Comparison of T2 high and T2 low asthma : Data from ISAR KOREA

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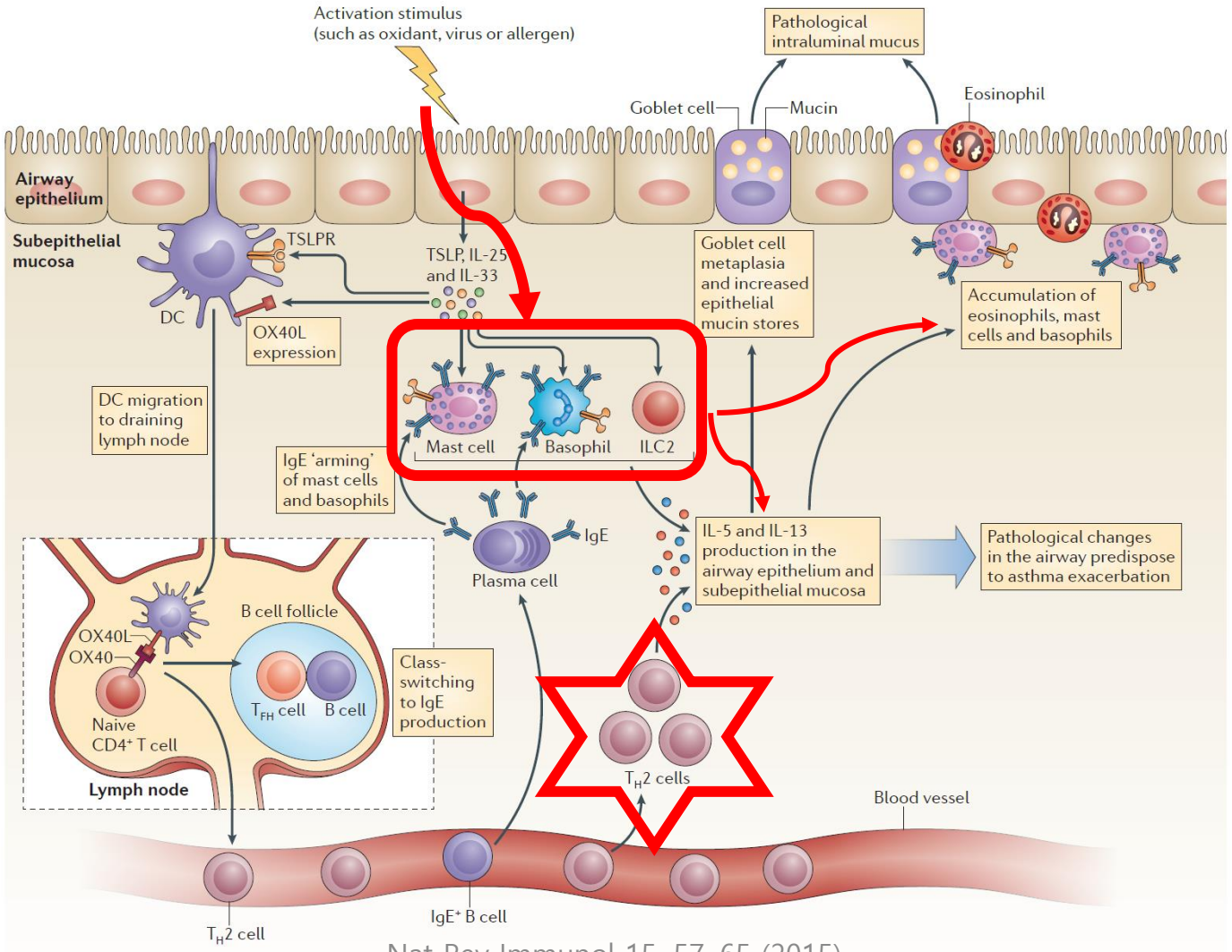
Today's Table

- T2 high vs. T2 low in asthma

- Data from ISAR KOREA

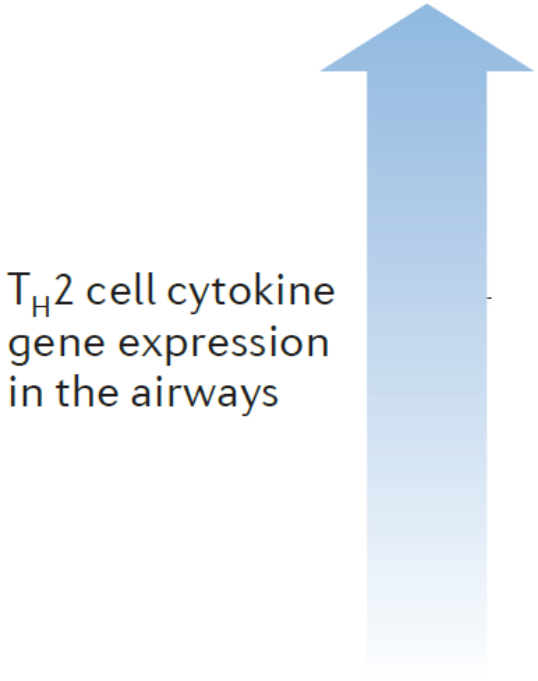
T2 high vs. T2 low in asthma

T2 inflammation in asthma



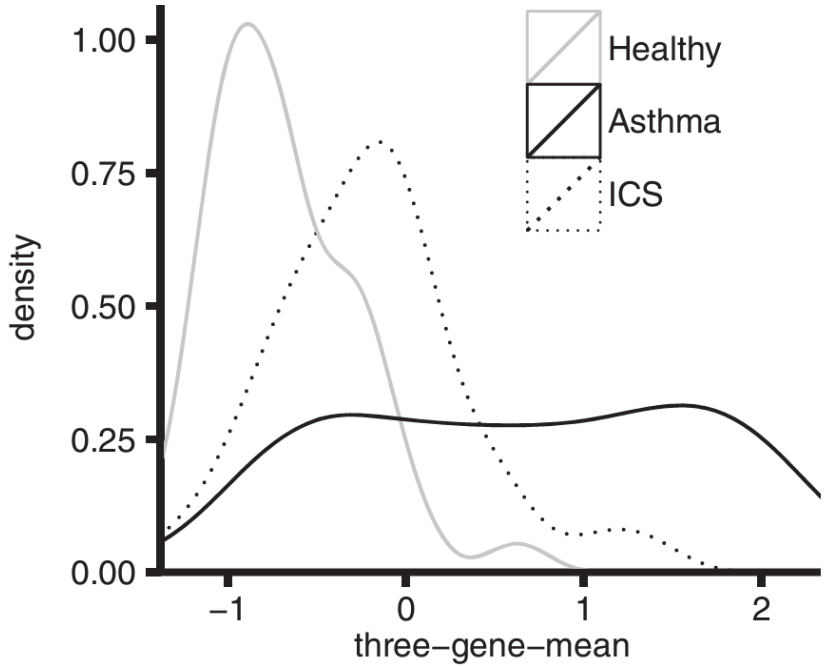
Nat Rev Immunol 15, 57–65 (2015).

T2 high vs. T2 low in asthma



Nat Rev Immunol 15, 57–65 (2015).

Continuous expression of airway T2 cell in asthma



- Gene expression for T2 cell cytokines
- Activation of epithelial cells by T2 cell cytokines

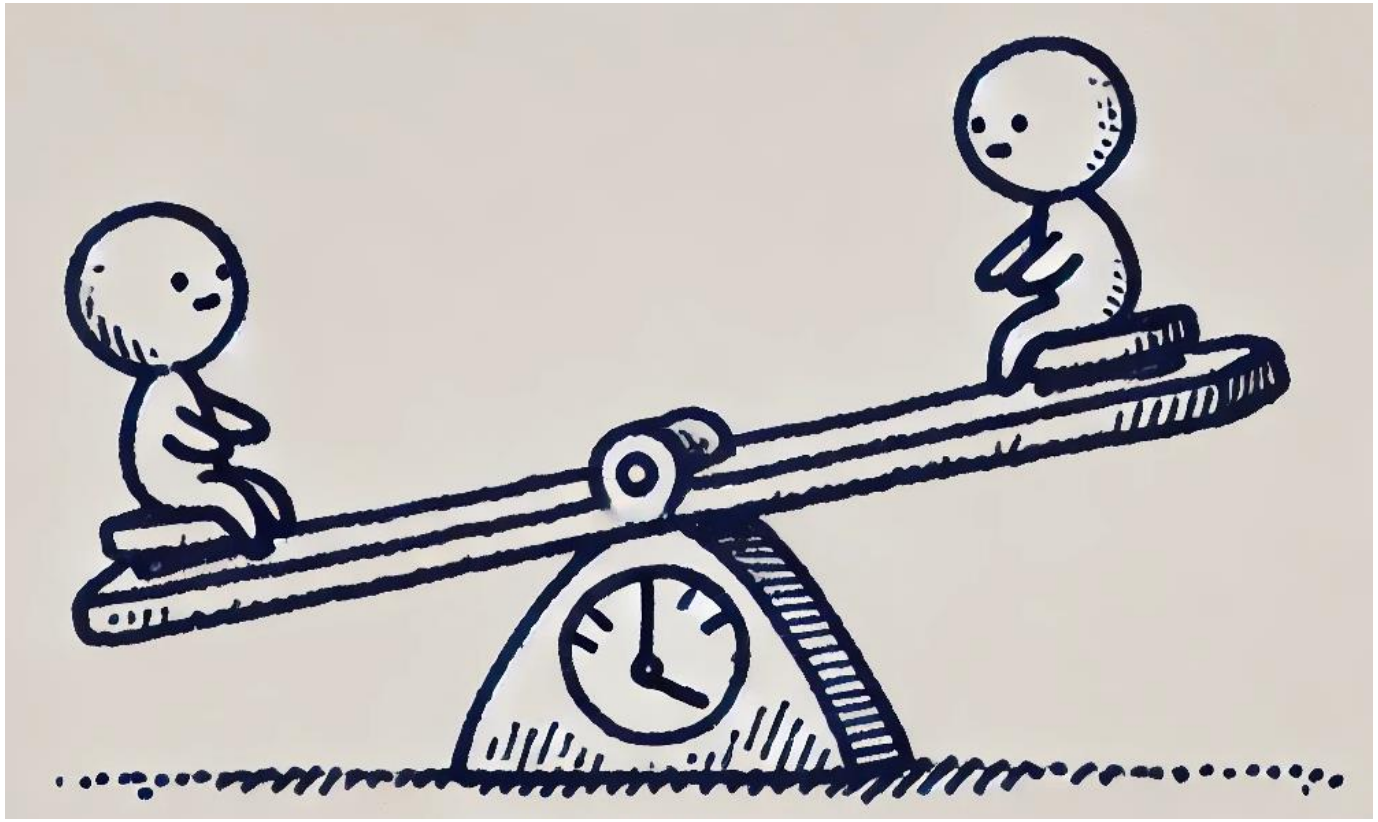
→ A continuum in the asthma airways
(rather than a bimodal distribution)

T2-high molecular expression of *periostin, CLCA1 and serpinB2*

Nat Rev Immunol 15, 57–65 (2015).
Clinical and Translational Allergy 2013, 3:24

Seasaw-like T2 inflammation in asthma?

T2 high



T2 low

What is different? T2 high vs. T2 low in asthma

TABLE I. Common features of T2-"high" vs T2-"low" asthma

Feature	T2-"high"	T2-"low"
Age of onset	Earlier onset	Later onset
Symptoms	May be significant	May be significant
Life-threatening exacerbations	More exacerbations	Fewer exacerbations
Obesity/metabolic dysfunction	May be present	Often present
Lung function	More obstruction	Less obstruction
Short-acting bronchodilator response	More responsive	Less responsive
Allergic sensitization	Present	Absent
Exhaled nitric oxide	Normal to elevated	Low to normal
Airway eosinophilia	Present	Absent
Airway neutrophilia	May be present	May be present
Medication requirements	More responsive to corticosteroids	Less responsive to corticosteroids

Allergy Clin Immunol Pract 2020;8:452-63)

Priority research questions for T2 low asthma

Allergy Clin Immunol Pract 2020;8:452-63)

Data from ISAR KOREA

Question from ISAR KOREA T2 high vs low

- Q1. BEC → Transient or Consistent?
- Q2. Demographic feature: Age, Sex, Smoking, and BMI
- Q3. Comorbid condition: Atopy, Eczema, AR, CRS, nasal polyp
- Q4. Baseline Asthma feature: (onset, day/activity/night/reliever/FEV1 180ml/Asthma control/future plan)
- Q5. Prospective event: lung functions, AE

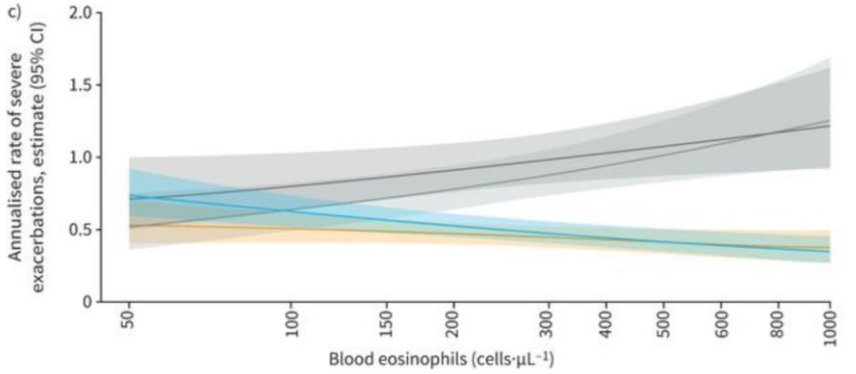
Q1. Blood Eosinophil Count → Transient or Consistent?

- Definition of 'T2 High and Low' ?

→Higher is better for prediction

→Best cut-off value?

  - BEC: 150? 200? 300? 500? Cells/uL
  - FENO: 25? 45? 50? Ppb



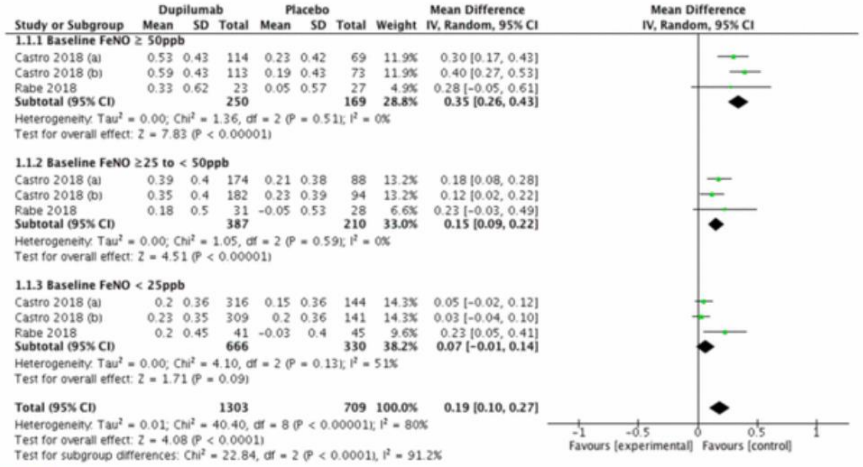
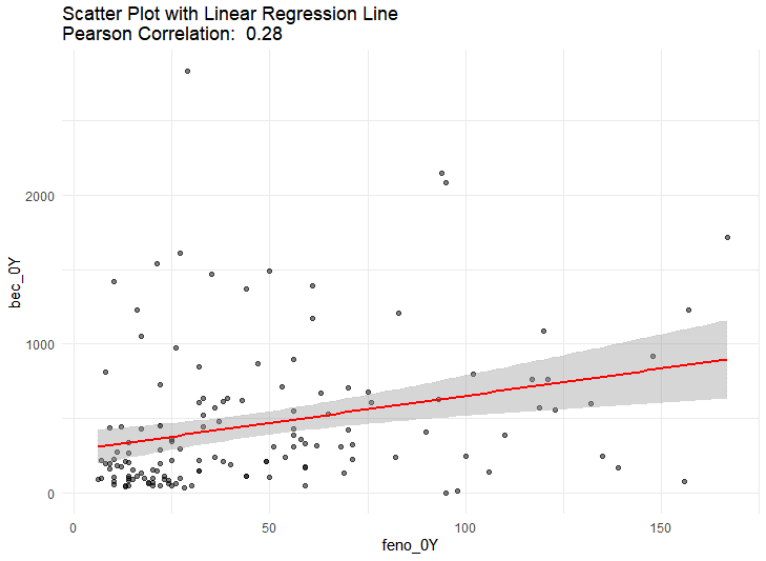


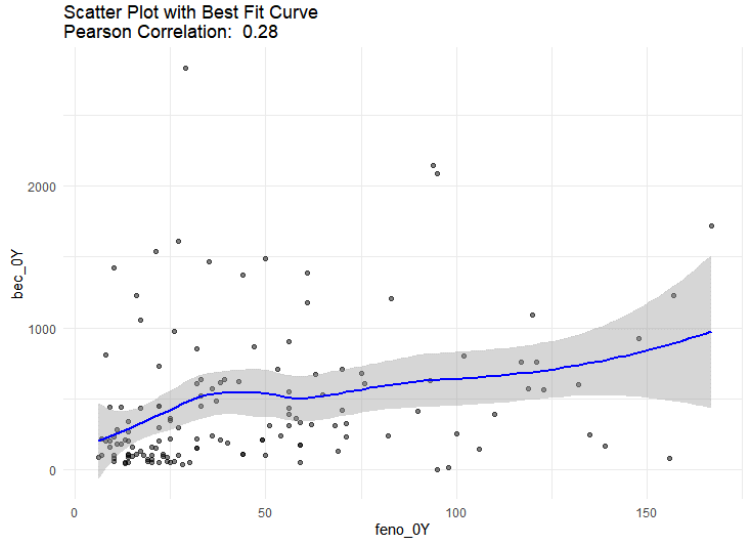
Figure 1. Effects of FEV1 (change from baseline) with 95% CIs on dupilumab and placebo by baseline FeNO level FEV1: forced expiratory volume in one second; FeNO: fraction of exhaled nitric oxide.

N Engl J Med 2018;378:2486-2496, N Engl J Med 2014;371:1198-1207, European Respiratory Journal 2022 59: 2102577
J Allergy Clin Immunol Pract. 2023 Apr;11(4):1213-1220.e2., Journal of Asthma, 57(1), 79–81 2020, eClinicalMedicine 2022;50: 101533

Q1. Blood Eosinophil Count → Transient or Consistent?

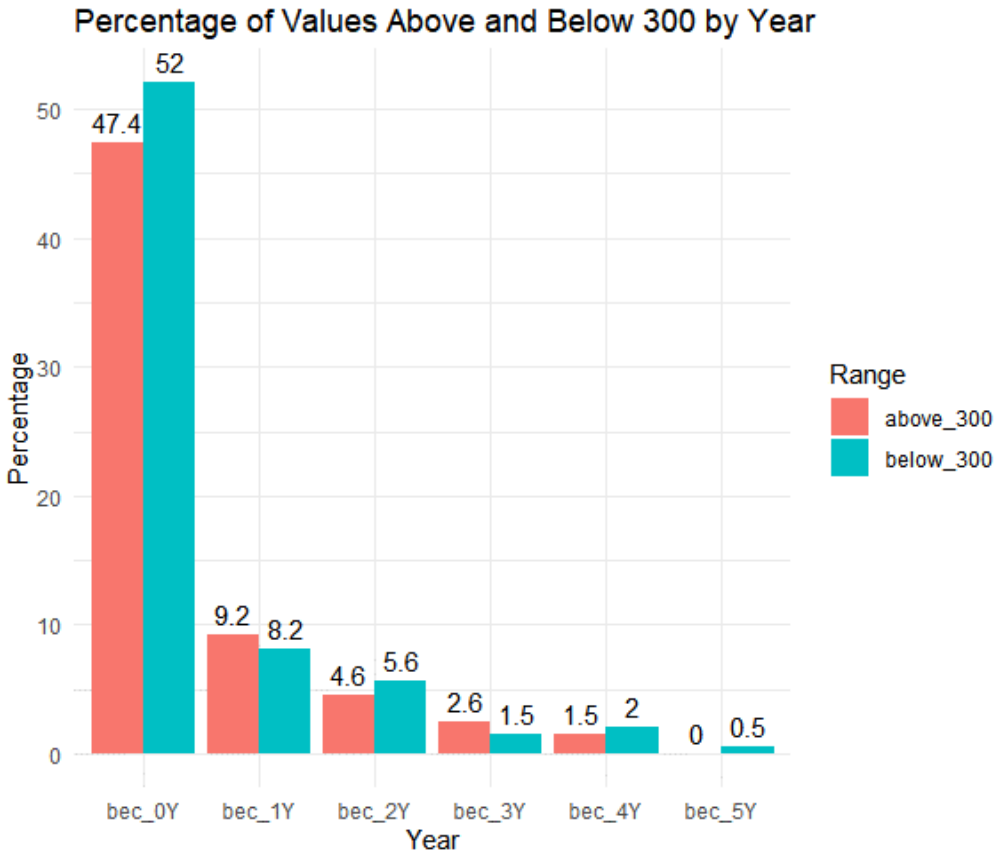
- Correlation of BEC and FENO in ISAR KOREA
  - Weak linear correlation (r=0.28)





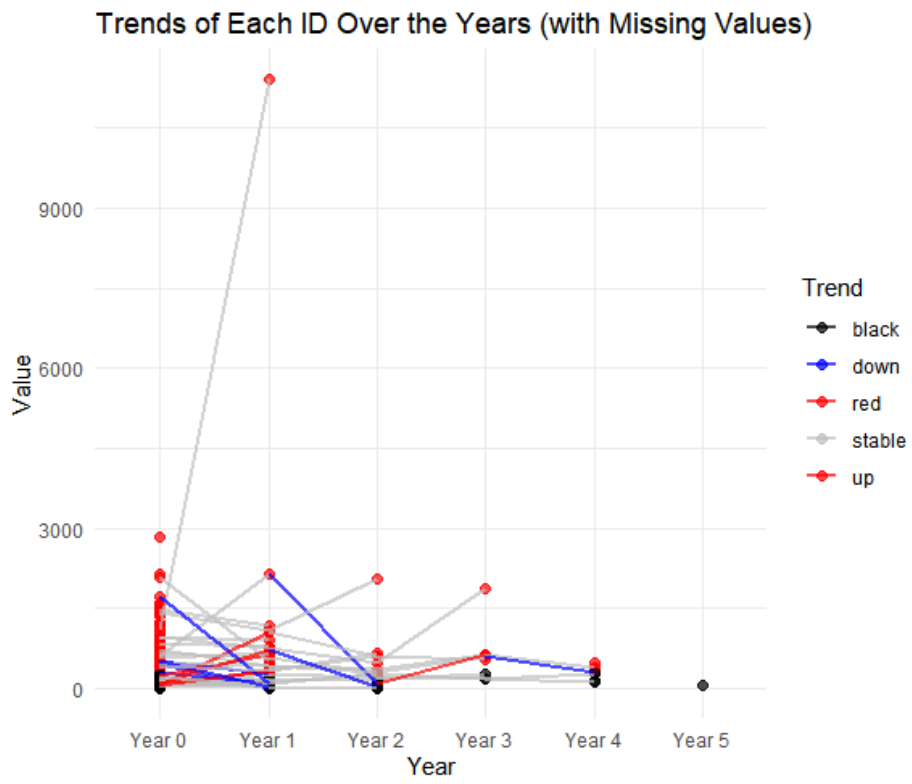
Q1. Blood Eosinophil Count → Transient or Consistent?

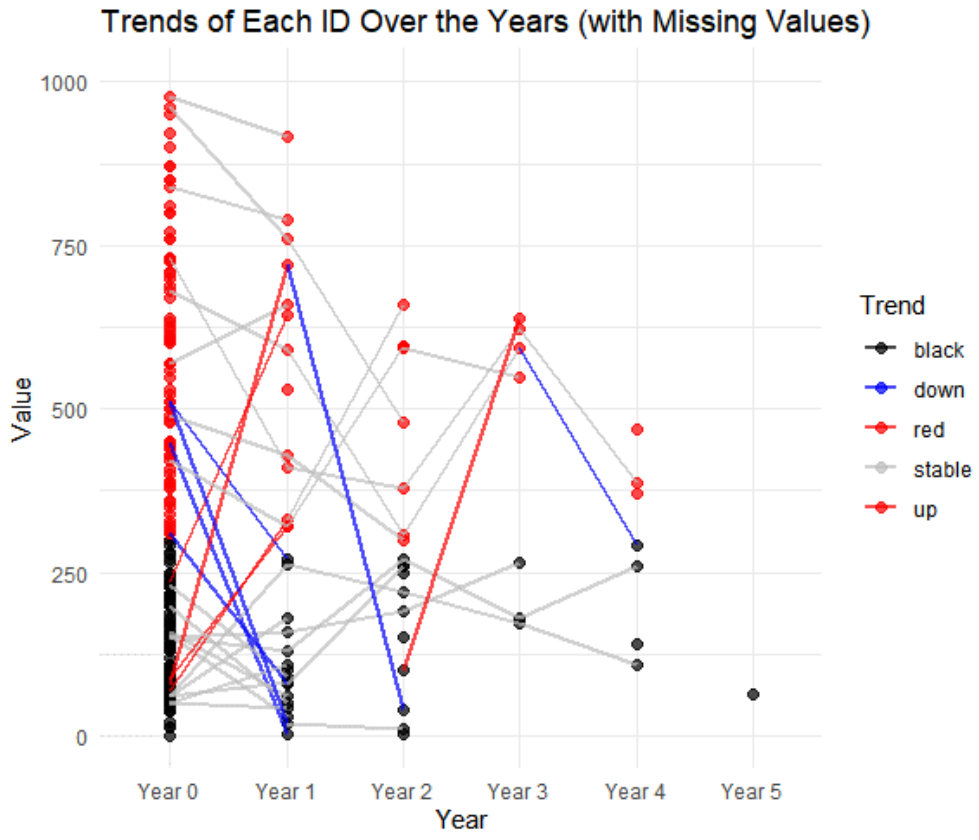
- T2 high vs. T2 Low in ISAR Korea
  - Relatively higher % of T2 low
    - Baseline: 52.3%
    - 1st year: 47.1%
    - 2nd year: 54.9%
    - 3rd year: 36.6%
    - 4th year: 57.1%



Q1. Blood Eosinophil Count → Transient or Consistent?

- Trends





Q1. Blood Eosinophil Count → Transient or Consistent?

Year	Trend	n (%)
0Y	Down	5 (14.7)
0Y	Stable	24 (70.6)
0Y	Up	5 (14.7)
1Y	Down	2 (13.3)
1Y	Stable	13 (86.7)
2Y	Stable	7 (87.5)
2Y	Up	1 (12.5)
3Y	Down	1 (25.0)
3Y	Stable	3 (75.0)

Q1. Blood Eosinophil Count → Transient or Consistent?

- Relatively consistent → Using baseline T2 marker

- Weak correlation between BEC and FENO
  - Not proper using single marker → BEC and/or FENO
  - BEC 150/300 cells/uL
  - FENO 25/45ppb

- 243명중 20명 제외하고 분석 (BEC/FENO 데이터 없는 그룹)

Q2. Demographic feature: Age, Sex, Smoking, and BMI

	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
Male Sex	50 (43.9)	40 (37.0)	0.37	61 (43.3)	29 (35.8)	0.34	63 (43.4)	27 (35.1)	0.29
Age	55.8±13.3	58.5±16.5	0.18	55.9±13.7	59.0±16.8	0.16	56.2±13.8	58.6±17.0	0.28
Height	1.6±0.2	1.6±0.1	0.72	1.6±0.2	1.6±0.1	0.52	1.6±0.2	1.6±0.1	0.66
Weight	66.0±12.7	64.2±12.2	0.30	65.5±12.4	64.6±12.7	0.61	65.6±12.5	64.4±12.5	0.50
BMI	25.2±4.6	24.7±4.1	0.45	25.1±4.4	24.7±4.3	0.57	25.1±4.4	24.7±4.2	0.57
BSA	1.7±0.2	1.7±0.2	0.55	1.7±0.2	1.7±0.2	0.92	1.7±0.2	1.7±0.2	0.76
Current Smoker	9 (7.9)	14 (13.0)		13 (9.2)	10 (12.3)		13 (9.0)	10 (13.0)	
Ex-smoker	34 (29.8)	24 (22.2)	0.27	40 (28.4)	18 (22.2)	0.52	43 (29.7)	15 (19.5)	0.22
Never smoker	71 (62.3)	70 (64.8)		88 (62.4)	53 (65.4)		89 (61.4)	52 (67.5)	
Pack-Year	17.1±12.6	14.0±14.4	0.30	17.0±12.7	13.1±4.7	0.22			0.16

Q3. Comorbid condition: Atopy, Eczema, AR, CRS, nasal polyp

	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
Current	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
Allergic Rhinitis	**71 (61.7)**	49 (45.8)	0.04	79 (56.0)	41 (50.6)	0.69	80 (55.2)	40 (51.9)	0.88
Chronic Rhinosinusitis	29 (25.9)	16 (15.0)	0.13	32 (23.2)	13 (16.0)	0.43	32 (22.5)	13 (16.9)	0.57
Eczema	5 (4.5)	3 (2.9)	0.31	7 (5.1)	1 (1.3)	0.34	7 (5.0)	1 (1.4)	0.38
Nasal polyp	13 (11.5)	5 (4.7)	0.16	14 (10.1)	4 (4.9)	0.41	14 (9.8)	4 (5.2)	0.49
Atopy	**71 (61.7)**	50 (46.3)	0.03	80 (56.3)	41 (50.6)	0.49	81 (55.5)	40 (51.9)	0.72

Q4. Baseline Asthma feature: asthma feature

	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
BEC	677.3±477.8	129.4±71.5	<0.01	590.5±461.7	79.4±34.8	<0.01	590.5±461.7	79.4±34.8	<0.01
FENO	65.1±38.5	19.4±9.8	<0.01	53.4±38.5	27.3±26.7	<0.01	52.8±37.9	26.7±27.4	<0.01
Asthma Onset Age	43.2±16.0	43.1±21.6	0.96	43.2±17.4	43.0±21.3	0.96	43.2±17.4	43.1±21.4	0.98
GINA 5	63 (54.8)	47 (43.5)	0.12	**78 (54.9)**	32 (39.5)	0.04	**81 (55.5)**	29 (37.7)	0.02
GINA 4	52 (45.2)	61 (56.5)	0.12	64 (45.1)	**49 (60.5)**	0.04	65 (44.5)	**48 (62.3)**	0.02
GINA 4 - Frequent AE	18 (34.6)	19 (35.8)	1.00	21 (32.3)	16 (40.0)	0.56	22 (33.3)	15 (38.5)	0.75
GINA 4 – severe Sx	45 (86.5)	40 (75.5)	0.23	**57 (87.7)**	28 (70.0)	<0.05	57 (86.4)	28 (71.8)	0.11

1. GINA Step 5
2. Uncontrolled on GINA Step 4
   (a) Uncontrolled defined as: Has frequent severe asthma exacerbations requiring OCS
   (b) Uncontrolled defined as: Has severe asthma symptoms

Q4. Baseline Asthma feature: Asthma control status

	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
Day Sx	65 (61.3)	51 (54.8)	0.56	78 (60.0)	38 (55.1)	0.60	82 (61.2)	34 (52.3)	0.30
Activity	52 (49.1)	32 (34.4)	0.05	57 (43.8)	27 (39.1)	0.62	61 (45.5)	23 (35.4)	0.23
Night Sx	38 (35.8)	20 (21.7)	0.04	41 (31.8)	17 (24.6)	0.37	42 (31.6)	16 (24.6)	0.40
Reliver	48 (45.3)	30 (32.3)	0.08	55 (42.3)	23 (33.3)	0.28	57 (42.5)	21 (32.3)	0.22
FEV1 180ml	83 (79.8)	72 (80.0)	1.00	100 (79.4)	55 (80.9)	0.95	104 (80.0)	51 (79.7)	1.00

In the past 4 weeks, has the patient had Day time symptoms? (more than twice per week)	Day Sx
In the past 4, has the patient had Any activity limitation?	Activity
In the past 4 weeks, has the patient had: Any nocturnal symptoms/awakening?	Night Sx
In the past 4 weeks, has the patient had: Reliever medication use? (more than twice per week)	Reliver
In the past 4 weeks, has the patient had: Lung function (PEF or FEV1)< 80% of predicted or personal best(if known)?	FEV1 180ml

Q4. Baseline Asthma feature: Asthma control

	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
Asthma Control status in last year									
Well	8 (7.5)	8 (8.6)		10 (7.7)	6 (8.7)		10 (7.5)	6 (9.2)	
Partial	40 (37.7)	**49 (52.7)**	0.07	57 (43.8)	32 (46.4)	0.89	57 (42.5)	32 (49.2)	0.53
Not	**58 (54.7)**	36 (38.7)		63 (48.5)	31 (44.9)		67 (50.0)	27 (41.5)	
Medication Switch to biologics	3 (15.8)	0 (0.0)	0.22	3 (13.6)	0 (0.0)	0.93	3 (13.6)	0 (0.0)	0.93
d/t Poor Adherence	67 (58.3)	64 (59.8)	0.22	81 (57.0)	50 (62.5)	0.64	85 (58.2)	46 (60.5)	0.82

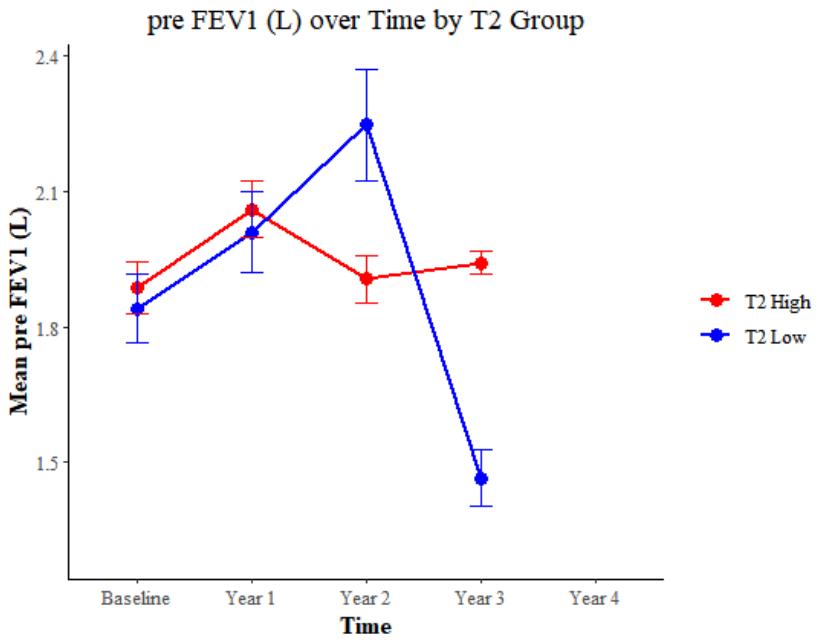
Q4. Baseline Asthma feature: current management plan

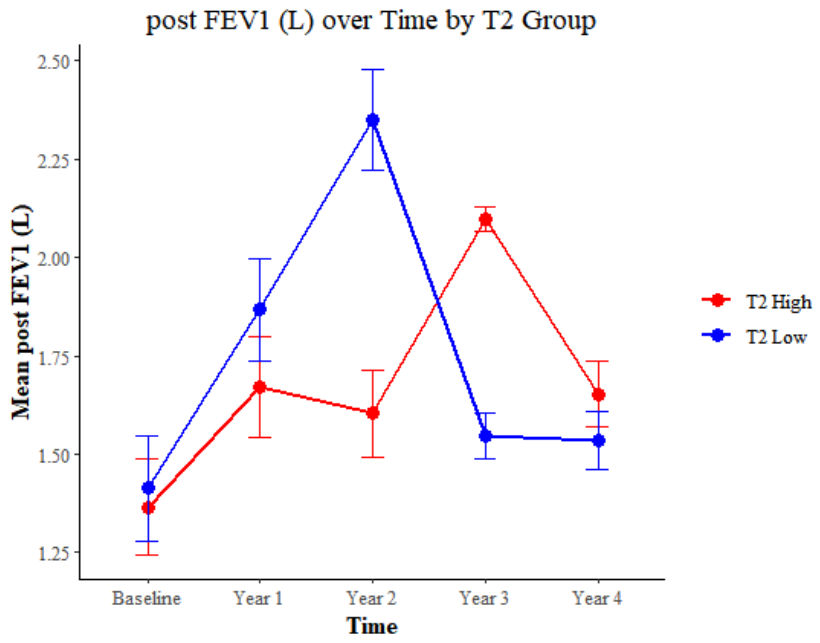
	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
Optimization	106 (92.2)	104 (96.3)	0.30	130 (91.5)	80 (98.8)	0.10	134 (91.8)	76 (98.7)	0.07
Biologics	19 (16.5)	10 (9.3)	0.16	23 (16.2)	6 (7.4)	0.06	23 (15.8)	6 (7.8)	0.14
OCS	8 (7.0)	2 (1.9)	0.13	7 (4.9)	3 (3.7)	0.93	7 (4.8)	3 (3.9)	1.00
Steroid sparing	4 (3.5)	1 (0.9)	0.40	4 (2.8)	1 (1.2)	0.77	4 (2.7)	1 (1.3)	0.83
Trial	1 (0.9)	1 (0.9)	1.00	2 (1.4)	0 (0.0)	0.74	2 (1.4)	0 (0.0)	0.78

Q4. Baseline Asthma feature: Previous AE history

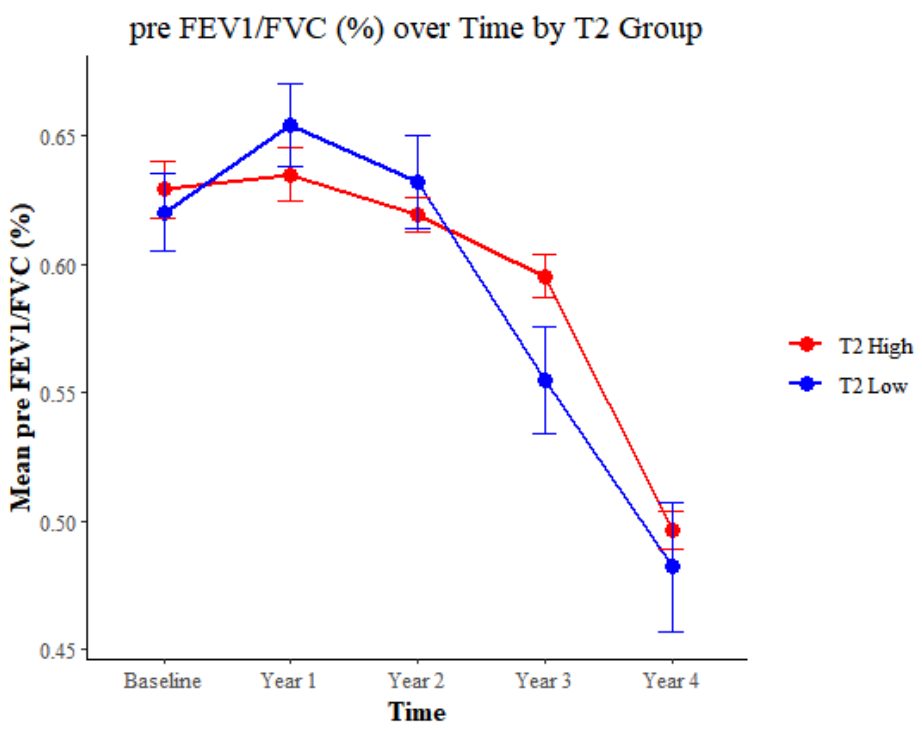
	BEC 300 / FENO 45			BEC 150 /FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
MV	0.1±0.6	0.1±0.3	0.23	0.1±0.5	0.1±0.4	0.75	0.1±0.5	0.1±0.4	0.64
ER visit	0.5±1.6	0.3±1.2	0.57	0.4±1.5	0.4±1.4	0.98	0.4±1.5	0.4±1.4	0.94
Admission	0.5±1.2	0.3±1.0	0.12	0.4±1.1	0.3±1.1	0.53	0.4±1.1	0.4±1.1	0.67

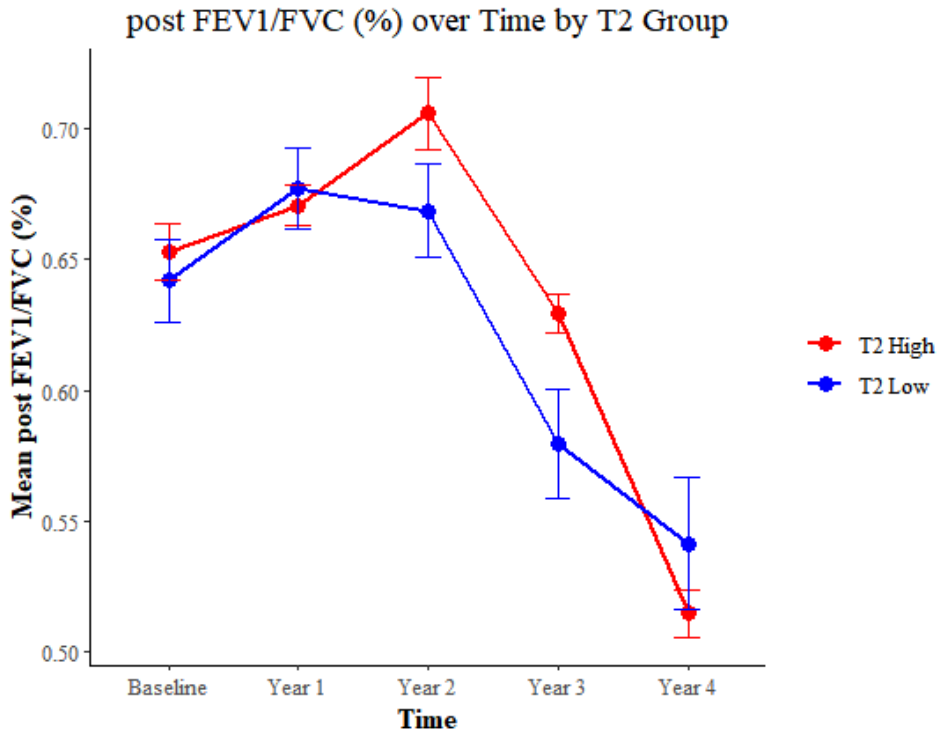
Q5. Prospective event: lung functions – FEV1





Q5. Prospective event: lung functions – FEV1/FVC

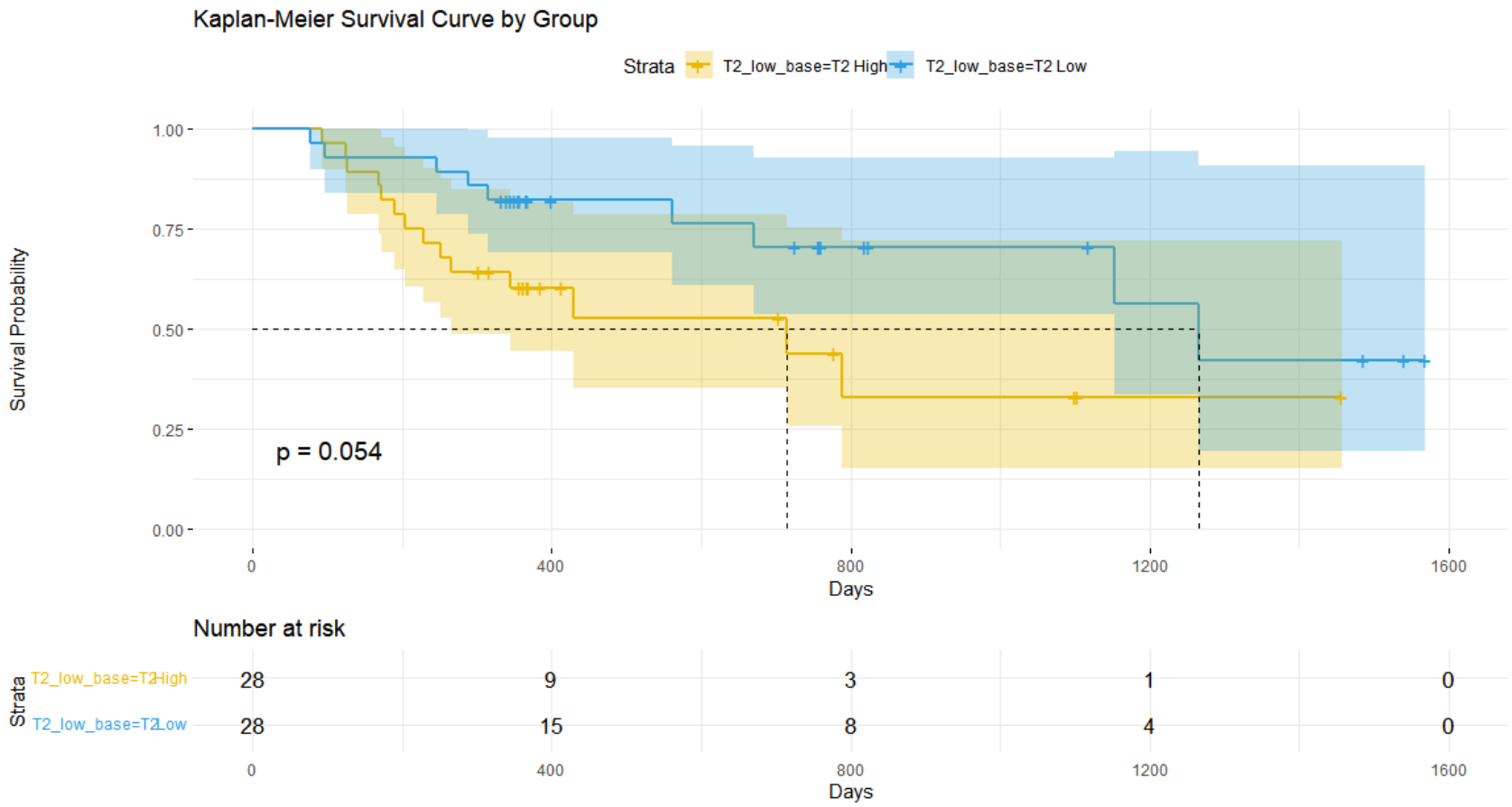




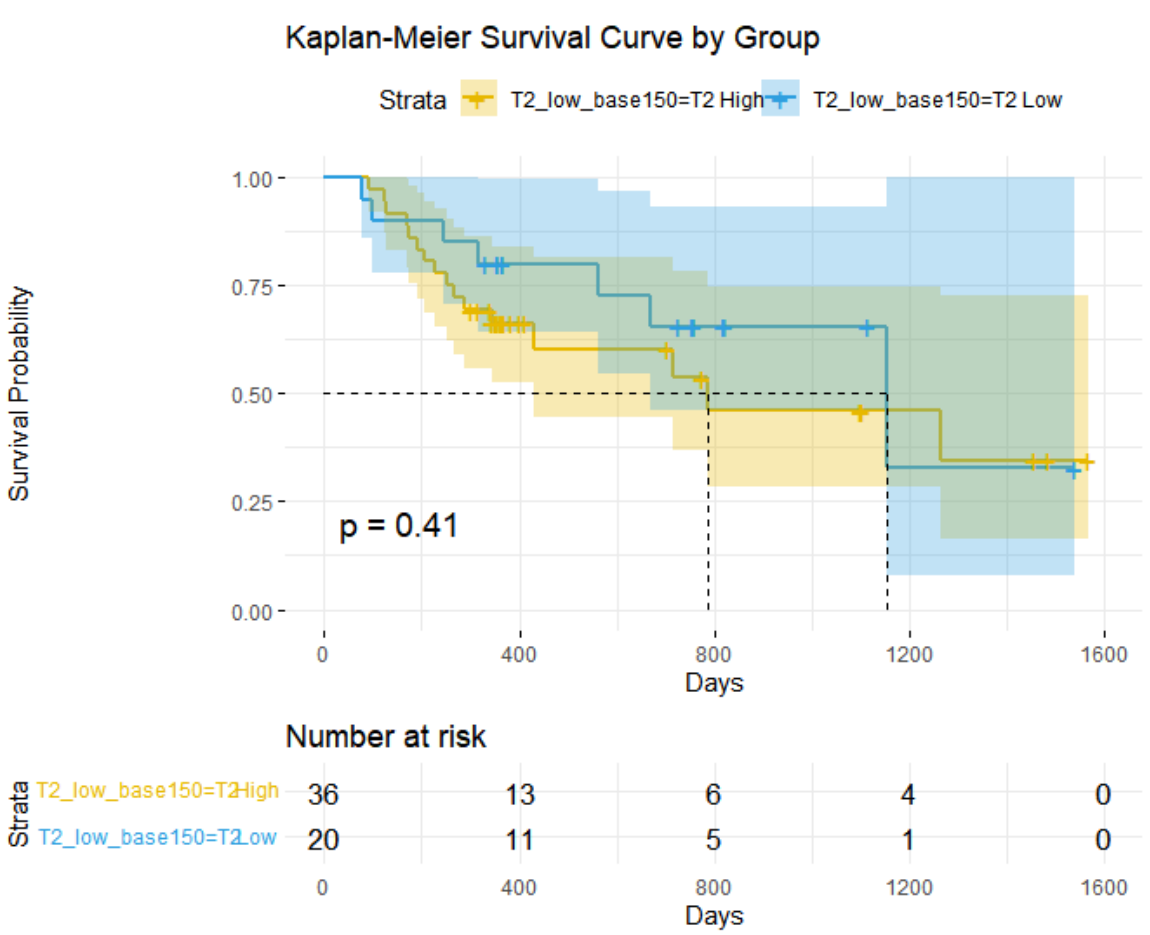
Q5. Prospective event: AE

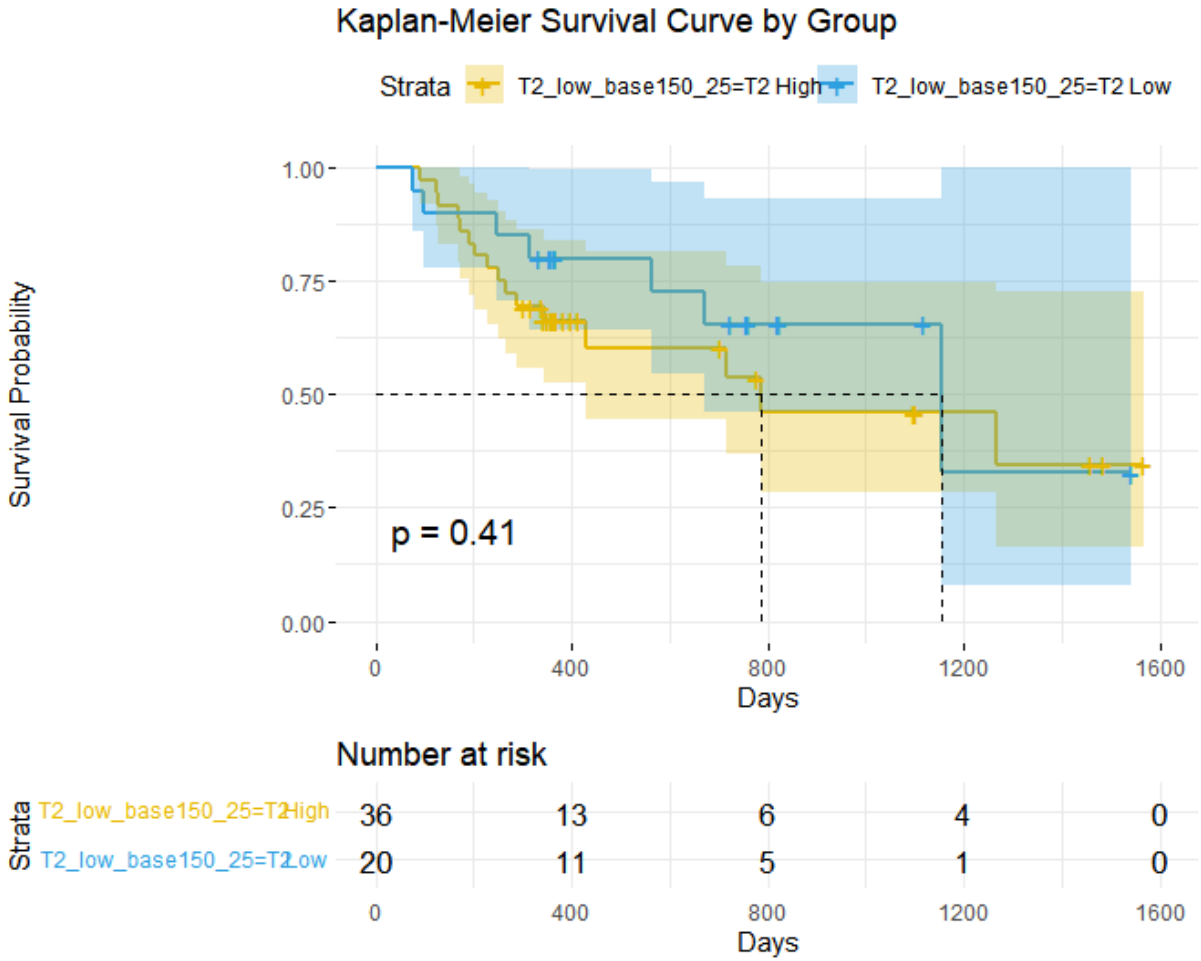
	BEC 300 / FENO 45			BEC 150 / FENO 45			BEC 150 / FENO 25		
	T2 high (n=115)	T2 low (n=108)	P-value	T2 high (n=142)	T2 low (n=81)	P-value	T2 high (n=146)	T2 low (n=77)	P-value
AE during f/u	14 (50.0)	9 (32.1)	0.28	16 (44.4)	7 (35.0)	0.69	16 (44.4)	7 (35.0)	0.69
AE frequency	1.0±1.6	0.6±1.1	0.29	0.9±1.4	0.7±1.3	0.68	0.9±1.4	0.7±1.3	0.68
1st year	11 (39.3)	5 (17.9)	0.14	12 933.3)	4 (20.0)	0.45	12 (33.3)	4 (20.0)	0.45
2nd year	7 (53.8)	4 (25.0)	0.23	7 (43.8)	4 (30.8)	0.74	7 (43.8)	4 (30.8)	0.74
3rd year	5 (62.5)	2 (22.2)	0.23	5 (45.5)	2 (33.3)	1.00	5 (45.5)	4 (30.8)	1.00
4th year	3 (75.0)	3 (50.0)	0.90	4 957.1)	2 (66.7)	1.00	4 (57.1)	2 (33.3)	1.00
Steroid Exposure during f/u	166.8±418.0	110.7±221.4	0.53	143.1±373.5	131.0±251.4	0.90	143.1±373.5	131.0±251.4	0.90

Q5. Prospective event: time to first AE



Q5. Prospective event: time to first AE





Q5. Prospective event: time to first AE

- Crude OR (95% CI) vs. T2 high
  - T2 Low (BEC 300 / FENO 45) : 0.47 (0.16-1.40)
  - T2 Low (BEC 150 / FENO 45) : 0.67 (0.22-2.08)
  - T2 Low (BEC 150 / FENO 25) : 0.67 (0.22-2.08)

- Adjusted OR (95% CI) vs. T2 high
  - T2 Low (BEC 300 / FENO 45) : 0.60 (0.18-2.03)
  - T2 Low (BEC 150 / FENO 45) : 0.70 (0.20-2.43)
  - T2 Low (BEC 150 / FENO 25) : 0.70 (0.20-2.43)

  - Variable: age, sex, BMI, smoking status, AR, atopy

Summary

Summary

- Definition of T2 high & T2 low : still debating
- Blood Eosinophil: relatively consistent? → maybe consistent in most cases
- Weak correlation of BEC and FENO
- High proportion of T2 Low Asthma in ISAR Korea (35~48%)
- Not obese actually
- Smoking
- Low steroid sparing agent

Summary

- BEC 300/ FENO 45 → baseline atopy, AR, night Sx.
- BEC 150 or FENO 25 → baseline status of GINA 5 high (T2 high), GINA 4 high (T2 low)
- T2 Plan : low level of steroid sparing → not effective? Not treated?
- AE in T2 high vs. T2 low
  - Crude / Adjusted OR for AE risks : not significantly different
  - Time to first: higher in T2 high
  - Future : slightly higher in T2 high (BEC 300 / FENO 45) : or higher cut off?

Limitation

- More patients and more data: BEC, FENO, PFT, and AE

T2 low asthma feature and treatment

- Obesity/Weight loss
- Smoking cessation
- ICS/LABA
  - Baseline therapy
- **LAMA**
  - **Always?**
- **Macrolide**
  - **AZISAST etc → not for T2 low study**
- **Upper immune cascade**
  - **e.g.: anti-TSLP**

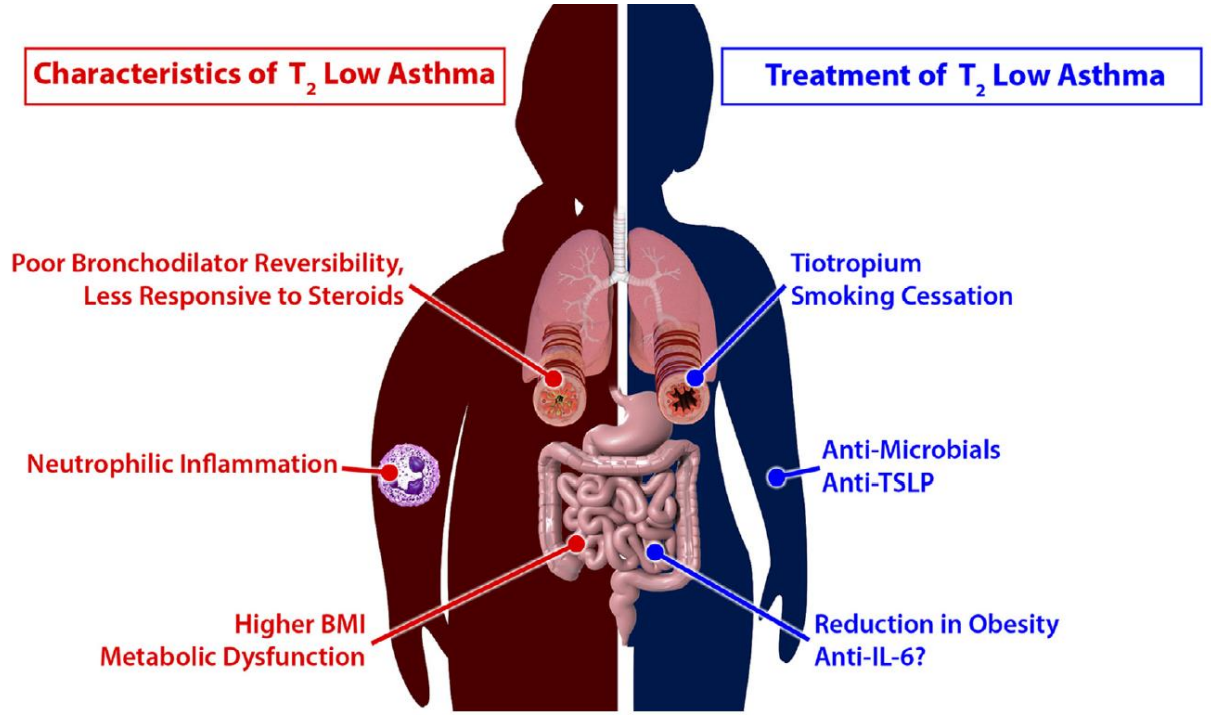


Figure 1. Clinical characteristics and focused interventions for T2 low asthma.

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Thank you