative monitoring for fetal complications, and a 54 year-old SSc female patient on mycophenolate was admitted with a one-week history of fever > 37.5 °C, cough and fatigue. She was treated with hydroxychloroquine and azithromycin, low-flow oxygen (2 L/min) and discharged after 9 days. No deaths were registered. Notably, the rate of confirmed COVID-19 cases among our patients was similar to that observed in the general population of the Veneto Region according to data from Civil Protection Department [14].

Thirty-one patients discontinued at least part of their therapeutic regimen in response to the COVID-19 epidemic, more frequently immunosuppressants or biologics (Table 3). Among these 31 patients, the majority were asymptomatic (23 patients, 74.2%), six (19.3%) were tested by nasopharyngeal swab, one resulted positive for SARS-CoV-2 (Table 3). Discontinuation events were observed in 3.3% of SLE patients, 10% of RA patients, proportions higher than that observed in other ARDs ($p = 0.0003$). Among SLE patients who discontinued therapy, 8 (61.5%) were in remission and 5 (38.5%) were unremitted, including 3 patients with nephritis; among RA patients 5 were remitted (41.6%), 4 (33.3%) had low and 3 (25%) moderate disease activity. A combination of ≥3 drugs previously prescribed for the ARD was associated with therapy discontinuation ($p < 0.001$); no influence upon discontinuation was observed by gender, age, concomitant fibromyalgia/depression, and development of symptoms (15.8% vs. 25.8%, $p = 0.13$). Modification to patients own habits was highly prevalent in response to COVID-19 (93.9%). Notably, 6.1% of patients did not notice significant changes to their habits during lockdown: this group was mainly comprised of pensioners (32.1%) or workers having no contact with the public (46.4%). Overall, 335 patients (36.6%) adopted social distancing measures before official lockdown declaration by Italian Authorities (Table 1). The proportion of patients who early adopted such measures was not different among the disease groups, apart from AAV patients who mainly embraced them from lockdown date onwards ($p < 0.001$). Patients with early adoption of social distancing were taking a higher mean number of drugs ($p = 0.006$), were more frequently female ($p = 0.036$) and were more frequently unremitted at last follow-up ($p = 0.025$) compared to patients with late adoption; no difference in age, occupational exposure, use of immunosuppressants, immunomodulants or biologics, and concomitant fibromyalgia was observed (Supplementary Table S2).

Six patients had nasopharyngeal SARS-CoV-2 swab-positive cohabitants; of these, 3 (50%) were tested (all negative), 1 was symptomatic for anosmia/ageusia, 5 were asymptomatic.

4. Discussion

Patients with ARD are considered at higher risk of infections [2,3]. Data on SARS-CoV-2 infection in ARD patients are scanty, and the rate and outcome of COVID-19 in this heterogeneous group of patients are still elusive. Additionally, case-series published to date were collected in Italy before the peak incidence [12,13].

The proportion of patients with ARD who underwent SARS-CoV-2 testing in our study is in line with the regional standard (7.1% vs. 6.1%, respectively [14,15]). Between February 21st and April 25th, a total of 306.977 SARS-CoV-2 swabs were performed in the Veneto region in

Table 1
Baseline characteristics of the cohort. Number (%) or mean ± SD are reported.

	Overall (916)	SLE (397)	AAV (182)	SSc (176)	AR (111)	IIM (50)
Age (mean ± SD)	53.6 ± 14.3	47.8 ± 13.4	59.3 ± 15.3	55.5 ± 11.9	60.8 ± 12.6	56.2 ± 11.6
Female	720 (78.6)	340 (85.6)	100 (54.9)	154 (88)	87 (78.4)	39 (78)
Remission	583/740 (78.7)	319 (84.8)	161 (88.5)	–	81 (72.9)	22 (44.9)
Immunosuppressants/Immunomodulant agents						
Prednisone > 7.5 mg/day	91 (9.9)	42 (10.9)	25 (13.7)	8 (4.5)	8 (7.3)	8 (16.3)
Methotrexate	139 (15.1)	14 (3.8)	36 (19.8)	12 (6.8)	53 (48.6%)	24 (48)
Cyclosporin	11 (1.2)	4 (1.1)	3 (1.6)	1 (0.6)	0	3 (6.1)
Mycophenolate	181 (19)	118 (31.3)	25 (13.7)	28 (15.9)	1 (0.9)	9 (18.8)
Tacrolimus	9 (0.9)	7 (1.9)	1 (0.5)	1 (0.6)	0	0
Azathioprine	61 (6.6)	31 (8.4)	27 (14.9)	0	0	3 (6.3)
Cyclophosphamide	4 (0.4)	1 (0.3)	2 (1.1)	0	0	1 (2.1)
Antimalarial drugs	336 (36.6)	298 (77)	2 (1.1)	16 (9.1)	13 (11.9)	7 (14.6)
Leflunomide	17 (1.8)	6 (1.6)	0	0	11 (10.1)	0
Salazopyrin	5 (0.5)	0	0	0	5 (5.2)	0
Biologics						
Anti-TNF	42 (4.6)	0	0	0	42 (38.5)	0
CTLA4-Ig	12 (1.3)	0	0	0	12 (11)	0
Anti-IL6R	9 (0.9)	1 (0.3)	0	3 (1.7)	5 (4.6)	0
Anti-CD20	40 (4.3)	1 (0.3)	29 (15.9)	5 (2.8)	3 (2.8)	2 (4.2)
JAK-i	21 (2.3)	2 (0.5)	0	0	19 (17.4)	0
Anti-BLYSS	47 (5.1)	47 (11.8)	0	0	0	0
Professional exposure						
Healthcare professional	44 (4.9)	26 (6.8)	3 (1.6)	6 (3.4)	7 (6.3)	2 (4)
Contact with public	218 (24.2)	128 (32.2)	15 (8.2)	42 (23.9)	24 (21.6)	9 (18)
No contact with public	393 (42.9)	165 (43.4)	66 (36.3)	61 (34.7)	65 (58.6)	19 (38)
Pensioner	261 (29)	61 (15.4)	98 (53.8)	67 (38.1)	15 (13.5)	20 (40)
SARS-CoV-2 related variables						
COVID-19 positive cohabitant	6 (0.6)	3 (0.8)	0	2 (1.1)	1 (0.9)	0
Social distancing adoption	860 (93.9)	377 (95)	176 (96.7)	153 (87)	107 (96.4)	47 (94)
Social distancing measures before March 12th	335 (36.6)	169 (42.6)	34 (18.7)	67 (38.1)	42 (37.8)	23 (46)
Social distancing measures after March 12th	525 (57.3)	208 (52.4)	142 (78)	86 (48.9)	65 (58.6)	24 (48)
Symptomatic, any symptom	148 (16.1)	75 (18.9)	26 (14.3)	23 (13.1)	8 (7.2)	16 (32)
SARS-CoV2 nasopharyngeal swab	65 (7.1)	31 (7.8) [1 Positive (0.3)]	14 (7.7)	10 (5.7) [1 Positive (0.6)]	9 (8.1)	1 (2)
Therapy adherence						
Discontinued any therapy	31 (3.4)	13 (3.3)	2 (1.1)	4 (2.3)	12 (10.8)	0 (0)
Considered discontinuing	11 (1.2)	1 (0.3)	6 (3.2)	4 (2.3)	0 (0)	0 (0)
Did not discontinue	874 (95.4)	383 (96.4)	175 (95.6)	168 (95.4)	99 (89.2)	50 (100)

SLE, systemic lupus erythematosus; AAV, ANCA-associated vasculitis; SSc, systemic sclerosis; RA, rheumatoid arthritis; IIM, idiopathic inflammatory myopathies; TNF, tumor necrosis factor; CTLA4-Ig, CTLA4-binding monoclonal immunoglobulin; Anti-IL6R, anti-interleukin 6 receptor; JAK-i, Janus Kinase inhibitors; Anti-BLYSS, anti B lymphocytes stimulating factor; SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2; COVID-19, SARS-CoV-2 disease.

symptomatic and asymptomatic individuals, vs. 326.940 swabs performed in Lombardy region, with almost twice the number of inhabitants [14]. Only 2 cases of COVID-19 were confirmed by nasopharyngeal swab in our cohort, a finding consistent with other reports [12,13] and in line with general prevalence of COVID-19 cases in the Veneto region, where cumulative COVID-19 cases up to 25th April were 17.391, accounting for approximately 0.3% (3/1000) of the total population of the Region.

Clinical course of the observed cases was benign [16]. Although the study design prevents from far-reaching assumptions, the currently available evidence does not indicate a higher incidence of COVID-19 among ARD patients.

Unfortunately, at the time of the survey administration SARS-CoV-2 antibody testing was not routinely available to the general population and none of our patients was screened for SARS-CoV-2 antibodies.

Discontinuation of therapy was overall rare in our cohort, being higher in RA and SLE. Discontinuation events were driven by immunosuppressant withdrawal in SLE and biologics in RA. These

Table 2
Symptoms compatible with COVID-19 in the overall cohort and according to disease diagnosis. Symptoms developed between February 1st and the survey administration are presented. Number (%) are reported.

	Overall (916)	SLE (397)	AAV (182)	SSc (176)	AR (111)	IIM (50)
Any symptom compatible with COVID-19	148 (16.2)	75 (18.9)	26 (14.3)	23 (13.1)	8 (7.2)	16 (32)
Fever > 37.5 °C	64 (6.9)	40 (10.1)	8 (4.4)	7 (4.0)	3 (2.7)	6 (12)
Cough	96 (10.5)	43 (10.8)	24 (13.2)	11 (6.3)	8 (7.2)	10 (20)
Sore throat	64 (6.9)	41 (10.3)	2 (1.1)	12 (6.8)	5 (4.5)	4 (8)
Arthromyalgias	59 (6.4)	35 (8.8)	0	8 (4.5)	2 (1.8)	14 (28)
Diarrhea	26 (2.8)	18 (4.5)	0	5 (2.8)	1 (0.9)	2 (4)
Ageusia/hyposmia	18 (1.9)	11 (2.8)	2 (1.1)	3 (1.7)	1 (0.9)	1 (2)
Conjunctivitis	18 (1.9)	13 (3.3)	0	3 (1.7)	0	2 (4)
Three or more symptoms	45 (4.9)	30 (7.6)	1 (0.5)	7 (4.0)	1 (0.9)	6 (12)
Fever plus cough plus one more symptom	23 (2.5)	14 (3.6)	0	5 (2.8)	0	4 (8)

SLE, systemic lupus erythematosus; AAV, ANCA-associated vasculitis; SSc, systemic sclerosis; RA, rheumatoid arthritis; IIM, idiopathic inflammatory myopathies; COVID-19, SARS-CoV-2 disease.

Table 3
Therapy discontinuation events overall and according to disease groups. Number (%) are reported.

	Overall (31)	SLE (13)	AAV (2)	SSc (4)	AR (12)	IIM (0)
Female	25 (80.6)	11 (84.6)	1 (50)	2 (50)	11 (91.6)	–
Therapy						
Prednisone	1 (3.2)	0	1 (50)	0	0	–
Antimalarial drugs	2 (6.5)	2 (15.4)	0	0	0	–
Immunosuppressants*	18 (58.1)	9 (69.2)	1 (50)	3 (75)	5 (41.6)	–
Biologics	13 (41.9)	2 (15.3)	1 (50)	0	10 (83.3)	–
Anti-TNF	4 (12.9)	0	0	0	4 (33.3)	–
CTLA4-Ig	4 (12.9)	0	0	0	4 (33.3)	–
Anti-IL6R	2 (6.4)	0	0	0	2 (16.6)	–
Anti-CD20	0	0	0	0	0	–
Anti-BLYSS	2 (6.4)	2 (15.3)	0	0	0	–
Anti-IL5	1 (3.2)	0	1 (50)	0	0	–
tsDMARD						
JAK-i	2 (6.4)	0	0	0	2 (16.6)	–
Symptomatic, any symptom	8 (25.8)	4 (30.7)	0	1 (25)	3 (25)	–
SARS-CoV2 nasopharyngeal swab	6 (19.3)	2 (15.3)	0	1 (25)	3 (25)	–
Positive swab	1 (3.2)	0	0	1 (25)	0	–
Fibromyalgia	4 (12.1)	2 (15.3)	0	0	2 (16.6)	–
Depression	2 (6.4)	2 (15.3)	0	0	0	–

SLE, systemic lupus erythematosus; AAV, ANCA-associated vasculitis; SSc, systemic sclerosis; RA, rheumatoid arthritis; IIM, idiopathic inflammatory myopathies; COVID-19, SARS-CoV2 disease; anti-TNF, anti-tumor necrosis factor drugs; CTLA4-Ig, CTLA4-binding monoclonal immunoglobulins; Anti-IL6R, anti-interleukin 6 receptor; Anti-BLYSS, anti B lymphocytes stimulating factor; anti-IL5, anti-interleukin 5; tsDMARD, targeted synthetic disease modifying anti-rheumatic drugs; JAK-i, Janus Kinase inhibitors; SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2.

observations show the positive impact of current national and international recommendations [4–7]. Conversely, it has to be underlined that, despite unhindered access to counselling with their rheumatologists through email or telephone, 3.4% of patients autonomously withdrew at least 1 medication. Interestingly, the development of infectious symptoms seems not to be the main driver of discontinuation, as approximately 75% of patients who discontinued part of their therapeutic regimen were asymptomatic.

Disease activity of patients who discontinued therapy represents another concern: we found that almost half of SLE and RA patients who discontinued their therapy were unremitted.

These findings call for vigilance by healthcare providers about patient concerns on SARS-CoV-2 infection during DMARD therapy.

Patients displayed a high degree of compliance with social distancing measures: 42.2% of SLE patients declared they had already adopted social distancing measures by the time official widespread lockdown was declared by Italian Authorities. This behavior, likely dictated by patients' perceptions about their disease as a risk factor for infections, may exert a protective effect on SARS-CoV-2 infection among patients with ARD. The extent of this effect is uncertain, as we did not observe significant differences in the rates of COVID-19 in our cohort compared to the general population of Veneto Region. Notably, no patients at high risk of contagion (e.g. with a swab-positive cohabitant) tested positive or developed a suspicious symptom complex.

In conclusion, the incidence of SARS-CoV-2 infection as defined by positive nasopharyngeal swab test was low and seems to be comparable to that of the general population in a large, real-life, referral-center cohort encompassing different ARD interviewed in a short time interval (sixteen days), after peak incidence in Italy. Clinical course of confirmed and suspect cases was benign. Spontaneous discontinuation of therapy was rare, but it was also undertaken by patients with active disease. Enhanced vigilance by health professionals about patients' concerns about their therapy in the midst of the COVID-19 epidemic is warranted, taking also into consideration that the duration of this pandemic is still uncertain.

CRediT authorship contribution statement

M. Zen: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **E. Fuzzi:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **D. Astorri:** Conceptualization, Methodology, Software, Investigation, Writing - original draft. **F. Saccon:** Investigation. **R. Padoan:** Investigation. **L. Ienna:** Investigation. **G. Cozzi:** Investigation. **R. Depascale:** Investigation. **E. Zanatta:** Investigation. **M. Gasparotto:** Investigation. **F. Benvenuti:** Investigation. **S. Bindoli:** Investigation. **M. Gatto:** Investigation. **M. Felicetti:** Investigation. **A. Ortolan:** Investigation. **D. Campaniello:** Investigation. **M. Larosa:** Investigation. **M. Lorenzin:** Investigation. **R. Ramonda:** Investigation. **P. Sfriso:** Investigation. **F. Schiavon:** Investigation. **L. Iaccarino:** Investigation. **A. Doria:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

All Authors declare they have no competing interests to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2020.102502.

Authors' contributions

MZ contributed to the conception and design of the work, the follow-up of patients with SLE, RA and IIM, acquisition, analysis and interpretation of data, and drafted the work; EF contributed to the conception and design of the work, the follow-up of RA patients, acquisition and interpretation of data, and helped in drafting the work; DAs contributed to the design of the work, the follow-up of RA and SLE

patients and acquisition and interpretation of data; FSa, LIe, RD and SB contributed to acquisition of data of SLE patients; EZ contributed to follow-up and acquisition of data of SSc patients; GC, FB and MLo contributed to acquisition of data of SSc patients; RP contributed to follow-up and acquisition of data of AAV patients; MGas and DC contributed to acquisition of data of IIM patients; MGat contributed to follow-up and acquisition of data of patients with SLE; MF contributed to follow-up of patients with AAV; AO and MLa contributed to follow-up of SLE patients; RR, PS, FSc, LIa are in charge of the follow-up of patients affected with autoimmune rheumatic diseases at Padua University-Hospital; Prof AD led the team that followed-up patients, contributed to the conception of the work and revised the manuscript for important intellectual content.

All the authors approved the final version of the manuscript and gave their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethical approval information

The study was approved by the Ethics Committee of the “Azienda Ospedaliera- Università degli Studi di Padova”, Padova, Italy.

Patient consent

Obtained.

Data sharing

All data relevant to the study are included in the article or uploaded as supplementary material. Data are available upon reasonable request to Prof AD, adoria@unipd.it. The use of data from third party is not allowed without permission.

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