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Efficacy of Benralizumab in severe asthma in real life and focus on nasal polyposis

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ABSTRACT

Introduction: Severe asthma occurs in 5–10% of asthmatic patients, with nasal polyposis as one of the most frequent comorbidity. Benralizumab was recently marketed, thus we could analyse its effects in real-life in severe asthma, and compare the effects of the drug in patients with and without polyposis.

Methods: Patients with severe asthma, receiving Benralizumab were enrolled in Italian asthma centres. The efficacy criteria for asthma (exacerbation rate, oral corticosteroid intake, hospitalizations, pulmonary function, exhaled nitric oxide) were evaluated at baseline and after 24 weeks of treatment. Patients were then sub-analysed according to the presence/absence of nasal polyposis.

Results: Fifty-nine patients with severe uncontrolled asthma (21 males, age range 32–78) and treated with benralizumab for at least 24 weeks has been evaluated, showing significant improvements in asthma-related outcomes, except for pulmonary function and exhaled nitric oxide. This included a reduction in the sino-nasal outcome-22 score versus baseline of 13.7 points ($p = .0037$) in the 34 patients with nasal polyposis. Anosmia disappeared in 31% patients ($p = .0034$). When comparing the groups with and without nasal polyposis, a similar reduction of exacerbations was seen, with a greater reduction of the steroid dependence in patients with polyposis (−72% vs −53%; $p < .0001$), whereas lung function was significantly more improved (12% vs 34%, $p = .0064$) without polyposis patients.

Conclusions: Benralizumab, after 6 months of treatment, confirmed its efficacy in severe asthma, and also in nasal polyposis, which is the most frequent comorbidity. The efficacy of Benralizumab in reducing steroid dependence was even higher in patients with polyposis.

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1. Introduction

Bronchial asthma is a chronic respiratory disease of increasing prevalence that affects an estimated 300 million people worldwide [1,2]. Among asthmatic patients 5–10% meet consensus criteria for severe asthma [3]; specifically they have poor control of symptoms despite a maximal inhaled therapy, frequent exacerbations, and/or the need for oral corticosteroid (OCS) (American Thoracic Society/European Respiratory Society (ATS/ERS) [4]. With the aim to reduce OCS intake, due to its well-known side effects (diabetes, cataract, osteoporosis, hypertension, weight gain) [5,6], maintaining controlled asthma symptoms, to omalizumab [7,8] has been added mepolizumab, reslizumab, against interleukin (IL) 5 or its receptor alpha, in case of benralizumab [9–11]. The awareness that these molecules act on mechanisms of type-2 inflammation, common between asthma and several of its of comorbidities, including chronic rhinosinusitis with nasal polyps (CRSwNP, briefly **NP**) [12–16], prompt clinicians to observe the efficacy of monoclonal antibodies on both diseases [17]. The importance of NP in asthmatic patients stem from the fact that, it appeared to be one of the most frequent comorbidity both in clinical trials [14,18,19] and in the real-life setting [20]. Although not life-threatening, NP severely affects the quality of life of patients, contribute to the poor control of asthma, and is associated with a significant socio-economic burden, due to repeated surgery and use of OCS [21]. Particularly in severe asthmatic patients NP needs to be evaluated and an accurate follow-up program must be set, in the first instance with nasal fiberotic endoscopy eventually followed by CT scan [22,23].

The use of biological drugs in the treatment of severe asthma has become a proven practice for some years now. Favourable effects in reducing exacerbations, the use of OCS, in improving disease control in patients with severe asthma are well known. In recent years, research has been carried out with trials to evaluate the efficacy of biological drugs marketed for asthma on nasal polyposis [24]. Anti IL-5 drugs, both mepolizumab [25] and reslizumab [26], demonstrated a significant reduction of NP size after their administration. Also omalizumab (anti IgE), demonstrate its efficacy in reduction of NP size after administration [27]. Finally dupilumab (anti IL-4r) has proved its effectiveness in NP size reduction and impact of the disease in affected patients [28].

There are much less data about Benralizumab (BEN), an antagonist of the IL-5 receptor. It inhibits the maturation, activation and survival of eosinophils and, via a cell-mediated cytotoxicity mechanism, also provoke apoptosis and induce eosinophil depletion (ADCC). BEN was recently commercialized in Italy for severe asthma.

Given the increasingly central role of real life studies, following the suggestions of Thorpe et al., and their PRECIS tool [29], in the present study we describe the effects of BEN, given for at least 6 months in asthma and compare the effect of the treatment in subjects with or without NP.

List of abbreviations

OCS	Oral Corticosteroids
FEV1	Forced Expiratory Volume in 1 s
FVC	Forced Vital Capacity
FeNO	Fractional exhaled Nitric Oxide
BEN	Benralizumab
NP	Nasal Polyposis
CRS	Chronic RhinoSinusitis
SNOT-22	Sino Nasal Outcome Test 22 items

2. Methods

Study design is an observational retrospective multicentre study. Source of population are database about multiple Italian Centres (Genoa, Arenzano, Turin, Verona, Brescia, Sestri Levante, Naples, Rome, Cuneo, Pietra Ligure, Bergamo, Milan and Bari).

Inclusion criteria. Patients aged ≥18 year old, with diagnosis of severe asthma, according to ATS/ERS definition, eligible to BEN treatment according to GINA guidelines and to the Italian prescription rules (blood eosinophils ≥300 cell/mcl, ≥2 exacerbations requiring systemic steroids in the previous 12 months or steroid dependence for at least 6 months). All patients were fully adherent to the prescribed maximal inhaled therapy (GINA step 5) and underwent a detailed diagnostic work-up before receiving the diagnosis of severe asthma, and BEN prescription, including thoracic CT-scan, allergy testing and plethysmography. When needed, in the clinical suspect of NP, maxillary CT-scan and/or fiber-optic rhinoscopy were performed. The first consecutive patients, who were treated with BEN in the various clinics involved in the study, were considered. Patients needed to be treated for 6 months, with BEN, in the period from December 1, 2018 to August 31, 2019.

No exclusion criteria were envisaged for this study.

The evaluated parameters were: exacerbation rate and hospitalizations (compared to the previous 12 months), asthma control test (ACT) score, Forced Expiratory Volume 1 s (FEV1), Forced Vital Capacity (FVC), fractional exhaled nitric oxide (FeNO), eosinohil blood count. All the parameters were recorded at baseline (before treatment) and at 24 weeks. Also, the OCS intake, and the chronic need for OCS were carefully assessed at the same time points. NP was evaluated, in addition to the instrumental diagnosis, by the sino-nasal outcome test with 22 items (SNOT-22) and by the subjective patient's perception of anosmia (yes/no).

Main study endpoints was to observe the efficacy of BEN in the whole population, about the variation of exacerbations, OCS dependence and dosage, lung function tests and asthma control (measured with ACT). Further endpoint was to observe the effect of BEN in two distinct population, patients with or without NP, also evaluating the efficacy on nasal symptoms (measured with SNOT-22 test).

Data were analysed by descriptive statistics. Comparisons between groups were made by *t*-test, chi-square test, Fisher's exact test where necessary. A p value of ≤.05 was considered significant.

3. Results

Fifty-nine patients (64% female, age range 32–78), referred to 12 severe asthma clinics in Italy starting from December 1st, 2018 received BEN and could be evaluated for at least 24 weeks. The clinical and demographic data of the population are summarized in Table 1. After 24 weeks of treatment, there was a significant improvement in almost all of the considered asthma-related parameters, as shown in Table 2. The control of the disease, measured with ACT score, showed an overall improvement of 47% ($p < .0001$ versus baseline). The results are detailed in Table 2 and Fig. 1. After 24 weeks of therapy 48 (81%) patients have reached the minimal clinical important difference (MCID) for ACT, fixed at 3 points [30]. No further observations about MCID could be done due to the unviability of similar parameters in other evaluated outcomes [31].

The mean number of asthma exacerbations decreased from 4.44 to 0.39 (−91%; $p < .0001$) and hospitalizations decreased from 0.31 to 0.03 (−89%; $p < .0001$). The number of patients chronically receiving OCS went down from 41/59 to 15/59 and the mean OCS daily dose decreased by 54% (12.0–5.6 mg, $p < .0001$). There was also an increase in the absolute values of FEV1 and FVC, 17% and 11%, respectively.

Thirty-four (58%) out of 59 patients (19 female, mean age 56 ± 11 years, age range 32–78 years) had an ascertained concomitant NP, confirmed by TC scan and/or fiber-optic rhinoscopy. In those patients the mean number of previous surgical interventions (ranged between 1

Table 1
Descriptive statistics of the population at baseline.

Baseline (n = 59)	Total population (n = 59)	NP (n = 34)	No NP (n = 25)
Male/Female	21/38	19/15	19/6
Age range	32–78	32–78	47–78
ACT score, mean ± SD (range)	15 ± 4 (6–23)	15 ± 4 (6–23)	13 ± 3 (8–19)
Exacerbations per year, mean ± SD (range)	4.44 ± 3.52 (0–20)	4.7 ± 3.8 (0–20)	4.1 ± 3.15 (0–12)
Hospitalizations per year, mean ± SD	0.31 ± 0.56 (0–2)	0.18 ± 0.39 (0–1)	0.48 ± 0.71 (0–2)
OCS-dependent, n (%)	41 (69)	25 (73)	19 (76)
OCS intake mg/day, mean ± SD	12.0 ± 8.1 (2.5–25)	9.04 ± 8.01 (2.5–25)	14.4 ± 9.4 (5–25)
FEV1 L, mean ± SD	1.92 ± 0.76 (0.61–4.43)	2.16 ± 0.73 (0.66–4.43)	1.47 ± 0.63 (0.61–2.79)
FeNO ppb, mean ± SD	70 ± 58 (5–406)	59 ± 31 (17–156)	82 ± 79 (5–406)
Eosinophils cells/μl, mean ± SD	581 ± 556 (70–3350)	632 ± 397 (70–1600)	567 ± 733 (100–3350)
Perceived anosmia (%)	26 (44)	26 (76)	-

Table 2
Changes in the severe asthma-related outcomes (whole population N = 59). All data are expressed in mean ± standard deviation. * previous 12 months before treatment; **geometric mean; n.s. = not significant.

	Baseline	24 weeks	p-value
ACT	15 ± 4	21 ± 4	<.0001
Exacerbation rate*	4.44 ± 3.52	0.39 ± 1.12	<.0001
Hospitalizations*	0.31 ± 0.56	0.03 ± 0.18	0.0006
OCS dependent n (%)	41 (69)	15 (25)	<.0001
OCS dose (mg prednisone)	12.0 ± 8.1	5.6 ± 3.58	<.0001
FEV1 (L)	1.92 ± 0.76	2.25 ± 0.82	n.s.
FEV1 (%)	72 ± 20	86 ± 18	0.0002
FeNO ppb	70 ± 58	42 ± 42	0.017
Eosinophils (cell/mcl)**	581 ± 556	24 ± 48	<.0001

and 8) was 2.8 ± 2.0, the SNOT-22 score was 58 ± 18, and 76% of them reported a concomitant anosmia. After 24 weeks of treatment 20 (54%) patients reduced their SNOT-22 score more than 8.9, fixed value for MCID of the test [32]. The details of patients with and without NP are summarized in Table 3. When comparing the two subpopulations (with and without NP), some differences could be seen. The pulmonary function (FEV1 in absolute value and % predicted) improved significantly versus baseline only in patients without NP, and the same happened for FeNO. On the contrary, the percentage of subjects who were on chronic OCS treatment decreased significantly only in patients with NP (Table 4, Fig. 2).

Concerning the safety, no patient had to discontinue the treatment due to adverse events. Adverse events occurs in 9 (15%) patients, with fever on the day of first administration as the most common one (4 patients; 6.8%) and 2 (3.4%) patients with Herpes Zoster Virus infection. Other adverse events individually reported were headache, back pain and urticarial.

4. Discussion

In the last two decades, biological treatments were commercialized for severe asthma, and the results obtained firstly with anti-IgE (Omalizumab) and subsequently with IL-5 antagonists (Mepolizumab, Benralizumab) lead to relevant advances in the management of the disease. These include the direct clinical aspect (asthma control, pulmonary function, exacerbation rate, hospitalizations) and the sparing effect on OCS use, with its long-term implications. It was observed that real-life data and patients' characteristics [18,21] partly diverge from the results of regulatory trials, therefore real-life data improved our knowledge on the clinical effects, safety and indications of the new drugs [33,34]. BEN was licensed in many Countries for the treatment of severe asthma, and in Italy less than one year ago. We can provide nowadays the efficacy data of this recently marketed drug, over a period of at least 6 months in real life.

Comparing several aspects of RCTs and RL studies, particularly about our patients and the one randomized in main BEN studies, was possible to observe several differences. One of the first observation is regard

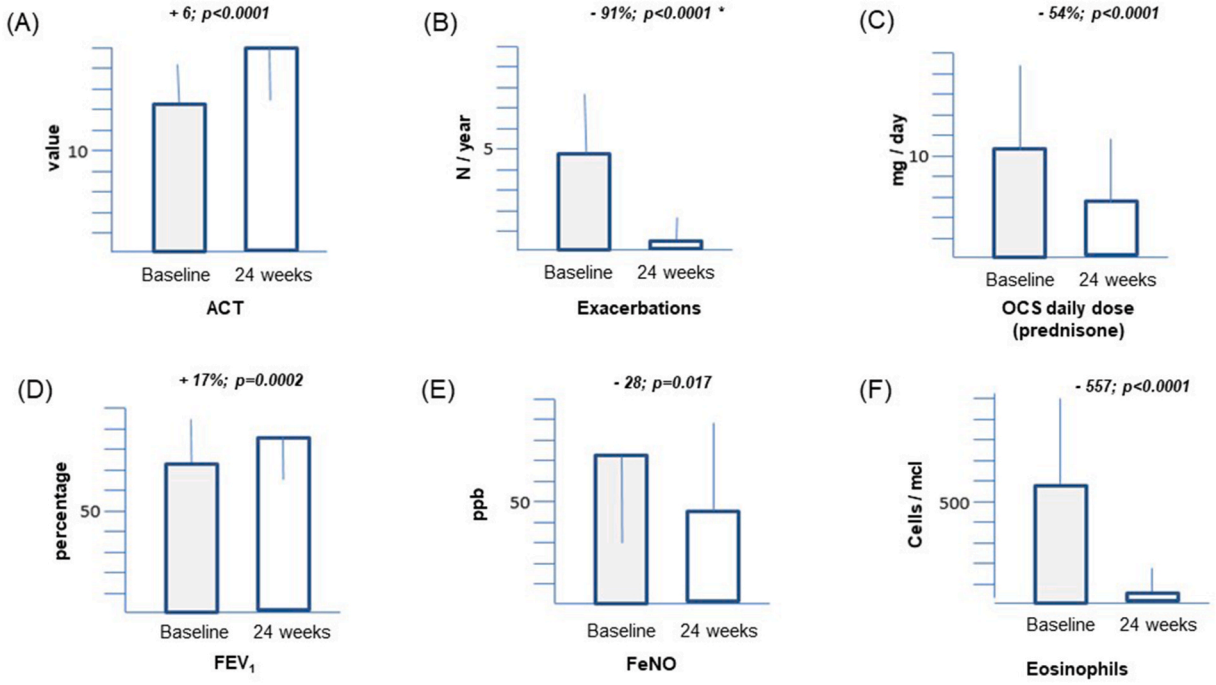

Fig. 1. Changes in the main asthma evaluation parameters between baseline and 6 months. * change in exacerbation comparing 12 months before with 24 weeks after Benralizumab administration.

Table 3
Difference of outcomes, after 6 months of therapy, in population with and without NP.

	NP (n = 34) baseline	NP (n = 34) 24 weeks	Change from baseline (%)	p-value	No NP (n = 25) Baseline	No NP (n = 25) 24 weeks	Change from baseline (%)	p-value
ACT	15 (4)	21 (4)	6 (39%)	<.0001	13 (3)	21 (4)	8 (62%)	<.0001
Exacerbations¥	4.7 (3.8)	0.35 (1.37)	- 4.36 (- 93%)	<.0001	4.1 (3.15)	0.44 (0.71)	−3.64 (- 89%)	<.0001
Hospitalizations	0.18 (0.39)	0.06 (0.24)	- 0.12 (- 67%)	n.s.	0.48 (0.71)	0.0 (0.0)	- 0.48 (100%)	.0015
OCS dependent	25 (73%)	7 (21%)	- 18 (- 72%)	<.0001	19 (76%)	9 (36%)	−10 (- 53%)	.0096
OCS dose#	9.04 (8.1)	3.5 (1.7)	- 5.54 (- 61%)	<.0001	14.1 (9.4)	6.25 (4.2)	- 7.85 (- 56%)	.0002
FEV1 (L)	2.16 (0.73)	2.34 (0.79)	0.18 (8.3%)	n.s.	1.47 (0.63)	2.09 (0.90)	0.62 (42%)	.0318
FEV1 (%)	76 (18)	85 (18)	9 (12%)	n.s.	66 (22)	88 (18)	22 (34%)	.0005
FVC (L)	3.27 (1.07)	3.43 (1.05)	0.16 (4.9%)	n.s.	2.31 (0.77)	3.00 (1.20)	0.68 (30%)	n.s.
FVC (%)	94 (18)	101 (21)	7 (5%)	n.s.	80 (26)	98 (24)	18 (22%)	n.s.
FeNO	59 (31)	49 (44)	−10 (- 18%)	n.s.	82 (79)	36 (41)	- 45 (55)	.0280
Blood eosinophils*	632 (397)	14 (47)	- 618 (- 98%)	<.0001	567	36 (49)	531 (94%)	<.0001
SNOT-22	57.6 (18)	44.0 (19.8)	- 13.7 (- 23.8%)	.0037	n.a.	n.a.	n.a.	n.a.
Anosmia	26 (76%)	18 (53%)	- 8 (31%)	.0034	n.a.	n.a.	n.a.	n.a.

All data are expressed as mean and standard deviation (SD) or value and percentage (%) where not differently specified. ¥ 12 months at baseline and in the period of treatment after 6 months, *value expressed in geometric mean. # expressed in prednisone equivalent. n.s. = statistically not significant.

Table 4
Comparison of the change in the evaluated parameters between patients with and without NP.

	NP (Δ 24 week – baseline)	No NP (Δ 24 week – baseline)	p-value
ACT	6 (39%)	8 (62%)	n.s.
Exacerbations¥	−4.36 (−93%)	−3.64 (−89%)	n.s.
Hospitalizations	−0.12 (−67%)	−0.48 (100%)	.0168
OCS dependent	−18 (−72%)	−10 (−53%)	<.0001
OCS dose#	−5.54 (−61%)	−7.85 (−56%)	n.s.
FEV1 (L)	0.18 (8.3%)	0.62 (42%)	.0414
FEV1 (%)	9 (12%)	22 (34%)	.0064
FeNO	−10 (−18%)	−45 (−55%)	.0358
Blood eosinophils*	−618 (−98%)	−531 (−94%)	n.s.

¥ 12 months at baseline and in the period of treatment after 24 weeks, *value expressed in geometric mean. # expressed in prednisone equivalent. n.s. = statistically not significant.

baseline eosinophils count, resulted highest in our patients if compared with the one of CALIMA [35] and SIROCCO [36]. A second interesting difference regards the prevalence of nasal polyps in the two different population. As already observed in mepolizumab trials [20], if compared with RCTs, NP prevalence is considerably higher in RL also in this trial with BEN. A reason of these variance could be find in the different inclusion and exclusion criteria about RL and RCTs studies, where the real patients have less restrictions to be enrolled in a study. In our trial, in fact, inclusion and exclusion criteria, above described, are less strict, requiring almost only the diagnosis of asthma and the prescription criteria for BEN.

The herein reported results confirm the clinical efficacy and the biological effects of BEN in real life and its safety. In particular, there was an apparent improvement in asthma control, in the exacerbation rate, in OCS intake and biological markers (FeNO, blood eosinophils). It is true that the efficacy results in this real-life population, still not allow to identify the right patient for the right prescription. Another limitation of our study is that we could assess the data of exacerbations and OCS intake over a 6-month period, and those data are compared to the historical over 1 year. Nonetheless, the difference between baseline and 6 months were apparent.

There is another aspect of clinical relevance: in severe eosinophilic asthma, NP represents a frequent comorbidity, with a well-recognized impact on the quality of life, on the costs and on the control of asthma itself. In the herein observed population, an ascertained NP was present

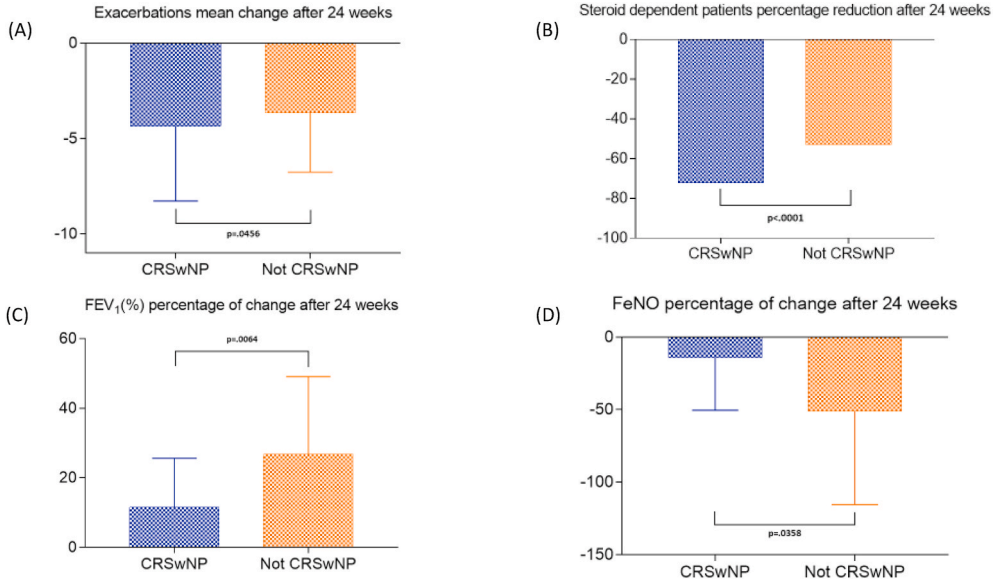

Fig. 2. A) Exacerbations mean change, B) steroid dependent patients percentage reduction, C) FEV_1 improvement, D) FeNO percentage of change after 24 weeks of treatment.

in 58% of patients, thus we could evaluate both the effects of the drug, and to dissect those effects between patients with or without NP.

After 24 weeks of therapy, the cohort of patients with NP had a significant improvement in SNOT-22, by 23.8% compared with the baseline value. Actually, the literature on the possible effects of BEN in NP associated to severe asthma is, so far, scarce [36–38]. One of the worst symptom associated with NP is anosmia. Patients with this symptom are more commonly anxious and depressed than patients without anosmia [39]. We could evidence the improvement of the symptom in 31% of patients affected by anosmia at baseline ($p = .0034$), as previously reported as case description [40].

Overall, after 24 weeks, BEN treatment in real life was confirmed and the efficacy was also apparent on the concomitant NP, when present. In the subset of patients with NP the reduction of OCS dependence was greater than in patients without NP, while the opposite was seen for the respiratory function.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Diego Bagnasco: Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Luisa Brussino:** Data curation, Visualization, Validation. **Marco Bonavia:** Data curation, Visualization, Validation. **Elisa Calzolari:** Data curation, Visualization, Validation. **Marco Caminati:** Data curation, Visualization, Validation. **Cristiano Caruso:** Data curation, Visualization, Validation. **Maria D'Amato:** Data curation, Visualization, Validation. **Laura De Ferrari:** Data curation, Visualization, Validation. **Fabiano Di Marco:** Data curation, Visualization, Validation. **Gianluca Imeri:** Data curation, Visualization, Validation. **Danilo Di Bona:** Data curation, Visualization, Validation. **Andrea Gilardenghi:** Data curation, Visualization, Validation. **Giuseppe Guida:** Data curation, Visualization, Validation. **Carlo Lombardi:** Data curation, Visualization, Validation. **Manlio Milanese:** Data curation, Visualization, Validation. **Antonello Nicolini:** Data curation, Visualization, Validation. **Anna Maria Riccio:** Data curation, Visualization, Validation. **Giovanni Rolla:** Data curation, Visualization, Validation. **Pierachille Santus:** Data curation, Visualization, Validation. **Gianenrico Senna:** Data curation, Visualization, Validation. **Giovanni Passalacqua:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing.

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