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REVIEW ARTICLE **OPEN ACCESS**

Diagnosis and management of COVID-19 from laboratory medicine and operative room to Anesthetic care of critically ill patients: A review from updated literature

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ABSTRACT
In December 2019, an outbreak of the new disease occurred in the Wuhan city of china and spread very quickly in the world due to the high rate of transmission. From the outbreak to date 2/5/2020 confirmed cases of COVID-19 are 6,194,533 and 376,320 deaths reported by WHO.The main route of transmission for COVID-19 is respiratory droplets and human contact. Most scientists agree that aerosol propagation also plays a role in the transmission of diseases. Symptoms of the disease may appear 2-14 days after in contact with COVID-19 patients and incubation duration takes 4-7 days. Symptoms of COVID-19 include fever, sense of smell loss, cough, myalgia, or fatigue but fewer ratios of patients also present dyspnea. Laboratory medicine play a critical role in trying times of pandemic from screening of patient to diagnosis, treatment as well as public health surveillance. Special procedures were required for critically ill COVID-19 patient's management in operative rooms and during anesthetic care. About a third of patients infected with COVID-19 come to be critically ill and need critical care. This review summarized the important points from laboratory perspective to operative room and anesthetic care of critically ill COVID-19 patients.
Keywords: *COVID-19, laboratory medicine, operative room, Anesthetic*

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INTRODUCTION

COVID-19 name given by WHO on Feb, 11 2020 that affect primarily respiratory system. Disease caused by new coronavirus formerly called 2019-nCoV (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. The first case was reported in Wuhan city of china in December 31 2019 and then it export to other parts of world and tackle the pandemic situation [3,4].Upto 02 june 2020 the disease spread to 216 countries, area and associated territories and affect 6057853 individual with the status of confirm cases and 371166 confirm death reported by World Health Organization(WHO) [5]. Transmission of COVID-19 is reported through animal to humans and from person to person. When infected person cough or sneeze their respiratory droplets contain the nCoV which enter quickly through respiratory tract of person in close contact. Fomites may also play significant role in transmission of virus as persistence of 96hr is reported by [6,7]. There is no such evidence of vertical transmission is reported which cause intrauterine infection [8].

Clinical manifestation of nCoV is similar with other SARS-CoV with most frequent and common symptoms are dyspnea (Shortness of breath), a low grade fever, cough having severity over time , myalgia and fatigue overtime. Other symptoms also experience and less common is headache, sore throat, loss of taste and smell nausea and vomiting [6,9]. Sample for diagnosis of COVID as recommended by WHO and CDC are naso- and oropharyngeal samples for upper respiratory and Broncho alveolar lavage, expectorated sputum, endotracheal aspirate for lower respiratory samples [9,10].Institute quarantine, social distancing and isolation measure and management of clinically ill COVID-19 patients are required for diagnosis and

screening purpose. In community the fundamental approach for interrupting transmission is isolation [11].

WHO stated definition of suspected and confirmed case and reported fever, dyspnea , low WBC and lymphocyte count ,pulmonary infiltrates and symptoms sustained after 3 days of antibiotic treatment for confirm case while patient with respiratory acute illness and in the absence of alternative diagnosis is suspected case [12]. Understanding of COVID-19 is now advanced and many studies reported aspect of COVID-19 such as critically care(13), medical and intensive care, infection control measure ,air way management and surgical perspectives of COVID-19 management [14,15]. Therefore, this review aims to discuss the current approaches for diagnosis and management of COVID-19 patient's from laboratory perspectives to surgical, airway management and critically ill patient.

METHODS

We performed extensive literature search in May 2020 through variety of scientific databases such as PubMed, Scopus, web of science, Science direct, Directory of Open Access Journals (DOAJ) using the Key word, Medical subject Heading (MeSH) and database appropriate syntax such as "COVID-19 Pandemic", "Diagnosis of COVID-19", "management and diagnosis", "Air way Management" using Boolean Operators for eluding inappropriate hits. We included peer reviewed original article of observational studies i.e Cohort, cross sectional, case control that evaluated the management protocol and laboratory diagnosis of COVID-19 airway management of COVID-19, management of critically ill patients infected with COVID-19, lab diagnosis of COVID-19, allied health technologist role and Self-protection of health professionals. Additional article through bibliographic finding were also included. Article were reviewed independently by authors and search for potential biasness and checked for agreement. All those article were excluded after screening their title and abstract for non-similarity. Exclusion criteria for final selection of article were: opinion and editorials, gender age and race specific studies, non-English language, commentaries or studies focusing other area beside diagnosis and management of COVID-19 patients.

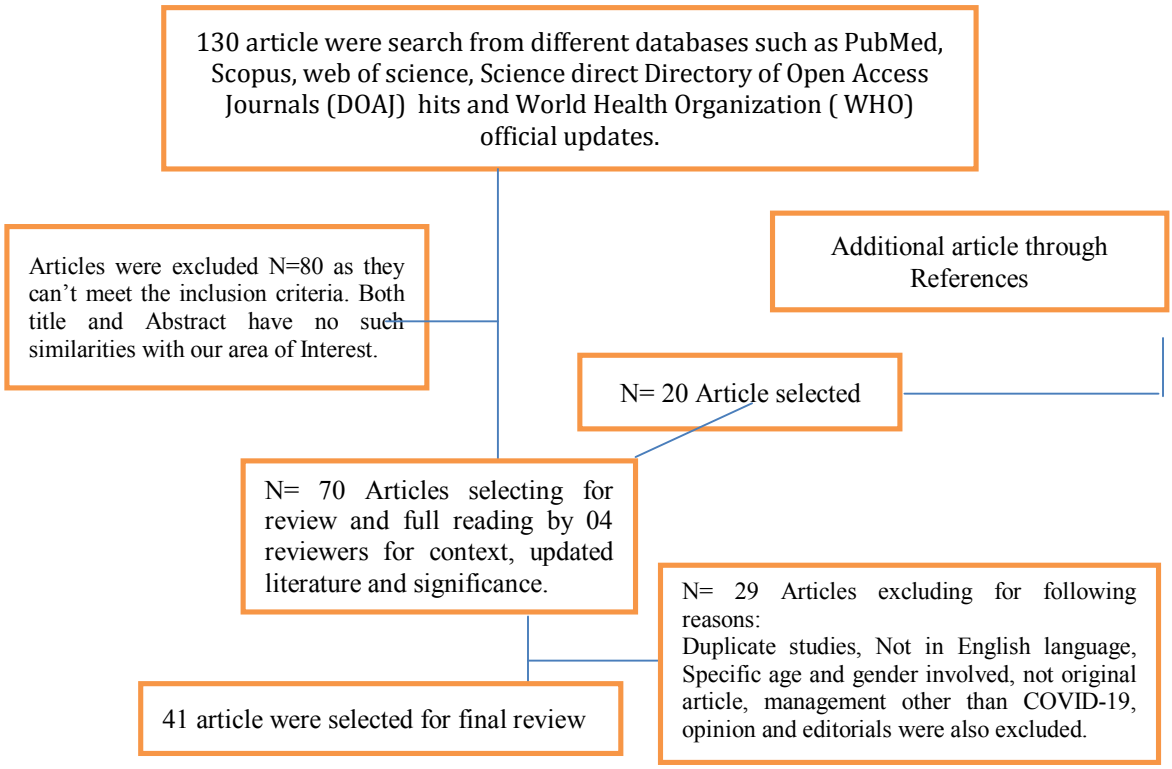

Figure: 1 Flow chart of selection of article and method of inclusion.

DIAGNOSTIC FRAME AND METHODS FOR COVID-19

Various factor responsible in diagnosis of COVID-19 such as where the person live, close contact with infected case, travelled to or live in epidemic area in previous 14 days. COVID-19 involve respiratory system particularly , at minimum respiratory sample were required for testing i.e nasopharyngeal and oropharyngeal swab, bronchoalveolar lavage, sputum and endotracheal aspirated specimen.

Moreover stool, blood and autopsy material (in case of disease patient) should be considered for testing of COVID-19.Figure:1 sketch about diagnostic frame and pathway of work flow for COVID-19 diagnosis.

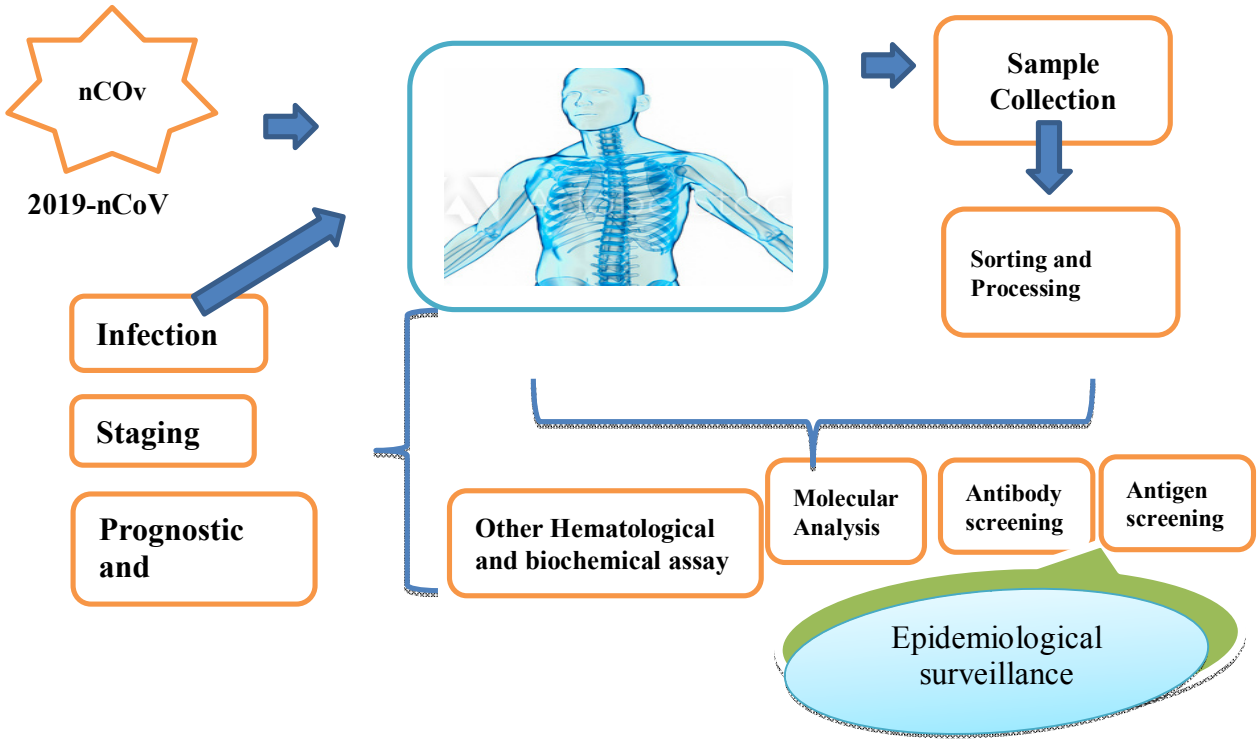

Figure:1 Diagnostic frame of COVID-19. Sample were collected by trained technologist/Nurse /health professional based on principal of biosafety according to CDC guidelines and transported to laboratory. After sorting and processing molecular assay, antibody screening and other biochemical finding revealed the screening and diagnosis using different techniques. Molecular assay confirm diagnosis while biochemical and other test used for staging and prognosistic measure and therapeutic monitoring of COVID-19 overt disease.

Case definition:

- **Confirmed:**
  A person with laboratory confirmation of infection from 2019-nCoV irrespective of sign and symptoms.
- **Suspected:**
  Global Surveillance for human infection with novel coronavirus (2019-nCoV) by WHO define suspected case as individual with sign and symptoms of respiratory infection with no other background etiology of such clinical presentation with history of recent travel prior to onset of symptoms or those having sign and symptoms along with contact with confirm case or worked in health care facility where COVID-19 patients are treated [17].
- **Probable case:**
  Suspected individual with status of inconclusive result for COVID-19 molecular testing or testing positive for pan coronavirus testing or suspect case whose test is not performed for any reason [17].

METHODS FOR LAB DIAGNOSIS

NAAT Testing:

CDC and WHO recommends Real-time reverse transcription polymerase chain reaction (rRT-PCR) as a gold standard for diagnosis of COVID-19. The test is specifically designed to determine the special sequence in viral nucleic acid. A study published by Cormon *et al* specify diagnostic workflow for targeting region and sequence for screening of nucleic acid. They reported first line screening by targeting E gene, for confirmatory screening RdRP gene and for additional screening for confirmation is screening N gene [18]. International federation of clinical chemistry and laboratory medicine (IFCC) define case location and their confirmation criteria for COVID-19. The criteria for area with known COVID-19 virus circulation are a positive nucleic acid test for a single discriminatory target in the viral genome and area with no prior viral circulation are a positive result for at least two distinct target among which one is specific for SARS-COV-2 genome. Negative test result for suspected and high likelihood often required repeat testing with both upper and lower respiratory tract sample for sequential testing.

Antigen Testing:

Blairon L et al reported poor sensitivity for antigen testing which is an alternative to other diagnostic assays. Having high specificity but low sensitivity as compared to molecular assay however antigen testing is advantageous with lower cost, instant results and early rule-in of patients. Recommendation are there from different authors for larger scale studies and appropriate validation for specific population and settings [19].

Serological Testing:

Specific antibodies are produced by the immune system of body in response to infection. Clinician and physicians mostly refer serological testing for detecting previous infection called antibody testing. When virus is exposed to the immune system it produces antibodies as protection against that foreign invader.

Serologic testing is determined by both qualitative and quantitative manner where emphasis on Enzyme linked Immune Sorbent Assay (ELISA) for identification of true rate counts along with rate of asymptomatic infection. However for acute infection, testing strategy only limits to antigen and molecular assays because it take 1-3 weeks for antibody production from symptoms onward [20].

Serologic testing is not currently recommended by CDC because of general concern of negative in acute phase of infection as well as rate of cross reactivity to other seasonal infection of other corona viruses however recommended for public health surveillance and occupational health monitoring [21].

SURGICAL PERSPECTIVES OF COVID-19 MANAGEMENT

Operating room:

Worldwide operating rooms should be prepared according to the stranded protocol to minimize the spread of COVID-19 from patients to the operating personal. The Surgical suite consists of patient holding area, changings rooms, waiting area, central sterile core, operating rooms, and recovery rooms. the Central and peripheral corridor should be used for operating confirmed or suspected COVID-19 patients because this design has both central and peripheral corridor which help in reduce traffic pattern and spreading for COVID-19 [22]. Operating rooms have positive pressure air circulation normally but negative pressure operating room would be ideal for reducing the risk of infections [23]. Viral load is reduced by exchanging the air cycle up to 25 cycles/hour within OR [24]. All necessary supplies kept in each OR to minimize out the flow of surgical technologists from OR to minimize infection risk. Surgical planning is started when patients arrive from the isolation ward to the operating room. Each step is taken according to the plan and stranded protocol to reduce accidental exposure of COVID-19. All staff should be informed to wear proper Personal Protective Equipment (PPE).

Preoperative duties:

All those diseases which are transmitted by human to human contact are a critical factor for operating personal it should be addressed timely. In the preoperative environment, COVID-19 transmission is controlled in the operating room environment by giving proper attention to make the preoperative environment clean and make proper hand hygiene. Viral load is reduced with povidone-iodine and chlorhexidine gargle and proper hand hygiene practice before entering to OR [25]. Before surgery COVID-19 test should be mandatory for a patient. In the assessment of the case, the emergency procedure is a prime concern if the procedure is not too urgent preferable postpone it. Protective material uses and availability is mandatory in the right situation to avoid shortage. PCR test, chest x-ray, and computed tomography scan of the chest are recommended tools to identify the status of \asymptomatic schedule patients hospitalized 48 hours before surgery. If surgery is performed on an emergency basis all those staffs in the operating room is allowed to assist surgeon who are trained and have proper knowledge regarding risk management and awareness of protocol established in the institution. When a patient is transferred to the operating room it is mandatory to wear a surgical mask [23,26].

Intraoperative duties:

After entering the patient immediately close the OR door at all times to stop unnecessarily entry to the operating room. The supply material should also be discouraged during the surgery. During surgery no one is allowed to leaves the OR. The surgical team will drape the patient according to the surgical procedure, wearing shoe covers and exchanging surgical mask with Filtering Face piece(FFP2) filter. Double pair of gloves must wear by all those Operating personnel who are in direct contact with the patient, even while operating [26]. Surgical team is divided into two main teams intraoperatively "contaminated team" should wear proper PPE along with an N95 mask, goggles when contacting a patient [22,23]. "Clean Team" responsible for providing additional support to deliver equipment and instruments to and from the contaminated team. Equipment will be left in the anteroom for the contaminated team to retrieve. The same process in reverse will be used when sending out specimens. This will be particularly

pertinent in musculoskeletal tumor surgical procedures in which frozen sections are commonly sent intraoperatively for histopathological review [27].

Postoperative duties:

Surfaces and attachments of an operating table, mayo stand, standing stool, instruments table, surgeon stool, and electro medical devices (i.e., ultrasound) must be cover with proper protection and proper sanitization is done at the end of the procedure. Contaminated PPE should be discarded in negative pressure areas postoperatively and perform proper hand hygiene to control the risk of infection. In routine practice, the patient is recovered first in the post-anesthesia care unit (PACU) than transfer to the surgical ward by common staff. Regardless of routine practice recovery of COVID-19 Patients is mandatory within the OR and transfer back to isolation ward by the specialized team has worn Proper PPE [28]. Face mask should always be placed on the patient before transfer. Patient with postoperative nausea and vomiting is treated with antiemetic's hence minimizing potential aerosolization. Fang et al. reported in The Lancet Respiratory Medicine that the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen) can potentially worsen symptoms in patients with COVID-19 [29]. This is attributed to their increased expression of angiotensin-converting enzyme 2 (ACE-2), which enables SARS-CoV-2 (the coronavirus responsible for COVID-19) to bind to its target cells in the lungs. This theory is still highly controversial and is as yet unproven. However, it might be careful to choose alternative classes of analgesia when managing patients with COVID-19 [10]. At the time of transfer, a surgical mask should be worn by the patient when leaving the OR and strict disinfection of the OR should be achieved [30].

Air way Management:

Coronavirus can effect different body system like CNS, GIT but Respiratory system especially lungs are primary target which result in rapid respiratory decompensation and need to ventilate the patient invasively [31]. About 2-3% Critical ill covid-19 patient need tracheal intubation and approximately 3-17% patient required mechanical ventilation [32].The highest amount of viral load found in sputum and upper airway secretion which make the tracheal intubation count in high risk aerosol generating procedure. Tracheal intubation cause high risk transmission to the anesthetist which is performing to secure patient airway in order to provide invasive ventilation. This novel virus spread via droplets and through natural aerosol from person to person which may put the Anesthesiologist and his team at high risk to perform intubation [8,9,10]. Others aerosol generating procedure includes tracheostomy, bronchoscopy, bag mask ventilation, disconnection of ventilatory circuits and suctioning [33]. This Aerosol generating procedure requires much care and precaution in Covid-19patient. Management of endotracheal intubation performed using RAPID approach which is quite different from routine intubation.

Ideally a separate negative pressure room required with a High frequency particulate air (HEPA) for Covid-19 patient to perform intubation under special experience care team which include Senior Anesthetist, Technologist, Technician and Charge Nurse. Donning and Doffing required for 3 member of the team while 4th one are helper which are outside of the room. Drug and all essential equipment should be prepared in advance outside the room and make sure use disposable equipment as much as you can [33]. Using MACOCHA score for evaluating quick assessment of airway. If score >2 key indicator for anticipated difficult intubation. Adequate pre oxygenation should be performed for 3-5 minutes with low pressure and flow system by two hand technique using Mepelson C circuit. Most of the senior anesthetist use video laryngoscopes if available and perform the modified RSI technique to provide rapid intubation and minimize the exposure of anesthetic care team. Monitoring will be on recommendation of ASA with End tidal carbon dioxide detector. Smooth induction performed using lidocaine with induction agent to blunt airway reflex in order to avoid coughing and straining. Extreme precaution should be taken to place HEPA filter and removing bougie to avoid contamination of airway surfaces. After inflating ETT cuff with a pressure of 20-30cmH2O start ventilation but avoid auscultation or confirming of the endotracheal tube. However use the intubation box or transparent sheet for Covid-19 in limited resources setup [33].

Management of critical COVID-19 Patient:

World Health Organization (WHO) has proclaimed pandemic for COVID-19 which was began in Wuhan province of China and spread across the globe. This pandemic is considered as a viral pneumonia pandemic not a simple flu, and so intensive care unit (ICU) admission, follow-up, and care of the critically ill patients with COVID-19 is very significant. Due to the insufficient studies on COVID-19, ideas that are developed from the experience framework of China, Italy, USA, and United Kingdom that have the major battle against this pandemic. About a third of patients infected with COVID-19 come to be critically ill and need critical care unit [25,36].

Admission to ICU:

Through 5% of total COVID-19 cases becoming seriously or critically ill and 20-30% of admitted hospitalised patients in a health care facility need intensive care management, it is vital that up-to-date recommendation are in place to help management. Those patients who are failing with standard oxygen therapy are prospective to need advanced oxygen therapy or ventilator support. National institute of health and care excellence inspire intensivists to initiate critical care treatment with clear goal or objective from the beginning. It endorses most reviews with immediate assessment of response to therapy. Critical care therapy should be stop when the goal set at the beginning of treatment is not reached and the victims fail to improve. Consult with patient ,their family, carers and/or independent mental capacity advocate if possible [37].

Respiratory support:

Critical illness most commonly occurs between 1 and 2 week after the onset of symptom. There is some ground glass dullness with basal consolidation seen on the chest radiography of critical COVID-19 patient[38]. Furthermore patients can develop rapid deterioration and acute respiratory distress syndrome. Acute respiratory distress syndrome caused by COVID-19 should not vary from conventional ARDS management, which involve protective lung ventilation a fluid conservative strategy when applicable, and for sever ARDS the early initiation of prone ventilation ,for moderate to severe ARDS early neuroblocker may be considered when appropriate [39]. Low tidal volume's (4–6mL/kg) and low inspiratory pressure (plateau pressure < 30 cm H2O, driving pressure which is plateau pressure minus positive end expiratory pressure < 14 cm H2O) should be provided to those patient who are developing acute respiratory distress syndrome (ARDS) [40].

Type-2 or Hypoxemic respiratory failure should be determined as soon as possible. Hypoxemia and respiratory rate progressively become more sever despite of conventional oxygen therapy. Various airway such as nasal cannula (1-6 L/min to provide FiO2 of 0.24–0.45), simple face mask (5–8 L/min to provide FiO2 up to 0.50–0.60), non-rebreather masks with reservoir providing FiO2 up to > 0.85 with 10–15 L/min oxygen, should be used for supplemental oxygen through low oxygen delivery system, titrated according to SpO2.Venturi and diffuser masks are recommended to be not used. This should be remember that oxygen may be produced toxicity when FIO>0.60 for greater than 6 hours. In some selected patient of hypoxemic respiratory failure high flow nasal oxygen therapy (HFNO) and non-invasive mechanical ventilation (NIMV) support may be provided with proper PPE because of high risk of aerosol production. Although these patient should be monitored closely in term of clinical severity (tidal volume > 9 mL/kg meaning increased minute ventilation and work of breathing, tachypnea, refractory hypoxemia) if there is positive outcome in the first few hours. A helmet mask applied with intensive care ventilator or dual circuit ventilator may be used, to the circuit a viral/bacterial filter should be added. Those patients whose secretion cannot be controlled, or have greater risk of aspiration, altered mental status ,cardiac complication and multiple organ failure or those who are hemodynamically unstable should not provide non-invasive mechanical ventilation(NIMV) [41].

Invasive mechanical ventilation is required by almost 10% of patients. A trained and most experienced physician with a rapid sequential intubation protocol will be responsible for endotracheal intubation. If possible video-laryngoscope should be used for intubation for difficult intubation flexible bronchoscopy should be used but there is high risk of aerosol formation during bronchoscopy.during preoxygenation the use of bag mask ventilation(BMV) should be avoided and preoxygenation will be performed with non-rebreather mask with reservoir. A filter should be connected with bag mask if beg mask would be used. Before intubation the administration of neuromuscular blocker can be used to suppress cough. Before the inflation of endotracheal tube positive pressure ventilation should not be started and without bag mask ventilation patient should be connected directly to mechanical ventilator [42].

CONCLUSION

Current COVID-19 is global emergency and required strict adherence to the guidelines stratified by WHO for diagnosis management and critical care of critically ill patients. Advanced diagnostic tools and sensitive methods required for ongoing population screening, diagnosis, monitoring and epidemiologic surveillance. Hospital and emergency services should adapt respond services and readiness according to clinical characteristics.

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