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Cardiothoracic Imaging

Coronavirus Disease 2019 (COVID-19) diagnostic technologies: A country-based retrospective analysis of screening and containment procedures during the first wave of the pandemic

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ABSTRACT

Since first report of a novel coronavirus in December of 2019, the Coronavirus Disease 2019 (COVID-19) pandemic has crippled healthcare systems around the world. While many initial screening protocols centered around laboratory detection of the virus, early testing assays were thought to be poorly sensitive in comparison to chest computed tomography, especially in asymptomatic disease. Coupled with shortages of reverse transcription polymerase chain reaction (RT-PCR) testing kits in many parts of the world, these regions instead turned to the use of advanced imaging as a first-line screening modality. However, in contrast to previous Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome coronavirus epidemics, chest X-ray has not demonstrated optimal sensitivity to be of much utility in first-line screening protocols. Though current national and international guidelines recommend for the use of RT-PCR as the primary screening tool for suspected cases of COVID-19, institutional and regional protocols must consider local availability of resources when issuing universal recommendations. Successful containment and social mitigation strategies worldwide have been thus far predicated on unified governmental responses, though the underlying ideologies of these practices may not be widely applicable in many Western nations. As the strain on the radiology workforce continues to mount, early results indicate a promising role for the use of machine-learning algorithms as risk stratification schema in the months to come.

1. Introduction

In the short while since its first documented appearance in December of 2019, Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has escalated expeditiously to become a worldwide threat to human life and global commerce\textsuperscript{[1,2]}. Originating from the Wuhan Province of China, the virus spread with alarming rapidity in large part due to sustained human-to-human transmission despite arising from zoonotic vectors linked to the province’s Huanan Seafood Market\textsuperscript{[1–5]}. On January 30, 2020, the World Health Organization (WHO) initially declared the local outbreak in China a global health emergency due to increasing need for coordinated international response and containment procedures\textsuperscript{[1,2,6]}. Eventually, on March 11, 2020, unabated spread led the WHO to issue a follow-up statement officially declaring COVID-19 a global pandemic\textsuperscript{[7,8]}. With over 7,000,000 reported cases across 210 countries at the time of this writing, COVID-19 has since claimed over 405,000 lives\textsuperscript{[9]}

Response to the global outbreak has been varied, with many countries employing mitigation strategies ranging from social distancing and travel restrictions to quarantine and contact tracing for known or suspected cases\textsuperscript{[7,10–12]}. Recommendations from the United States (US) Centers for Disease Control (CDC) and the WHO included screening for high priority individuals by reverse transcription polymerase chain reaction (RT-PCR)\textsuperscript{[13,14]}, however implementation of standardized and widespread protocols were hampered in many
countries by cost and availability of medical technologies [7,12,15,16]. Studies initially suggested that chest computed tomography (CT) was actually the most sensitive diagnostic modality, especially in early-stage asymptomatic disease when RT-PCR was prone to false negative results [1,3]. Bilateral ground glass opacities in a peripheral, subpleural distribution were characteristically described, with or without superimposed consolidation (Fig. 1) [1-4,17]. Furthermore, in confirmed COVID-19 cases from China with initially negative RT-PCR results, as many as 70% of patients manifested typical CT findings [18]. Though curiously, despite early data reporting overall sensitivities as high as 98% for chest CT as compared to 71% for RT-PCR [19], more recent iterations of the Diagnosis and Treatment Protocol issued by the National Health Commission and National Administration of Traditional Chinese Medicine have instead deferred to serologic diagnosis without mention of radiographic diagnostic criteria [20]. Yet, as opposed to earlier Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronavirus epidemics, initial chest radiography has proven less useful in early disease and may in fact be normal in up to 20% of cases [1,3,21,22].

Recommendations for implementation of chest CT in COVID-19 screening protocols were initially hindered by cost and scanner availability [18,19]. To this point, cost-effectiveness analyses of chest imaging for lung cancer screening suggest that a single plain film radiograph costs as much as 92 US dollars, with a single chest CT more than quintuple at 527 US dollars [23]. These are in stark contrast to the significantly lower cost of a single RT-PCR test, which can be obtained for as little as 15 US dollars [24]. Moreover, many lower- and middle-income African, Asian, and Latin American countries require technical and financial support to even implement comprehensive RT-PCR testing, let alone capability to provide widespread access to advanced imaging [7,25]. Even in the developed world, Japan far outpaces the field with 101.3 CT scanners per million population, double that of its next closest competitors in the US and Australia. In comparison, Chile and Mexico lag behind at 12.3 and 5.1 CT scanners per million population, respectively [26].

Yet, this must be juxtaposed with the fact that low sensitivity of RT-PCR testing often necessitated multiple negative examinations over time for definitive rule-out of SARS-CoV-2 infection. Thus, overreliance on RT-PCR ran the risk of only further exacerbating testing kit shortages in resource-strapped regions [27]. While some recommendations ideally called for both chest CT and RT-PCR in febrile cases for which there was a high index of clinical suspicion [28], institutional and national protocols were in reality driven by regional availability of resources. Additionally, time to diagnosis was also a factor. Early viral assays took as long as 2 days to return results [29-31], though accelerated development of commercially available real-time RT-PCR testing kits for SARS-CoV-2 have since cut turnaround times to as little as 4–6 h [24,32]. Even still, chest CT can be read within minutes of acquisition [33], making it the most rapidly available screening tool for diagnosing COVID-19. However, institutions must consider that CT suite sanitization protocols can take up to an hour, and screening with advanced imaging places technologists and other staff at risk for nosocomial transmission [34,35]. In this review, we examine implementation of these diagnostic technologies in resource-driven healthcare environments using a targeted, country-centered approach.

2. Lessons from China

Since initiating complete lockdown of the city of Wuhan on January 23 [36], China has, for the most part, managed to contain their viral spread. A host of nationwide precautionary initiatives, including dedicated fever clinics and a vast network of temporary hospitals, helped segregate infected cohorts in designated areas away from susceptible, healthy individuals [37,38]. In Wuhan, authorities went so far as to perform door-to-door health checks and asked local caretakers of large apartment buildings to perform regular temperature checks on residents [37]. During the early days of infection when RT-PCR testing kits were in short supply, suspected cases were triaged by pulse oximetry, complete blood count, and C-reactive protein levels. If febrile, patients were additionally screened with chest CT and nonspecific viral testing. Subsequently, only patients with findings concordant with viral pneumonia received SARS-CoV-2 specific testing [38].

In the province of Zhejiang, government officials heeded the early warning signs from Wuhan and preemptively implemented risk management strategies, even before any cases were confirmed in the region. These included Health QR codes for all travelers in to and out of cities that restricted movement based on perceived infectious risk. Individuals at moderate or severe risk were placed on mandatory 7- and 14-day quarantines, respectively [39]. QR codes were surveilled at regularly interspersed health check points that also required individuals to submit to temperature checks [40]. Nonessential businesses were only reopened systematically based on societal priority. Essential supplies and food were distributed in an organized fashion with governmental oversight [39]. Though perhaps excessive, China has managed to stem the tide of infection, having reported only a modest 0.11% increase in cases in the last 2 weeks [9].

Starting in February, China began rolling out artificial intelligence (AI) platforms in hospitals around the country to support detection of SARS-CoV-2-associated lung changes on CT. Whereas radiologists conventionally spend up to 15 min reading a chest CT, AI-assisted detection algorithms are capable of triaging problem cases in seconds, with accuracies cited as upwards of 90% [33,41,42]. Machine-learning algorithms have even shown promise in segregating COVID-19 from other causes of viral pneumonia, with an area-under-the-curve of 0.78 on external validation testing sets [43]. While quantitative imaging metrics and machine-learning algorithms have for some time shown applicability in a wide range of pathologies ranging from soft-tissue masses to renal cancer, integration of radiomics analyses into clinical workflows is still in its infancy [44-46]. Nevertheless, surging demand for subspecialty-trained cardiothoracic radiologists may necessitate more widespread implementation of computer-aided detection systems as the need for rapid risk prioritization continues to rise [47].

Despite the fact Chinese researchers successfully sequenced SARS-CoV-2 within a week of identifying a novel infectious agent, it was not until a full 2 weeks later that the first testing kits were made available on January 13 [39,48]. Early confirmatory testing required nucleic acid sequencing, which was both costly and time consuming [39]. Thus, initial triage protocols centered around diversion of suspected cases to Fig. 1. 3-Dimensional reconstruction of a chest CT showing bilateral ground glass opacities in a peripheral, subpleural distribution in a COVID-19 patient.
designated healthcare sites that were segregated from the healthy populace. Chest CT and non-specific laboratory testing proved to be valuable first-line screening tools, with specific confirmatory testing by RT-PCR to follow in cases with positive results. Though not a replacement for human radiologist evaluation, early results indicate that AI and machine-learning may come to play a vital role in risk stratification of suspected cases as the burden on the radiology workforce continues to mount. While China’s extreme social mitigation policies proved to be effective containment strategies, implementation was only possible because of homogeneous governmental authority. It is unlikely that these policies will be replicated in Western democracies, which place too much value on individual freedoms and personal privacy [12,38].

3. Lessons from Iran

In Iran, a shortage of RT-PCR testing kits led local medical authorities to establish an imaging-driven triage system, whereby chest CT represented the first-line diagnostic modality [27]. Paradoxically, supply-and-demand factors were such that while the cost of a single RT-PCR test could range anywhere between 3 and 17 US dollars, a single non-contrast chest CT costed as little as 1.5 US dollars. At 6.5 CT scanners per million population [49], chest CT was thus much more widely accessible to the average citizen than RT-PCR testing [50]. However, complex morphological patterns of SARS-CoV-2-associated pneumonia in combination with a paucity of subspecialty-trainedcardiothoracic radiologists led the Iranian Society of COVID-19 Consultant Group to develop a massive teleradiology network to support their increased demands for advanced imaging. In brief, anonymized clinical images are uploaded to WhatsApp social messaging software and subsequently assigned a case number by a volunteer network coordinator. The cases are then shared to a private WhatsApp group, whereby undertrained Iranian clinicians can connect with volunteer subspecialists in North America and the Iranian capital. This system allows Iranian clinicians across the country to access consultative support in real-time while avoiding referrals to tertiary care centers, thereby minimizing unnecessary community exposures [27].

For countries without widely available RT-PCR screening, chest CT provides a reusable testing modality for the diagnosis of COVID-19. Widespread use of CT is primarily limited by scanner availability, subspecialist expertise, and cost; however, costs can be subsidized and expertise can be supported on a global scale, provided there is an existing framework of scanner availability. As of this writing, Iran has managed to level their doubling time of confirmed cases to 47 days, notably 1.1 times that of the US [9]. Though WHO officials have been skeptical that reports from Iran are underestimating the infectious burden, these data nevertheless suggest a promising role for CT-driven triage strategies in supply-restricted regions [51].

4. Lessons from Italy

With almost 34,000 COVID-19-related deaths as of June 9, Italy is currently reporting the fourth-highest death toll in the world [9]. While this number may be somewhat suspect due to heterogeneous reporting of case-fatality rates and difficulties separating deaths due to co-morbidities from deaths due to primary infection [52], it is curious that such a highly-regarded healthcare system has suffered disproportionately. The Italian healthcare system boasts 3.2 hospital beds per 1000 people, notably higher than the US, which stands at 2.8 beds per 1000 people [53]. Italy is also ranked in the top 10 of all European nation in critical care beds at 12.5 per 100,000 capita, for which the European average stands at 11.5 beds per 100,000 capita [54]. However, progressive healthcare privatization over the years combined with governmental decentralization ultimately inhibited the nation’s ability to implement early coordinated mitigation measures, contact tracing, and isolation efforts [55,56]. Though a state of emergency was declared on January 31, 1 day after first viral detection, it was not until March 9 that the country issued nationwide lockdown orders [54,57]. Additionally, severe shortages of personal protective equipment have also exacerbated viral spreading among healthcare workers, who carry an estimated 9% of the country’s total infectious burden [52,58].

The “Vò Experiment” made headlines in late winter, whereby scrupulous mass testing and isolation protocols were seemingly able to eradicate the virus in a matter of days. Beginning March 6, researchers from the University of Padua and the Red Cross began testing every citizen living in the town of Vò, regardless of symptoms. It was discovered that 3% of the population was carrying the virus at that time, with about half of them in the asymptomatic phase. Retesting after strict quarantine measures revealed over 90% drop in viral positivity over the ensuing days [59–63]. While nearly impossible to replicate, the Vò Experiment lends credence to the mantra that appropriate testing and isolation measures do, in fact, drastically impact viral spread if implemented on a large enough scale. Given concerns over low specificity of chest CT, specifically in patients with pre-existing pulmonary conditions, many Italian medical practitioners have instead relied heavily on RT-PCR as their first-line screening tool [64].

Italy has also faced a problem of unequal distribution of resources. Despite a national tally of 33.3 CT scanners per million population [26], many of the country’s resources are clustered in the richer northern and central regions, which collectively yield 40% of the Gross Domestic Product [53,65]. However, in regions where chest CT is not easily accessible in the emergency department setting, lung ultrasound has shown promise in detecting COVID-19-associated lung changes. Preliminary data have suggested that findings of diffuse B-pattern with spared areas correlate well with chest CT positivity. Given that lung ultrasound has for some time been a useful adjunctive imaging modality in acute respiratory failure, point-of-care testing may come to serve as an invaluable detection tool in regions without readily available access to alternative modalities [66].

It is apparent that social distancing and isolation measures do work, however implementation of effective mitigation strategies is contingent upon strong governmental frameworks with centralized authority. While screening and isolation of asymptomatic carriers may be an effective containment strategy, this methodology is inhibited by practical considerations and testing kit availabilities. In regions for which there is not an existing framework of CT scanner availability, lung ultrasound has preliminarily delivered promising results as an alternative imaging modality for the diagnosis of COVID-19 [66].

5. Lessons from South Korea

By March, South Korea had become one of the hardest hit countries after a superspreading event resulted in close to 4000 cases in the country’s third largest city of Daegu [67,68]. After the index case for this infectious cohort tested positive for COVID-19 on February 23, the number of daily new confirmed cases began increasing exponentially, eventually peaking on February 29 at 909 [9,29,68]. Even so, by March 16, the number of daily new confirmed cases had fallen sharply to 74 [29], attributed in large part to the government’s rapid implementation of widespread RT-PCR testing, strict isolation measures, and extensive contact tracing [69,70]. Accelerated production of emergency diagnostic kits combined with drive-through and walk-through testing centers allowed South Korea to administer up to 20,000 tests per day [71,72]. Notably, South Korea’s success with using RT-PCR as the primary first-line screening diagnostic – almost to the exclusion of chest CT – was predicated upon strict isolation policies and national legislation which allowed the government to track and make public the movements of infected individuals prior to the onset of symptoms [29,69,73].

Despite South Korea’s heavy reliance on RT-PCR, clinicians are also actively incorporating machine-learning algorithms from China to facilitate computer-aided detection of COVID-19 on chest CT in hospitalized patients [74]. Additionally, South Korea is even expanding their
use of AI to encompass analysis of chest X-ray. Developed by Lunit, a Seoul-based AI company, INSIGHT CXR is capable of detecting lung nodules, consolidation, and a host of other radiologic findings, with reported accuracies as high as 99%. Since releasing their software online free of charge, Lunit's INSIGHT CXR has also been deployed in hospitals in Brazil, where it has already been analyzed over 3000 chest X-rays. While low sensitivity of chest X-ray by human radiologist assessment alone may be prohibitive to its use as a primary screening tool [1,3], bolstering radiographic assessment with AI-driven decision support tools may be vital to preserving hospital resources and CT scanner availability. Nonetheless, further study is needed to confirm generalizable applicability in clinical practice.

The success of South Korea's mass screening by RT-PCR was contingent upon emergency governmental powers that allow for detailed contact tracing. Travel logs compiled by accessing personal data, such as credit card transactions and cellular phone locations by global positioning systems, allowed for the generation of publicly accessible infection maps. Individuals were encouraged to self-monitor for exposure risks and seek testing as appropriate. Such a coordinated effort was only possible with the help of overwhelming public backing, whereby 78.5% of respondents voiced support in favor of foregoing personal privacy to help curb the pandemic [69,75]. South Korea's successful expansion and implementation of AI-driven computer-aided detection systems to the realm of chest X-ray is further indication that decision support tools may be key in mitigating strain on the radiology workforce. Export of accurate and efficient computer-aided detection systems may lend invaluable support to developing countries during this pandemic, who are at baseline operating in resource-scarce practice environments.

6. Lessons from other countries

6.1. Turkey

Less than 2 weeks after millions gathered for an in-person prayer ceremony on March 13, an explosion of cases left Turkey scrambling to ramp up RT-PCR testing [76,77]. Costs and acquisition time limited the use of chest CT, however researchers are actively developing X-ray based convolution neural networks to aid in rapid detection and triage [78]. Perceived lack of government transparency has only further exacerbated poor public compliance with social mitigation measures in the wake of exponentially rising case numbers [77].

6.2. Japan

The Diamond Princess cruise ship that docked in Yokohama, Japan on February 5 was infamously quarantined for 2 weeks after an onboard traveler from Hong Kong tested positive for SARS-CoV-2 [29,79]. Accounting for nearly 700 cases [29], the Diamond Princess cruise ship was an unexpected observational cohort of a homogenously infected group of people. Analysis of transmission dynamics aboard the ship indicated that screening and prioritization of high-risk groups by RT-PCR with subsequent quarantine measures substantially decreased the effective reproduction number [79]. Yet curiously, the Japanese government has been hesitant to implement any sort of widespread screening protocol, throwing up numerous bureaucratic barriers and highly restrictive eligibility criteria to allow an individual to qualify for an RT-PCR test [80]. Use of imaging appears to be inconsistent at best [81], and official guidelines at this time are virtually nonexistent.

6.3. Germany

A Letter to the Editor of European Radiology from Beijing radiologists recommending for chest CT as a first-line screening diagnostic in major epidemic areas was not supported by joint guidelines published by the European Society of Radiology and the European Society of Thoracic Imaging [82]. The joint consensus statement states that while chest CT findings may be suggestive of COVID-19, final diagnosis must be made with RT-PCR, and that negative findings should be followed-up by repeat RT-PCR in highly suspect cases [83]. In accordance with recommendations from the European Centre for Disease Prevention and Control [84], Germany has ramped up their RT-PCR testing capacity to an excess of 50,000 tests per day [85]. How these recommendations will hold up if and when RT-PCR testing kit supplies begin to dwindle remains to be seen.

6.4. Canada

Canadian society guidelines are mostly concordant with the WHO recommendations for primary screening of suspected cases by RT-PCR. Furthermore, the Canadian Society of Thoracic Imaging also put forth a position statement that chest CT should not be used routinely for rule-out of COVID-19 [86]. Nevertheless, chest CT has been utilized to monitor disease progression in hospitalized patients and as auxiliary testing in cases for which there is a high index of suspicion following negative RT-PCR screen [87,88].

6.5. Thailand

Currently, Thailand's RT-PCR maximum testing capacity stands at 8804 tests per day [9]. Yet, production of over-the-counter IgG and IgM antibody tests for SARS-CoV-2 are reportedly ready for implementation and deployment. These screening tests are capable of delivering at-home results in as little as 15 min, and claim to more precisely identify high-risk individuals in need of follow-up testing [89,90]. Though Thailand Medical News published an article in late February encouraging citizens to seek out chest CT if they had concern for SARS-CoV-2 exposure [91], local medical authorities have been more conservative and have instead cautioned against the use of chest CT to rule out the presence of disease [92].

7. Updates from the United States

As of June 9, the total number of confirmed COVID-19 cases in the US has eclipsed the rest of the world at 1,961,185 [9]. In recent months, the US has, unfortunately, struggled with many of the same challenges as Italy in mounting a homogenous governmental response. Conflicting guidelines and regional resource availability forced many institutions to internally devise their own policies and screening protocols, resulting in a patchwork of inconsistent practices regarding appropriate use of diagnostic technologies around the country [15,93–97,103]. Due to concerns over specificity of findings and unclear effect on clinical outcomes, the American College of Radiology is currently recommending against the use of both chest X-ray and chest CT to screen for COVID-19 [95]. Moreover, inconsistent health insurance coverage of inflated consumer costs severely limited the use of chest CT as a frontline diagnostic; however, a lack of centralized coordination and slow ramp up of testing capacity during the early days of the pandemic resulted in wait times for RT-PCR results on the order of multiple days [98]. Combined with severe testing kit shortages in many states, a number of institutions were forced to begin diagnostic workflows with some kind of chest imaging – often chest X-ray – while awaiting definitive confirmatory testing [15,97,99]. While this may have proved to be a useful practice in places such as New York, where patients without severe features were instructed to self-isolate at home, the utility of first-line screening with chest X-ray was less clear in regions where patients were encouraged to present earlier in the disease course. In departure from many other published guidelines, consensus recommendations from the Fleischner Society do endorse use of chest imaging to support rapid triage of patients in resource-limited environments in which point-of-care SARS-CoV-2 testing is not available [96]. Despite low sensitivities for initial diagnosis, emerging data has suggested a role for the use of chest X-ray in severity scoring and
outcome prediction in younger populations [100]. Yet, as countless continue to gather en masse nationwide to protest police brutality, many officials fear triggering a second wave reminiscent of the superspreader event that propagated the virus in South Korea in February [67,101,102]. As the pandemic continues to unfold, the need for streamlined communication and unified decision making regarding best practices among leading authorities has never been clearer.

8. Conclusion

Diagnosis of COVID-19 is challenging, much in part due to a prolonged asymptomatic phase and a lack of consensus surrounding appropriate use of diagnostic technologies. RT-PCR has been considered the gold standard, however suboptimal sensitivity in early disease and regional shortages of testing kits have limited its use. Early data suggested that chest CT offered superior sensitivity for the diagnosis of COVID-19, though its use was constrained by cost, concerns for undue radiation burden, subspecialist expertise, and scanner availability. Institutions must consider regional availability of resources and cost when determining universal screening protocols. No matter the choice of screening tool, social mitigation measures and containment procedures upon positive case identification are essential to curtailting uncontrolled viral spread.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Author contributions

BKF and NLD drafted the manuscript with support from AG, who conceived the idea. BKF and NLD contributed equally to the work and should be considered as co-first authors.

The authors declare that they had full access to all of the data in this study and the authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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