Liver Care and Surveillance: The Global Impact of the COVID-19 Pandemic

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As social distancing and strict stay-at-home orders have been instituted to slow the spread of coronavirus disease 2019 (COVID-19), unintentional outcomes among those with chronic diseases including screening for the lethal hepatocellular carcinoma (HCC) may be occurring. We aimed to describe the changes in liver care before and after COVID-19 restricted access to health care. We obtained data on the number of liver clinic visits, abdominal ultrasound, computed tomography, and magnetic resonance imaging using electronic query or clinic registry at three medical centers in the United States, Japan, and Singapore for the following periods: February 1 to March 14, 2018, 2019, and 2020; and March 15 to May 1, 2018, 2019, and 2020. We performed trend analysis using logistic regression. In total, 14,403 visits were made to the liver clinics at the three centers: 5,900 in 2018, 5,270 in 2019, and 3,233 in 2020. Overall, there were no significant changes in the distribution of males and females between February 1 and May 1 from 2018 to 2020, but there was a lower proportion of seniors ages 65 years and older ($P < 0.001$). There were significant decreasing trends in the total number of liver clinic visits overall (p-trend = 0.038) and in the subanalysis for chronic hepatitis B, C, and other liver diseases. HCC/cirrhosis visits also dropped from 883 to 538 (39.07% decrease) overall and 665 to 355 (46.62% decrease) for the US site. In addition, there was a significant decreasing trend in the number of abdominal ultrasounds (*P*-trend = 0.004) and computed tomography/magnetic resonance imaging (*P*-trend = 0.007) performed overall. *Conclusion:* Liver clinic visits, hepatoma surveillance, and diagnostic abdominal imaging fell dramatically as social distancing measures were instituted. Care providers must find ways to recall patients for important care monitoring, including HCC surveillance. (*Hepatology Communications* 2020;0:1-7).

The coronavirus disease 2019 (COVID-19) pandemic has claimed 307,296 deaths globally and 89,420 deaths in the United States as of May 16, 2020.[1] Worldwide, countries responded to the pandemic by instituting social distancing and stay-at-home orders (e.g., United States) or stay-at-home request (e.g., Japan), to slow down disease spread. However, unintended consequences of these draconian measures are potentially harming others. For example, the American Heart Association recently reported a 40%-50% decrease in emergency-room visits for stroke and acute myocardial infarction, with the European Union reporting similar findings, while cardiac catherization labs are reporting a decrease of up to 40% for life-saving treatment for those in the throes of a myocardial infarction.[2-4] Public health organizations have reported a decrease in childhood immunizations, to include immunizations for the highly contagious diseases of mumps and measles.[5] Recently, the American Cancer Society reported a decrease in cancer screenings and diagnoses.[6,7]

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; NUH, National University Hospital, Singapore.

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As has been reported, liver cancer, specifically hepatocellular carcinoma (HCC), has been on the rise globally before COVID-19. These findings have been quite disturbing, as HCC has a high mortality rate in which less than 10% of those diagnosed with HCC are alive at 5 years.[8] Therefore, extensive efforts have been undertaken to try to improve HCC surveillance by focusing on awareness of who is at risk as well as appropriate screening methods and time intervals.[9-12] This report will briefly describe the experience of three hospitals located in the United States, Japan, and Singapore, to illustrate the impact of COVID-19 on liver clinic visits and surveillance for HCC.

Methods

This study was conducted using data from three clinical sites: Stanford University Medical Center (Palo Alto, CA), Ogaki Municipal Hospital (Ogaki, Japan), and National University Hospital, Singapore (NUH). We included all patients seen in a liver specialty clinic for follow-up. Patients were identified through several means that included using electronic search to obtain the number of patients seen at the liver specialty clinic using ultrasound CPT codes for "hepatoma surveillance," and/or using a hand search of all patients seen in the liver specialty clinics for the assigned time periods, identifying those who underwent ultrasound, computed tomography (CT), or a magnetic resonance imaging (MRI) for HCC surveillance. Using a data collection form, we obtained the number of liver clinic visits, number of abdominal ultrasounds, and number of abdominal CT or MRI scans at each study center for the following 1.5-month time periods: February 1 to March 14, 2018; March 15 to May 1, 2019; February 1 to March 14, 2019; March 15 to May 1, 2019; February 1 to March 14, 2020; and March 15 to May 1, 2020. The time periods were chosen to correspond with the beginning of social distancing initiative and orders for 2020, and data from 2018 and 2019 served as controls. We also obtained demographic characteristics (age, sex, and race/ethnicity) and liver disease etiology associated with liver clinic visits. To study patients with more advanced liver disease, we obtained data for patients with HCC and/or cirrhosis. The study was approved by the Institutional Review Board at Stanford University (Stanford, CA) and was conducted according to the Helsinki Declaration of 1975, as revised in 2008.

We used chi-square test to compare demographic characteristics associated with liver clinic visits among the different time periods. We performed trend analysis using logistic regression to compare the number of liver clinic visits or abdominal imaging across time periods. Statistical significance was defined with a two-tailed *P* value less than 0.05. We performed all analyses using STATA, version 14 (Stata Corp., College Station, TX).

Results

During the selected time periods, 14,403 visits were made to the liver clinics at the three participating centers (9,345 in Stanford, 3,657 in Ogaki, 1,401 in Singapore): 5,900 in 2018, 5,270 in 2019, and 3,233 in 2020. Most clinic visits at the Stanford site were through telemedicine after March 15, 2020, while most visits at the Ogaki and Singapore sites continued to be regular in-person visits. Overall (Table 1), there were no significant changes in the distribution of males and females between February 1 and May 1 from

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TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE TOTAL STUDY POPULATION

	2018 (2/1/2018-5/1/2018)	2019 (2/1/2019-5/1/2019)	2020 (2/1/2020-5/1/2020)	
Variable	n = 5,900	n = 5,270	n = 3,233	*P* Value
Age group, years				
<45	908 (16.17%)	814 (16.25%)	562 (18.11%)	0.043
45-55	800 (14.25%)	733 (14.63%)	468 (15.08%)	0.57
55-65	1,597 (28.44%)	1,544 (30.82%)	948 (30.55%)	0.016
65+	2,310 (41.14%)	1,919 (38.30%)	1,125 (36.26%)	<0.001
Sex	0.69			
Male	3,365 (57.03%)	2,966 (56.28%)	1,822 (56.36%)	
Female	2,535 (42.97%)	2,304 (43.72%)	1,411 (43.64%)	

2018 to 2019 and 2020 (P = 0.69) or in the age group 45-55 years (P = 0.57). However, there was a slight increase in 2020 for the age group less than 45 and 55-65 years, but a decrease for seniors ages 65 years or older (41.14% in 2018, 38.30% in 2019, and 36.26% in 2020; P < 0.001). Table 2 lists the number of patients seen at each study site and demographic characteristics associated with liver clinic visits by study center and by time period. The sex distribution remained consistently stable over the study periods at all three centers. However, while the age distribution remained relatively stable without significant changes at the Japan and Singapore centers, there was a significant and notable drop in clinic visits by seniors ages 65 years or older in the U.S. center (44.94% in 2018, 40.69% in 2019, and 37.88% in 2020; P < 0.001). Race/ethnicity data were available for the U.S. sites only, and showed that the distribution did not differ significantly over time.

Trend analysis of a total number of liver clinic visits for the month of February, March, and April for the 2018, 2019, and 2020 years showed significant decreasing trends overall (p-trend = 0.038), for the U.S. (p-trend = 0.046), and Singapore sites (p-trend = 0.026), but not the Japan site (p-trend = 0.103) (Fig. 1). Fig. 2A-D provides liver disease etiology–specific data, in which we again found a significant decreasing trend overall and for the U.S. site, but not the Japan site (p-trend = 0.281) for chronic hepatitis C diagnosis (number of hepatitis C virus visits at the Singapore site were too few for analysis) (Fig. 2A). For chronic hepatitis B visits (Fig. 2B), the trend also significantly decreased for the total cohort (p-trend = 0.003), as well as for the Japan (p-trend = 0.016), and Singapore (p-trend = 0.001) sites. A similar decreasing trend was also observed for visits associated with other liver disease at the U.S. site (Fig. 2C). However, there was no significant decrease in the number of visits for patients with more advanced disease, namely those with HCC and/or cirrhosis overall (p-trend = 0.11) or by individual study sites, although there was a non-signficant decreasing trend at the U.S. site (p-trend = 0.094) (Fig. 2D). Nevertheless, between February 1 to March 14, 2020 and the March 15 to May 1, 2020 period, the total number of HCC/cirrhosis visits dropped from 883 to 538 (39.07% decrease) overall, from 665 to 355 (46.62% decrease) for the U.S. site, and 120 (26.6% decrease) for the Japan site.

Regarding liver imaging, there was a significant decreasing trend in the number of abdominal ultrasounds overall (p-trend = 0.004) and at the U.S. site (p-trend = 0.010), but not the Japan (p-trend = 0.572) or the Singapore site (p-trend = 0.753) (Fig. 3A). A similar decreasing trend was also observed for CT/MRI overall (p-trend = 0.007) and for the U.S. and Singapore sites, but not the Japan site (p-trend = 0.838) (Fig. 3B).

Discussion

Although the COVID-19 measures instituted were meant to stop the spread of COVID-19 and to protect the general public as a whole, the measures appear to have adversely affected the routine monitoring of chronic liver disease, to include HCC surveillance. In this brief report, not surprisingly, we found that clinic visits for patients with chronic liver disease and surveillance imaging for HCC fell dramatically as the social distancing and COVID-19 stay-at-home measures were instituted. In fact, the decrease in clinic visits and screening tests was noted to begin before the strict implementation of stay-at-home orders but then

TABLE 2. PATIENT DEMOGRAPHIC CHARACTERISTICS BY STUDY SITE

Variable	2018 (2/1/2018-5/1/2018)	2019 (2/1/2019-5/1/2019)	2020 (2/1/2020-5/1/2020)	*P* Value
Stanford	n = 3,990	n = 3,430	n = 1,925	—
Age group, years				
<45	535 (14.44)	465 (14.67)	295 (16.43)	0.13
45-55	445 (12.01)	405 (12.78)	225 (12.53)	0.62
55-65	1,060 (28.61)	1,010 (31.86)	595 (33.15)	0.001
65+	1,665 (44.94)	1,290 (40.69)	680 (37.88)	<0.001
Sex	0.79			
Male	2,275 (57.02)	1,945 (56.71)	1,110 (57.66)	
Female	1,715 (42.98)	1,485 (43.29)	815 (42.34)	
Ethnicity				
White	1,600 (46.85)	1,265 (44.15)	775 (46.69)	0.075
Black	95 (2.78)	75 (2.62)	35 (2.11)	0.36
Hispanic	980 (28.70)	850 (29.67)	490 (29.52)	0.67
Asian	660 (19.33)	615 (21.47)	315 (18.98)	0.052
Pacific Islander/ Native	80 (2.34)	60 (2.09)	45 (2.71)	0.42
Ogaki	n = 1,326	n = 1,281	n = 1,050	—
Age group, years				
<45	280 (21.12)	273 (21.31)	235 (22.38)	0.73
45-55	259 (19.53)	258 (20.14)	199 (18.95)	0.77
55-65	325 (24.51)	313 (24.43)	259 (24.67)	0.99
65+	462 (34.84)	437 (34.11)	357 (34.00)	0.89
Sex	0.44			
Male	714 (53.85)	659 (51.44)	546 (52.00)	
Female	612 (46.15)	622 (48.56)	504 (48.00)	
NUH	n = 584	n = 559	n = 258	—
Age group, years				
<45	93 (15.92)	76 (13.60)	32 (12.40)	0.327
45-55	96 (16.44)	70 (12.52)	44 (17.05)	0.106
55-65	212 (36.30)	221 (39.53)	94 (36.43)	0.482
65+	183 (31.34)	192 (34.35)	88 (34.11)	0.514
Sex	0.989			
Male	376 (64.38)	362 (64.76)	166 (64.34)	
Female	208 (35.62)	197 (35.24)	92 (35.66)	

accelerated as the stay-at-home orders were more forcefully enforced. The decreasing trend was observed for both sexes, all race/ethnicity (in the United States), and all liver disease etiologies studied, including patients with HCC and/or cirrhosis, although p-trend for this population at the U.S. site was only trending toward statistical significance. Indeed, between the February 1 to March 14, 2020 and the March 15 to May 1, 2020 period, there was a 40% decrease in the number of HCC/cirrhosis visits overall, almost 50% at the U.S. site, and about 25% at the Japan site. In Japan, the range of the number of patients seen in Japan decreased from 1,326 patients seen in 2018, 1281 patients were seen in 2019 while only 1050 patients were seen in 2020.

A recent informal Gallup poll found that over 80% of patients were afraid to go to the hospital due to fears of contracting COVID-19.[13] To overcome this fear, the American College of Cardiology has started a campaign, CardioSmart, in which they use social media and local news stations to let people know that it is safe to come to the hospital if one is sick.[14]

Given the lethality of HCC, we must also find ways to reach out to patients to bring them in for their surveillance. In fact, a delay of just a few months in HCC surveillance may be catastrophic for patients, given that the doubling time for HCC tumor volume is 85.7 days.[15] Therefore, any delay may result in either more aggressive treatment than would have

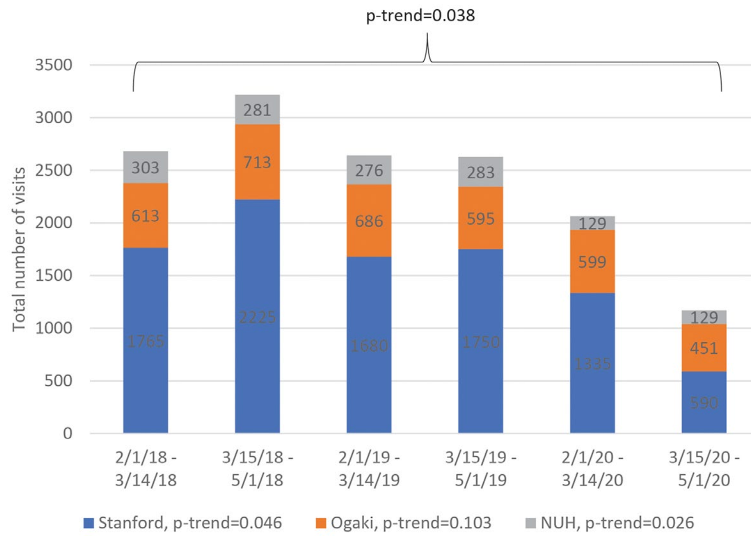

FIG. 1. Trends in total number of liver clinic visits.

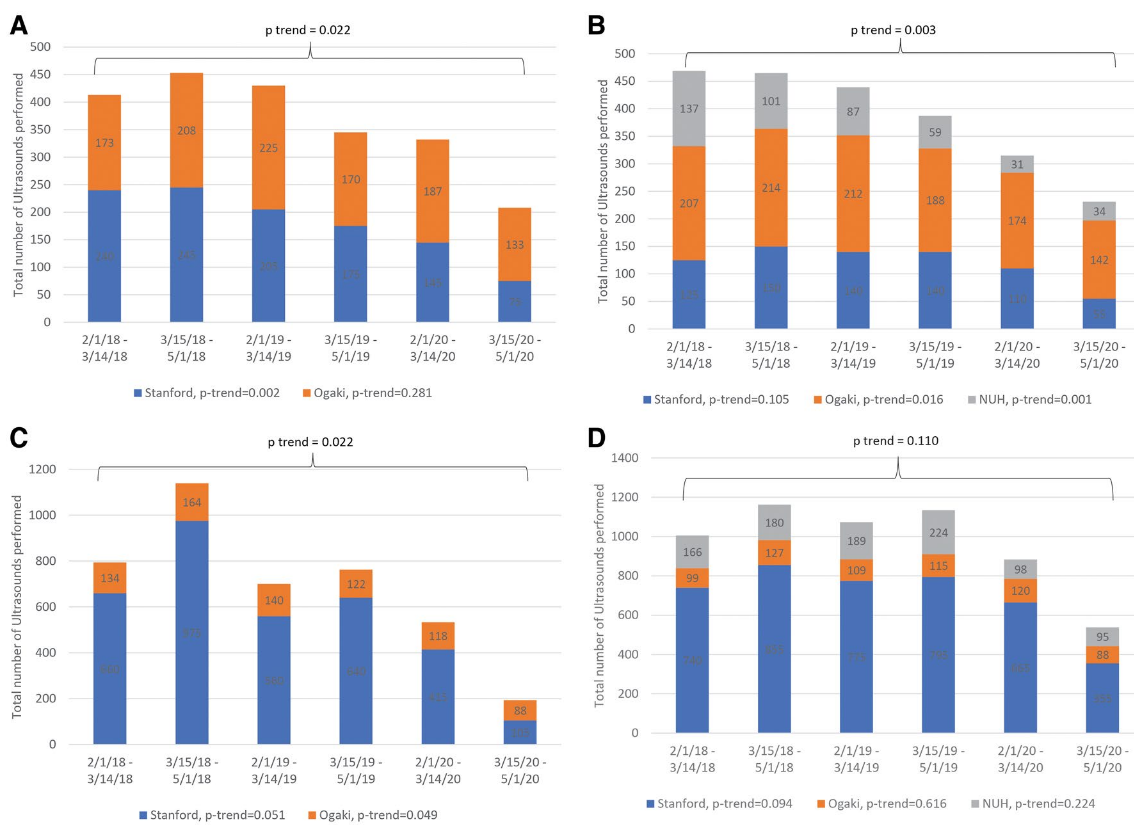

FIG. 2. (A) Trends in liver clinic visits by etiology, HCV (data too few for NUH). (B) Trends in liver clinic visits by etiology, HBV. (C) Trends in liver clinic visits by etiology, other liver disease (data unavailable for NUH). (D) Trends in liver clinic visits in advanced patients, HCC, and/or cirrhosis. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

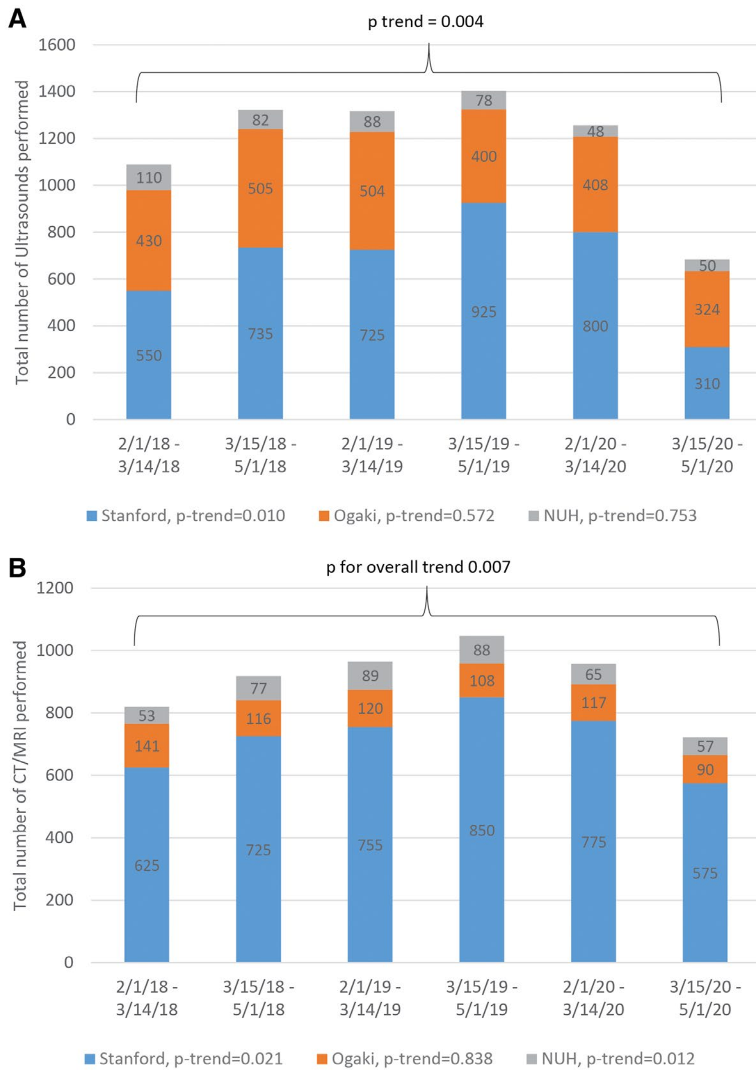

FIG. 3. (A) Trends in the number of abdominal ultrasounds performed. (B) Trends in the number of CT/MRI performed over time.

possibly been needed or the potential for no longer being eligible for curative treatment. In addition to decreased hepatoma surveillance ultrasound, there was also a decreasing trend for CT/MRI, which was even more concerning, as these are usually performed for diagnostic purposes. Using the telehealth platform may be one way of directly linking with patients, to assure them that they are safe coming to the hospital and that the need to for continual follow-up of their liver cancer is vitally necessary. However, given the average age of patients with HCC, the use of social media may not be as effective, so sending letters through the postal system may be a necessary means to reach the patients. As seen in our report, the age group with most pronounced decrease in the number of clinic visits was those of seniors 65 years or older. Elderly patients may have a more limited capability with technology which may impair their use of telehealth. Elderly patients may also be more fearful about COVID-19 exposure based on reports of higher mortality within the elderly as reported by the media and the Center for Disease Control and Prevention.[16]

Another important observation from our study is the heterogeneity of observations among the study sites. Some of these may be due to cultural differences and some may be due to differences in the local government's response to COVID-19 and subsequent morbidity and mortality. These findings were most pronounced at the U.S. site, where when shelter-in-place was ordered by local government, all regular in-person clinic visits were discontinued almost immediately replaced by almost exclusively telemedicine clinics. In the U.S., the first COVID-19 death was only reported on March 1, 2020, but the death toll quickly rose to 40 on March 13, 2020, and over 87,000 on May 16, 2020, prompting extended government lock-down orders in the area of the U.S. study site of this report. Although Japan reported the first COVID-19 death earlier on February 13, 2020, the death toll has risen to only 725 as of May 16, 2020. Although the government of Japan has closed school since early March 2020 and has requested citizens to stay home, the government has not ordered a severe shelter-in-place order, and this may explain the less severe drop in health care visits at the Japan center. Singapore has a small population and has reported only 21 COVID-19 deaths as of May 16, 2020, although it has more confirmed cases than Japan (26,891 vs. 16,237). Singapore shifted its public health response level to "enhanced preparedness" on February 7, and on April 7, instituted "circuit breaker" measures that included closure of nonessential services and social distancing measures.[17] We also recognize that patients may have been seen at another clinic during our study time, and therefore would not have been counted in our study. However, due to the restrictions of the pandemic as noted, we feel it is highly unlikely that a patient would go to another clinic or would have been able to be seen at another clinic. We also used internal controls as a means of controlling for this potential phenomenon and did not see such a pattern. Finally, although we were not able to provide outcome data with our study, we have highlighted an area that requires study to determine the effects of delaying HCC surveillance. When future pandemics happen, health care will be better prepared to identify areas that need to continue to function, so as not to increase morbidity and mortality as an unintended consequence.

Summary

Due to the stay-at-home measures that have been instituted as a means of stopping the spread of COVID-19, liver care for patients with chronic liver disease has been suboptimal, and HCC surveillance has incurred a dramatic drop. Given the lethality of HCC, health care workers must find effective ways to reach out to patients to provide assurance that it is safe to come for their HCC testing so that we do not see an increase in mortality, in which by trying to avoid one disease, patients succumb to another potentially preventable disease.

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