

Format for ANSWERING REVIEWERS

October 12, 2013



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5351-review.doc).

Title: Anxiety and depression propensities in patients with acute toxic liver injury

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated. The English of this paper was revised by professional English language editing company: American Journal Experts: <http://www.aje.com>; We attached "EDITORIAL CERTIFICATE" from AJE.

2 Revision has been made according to the suggestions of the reviewer

(1) Answers for reviewer 00058104

Thank you for your good comments.

[1] We have revised the manuscript as you pointed out.

[2] page 5; Since the WJG needs CONCLUSION (no more than 26 words), we delete following sentence.

Not only treatment of the toxic liver injury, but also appreciation [please, reconsider the

use of the term

“evaluation”] of anxiety and depression propensities is a good management tool to prevent recurrence of the toxic liver injury.

--- So, we have revised:

CONCLUSION: Psychological factors that present vulnerability to the temptation to use alternative

medicines, such as herbs and plant preparations, are important for understanding toxic liver injury.

[3] The retrospective multi-center preliminary study, which was performed in 7 university hospitals in Korea across the country in 2003, reported that about two patients (23.4 patients per year) with the liver injury [please, reconsider this phrase] caused by plant preparations were hospitalized in the 1,000-bed class hospital.⁵

--- We have revised:

A retrospective multi-center preliminary study, which was performed in 7 university hospitals in Korea across the country in 2003, reported that the estimated annual incidence of hospitalization of patients with toxic hepatitis at a university hospital in Korea was 2,629.8^[5].

Followings are answers for your questions.

- How was defined the acute nature of the liver injury?

Answers: The acute nature of the liver injury was defined as the case that the liver injury had been recovered within 3 months. We have added these point in the material and methods section.

- What was the AST/ALT cutoff value in order to exclude patients that answered the questionnaires? **Answers:** Normal AST/ALT levels were defined as 37/43 IU/L and these values were applied to screen out patients who did not meet our definition of acute liver injury. In this study, AST/ALT levels had to be increased twice or more of the defined normal value in order to meet our standard for acute liver injury.

- Why patients with drug-induced acute liver injury were excluded? Could not these patients qualify as control group (2nd group)?

Answers: When this study was designed, we took into consideration that acute liver injury alone could cause anxiety and depression. Therefore we divided the acute liver injury group into toxic/non-toxic groups. Generally, toxic or drug-induced liver injury displays similar increases in AST and ALT levels. However, causes of the damage are of different nature: drug induced liver injury is usually due to passive intake of prescribed medication instructed by physicians whereas toxic liver injury is due to active self medication.

Therefore, patients with drug-induced acute liver injury were excluded in this study. As it was pointed out, we have plan to separately study drug induced liver damage and toxic liver damage.

We have added these point in the discussion section.

- Why patients with already known psychiatric pathology were excluded? Should this contribute to selection bias?

Answers: Thank you for your good comment.

We wanted to know the net psychiatric states in toxic hepatitis patients without already known psychiatric pathology. If patients with already known psychiatric pathology were included in the study, we could not know the net psychiatric states in toxic hepatitis patients and it would be selection bias which can affect on results.

- In the 2nd group were included patients with alcoholic hepatitis; how was defined the acute onset of liver injury? Also, are these patients considered free of anxiety and / or depression given their underline disease? **Answers:** All three patients with alcoholic hepatitis were included in the study because they had sudden increase of AST/ALT levels after short-term or temporary drinking. Their medical records were checked to make sure that they did not have any history of psychiatric pathology.

- 34 of 124 patients in the 2nd group have acute liver injury of unknown etiology; do they

qualify as control?

Answers: I do feel that 34 patients is not a small number. However, none of these patients had history of intake of drugs, herbal medication or plant preparation. Also, lab results showed that they were all negative on type A/B/C hepatitis virus, herpes virus, CMV or EBV. ANA and AMA were also negative, and there were no evidence of fatty liver (observed via abdominal sonography or CT), muscular disease or ischemic liver disease; their AST/ALT levels were temporarily raised. Thus we concluded that they were cryptogenic patients. There may have been other possible cause of the temporarily condition such as hidden bacterial or other viral infection, but because the cause could not be found, we concluded that they were patients of unknown etiology, and assigned them into control group.

- We have revised the part of language polishing.

Our manuscript was edited by English language editing companies: American Journal Experts: <http://www.aje.com>

(2) Answers for reviewer 00053786

Thank you for your good comment.

[1] We have revised the manuscript as you pointed out.

[2] The retrospective multi-center preliminary study, which was performed in 7 university hospitals in Korea across the country in 2003, reported that about two patients (23.4 patients per year) with liver injury caused by plant preparations were hospitalized in the 1,000-bed class hospital.⁵

--- We have revised:

A retrospective multi-center preliminary study, which was performed in 7 university hospitals in Korea across the country in 2003, reported that the estimated annual incidence of hospitalization of patients with toxic hepatitis at a university hospital in Korea was 2,629.8^[5].

[3] We have added a brief explanation of RUCAM as you indicated.

- We have revised the part of language polishing.

Our manuscript was edited by English language editing companies: American Journal Experts: <http://www.aje.com>

(3) Answers for reviewer 00053724

The most important point is the selection of the control group. There are three groups, however, all of these patients suffer from a certain medical condition that per se might cause anxiety and depression. The sole presence of a higher level of anxiety and depression in the patients with toxic liver injury compared to patients with other causes of liver injuries is not evidentiary that this is because of a certain personality pattern in the patients who take herbal remedies. It is well possible that the patients have higher anxiety levels because of the liver injury (cholestatic toxic liver injury for example might cause severe pruritus that itself might cause depression). To prove their findings, the authors need a control group of patients who take herbal remedies but do not have toxic liver injury.

Answers: Thank you for your good comment.

This study is a cross-sectional study that was designed to try to understand the psychological states, such as anxiety and depression, in patients with toxic liver injury who are taking herbal or folk remedies. The primary purpose of our study was achieved by determining the proportion of psychological conditions, such as anxiety and depression, suffered by patients with toxic liver injury taking herbal or folk remedies. However, there are issues that may be pointed out as a limitation of this cross-section study, such as “Does psychological state induce toxic liver injury?” and “Are changes in psychological state caused by toxic liver injury?” The relation can be demonstrated, but this research design that may be limit our understanding of causalities. To overcome some of these limitations, we tried to compare the non-toxic acute liver injury group with the normal group. Through this process, we attempted to distinguish between anxiety and depression induced by hospitalization alone. This study demonstrated that the rate of anxiety and depression in patients with toxic liver injury is significantly higher than that of cases without toxic liver injury, even when taking into account the change in the psychological states due to hospitalization. We believe that this finding is a key result of our research. We plan to promote research to clarify the psychological risk factors such as anxiety and

depression by comparing healthy individuals who are taking herbal preparations with toxic hepatitis patients taking herbal preparations through a case-control study.

We have added above descriptions to the discussion section.

A control group of patients with chronic liver disease would be of interest.

Answers:

We are very sorry that we did not enroll patients with chronic liver disease. Originally, this study was designed to evaluate psychiatric states in patients with acute toxic liver injury. We have plan the research about psychologic difference between acute and chronic liver disease. It might be a interesting result.

Language polishing is necessary.

Answers:

We have revised the part of language polishing.

Our manuscript was edited by English language editing companies: American Journal Experts: <http://www.aje.com>

(4) Answers for reviewer 00061678

- Authors did not mentioned what are the parameters of diagnosis of toxic or non toxic (clinical and laboratory)

Answers: Thank you for your good comment.

To identify the cause of acute liver injury, careful history taking, physical examination, liver function test, viral hepatitis serological testing (anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV antibody, CMV, EBV, HSV), anti-nuclear antibody, anti-mitochondrial antibody, or imaging studies (abdominal sonography or CT) were performed

We have added this point in MATERIAL and METHODS section.

- What are the degree of liver affection and is it related to search result or not??

Answers:

The degree of liver affection did not influence the psychologic results such as anxiety and depression.

- What are exactly types and doses of remedies used because special types might lead to these psychological effects others not .

Answers: Thank you for your good comment.

We are very sorry that we did not mentioned exactly types and doses of remedies used.

Some patients with toxic liver injury have taken multiple herbal preparations. Moreover, because of irregular taking of herbal preparations during several days to weeks, we could not mention exactly doses of remedies used. So we described just as “medicinal herbs, plant preparations, health foods and folk remedies” in this manuscript.

Followings are the types of remedies used.

Acanthopanax snticosus, Amanita virosa, Angelica dahurica Bentham et Hooker, Angelica gigas Nakai, Angelica tenuissima, Artemisia capillaries, Asparagus cochinchinensis (Lour.) Merr, Anemarrhena asphodeloides, Astragalus membranaceus, Atractylodes macrocephala, Catalpa ovata, Channa argus, Chelidonium majus var. asiaticum, Chrysanthemum morifolium, Chrysanthemum zawadskii var. latilobum, Cimicifuga heracleifolia Komarov, Citrus unshiu Markovich, Coix lachryma-jobi var. mayuen, Cornus offi cinalis, Crataegus pinnatifi da Bunge var. typica Schneider, Carassius carassius, Dimocarpus longan Lour, Ephedra sinica Stapf, Epimedium koreanum Nakai, Forsythia viridissima Lindley, Ganoderma lucidum Karsten, Gingko biloba L, Glycyrrhiza uralensis fischer, Hovenia dulcis, Ligusticum chuanxiong Hort., Liriope platyphylla, Lycium chinense Miller, Pachyma Hoelen Rumphius, Paeonia japonica, Paeonia lactifl ora Pallas, Phellinus linteus, Platycodon grandifl orus, Polygala tenuifolia, Polygonatum odoratum var. plurifl orum, Polygonum multifl orum, Poria cocos Wolf, Pueraria lobata, Raphanus sativus L., Rehmannia glutinosa, Rhododendron brachycarpum, Rutaceae, Scutellaria baicalensis, Ulmus davidiana var. japonica, Zingiber offi cinale, Zizyphus jujuba Miller, Antler, Chestnut, White chestnut, Red ginseng, Snakehead fish

- There is lack of inclusion and exclusion criteria for patients, eg what are psychological history or background for such patients.

Answers: Thank you for your good comment.

All the subjects in this study had only acute non-toxic or toxic liver injury without any chronic illness. Therefore all patients did not have previous psychological history or

underline non-psychological medical disorders such as chronic chronic liver disease, or chronic medical disease such as hypertension, diabetes or chronic respiratory disease etc which might affect on results.

(5) Answers for reviewer 00057978

Title: it partly reflects the major topic and contents of the study. The authors investigated only patients with the toxic acute liver injuries. Therefore the title "Study on anxiety and depression propensities in patients with the toxic liver injury in Korea: A multi-center, nation-wide, prospective study" is incomplete. The title "Study on anxiety and depression propensities in patients with the acute toxic liver injury in Korea: A multi-center, nation-wide, prospective study" would be more precise for this article.

Answers: Thank you for your good pointing out..

We considered the title as you pointed: "Study on anxiety and depression propensities in patients with acute toxic liver injury in Korea: A multi-center, nation-wide, prospective study"

But, the title of the manuscript should be less than 12 words according to the requirement of the WJG.

So, we changed the title into "Anxiety and depression propensities in patients with acute toxic liver injury"

Why was the toxic liver injury caused by drugs excluded from this study?

Answers:

Generally, drug or toxic induced liver damage displays similar increase in AST/ALT. However, causes of the damage are of different nature: drug induced liver damage is usually due to passive intake of prescribed medication instructed by physicians whereas toxic liver damage is due to active self medication. As it was pointed out, we have plan to separately study drug induced liver damage and toxic liver damage.

We have added these point in the discussion section.

Also, sources for criteria for diagnosis of " the acute liver injury" as follows: "The acute liver injury was defined as the case that ALT or the conjugated bilirubin value was

increased two times or more than the normal upper limit thereof, or that AST, alkaline phosphatase and total bilirubin were increased together and at least one of them was two times or more as much as the normal upper limit thereof" should be presented, and adequate references should be cited.

Answers: Thank you for your good comment.

In 1989, a panel of 12 European and American experts by consensus defined liver injury as an increase of more than twice the upper limit of the normal range in the levels of serum alanine aminotransferase or conjugated bilirubin, or a combined increase in the levels of aspartate aminotransferase, alkaline phosphatase, and total bilirubin, provided that one of these was more than twice the upper limit of the normal range.

And reference cite was added: "Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990; **11**: 272-276 "

We have added these point in the material and methods and references section.

(6) Answers for reviewer 00043561

Inclusion of people without liver disease and people with increased liver transaminases due to other causes of liver injury are appreciated in the design of the study. However, the positive control group with non-toxic liver injury is quite heterogeneous. In such a case, I would recommend inclusion patients with the same or similar duration of illness. While HAV infection and liver injury occurs suddenly, HBV infection causes slower progression.

Answers:

It is good opinion. The cause of the group with non-toxic liver injury is heterogenous, but in terms of acute liver injury, the patients have similar nature. Originally, we wanted to find out the psychological difference between non-toxic liver injury group and toxic liver injury group. Both group have the similarity of acute liver injury regardless of cause. Because the questionnaires survey was performed at the time of admission, psychologic states might be non-dependent of disease progression.

Introduction: This section is too long. The readers can read general information regarding toxic liver injury in specific papers that can be found in the past issues of this journal.

Answers:

We have modified shortly some portion of description as you pointed out.

The phrase “the inadvertent use of plant preparations in the form of an oriental medicine and a supplementary health food has become a frequent cause of toxic hepatitis” was deleted.

And we have summarized the phrase “Shepherd et al. reported the correlation between physical diseases and psychiatric diseases.¹¹ Finn and Huston reported that an emotional factor was one of the major causes of physical diseases in 18.5% of the internal medicine patients.¹² Schweb et al. reported that about 20% of 153 patients with non-cancer diseases who were hospitalized in the internal medicine ward showed depression symptoms.¹³ Lee et al. reported that 37-50% of non-psychiatric hospitalized patients showed depression and 50% of them showed anxiety.¹⁴ In 1995, Clarke and Smith reported that 55% of the subjects had mood disorder.¹⁵ In 1997, Olfson et al. reported that 11.6% of outpatients had anxiety disorder and 8% of them had depression disorder.¹⁶ Kroenke et al. reported that anxiety disorder was found in 15% of the subjects and depression disorder in 22%.¹⁷ ” into “Symptoms of anxiety and depression are often observed in psychiatry, and they are often discovered in patients with any non-psychiatric physical disease as well. Considerable research has been conducted regarding the anxiety or depression in non-psychiatric general or medical practice^[11-14]”.

I could not understand why the authors excluded those subjects with previously diagnosed mood disorders from the study. This causes reduction in the number of the disease cases in the real life. Nevertheless, this issue is a matter of choice but, in such case, the title and the content of the paper should be modified into something like “Frequency of undetected mood disorders in ...”.

Answers:

This study is a cross-sectional study that was designed to try to understand the psychological states, such as anxiety and depression, in patients with toxic liver injury who are taking herbal or folk remedies. The primary purpose of our study was achieved by determining the proportion of psychological conditions, such as anxiety and depression, suffered by patients with toxic liver injury taking herbal or folk remedies. However, there are issues that may be pointed out as a limitation of this cross-section study, such as “Does

psychological state induce toxic liver injury?" and "Are changes in psychological state caused by toxic liver injury?" The relation can be demonstrated, but this research design that may be limit our understanding of causalities. To overcome some of these limitations, we tried to compare the non-toxic acute liver injury group with the normal group. Through this process, we attempted to distinguish between anxiety and depression induced by hospitalization alone. This study demonstrated that the rate of anxiety and depression in patients with toxic liver injury is significantly higher than that of cases without toxic liver injury, even when taking into account the change in the psychological states due to hospitalization. We believe that this finding is a key result of our research. We plan to promote research to clarify the psychological risk factors such as anxiety and depression by comparing healthy individuals who are taking herbal preparations with toxic hepatitis patients taking herbal preparations through a case-control study. We have added above descriptions to the discussion section.

The timing of neuropsychological testing is not clear in the text and this is a major issue.

Answers: We have described the timing of neuropsychological testing in MATERIALS AND METHODS section, as follows "The questionnaire surveys were conducted during the hospital visit for Group 1 and at the time of admission for Groups 2 and 3."

Discussion: A brief summary of the result could be suitable at the beginning of this section.

Answers:

We have added a brief summary of the result at the beginning of discussion section, as follows "The present study demonstrate that patients with toxic liver injury had high anxiety and depression propensities".

The frequency of anxiety and depression all increases in hospitalized subjects. The frequency of mood disorders in these individuals increases with the number of comorbidities and polypharmacy.

Answers:

We agree your opinion. As already mentioned, this study is cross-section study. However,

there are issues that may be pointed out as a limitation of this cross-section study, such as “Does psychological state induce toxic hepatitis?” and “Are changes in psychological state caused by toxic hepatitis?” Relation can be demonstrated, but this is a research design that maybe restrictive to our understanding of the causalities. To overcome some of these limitations, we have tried to compare an acute hepatitis without toxic liver injury patient group with the normal group. Through these processes, we have attempted to distinguish between depression and anxiety induced by hospitalization alone. In conclusion, the rate of depression and anxiety suffered by toxic hepatitis patients taking folk remedies is significantly higher, even taking into account the change in the psychological states due to hospitalization. We believe this finding is a key result of our research. We plan to promote research to clarify the psychological risk factors, such as anxiety and depression, by comparing healthy individuals who are taking folk remedies with toxic hepatitis patients taking folk remedies through case-control study. We have added above descriptions to the discussion section.

The major limitation of the present study is the lack of in-depth analyses of depression with special reference to age groups.

Answers: Thank you for your good comment.

We are very sorry that we cannot provide age-dependent in-depth analysis.

3 Title, References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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