Research Article

DOI: 10.4274/vhd.galenos.2023.2022-11-2
Viral Hepatitis Journal 2023;29(2):52-57

The Effect of HCV-RNA, HCV-Genotype 1b, and Anti-HCV Positivity on Laboratory Parameters

HCV-RNA, HCV-Genotip 1b ve Anti-HCV Pozitifliğinin Laboratuvar Parametrelerine Etkisi

Sanem Karadağ Gencer[1], Yasemin Üstündağ[2], Kağan Huysal[2]

[1]*University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Department of Microbiology, Bursa, Turkey*
[2]*University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Department of Biochemistry, Bursa, Turkey*

ABSTRACT

Objectives: We aimed to compare the effect of hepatitis C virus (HCV)-RNA, HCV-genotype 1b, and anti-HCV positivity on laboratory parameters in our study.

Materials and Methods: HCV-RNA and anti-HCV tests were analyzed from 500 patients and the HCV genotyping test was applied to 100 patients between January 2018 and September 2020. Hemoglobin, white blood cell, platelet (PLT), mean platelet volume (MPV), platelet distribution width, the volume of platelet of total blood volume-plateletcrit, mean corpuscular volume, red cell distribution width, alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, prothrombin time, partial thromboplastin time (PTT), International Normalized Ratio values were analyzed simultaneously.

Results: Age, AFP levels, AST, ALT, GGT, ALP, PTT, and MPV values were detected to be significantly higher in HCV-RNA positive patients than in HCV-RNA negative patients. Anti-HCV titer, PLT, and albumin values were found to be lower in HCV-RNA positive patients compared with HCV-RNA negative patients. HCV-RNA, AST, ALP, and GGT values were higher in anti-HCV positive patients compared to anti-HCV negative patients. Albumin values were lower in anti-HCV positive patients than in anti-HCV negative patients. The average age of patients with HCV-genotype 1b was determined to be higher than that of patients with non-HCV-genotype 1b.

Conclusion: HCV-RNA is the most important specific biomarker that affects other non-specific parameters used to evaluate HCV infection. The detection of genotype 1b in patients with HCV infection may be guiding in the treatment of older patients than non-genotype 1b.

Keywords: HCV-RNA, anti-HCV, HCV-genotype 1b

ÖZ

Amaç: Çalışmamızda hepatit C virüs (HCV)-RNA, HCV-genotip 1b ve anti-HCV pozitifliğinin laboratuvar parametrelerine etkisini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza Ocak 2018-Eylül 2020 tarihleri arasında hastanemize başvurup HCV-RNA, anti-HCV testleri yapılan 500 hasta ve HCV genotiplendirme testi yapılan 100 hasta dahil edildi. Hastaların eş zamanlı alınan kanlarından hemoglobin, beyaz kan hücresi, trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği, kandaki trombosit oranı, ortalama hücresel hacim, kırmızı hücre dağılım genişliği, alfa-fetoprotein (AFP), aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP), gama-glutamil transferaz (GGT), albümin, protrombin zamanı, parsiyel tromboplastin zamanı (PTT), Uluslararası Normalleştirilmiş Oran değerleri eş zamanlı, retrospektif olarak incelendi.

Bulgular: HCV-RNA pozitif hastalarda HCV-RNA negatif hastalara göre, yaş, AFP, AST, ALT, GGT, ALP, PTT ve MPV değerleri anlamlı yüksek saptandı ($p<0.01$). HCV-RNA pozitif hastalarda HCV-RNA negatif hastalara göre, anti-HCV titresi, PLT ve albümin değerleri düşük bulundu. Anti-HCV pozitif hastalarda anti-HCV negatif hastalara göre, HCV-RNA, AST, ALP ve GGT değerleri yüksek saptandı. Anti-HCV pozitif hastalarda, anti-HCV negatif hastalara göre albümin değerleri düşük belirlendi. HCV-genotip 1b saptanan hastaların yaş ortalaması, HCV-genotip 1b dışındaki genotip saptanan hastalara göre yüksek belirlendi.

Sonuç: HCV-RNA pozitifliği, HCV enfeksiyonunu değerlendirmek için kullanılan diğer spesifik olmayan parametreleri etkileyen en önemli spesifik biyobelirteçtir. HCV enfeksiyonu olan hastalarda genotip 1b'nin saptanması, genotip 1b olmayanlara göre daha yaşlı hastaların tedavisinde yol gösterici olabilir.

Anahtar Kelimeler: HCV-RNA, anti-HCV, HCV-genotip 1b

Cite this article as: Karadağ Gencer S, Üstündağ Y, Huysal K. The Effect of HCV-RNA, HCV-Genotype 1b, and Anti-HCV Positivity on Laboratory Parameters. Viral Hepatitis Journal 2023;29(2):52-57

Address for Correspondence: Sanem Karadağ Gencer MD, University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Microbiology, Bursa, Turkey
Phone: +90 224 295 50 00 **E-mail:** sanemkaradag@yahoo.com **ORCID ID:** orcid.org/0000-0002-3567-4262 **Received:** 03.11.2022 **Accepted:** 16.06.2023

Introduction

It is estimated that 71 million people worldwide are infected with the hepatitis C virus (HCV) (1,2). Acute HCV infection usually has an asymptomatic course and, if left untreated, becomes chronic and progresses to clinical conditions up to cirrhosis and hepatocellular cancer. The diagnosis of HCV infection is primarily based on an anti-HCV test that provides the detection of the HCV antibody. Anti-HCV tests may not be sufficient for the diagnosis of acute HCV infection because of the window period. Also, the establishment of false positivity and HCV-RNA negativity in low anti-HCV positive titrations may result in delays in the diagnosis and treatment of HCV infection (3). The polymerase chain reaction (PCR) test is based on viral RNA detection and is used more advantageously in the diagnosis of acute HCV infection, where serological tests are negative or false positivity should be evaluated with serological tests (4). The HCV-RNA test is used for scanning and diagnostic purposes, verification, monitoring, and treatment of active HCV infection. Another test used in HCV infection allows HCV genotyping testing to determine HCV subtypes and allows treatment response and disease prognosis to be evaluated (5,6,7). Different HCV genotypes show characteristic distributions in different parts of the world. Genotype 1 (subtype 1b) has the highest global prevalence (8,9,10,11). The persistence treatment of genotype 1b is more difficult than other genotypes, and therefore the requirement for HCV genotyping has been highlighted in many studies (12,13,14). In addition, non-specific biochemical and hematological parameters related to liver function are evaluated in the diagnosis and follow-up of HCV infection (15). Early diagnosis and effective management of HCV infection can prevent the progression of the disease (16,17).

In our study, we aimed to compare the effect of HCV-RNA, HCV-genotype 1b, and anti-HCV positivity on laboratory parameters.

Materials and Methods

Our study was conducted at University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, which serves the South Marmara region with a population of approximately 5 million. The study protocol was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2022/01-15, sate: 26.01.2022).

HCV-RNA and anti-HCV tests were analyzed from 500 patients and the HCV genotyping test was retrospectively applied to 100 patients between January 2018 and September 2020 hemoglobin (HGB), white blood cell (WBC), platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), the volume of platelet of total blood volume-plateletcrit (PCT), mean corpuscular volume (MCV), red cell distribution width (RDW), alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin, prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR) values were analyzed simultaneously and retrospectively.

The anti-HCV test was performed in a fully automated COBAS e601 (Roche, Germany) device with the chemiluminescent method in the ELISA laboratory of our hospital. HCV-RNA and HCV genotyping tests were conducted at our hospital PCR laboratory. The HCV-RNA extraction was done in a Qiasympony RGQ (Qiagen, Germany) device with the fully automated system. HCV-RNA amplification was performed in a Rotor-Gene Q (Qiagen, Germany) device with the real-time PCR method. RNA extraction for HCV genotyping was performed in a Qiasympony RGQ (Qiagen, Germany) device with the fully automated system. The HCV genotyping assay was manually performed using the Qiagen HCV genotyping kit. HGB, WBC, PLT, MPV, PDW, PCT, MCV and RDW values were analyzed with the Hematology Analyzer (Mindray, BC-6000, China) device in the Hematology Laboratory of our hospital. AFP, AST, ALT, ALP, GGT, and albumin levels were studied with COBAS 8000 (Roche, Germany) in the Biochemistry Laboratory of our hospital. PT, PTT, and INR tests were performed with a SYSMEX C55160 (Siemens, Germany) device in the Biochemistry Laboratory of our hospital.

Statistical Analysis

Data were expressed as frequency or related percent values. Normality analyzes were performed for data (n>50) with the Kolmogorov-Smirnov test. A comparison of the two groups was done with the Independent sample t-test for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters. Comparison of more than two groups was done with Kruskal-Wallis tests for non-normally distributed parameters. Data were analyzed using SPSS Statistics for Windows, version 23.0 (IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp). $P<0.05$ and $p<0.01$ were accepted as statistically significant.

Results

Biomarkers of patients were compared according to HCV-RNA positivity in Table 1. Age, AFP levels ($p<0.05$, $p<0.05$), and AST, ALT, GGT, ALP, PTT, and MPV values ($p<0.01$) were detected to be significantly higher in HCV-RNA positive patients than in HCV-RNA negative patients. Anti-HCV titer, PLT, and albumin values were found to be lower in HCV-RNA positive patients compared to HCV-RNA negative patients ($p<0.05$) ($p<0.01$) ($p<0.01$). There was no significant difference in the WBC, HGB, MCV, RDW, PT, INR, PDW, and PCT values of the patients according to HCV-RNA positivity.

Comparison of biomarkers of patients according to anti-HCV positivity is shown in Table 2. HCV-RNA, AST, ALP, and GGT values were higher in anti-HCV positive patients compared to anti-HCV negative patients ($p<0.05$) ($p<0.05$) ($p<0.01$) ($p<0.05$). Albumin values were lower in anti-HCV positive patients than in anti-HCV negative patients ($p<0.05$). There was no significant difference in age, WBC, HGB, PLT, MCV, RDW, AFP, ALT, PT, PTT, INR, MPV, PDW and PCT values according to anti-HCV positivity.

Comparison of biomarkers of patients with genotype 1b and genotypes other than HCV-genotype 1b detected is shown in Table 3. The average age of patients with HCV-genotype 1b was determined to be higher than that of patients with non-HCV-genotype 1b ($p<0.01$). HCV-RNA, anti-HCV titer, WBC, HGB, PLT, MCV, RDW, AFP, AST, ALT, ALP, GGT, albumin, PT, PTT, INR, MPV, PDW, and PCT values showed no significant difference in patients with HCV-genotype 1b according to genotypes other HCV-genotype 1b detected.

Discussion

Accurate determination of the presence of HCV infection and advanced description of the HCV with HCV-genotyping is essential for effective treatment (18). According to our study, there was no significant difference between HCV genotyping and HCV-RNA values, anti-HCV titration, and biochemical and hematological parameters, although the average age of patients was higher with genotype 1b than patients with non-genotype 1b genotype. According to studies, the effect of the HCV genotype on biochemical biomarkers is contradictory. In some studies, there is no relationship between viral genotypes and biomarkers, whereas in some studies, AST, ALT, and ALP values were higher in patients with genotype 1 (12). In addition, some studies showed that high viral load was associated with HCV genotype 1 or found no association with HCV genotype (8).

The HCV-RNA test must be studied for anti-HCV positive patients, and the genotype test should be studied for HCV-RNA positives, but the combined use of HCV-RNA and genotyping tests together to evaluate HCV infection has remained only 50% in the last 10 years in Turkey (19). Although some studies showed that anti-HCV antibody titration can be used to determine HCV viremia and indicates a positive correlation with HCV-RNA, some studies showed the opposite (2,20,21). According to our study, the detection of HCV-RNA and genotype 1b positivity without higher anti-HCV levels shows that HCV-RNA values are more valuable than anti-HCV values in assessing HCV acute infection and activation.

Hypoalbuminemia has been reported as an important prognostic factor in HCV infection (22,23). In our study, the determination of lower albumin values in patients with anti-HCV-positive and HCV-RNA-positive that the albumin values guide the evaluation of the prognosis of HCV infection in HCV-RNA- and anti-HCV -positive HCV patients regardless of genotype.

HCV viral load was found to be associated with lower PLT values, and the HCV-RNA viral load was identified as a biomarker of disease prognosis and treatment response (15,24,25). According to our study, the detection of lower PLT values in HCV-RNA positive patients shows that lower PLT values can provide information on disease behavior, regardless of anti-HCV and genotyping in HCV-RNA-positive patients.

MPV, which shows PLT function and activation, was associated with advanced fibrosis and disease severity in patients

Table 1. Comparison of biomarkers according to HCV-RNA positivity

	HCV-RNA negative	HCV-RNA positive	p
	Mean ± SD	Mean ± SD	
Age	51±19	55±19	**0.017**[a*]
HCV-RNA	0	4269331±5640479	**0.001**[b**]
Anti-HCV titer	48.8±52.0	45.9±25.4	**0.023**[b*]
WBC	7.6±2.5	8.1±6.2	0.236[a]
HGB	13.2±1.9	13.5±2.3	0.282[b]
PLT	247±81	224±92	**0.004**[a**]
MCV	87.1±6.4	87.5±7.0	0.579[a]
RDW	14.1±1.7	14.2±2.0	0.388[b]
Alpha-fetoprotein	5.5±13.1	46.5±306.6	**0.023**[b*]
AST	34±58	67±99	**0.001**[b**]
ALT	34±72	82±162	**0.001**[b**]
ALP	102±133	241±1070	**0.006**[b**]
GGT	34±54	101±181	**0.001**[b**]
Albumin	4.5±0.6	4.4±2.8	**0.001**[b**]
PT	13.6±2.5	13.6±2.0	0.887[a]
PTT	26.3±4.8	27.8±4.9	**0.006**[a**]
INR	1.2±2.0	1.0±0.1	0.345[b]
MPV	9.70±1.52	10.08±1.18	**0.002**[b**]
PDW	16.14±1.09	16.06±1.27	0.463[b]
PCT	0.24±0.13	0.22±0.09	0.089[b]

[a]: Independent t-test, [b]: Mann-Whitney U test, *p<0.05 **p<0.01, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 2. Comparison of biomarkers of patients according to anti-HCV positivity

	Anti-HCV negative	Anti -HCV positive	p
	Mean ± SD	Mean ± SD	
Age	44±18	52±19	0.174[a]
HCV-RNA	0	1825303±4403095	**0.008**[b]
Anti-HCV titer	0.3±0.5	49.0±43.0	**0.001**[b]
WBC	7.8±2.9	8.0±5.0	0.916[a]
HGB	12.7±1.8	13.3±2.1	0.328[b]
PLT	256±84	242±88	0.602[a]
MCV	86.9±4.6	86.9±6.9	0.984[a]
RDW	13.9±1.0	14.2±2.0	0.774[b]
Alpha-fetoprotein	2.0±1.1	32.0±248.6	0.109[b]
AST	18±7	51±88	**0.012**[b]
ALT	17±9	56±127	0.076[b]
ALP	52±15	139±204	**0.001**[b]
GGT	19±9	64±102	**0.027**[b]
Albumin	4.8±0.4	4.4±2.4	**0.016**[b]
PT	14.3±0.8	13.5±2.4	0.421[a]
PTT	28.9±3.2	26.5±5.1	0.266[a]
INR	1.0±0.0	1.2±1.7	0.452[b]
MPV	9.78±1.39	9.88±1.41	0.502[b]
PDW	16.25±0.44	16.06±1.31	0.128[b]
PCT	0.22±0.07	0.24±0.13	0.060[b]

[a]: Independent t-test, [b]: Mann-Whitney U test, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 3. Comparison of biomarkers of patients with genotype 1b and genotypes other than HCV-genotype 1b detected

	HCV-genotype 1b	Genotypes other than HCV-genotype 1b	p
	Mean ± SD	Mean ± SD	
Age	61±15	46±18	**0.001**[a]
HCV-RNA	3524425±5254788	4109971±6109528	0.521[b]
Anti-HCV titer	46.9±21.2	41.4±27.7	0.245[b]
WBC	7.4±2.3	9.1±10.2	0.185[a]
HGB	13.5±2.1	13.6±1.9	0.901[b]
PLT	208±70	232±106	0.060[a]
MCV	88.3±7.2	87.6±6.5	0.488[a]
RDW	14.0±1.6	14.2±2.8	0.381[b]
Alpha-fetoprotein	69.6±397.2	16.3±47.6	0.425[b]
AST	62±99	56±78	0.802[b]
ALT	80±179	61±87	0.479[b]
ALP	124±142	390±1874	0.080[b]
GGT	81±99	94±258	0.230[b]
Albumin	4.6±3.4	4.3±0.6	0.529[b]
PT	13.6±1.9	13.5±2.0	0.706[a]
PTT	26.8±5.2	27.5±5.0	0.442[a]
INR	1.3±2.4	1.0±0.1	0.963[b]
MPV	10.20±1.15	10.08±1.23	0.500[b]
PDW	16.14±0.44	16.16±0.50	0.723[b]
PCT	0.21±0.07	0.26±0.26	0.102[b]

[a]: Independent t-test [b]: Mann-Whitney U tests, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

with chronic hepatitis C (26,27,28,29,30). Our study shows that higher MPV values in HCV-RNA-positive patients regardless of anti-HCV and genotype 1b positivity can be a non-invasive guide in evaluating the severity of liver disease in HCV infection.

Elevated AFP values have been accepted as cautionary biomarkers for advanced fibrosis, end-stage liver disease, and hepatocellular cancer in chronic HCV infection (31). Although higher AFP levels were correlated with lower albumin levels in studies, its association with genotype 1b and HCV-RNA positivity is unclear (32,33). In our study, the detection of higher AFP values in HCV-RNA-positive patients except for anti-HCV and genotype 1b positivity shows that determination of higher AFP values with HCV-RNA positivity together is more useful in assessing serious liver damage.

According to studies, higher GGT values, which are a non-invasive significant marker of advanced severe liver disease in chronic hepatitis C, can indicate the effectiveness of interferon therapy (34,35). In our study, the higher GGT values in HCV-RNA-positive patients, irrespective of anti-HCV and genotype 1b positivity, illustrate the importance of higher GGT values in HCV-RNA-positive patients for diagnosis and treatment of advanced liver disease.

According to the studies conducted, HCV viral load and higher ALT values are clinically related parameters that indicate treatment activity, especially in chronic HCV patients (36,37). In addition, Ijaz et al. (38) demonstrated that the evaluation of ALP levels with viral load independent of the genotype determination can help to estimate disease progression in patients with hepatitis C.

Doğan et al. (39) showed that albumin, AST, ALT, GGT, and AFP values in compensated cirrhosis patients with genotype 1b after treatment and ALT, AST, GGT, ALP, and AFP values in non-cirrhosis patients after treatment were significantly changed. In our study, higher AST, ALT, and GGT values were determined in anti-HCV and HCV-RNA-positive patients, in addition to higher ALP values in HCV-RNA-positive patients. According to our study, higher AST, ALT, and GGT values in HCV-RNA and anti-HCV positive patients and higher ALP values with HCV-RNA positivity are the guiding factors for the diagnosis and treatment evaluation of advanced HCV infection, regardless of genotype 1b positivity.

Study Limitations

The limitations of our study were the inability to evaluate the clinical data of the patients and the inability to evaluate the development of hepatocellular cancer and mortality due to advanced HCV infection.

Conclusion

In conclusion, according to our study, HCV-RNA is the most important specific biomarker that affects other non-specific parameters used to evaluate HCV infection. The detection of genotype 1b in patients with HCV infection may be guiding in the treatment of older patients than non-genotype 1b.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2022/01-15, sate: 26.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K.G., Concept: S.K.G., Y.Ü., Design: S.K.G., Y.Ü., K.H., Data Collection or Processing: S.K.G., Analysis or Interpretation: S.K.G., Literature Search: S.K.G., Writing: S.K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

References

1. Yu ML, Yeh ML, Tsai PC, Huang CI, Huang JF, Huang CF, Hsieh MH, Liang PC, Lin YH, Hsieh MY, Lin WY, Hou NJ, Lin ZY, Chen SC, Dai CY, Chuang WL, Chang WY. Huge gap between clinical efficacy and

community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. Medicine (Baltimore). 2015;94:e690.

2. Liu HY, Lin YH, Lin PJ, Tsai PC, Liu SF, Huang YC, Tsai JJ, Huang CI, Yeh ML, Liang PC, Lin ZY, Dai CY, Huang JF, Chuang WL, Huang CF, Yu ML. Anti-HCV antibody titer highly predicts HCV viremia in patients with hepatitis B virus dual-infection. PLoS One. 2021;16:e0254028.
3. Aydın G, Adaleti R, Boz ES, Yücel FM, Özhan HK, Aksaray S. Investigation of Anti-HCV S/CO Value in Detecting Viremia in Patients with Hepatitis C Virus Infection. Mikrobiyol Bul. 2020;54:110-119.
4. Şanlıdağ T, Şanlıdağ T, Akçalı S, Ecemiş T, Süer K, Erbay Dündar P, Arıkan A, Güvenir M, Güler E. Investigation of the correlation between anti-HCV levels (S/Co) with HCV-RNA in the diagnosis of hepatitis C virus (HCV) infection. Mikrobiyol Bul. 2016;50:508-510.
5. Albertoni G, Arnoni CP, Araújo PR, Carvalho FO, Barreto JA. Signal to cut-off (S/CO) ratio and detection of HCV genotype 1 by real-time PCR one-step method: is there any direct relationship? Braz J Infect Dis. 2010;14:147-152.
6. Sreevatsan S, Bookout JB, Ringpsis FM. Algorithmic approach to high-throughput molecular screening for alpha interferon-resistant genotypes in hepatitis c patients. J Clin Microbiol. 1998;36:1895-1901.
7. Petruzziello A, Coppola N, Loquercio G, Marigliano S, Giordano M, Azzaro R, Diodato AM, Iervolino V, Di Costanzo G, Di Macchia CA, Di Meo T, Paradiso L, Ferro R, Giuliano P, Russo F, Pasquale G, Cacciapuoti C. Distribution pattern of hepatitis C virus genotypes and correlation with viral load and risk factors in chronic positive patients. Intervirology. 2014;57:311-318.
8. Castro GLC, Amoras EDGS, Araújo MSM, Conde SRSDS, Vallinoto ACR. Hepatitis C virus genotypes and associated risk factors in the state of Pará, Northern Brazil. Braz J Infect Dis. 2020;24:304-309.
9. Haldeda M, Baume J, Tamalet C, Bizhga M, Colson P. Hepatitis C virus genotypes in Tirana, Albania. Int J Infect Dis. 2014;18:90-93.
10. Oh DJ, Park YM, Seo YI, Lee JS, Lee JY. Prevalence of hepatitis C virus infections and distribution of hepatitis C virus genotypes among Korean blood donors. Ann Lab Med. 2012;32:210-215.
11. Üçbilek E, Abayli B, Koyuncu MB, Midikli D, Gözüküçük S, Akdağ A, Özdoğan O, Altintaş E, Sezgin O. Distribution of hepatitis C virus genotypes among intravenous drug users in the Çukurova region of Turkey. Turk J Med Sci. 2016;46:66-71.
12. Saravanan S, Velu V, Kumarasamy N, Shankar EM, Nandakumar S, Murugavel KG, Balakrishnan P, Solomon SS, Solomon S, Thyagarajan SP. The prevalence of hepatitis B virus and hepatitis C virus infection among patients with chronic liver disease in South India. Int J Infect Dis. 2008;12:513-518.
13. Podzorski RP. Molecular testing in the diagnosis and management of hepatitis C virus infection. Arch Pathol Lab Med. 2002;126:285-290.
14. Zein NN. Clinical significance of hepatitis c virus genotypes. Clin Microbiol Rev. 2000;13:223-235.
15. Basharkhah S, Sabet F, Ghezeldasht SA, Mosavat A, Jahantigh HR, Barati E, Shamsian K, Saleh-Moghaddam M, Sharebyani H, Hassannia T, Shamsian SAA. Prediction of HCV load using genotype, liver biomarkers, and clinical symptoms by a mathematical model in patients with HCV infection. Microbiol Immunol. 2019;63:449-457.
16. Cavalcante LN, Lyra AC. Predictive factors associated with hepatitis C antiviral therapy response. World J Hepatol. 2015;7:1617-1631.
17. Mukherjee R, Burns A, Rodden D, Chang F, Chaum M, Garcia N, Bollipalli N, Niemz A. Diagnosis and management of hepatitis C virus infection. J Lab Autom. 2015;20:519-538.
18. Kumar A, Rajput MK, Paliwal D, Yadav A, Chhabra R, Singh S. Genotyping & diagnostic methods for hepatitis C virus: A need of low-resource countries. Indian J Med Res. 2018;147:445-455.
19. Balaban HY, Dağ O, Alp A, Tseveldorj N, Vahabov C, Göktaş MA, Pürnak T, Hasçelik G, Demir H, Sivri B, Şimşek H. Retrospective Evaluation of Hepatitis C Awareness in Turkey Through Two Decades. Turk J Gastroenterol. 2021;32:88-96.
20. Ranjbar Kermani F, Sharifi Z, Ferdowsian F, Paz Z, Tavassoli F. The Usefulness of Anti-HCV Signal to Cut-off Ratio in Predicting Viremia in Anti-HCV in Patients With Hepatitis C Virus Infection. Jundishapur J Microbiol. 2015;8(4):e17841.
21. Li Y, Zhao L, Geng N, Zhu W, Liu H, Bai H. Prevalence and characteristics of hepatitis C virus infection in Shenyang City, Northeast China, and prediction of HCV RNA positivity according to serum anti-HCV level: retrospective review of hospital data. Virol J. 2020;17:36.
22. Nagao Y, Sata M. Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan. Virol J. 2010;7:375.
23. Erdal H, Bakır A, Güney M, Günal A, Erçin CN, Uygun A, Gülşen M. The relationship between histopathological stages of liver fibrosis and albumin–bilirubin score in chronic hepatitis C infection. The Turkish Journal of Academic Gastroenterology. 2020;19:25-30.
24. Gallotta A, Paneghetti L, Mrázová V, Bednárová A, Kružlicová D, Frecer V, Miertus S, Biasiolo A, Martini A, Pontisso P, Fassina G. Development of a novel diagnostic algorithm to predict NASH in HCV-positive patients. Int J Biol Markers. 2018;33:231-236.
25. Elbedewya TA, Ghazya MA, Mabroukb MM. Serum thrombopoietin and platelet antibodies in thrombocytopenic patients with chronic hepatitis C virus: clinical application of platelet indices. Egypt J Haematol. 2016;41:15-22.
26. Karaman H, Karakükcü C, Karaman A, Kayman T, Yalçın S, Taşdemir EA, Zararsız G, Poyrazoğlu O. Mean platelet volume as a fibrosis marker in patients with chronic hepatitis C. Turk J Med Sci. 2013;43:39-45.
27. Kosekli MA. Prediction of Fibrosis in Chronic Hepatitis C by Mean Platelet Volume and Platelet to Lymphocyte Ratio. Nat J Health Sci. 2021;6:48-52.
28. Karagöz E, Tanoğlu A, Ülçay A, Erdem H, Turhan V, Kara M, Yazgan Y. Mean platelet volume and red cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol. 2016;28:744-748.
29. Purnak T, Olmez S, Torun S, Efe C, Sayilir A, Ozaslan E, Tenlik I, Kalkan IH, Beyazit Y, Yuksel O. Mean platelet volume is increased in chronic hepatitis C patients with advanced fibrosis. Clin Res Hepatol Gastroenterol. 2013;37:41-46.
30. Uslu AU, Aydin B, Balta S, Yonem O, Uncu T, Seven D. The effect of standard therapy on mean platelet volume in patients with chronic hepatitis C. Prz Gastroenterol. 2016;11:200-205.
31. Bruce MG, Bruden D, McMahon BJ, Christensen C, Homan C, Sullivan D, Deubner H, Williams J, Livingston SE, Gretch D. Clinical significance of elevated alpha-fetoprotein in Alaskan Native patients with chronic hepatitis C. J Viral Hepat 2008;15:179-187.
32. Chu CW, Hwang SJ, Luo JC, Lai CR, Tsay SH, Li CP, Wu JC, Chang FY, Lee SD. Clinical, virologic, and pathologic significance of elevated serum alpha-fetoprotein levels in patients with chronic hepatitis C. J Clin Gastroenterol. 2001;32:240-244.
33. Chen CH, Lin ST, Kuo CL, Nien CK. Clinical significance of elevated alpha-fetoprotein (AFP) in chronic hepatitis C without hepatocellular carcinoma. Hepatogastroenterology. 2008;55:1423-1427.
34. Silva IS, Ferraz ML, Perez RM, Lanzoni VP, Figueiredo VM, Silva AE. Role of gamma-glutamyl transferase activity in patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol. 2004;19:314-318.
35. Hwang SJ, Luo JC, Lai CR, Chu CW, Tsay SH, Lu CL, Wu JC, Chang FY, Lee SD. Clinical, virologic and pathologic significance of elevated serum gamma-glutamyl transpeptidase in patients with chronic hepatitis C. Zhonghua Yi Xue Za Zhi (Taipei). 2000;63:527-535.
36. Akkaya O, Kiyici M, Yilmaz Y, Ulukaya E, Yerci O. Clinical significance of activity of ALT enzyme in patients with hepatitis C virus. World J Gastroenterol. 2007;13:5481-5485.
37. Beld M, Penning M, Mcmorrow M, Gorgels J, Van Den Hoek A, Goudsmit J. Different Hepatitis C Virus (HCV) RNA Load Profiles Following Seroconversion among Injecting Drug Users without Correlation with HCV Genotype and Serum Alanine Aminotransferase Levels. J Clin Microbiol. 1998;36:872-877.

38. Ijaz B, Ahmad W, Javed FT, Gull S, Sarwar MT, Kausar H, Asad S, Jahan S, Khaliq S, Shahid I, Sumrin A, Hassan S. Association of laboratory parameters with viral factors in patients with hepatitis C. Virol J. 2011;8:361.

39. Doğan M, Topçu B, Karaali R, Erdem I. Evaluation of Treatment Results with Direct Acting Antiviral Drugs of Cirrhotic/Non-cirrhotic Chronic Liver Disease Caused by Hepatitis C Virus Genotype 1b Infection. Viral Hepat J. 2020;26:43-48.