

DR. FRANCESCA ROMANA PONZIANI (Orcid ID : 0000-0002-5924-6238)

PROF. ALESSIO AGHEMO (Orcid ID : 0000-0003-0941-3226)

DR. GIUSEPPE CABIBBO (Orcid ID : 0000-0002-0946-3859)

DR. MARIO MASARONE (Orcid ID : 0000-0003-0550-8201)

DR. SARA MONTAGNESE (Orcid ID : 0000-0003-2800-9923)

DR. SALVATORE PETTA (Orcid ID : 0000-0002-0822-9673)

DR. FRANCESCO PAOLO RUSSO (Orcid ID : 0000-0003-4127-8941)

DR. QUIRINO LAI (Orcid ID : 0000-0003-1487-3235)

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**Management of liver disease in Italy after one year of the SARS-CoV-2 pandemic:
a web-based survey**

Francesca Romana Ponziani^{1,2}, Alessio Aghemo^{3,4}, Giuseppe Cabibbo⁵, Mario Masarone⁶,
Sara Montagnese⁷, Salvatore Petta⁸, Francesco Paolo Russo⁹, Quirino Lai¹⁰

on behalf of the AISF COVID-19 survey group

*1 Internal Medicine and Gastroenterology – Hepatology Unit, Fondazione Policlinico Universitario
Agostino Gemelli IRCCS, Rome, Italy*

2 Università Cattolica del Sacro Cuore, Rome, Italy

*3 Division of Internal Medicine and Hepatology, Humanitas Clinical and Research Center IRCCS,
Rozzano, Italy*

4 Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

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5 Section of Gastroenterology & Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy

6 Internal Medicine and Hepatology Division, Department of Medicine, Surgery and Odontostomatology, "Scuola Medica Salernitana", University of Salerno

7 Department of Medicine, University of Padova, Padova, Italy

8 Section of Gastroenterology and Hepatology, PROMISE, University of Palermo, Italy

9 Department of Surgery, Oncology and Gastroenterology, University Hospital Padua, Italy

10 General Surgery and Organ Transplantation Unit, Sapienza University of Rome

Correspondence to

Francesca Romana Ponziani MD PhD

Internal Medicine and Gastroenterology – Hepatology Unit

Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Università Cattolica del Sacro Cuore - Rome - Italy

e-mail: francesca.ponziani@gmail.com

phone: +393471227242

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has severely limited the clinical activity of most hospitals around the world. A previous survey of the Italian Association for the Study of the Liver (AISF) has demonstrated a negative impact of the first pandemic wave on all in-patient and outpatient hepatology activities.¹

Like other countries, Italy has subsequently experienced a second and a third wave, which occurred in November 2020 and in March 2021, respectively.² During the second and third wave many hospitals had already developed emergency management plans³ and improved knowledge on the management of mild-moderate COVID19 disease was available. However, it is unknown whether this approach has translated into improved care of patients with chronic liver diseases.⁴

The present study aims to evaluate the activity of Italian hepatological centers during the second and third waves, also by comparison with the first wave.

MATERIALS AND METHODS

An online survey was sent by email to all the active AISF members. The questionnaire was available from January 15 to March 15, 2021. The same questions were used as in the March 2020 survey¹ to allow comparisons between the activities of Italian hepatological centers between the first and the second/third waves. However, new questions were added concerning the re-organization of the centers based on previous pandemic experience.

At the end of the survey period, invalid/redundant answers and those of responders who did not consent to scientific use of the data were discarded. For each question, the percentages were calculated on the total number of responses from the centers where that service or activity was available.

Statistical analysis

Data were analyzed and reported as median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical ones. Comparisons between the frequency of responses to the questionnaires relative to the first and the second-third waves were performed using the chi-squared or Fisher's exact test, as appropriate. Variables with a

$p < 0.05$ were considered statistically significant. The R statistics program (version 3.6.2) was used for all analyses.

RESULTS

Fifty-eight questionnaires were received, of which three were discarded. Thus, 55 questionnaires were available for analysis.

Data were obtained from 55 different units, present in 43 Italian hospitals (25 [45.5%] north, 16 [29.1%] center, 14 [25.5%] south and isles). The responding centers corresponded to the 43.3% (55/127) of the entire number of centers receiving the survey.

The responders were mainly working in gastroenterology or internal medicine units and thirty-eight (69.1%) were located in a university hospital. A liver transplant (LT) center was available in about one-third of the facilities.

After the first wave, clinical activities returned to normal in 46/55 (79.3%) cases. At the beginning of the second/third pandemic waves, 24 (43.6%) participants perceived to be fully prepared and 23 (41.8%) to be only partially prepared to handle the situation. An *ad hoc* emergency plan was present in 21 (38.2%) hospitals, while in 20 (36.4%) a more informal re-organization was reported. Seven (12.7%) centers were converted to COVID-hospitals during the second/third pandemic waves.

Since the beginning of the pandemic, medical activities have been stopped because of SARS-CoV-2 infection of the healthcare personnel in 16 (29.1%) centers. Twenty-one (38.2%) of the survey participants have been, at some stage transferred to departments dedicated to COVID19-patients and for 61.9% of them this has impinged on their ability to look after patients with liver disease.

Modifications of inpatients wards, day hospital/services and outpatients activities

While clinical and hepatological activities continued, significant changes were reported. In 21/52 (40.4%) cases, inpatients wards had reduced beds available for non-COVID19 patients, while in 12/52 (23.1%) cases, the wards were completely dedicated to the assistance of COVID19 patients, similarly to what happened during the first wave (40.9% $p=0.97$ and 33.3% $p=0.17$,

respectively) (Figure 1). Conversely, a lower proportion of day hospital, day service activities, and outpatient reviews for non-oncology patients were reduced or stopped compared to the first wave (Figure 1).

Non-oncology outpatient visits, during the first wave, were mainly interrupted except for urgent cases, while during the second wave, this activity was not heavily affected (Figure 1). Reviews of patients with chronic non-cirrhotic liver disease (69.1%) or those with compensated cirrhosis (54.5%) were limited, while 74.55% of centers continued on-site follow-up for patients with decompensated cirrhosis. Although a substantial number of centers (65.5%) adopted telemedicine, it was implemented in the institutional organization in only 25% of them. The median percentage of patients who missed semiannual surveillance was 20% (interquartile range 10-40); similarly, 20% (interquartile range 5-50) did not attend the previously scheduled clinical evaluation. Only a small number of centers implemented decentralized care in collaboration with general practitioners (7.3%).

Changes in diagnostic and follow-up imaging activities

Diagnostic and follow-up imaging activities were reduced or suspended in 21/53 (39.6%) centers, compared to 71.0% during the first wave ($p=0.0001$). Ultrasound services reduced their activity in 18 (32.7%) centers, being dedicated to cirrhotic patients in 5/55 (9.1%). Endoscopic screening for portal hypertension was reduced or suspended in 31/52 (59.6%) centers, esophageal varices band-ligation in 29/51 (56.9%) of them, TIPS placement in 24/40 (60.0%). These rates were significantly lower compared to the first wave (76.3%, $p<0.00001$; 64.9%, $p=0.006$; 63.1%, $p=0.004$, respectively). Paracenteses continued to be performed in 43/53 (81.1%) centers compared to 69.6% ($p=0.12$) during the first wave.

Pre-procedural screening for SARS-CoV-2 infection was available in 39 (70.9%) centers, based on the antigenic nasopharyngeal swab (30.8%), molecular nasopharyngeal swab (82.1%), or serologic tests (12.8%) in varying proportions. This policy was mainly adopted for patients with scheduled day hospital, elective hospitalization, or endoscopic procedures.

Impact on antiviral treatments prescription, HCC management and liver transplant program

By contrast to the first wave (12.6%), in over half of the centers (33/55, 60.0%, $p < 0.0001$) the prescription of antiviral treatment continued.

Surgical or locoregional treatments for HCC were reduced or stopped in a significant number of centers (29/52 [55.8%] and 25/52 [48.1%], respectively), with similar rates compared to the first wave, while the prescription of systemic therapies continued in the majority (36/49 [75.5%]; Figure 2).

A small percentage of centers (14.5%) implemented home drug delivery.

Pre-LT evaluations were maintained in 41/55 (74.5%) of cases, 16/36 (44.4%) centers reduced their LT activity (Figure 2). Post-LT follow-up reviews were unaffected in 27/38 (71.1%) of the centers, while only urgent reviews were performed in 10/38 (26.3%).

DISCUSSION

This survey reports the changes in the clinical activity of Italian liver centers during the second and third waves of the SARS-CoV-2 pandemic.

As reported by over 80% of the study participants, most liver centers were prepared for a new emergency and a small number of centers were fully converted to COVID19 centers. To safely carry out procedures and hospital activities, more than 70% of the centers were equipped with screening measures. The most important elements involved in the limitation of clinical activities were the infection of health-care personnel, in about one-third of cases and, to a lesser extent, the secondment of hepatologists to COVID19 wards. This probably explains the reduction, observed also in other international centers,⁵ in the locoregional and surgical treatment of HCC, which was comparable to that of the first wave, and why the activities of day hospitals and day services have not been reduced as drastically as during the first pandemic wave. Indeed, these services have probably compensated, as far as possible, the shortage of beds in the wards. Outpatient reviews for non-oncology patients were never interrupted during the second and third waves. However, they were limited to the care of the most fragile patients, such as those with decompensated cirrhosis, safeguarding endoscopic procedures for portal hypertension, paracenteses, and the prescription of antiviral treatments, while reducing by half the assistance to patients with compensated cirrhosis or chronic hepatitis.

The growing awareness of the impact of COVID19 among patients with chronic liver diseases^{6,7} might have played a role in reducing clinical activities. As a result, nearly 20% of patients missed their scheduled clinical evaluation. Moreover, the use of telemedicine was underpowered, often informal and left to the initiative of individual doctors, as like as home drug delivery and networking with general practitioners. This might result in some patients discontinuing their follow-up (possibly the most socially and economically vulnerable) and in delays in diagnosing complications, such as HCC.

As for the potential negative impact of COVID-19 on the diagnosis and treatment of HCV, a recent international study has shown that a 1-year delay in hepatitis diagnosis and treatment could result in an additional 44800 liver cancers and 72300 deaths from HCV globally by 2030.⁸ Observing the the results of our survey, it was interesting to observe that more than half of the centers (60%) continued prescribing antiviral treatments during the second-third waves, therefore indicating that the predictions of the Markov model by Blach et al. were more severe respect to the real impact of COVID-19 on HCV elimination. Nevertheless, an impact of the pandemic waves should be taken into account in relation to the predicted elimination of HCV as a major public health threat by 2030.

Finally, our survey revealed that the SARS-CoV-2 pandemic has generated a bottleneck in the LT program, with 45% of centers reporting a reduction in their activities, without a parallel reduction in pre-LT assessments. It is likely an increase in waiting list mortality will be reported^{9,10}.

We acknowledge our study has some limitations: firstly, the small sample size and the fact that not all participants in the first wave questionnaire participated in the current study might have led to selection bias thus impinging the comparisons between first versus second/third wave responses. Nonetheless, our study raises considerable concerns about the reductions in in-patient procedures and LT activities, which are likely to have middle- and long-term morbidity and mortality consequences¹¹.

Another point to consider is the possibility of an underestimation bias in the reported data due to the non-participation of centers heavily affected by COVID19-related changes of the activities. However, the number of Italian centers involved in the study (43.3%; 55/127) appears to represent a relevant percentage of the total number of centers. Moreover, we should note that

the responding centers corresponded to the principal units of hepatology / gastroenterology present in Italy, therefore being a representative approximation of the Italian reality. Indeed, in among those who did not answer, at least 50 were AISF active members but working in peripheral centers without specific hepatological expertise.

In conclusion, the care of liver diseases was severely affected also during the second/third COVID-19 pandemic wave in Italy. Future data to quantify the weight of these consequences are strongly needed.

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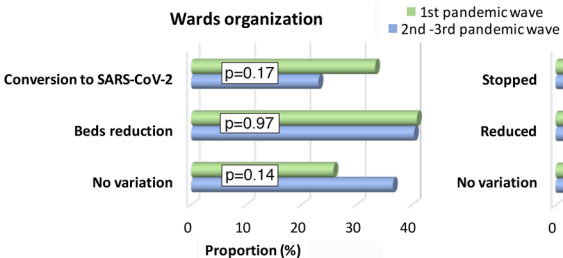
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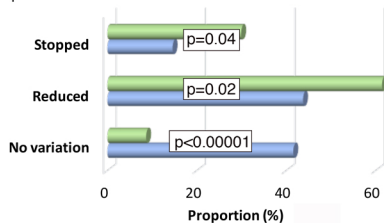
Figure 1: Re-organization of hepatology wards, day hospital/services activities and variation in non-oncologic outpatient visits during the second/third pandemic waves in the surveyed hepatology centers.

Figure 2: Management of hepatocellular carcinoma (HCC) treatments and liver transplant (LT) activities during the second/third pandemic waves in the surveyed hepatology centers.

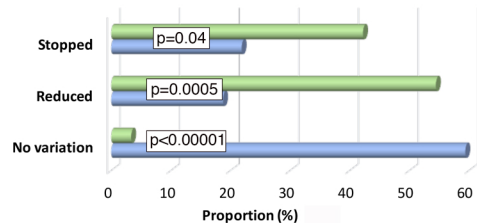
Wards organization



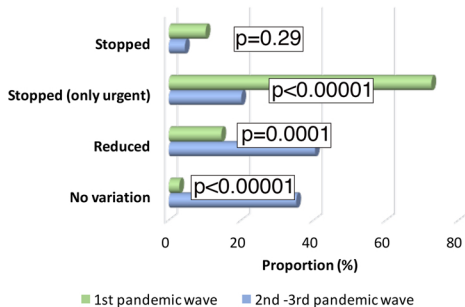
Day Hospital activities



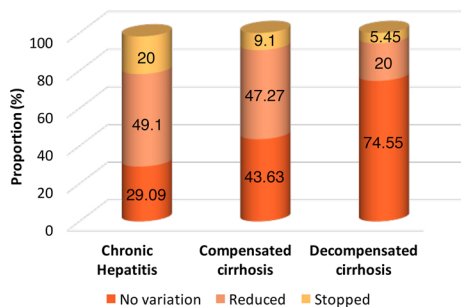
Day Services activities



Non-oncologic outpatient visits

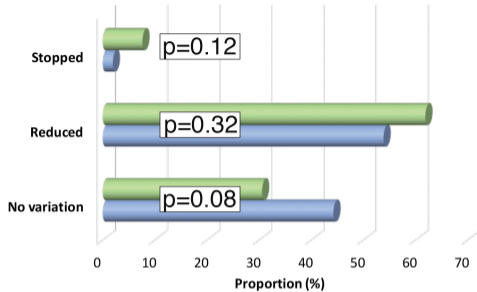
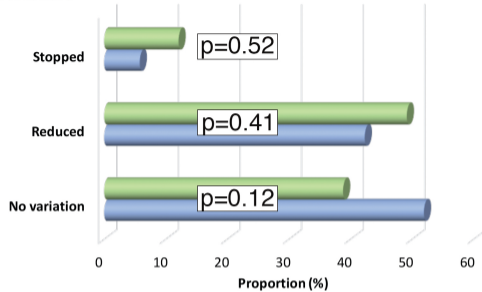
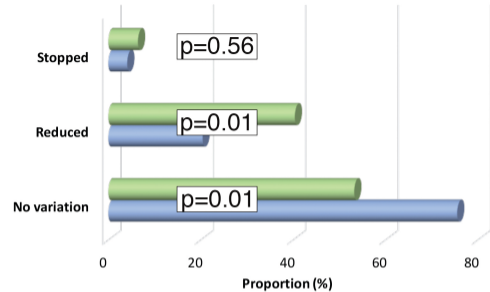
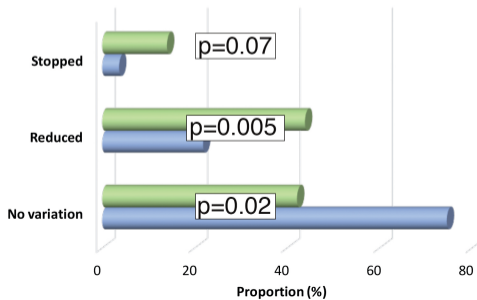
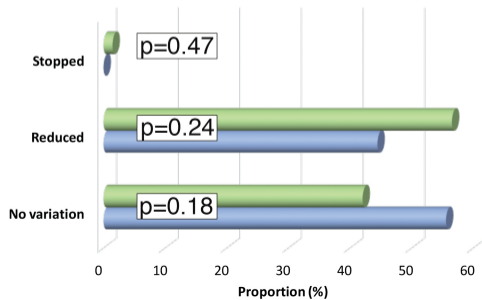


Outpatient visits during 2nd-3rd waves



HCC surgical treatments

■ 1st pandemic wave
 ■ 2nd -3rd pandemic wave

**HCC locoregional treatments****HCC systemic treatments****Pre-liver transplant evaluations****Liver transplant procedures****Post-liver transplant outpatient visits**