High antibody level: an accurate serologic marker of viremia in asymptomatic people with hepatitis C infection

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BACKGROUND: The screening and diagnosis of hepatitis C virus (HCV) infection is initiated by testing for antibody to HCV (anti-HCV). A positive anti-HCV test in blood donors represents ongoing infection in only a variable proportion of individuals. Because a high anti-HCV level has been associated with viremia, a study was conducted to determine whether a high antibody level is an accurate serologic marker for viremia in asymptomatic anti-HCV–positive persons.

STUDY DESIGN AND METHODS: In a diagnostic test study, we included 856 anti-HCV–positive blood donors in a blood bank at Guadalajara, Jalisco, Mexico, between 2002 and 2007. A third-generation amplified chemiluminescence assay (ChLIA HCV) was used to detect anti-HCV. A positive result of the qualitative nucleic acid test (HCV RNA) was considered the gold standard for viremia.

RESULTS: By receiver operating characteristic analysis, the signal-to-cutoff (S/CO) ratio of 20 or more was chosen as optimal to identify viremia and so was defined as high anti-HCV level. There was a significant difference in the proportion of viremia between subjects with high antibody level and those with lower levels (93.7% vs. 1.8%, respectively; $p < 0.001$). A high antibody level showed a sensitivity for viremia of 96.6% (95% confidence interval [CI], 93.8%-98.1%), a specificity of 96.6% (95% CI, 94.8%-97.8%), and a likelihood ratio of 28.6 (95% CI, 18.4%-44.6%).

CONCLUSION: A high antibody level (S/CO ratio ≥20 by ChLIA HCV) clearly divides the viremic from the nonviremic blood donors and functions as an accurate serologic marker to guide the use of routine HCV RNA testing to confirm hepatitis C infection.

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease in the world and most infected people are asymptomatic until complications appear. There has been a dramatic improvement in HCV testing over the past

ABBREVIATIONS: ChLIA = chemiluminescence assay; ROC = receiver operating characteristic; S/CO ratio = signal-to-cutoff ratio.

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decade with a variety of serologic and molecular tests.[1] The diagnosis of HCV infection begins with the detection of antibody to hepatitis C (anti-HCV), and the validation of every positive anti-HCV result is critical to confirm infection.[2-4] Testing directly for HCV RNA is the recommended practice in anti-HCV–positive patients with biochemical or clinical evidence of chronic liver disease, and ongoing hepatitis C infection is confirmed in more than 90% of these cases.[1] In contrast, in a population with low prevalence of HCV such as blood donors and general population, viremia is detected in as few as 30% to 40% of subjects with positive antibody,[2,5] and to proceed directly to HCV RNA testing may be a costly strategy.[6-8]

Anti-HCV test is automated and relatively inexpensive.[9] Second- and third-generation assays are used in laboratories around the world; an anti-HCV enhanced chemiluminescence assay (ChLIA HCV), FDA-approved, which is more sensitive than other assays, is now widely used.[10] Interestingly, although the concentration of antibodies is detected in a semiquantitative manner and expressed as a signal-to-cutoff (S/CO) ratio, the anti-HCV result is usually reported as positive (reactive, S/CO ratio $\geq$1) or negative (nonreactive, S/CO ratio <1). The level of the S/CO ratio is directly related to the antibody concentration.[9] To better define the use of supplemental testing in positive anti-HCV subjects, CDC guidelines recommend to include in the report a statement that samples with high S/CO ratios usually ($\geq$95%) confirm positive; for example, an S/CO ratio of 8 or more by ChLIA HCV predicts true-positive antibody results.[2]

It has been traditionally considered that the presence of the antibody does not distinguish between past acute infection with spontaneous viral clearance accompanied by antibody production and chronic hepatitis C infection with viremia.[2,11] In previous studies,[5,12-15] a high antibody level by ChLIA HCV was associated with viremia in patients with HCV infection but in these reports either a specific cutoff level was not established by an appropriate diagnostic test design or the number of the included subjects was too small to draw definitive conclusions. Because viral replication stimulates antibody production,[16-19] we hypothesized that a high anti-HCV level by ChLIA HCV would predict a positive HCV RNA test and could be used as an accurate serologic marker of viremia in antibody-positive blood donors with hepatitis C infection.

MATERIALS AND METHODS

Study population and setting

The study was conducted at the Central Blood Bank of the West National Medical Center of the Mexican Institute of Social Security, in Guadalajara, Jalisco, Mexico, between July 2002 and September 2007. This center serves approximately 3 million potential users and recruits 30,000 donors annually with a prevalence of 1% anti-HCV–positive donors. During the study period eligible subjects were those with positive anti-HCV results. Individuals without HCV RNA testing or coinfected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) were excluded. The study protocol and consent forms were approved by the National Board of Scientific Research of the Mexican Institute of Social Security.

The blood donors with positive antibody tests were contacted by telephone, telegram, or domiciliary visit, and we included only those willing to participate. After providing their written informed consent and before supplemental testing, the donors were interviewed to obtain information about demographic characteristics and hepatitis C risk factors.

Laboratory tests

A third-generation ChLIA HCV (VITROS, Ortho-Clinical Diagnostics, Johnson and Johnson, Raritan, NJ) was used to detect anti-HCV in the screened blood donors. The S/CO ratio was recorded directly from the automated equipment. Repeatedly reactive samples were considered positive when the S/CO ratio was 1 or more and negative when it was less than 0.90. Results of 0.90 or more but less than 1 were retested to define their reactivity. In addition, all participants were tested for HBV and HIV.

After the interview, two blood samples were obtained from all included subjects The first blood specimen was collected and handled in a manner suitable for performing a qualitative HCV RNA test with a commercially available, reverse transcription-polymerase chain reaction assay (Cobas Amplicor HCV test, Version 2.0; detection limit, 50 IU/mL; Roche Diagnostics, Branchburg, NJ). The assays were performed at the Molecular Diagnostic Laboratory of Specialties Hospital, West National Medical Center, and interpreted according to the manufacturer's recommendations. A recombinant immunoblot assay (RIBA, HCV 3.0, Chiron Corp., Emeryville, CA) was carried out on the second sample to identify true-positive anti-HCV results, in nonviremic subjects.

Definitions

Blood donors with positive HCV RNA were recorded as HCV viremic. Individuals with a negative HCV RNA and positive RIBA were considered as nonviremic, true antibody positive. Subjects with a negative HCV RNA result and a negative or indeterminate RIBA result were recorded as false-positive anti-HCV (non-hepatitis C).[2]

Follow-up

Patients with ongoing HCV infection were further evaluated at the clinic, where they received treatment when it

was indicated. The RIBA-positive blood donors without viremia were followed up with an HCV RNA test every 3 months to detect intermittent viremia. The blood donors with false-positive antibody results were informed of their results and received no further follow-up.

Statistical analysis

We required at least 700 anti-HCV–positive subjects to define the antibody level (S/CO ratio) with a 95% confidence interval (CI) within a range of ±3% of the point estimate for the specificity of viremia prediction. Receiver operating characteristic (ROC) analysis was applied to choose the optimal antibody level (sensitivity and specificity >95%) to identify viremia, using HCV RNA testing as the gold standard. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of the optimal S/CO ratio to predict viremia and these were compared to the S/CO level of 8 previously proposed by the CDC[2] to predict true anti-HCV–positive results. Because the antibody level does not have a normal distribution, the S/CO ratio is expressed as the mean and 2.5th, 25th, 50th, 75th, and 97.5th percentiles. Qualitative variables are presented as proportions, and age as mean and standard deviation (SD). General characteristics of the included subjects were compared with t test, the Mann-Whitney U test, and the chi-square test. Differences were considered significant at p values of less than 0.05. All data collection and analyses were performed with computer software (Visual Fox Pro, Version 9.0, Microsoft Corp., Redmond, WA; EPI-Info, Version 6, CDC, Atlanta, GA; and SPSS, Version 15.0, SPSS, Inc., Chicago, IL).

RESULTS

During the study period, 149,995 blood donors were evaluated for HCV antibody by ChLIA HCV. This test was positive in 1511 individuals (1.01%). Of these, 626 blood donors did not agree to participate for personal reasons (such as work or schedule restriction) or when they could not be located because their data were incompletely recorded. In addition we excluded 23 subjects because of unavailable HCV RNA testing and six because of coinfection with HBV or HIV. The records of all blood donors were available, in accordance with the institutional requirements; however, we did not make any analysis of the excluded subjects, because only blood donors who accepted participation were evaluated with supplemental testing (HCV RNA and RIBA). Thus, 856 asymptomatic subjects were available for analysis. The demographic, serologic, and virologic characteristics and hepatitis C risk factors of the included population are described in Table 1. HCV RNA was tested in all included individuals

TABLE 1. Demographic, serologic, and virologic characteristics of 856 anti-HCV–positive subjects

Characteristic	Viremic* subjects, n = 293 (34.2%)	Nonviremic subjects, n = 563 (65.8%)			p value§
		Positive RIBA,† n = 54 (6.3%)	Indeterminate or negative RIBA,‡ n = 439 (51.3%)	RIBA, not available, n = 70 (8.2%)	
Demographics					
Mean age, years (SD)	36.8 (10.2)	38.9 (10.6)	33.4 (9.8)	36.0 (9.1)	<0.001
Male sex, n (%)	194 (66.2)	28 (51.9)	289 (65.8)	38 (54.3)	0.06
No elementary school, n (%)	28 (9.6)	7 (13.0)	27 (6.2)	5 (7.1)	0.18
Risk factors, n (%)					
Transfusion before 1994	105 (35.8)	22 (40.7)	49 (11.2)	16 (22.9)	<0.001
Injection drug use	27 (9.2)	2 (3.7)	6 (1.4)	1 (1.4)	<0.001
Acupuncture	24 (8.2)	4 (7.4)	40 (9.1)	10 (14.3)	0.46
Tattoos	64 (21.8)	7 (13.0)	47 (10.7)	8 (11.4)	0.001
Glass syringes¶	99 (33.8)	20 (37.0)	136 (31.0)	23 (32.9)	0.69
Shared syringes	20 (6.8)	1 (1.9)	4 (0.9)	6 (8.6)	<0.001
Lifetime sexual partners ≥6	71 (24.2)	6 (11.1)	52 (11.8)	9 (12.9)	<0.001
Homosexual	8 (2.7)	0 (0.0)	9 (2.1)	4 (5.7)	0.18
Casual sex ever	56 (19.1)	8 (14.8)	47 (10.7)	8 (11.4)	0.015
Appropriate condom use	46 (15.7)	12 (22.2)	92 (21.0)	11 (15.7)	0.24
Sex with prostitutes ever	61 (20.8)	7 (13.0)	51 (11.6)	8 (11.4)	0.004
Any hepatitis family history	77 (26.3)	19 (35.2)	118 (26.9)	14 (20.0)	0.30
Any surgery history	188 (64.2)	31 (57.4)	216 (49.2)	43 (61.4)	<0.001
Alcoholism	35 (11.9)	1 (1.9)	18 (4.1)	7 (10.0)	<0.001
Any hospitalization	205 (70.0)	36 (66.7)	216 (49.2)	46 (65.7)	<0.001
Any invasive procedures	48 (16.4)	10 (18.5)	40 (9.1)	8 (11.4)	0.016
Any dental procedures	207 (70.6)	39 (72.2)	299 (68.1)	50 (71.4)	0.85

* Viremic: individuals with positive HCV RNA were recorded as HCV infected.
† Individuals with a negative HCV RNA and positive RIBA were considered as nonviremic, true antibody positive.
‡ Subjects with a negative HCV RNA result and a negative or indeterminate RIBA result were recorded as false-positive anti-HCV (non–hepatitis C).
§ For comparison of viremic with nonviremic donors; all p values are two-sided.
¶ Glass syringes means the former or current use of reusable crystal syringes.

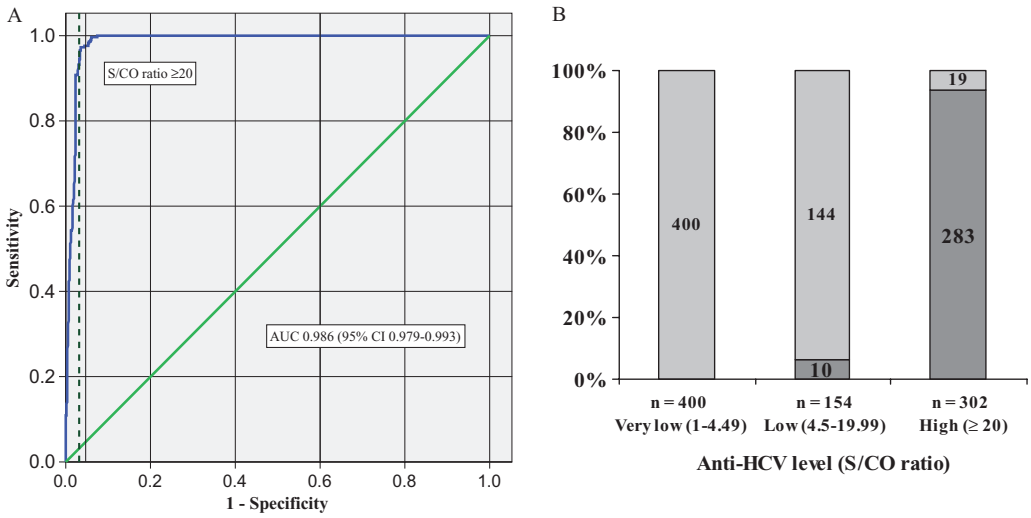

Fig. 1. The ROC curve and probability of viremia according to hepatitis C antibody levels. (A) Dashed line crosses the ROC curve at the S/CO ratio of 20 or more. A perfect test would have 100% sensitivity and 100% specificity and would include a point at the upper left-hand corner. The diagonal line would be a test with no discriminatory power. (B) Distribution of the screened subjects according to their antibody level; the values in the bars represent the number of subjects. (■) Viremic; (□) nonviremic. The percentages of HCV viremic subjects according to the antibody level were as follows: high level 93.7%, low level 6.5%, and none with very low level. AUC = area under the curve.

and viremia was detected in 293 (34.2%) samples representing viremic subjects, whereas 563 (65.8%) had a negative HCV RNA test (Table 1). RIBA testing was performed in 493 nonviremic donors and was deemed positive in 54, representing true-positive anti-HCV results without viral replication. The RIBA test result was not available for 70 subjects.

TABLE 2. Diagnostic performance of different cutoff points for the S/CO ratio of anti-HCV by ChLIA HCV as predictor of viremia

Performance measure	Cutoff value ≥8	Cutoff value ≥20*
Sensitivity, %	100 (98.7-100)†	96.6 (93.8-98.1)
Specificity, %	85.3 (82.1-87.9)	96.6 (94.8-97.8)
Negative predictive value, %	100 (99.2-100)	98.2 (96.7-99.0)
Positive predictive value, %	77.9 (73.5-81.8)	93.7 (90.4-95.9)
Negative likelihood ratio	0.00	0.03 (0.02-0.06)
Positive likelihood ratio	6.8 (5.6-8.3)	28.6 (18.4-44.6)

* Optimal level of the antibody (S/CO ratio) that identified viremia.
† Values in parentheses are 95% CIs.

On the basis of ROC analysis, we chose the value of 20 or more as the optimal cutoff point for the S/CO ratio to identify viremia (sensitivity and specificity >95%). Then, results with an S/CO ratio of 20 or more were classified as high antibody level. The ROC curve is shown in Fig. 1A. Those samples with an S/CO ratio between 4.5 and 19.99 were considered as low level, and ratios between 1 and 4.49 were designated as very low level. This last group was selected because it has been shown that the very low anti-HCV level indicates a null risk of having HCV infection.[5] A high antibody level was found in 302 samples (35.3%), a low level in 154 subjects (18%), and a very low level in 400 (46.7%) of the 856 blood donors (Fig. 1B). Viral replication was confirmed by positive HCV RNA testing in 283 of the 302 blood donors with high antibody level, whereas only 10 of the 154 subjects with low anti-HCV level were viremic ($p < 0.001$); none of the subjects with very low antibody levels showed viremia. There was a significant difference in the frequency of viral replication between patients with the high anti-HCV level and those below it (93.7% vs. 1.8%, respectively; $p < 0.001$). An S/CO ratio of 20 or more offered better discriminatory ability of the test to identify viremia in anti-HCV–positive subjects than did the value of 8, as can be seen in Table 2. Our method yields a higher specificity and positive predictive value to identify viremic individuals among true antibody positives and gives an excellent positive likelihood ratio of 28.6 (95% CI, 18.4-44.6).

As shown in Fig. 2, the 293 viremic subjects in the study population showed higher antibody levels (mean S/CO ratio, 27.6; 95% CI, 17.45-37.1) compared with the 54 individuals with serologically confirmed hepatitis C without viremia (mean S/CO ratio, 14.2; 95% CI, 1.06-32.23; $p < 0.001$). These nonviremic individuals with positive RIBA were followed up every 3 months with an HCV RNA test to identify intermittent viral replication. After a mean of five determinations, all of them remained

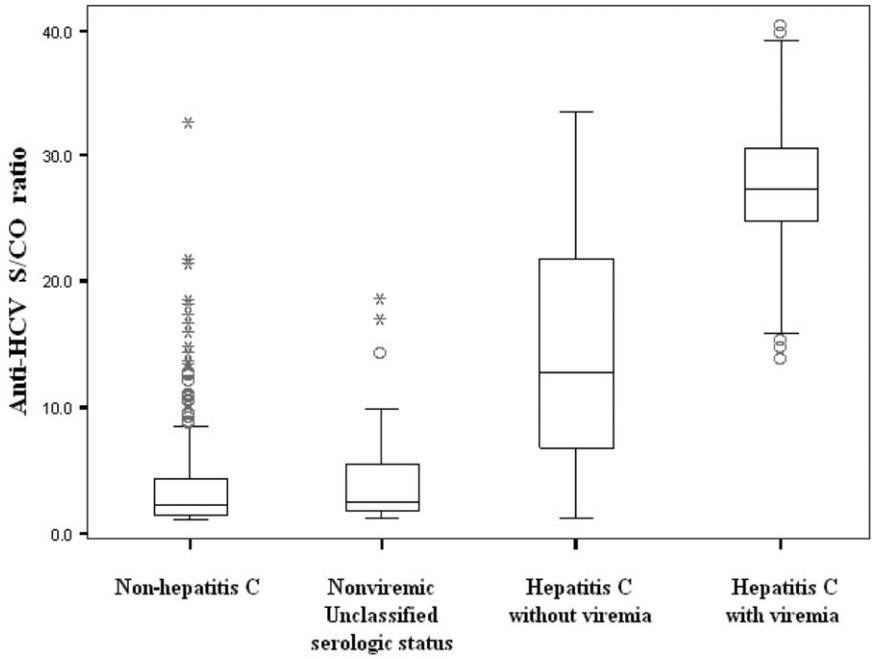

Fig. 2. Box-and-whisker figure for the level of the anti-HCV S/CO ratio according to the serologic and viral status. The horizontal line within each box represents the median, and the top and bottom of each box represent the 25th and 75th percentiles, respectively. The I bars represent the 2.5th and 97.5th percentiles. The circles represent mild outliers and the asterisks denote extreme outliers.

negative for HCV RNA (data not shown). The 439 blood donors with negative or indeterminate RIBA without viremia, defined as non–hepatitis C, showed a mean S/CO ratio of 3.5 (95% CI, 1.04-14.65). This value is comparable with that of 70 nonviremic individuals (mean S/CO ratio, 4.0; 95% CI, 1.06-17.22) with unclassified serologic status (no available RIBA).

DISCUSSION

Our study shows that a high anti-HCV level (S/CO ratio ≥20 by ChLIA HCV) provides an accurate marker for predicting viremia in asymptomatic antibody-positive blood donors. A high antibody level yields a higher specificity and positive predictive value to identify viremic individuals among true antibody positives and gives an excellent positive likelihood ratio. This is the first study to use ROC analysis to determine the optimal level of anti-HCV that functions as a serologic marker of viremia. A high antibody level does not obviate the need for HCV RNA testing, but it functions as a tool to guide the use of routine HCV RNA testing in blood donors.

Most of the asymptomatic HCV-infected patients around the world are detected when they donate blood, and only a variable proportion has viral replication. Evidence of viremia defines the diagnosis of ongoing HCV infection, independent of the liver histology findings.[20] Interestingly, the ability of the anti-HCV assay to differentiate viremic from nonviremic depends on the level of the S/CO ratio that is chosen. Our study in a population with low prevalence of HCV, such as the blood donors, demonstrates that an S/CO ratio of 20 or more by ChLIA HCV has a specificity higher than 95% for the presence of viremia, in contrast with the value of 8 (specificity of 85.3%), which is recommended to define true-positive anti-HCV results.[2] Two fundamental differences exist between CDC current guidelines[2] and our study. First, we used the ROC analysis to define the best cutoff point of the antibody level to identify the major proportion of viremic subjects, and so an S/CO ratio of 20 or more by ChLIA HCV was defined as high anti-HCV level, in contrast to CDC guidelines, which identified true-positive anti-HCV results using an S/CO ratio of 8 or more; this level does not distinguish between current or past infection. Second, we demonstrate that the high antibody level is an accurate serologic marker of viremia to identify asymptomatic people who need supplemental testing with routine HCV RNA to confirm hepatitis C infection, in contrast to CDC's recommendation to perform either HCV RNA or RIBA testing.[2] In addition, in a new confirmatory algorithm that integrates the multiplex nucleic acid test (HCV NAT), the high antibody level of the S/CO ratio is a criterion to establishing HCV infection with reactive HCV NAT results, and RIBA testing need not be performed.[21] Furthermore, the high

sensitivity and predictive value of the S/CO ratio of 20 or more by ChLIA HCV for viremia has been observed in different populations, including those with low and high prevalences of hepatitis C;[5,12-15] these studies support the hypothesis that regardless of the anti-HCV prevalence or characteristics of the population being tested, a high antibody level predicts viremia. The mechanism of the strong correlation between high anti-HCV levels and HCV RNA positivity has not been established. We speculate that continuous antigenic stimulation in the presence of viral replication maintains a high antibody level. To the best of our knowledge, ours is the first report that demonstrates a positive likelihood ratio greater than 10 for predicting viremia in asymptomatic antibody-positive blood donors, which is an excellent likelihood ratio.[22-24]

HCV infection presents an enormous health burden that is expected to increase two- to fourfold over the next decades.[7,25,26] Because, most infected persons are asymptomatic and are unlikely to be aware that they are infected, it is necessary to improve current HCV testing practices to identify HCV-infected people without overt clinical picture of liver disease. It has been proposed that HCV RNA testing should be performed only in subjects with a high likelihood of being viremic.[6] In our study, 93 of each 100 subjects with a high antibody level (S/CO ratio ≥20) by ChLIA HCV were viremic, and proceeding directly to HCV RNA testing of these patients only is an adequate and cost-effective strategy (Table 3). Using the high antibody levels as a serologic marker of viremia maximizes the accuracy of the interpretation of the positive antibody results. The use of the S/CO ratio to guide the decision for routine HCV RNA testing provides a "golden opportunity" to allow those who interpret anti-HCV tests to detect asymptomatic persons probably needing antiviral treatment before they develop fibrosis or cirrhosis.

In the course of the natural history of HCV infection, several changes in antibody kinetics can be observed.[16] In our study, low antibody levels (S/CO ratio between 4.5 and 19.99) occur in nonviremic RIBA-positive subjects and they did not show intermittent viral replication during follow-up. We hypothesized that the partial seroreversion with low antibody levels that occurs in RIBA-positive subjects, compared with high antibody levels in viremic subjects, may be related to a loss of antigenic stimulation in the absence of viral replication. In these cases, it is likely that the infection has undergone spontaneous clearance. Such clearance limits the consequences of infection: because patients no longer harbor the virus they will neither transmit infection nor be at risk of HCV-related disease.[19] On the other hand, we demonstrated that only 10 (1.8%) of the subjects with an S/CO ratio of less than 20 were viremic; to proceed directly to HCV RNA testing in all subjects with low antibody levels then seems not to be cost-effective. Testing with RIBA is still necessary in low-prevalence populations[2,6] such as blood donors to identify

TABLE 3. Guidelines for interpreting results of positive anti-HCV by antibody levels and type of recommended supplemental testing

Antibody level (S/CO ratio)*	Probability of HCV viremia (%)	Supplemental testing			Suggested action
		Recommended	Result	Interpretation	
Very low level	0†	None	—	Anti-HCV false positive (non–hepatitis C)	Notify
Low level	<10	RIBA	Positive‡	Anti-HCV true positive	HCV RNA testing
			Negative	Anti-HCV false positive (non–hepatitis C)	Notify
			Indeterminate§	HCV status not determined	Anti-HCV or HCV RNA testing
High level	>90	HCV RNA	Positive	Anti-HCV true positive with viremia (hepatitis C infection)	Notify and evaluate for antiviral therapy
			Negative¶	Nonviremic hepatitis C	Notify

* By amplified ChLIA: very low antibody level, S/CO ratio 1 to 4.49; low antibody level, S/CO ratio 4.5 to 19.99; high antibody level, S/CO ratio 20 or more.
† 95% or more represents false reactivity; less than 5% represents nonviremic true-positive anti-HCV.
‡ RIBA-positive indicates past or present HCV infection; these subjects require HCV RNA testing because of a low possibility of being viremic.
§ Perform HCV RNA testing or repeat anti-HCV testing (another sample collected >1 month later). Indeterminate RIBA and negative HCV RNA result is considered as false-positive anti-HCV.
¶ A single negative HCV RNA result does not rule out active infection because viremia may be intermittent; another determination of HCV RNA test should be considered (3 or 6 months later).

true-positive anti-HCV results when the S/CO ratio is between 4.5 and 19.99. In this scenario, only a RIBA-positive subject requires HCV RNA testing because of a low possibility of being viremic (Table 3). However, the RIBA test has disadvantages, such as the variable proportion of indeterminate results[27] and the extended time required for its execution. Therefore, its use is not currently recommended.[1,11,27-29] Simple assays of cellular immunity, such as interferon enzyme-linked immunospot, might be added to the methods for the diagnosis of HCV infections,[30] mainly in cases with low antibody levels.

Despite the accuracy of third-generation immunoassays in detecting antibodies and the high reliability of the automated equipment,[31] false-positive anti-HCV results occur at unacceptable frequencies (15%-62%), predominantly in low-prevalence populations.[2,5] The proportion of false-positive anti-HCV results is inversely related to the prevalence of the disease.[2] In our study, approximately half the subjects (400, 46.7%) had very low antibody levels. Recently, it has been reported that very low antibody levels (<4.5 S/CO ratio by ChLIA HCV) have more accuracy in detecting false-positive and even irrelevant indeterminate results; further diagnostic testing is not necessary in samples with an S/CO ratio of and 4.5. It has been shown that the very low anti-HCV level indicates a null risk of having HCV infection.[5] The application of this recommendation avoids an erroneous hepatitis C diagnosis associated with incorrect notification of false-positive anti-HCV results and the attendant costs for consultations and repeated HCV RNA testing (Table 3).

The robustness of our study derives from several factors. The sample size was sufficiently large and validation with HCV RNA testing results was obtained on all included samples. However, some limitations of the study should be considered. We did not include high-prevalence hepatitis C or immunocompromised populations and our proposal is only applicable when the third-generation ChLIA HCV assay is used. Because this and other commercially available automated chemiluminescence immunoassay analyzers are now replacing conventional enzyme immunoassays in clinical laboratories;[15] additional studies with other assays are required to define the optimal S/CO ratio predicting viremia with at least 95% accuracy.[2] All laboratories that provide anti-HCV testing should validate their own high-level S/CO threshold with the assay used for the screening.

In conclusion, based on our study, a high anti-HCV level (S/CO ratio ≥20), obtained by a third-generation amplified ChLIA HCV, is a predictor of viremia in anti-HCV–positive blood donors. The strategy based on the antibody level to determine the next step in hepatitis C diagnosis allows an efficient approach, in terms of time and cost, in most of the screened anti-HCV–positive subjects by ChLIA HCV. Anti-HCV testing is performed in multiple settings including blood banks or health department facilities, and asymptomatic people with a positive anti-HCV result are frequently evaluated by clinicians. Our new proposal is an acceptable alternative to the current algorithms because it provides superior accuracy in detecting viremic individuals who need routine supplemental HCV RNA testing (Table 3) and terminates the diagnostic evaluation in subjects with false-positive antibody results identified by very low antibody levels. This approach can be implemented without increasing test costs because the S/CO ratio is automatically generated in most analyzers. Because a general lack of understanding exists regarding the interpretation of anti-HCV results, when more specific testing should be performed, and which tests should be considered for this purpose,[2] we recommend the inclusion of the S/CO ratio and the type of the immunoassay in the written anti-HCV reports; the ordering physician should be informed that more specific testing with HCV RNA should be requested to confirm HCV infection in patients with high antibody levels. Moreover, this strategy would provide clinicians with accurate information for correctly identifying those anti-HCV–positive patients who are infected and need antiviral treatment.

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CONFLICT OF INTEREST

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