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Short communication

# Prevalence and features of IOS-defined small airway disease across asthma severities

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ABSTRACT

*Background:* Impulse oscillometry (IOS) is a noninvasive method based on the forced oscillation technique able to detect small airway dysfunction (SAD) in asthma. We aimed to analyze the prevalence and the functional features of IOS-defined SAD across the different Global Initiative for Asthma (GINA) steps.

*Methods:* A cross-sectional, single-center study in which 400 consecutive adult patients with physician-diagnosed, community-managed asthma underwent standard spirometry and IOS, and were stratified by stepwise GINA classification. SAD was defined by IOS as a fall in resistance from 5 to 20 Hz [R5–R20]>0.07kPa × s × $L^{-1}$.

*Results:* The prevalence of IOS-defined SAD ranged between 58.3% (GINA step 2) and 78.6% (GINA step 5), without statistically significant difference within GINA steps ($p > 0.05$ in all comparisons). Isolated SAD (i.e. without proximal airways involvement) was similarly represented across GINA steps 2–4. Peripheral airways resistance (R5-R20) tended to a progressive increase with the worsening of GINA steps, and was significantly higher in steps 4–5 compared to the other steps ($p < 0.05$).

The proportion of patients with $FEF_{25–75\%}$-defined SAD (<60%) was lower than the IOS-defined one in GINA steps 2–4 ($p < 0.05$). Only non-significant or weak inverse correlations between R5-R20 and $FEF_{25–75\%}$ were observed within each GINA step, with the exception of GINA step 5, which showed a strong, inverse correlation ($r = -0.80$, $p = 0.0005$).

*Conclusions:* This study shows that first, IOS-defined SAD is overwhelmingly present across asthma severities; second, airways resistance increases with the worsening of GINA steps; and third, SAD may be overlooked by standard spirometry, especially in milder asthma.

## 1. Introduction

Small airways are generally defined as bronchial airways with an internal diameter ≤2 mm [1–5], representing the major site of airflow limitation in both asthma and chronic obstructive pulmonary disease [5]. The small airways dysfunction (SAD), associated with worse asthma control and higher inhaled corticosteroid dosages [6,7], has been estimated to be around 50–60% in asthma [5–10]. However, Global Initiative for Asthma (GINA) guidelines [11] do not take into consideration SAD for the management of asthma, and only symptoms and spirometry guide asthma treatment.

Conventional spirometry measurements are unable to sensitively evaluate small airways [12,13]. Impulse oscillometry (IOS) is a simple and noninvasive method based on the forced oscillation technique, requiring minimal patient cooperation [14–16]. The contribution of the distal airways is determined by the difference between R5 and R20 (R5-20), as already performed in asthmatic patients in clinical trials and hospital cohorts [6–8,17,18]. Overall, we and others showed that

*Abbreviations:* SAD, Small airway dysfunction; IOS, Impulse oscillometry; FeNO, Fractional exhaled nitric oxide; BMI, Body Mass Index; FEV1, Forced expiratory volume in the first second; FVC, forced vital capacity; FEF25-75, Forced Expiratory Flow Between 25% and 75%; R5-R20, Resistances at 5 and 20 Hz; X5, Reactance at 5 Hz; Ax, Reactance area; FRes, Resonant frequency in Hz; ICS, inhaled corticosteroids; LABA, Long-acting β adrenoceptor agonist; LAMA, Long-acting muscarinic antagonist.

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particularly exercise-induced asthma symptoms, overweight, asthma-related night awakenings, smoking and older age are significantly associated with SAD in asthmatic patients [6,19].

In this study, we aimed to analyze the prevalence and the functional features of IOS-defined SAD across the different GINA steps (from 2 to 5), in an unselected sample of patients with physician-diagnosed, community-managed asthma.

## 2. Material and methods

### 2.1. Patients

This is a cross-sectional analysis of a single-centered, observational study on 400 adult (≥18 years old) asthmatic community-treated patients, consecutively recruited between January 1, 2017 and March 1, 2018. In this context, all the patients with a stable asthma (without new or worsening symptoms as episodes of wheezing, breathlessness, chest tightness, and coughing) at the time of the visit and during the 4 weeks before were recruited. All patients underwent to standard spirometry [20], IOS [21–23] (see **Supplementary Material 1** for details) and Fractional exhaled nitric oxide (FeNO) [24] measurements at the initial screening visit in our secondary-care asthma clinic. Demographic parameters, clinical features, asthma therapy as defined by Global Initiative for Asthma (GINA) guidelines [11] at first visit were recorded. See **Supplementary Material 2** for details.

The study was conducted according to STROBE guidelines (STrengthening the Reporting of Observational Studies in Epidemiology) for cohort, case-control, and cross-sectional studies.

### 2.2. Statistical analysis

Categorical data were summarized as percentages; significant differences or associations were analyzed using the $X^2$ test or Fisher exact tests. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on normality demonstrated by Kolmogorov–Smirnov test. Comparisons were performed with either Student's t-test for independent samples (2-tailed) or with analysis of variance (ANOVA) comparisons with Bonferroni correction when more than 2 means were being compared. Correlations between different variables were explored using Spearman's r coefficient.

## 3. Results

### 3.1. Characteristics of the patients with asthma

Baseline demographics, clinical, and functional features of 400 asthmatic, community-treated subjects by GINA steps were shown in Table 1. Overall, subjects in this cohort were mostly Caucasians (n = 397). Different GINA steps were associated with different frequencies of current or former heavy smoker status (≥10pack/years; p = 0.0042). Age at diagnosis and years of asthma duration progressively increased with the worsening of GINA steps (p < 0.0001), as well as the proportion of patients with FEV1<80%, FEV1/FVC ratio < lower limit of normal,

**Table 1**
Baseline clinical characteristics, spirometry and impulse oscillometry features of the 400 asthmatic patients according to GINA step stratification.

| Patient Characteristics | Total (n = 400) | GINA Classification Steps | | | | *p* value[a] |
|---|---|---|---|---|---|---|
| | | Step 2 (n = 84) | Step 3 (n = 212) | Step 4 (n = 90) | Step 5 (n = 14) | |
| **Clinical features and treatment** | | | | | | |
| Female sex, *n(%)* | 219 (54.8) | 35 (41.7) | 118 (55.7) | 58 (64.4) | 8 (57.1) | 0.0253 |
| Age, years, *mean (SD)* | 52.6 (31.4) | 42.3 (15.7) | 52.9 (17.4) | 56.3 (17.5) | 60.2 (17.1) | <0.0001 |
| BMI (kg/m$^2$), *mean (SD)* | 25.2 (8.8) | 25.1 (4.2) | 25.1 (4.8) | 25.6 (5.9) | 25.0 (4.0) | 0.8593 |
| Current or former smokers (≥10pack/years), *n (%)* | 127 (31.8) | 17 (20.2) | 65 (30.7) | 41 (45.6) | 4 (28.6) | 0.0042 |
| Asthma duration, years, *median (25%-75% IQR)* | 15.0 (5.0, 23.0) | 7.5 (3.0,15.75) | 15.0 (6.0, 25.0) | 16.5 (6.0, 25.25) | 20.0 (7.75, 31.25) | <0.0001 |
| Presence of Atopy[b], *n(%)* | 250 (62.5) | 60 (71.4) | 131 (61.8) | 53 (58.9) | 6 (42.8) | 0.1267 |
| Eosinophils, *mm$^3$, median (25%-75% IQR),* | 328 (191, 510) | 300 (180, 490) | 290 (190, 460) | 370 (210, 515) | 388 (314, 566) | 0.2153 |
| FeNO, ppb, *median (25%-75% IQR)* | 24 (14, 48) | 27 (13,48) | 24 (13, 43) | 25 (16, 56) | 35 (19, 52) | 0.4310 |
| ICS(BPD equivalent)/day[c], micrograms, *mean (SD)* | 483 (320) | 244 (83) | 399 (187) | 779 (290) | 1262 (465) | <0.0001 |
| Extrafine therapy, *n(%)* | 133 (33.3) | 14 (16.7) | 84 (39.6) | 33 (36.7) | 2 (14.3) | 0.0007 |
| **Spirometry values** | | | | | | |
| FEV1 <80%, *n(%)* | 98 (24.5) | 8 (9.5) | 46 (21.7) | 32 (35.6) | 12 (85.7) | <0.0001 |
| FEV1/FVC <70%, *n(%)* | 119 (29.8) | 14 (16.7) | 60 (28.3) | 35 (38.9) | 10 (71.4) | <0.0001 |
| FEF25-75 < 60%, *n(%)* | 157 39.3) | 16 (19.1) | 80 (37.7) | 48 (53.3) | 13 (92.9) | <0.0001 |
| **Spirometry values**, *mean (SD)* | | | | | | |
| FEV1, *(% predicted)* | 92.1 (19.5) | 97.3 (13.8) | 93.8 (18.9) | 87.5 (21.6) | 63.9 (13.3) | <0.0001 |
| FEV1/FVC ratio, (x100) | 77.7 (12.6) | 80.1 (11.0) | 78.0 (11.8) | 76.0 (14.1) | 63.0 (12.3) | <0.0001 |
| FEV1/FVC ratio, *(% predicted)* | 86.0 (12.9) | 90.0 (12.4) | 87.1 (11.9) | 82.5 (13.4) | 68.0 (8.8) | <0.0001 |
| FEF25-75, *(% predicted)* | 69.7 (31.4) | 83.19 (27.3) | 69.9 (29.5) | 62.8 (34.2) | 30.7 (12.3) | <0.0001 |
| **Impulse oscillometry values**, kPa/l/s, median [25%–75% IQR] | | | | | | |
| R5-R20 | 0.11 [0.04, 0.18] | 0.09 [0.04, 0.14] | 0.11 [0.04, 0.17] | 0.15 [0.04, 0.23] | 0.23 [0.15, 0.30] | 0.0007 |
| X5 | −0.14 [-0.21, −0.10] | −0.13 [-0.17,-0.09] | −0.14 [-0.18, −0.10] | −0.18 [-0.27, −0.10] | −0.23 [-0.34, −0.12] | 0.0002 |
| Ax | 1.13 [0.35, 2.11] | 0.95 [0.36, 1.40] | 1.04 [0.34, 1.76] | 1.62 [0.40, 3.00] | 3.07 [1.39, 4.25] | 0.0002 |
| $F_{Res}$ | 19.97 [11.94, 24.95] | 16.9 [11.05, 22.41] | 19.76 [11.74, 24.16] | 23.06 [13.47, 28.15] | 28.94 [18.74, 35.03] | 0.0001 |

Spirometry values were represented as mean (SD) because of their normal distribution, while the values of the impulse oscillometry were represented as median [25%–75% interquartile range], since they were not normally distributed. Variables of the different groups were compared with parametric methods for spirometry values, and with non-parametric methods for impulse oscillometry values.

BMI: Body mass index; IQR: interquartile range; FEV1: Forced expiratory volume in the first second; FVC: forced vital capacity; FEF25-75: Forced Expiratory Flow Between 25% and 75%, R5-R20: Resistances at 5 and 20 Hz; X5: Reactance at 5 Hz; Ax: Reactance area; $F_{Res}$: Resonant frequency in Hz, BPD: beclomethasone dipropionate.

[a] One-way ANOVA: cut-off for p value interpretation after Bonferroni correction**: 0.0125**.

[b] Atopy: the presence of at least 1 positive skin prick and/or specific serum IgE test for aeroallergens with clinically correlated symptoms.

[c] All ICS doses were converted to standard beclomethasone dipropionate potency equivalents for the purposes of statistical comparisons between groups.

and $FEF_{25–75\%}$<60% ($p < 0.0001$ for all comparisons).

Overall, standard spirometry measures and X5 progressively worsened from GINA steps 2 to 5, whereas all IOS measures but X5 progressively increased with the worsening of GINA steps 2 to 5. The difference between R5-R20 in each GINA steps was not primarily due to the skewed distribution of patients among GINA steps (Hedges' g coefficient ≤0.5; for GINA 2 vs. 3 = 0.2; for GINA 3 vs 4 = 0.3; for GINA 4 vs 5 = 0.5).

### 3.2. SAD among different GINA steps

While the prevalence of IOS-defined SAD was similar across all the classes (step 2, 58.3%; step 3, 60.9%; step 4, 63.3%; step 5, 78.6%; $p > 0.05$ in all comparisons) (Fig. 1A, black histograms), the peripheral airways resistance, as assessed by R5–R20, tended to progressively increase with the worsening of GINA steps, and was significantly higher in steps 4–5 compared to others ($p < 0.05$) (Fig. 1B).

The prevalence of IOS-defined "isolated SAD", i.e. SAD without proximal airway involvement (with a FEV1/FVC > lower limit of normality) (total n = 70), was non-significantly different across GINA steps 2–4 (step 2, 23.8%; step 3, 17.5%; step 4, 14.4%); while was absent in step 5 (0%) (Fig. 1A, red histograms).

Table 1 reported the prevalence of SAD by $FEF_{25–75\%}$. By direct comparison, the proportion of IOS-defined SAD were higher than $FEF_{25-75}$-defined SAD for GINA step 2 ($p = 0.0338$), step 3 ($p = 0.0001$), step 4 ($p = 0.0141$), but not step 5 ($p = 0.2143$).

### 3.3. Correlations between spirometric and oscillometric features

Overall, we found a weak inverse correlation between $FEF_{25-75}$ and R5–R20 ($r = -0.28$, $p < 0.0001$, Fig. 2), those indices of standard spirometry and IOS conventionally used to assess peripheral airways resistance. Only nonsignificant or weak inverse correlations between R5-R20 and $FEF_{25-75}$ were observed among GINA steps, with the exception of GINA step 5, which showed an inverse, strong correlation ($r = -0.80$, $p = 0.0005$).

## 4. Discussion

The main findings of this study are first that, in spite of a stable presence of SAD and "isolated" SAD (i.e. SAD without proximal airways involvement) across asthma severities, the level of peripheral obstruction progressively increased with the worsening of GINA steps, highlighting the contribution of small airways in asthma and directly linking the presence of SAD with asthma severity. Second, a significantly lower proportion of SAD was detected in GINA steps 2–4 by $FEF_{25–75\%}$ compared to IOS. In addition, with the exception of GINA step 5, there were only nonsignificant or weak inverse correlations between R5-R20 and $FEF_{25–75\%}$ within each GINA step. Altogether, this suggests that SAD is detected more frequently by IOS than by spirometry, especially in milder asthma. Therefore, IOS is an ideal complement to conventional lung function testing such as spirometry, body plethysmography and diffusion. It shows a comparatively high sensitivity in displaying peripheral obstructions of the respiratory tract (small airways) and detects instabilities in the bronchial system (i.e. trapped air), which supports early detection of lung disease and specific therapeutic approaches [8].

Our study also confirms in a large population of community-treated patients the previous finding of a high prevalence of SAD in asthma [10]. However, only a few studies previously showed that SAD is highly prevalent across different asthma severities or the correlation of SAD with asthma control, but results are overall heterogeneous and sometimes even conflicting [7,18,25,26].

Our findings showed that with the aggravation of asthma severity, the resistance in small airways (detected by both IOS and spirometry) worsened, becoming progressively more apparent by standard spirometry, as shown by the increase in the proportion of $FEF_{25-75}$-defined SAD from GINA step 2 to GINA step 5 and by the progressive increase in the Pearson's r correlation coefficient between R5-R20 and $FEF_{25–75\%}$. This supports the concept that the less severe is the asthma, the less spirometry is able to detect small airways resistance. Overall, conventional spirometry measurements are usually considered unable to sensitively evaluate small airways [12,13,27–30]. In addition, isolated SAD was observed approximately between 15% and 25% in asthmatic patients with GINA steps 2–4. To us, these results have important clinical implications, by supporting the use of IOS in the routine asthma assessment and ultimately by guiding the inhalator treatment choice (i.e. considering inhaled extra-fine therapy and biologics in those patients with SAD). Anderson et al. [7] analyzed the prevalence of SAD in 368 patients with asthma receiving treatment as defined by British Thoracic Society (BTS), and demonstrated that SAD is persistently present across asthma severities. Our findings are consistent with those of Anderson' study, since peripheral abnormalities persist across severity classes despite a greater daily dose of ICS at higher steps, suggesting a little effect of current therapies on the development of airway structural abnormalities, or a poor peripheral delivery of inhaled therapy.

Our study has several limitations, which may impair the generalizability of these findings to non-community-managed asthmatic patients. First, we used a physician-diagnosed asthma definition, with the potential risk of over-diagnosis. However, this is the gold standard used for several real life studies [7,27–30], and in the majority of cases diagnosis was supported by a standard spirometry and/or methacholine challenge. Second, there was a lack of data on treatment adherence, since this data

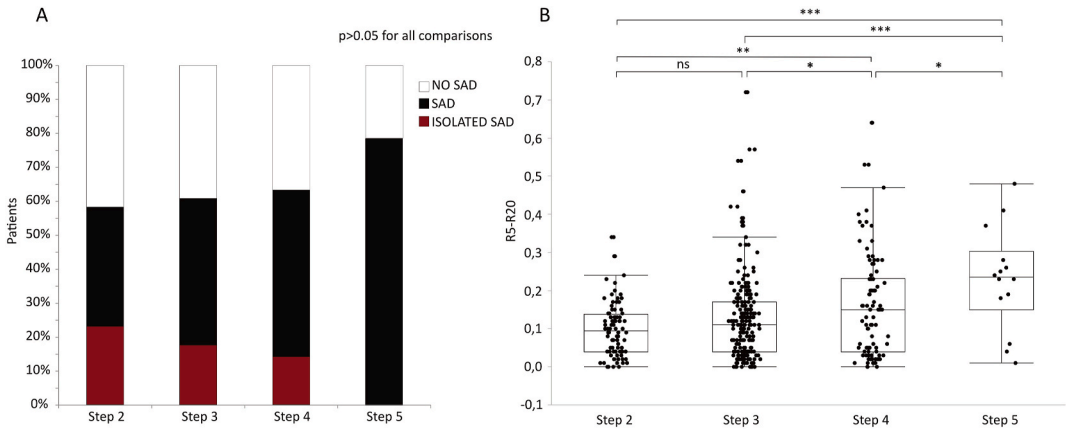


**Fig. 1.** Prevalence of small airways disease across GINA steps 2 to 5 (**A**): In black the prevalence of SAD, in red the prevalence of "isolated" SAD, i.e. SAD without proximal airways involvement. $P > 0.05$ for all comparisons for SAD and for "isolated" SAD within different GINA steps. Small airways resistance assessed by R5-R20 across GINA steps 2 to 5 (**B**). Significance: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

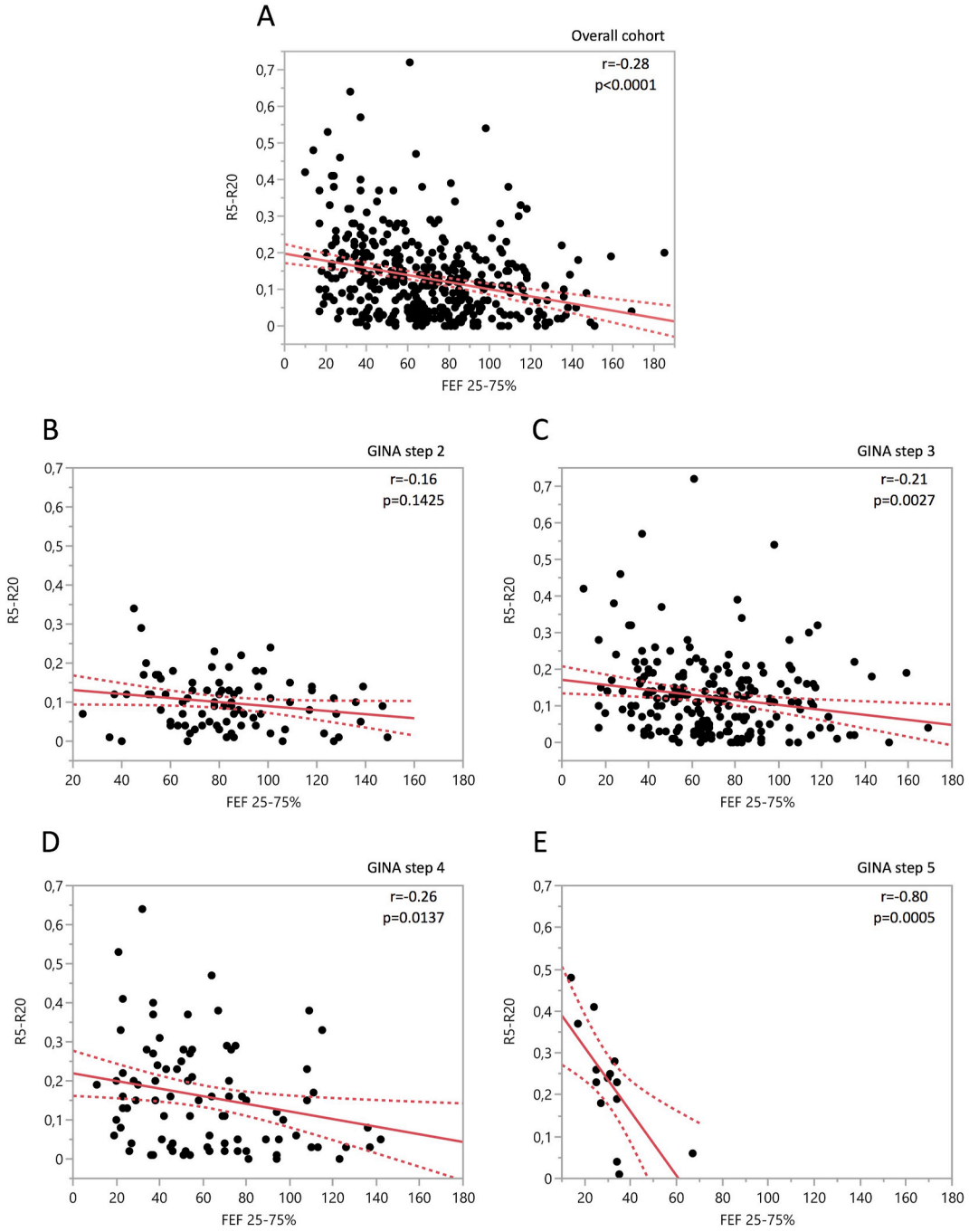


**Fig. 2.** Correlations between R5-R20 and $FEF_{25-75}$ for all the cohort of patients (**A**); for patients in GINA step 2 only (**B**), for patients in GINA step 3 patients only (**C**), for patients in GINA step 4 patients only (**D**), for patients in GINA step 5 patients only (**E**).

was difficult to be collected. Another limitation is the underrepresentation of GINA step 5; we tried to mitigate this potential issue by excluding that these results were a consequence of the effect size. However, this data is in line with previous reports [7,31] and ultimately represents the epidemiology of the community-treated asthma. Finally, we relied on IOS for the definition of SAD, which is not the only measure that can be used to assess SAD. However, R5-R20 was the marker that most strongly correlated with SAD in a recent large study [8].

In conclusion, this study shows that first, IOS-defined SAD is highly present across asthma severities in community-treated patients; second, airways resistance increases with the worsening of GINA steps. Third, SAD may be frequently overlooked by standard spirometry and especially in milder asthma cases, highlighting the needs of the IOS use for an accurate detection of SAD.

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## CRediT authorship contribution statement

**Marcello Cottini:** Writing - review & editing, conceived the study, designed the study, had full access to all of the data in the study and takes responsibility for the integrity of the data, drafted the article. approved the final version to be published. **Anita Licini:** Writing -

review & editing, acquired the data, approved the final version to be published. **Carlo Lombardi:** Writing - review & editing, conceived the study approved the final version to be published. **Alvise Berti:** Writing - review & editing, conceived the study, designed the study takes responsibility for the accuracy of the data analysis, drafted the article approved the final version to be published.

## Declaration of competing interest

The authors have no financial or non-financial potential conflicts of interest to declare related to this project.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmed.2020.106243.

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