Guidelines on the Preoperative Diagnostic Workup for COVID-19

A rapid review commissioned by RACS

1 July 2020

Royal Australasian College of Surgeons

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Recommendations:

1. Patient history should be thoroughly examined for potential sources of SARS-CoV-2 exposure (especially close contact with groups at high risk of contracting the disease), and equal weight should be given to these findings as to clinical presentation. Preoperative testing for COVID-19 is not recommended in patients with no risk factors.

2. Assessment of patient symptoms is insufficient as a sole method of diagnosing COVID-19, although it can inform necessary adjunctive investigations.

3. Hyposmia (loss of smell) or hypogeusia (loss of taste) should be considered important in considering the potential for SARS-CoV-2 infection.

4. Although crucial to the optimal management of patients with COVID-19, non-SARS-CoV-2 specific laboratory tests (such as haematology and biochemistry tests) have limited utility on their own within the diagnostic workup of potential SARS-CoV-2 infection.

5. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is the gold standard laboratory test for diagnosing SARS-CoV-2 infection, and within Australia and New Zealand there is good concordance in analytical performance between in-house developed and commercial tests. False negatives can decrease with repeated testing, however, the decision to repeat test should be made based on clinical history and the local supply of laboratory testing resources. Local microbiology services should be consulted regarding testing capability, particularly with regard to the availability of rapid RT-PCR testing.

6. Turnaround times for RT-PCR results detecting SARS-CoV-2 infection may be within 24 hours in Australia and New Zealand. There is considerable postoperative morbidity and mortality associated with operating on COVID-19 patients. Thus, any surgical operation that can be delayed for 24 hours or more without adverse effect to patients, should await the testing results prior to undertaking surgery in patients suspected of SARS-CoV-2 infection.

7. At present, serological testing has limited use within the routine preoperative diagnostic workup for SARS-CoV-2 infection. However, it may be used in the diagnosis of COVID-19, including where patients are RT-PCR negative, or as a supplemental test with an unexpected positive or inconclusive RT-PCR result. It can also be used for sero-epidemiologic studies to determine population exposure and infection, and for evaluating vaccine effectiveness.

8. The use of chest CT scanning alone to diagnose COVID-19 is not recommended due to non-specific findings that may overlap with other respiratory illnesses.

Proposed Preoperative Diagnostic Workup for COVID-19

Features of Patient History	Advised Preoperative Investigation
Any risk of potential SARS-CoV-2 exposure, including: • Close contact[#] with a confirmed case of COVID-19 in the past two weeks • Close contact with someone who displays symptoms of hyposmia (loss of smell), hypogeusia (loss of taste), cough, sore throat, or dyspnoea in the past two weeks (including in the three days prior to onset of symptoms) • Overseas or interstate (if state of journey's origin contains active cases of COVID-19) travel in the past two weeks, either by plane or cruise ship, or close contact with such a traveller • Presence within an aged care facility in the past two weeks, either as a resident, worker, or visitor • Presence within a detention facility in the past two weeks, either as a resident, worker, or visitor • Presence within a group residential setting in the past two weeks, either as a resident, worker or visitor • Presence within other facilities that have relatively high risk of COVID-19 transmission • Profession that includes regular interaction with potential COVID-19 cases (e.g. workers in healthcare, allied health facilities, supermarkets, schools, delivery, factories, farming, or transport)	**RT-PCR assay**
Any of the following symptoms in the past two weeks: • Hyposmia • Hypogeusia • Cough • Sore throat • Dyspnoea • Unexplained fever	**RT-PCR assay**
Over 70 years of age AND any new-onset respiratory symptoms, including: • Cough • Sore throat • Dyspnoea	**RT-PCR assay AND CT scan of chest**
Surgery required within 24 hours AND presence of ANY of the above history features	**No preoperative investigation for SARS-CoV-2 infection***

[#]The definition of a 'close contact' is outlined in Appendix A

*Proceed to surgery with surgical staff wearing full PPE and taking appropriate intraoperative precautions, especially for potential aerosol-generating procedures.[I,II,III] Isolate patient postoperatively and test for SARS-CoV-2 infection when possible.

[I] Royal Australasian College of Surgeons. *Surgery Triage: Responding to the COVID-19 Pandemic*. 2nd Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5254/2020-04-22_racs-triage-of-surgery-web.pdf

[II] Royal Australasian College of Surgeons. *Guidelines for Personal Protective Equipment*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5302/2020-05-05-covid19-ppe-guidelines.pdf

[III] Royal Australasian College of Surgeons. *Guidelines for Safe Surgery: Open versus Laparoscopic*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5214/2020-04-15-recommendations-on-safe-surgery-laparoscopic-vs-open.pdf

Balancing the Diagnostic Workup of COVID-19 with Surgical Urgency

Given the considerable postoperative morbidity and mortality associated with operating on COVID-19 patients,[IV,V] it is imperative that all surgical patients suspected of SARS-CoV-2 infection undergo appropriate testing prior to their operation. However, this need for diagnostic evaluation must be balanced with the urgency of surgery to ensure optimal outcomes for the patient, and surgery should not be delayed unnecessarily.

Fortunately, within Australia and New Zealand it is possible to have same-day return of results for the RT-PCR assay, meaning that surgery should be delayed by no more than 24 hours while awaiting a laboratory result for potential SARS-CoV-2 infection (not accounting for scheduling details within individual institutions). This means that protocols for surgical triage during both the initial and any successive phases of the COVID-19 pandemic[VI,VII,VIII] can be implemented with only slight modification to incorporate an appropriate diagnostic workup.

As outlined in previous RACS rapid reviews on this topic, emergency surgery should not be delayed for confirmation of COVID-19 diagnosis in suspected patients.[IX] It should proceed with surgical staff wearing full PPE[X] and undertaking appropriate intraoperative precautions.[XI] In order to optimise the efficient use of medical resources, surgery that can be delayed for 24 hours or more (the likely maximum duration to complete COVID-19 testing) without adversely affecting patient morbidity or mortality, should await test results prior to surgery where SARS-CoV-2 infection is suspected. This process of deliberation is summarised in the Box below.

[IV] Nepogodiev D, Glasbey JC, Li E, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *The Lancet*. 2020.

[V] Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*. 2020; 10.1016/j.eclinm.2020.100331:100331.

[VI] Royal Australasian College of Surgeons. *Surgery Triage: Responding to the COVID-19 Pandemic*. 2nd Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5254/2020-04-22_racs-triage-of-surgery-web.pdf, *op. cit.*

[VII] Brindle ME, Doherty G, Lillemoe K, Gawande A. Approaching Surgical Triage During the COVID-19 Pandemic. *Ann Surg*. 2020; 10.1097/SLA.0000000000003992.

[VIII] Argenziano M, Fischkoff K, Smith CR. Surgery Scheduling in a Crisis. *N Engl J Med*. 2020; 382:e87.

[IX] Royal Australasian College of Surgeons. *Surgery Triage: Responding to the COVID-19 Pandemic*. 2nd Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5254/2020-04-22_racs-triage-of-surgery-web.pdf, *op. cit.*

[X] Royal Australasian College of Surgeons. *Guidelines for Personal Protective Equipment*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5302/2020-05-05-covid19-ppe-guidelines.pdf, *op. cit.*

[XI] Royal Australasian College of Surgeons. *Guidelines for Safe Surgery: Open versus Laparoscopic*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5214/2020-04-15-recommendations-on-safe-surgery-laparoscopic-vs-open.pdf, *op. cit.*

Box. ***Balancing the diagnostic workup with surgical urgency when COVID-19 is suspected***

Possible to Delay Surgery for 24 hours	**Impossible to Delay Surgery for 24 hours**
• Delay surgery for 24 hours for appropriate testing for SARS-CoV-2 infection to be conducted preoperatively • Refer to *Proposed Preoperative Diagnostic Workup for COVID-19* above for appropriate diagnostic pathway depending on clinical presentation and exposure history	• Proceed to surgery with surgical staff wearing full PPE and appropriate intraoperative precautions taken, especially for potential aerosol-generating procedures[XII,XIII,XIV] • Isolate patient postoperatively and undergo testing for SARS-CoV-2 infection when possible

[XII] Royal Australasian College of Surgeons. *Surgery Triage: Responding to the COVID-19 Pandemic*. 2nd Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5254/2020-04-22_racs-triage-of-surgery-web.pdf, *op. cit.*

[XIII] Royal Australasian College of Surgeons. *Guidelines for Personal Protective Equipment*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5302/2020-05-05-covid19-ppe-guidelines.pdf, *op. cit.*

[XIV] Royal Australasian College of Surgeons. *Guidelines for Safe Surgery: Open versus Laparoscopic*. 1st Edition., cited 9 June 2020. Available from: https://umbraco.surgeons.org/media/5214/2020-04-15-recommendations-on-safe-surgery-laparoscopic-vs-open.pdf, *op. cit.*

Executive summary:

Introduction:

For surgical care following the initial peak of the COVID-19 pandemic, an effective and reliable preoperative diagnostic workup is necessary for patients suspected of having the disease to ensure their safety, and that of surgical staff and the wider community. This rapid review aims to evaluate the literature surrounding the clinical, laboratory and radiological methods that can contribute towards diagnosing infection of the causative virus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—for the purpose of producing evidence-based guidance for surgeons in Australia and New Zealand.

Methods:

A rapid review methodology was utilised by researchers from the RACS Evidence Synthesis Team (ASERNIP-S and Research, Audit & Academic Surgery) for an extensive search of the peer-reviewed literature using the PubMed database. This was supplemented with targeted searches of the peer-reviewed literature using both the PubMed and Google Scholar databases, informed by feedback from clinical experts within the RACS COVID-19 Working Group.

Results:

Due to the transmission dynamics of SARS-CoV-2, patient history should be thoroughly examined for potential sources of exposure. Hyposmia and hypogeusia may present as early symptoms that could be useful in distinguishing COVID-19 from other influenza-like illnesses. Non-SARS-CoV-2 diagnostic assays performed on persons with COVID-19 are useful in managing the disease, but diagnostic utility is limited as these are largely manifestations of the aggressive inflammatory response that typifies the immunopathogenesis of SARS-CoV-2 infection. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is the gold standard laboratory test for diagnosing SARS-CoV-2 infection, and within Australia and New Zealand there is concordance in efficacy between local and commercial test kits. False negatives can be decreased with repeated testing, however, the decision to repeat test should be made based on clinical history and the local supply of diagnostic resources. At present, routine serological testing has little utility within the preoperative diagnostic workup for SARS-CoV-2 infection. However, it does have future epidemiological usefulness, as it is the only method of estimating herd immunity within the community and evaluating large-scale effectiveness of potential vaccines. To appropriately integrate testing for SARS-CoV-2 infection into preoperative surgical triage protocols, the temporal dynamics of the virus must be considered, including the 4- to 5-day incubation period. The use of chest computed tomography (CT) alone to diagnose COVID-19 is not recommended due to non-specific findings that overlap with other respiratory illnesses. Lung ultrasound also has questionable utility for diagnosing SARS-CoV-2 infection in settings of low prevalence such as Australia and New Zealand.

Conclusions:

On the basis of this rapid review of the literature, evidence-based recommendations have been produced along with a proposed schema for the preoperative diagnostic workup of surgical patients suspected of having COVID-19. A printable questionnaire has also been provided which could be utilised for screening patients for symptoms of COVID-19 or those with a history of potential SARS-CoV-2 exposure, in either face-to-face or telemedicine consults.

Introduction

The coronavirus disease (COVID-19) global pandemic has caused considerable disruption to surgical care across Australia and New Zealand. Although a worldwide research effort has produced a sizeable literature base in a relatively short time, the causative virus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—and its effects on healthcare systems at both an individual and systemic level, are still not completely understood.

Three rapid reviews have already been produced and updated, in order to effectively evaluate the evolving literature surrounding COVID-19. This process was led by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) within the RACS Evidence Synthesis Team (ASERNIP-S and Research, Audit & Academic Surgery). These evidence-based guidelines for surgical care within Australia and New Zealand have been produced in the domains of safe intraoperative practice,[1] appropriate personal protective equipment (PPE),[2] and surgical triage.[3] However, as government regulations associated with the pandemic begin to ease within Australia and New Zealand, an important aspect of maintaining the suppression of caseload is the presence of effective diagnostic protocols that facilitate early identification of the disease.[4] In surgical care this is relevant to the preoperative setting, where the diagnostic workup for COVID-19 must be integrated within standard management for the safety of both surgical staff and the wider community.

A recent publication from the international COVIDSurg Collaborative demonstrated the importance of appropriate and effective preoperative diagnostic protocols for patients with suspected SARS-CoV-2 infection. They found that surgical patients with perioperative SARS-CoV-2 infection experienced a postoperative pulmonary complication rate of 51.2%, which was associated with high mortality.[5] Similarly, a small retrospective cohort study by Lei et al. investigated 34 COVID-19 patients who underwent elective surgery, finding that intensive care unit (ICU) admission was required for 44.1% of patients and there was a mortality rate of 20.5%.[6] This was also echoed by a matched cohort study of surgical patients by Doglietto et al. where surgical mortality and complications were found to be significantly higher in patients with COVID-19 compared to those without COVID-19.[7] An effective and reliable diagnostic workup is necessary to appropriately triage surgical patients with COVID-19 and reduce postoperative morbidity and mortality.

This rapid review aims to evaluate the literature surrounding the clinical, laboratory and radiological methods that can contribute towards diagnosing active SARS-CoV-2 infection in a setting with a low number of COVID-19 cases within the community. The diagnostic utility of each modality will first be considered on its own, and then also within the context of a complete multimodality workup. Pertinent findings will be synthesised in the context of the standard preoperative workup of surgical patients for the purpose of producing evidence-based guidance for surgeons to assist the long-term minimisation of COVID-19 in Australia and New Zealand.

Methods

A rapid review methodology[8] was utilised for an extensive search of the peer-reviewed literature using the PubMed database. The search was limited to articles published between 31 December 2019 and 6 May 2020 (search date) in order to correspond with the World Health Organization's (WHO) identification of the novel coronavirus.[9] The search strategy is provided in Appendix B. This search strategy has been saved and will be repeated at regular intervals for the purpose of updating this review as important new findings are published.

The PubMed search strategy was supplemented with targeted searches of the peer-reviewed literature using both the PubMed and Google Scholar databases. Targeted searches and the inclusion of articles after the formal search were informed by feedback provided by clinical experts within the RACS COVID-19 Working Group.

Study selection was performed by two ASERNIP-S researchers (JK and DT), and was expedited using the web application, Rayyan.[10] Study extraction used a standard template, with each extraction performed by a single reviewer (JK, PW, LT, HK) and a sample of the extractions checked by JK and DT. Inclusion was not limited by language, as any relevant non-English articles were translated using Artificial Intelligence translation tools where necessary. Case series were excluded based on sample size, apart from articles deemed important by the reviewers. Median values and interquartile ranges on the symptoms of COVID-19 were calculated based on objective data from the retrieved studies.

Results

Search Results

The electronic search yielded an initial pool of 5,762 citations, from which 1,395 human studies were identified (Appendix B). After screening based on title and abstract, this pool was refined to 255 relevant articles, for which full-text versions were retrieved. Information deemed pertinent from this pool of 255 articles was synthesised along with findings from the targeted searches to produce the following sections of this review.

COVID-19 Caseload in Australia and New Zealand

Throughout the course of the COVID-19 pandemic, both Australia and New Zealand have experienced a low number of cases relative to the rest of the world. As of 12 June 2020, Australia has had a total of 7,288 confirmed cases resulting in 102 deaths, and New Zealand has had a total of 1,504 confirmed cases resulting in 22 deaths.[11] Notably, New Zealand became free of active cases of COVID-19 on 8 June 2020[12] (maintained as of 12 June 2020).[13] In a global context, these data (as of 12 June 2020) produce case-fatality rates of 1.4% and 1.5% for Australia and New Zealand, respectively; both considerably lower than the global case-fatality rate of approximately 5.7% (as of 11 June 2020).[14]

It is important to note that this rapid review has been conducted for the purpose of providing evidence-based guidance for surgical staff in Australia and New Zealand, that is, recommendations have been developed for implementation within settings of relatively low COVID-19 caseload.

Clinical Presentation of COVID-19

The Importance of Exposure History for COVID-19

A considerable proportion of COVID-19 cases are asymptomatic.[15] Although it is impossible to discern the true rate of asymptomatic cases, an estimate can be derived from analysis of the 634 people with laboratory-confirmed SARS-CoV-2 infection aboard the Diamond Princess cruise ship in Japan, where the asymptomatic proportion was reported to be 17.9%.[16] Clinically silent carriers of SARS-CoV-2 are capable of transmitting the virus to others during both the pre-symptomatic incubation period[17] and at other times during the course of COVID-19.[18-20] This is due to the high level of SARS-CoV-2 shedding in the upper respiratory tract[21], which is estimated to begin two to three days prior to the onset of symptoms.[22] It has been estimated that approximately 44% of secondary cases in a given cohort could be infected during the pre-symptomatic stage of index cases.[22] This transmission capability means that SARS-CoV-2 can spread rapidly even when clinically undetectable.[23] It is thus imperative to thoroughly examine all patients' histories for potential sources of SARS-CoV-2 exposure, and to give equal weight to these findings and their clinical presentation. This is especially important in low-prevalence settings such as Australia and New Zealand.

Patients from any of the population groups at high risk of contracting COVID-19 should be treated with extra caution regarding PPE and triage considerations,[2, 3] and they should undergo RT-PCR assay for laboratory evaluation of potential SARS-CoV-2 infection. In Australia and New Zealand these groups include travellers who have recently been on either planes or cruise ships, aged care residents, people in detention facilities, people in group residential settings, and those who have been in close contact with someone who has been diagnosed with COVID-19 (including the two to three days prior to onset of symptoms).[22, 24] Further, people in 'essential' professions that are likely to place them in contact with any of these population groups (e.g. workers in healthcare, allied health facilities, supermarkets, schools, delivery, factory and farming, and transport)[25] should also be treated with caution and undergo RT-PCR testing if symptomatic.

Symptoms Associated with COVID-19

From the retrieved studies, the symptoms most frequently reported in association with COVID-19 include fever, cough, sore throat, dyspnoea (including shortness of breath or tachypnoea), diarrhoea, nausea or vomiting, and myalgia or arthralgia. In order to objectively evaluate these frequently reported symptoms, median values and interquartile ranges were calculated using 38 data-sets from 31 selected studies reporting symptoms associated with laboratory-confirmed SARS-CoV-2 infection.[5, 26-55] Studies with a sample size of fewer than 40 were excluded from analysis, apart from

those reporting on ICU[55] and paediatric[48] populations. The findings from this analysis are presented in Table 1.

Table 1. Findings from 31 selected studies with the most frequently reported COVID-19 symptoms[5, 26-55]

Finding	No. Data Points	Cohort Median	Interquartile Range
Fever	37	71.6%	53.6–82.6
Cough	35	62.6%	45.8–73.2
Sore throat	19	13.9%	6.4–35
Dyspnoea	31	28.7%	13–44
Diarrhoea	32	10.4%	5.3–22.1
Nausea/Vomiting	24	7.5%	4.3–17.5
Myalgia/Arthralgia	25	26.5%	15.0–54.2
Sample Size, n	38	253	100.5–883.8
Median Age, years	30	53.3	46.5–62.3
ICU admission	19	23%	6.8–32
Case-fatality rate	22	12.5%	0.9–23.3

An assessment of patient symptoms is insufficient as a sole method of diagnosing COVID-19, however, the collection of presenting systems can direct clinicians towards the involved organ systems and inform the necessary adjunctive investigations. Although characterised as a respiratory disease in the initial stages of the pandemic,[36, 51, 56-58] COVID-19 has demonstrated association with gastrointestinal,[59, 60] cardiovascular,[61] haematological,[62, 63] immunological[64] and neurological[65, 66] manifestations. Of these, evidence of gastrointestinal manifestations is the only one to have been found in the absence of respiratory symptoms.[41]

Olfactory and/or gustatory dysfunction can be key presenting features of COVID-19. Hyposmia or hypogeusia are potentially the two symptoms with greatest usefulness for the early detection of SARS-CoV-2 infection. In a survey of 417 laboratory-confirmed COVID-19 patients, Lechien et al. found that 85.6% and 88.0% of patients reported olfactory and gustatory dysfunction, respectively, leading to the conclusion that sudden anosmia or ageusia should be recognised as an important early manifestation of SARS-CoV-2 infection.[67] This early symptom has also been reported by others.[68-71] In the survey by Lechien et al., of the 357 (85.6%) patients that had acute onset olfactory dysfunction, 284 (79.6%) were anosmic and 73 (20.4%) were hyposmic. Similarly, amongst 68 laboratory-confirmed COVID-19 patients surveyed by Benezit et al., 62% had hypogeusia, 45% had hyposmia, and 43% had both, resulting in calculated specificities for COVID-19 of 89%, 90%, and 93% respectively.[72] Together, these studies provide evidence that the symptoms of hypogeusia and hyposmia have potential in discriminating COVID-19 from other influenza-like illness. This outcome is echoed by Yan et al. in their study of 1,480 patients with influenza-like symptoms.[73] Further, there is evidence within the literature to suggest that hyposmia may be associated with a milder clinical course of COVID-19.[74] Regardless, the loss of smell or taste can potentially be found in a considerable proportion of COVID-19 patients,[75] and these symptoms must be specifically screened for in patients suspected of having SARS-CoV-2 infection.

There is also limited evidence of possible SARS-CoV-2 reactivation. Ye et al. reported on 55 patients with laboratory-confirmed COVID-19, five of whom (9%) re-presented with COVID-19 following discharge from hospital.[76] Amongst this small group of cases, there were no specific clinical characteristics that allowed the reactivated cases to be distinguished.

Figure 1 outlines a questionnaire for verbally screening patients for symptoms of COVID-19 or history of potential SARS-CoV-2 exposure. This printable questionnaire may be clinically useful for face-to-face consultations, in addition to telemedicine consults.[77]

Figure 1. Printable questionnaire for screening patients for symptoms of COVID-19 or history of potential SARS-CoV-2 exposure

Question	Yes	No
Have you been diagnosed with COVID-19 in the past?		
Over the past two weeks, have you been in close contact with someone who has been suspected of, or diagnosed with COVID-19?		
Over the past two weeks, have you been unwell or experienced any of the following symptoms: • **Loss of smell** • **Loss of taste** • **Fever** • **Cough** • **Sore throat** • **Shortness of breath or difficulty breathing** • **Diarrhoea** • **Nausea or vomiting** • **Muscle aches**		
Over the past two weeks, have you been in close contact with someone who has been unwell or displayed any of the above symptoms (including in the three days prior to the onset of their symptoms)?		
Have you travelled overseas in the past two weeks, either by plane or cruise ship, or been in contact with someone who has?		
Have you travelled interstate in the past two weeks?*		
Have you been within an aged care facility, either as a resident, worker, or visitor, in the past two weeks?		
Have you been within a detention facility, either as a resident, worker, or visitor, in the past two weeks?		
Do you live in a group residential setting, or have you visited one in the past two weeks?		
Do you regularly interact with people with COVID-19 as part of your job?		

*Applicable only if active cases within state of journey's origin

Laboratory Findings Associated with COVID-19

The laboratory findings associated with SARS-CoV-2 infection within the retrieved studies confirm that COVID-19 is not a disease solely limited to the respiratory system. There is also immunological dysfunction resulting in the derangement of haematological, hepatic and renal laboratory markers.[26-28, 31, 32, 35, 36, 38, 39, 41, 44, 48, 49, 51-53, 78-82] Although these may be potentially useful for gauging disease severity,[31] no individual laboratory marker within a multisystem workup provides a method of definitively diagnosing SARS-CoV-2 infection. This was apparent in the early phase of the pandemic via a systematic review by Rodriguez-Morales et al. who determined that decreased albumin (75.8%; 95% CI 30.5–100.0%); high C-reactive protein (58.3%; 95% CI 21.8–94.7%), lactate dehydrogenase (57.0%; 95% CI 38.0–76.0%) and erythrocyte sedimentation rate (41.8%; 95% CI 0.0–92.8); and lymphopaenia (43.1%; 95% CI 18.9–67.3), were all commonly correlated with COVID-19.[83]

The immunopathogenesis of SARS-CoV-2 infection is typified by an aggressive inflammatory response.[84] Accordingly, elevated inflammatory markers including C-reactive protein, erythrocyte sedimentation rate, ferritin, D-dimer and lactate dehydrogenase are amongst the laboratory findings most commonly associated with COVID-19.[26-28, 31, 32, 35, 36, 38, 48, 49, 52, 53, 78-81] The importance of closely monitoring inflammatory markers, along with serum levels of cytokines and chemokines,[64, 85] in the management of COVID-19 cannot be overstated, because severe SARS-CoV-2 infection can result in the manifestation of a cytokine storm syndrome in a subgroup of patients.[86] Lymphopaenia and an increased neutrophil–lymphocyte ratio has been reported in 80% of cohorts of patients with SARS-CoV-2 infection.[38, 64] Tay and colleagues consider this to be the product of pulmonary recruitment of immune cells from the blood and infiltration of lymphocytes into the airways.[84]

Although crucial to the optimal management of patients with COVID-19, a lack of specificity means that laboratory findings have limited utility within the routine diagnostic workup of potential SARS-CoV-2 infection.

Diagnostic Laboratory Testing for COVID-19

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is the gold standard SARS-CoV-2 diagnostic test.[87] However, it is important to appreciate that no one test is perfect.[88] A recent review on COVID-19 testing found false negative rates (based on a negative first test followed by a positive second test) varied from 2–29%.[89] The site of sample collection can also influence the test outcome. In a study of 205 patients screened by RT-PCR, the highest SARS-CoV-2 RNA positive rates were detected in bronchoalveolar lavage fluid, followed by sputum, nasal swab, fibreoptic bronchoscope brush biopsy, pharyngeal swab, faeces and blood, but not urine samples.[90] Also Hong et al. noted that possible causes of false negative results may be attributed to inadequate specimen quality, specimens collected too early or too late in the disease progression, specimens improperly handled or transported, occurrence of viral genetic mutation, presence of PCR inhibitors or anti-viral administration prior to testing.[91] As reported by Kurcika et al., false negative rates of RT-PCR-based

tests varied significantly with time since exposure to the virus.[92] The authors reviewed seven studies that used naso- and oropharyngeal swab samples from the upper respiratory tract (n=1,330) and published data on RT-PCR patient results since symptom onset or SARS-CoV-2 exposure. The authors showed that the probability of recording a false negative was highest during the first four days leading up to symptom onset. The probability was lowest on the day of symptom onset (day five). These findings correspond with temporal fluctuations in viral load.[22, 93, 94] Hence, if any symptoms associated with COVID-19 are present, the decision to conduct RT-PCR testing to confirm SARS-CoV-2 infection status is justified, even if the patient has tested negative in the past.

Currently, diagnostic assays used by public and private pathology laboratories consist of commercially available diagnostic kits and/or in-house developed assays. In Australia and New Zealand, laboratories have participated in the proficiency testing program (PTP) as part of the Royal College of Pathologists of Australasia's Quality Assurance Program (RCPAQAP).[95, 96]

Diagnostic RT-PCR tests must demonstrate high sensitivity and specificity and minimal cross-reactivity with other coronaviruses, with a cycle threshold (Ct) value below 40 for real time RT-PCR assays as the criteria for positivity, in general.[97] The amount of virus present in the sample tested is inversely proportional to the Ct value. The SARS-CoV-2 genes selected for amplification vary depending on the manufacturer or diagnostic laboratories developing these assays.[98] For example, the Charité – Universitätsmedizin Berlin Institute of Virology, Berlin, used the SARS-CoV-2 RNA-dependent RNA polymerase (RdRP) as the gene to confirm amplification of coronavirus cDNA, and the envelope (E) and nucleocapsid (N) targets to confirm the presence of SARS-CoV-2.[99] By contrast, the Centers for Disease Control (CDC) in the United States (US) developed a SARS-CoV-2 PCR kit that targets two regions of the viral nucleocapsid gene (N1 and N2) plus the human RNAse P gene to confirm successful RNA extraction. Unlike the CDC, the kits from the World Health Organization (WHO) used primer/probe sets targeting the SARS-CoV-2 RdRP and E genes.[100]

Clinicians are encouraged to seek clarification on turnaround times of RT-PCR tests delivered by their local pathology service as these can range from 30 minutes to between 3-4 hours following receipt in the laboratory.

It is worth noting that investigators are developing other test methods for nucleic acid amplification (based on the principles of RT-PCR), such as the loop-mediated isothermal amplification (LAMP) assays, that have reasonably high sensitivity and specificity, but reduced turnaround times of 30–40 minutes.[101]

The US Food and Drug Administration (FDA) has given manufacturers of SARS-CoV-2 testing kits emergency use authorisation (EUA) to meet diagnostic testing demand in response to the speed of COVID-19 disease spread that has overwhelmed healthcare centres. These include point of care tests (POCTs). Many of these assays have been brought to market with the promise of rapid turnaround times of 20–60 minutes, an attractive feature for healthcare workers faced with an influx of patients requiring immediate COVID-19 status confirmation.[102] However, these kits have not undergone the standard rigorous testing because this would delay the supply of kits to healthcare units.

Similarly, the Therapeutic Goods Administration (TGA) has listed on its website approved nucleic acid and serology COVID-19 testing kits for inclusion in the Australian Register of Therapeutic Goods (ARTG), https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia. The Doherty Institute has been appointed to conduct post-market validation of POCTs.[103] Further, within Australia and New Zealand, irrespective of jurisdiction, there is good concordance in the analytical performance between in-house developed and commercial RT-PCR assays for detecting SARS-CoV-2 infection.

Repeat RT-PCR testing reduces the probability of reporting an incorrect result. However, the decision to repeat test should be made based on the pre-test probability of COVID-19, including clinical history and symptoms, recent travel history and close contact with persons with confirmed or probable COVID-19. This avoids testing of limited clinical utility and targets patients with a high probability of positive COVID-19 status. Local supply of medical resources must also be factored into this decision-making process. Given the reported poor outcomes of surgery in COVID-19 patients,[5] their identification is imperative when preparing for elective surgery.

Where the prevalence or pre-test probability of SARS-CoV-2 infection is low, false positive results may occur. Therefore, it is recommended that the initial positive result be confirmed by testing the sample using alternate RT-PCR assays and/or gene targets (if available) and also to collect another sample for testing as soon as possible.

Publications from the Public Health Laboratory Network of Australia (PHLN), including guidance and information regarding laboratory testing for SARS-CoV-2, can be found at the following link: https://www1.health.gov.au/internet/main/publishing.nsf/Content/Publications-13

Serological Testing

Serological detection of antibodies produced in the host immune response to SARS-CoV-2 infection can be utilised as a method of indirectly diagnosing COVID-19.[104, 105] Serology testing may be useful in confirming COVID-19 infection where RT-PCR is negative, not tested or inconclusive. It is also useful to define the degree of population infection (and therefore immunity potentially). Seroconversion or a four-fold or greater rise in antibody levels between acute and convalescent samples is definitive laboratory evidence of infection.

A recent publication by Xu et al. measured levels of immunoglobulins (Ig) M and G in 17,368 people in China between 9 March 2020 to 10 April 2020, which provides a useful perspective in future estimations of the cumulative prevalence of SARS-CoV-2 infection within lower caseload settings such as Australia and New Zealand.[106] Taking into account the limitation of potential bias due to lack of random sampling, seropositivity in the initial epicentre of Wuhan varied from 3.2% to 3.8% in different cohorts, and progressively decreased in other cities as the distance from Wuhan increased, corresponding to the geographic spread of the pandemic. Overall, of the 6,919 individuals included from hospital settings, 141 (2.0%) were IgG positive only, 41 (0.6%) were IgM positive only. Of the

10,449 individuals from community settings, 48 (0.5%) were IgG positive only, 44 (0.4%) were IgM positive only. Although the highest seropositive rates were observed for IgG, the presence of individuals with only IgM resulted in the authors recommending that serologic surveys should incorporate measurements of both antibodies. However, when analysing seropositivity in a population, groups at high-risk of SARS-CoV-2 exposure must be taken into account,[107] along with the population's overall duration of exposure to SARS-CoV-2.[108]

Of note, IgG and IgA are the antibodies that are most reliably detected following SARS-CoV-2 infection. The seroprevalence rate globally ranges from 0.1% - 47% following the first pandemic wave, and can vary widely between countries, between states within a country, and also between different parts of the same city.[109]

While serological tests may be useful in assessing whether potential vaccine candidates confer immunity[110], their diagnostic utility for acute SARS-CoV-2 infection is limited. Results from serological testing alone can neither confirm nor exclude a diagnosis of acute SARS-CoV-2 infection, nor provide information on potential infectivity, because the detection of antibodies may be due to either a past or present infection. Further, there is no evidence in the literature confirming that positivity for IgG or IgM is an assurance of protective immunity[111], and there is uncertainty as to how long any such immunity may last.[112] In settings where the necessary equipment for RT-PCR assay is not available, serology could potentially provide an imperfect alternative, but in all other instances it cannot be recommended as a sole diagnostic modality for acute SARS-CoV-2 infection.

In addition to questions regarding the perceived utility of serological testing within the diagnostic workup for potential SARS-CoV-2 infection, issues exist with various aspects of the testing modality itself at the time of this rapid review. The choice of immunoglobulin to be measured should be considered, as although IgG, IgM and IgA all figure in testing, IgG and IgM are more frequently analysed.[113, 114] The type of assay to use has been debated, with enzyme-linked immunosorbent assay (ELISA) possibly more reliable than the blotting assays.[115] Further, there have been questions regarding which antigen (derived from SARS-CoV-2) is best utilised within serological testing.[110, 116] Tests for antibodies to SARS-CoV-2 must also ensure that other coronaviruses do not cause cross-reactivity.[110, 117] Patient-collected samples (which have shown comparability to healthcare worker-collected samples for RT-PCR[118]), are rarely utilised for serological testing, and thus are unlikely to present a significant issue.

When reliable antibody tests are consistently available, they could provide important information that contributes to our understanding of which subgroups within the population have experienced differing rates of infection[106] and how to stop further spread of COVID-19. However, although multiple POCT kits are available both locally and internationally, most are unreliable and not accurate enough to confirm past exposure to SARS-CoV-2. The FDA has relaxed the rules surrounding the use of these tests[119] and consequently some available kits have not undergone the usual rigorous testing necessary to ensure reliability and accuracy. Given the presence of a disclaimer noting the lack of FDA review in these tests, their results should not be used as the sole diagnostic tool for confirming SARS-CoV-2 infection. Multiple serology tests have been approved by the FDA in the EUA category,

however there is significant variability in their performance.[120] In many instances it is likely advisable that serological testing not be conducted if reliability of the individual kit has not been adequately proven. PHLN has also expressed concerns about the quality and clinical utility of POCTs, and do not recommend them as first line tests for the diagnosis of acute viral infection.[121] PHLN also strongly recommends that validation of emerging tests be undertaken by a PHLN laboratory before they are approved for use or through post-market assessment, whichever is applicable.

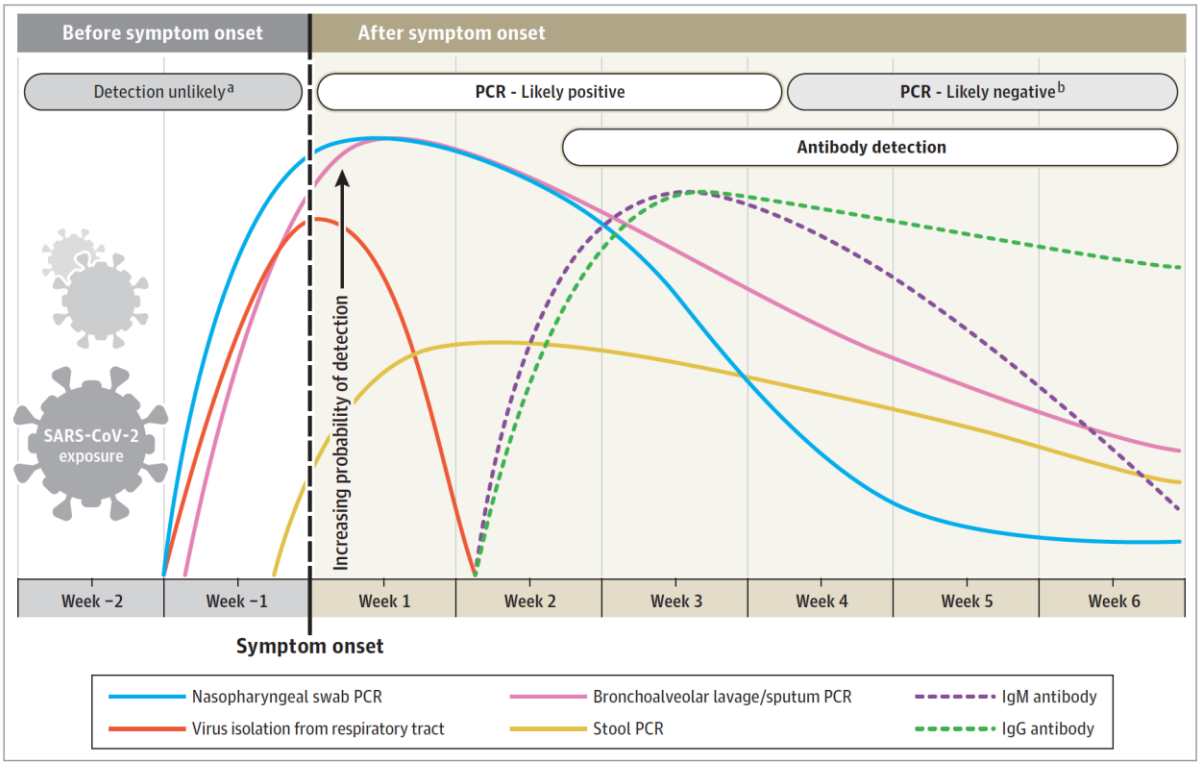
At present, serological testing has little utility within the preoperative diagnostic workup for SARS-CoV-2 infection. Further research is needed to explore descriptions of antibody profiles in the infection, presence of antibodies and correlations with protective immunity, and the duration of the protection.[112] However, serological testing does have future epidemiological usefulness as it is the only method of estimating herd immunity within the community and evaluating large-scale effectiveness of potential vaccines.[110]

Temporal Considerations for SARS-CoV-2

To appropriately integrate testing for SARS-CoV-2 infection into preoperative surgical triage protocols,[3] the temporal dynamics of the virus must be considered. The incubation period (time from exposure to onset of symptoms) of SARS-CoV-2 infection has been estimated to be approximately four to five days.[57, 122, 123] Viral load has been found to decrease after the onset of symptoms,[22, 93, 94]although SARS-CoV-2 RNA has been detected up to 37 days later.[50] However, infectiousness is likely to decline considerably after the first week of symptoms, when live virus may not be found on culture despite ongoing high viral loads.[21] SARS-CoV-2 RNA has been detected and also isolated from respiratory samples collected up to six days prior to symptom onset in persons infected with the virus (pre-symptomatic stage).[17]

In an evidence-based timeline of the various diagnostic markers of SARS-COV-2 infection (Figure 2),[105] Sethuraman et al. estimated that PCR detection (which merely confers the presence of viral RNA, not viable virus[21, 124]) is likely to produce a positive result in the first three weeks after symptom onset.[125] Antibodies are most likely to be detected on serology after approximately two weeks of symptoms,[126] with IgG levels generally greater than IgM levels from about four weeks after symptom onset.[127] It is important to note that PCR positivity has not been shown to correlate with clinical severity,[125] and has been found in cases when symptoms have completely resolved.[128] The temporal variance and utility of the RT-PCR assay based on clinical sample location is discussed earlier in this review (section: Reverse Transcription-Polymerase Chain Reaction [RT-PCR]), and in previous RACS COVID-19 reports.[1, 2]

Figure 2. Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Source: Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *JAMA*. 6 May 2020.[105]

Imaging for COVID-19

The inclusion of computed tomography (CT) in the diagnosis or clinical investigation of COVID-19 has rapidly evolved and been debated. While the fifth edition of the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia includes the use of CT findings to diagnose COVID-19, it is omitted from the sixth and seventh editions. [129] Multiple radiological societies around the world indicate that using CT alone to diagnose COVID-19 is inappropriate and not recommended[129-136] due to non-specific findings that overlap with other variants of pneumonia.[137] Most recommendations indicate that the use of CT should be part of parallel tests to determine if a patient is positive for COVID-19 pneumonia. Parallel patient workup must include a detailed patient history (i.e. overseas travel or contact with a COVID-19 positive case), clinical manifestations and laboratory tests.

Characteristic Features on CT Imaging

The most common lesion patterns based on the meta-analysis by Bao et al.[138] include Ground Glass Opacity (GGO) (83.3%), followed by GGO with consolidation (58.4%), adjacent pleura thickening

(52.4%), interlobular septal thickening (48.5%), and air bronchogram (46.4%). Despite frequently being mentioned, the incidence of crazy paving pattern was only 14.8%.

Lesion distribution was more likely to be bilateral (78.2% incidence) and located in the peripheral area (77.0% incidence), with far fewer lesions in the central or peribronchovascular area (10.8% incidence). Lesions were also more likely to be found in the lower lobes.[138]

Evolution of CT Features Over the Duration of COVID-19

The disease stages and features of COVID-19 pneumonia in CT images, as described by Pan et al.[139], are presented in Table 2. Disease severity will affect the length of time within each disease stage and progression to the absorption stage. Ding et al.[140] provided a variation on time estimation with minimal follow up for some patients, but no description of the severity of the patient's disease. This inhibits the ability to provide an overall disease stage and progression rate.

In the early or initial stages of disease, patients may have minimal abnormalities on CT imaging,[141, 142] as seen in the COVID-19 patients on the Diamond Princess, where 39% had no lung opacities, even in the 21% who were symptomatic.[143] As symptoms develop, CT images begin to reveal the effect of COVID-19 on the lungs, showing more lesions and greater involvement of the lungs and progression through a peak stage that includes 'white lungs'.[144]

Table 2. Disease stages and features of COVID-19 on CT imaging

Disease stage	Time estimate	Features visible on CT image
Initial	0–4 days	GGO distributed sub-pleurally either unilaterally or bilaterally in lower lobes
Progressive	5–8 days	Bilateral multilobe distribution of GGO, potential for crazy paving pattern and/or consolidation
Peak	9–13 days	Diffuse GGO, crazy paving pattern, consolidation and residual parenchymal bands
Absorption	>14 days	Consolidation being absorbed, crazy paving patterns less frequent, possible presence of extensive GGO as consolidation absorbed

Source: based on Pan et al.[139]

Disease Severity and Presentation on CT

Disease severity in COVID-19 ranges from mild (patient with no or minimal symptoms) to extremely severe (patient requiring intubation), with a considerable proportion of cases likely experiencing a mild version with minimal symptoms.[38] The literature has not adopted a consistent description of case severity, with many studies either creating a severity index[145, 146] or adapting a pre-existing definition.[142]

In a retrospective review of medical records, Guan et al[142] found that patients with a severe version of COVID-19 were more likely to have bilateral patchy shadowing on CT images (five to eight days after symptoms presented[139]) and/or a higher rate of GGO in comparison to those experiencing a less

severe version of COVID-19 (degree of severity defined according to the American Thoracic Society). The Society of Thoracic Radiology[136] has proposed reporting language to be used by radiologists when describing CT features in relation to COVID-19. The proposed reporting language allows for consistency across countries and organisations but removes the frequently used terms to describe features (e.g. GGOs, consolidation).

Comparison between CT and RT-PCR

Currently, there is debate over the sensitivity and specificity rates for both RT-PCR and CT to diagnose COVID-19. Reported ranges for RT-PCR vary according to the population tested, testing location (i.e. upper or lower respiratory tract), transportation of samples, and laboratory conditions and equipment. Ranges vary for CT due to ill-defined gold testing descriptions and testing only being conducted on RT-PCR positive cases. Many of the studies reporting sensitivity for CT provide minimal information about the opposing or gold standard test to which they are comparing, and frequently omit specificity, positive predictive value (PPV) and negative predictive value (NPV). This lack of information makes comparing CT and RT-PCR sensitivity and specificity rates difficult.

CT versus RT-PCR

A systematic review and meta-analysis on the performance of CT to diagnose COVID-19 identified 63 articles that provided a sensitivity score for CT diagnostic performance.[147] Only five articles stated a specificity score. Unfortunately, Kim et al[147] included studies comprising patients with laboratory-confirmed COVID-19 without including patients who were negative for COVID-19, or those who had another respiratory condition. Ultimately, the pooled rates of 94% sensitivity (95% CI 91–96%) and 37% specificity (95% CI 26–50%) can only be used as guidance. A second systematic review and meta-analysis pooled 16 studies to find a sensitivity value of 92% (95% CI 86–96%), but was only able to pool two studies to determine a specificity value of 31% (95% CI 22–42%).[148] The high sensitivity values from both Kim et al.[147] and Xu et al.[148] are discordant with Inui et al.[143] who found that a high proportion of patients confirmed positive with RT-PCR had no or minimal abnormalities on CT, bringing into question the high sensitivity and specificity rates found in the other studies. One possibility is that most studies are focusing on patients with high disease severity. Including those with less severe disease might reduce the sensitivity and specificity.

Chest X-Ray

The use of Chest X-rays (CXR) to diagnose COVID-19 is sparse in the literature and generally describes an inability to identify key characteristics of COVID-19 (i.e. GGO or consolidation).[149] The Royal Australian and New Zealand College of Radiologists[135] has clarified that the use of CXR is not ideal due to the reduced capacity of CXR to identify characteristics of COVID-19; however, this may be incidentally used on COVID-19-positive patients that have no clinical indication.

Ultrasound

There is a growing discussion and evidence base on the utility of ultrasound to identify COVID-19 characteristics in lungs[150-153], which stems from the use of lung ultrasonography to quickly identify artifacts during emergency situations.[154] Lung ultrasonography has a high sensitivity and specificity when diagnosing characteristics of pneumonia.[155, 156] Despite the emerging interest in lung

ultrasound, the Canadian Society of Thoracic Radiology and the Canadian Association of Radiologists provided a consensus statement indicating that lung ultrasound should not be used to diagnose COVID-19 due to the minimal evidence and the overlap of features with other diseases.[157] The Fleischner Society has also provided a consensus statement indicating that there is minimal evidence for using ultrasound in COVID-19 patients as of 7 April 2020.[132]

A panel of international experts has evaluated the challenges of using ultrasound during the current pandemic, discussing the requirement for personal protective equipment, caution around cleaning and disinfecting ultrasound equipment, and reproducibility between operators.[158] However, advice is mostly in favour of ultrasonography in a setting of high COVID-19 prevalence or low medical resources, because it provides a low-cost, accessible alternative to CT that is free of radiation and can be swiftly cleaned for infection control.[152, 159, 160] The lack of radiation with ultrasound confers an added benefit for assessing lung involvement in children and pregnant women.[161-163] However, in low prevalence settings such as Australia and New Zealand, where COVID-19 caseload and medical resources are less of an issue, lung ultrasound has questionable utility for diagnosing SARS-CoV-2 infection.

Characteristic Features of COVID-19 on Ultrasound

At present, reported studies are of low quality with low numbers of patients. Nevertheless, the case reports,[162, 164-167] case series,[153, 168] and retrospective studies,[152, 169-171] have informed the common characteristics found on ultrasound for COVID-19. Common features of COVID-19 are consolidation, the presence of B-lines, pleural thickening, and pleural effusion.[172, 173] It is important to note that these characteristics are also associated with other conditions,[172] therefore ultrasound should be used in combination with other supporting information to determine a diagnosis.

Evolution of Features through Disease Severity

There is a paucity of information relating to the evolution of characteristic features of COVID-19 on ultrasound over time. One low-level study has provided evidence that separated B-lines increased from the second week to the fourth week, while confluent B-lines were present mainly in the second and third week, reducing in the fourth week.[174] Consolidation was more likely to be present in the third week in the infrascapular area, decreasing again in the fourth week.

Sensitivity and specificity for diagnosing COVID-19 features using lung ultrasound

There is a lack of reliable evidence regarding the sensitivity and specificity of lung ultrasound in detecting COVID-19. One low-level retrospective study stated that lung ultrasound had higher sensitivity than chest CT in identifying pleural effusion, consolidation, regional alveolar-interstitial pattern and alveolar-interstitial syndrome.[170] These results should be considered with caution as the authors used multiple scans from the same patients identifying the same features to determine sensitivity values. Due to the inadequate information on sensitivity and specificity values, using lung ultrasound to diagnose COVID-19 is not advised.

N.B. The University of Melbourne is currently running courses on using ultrasound to identify the features of COVID-19 pneumonia: http://mdhs-study.unimelb.edu.au/short-courses/mms-short-courses/covid-19-lung-ultrasound/overview#overview

Conclusion

On the basis of a rapid review of the literature, evidence-based recommendations have been produced along with a proposed schema for the preoperative diagnostic workup of surgical patients suspected of having COVID-19. A printable questionnaire is provided for screening patients for symptoms of COVID-19 or a history of potential SARS-CoV-2 exposure, in either face-to-face or telemedicine consults.

Limitations of the review

The limitation to a single database for sourcing peer-reviewed publications may have overlooked some articles, and the expedited publication of peer-reviewed articles within the literature means that the relevance of information related to COVID-19 will change rapidly. However, throughout the process of developing this rapid review, iterative engagement with a working group of expert clinicians was maintained in order to optimise the clinical relevance of the presented evidence.

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Appendix A: Definition of a Close Contact

The following information is derived from the national guideline, *Coronavirus Disease 2019 (COVID-19)* from the Communicable Diseases Network Australia (CDNA), which is available at the following link: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm

For New Zealand, advice in this area can be found in the guidance document from the New Zealand Ministry of Health, *Updated advice for health professionals: novel coronavirus (COVID-19)*, which is available at the following link: https://www.health.govt.nz/system/files/documents/pages/updated-advice-health-professionals-22may20.pdf

A close contact is defined as requiring:

- face-to-face contact in any setting with a confirmed or probable case, for greater than 15 minutes cumulative over the course of a week, in the period extending from 48 hours before onset of symptoms in the confirmed or probable case, or
- sharing of a closed space with a confirmed or probable case for a prolonged period (e.g. more than 2 hours) in the period extending from 48 hours before onset of symptoms in the confirmed or probable case.

For the purposes of surveillance, a close contact includes a person meeting any of the following criteria:

- Living in the same household or household-like setting (e.g. in a boarding school or hostel) – referred to as 'household contacts'.
- Direct contact with the body fluids or laboratory specimens of a case without recommended PPE or failure of PPE.
- A person who spent 2 hours or longer in the same room (such as a GP or ED waiting room; a school classroom; communal room in an aged care facility).
- A person in the same hospital room when an aerosol-generating procedure is undertaken on the case, without recommended PPE.
- Aircraft passengers who were seated in the same row as the case, or in the two rows in front or two rows behind a confirmed or probable COVID-19 case. Contact tracing of people who may have had close contact on long bus or train trips should also be attempted where possible, using similar seating/proximity criteria.
- For aircraft crew exposed to a confirmed or probable case, a case-by-case risk assessment should be conducted by the airline to identify which crew member(s) should be managed as close contacts.
- If an aircraft crewmember is the COVID-19 case, contact tracing efforts should concentrate on passengers seated in the area where the crewmember was working during the flight and all of the other members of the crew. A case by case risk assessment should be conducted to identify which passengers and crew members should be managed as close contacts.
- Close contacts on cruise ships can be difficult to identify, and a case-by-case risk assessment should be conducted to identify which passengers and crew should be managed as close contacts.

Contact needs to have occurred within the period extending 48 hours before onset of symptoms in the case until the case is classified as no longer infectious. If the case is asymptomatic, see PCR positive tests in asymptomatic or pre-symptomatic persons for information on determining the asymptomatic (or pre-symptomatic) case's infectious period and to inform identification of contacts.

Note that:

- Healthcare workers and other contacts who have taken recommended infection control precautions, including the use of full PPE, while caring for a symptomatic confirmed or probable COVID-19 cases are not considered to be close contacts.
- Contact tracing is not required for close contacts arriving on international flights on or after 16 March 2020.

Appendix B: Search Strategy

No.	Reason	Query	Results (6 May 2020)
1	COVID-19 Pandemic	((((((("COVID-19" [tiab]) OR "SARS-CoV-2" [tiab]) OR "2019-nCoV" [tiab]) OR coronavirus [tiab]) OR "novel coronavirus" [tiab]) OR "corona virus" [tiab]) OR "severe acute respiratory syndrome coronavirus" [tiab]	19,687
2	Clinical Presentation	((((((((((infecti* [tiab]) OR pathology [tiab]) OR pathological [tiab]) OR sign [tiab]) OR signs [tiab]) OR symptom [tiab]) OR symptoms [tiab]) OR symptomatic [tiab]) OR asymptomatic [tiab]) OR "clinical presentation" [tiab]) OR "clinical findings" [tiab]) OR pneumonia [tiab]	3,494,934
3	Point-of-Care and Serologic Testing	((((((((((("Point-of-Care Testing"[Mesh]) OR (((point*of*care OR rapid OR bedside OR real*time OR near*patient OR fast OR prompt OR early) AND (test OR tests OR testing OR assay* OR PCR OR molecular OR diagnostic OR diagnosi* OR diagnostics OR diagnose* OR detection OR assessment* OR use*)))) OR ((Bedside AND (Computing OR Technology)))) OR ((“in field detection” OR POC OR POCT)))))) OR ((((((((((("Serologic Tests"[Mesh]) OR "Molecular Diagnostic Techniques"[Mesh]) OR ((“IgM” OR “IgG” OR “Ag”))) OR ((Immunoglobulin OR “antiviral immunoglobulin-G”))) OR ((Serologic* AND (test OR testing OR tests OR conversion* OR assay* OR analysis OR diagnostic OR diagnostics OR diagnosi* OR diagnose* OR screen*)))) OR ((Serology or seroconversion OR seroepidemiology OR serodiagnos* or seroprevalence*))) OR (((Antibod* AND (test OR tests OR testing OR serum OR detection* OR response*))))) OR ((Antigen OR antigeni* OR antigens*))) OR Immunoassa*) OR ((Molecular AND (diagnostic OR diagnostics OR diagnosi* OR diagnose*)))) OR Dynamic* profile))))	4,672,773
4	Diagnosis	((((((((((((("Diagnosis"[Mesh]) OR (("Diagnostic Techniques and Procedures"[Mesh]))) OR "Diagnostic Tests, Routine"[Mesh]) OR “Diagnostic Test Approval"[Mesh]) OR "Reagent Kits, Diagnostic"[Mesh]) OR "Predictive Value of Tests"[Mesh]) OR (("Sensitivity and Specificity"[Mesh]))) OR ((detect* OR laboratory OR evaluat* OR validat* OR clinical OR perform* OR sensitivity OR specificity OR area under the curve OR positive predictive value OR PPV OR negative predictive value OR NPV OR predictive value OR feasibility OR accuracy OR likelihood ratio OR false negative OR false positive OR Positive rate OR validation OR diagnostic odds ratio OR DOR OR valid*))) OR ((Diagnostic AND (value OR panel OR tool*)))) OR ((diagnosa* OR diagnosi* OR diagnose* OR diagnoss* OR diagnostic OR diagnostics))) OR (((Test OR tests OR testing) AND (infection OR virus OR disease OR diseases OR disease, OR antibod* OR blood OR nucleic acid or diagnostic OR diagnostics OR diagnosi* OR diagnose* OR diagnose*))))))	17,661,043
5	Computed Tomography Imaging	((((((((((("Radiography, Thoracic"[Mesh]) OR "Tomography, X-Ray Computed"[Mesh]) OR “Tomography, X-Ray” [Mesh]) OR ((CT X*Ray* OR CT))) OR (((CT OR CAT OR chest OR lung or lungs or thoracic* OR thorax*) AND (Scan or screen* or imaging or film or radiograph* or radiogram or radiolog*)))) OR Compute* tomograph*) OR ((Cine-CT or “Cine CT”))) OR (((Thoracic* OR thorax* OR lung OR lungs OR Chest) AND CT))) OR ((“Chest CT” AND (scan or imaging)))) OR ((X*ray* computed or x-ray compute*))) OR ((Compute* assist* tomograph* OR compute* axial tomograph*))) OR ((chest radiological imaging OR Roentgenolog* or roentgen ray*or roentgen OR Grenz Ray* or X*Radiation*))	664,529
6	X-ray Imaging	((((((“Radiography, Thoracic"[Mesh]) OR "Mass Chest X-Ray"[Mesh]) OR "X-Rays"[Mesh]) OR (((CXR OR CR OR x*ray* OR radiograph*)))) OR (((chest AND (film* OR radiograph*))))) OR ((((chest OR lung OR lungs OR thoracic* OR thorax*) AND (x*ray* OR radiograph* or radiogram* or radiolog*))))) OR (((Chest X-ray radiography OR chest radiological imaging OR thoracic radiology OR Roentgenolog* or roentgen ray*or roentgen OR Grenz Ray* or	1,438,818

		X*Radiation*)))	
7	RT-PCR Testing	((((((((((((((((((((((((("Polymerase Chain Reaction"[Mesh]) OR "Reverse Transcriptase Polymerase Chain Reaction"[Mesh]) OR "Real-Time Polymerase Chain Reaction"[Mesh]) OR (((polymerase chain reaction) OR "PCR" OR "PCRs" OR ((Inverse OR Nested OR Anchored OR Kinetic) AND (Polymerase Chain Reaction))))) OR ((reverse AND (transcriptase OR transcription) AND (PCR OR PCRs OR polymerase chain reaction)))) OR ((RT-PCR OR RT-PCR diagnostic panel OR RT-PCR assay* OR rRT-PCR OR qPCR OR qRT-PCR OR RT-qPCR OR mPCR OR WHO-PCR))) OR ((RT-PCR OR (RT-PCR diagnostic panel) OR (RT-PCR assay*) OR rRT-PCR OR qPCR OR qRT-PCR OR RT-qPCR OR mPCR OR WHO-PCR))) OR (((Real*Time AND (Polymerase Chain Reaction OR PCR OR PCRs OR RT-PCR))))) OR ((Real*time AND ((reverse AND (transcriptase OR transcription)) AND (PCR OR PCRs OR polymerase chain reaction))))) OR ((Real*time AND RT-PCR) OR ((reverse real*time) AND (PCR OR PCRs OR polymerase chain reaction)) OR ((real reverse AND (transcriptase OR transcription)) AND (PCR OR PCRs OR polymerase chain reaction)))) OR ((Quantitative Real*Time AND (Polymerase Chain Reaction OR PCR OR PCRs)))) OR ((((qualitative AND (real*time)) AND ((reverse AND (transcriptase OR transcription)) AND (PCR OR PCRs OR polymerase chain reaction)))))) OR ((Multiplex AND (PCR OR PCRs OR polymerase chain reaction)))) OR ((nucleic acid OR nucleic acid detection OR RNA))) OR (("Hologic Panther Fusion" OR "Hologic" OR "Hologic Panther" OR "DiaSorin Simplexa" OR "DiaSorin" OR "Roche Cobas 6800" OR "DiaSorin Simplexa COVID*19 Direct" OR "Cepheid Xpert Xpress SARS*CoV*2" OR "Cepheid Xpert Xpress" OR "QIAstat-Dx Respiratory SARS*CoV*2 Panel" OR "QIAstat-SARS" OR "QIAstat"))) OR (((lateral flow immunoassay) OR "LFIA"))) OR "LAMP assay" [Supplementary Concept]) OR ((((reverse AND (transcriptase OR transcription)) AND (loop*mediated isothermal amplification)) OR "RT-LAMP" OR (loop*mediated isothermal amplification) OR LAMP))) OR (((open reading frame 1ab) OR ORF1ab))) OR ((((magnetic chemiluminescence enzyme immunoassay) OR MCLIA)))) OR (((magnetic chemiluminescence enzyme immunoassay) OR MCLIA OR MCLA))) OR "Enzyme-Linked Immunosorbent Assay"[Mesh]) OR (((enzyme*linked immunosorbent assay*) OR ELISA))) OR "Luminescent Measurements"[Mesh]) OR (((chemiluminescence immunoassay) OR CLIA OR chemiluminescence))) OR spike protein) OR nucleocapsid protein	2,724,819
8	Ultrasound Imaging	(((((((("Ultrasonography"[Mesh]) OR ((POCUS OR LU OR LUS OR US))) OR ((((Point*of*care OR bedside OR rapid OR real*time OR near*patient OR fast OR prompt OR early))) AND ((Ultrasound OR ultrasonography OR ultrasonic OR sonography OR sonographic)))) OR ((((Chest OR thoraci* OR thorax* OR lung or lungs))) AND ((Ultrasound OR ultrasonography OR ultrasonic OR sonography OR sonographic)))) OR ((((Chest OR thoraci* OR thorax* OR lung or lungs))) AND US)) OR ((((Point*of*care OR bedside OR rapid OR real*time OR near*patient OR fast OR prompt OR early))) AND ((Image OR imaging OR images)))) OR ((((Chest OR thoraci* OR thorax* OR lung or lungs))) AND ((Image OR imaging OR images)))) OR ((((Ultrasound OR ultrasonography OR ultrasonic OR sonography OR sonographic))) AND ((diagnosa* OR diagnosi* OR diagnose* OR diagnoss* OR diagnostic OR diagnostics)))	2,361,046
9	Treatments for COVID-19 in Title	Ivermectin [TI] OR Stromectol [TI] OR Mectizan [TI] OR Eqvalan [TI] OR Ivomec [TI] OR "MK-933" [TI] OR "MK 933" [TI] OR MK933 [TI] OR Macrolide* [TI] OR "extracorporeal membrane oxygenation" [TI] OR ECMO [TI] OR "life support" [TI] OR Paracetamol [TI] OR Acetaminophen [TI] OR Antipyretic [TI] OR Amide* [TI] OR Ibuprofen [TI] OR NSAID [TI] OR Ibumetin [TI] OR Motrin [TI] OR Nuprin [TI] OR Rufen [TI] OR Salprofen [TI] OR Dolgit [TI] OR Brufen [TI] OR Phenylproprionate* [TI] OR "anti-inflammatory" [TI] OR "anti inflammatory" [TI] OR angiotensin [TI] OR "ACE-inhibitor*" [TI] OR "ACE inhibitor*" [TI] OR renin [TI] OR steroid* [TI] OR methylprednisolone [TI] OR tocilizumab [TI] OR atlizumab [TI] OR actemra [TI] OR roactemra [TI] OR heparin [TI] OR liquaemin heparin OR hydroxychloroquine [TI] OR oxychlorochin [TI] OR oxychloroquine [TI] OR hydroxychlorochin [TI] OR plaquenil [TI] OR sulfate [TI] OR quinolone* [TI] OR chloroquine [TI] OR chlorochin [TI] OR chingamin [TI] OR nivaquine [TI] OR khingamin [TI] OR aralen [TI] OR arequin [TI] OR arechine [TI] OR remdesivir [TI] OR alanine [TI] OR antiviral [TI] OR "anti-viral" [TI] OR "anti viral" [TI] OR vasodilator* [TI] OR corticosteroid* [TI] OR lipoic [TI] OR bevacizumab [TI] OR lopinavir [TI] OR protease [TI] OR pyrimidin* [TI] OR ritonavir [TI] OR cytochrome [TI] OR	1,115,209

		azole* [TI] OR interferon [TI] OR beta [TI] OR gamma [TI] OR “lopinavir-ritonavir” [TI] OR “lopinavir/ritonavir” [TI] OR azithromycin [TI] OR antibiotic* [TI] OR sumamed [TI] OR toraseptol [TI] OR vinzam [TI] OR Zithromax OR Azitrocin [TI] OR Ultreon [TI] OR oseltamivir [TI] OR interleukin [TI] OR lenzilumab [TI] OR monoclonal [TI]	
10	Sensitivity string	**2** OR **3** OR **4** OR **5** OR **6** OR **7** OR **8**	19,561,598
11	Specifying for COVID-19	**1** AND **10**	15,340
12	Eliminating treatments for COVID-19 in Title	**11** NOT **9**	14,178
13	Specifying to timeframe since WHO was alerted of COVID-19	Apply filter: Publication date from 31 Dec 2019	5,762
14	Specifying for humans	Apply filter: Humans, and results imported into EndNote	1,395