

Recommendations and algorithms to deal with gastroenterological procedures, inflammatory bowel diseases, liver diseases and transplantation during COVID-19 Pandemic: Review article and regional expert opinion

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) has emerged in Wuhan, China, in December 2019, then spread to become a worldwide pandemic with significant morbidity and mortality. This has left healthcare systems worldwide vulnerable to the surge in the number of patients. With the exponential spread of the disease and increasing demand for medical care, a significant proportion of medical procedures were canceled or delayed to decrease viral transmission. Most inflammatory bowel disease patients are on immunosuppressive agents, which are presumed to put them at a higher risk for acquiring the infection. However, some studies have shown that immunosuppressive agents did not increase mortality from COVID-19 at any age. Although most of the morbidity and mortality of this condition are related to respiratory manifestations, some patients develop extrapulmonary manifestations including gastrointestinal and hepatic derangements. Studies have shown that liver chemistry abnormalities are common with COVID-19. There is currently no vaccine or effective treatment for COVID-19, so the only thing we can do is reduce the virus's transmission. In this review, we addressed the dilemma of how to deal with gastroenterological procedures in times of a spreading pandemic, to decide which procedures can or cannot be postponed based on current international available data. As well as, to ensure the continuation of the essential management of inflammatory bowel diseases (IBDs) patients, many of whom are on immunosuppressive and biologic agents, thus, making the decisions about which medications the patient can stay on to prevent disease attacks. Finally, studying the hepatic manifestations during the COVID-19 pandemic. We have also postulated local recommendations that can serve as a guide for managing liver diseases during COVID-19 and when to go to liver transplantation with the least risk possible for viral transmission.

Keywords: Coronavirus, COVID-19, Gastroenterological procedures, Inflammatory Bowel Diseases, Liver disease, Liver transplantation.

INTRODUCTION

Coronaviruses are enveloped in non-segmented positive-sense RNA viruses. The new 2019 novel coronavirus (2019-nCoV), has emerged in Dec 2019 in China and has been declared in March 2020 by the World Health Organization (WHO) as a pandemic [1, 2]. Globally, over 55 million confirmed cases of COVID-19 have been reported. The reported cases of Coronavirus disease 2019 (COVID-19) in occupied Palestinian territory based on WHO data, were 93,700 confirmed cases in West Bank including Jerusalem, and 27,400 confirmed cases in Gaza Strip [3].

The increasing need for hospitalizations and intensive care unit admissions has urged health care systems around the world to cancel or postpone elective procedures in preparation for the expected surge in cases [4].

COVID-19 pneumonia is presumed to spread primarily by respiratory droplets (e.g., sneezing, coughing, etc.) [5]. Considering close person-to-person contact puts the individual at a higher risk of contracting the disease, health care professionals involved in direct clinical care, and those involved with procedural medicine are at high risk of developing COVID-19. It is estimated that 10% of the health care professionals have become

infected with the virus in western countries [6].

The spread of the disease via health care workers is particularly concerning because of the following reasons: 1) Scarcity of Personal Protective Equipment (PPE), 2) Shortage of healthcare workers due to illness or quarantine, 3) Concern for healthcare workers becoming vectors for transmission of the COVID-19 virus, and 4) Individuals, including health care workers, can be contagious without displaying any signs or symptoms of the disease [2, 7].

This study aims to address how to deal with gastroenterological procedures during the spreading pandemic with the least risk for viral transmission and classify the procedures to which can be postponed and that cannot be delayed based on current international available data and expert experience. Our second objective was recommendations concerning the management of inflammatory bowel diseases (IBDs) during the current pandemic to clarify which drugs should be continued to prevent IBD relapse or stopped to decrease viral transmission risk. Finally, we studied the approach and screening protocol to COVID-19 with liver function test abnormality. Also, we think that we should have regional guidance regarding liver diseases drugs continuation, drug-drug interactions, hepatitis reactivation, and doing or delaying liver transplantation.

METHODS

To date, the guidelines for dealing with gastroenterological procedures, managing inflammatory bowel diseases, managing liver diseases, and dealing with liver transplantation patients before and after transplant in patients with COVID-19 have already been established globally; however, there are no regional guidelines. Thus, the An-Najah National University Hospital gastroenterology and internal medicine expert group collected and summarized the current international available data of different literature and guidelines among different databases comprising Google Scholar, Medline, Pub Med, EMBASE, and Science Direct. Also, data obtained from WHO to create these recommendations in patients with COVID-19. The

experts followed the previous regional guidelines associated with COVID-19 [8, 9].

Gastroenterological procedures and COVID-19

While direct person-to-person contact puts the individual at higher risk of contracting the disease, aerosol-generating medical procedures generate small droplets and permit the virus's airborne transmission. Esophagogastroduodenoscopy (EGD), small bowel enteroscopy, endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and esophageal manometry are some of the aerosol-generating procedures that should be considered as high risk for viral transmission [4].

It is likely that COVID-19 will remain an issue for the foreseeable future and that it has and will continue to have a negative impact on our healthcare systems including its endoscopy capacity and its ability to deliver medical services on time. With a steadily rising number of COVID-19 cases around the globe, it is difficult to determine the appropriate time to resume medical services in endoscopy centers.

Considering the points mentioned above, we summarized the following recommendations for gastroenterological procedures during the COVID-19 pandemic to mitigate the virus's transmission.

Triage patients before scheduling an appointment

Telephoning the patient to ask about symptoms and signs of COVID-19 pneumonia before an appointment is made and 3 days before the procedure is planned along with using the (FTOCC) triage (Fever of more than 37.5 C, Travel history, Occupational exposure, Contact history, and Clustering type) can help in classifying the patients into high-risk and low-risk groups for having the virus [10]. This recommendation aims to ration the valuable resources at a time where they could be used more effectively to protect healthcare professionals while interacting with higher-risk patients.

All patients suspected to have coronavirus based on the mentioned screening tool should be offered a Real-Time Polymerase Chain Reaction (RT-PCR) antigen testing

before presenting to do the procedure, their procedure should be deferred for 14 days where clinically appropriate. It should have their procedure performed in a high risk or hot unit to minimize interaction between high-risk and low-risk patients.

On the day of the procedure

Dealing with patients should be done with caution at all times so we recommend using surgical masks by healthcare professionals and patients, maintaining a distance by staying at least two meters apart whenever possible, and using a physical barrier such as a face shield. These measures should be stuck to at all times including but not limited to the following interactions: patient assessment, taking vital signs, and informed consent for the procedure. Screening tools should also be implemented to risk stratify the patients and minimize interaction with high-risk patients.

For patients deemed at high risk of having COVID-19, we recommend using a separate unit for performing the procedure if available. As resources have been becoming more scarce since the beginning of this pandemic and a separate unit might not be available, using separate pre and post-endoscopy recovery areas might be an alternative. It is reasonable to postpone high-risk or COVID-19 positive patients at the end of the session. Using full PPE, including N95 respirator cannot be overemphasized and, where available, negative pressure rooms for performing high-risk aerosol-generating procedures on the high-risk patient [11].

For all patients, including those with low-risk, standard precautions should be implemented at all times including keeping a distance of 2 meters, using surgical masks, rigorous hand hygiene. Considering the urgency of the pandemic in the current period and lack of a reliable rapid COVID-19 test, only experienced endoscopists, anesthetists, and healthcare professionals should be present during the procedure. To minimize exposure, only personnel directly involved in the procedure should be present once the patient enters the endoscopy unit. It is important to keep ample time before and after the procedure for infection control measures.

Urgent, Semi-urgent and Non-Urgent Procedures

In general, Gastroenterological procedures can be divided into Urgent, Semi-urgent, and Elective (non-urgent) procedures according to the Asian Pacific Society for Digestive Endoscopy [12], please refer to figure 1.

Abbreviations: EMR (Endoscopic mucosal resection).

Needless to say, urgent procedures should be performed urgently but while using full protective equipment especially since the information is likely to be lacking on the risk of having COVID19. Likewise, Elective procedures can be postponed during the current surge of the virus after setting a new appointment or by using telemedicine. Semi-urgent procedures need a discussion on a case-by-case basis to decide on the urgency of the procedure. Figure 2 gives an algorithm on how to proceed when endoscopy is indicated.

Following the procedure

Standard cleaning and sterilization of the endoscopy unit and tools as per the American Society for Gastrointestinal Endoscopy guidelines has proven effective at deactivating coronaviruses [13].

Commonly used biocidal agents including hydrogen peroxide, alcohols, sodium hypochlorite, and benzalkonium chloride have been confirmed to decontaminate surfaces and tools from coronaviruses [14]. For infection control during GI endoscopy current guidelines Include mechanical and detergent cleaning, followed by high-level disinfection (HLD), rinsing and drying through sterilization.

Follow up phone calls at 7- and 14-days post endoscopy to inquire about COVID19 symptoms or positive testing is useful to determine if an endoscopy unit has been exposed to the virus and to take protective action in a timely manner to minimize exposure to other units and patients.

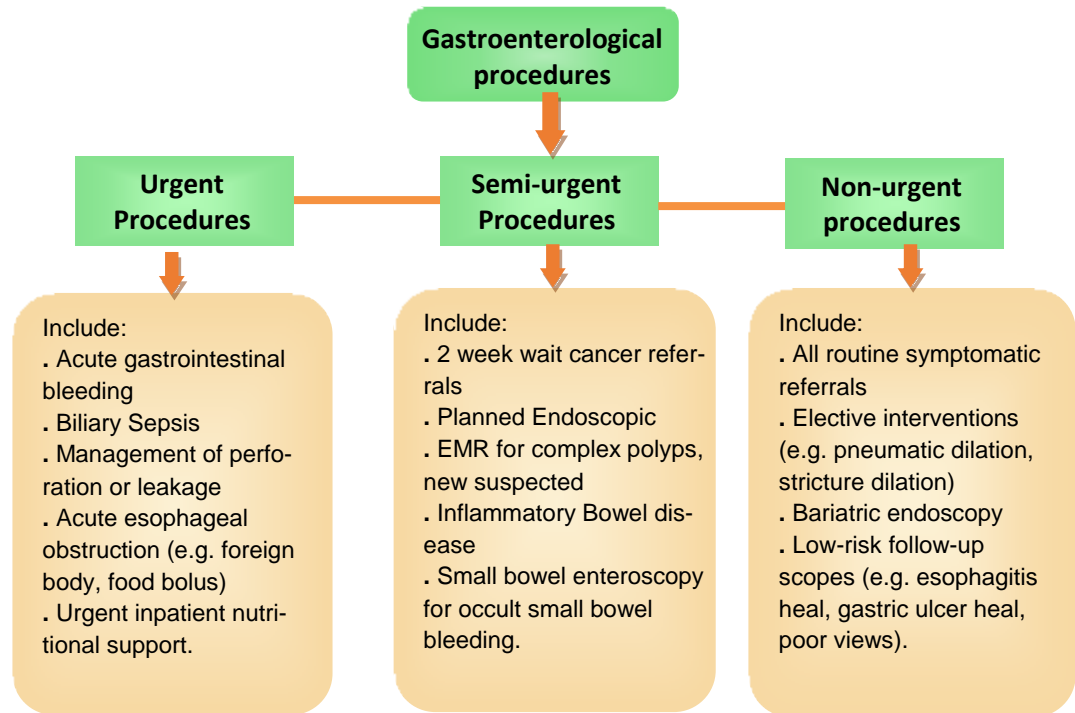


Figure (1): Gastroenterological procedures classification according to the Asian Pacific Society for Digestive Endoscopy.

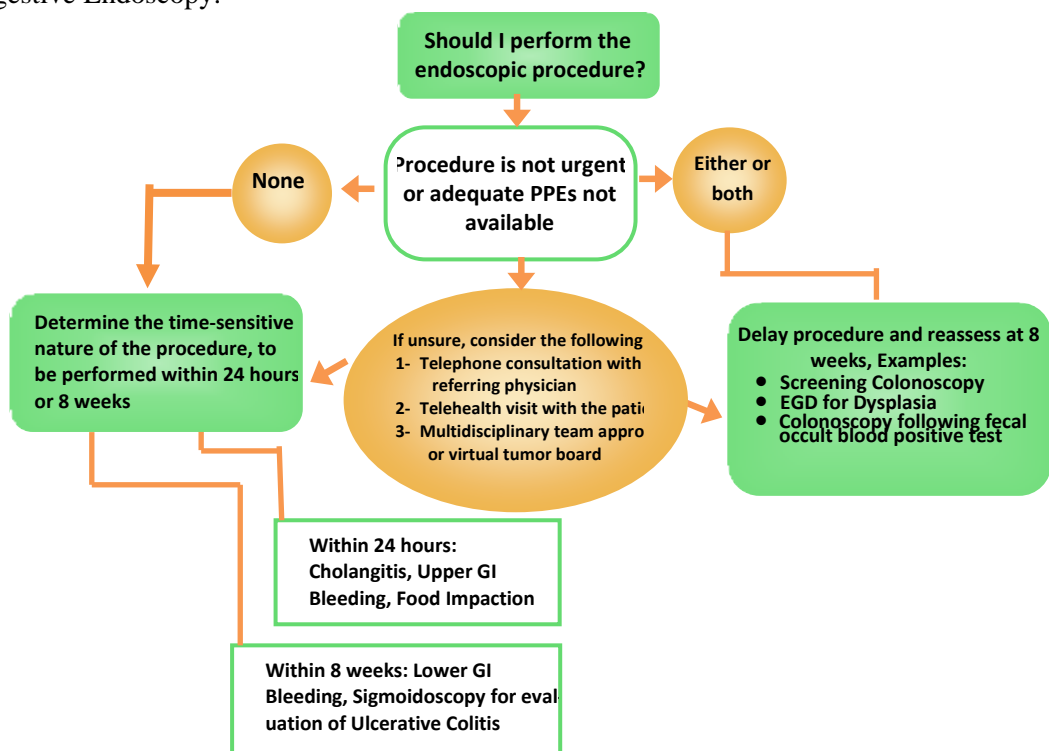


Figure (2): How to proceed when endoscopy is indicated.

Abbreviations: *PPEs* (personal protective equipment's), *EGD* (Esophagogastroduodenoscopy), *GI* (Gastrointestinal).

Inflammatory Bowel Disease (IBD) and COVID-19

As the outbreak spread to a worldwide pandemic, concerns that immunocompromised patients may be at high risk of developing coronavirus disease 2019 (COVID-19) were raised [15]. The treatment regimens for inflammatory bowel disease (IBD) patients comprising Crohn's disease (CD) and ulcerative colitis (UC), frequently involve immunosuppressive and/or biologic agents which are known to increase a patient's susceptibility to certain infections. We have gathered the available evidence on COVID-10 and its impact on IBD patients [16].

In contrast to those with comorbidities like diabetes, heart disease, lung disease, or kidney disease which are considered as risk factors for poor outcomes. Patients with impaired or suppressed immune response are not at a higher risk for severe or complicated COVID-19 infection [17].

One study conducted in Italy during the COVID-19 pandemic supports the above-

mentioned statement where 522 patients with inflammatory bowel disease were followed over one month (Feb-March 2020) [18]. Another similar study conducted in Wuhan and involved 319 patients with IBD reported no Confirmed COVID-10 cases of pneumonia in the IBD population [19]. This comes because no treatment regimens were adjusted [18, 19]. This was also true for the two previous epidemics caused by coronaviruses, Middle East respiratory syndrome caused by the coronavirus named MERS-CoV, and severe acute respiratory syndrome-associated coronavirus (SARS-CoV).

After a careful review of SARS-CoV mortality and morbidity reports, there is no mentioned report to link immunosuppression (including patients on immunosuppressive or chemotherapeutic medications and transplant recipients) as a risk factor for mortality at any age wither in the current pandemic or the previous coronavirus outbreaks [17, 18, 20].

Taking into account the previously mentioned points, we have gathered the following recommendations concerning the management of IBD during the current pandemic. Figure 2 summarizes those recommendations.

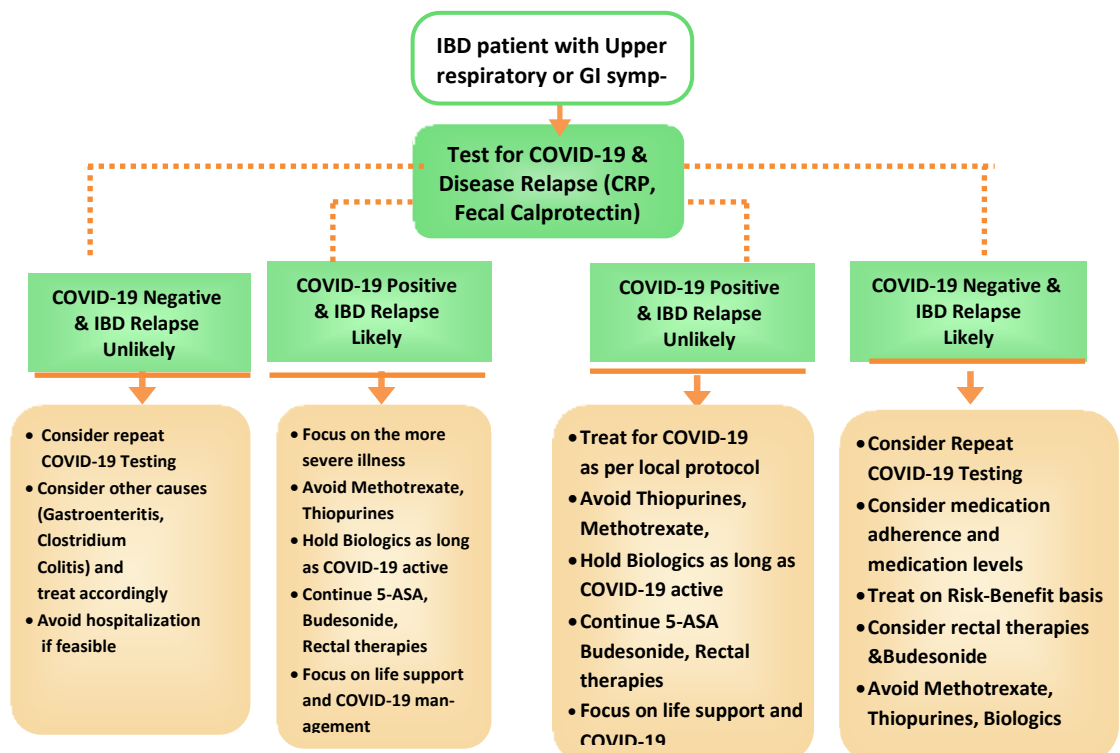


Figure (3): Management of IBD during the COVID-19 Pandemic. *Abbreviations:*

CRP (C-reactive protein), IBD (Inflammatory bowel disease), 5-ASA (5-aminosalicylic acid).

minosalicic Acid Derivative

We recommend that 5-aminosalicylic acid (5-ASA) (e.g. Mesalazine and sulfasalazine) should be continued as there is no data to support discontinuation of either oral or rectal preparations. This recommendation includes patients with symptoms suspicious of COVID-19 (such as new cough, fever of more than 100F, breathlessness) or even patients who tested positive for the disease [21].

Corticosteroids

In COVID-19 negative patients, it is recommended to avoid corticosteroids whenever possible especially in co-administration with other immunosuppressive agents. In the case of IBD relapse, corticosteroids use may be unavoidable. In such scenarios, consider using locally acting preparations. Systemic steroids should be prescribed after careful assessment of risks and benefits [21]. In patients with symptoms suspicious of COVID-19 and those confirmed to have the disease, systemic steroids should be used at a low dose and discontinued once the risks outweigh their benefit. However, tapering steroids could be used when other alternatives are unavailable or cannot be used [22]. According to the local corticosteroids (Budesonide, Beclomethasone dipropionate) should be continued regardless of the COVID-19 status [21].

Immunomodulatory drugs (immunosuppressive agents)

Immunomodulatory drugs including thiopurines (e.g. Azathioprine, 6-mercaptopurine), methotrexate and calcineurin inhibitors (e.g. Cyclosporine) should be continued to decrease the risk of disease recurrence, especially in COVID-19 negative patients as well as those with no symptoms of COVID-19 infection [16, 21, 22]. In high-risk endemic areas, changing the dose or the medication is not recommended unless clinically indicated [23]. Starting a new biologic agent could be sought if protective and supportive measures are available [16]. We be-

lieve that continuing immunomodulatory drugs would lead to the possibility of the rapid evolution of the infection so immunomodulatory treatments should be discontinued in the case of a positive test throughout the infection [21]. This does not include patients with a high risk of relapse (i.e. history of intestinal or colonic stricture, intra-abdominal abscesses or fistulae, complex perianal or severe rectal disease).

Biologic therapy and small molecule

The available data suggests that the risk of COVID-19 infection and its complications is not increased in IBD patients receiving biological treatment. Consequently, biological agents including (1) anti-TNF (Tumor necrosis factor) agents (e.g. infliximab and adalimumab), (2) anti-integrin (e.g. vedolizumab) and (3) anti-interleukin (e.g. ustekinumab) should be continued in COVID-19 negative patients. The risks and benefits of discontinuing those biological agents should be balanced to avoid the risk of disease relapse. This recommendation also applies to small molecule drugs (JAK inhibitors e.g. tofacitinib and baricitinib). However, in the case of a positive test, biological agents and small molecule drugs should be discontinued throughout the infection [21, 22].

Liver diseases and COVID-19

Recent studies indicated that 50-76% of patients with COVID-19 have elevated aspartate transaminase (AST) and alanine transaminase (ALT) during their illness [24, 25]. It's been shown that elevations of ALT & AST correlate with the severity of COVID-19 infection [26]. Though most COVID-19 patients have only mild elevations of Liver enzymes (i.e. 1-2 times the upper limit of normal).

It is recommended that every patient with COVID-19 infection and liver enzyme derangement undergo screening protocol (according to local prevalent causes) to establish the etiology of liver injury as multiple etiologies could be responsible including but not limited to COVID-19 or its complications, drug-induced or underlying liver disease. Therefore, establishing the cause behind the liver injury will facilitate management and

reduce overall mortality and morbidity. In Asia, for example, the high prevalence of Hepatitis B & C Viruses, Alcohol-related liver disease, and Nonalcoholic Fatty Liver Disease (NAFLD) necessitates directing screening protocol towards these etiologies

[27-29]. Screening for other causes of liver injury is only necessary when liver test abnormalities persist beyond recovery of COVID-19. Figure 3 represents an approach to COVID-19 patients with elevated liver function tests.

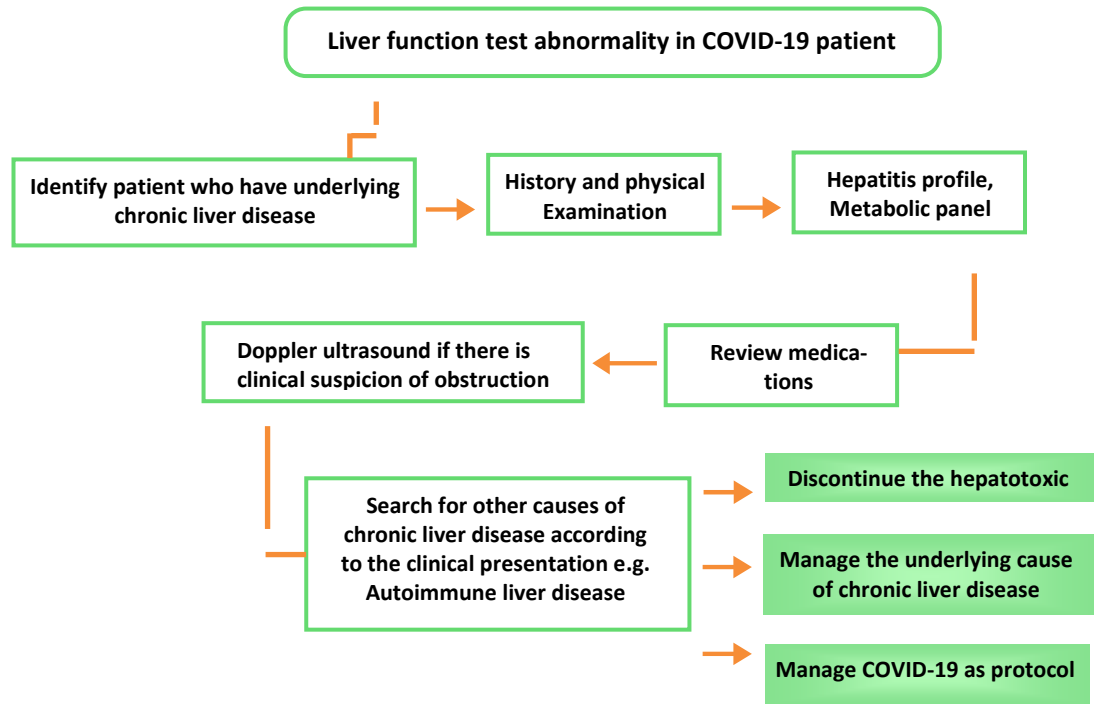


Figure (4): Approach to COVID-19 patient with liver function test abnormality.

Considering that COVID-19 infection can cause liver injury especially given that the severity of COVID-19 pneumonia and Liver injury is directly proportional, screening for Hepatitis-B Virus infection in all patients with severe COVID-19 pneumonia is recommended and those found to be positive should start antiviral prophylaxis with a nucleoside analogue [30].

Immunosuppressive agents including high dose systemic steroids and interleukin-6 (IL-6) monoclonal antibodies have been advocated for the treatment of critically ill COVID-19 patients and were found to be triggering factors for Hepatitis-B reactivation, chronic hepatitis-B infection flare, or acute liver failure [31]. For that, screening for hepatitis-B infection is recommended for patients planned for such treatments, and those found to be positive are recommended to start antiviral prophylaxis with a nucleoside analogues.

There are no major drug-drug interactions between current therapeutic options for COVID-19 and Nucleoside analogues used to treat hepatitis-B viral infection. Therefore, no absolute contraindications exist in the current period regarding drug-drug interactions. Our recommendation is to initiate or continue treatment for hepatitis-B infection in a patient being treated for COVID-19.

Most current therapeutic options for COVID-19 do not have significant drug-drug interactions with direct-acting antivirals against chronic hepatitis-C virus infection. The only significant interaction possible is the use of protease inhibitor direct-acting antivirals with lopinavir-ritonavir which may lead to a significant elevation in ALT. The pathophysiology behind this is related to lopinavir's ability to significantly increase the blood concentration of protease inhibitors. Therefore, the use of protease inhibitor direct-acting antivirals with lopinavir-ritonavir

is contraindicated. Furthermore, Hepatitis-C viral flare following termination of direct-acting antivirals is rare [32] and so, we recommend termination of or withholding direct-acting antivirals if a significant drug-drug interaction is discovered or if the patient is in critical condition (e.g. requiring invasive or non-invasive ventilation).

Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) have a higher probability of having metabolic comorbidities, namely Type II Diabetes Mellitus and Hypertension, which places them at a higher risk of having severe COVID-19 infection. Although studies looking into the severity of COVID-19 infection in patients with NAFLD are currently lacking, Diabetes is currently known to increase the risk of Intensive care unit admission mechanical ventilation and death due to COVID-19 [33]. As patients with NAFLD are at higher risk of developing a drug-induced liver injury, close monitoring of liver function is advised in those patients.

Ever since the beginning of the pandemic, Screening protocols have been a center of controversy and debate. Balancing the risk of contracting COVID-19 infection and the risk of developing the illness or complication under surveillance has been the target of many researchers and clinicians. Hepatocellular Carcinoma is the 3rd most common cause of cancer-related death worldwide and early detection increases the probability of curative management and therefore decreases mortality [34]. Considering those facts, in regions with a high prevalence of COVID-19 it is reasonable to delay screening for Hepatocellular Carcinoma by 3 to 6 months depending on the urgency of screening and availability of resources including health-care staff. Although screening every 6 months is recommended, screening every 1 year is beneficial with no difference in survival [35]. For patients diagnosed with stable Hepatocellular Carcinoma but not COVID-19, continuous follow up with telemedicine and Alpha-Fetoprotein (AFP) locally is recommended.

In patients with high risk for Hepatocellular Carcinoma (cirrhosis, chronic hepatitis B) continue screening as planned if possible. In such patients, a delay of 2 months is acceptable once risks and benefits are discussed

with the patient. Patients suspected to have Hepatocellular Carcinoma due to elevated AFP or Liver nodule should be prioritized. For a patient confirmed to have Hepatocellular Carcinoma, surgical resection and liver transplantation are the curative therapeutic options available if the disease is detected in its early stages. Considering COVID-19 is highly contagious and most patients recover within 2-4 weeks [33]. It is reasonable to defer treatment of Hepatocellular Carcinoma for a few weeks after recovery while using bridging therapy.

Bridging therapeutic options for Hepatocellular Carcinoma include transarterial chemo-embolization, radio-frequency ablation, and systemic chemotherapy. Coupling those options with close monitoring by using imaging studies and AFP reduces the risk of potential progression of the disease beyond the eligibility for liver transplantation or resection.

We recommend continuing treatment for Hepatocellular Carcinoma in COVID-19 free patients as deemed appropriate. Patients already on kinase inhibitors may continue their treatment given they are not infected with COVID-19. Those who become infected should withhold Hepatocellular Carcinoma directed immunotherapy until resolution of their infection.

Variceal bleeding is a potentially life-threatening complication in patients with liver cirrhosis [36]. Prognosis is even poorer if the patient presents with hemodynamic instability requiring urgent endoscopy [37]. Considering upper endoscopy is a high-risk procedure for transmission of COVID-19, patients planned for elective endoscopy who have a low-risk of variceal bleeding might be postponed. To identify patients with clinically significant varices and, hence, at high risk of future variceal bleeding, we recommend using non-invasive assessment methods with good predictive value, including Baveno IV criteria platelet-to-liver stiffness measurement ratio, liver stiffness measurement ratio, and spleen stiffness measurement with transient elastography. This recommendation is expected to reduce the need for upper endoscopy in 50% of the cases and therefore the need for scarce personal protective equip-

ment and personnel [38].

Liver transplantation and covid19

Liver transplantation is a curative therapeutic option for chronic liver disease. The comorbidities that commonly accompany the chronic liver disease, long term immunosuppressive therapy and regular follow up needed post-transplantation are risk factors for developing COVID-19 and need to be taken into consideration.

Given the whole picture, we composed the following recommendations concerning liver transplantation

1. Limiting liver transplantation to emergency cases (acute liver failure, high MELD score, and high rate of progression to hepatocellular carcinoma) conforming to local resources and status of the pandemic.
2. Before planned transplantation, the donor and recipient must be tested for coronavirus with a nasopharyngeal swab, bronchoalveolar lavage, or chest CT keeping in mind that negative testing does not rule out infection.
3. Risks of liver transplant in a COVID-19 positive patient should be balanced against benefits taking into consideration risks to healthcare personnel.
4. No adjustment to immunosuppressive medications is recommended in a COVID-19 negative liver transplant patient as any adjustment carries the risk of organ rejection.
5. Consider immunosuppressive therapy dose reduction in a patient with moderate COVID-19 infection. Doses are recommended to be reduced in patients with lymphopenia, fever, or worsening pneumonia.
6. Consider the risk of drug-drug interaction between immunosuppressive therapeutic medications and COVID-19 medications. Such risk is expected when using medications metabolized by Cytochrome P450 enzymes (sirolimus, tacrolimus) and lopinavir-ritonavir but no, or minimal, interaction is expected with azathioprine, cyclosporine, and mycophenolate mofetil. Reduce tacrolimus dose by 2-5% of the baseline when using lopinavir-ritonavir [17, 39].

7. Transplant recipients who develop severe COVID-19 infection should be treated according to local protocol taking into account drug interactions.
8. Follow-up should be maintained through altered pathways including telehealth/telephone consultation and local blood testing, immediate medical attention must be provided when indicated.
9. All liver transplant recipients should receive vaccination against influenza and pneumococcal infection.
10. If a steroid dose reduction is decided, a minimum of 10 mg daily of prednisone or equivalent should be continued to avoid adrenal insufficiency.

CONCLUSIONS

COVID-19 is a global pandemic with a high morbidity and mortality rate, affecting every aspect of the health system with an ongoing shortage of healthcare workers under the continuous risk of contracting the virus.

This paper provides scientific evidence in addition to expert opinion to guide the health care team on how to deal with gastroenterological procedures, to clarify the effect of COVID-19 on inflammatory bowel disease patients on immunosuppressive and biologic agents. Finally, it outlined a screening protocol for liver disease in COVID-19 patients and provided a set of recommendations concerning antiviral drugs and liver transplantation.

Our recommendations concerning gastroenterological procedures focused on standard cleaning and sterilization of the endoscopy unit and tools. They also emphasized the importance of maintaining standard precautions at all times and for all patients including keeping a distance of 2 meters, using surgical masks, and rigorous hand washing or hygiene.

Concerning IBD management, immunosuppressive and biological drugs should not be discontinued in patients asymptomatic for

COVID-19 especially considering that immunosuppressive medications were not shown to increase the risk of contracting COVID-19 or its mortality.

Screening for hepatitis B infection is recommended for patients planned for high dose systemic steroids or interleukin-6 (IL-6) monoclonal antibodies as these were found to be triggering factors for Hepatitis B reactivation. Those found to be positive are recommended to start antiviral prophylaxis with a nucleoside analogues.

Liver transplantation procedures should be limited to emergency cases. Before the procedure, the donor and recipient must be tested for COVID-19 to avoid unnecessary exposure. Generally speaking, immunosuppressive medications do not need to be adjusted solely to avoid COVID-19 infection or complications.

These recommendations and algorithms present an expert opinion that is based on a careful review of the available data. It aims to guide clinicians to provide excellent medical care with the least risk possible for viral transmission. We aspire to have provided a stepping stone to generating work protocols at times of a pandemic.

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