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Article

Comparison of Fourteen Rapid Point-of-Care Antigen Tests for SARS-CoV-2: Use and Sensitivity

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Abstract: Fast, sensitive techniques are advisable for SARS-CoV-2 detection. Various rapid SARS-CoV-2 antigen detection tests have been developed, but type and quality of the sample, stage of the disease and viral load can all have an impact on their sensitivity. For this study, a total of 486 swabs were processed and checked with various commercially available tests and then compared with q(RT)-PCR (the gold-standard method). Total sensitivity varied considerably; for example, 42.10% (nal von minden and Tody Laboratories), 68.42% (Cahnos) and 84.78% (PCL). Sensitivity reached 100% when the cycle threshold (Ct) was lower than 22 in almost all tests, although this dropped considerably when the Ct was higher above 30, where only 3 tests identified 40% or more positive samples and in 5 cases it was 0%. What is more, only 2 cases were 100% accurate when viral load was higher than 5 log/10^3 cells and accuracy was 0% in 12 cases when viral load was lower than 4 log/10^3 cells. These results, particularly taking into consideration the fact that they used normalized viral load, suggest that antigen detection tests have their role in the fast triage of positive patients, but that considerable care should be taken with negative results, which is even more important if they are used for massive screening.

Keywords: rapid antigen test comparation; SARS-CoV-2; COVID-19; normalized viral load; false negative

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1. Introduction

Since 11 March 2020, when the WHO declared COVID-19 a pandemic, and now with over 150 million infections and more than 3 million deaths worldwide [1,2], the long term management of this disease is imperative.

Although q(RT)-PCR is the gold-standard testing method, it can take at least 3 h from the point at which the sample suspected of containing SARS-CoV2 arrives at the laboratory and is properly processed for the result to be obtained [3]. In contrast, with the various rapid antigen detection tests that have been developed, a preliminary result can be obtained in 10–30 min [4,5], providing quick information for the triaging of patients.

However, the type and quality of the sample, stage of the disease and viral load can all have an impact on this latter type of test [5–8]. In order to provide more information on this, here, various different antigen detection tests were compared with q(RT)-PCR, paying close attention to two values of the sample, the cycle threshold (Ct) and the normalized viral load (VL) expressed by copies (log) by 10^3 cells.

Normalized VL was obtained by the quantification that both virus and human cells on the sample (using human β-globin gene) allow the normalization of the number of viral copies per cell on the sample, a value linked to the possible infectivity of patients [9,10].

2. Material and Methods

Samples: Between September 2020 and January 2021, 457 positive and 29 negative nasopharyngeal samples were collected from different adult patients (over 18 years old) at the Hospital Universitario Central de Asturias. All patients declared symptomatology compatible with COVID-19 at the moment of sample collection.

Genome detection: All samples were extracted and purified using MagNa Pure 96 system (Roche, Geneva, Switzerland), following the manufacturer's instructions.

An in-house q(RT)-PCR test able to detect two targets of the SARS-CoV2 genome (ORF1ab and N gene) as well as the human β-globin gene was performed for each sample. Briefly, 5µL of the sample was added to 10 µL of TaqMan Fast 1-Step Master Mix (Life Technologies, Carlsbad, CA, USA) and supplemented with a mixture of primers (Thermo Fisher Scientific, Massachusetts, USA) and taqman MGB probes (Applied Biosystems, Massachusetts, USA) (Table 1), as in reference [12].

Table 1. Primers and probes.

Target	Design	Function	Name	Sequence (5′-3′)	Position
SARS-CoV-2	In-house	Forward primer	CoV-2-OVI-S	ATCAAGTTAATGGTTACCCTAACATGT	ORF1ab
		Reverse primer	CoV-2-OVI-A	AACCTAGCTGTAAAGGTAAATTGGTACC	
		MGB FAM probe	CoV-2-OVI-FAM	CCGCGAAGAAGCTA	
SARS-CoV-2	CDC [1]	Forward primer	2019-nCoV_N1-F	GACCCCAAAATCAGCGAAAT	Gen N
		Reverse primer	2019-nCoV_N1-R	TCTGGTTACTGCCAGTTGAATCTG	
		MGB VIC probe	2019-nCoV_N1-P-VIC	CCGCATTACGTTTGGT [2]	
β-globin	In-house	Forward primer	Beta-TR-S	ACACAACTGTGTTCACTAGC	β-globin
		Reverse primer	Beta-TR-A	CCAACTTCATCCACGTTCACC	
		MGB Cy5 probe	Beta-Cy5	TGCATCTGACTCCTGAGGA	

[1] Sequences published by U.S. Centers for Disease Control and Prevention (CDC) [11]. [2] Due to the incorporation of MGB in the probes used for this work, the length of sequences was modified.

Rapid Antigen Detection Test: For this comparative assay, 13 different immunochromatography-based and 1 immunofluorescence-based SARS-CoV2 antigen detection tests were analyzed. All tests were performed following the manufacturer's instructions. The number of samples used for testing with each test is shown in Tables 2 and 3; each test was performed with different samples because of the need to rationalize the materials' disposable at each moment.

The different tests were:

1. Panbio COVID-19 Ag rapid test device (Abbott, Wiesbaden, Germany).
2. SIMPLE/STICK AG SARS-CoV-2 (COVID-19) (Operon, Zaragoza, Spain).
3. PCL COVID-19 Ag Gold Saliva (PCL, Seoul, South Korea).
4. SARS-CoV-2 Antigen Detection Kit (Assut Europe, Rome, Italy).
5. CLINITEST Rapid COVID-19 Antigen Test (Siemens Healthineers, Erlangen, Germany).
6. SARSCoV2 Rapid Antigen test (Roche, Mannheim, Germany).
7. Test Rapido de Antigenos de SARS-CoV-2 (Oro coloidal) (Cahnos, Madrid, Spain).
8. Test rápido de antígenos COVID-19 (hisopado nasofaríngeo) (Beright, Madrid, Spain).
9. NADAL® COVID-19 antigen rapid test (nal von minden, Moers, Germany).
10. Coronavirus (SARS-CoV-2) Rapid Tests Reagents (Tody Laboratories, Bucarest, Romania).
11. CerTest SARS-CoV-2 Card Test (CerTest Biotec, Zaragoza, Spain).
12. Test Rápido COVID-19 Ag (Lambra, Madrid, Spain).
13. STANDARD F COVID-19 AG FIA (SD Biosensor, Suwon, South Korea).
14. ESPLINE® SARS-CoV-2 (Fujirebio, Tokyo, Japan).

Table 2. Sensitivity, Ct average and CI 95% by test and cycle threshold (Ct).

	Total				Ct ≤ 22				23 ≤ Ct ≤ 29				Ct ≥ 30			
Test	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**
Abott	84	48 (57.14%)	23.28 ± 3.91	(22.17–24.39)	22	22 (100%)	19.72 ± 1.42	(19.13–20.31)	40	25 (62.50%)	25.92 ± 2.23	(25.05–26.79)	23	1 (4.35%)	33 [3]	-
Operon	79	40 (50.63%)	25.27 ± 4.64	(23.83–26.71)	13	12 (92.30%)	20.00 ± 1.48	(19.16–20.84)	38	19 (50.00%)	25.47 ± 1.87	(24.63–26.31)	28	9 (32.00%)	31.84 ± 1.76	(31.48–32.20)
PCL	46	39 (84.78%)	25.07 ± 4.06	(23.80–26.34)	11	11 (100%)	20.82 ± 1.54	(19.91–21.73)	24	21 (87.50%)	25.00 ± 1.67	(24.28–25.72)	11	7 (63.63%)	32.00 ± 1.41	(30.95–33.05)
Assut Europe	39	23 (58.97%)	23.78 ±4.67	(21.87–25.69)	10	10 (100%)	19.60 ± 2.12	(18.29–20.91)	15	10 (66.67%)	25.70 ± 2.41	(24.21–27.19)	14	3 (21.43%)	31.33 ± 1.53	(29.60–33.06)
Siemens	39	21 (53.84%)	25.00 ± 3.92	(23.32–26.68)	6	6 (100%)	20.17 ± 1.72	(18.79–21.55)	16	13 (81.25%)	26.23 ± 1.92	(25.19–27.27)	17	2 (11.76%)	31.50 ± 2.12	(28.86–34.14)
Roche	23	15 (65.21%)	23.00 ± 3.84	(21.06–24.94)	6	6 (100%)	19.16 ± 2.04	(17.53–20.79)	11	8 (72.72%)	25.00 ± 1.51	(23.67–26.33)	6	1 (16.67%)	30 [3]	-
Cahnos	19	13 (68.42%)	23.85 ± 2.12	(22.70–25.00)	4	4 (100%)	21.50 ± 0.58	(20.93–22.07)	13	9 (69.23%)	24.88 ± 1.62	(23.82–25.94)	2	0 (0%)	-	-
Beright	19	12 (63.15%)	25.00 ± 5.54	(21.84–28.16)	4	4 (100%)	19.50 ± 2.38	(17.17–21.83)	8	4 (50.00%)	24.25 ± 1.89	(22.39–26.11)	7	4 (57.14%)	31.25 ± 1.50	(29.78–32.72)
nal von	19	8 (42.10%)	21.12 ± 3.83	(18.46–23.78)	5	5 (100%)	19.00 ± 2.92	(16.44–21.56)	6	3 (50.00%)	24.67 ± 2.08	(22.31–27.03)	8	0 (0%)	-	-
Tody	19	8 (42.10%)	21.37 ± 4.31	(18.39–24.35)	5	5 (100%)	19.00 ± 2.92	(16.44–21.56)	6	3 (50.00%)	25.33 ± 3.21	(22.29–28.37)	8	0 (0%)	-	-
Certest	17	9 (52.94%)	23.67 ± 3.81	(21.18–26.16)	4	4 (100%)	20.25 ± 2.22	(18.08–22.42)	9	5 (55.56%)	26.40 ± 2.07	(24.58–28.22)	4	0 (0%)	-	-
Lambra	15	10 (66.67%)	23.80 ± 3.58	(21.58–26.02)	4	4 (100%)	20.50 ± 1.91	(18.62–22.38)	6	5 (83.33%)	25.20 ± 1.79	(23.63–26.77)	5	1 (20.00%)	30 [3]	-
SD Biosensor	12	8 (66.67%)	25.50 ± 3.89	(22.80–28.20)	2	2 (100%)	21.00 ± 1.41	(19.04–22.96)	5	4 (80.00%)	25.25 ± 2.06	(23.23–27.27)	5	2 (40.00%)	30.50 ± 0.71	(29.52–31.48)
Fujirebio	9	4 (44.44%)	23.75 ± 2.63	(21.17–26.33)	2	2 (100%)	21.50 ± 0.71	(20.52–22.48)	2	2 (100%)	26.00 ± 0.00 [1]	- [2]	5	0 (0%)	-	-

[1] As both positive samples in this range had a Ct of 26, deviation is 0. [2] As deviation has a value of 0, CI 95% cannot be calculated. [3] Ct values for the only positive sample by these tests.

Table 3. Sensitivity, viral load average and CI 95% by test and normalized viral load.

	Total				log ≥ 5				4 ≤ log ≤ 4.99				log ≤ 3.99			
Test	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**	**Samples**	**Sensitivity**	**± σ**	**CI 95%**
Abott	84	48 (57.14%)	6.47 ± 1.08	(6.16–6.78)	63	47 (74.60%)	6.62 ± 1.04	(6.32–6.92)	14	1 (7.14%)	4.77 [1]	-	8	0 (0%)	-	-
Operon	79	40 (50.63%)	6.72 ± 1.72	(6.19–7.25)	54	35 (64.81%)	7.17 ± 1.30	(6.64–7.70)	12	1 (8.33%)	4.76 [1]	-	13	4 (30.77%)	3.32 ± 0.48	(2.85–3.79)
PCL	46	39 (84.78%)	6.25 ± 1.36	(5.82–6.68)	35	33 (94.28%)	6.62 ± 1.12	(6.24–7.00)	6	4 (66.67%)	4.59 ± 0.33	(4.27–4.91)	5	2 (20.00%)	3.51 ± 0.01	(3.50–3.52)
Assut Europe	39	23 (50.00%)	6.47 ± 1.52	(5.85–7.09)	23	19 (82.60%)	6.81 ± 1.44	(6.16–7.46)	12	4 (33.33%)	4.82 ± 0.13	(4.70–4.94)	4	0 (0%)	-	-
Siemens	39	21 (53.84%)	6.13 ± 1.43	(5.52–6.74)	19	17 (89.47%)	6.55 ± 1.27	(5.95–7.15)	12	4 (33.33%)	4.37 ± 0.10	(4.27–4.47)	8	0 (0%)	-	-
Roche	23	15 (65.21%)	6.73 ± 1.26	(6.09–7.37)	15	14 (93.33%)	6.88 ± 1.17	(6.27–7.49)	7	1 (14.28%)	4.70 [1]	-	1	0 (0%)	-	-
Cahnos	19	13 (68.42%)	6.04 ± 0.51	(5.76–6.32)	18	13 (72.22%)	6.04 ± 0.51	(5.76–6.32)	1	0 (0%)	-	-	0	-	-	-
Beright	19	12 (63.15%)	6.31 ± 1.42	(5.51–7.11)	12	8 (66.67%)	7.16 ± 0.82	(6.34–7.98)	7	4 (57.14%)	4.60 ± 0.22	(4.38–4.82)	0	-	-	-
nal von	19	8 (42.10%)	6.61 ± 1.50	(4.97–8.25)	10	7 (70.00%)	6.85 ± 1.45	(5.77–7.93)	7	1 (14.28%)	4.98 [1]	-	2	0 (0%)	-	-
Tody	19	8 (42.10%)	6.82 ± 1.35	(5.88–7.76)	10	7 (70.00%)	7.08 ± 1.22	(6.18–7.98)	7	1 (14.28%)	4.98 [1]	-	2	0 (0%)	-	-
Certest	17	9 (52.94%)	6.11 ± 0.99	(5.46–6.76)	14	9 (64.28%)	6.11 ± 0.99	(5.46–6.76)	2	0 (0%)	-	-	1	0 (0%)	-	-
Lambra	15	10 (66.67%)	6.80 ± 1.22	(6.11–7.49)	10	10 (100%)	6.80 ± 1.22	(6.11–7.49)	4	0 (0%)	-	-	1	0 (0%)	-	-
SD Biosensor	12	8 (66.67%)	6.26 ± 1.15	(5.46–7.06)	8	7 (87.50%)	6.57 ± 0.82	(5.96–7.18)	3	1 (33.33%)	4.11 [1]	-	1	0 (0%)	-	-
Fujirebio	9	4 (44.44%)	6.02 ± 1.92	(4.14–7.90)	4	2 (50.00%)	7.65 ± 0.57	(6.86–8.44)	3	2 (66.67%)	4.39 ± 0.25	(4.05–4.73)	2	0 (0%)	-	-

[1] Viral load values, expressed in Copies (log)/10^3 cells, for the only positive sample by these tests.

3. Results

For results analysis, both cycle threshold (Ct) (Table 2) and viral load (VL) (Table 3) were considered, three subgroups being established in each case: Ct $\leq$ 22; 23 $\leq$ Ct $\leq$ 29; and Ct $\geq$ 30, and VL log $\geq$ 5; 4 $\leq$ VL log $\leq$ 5 and VL log < 4.

With respect to Ct: total mean sensitivity was 58.36%, while this figure was 99.45% when Ct $\leq$ 22; 68.48% for 23 $\leq$ Ct $\leq$ 29; and 29.66% when Ct $\geq$ 30. The full results are shown in Table 2 and Figure 1.

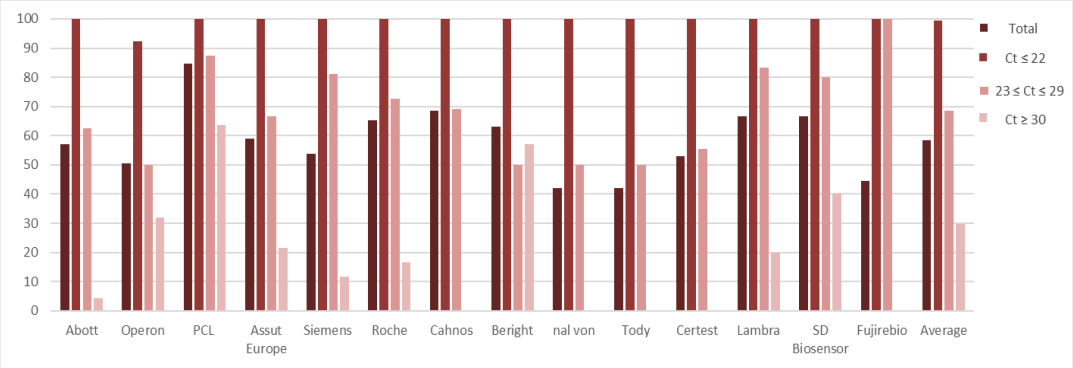

Figure 1. Representation of sensitivity percentage of each test by cycle threshold (Ct).

On the other hand, looking at normalized viral load, expressed on a logarithmic scale, total mean sensitivity was 57.72%. When the three different VL bands were considered, sensitivity was 77.60% when VL log $\geq$ 5; 31.70% for 4 $\leq$ VL log $\leq$ 5; and 25.38% on log $\leq$ 4. The full results are shown in Table 3 and Figure 2.

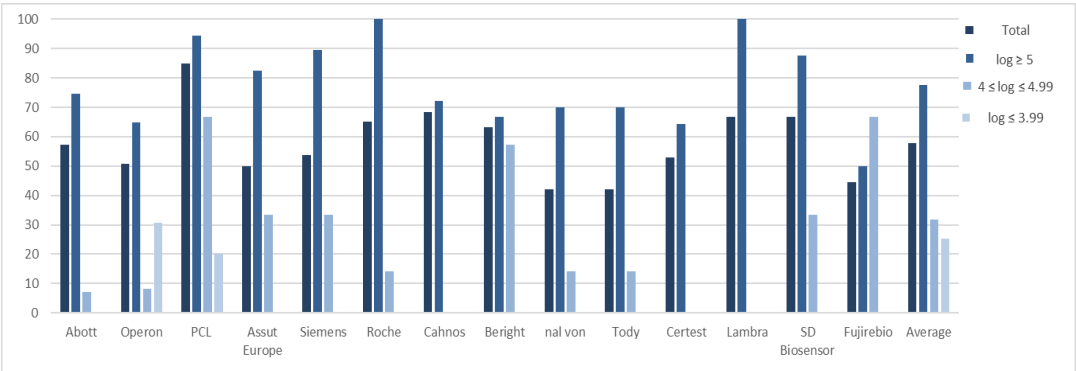

Figure 2. Representation of sensitivity percentage of each test by normalized viral load.

Specificity was always 100% except for with the PCL test, where there was one false positive of 4 samples tested.

4. Discussion

Under the current emergency measures in force in different parts of the world, and with the fourth wave of COVID-19 rising or feared in many countries, the time it takes to process samples is crucial to triage patients, making rapid antigen detection tests a very useful assay. But all efforts should be made to ensure that the tests used are as sensitive as possible.

When comparing the different tests examined in this study and using the Ct of the q(RT)-PCR as validation, a large range of sensitivity was found, from 42.10% using the tests by the nal von minden and Tody Laboratories, to 84.78% with the COVID-19 Ag Gold Saliva from PCL.

As would be expected, we found the correlation between sensitivities on rapid antigen detection tests and q(RT)-PCR for Cts under 23 to be practically complete (only the Operon test was not 100% accurate, although it did correctly identify over 90% of positives). However, as soon as Ct was higher, sensitivity decreased notably. With Cts over 23, 4 of the 14 tests correctly identified only 50% of positives, and just 5 were accurate in 80% or more of cases. The situation was even more marked when Ct was over 30, where just 2 tests correctly identified 50% or more of positives (PCL with 63.63% and Beright with 57.14%).

When the accuracy of the various tests was compared on the basis of the quantification of human β-globin, which allows the true measurement of viral load and validates the quality of the sample extraction [12,13], the results were somewhat different.

In this case, not all tests had a 100% correlation for samples with over 5 $\log/10^3$ cells, as might be expected. This is very important, both clinically and epidemiologically, because it implies a not insignificant percentage of false negatives that correspond to contagious patients [9,10]. This indicates, therefore, that these rapid antigen detection tests are not recommended for massive screenings.

For samples with VL of below 4 log, only two methods could detect SARS-CoV-2 antigens, and both at low rates: 31% (Operon) and 20% (PCL). This is to be expected and is not of great epidemiological significance given that patients with low viral load are not considered to be transmitters [14–16], even though they may in fact be at the beginning of the infection and could become transmitters at a relatively short later date.

To our knowledge, this is the first study that compares so many rapid antigen detection tests for SARS-CoV2. We counteracted any potential bias of the low number of samples used by checking each sample with each commercial test and, despite the variance derived from the manual procedure of this kind of probe, our results for specific tests were similar to those obtained in other studies [4,5,17–19]. They were, however, far from the promising results published by the manufacturers themselves or claimed by certain authors [19], and this emphasizes that special care should be taken with the general lack of sensitivity with higher Cts (or low viral load), as results show that the reliability of obtaining positive PCR and contagion capacity in this range are unclear [9,10].

This concern is confirmed when a normalized measure of viral load is considered. These results also confirm that sampling procedures are very important and rapid tests using easily recovered samples can have compromised sensitivity.

A limitation of this study was the low number of samples tested, especially with Fujirebio, SD Biosensor, Lambra and Certest.

In conclusion, this kind of immunoassay for antigen detection can be useful to ensure the quick isolation of positive patients, but the lack of sensitivity of some tests, even in patients with a high viral load, means they miss identifying patients who are positive for SARS-CoV2 who might be infectious, so they must be used with great care.

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