Archives of Anesthesiology and Critical Care (Winter 2022); 8(1): 18-24.

Available online at http://aacc.tums.ac.ir

Research Article

Comprehensive Analysis of Perioperative Anaesthesia Concerns in Covid Associated Mucormycosis: A Retrospective Study of Surgical Patients

Poonam Ghodki, Neha Panse*, Shalini Sardesai

Department of Anesthesiology, Smt.Kashibai Navale Medical College Pune, India.

ARTICLE INFO

Article history:
Received 24 June 2021
Revised 08 July 2021
Accepted 22 July 2021

Keywords:
Anaesthesia;
COVID-19;
Diabetes mellitus;
Mucormycosis

ABSTRACT

Background: Data regarding sudden surge of mucormycosis cases with COVID-19 outbreak and its impact on anaesthesia management are lacking. This retrospective study was designed to analyze the number and characteristics of patients posted for mucormycosis surgery in COVID19 pandemic while emphasizing upon the anaesthesia concerns.

Methods: Data was collected from all patients who were admitted with mucormycosis in our institute from the year 2020 onwards. Further analysis of patients who were surgically treated was carried out in terms of demographic characteristics, association with COVID19 and perioperative course of mucormycosis and anaesthetic management. All statistical analyses were performed with the Statistical package for social sciences (SPSS) version 25·0 software.

Results: We report an incidence of 30 operated patients of the average age 52.60 years with mucormycosis from August 2020 to May 2021. Diabetes as a comorbidity was common (86.90%). Previous infection with COVID-19 was observed in 29 (96.60%) out of which 80% patients had residual pulmonary involvement. Concomitant medical therapy with Amphotericin B was received by 90% patients and subsequently 70% had deranged renal profile. While 20 % patients had compromised airway, 60 % required blood transfusion and 76.6% patients were electively ventilated while 1 patient (3.3%) succumbed amounting to a survival rate of 96.6%.

Conclusion: To conclude elderly male diabetic patients with history of COVID19 infection is the most vulnerable population for developing mucormycosis. Airway management, glycemic control, concomitant Amphotericin B therapy and intraoperative bleeding are the major challenges for anaesthesiologist along with an element of post Covid respiratory compromise.

Mucormycosis is an opportunistic fungal infection occurring when favourable circumstances exist, e.g. diabetes (DM) or immunocompromised status [1]. The coronavirus disease 2019 (Covid-19) infection caused by the novel coronavirus 2 (SARS-CoV-2) is associated with a variety of disease patterns. After SARS- CoV-2 has had infected the human body the post Covid 19 sepsis sets in. This sepsis leads to an altered uncontrolled immune response, ciliary dysfunction, cytokine storm, thrombo-inflammatory response leading to microvascular coagulation and eventually the exhaustion of the immune system [2]. A variety of bacterial and fungal co-infections are being reported concomitantly or after recovery and mucormycosis is one among such [3].

Mucormycosis can be limited to a particular area or invade further increasing the severity [1]. Amphotericin B (AmB) is the preferred antifungal treatment;

The authors declare no conflicts of interest.

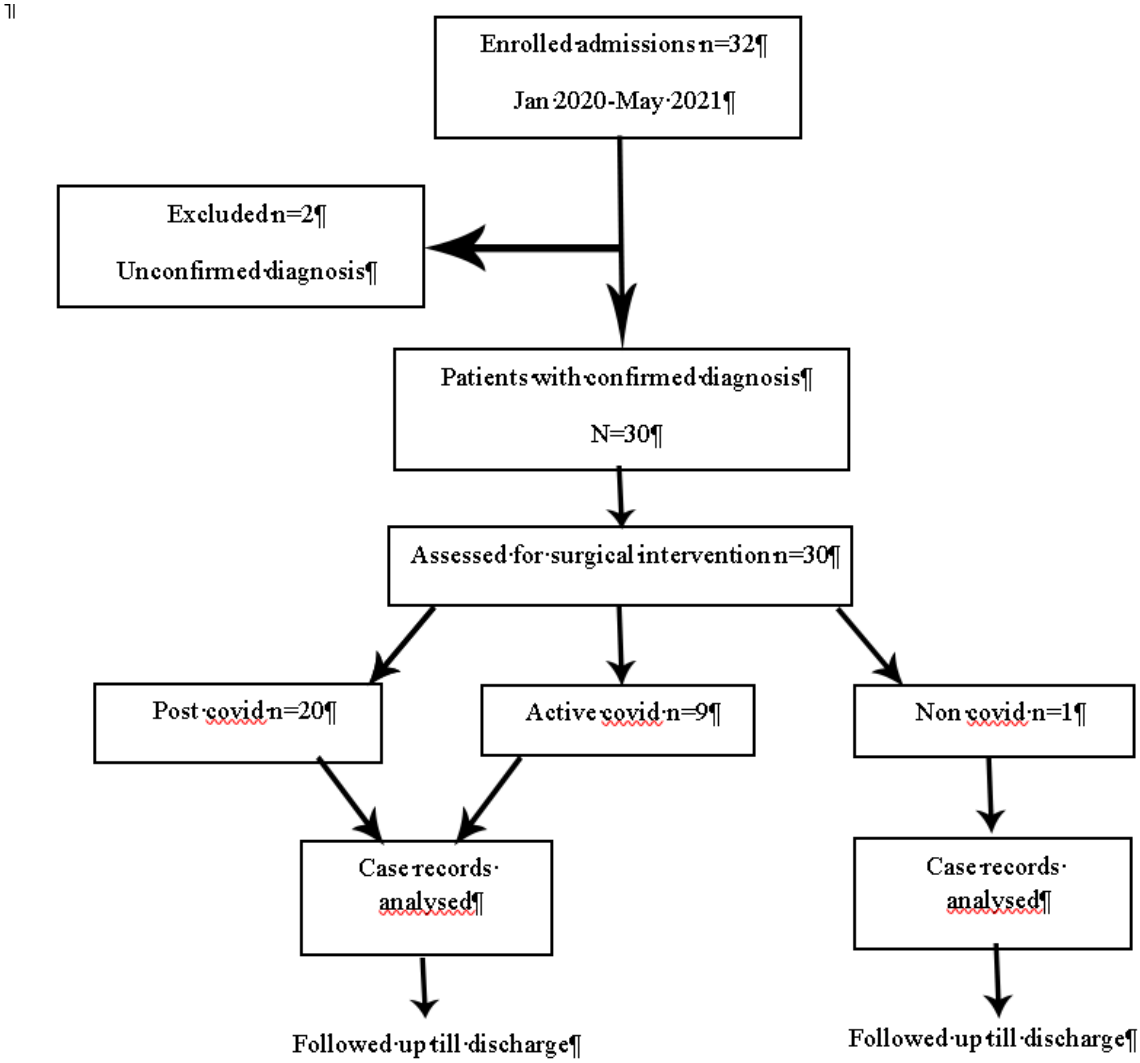
*Corresponding author.
E-mail address: drnehaghule@gmail.com

nevertheless, the medical management generally culminates into surgical intervention which becomes imperative for a better outcome. Anaesthetizing patients for maxillary mucormycosis surgery in itself is challenging to anaesthetist because of vascularity, likely airway involvement and complications of AmB [4]. With the increasing incidence of post Covid patients presenting for various surgeries, addressing mucormycosis in particular becomes relevant. We hypothesize that Covid 19 would disproportionately influence the occurrence of mucormycosis; significantly increasing the perioperative morbidity. To investigate this, we decided to conductthe present retrospective study on mucormycosis cases during Covid 19 outbreak. To our knowledge this is the largest pool of mucormycosis case series focusing upon the anaesthetic implications of mucormycosis in the Covid 19 pandemic. Our primary objective was to analyse the clinical data of patients with mucormycosis in relation to Covid 19 by studying the demography, incidence, association with DM and grade of severity. Secondly we aimed to bring forth the anaesthetic concerns in these patients and highlight the perioperative course of mucormycosis presenting for surgery.

Methods

After obtaining institutional ethics committee approval, (SKNMC/Ethics/App/2021/800) we conducted this retrospective observational study on patients admitted with all forms of mucormycosis, posted for debridement under general anaesthesia (GA) from January 2020 to May 2021(figure l). Our study is in strict accordance with guidelines of Helsinki declaration of 1975.

Figure1- Consort flow chart for the study



Two research investigators independently reviewed data collection to verify accuracy. Both manual and electronic data were collected from the medical records department of our institute. Data were retrieved from patients' clinical chart, operative records and also by computerized hospital information system (IMPAC medical system, Inc). Any missing or uncertain data was collected by direct communication with patients or family members and confirmed telephonically. While recording, only patients with microbiologically confirmed diagnosis of mucormycosis were included and they were grouped as post Covid and non Covid depending on the history of Covid infection in past.

The primary objective of the study was to analyse the clinical data with regards to the number and characteristics of patients posted for mucormycosis debridement under GA. This was done by studying the following parameters:

1. Demographic profile
2. Type and severity of mucormycosis,
3. History of Covid 19 infection
   a) Course of Covid infection with treatment details,
   b) Cardiorespiratory profile during Covid,
   c) Type of oxygen therapy required during Covid treatment,
   d) Drugs therapy post Covid,
4. Presence of comorbidities (DM and other illness),
5. Time lapse between Covid infection and mucormycosis,

The secondary objective was to study the anaesthesia concerns for mucormycosis surgery in lieu of Covid 19. For this following parameters were assessed-

1. Concomitant drug therapy in post Covid period.
2. Complications of AmB and its anaesthetic implications.
3. Intraoperative problems regarding airway management, blood loss and glycaemic control.
4. Recovery profile.

Data was entered and analysed using Statistical Package for Social Sciences (SPSS) version 25·0 software.Significant clinical findings, management and outcome characteristics were plotted on MS Excel spreadsheet. Results are presented in numbers/mean and expressed in terms of percentage.

Results

A total of 32 patients suspected of mucormycosis were admitted in our hospital from August 2020 to May 2021. Out of these, 30 patients with confirmed microbiological diagnosis of mucor hyphae who underwent FESS (functional endoscopic sinus surgery) under GA were included in the study. Rest 2 patients without confirmed diagnosis of mucor were excluded from the study. Out of the 30 patients, all but one were Covid associated mucormycosis.

The demographic and patient characteristics profile is depicted in Table 1.A significant demographic pattern was noted in our study. All our patients belonged to a common ethnic group from one state (100 %). Significant male preponderance was noted with the mean age of the patients being 52.6 years. Diabetes was seen in 86.90%; out of which63.60% were chronic diabetic and 23.30% developed diabetes post Covid. Sixty percent patients had poor glycaemic control as observed by the HbA1C values entered in (Table l).

Table II shows the analysis and course of Covid illness. The time lapse between Covid 19 and the occurrence of mucormycosis disease per se was evaluated. The average interval between Covid infection and onset of mucormycosis was detected to be38.93days. Post covid mucormycosis was seen in 68.90% patients, while 31.10% patients were actively Covid positive with concomitant mucormycosis. As is apparent from table II, no correlation between severity and oxygen therapy could be established between the covid course and covid associated mucormycosis. Drug therapy received for Covid illness appeared to be non-standardized due to variety of drug options and frequently changing protocols and available recommendations, hence not included. Typically, all the hospitalised patients had received steroids in the form of methylprednisolone (100%) and interleukin 6 inhibitors were administered in 30%. All the patients also received antiplatelet in the form of aspirin 150mg which was continued for 1 month following Covid recovery.

Mucormycosis severity, anaesthesia concerns and postoperative outcome are illustrated in Table III. All patients had primarily rhinomaxillary mucormycosis (73.33%), 20% patients had rhino-orbital mucormycosis and 6.66% had rhino-orbital with cerebral involvement. Out of all, 90% patients had concomitant AmB therapy going on; while 3 patients (10%)which were taken up for emergency debridement were not on any medical therapy. Deranged renal functions due to AmB were observed in 21patients (70%). Pre-existing mild to moderate pleural effusion and lower lobar atelectasis was diagnosed in 80% patients one of which needed tapping preoperatively. Sixty percent patients had fluctuating blood sugar levels while taking up for surgery and 86.6% (26) of patients had to be put on insulin therapy as per sliding scale to maintain blood sugars around 120 mg%. Blood loss above maximum allowable blood loss (MABL) requiring intra-operative blood transfusion was noted in 60% of cases. None of the post Covid patients was on anticoagulant therapy peri-operatively except for 2 cases for whom dabigatran and clopidogrel had to be continued in view of post Covid19 cerebellar and vertebral artery occlusion respectively. While20 % patients were extubated on table, 76.6% had to be electively ventilated for 24h postoperatively in intensive care unit (ICU). One Covid positive patient succumbed 6 hours postoperatively which may be attributed to delayed

presentation of invasive mucormycosis with likely severe Covid pneumonia.

Conventional GA protocol for mucormycosis was undertaken as per institute's practice. Except for the patients with difficult airway, all patients were induced with propofol and vecuronium after premedication with midazolam and fentanyl intravenously. Difficult airway was noted in 6 patients (20%) due to airway oedema and maxillary sinus communicating into oral cavity with the draining fungal debris (Fig II). Succinylcholine was used in these 6 patients instead of vecuronium to facilitate intubation anticipating difficult airway. Out of these, 2 patients had palatal perforation draining the fungal debris into the oral cavity. In these, the palatal rent was closed with wet cotton pellets before intubation. Maintenance was carried out with nitrous oxide, oxygen and isoflurane on circle system with vecuronium top-ups as and when required. Minimum monitoring standards as per ASA guideline were applied. While 68.90% patients were tested negative for Covid RT-PCR prior to surgery, 31.10 % patients had active covid infection at the time of surgery which had to be managed in dedicated Covid positive operation theatres with necessary universal precautions to limit transmission during aerosol generating procedures.

Table 1- Demographic Characteristics (N=30)

Mean Age (Yrs)	Sex M/F	ASA	H/o diabetes Mellitus		HbA1c	H/O Covid
52.6 yrs	M-80% F-20%	II-20% III-42% IV-28% IV E 10%	Chronic Recent Non Diabetic	63.6% 23.3% 13.3%	6-8%: 60% 5-6%: 26.6% <5%: 14.4%	96.60%

Table 2- Course of Covid illness (N-29)

Covid		Admission		O2 Therapy	Steroid Treatment In hospitalized Pts	Interleukin 6 inhibitors	Mean Duration between Mucormycosis & Covid (DAYS)
Post Covid infection	66.60%	Ward	20%	None:58.6%	100%	30%	38.93 Days
Active Covid infection	30%	ICU	30%	NIV-31.1%			
		Home	50%	Intubation-10.3%			

Table 3- Perioperative course of mucormycosis

Extent of Mucormycosis	Amphotericin B treatment	Laboratory Profile	Difficult airway	Respiratory involvement on Xray Chest	Perioperative anticoagulation	Post -Op Recovery
Rhinomaxillary 73.33%	90%	Deranged Renal Function Test 70%	Difficult airway with palatal perforation : 6.6%	80%	Asprin-80%	20% Extubated on Table
					Clopidogrel 13.3%	76.6% Ventilated for 24hrs
Rhinoorbital 20%		Hypokalemia 16.6%	Difficult airway due to facial oedema:13.3 %		Ribavirin -3.3%	3.3% Succumbed
Rhinoorbitocerebral 6.6%					Dabigatran-.3.3%	

Figure 2- Patient with palatal perforation

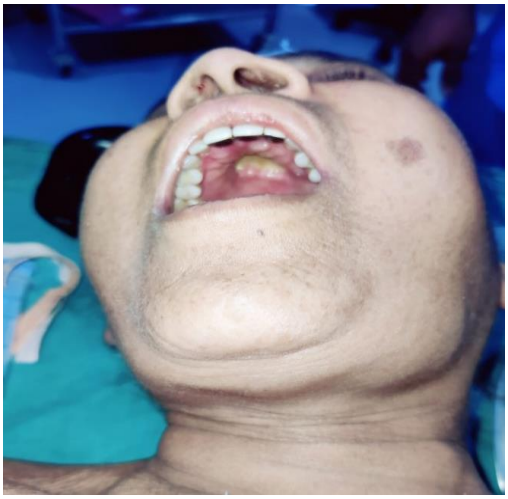


Figure 3- MRI showing ICA occlusi

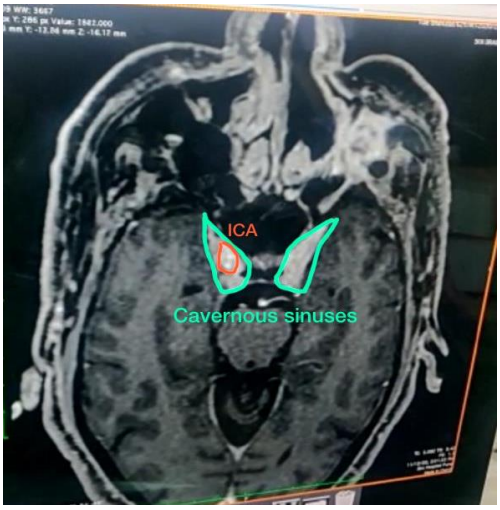


Figure 4- Patient with complete Right eye ophthalmoplegia.

Discussion

In this retrospective analysis we attempted to describe Covid associated mucormycosis and study the course, progression and prognosis of mucormycosis in the Covid pandemic. Notably, all the cases we reported were seen in the latter half of pandemic (August 2020 onwards) mirroring the post Covid period of patients infected earlier in the outbreak.

The initial phase of pandemic was dedicated in saving patients from Covid19 related mortality. With number of post Covid survivors rising exponentially, a separate set of maladies is seen lingering and mucormycosis is observed as one of them [5]. Mucormycosis infection flourishes wherever a compromised immune system provides it with an opportunity to multiply [1]. Most common predisposing factor includes DM which accounts for nearly 70% of patients suffering from mucormycosis [1,6]. We had 86.90% of our patients suffering from DM with poor glycaemic control in post Covid period. As this observation maybe a post hoc ergo propter hoc fallacy; a multi-centric trial is desirable to validate such conclusion. Post Covid elderly diabetics with male predominance is the key finding of our study. These results are in concordance with previous reports studying the demographic profile in patients affected by mucormycosis [4,7]. The free iron load in diabetes is further exacerbated during the course of Covid illness and the hyperglycaemia that is induced by the prolonged use of corticosteroids, both precipitate mucormycosis. The landmark RECOVERY trial published in June 2020has served as a 'license' to use steroids in patients with Covid19 [8]. However, some important messages regarding doses and duration of steroid therapy have been overlooked resulting in rampant use of methylprednisolone. Similarly, in our study injudicious use of methylprednisolone during Covid illness is apparent. Currently with more clarity regarding use of steroids in Covid infection, the immunity may be spared in future patients.

The blood sugars levels keep fluctuating in diabetics even after the patient is tested negative for Covid 19 [8]. Hyperglycaemia is a modifiable factor directly influencing the outcome of mucormycosis [9]. It is noteworthy that majority of patients presented in this report had extremes of blood sugar levels which were managed with intravenous insulin and appropriate intravenous fluids.

Although the severity of Covid 19 could not be established to be related to the severity of mucormycosis in our study, certain significant findings need a mention. Pulmonary complications form the most common residual effects of Covid 19 and adversely affect the respiratory function in perioperative period [10-11]. A high proportion of patients had lung involvement as evident on chest X-ray as pleural effusion and atelectasis

leading to a picture similar to restrictive lung disease. The role of anticoagulants/ antiplatelet that patients receive during the course of Covid illness remains debatable [12]. The vascularity of paranasal sinuses affected in mucormycosis poses a constant threat of excessive intraoperative blood loss which is another major concern for the anaesthetist [9]. Two patients in our analysis had atheromatous plaques in inferior cerebellar artery and vertebral artery respectively leading to hemiparesis. This history coincides with the course of Covid illness and stipulates the thromboembolic events often associated with Covid 19 infection [13-14]. We however cannot, from our study, suggest a linear relationship of blood loss and anticoagulant therapy; a larger scale multivariate studies need to be conducted to ascertain existence of any association between anticoagulants and post Covid surgical blood loss.

Handling the airway in active or post Covid patients, which has once harboured the novel corona virus is also arduous [6]. Airway management in mucormycosis is of paramount importance since the fungal debris in the oropharyngeal region from palatal perforation and the overall airway and supra-glottic oedema lead to difficult ventilation and endotracheal intubation [4, 15]. Such patients fall in to the category of anticipated difficult airway.

There is conflicting data in global registry on the optimum time for surgical intervention in mucormycosis. European federation of medical mycology for mucormycosis guidelines suggest an early surgical resection for the disease, more so in the presence of predisposing factors such as immunodeficiency and DM [16]. AmB, a polyene antifungal, used as the first line of medical management in mucormycosis confers excess risk that may require remodelling of plan of anaesthesia and the drugs used. AmB-induced hypokalaemia causes a synergistic effect on skeletal muscle relaxation [1,4]. Anaesthesia providers must pay particular attention for the maintenance of adequate mean arterial pressure and cardiac output while simultaneously avoiding further renal insults to the patients [17]. While the exact metabolic pathways of AmB are not known; a high degree of vigilance is required for renal, electrolyte, coagulopathy, haemodynamic, and respiratory complications when anaesthetizing patients receiving AmB therapy [4].

There is paucity of literature regarding best or safest anaesthetic drugs for mucormycosis in post Covid patients. All routine drugs can probably be used for induction and maintenance of anaesthesia after stratifying to individual patient. Interestingly, there are few reports demonstrating fungicidal effect of isoflurane in mucormycosis [18]. We too have used isoflurane for all the patients in our study.

Mucormycosis carries 50% mortality for in hospital patients despite prompt diagnosis and treatment [18]. In contrast, recovery was good in all the patients in our study with 96.6% survival rate. An explanation to the improved survival maybe due to more aggressive therapy and absence of acute renal failure commonly observed in non-survivors from published data.

The authors acknowledge several limitations to the study apart from the inherent drawback of performing a retrospective analysis. Although the demographic profile in our study disclosed a strong ethnic preponderance for males and elderly, this finding is limited by the fact that our study population included patients only from our state. Ours being a single centric study; the incidence of mucormycosis in relation to Covid 19 from other parts of the globe could not be addressed. Lastly our study was of a shorter duration, albeit the surge in the mucormycosis cases during this limited period cannot be over emphasized. We plan to address this aspect and continue follow up of similar cases in future.

Conclusion

Themes that emerge from this small study provide important pointers to anaesthesiologists to ensure appropriate care and safety in imminent patients presenting with mucormycosis in Covid pandemic. Mucormycosis has a direct relationship with diabetes and Covid 19 infection, though no correlation with the severity could be established in our study. Airway management, consequences of AmB therapy, blood loss and glycaemic control in the backdrop of Covid 19 have to be kept in mind while anesthetizing such patients.

Availability of data and materials- All the data generated or analysed during this study are included in the write up.

References

[1] Kulkarni PK, Reddy NB, Shrinivas B, Takkalki VV. Anesthetic considerations in the management of mucormycosis. Int J Med Public Health 2015; 5:387-90.

[2] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARSCoV-2 infected patients. EBioMedicine. 2020; 55:102763

[3] Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus. 2020; 12(9): 10726.

[4] Karaaslan E. Anesthetic management of rhinoorbitocerebral mucormycosis; Focus on challenges. J Mycol Med. 2019; 29(3):219-222.

[5] Peng M, Meng H, Sun Y, Xiao Y, Zhang H, Lv K, et al. Clinical features of pulmonary mucormycosis in patients with different immune status. J Thorac Dis. 2019; 11(12):5042–52. 4.

[6] Werth manEhrenreich A. Mucormycosis with

orbital compartment syndrome in a patient with COVID19. Am J Emerg Med. 2021; 42:264.e5-264.e8.

[7] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19–preliminary report. N Engl J Med. 2021; 384(8):693-704.

[8] Sen. M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a Viral Land: A Tale of Two Pathogens. Indian J Ophthalmol. 2021; 69(2):244-52.

[9] Afroze SN, KorleparaR, Rao GV, Madala J. Mucormycosis in a diabetic patient: A case report with an insight into its pathophysiology. Contemp Clin Dent. 2017; 8(4):662-6.

[10] George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, et al Respiratory follow-up of patients with COVID-19 pneumonia. Thorax. 2020; 75(11):1009-1016.

[11] Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020; 25100463.

[12] Banik J, Mezera V, Köhler C, Schmidtmann M. Antiplatelet therapy in patients with Covid-19: A retrospective observational study. Thrombosis Update. 2021; 2:100026.

[13] Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARSCoV-2 infection. New Engl J Med. 2020; 382(23):2268–70.

[14] Yusuff H, Zochios V, Brodie D. Thrombosis and Coagulopathy in COVID-19 Patients Requiring Extracorporeal Membrane Oxygenation. ASAIO J. 2020; 66(8):844-846.

[15] Eckmann DM, Seligman I, Cote´ CJ, Hussong JW. Mucormycosissupraglottitis on induction of anesthesia in an immunocompromised host. AnesthAnalg. 1998; 86:729-30.

[16] Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis:an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019; 19(12):e405–21.

[17] Choleva AJ. Anesthetic management for lobectomy in a patient withcoccidioidomycosis: A case report. AANA J 2010; 78(4):321-5.

[18] Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008; 47(4):503–9.