Measuring respiratory syncytial virus infection severity in hospitalized children using the Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System (PRESORS)

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Abstract
Background: The Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System (PRESORS) was developed to assess the severity of respiratory syncytial virus (RSV) infection in children. Because young children cannot report how they feel or function, ratings are based on observations by the child’s caregiver (Observer-Reported Outcome questionnaire [ObsRO]) and clinician (Clinician-Reported Outcome questionnaire [ClinRO]). This prospective study aimed to evaluate the psychometric properties of the PRESORS.

Methods: The PRESORS version 6 ObsRO and ClinRO were evaluated in children with RSV infection requiring hospitalization in centers in the United States, Argentina, and Chile. Assessments were performed from days 1 to 7 by the child’s caregiver and clinician. To assess inter-rater reliability, two clinicians independently performed the ClinRO near in time.

Results: A total of 124 children aged ≤36 months were enrolled (mean age, 8 months). Factor analysis demonstrated that RSV severity consists of two dimensions, respiratory signs and illness behavior, and that these dimensions were consistent over time. The inter-rater reliability for the ClinRO was 0.66 (95% confidence interval [CI], 0.55–0.75) but improved to 0.79 (95% CI, 0.71–0.86) after removing one outlying site, suggesting that quantifying RSV severity is not trivial, even using qualified raters, but that an adequate inter-rater reliability is achievable with the PRESORS through adequate training. ClinRO and ObsRO displayed acceptable internal consistency and acceptable convergent validity with the Respiratory Syncytial Virus Network Scale, global impression scores, and key hospital characteristics.

Conclusions: The PRESORS is relevant and appropriate for assessing the severity of RSV infection in infants requiring hospitalization.

Keywords
patient-reported outcome, pediatrics, psychometrics, respiratory syncytial virus

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Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract illness in young children. Most children will have experienced at least one RSV infection by 2 years of age. Globally, RSV is the most common cause of bronchiolitis and pneumonia in children <1 year of age. In the absence of specialized care, RSV infection can be fatal in neonates, as witnessed in developing countries. There exists a high unmet need for pediatric RSV vaccines and treatments to prevent infection, reduce the severity of symptoms and disease, and reduce the time to recovery.

Several treatments are in development; however, no widely accepted and validated tool yet exists to measure RSV disease severity in young children, and the development of such a tool to assist in assessing treatment efficacy is of high priority. Because young children cannot self-report how they feel and function, observations by their parents/caregivers and clinicians are essential to the evaluation of RSV severity in this population. The Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System (PRESORS) is under development to assess the severity of RSV infection in children based on the presence and severity of signs and symptoms of RSV disease as reported by clinicians (the PRESORS Clinician-Reported Outcome questionnaire [ClinRO]) and the child’s caregiver (the PRESORS Observer-Reported Outcome questionnaire [ObsRO]). The ClinRO and ObsRO measures were developed in parallel based on ethnographic and qualitative interview studies with clinicians and caregivers of children with RSV and consultations with pediatric clinical experts. Other tools in development include the Respiratory Syncytial Virus Network (ReSVINET) Scale, the Global Respiratory Severity Score (GRSS), and the Gilead RSV Caregiver Diary (GRCD).

For clinician ratings, an RSV severity rating scale needs to be reliable such that different clinicians provide the same rating for the same child. This characteristic is measured by inter-rater reliability and is a key aspect of any scale in which the patient cannot self-report outcomes. To assess inter-rater reliability, this study required multiple clinician ratings using the ClinRO of disease severity for the same child.

The PRESORS version 6 (PRESORSv6) ClinRO is a clinician-rated assessment of the severity of signs of RSV infection. ClinRO ratings are based on information that clinicians would ordinarily use to evaluate a pediatric patient: observed presentation of the child (assisted with clinical case notes), discussion with other medical staff, and interaction with the child’s parents or caregivers. The ClinRO includes 12 items reflecting signs of RSV infection that had been identified in earlier development steps: activity level, sleep, feeding, dehydration, apnea, retractions, tachypnea, breathing problems, cyanosis, cough, nasal secretions, and wheezing (Table S1). For each item, possible responses reflect potential diagnoses or other key elements. For example, the clinician can indicate for the item retractions whether any subcostal, intercostal, or tracheosternal retractions were observed in the relevant time window. By avoiding subjective Likert-type responses (e.g., mild, moderate, or severe), it was anticipated that choices based on diagnosis would increase reliability and validity. In addition to RSV severity items, the ClinRO includes questions regarding the degree of concern with the child’s present health status, a global impression of the child’s health, and a global impression of change in the child’s health from baseline.

The PRESORSv6 ObsRO is an assessment of the severity of signs of RSV infection from the perspective of the parent/caregiver. It comprises 16 items: activity level, sleep, crying, feeding, urination, dehydration, vomiting, apnea, retractions, tachypnea, tachycardia, breathing problems, cyanosis, cough, nasal secretions, and wheezing (Table S2). Items were generated and refined through focus group interviews involving concept elicitation and cognitive debriefing. Meaningful responses were selected for easily understandable items. Like the ClinRO, the ObsRO included questions on a global impression of the child’s health and a global impression of change in the child’s health from baseline.

Points for each response were initially assigned based on clinical guidance (Tables S1 and S2). These scoring rules were then evaluated based on study results. It was hypothesized that RSV severity consists of two main dimensions, respiratory signs and illness behavior, with overall RSV severity resulting from the combination of these two domains.

This study aims to develop the PRESORS further based on its psychometric properties.

2 | METHODS

2.1 | Study design

This was a prospective study conducted in children aged ≤36 months with a confirmed RSV infection requiring hospitalization. No study medication or experimental treatment was administered. The RSV diagnosis could be established by a rapid antigen assay or a polymerase chain reaction—based assay and was to have an onset of symptoms within 5 days of enrollment. A coinfection with another respiratory pathogen was allowed for inclusion, but the use of an investigational (RSV) drug or vaccine was a reason for exclusion.

At each study site, three to five health care providers were trained to complete the ClinRO. The primary ClinRO rating was completed as soon as possible after admission. Independent of this assessment, a second clinician would complete an additional ClinRO to assess inter-rater reliability. This second assessment was ideally performed within 30 min before or after the primary ClinRO to reduce potential changes in the child’s condition. Further evaluations were performed daily while the participant was hospitalized and on day 7, preferably by the same health care provider throughout. Participant demographics and medical history were captured at enrollment, and clinical evaluations (physical examination, feeding/hydration, vital signs, and oxygen saturation) were performed during hospitalization and on day 7. The parent/caregiver completed the ObsRO twice daily during the assessment period regardless of whether the child was an inpatient or discharged from the hospital and once on day 7. The
ObsRO was preferably completed by the same parent/caregiver throughout the study, but if another person was caring for the child during an interval, this person was to assess the ObsRO.

For the assessment of convergent validity, or how closely a scale relates to other measures of the same construct, the ReSViNET was included, which was considered the most established alternative scale. The ReSViNET also has clinician and caregiver versions, each including seven items related to symptoms and clinical management (feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnea, general condition, and fever). The same clinician who completed the ClinRO throughout the study also completed the clinician ReSViNET on day 1. The parent/caregiver completed the ReSViNET caregiver version on day 1.

To determine the sample size for the study, the objective was set to exclude an inter-rater reliability <0.65 for the ClinRO. Assuming a true inter-rater reliability of 0.75 and two to three raters per child, a sample size of 124 children would provide 80% power to exclude an inter-rater reliability <0.65 at an α level of 5%. A sample size of 124 was also considered sufficient to provide meaningful information for other study objectives.

### 2.2 | Statistical analysis

This study aimed to develop the PRESORS further based on the psychometric properties of the ClinRO and ObsRO. Methods used in the first step were exploratory factor analysis (EFA), variability assessment, reliability based on internal consistency (Cronbach α), and item-rest correlations. In this step, items were to be iteratively removed based on poor performance on these properties (in particular, based on low variability and/or low item-rest correlations). Simultaneously, the domain structure was established by examining EFA solutions with up to three factors. In a second step, confirmatory factor analysis (CFA) was used to confirm the domain structure by assessing the goodness of fit and to investigate domain structure and item behavior over time. Next, item response theory (IRT; graded response model) was applied to each dimension of the ClinRO and ObsRO to evaluate the scoring of item responses. IRT creates a unidimensional representation for each domain, whereby the probability of observing each response of an item is based on the score on the latent trait (unobservable characteristics) of the RSV severity domain. It expresses how item responses are expected to change as RSV severity increases and can help verify score assignment to responses. For each domain, plots were created showing switch points, whereby the first point to the left is where the response to the item is expected to switch from absent to present (binary items) or the next higher score level of the item (ordinal items). Based on this, revised scores were assigned to ClinRO and ObsRO. Finally, EFA and CFA were again performed on the revised PRESORS ClinRO and ObsRO.

Inter-rater reliability of the revised ClinRO was investigated using the intra-class correlation (ICC) in a one-way random-effects model. Statistical analyses were performed using R Statistical Software version 4.1.0 (http://www.r-project.org, RRID:SCR_001905); the R psych package (https://cran.r-project.org/web/packages/psych/index.html, RRID:SCR_021744) was used to estimate the ICC and corresponding confidence intervals (CIs). A two-way random-effects model was investigated as a sensitivity analysis but gave similar results, which are therefore not presented. Bland-Altman plots were used to assess whether score differences between raters depended on the mean score and whether the mean scores and score differences varied between sites.

Psychometric properties of the revised scales were investigated by examining internal consistency, convergent and divergent validity, and floor and ceiling effects. The correlation between the ClinRO and ObsRO scale was used to evaluate the correspondence between clinician and caretaker assessments. Both Spearman and Pearson correlations were used but generally yielded similar results.

### 3 | RESULTS

A total of 124 participants were enrolled across 10 sites in Argentina, Chile, and the United States. Baseline characteristics and features of hospitalization are summarized in Table 1. Approximately half of the participants were male (53.2%), the mean age was 7.6 months, and the mean duration of RSV symptoms from onset until day 1 was 3 days. Two participants (1.6%) were admitted to the pediatric intensive care. Completion information on ClinRO and ObsRO is available in Figure S1.

#### 3.1 | Evaluation of the ClinRO

The items dehydration, apnea, and cyanosis were rarely reported as present and showed little variability. In EFA, cyanosis correlated poorly with other items and did not fit well in either domain. Clinical experts noted that dehydration and apnea may be difficult to detect, and cyanosis is typically present only in more serious cases. Based on these findings, it was decided to remove these three items from the revised ClinRO for these analyses. EFA revealed that the items retractions, breathing problems, tachypnea, cough, nasal secretions, and wheezing loaded on one factor that was interpreted as respiratory signs; the items activity level, feeding, and sleep loaded on a second factor that was interpreted as illness behavior. This result supports the hypothesized structure that RSV severity has two distinguishable dimensions: respiratory signs and illness behavior.

IRT analysis was used to evaluate the scoring system, and few adjustments were made (Table S3). The switch points for responses to all items linked to the level of the latent trait are shown in Figure S2.

The revised PRESORSv6 ClinRO is shown in Table 2. The domain scores are obtained by summing the corresponding signs and rescaling this value to obtain a domain score of 0 to 8 points. Figure 1 (left) presents the factor analysis loading plot of the results of the primary rater on day 1. The two-factor CFA model consistently provided a good fit to the ClinRO data, as shown in item loadings (Table S4) and fit statistics (Table S5) from days 1 to 3.
TABLE 1 Summary of demographics, baseline disease characteristics, and features of hospitalization

|                               | N = 124 |
|-------------------------------|---------|
| **Age, mean (SD), months**    | 7.63 (7.52) |
| **Age group, n (%), months**  |         |
| 0 to <3                       | 53 (42.7) |
| 3 to <6                       | 14 (11.3) |
| 6 to <12                      | 37 (29.8) |
| 12 to <24                     | 16 (12.9) |
| 24 to ≤36                     | 4 (3.2)   |
| **Male sex, n (%)**           | 66 (53.2) |
| **Race, n (%)**               |         |
| White                         | 77 (62.1) |
| Black or African American     | 14 (11.3) |
| Other/not reported/unknown    | 33 (26.6) |
| **Ethnicity, n (%)**          |         |
| Hispanic or Latino            | 71 (57.3) |
| Not Hispanic or Latino        | 40 (32.3) |
| Not reported/unknown          | 13 (10.5) |
| **Duration of RSV symptoms from onset until day 1, mean (SD), days** | 3.15 (1.17) |
| **Presence of comorbid conditions, n (%)** | 26 (21.0) |
| **Presence of any past and/or concomitant diseases, n (%)** | 51 (41.1) |
| **Supplemental feeding/hydration during study, n (%)** | 84 (67.7) |
| IV line                       | 69 (82.1) |
| Mouth                         | 2 (2.4)   |
| Nasogastric tube              | 40 (37.4) |
| **Oxygen supplementation during study, n (%)** | 91 (73.4) |
| **Time to discharge readiness since day 1 visit, n (%), days** |         |
| 1                             | 4 (3.2)   |
| 2                             | 24 (19.4) |
| 3                             | 18 (14.5) |
| 4                             | 19 (15.3) |
| 5                             | 13 (10.5) |
| 6                             | 17 (13.7) |
| 7                             | 9 (7.3)   |
| 8                             | 5 (4.0)   |
| Unknown, but >1               | 1 (0.8)   |
| Unknown, but >6               | 7 (5.6)   |
| Unknown, but >7               | 7 (5.6)   |

Abbreviations: IV, intravenous; RSV, respiratory syncytial virus; SD, standard deviation.

aConditions from the concomitant diseases identified as conditions that predispose to severe RSV disease and complications in children.

bAll conditions recorded in the history of the participant entering the study. The most frequently reported past and/or concomitant disease category was “respiratory” in 76.5% of patients.

3.2 | Evaluation of the ObsRO

As seen in the ClinRO, illness behavior and respiratory signs factors explained most of the variance in the ObsRO data. Model fit was improved when rarely observed signs of severe RSV infection (apnea, cyanosis, and vomiting) were removed; for the purpose of these analyses, these items were omitted from the ObsRO scoring.

In IRT analysis of the original ObsRO scoring system, several adaptations were made in each domain based on the switch points of each of the items in the illness behavior domain and respiratory signs domain (Figure S3 and Table S6).

The revised ObsRO scale and scoring are shown in Table 3. The domain scores are obtained by summing the corresponding signs and rescaling the summed value to obtain a domain score between 0 and 8. Figure 1 (right) presents the factor analysis loading plot of the results on day 1. A two-factor CFA on days 1 to 3 was performed for the 13 items in the revised scale (Tables S7 and S8). The items loaded on each of the two factors corresponding to the hypothesized domain structure (illness behavior and respiratory signs). It was observed that dehydration, nasal secretions, and cough did not load well on day 1 but performed better in the hypothesized structure on days 2 and 3. It was concluded that the two-factor structure provided a satisfactory model fit across the first 3 days for the ObsRO. The results and interpretation were in line with those for the ClinRO.

3.3 | Inter-rater reliability of the PRESORS ClinRO

The multi-rater ClinRO was obtained for 121/124 participants (97.6%); all participants were rated by two health care providers. The mean (standard deviation [SD]) time between PRESORS ClinRO evaluations was 16.2 (14.5) min. The maximum time between two ratings was 71.8 min. The mean (SD) of the overall RSV severity score was 3.41 (1.4) for the revised measure. Among all raters, illness behavior summary scores were lower than respiratory signs summary scores for the revised ClinRO measure (mean [SD], 3.12 [1.60] vs. 3.55 [1.68]). Summary scores based on primary rater assessments were generally comparable to those based on the second rater’s assessments (Table S9). Scatterplots for all summary scores demonstrated a moderate association between the primary rating and the second rating (Figure S4). In the Bland–Altman plot of the overall RSV severity scores, the scores of the primary rater were not consistently higher or lower than those of the second rater, and differences between ratings were independent of the mean scores (Figure 2).

Based on the revised ClinRO scoring, the estimated ICC for the overall RSV severity summary score was 0.66 (95% CI, 0.55–0.75), with ICCs for respiratory signs and illness behavior of similar magnitudes (0.60 vs. 0.62, respectively; Table 4). One study site in the United States deviated markedly from the other sites (Figures S5 and S6). With this outlier site excluded, a sensitivity analysis yielded an estimated ICC for the overall RSV severity summary score that was
| Item                        | 0 points                                      | 1 point                                        | 2 points                                      | 3 points                                      |
|-----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Illness behavior domain** |                                               |                                               |                                               |                                               |
| Activity level              | Alert and active/normal sleep                 | Irritable/restless/agitated                   | Floppy/lethargic/poor interaction             | Only responds to pain/unresponsive            |
| Sleep                       | Normal                                        | Occasional restlessness/disturbed              | Restless/disturbed much of time               | Comatose                                      |
| Feeding                     | >75% of normal amount of feeds via usual route | 50%–75% of normal amount of feeds via usual route | <50% of normal feeds or needing NG feeds or IV fluids |
| **Respiratory signs domain**|                                               |                                               |                                               |                                               |
| Retractions                 | None                                          | Subcostal retraction                          | Intercostal retraction                        | Tracheosternal retraction                     |
| Breathing problems          | No signs of increased work of breathing       | 1 symptom of:                                 | 2 symptoms of:                               | 3 symptoms of:                               |
|                             |                                               | • head bobbing                                | • head bobbing                                | • head bobbing                                |
|                             |                                               | • grunting                                    | • grunting                                    | • grunting                                    |
|                             |                                               | • nasal flaring                               | • nasal flaring                               | • nasal flaring                               |
| Tachypnea                   | No                                            | Yes                                           |                                               |                                               |
| Cough                       | Little or none                                | Occasional strong cough, sometimes productive |                                               |                                               |
| Nasal secretions            | None or minimal, easily cleared with suctioning | Moderate, but could be cleared with suctioning |                                               |                                               |
|                             |                                               |                                               | Extensive, requires frequent suctioning      |                                               |
| Wheezing                    | None                                          | Terminal expiratory wheezing                   | Entire expiration or audible during expiration without stethoscope | Inspiration and expiration without stethoscope |

**Overall RSV severity** is the combination of the *illness behavior* and *respiratory signs* items.

*Note:* The PRESORS ClinRO consists of items that ask the severity of condition now and based on a 12-h recall question, and the score is the worst score of both items, with exceptions for marked items. The domain scores are obtained by summing the corresponding signs and rescaling the summed value to obtain a domain score between 0 and 8.

**Abbreviations:** ClinRO, Clinician-Reported Outcome questionnaire; IV, intravenous; NG, nasogastric; PRESORS, Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System; RSV, respiratory syncytial virus.

*There is only a recall item, not an item for the condition now.

*Score based on the condition now (however, 1 point in the case the symptom is “present” in recall and no point in the condition now).
FIGURE 1  EFA loading plot of the revised PRESORS ClinRO (left) and ObsRO (right). Abbreviations: ClinRO, Clinician-Reported Outcome questionnaire; EFA, exploratory factor analysis; ObsRO, Observer-Reported Outcome questionnaire; PRESORS, Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System. Results presented for data of the day 1 ratings of the primary rater for the PRESORS ClinRO (N = 132) and day 1 for the ObsRO (N = 120).

TABLE 3  Revised PRESORS ObsRO items, responses and scoring

| Item                  | 0 point                                      | 1 point                                      | 2 points                                     | 3 points                                      |
|-----------------------|----------------------------------------------|----------------------------------------------|----------------------------------------------|----------------------------------------------|
| **Illness behavior domain** |                                             |                                              |                                              |                                              |
| Activity level        | As active as usual                           | A little less active than usual              | A lot less active than usual                 | Floppy or limp, not responding to you as usual |
| Sleep                 | About as much as usual                       | A little less than usual OR A little more than usual | A lot less than usual OR A little more than usual |                                              |
| Crying                | Normal, no more crying than usual           | Cried more than usual but calm if held or soothed | Cried a lot, difficult to calm even if held or soothed | Cried a lot, would not stop crying even if held or soothed |
| Feeding               | Ate, drank, or nursed as usual              | A little less than usual                     | A lot less than usual                        | Did not eat, drink, or nurse at all           |
| Urination             | About as much as usual                       | A little less than usual                     | A lot less than usual                        | Did not wet a diaper or use the toilet        |
| Dehydration           | None of these                                | Dry skin or lips OR Dark yellow urine        | Soft spot on top of head sunk in OR Sunken eyes |
| **Respiratory signs domain** |                                             |                                              |                                              |                                              |
| Retractions           | None of these                                | Belly sucked in when breathing              | Belly sucked in when breathing AND          | Skin at the base of the throat sucked in when breathing in |
|                       | OR Ribs more visible than usual when breathing in |                              | Ribs more visible than usual when breathing in |                                              |
| Tachypnea             | None                                         | Breathing faster than normal                 |                                              |                                              |
| Tachycardia           | No                                           | Yes, child’s heart seems to be beating faster than usual |                                              |                                              |
| Nasal secretions      | None                                         | Breathing through mouth because of difficulties breathing through stuffy or runny nose |                                              |                                              |
| Breathing problems    | None                                         | Nostrils flared out when breathing in OR    | Nostrils flared out when breathing in AND    |                                              |
|                       |                                              | Made grunting sounds when breathing OR      | Made grunting sounds when breathing AND     |                                              |
|                       |                                              | Head bobbed back and forth when breathing   | Head bobbed back and forth when breathing    |                                              |
|                       | 2 of 3 for:                                  |                                              |                                              |                                              |
|                       | Nostrils flared out when breathing in OR    |                                              |                                              |                                              |
|                       | Made grunting sounds when breathing OR      |                                              |                                              |                                              |
|                       | Head bobbed back and forth when breathing   |                                              |                                              |                                              |
| Cough                 | None OR A little coughing                    | Coughing a lot                               | Coughing almost all the time                 |                                              |
| Wheezing              | No                                           | Yes, but only at the end of                 | Yes, throughout breathing out                | Yes, throughout breathing in and out         |
|                       |                                              | when the child breathes out                  |                                              |                                              |

Overall RSV severity is the combination of the illness behavior and respiratory signs items

Note: The PRESORS ObsRO was asked taking a 12-h recall period into account. The PRESORS ObsRO was completed once in the morning and evening, and the score for a day is defined as the worst score observed for an item. The domain scores are obtained by summatting the corresponding signs and rescaling the summed value to obtain a domain score between 0 and 8.

Abbreviations: ObsRO, Observer-Reported Outcome questionnaire; PRESORS, Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System; RSV, respiratory syncytial virus.
The psychometric properties (internal consistency, convergent validity, and floor and ceiling effects) of the revised ClinRO and ObsRO scoring were evaluated (Tables 5 and S10).

Convergent validity between the revised ClinRO overall RSV severity score and clinician ReSVINET total score was moderate (Pearson correlation: 0.45; 95% CI, 0.30–0.58). The Pearson correlation between the parent/caregiver ReSVINET total score and the revised ObsRO overall RSV severity score was lower (0.33; 95% CI, 0.16–0.48). Overall, convergent validity results with global impression scores and important hospital characteristics were in the anticipated directions for both ClinRO and ObsRO domain scores.

The Pearson correlation between revised ClinRO and ObsRO overall RSV severity scores was 0.32 on day 1 and increased on other days (day 2, 0.52; day 3, 0.42; day 4, 0.52; day 5, 0.47; day 6, 0.57; and day 7, 0.70). The illness behavior domain scores showed higher correlations than the respiratory signs domain scores (Table S11).

### 4 | DISCUSSION

This prospective multi-center study studied the use of the PRESORS for clinician-observed (ClinRO) and parent/caregiver-observed (ObsRO) RSV severity. Exit interviews with parents/caregivers and clinicians indicated that most found the PRESORSv6 ObsRO and ClinRO to be conceptually comprehensive, clinically relevant, and clear.

Results indicate that RSV severity measured by the PRESORS can be characterized by two domains, respiratory signs and illness behavior, as evidenced in responses given by clinicians and parents/caregivers. This structure was consistent over time, revealing that the domains do not change with declining RSV severity.

Vital sign measurements are not directly part of the PRESORS, which may seem an omission. In this study, vital signs were recorded but did not correlate substantially with PRESORS scores. Management of RSV in the hospital setting typically involves the administration of supplementary oxygen and antipyretics when needed, which likely limits the value of recorded vital signs to predict RSV severity throughout hospitalization.

An important limitation was the evidence of homogeneity of RSV severity among participants at the start of the study. By design, infants required hospitalization, but only 2 of 124 infants required admittance to the pediatric intensive care unit. For severely ill infants, it can be hypothesized that screening procedures were perceived as interfering with urgent medical needs and/or that parents/caregivers were not eager to consider participation. The lack of severely ill infants had consequences. The items cyanosis, dehydration, and apnea were rarely reported by clinicians or caregivers during the study; the association of these items with severe RSV infection may explain, in part, their low frequency. Without infants for whom these symptoms were observed, it was not possible to evaluate whether these items are well suited to the PRESORS. Validation of the PRESORS throughout the spectrum of RSV severity in infants is limited in this study.

Although reliability and validity are typically thought of as characteristics of scales, these attributes are not fixed. A homogeneous population implies a relatively low “true” score variance, which produces weaker reliability results (defined as “true” score variance divided by “true” score variance plus error variance). Validity results, which are based on correlations, are likewise weakened by homogeneous populations. The relative homogeneity of severity on day 1 was reflected in internal consistency and convergent validity associations that generally increased for days 2 and 3, which in turn also reflect positively on the ability of the PRESORS to reliably assess RSV severity.
## Table 5: PRESORS ClinRO Psychometric Results Per Domain

| Validity Type (Analysis) | Reference Measure | Day 1 ClinRO | Respiratory Signs | Illness Behavior | Overall RSV Severity |
|--------------------------|-------------------|--------------|-------------------|-----------------|---------------------|
| Internal Consistency (α, 95% CI) | | 0.77 (0.73-0.81) | 0.66 (0.59-0.73) | 0.76 (0.72-0.80) |
| | | 0.76 (0.71-0.82) | 0.70 (0.62-0.79) | 0.80 (0.75-0.84) |
| | | 0.72 (0.64-0.80) | 0.77 (0.69-0.84) | 0.79 (0.73-0.85) |
| Convergent Validity (r, 95% CI) | ReSViNET Clinical Scale Total Score | Day 1 | 0.35 (0.18-0.49) | 0.42 (0.26-0.55) | 0.45 (0.30-0.58) |
| Convergent Validity (mean ± SD, p*) | GC1: “Do you have any concerns relating to the participant’s overall condition?” | Day 1 | 0: 2.84 ± 1.74 | 0: 2.66 ± 1.48 | 0: 2.78 ± 1.42 |
| | | 2: 3.87 ± 1.60 | 2: 3.31 ± 1.45 | 2: 3.68 ± 1.31 |
| | | 3: 2.86 ± 1.67 | 3: 5.36 ± 2.20 | 3: 3.70 ± 1.12 |
| | | p < 0.001 | p < 0.001 | p < 0.001 |
| | Day 2 | 0: 1.80 ± 0.89 | 0: 1.44 ± 1.38 | 0: 1.68 ± 0.85 |
| | | 2: 3.77 ± 1.44 | 2: 3.02 ± 1.28 | 2: 3.52 ± 1.19 |
| | | 3: 4.56 ± 2.86 | 3: 5.50 ± 1.69 | 3: 4.88 ± 1.55 |
| | | p < 0.001 | p < 0.001 | p < 0.001 |
| | Day 1 | 0: 2.83 ± 1.04 | 0: 1.67 ± 0.58 | 0: 2.44 ± 0.77 |
| | | 1: 2.41 ± 1.19 | 1: 2.38 ± 1.59 | 1: 2.40 ± 1.05 |
| | | 2: 4.03 ± 1.60 | 2: 3.45 ± 1.33 | 2: 3.84 ± 1.25 |
| | | 3: 3.96 ± 2.35 | 3: 5.54 ± 1.56 | 3: 4.49 ± 1.50 |
| | | p < 0.001 | p < 0.001 | p < 0.001 |
| | Day 2 | 0: 0.88 ± 0.85 | 0: 0.25 ± 0.50 | 0: 0.67 ± 0.54 |
| | | 1: 2.11 ± 1.06 | 1: 1.54 ± 1.49 | 1: 1.92 ± 0.94 |
| | | 2: 3.78 ± 1.50 | 2: 3.12 ± 1.11 | 2: 3.56 ± 1.20 |
| | | 3: 4.50 ± 2.59 | 3: 5.44 ± 1.59 | 3: 4.81 ± 1.43 |
| | | p < 0.001 | p < 0.001 | p < 0.001 |
| Convergent Validity (mean ± SD, p**) | Oxygen Supplementation on Day 1 and/or Day 2 | Day 1 | No: 2.88 ± 1.43 | No: 2.72 ± 1.50 | No: 2.83 ± 1.14 |
| | | Yes: 3.87 ± 1.72 | Yes: 3.47 ± 1.57 | Yes: 3.74 ± 1.39 |
| | | p < 0.001 | p < 0.001 | p < 0.001 |
| Supplemental Feeding on Day 1 and/or Day 2 | Day 1 | No: 3.62 ± 1.73 | No: 2.65 ± 1.50 | No: 3.30 ± 1.46 |
| | | Yes: 3.55 ± 1.69 | Yes: 3.55 ± 1.54 | Yes: 3.55 ± 1.34 |
| | | p = 0.749 | p < 0.001 | p = 0.185 |
| | Day 1 | ≤ 3 days: 3.15 ± 1.64 | ≤ 3 days: 3.00 ± 1.48 | ≤ 3 days: 3.10 ± 1.31 |
| | | > 3 days: 3.81 ± 1.69 | > 3 days: 3.38 ± 1.63 | > 3 days: 3.67 ± 1.38 |
| | | p = 0.002 | p = 0.052 | p = 0.001 |
| Divergent Validity (mean ± SD, p**) | Sex | Day 1 | Female: 3.46 ± 1.74 | Female: 3.18 ± 1.70 | Female: 3.37 ± 1.40 |
| | | Male: 3.67 ± 1.66 | Male: 3.29 ± 1.49 | Male: 3.54 ± 1.37 |
| | | p = 0.381 | p = 0.519 | p = 0.389 |
| Floor and Ceiling Effects* | | Day 1 | 0.4%/2.0% | 6.4%/0.8% | 0.0%/0.0% |
| | | Day 2 | 2.5%/0.0% | 18.0%/1.2% | 1.9%/0.0% |
| | | Day 3 | 2.7%/0.0% | 26.4%/0.9% | 1.8%/0.0% |

Note: All analysis using data of both primary and second rater on a specific day.
Abbreviations: CI, confidence interval; ClinRO, Clinician-Reported Outcome questionnaire; GC, general condition; PRESORS, Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System; ReSViNET, Respiratory Syncytial Virus Network; RSV, respiratory syncytial virus; SD, standard deviation; r, Pearson correlation coefficient; α, Cronbach alpha.

*GC1: 0 – No concerns (condition is stable and improving); 2 – Some concerns (may become unstable/requires close observation); 3 – Extremely concerned (unstable, requires immediate medical review).

*GC2: 0 – Excellent; 1 – Good; 2 – Fair; 3 – Poor.

*The day when the clinician rated the child ready for discharge.

*Floor and ceiling effects calculated as the percentage of the PRESORS with a minimum/maximum score.

*p value from Kruskal–Wallis rank sum test.

**p value from two-sided Wilcoxon rank-sum test with continuity correction.
The inter-rater reliability of the clinician-rated RSV severity for hospitalized children assessed on day 1 was below expected levels overall (ICC = 0.66; 95% CI, 0.55–0.75). Interpretation of this result should take into account the relatively homogeneous RSV severity of participants on day 1. Additionally, for one site, there were high levels of disagreement between the raters. For the remaining nine sites, the inter-rater reliability on day 1 was better (ICC = 0.79; 95% CI, 0.71–0.86). This finding indicates that the PRESORS can provide satisfactory inter-rater reliability and illustrates the key importance of clinician training before rating RSV severity: disagreement, such as that witnessed in the outlier site, needs to be avoided.

In conclusion, the PRESORS ClinRO and ObsRO both produced summary scores with acceptable internal consistency and convergent validity. PRESORS could be reliably used for and provided valuable insights into the evaluation of the severity of signs of pediatric RSV by both clinicians (ClinRO) and parents/caregivers (ObsRO). Further development and validation of the PRESORS to measure RSV severity in clinical trials are recommended.

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CONFLICT OF INTEREST
YV, DH, WVDE, SR, and HF are employees of Janssen Research & Development, LLC. JS and JW are former employees of Janssen Research & Development, LLC.

AUTHOR CONTRIBUTIONS
Yannick Vandendijck: Data curation; formal analysis; methodology; software; writing-original draft; writing-review and editing. Jane Scott: Conceptualization; methodology; writing-original draft; writing-review and editing. Dirk Heerwegh: Formal analysis; writing-review and editing. Wim Van Der Elst: Formal analysis; writing-review and editing. James Witek: Conceptualization; methodology; writing-review and editing. Rekha Sinha: Supervision; writing-review and editing. Hein Fennema: Conceptualization; formal analysis; methodology; writing-original draft; writing-review and editing.

PATIENT CONSENT STATEMENT
Informed consent for participation was obtained from each participant’s parent or caregiver prior to screening and enrollment in the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES
Does not apply to this study. The authors declare that this manuscript does not contain any previously published material (including figures/diagrams, or short extracts, or content taken from websites), and all figures and tables are original.

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DATA AVAILABILITY STATEMENT
The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/Transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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