



Should electrochemiluminescence immunoassay (ECLIA) tests be used in the diagnosis of COVID-19?

Authors: Carol Stephanie Tan-Lim, MD, MScCE, Aldrich Ivan Lois D. Burog, MD, MScCE (cand.)

Date of Review: 16-AUGUST-2020 (version 1)

Last Updated: 16-AUGUST-2020 (version 1)

This rapid review summarizes the available evidence on the use of ECLIA tests in diagnosing COVID-19. This may change as new evidence emerges.

KEY FINDINGS

Current evidence does NOT support the use of ECLIA as a screening tool for the diagnosis of COVID-19.

- ECLIA is an immunoassay technique that qualitatively determines antibody concentrations in an individual's blood.
- This review included 18 studies that were appraised to have overall moderate quality of evidence.
- The sensitivity of ECLIA in detecting the presence of antibodies against SARS-CoV-2 varies depending on the timing of sample collection.
- The pooled sensitivity was 14.5% (95% CI 1.3 to 27.8%) if used 0 to 6 days from onset of symptoms, 70.1% (95% CI 55.9 to 84.3%) if used 7 to 13 days from onset of symptoms, 37.6% (95% CI 24.8 to 50.4%) if used 0 to 13 days from onset of symptoms, and 82.4% (95% CI 69.6 to 95.2%) if used at least 14 days from onset of symptoms.
- The overall pooled sensitivity of ECLIA is 83.0% (95% CI 72.0 to 90.2%, $I^2=98.3%$) and the overall pooled specificity is 99.8% (95% CI 99.6 to 99.9%, $I^2=45.3%$).
- Based on pooled evidence, ECLIA is not an accurate test when used to screen for close-contacts of COVID-19 confirmed and/or suspect cases, employees undergoing return-to-work screening, and asymptomatic patients in general.
- CDC guidelines do not recommend the use of antibody tests to diagnose COVID-19 infection or reinfection.

Disclaimer: The aim of these rapid reviews is to retrieve, appraise, summarize and update the available evidence on COVID-related health technology. The reviews have not been externally peer-reviewed; they should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent the views of the authors and not necessarily those of their host institutions. The views are not a substitute for professional medical advice.

Copyright Claims: This review is an intellectual property of the authors and of the Institute of Clinical Epidemiology, National Institutes of Health-UP Manila and Asia-Pacific Center for Evidence Based Healthcare Inc.



BACKGROUND

Accurate diagnostic tests are crucial in curbing the spread of COVID-19. Currently, there are 2 main types of tests available: viral tests and antibody tests. Detection of viral RNA through RT-PCR is considered the reference standard for diagnosing COVID-19. The limitations of this test include high costs, need for specialized equipment, and longer turnaround time of results.[1]

The antibody tests available in the Philippines can be classified based on the immunoassay techniques involved. The most commonly used tests include the lateral flow assays (LFA) and the electrochemiluminescence immunoassays (ECLIA).[2] Rapid tests are LFAs and are reviewed in a separate document.

ECLIA is an immunoassay technique that qualitatively determines antibody concentrations in an individual's blood. It uses electrochemical reactions to produce chemiluminescent signals which is measured by an analyzer.[3] The currently available ECLIA test is the Elecsys by Roche. It measures the total antibody in the blood. A positive result (indicating presence of antibodies to SARS-CoV-2) is a cutoff index of ≥ 1 , while a negative result is a cutoff index of < 1 . Results can be generated in as fast as 18 minutes.[4] ECLIA is currently offered in various areas in Luzon, including The Medical City, BloodWorks, St. Frances Cabrini Medical Center, and the drive-thru testing in Pasig City.[5-7]

Due to the urgent need to curb the transmission of COVID-19, a screening test that has high sensitivity values is critical to determine if individuals have active COVID-19 infection and are considered contagious. This review analyzes the current evidence on ECLIA to determine if it can be used as a screening test for COVID-19.

OBJECTIVE

The objective of this review is to determine the accuracy of ECLIA in the diagnosis of COVID-19.

METHODS

See General Methods Section.

Articles were selected based on the following inclusion criteria:

- Population: Patients with COVID-19 symptoms of any age, with any co-morbidities, any severity
- Intervention: ECLIA
- Comparator: PCR, viral culture
- Outcomes: Current COVID-19 infection
- Study designs: randomized controlled trials (RCTs), non-randomized studies, observational studies (e.g. cohort, case-control, cross-sectional)

Preplanned subgroup analysis to determine the utility of ECLIA depending on the timing of symptoms (< 14 days from symptom onset, and at least 14 days from symptom onset) was also done.

RESULTS

Characteristics of Included Studies

This review includes 18 studies involving a total of 16,865 specimens. There are 14 case control studies, 2 cross-sectional studies, and 2 cohort studies. The studies were conducted in various countries in Europe, Asia, and America.[8-25] Five of the 18 studies are preprints and have not yet been peer reviewed.

All studies compared ECLIA (Elecsys by Roche) to RT-PCR. Out of the 18 studies, 17 studies involved RT-PCR COVID-19 positive patients for the computation of the sensitivity values. One study involved RT-PCR COVID-19 positive patients and symptomatic patients with close contact to RT-PCR COVID-19 positive patients.

For the computation of specificity values, 10 studies used sera collected before the COVID-19 pandemic. One study involved RT-PCR COVID-19 negative individuals, 1 study involved both RT-PCR COVID-19 negative individuals and sera collected before the pandemic, 1 study involved patients with no suspicion for COVID-19 infection or acute respiratory illness. One study involved RT-PCR COVID-19 negative individuals, patients with other respiratory viral infection diagnosed, patients with chronic disease, and healthy controls. One study involved patients who are RT-PCR positive for a different respiratory pathogen, patients with positive ANA/dsDNA, healthy subjects, and sera collected before the pandemic. Three studies did not compute for specificity values.

The characteristics of the included studies are found in Appendix 1.

Critical Appraisal

Appraisal was done using the guide questions for diagnostics found in Painless Evidence-Based Medicine 2nd edition.[26] The included studies had overall some risk of bias. Three studies had low risk of bias, since these used an acceptable reference standard, had an independent definition of the index test and reference standard, performed the index test and reference standard independently. Since the results were automated and produced by an analyzer, the interpretation of the index test and reference standard can be considered independent. Fifteen studies had some risk of bias in the independent performance of the index test and reference standard. In 13 studies, PCR was not performed for the control group samples. In the study by Padoan et al, ECLIA results were not available for all included patients but the reason was not specified. In another study by Perkmann et al, RT-PCR was not performed for the symptomatic patients with close contact to COVID-19 patients as well as for the control group. Overall, the studies are appraised to have moderate quality of evidence. The summary of the appraisal is found in Appendix 3.

Accuracy Outcomes

The overall sensitivity and specificity of ECLIA for each included study, as well as the pooled values, is shown in Table 1. The study by Padoan 2020 was not included in the pooled analysis for both sensitivity and specificity due to inadequate data. There are 3 other studies (i.e. Weidner 2020, Schnurra 2020, Muecksh 2020) that were not included in the pooled analysis for specificity due to inadequate data. The pooled overall sensitivity of ECLIA is 83.0% (95% CI 72.0-90.2%) and the pooled overall specificity is 99.8% (95% CI 99.6 to 99.9%). There was significant heterogeneity ($I^2=98.3\%$) in the pooled sensitivity data, and no significant heterogeneity ($I^2=45.3\%$) for the pooled specificity data. The forest plots are found in Appendix 4.

Table 1. Overall sensitivity and specificity of ECLIA

Study	Sensitivity % (95% CI)	Specificity % (95% CI)
Egger et al 2020	48.1 (38 to 58)	99.8 (99 to 100)
Favresse et al 2020	73.2 (68 to 78)	100 (95 to 100)
Merrill et al 2020	64.8 (55 to 74)	100 (98 to 100)
Weidner et al 2020	94.9 (89 to 98)	-
Charlton et al 2020	71.4 (55 to 84)	100 (93 to 100)
Coste et al 2020	30.7 (26 to 35)	100 (93 to 100)
Pflugger et al 2020	62.7 (51 to 74)	99.7 (98 to 100)
Perkmann et al 2020	89.2 (79 to 96)	99.7 (99 to 100)
Lau et al 2020	68.3 (63 to 73)	99.9 (99 to 100)
Muench et al 2020	82.5 (79 to 86)	99.8 (99 to 100)
Ekelund et al 2020	100 (83 to 100)	98.0 (93 to 100)
Haselmann et al 2020	92.3 (75 to 99)	100.0 (86 to 100)
Horber et al 2020	86.6 (81 to 91)	100.0 (97 to 100)
Kohmer et al	75.6 (60 to 87)	97.1 (85 to 100)
Schnurra et al 2020	90.4 (81 to 96)	-
Muecksh et al 2020	98.7 (97 to 100)	-
Suhandynata et al 2020	84.8 (76 to 91)	99.4 (97 to 100)
Padoan et al. 2020	78.5 (70 to 85)	97.6 (87.4 to 99.9)
Pooled overall values	83.0 (72.0 to 90.2)	99.8 (99.6 to 99.9)

Subgroup analysis was done to determine the sensitivity of ECLIA depending on the timing of sample collection. The sensitivity of ECLIA for samples taken 0 to 6 days, 7 to 13 days, 0 to 13 days, and at least 14 days from onset of symptoms is shown in Table 2.

The pooled sensitivity is 14.5% (95% CI 1.3 to 27.8%) if used 0 to 6 days from onset of symptoms, 70.1% (95% CI 55.9 to 84.3%) if used 7 to 13 days from onset of symptoms, 37.6% (95% CI 24.8 to 50.4%) if used 0 to 13 days from onset of symptoms, and 82.4% (95% CI 69.6 to 95.2%) if used at least 14 days from onset of symptoms. Subgroup analysis depending on the timing of sample collection is shown in Table 2.

In the subgroup analysis of 0 to 13 days from onset of symptoms, data was derived from 4 studies. The reviewers included the studies that used a cutoff of every 5 days (i.e. 0 to 5 days, 6 to 10 days, 11 to 15 days from onset of symptoms). Due to the minimal difference in time period, the reviewers included the data for the samples collected 11 to 15 days from onset of symptoms.

In the subgroup of at least 14 days from onset of symptoms, data was derived from 7 studies. The study of Egger et al. reported sensitivity values from specimens collected 16-22 days from symptom onset, while the study of Coste et al were from specimens collected >15 days from symptom onset. Due to the minimal difference in time period, the reviewers included these 2 studies into the analysis for the subgroup of specimens collected at least 14 days from symptom onset.

Table 2. Subgroup analysis of sensitivity of ECLIA based on days from symptom onset (every 7 days)

Study	Sensitivity % (95% CI)
<i>0 to 6 days from onset of symptoms</i>	
Favresse et al 2020	13.6 (4.7 to 33.3)
Merrill et al 2020	20.0 (3.6 to 62.4)
Pooled sensitivity (0 to 6 days from onset of symptoms)	14.5 (1.3 to 27.8)
<i>7 to 13 days from onset of symptoms</i>	
Favresse et al 2020	71.4 (52.9 to 84.7)
Merrill et al 2020	66.7 (39.1 to 86.2)
Pooled sensitivity (7 to 13 days from onset of symptoms)	70.1 (55.9 to 84.3)
<i>0 to 13 days from onset of symptoms</i>	
Favresse et al 2020	46.0 (33.0 to 59.6)
Merrill et al 2020	52.9 (31.0 to 73.8)
Egger et al 2020	37.2 (27.7 to 47.8)
Coste et al 2020	24.2 (19.4 to 29.6)
Pooled sensitivity (0 to 13 days from onset of symptoms)	37.6 (24.8 to 50.4)
<i>At least 14 days from onset of symptoms</i>	
Egger et al 2020	100.0 (82.4 to 100)
Favresse et al 2020	91.1 (82.8 to 95.6)
Merrill et al 2020	91.7 (64.6 to 98.5)
Weidner et al 2020	94.9 (88.7 to 97.8)
Charlton et al 2020	76.2 (54.9 to 89.4)
Coste et al 2020	30.9 (22.6 to 40.7)
Perkmann et al 2020	89.2 (79.4 to 94.7)
Pooled sensitivity (at least 14 days from onset of symptoms)	82.4 (69.6 to 95.2)

Sensitivity analysis was done to exclude the 5 preprint studies. Pooled overall sensitivity was 79% (95% CI 71 to 85%) while pooled overall specificity was 99.8% (95% CI 99.7 to 99.9%)

Safety Outcomes

No adverse events were reported among the studies reviewed.

Ongoing studies

There are no ongoing studies as of the date of this search.

Recommendations from Other Guidelines

Based on the Center for Disease Control and Prevention (CDC) interim guidelines, antibody tests should not be used to diagnose COVID-19 infection or reinfection. Antibody tests should also not be used to determine immune status. Antibody tests may be offered in the following situations:

1. To support the diagnosis among patients with late complications of COVID-19 illness, such as multisystem inflammatory syndrome in children
2. To support the diagnosis of acute COVID-19 infection among patients who present 9 to 14 days after illness onset.

Furthermore, the CDC guidelines state that there is no identified advantage of whether the antibody tests measures total antibody (such as Elecsys), IgG and IgM, or IgG alone.[27]

The World Health Organization (WHO) recommends the use of antibody tests to aid investigation of an ongoing outbreak and as for retrospective assessment of the attack rate or extent of an outbreak. Paired

serum samples taken in the acute phase and convalescent phase can also be used to support diagnosis among patients with negative PCR but with a strong epidemiological link to COVID-19.[28]

The European Centre for Disease Prevention and Control states that antibody tests currently have limited diagnostic use. Antibody tests can complement PCR among patients presenting late after illness onset and among those who are PCR negative despite strong indications of infection. Antibody tests are used in their setting for sero-epidemiological surveys and research.[29]

The Chinese Center for Disease Control and Prevention state that antibody tests are used in the following conditions:

1. As a supplementary test for PCR negative patients
2. As a complement to PCR for suspected COVID-19 patients
3. Serologic surveys and past exposure surveys of concerned population groups

To be considered positive, an individual has to have positive IgM or IgG for SARS-CoV-2, or an individual has to seroconvert from negative IgG during the acute phase to positive IgG (with antibody levels at least 4x higher) in the convalescent phase.[30]

The Ministry of Health in New Zealand states that antibody tests are not useful in diagnosing new infections. It may be used in the future to determine who had past COVID-19 infection.[31]

The Infectious Diseases Society of America guidelines suggest against using antibody tests to diagnose COVID-19 in the first 14 days of symptom onset. Determination of SARS-CoV-2 IgG or total antibody levels may be done 3 to 4 weeks after symptom onset to detect past COVID-19 for clinical or epidemiological purposes. Determination of IgG may also be done among symptomatic patients with high clinical suspicion of COVID-19 and repeatedly negative PCR tests.[32]

The Department of Health in the Philippines recommends that only antibody tests approved by the FDA and locally validated by RITM or DOST, or those with >90% sensitivity and >95% specificity validated by WHO-Foundation for Innovative New Diagnostics (FIND) should be used. Antibody tests, particularly validated ELISA tests, can be used for seroprevalence surveys.[33]

APPLICATION

Current COVID-19 infection

Using the sensitivity and specificity values for 0 to 13 days from onset of symptoms, the computed positive likelihood ratio is 38.1 and the negative likelihood ratio is 0.62.

Based on locally observed data (i.e. from NIH; consensus from experts), the pretest probability of having current COVID-19 infection is 1% among asymptomatic individuals. Thus, individuals who obtain a positive ECLIA result have a posttest probability of 28% for having current COVID-19 infection. Meanwhile, individuals who obtain a negative ECLIA result have a posttest probability of 1% for having current COVID-19 infection. This is illustrated in Figure 1.

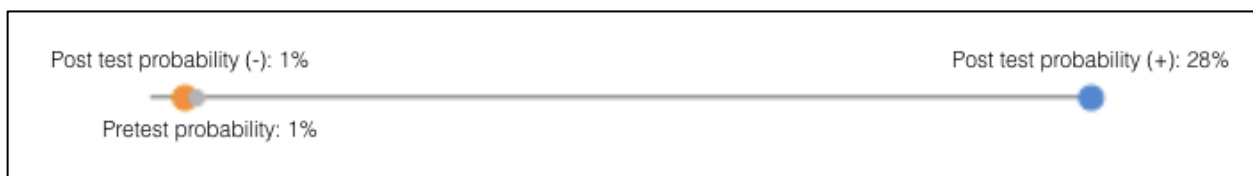


Figure 1. Posttest probability for asymptomatic individuals

Based on locally observed data (i.e. from NIH; consensus from experts), the pretest probability of having current COVID-19 infection is 10% among individuals with symptoms of COVID-19. Thus, individuals who

obtain a positive ECLIA result have a posttest probability of 81% for having current COVID-19 infection. Meanwhile, individuals who obtain a negative ECLIA result have a posttest probability of 6% for having current COVID-19 infection. This is illustrated in Figure 2.



Figure 2. Posttest probability for individuals with symptoms of COVID-19

Past COVID-19 infection

Using the sensitivity and specificity values for the subgroup of samples collected at least 14 days from onset of symptoms, the computed positive likelihood ratio is 83.4 and the negative likelihood ratio is 0.17.

Based on locally observed data (i.e. from NIH; consensus from experts), the pretest probability of having COVID-19 infection is 10% among individuals with previous symptoms of COVID-19. Thus, individuals who obtain a positive ECLIA result have a posttest probability of 90% for having past COVID-19 infection. Meanwhile, individuals who obtain a negative ECLIA result have a posttest probability of 2% for having past COVID-19 infection. This is illustrated in Figure 3.

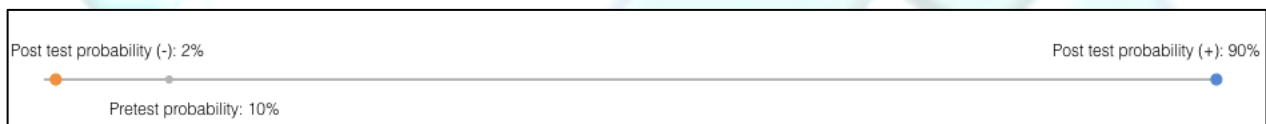


Figure 3. Posttest probability for individuals manifesting with symptoms of COVID-19 for at least 14 days

CONCLUSION

ECLIA has a high specificity of 99.8% but its usefulness is limited by poor sensitivity. The sensitivity is 37.6% when used less than 14 days from onset of symptoms, so it is not recommended for screening asymptomatic disease (eg. mass screening, contact tracing or return to work clearance). The sensitivity is 82.4% when used at least 14 days from onset of symptoms, so it may have some use in patients with prolonged illness of more than 14 days. It may also be useful for seroprevalence studies.

Declaration of Conflict of Interest

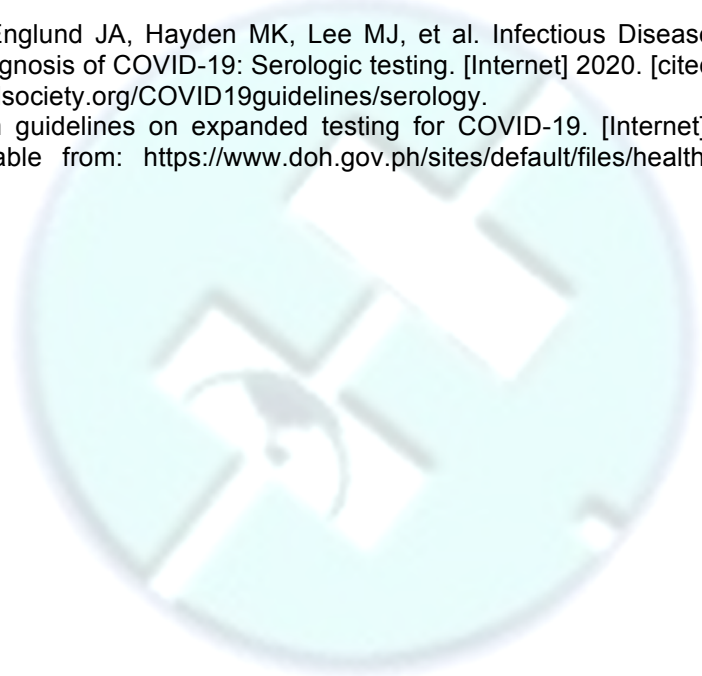
No conflict of interest

REFERENCES

1. Kumar R, Nagpal S, Kaushik S, Mendiratta S. COVID-19 diagnostic approaches: different roads to the same destination. *VirusDis.* 2020;21(2):97-105.
2. Diagnostic testing and screening for SARS-CoV-2. European Centre for Disease Prevention and Control. June 2020. Retrieved from <https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing>.
3. COVID-19 (SARS-CoV-2) serology total Ig. Retrieved from <https://www.eurofins-biomnis.com/en/services/test-guide/page/SCOV1/>.
4. Elecsys® anti-SARS-CoV-2. Roche. Retrieved from <https://diagnostics.roche.com/global/en/products/params/electsys-anti-sars-cov-2.html>.

5. FAQs on TMC drive-thru COVID-19 testing. The Medical City. August 13, 2020. Retrieved from <https://www.themedicalcity.com/news/faqs-tmc-drive-thru-covid-19-testing>
6. COVID-19 antibody test (ECLIA method) is now available! St. Cabrini. Retrieved from http://cabrinimed.com/blog.php?b_id=14/covid-19-total-antibody-test-eclia-method.
7. Casinas JA. Pasig provides residents free COVID-19 testing. August 13, 2020. Retrieved from <https://mb.com.ph/2020/08/13/pasig-provides-residents-free-covid-19-testing/>.
8. Egger M, Bundschuh C, Wiesinger K, Gabriel C, Clodi M, Mueller T et al. Comparison of the Elecsys® Anti-SARS-CoV-2 immunoassay with the EDI™ enzyme linked immunosorbent assays for the detection of SARS-CoV-2 antibodies in human plasma. *Clinica Chimica Acta*. 2020;509:18-21.
9. Favresse J, Euchet C, Elsen M, Laffineur K, Dogné J, Douxfils J. Response of anti-SARS-CoV-2 total antibodies to nucleocapsid antigen in COVID-19 patients: a longitudinal study. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020;0(0).
10. Lau C, Hoo S, Yew S, Ong S, Lum L, Heng P et al. Evaluation of an electrochemiluminescent SARS-CoV-2 antibody assay. *The Journal of Applied Laboratory Medicine*. 2020
11. Merrill A, Jackson J, Ehlers A, Voss D, Krasowski M. Head-to-Head Comparison of Two SARS-CoV-2 Serology Assays. *The Journal of Applied Laboratory Medicine*. 2020;
12. Muench P, Jochum S, Wenderoth V, Ofenloch-Haehnle B, Hombach M, Strobl M et al. Development and Validation of the Elecsys Anti-SARS-CoV-2 Immunoassay as a Highly Specific Tool for Determining Past Exposure to SARS-CoV-2. *Journal of Clinical Microbiology*. 2020;.
13. Weidner L, Gänsdorfer S, Unterweger S, Weseslindtner L, Drexler C, Farcet M et al. Quantification of SARS-CoV-2 antibodies with eight commercially available immunoassays. *Journal of Clinical Virology*. 2020;129:104540.
14. Charlton C, Kanji J, Johal K, Bailey A, Plitt S, MacDonald C et al. Evaluation of six commercial mid to high volume antibody and six point of care lateral flow assays for detection of SARS-CoV-2 antibodies. *Journal of Clinical Microbiology*. 2020;.
15. Coste A, Jaton K, Papadimitriou-Olivgeris M, Greub G, Croxatto A. Comparison of SARS-CoV-2 serological tests with different antigen targets. 2020;.
16. Ekelund O, Ekblom K, Somajo S, Pattison-Granberg J, Olsson K, Petersson A. High-throughput immunoassays for SARS-CoV-2, considerable differences in performance when comparing three methods. 2020;.
17. Haselmann V, Kittel M, Gerhards C, Thiaucourt M, Eichner R, Costina V et al. Comparison of test performance of commercial anti-SARS-CoV-2 immunoassays in serum and plasma samples. *Clinica Chimica Acta*. 2020;510:73-78.
18. Hörber S, Soldo J, Relker L, Jürgens S, Guthier J, Peter S et al. Evaluation of three fully-automated SARS-CoV-2 antibody assays. *CCLM*. 2020;
19. Kohmer N, Westhaus S, Rühl C, Ciesek S, Rabenau H. Brief clinical evaluation of six high-throughput SARS-CoV-2 IgG antibody assays. *Journal of Clinical Virology*. 2020;129:104480.
20. Pflüger L, Bannasch J, Brehm T, Pfefferle S, Hoffmann A, Nörz D et al. Clinical evaluation of five different automated SARS-CoV-2 serology assays in a cohort of hospitalized COVID-19 patients. *Journal of Clinical Virology*. 2020;130:104549.
21. Schnurra C, Reiners N, Biemann R, Kaiser T, Trawinski H, Jassoy C. Comparison of the diagnostic sensitivity of SARS-CoV-2 nucleoprotein and glycoprotein-based antibody tests. *Journal of Clinical Virology*. 2020;129:104544.
22. Muecksch F, Wise H, Batchelor B, Squires M, Semple E, Richardson C et al. Longitudinal analysis of clinical serology assay performance and neutralising antibody levels in COVID19 convalescents. 2020;.
23. Padoan A, Plebani M, Sciacovelli L, Bonfante F, Pagliari M, Bozzato D et al. Analytical and clinical performances of five immunoassays for the detection of SARS-CoV-2 antibodies in comparison with neutralization activity. 2020;.
24. Perkmann T, Perkmann-Nagele N, Breyer M, Breyer-Kohansal R, Burghuber O, Hartl S et al. Side by side comparison of three fully automated SARS-CoV-2 antibody assays with a focus on specificity. 2020;.
25. Suhandynata R, Hoffman M, Kelner M, McLawhon R, Reed S, Fitzgerald R. Multi-platform Comparison of SARS-CoV-2 Serology Assays for the Detection of COVID-19. *The Journal of Applied Laboratory Medicine*. 2020;.

26. Dans A, Dans L, Silvestre M. Painless evidence-based medicine. 2nd ed. Chichester, West Sussex: John Wiley & Sons Inc.; 2017.
27. Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing. [Internet] 2020. [cited August 17, 2020] Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html#anchor_1590264293982
28. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance. [Internet] 2020. [cited August 17, 2020] Available from: <https://apps.who.int/iris/handle/10665/331329>
29. European Center for Disease Control and Prevention. Diagnostic testing and screening for SARS-CoV-2. [Internet] 2020. [cited August 17, 2020] Available from: <https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing>
30. Chinese Center for Disease Control and Prevention. Technical guidelines for COVID-19 laboratory testing. [Internet] 2020. [cited August 17, 2020] Available from: <http://weekly.chinacdc.cn/en/article/doi/10.46234/ccdcw2020.085>
31. Ministry of Health New Zealand. How COVID-19 testing works. [Internet] 2020. [cited August 17, 2020] Available from: <https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-health-advice-general-public/assessment-and-testing-covid-19/how-covid-19-testing-works#types>
32. Hanson KE, Caliendo AM, Arias CA, Englund JA, Hayden MK, Lee MJ, et al. Infectious Disease Society of America guidelines on the diagnosis of COVID-19: Serologic testing. [Internet] 2020. [cited August 21, 2020] Available from: www.idsociety.org/COVID19guidelines/serology.
33. Department of Health. Updated interim guidelines on expanded testing for COVID-19. [Internet]. 2020 [cited August 17, 2020] Available from: <https://www.doh.gov.ph/sites/default/files/health-update/dm2020-0258.pdf>



Appendix 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	N (# of samples)	Key findings
1	Egger 2020	Case control study	Austria	1. RT-PCR confirmed COVID-19 patients 2. Healthy blood donors and ICU patients collected prior to December 2019	560	<p><5 days from symptom onset TP: 1/34 (2.9%) FN: 33/34 (97.1%)</p> <p>5 to 10 days TP: 18/35 (51.4%) FN: 17/35 (48.6%)</p> <p>10 to 15 days TP: 13/17 (76.5%) FN: 4/17 (23.5%)</p> <p>15-22 days TP: 18/18 (100%) FN: 0/18 (0%)</p> <p>FP: 1/456 (0.2%) TN: 455/456 (99.8%)</p>
2	Favresse et al 2020	Case control study	Belgium	1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to December 2019	348	<p>0 to 6 days from RT PCR + TP: 21/45 FN: 24/45 Sn: 46.7% (95% CI 31.7 to 62.1)</p> <p>7 to 13 days from RT PCR + TP: 26/35 FN: 9/35 Sn: 74.3% (95% CI 56.7 to 87.5%)</p> <p>14 to 20 days from RT PCR + TP: 23/24 FN: 1/24 Sn: 95.8% (95% CI 78.9 to 99.9%)</p> <p>21 to 27 days from RT PCR + TP: 13/15 FN: 2/15 Sn: 86.7% (95% CI 59.5 to 98.3%)</p> <p>At least 28 days RT PCR + TP: 19/21 FN: 2/21 Sn: 90.5% (95% CI 69.6 to 98.8%)</p> <p>0 to 6 days from symptom onset TP: 3/22 FN: 19/22 Sn: 13.6% (95% CI 2.9 to 34.9%)</p> <p>7 to 13 days from symptom onset TP: 20/28 FN: 8/28 Sn: 71.4% (95% CI 51.3 to 86.8%)</p> <p>14 to 20 days from symptom onset TP: 23/26 FN: 3/26 Sn: 88.5% (95% CI 69.9 to 97.6)</p> <p>21 to 27 days from symptom onset TP: 20/23 FN: 3/23 Sn: 87% (95% CI 66.4 to 97.2%)</p> <p>At least 28 days after symptom onset TP: 29/30 FN: 1/30 Sn: 96.7% (95% CI 82.8 to 99.9%)</p> <p>At least 14 days after onset of symptoms TP: 72/79 FN: 7/79 Sn: 91.1% (95% CI 82.6 to 96.4%)</p> <p>TN: 79/79 FP: 0/79 Sp: 100% (95% CI 95.44 to 100%)</p>

3	Lau et al 2020	Cross sectional study	Singapore	1. RT-PCR confirmed COVID-19 patients 2. Patients with no suspicion for COVID-19 or acute respiratory illness	1,064	0 to 6 days post-positive PCR TP: 91/189 FN: 98/189 PPA: 48.2% (95% CI 40.84 to 55.52%) 7 to 13 days post-positive PCR TP: 68/90 FN: 22/90 PPA: 75.6% (95% CI 65.36 to 84%) 14 to 20 days post-positive PCR TP: 68/70 FN: 2/70 Sn: 97.1% (95% CI 90.06 to 99.65%) At least 21 days post-positive PCR TP: 36/36 FN: 0/36 Sn: 100% (95% CI 90.26 to 100%) FP 1/715 Sp: 99.86% (95% CI 99.22 to 100)
4	Merrill 2020	Case control study	USA	1. RT-PCR confirmed COVID-19 patients 2. Patients with negative RT-PCR tests and sera collected prior to December 2019	282	<7 days from PCR + TP: 17/35 7-13 days from PCR + TP: 13/13 >13 days from PCR + TP: 5/6 <7 days from symptom onset TP: 1/5 7 to 13 days from symptom onset TP: 8/12 >13 days from symptom onset 11/12 Unknown symptom onset TP: 10/12 Asymptomatic patients TP: 5/13 Overall TP: 35/54 Sn 64.8% (95% CI 50.6 to 77.3) TN: 174/174 Sp: 100% (95% CI 97.9 to 100%)
5	Muench 2020	Case control study	Germany	1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to December 2019	10,949	0 to 6 days after PCR + TP: 97/161 FN: 64/161 Sn: 60.2% (52.3 to 67.8%) 7 to 13 days after PCR + TP: 128/150 FN: 22/150 Sn: 85.3% (95% CI 78.6 to 90.6%) At least 14 days after PCR + TP: 184/185 FN: 1/185 Sn: 99.5% (95% CI 97.0 to 100%) TN: 10432/10453 FP: 21/10453 Sp: 99.8% (95% CI 99.69 to 99.88%)
6	Weidner 2020	Cross sectional study	Austria	RT-PCR confirmed COVID-19 patients	99	26 to 61 days after symptom onset TP: 94/99 Sn: 94.95%
7	Charlton 2020	Case control study	Canada	1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to November 2019	92	0 to 14 days from symptom onset TP: 14/21 FN: 7/21 Sn: 67% (95% CI 43 to 85%) 15 to 21 days from symptom onset TP: 8/11

						<p>FN: 3/11 Sn: 73% (95% CI 39 to 94%) >21 days from symptom onset TP: 8/10 FN: 2/10 Sn: 80% (95% CI 44 to 97%)</p> <p>All time points TP: 30/42 FN: 12/42 Sn: 71% (95% CI 55 to 84%)</p> <p>TN: 50/50 Sp: 100% (93 to 100%)</p>
8	Coste 2020	Case control study	Switzerland	<p>1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to November 2019</p>	454	<p>0 to 5 days from symptom onset TP: 8/75 FN: 67/75 Sn: 0 (95% CI 0 to 32%) 6 to 10 days from symptom onset TP: 19/86 FN: 67/86 Sn: 47% (95% CI 27 to 68%) 11 to 15 days from symptom onset TP: 37/104 FN: 67/104 Sn: 86% (95% CI 72 to 94%) >15 days from symptom onset TP: 30/97 FN: 67/97 Sn: 93% (95% CI 79 to 99%)</p>
9	Ekelund 2020	Case control study	Sweden	<p>1. RT-PCR confirmed COVID-19 patients 2. Sera collected in 2018</p>	122	<p>>14 days after PCR + TP: 20/20 Sn: 100%</p> <p>TN: 100/102 Sp: 98%</p>
10	Haselmann 2020	Case control study	Germany	<p>1. RT-PCR confirmed COVID-19 patients 2. Control: atypical respiratory infection and RT PCR negative, other respiratory viral infection diagnosed, chronic disease, contact with COVID patient but negative PCR and no symptoms, healthy controls</p>	51	<p>7 to 13 days from PCR + TP: 5/5 At least 14 days from PCR + TP: 19/21 FN: 2/21 Sn 92.3%</p> <p>TN: 25/25 Sp 100%</p>
11	Horber 2020	Case control study	Germany	<p>1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to December 2019</p>	309	<p>0 to 6 days from PCR + TP: 15/23 FN: 8/23 Sn: 65.2% 7 to 13 days from PCR + TP: 28/31 FN: 3/31 Sn: 90.3% At least 14 days from PCR+ TP: 118/132 FN: 14/132 Sn: 89.4%</p> <p>TN: 123/123 FP: 0/123 Sp: 100%</p>
12	Kohmer 2020	Case control study	Germany	<p>1. RT-PCR confirmed COVID-19 patients (most were moderate to severe) 2. PCR negative or sera collected prior to the pandemic</p>	79	<p>Total time frame of 49 days after PCR + TP: 34/45 FN: 11/45 Sn: 75.6%</p> <p>TN: 33/34 FP: 1/34 Sp: 97%</p>

13	Pfluger 2020	Case control study	Germany	1. RT-PCR confirmed COVID-19 patients 2. Sera collected prior to the pandemic	395	1 to 10 days from symptom onset TP: 17/37 FN: 20/37 Sn: 46% (95% CI 31 to 61.6%) >10 days from symptom onset TP: 30/38 FN: 8/38 Sn: 79% (95% CI 63.7 to 88.9%) TN: 319/320 FP: 1/320 Sp: 99.7% (95% CI 98.3 to 100%)
14	Schnurra 2020	Prospective cohort study	Germany	RT-PCR confirmed COVID-19 patients (asymptomatic, mild or moderate)	73	2 to 3 weeks after PCR + TP: 20/25 FN: 5/25 Sn: 80% (95% CI 59.3 to 93.2%) At least 4 weeks after PCR + TP: 46/48 Sn: 95.8% (95% CI 85.7 to 99.5%)
15	Muecksh 2020	Prospective cohort study	USA	RT-PCR confirmed COVID-19 patients	319	21 to 40 days after PCR+ TP: 47/47 FN: 0/47 Sn: 100% (95% CI 92.5 to 100%) 41 to 60 days after PCR + TP: 135/137 FN: 2/137 Sn: 98.54% (95% CI 94.8 to 99.8%) 61 to 80 days from PCR + TP: 93/94 FN: 1/94 Sn: 98.94% (95% CI 94.2 to 100%) At least 81 days from PCR+ TP: 40/41 FN: 1/41 Sn: 97.56% (87.1 to 100%)
16	Padoan 2020	Case control study	Italy	RT-PCR confirmed COVID-19 patients (most were moderate or severe) RT-PCR negative individuals	172	Overall (total time frame of 93 days after symptom onset) Sn: 78.5% (95% CI 70.4 to 85.2%) At least 12 days from symptom onset Sn: 89.4% (95% CI 81.9 to 94.6%) Sp: 97.6% (95% CI 87.4 to 99.9%) Cannot compute for TN, Tp, FN, FP because it was not specified how many of the samples were PCR + or PCR -
17	Perkmann 2020	Case control study	Austria	Case: RT-PCR confirmed COVID patients, symptomatic patients with close contact to PCR + COVID patients, Control: sera collected before January 1, 2020	1,219	At least 14 days from symptom onset: TP: 58/65 FN: 7/65 Sn: 89.2% (95% CI 79.1 to 95.6%) TN: 1151/1154 FP: 3/1154 Sp: 99.7% (95% CI 99.2 to 100%)
18	Suhandynata 2020	Case control study	USA	Case: RT-PCR confirmed COVID patients Control: PCR positive for a different respiratory pathogen, patients with positive ANA/dsDNA, clinically elevated IgM/IgG, healthy subjects, sera stored since 2018	278	0 to 7 days post PCR + TP: 29/43 FN: 14/43 PPA: 67.4% 8 to 14 days post PCR + TP: 31/31 FN: 0/31 PPA: 100% At least 15 days post PCR + TP: 24/25 FN: 1/25 PPA: 96% TN: 178/179 FP: 1/179 NPA: 99.4%

Appendix 2. Literature search

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {ECLIA OR electroche electrochemiluminescence immunoassays OR Elecsys}	August 15, 2020 12:01:20 GMT+8	10	5
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {ECLIA OR electroche electrochemiluminescence immunoassays OR Elecsys}	August 15, 2020 12:01:20 GMT+8	1	0
Google Scholar	Coronavirus, ECLIA (since 2019)	August 15, 2020 12:01:20 GMT+8	51	9
Trial Registries				
ClinicalTrials.gov	ECLIA	August 16, 2020 12:01:20 GMT+8	10	0
Chinese Clinical Trial Registry	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
EU Clinical Trials Register	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
Republic of Korea - Clinical Research Information Service	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
CenterWatch	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
Other databases				
chinaxiv.org	ECLIA	August 16, 2020 12:01:20 GMT+8	0	0
Medrxiv.org	ECLIA	August 16, 2020 12:01:20 GMT+8	19	3
Biorxiv.org	ECLIA	August 16, 2020 12:01:20 GMT+8	16	0

Appendix 3. Critical Appraisal of Included Studies

Study	Was the reference standard an acceptable one?	Was definition of the index test and reference standard independent?	Was performance of the index test and the reference standard independent?	Was interpretation of the index test and the reference standard independent?	Overall
Egger 2020	Yes	Yes	No	Yes	Moderate risk of bias
Favresse et al 2020	Yes	Yes	No	Yes	Moderate risk of bias
Lau et al 2020	Yes	Yes	No	Yes	Moderate risk of bias
Merrill 2020	Yes	Yes	No	Yes	Moderate risk of bias
Muench 2020	Yes	Yes	No	Yes	Moderate risk of bias
Weidner 2020	Yes	Yes	Yes	Yes	Low risk of bias
Charlton 2020	Yes	Yes	No	Yes	Moderate risk of bias
Coste 2020	Yes	Yes	No	Yes	Moderate risk of bias
Ekelund 2020	Yes	Yes	No	Yes	Moderate risk of bias
Haselmann 2020	Yes	Yes	No	Yes	Moderate risk of bias
Horber 2020	Yes	Yes	No	Yes	Moderate risk of bias
Kohmer 2020	Yes	Yes	No	Yes	Moderate risk of bias
Pfluger 2020	Yes	Yes	No	Yes	Moderate risk of bias
Schnurra 2020	Yes	Yes	Yes	Yes	Low risk of bias
Muecksh 2020	Yes	Yes	Yes	Yes	Low risk of bias
Padoan 2020	Yes	Yes	No	Yes	Moderate risk of bias
Perkmann 2020	Yes	Yes	No	Yes	Moderate risk of bias
Suhandynata 2020	Yes	Yes	No	Yes	Moderate risk of bias

Appendix 4. Forest plots

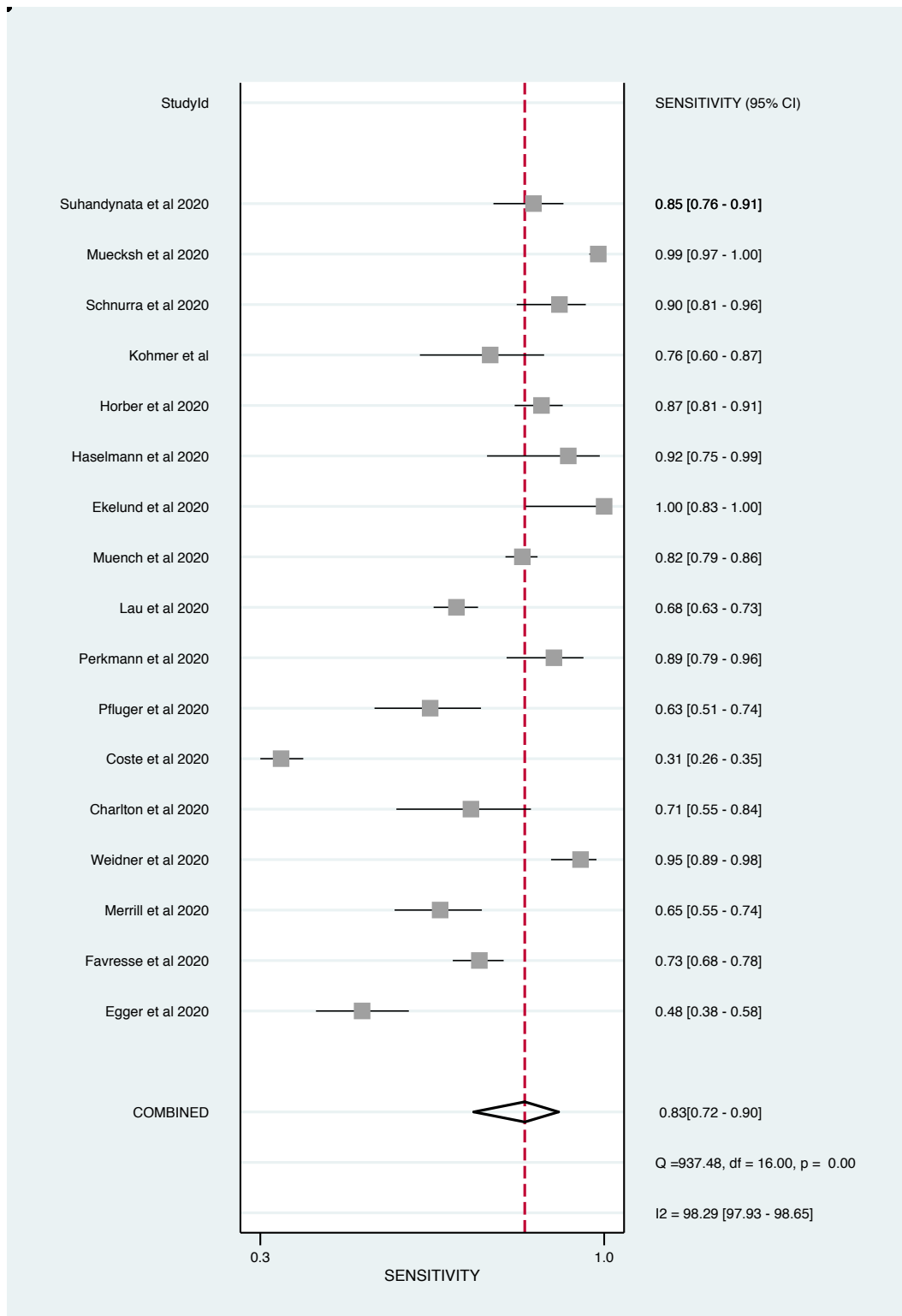


Figure 1. Pooled overall sensitivity

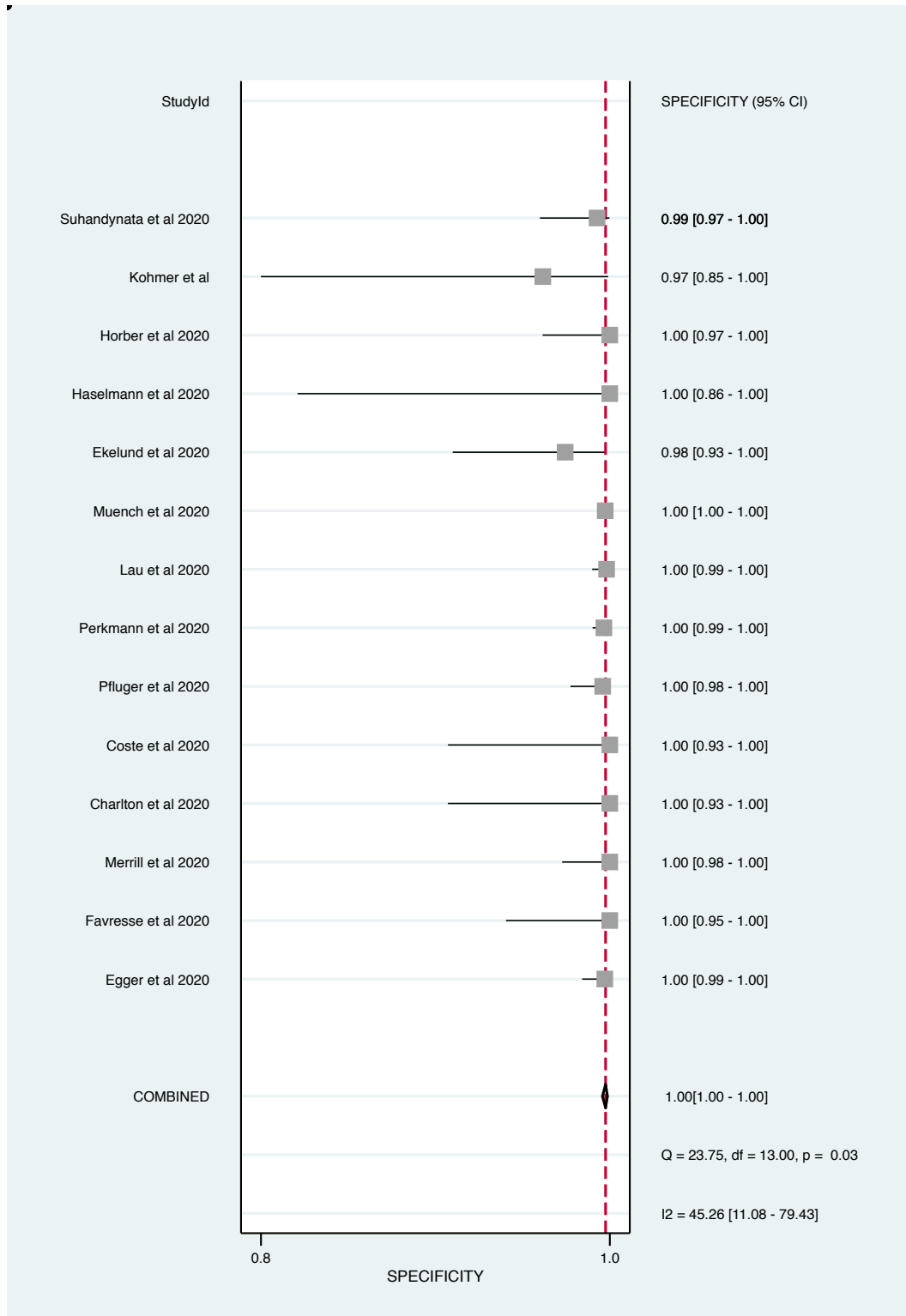


Figure 2. Pooled overall specificity

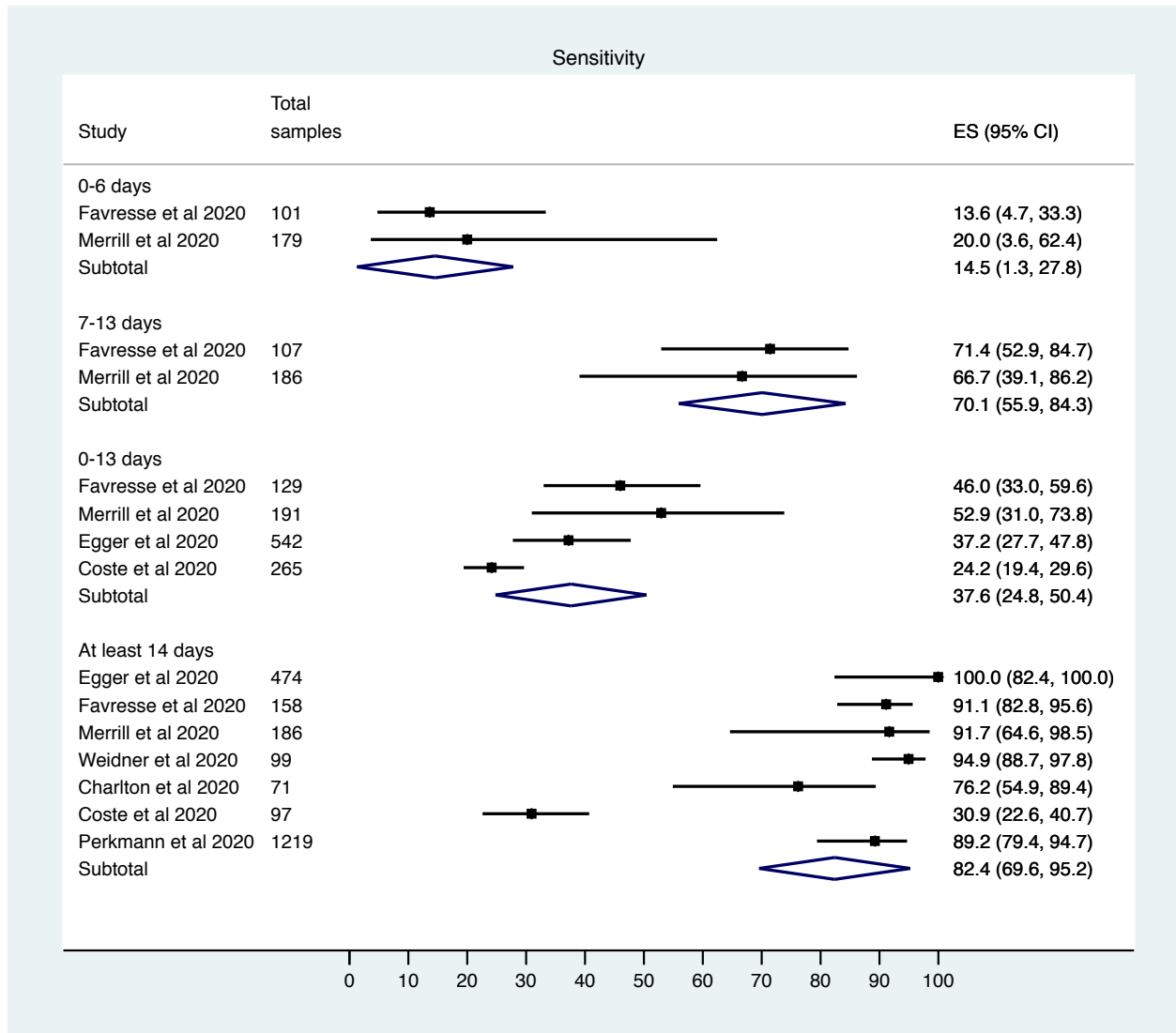


Figure 3. Subgroup analysis per timing of sample collection