BMJ Open

Integration of symptomatic, demographical and diet-related comorbidities data with SARS-CoV-2 antibody rapid diagnostic tests during epidemiological surveillance: a cross-sectional study in Jakarta, Indonesia

Rina Agustina [ID],[1,2] Ari Fahrial Syam,[3] Fadila Wirawan,[2] Indah S Widyahening,[4,5] Ahmad Jabir Rahyussalim,[6] Yusra Yusra,[7] Davrina Rianda,[2] Erlina Burhan,[8] Ngabila Salama,[9] Rebekka Daulay,[9] Ahmad Rhyza Vertando Halim,[9] Anuraj H Shankar[10,11]

For numbered affiliations see end of article.

Correspondence to
Dr Rina Agustina;
r.agustina@ui.ac.id

ABSTRACT

Objectives Affordable options for COVID-19 epidemiological surveillance are needed. Virus detection by reverse transcription-PCR (RT-PCR) is sensitive but costly, and antigen-based rapid diagnostic tests (RDTs) are cheap but with reduced sensitivity; both detect current infection but not exposure. RDT-IgM/IgG antibodies to SARS-CoV-2 detect exposure but have poor sensitivity for current infection. We investigated if the integration of symptomatic, demographical and diet-related comorbidities data with antibody RDTs improves their potential to assess infection rates in addition to exposure, thereby broadening their utility for surveillance.

Design We conducted a cross-sectional study using data from community surveillance for SARS-CoV-2. Health workers collected nasopharyngeal swabs for RT-PCR and RDT antigen assessments and venous blood for RDT-IgM/IgG from symptomatic and asymptomatic persons. Data on age, gender, contact history, symptoms (ie, fever, cough, runny nose, sore throat, headache, dyspnoea and diarrhoea), diet-related comorbidities (ie, diabetes and hypertension) and chest radiology were collected.

Setting High-risk communities in Jakarta, Indonesia, in May 2020.

Participants 343 community members' data were included.

Outcome measures RDT-IgM/IgG sensitivity, specificity and predictive values and area under receiver operating characteristic curve for RT-PCR positivity using RDT results alone and in combination with other predictors, including symptom components derived from principal component analysis.

Results There were 24 PCR-confirmed infections. RDT-IgM/IgG-positive tests were associated with infection (OR 10.8, 95% CI 4.43 to 26.4, p<0.001) with an area under the curve (AUC) of 0.708% and 50% sensitivity, 91.5% specificity, 30.8% positive predictive value (PPV) and 96.1% negative predictive value (NPV). RDT results combined with age, gender, contact history, symptoms and comorbidities increased the AUC to 0.787 and yielded 62.5% sensitivity, 87.0% specificity, 26.6% PPV and 96.9% NPV.

Conclusions SARS-CoV-2 RDT-IgM/IgG results integrated with other predictors may be an affordable tool for epidemiological surveillance for population-based COVID-19 exposure and current infection, especially in groups with outbreaks or high transmission.

Strengths and limitations of this study

► Data for symptoms, contact history, comorbidities, rapid diagnostic test (RDT)-IgM/IgG, RDT antigen and reverse transcription-PCR test were obtained on the same day from each person.

► The data were from COVID-19 active surveillance and self-reporting to SARS-CoV-2 screening centres in high-risk communities as part of routine surveillance and active case finding.

► Analyses used progressive integration of meta-data with RDT results, including the use of principal component analysis to identify patterns of data, assess predictive value and broaden the utility of RDT-IgM/IgG for concurrent infection, rapid surveillance and identification of high-transmission areas.

► The sensitivity of the first-generation RDTs used in this study may limit the ability to fully assess the value of progressive data integration for test interpretation.

INTRODUCTION

Since COVID-19 was first detected in Indonesia in early March 2020, cases increased rapidly. Indonesia became the country with the highest infections in Southeast Asia by mid-June 2020.[1] The municipal government

of Jakarta took action through case tracing, extensive testing and quarantine of infected and exposed persons.[2] By late November 2020, testing rates in Jakarta for SARS-CoV-2 through reverse transcription-PCR (RT-PCR) had reached 9.2 per 1000 persons per week, with a positivity rate of 8.3%,[3] much higher than the 5% threshold suggested by the WHO as adequate for reopening.[4] A surge in cases peaked in January 2021 before declining to a persistent plateau in April with spikes throughout the country. This underscores the need for intensified routine epidemiological surveillance and targeted action to detect and contain surges at an earlier stage. However, affordable surveillance and diagnostic tools for routine large-scale deployment remain limited.

The current gold standard for COVID-19 diagnosis is the detection of SARS-CoV-2 RNA by RT-PCR through nasopharyngeal or oropharyngeal swabs.[5] However, RT-PCR requires a certified laboratory, expensive equipment and trained personnel and can be time-consuming. These limitations create challenges for RT-PCR use for rapid mass screening for SARS-COV-2 infections, especially in countries with limited resources,[6] and it cannot detect past infection. An alternative is the immunochromatographic rapid diagnostic test (RDT), or lateral flow assay (LFA), as a quick and affordable point-of-care test that can detect SARS-CoV-2 antigens from swabs or IgM or IgG antibody in the blood.[5] However, the antigen RDT sensitivity for current infection is below that for RT-PCR and still provides no information on past infection. The IgM/IgG antibody RDT typically has poor predictive value for current infection due to the lag in onset of antibody production and is therefore much less sensitive than RT-PCR or antigen RDT and not suitable as a diagnostic tool.[7–10] However, the antibody RDT may be useful for rapid surveillance to help discern disease epidemiology.[5] Since disease surveillance is essential to control COVID-19,[11] improved population-based inference of both exposure and current infection from antibody RDT results could enable low-cost rapid mass surveillance to better detect and target community transmission.[12] We, therefore, hypothesised that real-time use of demographical and symptomatic data in conjunction with the results of the antibody RDT-IgM/IgG might enhance the value of such tests by enabling better estimation of both past exposure and current SARS-CoV-2 infection at the population level.

If there is added value of progressive integration of population-level and patient-level data to enhance inference of the RDT-IgM/IgG, then it may be a viable tool to help control COVID-19. Therefore, this study aims to assess the predictive value of progressive data integration with RDT results to detect SARS-CoV-2 infection, compared with RT-PCR alone. The results may provide insights for policy and action for surveillance and early detection and inform the design of mobile apps for point-of-use interpretation of RDT results.

METHODS
Study design and subject
A cross-sectional study was conducted using data from COVID-19 active case-finding surveillance activities of the Jakarta Provincial Health Office in seven high-transmission areas in May 2020. To assess the accuracy of screening and diagnostic tests for this study, a minimum of 339 samples was required, based on the previously known sensitivity and specificity of RDT-IgM/IgG for SARS-CoV-2 infection,[9] with an estimated positivity rate of 13%,[13] 95% CI (9.15% to 16.45%) and power of 90%.[14] A total of 379 subjects' data were available; however, two subjects were excluded due to missing PCR results, and 34 were excluded due to missing socio-demographics, symptoms and diet-related comorbidities, leaving 343 subjects who were included in these analyses, with complete data for RT-PCR, RDT-IgM/IgG, RDT antigen, socio-demographics, symptoms and comorbidities.

Patient and public involvement
Subjects of this study had no direct involvement in the design or conception of this study.

Data collection
The surveillance targeted densely populated hamlets with high COVID-19 transmission. The areas selected were based on the Jakarta Provincial Health Office's epidemiological indicators, including SARS-CoV-2 incidence rate (IR) per 100 000 population. The areas with IR in the highest quartile were designated as high-risk areas. The subjects were identified as high risk by the hamlet officers due to close contact with, or proximity to, a reported case and invited for active screening at a designated local primary or secondary health facility. The subjects included both genders, without age restrictions and regard to the presence of symptoms. Subjects were tested for SARS-CoV-2 by RDT-IgM/IgG, RDT antigen and RT-PCR. Information regarding age, sex, history of contact, area of residence, presence of signs or symptoms and coexisting comorbidities was collected through interviews. Venous blood samples were drawn to assess the RDT-IgM/IgG reactivity, and nasal swabs were taken on the same day for RDT antigen and RT-PCR confirmation assessment in an accredited laboratory. Three brands of RDT-IgM/IgG were used during the screening: Wondfo SARS-CoV-2 Antibody Test (n=223), Star Diagnostic Plus COVID-19 IgG/IgM (n=100) and GenBody COVID-19 IgM/IgG (n=20). Each subject was tested with only one brand, and reactivity data represent the pooled results of all the tests. The RDT antigen test was the Biocredit COVID-19. The RDT brand selection was based on its availability during the surveillance and permitted by the Ministry of Health to be used and distributed in Indonesia. All tests were carried out as per manufacturers' instructions.

Data analyses

Data were checked for duplicate and missing entries and analysed using STATA V.14. Subjects with missing variables were excluded from the analyses. The normal distributions of continuous data were checked using the Shapiro-Wilk test. RDT result, age, gender, contact history, symptoms, diet-related comorbidities and pneumonia findings were compared with the RT-PCR result, which was considered as the gold standard. Comparisons between these independent variables and RT-PCR results were performed using binary logistic regression for univariate and stepwise logistic regression for multivariate analyses. We included all the variables in the multivariate logistic regression. Firth logistic regression, a penalised likelihood-based method, was used where small to zero case numbers were present.[15] This is a preferred solution for small-to-medium-sized data sets wherein one parameter estimate may be infinite if responses and non-responses are perfectly separated by a single risk factor or combination of risk factors, for example, a contingency table with a cell populated with zero counts,[16] a phenomenon known as 'separation' or 'monotone likelihood'.[17 18] Principal component analysis (PCA) was carried out for symptom variables, and components were used as predictors in the multivariate logistic regression. We obtained the receiver operating characteristic (ROC) curve and area under the curve (AUC) to evaluate the RDT test vis-à-vis RT-PCR accuracy. The AUC value was used to determine the predictive quality of independent variables, with a minimum of zero and a maximum of one, with the latter indicating perfect differentiation by the test.[19] Specificities, sensitivities, positive predictive values (PPV) and negative predictive values (NPV) were calculated for each set of predictors based on the acquired ROC curve.[20] All analyses were two-tailed, and p values <0.05 were considered significant.

RESULTS

A total of 343 subjects were included in the analysis. The distribution of age, gender, COVID-19 contact history and Jakarta residence by infection status is presented in table 1. The median participant age was 41, ranging from 4 to 80 years old. There were 24/343 (7%) subjects who tested positive for SARS-CoV-2 by RT-PCR. The mean age of COVID-19-confirmed cases was 46 years, with 58% (14/24) older than 45 years, which was higher than the mean age of 40 for the uninfected subjects. Women comprised 58% of all cases, and most (71.7%) did not have a history of contact with patients with COVID-19. Residents of Jakarta formed 90.1% of the sample, as could be expected, given the designated survey area.

The distribution of the symptoms, RDT results and coexisting comorbidities is summarised in table 2. Only 15.5% (53/343) of all the subjects had any COVID-19 symptoms. Among the symptoms, cough was the most frequently reported at 9.6% (33/343) in all subjects and 20.8% (5/24) among the COVID-19 cases. There were 39/343 (11.4%) subjects reactive by RDT-IgM/IgG test, with 12/24 (50.0%) positive by RT-PCR. In contrast, only one subject was reactive by RDT antigen test, but was negative by RT-PCR. The data show that RDT-IgM/IgG had 30.8% PPV and 96.1% NPV, while RDT antigen had 0% PPV and 93.0% NPV. Table 3 presents the associations between demographical characteristics, symptoms, coexisting comorbidities and RDT results with RT-PCR results. In a multivariate model, an RDT-IgM/IgG reactive test was significantly associated with RT-PCR positivity with

Table 1 General characteristics of the study subjects by category of reverse transcription-PCR (RT-PCR) test results (n=343)

		RT-PCR test for SARS-CoV-2	
	All	**Positive**	**Negative**
Characteristics	**n=343**	**n=24**	**n=319**
Age (yr)*	41.3 (28.4, 51.4)	46.7 (38.7, 57.1)	40.9 (28.4, 51.2)
Age group (yr), n (%)			
<45	196 (57.3)	10 (41.7)	186 (58.3)
≥45	147 (42.7)	14 (58.3)	133 (41.7)
Gender, n (%)			
Man, n (%)	193 (56.3)	10 (41.7)	183 (57.4)
Woman, n (%)	150 (43.9)	14 (58.3)	136 (42.6)
Contact history, n (%)			
No	246 (71.7)	19 (79.2)	227 (71.2)
Yes	97 (28.3)	5 (20.8)	92 (28.8)
Residence of Jakarta province			
No	34 (9.9)	0 (0.0)	34 (10.7)
Yes	309 (90.1)	24 (100.0)	285 (89.3)

*Median (25th percentile and 75th percentile).

Table 2 Subjects' sign, symptom and coexisting diet-related comorbidities characteristics (n=343)

Characteristics	All n=343	Positive for SARS-CoV-2 n=24	Negative for SARS-CoV-2 n=319
Any symptoms, n (%)	53 (15.5)	6 (25.0)	47 (14.7)
Fever	26 (7.6)	2 (8.3)	24 (7.5)
Headache	15 (4.4)	1 (4.2)	14 (4.4)
Runny nose	16 (4.7)	2 (8.3)	14 (4.4)
Cough	33 (9.6)	5 (20.8)	28 (8.8)
Sore throat	18 (5.2)	3 (12.5)	15 (4.7)
Dyspnoea	13 (3.8)	0 (0.0)	13 (4.1)
GI track complaints	4 (1.2)	0 (0.0)	4 (1.3)
Coexisting diet-related comorbidities, n (%)			
Diabetes	8 (2.3)	1 (4.2)	7 (2.2)
Hypertension	17 (5.0)	1 (4.2)	16 (5.0)
RDT-IgM/IgG			
Non-reactive	304 (88.6)	12 (50.0)	292 (91.5)
Reactive	39 (11.4)	12 (50.0)	27 (8.5)
RDT antigen			
Non-reactive	342 (99.7)	24 (100)	318 (99.7)
Reactive	1 (0.3)	0 (0.0)	1 (0.3)
Chest radiograph abnormality, n (%)			
Pneumonia	5 (1.5)	0 (0.0)	5 (1.6)

GI, gastrointestinal; RDT, rapid diagnostic test.

an OR 9.19, 95% CI 2.46 to 23.8 and p value <0.001 after adjustment for age, gender, place of residence in Jakarta, cough and sore throat. Based on the ROC analyses using RT-PCR as the gold standard, the RDT-IgM/IgG tests had an AUC of 0.708. Overall sensitivity and specificity of the RDT-IgM/IgG test were 50.0% and 91.5%, respectively. The RDT antigen test performed poorly with a sensitivity of 0.0% and specificity of 99.7%. The adjusted ROCs integrating other predictors and RT-PCR as the gold standard are presented in figure 1. RDT-IgM/IgG antibody, combined with age, gender, and contact history, had a higher AUC of 0.757 (figure 1A) compared with age, gender and contact history without RDT, which had an AUC of 0.631 (figure 1B). RDT-IgM/IgG combined with age, gender, contact history, signs and symptoms showed an AUC of 0.787, 62.5% sensitivity, 87.0% specificity, 26.6% PPV and 96.9% NPV (figure 1C) and was similar to the AUC when RDT-IgM/IgG was analysed together with age, gender, contact history, signs and symptoms and with comorbidities, with an AUC of 0.787 (figure 1D). The ROC without RDT-IgM/IgG, but with age, gender, contact history, signs and symptoms and with and without comorbidities combined, yielded an AUC of only 0.696 (figure 1E) and 0.692 (figure 1F), respectively. We also included the primary component from the PCA of symptoms, together with RDT-IgM/IgG result, age, gender, contact history and comorbidities (figure 2), which yielded an AUC of 0.706 (figure 2A), compared with PCA

alone with an AUC of 0.552 (figure 2B); RDT-IgM/IgG and PCA with an AUC of 0.732 (figure 2C); and RDT-IgG/IgM, age, gender, contact history and PCA with an AUC of 0.751 (figure 2D).

DISCUSSION

The present findings indicate that integrating symptoms and demographical data broadens the utility of SARS-CoV-2 antibody RDTs for epidemiological surveillance of current and past infections. The predictive performance of the RDT-IgM/IgG for RT-PCR confirmed infection is enhanced by progressive data integration with demographical characteristics, contact information, symptoms and diet-related comorbidities, exceeding the predictive value of each variable individually or RDT alone. Interpreting RDT-IgM/IgG results with subject meta-data improves the sensitivity, thereby showing the value of this integration for population-level inference. These findings may be useful for enhancing COVID-19 surveillance.

Integrating the RDT-IgM/IgG result with the meta-data yielded a 12.5% absolute increase in the sensitivity, a 25% relative increase, with little loss of specificity. Better sensitivity would provide fewer false-negative results, leading to fewer actual cases being missed, thereby increasing the potential value for population-based screening and enumeration of possible active infections.[21] Additionally,

Table 3 Univariate and multivariate logistic regression of predictors of SARS-CoV-2 infection (n=343)

| Characteristic | Yes, n (%) | Positive for SARS-CoV-2 | | | |
| | | Univariate | | Multivariate* | |
		OR (95% CI)	P value	OR (95% CI)	P value
RDT-IgM/IgG					
Non-reactive	12 (50.0)	1.00		1.00	
Reactive	12 (50.0)	10.8 (4.43 to 26.39)	<0.001†	9.19 (3.46 to 23.8)	<0.001†
RDT antigen					
Non-reactive	24 (100)	1.00		1.00	
Reactive	0 (0)	0.08 (0.05 to 0.11)	<0.001†	3.63 (0.13 to 101.1)	0.450
Demographical					
Age category, year					
<45	10 (41.7)	1.00		1.00	
≥45	14 (58.3)	1.96 (0.84 to 4.54)	0.118	2.07 (0.83 to 5.16)	0.120
Gender					
Woman	14 (58.3)	1.00		1.00	
Man	10 (41.7)	0.53 (0.23 to 1.23)	0.140	0.65 (0.26 to 1.64)	0.428
History of contact					
No	19 (79.2)	1.00		1.00	
Yes	5 (20.8)	0.65 (0.24 to 1.79)	0.404	0.79 (0.27 to 2.32)	0.666
Residence of Jakarta province					
No	0 (0.0)	1.00		1.00	
Yes	24 (100.0)	5.92 (0.35 to 99.55)	0.217	6.23 (0.35 to 110.9)	0.213
Symptoms					
Fever					
No	22 (91.7)	1.00		1.00	
Yes	2 (8.3)	1.12 (0.25 to 5.04)	0.885	1.07 (0.18 to 6.31)	0.942
Cough					
No	19 (79.2)	1.00		1.00	
Yes	5 (20.8)	2.73 (0.95 to 7.88)	0.063	5.06 (0.84 to 30.6)	0.078
Sore throat					
No	21 (87.5)	1.00		1.00	
Yes	3 (12.5)	2.90 (0.78 to 10.80)	0.113	2.30 (0.42 to 12.6)	0.337
Runny nose					
No	22 (91.7)	1.00		1.00	
Yes	2 (8.3)	1.98 (0.42 to 9.27)	0.386	0.86 (0.09 to 8.08)	0.895
Dyspnoea					
No	24 (100.0)	1.00		1.00	
Yes	0 (0.0)	0.46 (0.03 to 8.03)	0.597	0.15 (0.02 to 7.24)	0.334
GI tract complaints					
No	24 (100.0)	1.00		1.00	
Yes	0 (0.0)	1.43 (0.07 to 27.35)	0.812	3.11 (0.02 to 476.9)	0.333
Headache					
No	23 (95.8)	1.00		1.00	
Yes	1 (4.2)	0.95 (0.12 to 7.53)	0.959	0.57 (0.05 to 6.47)	0.648
Radiology abnormalities					
Pneumonia					

Continued

Table 3 Continued

| Characteristic | Yes, n (%) | Positive for SARS-CoV-2 | | | |
| | | Univariate | | Multivariate* | |
		OR (95% CI)	P value	OR (95% CI)	P value
No	24 (100.0)	1.00		1.00	
Yes	0 (0.0)	1.17 (0.06 to 21.7)	0.918	1.11 (0.01 to 87.9)	0.964
Coexisting diet-related comorbidities					
Diabetes mellitus					
No	23 (95.8)	1.00		1.00	
Yes	1 (4.2)	1.94 (0.23 to 16.4)	0.554	1.42 (0.14 to 14.3)	0.767
Hypertension					
No	23 (95.8)	1.00		1.00	
Yes	1 (4.2)	0.82 (0.10 to 6.49)	0.854	0.69 (0.08 to 6.20)	0.918

*Firthlogit analyses were applied for the multivariable model.
†Significant at p<0.05.
GI, gastrointestinal; RDT, rapid diagnostic test.

our findings show that the RDT-IgM/IgG test has high specificity and high NPV but low PPV. Combined with other data, the RDT-IgM/IgG could be useful as a screen for hotspot surveillance, but not for individual diagnosis, and in high-risk groups, with the option for an RT-PCR assessment to complement surveillance as needed.

The antibody RDT performance results herein are comparable to, or somewhat below, previous studies[7 9 22–24] and below manufacturer and postmarket reports of the three antibody RDTs used in this study: Wondfo SARS-CoV-2 Antibody Test was reported to have 86% combined sensitivity and 99% combined specificity[25], Star Diagnostic Plus COVID-19 IgG/IgM was reported as 93% sensitivity and 97% specificity[26] and GenBody COVID-19 IgM/IgG was reported as 60% combined IgM/IgG sensitivity and 98.8% combined
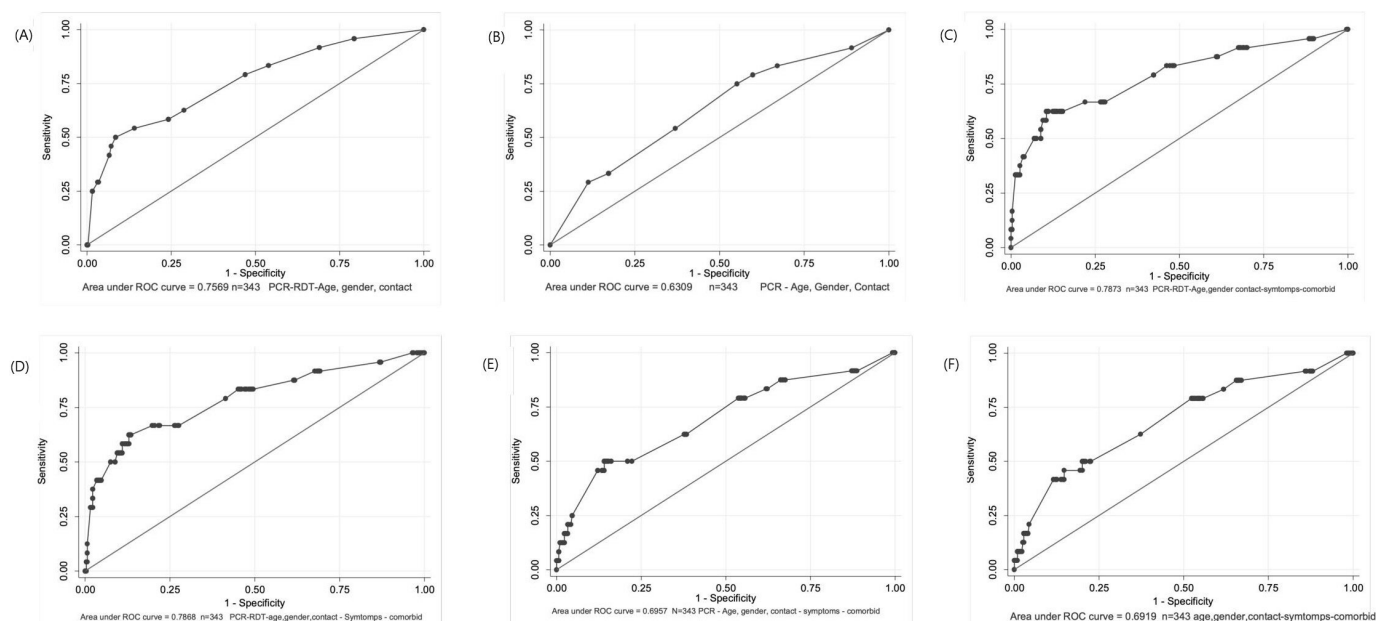
Figure 1 Adjusted receiver operating characteristic curves for integration of variables in comparison with reverse transcription-PCR test. (A) RDT-IgM/IgG, age, gender and contact history combined in comparison with PCR results; (B) age, gender and contact history combined, without RDT-IgM/IgG, in comparison with PCR results; (C) RDT-IgM/IgG, age, gender, contact history, signs and symptoms* combined in comparison with PCR results†; (D) RDT-IgM/IgG, age, gender, contact history, signs, symptoms* and diet-related comorbidities combined in comparison with PCR results; (E) age, gender, contact history, signs and symptoms*, without RDT-IgM/IgG, combined in comparison with PCR results; (F) age, gender, contact history, signs, symptoms* and diet-related comorbidities, without RDT-IgM/IgG, combined in comparison with PCR results. AUC, area under the curve; PCA, principal component analysis; RDT, rapid diagnostic test. *Excluding dyspnoea and diarrhoea. †Sensitivity, 62.5%; specificity, 87.0%; positive predictive value, 26.6%; negative predictive value, 96.9%.
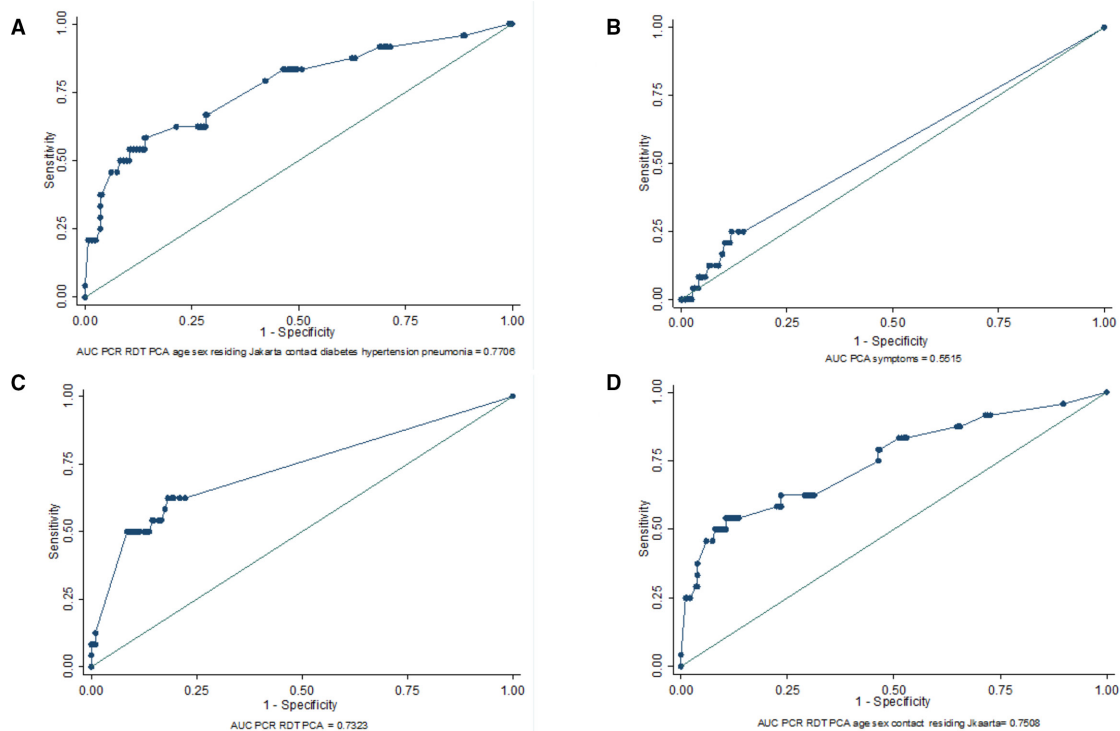
Figure 2 Adjusted receiver operating characteristic curves for principal component analysis (PCA) and combination of variables in comparison with reverse transcription-PCR test. (A) RDT-IgM/IgG, age, gender, contact history, diet-related comorbidities and PCA combined in comparison with PCR results; (B) PCA in comparison with PCR results; (C) RDT-IgM/IgG and PCA combined in comparison with PCR results; (D) RDT-IgM/IgG, age, gender, contact history and PCA combined in comparison with PCR results. PCA loading matrix: fever, 0.701; cough, 0.754; runny nose, 0.698; sore throat, 0.658; dyspnoea, 0.704; headache, 0.620; and diarrhoea, 0.579. AUC, area under the curve; RDT, rapid diagnostic test.

IgM/gG specificity.[27] For the RDTs with a combined IgM and IgG readout (ie, not separate lines on the test readout), a reactive test with negative RT-PCR result may be due to detected IgG but no IgM, which could indicate past, but not current, infection. Based on a report of SARS-CoV-2 antibody responses using a magnetic chemiluminescence enzyme immunoassay, expected to be more sensitive than an LFA-based RDT, IgM and IgG may appear within 2 days from onset of symptoms in approximately 30% of patients, with nearly 100% being positive by day 19.[28] Meta-analysis on the diagnostic accuracy of SARS-CoV-2 IgM/IgG tests reported that RDT accuracy was higher 2 weeks after the onset of symptoms compared with earlier than 2 weeks and reported up to 40% false-negative rates in the early onset of infection due to undetected IgM. Therefore, the RDTs provide low individual diagnostic capacity in the clinical setting but may have value in population surveillance.[22 23] Concerning the antigen RDT results herein, performance was very poor for these early-release 'first-generation' tests, even below other reports for early-release antigen RDTs,[8 10] but higher sensitivity and specificity of more recent RDT antigen tests are encouraging.[29 30] However, we note these would detect current infection and typically only during the first week of disease when viral shedding is high, thereby being useful primarily for early case diagnosis, with less epidemiological utility for discerning past

infection.[24 29] In general, RDT accuracy is known to be variable due to test differences from manufacturers, the timing of the test and the assay method.[31 32]

Limited studies have assessed RDTs in combination with symptoms to enhance the value of SARS-CoV-2 RDTs for exposure or infection. Some studies, however, reported a symptom-based model for COVID-19 diagnosis. Twenty-two multivariable, symptom-based diagnostic models were identified in a systematic review of diagnostic predictors for COVID-19.[33 34] The reported performance ranged from moderate to excellent. However, the risk of bias was high due to poor methodology in many studies. Most were based on hospital admission reports and therefore would not represent community-based results, as reported here.[33] Another study in the UK and the USA based on self-reported symptoms using a smartphone-based app reported an excellent association between symptoms and RT-PCR results, with a ROC curve analysis with AUCs of 0.76 in both UK and US sites.[35] The traits and symptoms included in the previous studies, including loss of smell and taste as predictors, were different from the symptoms in the current study. Further, the previous studies did not include RDT-IgM/IgG results as predictors. The current study showed RDT-IgM/IgG and data integration without including diarrhoea and dyspnoea improved the sensitivity of RDT-IgM/IgG, which could enhance support for early tracing. However, having more

symptoms included in the data integration would likely improve the inference.

Adaptive approaches in SARS-CoV-2 epidemiological surveillance using digital platforms to integrate data, such as real-time disease hotspot digital mapping and diagnosis, were reported to be effective in South Korea.[36] A study in the UK shows SARS-CoV-2-symptom-based mobile applications could facilitate health advice and guided medical direction at the population level.[37] Further, learning from past cases of the severe acute respiratory syndrome and the West African Ebola epidemic, separating RDT test results and epidemiological reporting led to under-reporting and difficulties in health service planning.[38 39] Cities in low-income and middle-income countries with dense populations are especially vulnerable to high COVID-19 transmission,[40] and systems capable of real-time tracking of RDT results and symptoms would bring more efficiency in mapping hotspot areas. Hence, follow-up steps such as PCR confirmation could be implemented more efficiently and effectively, avoiding over-burdening of laboratory capacity, thereby using public health capacities more efficiently. Ideally, open-source and free apps would be available to read an RDT result and interpret them based on patient or subject symptoms and other priors and facilitate swab collection for RT-PCR and further data integration.

This study had some limitations and potential bias. The subjects included in the surveillance may have been limited to those living and working in COVID-19-high-risk areas. In addition, RDT accuracy would be expected to be heterogeneous due to the three different RDT types that were pooled. The RT-PCR as the reference for diagnosis was performed by different laboratories and may be another source of variance. Moreover, the timing of the tests with respect to infection status or time after infection would be different for each person assessed, and this would interact differently with varying test methods. The data did not include time since symptom onset, nor certain additional symptoms such as loss of smell and taste.[35] Moreover, we used secondary data, wherein collection methods might have varied.

CONCLUSION

Data integration of RDT-IgM/IgG results with other predictors, namely, demographic characteristics, contact and clinical information, improves the population-based sensitivity for the number of current infections, thereby broadening the potential utility of RDT serology for inference of current and past infections. As such, the RDTs could serve as a useful tool for population-level surveillance, especially in hotspots such as high-prevalence areas and populations.

Author affiliations
[1]Department of Nutrition, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[2]Human Nutrition Research Center - Indonesian Medical Education and Research Institute (HNRC-IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[4]Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[5]Clinical Epidemiology and Evidence-Based Medicine Unit, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[6]Department of Orthopedic and Traumatology, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[7]Department of Clinical Pathology, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[8]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[9]Health Office, Government of DKI Jakarta Province, Jakarta, Indonesia
[10]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
[11]Eijkman-Oxford Clinical Research Unit, Eijkman Institute for Molecular Biology, Jakarta, Indonesia

ORCID iD
Rina Agustina http://orcid.org/0000-0002-8464-1037

REFERENCES

1 Task force for the acceleration of coronavirus handling. Available: https://covid19.go.id/ [Accessed 22 Jun 2020].
2 Djalante R, Lassa J, Setiamarga D, *et al*. Review and analysis of current responses to COVID-19 in Indonesia: period of January to March 2020. *Prog Disaster Sci* 2020;6:100091.
3 Provincial Government of DKI Jakarta. Available: https://corona.jakarta.go.id/id/data-pemantauan [Accessed 2 Dec 2020].
4 World Health Organization. *Public health criteria to adjust public health and social measures in the context of COVID-19*, 2020.

5 Tang Y-W, Schmitz JE, Persing DH, *et al*. Laboratory diagnosis of COVID-19: current issues and challenges. *J Clin Microbiol* 2020;58.
6 Ferrari D, Motta A, Strollo M, *et al*. Routine blood tests as a potential diagnostic tool for COVID-19. *Clin Chem Lab Med* 2020;58:1095–9.
7 Li Z, Yi Y, Luo X, *et al*. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol* 2020;92:1518–24.
8 Scohy A, Anantharajah A, Bodéus M, *et al*. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. *J Clin Virol* 2020;129:104455.
9 Zainol Rashid Z, Othman SN, Abdul Samat MN, *et al*. Diagnostic performance of COVID-19 serology assays. *Malays J Pathol* 2020;42:13–21.
10 Mak GC, Cheng PK, Lau SS, *et al*. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. *J Clin Virol* 2020;129:104500.
11 World Health Organization. *Surveillance strategies for COVID-19 human infection*. World Health Organization, 2020.
12 Peixoto VR, Nunes C, Abrantes A. Epidemic surveillance of Covid-19: considering uncertainty and Under-Ascertainment. *Port J Public Health* 2020;38:23–9.
13 Provincial Government of DKI Jakarta. Available: https://corona.jakarta.go.id/id/data-pemantauan [Accessed 8 Aug 2020].
14 Negida A, Fahim NK, Negida Y. Sample Size Calculation Guide - Part 4: How to Calculate the Sample Size for a Diagnostic Test Accuracy Study based on Sensitivity, Specificity, and the Area Under the ROC Curve. *Adv J Emerg Med* 2019;3:e33.
15 Firth D. Bias reduction of maximum likelihood estimates. *Biometrika* 1993;80:27–38.
16 Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med* 2002;21:2409–19.
17 Bryson MC, Johnson ME. The incidence of monotone likelihood in the Cox model. *Technometrics* 1981;23:381–3.
18 Albert A, Anderson JA. On the existence of maximum likelihood estimates in logistic regression models. *Biometrika* 1984;71:1–10.
19 Hajian-Tilaki K. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. *Caspian J Intern Med* 2013;4:627–35.
20 Tenny S, Hoffman M. *Prevalence*. StatPearls, 2020.
21 Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhalation Toxicology* 2019.
22 Castro R, Luz PM, Wakimoto MD, *et al*. COVID-19: a meta-analysis of diagnostic test accuracy of commercial assays registered in Brazil. *Sociedade Brasileira de Infectologia* 2020.
23 Chen M, Qin R, Jiang M, *et al*. Clinical applications of detecting IgG, IgM or IgA antibody for the diagnosis of COVID-19: a meta-analysis and systematic review. *Int J of Dis* 2021;104:415–22.
24 Riccò M, Ferraro P, Gualerzi G, *et al*. Point-of-Care diagnostic tests for detecting SARS-CoV-2 antibodies: a systematic review and meta-analysis of real-world data. *J Clin Med* 2020;9:1515.
25 Bond K, Nicholson S, Hoang T, *et al*. Post-market validation of serological assays for COVID-19 2020.
26 Labhouse. COVID-19 IgG/IgM WB/S/P cassette. Available: https://www.labhouse.id/products/detail/covid_19_igg_igm_wb_s_p_cassette [Accessed 15 Apr 2021].
27 Serology Test Evaluation Report for "GenBody COVID-19 IgM/IgG" from GenBody Inc, 2020. Available: https://www.accessdata.fda.gov/cdrh_docs/presentations/maf/maf3300-a001.pdf [Accessed 15 Apr 2021].
28 Long Q-X, Liu B-Z, Deng H-J, *et al*. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med* 2020;26:845–8.
29 Porte L, Legarraga P, Vollrath V, *et al*. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. *Int J Infect Dis* 2020;99:328–33.
30 Corman VM, Haage VC, Bleicker T. Comparison of seven commercial SARS-CoV-2 rapid point-of-care antigen tests 2020.
31 Hoffman T, Nissen K, Krambrich J, *et al*. Evaluation of a COVID-19 IgM and IgG rapid test; an efficient tool for assessment of past exposure to SARS-CoV-2. *Infect Ecol Epidemiol* 2020;10:1754538.
32 Lisboa Bastos M, Tavaziva G, Abidi SK, *et al*. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. *BMJ* 2020;24:m2516.
33 Wynants L, Van Calster B, Collins GS. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ* 2020;04:m1328.
34 Burhan E, Syam AF, Rahyussalim AJ. The emergence of COVID-19 in Indonesia: analysis of predictors of infection and mortality using independent and clustered data approaches 2020.
35 Menni C, Valdes AM, Freidin MB, *et al*. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med* 2020;26:1037–40.
36 Lee D, Lee J. Testing on the move: South Korea's rapid response to the COVID-19 pandemic. *Transp Res Interdiscip Perspect* 2020;5:100111.
37 Drew DA, Nguyen LH, Steves CJ, *et al*. Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* 2020;368:1362–7.
38 Al-Tawfiq JA, Zumla A, Gautret P, *et al*. Surveillance for emerging respiratory viruses. *Lancet Infect Dis* 2014;14:992–1000.
39 Cori A, Donnelly CA, Dorigatti I, *et al*. Key data for outbreak evaluation: building on the Ebola experience. *Philos Trans R Soc Lond B Biol Sci* 2017;372:20160371.
40 Reyes-Vega MF, Soto-Cabezas MG, Cárdenas F, *et al*. SARS-CoV-2 prevalence associated to low socioeconomic status and overcrowding in an LMIC megacity: a population-based seroepidemiological survey in Lima, Peru. *EClinicalMedicine* 2021;34:100801.