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Effectiveness of a targeted infant RSV immunization strategy (2024–2025): A multicenter matched case-control study in a high-surveillance setting

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SUMMARY

Background: Nirsevimab, a long-acting monoclonal antibody against respiratory syncytial virus (RSV), was recently introduced to prevent infant RSV-related hospitalizations. Although efficacy has been demonstrated in clinical trials, real-world data on targeted immunization strategies remain limited. We aimed to evaluate the effectiveness of nirsevimab in preventing RSV-associated hospitalizations in infants under 12 months, within a seasonal program prioritizing infants born from April onwards.

Methods: We conducted a prospective, multicenter, matched case-control study across seven Italian hospitals during the 2024–2025 RSV season. Infants hospitalized with PCR-confirmed RSV bronchiolitis were matched 1:2 by age and date of admission to controls hospitalized for non-respiratory causes. Data were collected via electronic medical records. Immunization effectiveness (IE) was estimated using conditional logistic regression adjusted for sex assigned at birth, gestational age, birth weight, and clinical risk factors. Two pre-specified stratified analyses and a sensitivity analysis using inverse probability of treatment weighting (IPTW) were performed.

Results: A total of 138 infants were included (46 cases, 92 controls). Adjusted IE was 89.5% (95% CI: 60.3–97.2%). Stratified analyses yielded similar results among infants born after April 1 (IE: 88.4%, 95% CI:

Abbreviations: ALRTI, acute lower respiratory tract infection; CI, confidence interval; IE, immunization effectiveness; IPTW, inverse probability of treatment weighting; IQR, interquartile range; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; RAENHoB, Real-world Assessment of Effectiveness of Nirsevimab in preventing Hospitalizations due to Respiratory Syncytial Virus Bronchiolitis; RSV, respiratory syncytial virus; STROBE, strengthening the reporting of observational studies in epidemiology

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56.5–96.9%) and those without risk factors (IE: 88.1%, 95% CI: 45.7–97.4%). IPTW analysis confirmed protection (IE: 79.6%, 95% CI: 53.5–91.0%).
Conclusions: This study provides real-world evidence supporting the effectiveness of nirsevimab in a targeted seasonal immunization framework. These findings may inform phased implementation strategies and RSV prophylaxis policies in varied healthcare settings.

Background

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory tract infections (ALRTIs) in infants worldwide. Each year, RSV accounts for an estimated 33·1 million episodes of ALRTIs in children under five years, resulting in approximately 3·2 million hospital admissions and over 100,000 deaths globally.[1,2] Until 2023, palivizumab was the only monoclonal antibody licensed for RSV prevention, but its use was limited to high-risk infants due to logistical and economic constraints.[3,4] Nirsevimab, a long-acting monoclonal antibody with potent neutralizing activity against RSV, has emerged as an effective preventive option suitable for all infants. Clinical trials have shown that a single dose significantly reduces the risk of medically attended RSV-related ALRTIs in preterm and full-term infants, with a favorable safety profile.[5–7] Following its approval by the European Medicines Agency in November 2022[8] and the Food and Drug Administration in July 2023,[9] several countries initiated immunization programs in autumn 2023. Preliminary real-world data from early-adopting countries, such as France, Spain, the United States, and Australia, have confirmed nirsevimab effectiveness.[10–20] These initial rollouts have adopted varying strategies in terms of eligibility criteria, timing, and delivery settings. Such heterogeneity offers an opportunity to assess the real-world performance of nirsevimab across different epidemiological contexts and delivery models.

This study evaluates the real-world effectiveness of a targeted immunization program prioritizing infants most likely exposed during peak RSV circulation. The strategy, implemented within a well-defined health system and birth cohort, offers insights into the impact of providing nirsevimab to all infants born after April 1st. We aimed to provide evidence on the effectiveness of a pragmatic and resource-conscious immunization approach that may inform public health planning in other settings.

Methods

Study design and population

We conducted a multicenter, observational, matched case-control study enrolling infants under 12 months of age who were hospitalized between November 1st, 2024, and March 31st, 2025, at one of seven participating pediatric centers in Tuscany, Italy (Real-world Assessment of Effectiveness of Nirsevimab in preventing Hospitalizations due to Respiratory Syncytial Virus Bronchiolitis, RAENHoB study, study protocol available at Supplementary Text S1).

Case patients were defined as infants hospitalized with respiratory infections related to RSV, confirmed through polymerase chain reaction (PCR) testing of respiratory samples. Control patients were infants admitted for non-respiratory conditions, such as urinary tract infections, gastroenteritis, surgical issues, feeding difficulties, jaundice, or poor weight gain, provided they had no respiratory symptoms. Case and control patients were matched in a 1:2 ratio based on age (± 1 month) and date of hospitalization (± 2 weeks). Children born before October 31st, 2024, were defined as out-of-season, while infants born between November 1st, 2024, and March 31st, 2025, were designated as in-season.

Exclusion criteria included parental refusal to participate, prior administration of palivizumab, and receipt of maternal RSV vaccine during pregnancy. Patients with missing data and unmatched case patients were not included.

By the approved indication of nirsevimab for all infants under 12 months of age, the primary analysis included all hospitalized infants in this age group, irrespective of their eligibility under the regional campaign. This approach aimed to reflect the potential effectiveness of nirsevimab across the whole infant population. Subgroup analyses were subsequently performed to specifically evaluate effectiveness among infants born on or after April 1st, 2024, those eligible under the Tuscan immunization campaign, and infants without predefined clinical risk factors for severe bronchiolitis. Risk factors for severe bronchiolitis were defined according to the eligibility criteria for palivizumab: birth at ≤35 weeks of gestational age and age < 6 months during the RSV season, bronchopulmonary dysplasia, and hemodynamically significant congenital heart disease.[3] This study did not address the immunization strategies for children older than 12 months with specific risk factors for severe bronchiolitis, who may still be eligible for RSV immunoprophylaxis under extended indications.

Enrollment was conducted prospectively and concurrently across all participating centers. Patients with incomplete matching or missing key data were excluded from the final analysis. Demographic and clinical data, including sex assigned at birth, were extracted from electronic medical records. The clinical variables analyzed included the need for oxygen (with its duration or type), the need for enteral feeding, pediatric intensive care unit (PICU) admission, the detection of other viruses, bacterial coinfections, and length of stay (LOS).

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary Table S2).

The RAENHoB study protocol was approved by the Regional Ethics Committee of Tuscany (approval number 218/2024). In accordance with regional regulations and ethical standards, written informed consent was obtained from the parents or legal guardians of all participating infants.

Nirsevimab immunization campaign and respiratory viruses' surveillance

In Italy, nirsevimab was introduced, allowing each region to tailor its implementation based on local epidemiology, resources, and healthcare infrastructure. In Tuscany, the immunization campaign officially began on November 1st, 2024, and targeted infants born on or after April 1st, 2024. Immunization was proposed and administered directly at birth centers for in-season born infants, while for out-of-season born infants, it was managed by family pediatricians. The nirsevimab immunization coverage in Tuscany in 2024 was about 90% of eligible infants.

The Tuscany region has developed a robust infrastructure for epidemiological surveillance, including the NETVAC project (Pediatric Regional Networking and use of low-cost molecular biology techniques as a new model for organizing and managing vaccine-preventable disease surveillance). This regional surveillance

network, coordinated by the Immunology Laboratory of Meyer Children's Hospital, encompasses all cases of vaccine-preventable infectious diseases, including respiratory syncytial virus (RSV). Implementing NETVAC has markedly enhanced diagnostic capabilities and substantially strengthened regional surveillance performance. Notably, all pediatric hospital departments in the region systematically perform PCR testing for major respiratory viruses in children admitted with respiratory symptoms, ensuring timely and accurate virological diagnosis.

Statistical analysis

Based on a very conservative nirsevimab coverage assumption of 60%, hypothesized on reports from countries that introduced the monoclonal antibody during the 2023–2024 season,[10–12,14] we calculated the required sample size to detect a 70% reduction in the odds of receiving nirsevimab among RSV-bronchiolitis cases compared to controls. This calculation assumed a two-sided alpha of 0·05, 90% power, and a 1:2 matching ratio, resulting in a required sample of 46 cases and 92 controls (total n = 138).

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as medians with interquartile ranges (IQR), and categorical variables were expressed as frequencies and percentages. Differences between groups were assessed using the Mann–Whitney *U* test for continuous variables and the Chi-square or Fisher's exact test for categorical variables, as appropriate.

To estimate the effectiveness of nirsevimab in preventing RSV-associated hospitalizations, we used conditional logistic regression models to account for the matched study design. Age and date of hospitalization were chosen as matching variables because they are strong potential confounders for both immunization status and the risk of RSV hospitalization. Matching on these variables allowed us to control for their potential non-linear effects and improve comparability between cases and controls while reducing model dependence.

The conditional logistic regression model was further adjusted for additional potential confounders not included in the matching process, specifically sex assigned at birth, gestational age, birth weight, and predefined risk factors for severe bronchiolitis. This two-step approach, matching followed by covariate adjustment, aligns recommended practices for matched case-control studies and enhances internal validity.

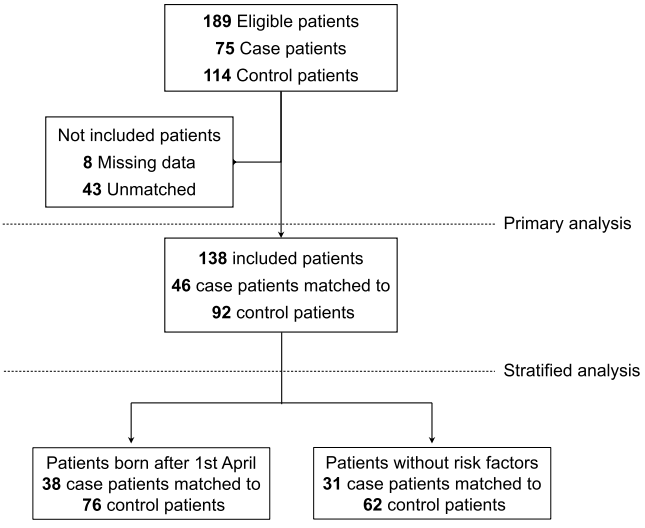

Fig. 1. Patients' inclusion flowchart.

Immunization effectiveness (IE) was calculated as IE = 100 × (1 − odds ratio), where the odds ratio refers either to the adjusted or unadjusted estimate, depending on the model.

We conducted two pre-specified stratified analyses to explore potential sources of heterogeneity in immunization effectiveness. The first included only infants born on or after April 1st, 2024, by the Tuscan campaign's eligibility criteria. This analysis assessed effectiveness within the population explicitly targeted by the program. The second excluded infants with predefined clinical risk factors to evaluate effectiveness in otherwise healthy infants, representing most of the birth cohort. In stratified analyses, matched sets were preserved to maintain internal validity.

As a sensitivity analysis, we used inverse probability of treatment weighting (IPTW) to estimate the average treatment effect. Propensity scores were derived via logistic regression using the same covariates described above, and weights were calculated as the inverse of the probability of treatment received.

All statistical analyses were performed using Stata version 18·5 (StataCorp, College Station, TX, USA), with two-tailed p-values < 0·05 considered statistically significant.

Results

During the study period, 189 eligible infants were identified, and 51 were excluded due to an unmatched status or missing data. One hundred thirty-eight infants under 12 months of age were enrolled across the participating centers, including 46 RSV-positive cases and 92 matched controls (Fig. 1 and Supplementary Fig. S3). The baseline characteristics of the two groups are summarized in Table 1. The median age at admission was 4·0 months for both case (IQR: 2·1–7·8) and control patients (IQR: 2·0–8·0). At least one clinical risk factor for severe bronchiolitis was present in 6 cases (13·0%) and 13 control patients (14·1%). Overall, 83 infants (60·1%) received nirsevimab: 19 (41·3%) among cases and 64 (69·6%) among control patients. Considering only infants eligible for immunization under the regional campaign criteria (i.e., born on or after April 1st, 2024, there were 38 cases and 76 controls), the coverage increased to 50·0% in cases and 84·2% in controls.

As shown in Table 2, immunized case patients had a significantly lower need for oxygen therapy than non-immunized ones, with a

Table 1
General cohort characteristics.

	Case patients n = 46	Control patients n = 92
Age at admission (months), median [IQR]	4·0 [2·1–7·8]	4·0 [2·0–8·0]
Male	26 (60·0)	47 (51·1)
Gestational age at birth (weeks), median [IQR]	39 [39,40]	39 [38–40]
Preterm birth[a]	5 (10·9)	17 (17·7)
Birth weight (kg), median [IQR]	3·1 [2·8- 3·4]	3·1 [2·8- 3·3]
Nirsevimab immunization	19 (41·3)	64 (69·6)
Immunization delay (days), median [IQR][b]	57 [41·2–76]	49 [37–83·2]
Non-immunized and non-eligible[c]	8 (17·4)	16 (17·4)
History of bronchiolitis	2 (4·3)	2 (2·2)
Requiring hospitalization	1 (2·2)	-
RSV detection	-	1 (1·1)
Risk factors for severe bronchiolitis[d]	6 (13·0)	13 (14·1)

Data are n (%) unless otherwise stated. IQR, interquartile range.
[a] Preterm was defined as birth at a gestational age < 37 weeks.
[b] Immunization delay corresponds to the days between nirsevimab immunization and hospital admission.
[c] Patients who were not eligible for nirsevimab immunization in Tuscany because they were born between 01.01.2024 and 31.03.2024.
[d] Risk factors for severe bronchiolitis were defined according to the eligibility criteria for Palivizumab administration: birth at ≤35 weeks of gestational age and age < 6 months during the RSV season, bronchopulmonary dysplasia of prematurity, and hemodynamically significant congenital heart disease.

Table 2
Clinical course and outcomes among infants hospitalized for RSV-related bronchiolitis, according to nirsevimab immunization status.

	All n = 46	Immunized n = 19	Non-immunized n = 27	*P-value*[a]
Age at admission (months), median [IQR]	4·0 [2·1–7·8]	2 [1·5–5]	7 [5–8]	< 0·001
< 3 months	17 (36·9)	12 (63·1)	5 (18·5)	
3 to 6 months	13 (28·3)	6 (31·6)	7 (25·9)	
> 6 months	16 (34·8)	1 (5·3)	15 (55·5)	
Gestational age at birth (weeks), median [IQR]	39 [39,40]	39 [39,40]	39 [38–40]	
Preterm birth	5 (10·9)	2 (10·5)	3 (1·1)	
Risk factors for severe bronchiolitis	6 (13·0)	3 (15·8)	3 (1·1)	
Need for oxygen therapy	41 (89·1)	14 (73·7)	27 (100·0)	0·008
Low-flow	15 (32·6)	5 (26·3)	10 (37·0)	
High-flow	26 (56·5)	9 (47·4)	17 (63·0)	0·29
Duration (days), median [IQR]	4 [3–6]	3 [3,4]	5 [3–7]	0·02
Need for ventilation[b]	5 (10·9)	-	5 (18·5)	
Noninvasive	4 (8·7)	-	4 (14·8)	
Invasive	1 (2·2)	-	1 (3·7)	
Duration (days), median [IQR]	5 [3–9]	-	5 [3–9]	
Need for enteral feeding	9 (19·6)	3 (15·8)	6 (22·2)	
Duration (days), median [IQR]	8 [4–8]	4 [2·5–3·2]	10 [5–12]	
PICU admission[c]	5 (10·9)	-	5 (18·5)	
Duration (days), median [IQR]	9 [6–12]	-	9 [6–12]	
Detection of other respiratory viruses	10 (21·7)	4 (21·0)	6 (22·2)	
Rhinovirus	5 (10·9)	2 (10·5)	3 (11·1)	
Bocavirus	1 (2·2)	-	1 (3·7)	
Adenovirus	3 (6·5)	1 (5·3)	2 (7·4)	
Metapneumovirus	1 (2·2)	1 (5·3)	-	
Coronavirus	1 (2·2)	-	1 (3·7)	
Parainfluenza 1	2 (4·4)	2 (10·5)	-	
Bacterial coinfection	4 (8·7)	-	4 (4·8)	
Length of stay (days), median [IQR]	5 [4–8]	4 [2·5–5·7]	7 [4–8]	0·05

Data are n (%) unless otherwise stated. PICU, pediatric intensive care unit; IQR, interquartile range.
[a] P-value of the Chi-2, Fisher, or Mann–Whitney test between immunized and non-immunized cases.
[b] Noninvasive ventilation: continuous positive airway pressure (CPAP) without endotracheal intubation.Invasive ventilation: mechanical ventilation delivered through endotracheal intubation.
[c] PICU admission: admission to a Pediatric Intensive Care Unit for any respiratory or clinical deterioration requiring advanced monitoring or treatment.

shorter median duration of respiratory support. No differences were observed in the type of oxygen therapy administered (low-flow vs. high-flow). Notably, none of the immunized infants required ventilatory support or admission to the PICU, whereas 5 out of 27 (18·5%) non-immunized infants did.

Conditional logistic regression estimated an immunization effectiveness (IE) of 88·8% (95% confidence interval (CI): 61·4% to 96·8%). This estimate remained stable in the multivariable model adjusted for sex, gestational age, birth weight, and clinical risk factors (adjusted IE: 89·5%, 95% CI: 60·3% to 97·2%)Fig. 2.

Stratified analyses confirmed consistent results. Among infants born after April 1st, 2024, the adjusted IE was 88·4% (95% CI: 56·5% to 96·9%). Among infants without predefined clinical risk factors, the IE was 88·1% (95% CI: 45·7% to 97·4%) (Fig. 2).

Inverse probability of treatment weighting sensitivity analysis confirmed the protective effect of nirsevimab, with an estimated IE of 79·6% (95% CI: 53·5% to 91·0%).

Discussion

This real-world, multicenter, matched case-control study provides robust evidence of nirsevimab effectiveness in preventing RSV-associated hospitalizations among infants under 12 months of age. The estimated IE of approximately 89% aligns with results from clinical trials and recent observational studies conducted during the 2023–2024 RSV season, reporting effectiveness ranging from 65% to 90%.[10,12–19,21] This protective effect remained stable after adjustment for key confounding variables and was confirmed across multiple stratified and sensitivity analyses.

To our knowledge, this is the first Italian study evaluating real-world nirsevimab effectiveness during the 2024–2025 season. It is also one of the few to adopt a matched case-control design, thereby contributing rigorous methodological evidence to the existing literature. The concurrent enrollment across multiple centers, strict matching on age and admission date, and robust adjustment for clinical covariates enhance the internal validity of the findings.

In line with the approved indication for all infants under 12 months, our primary analysis included the whole age group, regardless of regional eligibility criteria. This allowed for a broader evaluation of real-world impact in the infant population. Despite the selective rollout, we observed a markedly lower immunization rate among hospitalized RSV cases than controls, resulting in a high estimated effectiveness. These findings suggest that even phased or targeted approaches, when efficiently implemented, can achieve a substantial public health impact. Importantly, this high effectiveness was achieved despite a restricted target population, suggesting that prioritizing infants at the highest risk during early implementation may represent a cost-conscious strategy. By focusing resources on those most vulnerable to severe RSV disease, such programs could reduce the burden on healthcare systems while maintaining a substantial preventive impact. Further cost-effectiveness analyses will be essential to quantify the potential healthcare savings and to inform immunization policies, especially in resource-constrained settings.

Importantly, the decision to limit immunization to infants born after April mirrors strategies adopted in other countries, including Spain and Western Australia. Real-world studies from these settings reported effectiveness estimates above 70%, reinforcing the feasibility and value of a phased or targeted rollout, especially during initial implementation phases.[11,13–15]

Nevertheless, the exclusion of infants born between January and March, who remained unprotected during the RSV peak, raises important considerations. While older at the time of rollout, these infants may still be vulnerable to severe RSV infection, particularly in

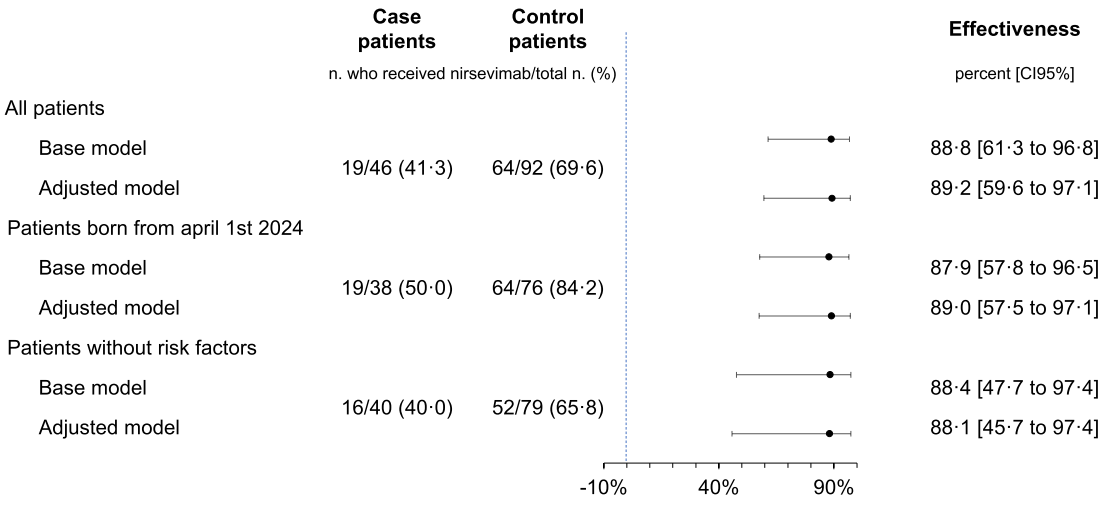

Fig. 2. Effectiveness of nirsevimab immunization against RSV-related hospitalization. Forest plot showing nirsevimab immunization effectiveness (IE) against RSV-related hospitalization in the overall population and stratified analyses. Base and adjusted models refer to conditional logistic regressions without and with covariate adjustment (sex, gestational age, birth weight, risk factors). Stratified analyses are presented for infants born after April 1st, 2024, and those without clinical risk factors. Immunization effectiveness was calculated using the formula: IE = 100 × (1 − odds ratio). IE, immunization effectiveness; CI, confidence interval.

years of early viral circulation. Expanding eligibility criteria or advancing the campaign start date could increase protection and equity in future seasons.

Regarding breakthrough infections, 41·3% of RSV cases in our cohort had received nirsevimab before hospitalization. This rate is consistent with the broad range reported in the literature (3% to 65%),[10,17,22–24] which reflects differences in case definitions, coverage, and follow-up duration. Unlike an Australian study,[15] we observed a lower need for and shorter duration of oxygen therapy among immunized RSV-positive infants compared to non-immunized cases, suggesting a potential role of nirsevimab in mitigating disease severity. Recent molecular surveillance data from France have shown that most breakthrough infections occurred in RSV-B cases, and only a small proportion harbored resistance-associated mutations, suggesting that viral escape remains rare at present. However, ongoing surveillance is warranted to detect emerging resistant strains.[25–27] Further studies are needed to understand the mechanisms underlying breakthrough infections and to identify potential risk factors.

Despite these strengths, several limitations warrant discussion. First, as an observational study, causal inference is limited, and residual confounding cannot be ruled out. Second, while we observed strong effectiveness, the design does not allow estimation of the absolute number of hospitalizations prevented. Third, the sample size, though adequate for primary analyses, limited the power of subgroup analyses and precluded regression modeling for rare but severe outcomes such as PICU admission and mechanical ventilation. Fourth, the absence of systematic RSV testing in control patients introduces the risk of undetected asymptomatic infections. Fifth, the study did not explore differences in effectiveness by sex assigned at birth, which may limit the understanding of potential sex-based variation in response.

Future studies will be essential to assess the long-term impact of nirsevimab, including its effect on RSV transmission, hospitalization burden, and population-level cost-effectiveness.

Conclusions

This study confirms that a targeted nirsevimab immunization strategy can significantly reduce RSV-related hospitalizations among infants under 12 months of age. Even with a phased rollout, the high effectiveness observed supports the feasibility and public health impact of prioritizing high-risk infants during the initial implementation phases. These findings may inform immunization policies aimed at sustainable and equitable RSV prevention.

Author contributions

FA, GI, and ST conceived the study and coordinated the project. All authors discussed the study protocol, participated in data collection, and patient enrollment. EL and FA conducted the statistical analysis. FA wrote the first draft of the manuscript. All authors contributed to data interpretation and critical revision of the manuscript. All authors approved the final version. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

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Data availability

Deidentified participant data and statistical analysis code will be made available upon reasonable request to the corresponding author (federica.attaianese@gmail.com) for academic purposes, following approval of a written proposal and data sharing agreement.

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.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT-4 (OpenAI, March 2025) to improve language clarity and grammar. All content was reviewed and edited by the authors, who take full responsibility for the final version.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106600.

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