Review

An Imaging Overview of COVID-19 ARDS in ICU Patients and Its Complications: A Pictorial Review

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Abstract: A significant proportion of patients with COVID-19 pneumonia could develop acute respiratory distress syndrome (ARDS), thus requiring mechanical ventilation, and resulting in a high rate of intensive care unit (ICU) admission. Several complications can arise during an ICU stay, from both COVID-19 infection and the respiratory supporting system, including barotraumas (pneumothorax and pneumomediastinum), superimposed pneumonia, coagulation disorders (pulmonary embolism, venous thromboembolism, hemorrhages and acute ischemic stroke), abdominal involvement (acute mesenteric ischemia, pancreatitis and acute kidney injury) and sarcopenia. Imaging plays a pivotal role in the detection and monitoring of ICU complications and is expanding even to prognosis prediction. The present pictorial review describes the clinicopathological and radiological findings of COVID-19 ARDS in ICU patients and discusses the imaging features of complications related to invasive ventilation support, as well as those of COVID-19 itself in this particularly fragile population. Radiologists need to be familiar with COVID-19's possible extra-pulmonary complications and, through reliable and constant monitoring, guide therapeutic decisions. Moreover, as more research is pursued and the pathophysiology of COVID-19 is increasingly understood, the role of imaging must evolve accordingly, expanding from the diagnosis and subsequent management of patients to prognosis prediction.

Keywords: COVID-19; ARDS; lung CT; mechanical intubation; intensive care; superinfection; pneumothorax; pneumomediastinum; pulmonary embolism

1. Introduction

Imaging studies performed at the time of admission can help in the risk stratification of patients with COVID-19. In particular, CT findings of COVID-19 pneumonia have been classified by the Radiological Society of North America (RSNA) expert consensus [1] and their variation over a period of time as well as their correlation with patient outcomes has been described by several studies [2–5].

Some studies have shown that a significant proportion of patients with COVID-19 pneumonia (20–67%) could develop acute respiratory distress syndrome (ARDS), thus requiring mechanical ventilation and resulting in a high rate of intensive care unit (ICU) admission (26–32%) [6–8].

According to the American Thoracic Society and the Infectious Diseases Society of America clinical guidelines [9,10], all patients who require invasive mechanical ventilation and/or present with hypotensive shock with the need for vasopressors should be admitted to ICU. Patients should be admitted to ICU also in the presence of at least two minor criteria,

i.e., a respiratory rate > 30 respirations/minute, $PaO_2/FiO_2 < 250$, multi-lobar infiltrates, confusion or disorientation, uremia (BUN > 20 mg/dL), leukopenia, thrombocytopenia (platelets < 100,000 cm/mm^3), hypothermia (temperature < 98.2 °F), and hypotension requiring aggressive fluid administration [11].

Several studies reported that COVID-19 patients who have been admitted to ICU had more comorbidities and, interestingly, were more frequently males, suggesting a sexual dimorphism in the innate response to infections [12].

Low flow nasal oxygen (<6 L/min), high flow nasal oxygen (10–20 L/min), continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BPAP) are some of the non-invasive techniques used in patients with COVID-19 ARDS to improve blood oxygenation while maintaining appropriate SpO_2 levels [13,14].

Moreover, several studies have demonstrated the benefit of putting patients with COVID-19 with hypoxemia into the prone position [15–17]. In fact, since the posterior surface of the lungs is larger than the anterior surface, the prone position allows to minimize the de-recruitment on this large surface area, thus improving lung oxygenation [18].

Intubation and mechanical ventilation should be considered in the case of rapid progression of hypoxemia and no improvement after high flow oxygen administration, worsening mental status, hypercapnia, hemodynamic instability or multiorgan failure, and is required in most patients with ARDS [19,20]. Recently, it has been demonstrated that admission computed tomography (CT) scans of COVID-19 patients can effectively and reliably be used to determine risk factors for invasive ventilation in ICU [21]. In fact, critically ill patients that required invasive ventilation exhibited more imaging findings associated with the later stages of the disease and superimposed findings, such as subpleural band-like consolidations predominantly in dorsal lower lobes. The decision to intubate patients with COVID-19 has been controversial, with some authors recommending early intubation and others trying a stepwise approach to avoid intubation, if possible [22]. This variation is largely due to the evidence that patients on mechanical ventilation are prone to complications, such as barotrauma with alveolar rupture and superimposed bacterial pneumonia, that can often be identified simultaneously on the same patient [23,24].

When a patient continues to have refractory hypoxemia despite optimal mechanical ventilator and medical therapy, extracorporeal membrane oxygenation (ECMO) should be considered for those without contraindications [25,26]. ECMO can bypass the lungs through a veno-venous circuit (VV-ECMO), providing quite complete respiratory support. In particular, the VV-ECMO circuit drains venous blood through a cannula commonly positioned in the inferior vena cava, oxygenates the blood with the external membrane oxygenator, and then pumps the blood back into the same venous compartment, generally through a return cannula positioned in the superior vena cava [27]. The use of veno-arterial ECMO (VA-ECMO) in COVID-19 patients is reserved for those with severe respiratory failure accompanied by severe heart failure or other causes of cardiogenic shock.

Several complications can arise during an ICU stay, from both COVID-19 infection and the respiratory supporting system, including barotraumas (pneumothorax and pneumomediastinum), superimposed pneumonia, coagulation disorders (pulmonary embolism, venous thromboembolism, hemorrhages and acute ischemic stroke) and abdominal involvement (acute mesenteric ischemia, pancreatitis and acute kidney injury) [11,28–30]. Therefore, the management of critically ill COVID-19 patients is complex, involving multiple interventions and requiring numerous and potentially interactive therapies that are delivered by a variety of healthcare professionals.

Imaging plays a pivotal role in the detection and monitoring of ICU complications, most of which are life-threatening, thus improving patient outcomes and overall survival. Moreover, proper and correct identification of COVID-19 complications in ICU patients is fundamental, since the comorbidities of this severely ill population may camouflage typical clinical and radiological findings, thus possibly delaying the appropriate treatment [31].

Conventional X-ray is the first-line imaging modality used to evaluate tube positions in the ICU and complications associated with mechanical ventilation. CT represents the

best modality choice to indicate vascular alterations, both pulmonary and visceral and can provide adequate information on the state of the gastrointestinal and renal systems, also allowing for the evaluation of possible brain injuries.

The present pictorial review will describe the clinicopathological and radiological findings of COVID-19 ARDS in ICU patients and will discuss the imaging features of complications related to mechanical ventilation and ECMO, as well as those of COVID-19 itself in this particularly fragile population.

2. COVID-19 ARDS

COVID-19 ARDS is diagnosed when a patient with confirmed COVID-19 infection develops acute respiratory distress and meets the Berlin 2012 ARDS diagnostic criteria which include: (i) acute hypoxemic respiratory failure (ii) developing within 1 week of onset of symptoms (iii) with bilateral air space opacities on X-ray or CT (iv) not explained by cardiac failure or fluid overload [32,33].

The imaging features of COVID-19 ARDS are similar to ARDS from other etiologies and consist of a rapid progression of lung opacities from unilateral to multifocal or bilateral involvement, with predominantly peripheral location, lymphadenopathy and pleural effusion [34–36]. In the acute phase, there is a predilection for dense consolidation to involve the dependent posterior lower lobes with relative sparing of the anterior or non-dependent areas [37]. This evidence represents the rationale behind the implementation of a prone position for ARDS patients. It is important to be aware of when ICU patients are imaged in this position, as they may demonstrate an apparent improvement in consolidations in imaging [38].

However, many differences between COVID-19 ARDS and ARDS caused by other conditions have emerged. First of all, COVID-19 ARDS has a slight delay in onset ranging from 8 to 12 days compared to non-COVID-19 ARDS from other causes where the onset is within 7 days [39]. Moreover, a discrepancy in lung compliance has been supposed, with a possible dissociation between relatively well-preserved lung mechanics and the severity of hypoxemia [40,41]. A possible explanation for severe hypoxemia occurring in compliant lungs could be attributed to the loss of lung perfusion regulation and the consequent hypoxic vasoconstriction. In fact, patients with COVID-19 ARDS develop significantly more thrombotic complications as compared to patients with non-COVID-19 ARDS [42–44], thus leading to worse clinical outcomes due to both pulmonary and extra-pulmonary complications [45,46].

Pulmonary fibrosis is a recognized sequela of ARDS caused by other viruses. In severe acute respiratory syndrome (SARS), reticular changes were seen in half of the patients after 4 weeks, but the 15-year follow-up demonstrated that the interstitial abnormalities recovered over the first 2 years, with only 4.6% of patients still having interstitial abnormalities at 15 years [47]. In Middle East respiratory syndrome (MERS), chest X-ray abnormalities consistent with fibrosis were reported in 33% of patients at a median of 43 days from recovery [48] while, in H1N1 influenza, pulmonary fibrosis was recorded in 40% of patients who developed ARDS [49].

However, the temporal evolution of COVID-19 ARDS imaging features is still unknown, and the majority of radiological studies involved a small number of patients or still have a short follow-up to complete, thus its long-term sequelae are yet to be identified [37,50]. A 3-month follow-up CT study [51] demonstrated that reticular or fibrotic lesions were present in approximately 50% of patients who were admitted to ICU for COVID-19 ARDS; moreover, these findings were higher compared to that of residual radiographic survivors with other viral pneumonias. However, a more recent study [52] reported that only approximately 14% of COVID-19 patients discharged from ICU kept fibrotic-like changes at the 1-year follow-up, thus suggesting a progressive regression of residual lung damage and, moreover, the residual lung damage rate was slightly lower compared to other causes of ARDS (Figure 1A,B). Therefore, the risk of developing long-term

pulmonary sequelae after COVID-19 pneumonia is still a matter of debate and requires further investigations due to the lack of longer follow-ups for this relatively novel disease.
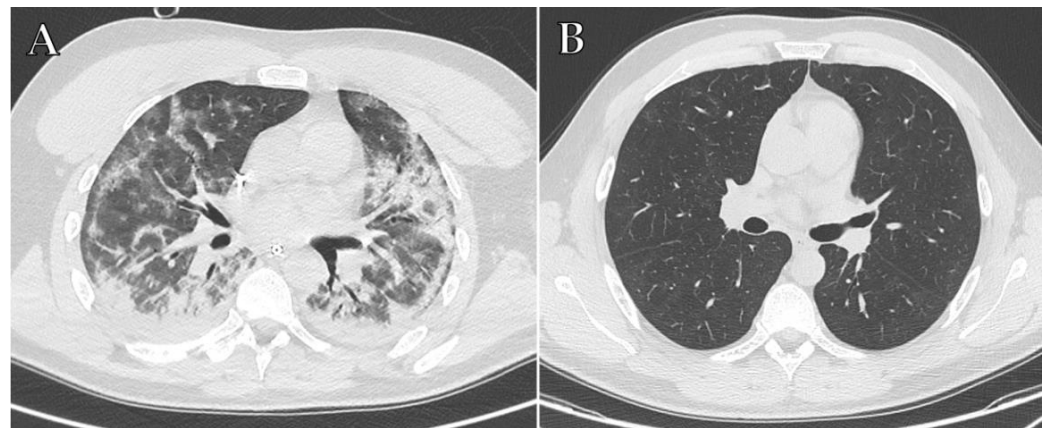

Figure 1. Axial HRCT images of a 38-year-old man with COVID-19 ARDS admitted to ICU at the same level, performed at different times: baseline scan (**A**) and 7-month follow-up (**B**). The baseline scan (**A**) shows typical imaging features indicative of severe COVID-19 pneumonia, including extensive bilateral parenchymal consolidations, mainly affecting the posterior regions of lower lobes, bilateral focal ground-glass opacities in the anterior regions and patchy consolidation, peripherally distributed, resembling pulmonary fibrosis. The 7-month scan (**B**) shows a complete resolution of the parenchymal consolidations and the apparent fibrotic abnormalities.

3. Pneumothorax

Pneumothorax represents the most common form of barotrauma [53] and develops whenever alveolar pressure increases, resulting in the rupture of alveoli, air dissection along the pulmonary interstitium and eventually air spreading into the pleural space (Macklin effect) [54].

The incidence of pneumothorax in ICU patients with COVID-19 is higher than what is reported for other ICU patients, ranging from 4% to 15%, regardless of the ventilatory strategies [55–57]. Moreover, its frequency further increased in the case of prolonged mechanical ventilation or refractory respiratory insufficiency requiring ECMO [58,59]. The occurrence of pneumothorax in ICU patients with COVID-19 has been associated with increased overall mortality [60], therefore, its prompt and correct detection is fundamental.

Pneumothorax is usually secondary to mechanical ventilation with high positive end-expiratory pressure (PEEP) or the cannulation of subclavian or neck vessels [23]. However, several studies [61] have interestingly pointed out that about 33–38% of air leaks occurred in COVID-19 patients who never received ventilatory support, raising the question of whether these patients are more prone to develop air leaks than patients with ARDS for other causes.

With this regard, it has been speculated that the air-filled cysts developing in the diseased areas of the lungs as a late consequence of ARDS, especially those peripherally located, may progress to pneumatocele and then spontaneously rupture, thus explaining the significant number of air leaks occurring in patients who had never received ventilatory support [56] (Figure 2A). Therefore, baseline CT imaging may be predictive for patients who may develop pneumothorax [61].
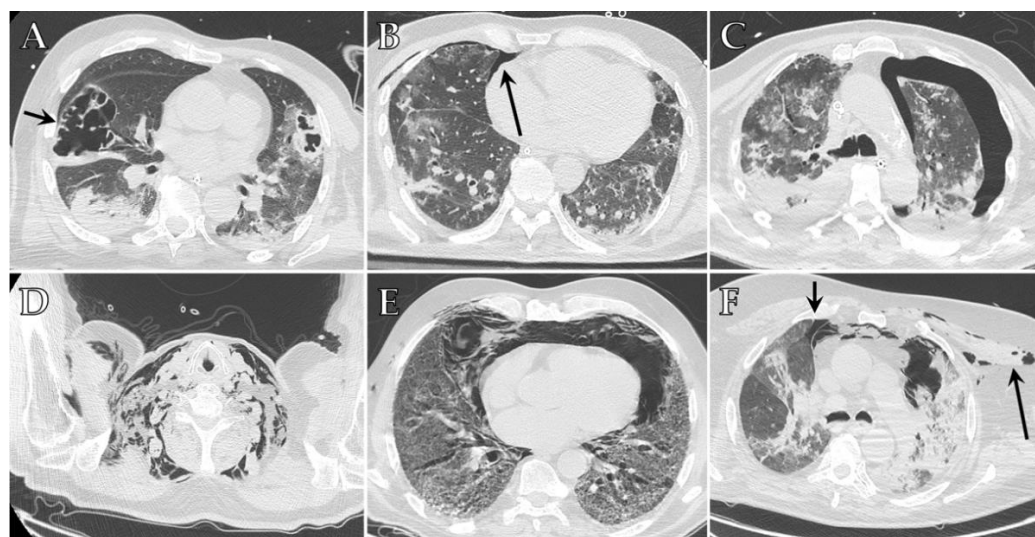
Figure 2. Axial HRCT images of different patients with COVID-19 ARDS admitted to ICU showing imaging features indicative of barotrauma secondary to mechanical ventilation: (**A**) large pneumatocele (black arrow); (**B**) small anterior pneumothorax (black arrow); (**C**) large left pneumothorax; (**D**) extensive bilateral subcutaneous emphysema of the neck; (**E**) pneumomediastinum; (**F**) pneumomediastinum associated with small anterior pneumothorax (small black arrow) and subcutaneous emphysema of the left upper chest (long black arrow).

Chest X-ray is an easy-to-use imaging technique to evaluate patients on ventilators but, despite its high specificity (99%), has a low sensibility for diagnosing pneumothorax (38%) [38].

Pneumothorax classically appears as a thin opaque line representing the visceral pleura outlined by lucent air on both sides, corresponding to the air in the pleural space on the chest wall side and in the lung parenchyma on the hilar side, respectively; other signs include the absence of distal lung markings and hypertranslucency of the pleural space [62]. On the standard upright view, air typically starts to collect in the apical region and laterally more than medially. However, in most ICU patients with suspected barotrauma, only supine X-rays are possible, thus pneumothorax becomes more difficult to detect [63]. In this position, the air is usually most visible at the anteromedial or subpulmonary location, outlines the structures of the mediastinum and may enlarge the costophrenic angle (the deep sulcus sign) [38].

Chest CT can easily identify pneumothorax on lung windows, though this imaging technique is not routinely recommended as the first diagnostic modality and is generally used as confirmatory for doubtful cases [64] (Figure 2B,C). Recently, Palumbo et al. [65] have demonstrated that early detection of the Macklin effect in CT scans could help to identify those patients at high risk for clinically relevant barotrauma, and therefore can benefit from different ventilation applications.

4. Pneumomediastinum, Pneumopericardium and Subcutaneous Emphysema

Pneumomediastinum has been identified as the second most common barotrauma-related event in patients with mechanical ventilation for COVID-19 ARDS [54]. The mechanism of development of pneumomediastinum is the same as pneumothorax and is linked to the Macklin phenomenon, so much so that the association between these two entities has been widely reported [66]. It can be either spontaneous or secondary to mechanical ventilation in COVID-19 patients and occurs when air leaks from ruptured alveoli into the mediastinum [62]. Rarely, the released air can track to the subcutaneous tissue, causing subcutaneous emphysema (Figure 2D), and/or to the pericardial tissue causing pneumopericardium [54,67,68].

The occurrence of pneumomediastinum in patients with COVID-19 ARDS is higher compared to patients who had ARDS due to other causes, despite protective mechanical ventilation strategies [69], and is associated with a poorer outcome and an increased mortality rate [70].

Pneumomediastinum can be identified on chest X-ray by radiolucent air surrounding the normal anatomic structures within the mediastinum, well demarcating the great vessel and the cardiac contour, especially along its left border. When air dissects inferiorly into the infracardiac region, it separates the cardiac and diaphragmatic densities, and the diaphragm can be seen in its entire extent [71]. When multiple vertically oriented lucencies are visualized extending superiorly into the neck, subcutaneous emphysema must be suspected [72]. Isolated pneumopericardium rarely occurs and manifests as a single band of gas that outlines the pericardium, especially along the left ventricle and right atrium contour [38].

On chest CT, pneumomediastinum is visualized as gas outlining the structures within the mediastinum (Figure 2E,F). Air collection in the extrapleural space may resemble pneumothorax, but the presence of thin connective tissue webs outside of the pleural line is typical of pneumomediastinum and can help achieve a correct differential diagnosis [38]. Chest CT is performed to confirm the diagnosis in equivocal cases on chest X-ray, to assess the extent of the pneumomediastinum, and to evaluate the presence of pneumopericardium, which may have a less favorable prognosis and might require treatment [73].

5. Ventilator-Associated Pneumonia (VAP) and Invasive Pulmonary Aspergillosis (IPA)

VAP is the most common ICU-acquired infection and is defined as an infection of pulmonary parenchyma developed in patients receiving mechanical ventilation for at least 48 h [74]. Previous reports indicated that COVID-19 patients have an increased risk of VAP compared to other ARDS, with a variable incidence of 29–79% (vs. 13%), and present even higher mortality rates [75,76]. The increased risk of VAP in ICU patients with COVID-19 is suspected to be due to multiple factors, including prolonged duration of mechanical ventilation, the extensive use of prone positioning, a higher risk for pulmonary infarction, disease, and therapy-associated immune impairment, possibly further amplified by ICU overcrowding during the pandemic outbreak [75].

The most common causative pathogens of VAP are bacteria, which can colonize in the endotracheal/tracheostomy tube of ICU patients. Several studies have demonstrated that the distribution of infecting organisms is similar between patients with and without COVID-19, with Enterobacteria (mainly *Escherichia coli* and *Klebsiella pneumoniae*) representing the most frequent pathogens (in about 40% of cases), followed by other Gram-negative bacilli (such as *Pseudomonas aeruginosa*) and Gram-positive cocci (such as *Staphylococcus aureus* and *Streptococcus pneumoniae*), both accounting for about another 25% of cases each [77–79].

Diagnosis of VAP is challenging in COVID-19 patients, due to the overlap of VAP imaging features with those of worsening COVID-19 pneumonia, and laboratory results provide essential support to both clinicians and radiologists [80]. Generally, a sudden increase in X-ray opacities should raise suspicion for VAP, especially if paired with rapid clinical deterioration of the patient [81].

Chest CT may show imaging features atypical for COVID-19 like lobar consolidation, pleural effusion, mediastinal lymphadenopathy and cavitation, which should prompt the radiologist to consider a bacterial co-infection [82] (Figure 3A,C,D).
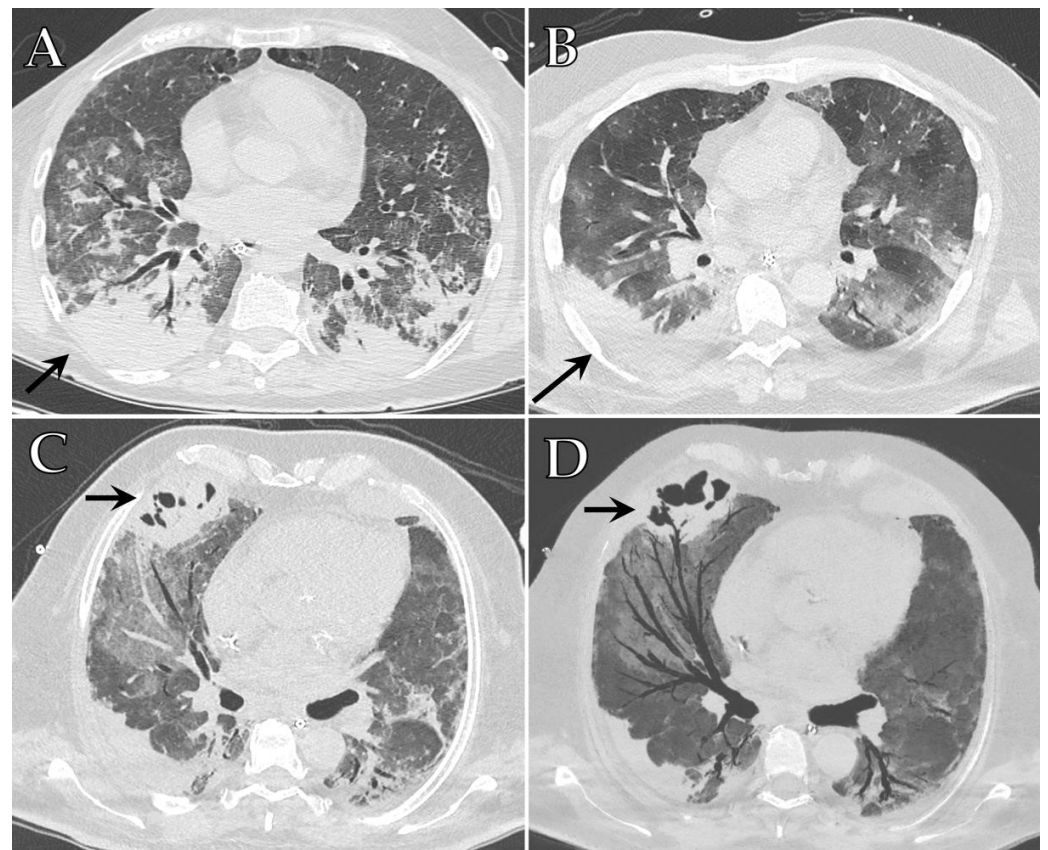
Figure 3. Axial HRCT images of different patients admitted to ICU demonstrating a sudden increase of large consolidations (black arrows) (**A**,**B**) associated with worsening of COVID-19 pneumonia. Superimposed infections of *Acinetobacter* (**A**) and *Aspergillus* (**B**) were detected. A different COVID-19 patient showed pulmonary consolidation complicated by cavitation located in the medium lobe (black arrow) (**C**), which demonstrates communication with the bronchial tree at minimum intensity projection (MIP) reconstruction (black arrow) (**D**); superinfection of *Pseudomonas aeruginosa* was detected.

Recently, IA secondary to *Aspergillus* invasion has been recognized as a severe complication of COVID-19 infection in ICU patients, with a higher mortality rate (up to 50%) and increased incidence (18–39% vs. 7% of patients) compared to ICU patients with other causes of ARDS [83,84]. Therefore, it is vital to raise awareness among radiologists and clinicians regarding fungal co-infection in COVID-19 patients, due to their immune dysregulation and wide administration of corticosteroids [85,86].

Chest CT is the imaging modality of choice to diagnose IA, as it can detect pulmonary nodules with surrounding ground-glass infiltrates (halo sign), which reflect angio-invasion and hemorrhage in the area surrounding the fungal infection. Sometimes these nodules may cavitate and a fungal ball can be seen within the cavity, with an air-crescent sign [87,88] (Figure 3B).

Although frequently secondary to bacterial, fungal, or mycobacterial co-infections [89–91], lung cavitation has also been reported as an atypical imaging feature of late stages of COVID-19 pneumonia [92]. In particular, COVID-19 cavities may be related to barotraumas, pulmonary embolism and infarction with a subsequent necrotic lesion of the lung tissue, or simply to necrotic evolution of the denser consolidations, as well as to all these factors working together [93].

Mechanically ventilated patients are also at increased risk of aspiration pneumonia (AP).

Worsening of X-ray opacities or the appearance of new ones, especially in the retro-cardiac and infrahilar regions, should raise the suspicion of AP. Confirmation chest CT

may demonstrate the presence of tree-in-bud, centrilobular nodules or consolidations in the dependent parts of the lungs, usually most pronounced in the lower lobes in supine patients or in the upper lobes and right middle lobe in prone patients [38].

6. Vascular Complications

The high prevalence of the thrombotic events in patients with COVID-19 may be induced by cross-talking between immune and coagulation systems since the high levels of inflammatory cytokines (such as IL-6 and TNF) induce activation of the endothelial cells and tissue factor, which triggers the coagulation cascade. Accordingly, D-dimer was reported as the most prominent factor in determining COVID-19 severity and subsequent complications [11].

COVID-19 patients in ICU showed a significant increase in the cumulative incidence of symptomatic venous thromboembolism compared with those not requiring ICU care [94], ranging between 31% and 69% [29,95]. Similarly, the percentage of COVID-19 ICU patients that were diagnosed with pulmonary embolism (PE) was higher compared to non-COVID-19 patients, despite having a similar severity to ARDS (23–47% vs. 7.5%) [42,95–98]. Moreover, thromboembolic complications have been described even in patients treated with anticoagulation therapy from admission, highlighting the intrinsic thrombogenicity of COVID-19 [95]. Due to prolonged immobility, mechanical ventilation and the use of sedatives and neuromuscular blockers, ICU patients experience a significant flow stasis, which could explain their increased risk for thromboembolic complications. Moreover, the frequent insertion of central venous catheters may cause vessel injury, which can further precipitate thrombotic risk in these vulnerable patients [99]. Finally, ECMO may significantly perturb the normal balance of hemostasis with biomaterial-mediated activation of coagulation, complement and inflammatory cascades, as well as increased platelet activation [100,101].

The imaging features of venous thrombosis in COVID-19 patients appear analogous to those associated with other diseases (Figure 4C,D). However, radiologists need to be familiar with the high prevalence in these patients, to achieve early detection and a more favorable outcome. The presence of a filling defect within a vessel with hypodense thrombus, venous distension, rim enhancement of the vein, and perivenous edema or fat stranding are the characteristic findings of venous thrombosis. Patients with a requirement for long-term vascular access may develop catheter-related thrombosis, especially when devices are in peripheral veins and in the context of hemodialysis [102].

In COVID-19 patients, PE is more commonly found in the segmental and lobar branches rather than in the central pulmonary arteries and is not confined to areas of the diseased lung, suggesting a diffuse vascular process [103] (Figure 4A,B). Moreover, vascular enlargement has been frequently described in COVID-19 pneumonia, possibly explaining the reason why many COVID-19 patients with PE only have mild symptoms or are even asymptomatic, since it might mitigate the increase of resistance in the pulmonary circulation [99].

Postprocessing vascular mapping using 3D MIP and volume rendering can be used to detect the filling defect more easily.

Besides thromboembolic complications, ICU patients with COVID-19 may also develop hemorrhagic events, with a higher incidence compared to patients on floor units (7.6–8% vs. 1.9%) [104].

Hemorrhages are more frequently observed in patients receiving therapeutic anticoagulation for the prevention of venous thromboembolism [105], but both high levels of proinflammatory cytokines and widespread endothelial cell damage may contribute to their occurrence [106]. Moreover, anticoagulant therapy to prevent the ECMO circuit from clotting and consequently minimize the risk of thromboembolic events may lead to an increased risk for spontaneous hemorrhages anywhere in the body [27].
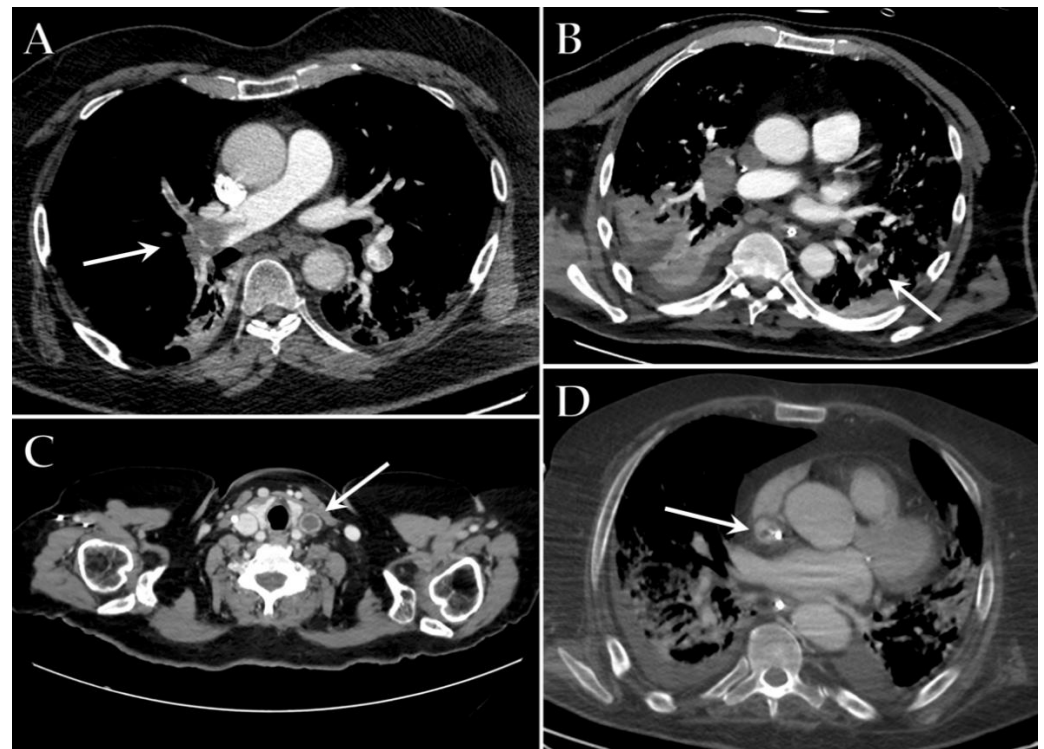
Figure 4. Axial contrast-enhanced CT images of different ICU patients with COVID-19 show filling defects indicative of a massive lung embolism in the right pulmonary artery (white arrow) (**A**), multiple embolisms in the left lower lobe artery (white arrow) (**B**), thrombosis of the left jugular vein (white arrow) (**C**) and thrombosis of the superior vena cava near the central venous catheter (white arrow) (**D**).

Hematomas appear as variable size hyperdense masses and can cause displacement and compression of surrounding structures (Figure 5A,B). A subacute hematoma might present a blood-fluid hematocrit level due to the evolution of blood products accumulated over time. Contrast-enhanced CT may provide confirmatory evidence of active bleeding, presenting as a blush in the arterial phase (Figure 5B,C).
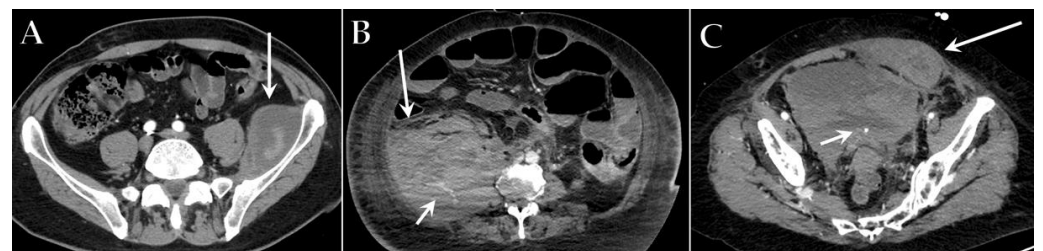

Figure 5. Axial contrast-enhanced CT images of different patients with COVID-19 admitted to ICU that developed hemorrhagic events: (**A**) a hematoma of the left iliopsoas muscle (white arrow); (**B**) a large retroperitoneal hematoma (long white arrow) that displaces the small bowel and shows a blush of active arterial bleeding (small white arrow); (**C**) a spontaneous hematoma of the anterior rectus abdominus (long white arrow) collecting in the pelvis that shows a small blush of active arterial bleeding (small white arrow).

Iatrogenic hemorrhages at the cannulation or surgical site reached an incidence of 26–31%, but the upper aerodigestive tract (including nose and mouth), the gastrointestinal tract, the genitourinary tract, and the thoracic and abdominal cavities are other relatively common sites of bleeding. The most common muscular site of hematoma is the iliop-

soas involving the retroperitoneum, followed by the rectus sheath involving the anterior abdominal wall [104,107–109].

7. Gastrointestinal Complications

Intestinal involvement related to COVID-19 results from either a direct viral infection, virus-induced inflammatory response, or bowel wall ischemia due to disease hypercoagulability [110,111]. Mesenteric ischemia, ileus, colitis and terminal ileitis are the most common gastrointestinal complications.

The prevalence of gastrointestinal symptoms and complications in ICU patients with severe COVID-19 is higher compared with those with mild disease (16.6% vs. 11.7%, respectively) [44,112–114] and with ICU patients without COVID-19 [115].

CT represents the gold standard for definitive diagnosis of acute mesenteric ischemia, since the US may be limited in obese patients and in the case of pneumoperitoneum or an excessive amount of bowel gas. Acute mesenteric ischemia appears as a filling defect within the lumen of the abdominal aorta, the celiac axis, the superior mesenteric artery and/or the inferior mesenteric artery, sometimes with poor contrast opacification of the mesenteric vascular arcade, which is indicative of hypoperfusion and is better seen on maximum intensity projection (MIP) (Figure 6D). Accordingly, the segment of the injured small bowel reveals absent or decreased contrast enhancement and wall thickening, with target appearance due to mural edema. In ICU patients, most cases of acute mesenteric ischemia involve the large bowel alone (56%) and less frequently, both the large and small bowel (24%) [116]. The early phase of bowel ischemia may only show contracted gasless bowel that, when progressed, may transform into dilated intestinal loops with a paper-thin wall and air-fluid levels (Figure 6C). In the late phase, transmural infarction may lead to intestinal wall pneumatosis (Figure 6B), mesenteric venous gas, pneumoperitoneum due to perforation (Figure 6E), and free fluid in the abdominal cavity [111,112,117].

Imaging findings suggestive of viral colitis or terminal ileitis include circumferential bowel wall thickening with edema, mucosal hyperenhancement, mesenteric hypervascularity, fluid-filled mildly distended intestinal lumen and pericolic fat stranding, and in absence of filling defects is suggestive of thrombi in the abdominal arteries [44].

Pancreatic damage has been observed in 1–2% of mild cases and 17% of severe COVID-19 cases, including patients in ICU [118]. It has been speculated that pancreatic injury could be a consequence of both viral cytotoxicity on pancreatic islet cells and the severe immune response triggered by the infection [119]. Despite this, in most of these reports, the diagnosis was made only based on the elevation of pancreatic enzymes levels, which can be secondary to a multitude of causes, and radiological findings were missing. Cases of acute pancreatitis related to COVID-19 without additional pathology in the etiology have been described [120,121], including one case of necrotizing pancreatitis [122].

At present, COVID-19 related pancreatitis is a diagnosis of exclusion and requires the presence of at least two of the three revised Atlanta criteria (upper abdominal pain, serum lipase or amylase level >3× for the upper limit of normal and/or characteristic imaging features) [123].

In COVID-19 related pancreatitis, the pancreas appears diffusely enlarged on the CT scan, with ill-defined borders and a heterogeneous enhancement of the parenchyma. Stranding of the surrounding retroperitoneal fat is usually present and a streak of fluid along the anterior conal fascia and in the retro-mesenteric plane may be seen [111] (Figure 6A).
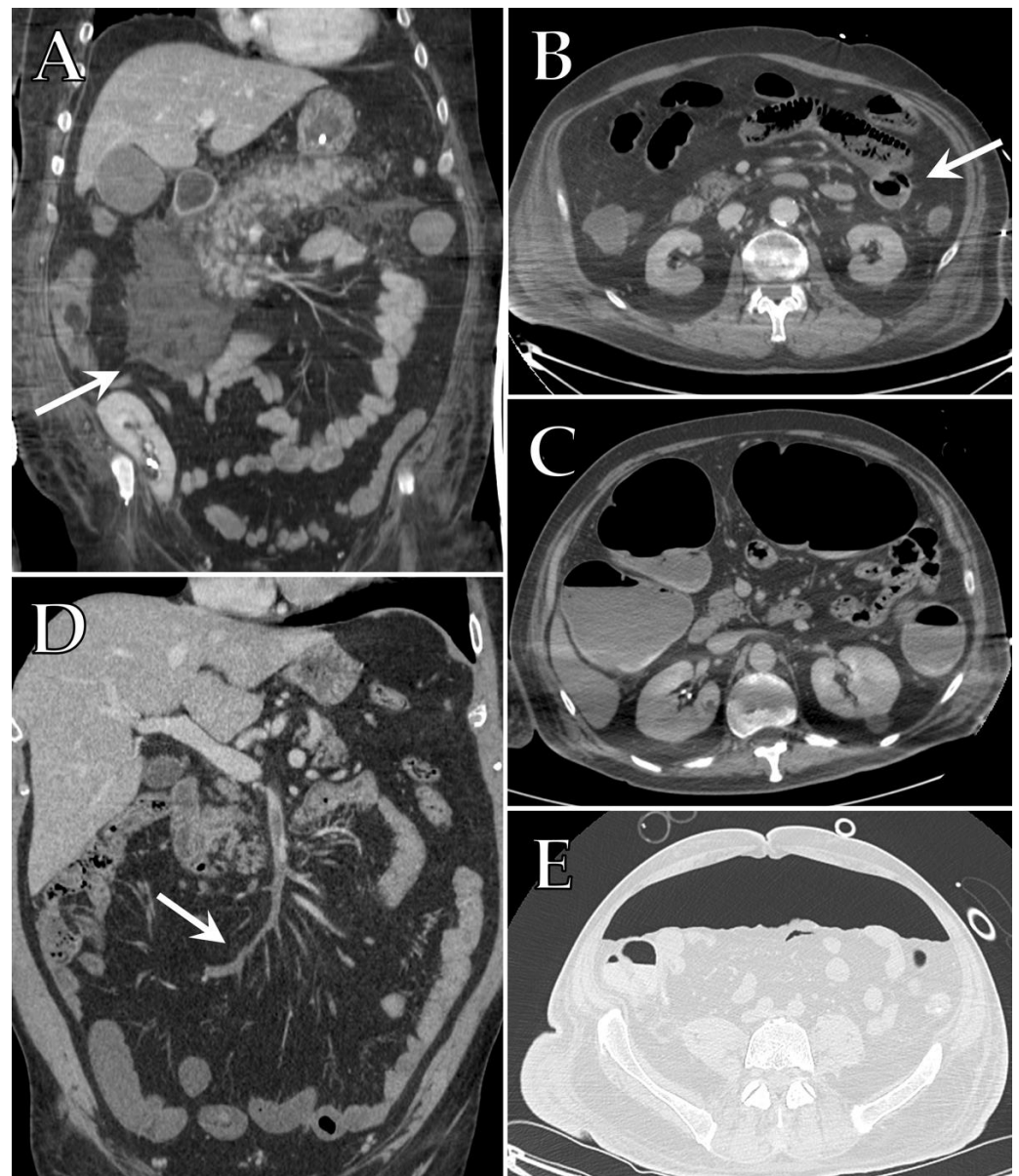
Figure 6. Coronal contrast-enhanced CT image of a patient with COVID-19 admitted to ICU with suspected pancreatitis reveals a diffusely enlarged pancreas, with ill-defined borders, stranding of the peri-pancreatic fat and streak of fluid along the anterior conal fascia (white arrow) (**A**). Axial contrast-enhanced CT scan of different COVID-19 patients with suspected acute mesenteric ischemia demonstrating the presence of linear collections of gas inside the small bowel wall referable to pneumatosis intestinalis (white arrow) (**B**) and dilated intestinal loops with a paper-thin wall and air-fluid levels (**C**). Coronal contrast-enhanced CT image of a COVID-19 patient admitted to ICU showing thrombosis of the superior mesenteric vein extending to several jejuno-ileal branches (white arrow), with consequent loss of contrast enhancement of the corresponding vascularized loops (**D**). Axial unenhanced CT scan with lung window of an ICU patient with COVID-19 and abdominal pain, showing a large quantity of free air (**E**).

8. Renal Complications

Patients with COVID-19 could experience high rates of acute kidney injury (AKI), especially those in ICU, with rates of approximately 20–40% [124–126].

Since ACE-2 receptors are highly expressed in kidney tubules, renal injury is most likely caused by a direct virus-induced cytopathic effect, with acute tubular necrosis, interstitial inflammation and protein leakage in the Bowman's capsule [127,128]; however,

a systemic cytokine storm developing in severely ill patients may also play a role [129]. Moreover, there have been several reports describing renal infarcts due to the severe hypercoagulability state which can occur in COVID-19 patients [130].

AKI during COVID-19 infection is considered a negative prognostic factor for survival and patients may require renal replacement therapy [131].

Abdominal CT with acquisition during the arterial and venous phases can easily detect AKI, showing the enlarged kidney with a loss of corticomedullary differentiation (Figure 7A). Renal infarctions appear as solitary or multiple, triangular-shaped areas of parenchyma with decreased perfusion and/or enhancement, with the apex pointing towards the medulla and base parallel to the subcapsular region [111,130,132] (Figure 7B). When a filling defect in the aorta or the renal arteries is not visible, microthrombi may be suspected, as they have been documented on histopathological samples [133].
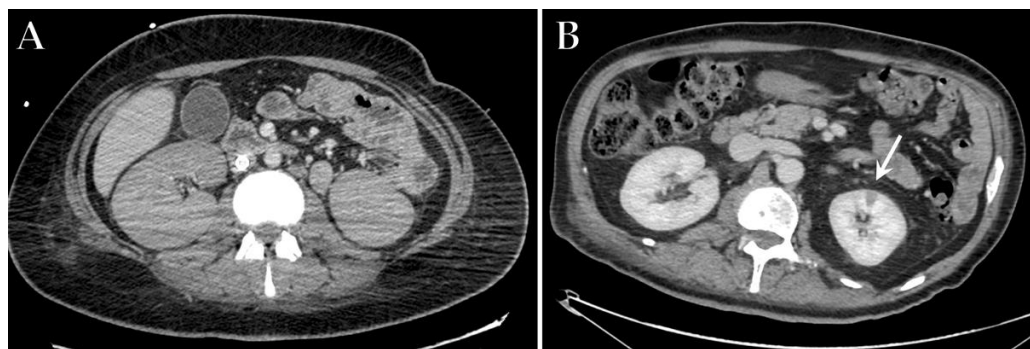

Figure 7. Axial contrast-enhanced CT image of an ICU patient with COVID-19 ARDS in ECMO treatment that developed kidney injury, showing enlarged kidney with a loss of corticomedullary differentiation (**A**). Axial contrast-enhanced CT image of a different patient with severe COVID-19 admitted to ICU demonstrating a wedge-shaped region of hypoattenuation in the left kidney (white arrow) consistent with renal infarction (**B**).

Since impaired renal function increases patients' susceptibility to contrast-induced nephropathy, contrast-enhanced imaging studies should be employed with caution and US, and despite its lower sensitivity, could represent a valid alternative.

9. Neurological Complications

Acute cerebrovascular events, such as acute ischemic stroke and intracranial hemorrhage (intraparenchymal and subarachnoid) are the most common neurological complications of COVID-19, but meningoencephalitis, encephalopathy and encephalomyelitis have also been reported [134].

COVID-19 neurological complications appear to involve both ischemic and hemorrhagic coagulation disturbances secondary to direct viral invasion through olfactory pathways or the bloodstream, with consequent endothelial damage [135]. Moreover, the exacerbated inflammatory response with the hypersecretion of cytokines, together with prolonged hypoxemia and a form of small vessel vasculitis, further increases the risk of acute cerebrovascular complications [136,137]. This could explain why cerebrovascular complications seem to affect patients with COVID-19 that are younger and have no history of vascular abnormality compared to patients with ischemic stroke/intracranial hemorrhages due to other causes [134].

Neurologic symptoms have been reported to be more common in patients admitted to ICU (84%), and are associated with a worse prognosis compared to patients with normal neurological examination [138]. Acute neurologic findings were recorded in 14% of patients on admission to the ICU [139], and stroke was demonstrated to be more frequent in this scenario compared to hospitalized patients (5–6% vs. 1–3%) [139,140]. In addition, despite the mortality benefit of ECMO demonstrated in patients with ARDS, the systemic

anticoagulation required to reduce circuit clotting further increases the risk of neurologic complications, especially extensive intracerebral hemorrhages [141–143].

Imaging features of acute ischemic stroke in COVID-19 patients are similar to those described in non-COVID-19 patients, including abnormal hypoattenuation of the brain parenchyma, a loss of gray-white differentiation, and sulcal effacement on unenhanced CT (Figure 8D–F). After contrast media administration, an extensive vascular occlusive disease may be revealed, typically involving the large vessel [43].
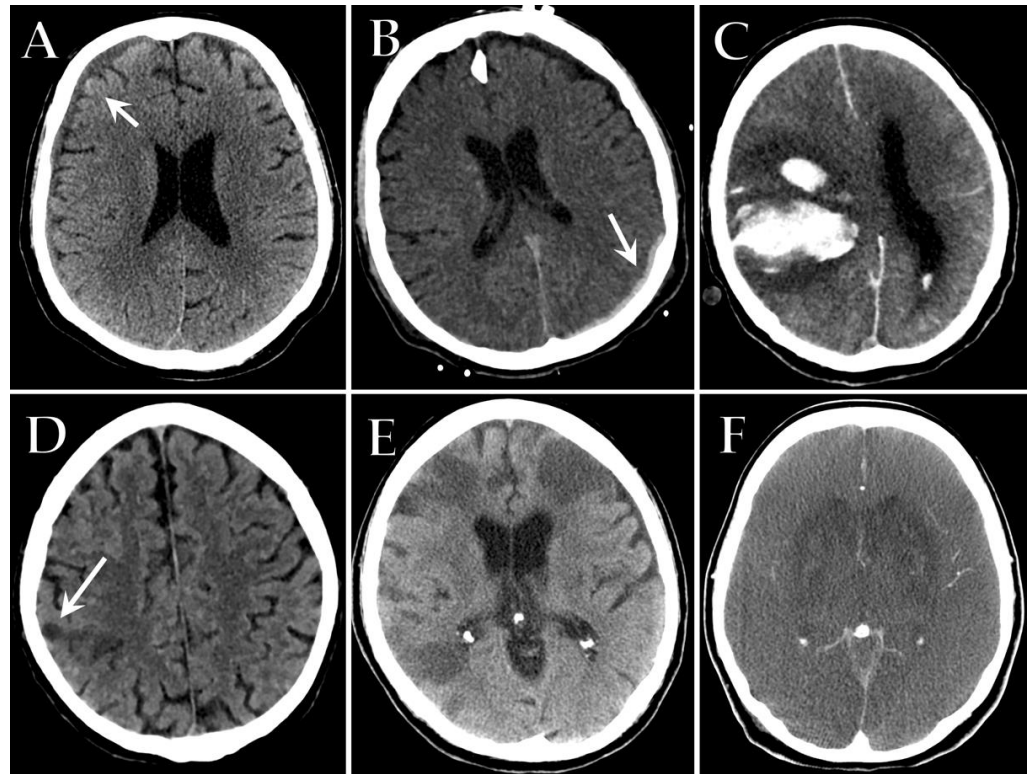

Figure 8. Axial unenhanced CT images of different patients with severe COVID-19 admitted to ICU showing spontaneous subacute right frontoparietal subdural hematoma (white arrow) (**A**), acute left parieto-occipital subdural hematoma (white arrow) (**B**) and massive right intracerebral hemorrhage with surrounding edema and significant midline shift (**C**). Axial unenhanced CT images show an acute ischemic stroke in the right parietal lobe (white arrow) (**D**) and multiple bilateral acute ischemic strokes (**E**) in two different COVID-19 patients admitted to ICU. Axial contrast-enhanced CT of a COVID-19 comatose patient reveals diffuse sulcal effacement with a decreased differentiation between gray and white matter, compatible with severe anoxic brain injury (**F**).

Intracerebral hemorrhages may occur spontaneously in critically ill patients, particularly in the context of circulation instability, or as a hemorrhagic transformation of acute ischemic stroke. Hemorrhages in COVID-19 patients resemble those secondary to anticoagulant therapy, appearing as a markedly hyperdense area with surrounding edema at unenhanced CT. In severely ill ICU patients, hemorrhages may be massive, with extensive hemispheric involvement and/or with multiple hematomas occurring in both supra and infra-tentorial locations, sometimes with intraventricular extension [140,144] (Figure 8A–C).

Finally, recent studies have analyzed brain MRIs of critically ill patients with COVID-19 after their discharge and described diffuse leuko-encephalopathy and microhemorrhages as late complications of the prolonged hypoxemia and/or the hyperinflammatory state in about 25% of cases [145,146]. These reports suggest that COVID-19 may produce protracted neurological sequelae, but further studies are needed to confirm these results.

10. Sarcopenia

It has been reported that ICU patients with COVID-19 show significant reductions in skeletal muscle mass and strength during their hospitalization [147,148], with increased morbidity and mortality and persistence in about one-third of cases, even post-discharge [149].

The acute inflammatory state and the procoagulant state described in the severe form of COVID-19 may play a role in the onset of sarcopenia, causing an increased glucocorticoid and catecholamine production with consequent hypercatabolism and anabolic resistance [150,151]. This process perturbs muscle homeostasis and decreases muscle quality and quantity, especially at the level of respiratory muscles, impairing the ability to produce appropriate tidal volumes and to perform high force expulsive airway clearance maneuvers [152].

CT is considered the gold standard for investigating quantitative and qualitative changes in muscle and fat, especially in the trunk area. In fact, besides the mere quantification of the muscle mass, CT can evaluate the quality of muscle based on identifying the fat portion within the muscle through the evaluation of specific attenuation [153].

Giraudo et al. [154] have recently demonstrated that a value above 34 HU in the right paravertebral muscle at the level of T12 is a highly sensitive CT prognostic factor for ICU admission in COVID-19 patients (Figure 9A,B). Similarly, Schiaffino et al. [148] reported that paravertebral skeletal muscle mass at T12 and, especially, T5, can predict ICU admission and death. Finally, Damanti et al. [155] have demonstrated that muscle quality perturbations were predictive of the length of hospitalization and in-hospital mortality, as well as the need for reintubation after the discontinuation of mechanical ventilation.
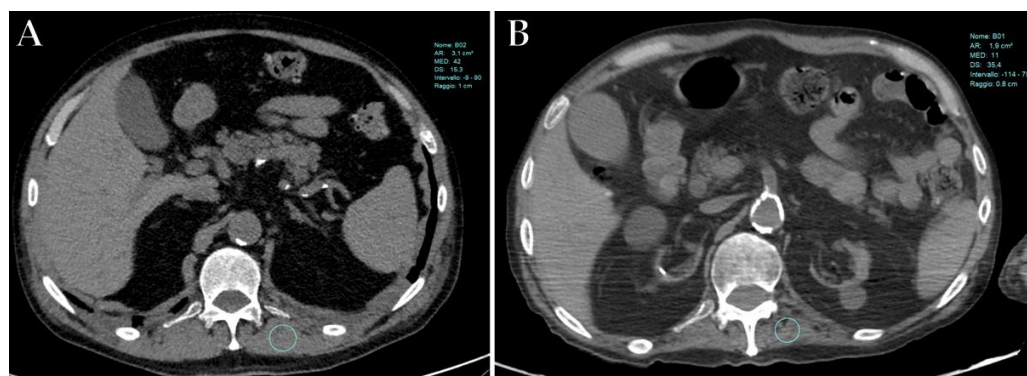

Figure 9. Axial unenhanced CT images of a patient with severe COVID-19 at the same level (T12), performed at the time of the ICU admission (**A**) and after a 3-month of ICU stay (**B**), demonstrates a reduction in muscle mass in the left paravertebral muscle (i.e., <30 HU) during hospitalization.

11. Current Limits of Imaging in Critically Ill COVID-19 Patients

X-rays, and especially CT, are highly reproducible and easy to perform imaging techniques, which provide a rapid and accurate estimation of disease progression. However, their excessive use during the pandemic has placed a substantial burden on radiology departments, which had to adapt their workflow and organize workforces accordingly. Moreover, diagnostic imaging examinations have been complicated by the need for strict infection control and prevention practices to contain the risk of transmission to other patients or healthcare workers [156], which have caused both delays in patient management and the consumption of personal protection equipment [157]. Therefore, in a global pandemic setting, it is particularly important that imaging examinations are performed with specific clinical indications and only after careful consideration, primarily reserving them for detecting and/or monitoring the complications in hospitalized and severely ill COVID-19 patients.

Despite imaging being an integral part of healthcare, the spread of the pandemic to developing countries, including those in sub-Saharan Africa, has highlighted and further stressed the huge inequality in healthcare access around the world [158]. In fact, as the

establishment of CT facilities is costly, it has been reported that developing countries have less than one CT scanner per one million inhabitants compared to almost forty scanners per one million inhabitants in high-income countries [159]. This shortage of equipment is also accompanied by a concomitant lack of trained healthcare manpower and reflects the higher risk of mortality in developing countries [160]. Therefore, while efforts should be made to expand the availability of critical imaging services to regions of great need, the providing of up-to-date evidence-based knowledge for diagnostic imaging may empower clinicians and radiologists in poor and underserved environments to choose proper imaging techniques with the aim to maximize patient benefits and ensure the optimal use of available financial resources.

12. Conclusions

During the COVID-19 pandemic, the growing request for prolonged pulmonary support for critically ill patients in ICU has increased the volume of imaging. Radiologists should be aware of the imaging features of COVID-19 ARDS and the complications of mechanical ventilation or other invasive supports. Moreover, it has been demonstrated that COVID-19 ARDS' evolution may be heterogeneous and unpredictable, and may also potentially involve other organs and systems. Therefore, radiologists need to be familiar with these extra-pulmonary complications and, through reliable and constant monitoring, guide therapeutic decisions. Moreover, as more research is pursued and the pathophysiology of COVID-19 is increasingly understood, the role of imaging must evolve accordingly, expanding from the diagnosis and subsequent management of patients to prognosis prediction.

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