



Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort

Liam Heaney, Luis Perez de Llano, Mona Al-Ahmad, Vibeke Backer, John Busby, Giorgio Walter Canonica, George Christoff, Borja Cosio, J. Mark Fitzgerald, Enrico Heffler, et al.

► To cite this version:

Liam Heaney, Luis Perez de Llano, Mona Al-Ahmad, Vibeke Backer, John Busby, et al.. Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest*, 2021, <10.1016/j.chest.2021.04.013>. <hal-03207485>

HAL Id: hal-03207485

<https://hal.science/hal-03207485v1>

Submitted on 13 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization



Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort

Liam G. Heaney, MD, Luis Perez de Llano, MD, PhD, Mona Al-Ahmad, MD, Vibeke Backer, MD, DMSci, John Busby, PhD, Giorgio Walter Canonica, MD, George C. Christoff, MD, PhD MPH, Borja G. Cosio, MD, PhD, J. Mark FitzGerald, MD, FRCPC, Enrico Heffler, MD, PhD, Takashi Iwanaga, MD, PhD, David J. Jackson, MBBS, MRCP (UK), PhD, Andrew N. Menzies-Gow, PhD, FRCP, Nikolaos G. Papadopoulos, MD, PhD, FRCP, Andriana I. Papaioannou, MD, PhD, Paul E. Pfeffer, MRCP(UK), PhD, Todor A. Popov, MD, PhD, Celeste M. Porsbjerg, MD, PhD, Chin Kook Rhee, MD, PhD, Mohsen Sadatsafavi, MD, PhD, Yuji Tohda, MD, PhD, Eileen Wang, MD, MPH, Michael E. Wechsler, MD, Marianna Alacqua, MD, PhD, Alan Altraja, MD, PhD, Leif Bjermer, MD, PhD, Unnur S. Björnsdóttir, MD, Arnaud Bourdin, MD, PhD, Guy G. Brusselle, MD PhD, Roland Buhl, MD PhD, Richard W. Costello, MB, MD, FRCPI, Mark Hew, MBBS, PhD, FRACP, Mariko Koh Siyue, MBBS, MRCP (UK), FCCP, Sverre Lehmann, MD, PhD, Lauri Lehtimäki, MD, PhD, Matthew Peters, MD, PhD, Camille Taillé, MD, PhD, Christian Taube, MD, Trung N. Tran, MD, PhD, James Zangrilli, MD, Lakmini Bulathsinhala, MPH, Victoria A. Carter, BSc, Isha Chaudhry, MSc, Neva Eleangovan, BSc, Naeimeh Hosseini, MD, Marjan Kerkhof, MD, PhD, Ruth B. Murray, PhD, Chris A. Price, LLB, David B. Price, FRCGP

PII: S0012-3692(21)00700-5

DOI: <https://doi.org/10.1016/j.chest.2021.04.013>

Reference: CHEST 4197

To appear in: *CHEST*

Received Date: 7 December 2020

Revised Date: 30 March 2021

Accepted Date: 5 April 2021

Please cite this article as: Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, Christoff GC, Cosio BG, FitzGerald JM, Heffler E, Iwanaga T, Jackson DJ, Menzies-Gow AN, Papadopoulos NG, Papaioannou AI, Pfeffer PE, Popov TA, Porsbjerg CM, Rhee CK, Sadatsafavi M, Tohda Y, Wang E, Wechsler ME, Alacqua M, Altraja A, Bjermer L, Björnsdóttir US, Bourdin A, Brusselle GG, Buhl R, Costello RW, Hew M, Siyue MK, Lehmann S, Lehtimäki L, Peters M, Taillé C, Taube

C, Tran TN, Zangrilli J, Bulathsinhala L, Carter VA, Chaudhry I, Eleangovan N, Hosseini N, Kerkhof M, Murray RB, Price CA, Price DB, Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort, *CHEST* (2021), doi: <https://doi.org/10.1016/j.chest.2021.04.013>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2021 Published by Elsevier Inc under license from the American College of Chest Physicians.

Word counts

Abstract: 300 words

Main Text: 3819 words

Title: Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort

Short title/running head: Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

Liam G. Heaney, MD¹; Luis Perez de Llano, MD, PhD²; Mona Al-Ahmad, MD³; Vibeke Backer, MD, DMSci^{4,5}; John Busby, PhD¹; Giorgio Walter Canonica MD^{6,7}; George C. Christoff MD, PhD MPH⁸; Borja G. Cosio MD, PhD⁹; J. Mark FitzGerald, MD, FRCPC¹⁰; Enrico Heffler MD, PhD^{6,7}; Takashi Iwanaga, MD, PhD¹¹; David J. Jackson, MBBS, MRCP (UK), PhD^{12,13}; Andrew N. Menzies-Gow, PhD, FRCP¹⁴; Nikolaos G. Papadopoulos, MD, PhD, FRCP^{15,16}; Andriana I. Papaioannou, MD, PhD¹⁷; Paul E. Pfeffer MRCP(UK), PhD^{18,19}; Todor A. Popov, MD, PhD²⁰; Celeste M. Porsbjerg, MD, PhD²¹; Chin Kook Rhee, MD, PhD²²; Mohsen Sadatsafavi, MD, PhD²³; Yuji Tohda, MD, PhD¹¹; Eileen Wang, MD, MPH^{24,25}; Michael E. Wechsler, MD²⁶; Marianna Alacqua, MD, PhD²⁷; Alan Altraja, MD, PhD²⁸; Leif Bjermer, MD, PhD²⁹; Unnur S. Björnsdóttir, MD³⁰; Arnaud Bourdin, MD, PhD³¹; Guy G. Brusselle MD PhD^{32,33}; Roland Buhl MD PhD³⁴; Richard W. Costello, MB, MD, FRCPI³⁵; Mark Hew, MBBS, PhD, FRACP^{36,37}; Mariko Koh Siyue, MBBS, MRCP (UK), FCCP^{38,39}; Sverre Lehmann, MD, PhD⁴⁰; Lauri Lehtimäki, MD, PhD⁴¹; Matthew Peters, MD, PhD⁴²; Camille Taillé, MD, PhD⁴³; Christian Taube, MD⁴⁴; Trung N. Tran, MD, PhD⁴⁵; James Zangrilli, MD⁴⁵; Lakmini Bulathsinhala, MPH⁴⁶; Victoria A. Carter, BSc⁴⁶; Isha Chaudhry, MSc⁴⁶; Neva Eleangovan, BSc⁴⁶; Naeimeh Hosseini, MD⁴⁶; Marjan Kerkhof, MD, PhD⁴⁶; Ruth B. Murray, PhD⁴⁶; Chris A. Price, LLB⁴⁶; David B. Price, FRCGP⁴⁶⁻⁴⁸

Affiliations:

¹UK Severe Asthma Network and National Registry, Queen's University Belfast, Belfast, Northern Ireland; ²Department of Respiratory Medicine, Hospital Universitario Lucus Augusti, Lugo, Spain; ³Al-Rashed Allergy Center, Ministry of Health, Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait; ⁴Centre for Physical Activity Research, Rigshospitalet, Copenhagen University, Copenhagen, Denmark; ⁵Department of ENT, Rigshospitalet, Copenhagen University, Copenhagen, Denmark; ⁶Personalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center

IRCCS, Rozzano, Milan, Italy; ⁷Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; ⁸Faculty of Public Health, Medical University of Sofia, Sofia, Bulgaria; ⁹Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain; ¹⁰Centre for Lung Health, Vancouver, Canada; ¹¹Department of Respiratory Medicine and Allergology, Kindai University Faculty of Medicine, Osakasayama, Japan; ¹²UK Severe Asthma Network and National Registry, Guy's and St Thomas' NHS Trust; ¹³School of Immunology & Microbial Sciences, King's College London, London, UK; ¹⁴UK Severe Asthma Network and National Registry, Royal Brompton & Harefield NHS Foundation Trust, London, UK; ¹⁵Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, UK; ¹⁶Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece; ¹⁷2nd Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; ¹⁸UK Severe Asthma Network; Barts Health NHS Trust; ¹⁹Queen Mary University of London, London, UK; ²⁰University Hospital "Sv. Ivan Rilski", Sofia, Bulgaria; ²¹Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark; ²²Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; ²³Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada; ²⁴Division of Allergy & Clinical Immunology, Department of Medicine, National Jewish Health, Denver, CO, USA; ²⁵Division of Allergy & Clinical Immunology, Department of Internal Medicine, University of Colorado Hospital, Aurora, CO, USA; ²⁶NJH Cohen Family Asthma Institute, Department of Medicine, National Jewish Health, Denver, CO, USA; ²⁷AstraZeneca, Cambridge, UK; ²⁸Department of Pulmonary Medicine, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia; ²⁹Respiratory Medicine and Allergology, Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden; ³⁰Department of Respiratory Medicine and Allergy, Landspítali The University Hospital of Iceland, Reykjavik, Iceland; ³¹PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France; ³²Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; ³³Department of Epidemiology and Respiratory Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; ³⁴Pulmonary Department, Mainz University Hospital, Mainz, Germany; ³⁵Clinical Research Centre, Smurfit Building Beaumont Hospital and Department of Respiratory Medicine, RCSI, Dublin, Ireland; ³⁶Allergy, Asthma & Clinical Immunology Service, Alfred Health, Melbourne, Australia; ³⁷Public Health and Preventive Medicine, Monash University, Melbourne, Australia; ³⁸Respiratory & Critical Care Medicine, Singapore General Hospital, Singapore; ³⁹SingHealth Duke-NUS Lung Centre, Singapore; ⁴⁰Section of Thoracic Medicine, Department of Clinical Science, University of Bergen, Bergen, Norway; ⁴¹Allergy Centre, Tampere University Hospital, and Faculty of Medicine and Health Technology, Tampere

University, Tampere, Finland; ⁴²Department of Thoracic Medicine, Concord Hospital, Sydney, Australia; ⁴³Department of Respiratory Diseases, Bichat Hospital, AP-HP Nord-Université de Paris; Paris, France; ⁴⁴Department of Pulmonary Medicine, University Medical Center Essen-Ruhrlandklinik, Germany; ⁴⁵AstraZeneca, Gaithersburg, MD, USA; ⁴⁶Optimum Patient Care, Cambridge, UK; ⁴⁷Observational and Pragmatic Research Institute, Singapore, Singapore; ⁴⁸Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom.

Corresponding author information

Professor David B. Price
Academic Primary Care
Division of Applied Health Sciences
University of Aberdeen
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
UK
E-mail: dprice@opri.sg

Summary conflict of interest statements

Liam G. Heaney declares he has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, and Teva; he has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

Luis Perez de Llano declares non-financial support, personal fees, and grants from Teva; non-financial support and personal fees from Boehringer Ingelheim, Esteve, GlaxoSmithKline,

Mundipharma, and Novartis; personal fees and grants from AstraZeneca and Chiesi; personal fees from Sanofi; and non-financial support from Menairi outside the submitted work.

Mona Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline.

Vibeke Backer, John Busby, George C. Christoff, J. Mark FitzGerald, Ruth B. Murray and Christian Taube declare no relevant conflicts of interest concerning this paper.

Unnur S. Björnsdóttir receives gratuities for lectures/presentations from AstraZeneca, Sanofi and Novartis.

Enrico Heffler participates in speaking activities and industry advisory committees for AstraZeneca, Sanofi-Genzyme, GSK, Novartis, TEVA, Circassia and Nestlè Purina.

G. Walter Canonica has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Abello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas.

Borja G. Cosio declares grants from Chiesi; personal fees for advisory board activities from Chiesi and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, Menarini, and AstraZeneca, outside the submitted work.

Takashi Iwanaga declares grants from Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Kyorin, MeijiSeika Pharma, Teijin Pharma, and lecture fees from Kyorin.

David J. Jackson has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Teva, Napp, Chiesi, Novartis and research grant funding from AstraZeneca.

Andrew N. Menzies-Gow has attended advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi and Teva, and has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Roche, Teva and Vectura. He has participated in research with

AstraZeneca for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca, Sanofi and Vectura.

Nikolaos G. Papadopoulos declares research support from Gerolymatos, Menarini, Nutricia, and Vian; and consultancy/speaker fees from ASIT, AZ, Boehringer Ingelheim, GSK, HAL Allergy, Medscape, Menarini, MSD, Mylan, Novartis, and Nutricia, OM Pharma, Sanofi, and Takeda.

Andriana I. Papaioannou has received fees and honoraria from Menarini, GSK, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi.

Paul E. Pfeffer has attended advisory boards for Novartis; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline and Novartis, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline.

Todor A. Popov declares relevant research support from Novartis and Chiesi Pharma.

Celeste M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme.

Chin Kook Rhee declares consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, MSD, Novartis, Sandoz, Takeda, and Teva-Handok.

Mohsen Sadatsafavi has received honoraria from AstraZeneca. He has also received research funding into his research account at The University of British Columbia.

Yuji Tohda declares honoraria from Kyorin Pharma and Teijin Pharma and research funding from Kyorin Pharma and Meiji Seika Pharma.

Eileen Wang has received honoraria from AstraZeneca and Clinical Care Options. She has been an investigator on clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Novartis, Teva,

and National Institute of Allergy and Infectious Diseases (NIAID) for which her institution has received funding.

Michael E. Wechsler reports receiving consulting honoraria from AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Novartis, Regeneron, Sanofi and Teva.

Marianna Alacqua and Trung N. Tran are employees of AstraZeneca, a co-funder of the International Severe Asthma Registry. **James Zangrilli** was an employee of AstraZeneca at the time this analysis was conducted.

Alan Altraja has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Novartis, and Orion; sponsorships from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Sanofi, and Novartis; and has been a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva.

Leif Bjermer has (in the last three years) received lecture or advisory board fees from Alk-Abello, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Genzyme/Regeneron, and Teva.

Arnaud Bourdin has received industry-sponsored grants from AstraZeneca/MedImmune, Boehringer Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, Sanofi-Regeneron and consultancies with AstraZeneca/MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi.

Investigator/Co-investigator for trials promoted by AstraZeneca/MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron- Sanofi, Chiesi, Actelion, Merck, Roche, Vertex, Galapagos,

Guy G. Brusselle has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva.

Roland Buhl reports grants to Mainz University and personal fees from Boehringer Ingelheim, GSK, Novartis, and Roche, as well as personal fees from AstraZeneca, Chiesi, Cipla, Sanofi, and Teva, outside the submitted work.

Richard W. Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence and prediction of exacerbations.

Mark Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, and Seqirus, for unrelated projects.

Mariko Koh Siyue reports grant support from AstraZeneca, and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Sanofi and Boehringer Ingelheim, outside the submitted work.

Sverre Lehmann declares receipt of lecture (personal) and advisory board (to employer) fees from AstraZeneca, Boehringer Ingelheim, and Novartis.

Lauri Lehtimäki declares personal fees for consultancy, lectures and attending advisory boards from ALK, AstraZeneca, Boehringer Ingelheim, Circassia, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma, Sanofi, and Teva.

Matthew Peters declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline.

Camille Taillé has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi and Novartis, for unrelated projects.

Lakmini Bulathsinhala, Victoria Carter, Isha Chaudhry, Neva Eleangovan, Naeimeh Hosseini,

Marjan Kerkhof, and Chris Price are employees of Optimum Patient Care, a co-funder of the International Severe Asthma Registry.

David Price declares advisory board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, and Teva; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, Pfizer, Teva, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, Pfizer, Respiratory Effectiveness Group, Teva, Theravance, UK National Health Service, and Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva; payment for manuscript preparation from Mundipharma and Teva; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp Pharmaceuticals, Novartis, and Teva; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva, and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

Funding information

ISAR research is supported by the Observational & Pragmatic Research Institute (OPRI), and dataset development is co-funded by Optimum Patient Care (OPC) Global and AstraZeneca.

221 **Notation of prior abstract publication/presentation**

222 The Demographic and Clinical Characteristics of Eosinophilic and non-Eosinophilic Phenotypes of
223 Severe Asthma in International Severe Asthma Registry (ISAR). *Accepted at Respiratory Effectiveness*
224 *Group (REG) Summit 2020. Meeting was cancelled due to the COVID-19 pandemic.*
225 Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes and proportion of
226 patients with these phenotypes in the International Severe Asthma registry (ISAR). *Accepted as a*
227 *virtual e-Poster presentation at the American Thoracic Society (ATS) 2020 Virtual Conference.*

228

Abstract

Background: Phenotypic characteristics of eosinophilic and non-eosinophilic asthma patients are not well-characterized in global, real life severe asthma cohorts.

Research Question: What is the prevalence of eosinophilic and non-eosinophilic phenotypes in the severe asthma population, and can they be differentiated by clinical and biomarker variables?

Study Design and Methods: This was an historical, registry study. Adult severe asthma patients with available blood eosinophil count (BEC) from 11 countries enrolled into the International Severe Asthma Registry (01/01/2015 to 09/30/2019) were categorized according to likelihood of eosinophilic phenotype using a pre-defined gradient eosinophilic algorithm based on highest BEC, long-term oral corticosteroid use, elevated fractional exhaled nitric oxide, nasal polyps, and adult-onset asthma. Demographic/clinical characteristics were defined at baseline (i.e. 1-year prior or closest to date of BEC).

Results: 1,716 patients with prospective data were included; 83.8% were identified as “most likely” (Grade 3), 8.3% were “likely” (Grade 2), and 6.3% “least likely” (Grade 1) to have an eosinophilic phenotype. 1.6% of patients had a non-eosinophilic phenotype (Grade 0). Eosinophilic phenotype patients (i.e. Grade 2 or 3) had later asthma onset (29.1 vs 6.7 yrs; $p<0.001$), and worse lung function (post-bronchodilator % predicted FEV₁: 76.1% vs 89.3%; $p=0.027$) than those with a non-eosinophilic phenotype. Non-eosinophilic-phenotype patients were more likely to be female (81.5% vs 62.9%; $p=0.047$), have eczema (20.8% vs 8.5%; $p=0.003$) and use anti-IgE (32.1% vs 13.4%; $p=0.004$) and leukotriene receptor antagonists (50.0% vs 28.0%; $p=0.011$) add-on therapy.

Interpretation: According to this multi-component, consensus-driven, and evidence-based eosinophil gradient algorithm (using variables readily accessible in real life), the severe asthma eosinophilic phenotype was more prevalent than previously identified, and phenotypically distinct. This pragmatic gradient algorithm utilizes variables readily accessible in primary and specialist care,

addressing inherent issues of phenotype heterogeneity and phenotype instability. Identification of treatable traits across phenotypes should improve therapeutic precision.

Clinical Trial Registration: None

Key words: International Severe Asthma Registry, Europe, North America, Asia, Middle East

Abbreviations:

ADEPT: Airways Disease Endotyping for Personalized Therapeutics

BEC: blood eosinophil count

EMR: electronic medical record

FeNO: fractional exhaled nitric oxide

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroids

IgE: immunoglobulin E

IL: interleukin

ISAR: International Severe Asthma Registry

ISC: ISAR Steering Committee

LABA: long-acting beta-agonists

LTRA: leukotriene receptor antagonists

mOCS: maintenance OCS

OCS: oral corticosteroid

OPC: Optimum Patient Care

ppb: parts per billion

REG: Respiratory Effectiveness Group

SARP: Severe Asthma Research Program

278 **U-BIOPRED:** Unbiased BIOmarkers for Prediction of Respiratory Disease

279

Journal Pre-proof

The knowledge that asthma represents a spectrum of diverse types is nothing new. In line with the Lancet Asthma Commission recommendations, asthma should be de-constructed into its various and heterogeneous types to answer the questions, ‘what sort of asthma does the patient have?’, ‘what are the components of the airway disease?’, and ‘what are the treatable traits?’^{1,2} In particular, the term severe asthma includes many different phenotypes and endotypes, which differ in their clinical presentation, underlying pathways, and their response to treatment.³

Eosinophilic airways inflammation has emerged as the hallmark of one type of severe asthma, so much so that asthma is routinely classified as eosinophilic or non-eosinophilic.⁴ Harry Morrow Brown was the first to identify the corticosteroid-responsive eosinophilic asthma phenotype in 1958.⁵ This eosinophilic inflammation is predominantly driven by Type 2 inflammation including T-helper cells Type 2 (Th2) and group 2 innate lymphoid cells (ILC2). It is mediated by interleukin (IL)-4, IL-5, IL-13 and granulocyte macrophage-colony stimulating factor (GM-CSF), and can be predicted (to some extent) from elevated fractional exhaled nitric oxide (FeNO) concentration and sputum/blood eosinophilia.⁶ Non-eosinophilic asthma has traditionally been more arbitrarily defined as asthma without features of Th2 asthma and is generally based on the presence of neutrophils in sputum, or the absence (or normal levels) of eosinophils or other T2 markers in sputum, biopsies or blood.⁷

Knowledge of the presenting phenotype can help predict asthma attack risk and healthcare resource utilisation,^{8,9} inform targeted treatment, and predict treatment response.^{10,11} This eosinophil-targeted approach also has the advantage of reducing oral corticosteroid (OCS) use, which decreases risk of serious adverse events¹² and attenuates rates of severe exacerbations.¹³ Non-eosinophilic severe asthma needs to be better characterized if there is to be a similar advancement in its treatment.

According to the Global Initiative for Asthma (GINA), the eosinophilic phenotype is found in approximately 50% of people with severe asthma.¹⁴ Cluster analyses from different asthma cohorts have identified several asthma phenotypes (mostly eosinophilic) using a range of demographic and clinical characteristics to describe them.¹⁵ However, substantial overlap was noted among phenotypes, most likely due to differences in sample population, geographic variation, variables assessed, and statistical methods used. Additionally, presence of co-morbidities, exposures, OCS use and FeNO were not included in all cluster descriptions. There is, therefore, a need to better characterize asthma phenotypes, in a large, multi-national, real-life cohort of severe asthma patients, considering the effect of steroids on type-2 biomarker concentrations and the importance of multiple blood eosinophil count (BEC) measurements when defining phenotypes. A more detailed deconstruction of asthma into its component types has the potential to make personalized treatment a reality for asthma patients, effectively jump-starting the 'stalled' asthma outcomes and asthma mortality trends that have remained unchanged for years.²

A combination of clinical characteristics and biomarkers may be a better way to characterize asthma types. GINA recommends using different combinations of factors to identify Type 2 inflammatory phenotypes, including BEC, FeNO, sputum eosinophils, need for maintenance OCS (mOCS) and presence of multiple co-morbidities.¹⁶ Only one study has previously proposed a diagnostic scheme to determine severe eosinophilic asthma, which has been agreed by severe asthma expert consensus.¹⁷ However, it has not yet been applied to a real-life clinical setting. The International Severe Asthma Registry (ISAR; <http://isaregistries.org/>), the largest adult severe asthma registry in the world, has sufficient power to investigate, characterize, quantify, and compare eosinophilic and non-eosinophilic phenotypes, and covers diverse jurisdictions, facilitating the generalizability of findings to the wider severe asthma population. ISAR captures BEC and many other variables associated with severe eosinophilic asthma (e.g. FeNO, age of onset, co-morbidities, atopic status,

330 and mOCS use),^{18,19} enabling the development of a multi-component, expert endorsed algorithm for
331 use in real life.

332 The aim of our study was to (i) describe an algorithm to better characterize severe eosinophilic and
333 non-eosinophilic asthma using both phenotype characteristics and biomarkers, (ii) quantify the
334 proportion of severe asthma patients with these phenotypes in the largest real-life severe asthma
335 cohort in the world (i.e. ISAR), and (iii) describe and compare their demographic and clinical
336 characteristics.

Journal Pre-proof

Materials & Methods

Study design and data source

This was a historical registry study to quantify and characterize eosinophilic and non-eosinophilic severe asthma for patients enrolled in ISAR from 1st January 2015 to 30th September 2019.¹⁹ Prospective, de-identified patient data incorporating standardized variables from new and pre-existing severe asthma registries were pooled from 11 countries (Bulgaria, Canada, Denmark, Greece, Italy, Japan, Kuwait, South Korea, Spain, the United Kingdom [UK], and the United States [US]). A full description of variables collected is provided in S-Table 1, including demographic variables (e.g. age, age of onset, sex, race) as well as details on asthma attack rate, asthma control status, presence of atopy and co-morbidities, biomarker concentrations (e.g. IgE and FeNO), lung function and treatment regimen. A full description of how ISAR works has previously been published.²⁰ Details on compliance with local and international codes and regulations are provided in the online supplement.

Patients

Patients were required to be aged ≥ 18 years at enrolment, have severe asthma (i.e. receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4)²¹ with ≥ 1 BEC recorded. A summary how each registry diagnoses asthma and categorizes severe asthma is provided in S-Tables 2 and 3.

Development of gradient eosinophilic phenotype algorithm

A gradient eosinophilic phenotype algorithm was developed following an extensive literature review as well as discussions with, and consensus of experts of the ISAR Steering Committee (comprising scientists, clinicians, and epidemiologists) (S-Figure 1). Consensus was achieved following several face-to-face meetings and via email correspondence (online supplement). This group of experts

selected variables used to inform the algorithm and agreed cut-off values, based on published evidence, feasibility of availability in real-life clinical practice, but without knowledge of how selection of these variables (or their cut-offs) would influence eosinophil phenotype grading in our cohort. These variables and cuts-offs included highest BEC ever (≥ 300 , ≥ 150 -300, < 150 cells/ μL), anti-IL-5/5R treatment, long-term OCS ever, elevated FeNO (≥ 25 ppb) ever, nasal polyps diagnosis ever, and adult asthma onset (≥ 18 years), and informed by the published evidence base and asthma management guidelines.^{16,22-27} Phenotypes were classified as Grade 3 (most likely eosinophilic), Grade 2 (likely eosinophilic), Grade 1 (least likely eosinophilic) and Grade 0 (non-eosinophilic) (Figure 1). Patients most likely to have an eosinophilic phenotype (Grade 3) were those with highest BEC ever of ≥ 300 cells/ μL OR on anti-IL-5/anti-IL-5R therapy, OR with BEC ≥ 150 -300 cells/ μL on (i) mOCS or (ii) ≥ 2 of nasal polyps, elevated FeNO, or late onset. The non-eosinophilic phenotype (Grade 0) was defined by experts as highest BEC ever of < 150 cells/ μL in the absence of nasal polyps, elevated FeNO, late onset, or mOCS. See Figure 1 for definitions of Grade 1 and 2 eosinophilic phenotypes.

Description of eosinophilic and non-eosinophilic severe asthma phenotypes

Both demographic and clinical variables were used to describe eosinophilic and non-eosinophilic severe asthma populations. All demographic and clinical characteristic were taken within one year prior to or closest to the highest BEC recording (pre-anti-IL-5).

Statistical analysis

The statistical analysis plan was pre-defined to reduce bias. Stata version 14.1 (College Station, TX, USA) was used to conduct all statistical analyses. Descriptive statistics were computed for all demographic and clinical characteristics by phenotype (Grade 0 to 3) as continuous variables or categorical measures as appropriate. For testing differences between groups, phenotypes were collapsed into an overall eosinophilic group (i.e. Grade 2 and 3) and a definitely non-eosinophilic group (i.e. Grade 0). Grade 1 was excluded from the non-eosinophilic group as patients in this group

had at least 1 eosinophilic characteristic. Between-group differences in categorical variables were tested using the Chi-square test or Fisher's exact test (if $n < 5$). The unpaired Student's t-test and Wilcoxon Mann Whitney tests were used to compare normally and non-normally distributed data across groups, respectively. A two-sample test was used to compare proportions across groups. Statistical significance was defined as $p < 0.05$.

Sensitivity post-hoc analyses

The original gradient eosinophilic phenotype algorithm was re-formulated without adult onset asthma and without FeNO as criteria. The number of patients (prospective ISAR data) in each eosinophilic/non-eosinophilic phenotype was re-calculated and demographic and clinical characteristics for each group re-assessed. The number (%) of patients in each phenotype and a summary of their demographic/clinical characteristics were also assessed for retrospective electronic medical record (EMR) data captured for patients with severe asthma actively managed in routine care in the US (i.e. have at least 2 visits).

Results

Patients

The ISAR prospective population comprised 1,716 patients (US: n=70; UK: n=712; Spain: n=217; Italy: n=163; Kuwait: n=158; Denmark: n=127; Bulgaria: n=87; Canada: n=85; Greece: n=35; Japan: n=34; South Korea: n=28). The ISAR retrospective population (utilizing EMR data) included a further 1,891 patients with severe asthma actively managed in routine care in the US.

Gradient eosinophilic phenotype algorithm

For the ISAR prospective population (n=1716) 83.8% of patients were identified as “most likely” (Grade 3) to have an eosinophilic phenotype, 8.3% were “likely” (Grade 2), and 6.3% were “least likely” (Grade 1) to have an eosinophilic phenotype. 1.6% of patients had non-eosinophilic asthma (Grade 0) (Table 1). These phenotype classifications were re-checked for robustness by cross-examining their defining characteristics, showing an increase of age of onset, incidence of nasal polyps, and high FeNO from Grade 0 (non-eosinophilic) to Grade 3 (eosinophilic) phenotypes (Table 4). Grade 3 (most likely) eosinophilic phenotype predominated for severe asthma patients in all countries, ranging from 64% of patients in South Korea to 93% of patients in Denmark (Figure 2). The eosinophilic phenotype distribution was similar when age of asthma onset and FeNO were excluded from the gradient algorithm (Table 1; S-Figure 2; S-Figure 3). For the ISAR retrospective population actively assessed in the US (n=1891). 74.3%, 4.1% and 11.5% “most likely,” “likely,” and “least likely” had an eosinophilic severe asthma phenotype, respectively; 10.1% of patients had a non-eosinophilic phenotype.

Demographic and clinical characteristics

Original algorithm (ISAR prospective population, n=1716)

Patients in our severe asthma cohort, irrespective of phenotype (i.e. eosinophilic or non-eosinophilic severe asthma) tended to be White (68.7% vs 74.1%), and overweight/obese (70.5% vs 74.0%), atopic (i.e. specific IgE testing or skin prick test; 88.3% vs 90.9%), had elevated (>150 IU/ml) IgE concentrations (61.8% vs 70.0%) and high AR prevalence (65.5% vs 60.0%), with the majority exhibiting poor asthma control (59.9% vs 59.3%) and multiple exacerbations (≥ 2 in last year; 62.0% vs 59.1%) (Table 2). The prevalence of ex-smokers (28.4% vs 34.6%), emergency department visits (≥ 1 in last year: 33.9% vs 32.0%), and hospitalizations (≥ 1 in last year: 28.6% vs 24.0%) was high in both groups (Table 2). Although an adherence variable was not included in the current dataset, all patients were on background asthma therapy with evidence of persistence and good adherence (in the opinion of the clinician or based on other evidence, such as prescription refills).

Some differences were noted. Patients with an eosinophilic phenotype (i.e. Grade 2 or 3) tended to be older (52.4 vs 38.8 yrs; $p < 0.001$), have later asthma onset (29.1 vs 6.7 yrs; $p < 0.001$), and worse lung function (i.e. % patients with $FEV_1/FVC < 0.7$: 46.6% vs 16.7%; $p = 0.039$ and post-bronchodilator % predicted 76.1% vs 89.3%; $p = 0.027$) than those with a non-eosinophilic phenotype (Table 2; Figure 3). Those with non-eosinophilic severe asthma (i.e. Grade 0) were more likely to be female (81.5% vs 62.9%; $p = 0.047$), have eczema (20.8% vs 8.5%; $p = 0.033$), and use anti-IgE (32.1% vs 13.4%; $p = 0.004$) and LTRA (50.0% vs 28%; $p = 0.011$) add-on to ICS/LABA therapy than those patients with an eosinophilic phenotype (i.e. Grade 2 + 3; Table 2; Figure 3).

Demographic and clinical characteristics along the eosinophil phenotype gradient (i.e. Grades 0, 1, 2 and 3) are provided in the online supplement (S-Table 5).

Original algorithm without age of onset and FeNO as phenotype-defining criteria (ISAR prospective population, n=1716) and for those actively managed in the US (n=1891; EMR data)

A similar distribution of demographic and clinical characteristics was observed when age of onset and FeNO were removed as defining criteria from the eosinophil gradient algorithm (S-Table 6 and S-Table 7). When age of onset was excluded from the algorithm, those with non-eosinophilic severe asthma still tended to be younger (49.6 vs 52.3 years; $p=0.145$), have earlier asthma onset (27.4 vs 28.9 years; $p=0.637$) and eczema (12.5% vs 8.4%; $p=0.291$), although the difference between non-eosinophilic and eosinophilic phenotypes was less marked (S-Table 6). When FeNO was removed from the gradient algorithm, those with non-eosinophilic severe asthma still tended to be female (75.0 vs 62.7 years; $p=0.096$), have eczema (13.9 vs 8.3; $p=0.229$) and add-on LTRA to ICS/LABA therapy (40.0% vs 28.0%; $p=0.078$), but the difference was no longer significant compared to those with eosinophilic severe asthma (S-Table 7). The demographic and clinical characteristics for those patients with severe asthma assessed actively in the US were slightly different to the ISAR prospective data (S-Table 8).

Discussion

We demonstrated that the eosinophilic severe asthma phenotype is larger than previously estimated (i.e. >80% vs ~50%),¹⁴ and identified distinct eosinophilic and non-eosinophilic severe asthma patterns based on a combination of clinical and biomarker variables. Our proposed multi-component, eosinophil phenotype classification algorithm is based on extensive literature review and expert consensus, uses variables readily accessible both in primary and specialist care, and is linked to morbidity and treatment response. Furthermore, the algorithm takes variability in BEC (using the highest ever value) and impact of OCS into account, both of which can confound phenotype classification. We have proposed a gradient approach (i.e. likelihood of eosinophilic asthma) rather than a dichotomous approach to severe asthma phenotype classification in recognition of inherent heterogeneity within phenotypes, and the fact that they can occur in isolation or combination in any given patient and may change over time, either due to natural history of the disease or as a consequence of treatment.¹ Finally, we have pooled diverse data from large severe asthma registries to provide a real-life phenotype snapshot at the global and country levels, quantifying and characterizing both the severe eosinophilic phenotype and also the often ignored non-eosinophilic severe asthma phenotype, which has historically been a diagnosis of exclusion.

A gradient and multi-component eosinophil classification algorithm is useful to reflect heterogeneity not only within severe asthma, but within eosinophilic and non-eosinophilic phenotypes too. Use of elevated BEC as the sole marker for defining an eosinophilic phenotype may be misleading for several reasons. The amount of eosinophils in the blood is both time- and treatment-dependent; eosinophil counts fluctuate in a circadian pattern and are also reduced during OCS therapy.^{28,29} Additionally, a low BEC does not necessarily rule out the presence of airway eosinophilia. Its use as a single surrogate marker for airway eosinophilia in patients with asthma “will lead to a substantial

number of false positives or false negatives.”³⁰ A combination of clinical parameters and biomarkers may safeguard against phenotype mis-classification, and is one explanation for the >80% of patients with severe eosinophilic asthma observed in the present study. Both the SARP and the Leicester cohorts have used this combination approach.³¹

Using a multi-component gradient eosinophil algorithm to characterize eosinophilic and non-eosinophilic phenotypes of severe asthma within ISAR (Figure 1) permitted us to take a phenotype snapshot.¹ We found that that the vast majority of patients (>80%) in severe asthma centers globally have background eosinophilic asthma (irrespective of algorithm used), and that the proportion of patients with a completely non-eosinophilic phenotype is very rare (only 1.6% in the current study). Others have recently validated our findings, showing a similarly high prevalence of eosinophilic asthma (83.4%), defined as ≥ 300 cells/ μ L ever in the past 10 years, in a real life difficult-to-treat UK asthma population.³² However, arguably the ISAR gradient eosinophil algorithm affords a more practical means of determining eosinophilic asthma status than reliance on protracted, sequential BEC.

The low prevalence of non-eosinophilic phenotype in the present study could be due to the strict non-eosinophilic phenotype definition employed, OCS over-treatment and/or possibly due to anti-IgE treatment and LTRA treatment which may have suppressed some algorithm variables (e.g. BEC).^{33,34} This low-eosinophilic phenotype prevalence remained when age of onset and FeNO were removed as criteria from the gradient algorithm. Those with an eosinophilic severe asthma phenotype have an elevated BEC (i.e. ≥ 150 cells/ μ L), and are more likely to have nasal polyps and FeNO ≥ 25 ppb (by algorithm definition), are older, and have adult-onset asthma and worse lung function (than those with non-eosinophilic severe asthma). On the flip side, our preliminary findings, based on small numbers, found that those with a non-eosinophilic severe asthma phenotype have a

relatively low BEC (i.e. <150 cells/ μ L), no nasal polyps, low FeNO (i.e. <25 ppb), and early onset disease, and are more likely to be female, have eczema, and be treated with anti-IgE and LTRA add-on to ICS/LABA therapy (presumably due to ineligibility for anti-IL5/5R treatment by virtue of low BEC). This finding highlights the lack of other treatment options, and the need to develop treatments targeted at this often overlooked sub-set of severe asthma patients. The higher likelihood of eczema reported relative to patients with an eosinophilic phenotype may be due to the greater prevalence of OCS and biologic use in the latter group, which may reduce the severity of both conditions so they are not currently active.

In common with most severe asthma cohorts, we found a clear female predominance (irrespective of phenotype). Interestingly, the prevalence of male sex appeared to be proportionately greater in the eosinophilic group (37.1% vs 18.5%), which in conjunction with older age and later onset seen in the eosinophilic group aligns with Azim and colleagues³⁵ who recently identified a male, adult-onset, eosinophilic, difficult asthma phenotype that has so far received scant attention in the literature. Similarity of healthcare resource utilization for both eosinophilic and non-eosinophilic severe asthma suggests comparable asthma severity across phenotypes. Similarity across phenotypes for asthma control and asthma attacks may be attributable to the fact that ISAR selects patients that are more likely to experience an asthma attack. However, this finding may suggest that despite complete suppression of eosinophilic inflammation (with corticosteroids or biologic therapy) in those with definite eosinophilic asthma, symptoms and asthma attacks can persist; that other factors (besides the eosinophil) are important (e.g. co-morbidities, healthcare access, and socio-economic factors). Characterization of non-eosinophilic mechanisms that persist when eosinophilic inflammation has been suppressed warrants further characterization. The relatively lower prevalence of the severe eosinophilic phenotype in the US retrospective population (74%), is mainly attributed to lack of nasal polyps and age of asthma onset data, and speaks to the benefit of standardized, prospective data collection and coding employed in ISAR as well as the importance of longitudinal assessment of BEC.

Table 3 compares this global view of eosinophilic phenotype description with cluster analyses from 3 large, asthma cohorts (SARP, U-BIOPRED, and ADEPT).¹⁵ All clusters identified a predominance of eosinophilic clusters, but differed in the size of the eosinophilic and non-eosinophilic clusters identified, ranging from 49-56% and 16-31%, respectively,^{36,37} and markedly differed from the results of the current study (Table 3). These differences may be due in part to inclusion of mild asthma in these clusters (e.g. the percentage of patients with an eosinophilic phenotype increases to 81.2% when mild patients are discounted from the SARP cohort), due to differences in choice of variables, and complicated by the inclusion of a mixed granulocyte phenotype in the UBIOPRED and ADEPT cohorts which includes neutrophilic types. Indeed, Burgel and colleagues³⁸ argue that cluster analyses should be viewed as an exploratory analysis and the results validated using clinically-relevant endpoints in multiple cohorts of patients. Use of multiple clinical biomarkers, a well-characterized cohort, and variables that are treatable to define phenotypes (as done in our study) may have a superior biological responsiveness predictive value.^{3,39}

One limitation of the study includes a potential selection bias for the eosinophilic phenotype within ISAR. Although the ISAR population may be enriched for those with high BEC, frequent asthma attacks, and suitability for biologic prescription in some countries (e.g. UK), thus positively selecting for the severe eosinophilic phenotype, this is not true for all countries. Indeed, a recent study including data from 7 ISAR-participating countries (US, UK, South Korea, Italy, Australia, New Zealand, and Singapore) found that only 25.4% of severe asthma patients were receiving biologic therapy (either anti-IgE or anti-IL-5).⁴⁰ A similarly high prevalence of eosinophilic asthma and low prevalence of non-eosinophilic asthma has also been reported in a primary care cohort using the same eosinophil phenotype gradient algorithm,⁴¹ and in the actively managed US EMR population presented in the current study). Furthermore, a similarly low prevalence of non-eosinophilic asthma

has been reported in the RASP-UK asthma cohort using a different algorithm.⁴² Our algorithm is intended to aid phenotype classification and does not capture all asthma sub-types. For example, there exists a sub-type of asthmatics with low BEC and elevated FeNO and nasal polyps who do respond well to anti-IL4/13.⁴³ This phenotype can be more fully explored within ISAR when IL4/13 use becomes more widespread.' Additional limitations include a reliance on BEC rather than sputum eosinophil count, possibility of recall bias (e.g. for onset of asthma), and the large imbalance in patient numbers between the groups when describing demographic and clinical characteristics. However, it should be noted that although sputum induced by hypertonic saline is generally considered a reliable, non-invasive method to assess and monitor eosinophilia, it can be problematic in patients with severe and uncontrolled asthma inducing airway narrowing and/or failure to produce an adequate sputum sample in about a quarter of patients.⁴⁴ Blood eosinophilia is an accurate surrogate marker for sputum eosinophils, with a reported ROC AUC of 89%.⁴⁵

It is recommended to apply this gradient algorithm in a different severe asthma study population with longitudinal BEC records to assess the specificity of the eosinophil phenotype definition and to assess the generalizability of the reported results. Future work could evaluate the internal and external validity of the gradient algorithm, more fully examine the eosinophil phenotype characteristics by country, characterize the ISAR cohort according to Type 2 and non-Type 2 endotypes and examine overlap between phenotypes and biomarkers.

Interpretation

This multi-component, expert-endorsed, eosinophil gradient algorithm, using variables readily accessible in real life, has shown that the prevalence of the severe asthma eosinophilic phenotype was higher than previously thought, and phenotypically distinct. Use of this algorithm may enable physicians to ascertain what type of asthma their patients have, the components of the airway

disease, and its treatable traits, bringing us one step closer to the practice of precision medicine and selection of targeted phenotype-specific treatments.

Take-Home Points

- Study Question: What is the prevalence of eosinophilic and non-eosinophilic phenotypes in the severe asthma population, and can they be differentiated by clinical and biomarker variables?
- Results: Of 1,716 patients included, 83.8%, “most likely” had an eosinophilic phenotype. These patients were older, had later onset asthma, and worse lung function compared to those with a non-eosinophilic phenotype (1.6%).
- Interpretation: The severe asthma eosinophilic phenotype is more prevalent than previously thought and phenotypically distinct, when defined using variables readily accessible in real life.

Acknowledgments

We thank Bassam Mahboub, Carlos A. Torres-Duque, Désirée Larenas Linnemann, Diahn-Warng Perng (Steve), Esther Garcia Gil, Jorge Maspero, Peter G. Gibson, Piotr Kuna, Riyad Al-Lehebi, Rupert C. Jones, and Sundeep Salvi as members of the ISAR Steering Committee for their valued contributions during the planning, analysis and drafting of this article.

Guarantor Statement

David Price agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition or analysis and interpretation, as well as the critical revision of the manuscript for important intellectual content. LGH, LP, MA, VB, JB, GWC, GC, BC, JMF, EH, TI, DJJ, AMG, NGP, AP, PEP, TAP, CMP, CKR, MS, YT, EW, MW, MA, AA, LB, USB, AB, GGB, RB, RWC, MH, MKS, SL, LL, MP, CT, ChT, TT, JZ, and DBP were involved in the conception and design of the study and in reaching consensus on the eosinophil gradient algorithm. LGH, LB, VC, IC, NE, NH, MK, RM, CP and DBP were responsible for drafting the manuscript. IC, NE and LB provided additional administrative, technical, and material support. The study was supervised by DBP. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

Financial/non-financial disclosures

Liam G. Heaney declares he has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, and Teva; he has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

Luis Perez de Llano declares non-financial support, personal fees, and grants from Teva; non-financial support and personal fees from Boehringer Ingelheim, Esteve, GlaxoSmithKline, Mundipharma, and Novartis; personal fees and grants from AstraZeneca and Chiesi; personal fees from Sanofi; and non-financial support from Menairi outside the submitted work.

Mona Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline.

Vibeke Backer, John Busby, George C. Christoff, J. Mark FitzGerald, Ruth B. Murray and Christian Taube declare no relevant conflicts of interest concerning this paper.

Unnur S. Björnsdóttir receives gratuities for lectures/presentations from AstraZeneca, Sanofi and Novartis.

Enrico Heffler participates in speaking activities and industry advisory committees for AstraZeneca, Sanofi-Genzyme, GSK, Novartis, TEVA, Circassia and Nestlé Purina.

G. Walter Canonica has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Abello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas.

Borja G. Cosio declares grants from Chiesi; personal fees for advisory board activities from Chiesi and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, Menarini, and AstraZeneca, outside the submitted work

Takashi Iwanaga declares grants from Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Kyorin, MeijiSeika Pharma, Teijin Pharma, and lecture fees from Kyorin.

David J. Jackson has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Teva, Napp, Chiesi, Novartis and research grant funding from AstraZeneca.

Andrew N. Menzies-Gow has attended advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi and Teva, and has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Roche, Teva and Vectura. He has participated in research with AstraZeneca for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca, Sanofi and Vectura.

Nikolaos G. Papadopoulos declares research support from Gerolymatos, Menarini, Nutricia, and Vian; and consultancy/speaker fees from ASIT, AZ, Boehringer Ingelheim, GSK, HAL Allergy, Medscape, Menarini, MSD, Mylan, Novartis, and Nutricia, OM Pharma, Sanofi, and Takeda.

Andriana I. Papaioannou has received fees and honoraria from Menarini, GSK, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi.

Paul E. Pfeffer has attended advisory boards for Novartis; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline and Novartis, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline.

Todor A. Popov declares relevant research support from Novartis and Chiesi Pharma.

Celeste M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme.

Chin Kook Rhee declares consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, MSD, Novartis, Sandoz, Takeda, and Teva-Handok.

Mohsen Sadatsafavi has received honoraria from AstraZeneca. He has also received research funding into his research account at The University of British Columbia.

Yuji Tohda declares honoraria from Kyorin Pharma and Teijin Pharma and research funding from Kyorin Pharma and Meiji Seika Pharma.

Eileen Wang has received honoraria from AstraZeneca and Clinical Care Options. She has been an investigator on clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Novartis, Teva, and National Institute of Allergy and Infectious Diseases (NIAID) for which her institution has received funding.

Michael E. Wechsler reports receiving consulting honoraria from AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Novartis, Regeneron, Sanofi and Teva.

Marianna Alacqua and Trung N. Tran are employees of AstraZeneca, a co-funder of the International Severe Asthma Registry. **James Zangrilli** was an employee of AstraZeneca at the time this analysis was conducted.

Alan Altraja has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Novartis, and Orion; sponsorships from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Sanofi, and Novartis; and has been a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva.

Leif Bjerner has (in the last three years) received lecture or advisory board fees from Alk-Abello, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Genzyme/Regeneron, and Teva.

Arnaud Bourdin has received industry-sponsored grants from AstraZeneca/MedImmune, Boehringer Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, Sanofi-Regeneron and consultancies with AstraZeneca/MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi.

Investigator/Co-investigator for trials promoted by AstraZeneca/MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron- Sanofi, Chiesi, Actelion, Merck, Roche, Vertex, Galapagos,

Guy G. Brusselle has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva.

Roland Buhl reports grants to Mainz University and personal fees from Boehringer Ingelheim, GSK, Novartis, and Roche, as well as personal fees from AstraZeneca, Chiesi, Cipla, Sanofi, and Teva, outside the submitted work.

Richard W. Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence and prediction of exacerbations.

Mark Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, and Seqirus, for unrelated projects.

Mariko Koh Siyue reports grant support from AstraZeneca, and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Sanofi and Boehringer Ingelheim, outside the submitted work.

Sverre Lehmann declares receipt of lecture (personal) and advisory board (to employer) fees from AstraZeneca, Boehringer Ingelheim, and Novartis.

Lauri Lehtimäki declares personal fees for consultancy, lectures and attending advisory boards from ALK, AstraZeneca, Boehringer Ingelheim, Circassia, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma, Sanofi, and Teva.

Matthew Peters declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline.

Camille Taillé has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi and Novartis, for unrelated projects.

Lakmini Bulathsinhala, Victoria Carter, Isha Chaudhry, Neva Eleangovan, Naeimeh Hosseini, Marjan Kerkhof, and Chris Price are employees of Optimum Patient Care, a co-funder of the International Severe Asthma Registry.

David Price declares advisory board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, and Teva; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, Pfizer, Teva, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp Pharmaceuticals, Novartis, Pfizer, Respiratory Effectiveness Group, Teva, Theravance, UK National Health Service, and Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva; payment for manuscript preparation from Mundipharma and Teva; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp Pharmaceuticals, Novartis, and Teva; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva, and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

Role of the sponsors

This ISAR research study was co-funded by AstraZeneca and Optimum Patient Care (OPC) Global Limited and overseen by the ISAR Steering Committee (ISC), Respiratory Effectiveness Group (REG), the Anonymised Data Ethics & Protocol Transparency Committee, and the ISAR Operational Committee. The ISC includes 1 member from OPC and 3 medical experts from AstraZeneca as well as 45 clinicians and researchers across 29 countries. OPC and AstraZeneca members of the ISC had input into study design, data analysis and interpretation, manuscript writing, and are authors of this article in line with ICMJE authorship criteria.

Other Contributions

The authors thank the following individuals who contributed substantially to the International Severe Asthma Registry.

Bulgaria: Cvetanka Odjakova, Darina Petrova Dimova, Diana X. Hristova, Eleonara M. Stamenova, Katya Vasileva Noleva, Nadezda K. Takovska, Plamen Hristov Yakovliev, Sonya Metodieva Genova, and Violina Milchova Vasileva.

Canada: Andreanne Cote, Celine Bergeron, Dloui-Philippe Boulet, Louis Phillipe Boulet, Mohit Bhutani, and Kenneth Chapman.

Denmark: Anders Christiansen, Charlotte Ulrik, Johannes Schmid, Karin Dahl Assing, Kirsten Rasmussen, Linda Rasmussen, and Ole Hilberg.

Greece: Giannis Paraskevopoulos, Konstantinos Kostikas, and Stelios Loukides.

Italy: Alessandro Farsi, Andrea Vianello, Angelo Guido Corsico, Antonio Spanevello, Barbaro Maria Pia Foschino, Carlo Lombardi, Caterina Bucca, Cecilia Calabrese, Concetta Sirena, Cristiano Caruso, Daniela Morrone, Eleonora Nucera, Elisabetta Favero, Erminia Ridolo, Fabio Luigi Massimo Ricciardolo, Francesco Blasi, Francesco Mazza, Francesco Menzella, Gabriella Guarnieri, Gianenrico Senna, Gianna Camiciottoli, Giovanni Passalacqua, Giovanni Rolla, Girolamo Pelaia, Giuseppe Guida,

Giuseppe Spadaro, Laura Pini, Lorenzo Cosmi, Luca Richeldi, Luigi Macchia, Luisa Ricciardi, Manlio Milanese, Marcello Montagni, Marco Bonavia, Maria Cristina Zappa, Maria D'Amato, Maria Elisabetta Conte, Maria Filomena Caiaffa, Maria Teresa Costantino, Mona-Rita Yacoub, Nicola Scichilone, Nunzio Crimi, Paolo Montuschi, Paolo Solidoro, Pierachille Santus, Pierluigi Paggiaro, Roberta Parente, Salvatore Lo Cicero, Simona D'Alò, Stefano Centanni, Stefano Del Giacco, Vincenzo Patella, and Vittorio Viviano.

Japan: Hiroshi Tanaka, Soichiro Hozawa, and Takahiko Horiguchi.

Kuwait: Ahmed Maher and Jasmina Nurkic.

South Korea: Jae Ha Lee, Ji-yong Moon, Youlim, Kim, Seung Won Ra, and Kwang Ha Yoo.

Spain: Vicente Plaza.

UK: We would like to thank the clinical staff and data entry teams at participating UK Severe Asthma Registry (UKSAR) centers.

US: Joy Zimmer and Pearlanne Zelarney.

References

1. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018;391(10118):350–400.
2. Bush A, Pavord ID. The Lancet Asthma Commission: towards the abolition of asthma? *European Medical Journal* 2018;3(4):10–15.
3. Bakakos A, Loukides S, Bakakos P. Severe Eosinophilic Asthma. *J Clin Med* 2019;8(9).
4. Kuruvilla ME, Lee FE-H, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. *Clin Rev Allergy Immunol* 2019;56(2):219–233.
5. BROWN HM. Treatment of chronic asthma with prednisolone; significance of eosinophils in the sputum. *Lancet* 1958;2(7059):1245–1247.
6. Pavlidis S, Takahashi K, Ng Kee Kwong F, et al. “T2-high” in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. *Eur Respir J* 2019;53(1).
7. Sze E, Bhalla A, Nair P. Mechanisms and therapeutic strategies for non-T2 asthma. *Allergy* 2020;75(2):311–325.
8. Price DB, Bosnic-Anticevich S, Pavord ID, et al. Association of elevated fractional exhaled nitric oxide concentration and blood eosinophil count with severe asthma exacerbations. *Clin Transl Allergy* 2019;9:41.
9. Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018;73(2):116–124.
10. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388(10056):2128–2141.
11. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6(1):51–64.
12. Bernstein JA, Virchow JC, Murphy K, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2020;8(5):461–474.
13. Lefebvre P, Duh MS, Lafeuille M-H, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015;136(6):1488–1495.
14. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2020 [Internet]. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf
15. Carr TF, Zeki AA, Kraft M. Eosinophilic and Noneosinophilic Asthma. *Am J Respir Crit Care Med* 2018;197(1):22–37.

- 836 16. GINA. Difficult-to-treat and severe asthma in adolescent and adult patients. Diagnosis and
837 management. A GINA Pocket Guide for Health Professionals. 2018 [Internet] Available from:
838 [https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-](https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf)
839 [wms-1.pdf](https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf)
- 840 17. Buhl R, Humbert M, Bjermer L, et al. Severe eosinophilic asthma: a roadmap to consensus. *Eur*
841 *Respir J* 2017;49(5).
- 842 18. Bulathsinhala L, Eleangovan N, Heaney LG, et al. Development of the International Severe
843 Asthma Registry (ISAR): A Modified Delphi Study. *J Allergy Clin Immunol Pract* 2019;7(2):578-
844 588.e2.
- 845 19. ISAR Study Group. International Severe Asthma Registry (ISAR): Mission Statement. *Chest*
846 2020;157(4):805–814.
- 847 20. FitzGerald JM, Tran TN, Alacqua M, et al. International severe asthma registry (ISAR): protocol
848 for a global registry. *BMC Med Res Methodol* 2020;20(1):212.
- 849 21. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis,
850 management, and prevention of chronic obstructive pulmonary disease. 2018. 2018 [Internet]
851 Available from: [https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-](https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf)
852 [revised-20-Nov_WMS.pdf](https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf)
- 853 22. Asano K, Ueki S, Tamari M, Imoto Y, Fujieda S, Taniguchi M. Adult-onset eosinophilic airway
854 diseases. *Allergy* 2020;
- 855 23. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic Rhinosinusitis with Nasal
856 Polyps and Asthma. *J Allergy Clin Immunol Pract* 2020;
- 857 24. Frøssing L, Silberbrandt A, Von Bülow A, Backer V, Porsbjerg C. The Prevalence of Subtypes of
858 Type 2 Inflammation in an Unselected Population of Patients with Severe Asthma. *J Allergy*
859 *Clin Immunol Pract* 2020;
- 860 25. Jeppegaard M, Veidal S, Sverrild A, Backer V, Porsbjerg C. Validation of ATS clinical practice
861 guideline cut-points for FeNO in asthma. *Respir Med* 2018;144:22–29.
- 862 26. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition,
863 evaluation and treatment of severe asthma. *Eur Respir J* 2014;43(2):343–373.
- 864 27. Kostikas K, Brindicci C, Patalano F. Blood Eosinophils as Biomarkers to Drive Treatment Choices
865 in Asthma and COPD. *Curr Drug Targets* 2018;19(16):1882–1896.
- 866 28. Prazma CM, Bel EH, Price RG, Bradford ES, Albers FC, Yancey SW. Oral corticosteroid dose
867 changes and impact on peripheral blood eosinophil counts in patients with severe eosinophilic
868 asthma: a post hoc analysis. *Respir Res* 2019;20(1):83.
- 869 29. Durrington HJ, Gioan-Tavernier GO, Maidstone RJ, et al. Time of Day Affects Eosinophil
870 Biomarkers in Asthma: Implications for Diagnosis and Treatment. *Am J Respir Crit Care Med*
871 2018;198(12):1578–1581.

- 872 30. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers
873 for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet*
874 *Respir Med* 2015;3(4):290–300.
- 875 31. Wu W, Bleecker E, Moore W, et al. Unsupervised phenotyping of Severe Asthma Research
876 Program participants using expanded lung data. *J Allergy Clin Immunol* 2014;133(5):1280–
877 1288.
- 878 32. Azim A, Newell C, Barber C, et al. Clinical evaluation of type 2 disease status in a real-world
879 population of difficult to manage asthma using historic electronic healthcare records of blood
880 eosinophil counts. *Clin Exp Allergy* 2021; Feb 2.
881 doi: 10.1111/cea.13841. Online ahead of print.
- 882 33. Busse WW, Humbert M, Haselkorn T, et al. Effect of omalizumab on lung function and
883 eosinophil levels in adolescents with moderate-to-severe allergic asthma. *Ann Allergy Asthma*
884 *Immunol* 2020;124(2):190–196.
- 885 34. Schäper C, Noga O, Koch B, et al. Anti-inflammatory properties of montelukast, a leukotriene
886 receptor antagonist in patients with asthma and nasal polyposis. *J Invest Allergol Clin*
887 *Immunol* 2011;21(1):51–58.
- 888 35. Azim A, Freeman A, Lavenu A, et al. New Perspectives on Difficult Asthma; Sex and Age of
889 Asthma-Onset Based Phenotypes. *J Allergy Clin Immunol Pract* 2020;8(10):3396–3406.e4.
- 890 36. Loza MJ, Djukanovic R, Chung KF, et al. Validated and longitudinally stable asthma phenotypes
891 based on cluster analysis of the ADEPT study. *Respir Res* 2016;17(1):165.
- 892 37. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster
893 analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181(4):315–
894 323.
- 895 38. Burgel P-R, Paillasseur J-L, Roche N. Identification of clinical phenotypes using cluster analyses
896 in COPD patients with multiple comorbidities. *Biomed Res Int* 2014;2014:420134.
- 897 39. Reihman AE, Holguin F, Sharma S. Management of Severe Asthma Beyond the Guidelines. *Curr*
898 *Allergy Asthma Rep* 2020;20(9):47.
- 899 40. Wang, E., Wechsler, M. E., Tran, T. N., et al. Characterization of severe asthma worldwide: data
900 from the International Severe Asthma Registry (ISAR). *Chest* 2020;157(4):805–814.
- 901 41. Kerkhof M, Tran TN, Zangrilli J, Carter VA, Price D. Eosinophilic asthma phenotypes in the UK
902 population. *European Respiratory Journal* 2020;56(Suppl 64).
- 903 42. Heaney LG. A randomized trial of treatment optimisation in patients with severe asthma using
904 composite type II biomarkers to adjust corticosteroid dose versus a symptom/risk-based
905 algorithm. *Lancet Respir Med* 2020;In press.
- 906 43. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe
907 Uncontrolled Asthma. *N Engl J Med* 2018;378(26):2486–2496.

908 44. Brinke A ten, Lange C de, Zwinderman AH, Rabe KF, Sterk PJ, Bel EH. Sputum induction in
909 severe asthma by a standardized protocol: predictors of excessive bronchoconstriction. *Am J*
910 *Respir Crit Care Med* 2001;164(5):749–753.

911 45. Wagener AH, Nijs SB de, Lutter R, et al. External validation of blood eosinophils, FE(NO) and
912 serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015;70(2):115–120.

913

Journal Pre-proof

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

914 **Table 1: Characterization of eosinophilic and non-eosinophilic phenotypes and the proportion of severe asthma patients with these phenotypes in ISAR**

Highest BEC available (cells/ μ L) ^a	Treatment or clinical characteristic	Eosinophilic phenotype	Prospective ISAR population (N=1,716) [Original algorithm]		Prospective ISAR population (N=1,716) [Original algorithm - age of onset]		Prospective ISAR population (N=1,716) [Original algorithm – FeNO]	
			N (%)	(%)	N (%)	%	N (%)	%
≥ 300		Grade 3: most likely	1196 (69.7%)	83.8%	1196 (69.7%)	82.6%	1196 (69.7%)	82.7%
Anti-IL5		Grade 3: most likely	178* (10.4%)		178* (10.4%)		178* (10.4%)	
≥ 150 to < 300	Long-term OCS	Grade 3: most likely	37 (2.2%)		37 (2.2%)		37 (2.2%)	
	Presence of ≥ 2 of the following: NP, FeNO ≥ 25 ppb or adult onset ^b (no long-term OCS)	Grade 3: most likely	27 (1.6%)		7 (0.4%)		8 (0.5%)	
	Either NP, FeNO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 2: likely	67 (3.9%)		45 (2.6%)		71 (4.1%)	
	No NP, elevated FeNO, adult onset or long-term OCS	Grade 1: least likely	27 (1.6%)		69 (4.0%)		42 (2.4%)	
< 150	Long term OCS	Grade 2: likely	75 (4.4%)	4.4%	75 (4.4%)	4.4%	75 (4.4%)	4.4%
	Either NP, FeNO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 1: least likely	81 (4.7%)	4.7%	40 (2.4%)	2.4%	64 (3.7%)	3.7%
	No NP, elevated FeNO, adult onset or long-term OCS	Grade 0: unlikely (non-	28 (1.6%)	1.6%	69 (4.0%)	4.0%	45 (2.6%)	2.6%

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

		eosinophilic)						
Anti-IL5/5R: anti interleukin 5/5-receptor; BEC: blood eosinophil count; eCRF: electronic clinical report form; EMR: electronic medical record; FeNO: fractional exhaled nitric oxide; ISAR: International Severe Asthma Registry; NP: nasal polyps; OCS: oral corticosteroids. ^a independent criteria specified in each row; pre-Anti-IL5/5R or long-term OCS was used wherever possible; ^b Onset of asthma: ≥ 18 years old; *Of 178 patients on Anti-IL-5, n=125 had a BEC < 150 (n=88 on mOCS; 37 never on mOCS) and 53 had a BEC ≥ 150 to <300 (n=38 on mOCS, n=15 never on mOCS). Of the 37 with BEC < 150 without OCS, n=26 did NOT have a pre-anti-IL5 BEC. N=11 (from Canada [n=1] Denmark [n=2], Spain [n=3] & USA [n=5]) had a pre-anti-IL5 BEC								

915

916

917

918

Table 2: Demographic and clinical characteristics according to eosinophilic (Grade 2 & 3) and non-eosinophilic (Grade 0) phenotype, categorized according to the original algorithm (ISAR prospective population; N=1,716)

	Non- Eosinophilic (Grade 0; N=28)	Eosinophilic (Grade 2 &3; N=1580)	P-value
Gender			
Non-missing, n (%)	27 (96.4)	1571 (99.4)	0.047 ^{a*}
Female, n (%)	22 (81.5)	988 (62.9)	
Age			
Non-missing, n (%)	26 (92.9)	1513 (95.8)	0.000 ^{b*}
Mean (SD)	38.8 (12.1)	52.4 (13.8)	
18-34, n (%)	10 (38.5)	177 (11.7)	0.000 ^{c*}
35-54, n (%)	14 (53.8)	631 (41.7)	
55-79, n (%)	2 (7.7)	683 (45.1)	
≥80, n (%)	0 (0)	22 (1.4)	
Ethnicity			
Non-missing, n (%)	27 (96.4)	1549 (98.0)	0.650 ^c
Caucasian, n (%)	20 (74.1)	1064 (68.7)	
Asian, n (%)	3 (11.1)	140 (9.1)	
African, n (%)	0 (0)	55 (3.5)	
Mixed, n (%)	0 (0)	12 (0.8)	
Other, n (%)	4 (14.8)	272 (17.6)	
Unknown, n (%)	0 (0)	6 (0.4)	
BMI*			
Non-missing, n (%)	27 (96.4)	1546 (98.0)	0.943 ^c
Underweight (<18.5), n (%)	0 (0)	25 (1.6)	
Normal (≥18.5-<25), n (%)	7 (25.9)	431 (27.9)	
Overweight (≥25 - <30), n (%)	10 (37.0)	504 (32.6)	
Obese (≥30), n (%)	10 (37.0)	586 (37.9)	
Smoking Status			
Non-missing, n (%)	26 (92.9)	1540 (97.5)	0.570 ^c
Current smokers, n (%)	1 (3.8)	53 (3.4)	
Ex-smokers, n (%)	9 (34.6)	438 (28.4)	
Never-smoked, n (%)	16 (61.5)	1049 (68.1)	
Age of asthma onset (years)			
Non-missing, n (%)	23 (82.1)	1493 (90.9)	0.000 ^{b*}
Mean (SD)	6.7 (4.1)	29.1 (18.0)	
<18, n (%)	23 (100.0)	424 (29.5)	
18-29, n (%)	0 (0.0)	283 (19.7)	
≥30, n (%)	0 (0.0)	729 (50.8)	
Comorbidities ever			
Non-missing, n (%)	24 (85.7)	1493 (94.5)	-
NP, n (%)	0 (0.0)	492 (32.9)	
Non-missing, n (%)	14 (50.0)	851 (53.9)	0.467 ^a
CRS	6 (42.9)	448 (52.6)	
Non-missing, n (%)	13 (46.4)	514 (32.5)	0.577 ^a
CRS without NP, n (%)	6 (46.1)	198 (38.5)	

Non-missing, n (%)	-	314 (19.9)	-
CRS with NP, n (%)	0 (0.0)	234 (74.5)	
Non-missing, n (%)	15 (53.6)	869 (55.0)	0.658 ^a
AR, n (%)	9 (60.0)	569 (65.5)	
Non-missing, n (%)	24 (85.7)	1275 (80.7)	0.033^{a*}
Eczema, n (%)	5 (20.8)	109 (8.5)	
Atopy			
Non-missing, n (%)	22 (78.6)	1362 (86.2)	P=0.701 ^e
Atopy, n (%)	20 (90.9)	1202 (88.3)	
Asthma Control			
<i>Asthma control, non-missing n (%)</i>	27 (96.4)	1296 (82.0)	
Poorly controlled, n (%)	16 (59.3)	776 (59.9)	0.828 ^a
Not well controlled, n (%)	5 (18.5)	190 (14.7)	
Well controlled, n (%)	6 (22.2)	330 (25.5)	
<i>Asthma attacks, non-missing n (%)</i>	22 (78.6)	1354 (85.7)	
Mean (SD)	3.2 (3.0)	3.4 (3.7)	0.919 ^b
0, n (%)	5 (22.7)	350 (25.9)	0.698 ^c
1, n (%)	4 (18.2)	166 (12.3)	
2, n (%)	1 (4.5)	180 (13.3)	
3, n (%)	2 (9.1)	129 (9.6)	
≥4, n (%)	10 (45.5)	529 (39.1)	
Health care resource utilization			
<i>Invasive ventilation, non-missing n (%)</i>	22 (78.6)	1395 (88.3)	
Mean (SD)	0.1 (0.5)	0.1 (0.6)	0.724 ^b
0, n (%)	20 (90.9)	1294 (92.8)	0.442 ^c
1, n (%)	1 (4.5)	75 (5.4)	
≥2, n (%)	1 (4.5)	26 (1.9)	
<i>ED visit, non-missing n (%)</i>	25 (89.3)	1461 (92.5)	
Mean (SD)	1.6 (4.2)	1.2 (3.2)	0.978 ^b
0, n (%)	17 (68.0)	965 (66.0)	0.912 ^c
1, n (%)	2 (8.0)	161 (11.0)	
≥2, n (%)	6 (24.0)	335 (22.9)	
<i>Hospitalization, non-missing n (%)</i>	25 (89.3)	1446 (91.5)	
Mean (SD)	0.6 (1.9)	0.7 (1.5)	0.676 ^b
0, n (%)	19 (76.0)	1033 (71.4)	0.808 ^c
1, n (%)	2 (8.0)	202 (14.0)	
≥2, n (%)	4 (16.0)	211 (14.6)	
Biomarkers			
<i>IgE (IU/mL), non-missing n (%)</i>	20 (71.4)	1270 (80.4)	
<150, n (%)	6 (30.0)	485 (38.2)	0.709 ^a
150-400, n (%)	7 (35.0)	357 (28.1)	
>400, n (%)	7 (35.0)	428 (33.7)	
<i>FeNO, ppb, non-missing n (%)</i>	23 (82.1)	1080 (68.4)	
<25, n (%)	23 (100.0)	299 (27.7)	-
≥25 - <50, n (%)	0 (0.0)	338 (31.3)	
≥50, n (%)	0 (0.0)	443 (41.0)	
Lung Function			
<i>Post-BD FEV₁ % predicted, non-missing n (%)</i>	14 (50.0)	823 (52.1)	0.027^{d*}

Mean (SD)	89.3 (18.2)	76.1 (22.1)	
Pre-BD FEV ₁ % Predicted	N=21	N=1174	0.427d
Mean (SD)	77.1 (23.2)	72.9 (24.1)	
Post-BD FEV ₁ /FVC, non-missing n (%)	12 (42.9)	641 (40.6)	0.429 ^d
Mean (SD)	0.7 (0.1)	0.7 (0.2)	
<0.7, n (%)	2 (16.7)	299 (46.6)	0.039^{e*}
Reversibility, non-missing n (%)	11 (39.3)	616 (39.0)	0.933 ^b
Mean (SD)	7.5 (8.0)	7.9 (8.6)	
<9%, n (%)	7 (63.6)	616 (64.1)	0.973 ^e
Therapy ever			
Non-missing, n (%)	28 (100.0)	1580 (100.0)	-
Anti-IL-5/5R	0 (0.0)	790 (50.0)	
Mepolizumab	0 (0.0)	638 (80.7)	
Benralizumab	0 (0.0)	129 (16.3)	
Reslizumab	0 (0.0)	23 (2.9)	
Long-term OCS	0 (0.0)	697 (44.1)	
Baseline Therapies			
Non-missing, n (%)	28 (100.0)	1580 (100.0)	
Anti-IgE	9 (32.1)	212 (13.4)	0.004^{a*}
Anti-IL4	0 (0)	2 (0.1)	0.576 ^a
Long-term OCS	0 (0.0)	581 (36.7)	-
Macrolide	1 (3.6)	78 (4.9)	0.596 ^c
Add on to ICS/LABA			
LAMA	11 (39.3)	503 (31.8)	0.402a
LTRA	14 (50.0)	443 (28.0)	0.011^{a*}
LAMA + LTRA	7 (25.0)	237 (15.0)	0.144 ^a
Theophylline	2 (7.1)	188 (11.9)	0.765 ^c
CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; FEV ₁ : forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroid; IgE: Immunoglobulin E; ISAR: International Severe Asthma Registry; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β ₂ -agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; SD: standard deviation ^a chi-square test, ^b Wilcoxon-Mann-Whitney Test, ^c Fisher's exact, ^d t-test, ^e two-sample test-of-proportions * p-value <0.05			

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

Table 3. Comparison of ISAR eosinophilic phenotypes versus clinical cluster analyses from 3 large, well-phenotyped asthma cohorts

ISAR cohort characteristics N=1716	%	SARP cluster ³⁷ N=726	%	U-BIOPRED cluster ³⁶ N=82	%	ADEPT clusters ³⁶ N=156	%
-		1. Early onset, mild , atopic, eosinophilic (n=110)		1. Mild asthma, good lung function, early onset, low inflammation (n=25)		1. Mild , normal lung function, early onset, low inflammation (n=28)	
1. Eosinophilic (BEC ≥150), adult onset, high FeNO (>25 ppb), nasal polyps, older, worse lung function	83.8%	1. Early onset, moderate, atopic, eosinophilic (n=321) 3. Late onset, non-atopic, eosinophilic , female, obese (n=59) 4. Early onset, severe atopic reversible, obstruction, eosinophilic (n=120)	68.9%	2. Moderate, hyperresponsive, eosinophilic (n=32) 3. Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n=8)	48.8%	2. Moderate, atopic, mild reversible obstruction, hyperresponsive, eosinophilic (n=44) 3. Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n=35)	50.6%
2. Non-eosinophilic (low BEC <150), early onset, low FeNO (<25 ppb), no nasal polyps, female, eczema, better lung function	1.6%	5. late onset, long duration, severe, fixed airflow obstruction (n=116)	16.0%	4. Mixed severity, mild reversible obstruction, non-eosinophilic, neutrophilic (n=17)	20.7%	4. Mixed severity, mild reversible obstruction, non-eosinophilic, neutrophilic (n=49)	31.4%

Table adapted from Carr et al, 2018.¹⁵

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

927 ADEPT: Airways Disease Endotyping for Personalized Therapeutics; BEC: blood eosinophilic count; FeNO: fractional exhaled nitric oxide; ISAR: International
928 Severe Asthma Registry; ppb: parts per billion; SARP: Severe Asthma Research Program; U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory
929 Disease
930

Journal Pre-proof

Legends to Figures

Figure 1: Original eosinophilic and non-eosinophilic severe asthma phenotype algorithm flow chart.

Anti-IL-5: anti-interleukin 5; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; OCS: oral corticosteroid

Figure 2: Eosinophilic severe asthma phenotype distribution by country for prospective ISAR population (defined according to the original algorithm)

Figure 3: Spider plot showing the clinical and biomarker variable distribution pattern for the eosinophilic (n=1580) and non-eosinophilic (n=28) severe asthma phenotype for the ISAR prospective population. BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; IgE: immunoglobulin E; LTRA: leukotriene receptor antagonist add-on to ICS/LABA therapy.

Figure 1

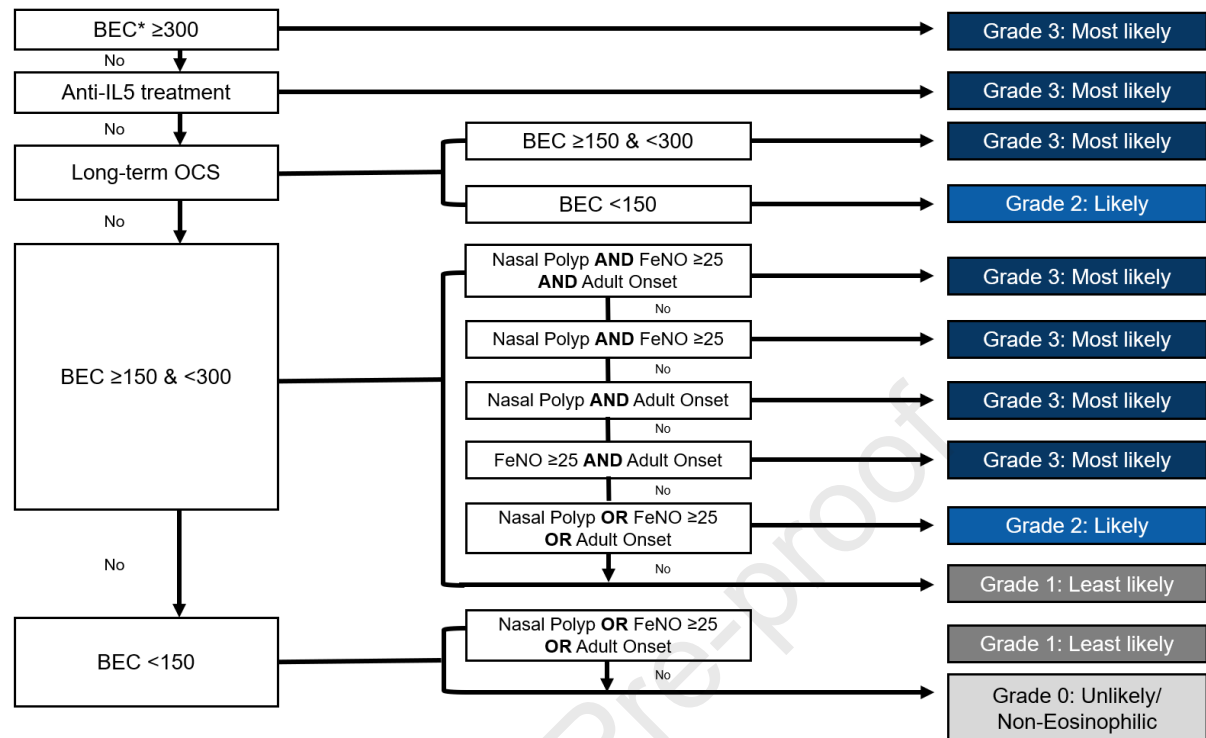


Figure 2

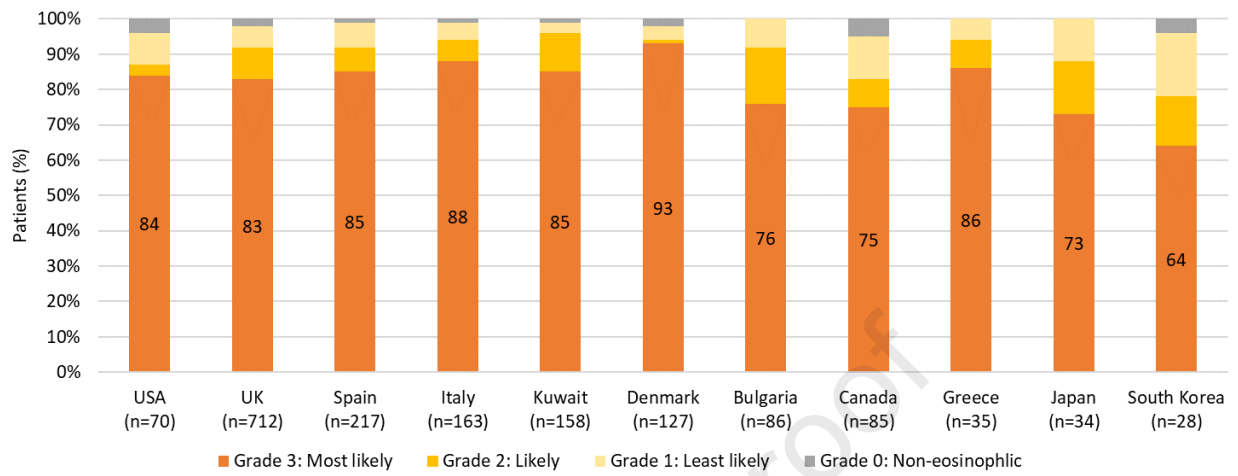


Figure 3

