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COVID-19-Induced Acute Respiratory Distress Syndrome (CARDS) Management

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Abstract

The lungs are the most affected organ due to SARS-CoV-2 infection. The lung damage due to severe COVID-19 is not similar to traditional ARDS. The histological analysis displayed Diffuse Alveolar Damage (DAD) with cellular fibro-myxoid exudates, desquamation of pneumocytes, pulmonary edema and hyaline membrane formation, which is similar histopathological changes seen in Acute Respiratory Distress Syndrome (ARDS). Patients with COVID-19 related lung injury full-fill the Berlin criteria of ARDS (i.e. PaO_2/FiO_2 ratio ≤ 200, measured at PEEP=5 cmH_2O) could present with certain characteristics, as compared to classical forms of ARDS. Such as refractory hypoxemia which doesn't correlate with relatively preserved lung mechanics, hypercapnia with high Ventilatory Ratio (VR) and also low alveolar recruitability which is improved by body positioning. The pathophysiology of COVID-19 related ARDS is different from ARDS induced by other causes; COVID-19 patients usually present with an intense endothelial dysfunction and thrombo-inflammatory state which leads to both micro-thrombosis and macro-thrombosis along with extreme pulmonary vasoconstriction which leads to significant alveolar dead space.

Keywords: COVID-19; Acute respiratory distress syndrome; Diffuse alveolar damage; Elastance; Recruitability

Introduction

The COVID-19 pandemic has emerged as a universal health crisis and the lung is the most affected organ by SARS-CoV-2 infection. The lung damage due to severe COVID-19 is not similar to traditional ARDS due to other pathology other than COVID-19 the pathophysiology of traditional ARDS is generally consistent with all types of abnormalities (gas exchange abnormalities, mechanics, the presence of physiological dead space, loss of lung volumes) and also the risk of development of ventilator-induced lung injury. So the sickest patients, i.e. those patients with severe hypoxemia are those patients with severe lung damage and more mechanics abnormalities and less aerated lung [1]. Where as in COVID-19 related lung injury largely depends on lung elastance, the unusual presentation of patients having relatively preserved lung mechanics i.e. good, or low elastance yet there is severe hypoxemia due to significant shunting [2]. The findings in autopsy as described in COVID-19 related lung injury, the patients could suggest an anatomical–pathological explanation for these findings, with distortion and abnormalities of capillary vascularization "Intussusceptive" angiogenesis along with the presence of microthrombi [3,4]. Intussusceptive angiogenesis is a fast development of intravascular-septation that creates two lumens from a single blood vessel within minutes [3]. This process is described in cancer, inflammatory disorders and tissue regeneration [5,6]. The micro-vascular abnormalities seen in COVID-19 related lung injury, the vasoconstriction and micro-thrombi in smaller blood vessels; results in hypoxia, shunting and elevation of pulmonary vascular resistance [7] and hence the discrepancy between a general well-preserved lung mechanics and the severity of hypoxemia could be justified by a reduced capacity of vascular tone in the pulmonary micro-vasculature and micro-thrombi [3].

The pathology of COVID-19 induced lung injury

In the initial case report of post mortem from China of the lung biopsy from patient died due to COVID-19 related lung injury. The histological analysis displayed Diffuse Alveolar Damage (DAD) with cellular fibro-myxoid exudates, desquamation of pneumocytes, pulmonary edema and hyaline membrane formation, which is similar histopathological changes seen in Acute Respiratory Distress Syndrome (ARDS). The interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes and multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, and in the intra-alveolar space; amphophilic granular cytoplasm, and prominent nucleoli were

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seen [8]. Later report suggests that COVID-19 related lung injury differs from typical ARDS at histopathological level. Some studies reported certain specific changes such as alveolar micro-vascular abnormalities the best example is 'Intussusceptive angiogenesis' and signs of micro-thrombi in smaller blood vessels. This changes leads to the activation of clotting pathway with consequent fibrin deposition so the vascular damage is more common in COVID-19 related lung injury, compared to other causes of ARDS, however ARDS in COVID-19 disease should not to be proposed as independent from DAD, but ARDS in these patients reflects the common denominator of DAD with the addition of vascular damage [9,10].

Respiratory mechanics and gas exchange in COVID-19–related lung injury

Patients with COVID-19 related lung injury full-fill the Berlin criteria of ARDS (i.e. PaO_2/FiO_2 ratio ≤ 200, measured at PEEP=5 cmH_2O) could present with certain characteristics, as compared to classical forms of ARDS [2]. Such as refractory hypoxemia which doesn't correlate with relatively preserved lung mechanics, hypercapnia with high Ventilatory Ratio (VR) and also low alveolar recruitability which is improved by body positioning [2,11,12]. Gattinoni et al. described two main distinctive types of COVID-19-related lung injury and probably comprise different pathophysiological mechanisms: COVID-19 pneumonia type L (Low elastance) or high compliance which characterized by low ventilation-to-perfusion ratio, and low recruitability, and COVID-19 pneumonia type H (High elastance) with high right-to-left shunt (i.e., less aerated areas of the lung are more perfused) and high recruitability, similar to what is faced in classic ARDS [2]. These changes lead to elevation of alveolar dead space as measured by Electrical Impedance Tomography (EIT) this observation could be a specific pathophysiological trait [13]. Recognizing the different types of Pneumonia (Type L *vs.* Type H) early is critical in the management of COVID-19 related lung injury, in first type (Type L), the Hypoxemia in these group of patients is due to ventilation/perfusion mismatch and hence delivering high flow oxygen is important to avoid intubation and mechanical ventilation where as in second type (Type H) the hypoxemia is related to right to left shunt and on these group of patients frequently necessitate earlier mechanical ventilation [14]. Gattinoni et al. descried four types of hypoxemia mechanisms in COVID-19 related lung injury: Hypoventilation (due to physiological alveolar dead space), diffusion impairment (as a result of thickening of inter-lobular septae), right to left shunt (i.e. hypo-ventilated areas of the lung are more perfused), and last but not the least is ventilation-perfusion mismatch which is the most important factor in these group of patients resulting from blood perfusing lung areas that have partial or no ventilation [2]. Based on large cohort study at baseline (i.e., first day on invasive mechanical ventilation), the following mechanics parameters ranges are found; tidal volume 6.3 ml/kg to 7.8 ml/kg predicted body weight, positive end-expiratory pressure 11 cmH_2O to 14 cmH_2O, respiratory system compliance ranges 27 ml/cmH_2O to 45 ml/cmH_2O, plateau pressure 22 cmH_2O to 29 cmH_2O, and driving pressure 10 cmH_2O to 16 cmH_2O, these ranges are comparable to values from non-COVID-19 ARDS [15]. These finding supported by Domenico et al. [16], he reported the following parameters in COVID-19 ARDS (CARDS) patients in comparison to non-COVID ARDS (nCARDS) patients; at low PEEP, the reported ranges of PaO_2/FiO_2 is 101 to 142 in CARDS and 87 to 154 in nCARDS. The compliance ranges 32 ml/cmH_2O to 52 ml/cmH_2O in CARDS *vs.* 27 to 42 in nCARDS with p=0.045) and ventilatory ratio 1.7 to 2.3 in CARDS *vs.* 1.4 to 2.1 in nCARDS, p=0.032 were somewhat greater in CARDS patients. In CARDS, PaO_2/FiO_2 was linearly interrelated with respiratory system compliance (r=0.52, p=0.003). Elevated PEEP more remarkably improved PaO_2/FiO_2 in CARDS compared to nCARDS, (p=0.005) however the recruitability seen in both group (CARDS *vs.* nCARDS) was similar but worth to note that CARDS patients, the recruitability was independent from oxygenation and respiratory mechanics changes due to PEEP [16,17].

COVID-19 and CT chest

Sana Salehi et al. [18], described the initial CT pattern (Figure 1), distribution and location in large series of COVID-19 patients: GGO 88%, Bilateral involvement 88%, posterior distribution 80%, multi-lobar involvement 79%, peripheral location 76% and consolidation in 32%. The left lower lobe was the most commonly involved 81% [19,20].

HRCT: Diagnosis and prognosis of COVID-19 infection

Generally the changes seen in HRCT is not specific for COVID-19 infection however the GGO and other described changes usually seen in COVID-19 patients revealed significant links with some clinical and laboratory findings, the C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase showed significantly positive correlation with the severity of initial CT opacifications (P<0.05) [21]. The highest temperature and the severity of radiological changes seen on initial CT were significantly linked to the advancement of radiological changes seen on follow-up CT (P=0.001–0.04), so high grade fever on initial presentation is a possible risk factor of aggressive CT outcomes so chest CT scans are not satisfactory to diagnose COVID-19 alone however it can be valuable complement to other tools such as PCR for diagnosing patients with COVID-19 and following their prognosis [20,21].

COVID-19 CO-RADS classification

The CO-RADS classification is a uniformed reporting system for patients suspected to have COVID-19 infection, this system is proposed for radiologists by COVID working group of the Dutch Radiology Society, the scoring system based on the presence or absence and the distribution of GGO and whether the COVID-19 PCR is negative or positive [22]. Basically the scoring system range from 1 to 6; CO-RADS 1; normal CT or radiological changes consistent with non-infectious abnormalities, has high negative predictive value, CO-RADS 5 has high positive predictive value and CT findings is typical of COVID-19 changes which includes multifocal GGO and consolidation, CO-RADS 6; Patient with positive PCR and bilateral GGO. The CO-RADS 2 to 4 has high inter-observer discrepancy and has a poor negative and positive predictive values [22].

HRCT: Management of COVID-19 infection

The use of CT in patient suspected to have COVID-19 infection to be isolated when there is delay on PCR result or suspected the result of PCR false negative, therefore improving patient management and outcome [23]. Pan describing four stages of CT changes in patients recovered from COVID-19 infection: (1) early stage (0 to 4 days) that revealed minor GGO located in sub-pleural areas in the lower parts of the lung, (2) progressive stage (5 to 8 days) when infection rapidly extended to both lungs and multi-lobes involvement with diffuse GGO, consolidation, and crazy-paving pattern, (3) peak stage (10 to 13 days) that demonstrate slow expansion of the involved part to the peak involvement, including diffused GGO, crazy-paving pattern, residual parenchymal bands, and consolidation, and lastly

(4) absorption stage which occurs two weeks after the beginning of first symptoms and shows that the disease is managed and the consolidation is slowly absorbed [24]. These stages help the physician in making the decision of type of management. CT scans also frequently used to demonstrate the progression and complications of COIVD-19 patients' when managed in critical care [22]. Not uncommon to have negative PCR more than once in highly clinically suspected infected with COVID-19 and hence the CT finding when it is classical findings, certain actions can be taken, such as strict isolation to prevent viral transmission, also normal CT in patient with COVID-19 positive PCR could be a good prognostic factor of the absence of lung involvement and hence early discharge of the patient [25,26]. Last but not least, there is good correlation between certain radiological findings; such as consolidation, air-trapping and or evidence of acute lung injury with oxygenation impairment as expressed by PaO_2/FiO_2 ratio [26].

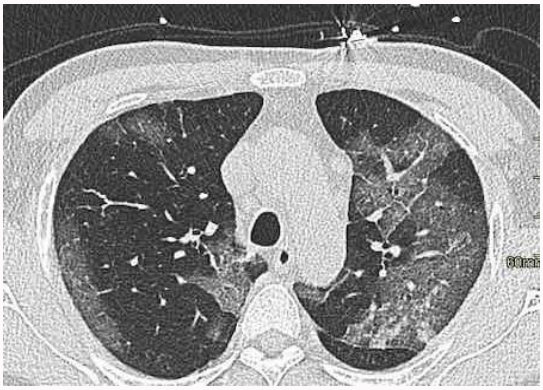

Figure 1: Ground Glass Opacity (GGO): GGO pattern is the most reported changes seen in COVID-19 infections in approximately 50% to 90% as solo changes and it can be seen with other changes. The classic pattern; multifocal, bilateral and peripheral, in early phase it can be unifocal [19,20].

COVID-related ARDS management in critical care

SARS-CoV-2, is responsible for the largest pandemic facing humanity since the Spanish flu pandemic in the early twentieth century, as there is no specific antiviral therapy, hence optimizing the support is the most critical element in the patient's clinical out-come [27]. Comprehensive understanding of lung mechanics is crucial to minimize the risk of developing Ventilatory-Induced Lung Injury (VILI) and, perhaps, improve the prognosis [28,29]. It is very important that physician working in intensive care have good information of physiological principles to correctly translate arterial oxygenation in clinical practice, and hence to intubate on the right time, to effectively achieve optimum mechanical ventilation, and, lastly, to commence weaning from the ventilator, as securely and as expeditiously as possible [30]. It has been clearly seen and documented in many studies that's the effects of ventilator settings (such as; tidal volume, Positive End-Expiratory Pressure [PEEP]) on VILI is variable from one patient to another based on the clinical condition of the patient and severity of the respiratory involvement such as lung stiffness and the compliance and hence it will influence the clinical outcome [31-33].

ICU admission criteria for patients infected with COVID-19: Severe patients with COVID-19 typically present respiratory rates ≥ 30 breaths per minute, oxygen saturation ≤ 93%, and lung infiltrates in the chest radiography >50% are at high risk for clinical deterioration and for developing critical illness, including Acute Respiratory Distress Syndrome (ARDS) and hence admission to the hospital should be merited for all patients developed such severe symptoms [34,35]. However, admission to intensive care has been kept for the utmost severe forms, however the criteria for ICU admission is vary from one hospital to another, depending on the capacity of the hospital, in generally around 25% of hospitalized patient was accepted to be admitted to intensive care unit [36,37]. Patients with the severe symptoms and signs must be carefully monitored, because the possibility of progression from moderate to severe form of ARDS un-expectedly can happen any time, acute hypoxemic respiratory failure is the most encountered complication happening in patients admitted to the ICU in about 60% to 70% of high risk group may develop ARDS are elderly patients, age >65 years, has high grade fever (T>39ºC), neutropenia, lymphopenia, elevated aspartate amino transferase, alanine amino transferase, elevated urea and creatinine, high acute phase markers such C-reactive protein, procalcitonin and serum ferritin and elevated coagulopathy indicators (such as prothrombin time, fibrinogen, and D-dimer) [35,36,38]. Admission to intensive care unit criteria include oxygen requirements ≥ 6 L/min to 8 L/min to reach a peripheral oxygen saturation ≥ 90% to 92%, respiratory failure, shock, acute organ failure, and patients at high risk for clinical deterioration. However, in many countries, due to the shortage of ICU beds in particular during the peak of the pandemic, usually only patients requiring mechanical intubation and ventilation were admitted to intensive care [27].

Mechanical ventilation strategies: Understanding the pathophysiology of COVID-19-induced ARDS is the key success in managing the critical COVID-19 patients; the pathophysiology of COVID-19 related ARDS is different from ARDS induced by other causes; COVID-19 patients usually present with an intense endothelial dysfunction and thrombo-inflammatory state which leads to both micro-thrombosis and macro-thrombosis along with extreme pulmonary vaso-constriction which leads to significant alveolar dead space [39,40]. Understanding the COVID-19 viral induced-lung injury is one of most important factor on patient's management, bellow is simplified pathophysiology of COVID-19 as described by Niraj Kumar Jha et al. [41]. In hospitalized patients, the ventilatory support varies from the need for O_2 supplementation through a nasal canula to invasive mechanical ventilation or extracorporeal membrane oxygenation (veno-venous ECMO) in patients with the most severe forms of ARDS. Generally the patients need to be maintained on oxygen therapy with oxygen saturation between 92 and 96%. The degree of hypoxemia can be calculated by SpO_2/FiO_2 ratios, with values ≤ 315 suggesting ARDS [42].

Many hospitals around the globe have implemented Non-Invasive Ventilation (NIV) as a therapeutic step to prevent further deterioration and development of respiratory failure requiring mechanical ventilation. Many international bodies such as European Society for intensive care Medicine (ESICM) with the international Surviving Sepsis Campaign recommended the use of NIV as an initial step for respiratory failure with COVID-19 in adult patient, however the recommendation remained low-quality evidence [43] (Figure 2).

The prone position in non-ventilated patients have been used in many centers with various success and it was noticed that's the patient who tolerated the prone position for more than three hours have great improvement in oxygenation, however only 50% of the patients maintain the benefit after resupination [44,45].

Invasive mechanical ventilation: Acute Respiratory Distress

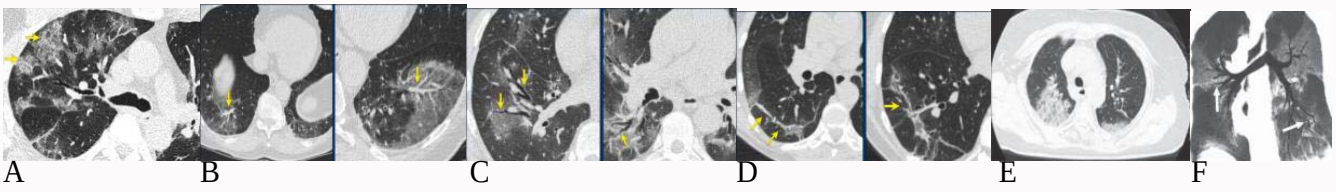

Figure 2: Other radiological changes; A: Crazy paving, B: Vascular dilatation, C: Traction Bronchiectasis, D: Sub-pleural bands and E: Consolidation with air bronchogram [20] and F: Bronchus deformation which leads to air trapping [21].

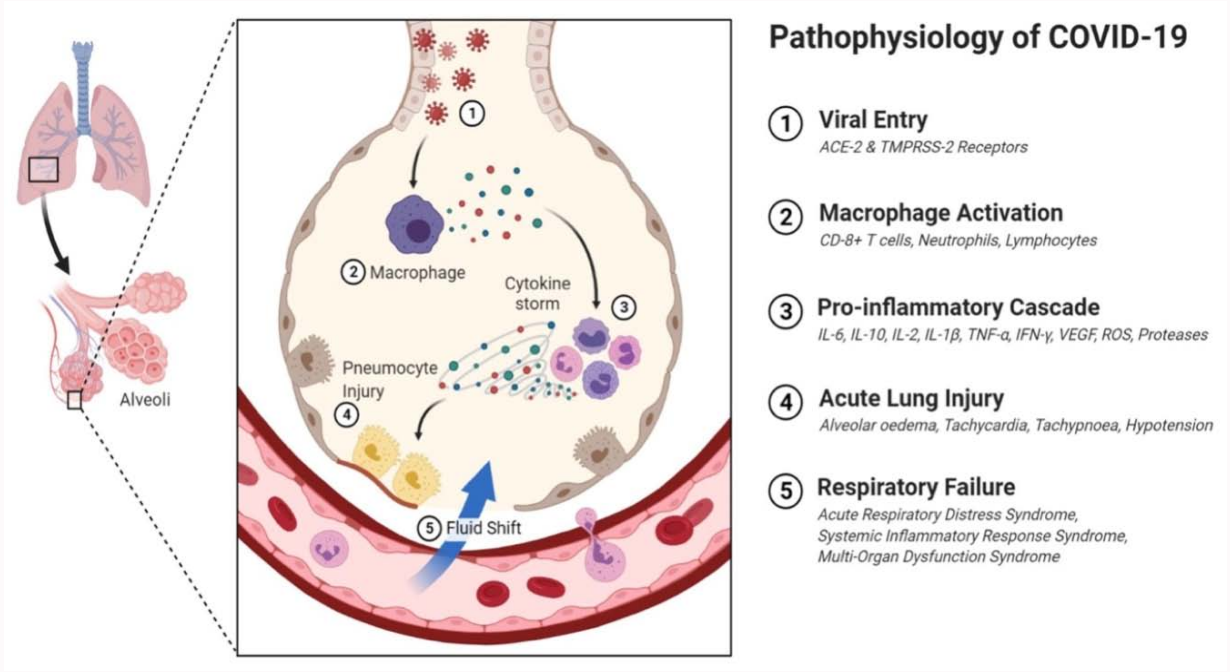

Figure 3: Pathophysiology of COVID-19.

Syndrome (ARDS) is non-cardiogenic pulmonary edema and according to Berlin definition, the proposed ARDS categories based on Hypoxemia degree:

- Mild (200 mmHg <PaO_2/ FIO_2 ≤ 300 mmHg),
- Moderate (100 mmHg <PaO_2/ FIO_2 ≤ 200 mmHg), and
- Severe (PaO_2/FIO_2 ≤ 100 mmHg)

and also based on variables for severe ARDS:

- Radiographic severity
- Respiratory system compliance (≤ 40 mL/cmH_2O),
- Positive end-expiratory pressure (PEEP) (≥ 10 cmH_2O), and
- Corrected expired volume per minute (≥ 10 L/min) [46].

There are certain maneuvers can be used to recruit the collapsed areas in the lung such as prone position, PEEP and alveolar recruitment maneuvers (brief and controlled increase in trans-pulmonary pressure) these leads to reduction in elastance and increased in compliance [47]. Prone position serves to relieve the severe hypoxemia by reducing the hyper-inflated areas in the lung, which then promoting alveolar recruitment and reduction of V/Q mismatch, this can be considered in patient with PO_2/FiO_2<150 [48,49].

The aim of mechanical ventilation in COVID-19 related ARDS patients is to preserve a lung-protective strategy, and this can be achieved by targeting a tidal Volume (Vt) of 4 mL/kg to 8 mL/kg Predicted Body Weight (PBW) and a plateau pressure of less than 30 cmH_2O, these values adopted by many centers around the globe [47].

Specific drug treatment

Antithrombotic treatment: One of the most important treatment strategy in COVID-19 patients, as in many studies showed there is severe pulmonary endothelial damage with extensive micro-thrombosis and angiopathy there also studies showed high incidence of Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) ranging from 35% to 78% in COVID-19 patients [4,50,51] (Figure 3). Hence most experts recommend pharmacologic Venous Thromboembolism (VTE) prophylaxis in all hospitalized COVID-19 patients as long as there is no contraindication [47,52]. The guidelines stressed that the anticoagulation regimens can be revised based on obesity (50% increases in dose), severe thrombocytopenia, or worsening renal function [53]. Based on expert opinions and retrospective studies the therapeutic dose can be considered for patients with severe COVID-19 and signs of 1 Sepsis-Induced Coagulopathy (SIC) and/or high D-dimer (6 × higher the reference values) in association with other biomarkers of severity and there is no contraindication for anticoagulation bellow is a proposed algorithm by Hajjar et al. [27], to assess thrombogenesis in patients with COVID- 19, as well as a treatment algorithm [54,55]. Unfortunately

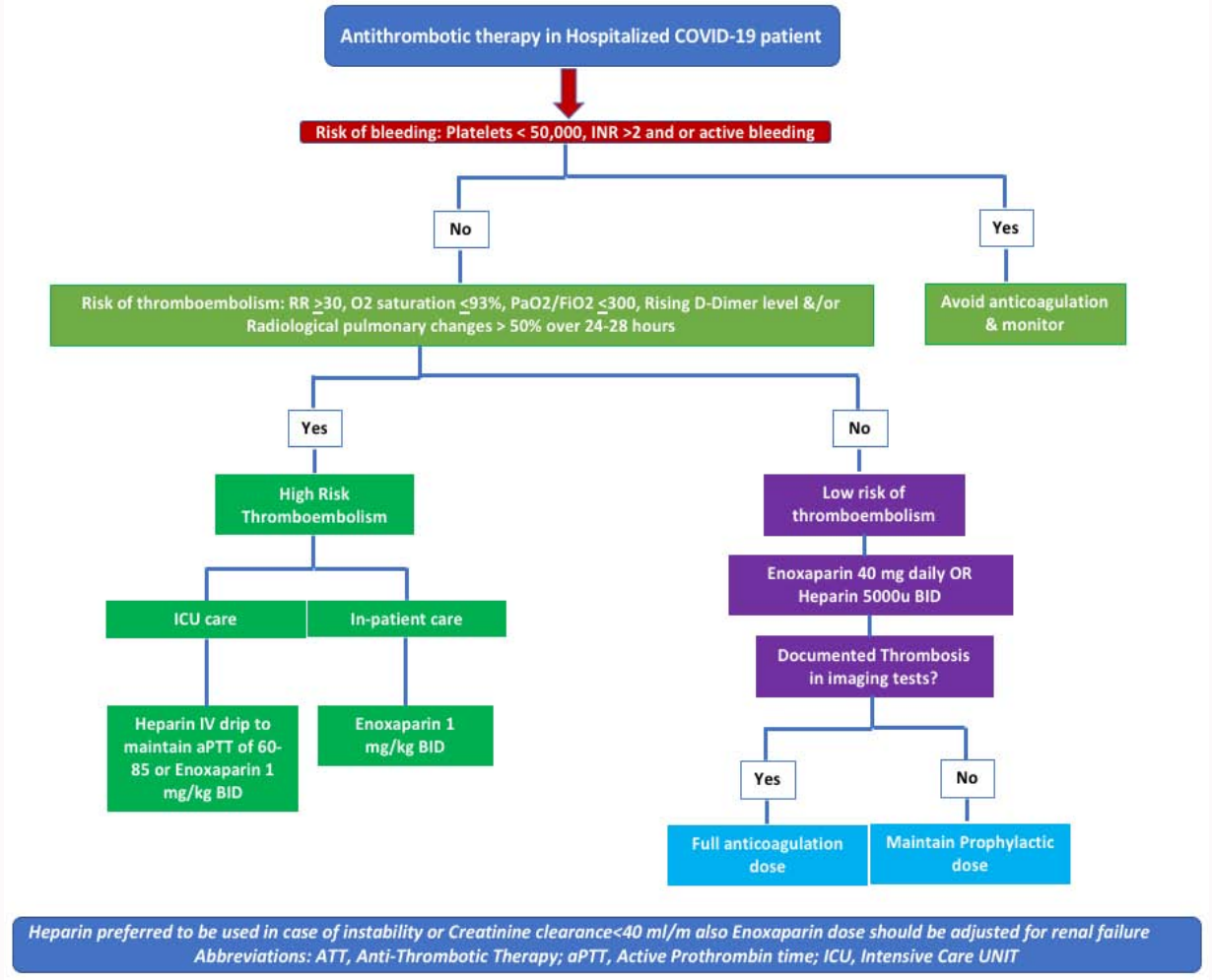

Figure 4: Antithrombotic treatment strategy in COVID-19 patients.

the available data are insufficient to identify the best drug used as anti-coagulant.

Systemic steroid: The National Institute for Health and Care Excellence (NICE) recommend the use of dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- Require oxygen supplement to meet their prescribed oxygen saturation levels or
- Have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Continue corticosteroids for up to 10 days unless there is a clear indication to stop early [56].

Tocilizumab: NICE recommend to use tocilizumab to adults in hospitalized COVID-19 patients if all of the following met:

- They are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- They have not had another interleukin-6 inhibitor during this admission
- There is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they either: Need supplemental oxygen and have a C-reactive protein level of >75 mg/liter, or are within 48 h of starting high-flow nasal oxygen, continuous positive airway pressure, Non-Invasive Ventilation (NIV) or invasive mechanical ventilation [56].

Conclusion

COVID-19 is one of the most challenging health care crises we have seen and faced in this century. Health care-giver is undergoing very difficult times, with a lot of limitation in resources and evidence based information, to date, there is no proven precise anti-viral therapy approved for COVID-19.

Early diagnosis and practicing on right time the appropriate interventional strategies are the key of treatment success, COVID-19 related lung injury and dysfunction is a unique characteristics and hence requires an individualized therapy, all physician taking care of COVID-19 patient should aware and have evidence based knowledge about the hemodynamic and cardio-pulmonary support.

Clearly the available COVID-19 vaccines are the way to go to eradicate COVID-19 infection or to minimize the severity of the infection.

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