Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A multidisciplinary evaluation of suspected, non-confirmed cases of COVID-19 including chest CT, as compared to World Health Organization recommendations

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AIM: To report an audit of the evaluation of suspected, unconfirmed cases of COVID-19 including chest computed tomography (CT), as compared to World Health Organization recommendations.

METHODS: A clinical audit was undertaken examining the evaluation of patients with suspected COVID-19 with negative SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) results, with comparison to WHO recommendations. A retrospective chart review was undertaken for 90 patients examining investigations, in particular CT, used to clarify the diagnosis.

RESULTS: Ninety patients underwent additional investigation. Seventy-five per cent adherence to WHO recommendations was observed. Fifty-two men (57.78%) and 38 (42.22%) women were investigated, with a median age of 69 years (range 20–96 years). Seventy-nine chest CT examinations demonstrated positive, indeterminate, and negative rates for COVID-19 of 3.79%, 24.1%, and 72.15% respectively. Three patients had discordant swab results with initially negative and subsequently positive results for SARS-CoV-2, resulting in false-negative rates of 5.1% for those retested. Combining discordant RT-PCR swab results, positive radiology, and patients treated as COVID-19-positive due to indeterminate radiology and highly consistent symptoms, resulted in a false-negative rate for initial SARS-CoV-2 RT-PCR swabs of 16.67%.

CONCLUSION: Seventy-five per cent compliance with relevant WHO guidance and a false-negative rate for initial swabs of 16.67% was demonstrated. Further evidence is needed to fully determine the utility of chest CT in the diagnosis of COVID-19 in the context of initial false-negative RT-PCR results.

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Introduction

Up to 27 October 2020, the COVID-19 pandemic has resulted in 43,598,033 cases worldwide, with 1,160,995 deaths, including 54,484 cases in Ireland causing 1,621 deaths.[1,2]

At present, detection of SARS-CoV-2 RNA via real-time reverse transcription polymerase chain reaction (RT-PCR) is the gold standard for diagnosing suspected cases of COVID-19.[3] Although this investigation is specific, test sensitivity varies according to a number of factors resulting in a false-negative rate of approximately 30%.[4]

Comprehensive guidelines on the use of chest computed tomography (CT) in the diagnosis of COVID-19 are lacking. Initial reports from China suggested a central role of CT in COVID-19 diagnosis,[5,6] with some citing higher sensitivity rates with use of CT thorax when compared to RT-PCR for SARS-CoV-2[5]; subsequent examination of these data has noted significant methodological limitations.[7] In clinical practice, chest CT has become a valuable adjunct to diagnosis[8]; however, its value in RT-PCR-negative COVID-19 cases has yet to be fully established.

In June 2020, the World Health Organisation (WHO) published "Use of chest imaging in COVID-19: a rapid advice guide". This guide makes recommendations for the use of chest imaging in the acute care of adult patients with suspected, probable, or confirmed COVID-19, including chest radiography, computed tomography (CT) and lung ultrasound (Table 1).[9]

The present authors undertook a clinical audit of the evaluation of suspected COVID-19 cases with negative SARS-CoV-2 RT-PCR results on oro/nasopharyngeal swabs, in comparison to recommendations set out by the WHO in the June 2020 rapid advice guide.

Table 1
World Health Organization (WHO) recommendations.

Relevant recommendation from "Use of chest imaging in COVID-19, A Rapid Advice Guide", WHO
R 2.1 - For symptomatic patients with suspected COVID-19, WHO suggests not using chest imaging for the diagnostic work-up of COVID-19 when RT-PCR testing is available with timely results
R 2.2 - For symptomatic patients with suspected COVID-19, WHO suggests using chest imaging for the diagnostic work-up of COVID-19 when: (1) RT-PCR testing is not available; (2) RT-PCR testing is available, but results are delayed; and (3) initial RT-PCR testing is negative, but with high clinical of suspicion of COVID-19
R 4 - For patients with suspected or confirmed COVID-19, not currently hospitalized and with moderate to severe symptoms, WHO suggests using chest imaging in addition to clinical and laboratory assessment to decide on regular ward admission versus intensive care unit (ICU) admission
R 5 - For patients with suspected or confirmed COVID-19, currently hospitalized and with moderate to severe symptoms, WHO suggests using chest imaging in addition to clinical and laboratory assessment to inform the therapeutic management

Materials and methods

Intrahospital COVID-19 pathway

In this Level 4 tertiary referral centre, as per national Health Service Executive (HSE) guidelines, at entry to hospital all patients are segregated into two parallel streams described as COVID-19 and non-COVID-19 pathways[10] (Fig 1). On presentation to hospital or during an inpatient stay, a decision to test for SARS-CoV-2 is made clinically, informed and supported by the national guidelines.[10]

In this institution, a patient with confirmed COVID-19 remains on the "COVID-19 pathway" in cohort wards throughout their inpatient stay until discharge or until they have undergone a 14-day period of isolation with resolution of respiratory symptoms. Following admission, to exclude COVID-19 as the primary diagnosis and leave the pathway, a patient must have at least one negative SARS-CoV-2 RT-PCR swab and a suitable alternative diagnosis. If clinical suspicion persists, despite the initial negative RT-PCR results, individual cases are discussed at a daily multidisciplinary team (MDT) meeting, attended by members of the infectious diseases, respiratory and admitting medical teams. Decisions regarding further investigation, including repeat SARS-CoV-2 RT-PCR testing and modality of chest imaging, are made on a case-by-case basis following specialist input. Patients with subsequently positive SARS-CoV-2 RT-PCR results, chest imaging reported as consistent with COVID-19, and highly consistent clinical presentations in addition to indeterminate imaging, in the absence of suitable alternative diagnosis, are treated as COVID-19 positive. The final decision to remove or keep a patient on the COVID-19 pathway following further investigation is made by the responsible treating physician.

Between 28 March and 4 May 2020, 90 patients with initial negative SARS-CoV-2 RT-PCR swab results were further investigated as per the MDT to further clarify the possible diagnosis of COVID-19. All included patients had, at minimum, moderate symptoms requiring admission to hospital or deterioration during an inpatient stay, necessitating MDT discussion.

CT images were categorised as (1) typical for COVID-19, (2) indeterminate for COVID-19, or (3) atypical or negative for COVID-19 by a consultant radiologist or by a registrar in radiology whose findings were confirmed by a consultant. This categorisation is derived from the Radiological Society of North America (RSNA) CT criteria related to COVID-19,[11] where "negative for COVID-19" cited is a combination of RSNA categories "atypical appearances" and "negative for pneumonia". Decision to use unenhanced chest CT versus CT pulmonary angiography (CTPA) was based on clinical presentation, supporting clinical tools (e.g., Well's score), and was made on an individual basis via MDT discussion.

Audit

A retrospective chart review was undertaken for patients with negative SARS-CoV-2 RT-PCR swab results, but for whom clinical suspicion for a diagnosis of COVID-19

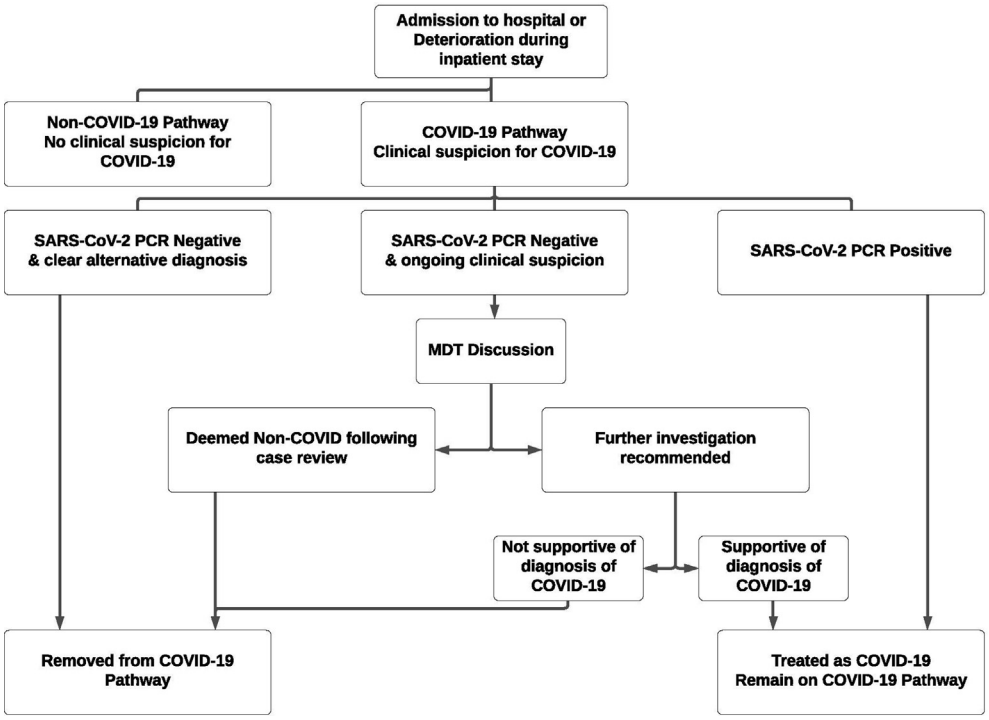

Figure 1 Intrahospital flow of patients via the "COVID-19" or "non-COVID-19" pathway.

remained, examining the investigations used to further clarify or exclude the diagnosis.

Due to lack of published standards during the study dates, the above WHO guideline was not applied prospectively, with comparison being made in retrospect. The aim of this audit was to assess the extent to which investigation of this patient population following MDT discussion, in particular with use of chest CT, is in keeping with the published guidance from the WHO and to formulate recommendations for future assessment. Approval to undertake this study was granted by the institution's Clinical Audit Committee.

Results

Due to ongoing clinical suspicion of COVID-19 in the context of at least one negative SARS-CoV-2 RT-PCR swab result, 90 patients underwent additional investigation under the guidance of the COVID-19 MDT between 28 March and 4 May 2020. Results are summarised in Fig 2.

Fifty-two men (57.78%) and 38 (42.22%) women were investigated, with a median age of 69 years (range 20–96 years). All 90 (100%) had initial negative RT-PCR swab results for SARS-CoV-2 and all had initial chest radiography performed either on admission to hospital or during their hospital stay.

Following MDT discussion, 55 patients (61.11%) underwent chest CT (non-contrast) and 22 (24.44%) underwent CTPA. One (1.1%) patient had both an unenhanced chest CT followed by CTPA. Twelve (13.33%) patients had no CT investigation.

Twenty-eight (31.11%) patients had CT alone (no repeat swab), nine had repeat RT-PCR testing alone (10%, two of which were positive), and 50 (55.56%) had both CT and repeat RT-PCR swabbing. Three (3.33%) patients had neither CT nor a second swab of which two were taken off the COVID pathway following clinical review alone by members of the infectious diseases team and one remained on the pathway but was later deemed non-COVID.

Of the 56 unenhanced chest CT examinations performed, two (3.57%) had findings consistent with COVID-19. Thirteen (23.21%) had indeterminate findings and 41 (73.21%) had CT findings negative for COVID-19. Both patients with chest CT examinations consistent with COVID-19 also had repeat SARS-CoV-2 RT-PCR testing, with negative results.

Of the 23 CTPA examinations performed, none confirmed a pulmonary embolism (PE). One (4.34%) had findings clearly consistent with COVID-19, 6 (26%) had indeterminate findings, and 16 (69.57%) were negative for COVID-19. The patient with CTPA findings consistent with COVID-19 did not undergo repeat RT-PCR testing.

Combining these results, for 79 CT examinations performed in 78 patients, chest CT resulted in positive, negative, and indeterminate rates for COVID-19 of 3.79%, 72.15%, and 24.1% respectively.

For those with indeterminate scans (CT/CTPA, n=19), the median age was 71 years (range 25–89 years). The median time from first swab to CT was 1 day (mean 1.47, range 0–5 days). Fourteen (73.7%) had second swabs an average of 0.64 days after CT (range from 3 days before CT to 7 days after). Non-specific ground glass changes were seen in 13 scans (68.42%) and consolidation was seen in two (10.52%). Six (31.58%) of these patients remained on the "COVID-19

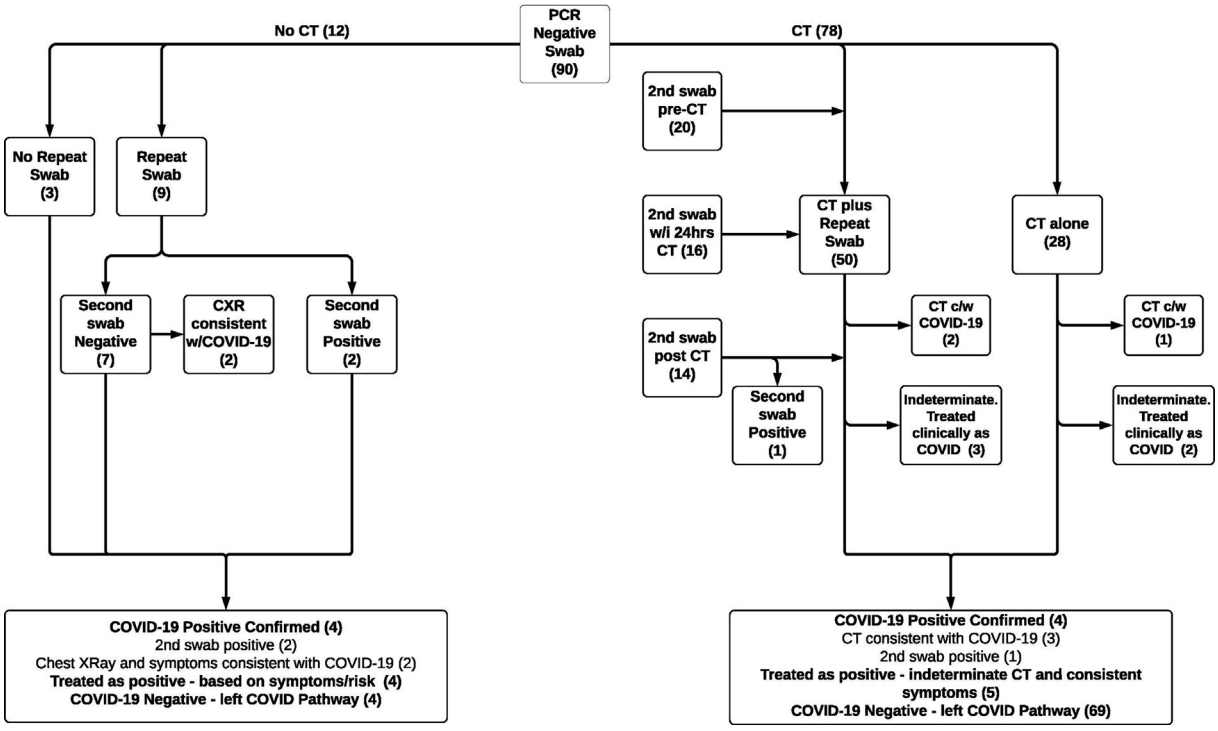

Figure 2 Patient flow through the "COVID-19 pathway" following initial negative SARS-CoV-2 RT-PCR swab: further investigations and outcomes.

pathway" with one having a subsequently positive RT-PCR swab, five treated as clinical COVID-19 disease (of whom three had repeat RT-PCR testing, all of which were negative). Thirteen (68.42%) were ultimately treated as non-COVID-19, with a mean time from CT to leaving the COVID-19 pathway of 1.54 days.

Fifty-nine (65.56%) patients had a second SARS-CoV-2 RT-PCR swab of which three (5.1%) were positive and 56 (94.92%) negative. Thirty-one (34.44%) were not re-swabbed. In the three discordant results, the time between negative and positive test was median 6 days (4, 6, 8 days, respectively). Two (2.22%) patients had subsequent de novo positive results on a third swab, 14 and 16 days after initial swabs. Of the three patients that had a second, subsequently positive swab, one underwent chest CT. This demonstrated diffuse interstitial changes not typical for COVID-19 and was performed 1 day after admission and initial swab. The second subsequently positive swab was taken 7 days later (8 days after first swab).

The mean number of days from first swab to CT scan was 2.2 days (median 2, range 0–8 days). The mean time from CT to leaving the hospital "COVID-19 pathway" in those determined to be COVID-19 negative was 1.35 days (median 1, range 0–4 days).

Seventeen (18.89%) patients remained on the "COVID-19 pathway" during their stay following further investigation (Fig 2.) comprising three (3.33%) with subsequently positive RT-PCR findings within their admission as above; three (3.33%) with CT results consistent with COVID-19; five (5.56%) with indeterminate CT findings and consistent symptoms, treated clinically as COVID-19; two (2.22%) with classical chest radiography findings and symptoms consistent with COVID-19 (with no CT performed); and four (4.44%) treated as clinical COVID without CT or definitive chest radiography findings: two of these patients were retrospectively deemed non-COVID post-discharge following review of results/contact tracing. Seventy-three (81.11%) patients left the "COVID-19 pathway" following MDT discussion and subsequent investigation.

Consistency with WHO guidance

R 2.1-The average turnaround time for SARS-CoV-2 RT-PCR in this institution is < 24 h. Despite the availability of rapid results, all 90 patients underwent initial chest imaging, with a minimum of chest radiography at assessment. Patients who underwent further radiological imaging are described above.

R 2.2-All patients in this audit underwent chest imaging with at least one method. All 90 patients had at least one chest radiography examination and 78 (86.67%) patients underwent CT. All patients included in this audit were considered to fall into the category "initial RT-PCR testing is negative, but with high clinical of suspicion of COVID-19" as a result of MDT discussion.

R 4-All patients met this criteria as chest imaging was used as part of clinical assessment on admission to hospital or during inpatient stay in all of the studied suspect COVID-19 cases. By supporting or aiding exclusion of a diagnosis of COVID-19, chest imaging contributed to decisions regarding location of care, i.e., COVID-19/non-COVID-19 wards. Clinical deterioration in a confirmed COVID-19 case may

prompt early review by intensive care teams; however, specific indications for this are outside the scope of this audit.

R 5-All patients in this audit were hospitalised with at least moderate symptoms requiring inpatient stay. Clinical symptoms together with radiological findings at the time of MDT discussion were used to determine further steps, such as CT. The presence of pneumonia on imaging was also used as a factor in decisions to prescribe COVID-19-directed therapy; however, the specifics of therapeutic agents prescribed is outside the scope of this audit.

Discussion

The present study reports a clinical audit of the evaluation of suspected COVID-19 cases with initial SARS-CoV-2 RT-PCR-negative swabs who merited further investigation for COVID-19. The MDT recommendations were compared to those made by the World Health Organization.

For three of the four relevant recommendations, this audit found that there was appropriate compliance with WHO advice in relation to the work-up of suspected COVID-19 cases. Recommendation 2.1 suggests withholding chest imaging in symptomatic patients in situations where RT-PCR swab results are known in a timely manner. The turnaround time for RT-PCR results in this institution is $<$ 24 h yet all 90 patients included in the audit had at least one chest radiography examination with 86.67% of patients going on to have some form of CT imaging. Although this is not in keeping with guidance of R2.1, the patients studied warranted admission regardless of ultimate diagnosis and chest X-Ray is a standard part of admission work-up for many infectious/acute respiratory presentations. Indeed the WHO advice guide notes that imaging is particularly useful in those with: “moderate–severe symptoms, require admission to hospital regardless of eventual diagnosis, or in those who are at risk of complications secondary to COVID-19, such as pulmonary embolism”.[9] All patients included in this audit met at least one of those criteria, and therefore, the use of at least one imaging technique in the reported work-up is consistent with the given guidelines.

Due to the limited evidence on the utility of specific imaging methods in the diagnosis of suspected/confirmed cases of COVID-19, the WHO advice guide acknowledges that radiological findings must be used as one element in the evaluation of a patient that also includes clinical and laboratory data.[12] This audit demonstrates full adherence to this advice, as all patients included were discussed in a MDT meeting, with consideration given to clinical presentation, laboratory findings, and initial imaging, e.g., chest radiography.

Preliminary results from the Study to Investigate COVID-19 Infection in People Living in Ireland (SCOPI), estimated the national seroprevalence of anti-SARS-CoV-2 antibodies in Ireland at 1.7%[13]; however, the true prevalence of COVID-19 in the Irish population is still unknown. The cumulative incidence rate per 100,000 population at the beginning of the audit and the end of the audit was 110.4 and 804.5 respectively.[14] Based on the incidence at the height of the pandemic, clinical presentations requiring admission, swabbing, and MDT discussion, it is reasonable to assume a moderate pre-test probability for COVID-19 in the analysed patient population in this audit.

Comprehensive guidelines on the use of CT in the diagnosis of COVID-19 are lacking. Findings early in the pandemic suggested a central role of CT in COVID-19 diagnosis with some reports citing sensitivities as high as 97% and 98%.[5,6] It has since been noted that significant methodological issues are present in these studies[7] necessitating some caution in interpretation. In clinical practice, however, CT has become a valuable adjunct to diagnosis, as well as detection of associated complications, of COVID-19, such as acute respiratory distress syndrome (ARDS), PE, superimposed pneumonia, or heart failure.[8] Chest CT is associated with high sensitivity but low specificity in most studies, resulting in weak positive likelihood ratios but stronger negative likelihood ratios.[12] A study by Ai *et al.*, found the positive likelihood ratio was 1.28 and the negative likelihood ratio was 0.16.[6] Indeed, in the present audit, no patient with a chest CT reported as negative for COVID-19, in addition to negative SARS-CoV-2 RT-PCR results on at least one RT-PCR swab, remained on the COVID-19 pathway. Most studies to date use a positive RT-PCR result for SARS-CoV-2 as a reference standard, so data regarding CT use in the diagnosis of suspected COVID-19 with negative SARS-CoV-2 RT-PCR swabs are limited.

The guidelines used in this audit are comparable to those provided by other sources, who similarly make broad recommendations, acknowledging persistent evidence gaps relating to diagnostic decisions. A consensus statement by The Fleischner Society recommends that imaging is indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results.[15] It is further noted that the decision regarding chest radiography versus chest CT in patient evaluation is dependent on time of presentation in the illness, local resources, and local public health policies. In March 2020, The American College of Radiology issued a statement regarding the use of CT in COVID-19 diagnosis and recommended its use only in those “with specific clinical indications for CT” and cited concerns regarding the overlap between the findings seen in COVID-19 and other viral illnesses.[16] Specific criteria for the use of chest CT are not provided by either body and the varying nature of guidance provided highlights the ongoing need for investigation into the use of this imaging modality in COVID-19 diagnosis.

At present, detection of SARS-CoV-2 RNA via RT-PCR is the gold standard for diagnosing suspected cases of COVID-19[4] and samples may be obtained from either the upper or lower respiratory tract. The test sensitivity varies according multiple factors including duration of illness,[17] the site of specimen collection,[18] the quality of specimen collection, and the viral load.[5] As a result, false-negative rates have been reported to occur in $\sim$30% of patients with COVID-19 (range $<$5%–40%),[4,19] and therefore, one initial negative swab should not be solely relied upon to confirm or exclude a diagnosis of COVID-19 if clinical suspicion is high. One

large study of 20,912 patients demonstrated that among those initially testing negative by SARS-CoV-2 RT-PCR of nasopharyngeal swabs, repeat testing within 7 days yielded a positive result in 3.5% of cases.[19]

In the present audit sample, three patients had discordant swab results with initial negative and subsequently positive results for SARS-CoV-2, 4, 6, and 8 days following initial sampling. This results in a false-negative rate of 5.1% for those retested, which is comparable to the rate of 3.5% reported by Long *et al.*[15] Two (2.22%) patients had subsequent de novo positive results on a third swab, 14 and 16 days after initial swabs. These two results likely represent nosocomial infection during prolonged admissions, and therefore, are not thought to be true delayed positive results from an existing infection at first assessment. As stated above, all cases were discussed on an individual basis via MDT evaluation and not all patients underwent repeat RT-PCR swabbing, the reason for which is multifactorial. Early in the course of the pandemic, laboratory capacity for retesting, including consumables required for SARS-CoV-2 RT-PCR were occasionally limited, therefore further investigations were rationalised by the MDT in keeping with available resources.

Fifteen of 17 patients who remained on the COVID-19 pathway were deemed to be COVID-19 positive by virtue of repeat swab positivity (n=3), positive radiology (n=5), or by having indeterminate radiology in combination with clinical syndromes significantly suggestive of COVID-19 (n=7). Combining these factors suggests a false-negative rate for the initial RT-PCR swabs of 16.67%.

Keeping patients in isolation such as those on the "COVID-19 pathway" in this institution, has significant implications for patient care including access to diagnostics, patient flow through the institution, institutional costs (PPE, cleaning), and infection control measures. In this audit, the mean number of days from first swab to CT was 2.19 days and for those deemed to be COVID-19 negative, 1.35 days from scanning to leaving the pathway. Reported negative likelihood ratios of chest CT in the diagnosis of COVID-19 may be of particular use in determining which patients can be removed efficiently from precautionary isolation. By ensuring diagnostic algorithms used for inpatient assessment adhere as closely as possible to best practice informed by emerging evidence and that adequate access to supporting radiology is efficient, institutions can ensure that patient care is not adversely affected by delayed intervention/diagnostics while minimising unnecessary care costs.

There are a number of limitations in this audit that need to be considered. Although 75% compliance with recommendations was determined, the guidance included in this and other similar guidelines to date are necessarily general until further data regarding utility of specific imaging methods emerge, in particular in the context of RT-PCR-negative COVID-19 cases. The WHO guidance[9] is subcategorised by symptom severity as mild/moderate/severe and patients in this analysis were not specifically given such designations; however, based on symptom criteria cited in the guide[9] and having clinical presentations severe enough to warrant admission, COVID testing and MDT discussion, all patients meet the criteria for "moderate" symptoms at a minimum. Lack of formal designation also limits the interpretation from this analysis of chest CT utility in diagnosis of COVID-19 by symptom severity in the context of negative RT-PCR results.

Furthermore, a limitation in determining the true sensitivity and specificity of chest CT in this audit group is the lack of a reference standard, as it is presumed that the initial negative RT-PCR result could possibly represent be a false negative itself. Fang *et al.*[5] utilised serial sampling as a way of defining which patients became truly positive and this could be used as a prospective method in future studies/audit to aid in this; however, this is not fully reliable, as discussed above due to reported sensitivity rates/timing of testing, etc.

Recommendations

Re-audit of this patient cohort and pathway will be undertaken as further guidelines from the WHO or comparable bodies are issued, to ensure best practice based on the available evidence. Recommendations for future evaluation of this pathway include classification of cases by symptom severity (mild/moderate/severe) to investigate the relative additional value CT imaging provides stratified by disease severity. Additionally, evaluation of benefit derived from chest CT imaging following indeterminate chest radiography will aid in refining patient criteria for this imaging technique. Finally, determining specific criteria for repeat SARS-CoV-2 RT-PCR testing, taking into consideration incidence of disease and community transmission, will further clarify the value of repeat RT-PCR-testing versus further radiological imaging such as chest CT in COVID-19 diagnosis.

In conclusion, a clinical audit was undertaken of the further evaluation of suspected COVID-19 cases with negative SARS-CoV-2 RT-PCR results on oro-nasopharyngeal swabs, in comparison to recommendations set out by the WHO in the June 2020 guidance.[9] At least 75% compliance with recommendations was determined. Chest CT resulted in a positive, indeterminate, and negative rate of 3.79%, 24.1%, and 72.15%, respectively, for COVID-19.

Further evidence is needed to fully determine the utility of chest CT in the diagnosis of COVID-19, in particular in the context of false-negative RT-PCR swab results for SARS-CoV-2. As diagnostic algorithms are refined, patient care, institutional patient flow and infection control measures will improve.

Conflict of interest

The authors declare no conflict of interest.

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