

Coronavirus Pandemic

Application of deep learning-based diagnostic systems in screening asymptomatic COVID-19 patients among overseas returnees

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Abstract

Introduction: Our study aimed to investigate the performance of deep learning (DL)-based diagnostic systems in alerting against COVID-19, especially among asymptomatic individuals coming from overseas, and to analyze the features of identified asymptomatic patients in detail.

Methodology: DL diagnostic systems were deployed to assist in the screening of COVID-19, including the pneumonia system and pulmonary nodules system. 1,917 overseas returnees who underwent CT examination and rRT-PCR tests were enrolled. DL pneumonia system promptly alerted clinicians to suspected COVID-19 after CT examinations while the performance was evaluated with rRT-PCR results as the reference. The radiological features of asymptomatic COVID-19 cases were described according to the Nomenclature of the Fleischner Society.

Results: Fifty-three cases were confirmed as COVID-19 patients by rRT-PCR tests, including 5 asymptomatic cases. DL pneumonia system correctly alerted 50 cases as suspected COVID-19 with a sensitivity of 0.9434 and specificity of 0.9592 (within 2 minutes per case); while the pulmonary nodules system alerted 2 of the 3 missed asymptomatic cases. Additionally, five asymptomatic patients presented different characteristics such as elevated creatine kinase level and prolonged prothrombin time, as well as atypical radiological features.

Conclusions: DL diagnostic systems are promising complementary approaches for prompt screening of imported COVID-19 patients, even the imported asymptomatic cases. Unique clinical and radiological characteristics of asymptomatic cases might be of great value in screening as well.

Advances in knowledge: DL-based systems are practical, efficient, and reliable to assist radiologists in screening COVID-19 patients. Differential features of asymptomatic patients might be useful to clinicians in the frontline to differentiate asymptomatic cases.

Key words: Deep learning; diagnostic systems; performance evaluation; COVID-19; asymptomatic cases.

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Introduction

Since December 2019, Coronavirus Disease 2019 (COVID-19) has broken out in many countries, and to date, over 37 million people have been diagnosed with COVID-19 globally [1]. Given the limited medical resources to accurately distinguish COVID-19 in developing countries, medical workers and researchers from all over the world utilized multiple approaches and techniques to cope with this pandemic, including data-driven artificial intelligence (AI) techniques represented by deep learning (DL) algorithms. DL has previously been applied to handle various tasks related to medical image analysis, such as automatic calcium

scoring based on CT [2] and breast cancer screening [3]. In the face of COVID-19, DL also shows great potential to assist frontline clinicians as an alternative initial screening and triage tool for COVID-19 [4-6], especially in combination with computed tomography (CT) examination. For example, previous studies showed that the DL model was a promising complementary diagnostic method for the early screening of COVID-19 patients [7-9], and could also facilitate the triage of suspected patients and aid the analysis of lesions based on CT [10]. Although over 200 prediction models to support decision-making in COVID-19 patients were developed [11], few of them

were deployed and validated in real-world clinical settings.

According to WHO, China, the Republic of Korea and some European countries have controlled the pandemic (current cases < 2500) [1]. For these countries, the prevention of widespread community transmission or the second outbreak caused by imported COVID-19 cases has become the current focus. Identifying asymptomatic COVID-19 cases is one of the keys to preventing imported cases-induced SARS-CoV-2 transmission [12-14]. Asymptomatic COVID-19 cases refer to SARS-CoV-2 infected patients without clinical symptoms, such as fever, cough, or fatigue. Although these individuals appear normal, they still carry the SARS-CoV-2 virus and are infectious to other people [15]. Given that nodular lesions might be an early manifestation of asymptomatic patients [16,17], a CT-based DL pulmonary nodule diagnostic system might also come in handy.

In this study, commercially available DL systems were implemented into clinical practice to screen COVID-19 cases among returnees from overseas who underwent routine examination after landing in our hospital and were evaluated according to the rRT-PCR test results. In addition to validating the performance of DL systems as initial screening tools in real-world scenarios, clinical features of identified asymptomatic overseas returnees were then analyzed in detail to gain more understanding of asymptomatic patients.

Methodology

Patients

A total of 1,917 returnees from overseas who underwent SARS-CoV-2 rRT-PCR tests and CT examinations in Beijing Xiaotangshan Hospital between March 16th and April 5th, 2020, were enrolled in this study. Epidemiological history, laboratory examination, treatment strategy, and prognosis were collected from the electronic medical records system.

CT Acquisition

All overseas returnees underwent CT examinations on the same day they underwent rRT-PCR testing for SARS-CoV-2 infection. In particular, multi-slice spiral CT low-dose scans were performed using the uCT760 (United Imaging, Shanghai, China), optimaCT680, or Brightspeed (GE Healthcare, Madison, WI, USA) instruments. The scanning parameters were as follows: tube voltage, 80-120KV; current, automatic exposure control, which usually ranged from 40 mA to 64 mA; reconstruction slice thickness, 1.25 mm; and interslice

gap, 1.25 mm. All CT scans were saved in the picture archiving and communication system, which was connected to the server of the DL systems.

DL Diagnostic Systems

Two commercially available DL diagnostic systems were utilized in our study, including the pneumonia system (InferRead CT Pneumonia, Infervision Medical Technology Co., Ltd, Beijing, China) and pulmonary nodules system (InferRead CT Lung, Infervision Medical Technology Co., Ltd, Beijing, China). Both DL diagnostic systems take CT images as input and output notifications and measurements of pneumonia or pulmonary nodular lesions. In particular, InferRead CT Pneumonia is a U-Net-based deep learning model that trained on more than 2000 scans from patients with rRT-PCR test results. The pneumonia system could segment abnormalities related to COVID-19 on chest CT scans at the pixel level, then flag suspected COVID-19 patients and provide automatic quantification analyses of lesions, in turn, serves as the screening and triage tools. InferRead CT Lung was modified from a Faster R-CNN network and trained on more than 11,000 chest CT scans to detect different types of pulmonary nodules. Training details and model performance of these two systems were previously described [10,18,19].

Study Workflow

As a designated hospital for screening imported COVID-19 in Beijing, DL diagnostic systems mentioned above were deployed and used to screen suspected cases of COVID-19 in the clinical workflow.

CT scans of all participants were directly sent to the DL systems server for analyses after the examination. Technicians are alarmed usually within 2 minutes once suspected patients with pneumonia lesions were detected; Pulmonary nodules were also acquired from the pulmonary nodules system as previous studies showed that pulmonary nodules might be the early manifestation of COVID-19 [16,17]. The performance and competence of the DL pneumonia system to identify suspected cases were assessed by referring to the results of rRT-PCR tests. The complementary roles of the pulmonary nodules system for early nodular manifestation were also discussed. Meanwhile, asymptomatic patients were identified by comparing the clinical symptoms with the rRT-PCR test results. Finally, the radiological features of identified asymptomatic patients were verified and described by three experienced radiologists with 10, 15, and 25 years

of experience according to the Nomenclature of the Fleischner Society [20].

IRB approval statement

The present study was approved by the Ethics Committee of Beijing Xiaotangshan Hospital (No.4 2020). Requirements for informed written consent were waived for emerging infectious diseases.

Results

Evaluation of DL systems in screening COVID-19 patients

Among the 1,917 participants, 53 patients were eventually confirmed as COVID-19 positive by rRT-PCR tests, accounting for 2.8% of the screened population. Five asymptomatic cases were identified in total. Accordingly, the DL pneumonia system correctly alerted 50 of them as suspected pneumonia cases on the day of admission, including two asymptomatic cases, presenting a high detection sensitivity of 0.9434 (95% CI [0.8434, 0.9882]) and specificity of 0.9592 (95% CI [0.9492, 0.9677]). Meanwhile, the DL pulmonary nodular system also alerted the radiologist to two of the three missed asymptomatic COVID-19 patients with nodular lesions. The results indicated the potential of DL systems in screening asymptomatic cases.

Radiological features of asymptomatic COVID-19 patients

Of the five identified asymptomatic COVID-19 patients, four were flagged by the DL systems because of either pneumonia lesions or pulmonary nodules. As for two cases with pneumonia lesions, one was characterized by multiple ground-glass shadows involving many lobes and segments, and the other case was characterized by ground-glass opacities along the

pleural region with thickening of blood vessels and grid shadows in the posterior basal segment of the left lower lobe. The rest three cases exhibited chest abnormalities other than pneumonia and showed no obvious progression or absorption in subsequent CT examination(s). In this study, no lymphadenopathy or pleural effusion was found on CT examination in any patient. Considering the different CT imaging presentations in each case, detailed features were analyzed case by case.

Case 1

A 9-year-old boy who returned from the United Kingdom presented a patchy shadow with partial consolidation in the medial segment of the right middle lung on initial CT examination (Figure 1). Three days later, subsequent CT re-examination revealed no changes in these lesions, suggesting that it was an old lesion instead of inflammation.

Case 2

A 38-year-old man who returned from Serbia exhibited multiple patchy ground-glass opacities in both lungs on admission (Figure 2A). The DL pneumonia system raised an alert for suspected COVID-19 (Figure 2B). After two days of treatment, increased density was observed in the first subsequent CT scan; two days later, the lesion density and area were significantly reduced. Six days later, the lesion was almost completely absorbed on CT imaging (Figure 2A). The dynamic change in lesion volume was monitored quantitatively using the DL pneumonia system (Figure 2C).

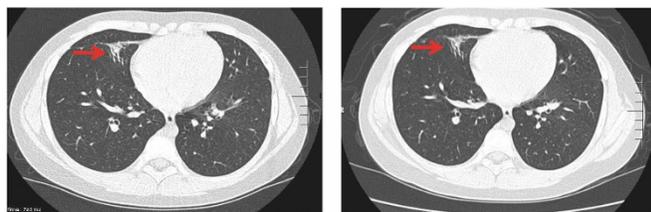
Case 3

A 10-year-old boy, who was a family member of case 2, was likely to have a small hard nodule in the lower lobe of the left lung (Figure 3). No further CT examinations were performed due to the stable condition of the patient. The DL pulmonary nodules system detected the nodule and alerted the radiologists.

Case 4

A 20-year-old woman, who returned from the United States, exhibited micro-nodules in both lungs, which were also detected by the DL pulmonary nodule system (Figure 4A and B). No visible changes were observed by the naked eye on the following CT re-examination. Meanwhile, the DL pulmonary nodules system also revealed no significant changes quantitatively. Given that, the possibility of an infected lesion could be ruled out.

Figure 1. Chest computed tomography (CT) scans for the patient in Case 1.

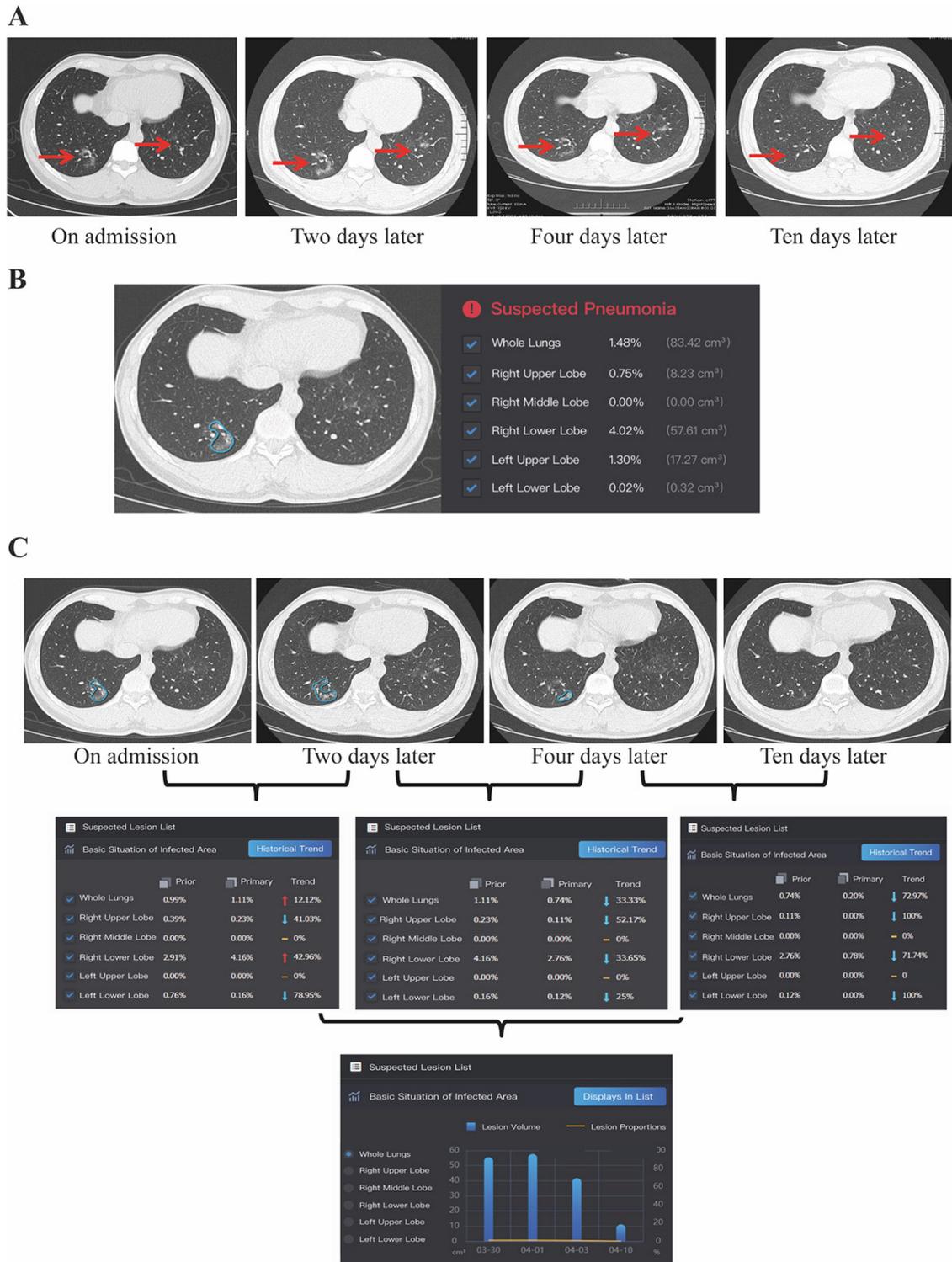


On admission

Three days later

He presented a patchy shadow with partial consolidation in the medial segment of the right middle lung on the initial CT examination (A); Three days later, no changes were observed in this lesion, such as progression or absorption (B).

Figure 2. Chest CT scans and DL diagnostic system alerts for the patient in Case 2.



(A) He demonstrated multiple patchy ground-glass opacities in both lungs on admission, followed by increased density and volume, reduction of density and volume, and absorption. (B) DL pneumonia system raised an alert for suspected COVID-19. Detailed abnormality proportions in the whole lungs, right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe were calculated. (C) DL pneumonia system monitored the dynamic change of lesion volume quantitatively. Detailed abnormalities alteration proportions in the whole lungs, right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe were calculated and compared between every two consecutive CT examinations; the overall trend was plotted as well.

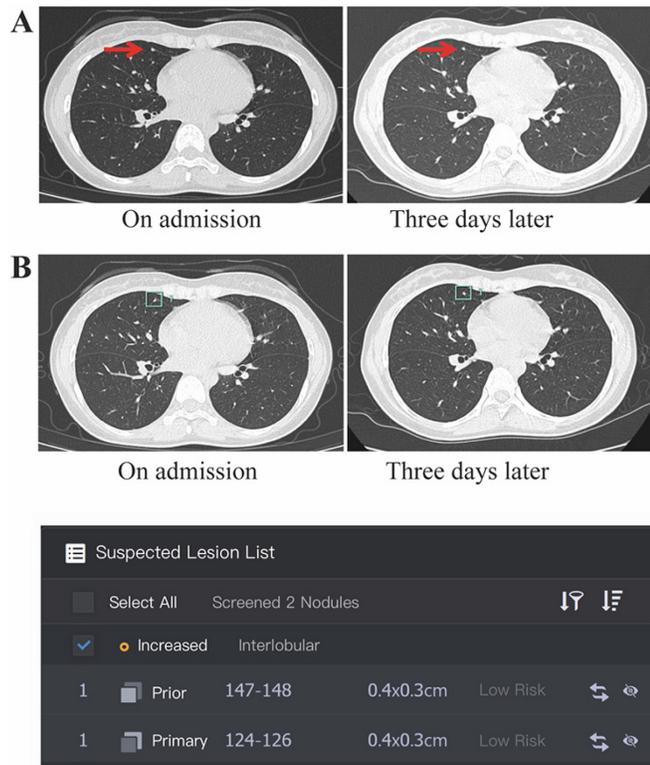
Case 5

A 57-year-old woman, who also returned from the United States, exhibited ground-glass opacities along the pleural region with thickening of blood vessels and a grid shadow in the posterior basal segment of the left lower lobe (Figure 5A). The DL pneumonia system raised an alert for suspected COVID-19 (Figure 5B). Lesion density and area visibly increased on subsequent CT examination two days later and gradually decreased (Figure 5A). The dynamic changes in lesion volume were monitored quantitatively by the DL pneumonia system and it gradually reduced (Figure 5C).

Clinical features of Asymptomatic COVID-19 Patients

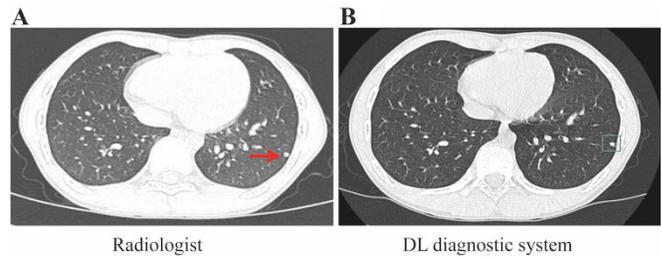
As for epidemiological history and laboratory examination tests, all but case 4 had a clear contact history with a confirmed COVID-19 patient(s) (Table 1). SARS-CoV-2 rRT-PCR tests were all positive upon admission. Only cases 2 and 5 were positive for serum immunoglobulin (Ig)G in the COVID-19 IgG and IgM rapid tests (Table 2).

Figure 4. Chest CT scans and DL diagnostic system prediction for the patient in Case 4.



The patient had micro-nodules in both lungs and no obvious volumetric changes were observed between CT examinations (A) which was quantitatively confirmed by DL pulmonary nodules system as well (B). Of note, the subtle changes (7mm³) reported by the system were within the measurement error tolerance scope.

Figure 3. Chest CT scans and DL pulmonary nodules system prediction for the patient in Case 3.



The patient had a small hard nodule in the lower lobe of the left lung (A). DL pulmonary nodules system detected the nodule and alerted the radiologist (B).

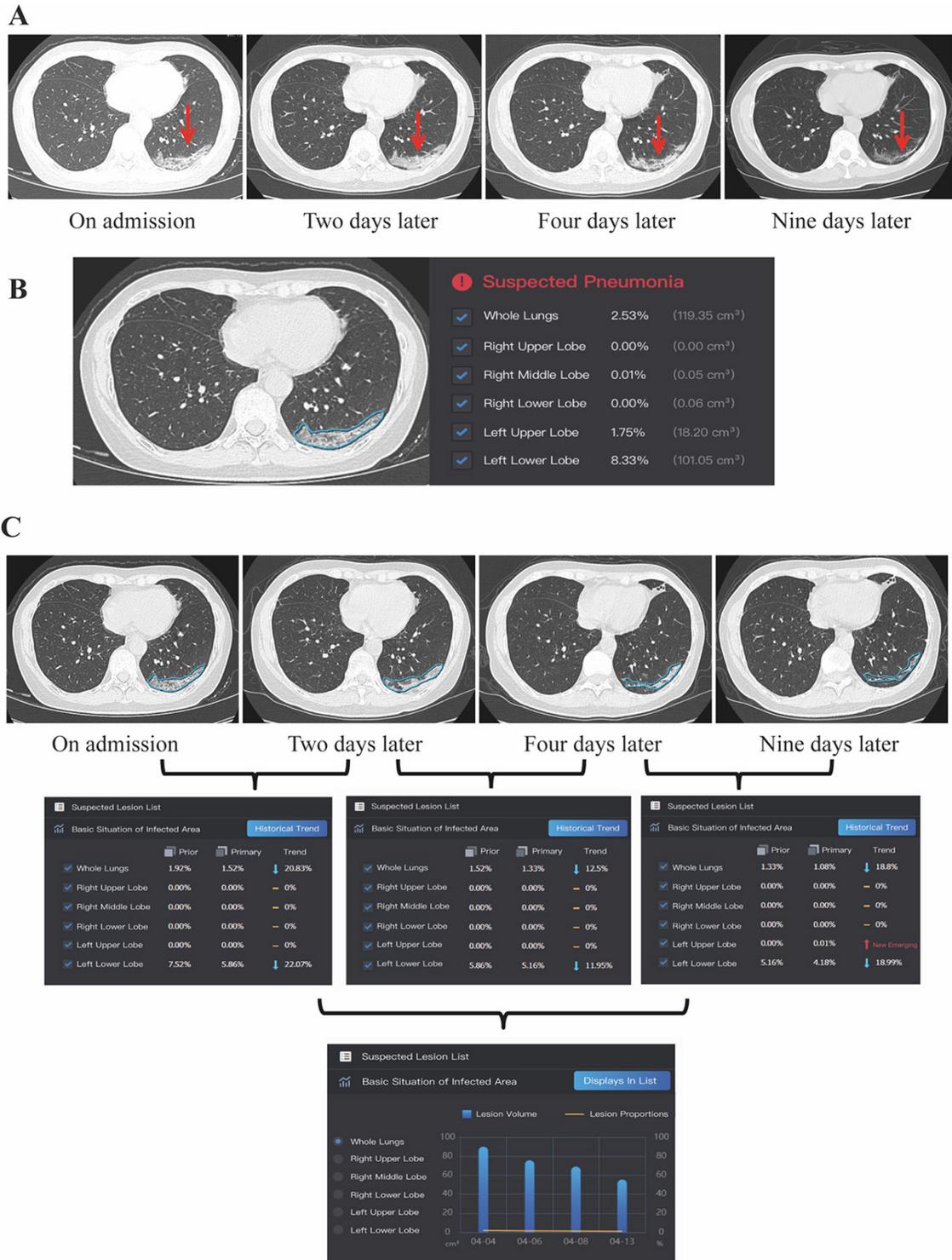
Laboratory examination revealed that the white blood cell (WBC) count and lymphocyte count were normal, while the neutrophil count in case 4 decreased. In addition, elevated levels of creatine kinase were observed in four of the five cases, while an increased level of lactate dehydrogenase was observed in three cases. Notably, prothrombin time was prolonged in all 5 cases; activated partial thromboplastin time was prolonged in three cases. C-reactive protein (CRP) levels were normal in all five cases, and D-dimer levels were elevated in two cases. Detailed laboratory examination information is summarized in Table 3.

With active treatment during quarantine, all five cases were discharged after several consecutive negative rRT-PCR test results.

Discussion

The practice has demonstrated that active prevention and control measures are the most trustworthy approach to containing the COVID-19 pandemic. With regard to countries where the COVID-19 pandemic was largely under-controlled, asymptomatic individuals and imported COVID-19 patients introduced new risks for a second-wave outbreak of the disease. As for other countries that still fight with the pandemic, early identification of asymptomatic patients could also contribute to disease prevention and control. However, the screening of asymptomatic or pre-symptomatic individuals brought even more challenges to current medical resources and workflow, as rRT-PCR tests require a large amount of manpower and resources, as well as a relatively long time. Thus, in the case of insufficient resources, patients with clinical symptoms or/and epidemiological contact history would undergo an rRT-PCR test preferentially.

Figure 5. Chest CT scans and DL diagnostic system alerts for the patient in Case 5.



Ground glass opacities along the pleural with thickening blood vessels and grid shadow were observed in the posterior basal segment of the left lower lobe (A). DL pneumonia system raised an alert for suspected COVID-19; detailed abnormality proportions in the whole lungs, right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe were calculated (B). DL pneumonia system monitored the dynamic change of lesion volume quantitatively; detailed altered abnormalities proportions in the whole lungs, right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe were calculated and compared between every two consecutive CT examinations; the overall trend was plotted as well (C).

Under such considerations, CT is an immensely helpful tool to complement the rRT-PCR tests [8,9] and dozens of CT-based artificial intelligence models were developed [11]. Unlike research on model development, we validated the performance of DL algorithms in real-world clinical settings and explored potential efficient (asymptomatic) COVID-19 screening workflow by implementing robust DL diagnostic systems in our clinical workflow to screen suspected patients based on chest CT scans, identified

asymptomatic patients, and then analyzed collected information of these asymptomatic patients in this study. It turned out that the DL pneumonia system showed high sensitivity to alert suspected patients with radiological features (50/53) and also identify asymptomatic patients with abnormalities on CT scans. In addition, DL pulmonary nodules system could complementarily flag asymptomatic patients presenting pulmonary nodules on CT scans, which are potential early manifestations of COVID-19 according to

Table 1. Clinical characteristics and demographics of asymptomatic COVID-19 cases.

Clinical characteristics	Case1	Case2	Case 3	Case 4	Case 5
Age, years	9	38	10	20	57
Sex	Male	Male	Male	Female	Female
Source	UK	Serbia	Serbia	USA	USA
Exposure to infected patients	Yes	Yes	Yes	No	Yes
Vital signs on admission					
Temperature, °C	36.9	37.1	36.7	36.4	36.9
Respiratory rate, breaths/min	22	19	22	19	20
Pulse oximeter O ₂ saturation, %	98	99	97	97	98
Systolic blood pressure, mmHg	115	131	118	119	113
Heart rate, beats/min	105	78	100	122	106

Table 2. SARS-CoV-2 test results of asymptomatic COVID-19 cases.

Tests for SARS-CoV-2 on admission	Case1	Case2	Case 3	Case 4	Case 5
PCR of throat swab	+	+	+	+	+
Serum immunoglobulin G	-	+	-	-	+
Serum immunoglobulin M	-	-	-	-	-

Table 3. Laboratory results of asymptomatic COVID-19 cases.

Laboratory findings on admission	Case 1	Case 2	Case 3	Case 4	Case 5	Normal range
White blood cell count, × 10 ⁹ /L	6.8	4.2	4.8	4.2	5.5	3.5-9.5
Neutrophil count, × 10 ⁹ /L	3.3	2.1	2.0	1.6 (↓)	3.8	1.8-6.3
Lymphocyte count, × 10 ⁹ /L	2.8	1.7	2.2	2.2	1.4	1.1-3.2
Hemoglobin, g/L	129	146	142	148	115	Female 115-150; Male 130-175; Child 120-140
Platelet count, × 10 ⁹ /L	310	273	252	239	283	125-350
Albumin, g/L	45.8	41.9	45.4	44.6	60.0 (↑)	40-55
Alanine aminotransferase, U/L	13.4	18.2	23.7	10.0	14.7	7-40
Aspartate aminotransferase, U/L	18.6	20.7	31.3	16.0	20.3	13-35
Total bilirubin, μmol/L	12.9	7.5	9.1	7.9	10.2	1.7-23
Potassium, mmol/L	4.6	4.7	4.9	4.6	4.1	3.5-5.3
Sodium, mmol/L	138.4	140.6	140.8	138.9	142.9	137-147
Creatinine, μmol/L	44.9	78.9	60.4	51.6	65.3	41-73
Creatine kinase, U/L	NA	51.8 (↑)	61.8 (↑)	40.0 (↑)	38.6 (↑)	13-35
Lactate dehydrogenase, U/L	205 (↑)	138	221 (↑)	158	219 (↑)	40-200
Cardiac Troponin I, pg/mL	0.01	0.01	0.01	0.01	0.01	0-0.04
B-type natriuretic peptide, pg/mL	12.9	13.5	10.0	10.0	10.0	0-95.5
Creatine kinase muscle-brain, U/L	8.2	7.3	11.0	8.8	9.0	0-24
Prothrombin time, s	14.3 (↑)	13.8 (↑)	14.4 (↑)	13.6 (↑)	13.1 (↑)	9.1-12.1
Activated partial thromboplastin time, s	42.9 (↑)	39.0 (↑)	36.4	43.7 (↑)	33.2	25.4-38.4
D-dimer, mg/L	220	250 (↑)	240 (↑)	220	220	0-231
Procalcitonin, ng/mL	NA	0.03	0.04	0.03	0.03	0-0.05
C-reactive protein, mg/L	0.6	1.1	0.1	0.7	0.8	0-6
Erythrocyte sedimentation rate, mm/hour	5	2	2	11	14	0-20

previous studies [16,17]. DL systems also help us with the quantification of chest lesions and therefore assist in the monitoring of disease progression.

Moreover, unique features and characteristics of asymptomatic cases are also valuable reference for frontline clinicians but are currently insufficiently described; whether imported cases exhibit the same features also remains unclear. Thus, we roundly described and analyzed the chest CT features, epidemiology history, and laboratory results of five identified imported asymptomatic cases.

Typical laboratory examination results for COVID-19 patients included increased or normal white blood cell count and decreased lymphocyte count. Some patients presented increased levels of creatine kinase, aminotransferases, and hemoglobin. C-reactive protein and erythrocyte sedimentation rates are increased in most cases, while D-dimer levels are elevated in individuals with severe COVID-19 [21]. In contrast, we observed an elevated level of creatine kinase and prolonged prothrombin time, instead of WBC count, lymphocyte count, or CRP level. Two individuals who returned from the United States exhibited increased D-dimer levels. In a previously published study [22], 55 asymptomatic patients who eventually developed mild, moderate, and severe COVID-19 during hospitalization exhibited typical laboratory examination results, to some extent, indicating the atypical results we observed may be representative of real asymptomatic COVID-19 cases. However, more cases need to be studied to further confirm this hypothesis.

Of note, approximately 97% of COVID-19 patients exhibited chest abnormalities, including multiple bilateral and peripheral ground-glass opacities and consolidation [23,24]. Consistent with a local study (50%) [25], we found that 40% of imported asymptomatic COVID-19 cases also exhibited typical presentations on chest CT imaging. One case featured multiple patchy ground-glass shadows, a typical early manifestation of COVID-19. The other presented ground-glass opacities with focal grid shadow and thickening of blood vessels; further progression and absorption were also consistent with the reported pattern of disease progression [15]. Of note, both patients were alerted as suspected COVID-19 by the DL pneumonia system. Although the rRT-PCR test for SARS-CoV-2 served as the gold standard diagnostic approach, false-negative results and time consumption still resulted in certain hidden dangers, especially with regard to asymptomatic patients. Given the presence of features of viral pneumonia on chest CT images of asymptomatic cases, the tandem DL-CT approach

demonstrated significant potential and value in complementing rRT-PCR testing.

In addition, we identified COVID-19 patients without either viral pneumonia abnormalities in the lungs or clinical manifestations, which accounted for 0.16% of the studied population. Notably, the DL pulmonary nodules system could detect old lesions or suspected early-stage infected lesions. By measuring lesion progression or absorption quantitatively, it is possible to detect the presence of early-stage infection and resulting lesions. As such, the modality demonstrated its utility and efficiency in this regard.

Our study had some limitations, the first of which was the selection bias that may be introduced by the screening criteria or treatment precautions, for example, clinical manifestation based on patients' self-description. More objective inclusion and exclusion criteria could be considered in future work. In addition, the DL systems only screened a small cohort coming from real-world scenarios in this study. To better evaluate the capabilities of the DL systems, the larger testing set containing more positive cases could be used to assess its performance.

Conclusions

The DL systems together serve as a reliable assistant for clinicians to screen COVID-19, even asymptomatic cases, based on either pneumonia lesions or other abnormalities like nodules on CT scans. Relatively atypical laboratory examination results were described in detail for asymptomatic cases, which could also be valuable for future early screening.

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