Research article

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Assessing the impact of COVID-19 on liver cancer management (CERO-19)

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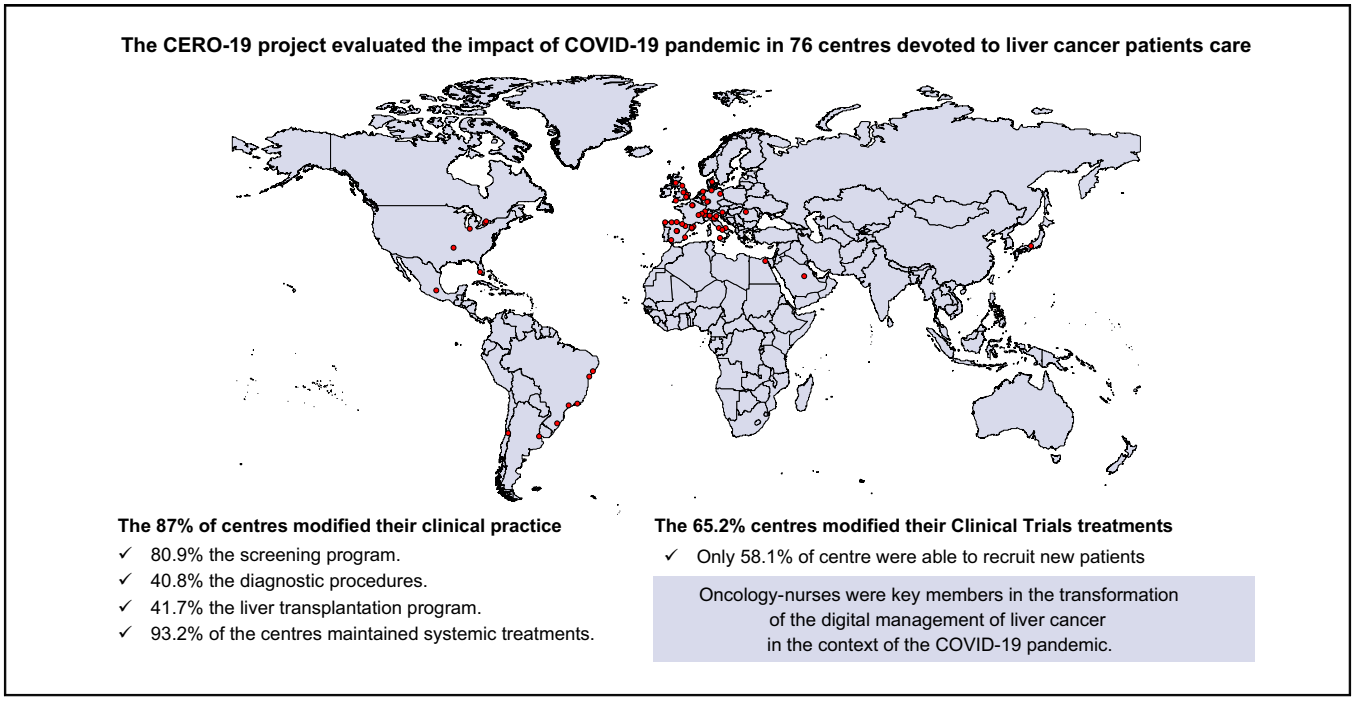
Graphical abstract



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Highlights

- The coronavirus disease 2019 (COVID-19) pandemic had a worldwide impact on liver cancer management.
- Screening programmes were modified or cancelled in 80.9% of participating centres.
- All but systemic treatments were cancelled or delayed in almost all centres.
- Phone call visits were the tools for patient follow-up during the first wave.
- The role of the nurses was key to maintaining clinical practice and clinical trials.

Lay summary

The coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges to healthcare systems globally. Herein, we assessed the impact of the first wave pandemic on patients with liver cancer and found that routine care for these patients has been majorly disrupted, which could have a significant impact on outcomes.

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Assessing the impact of COVID-19 on liver cancer management (CERO-19)

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Background & Aims: The coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges to healthcare systems and it may have heavily impacted patients with liver cancer (LC). Herein, we evaluated whether the schedule of LC screening or procedures has been interrupted or delayed because of the COVID-19 pandemic.
Methods: An international survey evaluated the impact of the COVID-19 pandemic on clinical practice and clinical trials from March 2020 to June 2020, as the first phase of a multicentre, international, and observational project. The focus was on patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma, cared for around the world during the first COVID-19 pandemic wave.
Results: Ninety-one centres expressed interest to participate and 76 were included in the analysis, from Europe, South America, North America, Asia, and Africa (73.7%, 17.1%, 5.3%, 2.6%, and 1.3% per continent, respectively). Eighty-seven percent of the centres modified their clinical practice: 40.8% the diagnostic procedures, 80.9% the screening programme, 50% cancelled curative and/or palliative treatments for LC, and 41.7% modified the liver transplantation programme. Forty-five out of 69 (65.2%) centres in which clinical trials were running modified their treatments in that setting, but 58.1% were able to recruit new patients. The phone call service was modified in 51.4% of centres which had this service before the COVID-19 pandemic (n = 19/37).
Conclusions: The first wave of the COVID-19 pandemic had a tremendous impact on the routine care of patients with liver cancer. Modifications in screening, diagnostic, and treatment algorithms may have significantly impaired the outcome of patients. Ongoing data collection and future analyses will report the benefits and disadvantages of the strategies implemented, aiding future decision-making.
Lay summary: The coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges to healthcare systems globally. Herein, we assessed the impact of the first wave pandemic on patients with liver cancer and found that routine care for these patients has been majorly disrupted, which could have a significant impact on outcomes.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has impacted all levels of society. In the absence of an available vaccine or therapy, healthcare authorities have mostly focused their efforts on reducing viral transmission to reduce the rate of COVID-19 pandemic-related deaths.

Although recent studies have described the mortality in cancer patients diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as reaching 28.9–33.6%, a relatively modest 4.4–5.5% has been reported in patient cohorts including hepatobiliary cancers.[1,2] In the case of hepatocellular carcinoma (HCC) and some intrahepatic

cholangiocarcinoma (iCCA), almost all patients also have underlying cirrhosis, Marjot *et al.*[3] and Iavarone *et al.*[4] reported that baseline liver disease stage and alcohol-related liver disease were independent risk factors for death from SARS-CoV-2 infection, increasing the risk of hepatic decompensation. Even in the absence of these significant complications in patients with liver cancer (LC) infected with SARS-CoV-2, treatments have been suspended or delayed, in line with national or institutional policies. As an example, Amaddeo *et al.*[5] have described how LC care changed in the metropolitan area of Paris alongside the evolution of the COVID-19 pandemic.

In addition to those infected by SARS-CoV-2, non-infected patients with LC may have also been affected by the COVID-19 pandemic-related modifications in clinical practice and the priorities established for population healthcare. For future decision-making, it is relevant to evaluate the consequences of interrupting or delaying the schedule of LC screening programmes or treatments, as established before the COVID-19 pandemic, on LC prognosis.

This is a multicentre, international, and observational project, the Liver Cancer Outcome in the COVID-19-pandemic (CERO-19) project, focused on patients with HCC or iCCA, managed during the COVID-19 pandemic. We describe here the results of the first part of the project, which was a survey to evaluate the impact of COVID-19 pandemic on international clinical practice and research.

Materials and methods

Centres around the world were invited to participate. The project was promoted through the European Network for the Study of Cholangiocarcinoma (ENS-CCA) network, organisers' personal Twitter accounts, and the Barcelona Clinic Liver Cancer (BCLC) account for a period of 4 weeks before starting the survey. The organisers of the project (MI, AF, and MR) elaborated the survey and 5 independent LC experts reviewed/tested it and sent their suggestions (JCN, GZ, LR, BS, JBruix). The survey had mandatory sections focused on clinical practice (related and non-related to COVID-19) and an optional section focused on clinical research. Survey and protocol details are summarised in the Supplementary material.

Statistical analysis

The answers to the survey were expressed as absolute frequencies and percentages (%). The survey was developed and performed using the SurveyMonkey® platform. Raw data and results were directly extracted from the platform. SAS software® (version 9.4; SAS Institute, Cary, NC, USA) was used when more accurate approaches were required and to generate the figures.

Results

The LC centres taking part in the survey

The survey was open from May 2020 to June 2020. Ninety-one centres were contacted or expressed interest to be involved and 81 survey responses were received (89% response). Five were excluded: 4 because of duplication and 1 because their data were incorporated with those from another centre.

The final analysis was based on information from 76 centres, including centres in Europe, South America, North America, Asia, and Africa (73.7%, 17.1%, 5.3%, 2.6%, and 1.3% respectively; Table 1). In combination, these centres cared in the pre-pandemic period for a total of 9,602 new LC patients per year, with a median (IQR) of 80 new visits/year (46.5–150), with the majority (77%) registered in Europe. In 2019, these centres, carried out 39,739 and 6,347 follow-up visits for HCC and iCCA, respectively (Tables S1 and S2). The profiles of the centres included in the survey were heterogeneous: 76.3% of them included nurses in their team and 47.4% had phone call visits as part of their clinical practice before the COVID-19 pandemic (Table S2).

Table 1. Distribution of the percentage of centres by continent included in the analysis.

Continent	Centres, %
Europe	73.7
South America	17.1
North America	5.3
Asia	2.6
Africa	1.3

LC management modification during the first wave of the COVID-19 pandemic

Eighty-seven percent of the centres (n = 66) modified their clinical practice during the COVID-19 pandemic, with almost half (48%) decreasing the number of physicians devoted to managing LC patients. Figure 1 describes the main areas where the clinical practice was modified: 80.9% modified the screening programme, 73.5% changed the imaging follow-up in LC patients after treatment, 63.2% rescheduled surgical treatments, and 52.9% amended locoregional therapies. Figures S1 and S2 describe the percentage of areas in which clinical practices were modified according to continent. Testing for SARS-CoV-2 infection before an outpatient visit for LC management was performed in 21.1% of centres (n = 16/76), increasing to testing in 76.3% (n = 58/76) before any pre-planned patient admission for LC treatment. Table 2 reports the criteria used for requesting a SARS-CoV-2 infection test in the different centres.

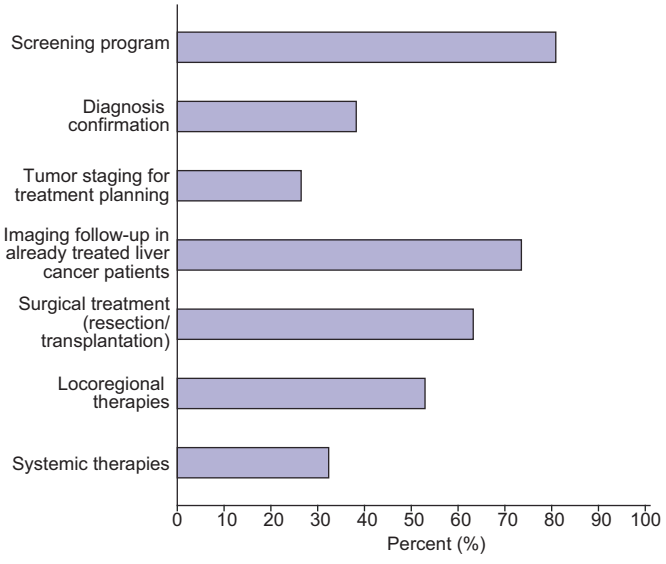

Fig. 1. Areas in which pre-pandemic clinical practices were modified expressed as percentages. Grey bars represent the percentage of centres that had to modify their clinical practice in the main areas mentioned in the left of the figure.

Table 2. Description of the criteria used for testing SARS-CoV-2 infection in clinical practice reported by the different centres.

Criteria for testing SARS-CoV-2 infection	Before any pre-planned patient admission for liver cancer treatment	Before doing an outpatient visit for liver cancer treatment
Number of centres which answer this part of the survey (n)	58/76 centres	16/76 centres
SARS-CoV-2 infection clinical suspicion	35 (57.4)	13 (81.3)
Pulmonary infiltrates suggestive of COVID-19 by imaging done for cancer work-up in otherwise asymptomatic patient	25 (41)	10 (62.5)
COVID-19 screening before hospital admission	47 (77.1)	9 (56.3)
COVID-19 screening before treatment indication	22 (36.1)	7 (43.8)
Others	9 (14.8)*	1 (6.3)*

Data are presented as n (%), unless otherwise indicated. *COVID-19 before invasive procedures. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Ten centres reported no modification of their clinical practice attributable to COVID-19 pandemic. Of note, despite these centres continuing to offer their full range of LC care, 3/10 of these centres reported that patients were reluctant to come to the hospital because of concerns about the possibility of SARS-CoV-2 infection.

Diagnostic strategy and staging procedures during the first wave of the COVID-19 pandemic

Based on the 76 centres, 40.8% modified their diagnostic procedure requests and timing (biopsy and imaging technique) during the COVID-19 pandemic. A total of 39.5% modified the magnetic resonance/computed tomography scan strategy for LC staging or treatment response evaluation. Figure 2 describes the criteria used to adhere to the pre-defined schedule of diagnostic procedures. The most frequent criteria were suspected tumour stage in 75% and degree of cancer suspicion in 68.8% of the centres. The most frequent criteria used to adhere to the staging procedures were the suspected tumour stage in 63.6% and the degree of cancer suspicion in 48.5% of the centres (these not shown in Figure 2).

In 28% of centres, at least 1 asymptomatic SARS-CoV-2 infected patient was incidentally diagnosed as a result of a radiology test done for the oncology indication.

Treatments options during the first wave of the COVID-19 pandemic

Despite the modifications made during the COVID-19 pandemic, 96% of the centres maintained their ability to perform LC treatments. From 48 centres with a liver transplantation (LT) programme before the COVID-19 pandemic, 28 (58.3%) (n = 28/48) of the centres did not modify their LT activity, 60.8% of centres (n = 45/76) were able to perform surgical resections, 68.9% (n = 51/76) percutaneous treatments, and 81.1% (n = 60/76) locoregional treatments.

The option to initiate systemic treatment was maintained in 93.2% of the centres.

Figure 3 describes the criteria adopted to maintain an unaltered therapy schedule. The survey was not designed to evaluate on an individual basis the criteria adopted by each centre.

In 50% of the centres (n = 38/76) curative and/or palliative treatments for LC were cancelled at least in 1 patient for each centre because of SARS-CoV-2 infection.

Phone call visits, face-to-face visits, and the role of nurses during the first wave of the COVID-19 pandemic

Based on 76 centres, a phone call visit service was part of routine clinical practice before the COVID-19 pandemic in 37 centres. It was modified in 19 of these centres (51.4%): an increase of the number of calls (more days and/or more hours/day) was the

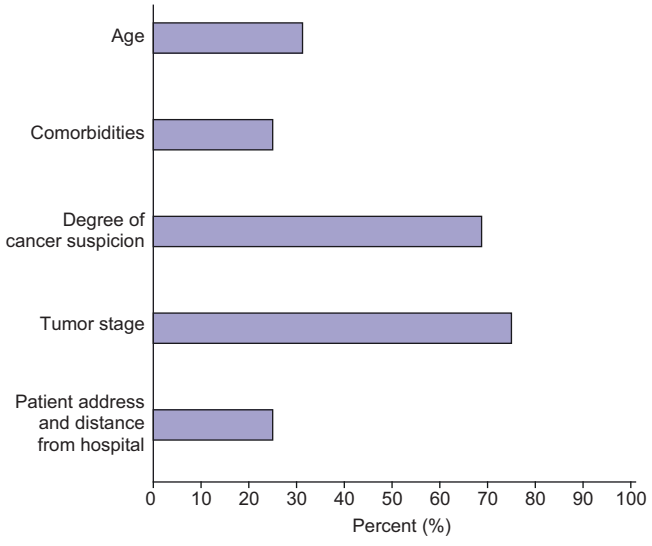

Fig. 2. Criteria used to maintain pre-defined schedules of diagnostic and staging procedures. Grey bars represent the percentage of centres that used each of the criteria mentioned in the left of the figure to maintain pre-defined schedules of diagnostic and staging procedures.

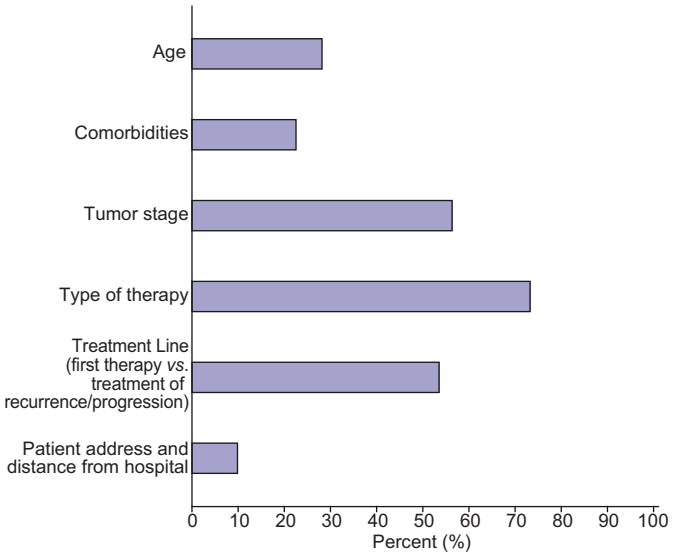

Fig. 3. Criteria used to maintain the therapy schedule unaltered. Grey bars represent the percentage of centres that used each of the criteria mentioned in the left of the figure to maintain their therapy schedule unaltered.

Table 3. Description of the criteria used for delaying visits in the clinical trials setting reported by the different centres.

Criteria	Centres, n (%)
Number of centres which answered this part of the survey (n)	69
Number of centres which answered 'yes' to this part of the survey (n)	20 (29.9)
Age	9 (35.5)
Comorbidities	11 (45.8)
Tumour stage	6 (25)
Clinical trial phase	6 (25)
Treatment line (first therapy *vs.* treatment of recurrence/progression)	8 (33.3)
Patient address and distance from hospital	10 (41.7)

most frequent modification in 84% of the centres, whereas 7 centres (17.9%) introduced phone call visits as a new practice during the COVID-19 pandemic.

Fifty centres included the type of visit (first *vs.* follow-up visit) and 53 centres the disease status (stable disease *vs.* progressive disease) in their criteria guiding decisions on whether to convert a face-to-face visit into a phone call visit (68.9% and 71.6%, respectively). The age of the patient and the patient address/distance to the hospital were adopted as criteria for phone call visits in 20 and 24 centres, respectively.

Focused on the 58 centres which had nurses integrated into the LC team, the liver-oncology nurses made decisions regarding face-to-face *vs.* phone call visits in 30.1% of the centres and organising the visits in 70.3%. The nurses undertook the phone call visits in 62.5%, to answer questions about treatment or follow-up events.

Treatments in clinical trials in LC patients during the first wave of the COVID-19 pandemic

Of the 69 (90.8%) centres which answered this part of the survey, 45 (65.2%) of them had modified their management of clinical trials activity. Human resources, feasibility, and sponsor's recommendation were the main reasons for these modifications.

Despite the modifications in management of clinical trials activities, 58.1% of the centres were able to recruit new patients during the COVID-19 pandemic, but only 9.7% of centres declared that the recruitment rate was similar to that before the pre-COVID-19 pandemic. In 46.2% of centres virtual visits by video or phone calls were done, and 29.9% of centres were forced to postpone visits (not transformed into virtual). Table 3 describes the most frequent criteria for delaying treatments in clinical trials visits.

Discussion

To ameliorate the impact of the COVID-19 pandemic on LC, several organisations advised multiple recommendations based on expert opinion data at the beginning of the first wave.[6–9] The results of this survey highlight the potential clinical significance of the implemented modifications, predicting a likely major impact of the COVID-19 pandemic on outcomes, given the magnitude of the disruption in patient care – from screening to diagnosis, staging, and treatment.

According to the present results, all areas of clinical practice were modified during the COVID-19 pandemic first wave. The major changes related to the suspension of screening programmes and surgical treatments (mainly LT), the decrease of face-to-face visits and the growing role of liver-oncology nurses as key members in the transformation of the digital management of LC in the context of the COVID-19 pandemic.

Notably, the approach maintained in almost all centres (93.2%) was systemic treatment of patients with LC. This may have been associated with the stage of the disease, stage being one of the priority criteria identified at the time of maintaining the planned schedule. The fact that the most widely used systemic therapies were oral tyrosine kinase inhibitors, which can be self-administered by the patient at home rather than requiring a visit to the hospital, is also likely to have played a role.

Unfortunately, the disruption in screening programmes as a result of this healthcare crisis raises the possible consequence of a shift towards a more advanced stage at diagnosis. Additionally, delays of interventional procedures such as transplant, resection, or ablation may impact on tumour progression, dissemination, and ultimately prognosis. Previous studies[10,11] indicated that progression associated with poorer outcomes occurred as a consequence of waiting or delaying interventions beyond 2 months. Hanna *et al.*[12] described a significant association between cancer treatment delay and increased mortality for 13 out of 17 indications analysed, although LC was not one of those analysed. Rich *et al.*[13] have recently shown that the rate of liver tumour growth at early stages is very heterogeneous. This may be something that could be further evaluated in the context of screening ultrasound delays because of the COVID-19 pandemic. Obviously, tumour stage at diagnosis will be one of the most relevant, as tumour growth is assumed to be faster along its evolution.[14–16] We should also keep in mind that the detection of changes in outcome or tumour progression during the delayed interventions may translate into a marginal impairment without clinically relevant consequences. It must also be noted in advance that any suggestion we raise in the future will not have the background that would be provided by a randomised controlled trial comparing conventional timing *vs.* delayed intervention. Despite this limitation, our future data will be instrumental in the identification of those areas where the changes induced by the pandemic have been beneficial or detrimental. If the outcome at any step of the healthcare pathway is clearly worse, we would have an estimation of the deleterious consequences of COVID-19 pandemic beyond the infection itself. This may inform us on the most appropriate measures to be adopted in the future; either while this pandemic persists or repeats, as is happening with the current second wave, or should another public health crisis emerge in the future.

The move from face-to-face visits to phone call visits encouraged during the pandemic may improve patient care going forward, being potentially acceptable and preferable in some patients. The pandemic also reinforced the role of nurses,[17,18] who were already part of LC teams in 76.3% of the centres, with their activity and responsibility appearing to have increased. In some groups, where nurses were not previously part of the team, the COVID-19 crisis has promoted investment in their growing roles, in education, and counselling of patients and their families.

The benefits and challenges related to the use of remote visits by nurses and physicians for cancer patients will be seen in the next months/years.[17–19] Not all patients and families will be successfully served by remote visits and our data already reveal that there are several characteristics that may favour face-to-face or phone call visits. The age of the patient (which is a factor associated with severity in SARS-CoV-2-infected patients in cancers other than LC)[2] as well as the patient address and

distance to the hospital (which could be associated with increased risk of exposure on their way to and from the hospital) were the less frequent factors considered to switch from a face-to-face visit to a phone call visit in clinical practice. However, in patients included in treatments in clinical trials we observed that younger age of the patients and lack of comorbidities were criteria to favour phone call visits. This difference could be mainly related to the type of information to be given during a conventional clinical practice visit related to diagnosis or/and tumour progression or the type of visit in the setting of treatments in clinical trials with experimental agents at risk of adverse events (first or follow-up visit). Indeed, as recruitment into treatments in clinical trials had been impacted (only 9.7% of centres maintained the same recruitment rate they had before the pandemic), almost all the visits within treatments in clinical trials have been devoted to follow-up assessments rather than new patient recruitment. As previous studies had shown,[20,21] maintaining treatments in clinical trials activities requires a great effort and reorganisation of the LC team, to define a protocol to continue with these activities while protecting patients from contracting SARS-CoV-2 infection.

The results of this survey describe the major changes that occurred in LC management in 76 high-volume centres around the world. However, 73.7% of centres that answered the survey were from Europe. In addition, the Italian and Spanish centres represented 55.4% of the European centres. Thus, the results of the survey could be overestimated by these 2 countries which were severely affected by the first wave. Table S3 describes the details of Europe without Italy and Spain and the data only from Italy and Spain, respectively.

In summary, despite the fact that the survey did not focus on individual patient information, the result of the survey reflects the consequence of the first wave of the COVID-19 pandemic. These modifications in LC management may have significantly impacted the outcome of patients and Public Health policy. The results of this survey may induce to predict that the profile of patients diagnosed after the first wave could be more advanced than we usually have in the pre-pandemic era, and will help us to identify confounding factors at the time of analysing the next phase of the CERO-19 project. Future analyses will provide invaluable information about the clinical effectiveness of the strategies that have been implemented during this devastating health crisis.

Abbreviations

BCLC, Barcelona Clinic Liver Cancer; CERO-19, Liver Cancer Outcome in the COVID-19-pandemic Project; COVID-19, coronavirus disease 2019; ENS-CCA, European Network for the Study of Cholangiocarcinoma; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; LC, liver cancer; LT, liver transplantation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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Conflict of interest

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Authors' contributions

Conceived and organised the study, planned the data management, organised data collection for the steering centre, wrote the manuscript and figures: M.R., M.I. Designed, reviewed, and tested the survey: M.R., M.I., A.F., J.C.N., G.Z., L.R., B.S., J.Bruix. Planned and realised the statistical analyses: V.S. Significantly contributed to the writing of the manuscript: S.M.-M., M.R., M.I., A.F., J.C.N., G.Z., L.R., B.S., H.R., J.B. Revised and edited the manuscript and gave their final approval before submission: all authors

Data availability statement

Research data are not available for sharing given their confidential nature.

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Supplementary data

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