Key Research Questions:

What patient demographic or clinical factors are associated with a positive COVID-19 test result?
What demographic, clinical, lab or radiologic features have a significantly positive predictive value for a COVID-19 infection?

Context

- Results from previous research have identified patient factors that are associated with a positive COVID-19 test result.
- This question was initially posed to determine if the more easily derived demographic and clinical predictor variables could potentially be used by AHS clinicians to help prioritize patients for COVID-19 testing, particularly if testing resources are limited.
- Overreliance on COVID-19 testing can lead to inappropriate cessation of isolation and PPE in the face of a false negative result despite clinical indicators suggesting a significant COVID-19 risk.
- There are variable sources of error in the collection and processing of swabs taken for COVID-19 RT-PCR testing which affect test sensitivity, raising questions about whether patients with a moderate or high pretest probability for COVID-19 should still be considered as possible COVID-19 despite a negative RT-PCR swab.

Key Messages from the Evidence Summary

- There is a lack of scientifically rigorous evidence to support the use of patient demographic, environmental or clinical factors as a means to estimate a higher pre-test probability for a positive COVID-19 PCR test result. Although research studies have identified various predictive factors with a suitable level of statistical significance, the quality of these studies is low due to small sample sizes, lack of control group, methodology shortcomings/flaws, risk of bias, risk of model overfitting, and study participants not being representative of the predictive models’ targeted populations.
- Those predictive factors that are statistically significant in more than one study, and are biologically plausible as well as clinically rational, might be considered (with suitable caution) by clinicians to very roughly estimate a potentially increased risk of COVID-19 infection in patients presenting with respiratory symptoms. These factors include advanced age, fever, shortness of breath, cough, high C-reactive protein, high lactate dehydrogenase, as well as ground glass opacification and bilateral lung involvement on chest imaging.
- Early predictive models have been developed using exposure history, demographic, clinical, lab and radiographic variables which perform well in initial derivation datasets. These studies, while more methodologically sound and demonstrating statistically and clinically reliable performance on Area under the receiver operating characteristic (AUROC) metrics, require further validation in other settings and more representative populations. The variables which have the strongest performance and validity includes: exposure to a COVID-19 positive case, male gender, fever, respiratory symptoms, evidence of pneumonia on CXR or CT and either an increased neutrophil lymphocyte ratio (NLR – calculated by
Factors that Predict a Positive COVID-19 Test Result

Committee Discussion

There was general agreement with the review and support for the recommendations with an additional recommendation to present the factors identified as predictive in the form of a table to make it easier to capture the weight of the factors. There was a desire to look for evidence, which would be predictive of a positive COVID test based on location of presentation to a community assessment centre or clinic versus emergency or inpatient setting. A request to ProvLab will be made to identify the likelihood of a positive test from these settings. Several committee members requested further information on whether the predictive value of imaging was considered as valid with an AP portable CXR vs PA CXR or CT of chest. There was support for creation of local datasets to allow for development and validation of similar criteria in representative local population of patients presenting with ILI. One committee member suggested consideration for addition of GI symptoms such as diarrhea or nausea which did have good predictive qualities in some of the models. Ongoing review of the developing literature will be needed as more representative patient populations from within North America are likely to be available in the near future.

Recommendations

1. Clinical risk factors for predicting a higher pretest probability of COVID-19 positive RT-PCR testing can be identified and should be documented at admission, in addition to consideration for transitions in care. The presence of recent travel to a high risk country or direct contact with a COVID-19 positive person in addition to the presence of fever and or cough, clinical evidence of pneumonia on imaging and the presence of lab abnormalities such as leukopenia or an elevated NLR (>3.53) can be currently considered as clinical features with sufficient evidence of predictive weight in multiple studies.

2. Further development and validation of these predictive tools using local datasets including exposure history, demographic, clinical, lab and radiological features should be prioritized and consistently documented to allow for ongoing development of risk stratification tools to support clinical and system decision making.

3. Risk assessment tools can not replace the need for RT-PCR testing, and repeated testing may be required in patients initially testing negative who had a high pre-test probability based on clinical assessment and the factors noted above.

Summary of Evidence

A literature search was conducted to describe patient demographic and clinical factors that are predictors of positive COVID-19 test results. Six (6) systematic reviews (SRs) on this topic were identified, and a synopsis of these systematic reviews is presented below. Wynants et al. concluded that the primary studies included in their SR were highly biased and fraught with methodological flaws. The remaining SRs were limited to primary studies that included COVID positive patients only. Lack of COVID-negative comparison group patients limits the conclusions that can be drawn from these SRs.

Two (2) primary research articles, published after the systematic reviews and which manifest a higher quality of research methodology, are also described.

Factors that Predict a Positive COVID-19 Test Result

**Search:** PubMed and Embase through Ovid, Arxiv, medRxiv, and bioRxiv; Jan 3, 2020 through Mar 24, 2020; all languages; preprint and peer-reviewed; studies must have developed or validated a multivariable model or scoring system to predict covid-19 outcomes.

**Number of Models Assessed:** 18 diagnostic models.

**Patient Population:** Majority are inpatients from hospitals in China (one study from Italy).

**Review Tools:** CHARMS, PROBAST, PRISMA and TRIPOD.

**Quality of Included Studies:** All models at high risk for bias and predictive performance is likely lower than reported and unreliable; study participants not representative of the models’ targeted populations; risk of model overfitting.

**Conclusions/Limitations:** “All models reported good to excellent predictive performance, but all were appraised to have high risk of bias owing to a combination of poor reporting and poor methodological conduct for participant selection, predictor description and statistical methods used.”

**Possible Pragmatic Predictive Factors:** Increased age, fever, shortness of breath (predictors with statistical significance in more than one model).


**Search:** PubMed, Cochrane Library, Embase and 2 Chinese databases: National Knowledge Infrastructure (CNKI) and China Biology Medicine disc (CBMdisc); up to Mar 1, 2020; English and Chinese language studies.

**Number of Studies & Patients:** Meta-analysis of single arm studies: 31 studies with 46,959 patients.

**Patient Population:** COVID-19 positive inpatients at hospitals in China.

**Review Tools:** Institute of Health Economics (IHE) scale.

**Quality of Included Studies:** “relatively high literature quality”

**Conclusions/Limitations:** This meta-analysis reports the pooled proportion of COVID-19 positive patients who have various demographic and clinical factors (i.e., no comparison with control/COVID-19 negative patients).

**Pragmatic Results:** Frequent clinical manifestations were: fever (87% of patients), cough (58%), high CRP (61%), lymphocytopenia (57%), high LDH (57%), bilateral lung lesions (76%) and ground glass shadows (70%) on chest imaging.


**Search:** PubMed, Cochrane Library, Embase; up to Feb 24, 2020; all languages.

**Number of Studies & Patients:** Meta-analysis of single-arm studies: 10 studies with 50,466 patients.

**Patient Population:** 9 studies include inpatients from China; 1 study includes inpatients from the USA.

**Review Tools:** Newcastle-Ottawa Scale (NOS).

**Quality of Included Studies:** NOS scores of 5-8 (possible range is 0-10 where higher score indicates higher quality).

**Conclusions/Limitations:** This meta-analysis reports the pooled proportion of COVID-19 positive patients who have various demographic and clinical factors (i.e., no comparison with control/COVID-19 negative patients).

**Pragmatic Results:** Frequent clinical manifestations were: fever (89% of patients), cough (72%), and “abnormal chest CT” (97%) where common findings were ground-glass opacity and bilateral patchy shadowing.


**Search:** Medline/PubMed, Scopus and Web of Science; Jan 1, 2020 through Feb 23, 2020; all languages.

**Number of Studies & Patients:** 19 studies with 2,874 patients.

**Patient Population:** 18 studies from China; 1 study from Australia.

**Review Tools:** PRISMA, Institute of Health Economics (IHE) scale.
Factors that Predict a Positive COVID-19 Test Result • 7

Quality of Included Studies: Scores of 12-19 (possible range is 0-20 where higher score indicates higher quality).

Conclusions/Limitations: This meta-analysis reports the pooled proportion of COVID-19 positive patients who have various demographic and clinical factors (i.e., no comparison with control/COVID-19 negative patients).

Pragmatic Results: Frequent clinical manifestations were: fever (89% of patients), cough (58%), decreased albumin (76%), high CRP (58%), high LDH (57%), bilateral involvement (73%) and ground-glass opacity (69%) on chest radiographs.


Search: PubMed, Embase, Google Scholar, and the World Health Organization database; up to Feb 24, 2020; English only;

Number of Studies & Patients: 30 studies with 919 patients.

Patient Population: inpatients; 29 studies from China; 1 study from Korea.

Review Tools: National Institutes of Health Quality Assessment Tool for Case Series Studies

Quality of Included Studies: "generally fair".

Conclusions/Limitations: includes ICU patients; reports the pooled proportion of COVID-19 positive patients who have various demographic and clinical factors (i.e., no comparison with control/COVID-19 negative patients).

Pragmatic Results: Ground glass opacification (88.0%), bilateral involvement (87.5%), posterior involvement (80%); peripheral distribution (76.0%), and multilobar involvement (78.8%).


Number of Studies & Patients: 13 studies with 2,738 patients.

Patient Population: inpatients; 13 studies from China.

Review Tools: PRISMA

Quality of Included Studies: Not provided.

Conclusions/Limitations: Reports the pooled proportion of COVID-19 positive patients who have various demographic and clinical factors (i.e., no comparison with control/COVID-19 negative patients).

Pragmatic Results: Ground glass opacity (83%), bilateral lung lesion distribution (78%), peripheral lesion distribution (77%), ≥3 lobes involved (71%).

Primary Research Studies:


Retrospective case-control study of 788 subjects presenting for assessment and testing for SARS-COV-2 at a Singapore Infectious Diseases Treatment facility between Jan 26 and Feb 16, 2020.

Used the TRIPOD criteria: Transparent Reporting of A Multivariable Prediction Model for Individual Prognosis or Diagnosis.

Used PCR of sputum, NP or throat swabs and collected data on demographic, clinical, laboratory and exposure risk variables to develop an algorithm for estimating the risk of COVID-19.

Akaike’s information criterion in a stepwise fashion to build logistic regression models which were translated into predictive scores and using ROC’s with adjustment for overconfidence.
Factors that Predict a Positive COVID-19 Test Result

4 prediction models created with the overlapping datasets of 788 with exposure, demographic and clinical criteria and 292 additionally with complete lab and radiological testing. Overall there were 54 cases, (6.9%), and 734 controls identified.

The significant features identified in model 1 with the highest ROC AUC value included: travel to Wuhan (AOR 23.05 95% CI 3.29-268), contact with a confirmed case in Singapore (AOR 6.04, CI 1.54-27.61), male gender (AOR 5.98, CI 1.23-36.05), fever (AOR 3.81, CI 1.97-13.12), CXR suggesting pneumonia (AOR 6.18, CI 1.68-25.75) and neutropenia (AOR 0.32, CI 0.19-0.49). In the other models using clinical and laboratory features also identified increasing age (AOR 1.03, CI 1.02-1.05).

The optimism-bias-corrected performance of Models 1, 2, 3 and 4 differentiated between patients who did and did not have COVID-19 with AUCs of 0.91 (95% CI: 0.86–0.96), 0.88 (95% CI: 0.83–0.93), 0.88 (95% CI: 0.83–0.93), 0.65 (95% CI: 0.57–0.73) respectively. The current proposed model is based on limited dataset and additional validation in larger datasets and across different contexts would increase confidence in its performance and implementation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.05)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>5.98 (1.2-136)</td>
<td>p=0.038</td>
</tr>
<tr>
<td>Contact with COVID Case</td>
<td>6.04 (1.54-27.61)</td>
<td>p=0.013</td>
</tr>
<tr>
<td>Travel to Wuhan</td>
<td>23.05 (3.29-268.08)</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Fever</td>
<td>3.81 (1.97-13.12)</td>
<td>3.27 (1.5-3.44)</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>3.73 (1.23-13.45)</td>
<td>3.28 p&lt;0.001</td>
</tr>
<tr>
<td>CXR/CT Suggestive of Pneumonia</td>
<td>6.18 (1.68-25.5)</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

Table 1: Covariates for the multivariate models for COVID-19 infection

From: Sun Y et al, 2020


Case-control study of 1311 patients presenting to the First Affiliated Hospital, School of Medicine, Zhejiang University between Jan 20 and Feb 5th, 2020 who completed an assessment and testing for SARS-CoV-2 nucleic acid detection analysis. Excluded asymptomatic patients.

Included exposure history, demographic and clinical characteristics, laboratory and radiology testing. Independent risk factor analysis was performed using multivariate logistic regression analyses with forward stepwise method.

The discrimination capacity of the diagnostic model and COVID-19 early warning score (COVID-19 EWS) were assessed by calculating the AUC for the ROC. Used a training and validation dataset with 711 and 600 patients each. There were 73 cases and 231 controls in the training dataset and 18 cases and 77 controls in the validation dataset. Overall the rate of positive COVID-19 testing of 6.9%. The predictive factors identified in the training data set included: male gender, higher age, Wuhan exposure and exposure to a COVID-19 positive contact, fever, dyspnea, cough, lower WBC count, NLR, CT finding of pneumonia. The EWS was created by converting the beta
coefficients into a score, with a score of 10 identified as the threshold to distinguish COVID-19 patient. Sensitivity and specificity were 0.932 and 0.874 respectively.

Probability (COVID-19) = 1 / (1 + exp [-9.106 + (2.79 x Fever) + (4.58 x History of close contact) + (5.10 x Signs of pneumonia on CT) + (0.97 x NLR) + (0.94 x Tmax) + (0.90 x Sex)].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Assessment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of pneumonia on CT</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>History of close contact with COVID-19 confirmed patient</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt;/= 44 yrs old</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Gender Male</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Tmax &gt;/= 37.8</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Meaningful respiratory symptoms &gt;/= 1 symptoms</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>NLR &gt;/= 5.8</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Highly suspect patient &gt;/= 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: COVID-19 Early Warning Score (EWS)
From: Song Cy et al, 2020

Date question received by advisory group: April 13, 2020
Date report submitted to committee: April 16, 2020
Date of first assessment: April 22, 2020
(If applicable) Date of re-assessment:

Authorship & Committee Members
This review was written by Susan Jelinski and Elizabeth Mackay, and scientifically reviewed by Elizabeth Mackay, Nathan Zelyas, and Melissa Potestio (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Lynora Saxinger (co-chair), Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

This copyright work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivative 4.0 International license. You are free to copy and distribute the work including in other media and formats for non-commercial purposes, as long as you attribute the work to Alberta Health Services, do not adapt the work, and abide by the other licence terms. To view a copy of this licence, see https://creativecommons.org/licenses/by-nc-nd/4.0/. The licence does not apply to AHS trademarks, logos or content for which Alberta Health Services is not the copyright owner.

Disclaimer: This material is intended for general information only and is provided on an "as is", "where is" basis. Although reasonable efforts were made to confirm the accuracy of the information, Alberta Health Services does not make any representation or warranty, express, implied or statutory, as to the accuracy, reliability, completeness, applicability or fitness
for a particular purpose of such information. This material is not a substitute for the advice of a qualified health professional. Alberta Health Services expressly disclaims all liability for the use of these materials, and for any claims, actions, demands or suits arising from such use.
Appendix

List of Abbreviations

AP  Antero-posterior
AUROC  Area under the receiver operating characteristic
CHARMS  Checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies
CRP  C-reactive protein
CXR  Chest x-ray
CT  Computed tomography
EWS  Early warning score
ILI  Influenza-like illness
LDH  Lactate dehydrogenase
NLR  Neutrophil lymphocyte ratio
NP  Naso-pharyngeal
PA  Postero-anterior
PCR  Polymerase chain reaction
PRISMA  Preferred reporting items for systematic reviews and meta-analyses
PROBAST  Prediction model risk of bias assessment tool
RT-PCR  Reverse-transcriptase – Polymerase chain reaction assay
SR  Systematic review
TRIPOD  Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
WBC  White blood cell

Literature Search Details

The literature search was done by Lauren Seal from the AHS Knowledge Resource Service.
- Inclusion Criteria: patients tested for COVID-19 (positive and negative results)
- Databases: Medline, CINAHL, PubMed, Google Scholar, Google.
- Only the systematic reviews obtained from this search were used in this report.