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The Results of the National Study of CLEIA Method for the Prevalence of HBV and HCV in the 40-64 Age Population of Mongolia

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Objective: Using high-sensitivity test results of CLEIA we aimed to investigate the prevalence of hepatitis B and C virus, and compare levels of AST, ALT, M2BPGI in the Mongolian population in the age between 40-64. **Methods:** In order to reflect the administrative and geographical features of Mongolia, the sampling was done at three levels: urban, province center, and rural. Immunological test was measured by chemiluminescence enzyme immunoassay (CLEIA). The statistical package for the social sciences (SPSS) version 25 was used for the statistical analyses. **Results:** The survey covered 3196 people. 71.8 percent of the patients surveyed had a negative in hepatitis test. 10.1 percent had a positive HBsAg test. 17 percent had a positive anti-HCV test. 1.1 percent had both a positive both HBsAg and anti-HCV (<.0001). AST and ALT increased more frequently during co-infection. M2BPGI protein average level in the non-infected group was 1.00 C.O.I, in the HBsAg positive group 1.65 C.O.I, in the anti-HCV positive group 1.83 C.O.I, and in the co-infection group 1.87 C.O.I (<.0001). **Conclusion:** 10.1 percent of 40-64year-olds in Mongolia were infected with hepatitis B virus, and 17 percent had Hepatitis C virus and 1.1 percent had hepatitis B and C virus co-infections. Serum M2BPGi is increasing in hepatitis C virus infection and in co-infection.

Keywords: Hepatocellular Carcinoma, Liver Fibrosis, Hepatitis B Virus, Hepatitis C Virus, Mongolia.

Introduction

Viral hepatitis infection is a major cause of cirrhosis and liver cancer and is still one of the world's most urgent health problems[1,2]. More than 2 billion people worldwide are infected with Hepatitis B virus (HBV), of which over 257 million are B virus carriers, leading to a high risk of chronic liver disease, particularly hepatocellular carcinoma[3]. 15-45% of people infected by

hepatitis C virus heal usually within six months, while the remainder shift to chronic infection, with according to the WHO Global Hepatitis report 2017. 1% of the world's population, or 71 million people are diseased with HCV chronic infection[4]. The most common etiology for hepatocellular carcinoma in our patients was hepatitis C virus infection which is 46%, hepatitis B virus infection 34%, co-infection B and C 14%[6-8].

Mongolia has recorded acute viral hepatitis since 1952, A and B hepatitis since 1981, and non-A and non-B hepatitis and C viral hepatitis since 1998. The hepatitis virus infection varies widely in every age due to socio-economic development, population behaviors, and immunizations in Mongolia. Therefore, researching the widening in different generations, early detection of liver disease, and prevention of complication is important.

According to a population-based survey in Mongolia, the prevalence of hepatitis in people born in the mid-1950's (currently 65 years old) was the highest, and the lowest was amongst young people (30s or younger) who are born since 1990's. Viral hepatitis is still decreasing when observing its movements, but the disease will remain highly prevalent until 2030. Mongolia belongs to the high-risk HBV and HCV epidemic. Also, (taslal nemne) complications of chronic viral hepatitis, liver cirrhosis, and hepatocellular carcinoma remain a major health problem in Mongolia. Hepatocellular carcinoma incidence has been increasing in recent years and is still the leading cause of cancer mortality. Hepatitis B and C viral infection is an important cause of hepatocellular carcinoma and chronic hepatitis. The study found that chronic HBV infection occurs in 60%-70% of chronic hepatitis and liver cancer in Mongolia. Worldwide, liver cancer morbidity ranking as fifth, mortality as third, and annual deaths as 1 million are indicative of global health problems. Mongolia is ranked first in the world with the death rate of 141 hepatocellular carcinoma deaths per 100,000 populations, which is eight times the global average[5].

Extensive research has been done on prevalence, treatment and diagnosis of hepatitis B and C virus in Mongolia. However, an epidemiological study with a large number of representative populations at the national level is rare. Viral markers are tested by the Immunochromatography assay (ICA), which confirm positive and uncertain responses by the enzyme-linked immunosorbent assay (ELISA) and CLEIA. We identified HBV and HCV by using a high-sensitivity CLEIA method, covering 3196 people aged 40-64 which is the innovation of our research.

The aim of our study is to determine the prevalence of hepatitis B and C among the 40-64 years of age population, including the capital city and countryside, assessing liver function by measuring AST and ALT, and identifying liver fibrosis M2BPGI marker levels in all participants.

Materials and Methods

Sampling

In order to reflect the administrative and geographical features of Mongolia, sampling was conducted at three levels: capital city, province centers, (taslal nemne) and rural. The 40-64 year old population of Bayanzurh district, Sukhbaatar district, Chingeltei district of Ulaanbatar city, Gobi-altai province and Uvs province in western region, Arkhangai, Khuvsgul provinces in khangai region, Tuv, Dornogobi and Umnugobi province in central region, Sukhbaatar province in eastern region. Totally 3196 participants were selected. The sample size was estimated using multi-stage random sampling method (simple random, well-organized, and cluster sampling) from October 2016 to January 2019.

Inclusion criteria

- 40-64 year old while participating in the study
- Citizen of Mongolia
- Participant and the caregiver must have given approval to participate in the study.

Laboratory testing

We evaluated qHBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc to detect and prove hepatitis B virus infection, and Anti-HCV to detect hepatitis C virus. Non-invasive liver fibrosis marker M2BPGI was determined by using chemiluminescence enzyme immunoassay (CLEIA) according to HISCL-5000 (Sysmex, Japan) of Sysmex Corporation of Japan, fully automated immunologic analyzer manufacturer's protocol. The sensitivity of this method is 100% and specificity is 99.94%.To evaluate liver function, the ALT and AST levels were evaluated using the kinase-UV method recommended by the International Clinical Chemistry Association (IFCC) and the Chemix-180 (Sysmex, Japan), Japanese Clinical Chemistry Association (JSCC) and measured by a biochemical full-automatic analyzer.

$$n = DE * \frac{Z^2 * p * (1-p) * 1.2}{e^2} = 1.5 * \frac{1.96^2 * 0.10 * (1-0.10) * 1.2}{0.014^2} = 3175$$

Parameters:
n- sample size
p-expected prevalence
z-statistic for a level of confidence
e- the acceptable sampling error
DE- desired margin of error

Statistical analysis

The statistical package for the social sciences (SPSS) version 25 was used for the statistical analyses. The collected data was expressed as the mean± standard deviation (SD), and categorical variables were summarized as frequency counts and percentages. Outcome measures (prevalence and mean variance) and differences between groups (age, gender and residence, and (and nemne) hepatitis virus infections) were calculated with 95 percent confidence intervals (95% CI), and Person chi-square test, Fisher's exact test, and one-way ANOVA test (p-value). One-way Anova and Tukey Honestly Significant Difference (HSD) tests were used when researching the correlation between the M2BPGI, ALT and AST levels of research participants and their rate of hepatitis infection. Differences at $p<0.05$ level were considered to be statistically significant.

Ethical statements

The research study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences (№8/3/2016-08). All participants gave written informed consent.

Results

Baseline characteristics of participants

3196 people were involved in the study, of which 1093 were

Table 1. Demographic characteristic of the study population

Variables		N	%
Area			
	Arhkhangai	270	8.5
	Govi-Altai	177	5.5
	Dornogovi	135	4.2
	Sukhbaatar	206	6.4
	Umnugovi	94	3.0
	Tuv	154	4.8
	Uvs	199	6.2
	Khuvsgul	132	4.2
	Ulaanbaatar	1829	57.2
Location			
	Rural	1367	42.8
	Urban	1829	57.2
Gender			
	Male	1093	34.2
	Female	2103	65.8
Age group			
	40-44	958	30
	45-49	758	23.7
	50-54	677	21.2
	55-59	522	16.3
	60-64	281	8.8

male and 2103 were female. There are 1829 people involved from Ulaanbaatar (57.2%), 177 from Govi-Altai, 199 from Uvs province, 270 from Arkhangai province, 132 from Khuvsgul, 154 from TuvAimag, 135 from Dornogovi province, 94 from Omnogovi province and 206 from Sukhbaatar province, and totally 1367 people from provinces (42.8%). By classifying age group 40-44 years old were 958 (30%), 45-49 years old were 758 (23.7%), 50-54 years old were 677 (21.2%), 55-59 years old were 522 (16.3%), and 60-64 years old were 281 (8.7 %) (Table 1).

Prevalence of Hepatitis B, and C virus infection

Of all participants, 71.8 percent were negative for virus markers, 10.1 percent were positive for HBsAg, 17 percent were positive for Anti-HCV, and 1.1 percent had co-infection of both HBV and HCV. 74 percent of respondents in Ulaanbaatar reported that viral markers were negative, 9.2 percent were HBsAg positive, 16 percent were anti-HCV positive, and 0.87 percent were positive for HBsAg and anti-HCV markers. In rural areas, 68.9 percent of 1367 people were negative on viral markers, 11.4 percent HBsAg positive, 18.4 percent positive anti-HCV and 1.32 percent were positive for HBsAg and anti-HCV markers. According to gender, there were 71.9% of males and 71.8% of women with negative result on viral markers, 7.7% of women and 14.8% of men with HBsAg positive, 12.8% of men and 19.2% of women with anti-HCV positive and 1.39% of women 0.46% of men HBsAg and anti-HCV both positive. Results were statistically significantly different (<.0001).The highest prevalence of hepatitis B virus was in 8 provinces: Sukhbaatar province with 18%, and the lowest prevalence in Umnugobi province with 5.3%, and hepatitis C virus was the highest in Tuv province with 27.3%, the lowest in Dornogobi province 9.6%. Hepatitis B and C co-

Table 2. Comparison of HBsAg, Anti-HCV marker result by gender, age and location

Variables Count	No Virus Hepatitis Infections		HBsAg positive		Anti-HCV positive		HBsAg+Anti-HCV positive		p-value
	% (95% CI)	Count	% (95% CI)	Count	% (95% CI)	Count	% (95% CI)		
Province									
Arhkhangai	174	64.4 (58.6-70.0)	16	5.9 (3.6-9.2)	79	29.3 (24.1-34.9)	1	0.37 (0.04-1.72)	
Govi-Altai	122	68.9 (61.8-75.4)	27	15.3 (10.5-21.1)	27	15.3 (10.5-21.1)	1	0.56 (0.06-2.61)	
Dornogovi	105	77.8 (70.2-84.2)	13	9.6 (5.5-15.5)	13	9.6 (5.5-15.5)	4	2.96 (1.01-6.89)	
Sukhbaatar	141	68.4 (61.9-74.5)	37	18.0 (13.2-23.6)	27	13.1 (9.0-18.2)	1	0.49 (0.05-2.25)	
Umnugovi	68	72.3 (62.7-80.6)	5	5.3 (2.1-11.3)	19	20.2 (13.1-29.2)	2	2.13 (0.44-6.65)	
Tuv	98	63.6 (55.8-70.9)	13	8.4 (4.8-13.6)	42	27.3 (20.7-34.7)	1	0.65 (0.07-2.99)	
Uvs	130	65.3 (58.5-71.7)	35	17.6 (12.8-23.3)	31	15.6 (11.1-21.1)	3	1.51 (0.43-3.97)	
Khuvsgul	104	78.8 (71.2-85.1)	10	7.6 (4.0-13.0)	13	9.8 (5.6-15.8)	5	3.79 (1.46-8.10)	
Ulaanbaatar	1353	74.0 (71.9-75.9)	168	9.2 (7.9-10.6)	292	16.0 (14.3-17.7)	16	0.87 (0.52-1.38)	
Residence									<.050
Province	410	68.1 (64.3-71.7)	58	9.6 (7.5-12.2)	127	21.1 (18.0-24.5)	7	1.16 (0.52-2.27)	
Soum	532	69.5 (66.2-72.7)	98	12.8 (10.6-15.3)	124	16.2 (13.7-18.9)	11	1.44 (0.77-2.47)	
Urban	1353	74.0 (71.9-75.9)	168	9.2 (7.9-10.6)	292	16.0 (14.3-17.7)	16	0.87 (0.52-1.38)	
Gender									<.0001
Male	786	71.9 (69.2-74.5)	162	14.8 (12.8-17.0)	140	12.8 (10.9-14.9)	5	0.46 (0.17-1.00)	
Female	1509	71.8 (69.8-73.6)	162	7.7 (6.6-8.9)	403	19.2 (17.5-20.9)	29	1.38 (0.94-1.95)	
Age group									<.0001
40-44	734	76.6 (73.9-79.2)	110	11.5 (9.6-13.6)	108	11.3 (9.4-13.4)	6	0.63 (0.26-1.29)	
45-49	575	75.9 (72.7-78.8)	76	10.0 (8.0-12.3)	101	13.3 (11.0-15.9)	6	0.79 (0.33-1.62)	
50-54	456	67.4 (63.8-70.8)	70	10.3 (8.2-12.8)	143	21.1 (18.2-24.3)	8	1.18 (0.56-2.22)	
55-59	351	67.2 (63.1-71.2)	46	8.8 (6.6-11.5)	118	22.6 (19.2-26.3)	7	1.34 (0.60-2.61)	
60-64	179	63.7 (58.0-69.2)	22	7.8 (5.1-11.4)	73	26.0 (21.1-31.3)	7	2.49 (1.12-4.83)	

HBsAg -Quantitative hepatitis B surface antigen; Anti-HCV - Antibodies against hepatitis C virus; [a]P value has been calculated with Pearson Chi Square Test;

infection were the highest rate in Khuvsgul province 3.79% and the lowest in Arkhangai province was 0.37% (<.0001). In the case of age group, HBsAg positive cases decreased to 11.5-7.8 percent, and positive hepatitis C virus cases increased by 11.3-26 percent (<.0001) due to increase in age (Table 2).

Among our whole study population, 13.5% of the HBsAg positive patients were HBeAg positive. When we compared HBsAg levels among HBeAg negative and positive group, HBsAg level mean was 1077.0 ± 342.19 IU/ml in the HBeAg negative group but as for the HBeAg positive group, it was 13346.4 ± 2494.2 IU/ml which is of statistical significance (<.0001)(Figure 1).

The results in changes of the biochemical analysis of ALT and AST, liver fibrosis M2BPGI protein.

We measured ALT and AST by biochemical analysis in HBsAg and anti-HCV positive participants, and M2BPGI was measured in all participants. The average ALT level in HBsAg positive group was 50.7 u/l, in anti-HCV positive group 49.7 u/l, and

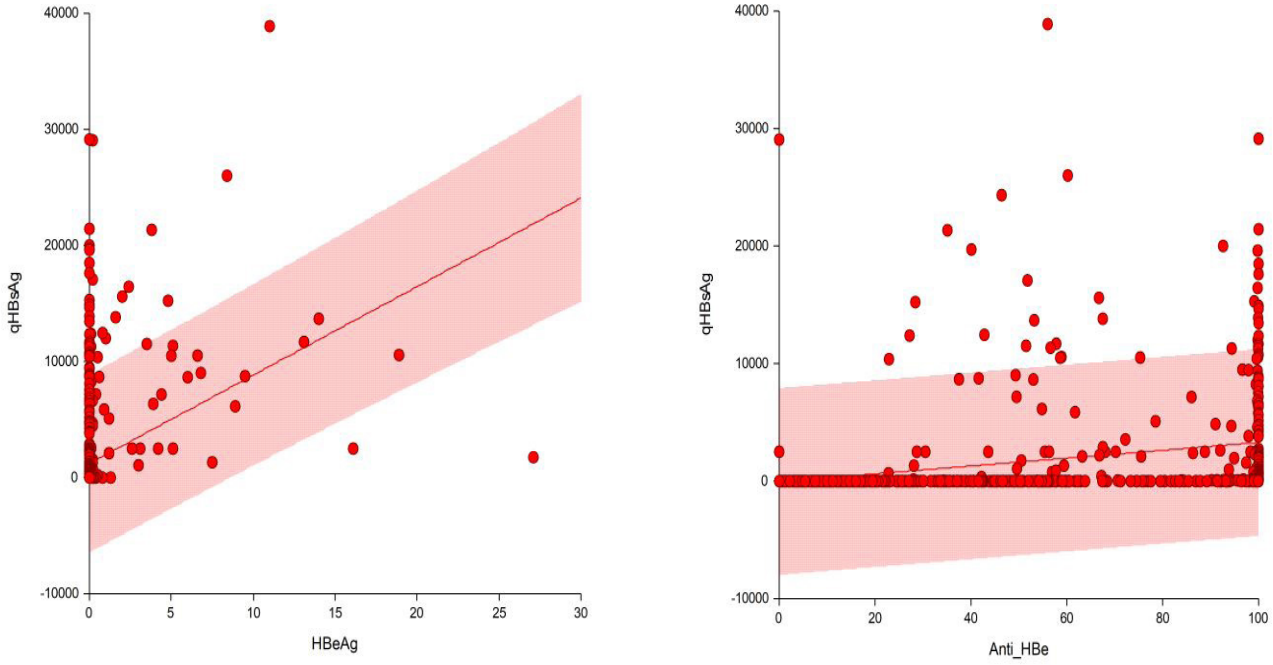

Figure 1. Results of numerical value comparison of HBsAg levels among HBeAg negative and positive group

Table 3. Results of liver function test

		N	Mean	Std. Deviation	95% CI Lower	95% CI Upper	Minimum	Maximum	p-value
ALT									.887
	Hepatitis B Virus Infections	176	50.7	54.3	42.7	58.8	14.0	508.0	
	Hepatitis C Virus Infection	192	49.7	38.4	44.3	55.2	15.0	214.0	
	Both Hepatitis B and C Virus Infections	16	55.8	33.6	37.9	73.6	23.0	134.0	
AST									.779
	Hepatitis B Virus Infections	173	47.0	39.2	41.2	52.9	18.0	297.0	
	Hepatitis C Virus Infection	186	48.3	37.5	42.9	53.7	14.0	275.0	
	Both Hepatitis B and C Virus Infections	16	53.8	25.3	40.3	67.3	24.0	119.0	

p-value has been calculated with Univariate Analysis of Variance (GLM),

Table 4. Multiple comparisons by liver function test.

Infection		Mean Difference	Std. Error	p-value Lower Bound	95% Confidence Interval Upper Bound
ALT					
	B vs C	1.00	4.825	.977	-10.36	12.35
	B vs BC	-5.02	12.074	.909	-33.43	23.39
	C vs BC	-6.02	12.032	.871	-34.33	22.29
AST					
	B vs C	-1.28	4.003	.946	-10.70	8.14
	B vs BC	-6.77	9.903	.773	-30.07	16.54
	C vs BC	-5.49	9.874	.843	-28.72	17.74

p-value was calculated Tukey HSD test.*The mean difference is significant at the 0.05 level. B - Hepatitis B Virus Infections, C - Hepatitis C Virus Infection, BC - Both Hepatitis B and C Virus Infections

Table 5. Defined Results of the mean value of M2BPGi

M2BPGi	N	Mean	Std. Error Lower	95% CI Upper		p-value
Infection						<.0001
No Virus Hepatitis Infections	2262	1.00	0.01	0.98	1.02	
Hepatitis B Virus Infections	319	1.65	0.08	1.48	1.81	
Hepatitis C Virus Infection	537	1.83	0.08	1.67	1.98	
Both Hepatitis B and C Virus Infections	34	1.87	0.19	1.48	2.26	
Total	3152	1.22	0.02	1.18	1.25	

M2BPGI– Mac-2-binding protein biomarker; [a]P value has been calculated with One-way ANOVA;

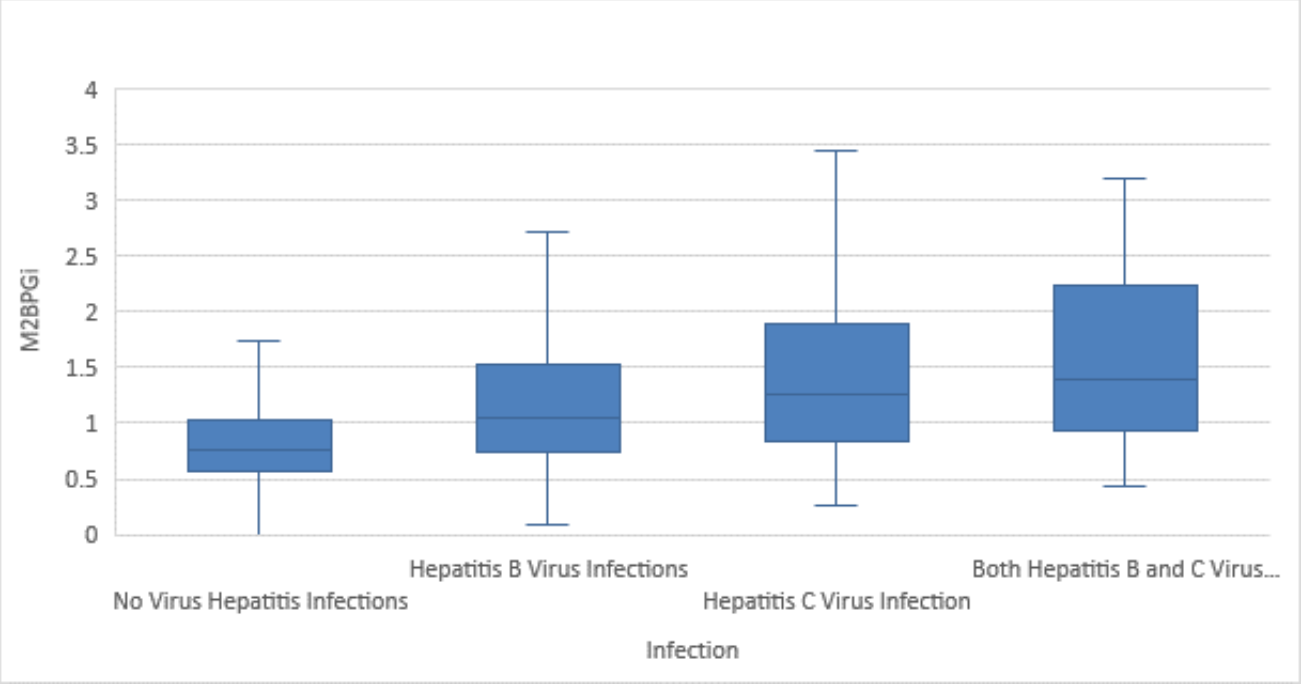

Figure 2. Result of M2BPGi marker

in co-infection group 55.8 u/l (p=.009) showing it's statistical significant. The average AST level in the first group was 47 u/l, in the second group 48.3 u/l and in the third group 53.8 u/l (p=.019) (Table 3).

Upon processing with the ANOVA test to estimate the results, we compared the people who have with the patients having HBV, HCV positive group and co-infection of both HBV and HCV under the multiple comparison test. Liver function tests of the infection groups had no significant difference (Table 4).

Liver fibrous change marker M2BPGI protein average level in non-infected group was 1.00 C.O.I, in HBsAg positive group 1.65 C.O.I, in anti-HCV positive group 1.83 C.O.I and in co-infection group 1.87 C.O.I (<.0001) (Table 5) (Figure 2).

Upon processing with the ANOVA test to estimate the results, we compared the non-infected hepatitis virus group with the patients having HBV, HCV positive group and co-infection of both HBV and HCV group under the multiple comparison test. As a result, liver fibrous change marker M2BPGi, of the non-infected group was identified as having the statistically significant difference (<.0001). M2BPGi, liver fibrosis marker, of the infection groups had no significant difference (Table 6).

Discussion

We have conducted this survey at 3 levels in cities, province centers, and rural areas, with 3196 people who are 40-64 years old. The survey involved 1829 (57.2%) people from the selected districts of Ulaanbaatar city, 1367 (42.8%) people from Gobi-Altai, Uvs, Arkhangai, Khuvsgul, Tuv, Dornogobi, Umnugobi, Sukhbaatar provinces, and 1093 of all participants were male, while 2103 were female. We used the latest analyzing technology in our research, the HISCL500 fully automatic immunologic analyzer which is highly sensitive to recognize the minimum titer of the virus in the serum by CLEIA method.

According to the results, 10.1% of the respondents had HBsAg positive, 17% had anti-HCV positive, and 1.1% had co-infection of both HBV and HCV. Percentage of the respondents from rural areas, who had positive HBsAg and anti-HCV results, was more than the respondents from Ulaanbaatar.

Gender disaggregated B virus was common in males, while C virus and B, C co-infection occurred mostly in women (<.0001). Hepatitis B infection decreased from 11.5 percent to 7.8 percent during the age-group increase, with hepatitis C virus infections increased from 11.3 percent to 26 percent (<.0001). According to a study on the prevalence of hepatitis C virus in the relatively healthy population of Mongolia, 11-16% of the population was infected with hepatitis C virus, which was higher than in other countries, and the prevalence of anti-HCV antibody in adults increased with the age group increase, therefore it shows that hepatitis C virus infections are poorly cured and have a high chronicity, which is the same as our research[9,10]. According to a study conducted in Mongolia, 9.6% of the relatively healthy adult population, 5.2-9.8% of the children, 8.2% of analysts with blood donors and 49.5-56.3% of patients with chronic hepatitis were diagnosed with hepatitis B virus in our country[11-17]. According to our survey, 10.1 percent of all respondents, 9.2 percent in Ulaanbaatar and 11.4 percent in rural areas, had a hepatitis B virus.

The hepatitis B virus "e" antigen (HBeAg) indicates that hepatitis B is rapidly replicating, and it is determined primarily

Table 6. Multiple comparisons by hepatitis virus infections.

Infection	Mean Difference	Std. Error	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
A vs B	-.64342*	0.0603	<.0001	-0.7984	-0.4884
A vs C	-.82592*	0.0484	<.0001	-0.9503	-0.7015
A vs D	-.86401*	0.17421	<.0001	-1.3118	-0.4162
B vs C	-0.1825	0.07128	.0510	-0.3657	0.0007
B vs D	-0.22059	0.1819	.6190	-0.6882	0.247
C vs D	-0.03809	0.17831	.9970	-0.4964	0.4202

p-value was calculated Tukey HSD test,A - No Virus Hepatitis Infections, B - Hepatitis B Virus Infections, C - Hepatitis C Virus Infection, D - Both Hepatitis B and C Virus Infections

with DNA in the blood. 13.5 % of the HBsAg positive patients enrolled in the study were HBeAg positive. In medical practices, qualitative method is commonly used for diagnosis of virus infection by the detecting the presence of viral markers. In recent years, quantitative HBsAg method has been used to monitor antiviral treatment efficacy and to estimate the hepatocellular carcinoma. When we compared HBsAg levels among HBeAg negative and positive groups, HBsAg level mean is 1077.0 ± 342.19 IU/ml in HBeAg negative group but as for the HBeAg positive group, it was 13346.4 ± 2494.2 IU/ml which is of statistical significance (<.0001).

AST and ALT increased more frequently during co-infection. Testing of ALT and AST levels which assess liver function is suitable for diagnosis of acute hepatitis but it can't assess chronic hepatitis or cirrhosis severity level[18]. Therefore, a diagnostic product is needed to measure cirrhosis levels. Japanese scientists have identified the structure changes glycoproteins on hepatocyte walls, thus in the result they found a specific M2BPGI glycol-biomarker. To the best our knowledge, this is the first study investigating M2BPGI level in people aged 40-64 in Mongolia. This study showed that M2BPGI levels in HBsAg and anti-HCV positive participants were significantly higher than in no hepatitis virus infection participants. The mean M2BPGI level in the HBsAg positive group was 1.65 COI, anti-HCV positive group was 1.83 COI, both HBsAg and anti-HCV positive group was1.83 COI. This finding is well in line with recent reports from Japan. Ishii et al. found that the median serum M2BPGI level was 1.2 COI in treatment of naive chronic hepatitis B patients[19]. Ichikawa et al. reported that the M2BPGI level was 0.97 COI in 112 treatment naïve patients with hepatitis B virus related chronic hepatitis and liver cirrhosis[20]. Sarantuya et al. reported that M2BPGI level was 2.1 COI in hepatitis D virus infection[21]. Biochemistry tests in this study showed that hepatitis virus infection groups have higher transaminase and higher fibrosis scores. These results support the fact that hepatitis virus infections cause more aggressive disease. M2BPGI is effective in assessing fibrosis in patients with hepatitis B virus[22], but studies have shown that it is very effective in diagnosing the fibrosis levels of patients with hepatitis C virus[23], and our study has shown that M2BPGI protein is higher in hepatitis C virus infection than hepatitis B virus result (<.0001). According to Yamasaki.K research, which involved 707 patients with hepatitis C virus, M2BPGI level increase is proportionally positive with liver cancer risk increase[24,25].

Mongolia is ranked first in the world with the death rate of hepatocellular carcinoma per 100,000 people, and this figure is eight times the world average[5] and new cases have not been decreased, with 2017 1.8 percent in 10000 population and 1.83 percent in 2018[26]. Our research aimed to describe prevalence of hepatitis B, C virus, therefore we did not include prevention and treatment issues into our research spectrum. We could not use liver biopsy to determine liver fibrosis in all patients for the reason that patients mainly hesitated to undergo a biopsy procedure. Further studies comparing M2BPGi with liver biopsy and/or Fibro Scan are necessary to confirm the efficacy of serum M2BPGi levels for assessing the stage of fibrosis among patients with hepatitis infection.

Our study's future direction is the first baseline study of the National Cancer Cohort study and will continue every five years to 2040.

Conclusion

Of population aged 40-64, 10.1 percent were positive for HBsAg, 17 percent were positive for Anti-HCV, and 1.1 percent had co-infection of both HBV and HCV. qHBsAg level shows a strong correlation with that of HBeAg. Serum M2BPGi is increasing in hepatitis C virus infection and in co-infection. Based on above mentioned facts, it is necessary to take action of control and need to detect liver cancer in an early stage (an nemeh), to determine risk factors and spread of disease and to take (to nemne) preventative measures.

Conflict of Interest

The authors declare that they have no competing interests.

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