

Journal of Asthma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijas20

Mild/Moderate Asthma Network in Italy (MANI): a long-term observational study

Fulvio Braido, Francesco Blasi, Giorgio Walter Canonica, Pierluigi Paggiaro, Bianca Beghè, Matteo Bonini, Giovanna Elisiana Carpagnano, Stefano Del Giacco, Federico Lavorini, Manlio Milanese, Vincenzo Patella, Pierachille Santus, Marco Contoli, On behalf of MANI Network, Chiara Allegrini, Ilaria Baiardini, Laura Bonzano, Maria Filomena Caiaffa, Paolo Castelnuovo, Angelo Guido Corsico, Lorenzo Cosmi, Maria Teresa Costantino, Marcello Cottini, Nunzio Crimi, Maria Angiola Crivellaro, Simona D'Alò, Ilenia Folletti, Dario Fornari, Maria Pia Foschino-Barbaro, Laura Franceschini, Domenico Gargano, Kim Lokar Oliani, Mauro Maniscalco, Laura Melissari, Marcello Montagni, Paolo Montuschi, Nicola Murgia, Alessandro Pannofino, Alberto Papi, Roberta Parente, Girolamo Pelaia, Laura Pini, Francesca Puggioni, Nolita Pulerà, Onofrio Resta, Luisa Ricciardi, Erminia Ridolo, Eleonora Savi, Francesca Savoia, Guglielmo Scala, Gianenrico Senna, Salvatore Tripodi, Alessandro Vatrella, Maria Teresa Ventura, Vittorio Maria Viviano & Mona-Rita Yacoub

To cite this article: Fulvio Braido, Francesco Blasi, Giorgio Walter Canonica, Pierluigi Paggiaro, Bianca Beghè, Matteo Bonini, Giovanna Elisiana Carpagnano, Stefano Del Giacco, Federico Lavorini, Manlio Milanese, Vincenzo Patella, Pierachille Santus, Marco Contoli, On behalf of MANI Network, Chiara Allegrini, Ilaria Baiardini, Laura Bonzano, Maria Filomena Caiaffa, Paolo Castelnuovo, Angelo Guido Corsico, Lorenzo Cosmi, Maria Teresa Costantino, Marcello Cottini, Nunzio Crimi, Maria Angiola Crivellaro, Simona D'Alò, Ilenia Folletti, Dario Fornari, Maria Pia Foschino-Barbaro, Laura Franceschini, Domenico Gargano, Kim Lokar Oliani, Mauro Maniscalco, Laura Melissari, Marcello Montagni, Paolo Montuschi, Nicola Murgia, Alessandro Pannofino, Alberto Papi, Roberta Parente, Girolamo Pelaia, Laura Pini, Francesca Puggioni, Nolita Pulerà, Onofrio Resta, Luisa Ricciardi, Erminia Ridolo, Eleonora Savi, Francesca Savoia, Guglielmo Scala, Gianenrico Senna, Salvatore Tripodi, Alessandro Vatrella, Maria Teresa Ventura, Vittorio Maria Viviano & Mona-Rita Yacoub (2022) Mild/Moderate Asthma Network in Italy (MANI): a long-term observational study, Journal of Asthma, 59:9, 1908-1913, DOI: 10.1080/02770903.2021.1968895

To link to this article: https://doi.org/10.1080/02770903.2021.1968895

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Published online: 01 Sep 2021.

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JOURNAL OF ASTHMA
2022, VOL. 59, NO. 9, 1908–1913
https://doi.org/10.1080/02770903.2021.1968895

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Fulvio Braido, MD[a], Francesco Blasi, MD[b,c], Giorgio Walter Canonica, MD[d,e], Pierluigi Paggiaro, MD[f], Bianca Beghè, MD[g], Matteo Bonini, MD[h], Giovanna Elisiana Carpagnano, MD[i], Stefano Del Giacco, MD[j], Federico Lavorini, MD[k], Manlio Milanese, MD[l], Vincenzo Patella, MD[m,n], Pierachille Santus, MD[o] and Marco Contoli, MD[p]; On behalf of MANI Network

CONTACT Fulvio Braido fulvio.braido@unige.it Respiratory Unit for continuity of Care, IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine (DiMI), University of Genoa, Genoa 16132, Italy.

On behalf of MANI network: Chiara Allegrini, Section of Respiratory Medicine, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

Ilaria Baiardini, Respiratory Unit for Continuity of Care, IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy.

Laura Bonzano, Dermatology Unit, Allergology Service, AOU Policlinico of Modena, Modena, Italy.

Maria Filomena Caiaffa, Department of Medical Sciences and Surgery, School and Chair of Allergology and Clinical Immunology, University of Foggia, Foggia, Italy.

Paolo Castelnuovo, Department of Biotechnology and Life Sciences, Otorhinolaryngology, University of Insubria, Varese, Italy.

Angelo Guido Corsico, Respiratory Diseases Division, IRCCS Policlinico San Matteo, Foundation and Department of Internal Medicine and Therapeutics, Pavia, Italy; Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy.

Lorenzo Cosmi, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

Maria Teresa Costantino, Medical Department, Allergy and Immunology Unit, Mantova, Italy.

Marcello Cottini, Allergy and Pneumology Outpatient Clinic, Bergamo, Italy.

Nunzio Crimi, Respiratory Medicine Unit, A.O.U. "Policlinico-Vittorio Emanuele", Catania, Italy; Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

Maria Angiola Crivellaro, Allergology Service, Department of Medicine and Public Health, University of Padova, Padova, Italy; Department of Cardiac Thoracic Vascular and Public Health Sciences, University of Padova, Padova, Italy.

Simona D'Alò, Allergology Unit, AV3 ASUR Marche, Hospital Civitanova Marche, Macerata, Italy

Ilenia Folletti, Department of Medicine, Section of Occupational Medicine, University of Perugia, Perugia, Italy.

Dario Fornari, Pulmonology Structure Montichiari Hospital Agency, Brescia, Italy.

Maria Pia Foschino-Barbaro, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; Respiratory Unit, Policlinico Riuniti Foggia, Foggia, Italy.

Laura Franceschini, SOS Allergology and Immunology, Prato Hospital, Prato, Italy.

Domenico Gargano, Department of Internal Medicine, Allergy and Clinical Immunology Unit, San Giuseppe Moscati Hospital, Avellino, Italy.

Kim Lokar Oliani, Department of Cardiac, Thoracic and Vascular Sciences, Section of Respiratorty Disease, University of Padova, Padova, Italy.

Mauro Maniscalco, Respiratory Rehabilitation of the Institute of Telese, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.

Laura Melissari, Respiratory Unit for Continuity of Care, IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy.

Marcello Montagni, UOC Allergology Department, Piacenza, Italy.

Paolo Montuschi, Pharmacology, Faculty of Medicine Catholic University of the Sacred Heart, Agostino Gemelli University Hospital Foundation IRCCS Rome, Rome, Italy.

Nicola Murgia, Department of Medicine and Surgery, Section of Occupational Medicine, Respiratory Diseases and Toxicology, University of Perugia, Perugia, Italy.

Alessandro Pannofino, Allergology and Immunology Clinic, Operative Unit of Medicine, Policoro Hospital, Matera, Italy.

Alberto Papi, Department of Translational Medicine, Research Center on Asthma and COPD, University of Ferrara, Ferrara, Italy.

Roberta Parente, Division of Allergy and Clinical Immunology, Department of Medicine, University of Salerno, Salerno, Italy.

Girolamo Pelaia, Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy.

Laura Pini, Department of Clinical and Experimental Sciences, Spedali Civili di Brescia, University of Brescia, Brescia, Italy.

Francesca Puggioni, Personalized Medicine, Asthma & Allergy, Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy.

Nolita Pulerà, Department of Pneumology, P.O. Livorno – AUSL Toscana Nord Ovest, Livorno, Italy.

Onofrio Resta, Department of Respiratory Diseases, University of Bari, Bari, Italy.

Luisa Ricciardi, Allergy and Clinical Immunology Unit, A.O.U. Policlinico "G. Martino", Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

Erminia Ridolo, Department of Medicine and Surgery, University of Parma, Parma, Italy.

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[a]Respiratory Unit for Continuity of Care, IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy; [b]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [c]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Respiratory Unit and Cystic Fibrosis Adult Center, Milan, Italy; [d]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [e]IRCCS Humanitas Research Hospital, Personalized Medicine, Asthma and Allergy, Rozzano, Milan, Italy; [f]Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Pisa, Italy; [g]Section of Respiratory Medicine, Department of Medical and Surgical Sciences, University Polyclinic of Modena, University of Modena and Reggio Emilia, Modena, Italy; [h]Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of Rome, Rome, Italy; [i]Respiratory Medicine Section, Policlinico of Bari, Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari Aldo Moro, Bari, Italy; [j]Unit of Allergy and Clinical Immunology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [k]Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence, Italy; [l]Pulmonology Unit, ASL2 Savonese, Pietra Ligure, Savona, Italy; [m]Division of Allergy and Clinical Immunology, "Santa Maria della Speranza" Hospital, Salerno, Italy; [n]Postprogram in Allergy and Clinical Immunology, School of Medicine, University of Naples Federico II, Naples, Italy; [o]Department of Biomedical and Clinical Sciences "L. Sacco" - Division of Respiratory Diseases, University of Milan, Sacco University Hospital, Milano, Italy; [p]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy

ABSTRACT

Objective: The prevalence of asthma in Italy is estimated to be around 4%; it affects approximately 2,000,000 citizens, and up to 80–90% of patients have mild-to-moderate asthma. Despite the clinical relevance of mild-to-moderate asthma, longitudinal observational data are very limited, including data on disease progression (worsening vs. improvement), the response to treatment, and prognosis. Studies are needed to develop long-term, observational, real-life research in large cohorts. The primary outcomes of this study will be based on prospective observation and the epidemiological evolution of mild and moderate asthma. Secondary outcomes will include patient-reported outcomes, treatments over time, disease-related functional and inflammatory patterns, and environmental and life-style influences.

Methods: This study, called the Mild/Moderate Asthma Network of Italy (MANI), is a research initiative launched by the Italian Respiratory Society and the Italian Society of Allergology, Asthma and Clinical Immunology. MANI is a cluster-based, real world, cross-sectional, prospective, observational cohort study that includes 20,000 patients with mild-to-moderate asthma. (ClinicalTrials.gov Identifier: NCT04796844).

Results and conclusion: Despite advances in asthma care, several research gaps remain to be addressed through clinical research. This study will add important new knowledge about long-term disease history, the transferability of clinical research results to daily practice, the efficacy of currently recommended strategies, and their impact on the burden and evolution of the disease.

Abbreviations: MANI: Mild/Moderate Asthma Network of Italy; SANI: Severe Asthma Network Italy; GINA: Global Initiative for Asthma; SABA: short acting β2-agonists; ICS: inhaled corticosteroids; CRF: Case Report Form

ARTICLE HISTORY
Received 20 July 2021
Revised 4 August 2021
Accepted 12 August 2021

KEYWORDS
Cross-sectional; prospective cohort study; patient-reported outcomes; registry

Introduction

Describing the natural history of asthma is challenging for several reasons. First, data sources are often questionable; in fact, information mainly comes from studies on patients with predominantly severe or difficult-to-treat asthma rather than studies on patients with mild or moderate asthma (1). Moreover, data retrieved from hospitals, prescription databases, and mortality records are often incomplete. Studies on general population cohorts can be criticized for their uncertain diagnoses and poor definitions of the participants. Furthermore, studies do not always include clinically important variables, such as lung function, daily symptoms, and biomarkers. The heterogeneity of airway diseases grouped under the

Eleonora Savi, Allergology and Pneumology Health Center Clinico Fiorenzuola, Piacenza, Italy.
Francesca Savoia, Pulmonology Unit, Cà Foncello Hospital, AULSS2 Marca Trevigiana, Treviso, Italy.
Guglielmo Scala, Allergy Unit, Loreto Crispi Hospital, Naples, Italy.
Gianenrico Senna, Allergy Asthma Unit, University of Verona, Verona, Italy.
Salvatore Tripodi, Allergology Service, Policlinico Casilino, Rome, Italy.
Alessandro Vatrella, Department of Medicine Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy.
Maria Teresa Ventura, Unit of Geriatric Immunoallergology, University of Bari Medical School, Bari, Italy.
Vittorio Maria Viviano, Allergology, Pneumology and Respiratory Department Biondo, Palermo, Italy.
Mona-Rita Yacoub, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy.

"asthma" label is a reflection of the different pathways involved and the specific signs of disease progression, including lung function decline, remission, reoccurrence, morbidity, and mortality (2,3). Several studies have identified disease-related factors that could predict disease progression, including long-standing disease, severe symptoms, frequent exacerbations, smoking, exposure to allergens/pollutants and occupational agents, chronic mucus hypersecretion, and high levels of airway hyperreactivity, IgE, and eosinophils (4). However, other factors can influence disease evolution, like the drugs administered (short acting β2-agonists [SABA], controllers, oral corticosteroids, etc.), the dosing schedules (symptom-driven or continuous), and the drug administration tool (e.g., manual devices, smart inhalers, digital interfaces), in addition to the individual's biological profile (comorbidities, concomitant disorders, inflammatory pattern) and sociodemographic profile (education, income, etc.). Furthermore, an over-reliance on inhaled SABAs increases the risk of asthma-related mortality (5). Although asthma-related mortality has been reduced substantially over the last few decades in most countries, it remains a concern, even among patients with mild asthma. It has become clear that some current clinical outcomes and behaviors in facing mild/moderate asthma need to be improved. The knowledge that morbidity was greater than previously appreciated among patients considered to have mild asthma has given rise to a document called the Global Initiative for Asthma (GINA) (6). This initiative recommended the use of inhaled corticosteroids (ICS)/rapid-onset β2-agonists, in preference to SABA alone, as a medication to alleviate symptoms in all patients with asthma (7). Although it has been shown that even low doses of ICS reduced the risks of severe asthma exacerbations and asthma-related death, the use of oral steroids in non-severe asthma was associated with substantial expense and comorbidities (8,9). Finally, albeit disease control is the goal of asthma management, severe exacerbations in mild asthma represent 30–40% of asthma exacerbations that require emergency consultations (10,11). Therefore, we need to improve the current understanding of the biology and pathophysiology of mild/moderate asthma by identifying a number of distinct phenotypes, similar to the approach previously taken for investigating severe asthma (12–14).

The prevalence of asthma in Italy is estimated to be around 4%; it affects approximately 2,000,000 citizens (15). Based on the minimum treatment needed to achieve asthma control, epidemiological studies have estimated that, among all patients with asthma, 50–75% have mild asthma, 15–45% have moderate asthma, and 5–10% have severe asthma. The individual burden of the pathology is strictly related to the level of control and the severity. However, the burden on the social and welfare systems (number of events × number of patients) due to mild and moderate asthma is not lower than that due to severe asthma. Indeed, if severe asthma requires more than 50% of the available resources, the remaining 50% are used for managing the milder forms of asthma. This long-term study (MANI) aims to observe a large patient population to provide an unparalleled source of data for defining the most appropriate management measures.

Methods

This study is a research initiative launched by the Italian Respiratory Society and the Italian Society of Allergology, Asthma and Clinical Immunology which have set up an intersocieties scientific committee.

The primary outcome of MANI will be the epidemiological evolution of mild and moderate asthma (disease severity, according to GINA), based on prospective observation.

The following items will be explored as secondary outcomes:

- Real-life assessments of asthma control over time
- Exacerbation rate over time
- Patient-reported outcomes (e.g., quality of life, patient engagement, disease awareness) from groups treated with different drugs and schedules
- Burden of oral corticosteroids in mild and moderate asthma
- SABA use in mild and moderate asthma
- Influence of infections and vaccinations on disease outcomes and progression
- Influence of upper airway disease on disease outcomes and progression
- Impact of inhalation techniques and smart inhalers on disease outcomes and progression
- Environmental exposure influences on disease outcome and progression
- Evolution of inflammatory patterns over time and their relationships to disease outcomes and progression
- Role of smoking and life style in lung function and disease progression

- Patient-reported outcomes over time
- Patient awareness and engagement in mild and moderate asthma
- Impact of digital therapy on disease management and outcomes
- Direct, indirect, and intangible costs of mild and moderate asthma
- Cost-efficiency of mild/moderate asthma treatments and management plans
- Sociodemographic issues related to disease progression and burden

MANI is a cluster-based, real world, cross-sectional, prospective, observational cohort study. A non-probability sample will include a population of male and female adult patients (18–80 years old) with a diagnosis of mild-to-moderate asthma, defined according to GINA 2020. Patients will be enrolled at 200 centers of pulmonology and allergology distributed throughout the national territory. We will enroll consecutive patients with asthma that are referred to the outpatient clinics of the recruiting centers. Exclusion criteria are: patients with severe asthma, according to the International European Respiratory Society/American Thoracic Society guidelines on the definition, evaluation, and treatment of severe asthma (15); patients with interstitial lung diseases, pulmonary neoplasms, or current lung infections; and patients with immunological disorders that require immunosuppressants or continuous treatment with oral steroids. To represent real-world Italian patients with mild or moderate asthma, the inclusion criteria are: all adults diagnosed with asthma by a specialist, according to the GINA document, that are scheduled to visit a respiratory or allergy clinic. Patients involved in previous or concomitant observational studies can be enrolled. Patients that meet the inclusion criteria will receive an informative leaflet for themselves and their general practitioner and must provide written consent to participate in the study. Follow-ups will be scheduled according to the GINA document and each center's plan.

The researchers will collect data on patient history, asthma features, comorbid diseases, and available spirometry and imaging results. At the time of enrollment, researchers will collect results from questionnaires. These data will include patient baseline characteristics, self-rated asthma control, and laboratory tests for allergy and airway inflammation. Follow-up data on asthma control, lung function, and environmental exposure will be collected by issuing questionnaires to participants at least every 6–12 months to assess outcome and exacerbation-related aggravating factors. The information collected in the Case Report Form (CRF) will coincide with patient data routinely reported in medical records. The transfer of data from the medical record to the analysis platform will be carried out by the physician that manages the therapy. Patients will be enrolled, starting in May 2021, and enrollment will continue until the established sample size is reached. Follow-up procedures will last 10 years, starting from the date that the last patient is enrolled. The study was registered at ClinicalTrials.gov under the identifier NCT04796844.

An *ad hoc* CRF on the Web platform, REDCap, has been created. A similar database has been adopted by the Severe Asthma Network Italy (SANI), which is an ongoing project (16–24). Each center that participates in the MANI study will have a username and password, which allows access to a reserved area of the Web application. Authentication is secure, with an https connection that encrypts the username and password. The passwords of each center are automatically stored in the database with MD5 coding. The web application is protected by Structured Query Language; therefore, it will not be possible to evade the authentication system or access data other than that which the application is allowed to return. For example, a given center will not be allowed, in any way, to display sensitive data from another center. Each patient registered in the database will be assigned a unique identification number, an identifiable code, which is used only by the physician providing therapy. The identification number is created by entering only the first three letters of the name, followed by the first three letters of the surname, the date of birth, the gender, and the province of residence, in the form of a cadastral code. Sensitive patient data can be viewed/edited only in the area reserved for the center treating that patient. Each center will have the ability to view the clinical data of its own patients, but it will only be able to view the general descriptive statistics (e.g., the number of patients enrolled) of patients from the other centers that share the platform.

A statistical plan has been defined. Qualitative variables will be expressed as the absolute and relative frequencies (percentages), and quantitative variables will be expressed as the mean (standard deviation) or the median (interquartile range), based on the parametric or non-parametric distribution. The incidence (and 95% confidence interval) of different forms of asthma will be calculated. Asthma severity will be defined according to the GINA document and a previous study (25). The role of demographic, clinical, and epidemiological variables in the evolution of asthma will be assessed with Cox proportional hazards regression analyses. All statistical analyses will be performed with STATA version 16 statistical software (StataCorp, Texas, US). Based on a previous study

(1), we assume that at least 20,000 subjects should be enrolled to detect an estimated incidence of 8% for the primary outcome, with a beta error of 0.1 and an alpha error of 0.05.

Discussion

Because asthma is heterogeneous, we assume that each subject will exhibit a different subset of risk factors for asthma exacerbation and a different rate of disease progression. Therefore, this MANI study aims to identify mild/moderate asthma clusters, based on sociodemographic data, clinical data, and patient-reported outcomes. Additionally, the study results might suggest cluster-specific analytical strategies, by focusing on each subject's individual aggravating factors during each exacerbation episode and by focusing on disease progression. We are aware that observational nature of the study and the recruitment in a secondary care in Italy will limit the generalizability of the results to different settings. However, we expect the cumulative results of the large number of patients would be helpful to improve the understanding of the epidemiological evolution of mild and moderate asthma and provide new insights in the clinical management of such patients.

GINA 2020 provides a new approach for the management of mild asthma. However, as recently underlined by Boulet et al. (26), despite recent advances in asthma care, several research gaps remain to be addressed through clinical research. Longitudinal, real-life studies will be exceptionally important for providing information on the translatability of clinical research results, the long-term efficacy of currently recommended strategies, and the ability to intervene in disease evolution.

Acknowledgements

The authors thank the Italian Respiratory Society and the Italian Society of Allergology, Asthma, and Clinal Immunology for providing professional guidance and Infomed Srl for the assistance in the preparation of the manuscript.

Declaration of interest

The author reports no conflicts of interest in this work.

Funding

This study is a nonprofit study, supported by the Italian Respiratory Society and Italian Society of Allergology, Asthma and Clinical Immunology.

Ethics approval and informed consent

The ethical conduct of the study is based on the latest revision of the Helsinki declaration and the Oviedo declaration. The study protocol was designed and will be conducted to ensure adherence to the principles and procedures of Good Clinical Practice and to comply with Italian laws, as described in the following documents, and accepted, with their own signatures, by the study investigators. Italian law documents: ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community; Italian Legislative Decree No. 211 of June 24, 2003; Italian Legislative Decree No. 200 6 November 2007; Italian Ministerial Decree December 21, 2007. All eligible participants that freely agree to participate in the study will sign an informed consent form.

ORCID

Fulvio Braido http://orcid.org/0000-0003-2460-4709
Francesco Blasi http://orcid.org/0000-0002-2285-9970
Giorgio Walter Canonica http://orcid.org/0000-0001-8467-2557
Pierluigi Paggiaro http://orcid.org/0000-0002-1213-2989
Bianca Beghè http://orcid.org/0000-0003-2894-1964
Matteo Bonini http://orcid.org/0000-0001-9326-1370
Giovanna Elisiana Carpagnano http://orcid.org/0000-0001-7931-4704
Stefano Del Giacco http://orcid.org/0000-0002-4517-1749
Federico Lavorini http://orcid.org/0000-0002-3293-2123
Manlio Milanese http://orcid.org/0000-0001-9626-6230
Vincenzo Patella http://orcid.org/0000-0001-5640-6446
Pierachille Santus http://orcid.org/0000-0003-3462-8253
Marco Contoli http://orcid.org/0000-0002-2731-5809

Data availability statement

The datasets used and/or analyzed during the current study will be available from the study steering committee upon reasonable request.

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