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Impact of COVID-19 on Incidence, Treatment, and Survival of Patients with Hepatocellular Carcinoma in the Netherlands

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Brief Report

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Abstract

Objective: The impact of the coronavirus disease 2019 (COVID-19) on hepatocellular carcinoma (HCC) care is unclear. This study reports on HCC patterns during the COVID-19 pandemic in the Netherlands.

Methods: Patients diagnosed with HCC between 2017 and 2020 were identified from the Netherlands Cancer Registration. Monthly incidence rates were compared between 2020 and 2017–2019. Patient, tumor, process, and treatment characteristics and survival were compared between 2020 and 2017–2019, and between COVID-high (April and May 2020) and COVID-low (June and July 2020) months.

Results: The incidence of HCC was lower in May 2020 (IRR 0.56, $P = 0.001$) and higher in June 2020 (IRR 1.32, $P = 0.05$) compared to the same months in 2017–2019. In 2017–2019, 2134 patients presented with HCC, compared to 660 in 2020. Time-to-treatment was shorter in 2020 (median 60 vs. 70 days, $P < 0.001$). The percentage of patients undergoing any treatment did not differ, yet if treatment was not performed this was more commonly due to comorbidity in 2020 (52 vs. 39%, $P < 0.001$). No other differences were found in patient, tumor, process and treatment characteristics and survival between COVID-high and COVID-low months.

Conclusions: This study demonstrated no impact of the COVID-19 pandemic on HCC patients, despite a decrease in HCC diagnoses.

Coronavirus disease 2019 (COVID-19) has had major impact on health care systems across the world. In oncological care, delays in diagnosis were observed, attributable to barriers to consulting a general practitioner for (non-specific) symptoms, delay of diagnostic evaluation, and halted screening programs for cancers.[1] Combined with potential treatment delay and decreased availability of certain treatment methods, this may have negatively impacted the prognosis of patients diagnosed with cancer during the COVID-19 pandemic.[2,3]

Globally, primary liver cancer is the second most common cause of cancer-related death. Hepatocellular carcinoma (HCC) is the most common primary liver cancer.[4] Studies thus far have shown a decreased incidence of HCC and a smaller percentage of patients being discussed at multidisciplinary team (MDT) meetings during the COVID-19 pandemic.[5,6] In addition, an increased treatment delay was observed.[5,6] However, results on the type of treatment are conflicting.[5,6] Studies on the impact on survival are currently lacking.

The collection of further evidence on the impact of the COVID-19 pandemic is essential in light of the unpredictability of the COVID-19 pandemic and potential future health care crises. Therefore, this study seeks to report on the impact of the COVID-19 pandemic on the incidence, treatment and overall survival of Dutch patients with HCC.

Methods

Study Design and Patient Inclusion

A retrospective, nationwide study was performed and reported according to the STROBE-statement and the declaration of Helsinki. The scientific committees of the Dutch Hepatocellular

& Cholangiocarcinoma Group (DHCG) and the Netherlands Cancer Registry (NCR, reference number K22.026) approved the study. The need for separate medical ethical approval was not required under the Dutch law "Wet medisch-wetenschappelijk onderzoek met mensen."

Adult patients diagnosed with HCC between 2017 and 2020 were identified from the NCR, using ICD-10 code C22.0. Patients were notified to the NCR using the Dutch National Hospital Care Registration (LBZ) containing data about hospital discharges and outpatient visits and the Dutch Nationwide Pathology Databank (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief, PALGA).[7] Specific informed consent for the study was not possible as data were processed anonymously. Patient, tumor, and treatment characteristics were collected from patient files by trained registrars. Survival data are established in the NCR by annual linkage to the Municipal Personal Records Database.

Data Collection and Definitions

Tumor stage was recorded according to UICC-TNM (Union for International Cancer Control 8th edition, pathological TNM supplemented with clinical TNM). Furthermore, recorded data included patient discussion in an multidisciplinary team (MDT) meeting with/without involvement of an expert (University Medical) center, year and month of HCC diagnosis (incidence date), and year and month of first hospital consultation (for evaluation of symptoms, or for imaging for surveillance or other indications) that led to the diagnosis (first consultation date). The presence or absence of liver cirrhosis was determined from clinical records. Registered cancer treatments for the stage at diagnosis were: surgical resection, liver transplantation, (radiofrequency or microwave) ablation, transarterial chemoembolization (TACE), systemic therapy (predominantly sorafenib), selective internal radiation therapy (SIRT), or stereotactic body radiation therapy (SBRT). Time to treatment was defined as number of days between first hospital consultation and start of (first) cancer treatment. Overall survival was defined as the time between the first consultation date and date of death. Patients were censored on February 1 2022, or earlier in case of emigration.

Statistical Analysis

For data analysis, IBM SPSS Statistics for Windows, version 26.0.0.1 (IBM Corp., Armonk, NY, USA) was used. Data were visually represented using GraphPad Prism version 8.0.2 for Windows (GraphPad Software, San Diego, CA, USA). Incidence rates were reported as diagnoses per 1 000 000 adult persons per month. To this end, the absolute number of patients diagnosed with HCC per month (based on incidence date) was divided by the number of adult inhabitants in the Netherlands on the first day of the year as determined from the Statistics Netherlands. The monthly incidence in 2020 was compared to the monthly incidence in 2017–2019 by calculating incidence rate ratios, using rate ratio function of the fmsb package, version 0.7.3, in RStudio, version 4.0.3 (Rstudio, PBC, Boston, MA, USA), and depicted visually. Subanalysis was performed according to the presence of liver cirrhosis.

Patient, tumor, process, and treatment characteristics and overall survival of patients first presenting in 2020 were compared with those presenting in 2017–2019, and patients first presenting in COVID-high months (April–May 2020) were compared with those presenting in COVID-low months (June–July 2020, based on first consultation date). Chi-squared tests were used to investigate differences between dichotomous/categorical variables. In cases of statistically significant differences between categorical variables, post-hoc testing was conducted to identify which categories were responsible for the difference. Bonferroni correction was employed to adjust the significance threshold in post-hoc testing. Student's t tests and Mann-Whitney-U tests were used to compare continuous variables, as appropriate. Survival data were compared using log-rank tests. P values < 0.05 were considered statistically significant.

Results

The annual incidence of HCC was 50.3, 53.3, 52.8, and 48.5 per 1 million adult inhabitants for 2017, 2018, 2019, and 2020, respectively. No significant difference was observed between 2020 versus 2017–2019 (incidence rate ratio [IRR] 0.93, 95% CI: 0.85–1.01, $P = 0.10$). The annual incidence of HCC occurring in patients with reported liver cirrhosis was 32.1 per 1 million adult inhabitants for 2017–2019 and 30.2 per 1 million inhabitants for 2020. The annual incidence of HCC occurring in patients without reported liver cirrhosis was 20.1 per 1 million habitants for 2017–2019 and 18.3 per 1 million inhabitants for 2020. The IRR of HCC occurring in patients with reported liver cirrhosis was 0.94 (95% CI: 0.84–1.05, $P = 0.29$) and 0.91 in patients without reported liver cirrhosis (95% CI: 0.79–1.05, $P = 0.20$).

In total, 2134 patients presented with HCC between 2017–2019 and 660 in 2020. Overall, 2129/2794 (76%) patients were male, with a mean age of 69 years (SD 10). The time to treatment was significantly shorter in 2020 (median 60 days, IQR: 38–87) compared to 2017–2019 (median 70 days, IQR: 44–103, $P < 0.001$). Actual treatment of patients did not significantly differ between 2020 versus 2017–2019. For patients whom did not undergo treatment, this was more often due to comorbidity in 2020 (52%) compared to 2017–2019 (39%, $P < 0.001$). Survival data were available for all but four patients. Median overall survival was 12.2 months in 2017–2019 versus 11.2 months in 2020 (hazard ratio [HR]: 0.99, 95% CI: 0.89–1.11, $P = 0.86$, Fig. S2A, Supplementary Material).

The monthly incidence in May 2020 was lower compared to 2017–2019, respectively 2.6 versus 4.6 per 1 million inhabitants (IRR 0.56, 95% CI: 0.39–0.80, $P = 0.001$, Fig. 1A). This significant decrease applied for HCC both occurring in patients with reported liver cirrhosis and HCC in patients without reported liver cirrhosis (Figure 1B and C; Table S1, Supplementary Material). The monthly incidence of HCC was higher in June 2020 compared to the range observed in 2017–2019, respectively 5.4 versus 4.1 per 1 million inhabitants, yet only reached borderline statistical significance (IRR 1.32, 95% CI: 1.00–1.72, $P = 0.05$).

In COVID-low months (April–May 2020), 81 patients presented with HCC, compared to 151 patients in COVID-high months (June–July 2020). Patients in COVID-low months presented with slightly larger tumors (median 5.0 cm, IQR: 2.4–10.0) than patients in COVID-high months (median 3.8 cm, IQR: 2.5–6.6, $P = 0.08$, Table 1). TACE was slightly more commonly applied in COVID-high months (15/81, 19%), compared to COVID-low months (16/151, 11%, $P = 0.09$, Figure S1, Supplementary Material). In COVID-high months, median overall survival was slightly shorter (10.7 months) than in COVID-low months (12.8 months), although not statistically significant (HR: 1.02, 95% CI: 0.72–1.45, $P = 0.90$, Figure S2B, Supplementary Material).

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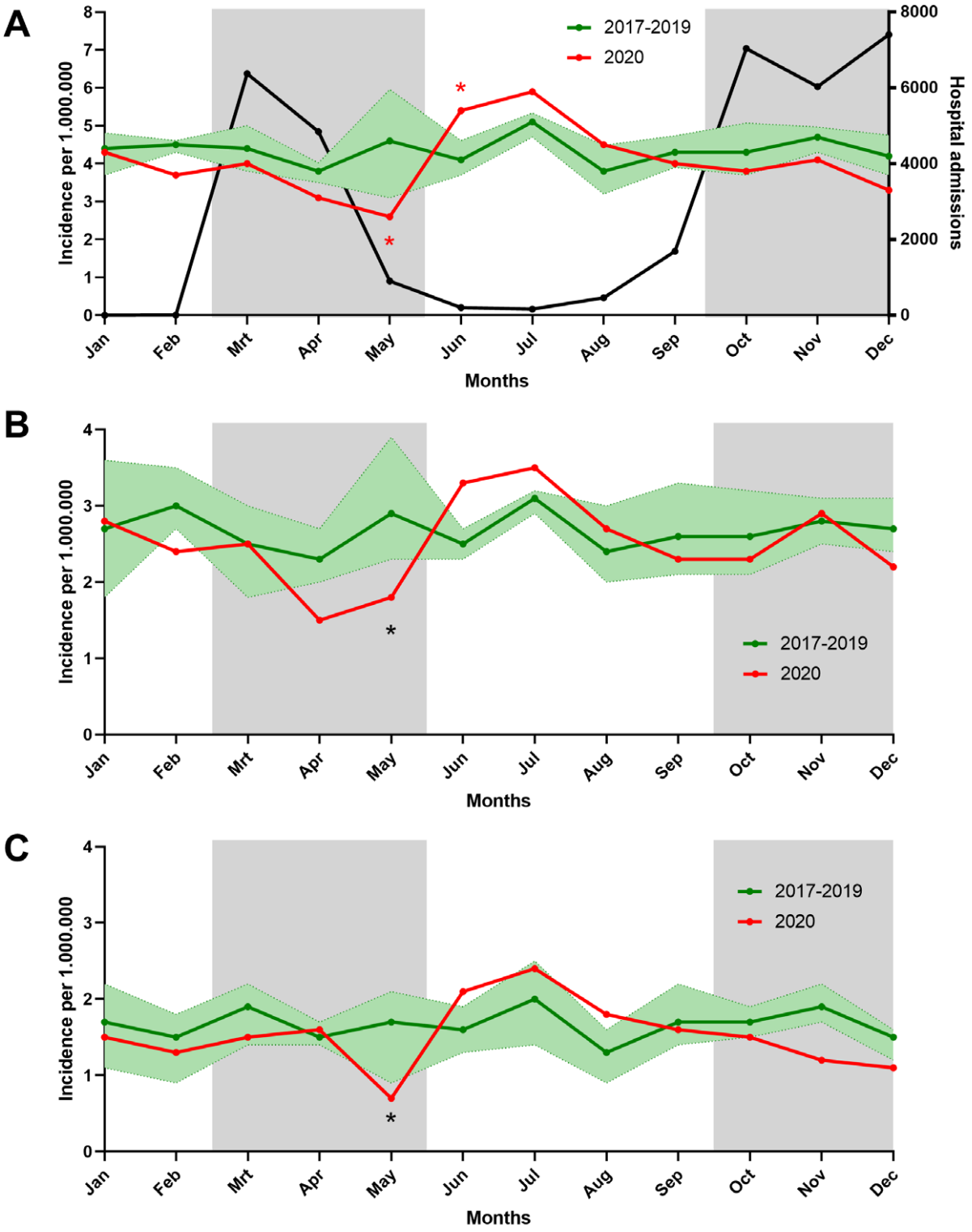

Figure 1. Monthly incidence rates of HCC. A. In 2017–2019 and 2020, overall. B. In 2017–2019 and 2020, in patients with reported cirrhosis. C. In 2017–2019 and 2020, in patients without reported liver cirrhosis. Red lines indicate the 2020 monthly incidence rate. Green lines indicate the average monthly incidence rate of 2017–2019; green areas indicate the minimum and maximum monthly incidence across 2017–2019. The black line shows the monthly absolute number of hospital admissions due to COVID-19. Grey filled areas indicate high COVID incidence months. Asterisks mark significantly difference incidence rate ratios between 2017–2019 and 2020.

Limitations

This study has some limitations. First, patients were included and the HCC incidence was calculated based on incidence date (date the diagnosis became certain). However, to compare characteristics between 2017–2019 and 2020, and COVID-high and COVID-low months, the date of first consultation was used to provide a more detailed estimate. However, in 3–6% of patients, this information was missing. Second, the absolute number of diagnoses per month was

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Table 1. Characteristics by period of first hospital consultation for HCC

	2017–2019	2020	*P*	April – May 2020	June – July 2020	*P*
N	2134	660		81	151	
Patient characteristics						
Sex (male)	1622 (76)	507 (77)	0.67	63 (78)	122 (81)	0.59
Age (years)[‡]	69.2 (10.4)	69.4 (10.5)	0.68	68.3 (9.7)	69.8 (10.0)	0.26
Performance Status	*1344 (63)*	*462 (70)*	0.17	*56 (69)*	*104 (69)*	0.71
WHO 0–1	926 (69)	300 (65)		38 (68)	72 (69)	
WHO 2	244 (18)	87 (19)		8 (14)	18 (17)	
WHO 3–4	174 (13)	75 (16)		10 (18)	14 (14)	
Liver cirrhosis	*2134 (100)*	*660 (100)*	0.80	*81 (100)*	*151 (100)*	0.97
Yes	1317 (62)	411 (62)		49 (61)	91 (60)	
No	817 (38)	249 (38)		32 (40)	60 (40)	
Tumor characteristics						
Pathology proven	*2134 (100)*	*660 (100)*	0.22	*81 (100)*	*151 (100)*	0.55
Yes	937 (44)	272 (41)		30 (37)	62 (41)	
No	1197 (56)	388 (59)		51 (63)	89 (59)	
Number of tumors	*2029 (95)*	*643 (97)*	0.96	*79 (98)*	*144 (95)*	0.50
Single	956 (47)	301 (47)		42 (53)	68 (47)	
2–3	454 (22)	142 (22)		14 (18)	35 (24)	
Multiple	619 (31)	200 (31)		23 (29)	41 (29)	
Tumor size (cm)[‡]	*1842 (86)*	*579 (88)*	0.14	*71 (88)*	*135 (89)*	0.08
	5.0 (2.8–9.1)	4.5 (2.6–8.7)		3.8 (2.5–6.6)	5.0 (2.4–10.0)	
TNM	*2095 (98)*	*648 (98)*	0.94	*81 (100)*	*147 (97)*	0.48
Stage 1	563 (27)	166 (26)		22 (27)	36 (25)	
Stage 2	561 (27)	177 (27)		25 (31)	37 (25)	
Stage 3	446 (21)	140 (22)		21 (26)	38 (26)	
Stage 4	525 (25)	165 (26)		13 (16)	36 (25)	
Process characteristics						
Time to treatment (days)[‡]	70 (44–103)	60 (38–87)	**< 0.001**	55 (43–84)	54 (35–89)	0.90
MDT meeting	*2051 (96)*	*646 (98)*	0.06	*79 (98)*	*147 (97)*	0.35
Yes, in expert center	1544 (75)	516 (80)		59 (75)	118 (80)	
Yes, not in expert center	114 (5.6)	30 (4.6)		3 (3.8)	8 (5.4)	
No	393 (19)	100 (16)		17 (22)	21 (14)	
Treatment characteristics						
Type of treatment[†]						
No treatment	912 (43)	276 (42)	0.68	32 (40)	57 (38)	0.79
RFA/MWA	379 (18)	113 (17)	0.71	24 (16)	77 (18)	0.83
Surgery	274 (13)	81 (12)	0.70	8 (9.9)	21 (14)	0.38
TACE	262 (12)	81 (12)	1.00	15 (19)	16 (11)	0.09
Systemic	188 (8.8)	64 (9.7)	0.49	8 (9.9)	20 (13)	0.45
SIRT	135 (6.3)	50 (7.6)	0.26	7 (8.6)	8 (5.3)	0.32
LTx	55 (2.6)	11 (1.7)	0.18	2 (2.5)	4 (2.6)	0.93
SBRT	21 (1.0)	11 (1.7)	0.15	2 (2.5)	3 (2.0)	0.81

(*Continued*)

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Table 1. (*Continued*)

	2017–2019	2020	*P*	April – May 2020	June – July 2020	*P*
Reason no treatment	*859 (40)*	*264 (40)*	**< 0.001**	*31 (38)*	*56 (37)*	0.36
Comorbidity	338 (39)	136 (52)	**< 0.001**	18 (58)	25 (45)	
Progression	261 (30)	67 (25)	0.12	6 (19)	14 (25)	
Patient choice	217 (25)	56 (21)	0.18	6 (19)	15 (27)	
Few symptoms	0 (0)	2 (0.8)	0.01	0 (0)	2 (3.6)	
Other	43 (5.0)	3 (1.1)	**0.006**	1 (3.2)	0 (0)	

Values in grey indicate the number of patients with data available for this variable. All outcomes are reported as *n* (%). Bonferroni correction gives an alpha of 0.05/5 = 0.01.
†Types of treatment percentages were not mutually exclusive; therefore, percentages may add up to more than 100%.
‡Age is reported as mean (SD) and tumor size and time to treatment as median (IQR).

relatively low and varied between 40-90 patients, as the Netherlands is a country with a relatively low COVID and HCC incidence.[4]

Discussion

The current study evaluates the impact of the COVID-19 pandemic on HCC care in the Netherlands. The incidence of HCC was significantly lower in May 2020, and subsequently increased in June compared to previous years (2017–2019). Nonetheless, the impact on HCC care and outcomes in the current study was limited. Comparing patients with a first consultation date in COVID-high (April-May 2020) periods with patients in COVID-low (Jun–Jul 2020) periods, there were no statistically significant differences on patient, tumor, process, or treatment characteristics or on overall survival.

Patients presenting in COVID-low months following COVID-high months had larger tumors, which could imply tumor progression caused by delay in diagnosis.[2,3] However, no differences were observed in tumor stage and the time to treatment remained stable comparing COVID-high and COVID-low months. A previous French study showed a time to treatment of more than one month in 21.5% during the first six weeks of the COVID pandemic compared to 9.5% in the same period in the prior year.[5] When comparing 2020 overall to previous years (2017–2019), time to treatment was even decreased. This is in line with studies in other cancers, and may indicate prioritization of cancer care and treatments with shorter access times.[8]

Based on the evidence emerging during the COVID-19 pandemic, national and international scientific collaborations provided guidelines for the management of HCC patients, recommending locoregional therapies as a bridge to surgery in case of unavoidable delay.[9] Yet, studies on the type of treatment applied during the COVID-19 pandemic are inconclusive. Certain studies show more TACE procedures applied in countries or periods with high COVID-19 prevalence, whereas others show less TACE procedures performed or no significant changes in treatment strategy.[5,6] In the current study, there was an slightly increased use of TACE in patients presenting during COVID-high periods compared to patients presenting during COVID-low periods. Although there was no statistically significant difference in type of treatment, if patients did not undergo treatment this seemed more often due to comorbidity in 2020 compared to 2017–2019. Despite possible inability or reluctance of patients to visit the hospital for treatment due to COVID-19, a registration artefact cannot be ruled out.

In the Netherlands, a 20–25% decrease was reported in the total number of cancer diagnoses in April 2020 compared to the weeks prior.[1] Another study showed a decrease in diagnoses of 30% for colorectal cancer, 16% for esophageal and gastric malignancy, and 7% for pancreatic and biliary neoplasia, comparing the first COVID wave to the reference weeks in 2019. The large decrease in colorectal cancer was attributed to the temporary halt of colorectal cancer screening and surveillance.[10] In comparison, the decrease in the incidence of HCC in the current study is even more pronounced, namely a decrease of 44% in May of 2020 compared to May of 2017–2019. This is perhaps related to the non-specific symptomology of HCC.[11] The decrease could also be attributed to a halt in HCC screening of patients with liver cirrhosis. Yet, this seems less likely, as the decrease was also observed in patients without reported liver cirrhosis who do not undergo HCC screening.

Conclusions

In conclusion, the current study suggests the COVID-19 pandemic was associated with a marked delay in HCC diagnosis in COVID-high months, yet without any indication for adverse sequelae. Thus, the Dutch HCC care system proved sufficiently resilient in face of the COVID-19 pandemic.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/dmp.2024.176.

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