

Second supplement;

Definition of cases in COVID-19¹

Suspicious case

A. A patient with clinical symptoms and epidemiological criteria

-Clinical findings

*Sudden onset of fever and cough

Or

*Sudden onset of at least three or more symptoms, including fever, cough, general weakness/excessive fatigue, headache, muscle pain, sore throat, runny nose, shortness of breath, anorexia/ nausea/ vomiting, diarrhea, loss of consciousness

-Epidemiological evidence

Residence, employment, or travel to areas where the virus is likely to spread (such as accommodation centers, crowded venues, conferences and ceremonies, health and therapeutic centers) during the last 14 days

-With the onset of symptoms during the last 10 days, a person with severe acute respiratory illness (SARI) requires hospitalization.

Probable case

A. A suspected patient who is in contact with a probable or definite patient or a cluster of patients among whom at least one definite case is reported.

B. A suspected patient with imaging findings in favor of COVID-19

E.g., unilateral or bilateral multilobular infiltration, especially infiltration of peripheral areas in the lung or CT scan or the ground glass and chest radiography on lung CT scan (Clinically confirmed)

C. A patient who has severely lost his sense of smell or taste

D. Death of a patient suspected of CPVID-19 (whose death cannot be justified by any other reason)

Definitive case

A person with laboratory confirmation of the virus caused by CPVID-19, regardless of the presence of clinical signs and symptoms. □

¹ Public health surveillance for COVID-19, WHO Interim guidance 7 August 2020

Definition of close contact

A person in contact with the patient under the following conditions, from two days ago to 14 days after the onset of possible or definite symptoms. The cases are as follows:

- Face-to-face contact at a distance of below 1 meter for at least 15 minutes
- Direct physical contact with a probable or definite person
- Probable or definite patient care with no use of appropriate personal protective equipment
- In other cases, assessment is based on the probability of regional transfer

Definition of COVID-19 death¹

Death of a probable or definite person, which is clinically from the COVID-19 disease and does not have another specific cause, non-relevant to COVID-19 (e.g., accidents, etc.). There is no full recovery period between active COVID-19 disease and death.

The report of deaths from COVID-19 disease should be prepared for positive and suspected cases.

The abovementioned definitions are of paramount importance from the point of view of the disease care system.

Flowchart of the diagnosis and treatment of COVID-19 disease

All doctors, including the public, private and charitable sectors, should have access to this flowchart and take it as the first measure in screening patients. It is necessary to observe the following steps of the flowchart approved by the Scientific Committee for any patient referred to outpatient medical centers:

All individuals with COVID-19 symptoms (namely cough, sore throat, chills with or without fever and so on) who refer to comprehensive health care centers, specialized clinics, hospitals, and private sector physicians should be first checked up in terms of respiratory symptoms. The patient may be with no fever in the early stages of the infection and exhibit other symptoms. Very high fever is generally not a common symptom.

According to the clinical signs and symptoms in the first step of the checkup, the patients are divided into three groups

- Patients with a need to be referred to hospitals
- High-risk patients with indications for outpatient antiviral therapy
- Patients without indication for outpatient antiviral treatment

First group: Patients with a need to be referred to hospitals

Regarding the significance of the issue at the patient's first visit to any public or private health center, it should be determined whether the patient needs to be referred to specialized centers or treated as an outpatient. Accordingly, it is vital to pay attention to reference indications.

Reference indications

¹ U 07.1 and U07.2 are death registration codes for definitive and suspected cases.

The following patients should be referred to the selected COVID-19 hospitals for further evaluation and, if necessary, hospitalization.

1. In addition to the symptoms in favor of COVID-19 disease, shortness of breath and hypoxemia $RR > 24$ or ($SpO_2 < 90\%$) should be concerned.

- Regarding patients with SpO_2 90- 93%, underlying diseases and clinical conditions should be concerned to decide whether they should be sent to hospitals or temporary hospitals/medical centers¹.

2. Patients with a decreased consciousness level

3. Patients with hypotension (Systolic blood pressure < 90 mmHg)

4. Patients with persistent dehydration and digestion intolerance after outpatient supportive care

5. Patients at risk of complication-bearing COVID-19 with no shortness of breath and hypoxia but with positive lung imaging findings based on the clinical condition and severity of the lung involvement in the CT scan, who may need to be referred to selected hospital centers for further evaluation upon the doctor's prescription

If the “pre-hospitalization intervention units (Temporary hospitalization)” are set up in the area, sending patients with SpO_2 90- 93% to these units should be done according to the relevant instructions.

Second group: High-risk patients with indications for outpatient antiviral therapy

As mentioned, about 80 patients need no hospitalization; hence, symptomatic and palliative care should be provided for most of the patients at home, and routine care includes the following cases:

Basically, for patients with no hospitalization indications, care measures and necessary precautions (care and isolation) and Chloroquine/hydroxychloroquine diet are recommended with regard to all relevant precautions as well as the prescription of symptomatic care.²

Since hydroxychloroquine, like other antiviral drugs, has the greatest effect in the first days of the disease, palliative and supportive treatments are helpful for patients who do not need to be hospitalized and have been referred one week after the onset of symptoms. Although the administration of hydroxychloroquine in the second week is also allowed, it is certainly much less useful than when prescribed in the first week (preferably the first three days).

If a person at the preliminary assessment has no hospitalization indication and is in the high-risk group with respiratory symptoms, it is recommended to refer to have lung imaging procedures if available. Note that all these procedures are adopted following a clinical examination and at the discretion of the physician.

Chloroquine/hydroxychloroquine for patients in each province is provided by the selected comprehensive COVID-19 health service centers (during 16-24 hours) announced by the University of Medical Sciences. The patient's information is recorded in the electronic health record systems (e.g., Sib, Sina, Nab, Parsa, etc.), and health personnel performs the follow-ups.

¹ If the patient needs to be hospitalized in temporary medical centers or hospitals and the patient does not obey, the patient's dissatisfaction should be recorded in the triage form.

² Drug doses and relevant precautions are described in the outpatient treatment section.

The principles of home quarantine, medicine administration, and important warning signs should be explained to the patients and their companions. Patients should be aware of the risk signs and refer to the selected COVID-19 treatment centers if the symptoms appear.

Hospitalization conditions

After sending the patient to the hospital, based on clinical examinations and checkups, a decision must be made for his hospitalization.

Hospitalization indications

It is necessary to pay attention to the following points to decide for hospitalization of patients:

1. Oxygen saturation level $<90\%$ ($SpO_2 <90\%$) and the need for respiratory support (including oxygen therapy)
2. Decreased level of consciousness,
3. A drop in blood pressure (systolic pressure $<90\text{mmHg}$)
4. Continued dehydration and oral intolerance after outpatient supportive care

The physician can hospitalize the patient based on the underlying diseases, clinical conditions, and paraclinical findings (Risk scoring).

The physician's clinical judgment about oxygen saturation level $<90\%$ for a patient's hospitalization should be based on his clinical conditions and underlying diseases.

According to the instructions, if the referred patient has no hospitalization indication, but he is eligible for outpatient hospitalization treatment, according to the instructions, receiving outpatient medicine will be in the form of an outpatient medicine application form (Selected hospitals are licensed to prescribe outpatient medicine).

Patient admission and hospitalization procedures (patient flow)

Patients referred to the selected hospitals by outpatient centers or referred directly to the hospital emergency wards, who are suspected of having COVID-19 disease and having hospitalization indications, will be monitored in the COVID-19 isolation unit and receive the necessary support services until the final decision is made based on paraclinical assessments and imaging findings.

If the diagnosis is confirmed (definitive diagnosis with positive molecular test result) or clinical confirmation (COVID-19 CT scan findings) is provided, and when, at the discretion of the physician, the patient is strongly suspected of COVID-19, he should be referred to the COVID-19 ward.

In this ward, it is necessary to pay sufficient attention to the patient's underlying diseases and, if necessary, provide expert advice for underlying diseases.

If the following symptoms persist and, at the discretion of the treating physician, the patient may need intensive care:

- Hypoxemia resistant to non-invasive treatment
- Decreased consciousness level

- Hemodynamic instability

- Hypercapnia-respiratory fatigue

Factors that can be the predictors of severe COVID-19 disease during hospitalization are as follows:

Table 1. Factors predicting the progression of the disease in the hospitalized person

Vital signs and clinical findings
>30 breaths per minute Heart rate >125 beats per minute (With the age increase, this rate is lower) SpO2 <90 despite receiving oxygen (Judgment will be different in the presence of underlying respiratory diseases) Blood pressure drop <90mmHg Elevated capillary filling to > 3 seconds Exacerbation of clinical symptoms/coagulation disorders/ and tendency to bleed Occurrence or progression of decreased consciousness level Allegory
Laboratory findings ¹
LDH> 2 × ULN ² Progressive lymphopenia (especially less than 500) PT, PTT, INR> ULN CRP> 2 × ULN, especially> 100 High ferritin (Ferritin> 500 ug / L) D-dimer> 1000 ng / ml ² CPK> 2 × ULN Elevated troponin Elevated SGOT, SGPT Elevated Procalcitonin

These patients need special care measures and, if necessary, specialized counseling appropriate to their symptoms.

Organ monitoring intervals should be reduced, and more specific support and treatment measures should be provided.

If necessary, highly intensive/critical care measures should be adopted in accordance with the Appendix "Managing care and treatment of patients with COVID-19.

Basic measures in hospitalized patients

In hospitalized patients, one of the main measures to save patients' lives is to provide oxygen, which should be specifically included in the treatment plan. In fact, in severe and critical stages, the patient fails to breathe normally to get enough oxygen into the bloodstream and thus deprives the body tissues of their required oxygen they. The process leads to organ failure and death.

To learn more about different types of respiratory failures and the concepts associated with oxygen, hypoxemia, and oxygen therapy, see Appendix 9.

Recommended tests for hospitalized patients

¹ ULN: Upper Limit of Normal

² D-dimer convert units: 0.5 mg / l = 500ng / ml

One of the measures in hospitalized patients is to send tests, the results of which allow the timeliest therapeutic interventions. Tests of patients suspected of COVID-19 are mainly divided into two categories:

- Tests sent to diagnose COVID-19 disease
- Recommended tests to assess the severity of the disease and its clinical course

It is noted that, as the course of the disease, in many cases, the course of the patient's tests is decisive for treatment decisions. For example, we can point to the decline in lymphopenia in such patients.

Accordingly, the timing of requesting tests and repeating them plays a vital role in the physicians' treatment decisions.

In Table 2, the necessary tests are suggested as inpatient tests, the test needed to determine the probable prognosis, tests to assess the likelihood of disease progression, and tests to assess the function of internal organs.

The request for a test will ultimately be based on the clinical decision of the concerned physician.

Managing care and treatment of hospitalized patients

According to the classification of patients based on the disease course in the "moderate pulmonary" phase, "severe pulmonary phase," and "inflammation exacerbation- highly severe phase," the patients are eligible for inpatient services.

Use of antiviral drugs in hospitalized cases

Due to insufficient evidence on the effectiveness of antiviral drugs in reducing mortality of COVID-19, there is no definite recommendation for their use; however, at the discretion of the physician, the following points should be considered in using antiviral drugs:

- The patient is in the moderate to the severe phase of the disease
- The patient is not in critical condition and does not need mechanical ventilation

If you are taking any of the antiviral drugs, you need to be careful about how you prescribe and monitor the patient.

It is emphasized that the drugs should be prescribed in the form of clinical trials to evaluate the effectiveness of these drugs.

Obviously, the patient's clinical history is recorded in the hospital file in cases of using antiviral drugs, and this must be done with sufficient care.

The role of corticosteroid administration in the treatment of COVID-19

According to the available evidence, corticosteroids, if given at the right time and used in the right dose in hospitalized patients in need of respiratory support, may be helpful in reducing mortality.

The members of the Scientific Committee of the Ministry of Health and Medical Education recommend that corticosteroids can be administered at low doses only if the patient's symptoms improve and there is a persistent oxygen demand despite supportive therapies and SpO₂ 90-93%.¹

¹ Corticosteroids for COVID-19, WHO Living guidance, 2 September 2020

Intravenous dexamethasone 8 mg per day for a maximum of 10 days

oral prednisolone tablets 0.5 mg / kg per day for a maximum of 10 days (prednisolone tablets are marketed in the forms of 5 mg and 50 mg. The full daily dose can be prescribed after breakfast.

Corticosteroids are recommended in severe cases.

Note: Higher doses of dexamethasone not only are less effective at this stage of the disease but may have side effects. Intravenous injection should be done slowly. Dexamethasone tablet is 0.5 mg, given the recommended dose, the oral administration of such a number of pills is not recommended, and patients with gastrointestinal tolerance and stable hemodynamics can take oral prednisolone in equal doses. It should be noted that different corticosteroids formulation should not be used at the same time to treat the patient. Using higher doses based on clinical judgment and condition may be considered as salvage therapy. Note that there are still questions about the definite use of corticosteroids in patients with COVID-19 as such future studies should be considered in this regard.¹.

1. Medium pulmonary phase

Diagnostic measures

- A. COVID-19 diagnostic tests: Molecular testing should be requested for all hospitalized cases.
- B. Serology COVID-19 diagnostic test (IgG, IgM): not currently recommended
- C. Other tests: They can be recommended based on the patient's clinical conditions and according to Table 2.
- D. Imaging measures: Imaging measures (Lung radiography/ CT scan) are recommended and are helpful in assessing the condition of the disease.

Care and treatment measures

Recommended measures for these patients are as follows:

Oxygen therapy is the most important step and should be performed under close supervision. Monitoring should be performed hourly, and if the patient does not respond, a decision should be made to improve the patient's oxygenation condition. Flow nasal Canula and high NIV are preferred.

- Water and electrolyte modification and other supportive treatments
- Observance of personal hygiene principles (e.g., hand washing, masks, etc.) □ □
- Separation from others and observing physical distance as long as necessary
- Careful monitoring of individuals in terms of symptom exacerbation and supportive therapies for various organs

¹ Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: evidence and hope during the pandemic. *Jama*. 2020 Oct 6; 324 (13): 1292-5.

- CAP Antibiotics are generally not necessary in the COVID-19 treatment and are not recommended. Decisions should be made in patients suspected of CAP¹ and other infectious causes.

It is noted that there is currently no therapeutic intervention or antiviral drug with proved effects for this disease. With continuous follow-ups of clinical trial results and the consequent reports, the guidance team will make therapeutic changes in future reviews.

Antiviral treatment

At present, there are drugs with relative effectiveness, which can be prescribed for hospitalized patients according to the proposal of the National Scientific Committee. They are mentioned in the section "Using antiviral drugs in hospitalized cases."

Anticoagulant treatment

Prophylactic anticoagulant treatment in hospitalized patients is recommended as follows:

Heparin 5000IU SC TDS

BMI \geq 40: Heparin 7500 IU SC TDS o

Or

Enoxaparin 40 mg SC once daily

BMI \geq 40: Enoxaparin 40 mg SC BID o

45 Community-Acquired Pneumonia

Corticosteroids

See "Prescription of Corticosteroids in COVID-19 Treatment "

Severe pulmonary phase

Diagnostic measures

A. Molecular COVID-19 test (RT-PCR): if not submitted since the onset of the disease

B. Serological COVID-19 test (IgG, IgM): not recommended

C. Other tests: They can be recommended based on the patient's clinical condition and Table 2.

As shown in Table 2, the following tests may be requested based on the patient's clinical condition and be repeated at appropriate intervals:

- ABG, ALT, AST, Ferritin, LDH, D-dimer

The following tests may be requested at the discretion of the physician with regard to their accessibility:

- NT-proBNP, IL6, Fibrinogen

- Radiological recommendations

Imaging measures (Lung radiography/ CT scan) are recommended and help assess the disease condition.

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Care and treatment measures

Recommended measures for these patients are as follows:

Oxygen therapy is the most critical step and should be performed under close supervision. Monitoring should be performed hourly, and if the patient does not respond, a decision should be made to improve the patient's oxygenation condition. Flow nasal Canula and high NIV are preferred.

- Water and electrolyte modification and other supportive treatments
- Careful monitoring of individuals in terms of symptom exacerbation and supportive therapies for various organs
- In general, antibiotics are not necessary for the COVID-19 treatment and are not recommended. In patients suspected of bacterial respiratory infection and other infectious diseases, other decisions are necessary.
- Observance of personal hygiene principles (e.g., hand washing, masks, etc.); separation from others and observing physical distance as long as necessary
- Careful monitoring of individuals for exacerbation of the symptoms

Note that there is currently no therapeutic intervention or antiviral drug with proved effects for this disease. With continuous follow-ups of clinical trial results and the consequent reports, the guidance team will make therapeutic changes in future reviews.

Antiviral treatment

At present, there are drugs with relative effectiveness, which can be prescribed for hospitalized patients according to the proposal of the National Scientific Committee. They are mentioned in the section "Using antiviral drugs in hospitalized cases."

Corticosteroids

Intravenous injection of dexamethasone 8 mg/day for a maximum of 10 days

Or

Oral prednisolone tablets 0.5 mg/day for a maximum of 10 days

□

The use of higher doses of corticosteroids and pulse therapy will be based on the clinical decision of the concerned physician and with regard to the patient's condition.

Anticoagulant therapy

Initiation of preventive anticoagulant therapy:

Heparin 5000IU SC TDS o

BMI \geq 40: Heparin 7500 IU SC TDS ☞

Or

Enoxaparin 40 mg SC once daily o

BMI \geq 40: Enoxaparin 40 mg SC BID o

3. Critical phase

Diagnostic measures

A. Molecular COVID-19 test (RT-PCR): if not submitted since the onset of the disease

B. Serological COVID-19 test (IgG, IgM): not recommended

C. Other tests: They can be recommended based on the patient's clinical condition and according to Table 2.

As shown in Table 2, the following tests may be requested based on the patient's clinical condition and be repeated at appropriate intervals:

- ABG, ALT, AST, Ferritin, LDH, D-dimer

The following tests may be requested at the discretion of the physician with regard to their accessibility:

- NT-proBNP, IL6, Fibrinogen

Radiological recommendations

Imaging measures (Lung radiography/ CT scan) are recommended and are helpful in assessing the disease condition.

Care and treatment measures

Recommended measures for these patients are as follows:

- In this phase, the patient needs intensive care services, and respiratory services should be provided in accordance with the instructions. They may need mechanical ventilation. See the section 'Referring to ICU.'

- Water and electrolyte modification and other supportive treatments

- Careful monitoring of individuals in terms of symptom exacerbation and supportive therapies for various organs

- In general, antibiotics are not necessary for the COVID-19 treatment and are not recommended. If necessary, the physician's prescription is required.

Observance of personal hygiene principles (e.g., hand washing, masks, etc.); separation from others and observing physical distance as long as necessary

Note that there is currently no therapeutic intervention or antiviral drug with proved effects for this disease. With continuous follow-ups of clinical trial results and the consequent reports, the guidance team will make therapeutic changes in future reviews.

Corticosteroids

Intravenous injection of dexamethasone 8 mg/day for a maximum of 10 days

The use of higher doses of corticosteroids and pulse therapy will be based on the clinical decision of the concerned physician and with regard to the patient's condition.

Anticoagulant therapy

Initiation of preventive anticoagulant therapy:

- Heparin 7500 IU SC TDS

Or

- Enoxaparin 40 mg SC BID

Other therapeutic treatments

Convalescent plasma

Convalescent plasma results of several small clinical trials have revealed no dramatic effect¹. On the other hand, the findings from the widespread use of Convalescent plasma in the United States indicate that if it is prescribed with the high d antibody titer, compared to convalescent plasma with low antibody titers, the mortality rate may decrease. Convalescent plasma is also recommended to be administered during the first three days after the onset of symptoms.^{2,3}

Plasma should contain the appropriate antibody titer. The possibility of the adverse effects raised by receiving plasma with low antibody titers is also put forth.⁴.

Convalescent plasma is only used in national or academic/hospital clinical trials. Note that the treatment data must be recorded and be extractable.

Other drugs or treatments are used only in the form of a research project as registered clinical trials until the international findings on the cost-effectiveness of such measures are finalized.

Any medication regimen or other therapeutic approach such as hemoperfusion recorded only in the form of clinical trial studies can be implemented in medical centers after being approved by the National Scientific Committee of Corona and obtaining permission from the University Ethics Committee, and providing the required resources. Medical centers conducting clinical trials are required to provide the results to the Corona State Scientific Committee. A list of registered clinical trials is available on IRCT.ir. Except in special cases (e.g., in MIS-C children), IVIg has no place and is not allowed in the treatment of COVID-19.

Prescribing anticoagulants in patients with COVID-19 infection

¹ Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020; 324: 460-70.

² Food and Drug Administration. Convalescent plasma COVID-19 letter of authorization. August 23, 2020 (<https://www.fda.gov/media/141477/download>).

³ Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. August 12, 2020 (<https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1>). preprint

⁴ Simonovich VA, Burgos Prax LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, Savoy N, Giunta DH, Pérez LG, Sánchez MD, Gamarnik AV. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. New England Journal of Medicine. 2020 Nov 24

Patients with COVID-19 disease have a type of coagulation disorder known as COVID coagulopathy.

In this type of coagulation disorder, there is an increase in the level of inflammatory markers, fibrinogen, and D-dimer, and at the beginning of their emergence, disorders are uncommon in PT and PTT tests and platelet counting. This type of coagulation is associated with the emergence of thromboembolic events. The presence of evidence of diffuse intravascular coagulation is also associated with an unfavorable prognosis in these patients. Previous studies have revealed that prophylaxis along with enoxaparin or heparin in severe cases of the COVID-19 disease or patients with D- dimer >6 average decreases mortality.

In this regard, it is essential to observe the following points:

1. Aspirin or anticoagulants are not recommended for the treatment of outpatients with COVID-19 disease.
2. In all patients admitted to the hospital, after assessing the risk of bleeding, prophylactic drug by enoxaparin or heparin is recommended.
3. In choosing the dose and type of anticoagulant prophylaxis, the risk of bleeding, renal function, platelet counting, and the patient's weight should be considered.
4. In all patients not having critical clinical conditions (not hospitalized in ICUs), the standard dose of anticoagulant prophylaxis is recommended after assessing the risk of bleeding.
 - a. Heparin 5000IU SC TDS
-BMI \geq 40: Heparin 7500 IU SC TDS
 - Or
 - b. Enoxaparin 40 mg SC once daily
-BMI \geq 40: Enoxaparin 40 mg BID
5. In all patients having critical clinical conditions (hospitalized in ICUs), a moderate dose of anticoagulant prophylaxis (i.e., enoxaparin 60 mg/day, or heparin 7500 units three times a day subcutaneously) is recommended.
6. Changing the dose of prophylaxis anticoagulant only based on D-dimer count is not recommended
7. In patients with impaired coagulation tests, if there is no active bleeding, anticoagulant prophylaxis is recommended, and anticoagulant use is stopped only if the platelet count is <25000 per microliter or fibrinogen <50 mg /dL.
8. In patients who are prohibited from using anticoagulants, mechanical prophylaxis methods such as compression stocking are recommended.
9. Patients treated with aspirin for other medical reasons, aspirin is recommended to be continued after hospitalization due to the COVID-19 disease.
10. IN patients treated with anticoagulants for reasons such as thromboembolism or atrial fibrillation, if the platelets are <30-50000 per microliter (Platelet <50,000 for heparin and <30,000 for low molecular weight heparin) or fibrinogen <100 mg/dL, the continuation or non-continuation of anticoagulants should be decided by the treatment team regarding the patients' conditions and the risk of thrombosis and bleeding.
11. If there is evidence in favor of thromboembolism according to the standard diagnosis and treatment method.

12. It is recommended to prescribe anticoagulants without diagnostic tests in the following cases.

- Intubated patients who suddenly have clinical (e.g., hypoxia) and laboratory evidence of thromboembolism.
- Presence of clinical signs consistent with thromboses such as superficial thrombophlebitis or ischemia and peripheral cyanosis or thrombosis filter or dialysis catheter, despite retiform purpura in the organs).
- In patients with respiratory failure, especially when the D-dimer or fibrinogen is very high. Other factors such as acute respiratory distress syndrome or overload do not justify the patient's symptoms, and thromboembolism is highly suspected.
- Patients treated with CRRT¹ or ECMO²

13. The use of prophylactic anticoagulants after discharging from the hospital is not routinely recommended. However, in patients with the lower risk of bleeding caused by coagulants, continuation of anticoagulant prophylaxis is recommended after discharge for 2-4 weeks.

A. Patients who have been intubated and sedated in ICUS for several days

D. Patients having thromboembolism (e.g., cancer, lack of mobility, and excessive muscle weakness) after discharge

Renal complications in COVID-19 disease

The prevalence of acute renal failure (AKI) mortality rate is about 5-15% in MERS and SARS infections, and its mortality rate is 60-90%. In the early studies, the risk of AKI in the COVID-19 infection was low and about 3-8%; however, the subsequent studies reported it to be 37%. A large prospective cohort study on approximately 700 patients in China revealed that 44% of the COVID-19 patients at the time of admission had proteinuria, and about 26% of these patients were suffering from Hematuria. About 13 to 14% of patients had increased urea and creatinine and decreased eGFR by <60ml/min per 1.73 m² of the body surface. In this study, AKI was noticed in 5% of cases. It also increased the risk of mortality in the hospital.

On the other hand, AKI was more prevalent (25%) in the ARDS patients, as documented in other studies, and worsened the prognosis and increased mortality risk. In another study in Italy on more than 2,000 patients with COVID-19, the prevalence of AKI in the ARDS patients was about 28%. However, the prevalence of renal involvement has been higher in recent reports. In a study, the patients with COVID-19 disease on the first day of hospitalization had severe albuminuria, 63% of the patients developed proteinuria during the remaining days of hospital stay. BUN was high in 27% of all patients and in two-third of patients who died. The prevalence of AKI is associated with the severity of the disease so that the prevalence was high (about 90%) in patients under the mechanical ventilator treatment; however, it was less common (about 22%) in patients who are not in critical conditions. The AKI predictors are aging, diabetes, hypertension, cardiovascular diseases, mechanical ventilation, and the use of vasopressor drugs.

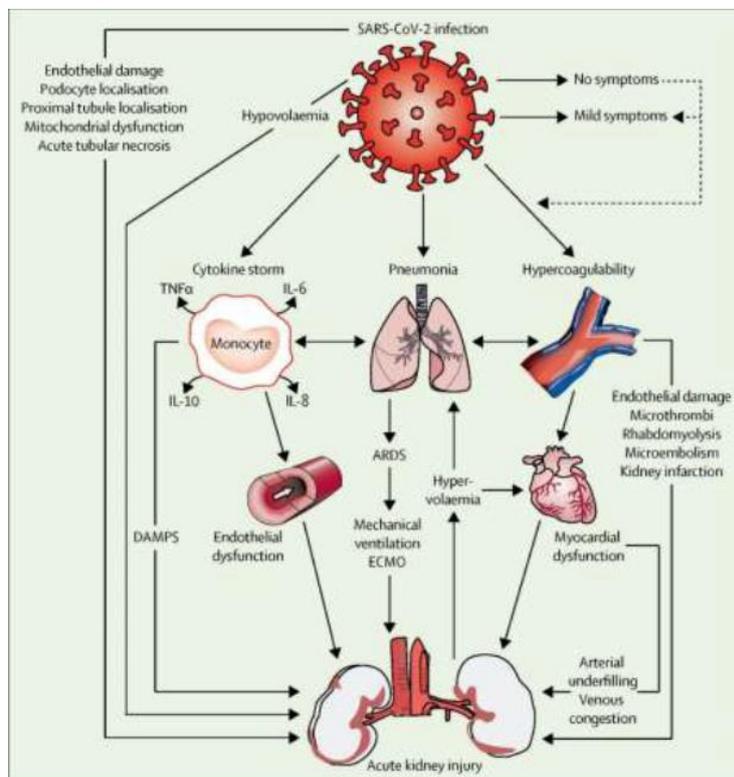
¹ Extracorporeal membrane oxygenation

² Continuous Renal Replacement Therapies

Hypokalemia is one of the most common findings in patients with COVID-19 infection, especially in severe cases. In a study, 93% of ICU patients had hypokalemia at the time of admission. This is because of increased caliversis induced by increased diarrhea, medications, and angiotensin II.

The mechanisms proposed for kidney involvement in the COVID-19 infection have been suggested to be multifactorial and includes direct cytotoxicity of the virus on renal endothelial cells, rhabdomyolysis, renal hypoperfusion, direct renal damage by cytokines in Cytokine Storm Syndrome or HLH Syndrome or increased cytokine production by ECMO or mechanical ventilator, cardiorenal syndrome due to secondary right ventricular failure to COVID-19 pneumonia and left secondary ventricular failure to viral myocarditis, medullary renal hypoxia caused by alveolar injury, and renal compartment syndrome caused by high peak airway pressure or intra-abdominal hypertension, eventually septicemic AKI.

AKI Mechanisms in COVID-19



Renal histopathological evidence in autopsy and biopsy includes RPGN, clamping glomerulopathy, and ATN.

Given the prevalence of renal involvement in this infection and its effect on the prognosis and outcome of the disease in patients with symptoms or those hospitalized for any reason, kidney function tests, and complete urinalysis are recommended to measure serum urea and creatinine. Moreover, calcium, phosphorus, uric acid, and serum potassium should also be measured to determine the likelihood of hypocalcemia. In hypocalcemia rhabdomyolysis, there are hyperphosphatemia, hyperuricemia, and hyperkalemia.

Evaluation of AKI in hospitalized individuals

Prerenal agents should be considered in AKI patients with suspected or positive COVID-19. The patient's hydration status should be checked and prevent hydration deficiency or over-hydration because it worsens respiratory status, especially in patients with ARDS. The etiological assessment of AKI is performed similar to those for critical patients in non-Coronavirus cases. Some tests such as complete urinalysis and urea and creatinine measurement are easily performed; however, the ultrasound of the kidneys and urinary tract in the evaluation of non-Coronavirus patients with AKI is difficult because staff should have less contact with COVID-19 patients.

AKI Treatment in hospitalized patients

In these patients, the AKI treatment is not different from the treatment in other non-COVID-19 patients; however, it should be noted that it should not cause over-hydration. Hemodialysis indications in COVID-19 patients (e.g., overload, severe refractory hyperkalemia, severe refractory acidosis, pericarditis, etc.) are not different from other those in non-COVID-19 patients.

It should be noted that these patients should be isolated from other patients undergoing hemodialysis to be hemodialyzed by only one person in a separate room, if possible. The concerned staff must observe all personal protection principles. In deadly sick patients, dialysis is better be conducted in the ICU. If the patient's hemodynamics are stabilized, a regular hemodialysis machine can be used. However, it is better to use CRRT for cases when the patient's hemodynamic condition is disturbed. In the care centers not equipped with CRRT, prolonged intermittent renal replacement therapy or sustained low-efficiency dialysis (SLED), which many new Hemodialysis devices can perform, can be adopted. Since the risk of thrombosis in these patients is high, heparin should be used.

Enoxaparin is prohibited for these patients.

Discharge criteria

The doctor's opinion and clinical decision are always the most important determinant of patients' discharge. It is also beneficial to consider the following points:

The following criteria must be met for the discharge of hospitalized patients:

- The fever should be stopped for at least 24-48 hours without using anti-fevers.
- Respiratory symptoms such as cough are improving (continuous coughing is stopped), and there is no shortness of breath. □
- SpO₂ ≥ 93% with no ventilator in the room. If it is lower and the other discharge criteria are met, the oxygen saturation level should be stabilized within an acceptable level (SpO₂ ≥ 90%) for two to three consecutive days and does not decrease (In patients with underlying respiratory disease, SpO₂ > 88% can be considered for stabilization based on clinical decisions.

- Other vital signs of the patient are stable at the discretion of the physician.

The following criteria can help you have a better decision about discharge:

-CBC should be getting normalized before discharge normal, and CRP and ESR should drop at least 20 and 50%, compared to the past.

- There has been a decrease in previous imaging findings, and no new lesion emerges in cases where CXR / CT scans are requested due to the severity of symptoms.

- The patient does not need intravenous therapy and has oral tolerance.

RT-PCR now is not one of the prerequisites of discharge; however, it may be recommended in the following cases and in accordance with facilities and the patient's conditions and post-discharge care place:

- Patients with underlying immunodeficiency

- Patients to be transferred to long-term care units

All patients and their families need to be educated before discharge about preventing the virus spread, isolation, self-assessment, and self-care, and becoming familiar with the warning signs of the disease relapse.

Post-discharge care and continued isolation of the patient

At the discharge time, the following points should be considered to ensure the health of the patient and those individuals around him:

Follow-up after discharge:

The patients' profiles should be recorded at the discharge time by the hospital caregivers on the Electronic Health Record Systems (Sib, Rial, Sina, Nab, and Parsa), and the necessary information should be provided to the patient.

Here are some possible recommendations to the patients:

-Full observance of isolation principles during the specified time at home

- Suggesting those in contact with the patient to refer to selected comprehensive health service centers (after 16-24 hours) to have relevant assessments.

- Returning to the hospital if the symptoms such as fever, shortness of breath, loss of consciousness, or severe coughs emerge.

Principles of isolation at home

-Place the patient in a room with proper ventilation (The doors and windows of the room can be opened).

- Restrict the patient's movement and transfer. If possible, the shared areas (e.g., kitchen, bathroom, restrooms, etc.) should have proper ventilation. Open windows for air circulation.