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Psychometric Properties of the Symptoms of Infection with Coronavirus-19: A Patient-reported Outcome Measure for COVID-19 Signs and Symptoms

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Introduction

- The patient experience with COVID-19 is highly heterogeneous and can vary over time, ranging from asymptomatic infection to life-threatening pneumonia and long-term complications[1-3]
- PRO measures are a standardized and patient-centered approach to the analysis of disease trajectory, experience, and impact, with applications in research and clinical practice[4-5]
- The SIC is a PRO measure designed to assess the **presence** and **severity** of COVID-19 signs and symptoms in adults (**Figure 1**)[6]
- Previous qualitative and cross-sectional studies supported the content validity and preliminary psychometric properties of the SIC[6-8]

Objective

- To assess psychometric properties of the SIC by evaluating reliability, responsiveness, known-groups validity, and meaningful change thresholds using data from the phase 3 trial ENSEMBLE2 and following best practices aligned with current regulatory guidance[9-10]

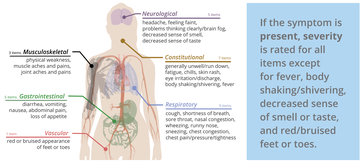
Figure 1. Development of the SIC.

Methods

The Symptoms of Infection with Coronavirus-19

- The SIC comprises 30 sign/symptom items, grouped by body system: respiratory (9 items), constitutional (7 items), gastrointestinal (5 items), neurological (5 items), musculoskeletal (3 items), and vascular (1 item; **Figure 2**)

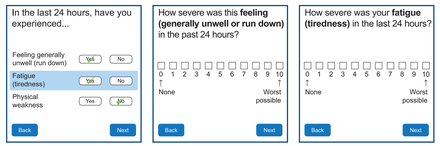
Figure 2. SIC conceptual framework.



If the symptom is **present**, **severity** is rated for all items except for fever, body shaking/shivering, decreased sense of smell or taste, and red/bruised feet or toes.

- Items are rated as present or absent (yes or no) during the prior 24 hours (**Figure 3**)

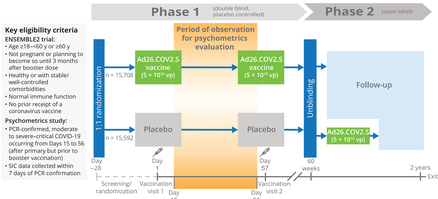
Figure 3. Sample SIC item scoring.



ENSEMBLE2

- ENSEMBLE2 (ClinicalTrials.gov Identifier: NCT04614948) was a multinational, randomized, double-blind, placebo-controlled, phase 3 trial assessing the safety, efficacy, and immunogenicity of the Ad26.COV2.S vaccine for the prevention of COVID-19 in adults[11] (**Figure 4**)
- ENSEMBLE2 followed the International Council for Harmonisation guidelines on Good Clinical Practice and principles of the Declaration of Helsinki; all participants provided informed consent

Figure 4. ENSEMBLE2 study design.



- In ENSEMBLE2, a total of 31,300 participants were enrolled and randomized 1:1 to receive a primary dose of Ad26.COV2.S (n = 15,708) or placebo (n = 15,592), plus a homologous booster dose or placebo dose at a 2-month interval
- Participants used an eCOA tool to complete the SIC at baseline before vaccination and throughout the study period for any suspected COVID-19 episode, defined as symptoms suggestive of COVID-19 and/or nonstudy positive PCR tests
- Two PRO measures were completed daily throughout each suspected COVID-19 episode:
  - SIC (to evaluate COVID-19 signs/symptoms)
  - PGIS (for validation of the SIC)
- A subset of ENSEMBLE2 participants from vaccine and placebo groups was included in the present psychometric analysis
  - Participants (n = 183) with PCR-confirmed moderate to severe–critical COVID-19 infection occurring from Days 15 to 56 and SIC data collected within 7 days of PCR confirmation were included in the psychometric analysis

Psychometric Properties

- In this trial, we evaluated psychometric properties of the SIC to expand the findings of a prior cross-sectional study (**Table 1**)[6-8]
- **Known-groups validity** was assessed by comparing mean differences in SIC item scores between subgroups using ANOVA
- **Internal consistency reliability** of the SIC composite scores at Day 1 of a COVID-19 episode was evaluated using Cronbach's coefficient alpha
- **Test-retest reliability** was evaluated among participants identified as stable by PGIS response via ICCs
- **Responsiveness** of the SIC was assessed via change in SIC composite scores from Days 1 to 2 (using ANOVA), with PGIS as an anchor variable
- **Meaningful change thresholds** of the SIC were calculated via ANOVAs and mean change scores (1- or 2-point improvement in PGIS)

Table 1. Psychometric Properties Assessed

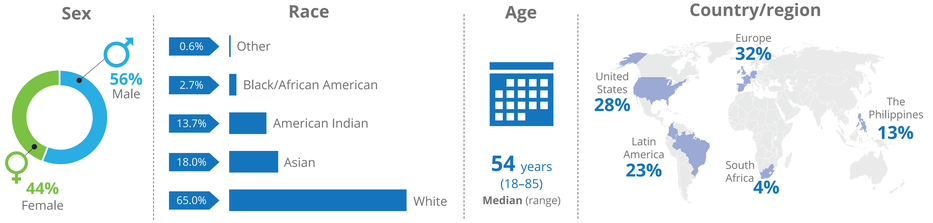
Psychometric analyses	Cross-sectional study[a]	Phase 3 trial (ENSEMBLE2)
Descriptive statistics	Item- and composite-level	
Inter-item correlations	Item-level	
Construct validity	Item- and composite-level	
Known-groups validity *Discriminating ability between groups known to differ on the variable of interest*	Item- and composite-level	Composite-level
Scoring	Preliminary	Confirmatory
Internal consistency reliability *How well items within an instrument measure aspects of the same construct and deliver reliable scores*	Composite-level	Composite-level
Test-retest reliability *Stability of scores when no change has occurred between assessment time points*		Composite-level
Responsiveness *The ability to detect change over time in a construct*		Composite-level
Meaningful change thresholds (based on PGIS) *The smallest change perceived as beneficial by participants*		Composite-level

Results

Participants

- 183 participants (**Figure 5**) from the ENSEMBLE2 trial met the inclusion criteria (ie, with PCR-confirmed moderate to severe–critical COVID-19 occurring between Days 15 and 56 after the first vaccination) and were included for the present psychometric evaluation; of these, 130 participants completed the SIC

Figure 5. Demographic and baseline characteristics.



Psychometric Evaluation

- Internal consistency reliabilities indicated that most SIC composite scores comprised items that were strongly related (**Table 2**)

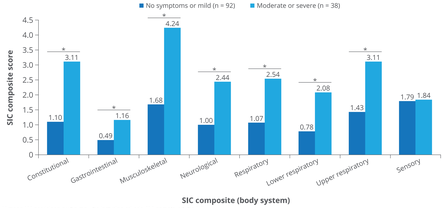
Table 2. SIC Internal Consistency Reliabilities at Day 1 of COVID-19 Episode

SIC composite score, N = 130*	Cronbach's alpha[b]	No. of items
Constitutional	0.71	6
Gastrointestinal	0.71	5
Musculoskeletal	0.82	3
Neurological	0.41	3
Sensory	0.87	2
Respiratory	0.82	9
Upper respiratory	0.80	4
Lower respiratory	0.75	5

*Among 183 participants who met the inclusion criteria, 130 completed the SIC.
[b]Cronbach's alpha ≥0.70 indicates strong internal consistency reliability.

- Known-groups analyses showed that mean differences in the SIC composite scores across PGIS severity levels were in the expected direction (**Figure 6**)
- Differences between severity groups were statistically significant ($P < 0.05$) for all composite scores except sensory, supporting known-groups validity and demonstrating that the SIC composite scores are an appropriate measure of COVID-19 symptom severity

Figure 6. Known-groups validity of SIC composite score by PGIS response at Day 1 of COVID-19 episode (N = 130*).



*Among 183 participants who met the inclusion criteria, 130 completed the SIC.
†P < 0.05.

- Test-retest reliabilities were strong for most SIC composite scores and were moderate for neurological and constitutional scores (**Table 3**)

Table 3. Test-retest Reliability Among Stable Patients at Days 1 and 2 of COVID-19 Episode

PGIS response of "no symptom" or "mild" at Days 1 and 2, n = 74	ICC (95% CI)
SIC composite score	
Constitutional	0.54 (0.39–0.70)
Gastrointestinal	0.67 (0.53–0.78)
Musculoskeletal	0.60 (0.44–0.73)
Neurological	0.50 (0.34–0.66)
Respiratory	0.73 (0.61–0.82)
Lower respiratory	0.67 (0.54–0.78)
Upper respiratory	0.72 (0.60–0.81)
Sensory	0.75 (0.63–0.83)
Same PGIS response at Days 1 and 2, n = 80	**ICC (95% CI)**
SIC composite score	
Constitutional	0.61 (0.46–0.73)
Gastrointestinal	0.72 (0.61–0.81)
Musculoskeletal	0.70 (0.57–0.80)
Neurological	0.52 (0.37–0.67)
Respiratory	0.70 (0.58–0.80)
Lower respiratory	0.64 (0.51–0.76)
Upper respiratory	0.70 (0.58–0.80)
Sensory	0.80 (0.70–0.86)

ICC scores of 0.20 to 0.40 indicate fair agreement, 0.41 to 0.60 indicate moderate agreement, 0.61 to 0.80 indicate strong agreement, and 0.81 to 1.00 indicate near complete agreement.

- Responsiveness was observed for all SIC composite scores
  - Improvement and worsening of PGIS ratings and SIC scores aligned directionally, supporting the ability of the SIC to detect changes over time in COVID-19 signs and symptoms
- Estimated meaningful change thresholds for the SIC composite scores, based on 1- or 2-point improvement in PGIS ratings, ranged from −0.22 for sensory (Day 3) to −2.11 for musculoskeletal (Day 5; **Table 4**)

Table 4. Meaningful Change Thresholds: Mean Change in Patients With 1- or 2-point PGIS Improvement, by Day of COVID-19 Episode

SIC composite score	Day 2 (n = 20)	Day 3 (n = 23)	Day 5 (n = 28)
Constitutional	−1.39	−1.53	−1.65
Gastrointestinal	−0.36	−0.21	−0.64
Musculoskeletal	−1.02	−1.77	−2.11
Neurological	−1.18	−1.36	−1.04
Respiratory	−1.09	−0.94	−0.98
Lower respiratory	−0.89	−0.74	−0.59
Upper respiratory	−1.35	−1.20	−1.47
Sensory	0	−0.22	−0.36

Conclusions

- This analysis builds on prior qualitative cross-sectional studies that supported the format of the SIC and the validity and reliability of individual items and composite scores
- Psychometric evaluation of SIC scores in a subset of participants from the global ENSEMBLE2 trial provided additional evidence for the SIC as a reliable and valid PRO measure for assessing COVID-19 signs and symptoms in adults
- These findings support the use of the SIC in both treatment and vaccine clinical trials
- Further studies are needed to validate the PRO measure for persistent symptoms following acute COVID-19 and the changing landscape of COVID-19 due to SARS-CoV-2 variants

Abbreviations

ANOVA, analysis of variance; CI, confidence interval; eCOA, electronic clinical outcome assessment; ICC, intra-class correlation; PCR, polymerase chain reaction; PGIS, Patient Global Impression of Severity; PRO, patient-reported outcome; SIC, Symptoms of Infection with Coronavirus-19.

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Disclosures

EKHC, JSt, YL, and EGK are employees of Janssen Global Services, LLC, and hold stock in Johnson & Johnson. YHL and KM were employees of Janssen at the time of the study. JSa is an employee of Janssen Research & Development and holds stock in Johnson & Johnson. IvD is an employee of Janssen Research & Development.

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