

The Psychometric Evaluation of the Immune Status Questionnaire in Indonesia

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ABSTRACT

Immunity is one of the key factors in Covid-19 transmission, thus, assessments of immune status are essential for evaluating transmission risks. This study aimed to assess the validity and reliability of the Immune Status Questionnaire (ISQ), a recently developed immune status measure, among Indonesian adults, during COVID-19 Pandemic.

Online Indonesian translated version of the ISQ and the Short Form 12 (SF-12) for measuring health-related quality of life were completed by 296 Indonesian adults (58% female, mean age=45±19 years old). Out of those, 102 (34%) completed a second survey one week later for the test-retest reliability assessment. The internal consistency reliability was assessed in both surveys. Confirmatory factor analysis was conducted to assess the construct validity. Correlations among ISQ items and between ISQ with SF-12 component summary were computed to assess the instruments' convergent and divergent validities.

Acceptable internal consistency reliabilities for the ISQ were found in the first and second surveys ($\alpha=0.87$ and 0.82 , respectively). Each ISQ item demonstrated excellent test-retest reliability, with intraclass correlations ranging from 0.70 to 0.88 . A good fit of the data was found with a root mean square error of approximation of 0.069 , after a model modification. Correlations among ISQ components and between ISQ with SF-12 components provided sufficient evidence for convergent validity of the scale while divergent validity was partially supported.

The validity and reliability of the Indonesian translated version of the ISQ for use in Indonesian adults are sufficiently demonstrated. The algorithm for computing ISQ in Indonesian adults, however, warrants further investigation.

Keywords: Validity, reliability, immune status questionnaire, cross-cultural adaptation, Indonesia, adults

Introduction

Indonesia, like many other countries worldwide, is greatly affected by the COVID-19 pandemic.(1,2) However, while many other countries have successfully contained the transmission rate, the COVID-19 cases in Indonesia continually increase exceeding 1.5 million confirmed cases, as reported in early 2021(2) Considered as one of the epicenters of the COVID-19 pandemic, Indonesia consistently has the highest case fatality rate (CFR) in Southeast Asia and has one of the highest CFR in the world.(1) To reduce the risk of community transmissions, social restriction policy is heavily imposed in Indonesia,(3,4) and elsewhere. (5,6). Although this policy has effectively flattened the cases,(7) it can also bring adverse effects on mental health,(5,8,9) physical activity level, (10) and quality of life (10). This could negatively affect the immune responses which could also further influence individuals' susceptibility to COVID 19 and the severity of COVID 19 infection. Therefore, the promotion of

healthy lifestyles to increase immunity is an important for curbing Covid-19 transmission and fatality rates. To assess the COVID-19 transmission risk, immune system assessments is also recommended both in the individual and population levels.

The immune system provides a defensive mechanism to overcome pathogen infection through myriad mechanisms involving a variety of immune system structures and cells.(11) Both innate and acquired immune responses encompass a variety of components which include physicochemical barriers, circulating molecules, cells, and soluble mediators.(11,12) Since there is no single marker of overall immune functional capacity in clinical and laboratory settings,(12) the status and functional capacity of the immune system, therefore, are assessed using a variety of approaches.(12)

In clinical settings, the assessments of immune status are frequently limited to only collecting blood and external secretions such as saliva, while in some experimental settings, biopsies of the gut

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or bronchoalveolar fluid may be collected.(12). Circulating cell counts, activation status, and responses to ex vivo stimulus may also be quantified in those circumstances.(12) The most common method in clinical settings is to count the number of plasma leukocytes.(12) It is followed by immunological labeling processes and associated analytical techniques such as flow cytometry to measure the total number of leukocytes and subclasses of leukocytes (e.g., neutrophils, monocytes, lymphocytes, T lymphocytes, B lymphocytes, CD4+ cells, CD8+ cells, natural killer cells) in the circulation.(12) In addition, assessment of immunoglobulin or antibodies,(13) interleukin,(14) and interferon in plasma(15) may also be conducted. However, these assessments tend to be expensive, difficult to perform, time-consuming, and invasive.(12) Even for the relatively non-invasive examinations using saliva or urine, specialist resources are required, thus, it is often considered as burdensome in clinical settings.(16) Thus, in the context when specialized laboratory test for assessing immunity status is unavailable, subjective immunity rating may be a more feasible approach. Moreover, to improve healthcare resource allocation in clinical practice, subjective immunity rating can be used as a screening tool to determine further biomarker assessments that are warranted.(16)

Several subjective immunity assessments have been developed to measure overall immune function using clinical indicators such as the 1-item perceived immune functioning,(16,17) Immune Function Questionnaire (IFQ),(18) the Immune System Assessment Questionnaire (ISAQ),(19) the Sickness Questionnaire (Sickness-Q),(20) and the Immune Status Questionnaire (ISQ).(16) Even though the 1-item perceived immune functioning has the advantage of being simple and the quickest to administer, it does not provide any information about the possible underlying causes. Thus, more complex multidimensional items such as the IFQ are usually preferred. However, an effort to simplify the questionnaire has been made which resulted in a 7-item scale ISQ, containing a third of the IFQ items.(16) Considered the most concise yet informative, this instrument may be the most suitable for screening purposes.

Similar to other subjective immune function scales, the ISQ is based on clinical symptoms related to the immune system.(16) During the instrument development, the ISQ has been validated in healthy adults and patients with

various forms of immune deficiency and chronic autoimmune diseases and demonstrated adequate face, content and construct validities as well as found to be reliable in assessing perceived immune status.(16) The use of the instrument has been reported in several studies in the adult population in the Netherlands,(17,21) Greece,(22) Saudi Arabia(23), Fiji(24), and Indonesia.(25,26) However, the ISQ has never been validated in the Indonesian context. Therefore, it is necessary to conduct cross-cultural adaptations of the instrument into the Indonesian context and language, to ensure that the instrument's validity and reliability are retained in the Indonesian version of the ISQ. Therefore, this study is aimed to evaluate the validity and reliability of the Indonesian version of the ISQ to justify the use of the instrument in evaluating the immunity status of the adult population in Indonesia.

Materials and Methods

Study Design, Study Sample and Ethical Consideration:

This study is a cross-sectional study on Indonesian adults, assessing the psychometric properties of the Indonesian version of the ISQ. The minimum sample size required for this study was 200 participants, as recommended by Myers (27) for confirmatory factor analysis. The number also exceed the minimum ratio of participants to number of items parameter of 20:1 as suggested by Jackson (28). Thus, our study participants, who were 296, was adequate for this analysis. Out of those 296 participants, 102 of them (34 %) participated in the second survey a week later for test and retest reliability analysis. Participants were provided with written informed consent. The study protocol was approved by the Human Ethics Committee of Gadjah Mada University (approval No. KE/0247/03/2021).

Data Collection Procedures and Measures:

Participants were invited to complete an initial survey and a second survey which was conducted 1 week later. In both surveys, participants self-completed the same online survey that included the socio-demographic questions, the ISQ, and the Short Form (SF-12).

Socio-demographic characteristics and anthropometric status: Participants were asked about their socio-demographic characteristics, such as age, sex, marital status, and two socio-economic status indicators: highest education and employment status. Participants were also asked to report their height and weight as indicators of anthropometric status.

squared and was categorized into underweight, normal weight and overweight according to a standard applicable to Asian population(33). The body mass index was also compared between groups using Pearson Chi-Square test. Means and standard deviations were calculated for each ISQ item, perceived immune function and perceived general health in the 1st and 2nd surveys. The proportion of participants reporting reduced immune function and with chronic illnesses were also calculated.

Test of Reliabilities: The internal consistency reliability of the ISQ was assessed using Cronbach's alpha, with an α of at least 0.70 to signify acceptable reliability.(34) We also calculated the 1-week test-retest reliability of each ISQ item by calculating the intra-class correlation (ICC) of the items (1-way single model). An ICC>0.60 was considered good, and an ICC>0.75 was judged excellent.(35)

Construct's Validity: Confirmatory factor analysis (CFA) was used to assess whether the original factor structure provided a good fit with the observed data. The calculation was based on the maximum likelihood estimation. If the fit was not satisfactory, model modification indices were created to guide a model specification. There were several criteria for the goodness of fit. First, a χ^2/df of less than 3.00 was required for a good fit.(36) Second, a root mean square error of approximation (RMSEA) of less than 0.08 suggested a good fit.(37) Lastly, a good fit was suggested by values of >0.90 for the Comparative Fit Index (CFI) and Tucker Lewis Index (TLI), as well as values of less than 0.08 for the standardized root mean square residual (SRMR).(38) We also calculated subscale factor loadings on each ISQ item. Factor loadings of 0.30 to 0.50 were considered low, 0.50 to 0.70 were considered moderate loading, and 0.70 were considered good loading.(39)

Divergent and Convergent Validity: Divergent validity was assessed by evaluating the correlations among the ISQ items and was demonstrated if the correlations were poor to fair ($r < 0.50$).(40) Convergent validity was assessed by evaluating the correlations between each item with the perceived general health and immune functioning of the ISQ and with the physical and mental component summary of the SF-12 and MCS. The convergent validity was demonstrated if correlations were strong ($r > 0.60$).(40) Spearman correlation coefficients were computed for these analyses, accounting for the non-normal distribution of the data.

Data were analysed using SPSS® version 21.0 (IBM Corp., Armonk, NY, USA), except for CFA, for which Stata 15 (Stata Corp, College Station,

TX, US) was used. For all tests, statistical significance was set at $p < 0.05$.

Results

Participants' Social Demographic Characteristics: In total, 296 participants completed the first data collection. Out of those, 102 participants completed the second survey for the test-retest reliability assessment (34%). Table 1 summarizes and compares characteristics of participants who completed only the 1st survey ($n=194$) and those who completed both the 1st and the 2nd survey for the test and retest assessment ($n=102$). Overall, the age of the participants ranged from 18 to 79 years, with a mean age of 45 ± 19 years. They were predominantly female, overweight, married, with primary or secondary education, and employed. The participants who completed the test-retest reliability assessment did not differ significantly on any of these characteristics from participants who only completed the first assessment ($p > 0.05$).

Descriptive Statistics and Immune Status Score Reliabilities: The Cronbach alphas for the ISQ in the first survey ($n=296$) and the second survey ($n=102$) were 0.87 and 0.82 thus indicated acceptable internal consistency reliability. All corrected item correlations for both assessments were acceptable and summarised in Table 2. The table also provides the ICC of each item which ranged from 0.70 to 88, thus demonstrated excellent test-retest reliability for all items.

Confirmatory Factor Analysis: Figure 1 illustrates the factor loadings for both the original (Figure 1a) and the modified factor structures (Figure 1b), while Table 3 summarises the goodness of fit statistics in both structures. All items loaded well into their composite summary except for skin which loaded poorly (factor loading < 0.50). The original factor structure indicated a poor fit (RMSEA=0.145). The model specification suggested a correlation between pain and headache, pain and skin, as well as headache and diarrhoea. Following the suggested modified structure resulted in all fit indices including the RMSEA of 0.069.

Convergent and Divergent Validity: As shown in Table 4, the divergent validity of the subscales was only partially supported with low and poor inter-subscale correlations ($r < 0.50$) among some of the ISQ items. Convergent validity, however, was supported by strong correlations between each item with the total ISQ score ($r = 0.63-0.82$) and between total ISQ score with the perceived general health ($r = -0.65$) and with perceived immune function ($r = -0.51$).

Table 1. Comparison of Participants' Sociodemographic Using Mann Whitney or Pearson Chi-Square

Characteristics	Total * (n=296)	Only completed the 1st survey (n=194)	Completed both surveys(n=102)**	p-value#
Age (years)	45±19	47±19	43±19	0.216*
Young adults (18-40)	129 (44%)	76 (39%)	53 (52%)	0.106
Mid-age adults (41-64)	101 (34%)	72 (37%)	29 (29%)	
Older adults (65-)	66 (22%)	46 (24%)	20 (19%)	
Sex				
Female	170 (57%)	117 (60%)	53 (52%)	0.167
Male	126 (43%)	77 (40%)	49 (48%)	
Body mass index				
Underweight <18.5	16 (6%)	10 (5%)	6 (6%)	0.425
Normal weight (18.5-23.5)	131 (44%)	81 (42%)	50 (49%)	
Overweight >23.5	149 (50%)	103 (53%)	46 (45%)	
Marital status				
Married	185 (62%)	125 (65%)	60 (59%)	0.343
Not Married	111 (38%)	69 (35%)	42 (41%)	
Education				
Primary/secondary	166 (56%)	114 (59%)	52 (51%)	0.200
Tertiary	130 (44%)	80 (41%)	50 (49%)	
Employment status				
Employed	222 (75%)	141 (73%)	81 (79%)	0.204
Unemployed/retired	74 (25%)	53 (27%)	21 (21%)	

#:P-values were derived from Pearson Chi-Square Except From Age Which Is Presented In Continuous Scale Was Compared Using Mann Whitney Test

It should be noted that fever, diarrhea, skin problems, cold, and coughing were not significantly correlated with PCS while fever and cold were also not correlated with MCS. However, a weak but significant correlation between total ISQ and PCS ($r=-0.25$) and MCS ($r=-0.29$) were found.

Discussion

After the initial development of the ISQ, to our knowledge, there has been only limited assessment of the ISQ psychometric properties in other population in the world,(21) while none were conducted in Indonesia. Although the ISQ had been used in several studies in Indonesia,(25,26) this study is the first study that thoroughly evaluates the validity and reliability of the cross-culturally adapted ISQ in the Indonesian population. The overall findings of this study provide satisfactory evidence that the Indonesian version of ISQ is a reliable and valid scale, thus can be used in monitoring and measuring immune status in Indonesian adults, which is important

amidst the height of the Covid-19 pandemic in this region.

Internal consistency reliability of the Indonesian translated version of the ISQ indicated acceptable internal consistency reliability (>0.7). The internal consistency values were much higher than what was reported by the ISQ developer which was conducted among Dutch students aged ranged from 18–30 years old (70 % female) that was 0.47.(16) The Cronbach alpha was also higher compared to a study in the Dutch general population (68% Female) during the Covid-19 pandemic which reported a Cronbach alpha of 0.67.(21) Women were slightly overrepresented in those surveys in the Dutch population compared to our study population (58%).(16,21) A substantial number of participants reported having underlying diseases (64.8%),(21) as opposed to ours which was 20%. The ISQ development study also reported that female participants reported significantly higher total ISQ scores than their male counterparts,(16) and this was not the case in our study. These differences may contribute to the discrepancies in the findings. The higher internal

Table 2. Descriptive Statistics and Reliabilities Assessments

	First Survey (n=296)				Second Survey (n=102)				ICC or Kappa*
	Mean or n	SD or %	Corrected item - subscale	α if item deleted	Mean or n	Mean or n	Corrected item - subscale	α if item deleted	
Sudden High Fever	0.61	0.82	0.63	0.85	0.43	0.71	0.51	0.81	0.82
Diarrhea	0.82	0.79	0.71	0.85	0.87	0.82	0.65	0.78	0.85
Headache	1.30	0.95	0.63	0.86	1.30	0.95	0.51	0.81	0.74
Skin Problem	1.35	0.95	0.52	0.87	1.30	0.97	0.50	0.81	0.88
Muscle and Joint Pain	1.39	0.90	0.61	0.86	1.34	0.94	0.51	0.81	0.87
Common Cold	1.03	0.80	0.71	0.85	1.02	0.87	0.60	0.79	0.87
Coughing	0.86	0.82	0.78	0.84	1.79	0.79	0.72	0.77	0.70
Total	7.37	4.54	-	-	7.07	4.21	-	-	0.85
Perceived immune function	7.81	1.07	-	-	7.88	1.02	-	-	0.79
Perceived General Health	7.88	1.05	-	-	8.14	1.03	-	-	0.73
Reduced immune function	n=62	21%	-	-	n=21	21%	-	-	0.95
Chronic illness	n=60	20%	-	-	n=16	16%	-	-	0.94

*=intraclass correlation

consistency in our study may also indicate that in a more diverse sample, the internal consistency reliability of the ISQ is improved. Our study also resulted in a good test re-test reliabilities which was comparable with those reported during the ISQ development(16) as well as in the study in the general Dutch population.(21) The overall findings provide evidence of good internal consistency and test and retest reliabilities of the Indonesian translated version of the ISQ.

To our knowledge, factor analysis of the ISQ has not been reported in the literature. In the factor analysis, we found that the original factor structure of the ISQ poorly fitted the data (RMSEA=0.145). The modification indices in the factor analysis then suggested that some components were correlated (i.e., headache and muscle/joint paint). Following the model

modification indices resulted in a significant model fit (RMSEA=0.069) and adequate loadings for each component. Our findings, thus, indicated that, while the suggested ISQ scoring assigns each component to equally contribute to the immune status score, the application of weighting each ISQ component in the ISQ scoring may be required. Further investigation is required to establish the most appropriate ISQ scoring algorithms, particularly in our target population.

Lastly, consistent with the findings from the factor analysis in a previous study.(16) Significant correlations among ISQ components and between the ISQ with the one-rated perceived immune function and general health were demonstrated,(16) thus, it supports the convergent validity of the ISQ. However, significant but only weak correlations were found between the total

Table 3. Goodness-of-fit Statistics of the Original and the Modified ISQ Structure (n=296)

	Hypothesised structure	Modified structure
χ^2/df	7.285	2.418
RMSEA (90%CI)	0.145 (0.120-0.173)	0.069 (0.036-0.103)
CFI	0.912	0.984
TLI	0.868	0.970
SMSR	0.063	0.031

Note: df, degree of freedom; RMSEA, Root Mean Square Approximation; CFI, Comparative Fit Index; TLI, Tucker Lewis Index; SMSR, Standardised Root Mean Square Residual

ISQ score with the PCS and MCS as the quality-of-life measures. The SF-12 consists of both physical and mental health components while the ISQ probed mostly physical health thus may limit the association. The overall evidence, however, suggests that the Indonesian version of the ISQ possesses adequate reliability and validity for use in populations of older adults in Indonesia.

Strengths and Limitations: A major strength of our study was that we thoroughly investigated the psychometric properties of the Indonesian ISQ using well-established guidelines.(29) Another strength was that our sample size exceeds the required sample size for factor analysis thus increasing the precision of the estimation.(28) However, the limitations of the study also need to be acknowledged. First, although our study sample was relatively heterogonous, our study recruited participants with internet access and social media, thereby limiting the generalizability of our findings to those who did not have access. Second, due to resource limitations, we did not confirm the ISQ data with the immune status assessments in the laboratory setting which is the assessment gold standard for convergent validity. Last, our cross-sectional design did not allow us to ascertain whether the ISQ is sensitive to time-related changes in health status, which is critical for use in clinical settings. Future research is recommended to involve participants with more heterogeneous characteristics, to use objective immune status assessment, and to employ longitudinal design to confirm the findings of this study.

This study provides the first evidence that the Indonesian-translated version of the ISQ is a reliable and valid measure of immune status among Indonesian adults. However, a more appropriate algorithm for computing ISQ scores for the Indonesian adult populations warrants further investigation. Longitudinal studies involving the use of objective immune system assessment in more heterogeneous samples which include healthy and immunosuppressed

populations are recommended to confirm the findings of this study.

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Conflict of Interest: No competing interest is declared.

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