

## **Clinical Research Study**

### **Characterization of T2-Low and T2-High asthma phenotypes in real-life**

**Fabio Luigi Massimo Ricciardolo<sup>1</sup>, PhD, MD, Andrea Elio Sprio<sup>1,2</sup>, PhD, Andrea Baroso<sup>1</sup>, MD, Fabio Gallo<sup>3</sup>, MSc, Elisa Riccardi<sup>1</sup>, MD, Francesca Bertolini<sup>1</sup>, PhD, Vitina Carriero<sup>1</sup>, PhD, Elisa Arrigo<sup>1</sup>, MSc, Giorgio Ciprandi<sup>4</sup>, MD.**

<sup>1</sup>Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga University Hospital, Turin, Italy

<sup>2</sup>Department of Research, ASOMI College of Sciences, Marsa, Malta

<sup>3</sup>Department of Health Science, University of Genoa, Genoa, Italy

<sup>4</sup>Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy

**Supplementary Table S1:** Output of the univariate analysis (N=503). Characteristic: variable taken into account; OR (95% CI): Odd Ratios (ExpB) with 95% Confidence Interval.

Characteristic	Univariate analysis			
	<i>Type 2 high vs Type 2 low</i>	<i>Type 2 high non-allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 high non- allergic</i>
<b>Age (years)</b>	0.960 (0.943-0.977)***	0.990 (0.970-1.012)	0.945 (0.927-0.963)###	0.952 (0.936-0.969)sss
<b>Gender (Male)</b>	1.453 (0.912-2.317)	1.679 (0.971-2.906)	1.359 (0.836-2.209)	0.809 (0.529-1.237)
<b>BMI</b>	0.926 (0.890-0.924)***	0.953 (0.909-0.999)#	0.913 (0.874-0.953)###	0.958 (0.921-0.998)§
<b>Age at asthma onset</b>	0.968 (0.955-0.981)***	0.988 (0.973-1.003)	0.957 (0.944-0.971)###	0.968 (0.956-0.980)sss
<b>Early onset</b>	2.161 (1.155-4.042)*	0.743 (0.328-1.686)	3.009 (1.592-5.686)##	4.047 (2.161-7.578)sss
<b>Asthma duration (years)</b>	1.016 (1.001-1.031)*	1.009 (0.993-1.026)	1.019 (1.003-1.035)#	1.007 (0.994-1.021)
<b>Smoking</b>				
<i>Never Smoker</i>	1.567 (0.981-2.504)	0.914 (0.529-1.580)	2.107 (1.273-3.490)##	2.305 (1.454-3.654)sss
<i>Past Smoker</i>	0.725 (0.436-1.205)	1.182 (0.657-2.218)	0.549 (0.317-0.951)#	0.464 (0.283-0.761)ss
<i>Current Smoker</i>	0.568 (0.253-1.276)	0.845 (0.330-2.168)	0.446 (0.182-1.094)	0.528 (0.222-1.256)
<b>Pack/Year 10PY (history)</b>	0.984 (0.973-0.995)**	0.996 (0.983-1.008)	0.975 (0.962-0.988)###	0.979 (0.965-0.992)ss
<b>BCM HFA dose (µg)</b>	1.000 (0.999-1.001)	1.001 (1.000-1.002)	1.000 (0.999-1.001)	0.999 (0.998-1.000)
<b>OCS (maintenance)</b>	0.755 (0.293-1.943)	1.169 (0.402-3.404)	0.572 (0.202-1.618)	0.489 (0.194-1.235)
<b>OCS (dependent)</b>	1.430 (0.722-2.830)	1.391 (0.629-3.079)	1.447 (0.714-2.933)	1.040 (0.579-1.869)
<b>LABA use</b>	0.994 (0.580-1.701)	0.964 (0.509-1.828)	1.008 (0.575-1.767)	1.045 (0.628-1.738)
<b>LAMA use</b>	0.624 (0.368-1.059)	0.996 (0.539-1.838)	0.475 (0.267-0.846)#	0.477 (0.280-0.813)ss
<b>Omalizumab use</b>	-	-	-	-
<b>Mepolizumab use</b>	5.572 (0.742-41.85)	6.521 (0.802-53.04)	5.144 (0.667-39.64)	0.789 (0.322-1.931)
<b>Nasal CS use</b>	2.749 (1.752-4.313)***	1.328 (0.783-2.253)	4.104 (2.524-6.673)###	3.090 (1.978-4.829)sss
<b>Theophylline use</b>	0.234 (0.058-0.954)*	0.376 (0.067-2.096)	0.170 (0.031-0.945)#	0.453 (0.063-3.252)
<b>Antileukotriene use</b>	2.825 (1.185-6.732)*	3.038 (1.176-7.849)#	2.729 (1.122-6.636)#	0.898 (0.507-1.591)
<b>Vitamin D (ng/mL)</b>	1.014 (0.990-1.038)	1.015 (0.987-1.043)	1.013 (0.989-1.038)	0.998 (0.978-1.019)
<b>Asthma severity grade</b>				
<i>GINA step 1</i>	0.717 (0.367-1.399)	0.810 (0.362-1.813)	0.675 (0.332-1.372)	0.833 (0.419-1.655)

<i>GINA step 2</i>	1.585 (0.725-3.461)	1.394 (0.560-3.469)	1.674 (0.749-3.737)	1.201 (0.623-2.315)
--------------------	---------------------	---------------------	---------------------	---------------------

**Supplementary Table S1:** Output of the univariate analysis (N=503). Characteristic: variable taken into account; OR (95% CI): Odd Ratios (ExpB) with 95% Confidence Interval (continued.)

Characteristic	Univariate analysis			
	<i>Type 2 high vs Type 2 low</i>	<i>Type 2 high non-allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 high non- allergic</i>
<b>Asthma severity grade</b>				
<i>GINA step 3</i>	0.899 (0.558-1.448)	0.668 (0.370-1.207)	1.018 (0.621-1.669)	1.523 (0.941-2.462)
<i>GINA step 4</i>	0.540 (0.331-0.882)*	0.822 (0.462-1.464)	0.429 (0.252-0.728)**	0.521 (0.316-0.869) <sup>§</sup>
<i>GINA step 5</i>	2.168 (1.200-3.914)*	2.023 (1.029-3.976)*	2.236 (1.217-4.107)*	1.105 (0.690-1.770)
<b>Exacerbations/years</b>	1.163 (0.975-1.388)	1.208 (0.999-1.461)	1.140 (0.951-1.367)	0.945 (0.849-1.051)
<b>FE phenotype</b>	1.811 (0.964-3.401)	1.846 (0.899-3.791)	1.795 (0.937-3.440)	0.972 (0.585-1.616)
<b>FVC (%pred.)</b>	1.008 (0.996-1.020)	1.003 (0.989-1.018)	1.010 (0.997-1.022)	1.006 (0.995-1.018)
<b>FEV<sub>1</sub> (%pred.)</b>	1.005 (0.994-1.015)	1.000 (0.988-1.012)	1.007 (0.996-1.018)	1.007 (0.997-1.017)
<b>FEV<sub>1</sub>/FVC (%)</b>	1.004 (0.987-1.022)	0.995 (0.974-1.015)	1.008 (0.990-1.027)	1.014 (0.997-1.031)
<b>-post-BD FEV<sub>1</sub> (mL)</b>	1.001 (1.000-1.003)	1.001 (0.999-1.002)	1.001 (1.000-1.003)	1.001 (0.999-1.002)
<b>-post-BD FEV<sub>1</sub> (%)</b>	1.004 (0.981-1.027)	1.007 (0.980-1.035)	1.002 (0.978-1.027)	0.996 (0.975-1.016)
<b>RV (%pred.)</b>	0.997 (0.991-1.003)	0.998 (0.991-1.002)	0.996 (0.989-1.002)	0.998 (0.992-1.004)
<b>RV/TLC (%)</b>	0.962 (0.940-0.984)**	0.986 (0.959-1.013)	0.950 (0.926-0.974)***	0.963 (0.943-0.984) <sup>§§</sup>
<b>TLC (%pred.)</b>	0.999 (0.982-1.015)	0.997 (0.977-1.016)	1.000 (0.983-1.017)	1.003 (0.988-1.019)
<b>FRC (%pred.)</b>	0.987 (0.975-1.000)	0.988 (0.973-1.003)	0.987 (0.974-1.000)	0.999 (0.987-1.011)
<b>Leukocytes (1000 cells/μL)</b>	1.044 (0.931-1.171)	1.177 (1.028-1.346)*	0.982 (0.874-1.103)	0.807 (0.720-0.906) <sup>§§§</sup>
<b>Neutrophils (1000 cells/μL)</b>	0.900 (0.769-1.053)	1.036 (0.865-1.241)	0.843 (0.714-0.996)*	0.786 (0.665-0.928) <sup>§§</sup>
<b>Eosinophils (100 cells/μL)</b>	2.363 (1.851-3.017)***	2.896 (2.109-3.975)***	2.400 (1.826-3.153)***	0.908 (0.839-0.982) <sup>§</sup>
<b>Lymphocytes (1000 cells/μL)</b>	1.759 (1.113-2.779)*	1.974 (1.115-3.496)*	1.671 (1.056-2.642)*	0.913 (0.656-1.271)
<b>Total IgE (100 IU/mL)</b>	1.188 (1.034-1.364)*	1.008 (0.904-1.124)	1.264 (1.087-1.471)**	1.259 (1.111-1.426) <sup>§§§</sup>
<b>FeNO (10 ppb)</b>	2.577 (2.016-3.294)***	3.827 (2.652-5.522)***	2.394 (1.853-3.093)***	0.962 (0.902-1.026)
<b>ACT</b>	1.067 (1.010-1.126)*	1.055 (0.988-1.127)	1.072 (1.012-1.136)*	1.015 (0.961-1.073)
<b>Activity limitation</b>	1.124 (0.906-1.394)	1.113 (0.858-1.444)	1.129 (0.901-1.414)	1.014 (0.824-1.247)

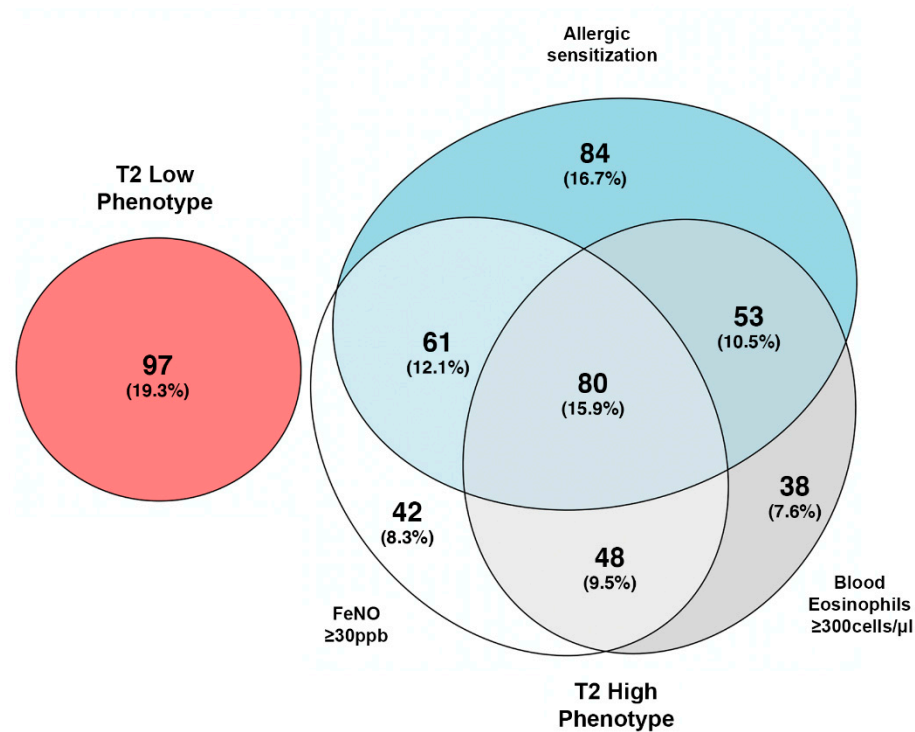
<b>SpO2 (%)</b>	1.075 (0.930-1.242)	0.919 (0.773-1.092)	1.161 (0.995-1.355)	1.260 (1.094-1.451) <sup>ss</sup>
<b>Heart Rate (bpm)</b>	1.013 (0.993-1.033)	1.001 (0.978-1.025)	1.019 (0.998-1.040)	1.017 (0.999-1.036)

**Supplementary Table 1:** Output of the univariate analysis (N=503). Characteristic: variable taken into account; OR (95% CI): Odd Ratios (ExpB) with 95% Confidence Interval (continued.)

<b>Characteristic</b>	<b>Univariate analysis</b>			
	<i>Type 2 high vs Type 2 low</i>	<i>Type 2 high non-allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 low</i>	<i>Type 2 high allergic Vs Type 2 high non- allergic</i>
<b>Comorbidities</b>				
<i>Aspirin intolerance</i>	1.006 (0.525-1.927)	1.080 (0.501-2.327)	0.973 (0.492-1.921)	0.901 (0.490-1.657)
<i>Rhinitis</i>	3.358 (2.129-5.297) <sup>***</sup>	3.092 (1.769-5.404) <sup>***</sup>	3.491 (2.156-5.652) <sup>***</sup>	1.129 (0.700-1.822)
<i>CRSsNP</i>	2.335 (1.406-3.878) <sup>***</sup>	3.528 (1.970-6.318) <sup>***</sup>	1.919 (1.113-3.250) <sup>*</sup>	0.544 (0.356-0.832) <sup>ss</sup>
<i>CRSwNP</i>	3.169 (1.481-6.778) <sup>***</sup>	4.451 (1.961-10.10) <sup>***</sup>	2.650 (1.212-5.796) <sup>***</sup>	0.595 (0.365-0.970) <sup>s</sup>
<i>Bronchiectasis</i>	1.165 (0.525-2.583)	0.858 (0.318-2.312)	1.310 (0.578-2.972)	1.527 (0.700-3.329)
<i>Emphysema</i>	0.618 (0.313-1.219)	0.948 (0.433-2.080)	0.478 (0.226-1.008)	0.504 (0.250-1.016)
<i>Pneumonia history</i>	0.788 (0.414-1.497)	0.927 (0.433-1.987)	0.726 (0.367-1.434)	0.783 (0.414-1.478)
<i>Recurrent bronchitis</i>	1.719 (0.384-7.690)	1.967 (0.373-10.36)	1.606 (0.341-7.565)	0.816 (0.268-2.487)
<i>OSAS</i>	0.325 (0.146-0.726) <sup>**</sup>	0.461 (0.172-1.238)	0.265 (0.106-0.660) <sup>**</sup>	0.574 (0.209-1.576)
<i>GERD</i>	0.485 (0.301-0.782) <sup>**</sup>	0.658 (0.372-1.164)	0.414 (0.248-0.691) <sup>**</sup>	0.629 (0.384-1.033)
<i>Obesity</i>	0.438 (0.273-0.703) <sup>**</sup>	0.532 (0.300-0.946) <sup>*</sup>	0.397 (0.240-0.659) <sup>***</sup>	0.747 (0.452-1.234)
<i>Diabetes</i>	0.554 (0.235-1.305)	0.656 (0.230-1.876)	0.508 (0.201-1.281)	0.773 (0.297-2.013)
<i>Arterial Hypertension</i>	0.393 (0.250-0.618) <sup>***</sup>	0.552 (0.322-0.947) <sup>*</sup>	0.331 (0.204-0.536) <sup>***</sup>	0.599 (0.379-0.946) <sup>s</sup>
<i>Acute myocardial infarction</i>	0.380 (0.161-0.897) <sup>*</sup>	0.665 (0.247-1.791)	0.255 (0.092-0.706) <sup>**</sup>	0.384 (0.136-1.084)
<i>Heart failure</i>	0.479 (0.086-2.652)	1.161 (0.190-7.088)	0.173 (0.016-1.933)	0.149 (0.015-1.449)
<i>Arrhythmia</i>	0.804 (0.353-1.828)	0.858 (0.318-2.312)	0.779 (0.327-1.853)	0.908 (0.396-2.080)
<i>Anxiety-depression</i>	1.049 (0.549-2.006)	1.222 (0.575-2.598)	0.973 (0.492-1.921)	0.796 (0.440-1.439)
<i>Osteoporosis</i>	1.596 (0.605-4.207)	2.491 (0.873-7.110)	1.211 (0.435-3.376)	0.486 (0.235-1.008)
<i>Chronic Pain</i>	0.386 (0.171-0.871) <sup>*</sup>	0.513 (0.188-1.401)	0.328 (0.132-0.815) <sup>#</sup>	0.640 (0.238-1.721)
<i>Arthropathy</i>	0.430 (0.211-0.875) <sup>*</sup>	0.440 (0.175-1.107)	0.426 (0.199-0.913) <sup>#</sup>	0.969 (0.407-2.308)

\* = P<.05; \*\* = P<.01; \*\*\* = P<.001 vs T2low; § = P<.05; §§ = P<.01; §§§ = P<.001 vs T2 high non-allergic; FE: frequent exacerbator (≥2 exacerbation/year); BCM HFA: beclomethasone hydrofluoroalkane; post-BD: post-bronchodilator.

### Supplementary figure legend



Supplementary Figure S1: Euler Diagrams of the type 2 biomarker positivity in the type 2 phenotypes including patients before biologic treatment.