

The background of the cover features a detailed, 3D-rendered illustration of a virus, likely SARS-CoV-2, shown in two sizes. The virus particles are spherical and covered in blue, cone-shaped spike proteins. The interior of the virus is filled with a complex arrangement of orange and purple particles, representing the viral genome and internal structures. The background is a gradient of blue and orange, with a diagonal split between the two colors.

# MANAGEMENT OF HCC DURING COVID-19 PANDEMIC: ILCA GUIDANCE



## **ILCA Guidance for Management of HCC during COVID-19 Pandemic**

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### **1. Background**

As of 4<sup>th</sup> April 2020, the coronavirus disease 2019 (COVID-19) pandemic has resulted in over 1 million confirmed cases across 208 countries, and over 60,000 deaths.[1] Already, the health services of many countries have been overwhelmed and many more will experience similar pressure over the coming weeks and months. The extra-ordinary resource required to meet the needs of this pandemic will have a major impact on the delivery care to patients with cancer who represent a population at high risk from severe disease or death from COVID-19. The purpose of this guidance is to provide up to date information on the impact of COVID-19 infection on liver function in those patients with chronic liver disease and hepatocellular carcinoma, and to offer recommendations for alternative treatment strategies where standard of care cannot be delivered for logistical or safety reasons related to COVID-19.

### **2. Impact of COVID-19 on liver function**

Most of the information available on liver injury in patients with COVID-19 is still based on early Chinese reports, unpublished data, and personal communication. Considering the limitations of this information, better understanding of COVID-19 related liver damage is needed.

Many COVID-19 cases are mild and resolve quickly; however 14% are severe and 5% critical or life threatening.[2] The incidence of liver injury ranges from 15 to 54%, mainly indicated by abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels accompanied by slightly elevated bilirubin levels.[3-10] Liver injury in mild COVID-19 cases is often transient and can return to normal without any specific treatment.[4] Serum albumin level is decreased in severe cases, but the mechanism of hypoalbuminemia is unclear and may be also related to the inflammatory status. Gamma-glutamyl transferase (GGT), a biomarker for biliary epithelial cell injury, is elevated in 54% of patients with COVID-19 during hospitalization.[4] The liver injury is significantly worse in the patients with severe COVID-19 as compared with those with mild disease.[11, 12] In addition, immune-mediated inflammation such as cytokine storm, pneumonia-associated hypoxia, myocardial damage and drug toxicity may also contribute to liver injury in patients with severe COVID-19.

The pathogenesis of liver damage in COVID-19 is largely unknown. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as its entry receptor as does SARS-CoV. Both hepatocytes and biliary epithelial cells express ACE2, and the ACE2 expression of biliary epithelial cells is much higher than that of hepatocytes suggesting that liver injury in COVID-19 might be mainly due to the damage of biliary epithelial cells or cholangiocytes; however, viral inclusions have not been observed in liver tissues to date [3, 13, 14]. Postmortem biopsies in patients who died of COVID-19 showed microvesicular steatosis and mild lobular and portal activities, indicating that the injury could have been caused by either SARS-CoV-2 infection or secondary drug-induced liver injury.[15]

No specific, evidence-based therapies are available for COVID-19. Several agents such as hydroxychloroquine, lopinavir/ritonavir (Kaletra), tocilizumab (Actemra), remdesivir, convalescent serum and azithromycin are being used under clinical trial and compassionate-use protocols based on in vitro activity with limited clinical experience.[16, 17] Lopinavir/ritonavir could increase liver enzyme levels, and administration of tocilizumab is associated with increased AST/ALT levels and risk of toxic hepatitis.

#### *Recommendations for assessing liver function in patients with COVID -19*

- When assessing patients with COVID-19, liver function tests, including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), albumin and total protein, total bilirubin, and prothrombin time (PT) or INR, is strongly recommended for obtaining baseline values.
- All patients with COVID-19 should be regularly monitored with liver function tests, particularly severe cases and those who are treated with tocilizumab, lopinavir/ritonavir, and other investigational or off-label drugs.
- In patients with COVID-19 who have jaundice or hyperbilirubinemia, the need for imaging tests (ultrasonography or computed tomography/magnetic resonance imaging) or endoscopic procedures such as ERCP, for differential diagnosis of biliary obstruction from hepatocellular damage should be carefully determined to minimize unnecessary exposure of patients and providers. It should be considered that ALP and GGT levels might increase disproportionately to ALT/AST levels owing to SARS-CoV-2 infection.

### **3. Impact of COVID-19 in patients with chronic liver disease and cancer**

Globally, approximately 1.5 billion population have chronic liver disease, mainly resulting from non-alcoholic fatty liver disease, chronic viral hepatitis B and C, and alcoholic liver disease.[18, 19] No evidence suggests that patients with controlled chronic hepatitis B or C virus infection are at increased risk of SARS-CoV-2 infection. However, these patients, often have other comorbidities such as diabetes, hypertension, and cardiovascular disease which increase the risk of serious illness from COVID-19.[20].

The CDC in the United States reported that 0.6% (N=41) of all COVID-19 cases with completed information (N=7162/total 74439, March 31, 2020) had underlying chronic liver disease, 22% of whom were hospitalized and 17% were treated in an ICU admission [21]. In other series of COVID-19 reported by Chinese centres, 2-11% of patients had comorbid chronic liver disease.[5, 7, 9-11, 22, 23] Infection with COVID-19 may impact existing chronic liver disease in three ways: First, the additional hepatic injury induced by the COVID-19 could lead to hepatic decompensation in patients with compromised hepatic reserves. Second, the potential immunosuppressive properties induced by the SARS-CoV-2 may lead to viral reactivation in patients with chronic viral hepatitis. More data are required to confirm these hypotheses.[15, 24] Third, drugs used for the treatment of COVID-19 or its complications may

produce hepatotoxicity. For liver transplant recipients, data of the impact of COVID-19 are also lacking. Experience from SARS in 2003 suggested that severe infection could occur in liver transplant recipient with high infectivity, presumably due to an immunocompromised state.[24]

Data on the prevalence and impact of COVID-19 on cancer patients have gradually emerged. According to a prospective nationwide cohort study in China, researchers identified 18 of 1590 (1%) patients with both confirmed COVID-19 and a history of cancer.[25] The cancer cohort experienced more severe disease and were more likely to be admitted to intensive care or die. Cancer therapy within 1 month also increased the risk of severe disease. A retrospective study in Wuhan of China reported that 12 of 1524 (0.79%) patients with COVID-19 suffered from cancer and those with non-small cell lung cancer and age greater than 60 appeared to be at higher risk of infection or symptomatic disease.[26] In a different retrospective cohort of 28 cancer patients admitted for COVID-19 infection across three hospitals in Wuhan, China, receipt of cancer therapy within 14 days was associated with substantially higher risk of mortality. [27] Collectively, these studies raise the possibility that patients with cancer may be more susceptible to severe COVID-19 infection than the general population but interpretation is limited by the small sample size and heterogeneity of cancer types and treatment.[25, 26, 28]. Moreover, the impact immunotherapy on the course of COVID-19 is also not known. Guidelines by international oncology associations generally recommend an individualized approach, including continuation of essential treatment for cancer and to consider stepping down treatment (e.g. treatment break, stopping maintenance therapy) in selected patients after careful evaluation risk-benefit ratio.[29, 30] In patients with advanced HCC who require systemic therapies, oral tyrosine kinase inhibitors may be preferred over infusional regimens in areas with high COVID-19 infection rates to minimize nosocomial exposures.

#### **4. Impact of COVID-19 on therapy for HCC**

The time-critical nature of treatment for COVID-19 and the huge numbers of patients requiring hospital admission, critical care and ventilation has diverted resources away from patients with other medical conditions including cancer. Additionally, the risk of infection associated with attending hospital visits is of particular concern for those patients with cancer who represent a high risk group, generally older with additional comorbidities and often immunosuppressed as a consequence of anti-cancer treatment. The demand to expand ventilation capacity for COVID-19 patients has resulted in shortage of anaesthetists to support cancer surgery and other procedures such as ablation which require a general anaesthetic. Nurses and physicians from all specialties are increasingly co-opted to provide supportive medical care for COVID-19 patients such that usual medical care is compromised resulting in the need to prioritise cancer therapy.

Given these limitations, it has become necessary to consider deviations from the current standard of care (SOC) in order to temporise until definitive therapy can be delivered. The recommendations below are intended to help guide treatment decisions during this unprecedented time but it is recognised that regional variations in practice will also influence treatment decisions.

#### **5. Recommendations for treatment of HCC during COVID-19 Pandemic**

##### **General**

- The risks and benefits of intervention will vary according to the type of treatment proposed and the level of infection risk. This will need to be assessed on an individual basis and fully discussed with the patient

- Deviations from SOC due to COVID-19 should be made in the context of multidisciplinary meetings and clearly document so that principals of clinical governance and accountability are maintained, and the impact of COVID-19 on cancer outcomes can be demonstrated
- To avoid nosocomial infection, appropriate use should be made of telemedicine to reduce visits to healthcare facilities. Where visits cannot be avoided, personal protective equipment (PPE) should be used in line with national guidance
- When bridging therapy or active monitoring is offered in place of potentially curative interventions, close monitoring including imaging and AFP should be used to reduce the risk of patients progressing beyond criteria for transplant, resection or ablation
- Where feasible cancer therapy should be offered in a 'COVID –free' institution

### **Surgical resection**

#### *Impact of COVID-19*

- Lack of anaesthetic capacity
- Lack of ITU and inpatient beds for post-operative care
- Risk of SARS-CoV-2 infection causing excess morbidity and mortality

#### *Mitigation*

- Select patients with lower risk of decompensation
- Select patients without comorbidities that increase risk of severe COVID-19.

#### *Alternative/Holding therapy*

- Ablation if anaesthetic capacity allow
- Bridging TA(C)E
- SBRT
- Bridging systemic therapy
- Active monitoring with imaging

### **Transplant**

#### *Impact of COVID-19*

- Lack of anaesthetic capacity
- Lack of ITU and inpatient beds for post-operative care
- Risk of COVID-19 causing excess morbidity and mortality in immunosuppressed patient
- SARS-CoV-2 donor derived infection
- Limited capacity for transplant assessment
- Acute liver failure is being be prioritised

#### *Mitigation*

- Temporary suspension of elective living donor transplantation may need to be considered to protect the potential donor as well as the recipient

- Consider delayed transplant in those with complete response to bridging therapy on transplant list; however, risk of delaying transplant in patients with viable tumors and/or significant liver dysfunction should be discussed with patient

*Alternative/holding therapy*

- Ablation if anaesthetic capacity allows
- Bridging TA(C)E
- Bridging SBRT
- Bridging systemic therapy (excluding checkpoint inhibition given risk of rejection)
- Active monitoring with imaging

**Ablation**

*Impact of COVID-19*

- Lack of anaesthetic capacity
- Lack of inpatient beds for post-procedure care if necessary
- Risk of COVID-19 infection causing excess morbidity and mortality

Mitigation

- Select patients at low risk due to tumour position
- Select patients with highest chance of cure; single tumours less than 3cm
- Assess risk benefit in those with comorbidities that increase risk of serious infection from COVID-19

*Alternative/holding therapy*

- TA(C)E
- SBRT
- Systemic therapy
- Active monitoring with imaging

**Arterial (Chemo) Embolisation or radioembolisation**

*Impact of COVID-19*

- Reduced capacity for interventional radiology
- Reduced inpatient beds for post-procedure care
- Increased risk of serious COVID 19 particularly in those receiving cTACE

Mitigation

- Select patients least at risk of decompensation
- Assess risk benefit in those with comorbidities that increase risk of serious infection from SARS-CoV-2
- Consider use of prognostic scores such as HAP [31] or beyond 7 criteria [32] to select those most likely to benefit
- Consider use of TAE, DEB-TACE or TARE to reduce risk of immunosuppression [33, 34]

*Alternative therapy*

- Systemic therapy

- Active monitoring with imaging

### **Systemic therapy**

#### *Impact of COVID-19*

- Suspension of clinical trial recruitment
- Challenging to maintain compliance with protocol for patients on trial
- Outpatient capacity limited resulting in second line therapy deprioritised
- Increased risk of serious COVID 19 infection in patients receiving immunosuppressive therapy
- Limited data regarding infection risk or impact on course of COVID-19 for those receiving checkpoint inhibitors
- Reduced capacity for response imaging

#### Mitigation

- For patients on trial, discussion with sponsor required to accommodate variations in follow-up schedule, trial-related procedures and treatment location
- Select patients most likely to benefit according to performance status, Child-Pugh score and comorbidities
- First-line sorafenib or lenvatinib to replace trial recruitment and minimise hospital visits
- In regions where checkpoint inhibitors approved, the increased risk of attendance for infusion should be considered
- Patients to be managed by telemedicine to avoid hospital visits
  - Drugs to be dispensed by mail
  - Blood, urine dip and BP to be performed locally in community
  - Consider omitting radiology response assessment and continue to clinical progression according to tolerance

#### *Alternative therapy*

- Active monitoring (with imaging where appropriate)
- Supportive palliative care



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