Liver **C**anc**er O**utcome in the COVID**19**-pandemic. (**CERO-19**)

PROMOTOR:

Massimo Iavarone, PhD, MD.
CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

Alejandro Forner, PhD, MD
Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain**.**

Maria Reig, PhD, MD
Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain.

Principal Investigators:

Massimo Iavarone, PhD, MD.
CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

Alejandro Forner, PhD, MD
Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain**.**

Maria Reig, PhD, MD
Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain.

Background:

These days the COVID19 pandemic is impacting at all levels of the society and the HealthCare authorities are focusing their efforts on reducing the transmission and the rate of COVID19-related deaths. Once the peak of incidence and mortality has been exceeded, middle-term the aims will change and focus should be placed in assessing how to handle the impact of an abrupt change in the clinical practice of other conditions while facing this COVID19 crisis.

In the liver cancer field, the COVID19-pandemic has huge implications. Patients have a high risk of suffering a worse outcome if they are infected. Their median age (≅60-70 years-old) and comorbidities are independent predictors of worse outcome regardless of their tumor burden. In the case of HCC, almost all patients present underlying cirrhosis with an associated risk of decompensation in the context of the infection, and their liver cancer treatment has to be stopped or postponed due to the infection. On the other side, those patients who were not infected also could suffer the impact of the COVID19-pandemic due to the COVID19-related modification on clinical practice and priorities in the population health care. In this regard, it is key to evaluate the impact of interrupting or delaying the schedule of liver cancer screening programs or treatments as established before the COVID19-pandemic on the liver cancer evolution and death rate.

In the context of the COVID19 pandemic, the Liver Cancer Groups have organized their clinical practice according to their Country, Hospital policies and resources. However, regardless of the local organization, almost all centers have decreased the frequency of face to face visits, availability to perform surgical procedures, percutaneous ablation, loco-regional interventions or apply oral or intravenous treatments. On the other hand, centers which continue with all their facilities to perform treatments and/or maintain the screening programs available, will realize that the patients who attend the hospital for disease monitorization by imaging techniques are at risk of being infected by coronavirus-SARS-2 or just be diagnosed with coronavirus-SARS-2 at the time of imaging for tumor staging and follow-up monitoring. Finally, regardless of the feasibility to perform liver cancer screening, imaging follow-up or treatment, some patients may decline to attend hospital appointments or physicians may recommend to cancel or delay the treatments or the imaging evaluations due to the high-risk patient profile. Accordingly, COVID19-pandemic has impacted in the management of liver cancer patients worldwide and it has become a major challenge in the management of Liver cancer patients.

Hypothesis: The COVID19-pandemic is associated to a negative impact on the liver cancer outcome and this impact will be seen in the middle-long term follow-up.

Aim: The purpose of this observational study is to evaluate the impact of the COVID19-pandemic in patients with Liver Cancer.

Design: This is a multicenter, international and observational study focused on patients with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (iCC) attended in separate institutions around the world during the COVID19-pandemic of the year 2020.

Aim:

1. Identify the impact of COVID19 pandemic in the clinical practice (stop screening program, diagnostic and staging delays, criteria to maintain the imaging follow-up in treated liver cancer patients)
2. Evaluate the rate of tumor progression while treatment has been delayed.
3. Events and outcome of Liver Cancer Patients with COVID19 infection under any non-systemic therapy.
4. Events and outcome of Liver Cancer patients with COVID19 infection under different systemic treatments.

Methodology:

This is an observational, international, multicenter study. The data registry will start from the date of the first coronavirus-SARS-2 case described in each country. The inclusion period will be open until the COVID19 pandemic is over in each country (the expected date in which the pandemic will be partially solved in Europe could be September 2020).

For the first aim, individual data is not needed. All centers must answer the following survey or questionnaire to be part of the study.

Clinical Practice- No related to COVID19 pandemic *-Mandatory information-*

1. **How many liver cancer patients (HCC and iCC) do you visit in your Unit/Group?** (Number of new liver cancer patients/per year and total number of visit per year-HCC and iCC separately)
2. **How many clinicians and nurses are involved in the liver cancer management in your Unit/Group?** (regardless of their disciplines)

Clinical Practice- Related to COVID19 pandemic *-Mandatory information-*

3. **Have you modified your clinical practice due to the COVID19-pandemic? Yes/No**
    - If Yes, mention the modifications in the following points: screening program, diagnostic/staging, images follow-up in treated liver cancer patients, treatment.
    - If Yes, how many of the clinicians related to liver cancer patients needed to stop their activity to treat only COVID19 patients?
    - If No, describe your policy in the following points: screening program, diagnostic/staging procedures imaging follow-up in treated patients, treatment.
4. **If you modify your clinical practice from face to face visit to remote visit, which were the criteria to maintain the face to face visits?** Please, describe.
5. **In your clinical practice: Have you involved the nurses for liver cancer management? Yes/No**
    - If yes, what was their role in the context of COVID19-pandemic?
6. **In your clinical practice: Had you organized phone visits for your liver cancer patients prior to the pandemic? Yes/No**
    - If yes, have you modified the schedule of this service?
        i. If yes, please describe the modification-
7. **Have you modified the diagnostic procedures request and timing (biopsy and imaging technique) in the context of COVID19-pandemic? Yes/No**

- If yes, what was the criteria to indicate that procedures? Please, describe/exemplify: age, comorbidities etc

8. **Have you modified the MR/CT scan strategy for liver cancer staging, tumor response evaluation? Yes/No**
    - If yes, what was the criteria to indicate that procedures? Please, describe/exemplify: age, comorbidities etc
9. **Have you tested COVID19 before performing or receiving a schedule for liver cancer treatment. Yes/No**
    - If yes, how many tests have you done and how many of them were positive?
    - If yes, what was the criteria to indicate the test?
10. **Have you had the possibility to perform liver cancer treatment during the COVID19-pandemic? Yes/No:**
    - If yes, which kind of treatment have you been able to perform? Please describe.
    - If yes, what was the criteria to indicate and give priority to treatments? /example: age, comorbidities, tumor burden, type of treatment
    -

Clinical Research - Related to COVID19 pandemic ***-Optional information-***

(Only applicable for center that has Clinical Trials activity)

11. **Have you been able to maintain clinical trials activity without changes? Yes/No**
    - If yes, please describe the changes
    - If no, please describe the reason (Human resource, feasibilities)
12. **Have you been able to recruit any new patient into a clinical trial? Yes/No**
    - If yes, was the recruitment rate similar as you usually have?
    - If no, which was the reason?

13. **Have you performed virtual visits by video or phone calls? Yes/No**
14. **Have you been forced to delay any visit (not transformed into virtual)? Yes/No**
    - If yes, what was the criteria to delay the visits? Please, describe/exemplify: age, comorbidities etc

For aim 2-4, anonymized individual data is requested and the patients need to sign an informed consent, if the patient is unconscious a verbal consent from a relative is needed. The study will be approved by the Ethics Committee of the Hospital Clinic Barcelona. After its approval the study will be open to all the centers willing to participate.

Study Cohorts:

The study will have 3 cohorts of patients and the inclusion criteria will be the following:

1. **Cohort A: Newly detected liver mass during COVID-19 pandemic:** Patients >= 18 years old, the COVID19 infection should be acquired prior to liver cancer diagnosis, new diagnosis of hepatocellular carcinoma or intrahepatic cholangiocarcinoma in the context of COVID19 infection.

2. **Cohort B: Hepatocellular carcinoma Patients:** Patients >= 18 years old, diagnosis of hepatocellular carcinoma done before the date of COVID19 infection.

3. **Cohort C: Intrahepatic Cholangiocarcinoma Patients:** Patients >= 18 years old, diagnosis of Cholangiocarcinoma done before the date of COVID19 infection.

The following variables are requested in each cohort:

Cohort A: New Liver cancer diagnosis in the context of COVID19 infection.

Age, gender, etiology, BCLC stage at the time of COVID19 diagnosis. Time between detection, diagnosis, staging and first-liver cancer treatment and outcome (alive, COVID19-related death, death-not related to covid19).
If the patient received COVID19 treatment (type of treatment and date of start/finish)

Cohort B: Hepatocellular carcinoma Patients:

a. **HCC Patients under non-systemic treatment**:

Age, gender, etiology, BCLC at the time of COVID19diagnosis, date of COVID19 infection, HCC treatment received before COVID19 diagnosis (resection, percutaneous treatment, locoregional treatment others), date of HCC treatment, HCC treatment stopped-delayed due to COVID19 (yes/no) and outcome [tumor evolution (progression, response) and patient evolution (alive, COVID19-related death, death-not related to COVID19).

If the patient received COVID19 treatment (type of treatment and date of start/finish).

b. **HCC Patients under systemic treatment**:

Age, gender, etiology, BCLC at the time of COVID19 diagnosis, treatment received before COVID19 diagnosis (sorafenib, lenvatinib, regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab, others), date of COVID19 infection, current systemic therapy (sorafenib, lenvatinib, regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab, others), included in a trial (yes/no and phase 1-2 vs 3) date of HCC treatment start, HCC treatment stopped-delayed due to COVID19 (yes/no) and outcome [tumor evolution (progression, response) and patient evolution (alive, COVID19-related death, death-not related to covid19).

If the patient received COVID19 treatment (type of treatment and date of start/finish)

Cohort C: Intrahepatic Cholangiocarcinoma Patients

a. **Intrahepatic cholangiocarcinoma Patients under non-systemic treatment**:

Age, gender, presence of chronic liver disease and if yes, etiology, stage according to TNM 8th edition and according tumor burden (size larger tumor, liver only yes/no, vascular invasion yes/no, multifocal yes/no, adenopathy yes/no) at the time of COVID19 diagnosis, date of COVID19 infection, treatment received before COVID19 diagnosis (resection, percutaneous treatment, locoregional treatment others), date of iCC treatment, iCC treatment stopped-delayed due to COVID19 (yes/no) and outcome [tumor evolution (progression, response) and patient evolution (alive, COVID19-related death, death-not related to COVID19).

If the patient received COVID19 treatment (type of treatment and date of start/finish)

b. **Intrahepatic cholangiocarcinoma Patients under systemic treatment**:

Age, gender, presence of chronic liver disease and if yes, etiology, stage according to TNM 8th edition and according tumor burden (size larger tumor, liver only yes/no, vascular invasion yes/no, multifocal yes/no, adenopathy yes/no) at the time of COVID19 diagnosis, date of COVID19 infection, treatment line (first, second or third) and previous systemic therapies (GemCis, GemOx, FOLFOX, investigational drugs), current systemic therapy, date of start of current systemic treatment, iCC treatment stopped-delayed due to COVID19 (yes/no) and outcome [tumor evolution (progression, response) and patient evolution (alive, COVID19-related death, death-not related to covid19).

If the patient received COVID19 treatment (type of treatment and date of start/finish)

All centers must answer the survey. The centers will be part of the entire study or in part of it according to the population they contribute with (HCC and/or iCC).

Statistical analysis

Categorical variables will be described as frequencies and percentages and continuous variables as median and interquartile ranges (IQR). Comparisons between two groups for quantitative or ordinal variables were assessed by Mann–Whitney U test. Fisher's exact test will used to compare categorical variables. Survival rates and curves will be determined using the Kaplan-Meier method. Analysis will be done censoring survivals at the time of last follow-up or death. Wilcoxon signed-rank test was used to compare paired continuous variables.

Dissemination of the results and Authorship:

All centers which send the survey will be part of the study. The number of authors will be defined according to the number of patients included, Journal rules and implication in the project. The statistician will be excluded for the rule of patients included and will have an independent slot.

The 3 authors who have the conception of the project (Massimo Iavarone, Alejandro Forner and Maria Reig) will be the first, senior and/or corresponding authors of the studies they have coordinated. They could delegate the first position to young researchers involved in the study.

If the number of patients is large, the proposal will report the results of the study in the following manuscripts:

1- Report of the results of the survey and Cohort A
2- Report of the results of Cohort B
3- Report of the results of Cohort C

If the number of patients is low, we will report all the results in 1- 2 manuscripts.

Centers which only answer the survey:

- If there are no restrictions in term of number of authors, they will have 1 author position in the manuscript that is focus on the results of the survey and Cohort A.
- if the Journal has a limited number of authors, 1 member of the center will be a collaborator in this manuscript.

For those centers which send the survey and include patients in the different cohorts:

- If there are no restrictions in term of number of authors, they will have 1 author position in the manuscript that is focus on the results of the survey and the number of additional authors per center and position in the manuscript will be defined according to the number of patients include in Cohort A.
- They will be authors of the cohort where they included patients.
- If there are no restrictions in term of number of authors, the number of authors per center and position in the manuscript will be defined according to the number of patients included.
- If the Journal has a limited number of authors, all centers will have 1 place as an author and the others will be recognized as a collaborator in this manuscript.