Expert consensus on management of analgesia and sedation for patients with severe coronavirus disease 2019

Abstract

The coronavirus disease 2019 (COVID-19) has caused a global outbreak and became a major public health issue globally. Pain, agitation, delirium, and sleep disturbance are common in COVID-19 patients and are closely associated with the severity and poor prognosis of patients. It has been a challenge to manage the pain, agitation, and delirium in patients with COVID-19. Based on a literature review and front-line experience in Wuhan, a panel of experts in critical care medicine have developed an evidence- and opinion-based consensus on the management of analgesia and sedation in severe COVID-19 patients. The consensus includes 6 sections and 30 statements, including pain assessment and analgesia management, agitation assessment and sedation management, management of delirium, management of sleep disturbance, palliative care, and a protocol for the management of analgesia and sedation in severe COVID-19 patients. Our aims are mainly to standardize the management of pain, agitation, delirium, and sleep disturbance; formulate appropriate medication plan, and achieve optimal clinical status. Owing to the limited experience in the management of analgesia and sedation in severe COVID-19 patients, this expert consensus statement with specific suggestions should be helpful for clinicians worldwide.

Key words: COVID-19; analgesia; sedation; delirium; sleep disturbance; expert consensus.

Introduction

The coronavirus disease 2019 (COVID-19) has been declared a global pandemic and is a major public health issue worldwide[1,2]. As of June 9, 2020, more than 7 million laboratory-confirmed infections in more than 210 countries have been reported globally, and more than 406,000 people have died[3].

COVID-19 is a systemic disease damaging multiple organs, with the lung as the main target organ, leading to acute hypoxemic respiratory failure. Acute respiratory distress syndrome (ARDS) is the most common complication (affecting 60–70% of patients admitted to the intensive care unit [ICU]), followed by shock (30%), myocardial dysfunction (20–30%), and acute kidney injury (10–30%)[4-9].

Based on epidemiological data, approximately 14% of COVID-19 patients develop a severe disease that requires hospitalization and oxygen support, and 5% require admission to ICU[10]. Those critically ill patients are often in a state of stress, pain, and anxiety due to the pathophysiology of the acute stage of the disease, the underlying illness, psychological factors, and environmental factors[11,12]. COVID-19 increases organ function load, resulting in increased tissue oxygen consumption and respiratory dysfunction, which further damage organs and can even be life-threatening. In addition, various medical procedures including mechanical ventilation, arterial puncture, central venous catheterization, and hemodialysis could aggravate discomfort, anxiety, and pain. Appropriate analgesia and sedation treatment have been shown to block the sympathetic storm, increase patient comfort, and reduce the stress response as well as the duration of mechanical ventilation and length of stay in the ICU[13-15].
Unlike ordinary patients, patients with COVID-19 have greater mental health problems and sleep disorders, which not only cause emotional fluctuations and delirium but also delay tissue repair and suppress immune function\textsuperscript{[16-18]}. Thus, it is necessary to monitor mental health problems and sleep quality of patients with COVID-19 and to improve the environment and use some sedation drugs according to the severity of the disease to ensure patients get adequate sleep.

At present, there are no specific antiviral drugs or vaccines against COVID-19. The use of analgesics and sedation agents is appropriate as an initial strategy in critically ill, mechanically ventilated patients with COVID-19, which can not only improve the discomfort of intubation and reduce ventilator-associated lung injury but also reduce sympathetic stress and protect against organ damage. No specific data exist on the optimal use of analgesics, sedatives, and agents to control delirium in patients with COVID-19. It will be a challenge to manage pain, agitation, and delirium in patients with COVID-19. Our consensuses are aimed mainly at standardizing the management of pain, agitation, and delirium, formulating the appropriate medication plan and achieving the optimal clinical status.

Methods

The statements were drawn up by a group of 15 front-line intensive care experts who fought the COVID-19 epidemic in China. The group’s agenda was predefined. The expert group first defined clinical questions to be addressed and then designated the experts in charge of addressing each question after an initial meeting. All the questions were formulated according to the Population, Intervention, Control, and Outcome (PICO) format, which helps to define inclusion and exclusion criteria for literature searches and identifies relevant studies. The quality of evidence was assessed using the methodology described in Grades of Recommendation, Assessment, Development, and Evaluation (GRADE). The quality of evidence can be high, moderate, low, or very low. Because of the sudden outbreak of COVID-19, the proposed question could be the subject of a recommendation as an expert opinion due to non-existent or insufficient literature. Besides, the published data on Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and other coronavirus infections, as well as data on management of analgesia, sedation, delirium, and sleep disturbance in the ICU from studies on critically ill patients were used as indirect evidence. A total of four rounds of expert seminars and discussions were organized to provide trustworthy recommendations on the management of analgesia and sedation for severe COVID-19 patients [Supplementary Table 1].

We used the wording ‘we recommend’, ‘recommended’, ‘should’ or ‘should not’ for strong recommendations, ‘should probably’, ‘should probably not’ or ‘should probably be considered’ for weak recommendations, and ‘The experts suggest’, ‘The experts suggest against’, ‘suggested’ or ‘not suggested’ for expert opinion. The implications of the recommendation strength are presented in Supplementary Table 2. The proposed recommendations were discussed one by one. At least 75% of experts agree to approve a proposal for criteria, and at least 90% of experts must agree to
reach a strong agreement. In the absence of strong agreement, we chose to reformulate the proposal and re-rate it, in order to reach consensus. Only the expert opinions that had strong agreement were retained.

Areas of recommendations

The management of pain, agitation, delirium, sleep disturbance, and palliative care were defined. Literature was searched via PubMed and the Cochrane Library databases. Only articles published in English or with an English abstract were included in the analysis, which focused on recent data according to an order of appraisal ranging from meta-analyses to randomized trials to observational research studies.

Summary of results

According to the GRADE method and summary of the results, experts draw up 30 statements. Of these consensuses, 3 had a high level of evidence (GRADE 1±), 13 had a low level of evidence (GRADE 2±), and 14 were expert opinions. A strong agreement was reached for all statements after two rounds of scoring.

1 Pain assessment and analgesia management

COVID-19 patients are all treated in isolation wards, multiple factors can modulate patients’ pain. (1) viral infection: symptoms such as wheezing, dyspnea, insidious pain caused by tracheal intubation, and various clinical operations; (2) anxiety: fear of disease and worries about prognosis and family; (3) environment: prolonged bed rest, lights, noise from various machines, sleep fluctuations, and resuscitation or death of other patients. In a single-centered observational study, 71% of critically ill COVID-19 patients were treated with mechanical ventilation, 42% of them received tracheal intubation[8]. In addition, 63.5% of critically ill patients complained of dyspnea, 11.5% had muscle pain, 2% had chest pain, 2% had arthralgia, and 6% suffered from headache[8].

Statement 1: Analgesia should probably be considered as a high priority in the treatment of severe COVID-19 patients and the implementation of analgesia-based sedation should probably be preferred. (Grade 2+, weak recommendation)

Rationale: It is reported that pain could decrease the immune response and increase the risk of delirium and post-traumatic stress disorder (PTSD)[19-21]. Analgesia could improve comfort in mechanically ventilated patients and reduce stress[22]. However, analgesic agents could also inhibit important physiological functions of certain organs (e.g., respiration, circulation) or increase the metabolic burden of certain organs (e.g., liver, kidney) resulting in organ dysfunction or imbalance[22]. The effect of analgesic drugs on the function of the patient's organs is an issue that must be addressed. The patient's basic vital signs (mood, heart rate, respiration, blood pressure, urine volume, and temperature) should be closely monitored before analgesia is administered so that the appropriate medication and its dosage can be selected. High-quality clinical trials of analgesia-based sedation are rare. It is reported that an analgesia-based sedation
protocol could reduce the use of sedative agents and decrease periods of deep sedation, without increasing agitation[23, 24].

Statement 2: The Numeric Rating Scale (NRS) is suggested for COVID-19 patients with non-invasive ventilation (communicative patients), the Critical-Care Pain Observation Tool (CPOT) is suggested for COVID-19 patients with invasive mechanical ventilation (non-communicative patients). (Expert opinion)

Rationale: In isolation wards, simple and easy-to-use assessment tools are recommended due to limited conditions. A prospective study showed that the NRS score was valid and sensitive to capturing changes in pain response in critically ill communicative patients[25]. NRS was also found to be a valid assessment for dyspnea[26]. In patients who are unable to express themselves, and whose behavior can be observed, CPOT could be a valid and reliable pain assessment tool for patients from different areas[27] [Supplementary Table 3].

Statement 3: Non-pharmacological interventions should probably be considered as adjuvant pain management therapy in severe COVID-19 patients. (Grade 2+, weak recommendation)

Rationale: Music was able to reduce mechanical pain sensitivity in healthy volunteers[28]. One meta-analysis showed that music interventions could significantly reduce pain intensity, emotional distress, and the use of anesthetic, opioid, and non-opioid agents[29]. The use of slow deep breathing (SDB) techniques is increasing in the clinic. Breathing techniques have shown beneficial effects on the intensity of pain in several clinical studies[30]. The breathing patterns used in these studies were diverse. In practice, we should carefully characterize the targeted timing (breathing frequency, inspiration/expiration ratio), and volume (breathing depth) components of a breathing cycle[30].

Statement 4: It is recommended that opioid analgesia should be used as the first choice for critically ill patients with COVID-19. (Grade 1+, strong recommendation)

Rationale: Opioids are powerful central analgesics with strong analgesic effect, fast onset of action and high adjustability that are widely used in the ICU, such as morphine, fentanyl, remifentanil, sufentanil, etc. [Supplementary Table 4][22].

The adverse effects of opioids, which mainly cause respiratory depression, decreased blood pressure, and decreased gastrointestinal motility, are particularly pronounced in the elderly[31, 32]. Critically ill COVID-19 patients are mostly elderly, with long mechanical ventilation time and high incidence of acute gastrointestinal injury, requiring prolonged analgesic treatment; the smallest effective dose of opioids should be used as soon as possible. There is a lack of clinical trials assessing patients’ benefits from prolonged application of opioids. When a patient is on opioids for more than 2 weeks, the patient's status should be carefully monitored and the type and dose of analgesic medication should be evaluated. Morphine derivatives, such as the opioid receptor agonist-antagonist dezocine, may have advantages in reducing respiratory depression and gastrointestinal adverse effects, but further clinical trial validation is needed.
**Fentanyl:** The analgesic potency of fentanyl is 100–180 times that of morphine, and studies have found that fentanyl applied to ICU patients can significantly reduce pain scores and pain incidence\(^\text{[33, 34]}\). However, due to the large apparent distribution volume of fentanyl, in order to achieve an effective concentration, the dose often needs to be increased. When repeatedly administered multiple times it accumulates easily and in recent years it has been used less as a long-term analgesic treatment\(^\text{[32]}\).

**Remifentanil:** The analgesic strength of remifentanil is comparable to that of fentanyl, which binds mainly to the alpha-1-acid glycoprotein. One meta-analysis, which included 23 RCT studies, noted that remifentanil shortened the duration of mechanical ventilation, time to extubation after sedation, and ICU length of stay but made no difference to mortality and agitation compared to other opioids\(^\text{[35]}\). In addition, no dose adjustment is required in patients with renal and hepatic dysfunction\(^\text{[36]}\). There are no studies on the impact of remifentanil on the respiratory drive so far. Remifentanil may be used in COVID-19 patients during awake tracheal intubation\(^\text{[37]}\).

**Sufentanil:** The analgesic effect of sufentanil is 7 to 10 times that of fentanyl. It has a strong analgesic effect and is mainly used during surgery. Because of its fast effect, small accumulation, and respiratory inhibition, its use in ICU patients with severe illness is rising\(^\text{[38]}\).

**Dezocine:** Dezocine is widely used for pain management in ICUs in China. In vivo studies, dezocine showed a stronger analgesic effect than morphine by activating \(\kappa\) and \(\mu\) opioid receptors\(^\text{[39]}\). In addition, the sedative side effects of dezocine are limited and it has ceiling effects in moderate doses\(^\text{[39]}\). One RCT study has shown that dezocine, in combination with propofol, can improve analgesia, reduce propofol use, and reduce the risk of complications of respiratory depression\(^\text{[40]}\).

**Statement 5: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Dexmedetomidine should probably be considered as alternative or adjunctive analgesic drugs for severe COVID-19 patients. (Grade 2+, weak recommendation)**

**Rationale:** Critically ill patients with COVID-19 could have a long course of illness, resulting in a high cumulative dose of opioids and a great risk of complications, such as respiratory depression and decreased gastrointestinal motility. In recent years, studies have shown that NSAIDs are effective in reducing non-neuropathic pain in critically ill patients. For example, the application of acetaminophen and ibuprofen could significantly reduce opioid consumption without a significant increase in serious adverse events\(^\text{[41, 42]}\). Recently, researchers have expressed concern that ibuprofen may be at risk of exacerbating COVID-19 infection due to the upregulation of ACE2, but the limited evidence available does not yet demonstrate an interaction between ibuprofen and coronavirus\(^\text{[43]}\). Acetaminophen is another potential drug for antipyretic and analgesic use but we must beware of the acute liver injury it can cause\(^\text{[44]}\). Dexmedetomidine has both mild sedative and analgesic effects by antagonizing central and peripheral catecholamines. It has synergistic effects with other analgesic and sedative drugs, which can reduce mechanical ventilation time and ICU hospitalization time\(^\text{[22]}\) and opioid use\(^\text{[45]}\). Patients sedated with dexmedetomidine are more likely to be aroused and have less respiratory depression\(^\text{[22]}\). However,
dexamethomidine application does increase the incidence of bradycardia and hypotensive events compared to other drugs[46].

**Statement 6: Experts suggest formulating appropriate analgesic and sedative strategies during medical procedures based on an individualized evaluation of patients with severe COVID-19. (Expert opinion)**

**Rationale:** Among the commonly used drugs, midazolam has less effect on cardiovascular function and produces anterograde amnesia. For patients with extreme anxiety, midazolam can be used intravenously. At the same time, etomidate or ketamine combined with low-dose midazolam is recommended in these patients. Since propofol infusion in patients with COVID-19 has an obvious effect on hemodynamics, it is only recommended in patients with relatively stable hemodynamics. Intravenous lidocaine can effectively inhibit cough during medical procedures. Among neuromuscular blockers, rocuronium lasts longer and confers a lower risk of cough than succinylcholine. Patients can be given rocuronium sequentially after deep sedation. Early use of opioids may cause cough in patients, so opioid administrations can be given after neuromuscular blockers have suppressed laryngeal reflex, commonly used opioids include fentanyl, sufentanil, or remifentanil[47].

During endotracheal intubation, tracheotomy, and fiber optic bronchoscopy, in addition to evaluating the anatomical factors of the patients, it is also necessary to monitor the pathophysiological factors of the patients. Early use of intravenous infusion and/or vasoactive drugs to prevent the occurrence of adverse events such as hypotension, asphyxia, and hypoxia is recommended[48]. It should be noted that acute critical illness can greatly reduce the need for analgesic and sedative drug doses, and analgesic and sedation therapy may increase the risk of hemodynamics and respiratory decompensation in critically ill patients. It is more common in elderly patients, obese patients, and patients with underlying heart disease and/or hepatorenal insufficiency. Therefore, the selection of the best type and dose of analgesic and sedative drugs should be determined based on an individual evaluation of patients. Besides, deep sedation [Richmond agitation-sedation scale (RASS) -4 to -5] should be maintained before the neuromuscular blocker effect disappears. In the continuous use of neuromuscular blockers, adequate analgesia and sedation therapy should also be used continuously.

**II Agitation assessment and sedation management**

Sedation is a key technology to reduce oxygen consumption and maintain oxygen balance. Because of the pathophysiological changes brought about by the disease and the psychological factors of the patients, COVID-19 can easily cause oxygen imbalance and lead to tissue hypoxia, which makes sedation an effective measure of treatment.

**Statement 7: Sedation is an important strategy for the treatment of COVID-19 in ICU. (Expert opinion)**

**Rationale:** Due to the different degrees of consolidation, extensive monocyte and megakaryocyte exudate from the alveolus, focal hemorrhage and necrosis, hyaline membrane formation and pulmonary interstitial fibrosis [49], severe COVID-19
patients suffer from severe dyspnea and hypoxemia, which rapidly leads to ARDS, septic shock and multiple organ failure[7]. Severe COVID-19 and ARDS will intensify the respiratory drive of patients, increase trans-pulmonary pressure, and cause ‘secondary injury’ to the lungs[5]. At the same time, due to multiple factors such as disease injury response, psychological load, social and treatment environment, severe COVID-19 patients have strong anxiety, fear, and even delirium, which can enhance body stress, tissue oxygen consumption, and catabolism. This is not conducive to the curing of the disease and may produce long-term mental conditions such as PTSD and depression[50]. Therefore, as an important part of ICU treatment, sedation is of great significance in reducing respiratory drive and relieving anxiety and stress[31].

Statement 8: RASS should probably be used for sedation assessment in COVID-19 patients. (Grade 2+, weak recommendation)

Rationale: Sedation should first rely on assessing the needs of patients. ‘No assessment, no sedation’. The assessment tools were divided into the subjective scoring scale and objective assessment tool. The subjective scoring scale should be simple, accurate, relatively objective, and easy to repeat. RASS [Supplementary Table 5] had high reliability and validity in medical and surgical, ventilated and nonventilated, and sedated and non-sedated adult ICU patients[51]. We recommend RASS as the first choice of the sedation assessment tool in patients with COVID-19 because of the rapid change in condition and the need for continuity with delirium assessment[51]. Procedure for RASS assessment lists in [Supplementary Table 6]. The objective evaluation tool refers to the digital EEG after EEG signal transformation, commonly used as Bispectral index (BIS), Narcotrend index (Ni), state entropy (SE), etc. However, it still requires strong evidence to prove its effectiveness and is now mainly used as an auxiliary tool for subjective assessment.

Statement 9: Goal-directed sedation strategy should probably be used during respiratory support in severe COVID-19 patients. (Grade 2+, weak recommendation)

Rationale: Patients with severe COVID-19 will be exposed to different methods of respiratory support according to the severity of the disease, including high-flow nasal cannula oxygen therapy (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), muscle relaxation, prone position, and extracorporeal membrane oxygenation (ECMO).

In different respiratory support methods, the depth of sedation varies. Injury from excessive deep sedation and organ damage caused by insufficient sedation should both be avoided. For severe COVID-19 patients, a goal-directed sedation strategy is most recommended[52]. The goal of individual sedation should be based upon the degree of pulmonary consolidation and fibrosis combined with the patient's inflammatory reaction, mental state, and respiratory support method. According to the dynamic evaluation of the goal, treatment should be adjusted and sedation titrated.

Statement 10: It is suggested to maintain RASS at −1 to 0 during HFNC application in severe COVID-19 patients. (Expert opinion)

Rationale: Patients who need HFNC are conscious but their symptoms, such as chest
tightness and shortness of breath, are severe\textsuperscript{[53]}. They should have adequate analgesia and should not be deeply sedated. A small dose of short-acting sedative drugs could be used to ensure comfort and relieve anxiety. A RASS score of $-1$ to $0$ should be maintained. In addition, the respiratory rate of patients should be observed closely. The respiratory rate should be less than 30 breaths per minute with analgesia and sedation, but respiratory inhibition caused by excessive sedation should be avoided.

**Statement 11:** RASS should probably be maintained at $-1$ to $0$ during NIV in critically ill COVID-19 patients, and deep sedation (RASS < $-2$) should probably be avoided. (Grade 2+, weak recommendation)

**Rationale:** NIV is an important respiratory support method for severe COVID-19 patients. However, for NIV to play a therapeutic role, it must be based on patient tolerance and good coordination between humans and machines. Therefore, a light sedation strategy needs to be implemented on the premise of sufficient analgesia, and the RASS score maintained between $-1$ to $0$\textsuperscript{[54-56]}. At the same time, respiratory indices, especially tidal volume (VT) and respiratory rate (RR), should be monitored. In the first two hours of NIV support, in addition to maintaining oxygen saturation (SpO2) > 93\%, VT < 9 mL/kg, and RR < 30 breaths per minute, respiratory drive and oxygen consumption should also be reduced\textsuperscript{[57]}. During the implementation of an NIV light sedation strategy, we should also schedule appropriate times for eating, drinking, rehabilitation activities, and sleeping. Attention should be paid to communication and delirium avoided.

Deep sedation (RASS < $-2$) should probably be avoided because there is no artificial airway protection in the course of NIV\textsuperscript{[56]}. Deep sedation also increases the risk of aspiration and may increase the length of stay in ICU.

**Statement 12:** In general, RASS should probably be maintained at $-2$ to $0$ when using IMV in critically ill COVID-19 patients. (Grade 2+, weak recommendation)

**Statement 13:** It is recommended to maintain RASS at $-5$ to $-4$ with deep sedation strategy if their obvious discomfort, agitation, patient-ventilator dyssynchrony, and strong respiratory drive during IMV. (Grade 1+, strong recommendation)

**Statement 14:** It is recommended that deep sedation should probably be administered for a short duration. However, it could be adjusted according to the individual condition of patients. Daily interruption should probably be considered during long periods of deep sedation. (Grade 2+, weak recommendation)

**Rationale:** Most of the severe COVID-19 patients, especially those with ARDS, need IMV treatment. The core measure of IMV implementation is lung-protective ventilation strategy (VT $\leq$ 6–8 mL/kg, Pplat $<$ 30 cmH\textsubscript{2}O, reasonable PEEP, driving pressure $<$ 15 cmH\textsubscript{2}O). Analgesic and sedation strategies are important factors in the implementation of lung-protective ventilation. However, because of the specificity of pathology and pathophysiology\textsuperscript{[58]}, the depth and duration of sedation in COVID-19 patients are different from other ARDS patients in the past.

In general, maintaining light sedation of RASS from $-2$ to $0$ is a reasonable initial
setting during IMV[59, 60]. However, if the patient is experiencing obvious discomfort, agitation, and patient-ventilator dysynchrony is affecting gas exchange, then a deep sedation strategy should be considered to maintain the RASS at −5 to −4. Severe COVID-19 and ARDS patients usually have a strong respiratory drive, which increases trans-pulmonary pressure, aggravates air pressure injury, and induces patient self-inflicted lung injury (P-SILI)[61]. Therefore, deep sedation, and even combination with neuromuscular blocking drugs, is needed to interrupt spontaneous respiration[61, 62].

It is preferable to keep the duration of deep sedation short[60], otherwise, the probability of secondary infection will increase, and the duration of stay in ICU will be prolonged. However, COVID-19 patients often regain a strong respiratory drive once the depth of sedation is reduced, which means intensive care physicians need to make individual adjustments based on the specific conditions of the patients. If the respiratory drive is still strong (RR > 30 breaths/min, VT > 9 mL/kg, man-machine confrontation is obvious) after changing to light sedation, and adjustment of analgesia and communication is ineffective, then deep sedation should probably be considered. During the implementation of a deep sedation strategy, daily interruption to observe the condition of the patient is suggested[63].

**Statement 15:** It is recommended to maintain RASS at −5 when using neuromuscular blocking drugs during the early stage of IMV in severe COVID-19 patients. (Grade 1+, strong recommendation)

**Rationale:** For early patients with severe ARDS, neuromuscular blockers may be considered based on adequate analgesia and sedation[64]. Conscious muscle relaxation is extremely dangerous, as seen during anesthesia, which can cause a severe sympathetic storm, stress, and significantly increase the metabolic burden of the circulatory system. Therefore, the use of muscle relaxants should adhere to the premise of sufficient analgesia and sedation, and maintain RASS at −5. At this time, objective assessment can help to monitor the depth of sedation and avoid being too light or too deep. Cisatracurium besylate is recommended for muscle relaxation. The indication is severe ARDS (PaO2/FiO2 < 150) at an early stage (within 48 h of onset). The dosage should be titrated to the minimum dose needed to prevent spontaneous respiration. The duration is recommended to be 48 h[65].

**Statement 16:** It is suggested that the degree of sedation during prone position varies with the respiratory support method and period of the disease. (Expert opinion)

**Rationale:** Prone position is recommended for severe COVID-19 and ARDS patients without contraindication in the early stage (first 48 h) of IMV[66], which can improve lung compliance and viscous secretion drainage. In the early prone position, a muscle relaxant is often used simultaneously, and the duration is at least 12 h, so a deep sedation strategy is needed. Prone position can be implemented many times in COVID-19 patients. After the early stage with muscle relaxation, light sedation strategy can be considered during prone position and some conscious patients have good tolerance[59].

The prone position also can be implemented during HFNC in COVID-19 patients.
With sufficient communication, some patients can adopt a prone position in a conscious state. Mild analgesia can be used, but sedation should probably be avoided as much as possible.

**Statement 17:** The degree of sedation during ECMO varies with the different periods of the ECMO implementation. ‘Awake’ ECMO is probably reasonable after strict evaluation. (Grade 2+, weak recommendation)

**Rationale:** ECMO can be used as a salvage treatment for critically ill patients with ineffective mechanical ventilation\[67\]. In the early stage of ECMO administration, in order to achieve lung rest and avoid the aggravation of lung injury, the parameters of the ventilator will be lowered as much as possible. At this time, it is necessary to administer sufficient analgesia and deep sedation to reduce the secondary lung injury caused by an overly strong spontaneous respiratory drive\[68\].

If the pulmonary inflammatory response is reduced and the alveolar ventilation function is improved after a certain period of ECMO treatment, and there is no major damage in neurology and other organ functions can be compensated, the depth of sedation can be gradually reduced. After a full evaluation and testing, ‘awake’ ECMO with no intubation and self-breathing could probably be considered. This kind of support can avoid sedation, intubation, and mechanical ventilation related complications\[69\].

The ECMO circuit may affect medication absorption through larger volumes of distribution and drug retention by membrane oxygenators\[70\]. Therefore, ECMO support may alter drug dosing regimens. Midazolam, a sedative, is reduced by more than 50% with ECMO\[70, 71\].

**Statement 18:** Experts suggest a deep sedation strategy (RASS –4 to –5) combined with a neuromuscular blocking agent in severe COVID-19 patients when undergoing high-risk medical procedures such as endotracheal intubation, tracheotomy, and fiber optic bronchoscopy. (Expert opinion)

**Rationale:** Due to the severe decrease of respiratory function and the high load of the 2019-nCoV virus in sputum and upper respiratory tract secretions of patients with severe COVID-19, medical procedures such as endotracheal intubation, tracheotomy, and fiber optic bronchoscopy are high-risk procedures for such patients\[72\]. On the one hand, the medical procedure itself and its complications may increase the patient’s mortality, on the other hand, the airway secretions and the formation of spatter may also enhance the risk of cross-infection among medical workers\[4\]. Therefore, during these medical procedures, all necessary preventive measures should be taken, including personal protective equipment (PPE), sterilization of operating equipment, minimizing unnecessary contact with patients, and the management of medical waste. A deep sedation strategy combined with a neuromuscular blocking agent can not only help to reduce the occurrence of adverse events caused by the operational stimulation, but also effectively reduce the difficulty and course of operation for medical workers, and reduce the risk of cross-infection among medical workers\[73\].

**Statement 19:** Experts recommend sedatives should probably be used with attention to the effects on hemodynamics and organ functions, as well as the need for depth of sedation. (Grade 2+, weak recommendation)
**Rationale:** Midazolam is the most commonly used benzodiazepine, it acts on the reticular structure of the brain stem and the limbic system of the brain, enhances inhibition of GABA receptors. It results in anti-anxiety, hypnosis, memory loss, and antispasmodic effects, and has little effect on blood pressure\[74\]. Lorazepam can be used as a long-term benzodiazepine. The main side effect of benzodiazepines is respiratory inhibition. The drugs have fast action and slow metabolism. Thus, they accumulate easily, increasing the depth of sedation and prolonging the time of mechanical ventilation and hospitalization. At the same time, in order to avoid delirium, we should try to reduce the duration of benzodiazepine use. Propofol enhances GABA signaling; it is quick to take effect and is metabolized quickly, it is a strong anxiolytic and induces memory loss. At the same time, it can effectively reduce cerebral blood flow and reduce intracranial pressure, and should be used preferentially in patients with neurological diseases with increased intracranial pressure\[74\]. The disadvantage of propofol is mainly its impact on the cardiovascular system, resulting in decreased cardiac output, stroke volume, and peripheral vascular resistance, as well as the function of reducing sympathetic nerve activity, causing decreased blood pressure during rapid intravenous injection. In addition, due to its liposolubility, long-term use can cause hyperlipidemia, which is not suitable for patients with triglyceride elevation, pancreatitis, etc. Dexmedetomidine acts on the locus coeruleus mainly by activating the $\alpha_2$ adrenergic receptor subtype of the central nervous system, producing sedation and analgesia; the degree of sedation is mild, and the occurrence of delirium can be reduced\[75\]. Adverse reactions such as bradycardia, and hypotension tend to occur, so it is necessary to strengthen the monitoring of the circulatory system. Dexmedetomidine can be used as a basic sedative for light sedation of patients without artificial airway. Midazolam or propofol can be selected as basic sedation in patients with artificial airway and deep sedation, and then combined with other sedative drugs [Supplementary Table 7]. The sedative dose can be adjusted at any time based on evaluation\[76\].

**III Delirium management**

Delirium, the most frequent clinical expression of acute brain dysfunction, is especially important in the context of COVID-19. The incidence rate of delirium for ICU patients is about 30% – 50%, while it can be as high as 50% – 75% for patients undergoing mechanical ventilation\[31\]. Evidence indicates that delirium is not only a robust prognostic indicator of prolonged mechanical ventilation and hospitalization, and a higher mortality rate, but also of higher risk of long-term cognitive impairment\[77\]. So far, the exact incidence of delirium in COVID-19 patients remains unknown. Mao reported the prevalence of neurological symptoms, which, including impaired consciousness and acute cerebrovascular disease, reached 45% in severe cases of COVID-19\[78\]. Therefore, it is urgent that the standard prevention and management of delirium should be implemented during the COVID-19 epidemic.

**Statement 20:** Experts suggest that severe COVID-19 patients should be routinely screened for high-risk factors for delirium on admission and during the whole course of the disease. (Expert opinion)
Rationale: In addition to the common high-risk factors for delirium, such as severe systemic disease, advanced age, dementia, alcohol, and drug abuse, etc., the high incidence of delirium for COVID-19 patients can be attributed to the following. (1) The impact of COVID-19 infection: both direct invasion of 2019-nCOV on the central nervous system[79] and hypoxia can lead to the development of delirium. (2) The high prevalence of cardiac-cerebrovascular comorbidities in COVID-19 patients, especially in severe cases, which is a predisposing factor of delirium[80]. (3) Iatrogenic intervention factors: overuse of sedatives and long duration of mechanical ventilation, and constraints of mobility. (4) Environmental factors: isolation ward, a panic of the pandemic, restrictions on visits, minimal communication with medical care personnel that is hindered by PPE. We suggest those high-risk factors mentioned above should be screened frequently on admission and during the whole course of the disease, and prevention measures should be applied as early as possible.

Statement 21: Experts suggest implementing easy screening tools for COVID-19 patients’ delirium assessments. (Expert opinion)
Rationale: Previous literature showed 75% of delirium would be missed without validated assessment tools[81]. During the COVID-19 crisis, in light of heavy workload and relative lack of labor resources in healthcare professionals, we suggest that it is necessary to use simple and easy delirium assessment tools. Based on front-line experience in Wuhan, we suggest that the brief Confusion Assessment Method (bCAM) should probably be used to identify delirium [Supplementary Figure 1].

Statement 22: It is recommended that non-pharmacological interventions should probably be the first choice of management of delirium. A modified ABCDEF bundle is probably preferred to meet the need of COVID-19 patients. (Grade 2+, weak recommendation)
Rationale: 2018 “Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU” recommended the use of multiple non-pharmacological interventions for the prevention and management of delirium[31]. Evidence has demonstrated that ABCDEF bundle intervention (Assessment/treatment of pain, Both spontaneous awakening trials and spontaneous breathing trials, Choice of Sedation, Delirium management, Early mobility, and Family presence) can effectively reduce the incidence and duration of delirium[82, 83]. However, the COVID-19 epidemic situation poses great challenges and barriers to the implementation of the typical ABCDEF bundle, for example, social separation and lack of contact with the family. We suggest delirium prevention measures should be modified to meet the need of COVID-19 during this critical time.

It is necessary to resolve the reversible causes of delirium which include maintaining adequate oxygenation, applying adequate pain management, avoiding urinary retention and constipation and to decrease iatrogenic intervention risk factors as soon as possible. Meanwhile, medical care personnel should pay more attention to providing cognitive stimulation by reorienting patients with each interaction, ensuring the call button and telephone are within reach, providing daily telephone/video chat
with family, normalizing sleep/wake cycles by adjusting light, minimizing the use of physical restraints, and encouraging early mobilization.

**Statement 23:** It is recommended probably not to use haloperidol or other atypical antipsychotics routinely to prevent or treat delirium in severe COVID-19 patients. (Grade 2–, weak recommendation)

**Rationale:** Given the current study, there is no definitive evidence for the use of antipsychotic drugs for the prevention or treatment of delirium. Studies showed that neither haloperidol nor ziprasidone provided a significant benefit over placebo in critically ill delirium patients[84, 85]. Skrobik and colleagues reported low-dose nocturnal dexmedetomidine sedation prevents delirium in ICU patients[86]. We suggest not using haloperidol or other atypical antipsychotics as a matter of routine to prevent or treat delirium in severe COVID-19 patients. Avoidance of overuse of potent psychoactive agents like sedatives and neuromuscular blockers (NMB) is important and dexmedetomidine could probably be used if necessary.

**IV Sleep disturbance management**

Sleep is an important and complex physiology process, which is influenced by both biological and environmental factors. It also plays a critical role in ensuring metabolic homeostasis. Severe COVID-19 patients always suffer from varying degrees of sleep disturbance due to pathophysiologial factors and environmental factors.

**Statement 24:** Experts suggest that a sleep management strategy should be adopted in severe COVID-19 patients. (Expert opinion)

**Rationale:** Not only the pathophysiologial factors lead to sleep disturbances in severe COVID-19 patients, but also the witnessing of events and the environment in the isolation ward. Patients with COVID-19 always feel pain due to hypoxia, long-term immobility, inflammatory storm, organ dysfunction, and mental stress, all of which could lead to anxiety and depression. In addition to the main causes (disease severity and pathophysiology), the surrounding environmental factors such as excessive noise, light, enclosed management, and medical treatment could also cause sleep disruption and sleep quality degradation.

A previous study reported that the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system[87]. Unfortunately, a study reported there was a high rate of acute encephalopathy in patients with COVID-19[88]. The Society of Critical Care Medicine has identified sleep deprivation as a significant contributor to the development of delirium in adult patients in ICU[89].

Lack of sleep or poor sleep quality will lead to a host of adverse outcomes, such as pain, anxiety, dysphoria, delirium[90, 91], tissue damage, abnormal immune regulation, and changing hormone levels and pulmonary mechanics that are associated with poor prognosis[16, 92-95]. Therefore, a sleep management strategy should be adopted for patients with COVID-19.

**Statement 25:** Experts suggest that the Richards Campbell Sleep Questionnaire
(RCSQ) should be an assessment tool among severe COVID-19 patients who can self-report their sleep state. (Expert opinion)

Statement 26: Experts suggest that for critically ill patients with IMV, the systematic assessment of deep sedation such as bispectral index (bis) can be used to evaluate deep sedation instead of Polysomnography (PSG) sleep monitoring to provide comprehensive measures to reduce the incidence of sleep fragmentation and delirium. (Expert opinion)

Rationale: Sleep disturbances mainly include abnormal sleep duration (insomnia and excessive sleep) and sleep-wake rhythm disorders. No relevant studies or data have described the characteristics of sleep disturbance in patients with COVID-19. Several studies have demonstrated the characteristic sleep disturbances of patients in ICU to be prolonged sleep latency, sleep fragmentation, decreased sleep efficiency, numerous arousals, abnormal circadian rhythm, abnormal sleep structure such as a preponderance of stage 2 sleep, decreased or absent stage 3 (‘deep’) sleep, and decreased or absent rapid eye movement(REM) sleep[16, 96, 97]. Disruptions of the circadian rhythm may harm to critically ill patients with COVID-19 via the disrupted sleep-wake cycle and disrupted activity of normal physiologic processes.

PSG is the golden standard for sleep assessment in general patients. Ventilated critically ill adults may have abnormal sleep electroencephalogram patterns that meet the criteria for atypical sleep. Disease severity, the sedative type, depth of sedation, and delirium all affect the PSG pattern and recordings[98]. Thus, the traditional scoring of sleep like Rechtschaffen and Kales (R & K) is difficult to apply in those patients. For the above reasons, and the particularity of isolation wards, the high price of equipment, frequent monitoring procedures, and professional interpretation of EEG, etc.[99], PSG should not be applied in patients with COVID-19, as the guidelines suggest not routinely using physiologic sleep monitoring clinically in critically ill adults.

For sober COVID-19 patients, we should routinely inquire about patients’ sleep or try to monitor it either by using one of the validated assessment tools such as the RCSQ or by informal bedside assessment[31]. The RCSQ is a short 5-item questionnaire that uses a visual analog scale to assess sleep depth, latency, wakefulness, percentage of awake time, and sleep quality, which can be completed by self-assessment by awake patients[100].

Studies have reported that sleep fragmentation is higher during mechanical ventilation and NIV[101, 102]. In order to take comprehensive measures to reduce the incidence of sleep deprivation and delirium to promote recovery, it is necessary to use a deep sedation evaluation system (e.g. bis) instead of sleep monitoring (e.g. PSG) to further evaluate the degree of deep sedation in critically ill patients, who are undergoing treatment with mechanical ventilation, prone position, neuromuscular blocking agents, and ECMO.
Statement 27: Using a multi-component bundle of interventions for sleep management in critical patients with COVID-19 should probably be considered. This management strategy is based on human care, control of environmental factors, cognitive behavior therapy for insomnia (CBT-I), and other non-pharmacological interventions, supplemented by pharmaceutical strategies such as melatonin and dexmedetomidine to induce sleep. (Grade 2+, weak recommendation)

Rationale: We suggest that psychological and humane care should be provided for awake patients with COVID-19. Communication and comfort from medical staff and others could reduce the severity of symptoms like PTSD, anxiety, and depression. Psychologists could be allowed to enter the isolation ward early to perform psychological assessment and psychotherapy of the patients.

Based on the experience of sleep management of patients in the ICU setting, the sleep of critically ill patients with COVID-19 can also be managed by a multifaceted and multidisciplinary approach that includes sleep hygiene routines, nursing care plans, and appropriate medication regimens, which may improve patient outcomes. Avoiding the continuous lighting and noisy surroundings to simulate the day-night cycle is an appropriate initial goal for sleep management. For example, day-night light should be controlled, and noise levels kept between 44 and 45 dB during the day and less than 35 dB at night. Earplugs and eye masks promote sleep and hormone balance in critically ill patients. Other complementary interventions such as playing music may reduce patients' perception of stress and improve their sleep. CBT-I is an effective non-pharmacological treatment for abnormal sleep state and comorbid symptoms that includes stimulus control, sleep restriction, relaxation training, cognitive therapy, and sleep hygiene education.

Sometimes sleep-inducing pharmacotherapy should be applied to those who still have sleep disorders after trying non-pharmacological measures. Using melatonin as an endogenous synchronizer to regulate the sleep-wake rhythms can reduce sleep latency and improve the quality of sleep. Dexmedetomidine is the primary medication used for sleep-induction and sedation, and it also reduces the incidence of delirium. Drugs used for sedation and analgesia may affect the recognition of sleep fragmentation. Because of the above-mentioned facts, utilizing PSG to assess circadian rhythm and analyze the classical sleep elements in patients with COVID-19 could be considered.

At present, the relationship between sleep disturbance and outcomes in critically ill patients with COVID-19 infection is still unknown. Further, there is still a lack of analytical data such as circadian rhythm and sleep elements on the sleep patterns of patients. This issue must be paid attention, otherwise, sleep disorders may cause or aggravate patients’ pathological diseases and mental health problems. A multidisciplinary approach to understanding and treating problems will require commitment from all therapists to significantly improve the final prognosis.
V Palliative care

COVID-19 has caused a fast-moving, highly distressing global health crisis. Patients of all ages are under pressure from the disease, while healthcare systems are under the enormous pressure of the growing demand for services. On account of the shortage of medical resources during the outbreak, sometimes physicians have to set a priority for critically ill patients to decide who can receive intensive care. During the pandemic of COVID-19 in Wuhan China, older patients had equal opportunity to receive medical care, given the expected recovery. Nevertheless, many factors should be taken into account for this prudent decision in different regions with different cultural backgrounds and social systems, such as the expected possibility of recovery, individual willingness, and religious beliefs. For those who are not expected to survive or those who renounce aggressive therapy, high-quality palliative care, including end-of-life care, needs to be provided.

**Statement 28: Hospital palliative care is an essential part of COVID-19 therapy. (Expert opinion)**

**Rationale:** Palliative care is a specialized health care for patients and families facing serious illness. It is an important component of health care in pandemics, contributing to symptom control, psychological support, and supporting triage and complex decision making. COVID-19 has caused a fast-spreading global health crisis and a severe imbalance between demand and supply of intensive care. Strengthening hospice care to the greatest extent to ease the patient's pain is an ethical imperative, as well as the embodiment of social progress.

**Statement 29: The primary task of palliative care is to relieve the patient's symptoms. (Expert opinion)**

**Rationale:** Beyond providing life-sustaining treatments, clinical efforts should also address the relief of symptoms. The most prevalent symptoms were dyspnea, agitation, drowsiness, pain, and delirium. Relatively low doses of opioids and benzodiazepines were the most commonly used drugs for palliative sedation and analgesia, especially at the end of life. COVID-19 patients may also experience gastrointestinal symptoms or changes in smell and taste. Clinicians need to pay attention to these symptoms and address them to improve the patient's physical experience.

**Statement 30: Psychotherapy is another indispensable part of palliative care. (Expert opinion)**

**Rationale:** Fear of death and psychological loss are the most common psychological activities of critically ill patients. Psychotherapists are most important in the treatment of mental disorders during epidemics. Serious illness affects both COVID-19 patients and their families, therefore both the patients and their families need to be cared for. Communication and family meetings are also necessary. When death inevitably occurs, the greatest need and desire of the patients is the company of their relatives. In order to avoid spreading the disease through close contact, the use of many new technologies such as telemedicine, visual telephone, and web conferencing should be encouraged. By connecting the patients and their families through the internet, patients can feel the warmth from their relatives and families, which plays a good role
in emotional comfort and pain alleviation. The families should cooperate with the medical staff with a good attitude and behavior to reduce the patient's negative emotions. The families also should give more comfort and create the best environment for the patients at the end of their lives.

In conclusion, regardless of the prognosis, relief of symptom distress and improvement of emotional state are the key components of palliative care for all COVID-19 patients. A multidisciplinary team is needed for better palliative care. The collaborative efforts of the physicians, nurses, and respiratory therapists will help treat distressing symptoms, which applies to the current COVID-19 crisis. While non-palliative specialist physicians can learn to provide primary palliative care, palliative care specialists remain essential members in providing support for COVID-19 patients. Particular attention should also be paid to the bereavement management of the families and PTSD of the health workers involved in the COVID-19 pandemic.

VI Protocol for the management of analgesia and sedation for severe COVID-19 patients

In order to better implement the management of analgesia and sedation for severe COVID-19 patients, we formulated an algorithm based on this consensus [Supplementary Figure 2].

Summary

Pain, agitation, delirium, and sleep disturbance are commonly manifested in COVID-19 patients and are closely associated with the severity and poor prognosis of the disease. It has been a challenge to manage the pain, agitation, delirium, and sleep in severe COVID-19 patients in this time of global crisis. Our consensus is mainly aimed at providing a practical guideline to standardize the management of pain, agitation, and delirium, formulate the appropriate medication plan and achieve the optimal clinical status. This expert consensus statement should be helpful for clinicians worldwide with limited experience in the management of analgesia and sedation for severe COVID-19 patients, offering specific suggestions.
References

1. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5: 536-544. doi: 10.1038/s41564-020-0695-z.

2. Nanchal RS, Truwit JD. Recent advances in understanding and treating acute respiratory distress syndrome. F1000Res 2018; 7: F1000 Faculty Rev-1322 doi: 10.12688/f1000research.15493.1.

3. Johns Hopkins University. Covid-19 dashboard by the center for systems science and engineering (csse) at Johns Hopkins University. 2020, Jun 9. (Accessed at https://coronavirus.jhu.edu/map.html).

4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720. doi: 10.1056/NEJMoa2002032.

5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506. doi: 10.1016/s0140-6736(20)30183-5.

6. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020; 8: 506-517. doi: 10.1016/s2213-2600(20)30161-2.

7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020; 323: 1061-1069. doi: 10.1001/jama.2020.1585.

8. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481. doi: 10.1016/s2213-2600(20)30079-5.

9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020; 215: 108427. doi: 10.1016/j.clim.2020.108427.

10. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China (in Chinese). Chin J Epidemiol 2020; 41: 145-151. doi: 10.3760/cma.j.issn.0254-6450.2020.02.003.

11. Liu N, Zhang F, Wei C, Jia Y, Shang Z, Sun L, et al. Prevalence and predictors of PTSS during COVID-19 outbreak in China hardest-hit areas: Gender differences matter. Psychiatry Res 2020; 287: 112921. doi: 10.1016/j.psychres.2020.112921.

12. Payen JF, Chanques G, Futier E, Velly L, Jaber S, Constantin JM. Sedation for critically ill patients with COVID-19: Which specificities? One size does not fit all. Anaesth Crit Care Pain Med 2020;39:341-343. doi: 10.1016/j.accpm.2020.04.010.

13. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et
al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008; 371: 126-134. doi: 10.1016/s0140-6736(08)60105-1.

14. Wang J, Peng ZY, Zhou WH, Hu B, Rao X, Li JG. A National Multicenter Survey on Management of Pain, Agitation, and Delirium in Intensive Care Units in China. Chin Med J 2017;130:1182-1188. doi: 10.4103/0366-6999.205852.

15. Liu L, Wu AP, Yang Y, Liu SQ, Huang YZ, Xie JF, et al. Effects of Propofol on Respiratory Drive and Patient-ventilator Synchrony during Pressure Support Ventilation in Postoperative Patients: A Prospective Study. Chin Med J 2017;130:1155-1160. doi: 10.4103/0366-6999.205864

16. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395: 912-920. doi: 10.1016/s0140-6736(20)30460-8.

17. Sun L, Sun Z, Wu L, Zhu Z, Zhang F, Shang Z, et al. Prevalence and Risk Factors of Acute Posttraumatic Stress Symptoms during the COVID-19 Outbreak in Wuhan, China. medRxiv 2020; 2020.2003.2008.20032425. doi: 10.1101/2020.03.06.20032425.

18. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int J Environ Res Public Health 2020; 17: 1729. doi: 10.3390/ijerph17051729.

19. Lindenbaum L, Milia DJ. Pain management in the ICU. Surg Clin North Am 2012; 92: 1621-1636. doi: 10.1016/j.suc.2012.08.013.

20. Myhren H, Ekeberg O, Tøien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care 2010; 14: R14. doi: 10.1186/cc8870.

21. Sampson EL, West E, Fischer T. Pain and delirium: mechanisms, assessment, and management. Eur Geriatr Med 2020; 11: 45-52. doi: 10.1007/s41999-019-00281-2.

22. Society of Critical Care Medicine Chinese Medical Association. Guidelines for analgesia and sedation treatment in intensive care unit of Chinese adults (in Chinese). Chin Crit Care Med 2018; 4: 90-113. doi: 10.3760/cma.j.issn.2095-4352.2018.06.001

23. Bugedo G, Tobar E, Aguirre M, Gonzalez H, Godoy J, Lira MT, et al. The implementation of an analgesia-based sedation protocol reduced deep sedation and proved to be safe and feasible in patients on mechanical ventilation. Rev Bras Ter Intensiva 2013; 25: 188-196. doi: 10.5935/0103-507x.20130034.

24. Park G, Lane M, Rogers S, Bassett P. A comparison of hypnotic and analgesic based sedation in a general intensive care unit. Br J Anaesth 2007; 98: 76-82. doi: 10.1093/bja/ael320.
25. Rahu MA, Grap MJ, Ferguson P, Joseph P, Sherman S, Elswick RK, Jr. Validity and sensitivity of 6 pain scales in critically ill, intubated adults. Am J Crit Care 2015; 24: 514-523. doi: 10.4037/ajcc2015832.
26. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care 1998; 7: 200-204.
27. Gélinas C, Puntillo KA, Joffe AM, Barr J. A validated approach to evaluating psychometric properties of pain assessment tools for use in nonverbal critically ill adults. Semin Respir Crit Care Med 2013; 34: 153-168. doi: 10.1055/s-0033-1342970.
28. Chai PR, Gale JY, Patton ME, Schwartz E, Jambaulikar GD, Wade Taylor S, et al. The Impact of Music on Nociceptive Processing. Pain Med 2020; pnaa070. doi: 10.1093/pm/pnaa070.
29. Lee JH. The Effects of Music on Pain: A Meta-Analysis. J Music Ther 2016; 53: 430-477. doi: 10.1093/jmt/thw012.
30. Jafari H, Courtois I, Van den Bergh O, Vlaeyen JWS, Van Diest I. Pain and respiration: a systematic review. Pain 2017; 158: 995-1006. doi: 10.1097/j.pain.0000000000000865.
31. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slootert AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018; 46: e825-e873. doi: 10.1097/ccm.0000000000003299.
32. Erstad BL, Puntillo K, Gilbert HC, Grap MJ, Li D, Medina J, et al. Pain management principles in the critically ill. Chest 2009; 135: 1075-1086. doi: 10.1378/chest.08-2264.
33. Richman PS, Baram D, Varela M, Glass PS. Sedation during mechanical ventilation: a trial of benzodiazepine and opiate in combination. Crit Care Med 2006; 34: 1395-1401. doi: 10.1097/01.Ccm.0000215454.50964.F8.
34. Robleda G, Roche-Campo F, Sendra M, Navarro M, Castillo A, Rodríguez-Arias A, et al. Fentanyl as pre-emptive treatment of pain associated with turning mechanically ventilated patients: a randomized controlled feasibility study. Intensive Care Med 2016; 42: 183-191. doi: 10.1007/s00134-015-4112-7.
35. Zhu Y, Wang Y, Du B, Xi X. Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis. Crit Care 2017; 21: 206. doi: 10.1186/s13054-017-1789-8.
36. Hoke JF, Shlugman D, Dershwitz M, Michalowski P, Malthouse-Duflore S, Connors PM, et al. Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 1997; 87: 533-541. doi: 10.1097/00000542-199709000-00012.
37. Ahmad I, Wade S, Langdon A, Chamarette H, Walsh M, Surda P. Awake tracheal intubation in a suspected COVID-19 patient with critical airway...
obstruction. Anaesth Rep 2020; 8: 28-31. doi: 10.1002/anr3.12041.
38. Conti G, Arcangeli A, Antonelli M, Cavaliere F, Costa R, Simeoni F, et al. Sedation with sufentanil in patients receiving pressure support ventilation has no effects on respiration: a pilot study. Can J Anaesth 2004; 51: 494-499. doi: 10.1007/bf03018315.
39. Wang YH, Chai JR, Xu XJ, Ye RF, Zan GY, Liu GY, et al. Pharmacological Characterization of Dezocine, a Potent Analgesic Acting as a Partial Agonist and μ Partial Agonist. Sci Rep 2018; 8: 14087. doi: 10.1038/s41598-018-32568-y.
40. Li XT, Ma CQ, Qi SH, Zhang LM. Combination of propofol and dezocine to improve safety and efficacy of anesthesia for gastroscopy and colonoscopy in adults: A randomized, double-blind, controlled trial. World J Clin Cases 2019; 7: 3237-3246. doi: 10.12998/wjcc.v7.i20.3237.
41. Jelacic S, Bollag L, Bowdle A, Rivat C, Cain KC, Richebe P. Intravenous Acetaminophen as an Adjunct Analgesic in Cardiac Surgery Reduces Opioid Consumption But Not Opioid-Related Adverse Effects: A Randomized Controlled Trial. J Cardiothorac Vasc Anesth 2016; 30: 997-1004. doi: 10.1053/j.jvca.2016.02.010.
42. Thybo KH, Hägi-Pedersen D, Dahl JB, Wetterslev J, Neresjøen M, Jakobsen JC, et al. Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty: The PansaID Randomized Clinical Trial. JAMA 2019; 321: 562-571. doi: 10.1001/jama.2018.22039.
43. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020; 368 m1086. doi: 10.1136/bmj.m1086.
44. Rodríguez-Morales AJ, Cardona-Ospina JA, Murillo-Muñoz MM. Gastroenterologists, Hepatologists, COVID-19 and the Use of Acetaminophen. Clin Gastroenterol Hepatol 2020; pii: S1542-3565(20)30521-8. doi: 10.1016/j.cgh.2020.04.025. [Epub ahead of print]
45. Feng M, Chen X, Liu T, Zhang C, Wan L, Yao W. Dexmedetomidine and sufentanil combination versus sufentanil alone for postoperative intravenous patient-controlled analgesia: a systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiol 2019; 19: 81. doi: 10.1186/s12871-019-0756-0.
46. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012; 307: 1151-1160. doi: 10.1001/jama.2012.304.
47. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology 2020; 132: 1317-1332. doi: 10.1097/aln.0000000000003296.
48. Wu KK, Chan SK, Ma TM. Posttraumatic stress, anxiety, and depression in survivors of severe acute respiratory syndrome (SARS). J Trauma Stress 2005; 18: 39-42. doi: 10.1002/jts.20004.
49. Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. J Clin Pathol 2020; 73: 239-242. doi: 10.1136/jclinpath-2020-206522.
50. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open 2020; 3: e203976. doi: 10.1001/jamanetworkopen.2020.3976.
51. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166: 1338-1344. doi: 10.1164/rccm.2107138.
52. Shehabi Y, Forbes AB, Arabi Y, Bass F, Bellomo R, Kadiman S, et al. The SPICE III study protocol and analysis plan: a randomised trial of early goaldirected sedation compared with standard care in mechanically ventilated patients. Crit Care Resusc 2017; 19: 318-326.
53. Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann Intensive Care 2020; 10: 37. doi: 10.1186/s13613-020-00653-z.
54. Chawla R, Dixit SB, Zirpe KG, Chaudhry D, Khilnani GC, Mehta Y, et al. ISCCM Guidelines for the Use of Non-invasive Ventilation in Acute Respiratory Failure in Adult ICUs. Indian J Crit Care Med 2020; 24: S61-S81. doi: 10.5005/jp-journals-10071-G23186.
55. Matsumoto T, Tomii K, Tachikawa R, Otsuka N, Nagata K, Otsuka K, et al. Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital. BMC Pulm Med 2015; 15: 71. doi: 10.1186/s12890-015-0072-5.
56. Muriel A, Peñuelas O, Frutos-Vivar F, Arroliga AC, Abaira V, Thille AW, et al. Impact of sedation and analgesia during noninvasive positive pressure ventilation on outcome: a marginal structural model causal analysis. Intensive Care Med 2015; 41: 1586-1600. doi: 10.1007/s00134-015-3854-6.
57. Lucchini A, Giani M, Isgrò S, Rona R, Foti G. The "helmet bundle" in COVID-19 patients undergoing non invasive ventilation. Intensive Crit Care Nurs 2020; 58:102859. doi: 10.1016/j.iccn.2020.102859.
58. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? Crit Care 2020; 24: 198. doi: 10.1186/s13054-020-02911-9.
59. Cho YJ, Moon JY, Shin ES, Kim JH, Jung H, Park SY, et al. Clinical Practice Guideline of Acute Respiratory Distress Syndrome. Tuberc Respir Dis (Seoul) 2016; 79: 214-233. doi: 10.4046/trd.2016.79.4.214.
60. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the 'ABCDE' approach. Curr Opin Crit Care 2011; 17: 43-49. doi: 10.1097/MCC.0b013e3283427243.
61. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA 2020;323:2329-2330. doi: 10.1001/jama.2020.6825.

22
62. Xie Y, Cao L, Qian Y, Zheng H, Liu K, Li X. Effect of Deep Sedation on Mechanical Power in Moderate to Severe Acute Respiratory Distress Syndrome: A Prospective Self-Control Study. Biomed Res Int 2020; 2020:2729354. doi: 10.1155/2020/2729354.

63. Vagionas D, Vasileiadis I, Rovina N, Alevrakis E, Koutsoukou A, Koulouris N. Daily sedation interruption and mechanical ventilation weaning: a literature review. Anaesthesiol Intensive Ther 2019; 51: 380-389. doi: 10.5114/ait.2019.90921.

64. Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N Engl J Med 2019; 380: 1997-2008. doi: 10.1056/NEJMoa1901686.

65. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363: 1107-1116. doi: 10.1056/NEJMoa1005372.

66. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368: 2159-2168. doi: 10.1056/NEJMoa1214103.

67. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med 2020; 8: 518-526. doi: 10.1016/s2213-2600(20)30121-1.

68. deBacker J, Tamberg E, Munshi L, Burry L, Fan E, Mehta S. Sedation Practice in Extracorporeal Membrane Oxygenation-Treated Patients with Acute Respiratory Distress Syndrome: A Retrospective Study. Asaio J 2018; 64: 544-551. doi: 10.1097/mat.0000000000000658.

69. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, et al. "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care 2016; 20: 150. doi: 10.1186/s13054-016-1329-y.

70. Ahsman MJ, Hanekamp M, Wildschut ED, Tibboel D, Mathot RA. Population pharmacokinetics of midazolam and its metabolites during venoarterial extracorporeal membrane oxygenation in neonates. Clin Pharmacokinet 2010; 49: 407-419. doi: 10.2165/11319970-000000000-00000.

71. Harthan AA, Buckley KW, Heger ML, Fortuna RS, Mays K. Medication adsorption into contemporary extracorporeal membrane oxygenator circuits. J Pediatr Pharmacol Ther 2014; 19: 288-295. doi: 10.5863/1551-6776-19.4.288.

72. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020; 323: 1843-1844. doi: 10.1001/jama.2020.3786.

73. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth 2020;125:e28-e37. doi: 10.1016/j.bja.2020.03.026.

74. Ding J, Chen Y, Gao Y. Effect of propofol, midazolam and dexmedetomidine
on ICU patients with sepsis and on arterial blood gas. Exp Ther Med 2019; 18: 4340-4346. doi: 10.3892/etm.2019.8091.

75. Mateos Gaitan R, Vicent L, Rodriguez-Queralto O, Lopez-de-Sa E, Elorriaga A, Pastor G, et al. Dexmedetomidine in medical cardiac intensive care units. Data from a multicenter prospective registry. Int J Cardiol 2020; 310: 162-166. doi: 10.1016/j.ijcard.2020.04.002.

76. Winings NA, Daley BJ, Bollig RW, Roberts RF, Jr., Radtke J, Heidel RE, et al. Dexmedetomidine versus propofol for prolonged sedation in critically ill trauma and surgical patients. Surgeon 2020; S1479-666X(20)30047-0. doi: 10.1016/j.surge.2020.04.003. [Epub ahead of print]

77. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013; 369: 1306-1316. doi: 10.1056/NEJMoa1301372.

78. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020; 77: 1-9. doi: 10.1001/jamaneurol.2020.1127.

79. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 92: 552-555. doi: 10.1002/jmv.25728.

80. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020; 109: 531-538. doi: 10.1007/s00392-020-01626-9.

81. Marra A, Kotfis K, Hosie A, MacLullich AMJ, Pandharipande PP, Ely EW, et al. Delirium Monitoring: Yes or No? That Is The Question. Am J Crit Care 2019; 28: 127-135. doi: 10.4037/ajcc2019874.

82. Barnes-Daly MA, Phillips G, Ely EW. Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. Crit Care Med 2017; 45: 171-178. doi: 10.1097/ccm.000000000002149.

83. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. Crit Care Med 2019; 47: 3-14. doi: 10.1097/ccm.0000000000003482.

84. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. N Engl J Med 2018; 379: 2506-2516. doi: 10.1056/NEJMoa1808217.

85. van den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, et al. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. Jama 2018; 319: 680-690. doi: 10.1001/jama.2018.0160.

86. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled
87. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.

88. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22. doi: 10.1016/j.bbi.2020.03.031.

89. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.

90. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22. doi: 10.1016/j.bbi.2020.03.031.

91. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.

92. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22. doi: 10.1016/j.bbi.2020.03.031.

93. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.

94. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22. doi: 10.1016/j.bbi.2020.03.031.

95. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.

96. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22. doi: 10.1016/j.bbi.2020.03.031.

97. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373-377. doi: 10.1126/science.1241224.
101. Cordoba-Izquierdo A, Drouot X, Thille AW, Galia F, Roche-Campo F, Schortgen F, et al. Sleep in hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators. Crit Care Med 2013; 41: 60-68. doi: 10.1097/CCM.0b013e31826764e3.

102. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. Crit Care 2013; 17: R46. doi: 10.1186/cc12565.

103. Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia 2014; 69: 540-549. doi: 10.1111/anae.12638.

104. Akansel N, Kaymakçı S. Effects of intensive care unit noise on patients: a study on coronary artery bypass graft surgery patients. J Clin Nurs 2008; 17: 1581-1590. doi: 10.1111/j.1365-2702.2007.02144.x.

105. Voigt LP, Reynolds K, Mehryar M, Chan WS, Kostelecky N, Pastores SM, et al. Monitoring sound and light continuously in an intensive care unit patient room: A pilot study. J Crit Care 2017; 39: 36-39. doi: 10.1016/j.jcrc.2016.12.020.

106. Hu RF, Jiang XY, Zeng YM, Chen XY, Zhang YH. Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. Crit Care 2010; 14: R66. doi: 10.1186/cc8965.

107. Litton E, Carnegie V, Elliott R, Webb SA. The Efficacy of Earplugs as a Sleep Hygiene Strategy for Reducing Delirium in the ICU: A Systematic Review and Meta-Analysis. Crit Care Med 2016; 44: 992-999. doi: 10.1097/ccm.0000000000001557.

108. Pagnucci N, Tolotti A, Cadorin L, Valcarenghi D, Forfori F. Promoting nighttime sleep in the intensive care unit: Alternative strategies in nursing. Intensive Crit Care Nurs 2019; 51: 73-81. doi: 10.1016/j.iccn.2018.11.010.

109. Sadler P, McLaren S, Klein B, Harvey J, Jenkins M. Cognitive behavior therapy for older adults with insomnia and depression: a randomized controlled trial in community mental health services. Sleep 2018; 41: 1-12. doi: 10.1093/sleep/zsy104.

110. Taylor DJ, Peterson AL, Pruiksma KE, Hale WJ, Young-McCaughan S, Wilkerson A, et al. Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: a randomized clinical trial. Sleep 2018; 41: 1-11. doi: 10.1093/sleep/zsy069.

111. Wu YT, Wang J, Chen YW, Guo W, Wu EL, Tang CR, et al. The efficacy of cognitive behavioral therapy in insomnia patients with or without comorbidities: a pilot study (in Chinese). Chin J Intern Med 2018; 57: 731-737. doi: 10.3760/cma.j.issn.0578-1426.2018.10.007.

112. Quera-Salva MA, Claustrat B. Melatonin: Physiological and pharmacological aspects related to sleep: The interest of a prolonged-release formulation (Circadin®) in insomnia. Encephale 2018; 44: 548-557. doi: 10.1016/j.
Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. Jama 2007; 298: 2644-2653. doi: 10.1001/jama.298.22.2644.

Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. Jama 2009; 301: 489-499. doi: 10.1001/jama.2009.56.

Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. Crit Care Clin 2006; 22: 313-327 doi: 10.1016/j.ccc.2006.02.010.

Response and role of palliative care during the COVID-19 pandemic: A national telephone survey of hospices in Italy. Palliat Med 2020; 34:889-895. doi: 10.1177/0269216320920780.

The Role and Response of Palliative Care and Hospice Services in Epidemics and Pandemics: A Rapid Review to Inform Practice During the COVID-19 Pandemic. J Pain Symptom Manage 2020; 60: e31-e40. doi: 10.1016/j.jpainsymman.2020.03.029.

Characteristics, Symptom Management, and Outcomes of 101 Patients With COVID-19 Referred for Hospital Palliative Care. J Pain Symptom Manage 2020; 60: e77-e81. doi: 10.1016/j.jpainsymman.2020.04.015.

Characteristics and Palliative Care Needs of COVID-19 Patients Receiving Comfort-Directed Care. J Am Geriatr Soc 2020; 68:1162-1164. doi: 10.1111/jgs.16507.

Brief Confusion Assessment MEthond (bCAM) Flow Sheet. 2012. (Accessed at http://www.icudelirium.org/docs/bCAM_Flowsheet.pdf).

Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41: 263-306. doi: 10.1097/CCM.0b013e3182783b72.
Supplementary Figure 1. Brief Confusion Assessment Method (bCAM)\textsuperscript{[120]}

Supplementary Figure 2. Algorithm of protocol for the management of analgesia and sedation in severe COVID-19 patients. COVID-19: Coronavirus disease 2019; NRS: Numeric Rating Scale; NIV: Non-invasive ventilation; HFNC: High-flow nasal cannula; CPOT: Critical-Care Pain Observation Tool; IMV: Invasive mechanical ventilation; RASS: Richmond agitation-sedation scale; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ECMO: extracorporeal membrane oxygenation; BZ: benzodiazepines; bCAM: Brief Confusion Assessment Method; ICU: Intensive care unit; ARDS: acute respiratory distress syndrome
Discomfort (regardless if it is pain, anxiety or delirium)

Improve environment, increase family video visitation, satisfy demands, music therapy

Still feel uncomfortable

**Pain assessment:**
NRS for HFNC/NIV
CPOT for IMV

**Agitation assessment:**
RASS for HFNC/NIV/IMV/ECMO

**Delirium screening:**
bCAM

**Sleep disturbance assessment:**
RCSQ

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1. Opioids as the first choice;
2. In consideration of safety and weak analgesia effect, dexmedetomidine is best for HFNC and NIV.

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Keep RASS at:
1. -1 to 0 for HFNC;
2. -1 to 0 for NIV;
3. -2 to 0 for IMV;
4. Different for ECMO

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1. Remove risk factors;
2. Discharge from ICU;
3. Do not use haloperidol;
4. Reduce sleep disturbance;
5. Dexmedetomidine

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Combination of opioids and BZ to reach target. NSAIDs can be used to reduce opioid dose if analgesia is needed for long time.

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Combine with neuromuscular blockers and maintain RASS at -5 to -4 in those receiving IMV in prone position or with patient-ventilator dyssynchrony, and those in whom ECMO is anticipated to be used for more than two weeks, and those who will receive invasive procedures.

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RASS should be kept at -4 to -5 under such situations. DSI should not be used in COVID-19 patients with severe ARDS especially with patient-ventilator dyssynchrony, but can be used in those who require long-term and deep sedation. Drug types and doses should be adjusted according to changes in hemodynamics and organ dysfunction.
**Supplementary Table 1. Consensus timeline**

| Time             | Works on the Consensus                                                                 |
|------------------|----------------------------------------------------------------------------------------|
| April 28, 2020   | Designating the experts in charge of addressing each question                          |
| May 13, 2020     | 1) Each expert made a detailed outline of their respective question                    |
|                  | 2) Discussing and resolving the problems encountered by the experts in the process of |
|                  | making the statements                                                                  |
| May 20, 2020     | 1) Discussing the experts’ respective statements and rationale after revision          |
|                  | 2) First round of scoring                                                               |
| May 30, 2020     | Guideline finalization meeting for the second round of scoring                          |

**Supplementary Table 2. Recommendations according to the GRADE methodology**

| Strength | Recommendations | Definition                                      |
|----------|-----------------|-------------------------------------------------|
| Grade 1+ | Strong recommendation | High level of evidence                  |
|          | “…we recommend…”, “…recommended…” or “…should…” |                                 |
| Grade 2+ | Weak recommendation | Low level of evidence          |
|          | “…should probably…” or “…should probably be considered…” |                                     |
| Expert opinion | Recommendation in the form of an expert opinion | Insufficient level of evidence |
|          | “…The experts suggest…”, “…suggested…”, “…The experts suggest against…”, or “…not suggested…” |                    |
| Grade 2- | Weak recommendation | Low level of evidence |
|          | “…should probably not…” |                                |
| Grade 1- | Strong recommendation | High level of evidence |
|          | “…should not…” |                                            |

**GRADE: Grades of recommendation, assessment, development, and evaluation**
**Supplementary Table 3. Critical-Care Pain Observation Tool (CPOT)**[27]

| Indicator | Description | Classification | Score |
|-----------|-------------|----------------|-------|
| Facial expression | No muscular tension observed | Relaxed, neutral | 0 |
| | Presence of frowning, brow lowering, orbit tightening, and levator contraction | Tense | 1 |
| | All of the above facial movements plus eyelid tightly closed | Grimacing | 2 |
| Body movements | Does not move at all (does not necessarily mean the absence of pain) | Absence of movements | 0 |
| | Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements | Protection | 1 |
| | Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed | Restlessness | 2 |
| Muscle tension | No resistance to passive movements | Relaxed | 0 |
| Evaluation by passive flexion and extension of upper extremities | Resistance to passive movements | Tense, rigid | 1 |
| | Strong resistance to passive movements, inability to complete them | Very tense or rigid | 2 |
| Compliance with the ventilator (intubated patients) | Alarms not activated, easy ventilation | Tolerating ventilator or movement | 0 |
| | Alarms stop spontaneously | Coughing but tolerating | 1 |
| | Asynchrony: blocking ventilation, alarms frequently activated | Fighting ventilator | 2 |
| or Vocalization (extubated patients) | Talking in a normal tone or no sound | Talking in a normal tone or no sound | 0 |
| | Sighing, moaning | Sighing, moaning | 1 |
| | Crying out, sobbing | Crying out, sobbing | 2 |
| Total, range | | | 0–8 |
### Supplementary Table 4. Pharmacokinetics of opioids\textsuperscript{[22]}

| Medicine     | Onset Time (min) | Half-life (min) | Loading Dose | Maintenance Dose | Side Effect                                                                 |
|--------------|------------------|-----------------|--------------|------------------|-----------------------------------------------------------------------------|
| Fentany      | 1–2              | 120–240         | 0.35–0.50 μg/kg | 0.7–10.0 μg·kg\(^{-1}\)·h\(^{-1}\) | Less hypotension than morphine, cumulative liver injury.                     |
| Morphine     | 5–10             | 180–240         | 2–4 mg       | 2–30 mg·h\(^{-1}\) | Cumulative liver injury, some histamine release.                             |
| Remifentanyl | 1–3              | 3–10            | 0.5–1.0 μg/kg | 0.02–0.15 μg·kg\(^{-1}\)·min\(^{-1}\) | No liver or kidney injury.                                                  |
| Sufentanil   | 1–3              | 784             | 0.2–0.5 μg/kg | 0.2–0.3 μg·kg\(^{-1}\)·h\(^{-1}\) | Doses vary widely among individuals, with short distribution half-lives and long metabolic half-lives, and long-term use may increase mechanical ventilation time. |
### Supplementary Table 5. Richmond agitation-sedation scale (RASS)\(^{[51]}\)

| Score | Classification | Interpretation |
|-------|----------------|----------------|
| +4    | Combative      | Combative or violent; danger to care team |
| +3    | Very agitated  | Pulls or removes tubes or catheters; aggressive |
| +2    | Agitated       | Frequent non-purposeful movements or patient-ventilator dyssynchrony |
| +1    | Restless       | Anxious or apprehensive; Not aggressive |
| 0     | Alert and calm | Spontaneously pays attention to caregiver |
| −1    | Drowsy         | Awakens to voice (e.g. eye opening with eye contact) >10 s |
| −2    | Light sedation | Briefly awakens to voice (e.g. eye opening with eye contact) <10 s |
| −3    | Moderate sedation | Movement or eye opening to voice; no eye contact |
| −4    | Deep sedation  | No response to voice; movement or eye opening to physical stimulation |
| −5    | Unarousable    | No response to voice or physical stimulation |

### Supplementary Table 6. Procedure for RASS assessment

| Steps for RASS assessment | Score |
|---------------------------|-------|
| 1. Observe patient: alert, restless or agitated | 0 to +4 |
| 2. If not alert, state the patient’s name and say to open eyes and look at the speaker.  
  • Patient awakens with sustained eye opening and eye-contact | −1 |
|  | • Patient awakens with eye opening and eye contact, but not sustained (<10 s) | −2 |
|  | • Patient has any movement in response to voice but no eye contact. | −3 |
| 3. When no response to verbal stimulation, physically stimulate the patient by shaking shoulder and/or rubbing sternum.  
  • Patient has any movement to physical stimulation | −4 |
|  | • Patient has no response to any stimulation | −5 |

**RASS**: Richmond agitation-sedation scale
| Medicine   | Onset Time (min) | Elimination Half-life (h) | Loading Dose | Maintenance Dose | Side Effect                                                                 |
|------------|-----------------|--------------------------|--------------|-----------------|-----------------------------------------------------------------------------|
| Midazolam  | 2–5             | 3–11                     | 0.01–0.05 mg/kg over several minutes | 0.02–0.10 mg⋅kg⁻¹⋅h⁻¹ | Respiratory depression, hypotension                                           |
| Propofol   | 1–2             | 3–12                     | 5 μg⋅kg⁻¹⋅min⁻¹ over 5 min. Administer IV loading dose only in hypotension is unlikely to occur. | 5–50 μg⋅kg⁻¹⋅h⁻¹ | Hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, allergic reactions, propofol-related infusion syndrome |
| Dexmedetomidine | 5–10          | 1.8–3.1                  | 1 μg/kg over 10 min. Avoid IV loading doses in hemodynamically unstable patients. | 0.2–0.7 μg⋅kg⁻¹⋅h⁻¹ | Bradycardia, hypotension; loss of airway reflexes |