Hepatitis A Virus Antibodies in Patients with Chronic Hepatitis B and C; A Cross-Sectional Study in Egyptian Patients.

Lobna Abd El Wahed Ahmed [1], Essam El-Deen Abdelmohsen [1], Wael Ahmed Abbas [1], *Kerollos Latif Labib Garas* [1], Enas Ahmed Reda Alkareemy [1].
Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt.
Dr.kerolloslatuf @gmial.com

Abstract

Background: Acute viral hepatitis A has a wide range of presentation; it may result in mild symptoms and self-limited disease or lead to fulminant liver cell failure. It infects 1.4 million people worldwide annually. Super-infection of HAV on top of chronic viral infections, including HBV, HCV, HIV, and dengue virus, or even chronic non-viral liver disease may affect the natural course of the basic disease and lead to fulminant liver failure and higher mortality rate.
Aim of the work: To detect the seroprevalence of previous HAV infection in chronic hepatitis B and C patients in Assiut to clarify its effect on these patients and the different impacts of HAV infection on hepatitis B and hepatitis C patients.
Results: **235** patients **(94 %)** were HAV IgG **positive,** and **15 (6%)** were negative. The Child-Pugh score showed **more deterioration** in HAV IgG-**positive** patients than negative patients. Of **235** HAV IgG-positive patients, **160** (68%) were HCV antibody-positive, and 75 **(32%)** were HBsAg positive. Patients with HAV/HCV have more impaired liver functions and lower Child-Pugh scores than HAV/HBV patients.
Conclusion: Our study showed that the prevalence of HAV infection in chronic liver disease patients is very high, as (94%) of them were positive for HAV IgG antibody. This high prevalence was associated with a significant deterioration in liver functions in chronic liver disease patients, leading to a worse prognosis. Also, we found that HAV/HCV patients showed more deteriorated liver functions than HAV/HBV patients, lower Child-Pugh scores, and worse general conditions.
Keywords: Hepatitis A virus antibody, HAV IgG, seroprevalence, chronic liver disease, hepatitis B, hepatitis C, Child-Pugh score, liver function tests

Background

Acute viral hepatitis A is an inflammation of the liver with a wide range of presentations; it may result in a self-limited disease or fulminant liver cell failure. It is a significant cause of morbidity and mortality in Egypt (1,2). Recent studies showed significant reductions in the proportions of HBV and HCV among acute viral hepatitis and an increase in HAV(3). The incidence of HAV infection is affected by socio-economic conditions, including water quality, sanitation, housing density, education, and income. (4,5)

It is endemic in Egypt; however, only a few publications provide epidemiological information based on prospectively collected sera in the general population with an adequate sample size. Specifically, more recent data from developing countries are limited. (5,6)

Unlike hepatitis B and C, HAV infection does not cause chronic liver disease. Still, infrequently, it may lead to fulminant hepatitis and more deterioration in liver functions (acute liver failure), with a reported incidence of 0.015–0.5%. Co- or superinfection of HAV with some viruses, including HBV, HCV, HEV, HIV, and dengue virus, or even in chronic non-viral liver disease, markedly affects the natural course of the basic disease and leads to the more severe outcome and liver cell failure. (7,8)

Immunoglobulins are formed once the patient gets infected by HAV. Immunoglobulin G (IgG) antibody appears simultaneously with Immunoglobulin M (IgM), but IgG dominates the antibody response, persisting for many years, if not life-long, in most individuals after infection. (4)

Total anti-HAV, including both IgM and IgG, remains positive for life after vaccination; it is useful only to identify unimmunized patients at risk. (9)

The high incidence of fulminant hepatitis in patients with combined HAV/HCV infection remains controversial; however, the Center for Disease Control and Prevention (CDC) survey demonstrated that HAV infection in patients with underlying chronic liver disease is associated with a higher mortality rate than isolated HAV infection. So, chronic liver disease is a very important risk factor in the development of fulminant hepatitis due to HAV infection in these patients with underlying liver disease such as hepatitis B and C. (10,11)

Methods

Our study included **250** patients with chronic liver disease due to HBV or HCV in 2017/2018. The study design was observational, a cross-sectional study that included patients diagnosed with chronic liver disease based on laboratory and ultrasonographic evidence. They underwent full history taking and clinical examination. Laboratory investigations were done to detect the Child-Pugh score: HAV IgG antibody, HBsAg, HCV Ab, AST, ALT, Bilirubin level, Albumin, and INR. Patients were divided into two main groups according to HAV IgG seropositivity: HAV IgG **positive** group and HAV IgG **negative** group, and a comparative analysis of liver function tests and Child-Pugh scores was done. Also, a comparative analysis of HBV and HCV seropositivity in the HAV IgG-positive group showed significant results.

Inclusion Criteria:

All patients who were attending the outpatient clinic and had chronic liver disease either due to HBV or HCV in 2017/2018. The patients' age was between 55 – 70 years old. We defined chronic HBV as a patient with Hepatitis B surface antigen (HBsAg) positive and chronic HCV as a patient with Hepatitis C virus antibody (HCV Ab) positive.

Exclusion Criteria:

Patients who were previously vaccinated against hepatitis A virus and patients with hepatocellular carcinoma (HCC) were excluded from the study.

Patients with other liver diseases concomitant with HBV or HCV (Autoimmune hepatitis, Hemochromatosis, Wilson's disease, and HIV) were excluded from the study.

Statistical Analysis

Data were verified, coded, and analyzed using IBM-SPSS (Statistical Package for the Social Science, Version 22 and Armonk, New York, USA). (12)

Descriptive statistics: means, standard errors, medians, and percentages were calculated. Test of significances: Chi-square and Fisher Exact tests were used to compare the difference in the distribution of frequencies among different groups. For continuous variables with more than two categories, the ANOVA test was calculated to test the mean differences of the data, and the post-hoc test was calculated using Bonferroni corrections. A

p-value equal to or less than 0.05 was considered significant.

Results

250 patients were enrolled in the study. Results showed that **235** patients **(94%)** were HAV IgG **positive,** and only **15 (6%)** were **negative**. (Fig1)

We found the Child-Pugh scores in the HAV IgG **positive** group were as follows: **19** patients were Child **A** (8.3%), **113** patients were Child **B** (47.9 %), and **103** patients were Child **C** (43.8%). **Bilirubin, INR,** and **liver enzymes** (ALT & AST) in the HAV IgG **positive** group were **higher than the** HAV IgG **negative** group with statistical significance. At the same time, serum **Albumin** was **lower** in the HAV IgG-**positive** group.

However, in the HAV IgG negative group, all patients were Child A and had much better liver function tests, representing a P-value of 0.006 and statistically significant. (Fig 2, Tabel1)

Comparative analysis between HBV and HCV patients who were found positive for HAV IgG antibody.

In the **HBV** group, **75** patients were HAV IgG **positive**. Child-Pugh score analysis was: **15** patients (**20%)** were Child **A**, **60** patients (**80%)** were Child **B,** and **no** patients found Child **C** in the **HBV** group.

However, in the **HCV** group, **160** patients were HAV IgG **positive**, we found **7** patients (**4%)** were Child **A**, **19** patients (**12%)** were Child **B,** and **134** patients **(84%)** were Child **C** with a **P-value of < 0.001,** and that was statistically significant. (Fig 3)

Serum **Albumin** and **liver enzymes** appeared **higher** in the **HBV** group **than** in the **HCV** group. However, serum **Bilirubin** and **INR** levels were **higher** in the **HCV** group **than** in the **HBV** group, which was statistically significant with a P-value of **< 0.**001. (Tabel 2)

Discussion

Egypt has a high prevalence of chronic liver disease due to chronic HCV and HBV infections. The highest HCV prevalence in the world, estimated to be 15% in some studies is in Egypt, and hepatitis B prevalence reaches (4.4%) in most studies. (13) The concomitant or superimposed infection of acute HAV leads to fulminant hepatic failure. (10,11) While the previous HAV infection has not proved to affect the progress of chronic liver disease course in our country, we conducted our study.

Serological tests showed that **31 %** were **HBsAg** positive and **69%** were **HCV Ab** positive with **no** statistical significance. In Turkey, it was found that (81%) of patients tested for anti-HAV IgG were positive to HbsAg, only (11.1%) were HCV Ab positive, and (7.9%) were cirrhotic patients; the reverse occurred in Italy, where about (75%) of tested patients were HCV Ab positive, (25%) were HBsAg positive, and both studies did not show any significance. (14,15)

All patients in our study were tested for HAV IgG antibody. Results showed that **235** patients **(94 %)** were **positive** for anti-HAV IgG and **15** patients **(6%)** were **negative**, with near incidence to study conducted in Saudi Arabia, anti-HAV IgG seropositivity was 134 patients (98.5%) out of a total 136 chronic liver disease patients tested. (16)

In the Kerala region of India, anti-HAV IgG seropositivity was (93.3%) in chronic liver disease patients. (17) In Brazil, it was (98.1%). (18) In Iran, it was (79.2%) in patients with chronic viral hepatitis, and hepatitis A vaccination was subsequently recommended for all patients with chronic viral hepatitis who were younger than 30 years old. (19) Also, in Korea, in one of the two recent studies, the anti-HAV IgG seropositivity was (86.61%) in chronic hepatitis patients. In another study where only patients with chronic hepatitis B were assessed, the anti-HAV IgG seropositivity was found to be (49.1%). (20,21)

Compared with two developed countries, in the USA, anti-HAV IgG seropositivity was (55%) in patients with chronic liver disease. (22) However, in Italy, they found (53.5%) were positive for total anti-HAV antibodies. (23)

We concluded from these studies that HAV seroprevalence in chronic liver disease patients is very high, especially in developing countries, so improving socioeconomic status, more sanitary environments, and advanced hygienic practices, all play a role in reducing the incidence of HAV infection in the general population reducing subsequent morbidity and mortality.

Analysis of liver functions in the **HAV IgG positive** group showed more deteriorated liver functions, lower Child-Pugh scores, and worse general condition than the **negative** group. This clearly showed the effect of previous HAV infection on chronic liver disease course as the mean Child-Pugh score in most HAV IgG **positive** patients is between **Child B and C**. However, **all** patients (100%) **negative** to HAV IgG antibody were **Child A**.

Other studies confirmed this result as they showed that HAV concomitant infection in chronic liver disease patients led to more laboratory abnormalities and more severe disease, including fulminant hepatic failure and a higher case fatality rate. (24)

In Thailand, they found that no one of **100** patients with **isolated acute** HAV infection developed severe hepatitis. However, in HBsAg carriers and chronic liver disease patients due to either HBV or HCV, they found (55%) of the HBsAg carriers and (33%) of total chronic liver disease patients developed fulminant or submassive hepatitis with high mortality rates reached about (25%) and (33%) respectively. (25)

Also, a study done in Turkey confirmed that hepatitis A is a self-limiting disease generally, but it may lead to more severe disease and worse outcomes if it is concomitant with chronic hepatitis B. (26,27)

Analysis based on **HBV or HCV** serological tests revealed that HAV/HCV patients were more affected. They had more deteriorated liver functions and lower Child-Pugh scores than HAV/HBV patients. The most dramatic observation of this result was seen in a well-cited Italian study where most **HAV/HCV** patients developed acute or fulminant hepatitis with a high mortality rate; however, **HAV/HBV** patients showed a much **better** prognosis, and this matches our results. (28,29)

Our current study needs to be performed on more patients and in multiple centers all over Egypt. Further research is required to clarify worse prognosis in HAV/HCV patients than in HAV/HBV patients.

Conclusions

Sero-prevalence of HAV infection in our society is very high, similar to other developing countries, and this could be minimized by enhancing socio-economic levels, advanced hygienic practices, and education.

Old or previous HAV infection in patients with chronic hepatitis B and C greatly affects disease progress. It carries a higher risk and worse prognosis, so we highly recommend close observation and follow-up of this high-risk group as well as empiric vaccination against HAV for all patients who were newly diagnosed to be HBV or HCV positive.

Our study revealed that previous HAV infection is much more serious in HCV patients and carries a worse prognosis than in HBV patients. However, more studies are needed on a larger number of patients.

List of Abbreviations

Ab	Antibody	HBsAg	Hepatitis B surface antigen
ALB	Albumin	HBV	Hepatitis B virus
ALT	Alanine transferase	HCV	Hepatitis C virus
AST	Aspartate transferase	HCC	Hepatocellular Carcinoma
Bil	Bilirubin	HIV	Human Immunodeficiency virus
CDC	Centers for Disease Control and Prevention	IgG	Immunoglobulin G
CLD	Chronic Liver Disease	IgM	Immunoglobulin M
HAV	Hepatitis A virus	INR	International Normalized Ratio

Figure Legends

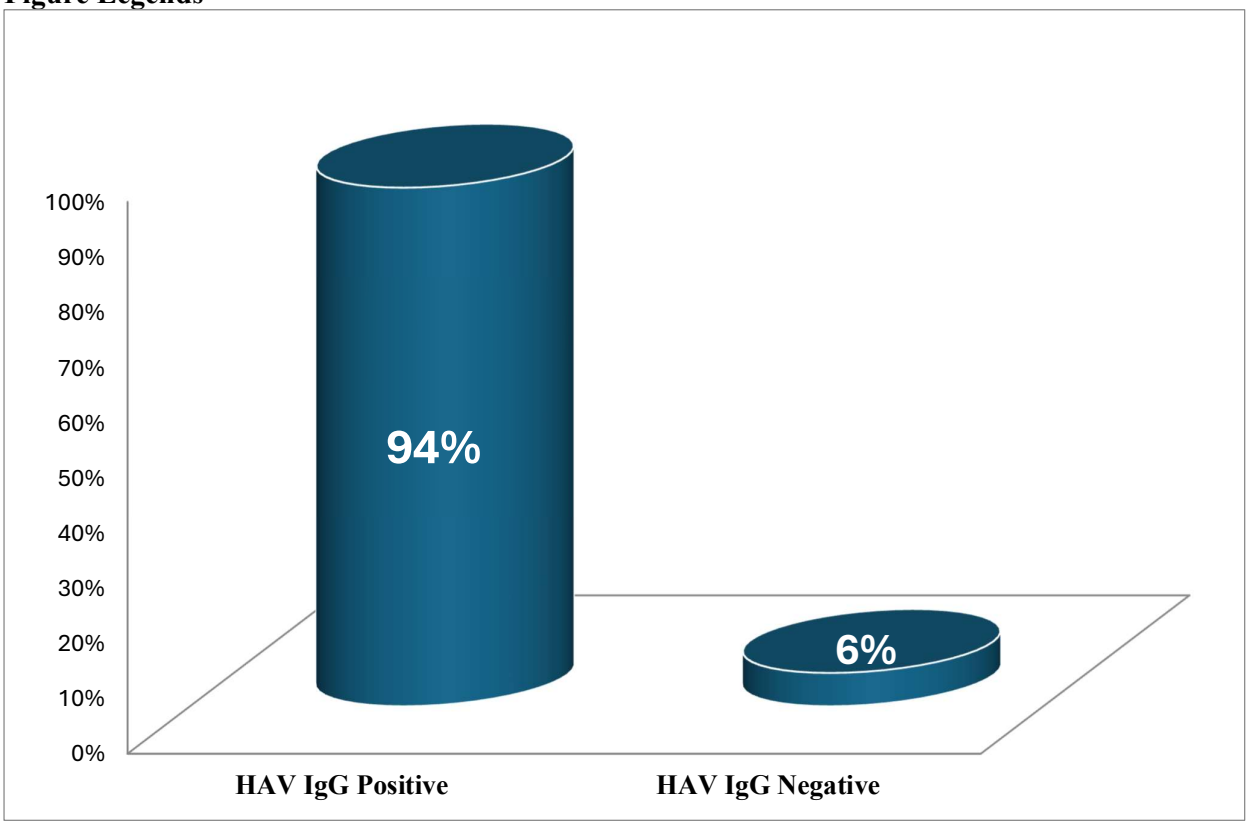

Fig. 1: Classification of patients according to HAV IgG seropositivity.

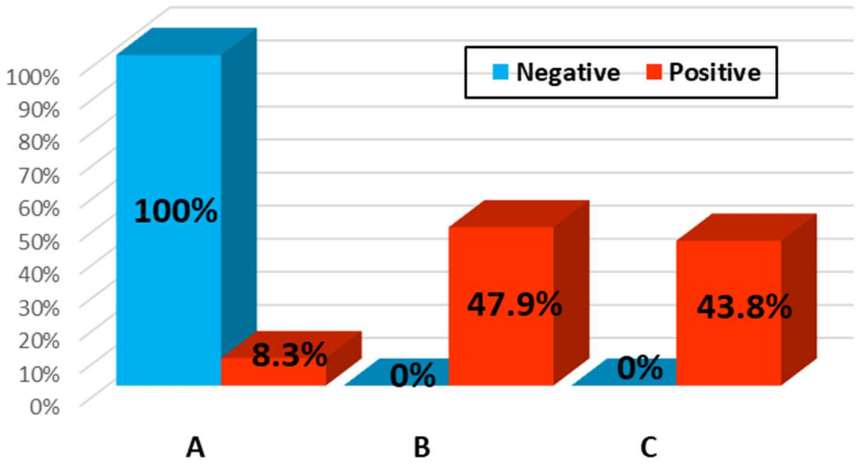

Fig. 2: Child-Pugh score classification categories according to HAV IgG seropositivity.

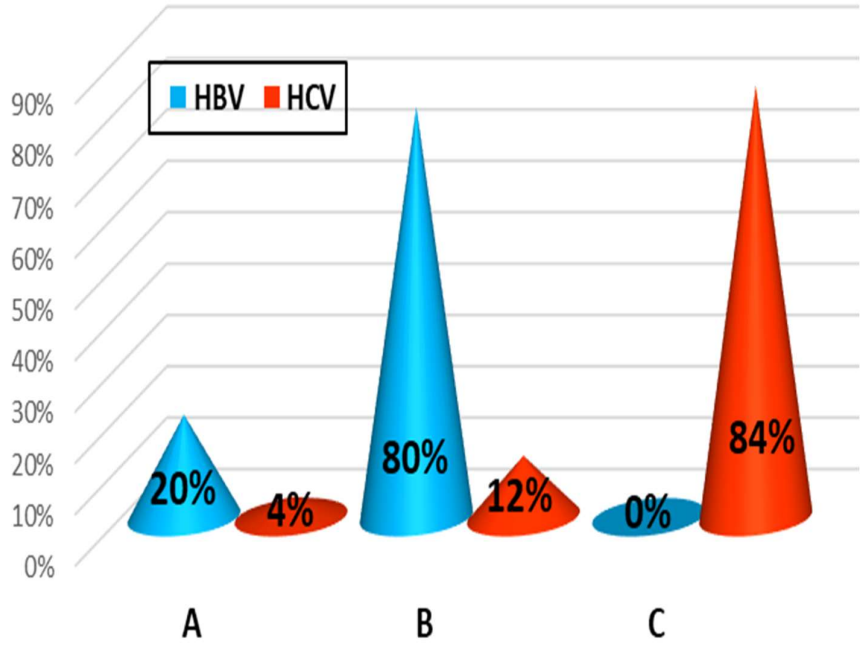

Fig.3: Distribution of Child-Pugh score classification categories of HBV and HCV patients.

Tables

Table 1: Comparative analysis according to HAV IgG seropositivity.

	HAV IgG Negative (No.=15)	HAV IgG Positive (No.=235)	P-value
Albumin	36.50 ± 0.7	28.50 ± 3.5	**< 0.001***
Bilirubin	32.50 ± 0.7	43.08 ± 7.7	**< 0.001***
INR	1.55 ± 0.1	2.02 ± 0.2	**0.020***
AST	55.00 ± 1.4	69.75 ± 4.9	**0.006***
ALT	53.00 ± 4.2	63.65 ± 4.1	**0.027***

*An independent t-test was used to compare the mean difference between groups.
**The Fisher Exact test was used to compare the proportion differences.

Table 2: Comparative analysis in HAV positive group between HBV and HCV patients.

	HBV (No.=75)	HCV (No.=160)	P-value
Albumin	31.68 ± 2.4	25.96 ± 2.4	**< 0.001***
Bilirubin	36.72 ± 5.9	48.60 ± 4.2	**< 0.001***
INR	1.82 ± 0.1	2.18 ± 0.2	**< 0.001***
AST	84.76 ± 7.8	53.56 ± 3.9	**0.001***
ALT	75.76 ± 6.5	50.68 ± 3.1	**0.001***

***The Chi-square test was used to compare the proportion differences.**

References

1. Matheny SC, Kingery JE. Hepatitis A. American Family Physician Journal. 2012 Dec;86(11):1027-34, quiz 1010-1012.
2. GBD study collaborators: Theo Vos, Barber RM, Bell B, Villa AB, Biryukov S, Bolliger I, Charlson F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Journal. 2016 Oct 8;388(10053):1545-1602.
3. Maha T, Salma A, Erik J, Hanaa A, Amany E, Samir R, Radi H, Mostafa A, Amr K. Evidence of sustained reductions in the relative risk of acute hepatitis B and C virus infections, and the increasing burden of hepatitis A virus infection in Egypt: comparison of sentinel acute viral hepatitis surveillance results, 2001–17. BMC Infectious Diseases. 2019;19:159.
4. World Health Organization. Hepatitis A Fact sheet N 328. July 2013.
5. World Health Organization. WHO Position paper on hepatitis A vaccines-June 2012. Weekly epidemiological record. 2012 Jul 13; No. 28-29, 87:261-276.
6. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine Journal. 2010 Sep 24;28(41):6653-6657.
7. Glikson M, Galun E, Oren R, Tur-Kaspa R, Shouval D. Relapsing hepatitis A. Review of 14 cases and literature survey. Medicine Journal. 1992;71:14-23.
8. Radha Krishna Y, Saraswat VA, Das K, Himanshu G, Yachha SK, Aggarwal R, Choudhuri G. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. Liver International Journal. 2009 May 29:392-398.
9. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and mortality weekly report series (MMWR), Center for Disease Control and Prevention. 2006 May 19;55(RR-7):1-23.
10. Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. The Journal of Infectious Diseases. 2008;197(9):1282-1288.
11. Vento S. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. Journal of Viral Hepatitis. 2000 May 7(suppl 1):7-8.
12. IBM_SPSS. Statistical Package for Social Science. Ver.21. Standard version. Copyright © SPSS Inc., 2011-2012. NY, USA. 2012.
13. Gamal S, Mahmoud S, Tarek H, F. DeWolfe. Mass screening for hepatitis B and C in Southern Upper Egypt. BMC Public Health. 2019;19:1326.
14. Sagnelli E, Rossi G, Coppola N, Scolastico C, Onofrio M, Fillipini P, et al. Antibodies to hepatitis A virus in Italian patients with chronic liver disease. Epidemiology and Infection Journal, Cambridge. 2001 Oct;127:341-346.
15. Hale TÖzden. Hepatitis A seroprevalence in patients with chronic viral hepatitis in Konya, Turkey. European Journal of Gastroenterology and Hepatology. 2016 Mar;28(3):333-337.
16. Singal AK. Hepatitis A vaccine is not required in adult patients with chronic liver disease in Saudi Arabia.

Singapore Medical Journal. 2009 Apr;50:442-443.

17. John A, Chatni S, Narayanan VA, Balakrishnan V, Nair P. Seroprevalence of hepatitis A virus in patients with chronic liver disease from Kerala: impact on vaccination policy. Journal of the Indian Medical Association. 2009 Dec;107:859-861.

18. Oliveira LC, Comácio SM, Santos Jde F. Seroprevalence of hepatitis A immunity among Brazilian adult patients with liver cirrhosis: is HAV vaccination necessary? The Brazilian Journal of Infectious Diseases. 2011 May-Jun;15:268-271.

19. Ahmadi Vasmehjani A, Javeshghani D, Baharlou R, Shayestehpour M, Mousavinasab SD, Joharinia N, Enderami SE. Hepatitis A infection in patients with chronic viral liver disease: a cross-sectional study in Jahrom, Iran. Epidemiology and Infection Journal. 2015 Feb;143:534-539.

20. Cho HC, Paik SW, Kim YJ, Choi MS, Lee JH, Koh KC. Seroprevalence of anti-HAV among patients with chronic viral liver disease. World Journal of Gastroenterology. 2011 Jan 14;17:236-241.

21. Lee SH, Kim HS, Park KO, Park JW, Chun SY, Lim SJ. Prevalence of IgG anti-HAV in patients with chronic hepatitis B and in the general healthy population in Korea. Korean Journal of Hepatology. 2010 Dec;16:362–368.

22. Saab S, Lee C, Shpaner A, Ibrahim AB. Seroepidemiology of hepatitis A in patients with chronic liver disease. Journal of Viral Hepatitis. 2005 Jan;12:101-105.

23. Sagnelli E, Stroffolini T, Almasio P, Mele A, Coppola N, Ferrigno L, et al. Exposure to HAV infection in patients with chronic liver disease in Italy, a multicentre study. Journal of Viral Hepatitis. 2006 Jan;13(1):67-71.

24. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? The American Journal of Gastroenterology. 1995 Feb;90(2):201-205.

25. Pramoolsinsap C, Poovorawan Y, Hirsch P, Busagorn N, Tamasirikul K. Acute hepatitis A super-infection in HBV carriers, or chronic liver disease related to HBV or HCV. Annals of Tropical Medicine and Parasitology Journal. 1999 Oct;93:745-751.

26. Tulek N, Ozsoy M, Moroglu C, Sonmezer MC, Temocin F, Ertem GT, Erdinc FS. Seroprevalence of Hepatitis A Virus Antibodies among the Patients with Chronic Hepatitis B in Turkey. Euroasian Journal of Hepatogastroenterology. 2015 Jul-Dec;5(2):95-97.

27. Rezende Guilhermo, Anne Marie Roque-Afonso, Didier Samuel, Michele Gigou, Elisabeth Nic. Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatology Journal. 2003 Sep;38(3):613-618.

28. Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G. Fulminant hepatitis associated with hepatitis A superinfection in patients with chronic hepatitis C. The New England Journal of Medicine. 1998 Jan;338:286-290.

29. Mele A, Tosti ME, Stroffolini T. Hepatitis associated with hepatitis A superinfection in patients with chronic hepatitis C. The New England Journal of Medicine. 1998 Jun;338(24):1771.