Consensus

Expert consensus of perioperative intensive care and management of critically ill cancer patients (2021)

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Introduction

According to the guidelines of Chinese Society of Critical Care Medicine, critically ill patients who fulfill the following criteria should be admitted to intensive care unit (ICU) for intensive care (1). First, acute, reversible and life-threating organ or system failure patients should be admitted to ICU, who may recover after a short period of intensive care. Second, high-risk patients with potentially life-threating diseases may benefit from intensive care monitoring and effective treatment. Third, acute on chronic organ or system failure patients may recover to original or near original state after intensive care monitoring and effective treatment. Four, other critically ill patients who may benefit from intensive care monitoring and effective treatment. However, patients with chronic wasting disease or terminal state cancer will not benefit from intensive care monitoring, and should not admitted to ICU.

With the development of surgical procedures, radiotherapy, target therapy and immunotherapy, the survival rate of patients with advanced stage cancer has improved greatly (2). Cancer patients who developed complications such as sepsis, acute kidney injury or acute respiratory failure after neoadjuvant therapy may

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have similar short-term or improved long-term survival after intensive monitoring and treatment compared with patients with no neoadjuvant therapy (3). Rescue anti-cancer treatment may alleviate organ failure in some hematological malignancies who present with acute kidney injury or acute respiratory failure. Most importantly, advanced staged cancer does not equal to terminally ill diseases. Currently, only German Society of Hematology and Medical Oncology (DGHO), Austrian Society of Hematology and Oncology (OeGHO), German Society for Medical Intensive Care Medicine and Emergency Medicine (DGIIN), and Austrian Society of Medical and General Intensive Care and Emergency Medicine (ÖGIAIN) jointly issued consensus statement on cancer patients requiring intensive care support (4). It mainly focuses on patients who received non-operative therapies. A recent meta-analysis including nine trials showed no significant differences in postoperative mortality and complications rate between goal directed therapy group and control group in cancer patients undergoing high-risk surgery, but a reduced hospital length of stay was seen in goal directed therapy group (5). However, there are no consensuses or guidelines regarding perioperative intensive care and/or management of critically ill cancer patients. Therefore, we organized experts of some medical centers in China to draft consensus which focused on common important clinical problems in perioperative critically ill cancer patients, which provide reference for clinical intensivists and policymakers.

Methods

Details about the methods can be found in the Appendix 1. The quality of evidence was graded according to GRADE system as followed (6). High quality, further research is very unlikely to change our confidence in the estimate of effect. Moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality, any estimate of effect is very uncertain. The strength of recommendations is classified as strong if more than or equal to 1/2 experts agree with the statement. Recommendation is classified as weak if less than 1/2 experts agree with the statement.

The consensus was first prepared by two members (Wang HJ and Xing XZ) using search strategies in the Supplement, and twenty-one consensuses were formed. Then these consensuses were sent to thirty experts of Critical Care Medicine Committee of Beijing Association of Oncology (CCMBAO) by electronic questionnaire and were graded. Finally, twenty-four experts responded. We present the following article in accordance with the RIGHT reporting checklist (available at https://dx.doi.org/10.21037/apm-21-870).

Results

Question 1. Which kind of cancer patients may benefit from postoperative intensive care monitoring?

Traditional definition of high-risk cancer patients is limited to patients with American Society of Anesthesiology (ASA) grade 3–4 or patients who underwent thoracic, abdominal or pelvic procedures (7-9). Experts from Massachusetts General Hospital proposed a new high-risk definition which includes twenty-three pre- and postoperative variables (10). In their study, patients who were rated as high propensity admission to ICU had decreased length of stay and costs after intensive care monitoring in ICU. On the contrary, patients who were rated as low propensity admission to ICU had increased length of stay and costs after intensive care monitoring in ICU, therefor these patients may return to surgical ward directly. However, external validation of the definition was not carried out owing to calculation method was not open.

(I) Consensus 1.1: the definition of high-risk patients refers to patients with ASA grade 3–4 who underwent surgical procedures or patients who underwent thoracic, abdominal or pelvic procedures (moderate quality, strong recommendation).

Traditional, high-risk surgical cancer patients including patients with ASA grade 3–4 and patients who underwent complex procedures may benefit from intensive care with reduced complications and mortality (7-9). Recently, several meta-analyses demonstrated no survival benefit for high-risk cancer patients after goal directed therapy in ICU (5,9,11). However, for selected high-risk cancer patients, shortened hospital length of stay and reduced hospital cost were still found after goal directed therapy (10).

(II) Consensus 1.2: selected high-risk cancer patients may benefit from goal directed therapy with shortened hospital length of stay and reduced hospital cost (moderate quality, strong recommendation).

Table 1 Surgical Apgar score

Variables	0 point	1 point	2 points	3 points	4 points
Estimated amount of blood loss (mL)	>1,000	601–1,000	101–600	≤100	–
Lowest mean arterial pressure (mmHg)	<40	40–54	55–69	≥70	–
Lowest heart rate (bpm)	>85	76–85	66–75	56–65	≤55

Modified from reference (12).

Surgical Apgar score (SAS) was proposed in 2007, which includes three variables, estimated amount of blood loss, lowest mean arterial pressure and lowest heart rate. Zero to four points were assigned for each variable (*Table 1*) (12). SAS is calculated as sum of three variables and is predictive of postoperative death rate. The lower the score, the higher the mortality rate, and vice versa. SAS has been tested in various surgeries with satisfactory results. Calculation of SAS is simple, and it does not require biochemical workups, acute or chronic disease category, clinical assessment, or depend on the nature of the surgery (elective, urgent, emergency) (13). Therefore, SAS is a simple and useful triage tool for anesthesiologist, surgeons and intensivists.

(III) Consensus 1.3: SAS may serve as a new triage tool in high-risk patients (moderate quality, strong recommendation).

Calvo-Vecino *et al.* conducted a randomized controlled trial in 2018 which included 450 low-moderate risk surgical patients (14). They found that compared with control group, patients who received esophageal Doppler monitor-guided goal-directed haemodynamic therapy had decreased complication rate (8.6% *vs.* 16.6%, P=0.018). However, there was no significant difference in mortality between two groups. The limitation of the study lies in small sample, and large study is needed to validate the conclusion.

(IV) Consensus 1.4: low-moderate risk surgical patients may benefit from esophageal Doppler monitor-guided goal-directed haemodynamic therapy with decreased complication rate (moderate quality, strong recommendation).

Perioperative goal-directed therapies consist of cardiac output-guided hemodynamic therapy, or esophageal Doppler monitor-guided goal-directed haemodynamic therapy, or cardiac index (CI)-guided goal-directed hemodynamic therapy, *et al.* (5,9,11,14), which make it difficult to compare the results of different studies. Recently, a network meta-analysis demonstrated that goal-directed hemodynamic therapy aimed at intravascular volume, stroke volume, and cardiac output optimization are likely most effective (15). However, there is no universally accepted definition of goal-directed hemodynamic therapy. Therefore, unification of goal-directed therapy may help compare and popularize the results of the study.

(V) Consensus 1.5: inconsistency of perioperative goal-directed therapy deserves further high-quality studies with uniform definition (moderate quality, strong recommendation).

Question 2. Does neoadjuvant therapy increase the mortality rate of critically ill cancer patients?

Although neoadjuvant therapy may improve long-term survival of some resectable solid tumors, it increased the incidence of pulmonary embolism, decreased cardiopulmonary reserve (16,17). It may also affect short-term outcome of critically ill cancer patients. In a recently retrospective study involving 963 surgical patients, after propensity score matching, neoadjuvant therapy does not adversely affect the short-term outcome of critically ill cancer patients (3). In multivariable analysis using the same database after adjusting for age, gender and tumor staging, neoadjuvant therapy still does not adversely affect the short-term outcome of critically ill cancer patients.

(I) Consensus 2.1: neoadjuvant therapy does not increase hospital mortality of critically ill cancer patients (moderate quality, strong recommendation).

Question 3. Can extracorporeal membrane oxygenation (ECMO) be used in the treatment of perioperative severe/refractory acute respiratory distress syndrome (ARDS) cancer patients?

According to a meta-analysis in 2019 involving 429 severe/refractory ARDS patients, usage of ECMO was associated with reduced 60-day mortality compared with controls, and 60-day mortality was 34% and 47% in ECMO and control group respectively (18). In an international multicenter retrospective study, 6-month mortality was 34% and 66%

for severe ARDS patients without or with immunodeficiency who received ECMO (19). Subgroup analysis demonstrated that hematological malignancies had the lowest 6-month survival compared with other immunodeficiency severe ARDS patients and patients with solid tumor (P=0.02). In another study including 68 nonhematologic malignancy patients with respiratory or cardiac failure who received ECMO as salvage therapy despite conventional therapy, the 6-month survival was 26.5% (20).

(I) Consensus 3.1: highly selected critically ill cancer patients with severe/refractory ARDS may benefit from ECMO therapy (moderate quality, strong recommendation).

There are case reports that ECMO therapy serves as a bridge therapy for refractory respiratory failure after esophagectomy (21,22). Besides, ECMO has been successfully used for perioperative support in thoracic and airway surgery with a low perioperative mortality rate (23).

(II) Consensus 3.2: ECMO may be used as a bridge therapy for perioperative refractory respiratory failure and perioperative support for high-risk surgery (high quality, strong recommendation).

Question 4. How is the prognosis of critically ill cancer patients with acute kidney injury?

Results from South Korea demonstrated that the prevalence of acute kidney injury (AKI) was 33.8% in 67,896 cancer patients according to risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria (24). Another study from China showed that there were 1,418 malignancy-related AKI in 7,604 AKI patients according to KDIGO criteria (25). Both patient-specific and cancer-related risk factors including age, co-morbid conditions, chemotherapy, surgery and radiotherapy increase the risk of AKI in cancer patients (26). Critically ill cancer patients with AKI had increased mortality compared patients without AKI (27).

(I) Consensus 4.1: many factors including surgery, chemotherapy, radiotherapy, and sepsis increase the risk of acute kidney injury in cancer patients. Acute kidney injury was associated with increased mortality in critically ill cancer patients (high quality, strong recommendation).

Several studies demonstrated that whether solid tumor or hematological malignancy patients, the prognosis of AKI was related to disease severity and AKI grading, but not cancer staging (28-31). Critically ill cancer patients with AKI who received renal replacement therapy had similar short-term outcomes compared with AKI patients without cancer (29).

(II) Consensus 4.2: short-term outcome of cancer patients suffered from acute kidney injury was related to disease severity and acute kidney injury grading, but not cancer staging. Therefore, the indication of renal replacement therapy in cancer patients with acute kidney injury should not be different from non-cancer patients with acute kidney injury (moderate quality, strong recommendation).

Question 5. Could ECLS be used in critically ill cancer patients with post-hepatectomy liver failure (PHLF)?

PHLF comes from two aspects, primary or secondary causes. Primary PHLF refers to liver failure caused by small-for-size situation, coupled with intraoperative bleeding or not. Secondary PHLF refers to liver failure caused by late complications (32). According to definition and grading of International Study Group of Liver Surgery (ISGLS), PHLF was divided into three groups. Grading A PHLF refers to patients with abnormal laboratory parameters but require no change in the clinical management. Grading B PHLF is a state that patients have abnormal laboratory parameters, require albumin infusion, daily diuretics, or noninvasive ventilation. Grading C PHLF means patients not only have abnormal laboratory parameters, but require ICU admission and invasive treatment including vasoactive drugs, or hemodialysis, or intubation and mechanical ventilation, or ECLS, or rescue hepatectomy/liver transplantation (33). In the ISGLS study, the incidence of grading B and grading C was 8.1% and 2.2%, with a mortality 12% and 54% respectively. In a Germany study which included 415 PHLF patients, the incidence of grading B and grading C was 5.7% and 1.6%, with a mortality 12.5% and 85.7% respectively (34). In a China study which involving 1,683 patients, the incidence of grading B and grading C was 0% and 1.6%, with a mortality 0.5% and 50% respectively (35).

(I) Consensus 5.1: the mortality of posthepatectomy liver failure was high although its incidence was low (high quality, strong recommendation).

There are no randomized controlled trials because of low incidence of PHLF. Treatment strategy of PHLF was based on the experiences of medical treatment of acute liver failure, which included elimination of possible etiology, supportive therapy of organ dysfunction, and treatment of postoperative reversible factors (36). Specific treatment measures consist of maintaining hemodynamic stability, blood purification for acute kidney injury or hepatic encephalopathy, prevention of gastrointestinal bleeding, treatment of postoperative infection. The outcome of ECLS was related to the etiology of PHLF. In a meta-analysis in 2020, of 34 PHLF patients who received ECLS, ninety-day mortality was 60% and 17% respectively for primary PHLF (n=25) and secondary PHLF (n=7) patients (32). Liver transplantation may be the only treatment measure for primary PHLF which was refractory to conventional measures. In a recent study, five-year and ten-year survival was 57% and 38% respectively for seven primary PHLF patients after liver transplantation (37).

(II) Consensus 5.2: specific treatment measures for posthepatectomy liver failure included elimination of possible etiology, supportive therapy of organ dysfunction. ECLS and liver transplantation may be an option for selected posthepatectomy liver failure patients (moderate quality, strong recommendation).

Question 6. What is the clinical characteristic and prognosis of perioperative stress cardiomyopathy?

In a national study in US, of 5,991,314 patients, patients with a prior intrathoracic/mediastinal malignancies and radiotherapy had increased risk of stress cardiomyopathy (38). Many anti-tumor agents were also associated with increased risk of stress cardiomyopathy in cancer patients (39). Patients who underwent major cancer surgeries were also at risk of developing stress cardiomyopathy (40). Compared with non-cancer patients who developed stress cardiomyopathy, cancer patients who diagnosed as stress cardiomyopathy had increased risk of respiratory insufficiency, prolonged hospital length of stay, slower recovery of cardiac function, and were more likely to develop cardiac arrest (41,42).

(I) Consensus 6.1: anti-tumor therapies were associated increased risk of stress cardiomyopathy. Cancer patients who developed stress cardiomyopathy had worse outcome compared with patients without cancer (high quality, strong recommendation).

For stress cardiomyopathy patients with stable hemodynamics, treatment strategies were similar to cardiac failure patients with reduced heart function, which consists of usage of β-blocker, angiotensin conversion enzyme inhibitor or angiotensin II blocker, giving diuretics in fluid overload, avoiding inotropes in patients with left chamber outflow obstruction in case of obstruction aggravation (39). The annual recurrence rate of stress cardiomyopathy in patients who stop medical agents is 1.5%, while β-blocker or angiotensin II blocker reduce the risk of recurrence (43). A retrospective study conducted in MD Anderson cancer center showed that of twenty-one stress cardiomyopathy patients who re-received anti-tumor systematic therapy, sixteen patients received treatment safely without recurrence of stress cardiomyopathy (44). However, there is also case report that stress cardiomyopathy patient developed cardiac arrest after re-received 5-fluorouracil chemotherapy (45).

(II) Consensus 6.2: treatment strategies of stress cardiomyopathy were similar to cardiac failure patients. Cancer patients who had a history of stress cardiomyopathy should be assessed cautiously when re-receiving anti-tumor systematic therapy is needed (moderate quality, strong recommendation).

Question 7. Does perioperative use of analgesic and sedation affect the outcome of cancer patients?

Sedation is an important part of treatment of critically ill cancer patients. A follow-up study of randomized controlled trial demonstrated that low dose infusion of dexmedetomidine between the day during surgery and the first day of surgery was associated with increased two-year survival in cancer patients compared with controls, although no significant difference was found (46). The beneficial effect of dexmedetomidine lies in inhibition of inflammatory response and related tissue injury (47). However, a propensity score-matched retrospective study demonstrated that no association was found between intraoperative use of dexmedetomidine and 10-year survival in non-small cell lung cancer patients (48). In a large study included over 10,000 patients, increasing dose of propofol was associated with lower thirty-day postoperative complications, but not one-year mortality in solid tumor patients (49). In a meta-analysis including 7,866 cancer patients, the use of propofol was associated with improved survival compared with use of volatile anesthesia (50). However, in a recent randomized controlled study, combination use of paravertebral block and propofol was not associated with reduced recurrence rate in breast cancer after surgery compared with volatile anaesthesia and analgesic (opioids) (51).

(I) Consensus 7.1: sedation may improve short-term and long-term survival in perioperative cancer patients. However, further studies are needed to clarify the association between sedation and outcome of surgical cancer patients (moderate quality, strong recommendation).

In a prospective multicenter study including 1,381 post-procedural patients, 42% patients received pain assessment and 90% patients received opioids (52). In another study involving 151 patients receiving mechanical ventilation, the development of overt pain which was defined as a behavioral pain scale (BPS) of >5 was associated with increased thirty-day mortality and prolonged duration of mechanical ventilation (53). Study also showed that pain assessment and timely use of analgesia was associated shortened duration of mechanical ventilation (54). In a special article of American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anaesthesia and Pain Therapy, there were two recommendations regarding analgestics and immune function. First, animal and human data demonstrated that morphine has negative effects on immune function. Second, non-opioid analgesia such as non-steroidal agents do not comprised immune function (55).

(II) Consensus 7.2: pain assessment and analgesia were associated with improved short-term outcome in cancer patients. Further studies are needed to assess the association between analgestics and cancer relapse and recurrence (moderate quality, strong recommendation).

Question 8. What is the role of adjuvant hemodialysis therapy in the treatment of postoperative severe intra-abdominal infection?

According to a Chinese guideline for the diagnosis and management of intra-abdominal infection, severe intra-abdominal infection was defined as intra-abdominal infection leads to sepsis, or patients suffers from intra-abdominal infection with acute physiologic and chronic health evaluation (APACHE) II large than 10, or intra-abdominal infection coupled with grading III or IV gastrointestinal injury (56). Therapeutic strategies of intra-abdominal infection consist of source control, antibiotic therapy and organ supportive therapy, nutritional therapy and adjuvant renal replacement therapy. A meta-analysis including ten studies involving 541 septic patients demonstrated that compared with controls, continuous blood purification increased 28-day survival rate and reduced duration of mechanical ventilation (57). A single center study in 2019 demonstrated that compared with controls, continuous renal replacement therapy reduced disease severity (APACHE II and sepsis-related organ failure assessment score) in severe intra-abdominal infection patients. Levels of inflammatory mediators dropped greatly in continuous renal replacement therapy group than controls. However, there was no significant difference in 28-day mortality between two groups (58).

(I) Consensus 8.1: adjuvant hemodialysis therapy may improve the severity of severe intra-abdominal patients (moderate quality, strong recommendation).

Question 9. What is the role of metagenomic next-generation sequencing (mNGS) tests in the diagnosis and treatment of pulmonary infection after cancer surgery?

Palacios *et al.* first using high-throughput sequencing discovered a new arenavirus in three patients who died of a febrile illness 4 to 6 weeks after receiving visceral-organ transplantation from a single donor (59). Currently, mNGS tests have been used in detecting virus, fungus, bacteria, parasite and other rare pathogens. However, it was not commonly used in clinical practice owning to its relative high cost (60). Multiple studies demonstrated that for suspected pulmonary infections, mNGS tests have a higher sensitivity than conventional measures in detecting sample from bronchoalveolar lavage fluid or sputum (61,62). In addition, mNGS test is less affected by prior antibiotic exposure.

(I) Consensus 9.1: meagenomic next-generation sequencing has a higher sensitivity than conventional tests in detecting pulmonary infections (high quality, strong recommendation).

Grumaz *et al.* reported that 48 patients suffering septic shock received mNGS tests. After majority experts voting, 53% of patients (n=24) received adjustment of antibiotic regimen, 38% (n=18) continued the original regimen (63). Of 24 patients who received antimicrobial therapy adjustment, experts recommended a de-escalation in 80% and escalation in 40% patients. In addition, patients who received antimicrobial therapy adjustment based on a combination of mNGS tests and experts' opinions had absolute increasement of 28- and 90-day survival 13% and 14% respectively compared with patients who remained original antibiotic based on experts' opinions alone. However, there were only 3 patients diagnosed as pulmonary infections. In Lin *et al.* study, there were 32 patients diagnosed as pulmonary infections. Of 20 patients who received antimicrobial therapy adjustment based on a combination of mNGS tests and experts' opinions, 14 patients (70%) had symptoms improvement (64).

(II) Consensus 9.2: meagenomic next-generation sequencing tests have a positive role in the treatment decision making of pulmonary infection (moderate quality, strong recommendation).

Question 10. What is the role of cerebral oximetry in the monitoring of critically ill cancer patients after brain surgery?

Sekhon *et al.* prospectively assessed the relationship between regional saturation of oxygen (rSO_2) and mean arterial pressure (MAP) using near-infrared spectroscopy in cardiac arrest patients (65). They found that there is positive relationship between rSO_2 and MAP when cerebral autoregulation is damaged. Rivera-Lara *et al.* demonstrated that rSO_2 was a useful tool in determining the upper and lower limits of cerebral autoregulation in the case of acute neurologic injury whose cerebral autoregulation is dynamic, but not static (66). Hence rSO_2 may serve as an alternative non-invasive tool in determining cerebral perfusion pressure, instead of invasive intracranial pressure measurement. Rivera-Lara *et al.* also found that cerebral oximetry index (COx), a derivative parameter calculated using the relation between rSO_2 and MAP, is associated with in-hospital mortality, 6-month mortality rate, and 6-month severe disability in acutely comatose adults with neurological injury (67,68).

(I) Consensus 10.1: rSO_2 and its derivative parameter may aid in clinical treatment decision and predicting the prognosis of acutely comatose patients after surgery (moderate quality, strong recommendation).

In a meta-analysis including five randomized controlled studies involving 446 patients, Liu *et al.* found that intraoperative cerebral oxygen saturation monitoring and intervention effectively reduced the occurrence of postoperative delirium in patients undergoing non-cardiac surgery (69). In their study, the treatment cutoff was absolute value 50% of rSO_2, or decreased by 20% from baseline level. Treatment measures included adjustment of mean arterial pressure, pressure of CO_2, hemoglobin level and cardiac function. There was significant difference in postoperative delirium rate between treatment group and controlled group (25.2% versus 34.1%, P=0.04). However, owing to the lack of high-quality, there is no sufficient evidence to support the routine use of rSO_2 measure to decrease mortality rate of patients who undergoing non-cardiac surgery (70).

(II) Consensus 10.2: goal-directed rSO_2 monitoring during non-cardiac surgery may decrease postoperative delirium rate (moderate quality, strong recommendation).

Future research

In summary, we make some recommendations about critical care for perioperative critically ill cancer patients. However, there are some limitations in our consensuses. First, few recommendations are based on high qualities, while most recommendations are based on moderate qualities evidences. Second, consensus development group consisted of clinical intensivists oncologist without surgeons. Cost-effective analysis was not conducted owing to the shortage of relevant literatures. Therefore, more trials regarding perioperative critical care for cancer patients are needed to provide high quality evidences for the updated consensus. For example, prospective studies are needed to determine whether usage of SAS as an ICU triage tool is a promising strategy in high-risk cancer patients in resource-limited hospitals, whether timing of renal replacement therapy impacts on the recovery of postoperative cancer patients with stage 2–3 AKI, whether adjuvant hemodialysis improve the short-term outcome of postoperative critically ill cancer patients with severe intra-abdominal infection.

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Supplementary

Appendix 1

Using search strategies in Appendix 1, two authors (Wang H, Xing X) identified relevant studies in PubMed, Wanfang, from inception through April 2021 without language restrictions. We also manually screened the reference lists of all relevant articles to supplement the systematic search.

Search strategy

For question 1, high risk surgery AND goal directed therapy, were used.

surgical apgar score AND high risk, were used.

For question 2, neoadjuvant therapy AND critically ill AND cancer were used.

For question 3, extracorporeal membrane oxygenation AND acute respiratory distress syndrome AND immunocomprised were used.

extracorporeal membrane oxygenation AND surgery AND perioperative were used.

For question 4, acute kidney injury AND cancer AND prognosis were used.

For question 5, post-hepatectomy AND liver failure were used.

For question 6, perioperative stress cardiomyopathy were used.

For question 7, cancer AND (anesthesia OR sedation) AND (dexmedetomidine OR propofol) AND surgery were used.

For question 8, hemodialysis AND postoperative intra-abdominal infection were used.

For question 9, next-generation sequencing tests AND pulmonary infection were used.

For question 10, cerebral oximetry AND critically ill were used.

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