

Title

The Rate of Referral of Hepatitis Virus Carriers to Hepatologists and the Factors
Contributing to Referral

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Abstract

Objective: The aims of the present study were to determine the proportions of hepatitis B surface antigen (HBsAg)-positive and anti-hepatitis C virus (HCV)-positive patients, and identify the characteristics that influenced referral to a hepatologist.

Methods: The present study included patients who were positive for HBsAg (n = 153) or anti-HCV (n = 574); their viral status was tested by non-hepatologists between January 2008 to December 2012. We performed a multivariate analysis to investigate the factors associated with the referral of patients to hepatologists.

Results: The rates of hepatitis B virus (HBV) and the percentage of suspected HCV carriers at the hospital were 1.4% and 3.5%, respectively. Among the 727 patients who were seropositive for HBV or HCV, 107 (14.7%) were referred to a hepatologist. A multivariate analysis to investigate the factors contributing to referral revealed that (i) an alanine aminotransferase (ALT) level of >30 IU/L (odds ratio [OR], 3.24; 95% confidence interval [CI], 2.10–5.03; P < 0.001); (ii) undergoing testing at an internal medicine department (OR, 2.79; 95% CI, 1.80–4.38; P < 0.001); and (iii) HBsAg-positivity (OR, 2.22; 95% CI, 1.35–3.61; P = 0.002) were factors that significantly influenced referral.

Conclusions: Hepatologists must educate non-hepatologists, especially non-internists, to

promote the referral of hepatitis-virus carriers, especially HCV carriers, even in patients with ALT levels of <30 IU/L.

Key words: hepatitis virus carriers, medical collaboration, non-hepatologist, HBV, HCV

Introduction

The prevalence rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in Japan are estimated to be 0.71% and 0.63%, respectively (1). As HBV and HCV are major causes of cirrhosis, liver failure, and liver cancer, the initiation of appropriate treatment is important for achieving a better prognosis (2, 3).

Although recent advances in antiviral therapy have caused dramatic improvements in the treatment of hepatitis virus infection, only a minority of HBV- or HCV-infected patients receive treatment due to multiple barriers, including patient factors (e.g., ongoing drug or alcohol abuse or psychiatric contraindications), provider factors (e.g., the physician's lack of knowledge or a reluctance to treat past drug abusers), and system factors (e.g., referral-associated delays or a lack of funds) (4-12). In addition, treated patients are significantly more likely to be referred to a hepatologist, in comparison to untreated patients (11). A previous study indicated that developing collaboration between specialists and primary care providers had the potential to improve the quality of HCV care (13). However, little attention has been paid to the actual collaboration between hepatologists and non-hepatologists in the hospital setting.

The Hakujuji Hospital provides health care for an almost exclusively urban population of 1,500,000 inhabitants. The medical departments within the hospital

function independently. The aims of the present study were to determine the proportion of hepatitis B surface antigen (HBsAg)-positive and anti-HCV-positive patients, and identify the characteristics of the patients who were referred (or not referred) to hepatologists in order to provide information for future interventions and to improve the rate of referral.

Materials and Methods

This retrospective study included the patients who tested positive for HBsAg and/or anti-HCV at our hospital over the 5 years from January 2008 to December 2012. Patients who were both HBsAg and anti-HCV-positive were excluded from the assessment of the effect of the virus type on referral. Patients who were already being tested and managed by hepatologists were excluded from the study. Ethical approval was obtained from the ethics committee of the hospital.

HBsAg was detected using the Architect-HBsAg QT assay (Abbott Laboratories, Tokyo, Japan); the cutoff level was 0.05 IU/mL. Anti-HCV was detected using the Architect-HCV assay (Abbott Laboratories); the cutoff point was a signal to cut-off ratio of 1.0.

The patients were classified into two groups: those who were referred to

hepatologists (referrals) and those who were not referred to hepatologists (non-referrals).

We retrospectively collected the following 12 characteristics of these patients: sex, age on the day of the test, the department in which the viral status was tested (internal medicine or a non-internal medicine department), the physician's years of experience on the date of the test, the presence of a family doctor (present or absent), platelet count, prothrombin time (%), viral hepatitis markers (HBsAg and anti-HCV), and the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total bilirubin.

The internal medicine departments at our hospital included Diabetes, Neurology, Gastroenterology, Nephrology, Cardiology, Hematology, and Endocrinology. The non-internal medicine departments included General and Gastroenterological Surgery, Breast Surgical Oncology, Orthopedic Surgery, Plastic Reconstructive Surgery, Neurosurgery, Urology, Ophthalmology, Oral Surgery, Physical Medicine, and Rehabilitation. The presence of a family doctor was determined by reviewing the patients' electronic medical records; "present" was defined by management of the patient's hepatic condition at another clinic, and absent was defined by the absence of another location of management. The most recent blood test result at the time of viral testing was included in the analysis.

In addition, we used the aforementioned data to create a decision tree from the factors that were found to affect referral to a hepatologist and performed a data mining analysis to further determine the reasons for referral.

The differences in the baseline characteristics of the groups were analyzed using Wilcoxon's signed test for continuous variables and Pearson's chi-squared test for categorical variables. A multivariate analysis was performed using stepwise logistic regression models. P values <0.05 were considered to indicate statistical significance. All of the analyses were performed using the JMP software program (version 10; SAS Institute, Cary, NC).

Results

The prevalence of HBsAg or anti-HCV seropositivity

Among the 11,823 patients who were tested for HBsAg, 163 (1.4%) tested positive.

Among the 11,320 patients who were tested for anti-HCV, 584 (5.2%) tested positive. Ten patients were positive for both HBsAg and anti-HCV (Figure 1).

The referral status and the characteristics of the seropositive patients

The overall, referral rate for seropositive patients was 14.7% (107/727). The referral

rates for HBsAg-positive and anti-HCV-positive patients were 20.9% (32/153) and 13.1% (75/574), respectively (Figures 1, 2). Among the 75 anti-HCV-positive patients who were referred to a hepatologist, 47 patients whose general condition could be treated with antiviral therapy or who did not have liver cancer or cirrhosis underwent an HCV RNA test; HCV RNA was detected in the serum of 32 patients (68.1%) by a polymerase chain reaction. Eighteen of these 32 (56.3%) patients were infected with non-1 HCV genotypes. The patients in the referral group were significantly younger than those in the non-referral group (Table 1). The rate of referral from internal medicine departments was significantly higher than that from non-internal medicine departments. The serum AST, ALT, and GGT levels were significantly higher and the platelet count was significantly lower in the referral group. A significantly greater number of patients in the referral group were HBsAg-positive, while significantly fewer were anti-HCV-positive.

The multivariate analysis showed that hepatitis virus-positive patients were referred to a hepatologist from a non-hepatologist based on the following factors: an ALT level of ≥ 31 IU/L (odds ratio [OR], 3.24; 95% confidence interval [CI], 2.10–5.03; $P < 0.001$), undergoing testing in an internal medicine department (OR, 2.79; 95% CI, 1.80–4.38; $P < 0.001$), or HBsAg positivity (OR, 2.22; 95% CI, 1.35–3.61; $P = 0.002$) (Table 2 and Figure 2).

The data mining analysis

A data mining analysis was performed to assess the reasons why the patients were referred to a hepatologist. The results are shown in Figure 3. This analysis classified four subgroups based on the three factors that influenced the decision to refer a patient to a hepatologist. The serum ALT value was selected as the best influential factor. Patients with an ALT level of ≥ 31 IU/L had a higher referral rate than those with an ALT level of < 31 IU/L (25.7% vs. 9.9%, $P < 0.001$). Among the patients with an ALT level of ≥ 31 IU/L, the type of department was strongly associated with referral. The referral rate of patients who underwent testing at an internal medicine department was higher than that of patients who underwent testing at a non-internal medicine department (38.5% vs. 12.8%, $P < 0.001$). In patients with an ALT level of < 31 IU/L, the type of the hepatitis virus was strongly associated with referral. HBsAg-positive patients had a higher referral rate than those who were anti-HCV-positive (17.8% vs. 7.5%, $P = 0.001$). Furthermore, among the four subgroups, most patients had an ALT level of < 31 IU/L, and the anti-HCV-positive group had the lowest referral rate.

Discussion

Our study showed that among the patients who were tested for the hepatitis virus by a non-hepatologist at our hospital, 1.4% were HBsAg-positive and 5.2% were anti-HCV-positive. The true rate of HCV positivity among the anti-HCV-positive referrals was 3.5%, because HCV RNA was detected in 68.1% of these patients—which is similar to the rate reported in previous studies (14, 15). However, this result should be interpreted carefully, as there may be selective bias since only treatable patients were tested for HCV RNA. In the present study, both the HBsAg-positive rate and the estimated HCV carrier rate were higher than the recently reported prevalence rates in Japan of 0.71% and 0.63%, respectively (1). One potential reason for this difference may be the high proportion of elderly patients in the study, particularly because the prevalence of HCV was shown to increase with age in reports from Japan (1, 15). Another potential reason is the area. In the Kyushu area, in which our hospital is located, the HBV and HCV carrier rates are high (0.96% and 0.80%, respectively) in comparison to the rest of Japan (1). Moreover, 56.3% of the anti-HCV-positive patients at our hospital were infected with non-1 HCV genotypes, which is higher than the estimated 30% in the entire Japanese population (1, 15). As intravenous drug abuse and tattoos are the major routes of non-genotype 1 HCV transmission in Japan (16, 17), the high prevalence of hepatitis virus at our hospital was likely associated with regional variations in these behaviors.

Despite the high prevalence of hepatitis virus infection, at only 14.7%, the rate of referral to hepatologists was suboptimal. Our data demonstrated a greater tendency for referral if the patient had an ALT level of ≥ 31 IU/L, underwent testing at an internal medicine department, or was HBsAg-positive.

Among the three factors that were analyzed, the factor that most strongly influenced referral to a hepatologist was the ALT level. Regarding the high rate of referrals in patients with an ALT level of ≥ 31 IU/L, the upper limit of normal for ALT at our hospital is 30 IU/L—at this cutoff point, the value is flagged in red in electronic medical records to attract the health care providers' attention. Consequently, non-hepatologists were more likely to refer patients to hepatologists due to high ALT values. Moreover, hepatitis virus carriers with normal ALT levels have a higher risk of cirrhosis and liver cancer in comparison to non-carriers (18-20). Thus, physicians need to be aware that referral to a hepatologist is necessary, even for patients with normal ALT levels.

In the subgroup of patients with an ALT level of ≥ 31 IU/L, the referral rate among patients who underwent testing in an internal medicine department was higher than that among patients underwent testing in a non-internal medicine department. This may indicate the different reasons for testing patients for hepatitis virus. For instance, internists may tend to perform hepatitis viral testing to identify the cause of liver

dysfunction, whereas non-internists may be more likely to perform these tests for preoperative surveillance. This gap in perception by internists and non-internists might have influenced the referral rate.

The referral rate of patients with an ALT level of <31 IU/L, was higher for patients who were HBsAg-positive. It is thought that the physicians were more careful about the management of HBV carriers, because there is a general agreement that the infectious capacity of HBV is stronger than that of HCV. In addition, HBV often causes serious clinical conditions, such as severe hepatitis (21-23). In the present study, there was a similar result in cases with a normal ALT level (24, 25). Furthermore, this result showed importance of measures for identifying anti-HCV-positive patients, who have a low referral rate. Given the recent and remarkable progress in the treatment of HCV, these measures will become increasingly necessary in order to identify hepatitis virus carriers in hospitals and determine an appropriate treatment strategy.

The perceived barriers to referral to hepatologists are significantly associated with the physician's knowledge (10). The findings of the current study suggest that among non-hepatologists, there is a gap in the knowledge of viral hepatitis between internists and non-internists. In particular, there was disparity in recognizing HCV infection in patients with a normal ALT level.

The present study is associated with some limitations. First, this study was retrospective in nature and was conducted at a single institution in Japan. Thus, the results may not be generalizable to other patient settings. Second, the reason for referral (or a lack of referral) by chief doctors to hepatologists was unclear. To improve the referral rate, these reasons should be elucidated.

In conclusion, to improve the current low rate of referral of hepatitis virus carriers, hepatologists should encourage and instruct non-hepatologists, especially non-internists to refer patients with hepatitis virus, especially those who are anti-HCV-positive, to a hepatologist—even if the patient's ALT level is normal.

The authors declare no Conflicts of Interest (COI) in association with the present study.

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Table 1 Characteristics of the patients with hepatitis virus between those with and without the consultation to a hepatologist

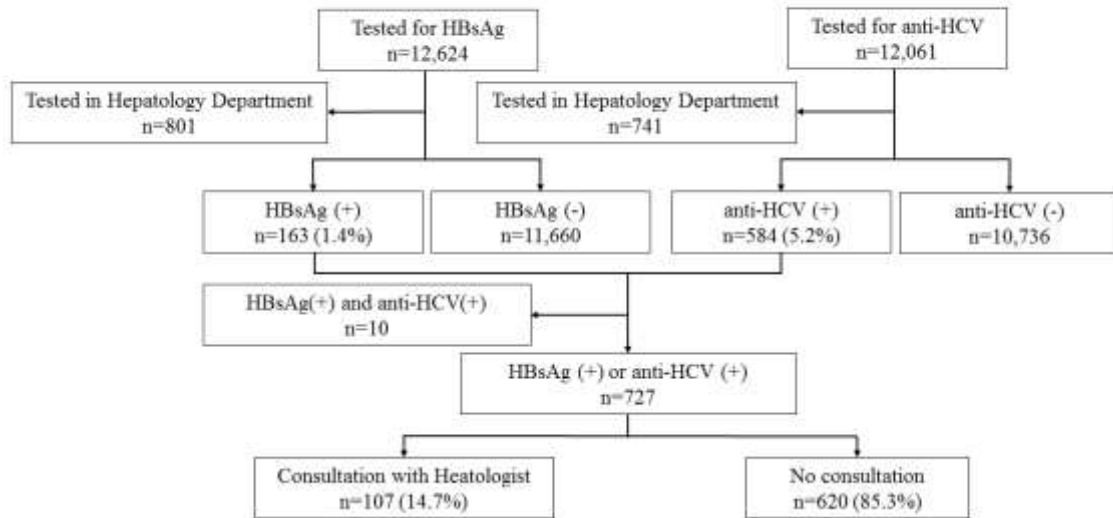
| Factor | Consultation (n=107) | No consultation (n=620) | P-value |
|--|-------------------------|----------------------------|---------|
| Sex (Male/Female) | 71/36 | 364/256 | 0.136 |
| Age | 62 (21-95) | 74 (17-99) | <0.001 |
| Department (Internal Medicine/others) | 70/37 | 248/372 | <0.001 |
| The years of experience of the physician | 15 (3-51) | 16 (3-51) | 0.365 |
| Family doctor (+/-) | 28/79 | 186/434 | 0.422 |
| HBsAg/anti-HCV | 32/75 | 121/499 | 0.015 |
| AST (IU/L) | 35 (12-1036) | 25 (9-5000) | <0.001 |
| ALT (IU/L) | 34 (6-2530) | 20 (2-2635) | <0.001 |
| GGT (IU/L) | 44 (10-839) | 25 (5-867) | <0.001 |
| Total Bilirubin (mg/dL) | 0.75 (0.3-28.9) | 0.7 (0.1-7.0) | 0.007 |
| Platelet ($\times 10^4/\mu\text{g}$) | 19.8 (3.21-65.3) | 22.0 (2.88-57.8) | 0.009 |
| PT (%) | 89.5 (9.1-156.6) | 89.1 (9.8-184.3) | 0.245 |

Table 2 Multivariate analysis of factors associated with a consultation with a hepatologist from non-hepatologist for the patients with hepatitis B surface antigen (HBsAg)-positive or anti-hepatitis C virus (HCV)-positive

| Factor | Multivariate analysis | |
|--------------------------------|-----------------------|---------|
| | OR (95% CI) | P-value |
| ALT \geq 31 IU/L | 3.24 (2.10-5.03) | <0.001 |
| Department (Internal Medicine) | 2.79 (1.80-4.38) | <0.001 |
| HBsAg positive | 2.22 (1.35-3.61) | 0.002 |

Figure Legends

Figure 1. A flow chart of patients included in this retrospective study



HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus

Figure 2. The referral rate of hepatitis virus-positive patients to a hepatologist from a non-hepatologist based on an alanine aminotransferase (ALT) level of ≥ 31 IU/L, undergoing viral testing at an internal medicine department, and hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) positivity.

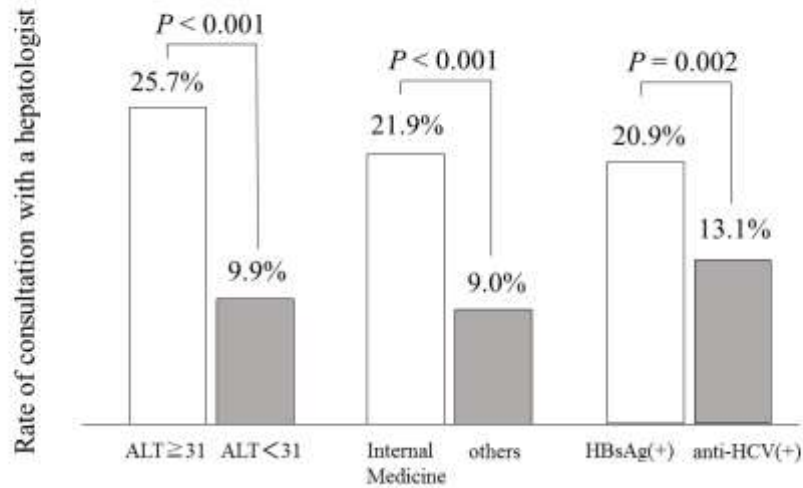
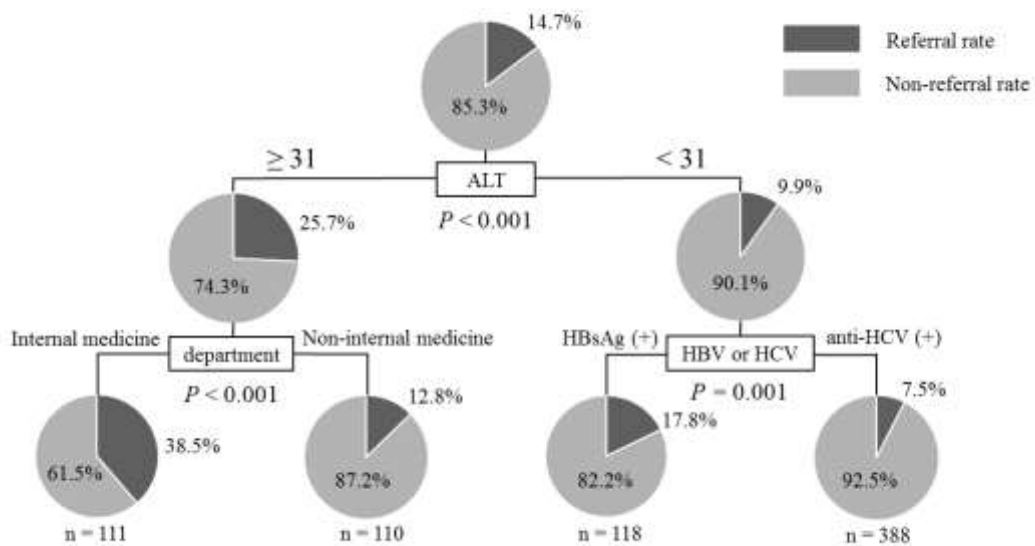


Figure 3. A decision tree model of the factors associated with referral to a hepatologist.



The rectangles indicate the variables that were used to differentiate the patients. The pie charts indicate the referral rate to a hepatologist for each group. The groups were

further classified into four subgroups by the three factors. The serum ALT value was selected as the factor that had the greatest influence on referral. Patients with an ALT level of ≥ 31 IU/L had a higher referral rate than those with an ALT level of < 31 IU/L. In patients with an ALT level of ≥ 31 IU/L, the clinical department in which the patient underwent testing was strongly associated with the referral rate. Patients who underwent testing in an internal medicine department had a higher referral rate. In patients with an ALT level of < 31 IU/L, the type of hepatitis virus was strongly associated with the referral rate. HBsAg-positive patients had a higher referral rate than anti-HCV-positive patients.

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HBV, hepatitis B virus

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