14-DAY SYMPTOM-BASED TEST

RECOMMENDATION

We suggest an initial screening for COVID-19 by checking for any influenza-like illness symptoms and typical COVID-19 symptoms* within the past 14 days in apparently healthy adults. *(Low quality of evidence; Conditional recommendation)*

Symptoms include: fever, cough, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, anosmia, ageusia, shortness of breath/dyspnea

Consensus Issues

14-day symptom-based test is a screening strategy wherein the presence of any influenza-like illness symptoms within the past 14 days is designated as presumptive for COVID-19. It should be noted that since the recommendation is for initial screening, a follow-up confirmatory diagnostic test should be done.

See updated WHO Surveillance Case Definition December 2020.

EVIDENCE SUMMARY

Should the 14-day symptom-based test be used in screening for COVID-19 infection in apparently healthy adults?

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Key Findings

Limited evidence was found from two (2) observational studies (n= 8,290) to support the use of the 14-day symptom-based test in screening for COVID-19 in apparently healthy adults. This symptom-based test had moderate sensitivity and specificity in detecting COVID-19 among adults. We found no randomized trials showing the benefits and harms of a symptom-based screening strategy. The studies were of moderate risk of bias due to inability to assure independent test performance and potential bias in patient selection.

Introduction

Earlier local and international recommendations using symptom-based screening were based on the incubation period of COVID-19. An earlier rapid review pooled three cohorts (n = 234) and estimated the proportion of symptomatic SARS-CoV-2 positive cases who developed symptoms within 14 days, or sensitivity, to be at 92.8% (95% CI 89.5-96.1%) [1]. They also used indirect evidence from an influenza vaccine study on elderly patients and found that development of influenza-like illness within 14 days had a specificity of 98.3% (95% CI 97.2, 99.2).

Review Methods

We conducted a search on several electronic databases (MEDLINE, Cochrane CENTRAL, HERDIN Plus), preprint servers (medRxiv, bioRxiv, ChinaXiv) and trial registries (ClinicalTrials.gov, WHO ICTRP, ChiCTR) on January 3, 2021 for studies investigating the accuracy of a 14-day symptom-based test in adults to screen for SARS-CoV-2 infection or COVID-19. Search terms included the following and their variations: screening, influenza-like illness, influenza symptoms, sensitivity, specificity, predictive value, COVID-19, SARS-CoV-2 and novel coronavirus. We excluded studies that did not specify a 14-day timeframe for symptoms, those involving hospital workers, and studies with small sample sizes (n < 30).

Results

Characteristics of included studies

We found two (2) eligible studies which compared the presence of symptoms of an influenza-like illness within two weeks with reverse transcription polymerase chain reaction (RT PCR) as a reference standard for SARS-CoV-2 infection [2,3]. Both studies used symptoms found in COVID-19 and influenza-like illnesses such as fever, cough and dyspnea. Nasopharyngeal swab (NPS) specimens were used in one study while both NPS and oropharyngeal swab (OPS) specimens were analyzed in the other.

One cross-sectional study (n = 8214) in the United States evaluated the diagnostic performance of individual symptoms, and various symptom combinations, against a positive RT PCR test[1] on NPS specimens collected by trained personnel using Dacron swabs [2]. Specimens were collected during the same encounter as the symptom screening and were sent to laboratories in Indianapolis, IN. Blinding of those who interpreted the RT PCR test was not specified.

The study recruited 8,214 patients, ages 12 years and older, who sought testing in statewide open-testing sites in Indiana. All participants were screened for presence of the following symptoms within the last 14 days using a standardized checklist: anosmia, ageusia, fever, chills, chest pain, vomiting, myalgia, cough, shortness of breath, sore throat, diarrhea, fatigue, headache and runny nose. Of these, 4,772 (58%) participants were asymptomatic in the past two weeks. There were 368 (4.6%) individuals with a positive RT-PCR result and 91 (24.7%) were asymptomatic.

Another smaller cross-sectional study (n = 76) investigated residents in a long-term skilled nursing facility in a Washington county where a COVID-19 outbreak occurred [3]. All consenting participants were screened for both typical (fever, cough, shortness of breath) and atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptoms of COVID-19 by records review and clinician interview. The study considered patients with only stable, chronic symptoms as asymptomatic. The presence of at least one typical or atypical COVID-19 symptom was considered positive for the symptom-based test. NPS for all, and OPS for some participants were collected at the time of screening and sent for one-step real-time RT-PCR assay using the SARS-CoV-2 CDC assay protocol (Washington State Public Health Laboratory). A Ct value < 40 cycles was the threshold for a positive result.

[1] Lilly Clinical Diagnostics Lab SARS-CoV-2 test, Luminexon NxTAG CoV Extended Panel or Roche cobas SARS-CoV-2 test, unspecified Ct value

There were 53 residents (69.7%) considered asymptomatic and 13 (24.5%) of them tested positive on RT PCR.

Methodological quality

Studies were assessed to be of moderate quality. Independence of test performance could not be assured. Patient selection could have also introduced bias due to voluntary enrollment.

Benefit and Harms of Screening

We did not find any randomized clinical trials on the effectiveness or harms of a universal 14-day symptom-based screening strategy in reducing SARS-CoV-2 transmission, mortality, or other patient-centered outcomes.

Diagnostic Accuracy

The pooled results from these two studies provide a moderate sensitivity of 61.7% (95% CI 36.6-81.8%) and similar specificity, 66.7% (95% CI 55.3-76.5%), for the 14-day symptom-based test in detecting COVID-19 among adults (**Figure 1** and **Table 1**).

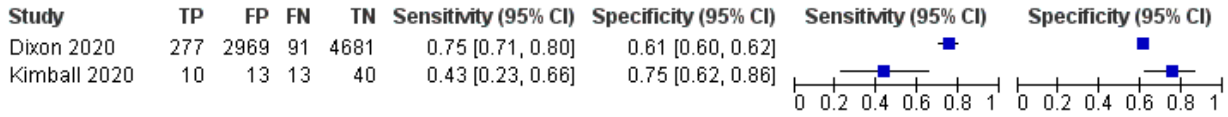

Figure 1. Forest plot of studies evaluating the sensitivity and specificity of the 14-day symptom-based test versus SARS-CoV-2 RT PCR testing in detecting COVID-19.

Table 1. Summary of diagnostic test performance of 14-day symptom-based test versus SARS-CoV-2 RT PCR testing in detecting COVID-19 from individual studies

Study	n	Sensitivity, % (95% CI)	Specificity, % (95%CI)	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)	Diagnostic Accuracy (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Dixon 2020	8,214	75.3 (70.5-79.6)	61.2 (60.1-62.3)	8.53 (8.04-9.05)	98.1 (97.7-98.4)	61.8 (60.8-62.9)	1.94 (1.82-2.07)	0.40 (0.34-0.48)
Kimball 2020	76	43.5 (23.2-65.5)	75.5 (61.7-86.2)	43.5 (28.4-59.9)	75.5 (67.6-82.0)	65.8 (54.0-76.3)	1.77 (0.91-3.44)	0.75 (0.51-1.11)

Assigning the presence of any one symptom as a positive test, the diagnostic accuracy of a 14-day symptom-based test for COVID-19 were as follows: sensitivity 75.27% (95% CI 70.53-79.60) and specificity 61.19% (95% CI 60.09-62.28). In this study setting with a disease prevalence of 4.59%, the positive and negative predictive values were 8.53% (95% CI 8.04-9.05) and 98.09% (95% CI 97.73-98.4) respectively. This test has a strongly negative LR, 0.40 (95% CI 0.34-0.48), but a weakly positive LR, 1.94 (95% CI 1.82-2.07) (**Table 1**). Individual symptoms with the highest specificity for COVID-19 were anosmia (98.9%), ageusia (98.7%) and fever (98.1%).

In the smaller study, the 14-day symptom-based test had a sensitivity of 43.48% (95% CI 23.19% to 65.51%) and specificity of 75.47% (61.72% to 86.24%). In this cohort with a higher prevalence

of SARS-CoV-2 infection (30%), the positive and negative predictive values were at 43.48% (28.38% to 59.89%) and 75.47% (67.57% to 81.96%) respectively, and both negative and positive LRs were weak (0.75 and 1.77 respectively) (**Table 1**).

Variability in diagnostic performance between the studies appears to be influenced by patient population and reference standard. While the first study performed a statewide community-based screening, individuals in the second study were screened after an identified COVID-19 outbreak in the facility. Conversely, COVID-19 prevalence was higher in the second study. OPS specimens, which have lower sensitivity for COVID-19 compared with NPS specimens [4], were also included in the reference standard of the smaller study [4].

Recommendations from Other Groups

The World Health Organization [WHO] (2020 Dec 16) definition for suspected case of SARS-CoV-2 infection includes the development of symptoms and meeting exposure criteria within 14 days before symptom onset [5]. Similarly, local societies forming the Healthcare Professionals Alliance Against COVID-19, including PSMID, PCCP, PCP, PSGIM and PCOOM, produced in November 2020 unified clinical decision algorithms that consider individuals without COVID-19 symptoms in the past 14 days as non-COVID-19 cases [6].

The latest WHO Living Guidance (2021 Jan 25) recommends screening all persons at the first point of contact with the health system, e.g., emergency unit, primary care clinic, community, telemedicine. A simple set of questions with symptoms including fever, cough, fatigue, anorexia, shortness of breath and other non-specific symptoms should be used [7]

The US Centers for Disease Control and Prevention (CDC) (2020 Oct 21) recommends SARS-CoV-2 diagnostic (molecular or antigen) testing in patients with symptoms of COVID-19. The CDC does not routinely recommend SARS-CoV-2 testing “if you do not have COVID-19 symptoms and have not been in close contact with someone known to have SARS-CoV-2 infection (meaning being within 6 feet of an infected person for at least 15 minutes).”[8]

Research gaps

We found no ongoing trials investigating the accuracy of the 14-day symptom-based test in detecting SARS-CoV-2 infection.

References

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Appendix 1: Characteristics of Included Studies

Author / Study Design	Population / Setting	Intervention/s	Control	Outcomes	Sample Size
Dixon 2020	≥ 12 years old, statewide open-testing sites in Indiana	Any symptom within 14 days on standardized checklist	RT PCR (NPS)	Diagnosis of SARS-CoV-2 infection	8,214
Kimball 2020	Residents in a long-term skilled nursing facility in Washington	Any typical (fever, cough, SOB) or atypical (malaise, nausea, sore throat, increased confusion, dizziness, diarrhea, rhinorrhea, myalgia, headache, chills) symptom within 14 days	RT PCR (NPS or OPS)	Diagnosis of SARS-CoV-2 infection	76

Appendix 2: GRADE Evidence Profile

Question: Should the 14-day symptom-based test be used to screen for COVID-19 in apparently healthy adults?

Sensitivity	0.62 (95% CI: 0.37 to 0.82)
Specificity	0.67 (95% CI: 0.55 to 0.77)

Prevalences	5%	7.8%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 7.8%	pre-test probability of 10%	
True positives (patients with COVID-19)	2 studies 391 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	31 (18 to 41)	48 (29 to 64)	62 (37 to 82)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having COVID-19)								19 (9 to 32)	30 (14 to 49)	38 (18 to 63)	
True negatives (patients without COVID-19)	2 studies 7703 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	634 (525 to 727)	615 (510 to 705)	600 (498 to 689)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having COVID-19)								316 (223 to 425)	307 (217 to 412)	300 (211 to 402)	

Explanations

a. Downgraded once due to inability to determine independence of test performance and possible bias in patient selection
b. Downgraded once due to the wide confidence interval of the pooled effect