Development and Validation of the Risk of Exacerbation in Severe Asthma (RESA) Model

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Aim and Methods

Aim

To develop and validate the Risk of Exacerbation in Severe Asthma (RESA) model for estimating the 12-month risk of ≥1 and ≥2 severe exacerbations in adults with severe asthma.

Methods

Data Processing

ISAR (2015-2022) & NOVELTY (2016-2023)
(N = 8,371 + 1,534)

- Aged ≥18 years at enrolment
- Severe asthma (with or without biologic use)

Predictor Selection

- Initial long list of predictors
- Expert opinion
- Machine learning
- Bayesian network

Predictors

Sociodemographic

- Age, sex

Clinical

- Exacerbation history
- Asthma control
- FEV1 %, FEV1/FVC
- BEC, FeNO
- Chronic rhinosinusitis (w/wo nasal polyps)

Medication

- Long-term OCS
- Macrolide

Final Model

Prediction endpoint: 365-day risk & rate of severe asthma exacerbation (SAE)

- Zero-inflated negative binomial model
- Country-setting random effects
- Biologic drop-in effects adjustment
- Internal-external cross-validation across settings.

ISAR: International Severe Asthma Registry; NOVELTY: NOVEL observational longiTudinal studY; RESA: Risk of Exacerbation in Severe Asthma; ZINB: zero-inflated negative binomial; SA: severe asthma.

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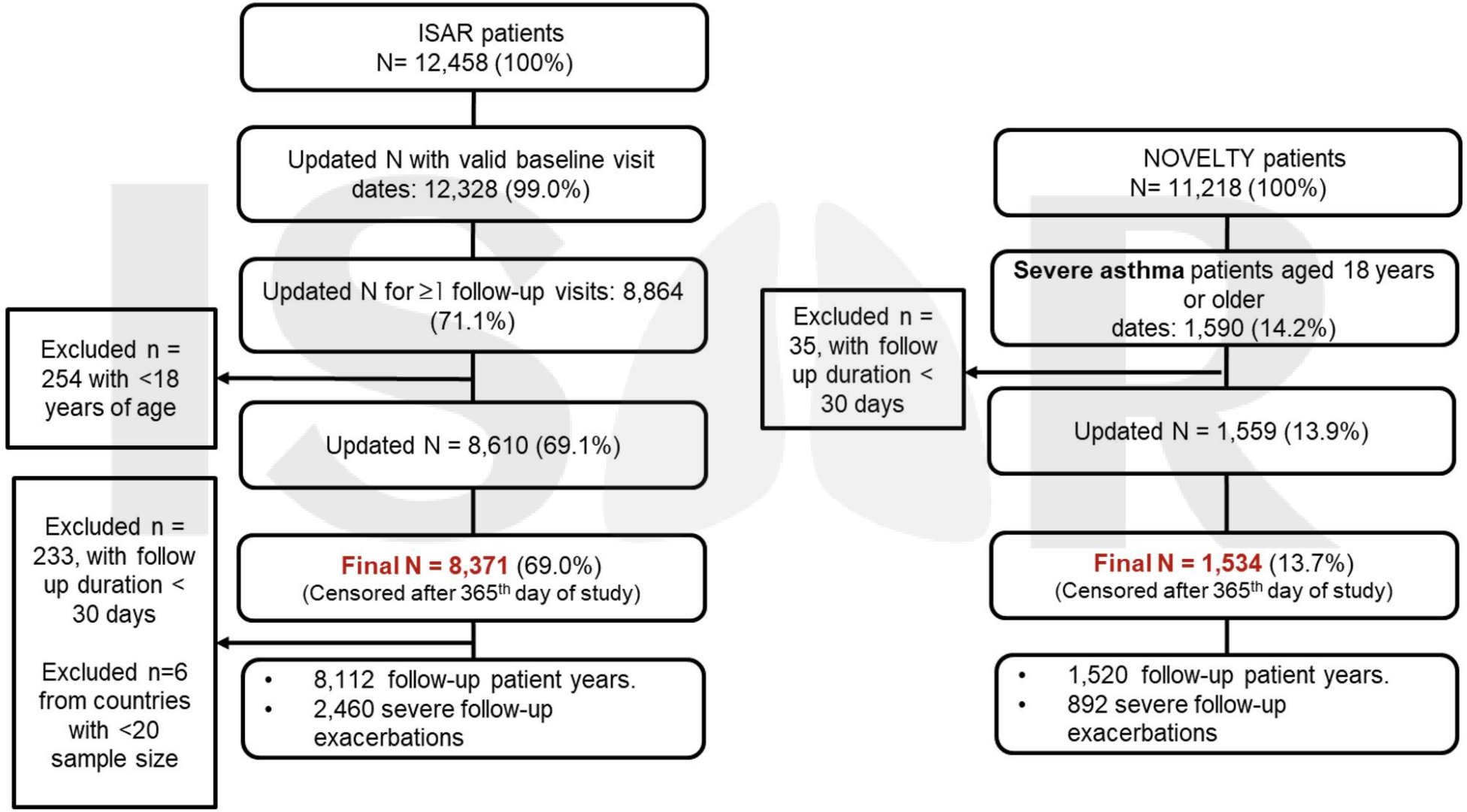
Patient Selection Flowcharts



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RESA: A Web App for individualized prediction of Risk of Exacerbation in Severe Asthma (Dr WenJia Chen, Dr Mohsen Sadatsafavi)

- **How RESA Generates Individualized Risk Estimates**

resascore.com

Input | Output

Do you know the average annual risk of severe asthma exacerbations in your setting (e.g., clinic, hospital, region)? With this information, RESA can better help you predict the risk of future exacerbations.

Yes, I know the average annual risk in my setting.

CALCULATE

RESET

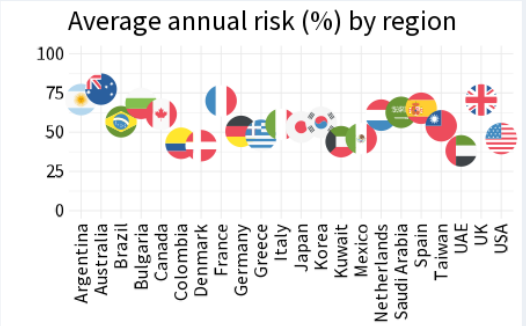
Out of 100 typical patients aged 18 years or older with severe asthma in your setting, how many will experience severe exacerbations in the next 365 days?

The value must be between 1 and 99.

4

This implies that the average annual risk in your setting is **4%.**

For your reference, the figure on the right provides the average annual risk values in other regions based on the ISAR and NOVELTY databases.



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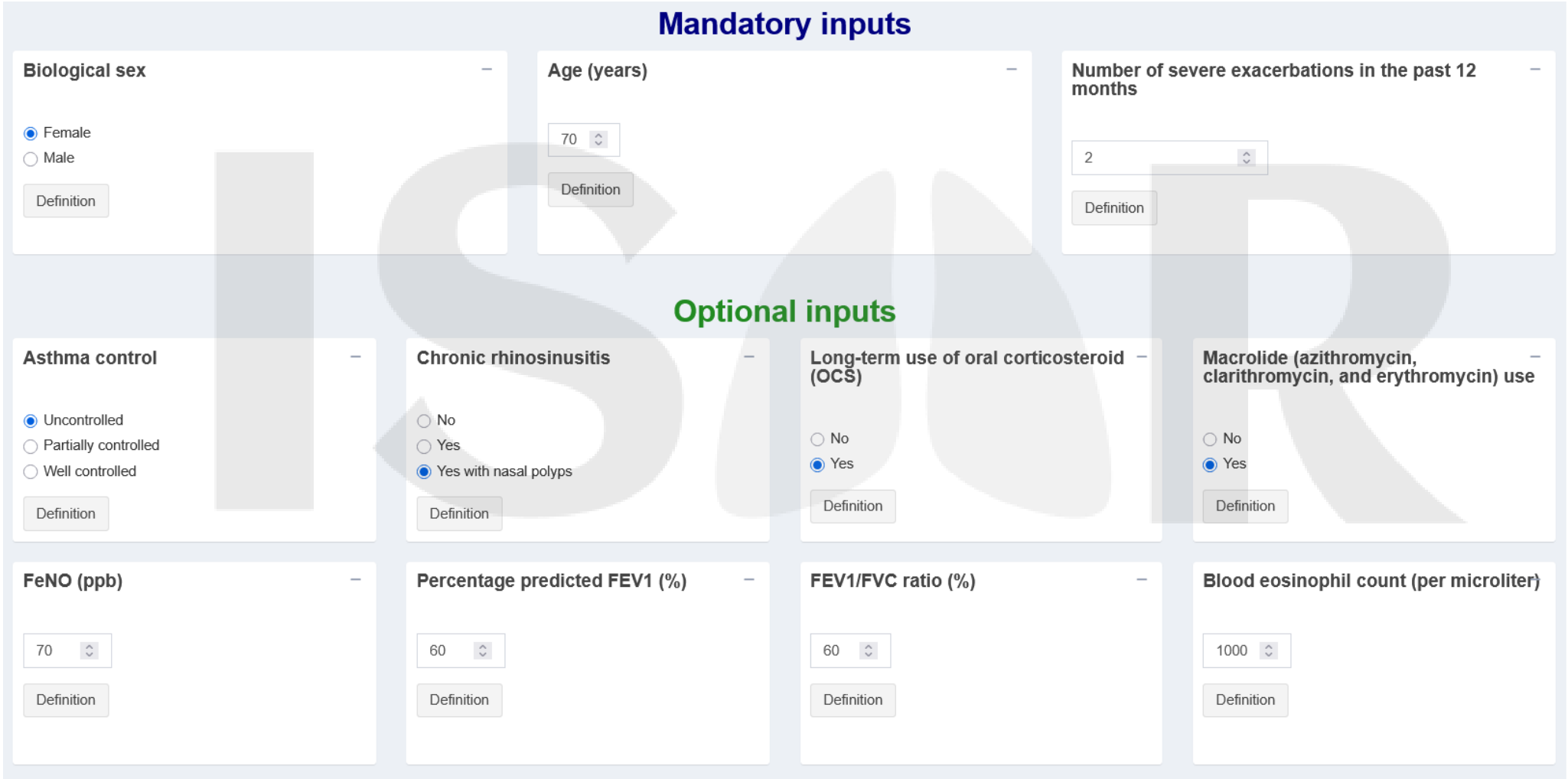

FeNO: Fractional Exhaled Nitric Oxide, PPB:Parts Per Billion, FEV1:Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity

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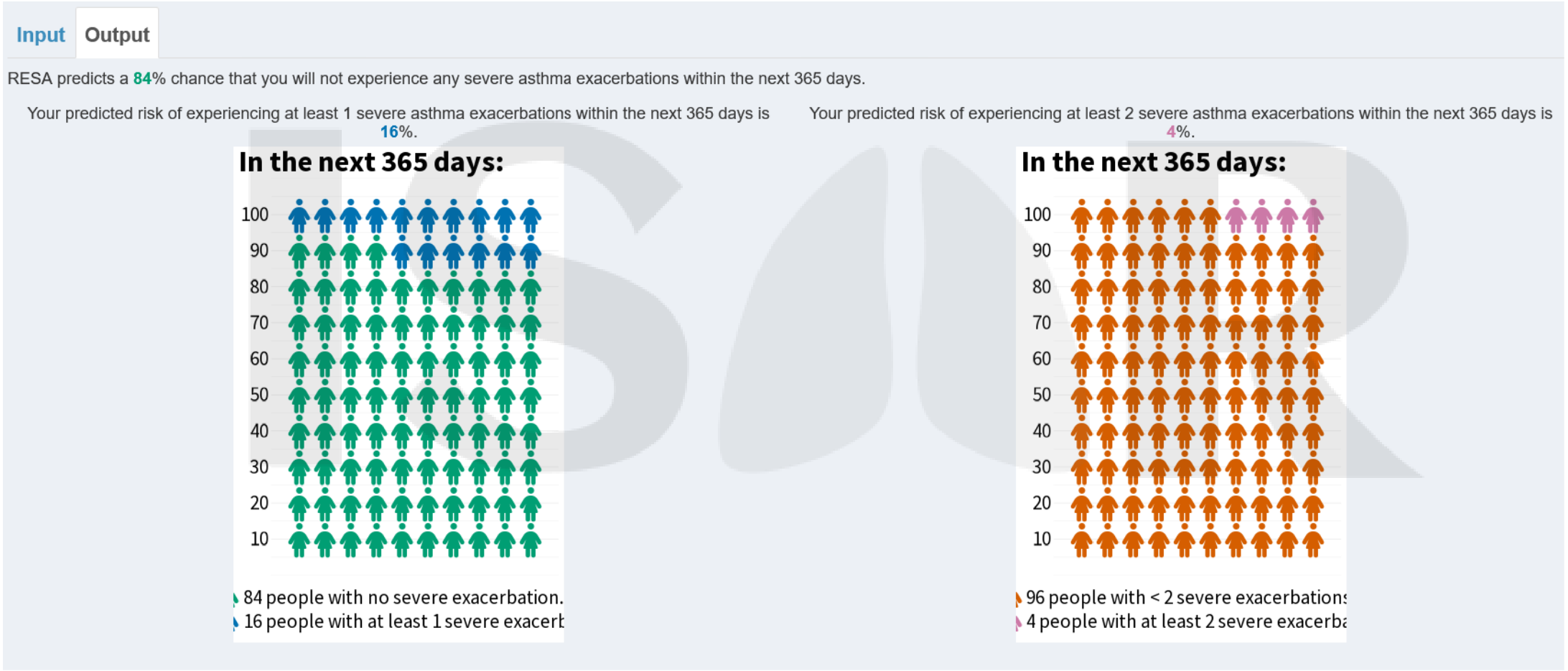

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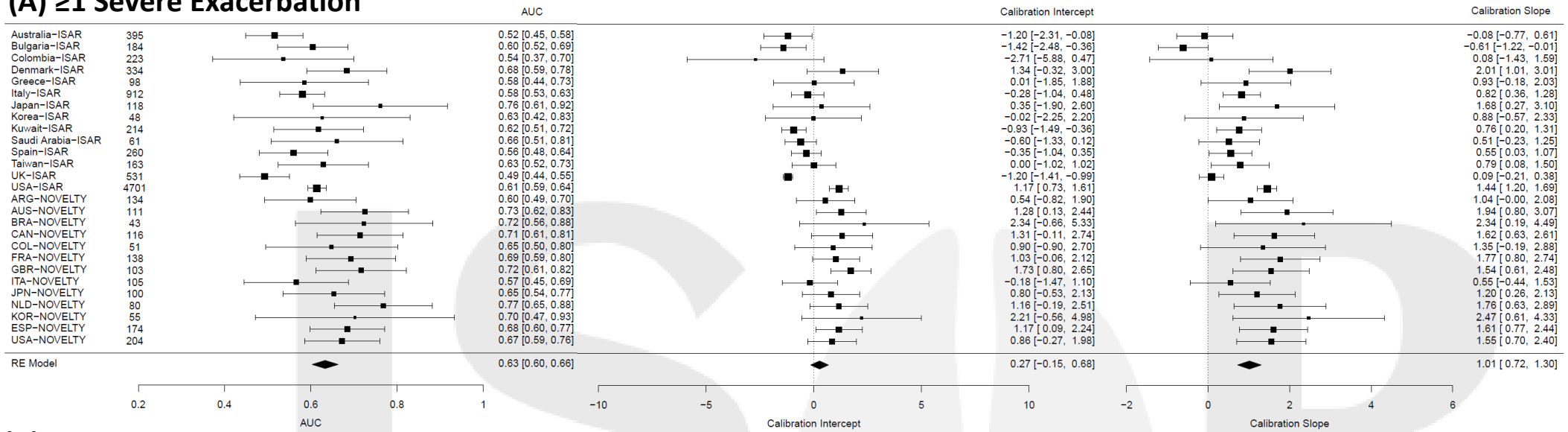
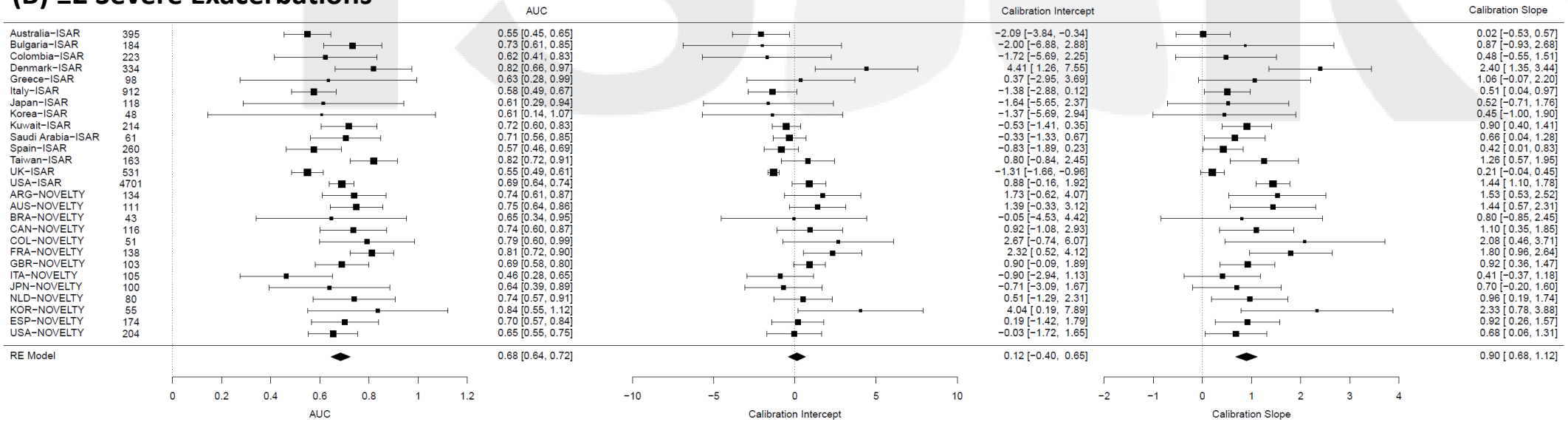
Internal–External Validation Across Country-settings

(A) ≥1 Severe Exacerbation



(B) ≥2 Severe Exacerbations



Meta-analysis

AUC

0.63 for ≥1 SAE

0.68 for ≥2 SAEs

Calibration *Intercept*

0.27 for ≥1 SAE

0.12 for ≥2 SAEs

Slope

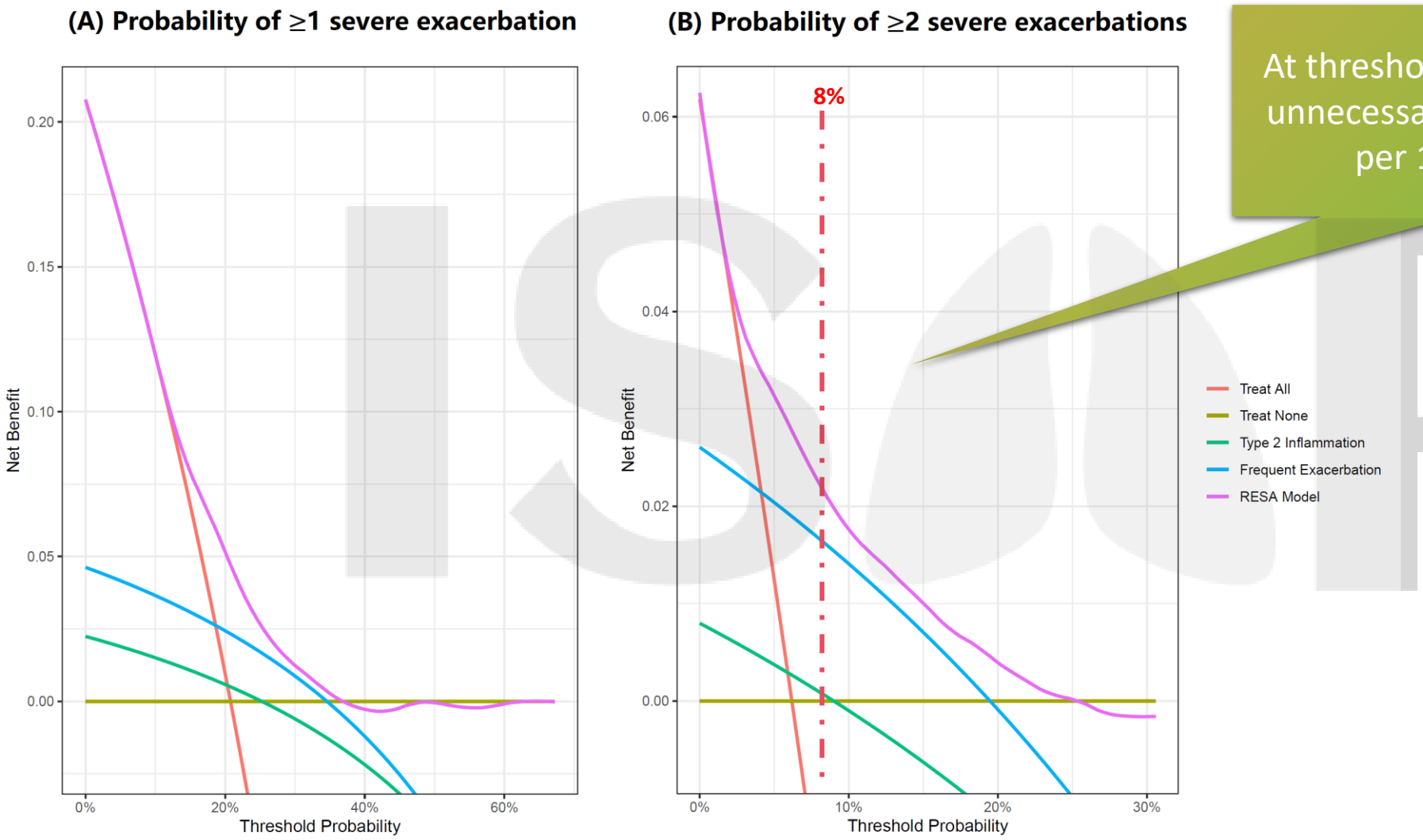
1.03 for ≥1 SAE

0.90 for ≥2 SAEs

Better performance for predicting ≥2 SAEs, which is also a more clinically meaningful endpoint

AUC: area under the time-dependent receiver-operating characteristic curve; SAE: severe asthma exacerbation; CI: confidence interval.

Decision Curve Analysis: Net Benefit Across Risk Thresholds



At threshold 8%, RESA reduces unnecessary treatments by 23 per 1000 decisions

- RESA outperformed all other strategies, including treat all, treat none, treating by type 2 inflammation, and by past-12mo frequent exacerbations.
- Net benefit was clearest for predicting ≥2 SAEs.
- RESA supports more efficient, risk-informed decisions for severe asthma management.

SAE: severe asthma exacerbation

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Conclusions

- **Flexible risk prediction model:** RESA predicts the risk of ≥1 and ≥2 severe exacerbations, exacerbation-free days and exacerbations over the next 365 days in adults with severe asthma. 11 key predictors are all routinely collected, capturing both eosinophilic and non-eosinophilic phenotypes.

- **Local risk-adapted prediction:** By combining patient-level clinical information with local background exacerbation risk, RESA provides individualized estimates that can be adapted across different health systems and care settings.

- **Clinical utility for personalized care:** RESA showed good calibration, generalizable discrimination, and positive net benefit across clinically relevant risk thresholds, supporting risk-informed severe asthma management.

Future direction: Further validation and model updates in new settings and broader asthma populations will help enhance RESA's transportability and clinical applicability.

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