

Full Length Research Paper

Evaluation of psychiatric morbidity and quality of life in inactive HbsAg carriers

Abdulkadir Küçükbayrak^{1*}, Fatih Canan², Aytekin Alçelik³, Gülali Akta³, Esra Koçoğlu⁴ and Tekin Ta⁴

¹Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Abant İzzet Baysal University Bolu, Turkey.

²Clinic of Psychiatry, Bolu İzzet Baysal Mental Health Hospital, Bolu, Turkey.

³Department of Internal Medicine, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey.

⁴Department of Medical Microbiology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey.

Accepted 22 March, 2019

Hepatitis B virus (HBV) infection develops in forms from asymptomatic carrier to cirrhosis. There are several studies examining the quality of life of patients with HBV in literature. However, only two studies have investigated the psychiatric morbidity in hepatitis B patients. In this study, we evaluated psychiatric morbidity and quality of life in inactive HbsAg carriers. This case-controlled study was performed among 26 healthy volunteers as control group and 31 inactive HbsAg carriers. Seven (22.5%) of our Hepatitis B patients were found to have an Axis I psychiatric diagnosis. For the carriers, the diagnoses made were major depression (3 patients), major depression with conversion disorder (1 patient), moderate depressive disorder (1 patient), cyclothymic disorder (1 patient), and obsessive-compulsive disorder (1 patient). No significant difference was found between carriers and controls in terms of quality of life scores and anxiety and depression scores. According to these findings, the patients with hepatitis should undergo psychiatric evaluation by a specialist. Also, physicians should be aware that emotional and psychiatric support is not necessary for all of the patients with hepatitis B.

Key words: Inactive HbsAg carrier, psychiatric morbidity, quality of life.

INTRODUCTION

Hepatitis B virus is a member of Hepadnaviridae family and contains circular double strain DNA genom. Although,

it primarily infects hepatocytes, virutic DNA can also be obtained from other types of cells. More than 500 million people worldwide are estimated to be infected with Hepatitis B. Hepatitis B virus infection may cause chronic hepatitis, cirrhosis, and hepatocellular carcinoma and more than one million deaths may occur annually because of factors related to chronic infection. The infection may occur in different clinical forms from asymptomatic carriage to end stage hepatic failure (Koziel et al., 2010).

There are many studies about health related quality of life (HRQOL) among hepatitis patients in the literature. These studies are focused particularly on therapy receiving patients with hepatitis C. There are few studies investigating the quality of life of patients with hepatitis B in the previous literature. Additionally, majority of HRQOL studies have been performed on patients on treatment. In

*Corresponding author. E-mail: abdulbayrak@yahoo.com. Tel: +90.533.8114215 or +90.374.2534656. Fax: +90.374.2534615.

Abbreviations: BDI-II, Beck depression inventory-II; CVH, chronic viral hepatitis; GAF, global assessment of functioning; HRQOL, health related quality of life; HBV, hepatitis B virus; HCV, Hepatitis C virus; HAD, hospital anxiety and depression scale; IDSA, infectious diseases society of America; SF-36, short form-36 health survey; SCID-I, Structured clinical interview for DSM-IV Axis I Disorders; WHO, world health organization; WHOQOL-BREF TR, WHO quality of life measurement instrument, short form, Turkish Version.

Table 1. Criteria of inactive HbsAg carriage (5).

Criteria	AST-ALT	HBsAg	Anti-HBe/HBeAg	HBV-DNA (IU/L)
Inactive HBsAg Carriage	Lower than upper limit for at least 6 months	Positive at least for six months	Positive/Negative	<2000

ALT: Alanin Aaminotferaz, AST: Aspartat aminotferaz.

those studies, however, psychiatric scales instead of psychiatric interviews were used (Karaivazoglou et al., 2010; Kunkel et al., 2000; Pojoga et al., 2004).

To our knowledge, there are only two studies investigating psychiatric morbidity in hepatitis B patients. Only one of these two studies, using previous guideline, was designed to include Hepatitis B carriers. The other study was performed in chronic hepatitis B and C patients. In this study, we evaluated psychiatric morbidity in inactive HbsAg carriers based on 2009 IDSA guidelines (Anna et al., 2009). Psychiatric interviews were conducted according to DSM-IV criteria and the patients were also asked to complete hospital anxiety depression inventory and World Health Organization Quality of Life questionnaire. We believe, this is the second psychiatric morbidity study in hepatitis B carriers. But our study is the first one in use in the new guidelines.

MATERIALS AND METHODS

This study was performed among the patients who had been followed up due to inactive HbsAg carriage between June 2011 to August 2011 in Abant İzzet Baysal University, Faculty of Medicine. A total of 31 inactive HBsAg carriers and 26 healthy volunteers as control group were enrolled in this case-controlled study. 2009 IDSA guidelines were used to detect HBsAg carriage. Eighteen were male and 13 were female; 28 were married and 3 were single; 11 were graduated from high school, 18 were graduated from primary school and 2 were graduated from university in HBsAg carriers. Mean age of the study population was 36.87 years (females: 39.69 years and males: 34.83 years). Nine of the carriers also had a chronic comorbidity (except malignancy). Duration of the awareness of the hepatitis diagnosis for the patients was in a range between 6 months and 20 years at the time of entry into the study.

The patients from our records were called by phone and 31 had accepted to enter the study. All had given written informed consent, and the study had been approved by the local ethical committee. In their first admission, we routinely inform all the patients about hepatitis disease and follow-up process. Control group, which was consisted of individuals with positive Anti HBs, and negative Anti HCV and anti HIV, had similar socio-demographic features with HBsAg carriers. Neither control subjects nor HBsAg carriers were excluded because of other comorbid diseases. Patients with positive anti HCV or anti HIV were excluded from the study. We also excluded patients who did not meet criteria in Table 1.

Axis I disorders were diagnosed using the Structured Clinical Interview for DSM-IV. Additionally, both patients and controls were asked to complete hospital anxiety depression inventory and Turkish version of World Health Organization Quality of Life questionnaire. Control group was not assessed with the Structured Clinical Interview.

Data gathering tools

Inactive HBsAg carriers

Patients providing following criteria were regarded as HBsAg carriers: at least two positive HBsAg and anti HBe-Ag values within 6 months, at least two normal liver function tests within 6 months, HBVDNA value is less than 10000copy/ml in PCR and HAI index in liver biopsy is less than 4 if performed.

Structured clinical interview for DSM-IV Axis I disorders (SCID-I)

SCID-I is a structured interview developed by First et al. (1997) for making the major DSM-IV Axis I diagnoses. The clinical version of SCID-I was used in the present study. SCID-I was translated into Turkish by Çorapçioğlu et al. (1999). The adaptation, validity and reliability studies of SCID-I have been conducted.

Hospital anxiety and depression scale (HAD)

HAD is a simple and reliable test that can be used in medical practice (Zigmond, 1983). Validation of the Turkish version of HAD has been conducted by Aydemir (1997). It can be used both in hospital and community settings. It has 14 items in total, 7 for anxiety and 7 for depression. Each item is evaluated on a 4 point scale. The total scores can range between 0 to 21 both for anxiety and depression. The scores between 0 to 7 indicate normal emotional status.

WHO quality of life measurement instrument, short form, Turkish version (WHOQOL-BREF TR)

WHOQOL-BREF-TR is an assessment tool that was initially developed by WHO, with the contribution of 15 centers from various countries, for the subjective evaluation of quality of life (WHOQOL GROUP, 1994). It is composed of 26 questions in 4 domains (World Health Organization, 1997). The 4 domains are physical health, psychological health, social relationships, and environment. It measures how a person perceives and the symptoms of physical or mental diseases and what kinds of interactions there are between the disease, physical activity, and environment. The questions measure the severity and frequency of the patient's experiences and interpretation about those experiences. The physical domain consists of questions about daily activities, dependence on medication and treatment, energy and exhaustion, mobility, pain and discomfort, sleep and rest, and capacity to work. The psychological domain consists of questions about positive and negative feelings, self-esteem, body image and external image, personal beliefs, and attention. The social relationships domain consists of questions about relationships with others, social support, and sex life. The environmental domain of the scale

Table 2. Quality of life and anxiety-depression scores.

Independent Samples t test	Inactive HbsAg carrier (Mean±SE)	Control (Mean±SE)	P
Depression scores	7.00±0.63	7.19±0.86	>0.05
Anxiety scores	8.00-0.00-17.00	8.00-1.00-17.00	>0.05
qol physics	67.70±2.93	63.46±4.23	>0.05
qol env	63.41±2.15	61.78±4.27	>0.05
Mann-Whitney U Test	Carrier Median-min-max	Control Median-min-max	P
qol psycho	72.91-16.67-100.00	72.91-0.83-95.83	>0.05
qol soc	66.67-25.00-100.00	66.67-8.33-100.00	>0.05

qol physics: Physical quality of life scores, qol env: Environmental quality of life scores, qol psycho: Psychological quality of life scores, qol soc: Social quality of life scores.

consists of questions about the home environment, physical security and safety, financial resources, availability of health services, leisure activities, physical environment, and transportation. The domain scores can be calculated separately between 4 and 20 or between 0 and 100 (WHOQOL GROUP, 1998)). There is no total score for the scale. In this study the score range of 4 to 20 was used. The validity and reliability of the Turkish form was performed by Eser et al. (1999).

Statistical analysis

Statistical analyses were performed with the SPSS 15.0 (Chicago IL) computer program. Parameter values were reported as mean ± standard deviation (SD) and group differences. The normality of distribution of the data was evaluated by running a one-sample Kolmogorov-Smirnov test both for the HBsAg carriers group and control group. In the comparisons between the patients and controls, the data that fit to the normal distribution (depression, qol-physics, and qol-environment scores) were compared using Student's t-test and data that did not fit the normal distribution (anxiety, qol-soc, and qol-psycho scores) were compared with the Mann-Whitney U-test. A p value of < 0.05 was considered significant.

RESULTS

Seven (22.5%) of our Hepatitis B patients were found to have an Axis I psychiatric diagnosis. Carriers were diagnosed with major depression (3 patients), major depression and conversion disorder (1 patient), moderate depressive disorder (1 patient), cyclothymic disorder (1 patient) and obsessive-compulsive disorder (1 patient). No significant difference was found between patients and controls in terms of quality of life scores and anxiety and depression scores (Table 2).

Personality disorders were detected in 2 of the carriers (antisocial and narcissistic personality disorders), however, Axis I diagnosis was not assigned. Three of the patients were currently being followed-up by a psychiatry clinic. Two of these patients had major depression (one has attempted suicide three times) and the other was

diagnosed as obsessive compulsive disorder. One of the patients that did not meet criteria for any Axis I psychiatric diagnosis at the entry to the study stated he received treatment for major depression previously.

Contrary to our expectation, two carriers with major depression had low depression scores. One of the major carriers with depression had higher than expected anxiety score although he was not diagnosed with any anxiety disorders. Moreover, a patient with obsessive-compulsive disorder had normal levels of anxiety scores, which is inconsistent with our expectations. Quality of life scores of the carriers with a psychiatric disorder were found to be lower than those of carriers without a psychiatric disorder, as expected. However, 3 of the carriers who were not diagnosed with an Axis I psychiatric disorder also had low quality of life scores. The rest of the patients in the study had high quality of life scores. Anxiety depression scores of the patient with anti-social personality disorder were low and his quality of life scores were high. Both anxiety-depression scores and quality of life scores were low in the patient with narcissistic personality disorder.

DISCUSSION

In the present study, inactive hepatitis B carriers were found to have similar rates of Axis I psychiatric diagnosis with general Turkish population. There was no significant difference between carriers and control group in terms of anxiety and depression scores and quality of life scores. These results confirm that inactive hepatitis B carriers do not differ from non-carriers in regards to social, psychological, environmental, and physical quality of life.

Psychiatric morbidity in the patients with hepatitis B in the literature is firstly described by Atesci et al. (2005). The authors evaluated psychological state of asymptomatic hepatitis B carriers. This study included 43 asymptomatic hepatitis B carriers (former name) and 43

healthy individuals. Psychiatric disorders and psychosocial functions in the participants were evaluated by SCID-I and the Global Assessment of Functioning (GAF) scales. Psychiatric disorder rate was 30.2% (13 patients) in Hepatitis B virus carriers and 11.6% (5 subjects) in controls. Psychiatric disorders diagnosed in the carriers were major depressive disorder (n=6), anxiety disorder not otherwise specified (n=2), adjustment disorder with depressive mood (n=2), obsessive-compulsive disorder (n=1), adjustment disorder with anxiety mood (n=1), and dysthymic disorder (n=1). The patients with asymptomatic hepatitis B had significantly higher depression and anxiety scores and lower GAF scores than control group. Authors have suggested emotional support for carriers. However, as a limitation, the authors have not explained the criteria of asymptomatic hepatitis B carriage in the study. Additionally, 5 patients enrolled to study were aware of the diagnosis for less than 3 months before enrolling to the study. Thus, we think that it is debatable to consider these 5 patients as carriers.

Psychiatric morbidity rate in general Turkish population has been reported to range between 10 and 20% (Rezaki et al., 1995; Kuey et al., 1987; Ögel, 1998). In the present study, the rate of psychiatric diagnosis in hepatitis B carriers was found to be similar with general population (22.5%). Additionally, anxiety-depression and quality of life scores were not different from the control group.

The second study about psychiatric morbidity in hepatitis patients was performed by Özkan et al. (2006) in 2006. They observed psychiatric diseases and HRQOL of chronic hepatitis B and C patients. They enrolled 107 patients to their study. Their inclusion criteria were as follows: patients with compensated hepatic disease with no cirrhosis, patients who receive antiviral therapy for at least 6 months, and patients without an active period related to hepatitis. Hepatitis B was described in 43.9% of the patients in that study. At least one psychiatric disease was diagnosed in 44.7% of the hepatitis B patients using SCID-1 structured interview. There were no significant difference between type of hepatitis and rate of the psychiatric diseases. On the other hand, types of the psychiatric disease differed between each hepatitis group.

The psychiatric diseases and rates in HBV and HCV groups were as follows: depressive mood (6.4 and 13.3%, respectively), alcohol related diseases (2.1 and 13.3%, respectively) and anxiety disorders (10.6 and 5%, respectively). Depression rates of HBV and HCV groups were not different. Physical and mental SF-36 scores of both hepatitis groups were significantly lower than control group. Physical and social functions and general wellness were worse in two hepatitis groups. Reduction in physical and social functions and general wellness was especially significant in females, in patients diagnosed with psychiatric disorder and in patients with severe depression. In addition, physical functions and general wellness tended to worsen as education levels

decreased. This study indicated that chronic hepatitis patients had higher psychiatric disease rates and significantly lower HRQOL than control group. Moreover, authors have recommended that hepatology, infectious diseases, and liaison psychiatry departments should follow up patients with chronic hepatitis together. Awareness of the disease by the patients in this study varied between 1 to 288 months. They did not explain how they diagnosed chronic hepatitis in a patient with a 1 month history of hepatitis disease. This was an apparent limitation of the study.

As they were psychiatric morbidity studies which used psychiatric interviews rather than psychiatric scales, the two studies mentioned above differs from other studies in the literature. Extent of fatigue and depressive symptoms in the patients with chronic hepatitis B or C were observed in a study, which was published in 2010. Short Form-36 Health Survey (SF-36), the Beck Depression Inventory-II (BDI-II) and the Fatigue subscale of the Functional Assessment of Cancer Therapy-Anemia Scale had been used to assess patients' symptoms in this study. HRQOL of HBV patients had been similar to HCV patients. Activity of infection, stage of fibrosis or grade of inflammation, depressive symptoms and fatigue in the patients with chronic viral hepatitis (CVH) had been found to be associated with HRQOL. Authors suggested that HRQOL in the patients with CVH had been impaired. Fatigue and impaired psychological functioning was associated with reduced HRQOL and this relationship was independent from the disease etiology. They proposed that management of fatigue and depressive symptoms in these patients was very important and should be done by a specialist (Karaivazoglou et al., 2010). In another study, 50 Korean immigrants with chronic viral hepatitis or healthy hepatitis B carriers had been evaluated. The relationship between their depression scores, psychosocial stressors, social support, and biological markers of dysfunction had been assessed. BDI-sf total scores were significantly associated with transaminase elevations but was not associated with other parameters of hepatic dysfunction (albumin levels, and prothrombin time) or other medical causes of depression. Authors determined that patients with higher BDI-sf total scores had more psychosocial stressors and lower GAF scores (Kunkel et al., 2000). In a further study, Foster et al. (1998) had investigated quality of life by SF-36 scale in the patients with chronic hepatitis B and C. The patients with chronic viral hepatitis B or C and without cirrhosis had been enrolled in the study if they were untreated or if their treatment had been stopped for at least six months. "Mental health" and "general health perception" in HBV infected patients had been decreased. However, the SF-36 scores (for the physical and social functioning, role limitation, energy, and fatigue and pain) in patients with chronic HBV was only minimally decreased. Authors reported that these patients did not have any significantly impaired physical

functions. There was no correlation between severity of hepatic inflammation and serum ALT levels in chronic hepatitis B and C patients with SF-36 scores.

Pojoga et al. (2004) had evaluated health-related quality of life by SF-36 in the patients with chronic viral hepatitis B and C. Several quality of life scores of hepatitis B patients were better than hepatitis C patients (general health, social functioning, mental health). However, they found no significant correlation between transaminase levels and the SF-36 scores. They noted that quality of life was affected negatively in the patients with chronic viral hepatitis who did not receive antiviral therapy. Another study Park et al. (2003) had also examined life quality before treatment in chronic viral hepatitis. The study showed that most of the HRQOL scores were significantly lower in the control group. The factors that affect SF-36 scores were evaluated and a weak correlation was found between age, serum albumin, serum bilirubin and prothrombin time. There was no correlation between histological activity index in liver biopsy, transaminase levels, duration of the disease, type of the virus (HBV or HCV) and HBV DNA levels. Chronic viral hepatitis patients were grouped into child A, B and C groups by modified Child-Pugh classification in the studies which evaluated life quality scores and severity of illness before treatment. It is reported in these studies that HRQOL scores were decreased as the liver disease became more severe (Ware et al., 1992; Younossi et al., 1999; Dan et al., 2006; Park et al., 2003; Cordoba et al., 2003; Younossi et al., 2001; Yao et al., 2003). Younossi et al. (2001) have observed 353 patients with chronic hepatitis B and C patients who had cholestatic disease (primary biliary cirrhosis or primary sclerosing cholangitis) or hepatocellular carcinoma. They found significantly different HRQOL scores in these patients than normal population. But there was similar HRQOL scores in patients with COPD and with congestive heart failure to those patients mentioned above. Some of the HRQOL scores of the cirrhotic patients with cholestatic disease were not as low as cirrhotic patients with hepatocellular carcinoma. Furthermore, scores of liver disease questionnaire and physical activity scores of SF-36 scales were lower in older patients. Lamivudin, an anti viral agent in treatment of hepatitis B, was reported to affect physical health scores (especially mental scores) positively when compared to the scores before treatment (Yao et al., 2003).

Depressive mood diagnoses were more than anxiety diagnoses in the patients in our study because we routinely inform the patients about treatment and follow up process in their first admission. We believe that this information makes it easy for the patients to skip anxiety period to the acceptance of the illness.

In conclusion, psychiatric evaluation of the patients with hepatitis should be done by a specialist. Also, physicians should be noted that emotional and psychiatric support is not necessary for all of the patients with hepatitis B. We

know that interferones which are used for the treatment of these patients with chronic viral hepatitis may cause major depression. For this reason, interferon receiving patients should be closely monitored both in pre- and posttreatment periods.

REFERENCES

- Anna SF, Lok, Brian J, McMahon (2009). Chronic Hepatitis B: Update. *Hepatology*. 2009.
- Atesci FC, Cetin BC, Oguzhanoglu NK, Karadag F, Turgut H (2005). Psychiatric Disorders and Functioning in Hepatitis B Virus Carriers. *Psychosomatics*. 46: 142-147.
- Aydemir Ö (1997). Hastane Anksiyete ve Depresyon Ölçeği Türkçe formunun geçerlilik ve güvenilirlik çalışması. *Türk. Psikiyatri. Dergisi.*, 8: 280-287.
- Cordoba J, Reyes J, Esteban JI, Hernandez JM (2003). Labeling may be an important cause of reduced quality of life in chronic hepatitis C. *Am. J. Gastroenterol.*, 98: 226-227.
- Çorapcıoğlu A, Aydemir Ö, Yıldız M Danacı AE, Köroğlu E (1999). Structured Clinical Interview for DSM-IV (SCID-I), Turkish Form. Ankara; Hekimler Yayın Birliği. (Turkish).
- Dan AA, Martin LM, Crone C, Ong JP, Farmer DW, Wise T (2006). Depression, anemia and health-related quality of life in chronic hepatitis C. *J. Hepatol.*, 44: 491-498.
- Eser SY, Fidaner H, Fidaner C, Elbi H, Eser E (1999): Yaşam kalitesinin ölçülmesi, WHOQOL-100 ve WHOQOL-BREF. *3P Dergisi.* ;(7): 5-13 (Ek 2) (Turkish).
- First MB, Spitzer RL, Gibbon M, Williams JBW (1997): Structured Clinical Interview for DSM-IV Clinical Version (SCID-I/CD). Washington, DC, American Psychiatric Pres.
- Foster GR, Goldin RD, Thomas HC (1998). Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology*, 27: 209-212.
- Kozziel JM, Lynne Thio C (2010). Hepatitis B Virus and Hepatitis Delta Virus. Mandell GL, Bennet JE, Dolin, R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, seventh ed., Philadelphia: Churchill Livingstone, pp. 2059-2086.
- Karaivazoglou K, Iconomou G, Triantos C, Hyphantis T, Thomopoulos K, Lagadinou M, Gogos C, Labropoulou-Karatzas C, Assimakopoulos K (2010). Fatigue and depressive symptoms associated with chronic viral hepatitis patients. health-related quality of life (HRQOL). *Ann. Hepatol.*, 9: 419-427.
- Kuey L, Ustun TB, Gulec C (1987). A study that examine the epidemiology of psychiatric disorders in Turkey. *Toplum. Ve. Hekim.*, 44: 16-30.
- Kunkel EJS, Kim JS, Hann HW, Oyesanmi O, Menefee LA, Field HL (2000). Depression in Korean Immigrants with Hepatitis B and Related Liver Diseases. *Psychosomatics*, 41: 472-480.
- Ögel K (1998). Social psychiatry, in *Basic Psychiatry*. Güleç C, Koroglu E (ed.). Ankara, Physicians Publications, pp. 1319-1328.
- Özkan M, Karayün D, Çorapcıoğlu A, Ünsalver BÖ, Balcıoğlu Đ, Kocaman N (2006). Kocaman N. Psychiatric Morbidity and Its Effect on The Quality of Life of Patients with Chronic Hepatitis B and Hepatitis C. *Int. J. Psychiatry Med.*, 36(3): 283-297.
- Park CK, Park SY, Kim ES, Park JH, Hyun DW, Yun YM (2003). Assessment of quality of life and associated factors in patients with chronic viral liver disease. (Abstract) *Taehan. Kan Hakhoe Chi*, 9: 212-221.
- Pojoga C, Dumitrascu DL, Pascu O, Grigorescu M, Radu C, Damian D (2004). Impaired health-related quality of life in Romanian patients with chronic viral hepatitis before antiviral therapy. *Eur. J. Gastroenterol. Hepatol.*, 16: 27-31.
- Rezaki M, Kaplan I, Özgen Üçok G, Sağduyu A, Gürsoy B, Öztürk MO (1995). Temel Sağlık Hizmetlerinde Ruhsal Sorunlar Üzerine Bir Alan Araştırması. *Türk. J. Psychiatry*, 6: 3-11.
- Ware JE, Sherbourne CD (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med.*

- Care, 30: 473-483.
- WHOQOL GROUP (1994) Development of the WHOQOL: rationale and current status. *Int. J. Mental Health*, 23: 24-56.
- WHOQOL GROUP (1998) The World Health Organization quality of life assessment (WHOQOL): development and general psychometric properties. *Soc. Sci. Med.*, 46: 1569-1585.
- World Health Organization (1997). WHOQOL, Measuring Quality of Life. World Health Organization, WHO/MSA/MNH/PSF/4.
- Yao GB, Cui ZY, Yao JL, Zhang DF, Ji NX, Huang Y (2003). Chronic hepatitis B treated with domestic manufactured lamivudine in 2200 patients: a phase IV study. (abstract) *Zhonghua Gan. Zang. Bing. Za. Zhi*11, pp. 103-108.
- Younossi M, Guyatt G, Kiwi M, Boparai N, King D (1999). Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut.*, 45: 295-300.
- Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G (2001). Health-related quality of life in chronic liver disease: the impact of type and severity of disease. *Am. J. Gastroenterol.*, 96: 2199-2205.
- Zigmond AS, Snaith RP (1983). The hospital anxiety and depression scale. *Act. Psychiatr. Scand.*, 67: 361-370.