

Letter to the Editor

Minimally important differences and risk levels for the Composite Asthma Severity Index*To the Editor:*

The Composite Asthma Severity Index (CASI) is a comprehensive severity scale combining multiple facets of asthma severity: impairment, risk, and treatment.¹ The CASI score, which was developed as a research tool for intervention studies, ranges from 0 to 20 points, with higher scores indicating higher levels of severity, and includes 5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations. This report expands on the introduction of the CASI score in Wildfire et al¹ by determining risk levels, the minimally important difference (MID), and the suggested effect size for the score. Information about CASI, including study forms and an online calculator, is available at www.asthmaseverity.org.

This report uses data from the Asthma Phenotypes in the Inner City (APIC) study to describe the relationship between CASI and the global clinician assessment of severity, establish cutoff points of the CASI score discriminating low versus medium or high asthma severity, and provide preliminary estimates of the MID and a treatment effect for the CASI. Data from the Inner City Anti-IgE Therapy for Asthma Study (ICATA), a double-blind randomized clinical trial evaluating the impact of the addition of omalizumab to guidelines-based therapy, are used to evaluate the MID and effect size developed.²

The MID,^{3,4} which is defined as the smallest difference in a measure that is considered clinically meaningful, can vary depending on the context. The MID presented in this report refers to an individual's change over time. In addition, we present the difference between 2 populations as the minimal important effect size, which serves as a benchmark for a treatment effect in a study.

The APIC study⁵⁻⁷ was an observational study designed to identify determinants of asthma severity. During the APIC study, children aged 6 to 17 years, with a wide range of asthma severity, received standardized guidelines-directed asthma treatment for 1 year. At screening and the final visit, the CASI score was calculated and the children were assigned numeric (0-100) and categorical ("low," "medium," or "high") global severity assessments by study clinicians.

We examined the relationships between CASI and the numeric (0-100) clinician assessment at screening to establish CASI risk levels and an MID for CASI. Traditional measures of risk and impairment, such as clinical and lung function measures, were not appropriate "criterion standards" for the CASI because it contains elements of both.

The mean CASI score at screening was 4.8 ± 3.22 ; the maximum possible CASI score is 20. There was a strong relationship between CASI and the numeric (0-100) clinician assessment of severity ($\rho = 0.65$; 95% CI, 0.60-0.69), indicating that any increase in CASI translates to an increase in clinician estimate of asthma severity. The categorical clinician assessment rated 294 participants (41%) as "low" severity, 309 (43%) as "medium" severity, and 113 (16%) as "high" severity at the screening visit.

To establish CASI risk levels, we examined the relationship between CASI and the clinician categorical assessment of severity

using receiver operator curve analysis. Of the 294 low severity participants, 75% had CASI scores of 3 or lower, and a CASI score of 3 was found to be optimal to discriminate a low severity rating from a medium or high severity rating (area under the curve = 0.86; Fig 1, A). The same optimal cutoff point of 3 was identified using data available for 557 participants from the final visit (data not shown). Similar receiver operator curves were created to discriminate between participants with medium and high categorical clinician assessments, but based on area under the curve, no recommended cutoff point was identified. In addition, as a continuous score, the CASI is shown to have a high correlation with asthma severity, and increases in CASI values both above and below the established cutoff point of 3 are associated with significant increases in severity (correlation with clinician assessment for CASI score 0-3 = 0.37; 95% CI, 0.27-0.46; CASI score from 3 to 20 = 0.47; 95% CI, 0.40-0.54; Fig 1, B).

The MID for CASI is informed by its design. CASI scores in each of the 5 domains were aligned with the National Asthma Education and Prevention Program Expert Panel Report asthma guidelines.⁸ As a result, a 1-point change in CASI score corresponds to either a 1-point increase in the participant's asthma control level (for day symptoms/albuterol use, night symptoms/albuterol use, and lung function measure) or a change in medication (inhaled corticosteroids for the controller treatment domain and prednisone for the exacerbation domain). Therefore, a 1-point difference in any domain constitutes a change that could be considered clinically significant, serving as a lower bound for the MID. To further define the MID, anchor-based analysis, a methodology for estimating the MID on the basis of a clinical reference measure, was performed by categorizing the numeric clinician rating of severity into 10-point intervals (Table 1). Mean differences in CASI scores were calculated between adjacent anchor categories and yielded an MID of 0.9 with Hedges g statistic of 0.36 (0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect). The validity of 0.9 change was evaluated using data from the ICATA study, where 52% (98 of 189) of the participants in the treatment arm demonstrated a CASI score decrease of 0.9 points between randomization and the end of the study, compared with only 40% (69 of 172) of participants in the placebo arm ($\chi^2 P = .03$). Because changes in CASI occur in no less than a 1-point increment, we rounded this value to propose an MID of 1 CASI point.

To determine the minimal important effect size, which is not limited to whole numbers as it represents the average of a population of individuals, a statistical simulation was performed using APIC data by creating a simulated placebo group and an active treatment group ($n = 250$ for each). The simulation yielded a mean difference of 0.49 CASI points between 2 treatment arms (95% CI, 0.01-0.99). In the ICATA study, participants in the treatment arm showed a significant improvement in CASI over participants in the placebo arm (0.67 points improvement, $P < .001$). Additional details regarding this result, including methodology and estimates based on several population sizes, are available as an online supplement at https://github.com/RhoInc/CASI_MID.

More research in high-risk populations, to include larger numbers of participants, is needed to discriminate between the medium- and high-risk levels of asthma severity using the CASI score. In addition, further research is needed to determine whether

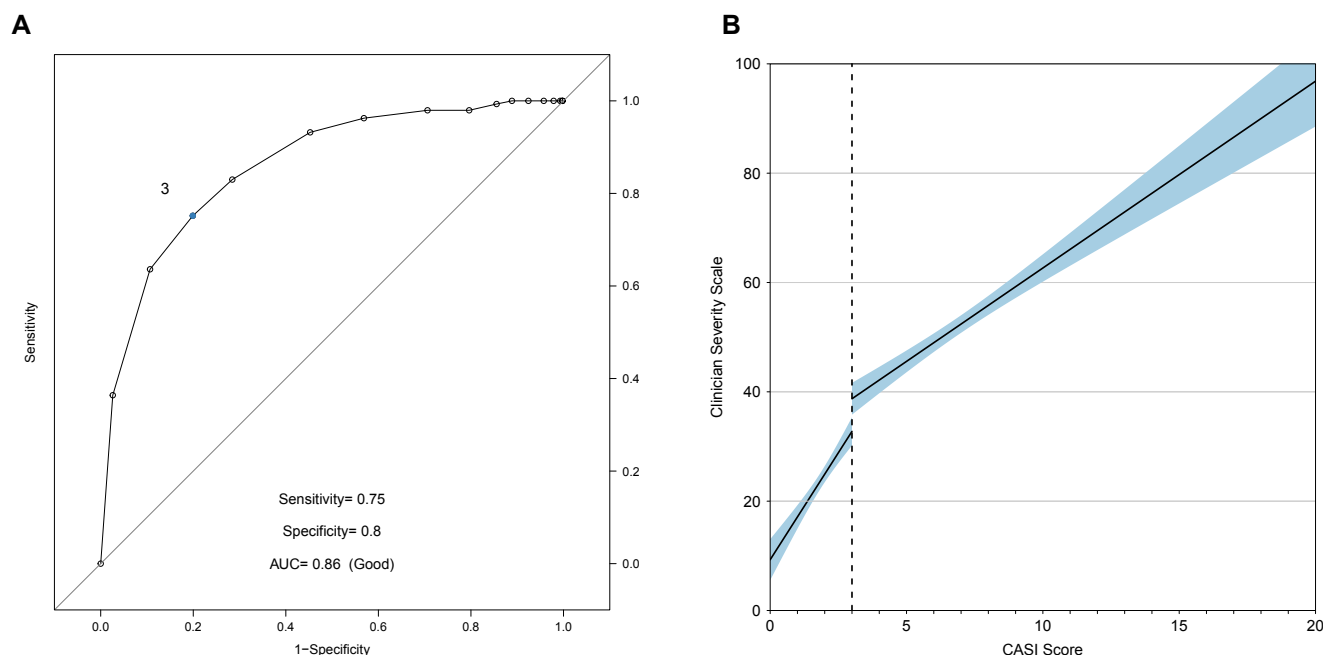


FIG 1. Risk level for discriminating a low CASI score from a medium or high CASI score. **A**, Receiver operating curve for CASI versus clinician assessment of severity (dichotomized as low and medium/high). Optimal cutoff point of 3 (corresponding to low severity) is annotated. **B**, Continuous relationship between CASI score and continuous clinician assessment of asthma severity. Optimal cutoff point is illustrated by dotted line. Linear relationship estimated separately for a CASI score of 0 to 3 and for a CASI score of 3 to 20. Shaded interval represents a 95% CI band. AUC, Area under the curve.

TABLE I. Anchor-based approach to determining the MID for the CASI

Baseline clinician severity (numeric rating) – 10 cats	Absolute difference (95% CI)	Effect size* (95% CI)
[0,10] vs [11,20]	0.48 (0.00 to 0.98)	0.26 (0.01 to 0.53)
[11,20] vs [21,30]	1.19 (0.64 to 1.75)	0.57 (0.29 to 0.85)
[21,30] vs [31,40]	1.13 (0.40 to 1.83)	0.49 (0.18 to 0.80)
[31,40] vs [41,50]	0.66 (–0.03 to 1.37)	0.25 (0.05 to 0.56)
[41,50] vs [51,60]	0.60 (–0.18 to 1.42)	0.22 (0.08 to 0.53)
[51,60] vs [61,70]	0.85 (–0.25 to 1.94)	0.31 (0.10 to 0.72)
[61,70] vs [71,80]	0.87 (–0.36 to 2.01)	0.27 (0.12 to 0.67)
[71,80] vs [81,90]	1.88 (0.02 to 3.57)	0.57 (0.01 to 1.13)
[81,90] vs [91,100]	1.65 (–1.20 to 4.11)	0.51 (0.64 to 1.65)
10 cats: weighted average	0.90	0.36

*Effect sizes were computed by using the Hedges *g* statistic: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect.

CASI and its associated risk levels differ in suburban or adult populations. Finally, APIC's observational design presents a limitation to the analysis; validation of the results using a true case-control population would be valuable.

Wildfire et al¹ demonstrated that the CASI was a better discriminator of treatment response than a symptoms-based outcome. The information provided in this report extends the utility of the CASI. A change of 1 point or greater in the CASI score suggests a change in the individual's asthma severity. For defining asthma risk levels, a CASI score of 3 or less identifies an individual with mild asthma; however, this may oversimplify asthma severity because an increase in CASI represents increased

severity both above and below the cutoff point. When using CASI in clinical studies, a difference of 0.49 represents a minimally important effect size (difference between the 2 groups). CASI is free to use and sample forms and other resources are publicly available at www.asthmaseverity.org.

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