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Low accuracy of the national reporting system of acute hepatitis C infection in Taiwan, 1995–2004

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Abstracts

Background and Aim: This study attempted to clarify accuracy of acute hepatitis C (AHC) and its clinical characteristics.

Methods: We reviewed 632 reported cases from national surveillance data of the Taiwan Center for Disease Control between 1995 and 2004, and reclassified diagnoses. A definite case was defined as alanine aminotransferase (ALT) > 10 × the upper limit of normal (ULN) with seroconversion of anti-hepatitis C virus antibody (anti-HCV). A probable case was defined as (i) seroconversion of anti-HCV and/or elevated ALT levels; or (ii) anti-HCV(+) but titers increased (from < 40 S/CO to ≥ 40 S/CO) and ALT > 10 × the ULN. A suspected case was defined as initial anti-HCV(+) and ALT level > 10 × the ULN and/or jaundice. Excluded cases were defined as ALT levels less than 10 × ULN with initial positive anti-HCV Ab.

Results: A total of 310 (49%) cases were confirmed as AHC; these included 95 (15%) definite and 215 (34%) probable cases. Higher incidence rates and accuracy of AHC were demonstrated in the southern area significantly if compared with northern, eastern and central areas, respectively (all $P < 0.05$). On comparison between blood centers and hospitals, more AHC cases were found in Southern Taiwan than in other areas (157/73 vs 24/40, $P < 0.001$), younger mean age (33.3 ± 11.1 vs 49.3 ± 16.4, $P < 0.001$), lower ALT levels (263.1 ± 200.9 vs 1264.2 ± 706.8, $P < 0.001$) and male predominance (191/39 vs 46/18, $P = 0.046$).

Conclusions: This study showed our reporting system over-estimated the AHC diagnosis, which is also a common issue worldwide. Greater efforts are needed to establish appropriate reporting systems, as well as more supplemental methods to distinguish between prevalent and incident cases.

Introduction

Chronic hepatitis C virus (HCV) infection is a global public health issue; long-term infection may lead to chronic liver disease, liver cirrhosis and hepatocellular carcinoma.[1] Recent estimated prevalence of HCV infection is 2% worldwide.[2] Approximately 55–85% of individuals with acute hepatitis C (AHC) infection will eventually develop chronic liver disease.[3–5] There is little epidemiological data regarding AHC infection, and this might be partly due to high percentages of AHC cases being unrecognized at early infection stages. Only about 10–20% of AHC cases develop jaundice and mild constitutional symptoms (fever, abdominal pain, nausea, vomiting) after exposure.[6] Due to asymptomatic and subclinical hepatitis in the majority of AHC infected cases, early detection and clinical diagnosis is difficult.[7–12]

Diagnosis and identification of AHC cases by current diagnostic criteria have some difficulties. To date, definite diagnosis of AHC still relies on seroconversion of the anti-HCV antibody (anti-HCV) in cases of elevation of serum alanine aminotransferase (ALT) levels.[10,12] Improvement of sensitivity and specificity of current second- or third-generation anti-HCV assays leads to earlier detectable anti-HCV and shortens the window period.[13–14] Most cases show detectable anti-HCV when diagnosed.[15] However, it is usually not possible to distinguish between acute, chronic with acute exacerbation, and past infections of HCV by using current anti-HCV assays. Detectable serum HCV RNA followed by anti-HCV seroconversion could make an even earlier diagnosis of AHC within 2 weeks after HCV exposure, but only a small proportion of cases identified as current HCV exposure that were subsequently monitored were available with this criterion to diagnose AHC, such as injecting drug users.[16]

Our previous studies showed that raising the titer of anti-HCV (AxSYM, version 3.0; Abbott, Chicago, IL, USA) might be used as a supplemental diagnostic criterion for AHC in those without documented seroconversion.[5,17] An initial signal/cutoff (S/CO) value < 40 with a rising pattern (≥ 40) might be the most common change of serial anti-HCV in those with suspected AHC infection without documented seroconversion.

Identification of AHC cases is an important public health issue that could be provided by a surveillance system. Accurate epidemiology of AHC might provide adequate information and control of the disease, so that the infection source of AHC could be identified earlier in this situation, leading to reduction of further spreading of HCV infection.

Many countries, such as those in the EEC and the United States, have surveillance systems that report AHC cases.[18–20] Some surveillance systems in Europe include incidental and prevalent cases for reporting. The diagnosis of AHC must be over-estimated and over-diagnosed if prevalent cases are to be included in the reporting systems. The majority of the reported systems could not distinguish between acute and chronic HCV infections. The accuracy of the AHC diagnosis in reporting cases has become a major issue worldwide, even in industrialized countries.

This study attempted to clarify accuracy of AHC by using the current national AHC reporting system in Taiwan, and by investigating clinical characteristics of AHC cases.

Patients and methods

Patients

In Taiwan, the case definition of the Taiwan Center for Disease Control (TCDC) for notifications of AHC is seroconversion of anti-HCV from a past negative to a positive test, with acute hepatitis as confirmed by a physician clinically.[21] All suspected AHC cases are reported to TCDC. The reporting cases are mainly reported from clinics, hospitals and blood donation centers. Basic demographic information such as age, sex, address and date of diagnosis are also reported.

This study was supported by the TCDC. We obtained the national database of reported cases between 1995 and 2004 from the TCDC. Based on the database, we retrospectively reviewed the medical charts and data of reported cases from the original notified sites. A form was created and basic demographic data such as age, sex, symptoms, date of diagnosis, place of residence, history, risk factors and laboratory data were collected from chart records retrospectively. In Taiwan, we used standard laboratory criteria in examining ALT among hospitals. We expressed ALT levels as a multiplication of the upper limit of normal (ULN).

The diagnostic accuracy for AHC of these reported cases was re-evaluated according to the criteria classified as follows.

Methods

Diagnostic criteria of acute hepatitis C

Diagnosis of AHC infection in most studies required recent seroconversion of anti-HCV from a past negative to a positive test, with elevated aminotransferase levels that was at least > 2× the ULN.[22] The Center for Disease Control of the United States used ALT > 7× ULN as cut off levels for AHC.[23] In this study, we use ALT level > 10× the ULN as diagnostic threshold to increase specificity of definite cases.[24]

We re-classified reported cases with the following diagnostic criteria as summarized in Table 1.

1. Definite cases were defined as ALT level > 10× ULN with one of the following: (i) seroconversion of anti-HCV from a past negative to a positive test; or (ii) positive serum HCV RNA and negative anti-HCV.
2. Probable cases were defined as: (i) seroconversion of anti-HCV and/or elevated ALT levels; or (ii) based on our previous study.[17] ALT level > 10× ULN with positive third generation anti-HCV EIA (AxSYM, version 3.0; Abbott, Chicago, IL, USA) but low titer level which was defined as < 40 S/CO at acute phase, and increasing titer to ≥ 40 S/CO at recovery phase.
3. With no previous history of hepatitis and drugs, suspect cases were defined as ALT level > 10× ULN and/or associated jaundice without history of hepatitis C, but initial positive anti-HCV.
4. Excluded cases were defined as ALT levels less than 10× ULN with initial positive anti-HCV Ab.

A small proportion of cases from the blood center ($n = 18$) had seroconversion of anti-HCV but with persistent normal ALT levels; these cases had a high probability of AHC but did not meet the AHC criteria of current TCDC, so we classified these cases as probable cases.

The cases that were identified as definite and probable cases in the study were reclassified as AHC cases. The geographic areas in Taiwan were classified into four areas: Northern, Central, Southern and Eastern. For cases from blood donation centers, serial

Table 1 Re-classified reported cases of acute hepatitis C according to diagnostic criteria ($n = 632$)

Cases	Diagnostic criteria	*N* (Hospital and clinics/Blood centres)	(%)
Acute hepatitis C		310	49%
Definite	1. Seroconversion and ALT > 10× ULN	79 (43/36)	12.5%
	2. HCV RNA(+), anti-HCV(–) and ALT > 10× ULN	16 (16/0)	2.5%
Probable	1. Seroconversion and/or elevated ALT	212 (0/212)	33.5%
	2. Anti-HCV titre increase (from < 40 S/CO to ≥ 40 S/CO) and ALT > 10× ULN	3 (3/0)	0.5%
Suspected	Initial anti-HCV(+) and ALT level > 10× ULN and/or jaundice	120 (118/2)	19%
Excluded	Initial anti-HCV(+) and ALT < 10× ULN	202 (152/50)	32%

ALT: alanine aminotransferase; Acute hepatitis C includes definite and probable cases; ULN: upper limit of normal.

anti-HCV data could be obtained in those who donate blood at least twice, so seroconversion of anti-HCV was more easily identified in these cases. Because of obvious different characteristics having been demonstrated between hospital/clinics and blood donation centers, such as gender, age, reporting area and ALT levels, we separated these two different report sites into two groups for analysis.

Statistical analysis

The *t*-test was used for continuous variables, the chi-square test was used for category variables and the Bonferroni correction for multiple comparisons. A *P*-value of less than 0.05 was considered statistically significant. Accuracy was calculated as AHC cases divided by report cases (percentage). Incidence rates were calculated as (AHC cases/population) × 1 000 000.

Results

Patient selection

A total of 865 reported cases were obtained from the TCDC official database. Of these, cases with insufficient data to confirm diagnosis ($n = 57$) and error report ($n = 61$) were not included in the study. Information and medical records of 115 reported cases were not obtained from original reporting hospitals, including 101 cases that did not support the study and 14 cases where the original hospitals had been closed down. Both of them were also excluded in this study. Risk factors were not analyzed because of lack of data record in many cases.

A total of 632 reported cases with available data were reviewed and analyzed (Table 1). Of these, 310 (49%) cases met the diagnostic criteria of AHC. These included 95 (15%) definite and 215 (34%) probable cases. The clinical characteristics of these cases will be discussed following. In suspect cases ($n = 120$, 19%), ALT levels were 1338.7 ± 626 U/L, 71.4% (80/112) of cases developed jaundice. 18 probable cases reported from blood centers had persistent normal ALT levels with seroconversion. Among them, 4 in 12 (33%) cases became negative for anti-HCV during follow-up. These cases were most likely spontaneous recovery from AHC infection. In excluded cases ($n = 202$), all cases had initial positive anti-HCV and ALT levels less than 10× the ULN (130.5 ± 93.5 U/L). Among them, 25% (21/84) developed jaundice.

Clinical characteristics of acute hepatitis C cases

Baseline characteristics of AHC (definite and probable) cases are shown in Table 2. Table 3 shows incidence rates and accuracy of AHC in reporting cases according to geographical distribution. Higher incidence rates and accuracy of AHC were demonstrated in the southern area significantly when compared with northern, eastern and central areas, respectively (all $P < 0.05$). Table 4 demonstrates the clinical characteristics of AHC cases comparing hospitals and clinics with the blood donation centers. Some different clinical characteristics were illustrated between them. For AHC cases in blood donation centers, these were mainly localized in Southern Taiwan, were younger in age, and had lower ALT levels significantly when compared with the AHC cases at hospitals and clinics.

Table 2 Baseline characteristics of acute hepatitis C cases ($n = 310$)

Age (years, mean ± SD)	36.5 ± 13.9
Gender (male/female)	246/64
ALT levels	448.7 ± 546.6
Report year	
1995–2000	8
2001	51
2002	80
2003	80
2004	91
Geographical distribution	
Northern	66
Central	37
Southern	197
Eastern	10
Report source	
Hospital	62
Blood donation centre	248

ALT: alanine aminotransferase; Acute hepatitis C includes definite and probable cases.

The mean ALT levels of definite and probable cases were 1039.5 ± 658.3 and 187.7 ± 132.9 U/L, respectively. For AHC cases at hospitals, higher ALT levels were observed and 69.5% (41/59) among them developed jaundice. In probable AHC cases, 98.6% (212/215) cases were reported from blood centers; all of them were subclinical hepatitis with ALT levels < 10× the ULN and asymptomatic. These asymptomatic cases were defined as AHC cases by documented anti-HCV seroconversion by using two blood donation tests, with median duration of 19.3 months (2–124 months).

Discussion

Current diagnostic criteria of AHC still relies on clinical presentation of acute hepatitis accompanied with anti-HCV seroconversion. Inaccuracy of AHC reporting in this study represents the current difficulty and challenge in AHC diagnosis. We identified definite and probable cases as AHC cases ($n = 310$) after re-classifying reporting cases by current diagnostic criteria. These 'AHC' cases may have the potential to highlight and provide some clinical characteristics and information of AHC.

Surveillance systems for reporting newly diagnosed HCV infections exist in many countries.[18–20,26] However, there is heterogeneity in case definitions among different countries and it is difficult to compare surveillance systems. Current case definition in the Unites States and many European countries is still unable to distinguish between AHC and acute exacerbation of chronic HCV infection. Some countries in Europe even include prevalent as well as incident cases in HCV notification. Over-estimation of the AHC diagnosis is credible in this situation. Present surveillance systems have difficulty in reflecting precise epidemiology of AHC infection, which is important in understanding the status of the disease burden.

Table 3 Incidence rates and accuracy of acute hepatitis C in reporting cases according to geographical distributions

Geographical areas	Population[25]	Report cases (*n*)	Report rates (/10^6)	AHC cases (*n*)	Incidence rates (/10^6)†	Accuracy (%)‡
Northern	8 970 668	171	19.1	66	7.4	38.6
Central	5 559 640	133	23.9	37	6.7	27.8
Southern*,**	6 262 614	299	47.7	197	31.5	65.9
Eastern	1 070 329	29	27.1	10	9.3	34.5
Total number	21 863 251	632	28.9	310	13.4	46.2

*Chi-square test for incidence rates: $P < 0.001$; and Bonferroni correction for multiple comparisons: northern versus central ($P = 0.625$), central versus southern ($P < 0.001$), southern versus eastern ($P < 0.001$), northern versus southern ($P < 0.001$), central versus eastern ($P = 0.508$), northern versus eastern ($P = 0.576$).

**Chi-square test for accuracy: $P < 0.001$; and Bonferroni correction for multiple comparisons: northern versus central ($P = 0.073$), central versus southern ($P < 0.001$), southern versus eastern ($P = 0.017$), northern versus southern ($P < 0.001$), central versus eastern ($P = 0.568$), northern versus eastern ($P = 0.673$).

†Incidence rates was calculated as (AHC cases/population) × 1 000 000.

‡Accuracy was calculated as AHC cases divided by report cases (%).

AHC, acute hepatitis C.

Table 4 Clinical characteristics of acute hepatitis C cases between hospitals/clinics and blood donation centers ($n = 310$)

Variables	Hospitals and clinics	Blood donation centers	*P* value
Gender (Male/female)	44/18	202/46	0.046†
Geographical area (Southern vs. other areas)	22/40	175/73	< 0.001†
Age, years (mean ± SD)	49.3 ± 16.4	33.3 ± 11.1	< 0.001‡
ALT levels	1264.2 ± 706.8	244.9 ± 204.2	< 0.001‡

†Chi-square test.

‡*t*-test.

ALT: alanine aminotransferase; Acute hepatitis C includes definite and probable cases.

In suspected cases, positive serum anti-HCV was confirmed when first detected. It was difficult to differentiate whether these cases were AHC or chronic hepatitis C with acute exacerbation. Increased sensitivity of the second and third ELISA kit for detection of anti-HCV shortens the window period and allows earlier detection of serum anti-HCV.

Our previous study demonstrated that the rise in S/CO ratios using a third generation anti-HCV assay might be used as a supplemental diagnostic criterion for AHC infection cases without documented seroconversion.[17] An initial S/CO value < 40 with a rising pattern (≥ 40) might be the most common change of serial anti-HCV in such suspected cases. In addition, the study showed that the S/CO ratio remained unaltered in chronic hepatitis C with acute exacerbation. The stimulation of the HCV antigen over time increases the production of anti-HCV antibodies. We believed some of the suspected cases were AHC infection. It is possible to differentiate between AHC and acute exacerbation of chronic hepatitis C by this method. Only three cases (0.5%) met the AHC criterion in this study by measuring the rise in anti-HCV titer, and because no serial serum anti-HCV could be obtained in this retrospective study, we expect that more AHC cases will be diagnosed by using this method.

In fact, the majority of AHC cases are asymptomatic and difficult to identify, and only about 15% cases develop jaundice. In this study, almost all probable AHC cases at blood donation centers were subclinical hepatitis and asymptomatic, and the diagnosis of AHC for these cases depended on serial blood samples of anti-HCV with confirmation of seroconversion. Our previous hospital-based study identified more AHC cases by using the diagnostic criterion of rising anti-HCV titer without documented seroconversion, but the result showed only 7.3% (9/123) of AHC cases had been reported to TCDC.[5] Under-diagnosis and under-reporting of AHC are common problems worldwide, as the majority of AHC cases are asymptomatic and patients rarely seek medical help. Accordingly, enhancing current surveillance systems for AHC notifications is a real challenge to minimize under-reporting.

Southern Taiwan is one of the HCV endemic areas shown in some previous community and epidemiological studies in Taiwan.[27–29] There exist geographic variations of HCV infection; a hospital-based study in Taiwan showed significant geographic variation of HCV prevalence even among different townships within the same county.[27] Tsai *et al.* showed that the prevalence of anti-HCV in Tainan County (located in southern Taiwan) was 10.2%, with a range of 2.6–30.9% and 0–90.5%, at township and village levels, respectively.[28] Tzukuan, one of the HCV endemic townships in southern Taiwan, had an anti-HCV prevalence of 37% in men and 38% in women.[29]

There were some limitations of this epidemiological and retrospective study in a small proportion of AHC cases. A few AHC cases can clear HCV virus spontaneously without antibody seroconversion.[7] In addition, some of the excluded cases may be recent HCV infection within 6 months. Such cases might lead to underestimation of AHC diagnosis. On the other hand, some of the definite cases with positive HCV RNA plus negative anti-HCV may be immuno-compromised chronic HCV infection or false-positive HCV RNA results.[30] This retrospective study had no

available HCV RNA data for analysis, which also creates a potential bias. Among 447 reported cases from hospitals/clinics, 115 cases (26%) were not included because of lack of support for the study ($n = 101$) and some hospitals had been closed down ($n = 14$). This may lead to potential bias in the study. For analysis between two the groups; no significant difference in gender ($P = 0.32$) or report year ($P = 0.45$) was found, although the analyzed group (53.6 ± 18.0 vs 59.3 ± 18.3, $P = 0.04$) was younger in age.

The establishment of epidemiological data of AHC still presents many challenges. An appropriate AHC reporting system is necessary for epidemiologic research, and diagnostic accuracy of AHC reporting might improve through educating and training primary clinicians to be alert to AHC, and improving diagnostic methods of AHC to differentiate incidence and prevalent cases. Identification and active surveillance of HCV endemic areas and high-risk groups such as intravenous drugs users could also help the recognition of more AHC cases. Identification of AHC cases will allow further intervention and control of the disease, to decrease the spreading of HCV infection. Over-estimation of AHC diagnosis in reported cases is common by using current notification systems. On the other hand, a relatively high percentage of under-estimation also exists, because many AHC cases are asymptomatic.

In summary, our study showed over-diagnosis of AHC cases by using current diagnostic criteria. Greater efforts are needed to establish appropriate surveillance systems as well as supplemental methods to identify more AHC cases.

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Conflict of interest

None declared.

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