COVID-19 Diagnosis

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3.1 Laboratory Testing for SARS-CoV-2 Infection

Hui Xing

Laboratory indicators can be used as the basis for the diagnosis, treatment, judgment of treatment efficacy, and prognosis of patients infected with SARS-CoV-2. Currently, the general laboratory indicators include nucleic acid tests, serum antibody tests, immunological tests, hematological tests, and bacteriological and mycological tests. The rational use of laboratory indicators is of great significance in guiding clinical diagnosis and treatment. Meanwhile, the laboratory staff should be careful to determine biosecurity measures to avoid infection based on the operational risk level of different test items.

3.1.1 Nucleic Acid Test

3.1.1.1 Sample Collection

Nucleic Acid Test (NAT) is the gold standard for diagnosing viral pneumonia caused by SARS-CoV-2 infection. Qualified specimens are a prerequisite for NAT. Wearing personal protective equipment (PPE) is required to collect specimens from patients infected with SARS-CoV-2. Specimens shall be obtained from the upper respiratory tract (nasopharyngeal swab, nasopharyngeal extract), the lower respiratory tract (sputum from deep cough, bronchial extracts, tracheal or alveolar lavage fluid, lung tissue biopsy specimens, etc.), and from blood, feces, urine, and conjunctival secretions. If possible, specimens should be collected from both the upper and the lower respiratory tracts of each case. Specimens from the lower respiratory tract have a
high positive rate of nucleic acid, so the collection should be given priority [1]. It is required to master the method and timing of specimen collection to improve the NAT sensitivity. Multiple sampling can be performed according to the patient’s process or if the research requires, improving the positive rate of NAT and avoiding missing diagnosis. The combination testing on multiple specimens from the respiratory tract, feces, blood, saliva, etc. is conducive to improving the diagnostic sensitivity of suspected cases, as well as to observe the efficacy on patients and formulate reasonable isolation management measures after their discharge. If the specimens are collected in a noninvasive manner, such as from the saliva, it can reduce the patient’s pain and be easily accepted by the patient [2].

### 3.1.1.2 Nuclei Acid Testing

In general, the real-time reverse transcription PCR (rRT-PCR) is used for NAT [3]. Proceed the NAT as directed by the kit instructions. The general procedure is: pre-treat the specimens from nasopharyngeal swab, sputum, saliva, etc. for inactivation of virus, lyse the virus, and extract the nucleic acid, then use rRT-PCR to amplify 3 specific genes in the SARS-CoV-2 genome: open reading frame la/b (ORFla/b), envelope protein (E) and nucleocapsid protein (N). Results were obtained by measuring the fluorescence intensity after amplification. Criteria for NAT positive: ORF1a/b gene positive, and/or N gene and E gene positive.

### 3.1.2 Specific Neutralizing Antibody Test

When a pathogen infects the body, the immune system defends against it and produces specific antibodies. A positive result of specific IgM antibody test indicates current infection or recent infection, while a positive result of IgG antibody test indicates convalescence or previous infection. The combined tests of viral RNA and serology in patients infected with SARS-CoV-2 can both improve the sensitivity of diagnosis and maintain a high specificity. Serum antibody determination methods include colloidal gold immunochromatography assay (GICA), ELISA, chemiluminescent immunoassay (CLIA) and so on. The following can be taken as a basis for diagnosis: novel coronavirus-specific antibodies IgG and IgM are positive; or specific IgG antibodies changed from negative to positive; or compared with the acute stage, there is a fourfold or more increase in the recovery period [4]. GICA operation is easy to manipulate without special equipment, but the quantitative analysis is unavailable. Special equipment is required for CLIA, but the results are objective and reliable, and the quantitative results are provided. The serum antibodies test can effectively avoid the risk of a missed test in NAT.

### 3.1.3 Pathogen Detection in Secondary Infection

Severe COVID-19 patients are prone to bacterial and fungal infections, so attention should be paid to the clinical microbiological detection of patients with severe and
critical diseases. Different testing methods are required based on different conditions, including bacterial testing, blood analysis, cerebrospinal fluid testing, secretion analysis, molecular biology testing, and so on. Elevated C-reactive protein has poor specificity for the diagnosis of secondary infection. Elevated procalcitonin levels are of great significance for clinical diagnosis of sepsis. Qualified specimens should be collected for bacterial and fungal cultures depending on the infected location. In case of the suspected fungal infection, in addition to fungal culture, G test, GM test, Cryptococcus antigen detection can also be performed.

### 3.2 Biochemical Examination

Hui Xing

Certain COVID-19 patients may have elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), phosphocreatine kinase (CK), and myoglobin (Mb), suggesting that the patient has suffered with multiple organ dysfunction. Elevated troponin (cTnI) can be observed in critically ill patients, indicating a poor prognosis. Corresponding clinical strategies should be developed according to the change of biochemical indicators to improve the therapeutic effect.

Indicators reflecting body’s inflammation and immune status, such as C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation, total lymphocytes and subpopulations, IL-6, and blood lactic acid, can facilitate the clinical stages judgment, which can be used as a clinical warning indicator for severe and critical cases, and provide a basis for the formulation of treatment strategies [4].

Most patients infected with SARS-CoV-2 have normal procalcitonin and significantly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein. IL-6 and IL-10 expressions in severe patients are elevated significantly, and the numbers of CD8+ T lymphocytes are decreased significantly. Dynamic monitoring of IL-6, IL-10, and CD8+ T lymphocyte levels can help assess the risk of worsening conditions of COVID-19 patients [5].

At the beginning of the onset, the total peripheral blood leucocyte is normal or decreased, and the lymphocyte count is decreased. Patients with a lower absolute lymphocyte value generally have a poor prognosis, and peripheral blood lymphocytes in critical patients show a progressive decrease. Elevated Neutrophil to Lymphocyte Ratio (NLR) is an independent risk factor affecting the occurrence of severe illness [6]. Patients with SARS-CoV-2 infection may develop hypoxemia, multiple organ dysfunction, etc., leading to coagulopathy and even DIC. Close monitoring of coagulation indicators in critical patients can facilitate early intervention and reduce mortality. Certain severe patients have decreased platelet counts, prolonged prothrombin time, prolonged activated partial thromboplastin time, decreased fibrinogen concentration, and significantly elevated D-dimer and FDP levels. These are potential risk factors for poor prognosis of patients [7].
3.3 Lung Imaging

Lian Yang

3.3.1 Imaging of Lungs [8–10]

Lung imaging has great value in COVID-19 diagnosis, efficacy monitoring, and discharge assessment. CT with high resolution to the lungs is preferred. For critical patients who cannot be mobilized easily, bedside X-ray scan can be selected. Generally, a baseline lung CT scan is performed on the day of admission. If the curative effect is not satisfactory after the treatment, lung CT can be performed after 2–3 days for review. If symptoms are stable or improved after treatment, and it can be performed after 5–7 days. For critical patients, follow-up and recheck with bedside X-ray scan can be taken as needed.

3.3.1.1 CT Scan

3.3.1.1.1 Preparation Before Admission

1. Reserve a CT scanner for suspected or confirmed cases; if available, prepare a separate CT scanner for suspected and confirmed cases respectively. Preference is given to movable CT scanner (if available) or the CT scanner that can lift the examination bed through the console, a separate control room (operating room) is required; if not, when disinfecting after examination, air disinfection of other computer rooms connected to the control room (operating room) is also required.
2. If a central air-conditioning fresh air system is used in the examination room, adjust the air supply and exhaust to the maximum; if an ordinary central air-conditioning is used, turn off the central air-conditioning in the examination room and operation room, and turn on the standby separate air-conditioning; if no spare separate air conditioner is available, turn on the central air conditioner after examination and disinfecting.
3. In order to reduce the viral transmission, a disposable medical middle sheet is needed during the examination to isolate the equipment from patients;
4. two technicians are required, with one operating the CT scanner, and the other one enter to be in the examination room for positioning (According to the requirements of the National Center for Disease Control and Prevention, both technicians for the operation and positioning require secondary or higher protection).

3.3.1.1.2 Preparation for Patient

The patient must wear a mask and lie down in a supine position. The technician trains the patient to hold his or her breath at the end of inspiration during the examination.

3.3.1.1.3 Scope and Direction of Scanning

Scan from apex pulmonis to costophrenic angle. For severe and critical patients (who are difficult to hold their breath), the scanning can be from costophrenic angle to apex pulmonis to reduce respiratory motion artifacts caused by difficulty in holding breath in the lower lung field, so as to ensure image quality.
3.3.1.4 Scanning Parameters
The technician uses a low-dose chest CT protocol to scan the patient. The automatic tube voltage, selected 100–120 kV of tube voltage, smart mAs of 20–50 mAs. Collimator with 0.5–1.5 mm width. Layer thickness, and layer spacing of 1–5 mm. For severe and critical patients, a larger pitch (1.0–1.5 pitches) can be used to reduce scanning time and respiratory motion artifacts.

3.3.1.2 Keys for CT Diagnosis

3.3.1.2.1 CT Manifestations in the Early Stage
Commonly, there are multiple lesions in the bilateral lungs, and a single side is rare. The lesions are mostly observed in the periphery of the lungs or under the pleura, and are more common in the lower lungs. They are irregular and fan-shaped, and can also be flaky or nearly round. They generally do not involve the entire lung segments. The density is uneven, often limited to small patches or large ground glass opacities, in which thickened blood vessels and thick-walled bronchi are seen, with or without localized grid-like interlobular septal thickening. The consolidation range is small and limited, with air bronchial signs visible.

3.3.1.2.2 CT Manifestations in the Advanced Stage
The distributions of the lesions are increasing, and the fusion of some lesions expanding, which can involve multiple lung lobes. The density of the lesion is increased because there appear consolidations that are irregular, wedge-shaped or fan-shaped, and the boundary is unclear. Bronchial vascular bundle thickening or multifocal lung consolidation can be seen under the pleura. The lesion progresses and changes rapidly, and the morphological changes are evident in the short-term review, which can be combined with the necrosis of lung tissue to form a small cavity. There are air bronchogram, usually with no pleural effusion and mediastinal and hilar lymph node enlargement.

3.3.1.2.3 CT Manifestations in the Severe Stage
Diffuse lesions of both lungs can be seen. When most of the lungs are affected, they appear as “white lungs” and the diaphragm is elevated. The density of the lesions is uneven, and air bronchial signs and bronchiectasis are seen. The nonconsolidated area can be patchy with ground glass opacities. The interlobular pleura and bilateral pleura are commonly thickened, with certain pleural effusion, showing free effusion or local wrapping.

3.3.1.2.4 CT Manifestations in the Absorption Stage
For most patients, after isolation and treatment for about 1 week, with the gradual improvement of the patient’s defense function, the scope of the lesion narrows, the lesions decreases, and the density become lighter, the lung consolidation lesion gradually disappears, the ground glass opacities can be completely absorbed, and the exudate is absorbed or organized by the body. The characteristic changes in imaging are generally later than the improvement of clinical symptoms (Figs. 3.1 and 3.2).
Fig. 3.1  Typical manifestations of lung CT for patients with mild COVID-19: (a) Ground glass opacity; (b) Crazy-paving sign; (c) Partial absorption of primary lesion with new lesions developed; (d) Re-examination after 1 month, the lesions are basically absorbed, with a low-density opacity (picture source F PAN, PMID: 32053470; authorized by the author)

3.3.1.3 Key for Examination and Imaging Diagnosis of Beside X-Ray

For mild patients, the early manifestation is locally ground glass opacities. Extensive ground glass opacities can appear in the advanced stage. The density is relatively low, DR is overlapping images, and the observation is limited, so a low dose is recommended for CT examination. For patients with severe and critical COVID-19, normal CT examination is unavailable due to the serious condition. Therefore, the movable bedside Chest Plain X-ray (abbreviated as chest radiography) have become the main imaging method for patients with severe and critical COVID-19. The technician should manage personal protection well: put on and take off the protective equipment and disinfect the movable imaging equipment according to the management procedure of the ward area.
At the early stage of a mild case, DR showed no obvious lesion. CT showed multiple patchy ground glass opacities in the lower lobes of both lungs.

Fig. 3.2 Typical manifestations of lung CT for patients with severe COVID-19: (a) Ground glass opacity; (b) The scope of the disease is enlarged, and the crazy-paving sign combined with consolidation appears; (c) The range of lesions continues to expand, and the consolidation is obvious; (d) The range of lesions continues to expand; “white lung” can be seen.

At the early stage of a mild case, DR showed no obvious lesion. CT showed multiple patchy ground glass opacities in the lower lobes of both lungs.
At the absorption stage of a severe case, DR vs. CT suggests the limit of DR in displaying ground glass opacities

### 3.3.1.4 Key Points in Imaging Diagnosis of Severe Pneumonia on Bedside X-Ray Plain Film

The imaging findings in the lungs are the same as the CT findings in severe pneumonia, including consolidation shadow, patchy shadow, reticular shadow, stripe shadow, hilar and mediastinal changes, pneumothorax, pleural effusions, pleural thickening, etc.

Large-scale consolidations in both lungs
Consolidation area is reduced and patchy and renticular shadows are present, indicating the lesion is at absorption stage.

Right costophrenic angle disappeared, indicating pleural effusions.
3.3.1.5 COVID-19 Pneumonia Follow-Up
Examination status, lesion area shall be recorded in the assessment. In the event of re-examination case, the lesion evolution shall be also recorded.

3.3.1.5.1 Examination Status
Including preliminary examination or re-examination.

3.3.1.5.2 Lesion Area
The number of involved lung segments and the number of significantly involved lung segments are recorded according to the method of 18-segment segmentation in lungs. The involved lung segment is defined as the lung segment involved by the lesion, regardless of the size of the lesion in it. Significantly involved lung segment is defined as the lung segment involved by the lesion, in which the lesion is at least 1/2 of the lung segment in size. The record shall be made in the manner of significantly involved lung segment/involved lung segment, for example, lesion area of 6/12 means there are 12 involved lung segments, of which significantly involved lung segments accounted for 6.

3.3.1.5.3 Evolution of Pulmonary Lesions
The evolution of pulmonary lesions evaluated using a serial chest CT scan presented different patterns with six manifestations: progression, stability, stalemate, improvement, sequelae, and complete radiological resolution.

- **Progression**: Increased pulmonary involvement of lesions with more consolidation.
- **Stability**: No obvious changes from previous chest CT images.
- **Stalemate**: De novo lesions could be observed but with partial absorption of old lesions.
- **Improvement**: Decreased pulmonary involvement with reduced density of the previous lesions.
- **Sequelae**: Clinical recovery but with the typical CT abnormalities, such as bronchiectasis and subpleural bullae.
- **Complete radiological resolution**: Complete absorption of lung lesions observed on chest CT scan.

3.3.1.6 Discharge Criteria
Discharge is recommended as per the following criteria: ① Lung lesions are significantly reduced in area, completely absorbed or resolved; ② Only a few fibrotic stripe shadows remained in lungs; ③ No new lesion is found. After discharge, it is recommended that patients should have a 14-day self-monitoring for health and CT re-examination timely according to the clinical needs.

3.3.2 Interventional Radiology Therapies
Interventional radiology plays an important role in the diagnosis and treatment of COVID-19 when underlying neurovascular, peripheral vascular, cardiovascular, and nonvascular and tumor diseases.
3.3.2.1 Reception and Operation Indication
(1) An interventional radiologist can use remote video and telephone for the consultation with the doctor in charge and patient, and shall contact the patient, if necessary, with level III protection; (2) The judgment of operation indications is consistent with that of non-COVID-19 patients, and the operation for general case can be delayed as much as possible according to the actual condition of patients, giving priority to the interventional operation necessary for emergency case, such as acute upper gastrointestinal hemorrhage caused by portal hypertension; (3) The principle for making operation procedures is that the interventional operation shall be performed with sufficient reference of preoperative imaging examination, such as enhanced MRI or CT examination of the operation area, and the balance between the effectiveness and short operation time shall also be kept; (4) A surgeon can communicate with patients through remote video, telephone and talk recording, or with level III protection, to obtain informed consent of the patient in the ward; if the patient is not capable of consent, the informed consent shall be obtained from his or her direct relatives; if the patient is not capable of consent and has no direct relatives, the operation shall be reported to the Medical Office for informed consent and recorded.

3.3.2.2 Patient Transportation
(1) The patient shall be transported to the interventional operating room through exclusive passage and an exclusive elevator, accompanied by his or her doctor in charge, nurse, and anesthetist. The transportation shall be completed along the shortest route without any stop to ensure the least time consuming. After putting on protective equipment, the interventional medical technician and nurse shall enter the interventional operating room through a clean passage and buffer area; (2) After arriving at the interventional operating room, the patient for local anesthesia shall wear a disposable protective cap and be given oxygen face mask; (3) Medical staff shall not enter the interventional operating room during and after the operation to ensure their personal protection.

3.3.2.3 Perioperative Preparation and Intraoperative Blood Oxygen Management
Since there is no adverse effect of COVID-19 on the coagulation function of patients and increasing the risk of interventional surgery, perioperative preparation shall be made as routine interventional preparation. For mild and severe patient, perioperative preparations shall be made for mask oxygen inhalation, ECG and blood oxygen monitoring, tracheal intubation kit, and ventilator shall be kept standby.

3.3.2.4 Protection from Patient’s Secretions
All areas that may come into contact with the patient’s blood, body fluids, vomitus, etc., shall be protected with disposable barrier sheet. The contamination of unprotected areas shall be recorded and targeted for postoperative disinfection (see below).
3.3.2.5 Postoperative Cleaning and Disinfection
(1) After the operation, the medical staff shall leave the operating room, enter the buffer area to successively remove the face shield, protective suit, foot coats, gloves, protective goggles and outer surgical protective mask, and discard them in the medical waste bucket. Then the hands shall be disinfected according to the “seven-step” washing method and then wear clean clothes after showering in the bathroom for half an hour. (2) The lead clothes shall be disinfected with a disinfectant paper towel, then wiped with clean water-moistened gauze and placed in a lead clothing disinfection cabinet for disinfection. (3) After the operation, disinfect object surfaces: Splash 2000–5000 mg/L effective disinfectant containing chlorine on the ground and allow to steep for 30 min before mopping the ground with clean water; wipe the surface of instrument table and operating table with 2000 mg/L effective disinfectant containing chlorine; as for the recorded unprotected area contaminated by the patient body fluid, use 5000 mg/L disinfectant containing chlorine to mop the area repeatedly. (4) After cleaning, close the operating room for at least 2 h and perform ultraviolet disinfection for an hour. (5) After disinfection, contact the infection office for object surface and air sampling. (6) All medical wastes shall be discarded into the double-layer medical waste bag and sealed for transportation. The bag shall be specially labeled with “Corona Virus Disease 2019” (referred as COVID-19) and disposed strictly as per regulations.

3.4 Ultrasonography and Treatment

Mingxing Xie and Jing Wang

Corona Virus Disease 2019, referred as “COVID-19,” is characterized by rapid transmission, rapid progression, and high rate of sever and critical cases [11]. Clinical imaging examination for this disease is mainly based on CT chest scan, but also ultrasound imaging examination. In this battle against COVID-19, ultrasound, as a quick and simple noninvasive imaging examination tool, plays an indispensable and important role in the diagnosis, efficacy evaluation, and follow-up observation of COVID-19 patients. The contents on ultrasound in the circulatory support treatment of COVID-19 were added in COVID-19 Diagnosis and Treatment Plan (Trial Version 7) issued by the State, with further emphasizing the important application value of ultrasound in the diagnosis and treatment of acute and severe COVID-19.

3.4.1 Ultrasonography

Because of the high contagiousness of COVID-19 and a large number of suspected and confirmed patients in affected areas, ultrasound examination for COVID-19 patients is recommended to be performed at the bedside of isolation ward area and
fever clinics to reduce nosocomial infections caused by instrument transport. In addition to conventional whole-body ultrasonic Doppler method diagnostic equipment, the application of bedside portable ultrasound should be valued, and new ultrasonic examination modes such as palmtop ultrasound, robotic ultrasound, and telemedicine platform can also be used.

The ultrasound examination for COVID-19 case is focused on heart and lungs. Besides, severe patients may present with multiple organ failure. Timely and dynamic ultrasonography of important abdominal solid organs such as liver and kidney and vascular lesions is also important for comprehensive assessment of the patient’s condition. The ultrasound instruments for COVID-19 cases are comprehensively equipped with multiple types of probes such as phased array, convex array, and linear array as well as various ultrasonic examination conditions for heart, abdomen, blood vessels, and superficial organs. In order to reduce the exposure time of sonographer, relevant dynamic and static image data shall be collected quickly and fully in an isolation ward area and analyzed after the sonographer leaves the infectious environment.

The main principle of emergent ultrasound examination is focused and targeted on rapid ultrasonography rather than comprehensive routine measurement.

3.4.1.1 Pulmonary and Thoracic Examination

3.4.1.1.1 Quantification and Localization of Pleural Effusion
Make qualitative and quantitative diagnosis on pleural effusion, and make identification and localization for the patients in need of catheter drainage therapy.

3.4.1.1.2 Auxiliary Diagnosis of Pneumonia
The lesions around the lungs caused by COVID-19 will increase the ultrasound penetration of pulmonary tissue. Therefore, the changes in the lungs should be determined through echo observation for lung ultrasound: including water content increases in lungs, inflammatory lesions, and severity and consolidation of inflammation. This observation method is applicable for the dynamic observation of lung lesions in the early, progression and severe stages of COVID-19, and for the determination on the effect of drug and nondrug intervention. Abnormal ultrasonographic signs of pneumonia include: disappearance of line-A and lung sliding sign, disappearance of B-line, pulmonary consolidation, air bronchogram, and localized or small amount of pleural effusion [12, 13] (Figs. 3.3 and 3.4).

3.4.1.1.3 With Pneumothorax Diagnosis for Auxiliary, Ultrasound Abnormal Signs of Pneumothorax Include
I disappearance of lung sliding sign and appearance of “lung point.”

3.4.1.1.4 Pediatric Lung Examination
Children are the vulnerable population for COVID-19 infection. The application of lung ultrasound in pediatrics is relatively mature. Normal characteristics of lung ultrasound image: same as those of adult lung ultrasound. It should be noted that
newborn infants may develop sparse B lines in some lung fields within Days 3–7 after birth, which disappears after a few days with the infant development.

### 3.4.1.2 Cardiac Examination

The disease progresses rapidly in severe COVID-19 patients, and cardiac injury occurs in approximately 31% of critical patients. Bedside echocardiography in COVID-19 can timely help clinical medical decision-making via combined cardiopulmonary and vascular diagnostic assessment. For clinical heart, focused and targeted assessment of heart damage is required (Fig. 3.5).

Rapid assessment of left and right heart function: (1) Visual measurement of left heart function is recommended in patients with normal ventricular wall motion. (2) M-mode assessment of left heart function is recommended for diffuse attenuation of ventricular wall motion. (3) Abnormal regional wall motion can be assessed using the uniplanar or biplanar Simpson method. (4) The maximum systolic excursion of the tricuspid annular plane (TAPSE) is measured by visual inspection of right ventricular wall motion or M-mode method, if necessary, and the right ventricular fractional area change rate (RVFAC) is estimated by the two-dimensional method.
Assessment of pulmonary artery pressure: Pulmonary artery pressure changes can be dynamically observed via ultrasound so as to adjust diagnostic and therapeutic strategies in a timely manner. Pulmonary artery systolic pressure is estimated using tricuspid regurgitation method or pulmonary venous reflux in the absence of right ventricular outflow tract stenosis.

Measurement of the width of the vein and its variation with respiration.

Rapid identification of pericardial effusion and localization: Observation of subxiphoid and parasternal sections is recommended.

Exclusion of other cardiac structural abnormalities, valvular heart disease, cardiomyopathy, myocardial infarction, infective endocarditis, aortic dissection, and other diseases. Comprehensive routine measurement is not necessary.

Ultrasound monitoring supported by ICU and ECMO: In ICU patients, left atrial pressure and vein width are dynamically monitored to determine whether fluid therapy shall be terminated [14, 15]. During the ECMO support, echocardiography can detect the size of the cardiac chamber, monitor whether the blood flow is emptied, and evaluate cardiac function and lung changes; ultrasound is used to determine the presence or absence of lung recruitment before weaning.

![Fig. 3.5](image)

(a) Left heart enlargement and reduced left heart function in patients with COVID-19 (b) Mitral regurgitation
3.4.1.3 Examination for Peripheral Vascular Thrombosis
Ultrasound examination shall rule out the presence or absence of deep venous thrombosis and arterial embolism in the peripheral vessels of the extremities in the early phase, determine the distribution range of thrombosis, etc., so as to reduce the risk of systemic and pulmonary embolism, especially the increased risk of deep venous thrombosis in bedridden patients with COVID-19. Severe patients with COVID-19, especially the elderly and those with underlying diseases, may have multiple other risk factors that further increase the risk of embolism. Bedside high-frequency ultrasound has irreplaceable advantages in the detection and dynamic observation of lower extremity deep venous thrombosis in COVID-19 patients. Focused and targeted rapid examination of blood vessels shall still be emphasized during the epidemic.

3.4.1.4 Blood Volume Assessment
Volume assessment shall include assessment of volume status and volume responsiveness. The common evaluation indicators of ultrasound examination include left ventricular end-diastolic dimension (LVEDD), Left ventricular end-diastolic volume (LVEDV), and internal diameter of the inferior vein. The internal diameter of the inferior vein is narrowed in the hypovolemia patients. Under conditions of spontaneous quiet breathing, the diameter of the vein less than 9 mm indicates hypovolemia. LVEDD less than 35 mm, etc., also indicates possible volume depletion. Ultrasound indicators can be used for volume or volume responsiveness assessment, but cannot completely replace other assessment means, so a comprehensive analysis is still required.

3.4.2 Interventional Ultrasound
Interventional ultrasound examination in the isolation ward area shall be strictly performed for the relevant indications as per the standards for ultrasound interventional diagnosis and treatment. Level III protection is required.

Interventional ultrasound can be used for quantitation of serous membrane effusion and ultrasound-guided puncture localization and catheterization.

Ultrasound-guided peripheral and central venous puncture, catheterization, and other related interventional therapy. In the rescue of emergent and critical cases, venous access can be rapidly established by ultrasound-guided peripheral and central venous catheterization. Interventional ultrasound is applicable for many conditions such as difficulty in blind venous puncture, urgent need for blood sample collection or intravenous infusion; long-term central venous catheterization and thrombolysis [16].

Ultrasound-guided lower extremity venous filter placement in real time to prevent lower extremity venous thrombosis from entering into the right heart system, resulting in the risk of pulmonary embolism (Fig. 3.6).
3.5 Primary Screening for Disseminated Intravascular Coagulation

Yadan Wang, Fanjun Cheng, and Yu Hu

3.5.1 Overview

Disseminated Intravascular Coagulation (DIC) is a clinical syndrome characterized by hemorrhage and microcirculatory failure on the basis of various diseases, in which pathogenic factors damage the microvascular system, leading to coagulation activation, systemic formation of microvascular thrombosis, massive consumption of coagulation factors, and secondary hyperfibrinolysis [17]. Multiple organ damage, inflammatory factor storm, and secondary bacterial and fungal infections in critical COVID-19 patients are most of the important factors that can induce DIC.

3.5.2 Diagnoses

The diagnosis of DIC depends on dynamic observation and comprehensive judgment of clinical pictures and laboratory parameters [17].

3.5.2.1 Clinical Characteristics

Multiple bleeding tendencies are one of the most common clinical pictures of DIC, but rarely occurs to the critical COVID-19 patients based on our observation, while microcirculatory disturbances and organ function injuries or even failure are commonly observed [18, 19]. The specific manifestations included: increased

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**Fig. 3.6** Image after the filter released via ultrasound-guided vein filter implantation (yellow arrow shows the echo of the filter)
respiratory distress in a short period, abnormal liver and renal function/disturbance of consciousness, myocardial damage, and shock, which cannot be explained by other causes. The old age and various complications of COVID-19 patients, combined with the effects of therapeutic drugs, disturbing clinical judgment. Dynamic observation and careful screening are required during the diagnosis and treatment process to detect early warning signs and perform early intervention as soon as possible.

3.5.2.2 Laboratory Indicators
The sensitivity and specificity of a single indicator for the diagnosis of DIC are poor, so comprehensive analysis and dynamic observation are required. The value of laboratory parameters for the early warning on COVID-19 with DIC varies, and their sensitivities are as follows: increased D-dimer > decreased platelet > prolonged PT > decreased fibrinogen > prolonged APTT; and specificities are as follows: progressive decreases in fibrinogen > progressive decreases in platelets > prolonged APTT > increased D-dimer (the above sequences are defined as per clinical practice experiences and shall be confirmed by clinical studies).

3.5.2.2.1 D-Dimer
According to the published descriptive literature on the clinical characteristics of COVID-19 patients [20–22], the high proportion of increased D-dimer is at 36–46.4% and at 59.6% in critical patients. The D-dimer level is significantly different between ICU patients and non-ICU patients (414 mg/L vs. 166 mg/L); Progressive increase in D-dimer is an early warning sign of disease aggravation and DIC occurrence. D-dimer presents high sensitivity and low specificity for the diagnosis of DIC.

3.5.2.2.2 Platelets
Most COVID-19 patients showed with normal or with mildly increased platelet counts, sometimes with decreased ones especially in severe and deadly patients [20, 22, 23]. The absolute value of platelets is of limited value in the assessment of DIC, and a dynamic decrease in platelet count indicates the occurrence of DIC better.

3.5.2.2.3 Fibrinogen
Fibrinogen, as an acute reactive protein, can be significantly increased in mild COVID-19 patients and in the early stages of disease in severe patients [20–23] and possibly decreased in the late stages of severe patients in the presence of DIC with consumptive hypocoagulability [18, 24]. Therefore, for the diagnosis of DIC, fibrinogens have low sensitivity and high specificity. For critical patients, a progressive decrease in fibrinogen requires vigilance.

3.5.2.2.4 Prothrombin Time/Activation of Partial Thromboplastin Time
30% of COVID-19 patients exhibit a shortened prothrombin time (PT), 16% of them exhibit a shortened activation of partial thromboplastin time (APTT), while PT and APTT are prolonged only in 5 and 6% of patients [20]. At different stages of
DIC in COVID-19, PT and APTT showed different characteristics as hypercoagulability, PT and APTT are shortened or normal at early stage, and consumptive hypocoagulability at late stage, PT and APTT are prolonged with higher sensitivity in PT than APTT.

3.5.2.3 DIC Diagnosis and Scoring System and WeChat APP

In order to accurately quantify the diagnostic criteria of DIC, the Thrombosis and Hemostasis Group of Chinese Society of Hematology of the Chinese Medical Association established the Chinese DIC scoring system (CDSS) through multicenter retrospective and prospective study on large size of sample in 2014 (see Table 3.1 [16]). This system highlighted the importance of underlying diseases and

| Item                                                                 | Score |
|---------------------------------------------------------------------|-------|
| Primary disease leading to DIC exists                              | 2     |
| Clinical picture                                                   |       |
| Severe or multiple bleeding tendency that cannot be interpreted with primary disease | 1     |
| Microcirculatory disturbance or shock that cannot be interpreted with primary disease | 1     |
| Extensive skin, mucous embolism, focal ischemic necrosis, falling off and eclosion, functional failure of lung, kidney, brain, and other organs with cause unknown | 1     |
| Laboratory indicators                                              |       |
| Platelet count                                                     |       |
| Nonmalignant blood disease                                         |       |
| ≥100 × 10^9/L                                                      | 0     |
| 80–< 100 × 10^9/L                                                  | 1     |
| <80 × 10^9/L                                                       | 2     |
| Decrease within 24 h ≥50%                                          | 1     |
| Malignant blood disease                                            |       |
| <50 × 10^9/L                                                       | 1     |
| Decrease within 24 h ≥50%                                          | 1     |
| D-dimer                                                            |       |
| <5 mg/L                                                            | 0     |
| 5 – <9 mg/L                                                        | 2     |
| ≥9 mg/L                                                            | 3     |
| PT and APTT extension                                              |       |
| PT extension ≤3 s and APTT extension<10 s                          | 0     |
| PT extension ≥3 s or APTT≥10 s                                     | 1     |
| PT extension ≥6 s                                                  | 2     |
| Fibrinogen                                                         |       |
| ≥1.0 g/L                                                           | 0     |
| <1.0 g/L                                                           | 1     |

Note: For patients with nonmalignant hematological diseases, DIC will be diagnosed if their scores were no less than 7; if their scores were less than 7, the scoring shall be repeated daily. For patients with malignant hematological diseases, DIC will be diagnosed if their scores are no less than 6; if their scores were less than 6, the scoring shall be repeated daily.
clinical pictures, strengthened the principle of dynamic monitoring, and included simple and easy popularization of laboratory test indicators. After clinical practical examination in Union Hospital, Tongji Medical College (Wuhan), CDSS scoring system can early identify DIC and its severity as a complication in COVID-19 patients [17].

According to the CDSS, we designed a WeChat APP for mobile use (Fig. 3.7). With this simple, quick, and intelligent APP, accurate scores can be very easily obtained by simple selections according to the clinical pictures and laboratory tests, so as to perform further dynamic scoring management, historical data export, and provide a reference for management.

3.5.2.4 Prevention of DIC
The viral infections may activate the body’s coagulation system, inflammatory factor storms, and secondary infections, which may cause damage to blood vessels in organs. These are high-risk factors in the formation of thrombosis (deep venous thrombosis or DIC). Literatures have been shown that the proportion of cases with increased D-dimer is 36–46.4%, and can be as high as 59.6% in critical patients with higher grade of increase [4–6]. Therefore, for critical and severe COVID-19 patients, if their D-dimer is increased with no significant bleeding tendency, or Caprini score is above intermediate risk, or Padua score is greater than 4, they can be treated with anticoagulant therapy and a prophylactic dose of low molecular weight heparin. The patients shall be closely monitored for bleeding tendency while receiving prophylaxis for venous thromboembolism and DIC.

3 COVID-19 Diagnosis
3.6 Blood Gas Analysis

Weimin Xiao

3.6.1 Concept and Definition

Blood gas analysis (BGA) aims to determine the pH, partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), and electrolyte concentration in the blood, providing references for a quick judgment on the presence of respiratory dysfunction and acid–base imbalance in COVID-19 patients during practice. It is an objective laboratory indicator for assessing the severity of the disease and helps to guide the diagnosis and treatment of COVID-19 patients.

3.6.2 Personal Protections for Sampling and Testing Personnel

According to the level III prevention criteria, the personnel shall wear a medical protective mask and eye protection (such as protective goggles or face shield) and test the tightness. The wearing order is as follows: clean hands → medical protective mask → disposable cap → working clothes → working shoes → isolation gown/protective suit → protective goggles/protective face shield/medical mask with eye protection → gloves → shoe cover.

3.6.3 Sample Collection

3.6.3.1 Selection of Puncture Site

The radial artery is preferred, followed by the brachial artery (not recommended for children, especially infants), dorsalis pedis artery and femoral artery (contraindicated for newborns), and scalp artery (used for infants) [25].

3.6.3.2 Arterial Blood Sampling Procedure: Operation for Puncturing Radial Artery [26]

1. The patient shall be introduced to the knowledge about arterial blood sampling and then informed consent shall be obtained for the patient.
2. The puncture site shall be selected according to Allen’s test (Allen’s test), and if the test failed, try the other arm.
3. The patient is placed in supine position, the arm is extended and abducted by 20–30° on the support frame with palm up, the patient’s wrist is padded by about 5–8 cm, the index finger and middle finger of the patient’s non-dominant hand are gently placed at the site with the strongest radial pulse, the syringe is held in the dominant hand of the sampling personnel, the needle is tilted about 45° to aim the artery for needle insertion, until flashback or the syringe is self-filled.
4. The needles are discarded into sharp boxes. Cap the syringe, roll the syringe on the palm to defoam, and mix well before delivery for testing.
5. The punctured sites should be pressed for at least 5 min or until signs of bleeding subside. Longer pressing time may be needed if the patient has hypertension, bleeding disorders, or when patient is taking anticoagulants.

### 3.6.4 Sample Deliveries

After the collection, the samples shall be tested with the analyzer as soon as possible. The test will be completed within 30 min at room temperature; if lactic acid test is performed, the test will be completed within 15 min. If the test cannot be completed within 30 min after blood collection, the blood sample shall be stored at 0–4 °C to avoid hemolysis by no direct contact with ice [25]. Before the delivery, the samples shall be placed into a sealed container, which shall be labeled with biological hazards. In the process of delivery for test, sample shaking shall be avoided so as to prevent hemolysis and inaccurate test values of PO2, etc. [25].

### 3.6.5 Computer Testing

Select the arterial blood on the blood gas analyzer, click Start, the injection needle automatically extends, remove the needle and discard the first drop of blood sample to ensure that there is no air at the tip. The tip of injection needle shall go deep into the bottom surface of blood sample as far as possible, avoiding air sucked during injection. After the completion of injection, the tube is removed, the injection needle is automatically retracted, and the syringe piston is inserted.

Input the patient information including operator number, patient name, hospitalization number, oxygen concentration, and body temperature, so as to avoid calculation error or correction error of test results [25].

Note: 1. Patient’s mood and body temperature: In order to accurately reflect the patient’s condition, the blood shall be sampled when the patient is rested and quiet to prevent overbreathing or breathe holding; if the body temperature is not easy to control, it is necessary to input the body temperature value for correction during the test. 2. Oxygen supply state: If the patient’s oxygen administration mode changes, a stable oxygen state shall be ensured for at least 20–30 min before blood collection, and the oxygen inhalation parameters shall be input during the test to ensure the accuracy of the test results (1).

Print Test Results.

### 3.7 Accurate Diagnosis and Treatment of COVID-19 Pneumonia with Assist of Metagenomic Sequencing

Fanjun Cheng

Metagenomic sequencing (mNGS) [27–30] aims to directly extract the nucleic acid of all microorganisms in the infected specimen for high-throughput sequencing, obtain the species information of suspected pathogenic microorganisms through the
comparison of microorganism special databases and intelligent algorithm analysis, and detect 12,593 pathogens such as bacteria, fungi, viruses, and parasites without bias. mNGS has the characteristics of comprehensive detection, high accuracy, high sensitivity, and fast identification. mNGS significantly improves the detection rate of infectious pathogens, especially for the detection of new pathogens, rare or special pathogens, and mixed infections.

As gene sequencing is one of the two methods for the diagnosis of SARS-CoV-2, mNGS can achieve rapid identification and in-depth sequence analysis of SARS-CoV-2. Viral pneumonia occurs frequently in winter and spring, so COVID-19 suspects cannot be excluded from the possibility of infection with other pathogens. In addition, according to the clinical features, mostly severe COVID-19 patients are elderly and/or with underlying disease. These patients, because of the relatively weak immunity, are easily coinfected with bacteria and/or other viruses. At the same time, these patients with long-term hospitalization are more likely infected by secondary bacterial and/or fungal. The above situations may enhance the difficulty of diagnosis and treatment, and affect the prognosis of COVID-19 patients. mNGS can simultaneously detect multiple pathogens, quickly providing the etiological evidence for differential diagnosis of suspected COVID-19 cases and coinfection or secondary infection of confirmed COVID-19 patients, and ultimately assist clinical targeted treatment.

Etiological metagenome sequencing shall be implemented by qualified institutions.

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