Performance Ranking of Diagnostic SARS-CoV-2 IgG Antibody Tests by Using Multi-Criteria Decision-Making Theory

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***Abstract*—Many different serological tests have been developed to support healthcare workers to identify individuals who may have developed an adaptive immune response to SARS-CoV-2. The study aimed to evaluate the test performances of the FDA EUA Authorized SARS-CoV-2 IgG antibody tests that are currently being used in coronavirus disease 2019 management. The study involved 48 SARS-CoV-2 IgG antibody tests. Different criteria of rapid diagnostic tests, plate-based tests, and immunoassay-based tests were evaluated by using multi-criteria decision making (MCDM) theory. While comparing the antibody tests, main criteria such as analytic sensitivity, specificity, positive predictive value, negative predictive value, specimen type, test technique, antigen target, time to first result, time of sampling days post infection, reagent storage conditions, practicability, etc. were assessed and used for determining the ranking of tests. The results showed that, Siemens ADVIA Centaur was the most representative of expected test performance, followed by QUANTA Flash and Siemens Dimension Vista S, while EUROIMMUN was the least favorable one. Fuzzy PROMETHEE technique can be applied in aiding decision-makers in choosing the right antibody test for the management of COVID-19.**

Keywords— SARS-CoV-2 IgG, COVID-19, Fuzzy PROMETHEE, MCDM

I. Introduction

The new Coronavirus Disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected in December 2019, has quickly spread worldwide, becoming a pandemic. Globally, more than 260 million infections involving over 5.2 million deaths have been reported up to date [1]. Novel Coronavirus is highly contagious and transmissible mainly by droplets and close contact; therefore, besides vaccination, early detection, isolation, and treatment undoubtedly play a crucial role in limiting the spread of the new virus [2].

Antibody testing is a significant and useful tool as a complementary approach to the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test in managing the COVID-19 pandemic [3]. Especially for the retrospective assessment of the infected population, mainly virus-specific IgG antibodies are measured, which generally develop several days after symptom onset in people infected with the virus [4-6]. In serological testing assays, S and N viral antigens of SARS-CoV-2 are most commonly used as targets [7]. The United States Food and Drug Administration (US FDA) has recently authorized several diagnostic kits for emergency use for the serological diagnosis of COVID-19 in clinical samples [8]. These tests include; colloidal gold and conventional lateral flow immunoassays (LFA) as rapid diagnostic approaches provide test results within <30 minutes without requiring complex laboratory equipment, immunoassays including enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA), chemiluminescent micro-particle immunoassay (CMIA), enzyme-linked fluorescence assay (ELFA), photonic ring immunoassay, multiple fluorescence immunoassay (FIA) and fluorescence-based fluorescence immunoassay (FMIA) [4-6]. Diagnostic test manufacturers worldwide are developing powerful diagnostic tools to support healthcare professionals and contribute to fighting against COVID-19. Since there is limited data on the clinical performance of commercially available serological tests in clinical samples, the performance verification of commonly used SARS-CoV-2 IgG antibody tests has been widely evaluated using samples from COVID-19 cases in different countries. [9-11]. To predict the diagnostic feasibility of different antibody platforms used for diagnosis and epidemiological investigations, IgG measurements obtained from COVID-19 cases in various serological platforms such as point of care or automated systems, nucleocapsid or spike protein-based ELISAs, LFAs, CMIAs, etc., have been investigating during different phases of the infection (5-9 days / ≥15 days of symptom onset) [9],[12],[13]. As with such difficult and time-consuming analyzes, the performance of only a limited number of serological tests can be compared, more practical applications should be preferred. Therefore, our purpose is to compare the performances of different SARS-CoV-2 IgG antibody assays used in COVID-19 management with an analytical technique. For this aim, we applied to Fuzzy Preference ranking organization method for enrichment evaluation (F-PROMETHEE) technique. This method is an

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analytical MCDM method that provides significant support to the decision maker in decision making for a complex or uncertain environment [14]. Fuzzy logic, which was created by Zadeh in 1965 [15,16], is an important logic process that enables decision makers or analysts to work even with uncertain or imprecise data and to obtain information from such complex environments [17]. PROMETHEE is an MCDM technique, which is defined by Brans in 1984, compares the alternatives based on the pairwise comparison and provides the decision-makers different preference functions for each criterion for calculating the preference values of each alternative [18]. Fuzzy based MCDM techniques are became a popular tool since 2000's for the solution of the real world problems. Fuzzy based MCDM techniques became a successfully used tool in the 2000s for the solution of real-world problems [19].

II. Materials and Methods

The study involved 48 SARS-CoV-2 IgG antibody test assays with different criteria using multi-criteria decision-making (MCDM) theory. These tests have been authorized for emergency use by FDA and are involved in this study based on the information provided on FDA official web page [8]. The criteria not provided for each kit in the package insert, such as the 'limit of detection (LoD)', which is common for all kits like 'cross-reaction may occur', were excluded from the study. Distribution of 48 SARS-CoV-2 IgG antibody tests involved in the study as follow; (n=19, 40%) LFA; (n=13, 27%) CLIA; (n=8, 17%) ELISA; (n=5, 10%) CMIA; (n=3,6%) FMIA, ELFA and FIA. PROMETHEE method of multi-criteria decision making (MCDM) theory was used for analysis. While comparing the antibody tests, different criteria such as minimum amount of sample required (2-10 µl /10-100 µl / >100), specimen type (serum/plasma/fingerstick blood), test procedure (manual/automated), antigen target (spike/ nucleocapsid), requiring laboratory equipment and device (point of care testing/requiring laboratory) test technique (LFA, ELISA,CMIA,ELFA etc.), practicability of the system (manual-rapid flow assay/manuel-plate based system/kit-automated system), time to first result (within 15 minutes/30 minutes/ more than 1 hour), result interpretation (qualitative/semi-quantitative/quantitative), analytic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), time of sampling days post infection (8-14 days / ≥ 15 days / ≥22 days), reagent storage conditions (2-8°C / 2-8°C upright position away from light and heat / 2-30°C), loading capacity (single /up to 100 / more than 250) and the maximum throughput for each run, test kit size per each pack, accessibility to the kit (availability in all countries / available only in Unites States), calibration frequency (each run / each kit), sample result storage capacity (low / moderate / high) and obtaining result (evaluation by direct observation, evaluation by optic reader /results by system) were assessed and used for determining the ranking of the kits [8].

SARS-CoV-2 Ig G Rapid diagnostic tests

Rapid diagnostic tests evaluated in the study were; LYHER Nove Coronavirus (2019-nCoV) (Hangzhou Laihe Biotech Co.Ltd., Zhejiang, China), ACON (ACON Laboratories, Inc., San Diego, USA), Assure (Assure Tech. (Hangzhou Co., Ltd, Zhejiang, China), etc.

SARS-CoV-2 IgG plate-based tests

Plate-based tests evaluated in the study were; EUROIMMUN Ig G (EUROIMMUN, New Jersey, USA), InBIOS ELISA (In Bios International, Inc., Seattle, Washington), etc.

SARS-CoV-2 IgG Immunoassays

Immunoassays evaluated in the study were; BioCheck (BioCheck, Inc., SanFrancisco, USA), The Babson Diagnostics aC19G1 (Babson Diagnostics, Inc.), Access IgG II (Beckman Coulter Inc., Kraemer Blvd, Brea, USA), Dimension Vista (CoV2G) (Siemens Healthcare Diagnostics, Inc., Newark, NY), SARS-CoV-2 Ig G Alinity i /ARCHITECT (Abbott Laboratories, Abbott Park, USA), bioMeriux VIDAS (bioMerieux SA, Marcy-I Etoile, France), etc.

The importance weights of each criterion have been defined based on the expert's opinion by the triangular linguistic scale (see in Table 1).

Table 1. Fuzzy scale and importance weights of the parameters of the Diagnostic SARS-CoV-2 IgG Antibody Tests

Linguistic /Triangular fuzzy scale	**Criteria / Parameter**
Very high (VH)/ (0.75, 1, 1)	Sensitivity, Specificity, PPV, NPV, Calibration frequency/CONTROL
High (H)/ (0.50, 0.75, 1)	Target, Time to first result, Storage, Time of sampling days post symptom onset, Maximum throughput, Result interpretation
Moderate (M)/ (0.25, 0.50, 0.75)	Specimen types, Technology/ease of operation, Systems/Ease of operation, Requiring special laboratory, Loading capacity/each run, Access to kit, obtaining result/storage
Low (L)/ (0, 0.25, 0.50)	Sample volume, Test kit size/pack
Very Low (VL)/ (0, 0, 0.25)	Not determined

The Yager index was used to define the given triangular numbers as a single number. Following this, Gaussian preference functions were assigned to each criterion to determine the alternatives' priorities using the PROMETHEE technique. Since PROMETHEE I only gives the partial ranking result by comparing the positive and negative outranking flow, the ranking results were obtained with the PROMETHEE II method, which gives the net ranking based on the differences between the positive and negative outranking flows [20].

III. Results and Discussion

The results showed that Siemens ADVIA Centaur (Cov2G) was the most representative of expected test performance for IgG against for SARS-CoV-2, followed by QUANTA Flash SAR IgG and Siemens Dimension Vista IgG

(CoV2G), while EUROIMMUN ELISA (IgG) was the least favorable one (see in Table 2). This ranking is a result of the main superiority of criteria: sensitivity, specificity, PPV/NPV, antigen target, and practicability.

Table 2. Complete ranking results of FDA EUA authorized SARS-CoV-2 IgG antibody tests

Rank	Antibody tests (IgG)	Tech.	Phi	Phi+	Phi-
1	*Siemens ADVIA Centaur (CoV2G)*	CLIA	0,1838	0,2138	0,0301
2	*QUANTA Flash*	CLIA	0,1561	0,2151	0,0591
3	*Siemens Dimension Vista (CoV2G)*	CLIA	0,1382	0,2100	0,0718
4	*Babson Diagnostics aC19G1*	CLIA	0,1352	0,1990	0,0638
5	*Siemens Atelica IM (CoV2G)*	CLIA	0,1251	0,1959	0,0708
6	*Abbott Architect*	CMIA	0,1056	0,1895	0,0838
7	*Abbott Alinity*	CMIA	0,1050	0,1913	0,0863
8	*Abbott Advise DX (Architect)*	CMIA	0,0860	0,1788	0,0928
9	*RightSign*	LFA	0,0852	0,1429	0,0577
10	*Abbott Advise Dx (Alinity)*	CMIA	0,0843	0,1766	0,0922
11	*LYHER Nove*	Colloidal gold LFA	0,0702	0,1314	0,0612
12	*Beckman Access II*	CLIA	0,0690	0,1493	0,0803
13	*DiaSorin LIAISON*	CMIA	0,0687	0,1371	0,0685
14	*Siemens Dimension EXL (CoV2G)*	CLIA	0,0665	0,1526	0,0862
15	*CareStart*	LFA	0,0567	0,1257	0,0690
16	*Innovita*	Colloidal gold LFA	0,0558	0,1304	0,0745
17	*COVID-19 IgG/IgM Rapid Test*	LFA	0,0536	0,1216	0,0680
18	*IDS*	CLIA	0,0500	0,1611	0,1111
19	*Diazyme DZ-Lite CLIA kit*	CLIA	0,0429	0,1409	0,0980
20	*bioMeriux VIDAS*	ELFA	0,0423	0,1400	0,0977
21	*SGTi-flex COVID-19 IgG*	LFA	0,0380	0,1285	0,0905
22	*Xmap*	FMIA	0,0317	0,1491	0,1173
23	*Beckman Access*	CLIA	0,0288	0,1304	0,1016
24	*Orawell*	LFA	0,0265	0,1187	0,0922
25	*MidaSpot Combo*	LFA	0,0240	0,1243	0,1003
26	*BioCheck*	CLIA	0,0234	0,1290	0,1055
27	*MAGLUMI*	CLIA	0,0232	0,1400	0,1168
28	*BIOTIME*	LFA	0,0170	0,1197	0,1027
29	*Assure*	LFA	0,0033	0,1303	0,1270
30	*Nirmidas*	LFA	-0,0003	0,1041	0,1044
31	*Rapid COVID-19 IgM/IgG Combo*	LFA	-0,0081	0,1222	0,1303
32	*ACON*	LFA	-0,0393	0,1094	0,1487
33	*EliA*	FIA	-0,0406	0,1211	0,1617
34	*Kantaro Semi-Quantitative*	ELISA	-0,0427	0,1048	0,1476
35	*Sienna-Clarity COVIDBLOCK*	LFA	-0,0492	0,1025	0,1517
36	*Biohit*	Colloidal gold LFA	-0,0608	0,0979	0,1588
37	*InBİOS*	ELISA	-0,0700	0,0916	0,1616
38	*Simoa*	ELISA	-0,0719	0,0879	0,1598
39	*qSARS-CoV-2*	LFA	-0,0975	0,0935	0,1910
41	*Bican Tell Me Fast Novel*	LFA	-0,1057	0,0880	0,1937
41	*Q-Plex*	ELISA	-0,1413	0,0679	0,2092
42	*TBG*	LFA	-0,1414	0,0836	0,2250
43	*SARS-CoV-2 RBD IgG test*	LFA	-0,1658	0,0669	0,2327
44	*RapCoV*	LFA	-0,1680	0,0831	0,2511
45	*ZEUS ELISA*	ELISA	-0,1727	0,0609	0,2336
46	*VITROS Anti-SVITROS*	CLIA	-0,1837	0,0984	0,2821
47	*UBI SARS-CoV-2 ELISA*	ELISA	-0,2142	0,0557	0,2699
48	*EUROIMMUN*	ELISA	-0,2230	0,0528	0,2758

Abbreviations: CLIA: chemiluminescent immunoassay; CMIA: chemiluminescent micro-particle immunoassay; LFA: lateral flow immunoassays; FMIA: fluorescence-based fluorescence immunoassay; ELISA: enzyme-linked immunosorbent assay; Tech.: Technique; ***P**hi: Net ranking; Phi+: Positive Outranking Flow; Phi-:Negative Outranking Flow*

Detection of viral-specific antibodies enables accurate diagnosis of COVID-19. These tests provide information regarding the progression of infection and enable monitoring therapeutic responses and immune responses to COVID-19 in vaccine studies. The antibody test is widely used to measure the immune response after infection and vaccination. It enables the estimation of the persistence of immune responses created by the human body and a retrospective evaluation of the infected population in the population for sero - surveillance studies [21-24]. To establish the most appropriate antibody testing systems for reliable COVID-19 detection, the analytical sensitivity and specificity of antibody testing systems were investigated primarily in clinical specimens at various stages of infection [10], [11], [25]. During pandemic conditions, besides the sensitivity and specificity of the platforms, criteria like accessibility to kits, storage conditions of the kits, point-of-care testing, and providing rapid test results with high throughput are also crucial. The fuzzy method used in this current study allows many criteria to be evaluated simultaneously in different antibody systems. Thus, decision-makers can decide the most suitable tests according to the importance of the criteria for their countries.

IV. Conclusion

Throughout the COVID-19 pandemic, detection of antibodies specific to SARS-CoV-2 can be used in screening large populations such as schools, factories, outpatient clinics, inpatient services, emergency services, etc., as they contribute more accurate diagnosis of COVID-19. This study shows that the Fuzzy PROMETHEE techniques can effectively aid decision-makers in choosing the most appropriate SARS-CoV-2 antibody assay. Fuzzy PROMETHEE can guide decision-makers about which SARS-CoV-2 antibody assay should be preferred. Therefore, SARS-CoV-2 IgG antibody tests available in different countries can be ranked with MCDM theory, and the most favorable ones can be used in the management of COVID-19 in each country.

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