Psychiatric Insights into Liver Cirrhosis and Their Correlations with Traditional Chinese Medicine Diagnostics

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***Abstract* — We studied various psychiatric attributes in the categories of depression, anxiety and insomnia on 208 patients with liver cirrhosis, 61 patients with non-cirrhosis chronic diseases, and 60 healthy people. A set of psychiatric attributes were found to be uniquely associated with cirrhosis. Literature shows that these attributes are related to some mechanisms underlying liver cirrhosis, such as zinc/selenium deficiency and vitamin D deficiency. In addition, we investigated the relationships between those psychiatric attributes unique to cirrhosis and the "four diagnostic methods" of Traditional Chinese Medicine (TCM), and discovered interesting correlations. The above two findings can shed new light on the diagnosis and prognosis of liver cirrhosis, and the integration of Traditional Chinese and Western Medicine in the future.**

Keywords—liver cirrhosis; psychiatric attributes; four diagnostic methods, Traditional Chinese Medicine (TCM)

I. INTRODUCTION

Cirrhosis of the liver, usually caused by alcoholism, chronic hepatitis B, hepatitis C and fatty liver disease, is one of the most common chronic liver diseases characterized by the replacement of normal liver tissues by non-functional tissues. It is a leading cause of illness and death in the United States with approximately 5.5 million infections (the number is only 0.4 million in 1998) and 26,000+ deaths per year (816,000 worldwide). The number of infections is still increasing. Cirrhosis can hardly be cured completely. Medications may slow the progression of some types of cirrhosis, and a liver transplant will be needed in advanced cases when the liver ceases to function [1]. Many attributes, such as, large numbers of infections, high risks of death, incapability of complete cure, and so on, make cirrhosis one of the leading life threats to human beings. Similar to patients with other chronic diseases, patients with cirrhosis are accompanied with notable negative emotional developments after long-term treatment [2-6]. These emotional changes, such as depression, anxiety and insomnia, are usually considered to be the consequences of long-term treatment, pain, limited mobility, losing hope, change in life, and so on [7].

Recently, growing attentions have been paid to the life quality of patients suffered from chronic diseases. Studies have identified that emotional problems experienced by patients with chronic diseases were among the most critical factors influencing their life quality [8-12]. However, existing works have not yet shown for patients with cirrhosis whether those emotional problems are unique to liver cirrhosis or just commonly brought by any chronic disease. For example, many non-liver chronic diseases (e.g. kidney diseases [13, 14], heart diseases [15, 16], chronic obstructive pulmonary diseases [17-19], etc.) have also been reported to be related to various emotional issues such as depression and anxiety. In addition, it was reported that the depressive symptoms associated with hepatitis C were more likely to be a psychological and social issue rather than a consequence of liver injury [20]. Hence, it remains an open question whether any of those emotional problems suffered by patients with cirrhosis are uniquely related to cirrhosis. If some of them show characteristics unique to patients with cirrhosis, it is possible to make use of them to design better treatment and provide early prognosis for patients with cirrhosis.

In this study, we are interested in identifying psychiatric attributes that may shed new light on mechanisms causing patients with cirrhosis to develop negative emotional problems. Such attributes should be statistically significantly associated only with patients with cirrhosis, or at least much more severe than patients with other chronic diseases. Understanding these attributes can be extremely valuable for providing better treatment and early prognosis. To this end, we examined 208 patients with cirrhosis diagnosed between May 2011 and Feb 2012 using three widely used psychiatric assessment standards: the Hamilton Depression Scale [21], the Hamilton Anxiety Scale [22-25] and the Pittsburgh Sleep Quality Index [26]. These patients were compared with two control groups that contain 61 patients with non-cirrhosis chronic diseases and 60 healthy people, respectively. All data were collected by certified psychiatrists.

Our analyses showed that 7 attributes in the Depression and Anxiety categories were significantly associated only with patients with cirrhosis. These attributes are very likely to be highly related to cirrhosis and liver functions. Moreover, we identified 20 attributes (11 out of them are in the Insomnia

category) to be significantly associated with patients with chronic diseases. We provided evidences from the literature to support our novel findings.

Another important aspect of our study is to explore the connections between Western Medicine and Traditional Chinese Medicine in the context of liver cirrhosis. Our liver cirrhosis subjects were assessed by 46 attributes (**Table III**) used in the "four diagnostic methods" of Traditional Chinese Medicine (TCM) [27]. The TCM four diagnostic methods include inspection, listening/smelling, inquiry and palpation, and are essential tools in TCM practice [28]. Our analyses demonstrated that there are interesting relationships between the TCM attributes and the psychiatric practice/research instruments used in Western Medicine. These findings provide an empirical foundation to facilitate the modernization of TCM, and contribute to combining TCM and Western Medicine in a more scientific way to treat liver cirrhosis and other chronic diseases.

The rest of the paper is organized as follows: Section II describes the details of the dataset and the assessment tools utilized in this work. Our methods and analysis results are explained in Section III. In section IV, we discuss the potential clinical indications and applications of our findings. Finally, we conclude this paper in Section V.

II. DATASET

In total, we studied 329 patients, which include (a) 208 patients with liver cirrhosis (127 males, 81 females, aged between 26 and 86 years with a median of 57.5 years), referred as the "Cirrhosis group" in the rest of the paper; (b) 61 patients with non-cirrhosis chronic diseases of internal organs (e.g., kidney, intestine, breast, stomach, heart, etc.), referred as the "Non-cirrhosis group" in the rest of the paper; and (c) 60 healthy persons, referred as the "Healthy group" in the rest of paper. The size of our cohort is much larger compared to two preliminary studies [29, 30], which investigated 53 and 125 patients with cirrhosis, respectively. Every participant in our cohort was assessed by three scaling psychiatric assessment tools: the Hamilton Rating Scale for Depression (25 attributes), the Hamilton Rating Scale for Anxiety (14 attributes) and the Pittsburgh Sleep Quality Index (18 attributes). The liver patients with cirrhosis were also assessed by the "four diagnostic methods" of Traditional Chinese Medicine.

The Hamilton Rating Scale for Depression (HRSD, a.k.a. HAM-D) was first introduced in 1960 [21] to indicate and study the depression status of patients, and has been practiced as a gold standard since then. The HRSD scale has a couple of extended versions to the original one, which include HRSD-21, HRSD-24, HRSD-29 and etc. In this study, we employed HRSD-24 and only focused on the individual attributes of the questionnaire rather than the total score. The HRSD-24 has the following 25 psychiatric attributes: 1) depressed mood, 2) feelings of guilt, 3) suicide, 4) insomnia (early), 5) insomnia (middle), 6) insomnia (late), 7) work and activities, 8) retardation, 9) agitation, 10) anxiety (psychic), 11) anxiety (somatic), 12) somatic symptoms (gastrointestinal), 13) somatic symptoms (general), 14) genital symptoms, 15) hypochondriasis, 16) loss of weight, 17) insight, 18A) diurnal variation (A.M.), 18B) diurnal variation (P.M.), 19) depersonalization and derealization, 20) paranoid symptoms, 21) obsessional and compulsive symptoms, 22) helplessness, 23) hopelessness and 24) worthlessness. We referred these 25 attributes as the "Depression attributes" in the rest of the paper.

The Hamilton Rating Scale for Anxiety (HRSA, a.k.a. HAM-A) has been widely practiced to measure the severity of anxiety symptoms since its introduction in 1959 [22-25]. Similar to HRSD, we only focused on the individual attributes rather than the total score. The HRSA-14 has 14 attributes: 1) anxious mood, 2) tension, 3) fears, 4) insomnia, 5) intellectual, 6) depressed mood, 7) somatic (muscular), 8) somatic (sensory), 9) cardiovascular symptoms, 10) respiratory symptoms, 11) gastrointestinal symptoms, 12) genitourinary symptoms, 13) autonomic symptoms and 14) behavior at interview. We referred these 14 attributes as the "Anxiety attributes" in the rest of the paper.

The Pittsburgh Sleep Quality Index has been an assessment tool of proven validity and reliability for measuring the quality and patterns of sleep in old adults [26]. The tool measures seven aspects of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month [31]. Sleep latency refers to the time it takes to fall asleep, and habitual sleep efficiency refers to the ratio of total sleep time to time in bed [32]. This tool can be used in a variety of clinical settings, with answers self-reported by the patient. It has 18 attributes: 1) bed time, 2) time taken to fall asleep, 3) getting up time, 4) hours of sleep per night, 5) cannot get to sleep within 30 minutes, 6) wake up in the middle of the night or early morning, 7) have to get up to use the bathroom, 8) cannot breathe comfortably, 9) cough or snore loudly, 10) feel too cold,11) feel too hot, 12) have bad dreams, 13) have pain, 14) other reasons, during the past month 15) self rating of sleep quality, 16) take medicine to help sleep, 17) have trouble stay awake, 18) have problem to keep up enthusiasm. We referred these 18 attributes as the "Insomnia attributes" in the rest of the paper.

Traditional Chinese Medicine (TCM) originated in ancient China and has been practiced and developed for more than 5,000 years in Eastern Asia. Different from Western Medicine that emphasizes anatomical structures, TCM mainly concerns functional systems that regulate digestion, breathing, aging, and so on. In the practice of TCM, a doctor diagnoses a patient by measuring the pulse, inspecting the tongue, skin, eyes, looking at the eating and sleeping habits of the patient, as well as many other things. These methods can be summarized into the "four diagnostic methods": inspection, listening/smelling (listening and smelling are sometimes treated as different diagnostic methods), inquiry and palpation. In this project, we selected 46 most typical attributes of the "four diagnostic methods" attributes (referred as "TCM attributes" in the rest of the paper). Every patient with liver cirrhosis received a rating from 0 to 3 based on the severity of each TCM attribute: 0 indicates lowest severity (Never appears), 1 indicates median low severity (Occasionally appears), 2 indicates median high severity (Frequently appears) and 3 indicates the highest severity (All day).

TABLE I. SIGNIFICANT ANALYSES IDENTIFIED 7 PSYCHIATRIC ATTRIBUTES UNIQUE TO LIVER CIRRHOSIS. SEE MAIN TEXT FOR MORE DETAILED EXPLANATIONS AND DISCUSSIONS. IN THE ***SEVERITY*** COLUMN, "+" INDICATES THAT THE CORRESPONDING ATTRIBUTE IS MORE SEVERE IN THE 1ST GROUP THAN IN THE 2ND GROUP.

Attribute	Cirrhosis *vs.* Non-cirrhosis			Cirrhosis *vs.* Healthy			Non-cirrhosis *vs.* Healthy		
	$p_{C\text{-}N}$	$\text{FDR}_{C\text{-}N}$	*Severity*	$p_{C\text{-}H}$	$\text{FDR}_{C\text{-}H}$	*Severity*	$p_{N\text{-}H}$	$\text{FDR}_{N\text{-}H}$	*Severity*
DEP_2 (feelings of guilt)	0.000	0.000	+	0.000	0.000	+	0.144	0.255	+
DEP_3 (suicide)	0.002	0.007	+	0.001	0.002	+	0.657	0.779	+
DEP_13 (somatic symptoms (general))	0.000	0.000	+	0.000	0.000	+	0.761	0.844	+
DEP_16 (loss of weight)	0.009	0.031	+	0.007	0.016	+	0.986	1.000	+
ANX_5 (intellectual)	0.000	0.000	+	0.000	0.000	+	0.669	0.779	+
ANX_6 (depressed mood)	0.008	0.027	+	0.012	0.026	+	0.770	0.844	+
ANX_12 (genitourinary symptoms)	0.000	0.000	+	0.000	0.000	+	0.349	0.474	+

III. RESULTS

A. Identify significant psychiatric attributes

We applied the Wilcoxon-Mann-Whitney Ranksum test (referred as the "ranksum test" for conciseness in the rest of the paper) to identify psychiatric attributes showing significant differences in their distributions between two populations [33, 34]. In the ranksum test, all samples were ordered based on each individual attribute. Let R_1 denote the sum of the sample ranks in group 1. Let n_1 and n_2 denote the number of samples in groups 1 and 2, respectively. The ranksum statistics U is calculated as:

$$\mathrm{U} = \left(R_1 - \frac{n_1(n_1+n_2+1)}{2} \right) \Big/ \sqrt{\frac{n_1 n_2 (n_1+n_2+1)}{12}} \tag{1}$$

We obtained a *p*-value for a given U value (using MATLAB 2013 Statistic toolbox), and then calculated the corresponding false discovery rate of each attribute. False discovery rates (FDR) were controlled in selecting significant attributes. FDR control is a widely practiced method in multiple hypotheses testing to correct for multiple comparisons. It controls the expected proportion of incorrectly rejected null hypotheses, i.e., non-significant attributes however called significant by accident in analysis. Given an attribute A_i, we applied the Benjamini-Hochberg (BH) approach [35] to calculate $\text{FDR}_{C\text{-}N}(A_i)$, $\text{FDR}_{C\text{-}H}(A_i)$, and $\text{FDR}_{N\text{-}H}(A_i)$, which represented the Benjamini-Hochberg FDRs for the Cirrhosis group *vs.* the Non-cirrhosis group, the Cirrhosis group *vs.* the Healthy group, and the Non-cirrhosis group *vs.* the Healthy group, respectively.

B. Psychiatric attributes unique to liver cirrhosis

Psychiatric attributes unique to liver cirrhosis are more likely to be closely related to underlying mechanisms unique to liver cirrhosis rather than those shared by general chronic diseases. We named these attributes the "cirrhosis-driven" attributes. Such an attribute must be significantly more severe in patients with cirrhosis than in other subjects, while its difference between the Non-cirrhosis group and the Healthy group should not be significant. To identify such attributes, we applied the following criteria: $\text{FDR}_{C-N}(A_i) < 0.05$, $\text{FDR}_{C-H}(A_i) < 0.05$ and $p_{N-H} \geq 0.1$. Seven attributes, including 4 Depression attributes and 3 Anxiety attributes satisfied these criteria (**Table I**). No Insomnia attribute satisfied these criteria. All 7 attributes were significantly more severe in the Cirrhosis group than in the Non-cirrhosis and Healthy groups.

C. Psychiatric attributes commonly associated with general chronic diseases

In this experiment, we searched for attributes commonly associated with general chronic diseases, namely the "chronic-driven" attributes, which are significantly more severe in patients with chronic diseases than in healthy participants. We first combined the Cirrhosis group and the Non-cirrhosis group together into "Chronic" group. Given an attribute A_i, we calculated its ranksum test *p*-value by comparing the Chronic group with the Healthy group, and then calculated the corresponding Benjamini-Hochberg FDR: $\text{FDR}_{CN\text{-}H}(A_i)$. We set the threshold $\text{FDR}_{CN\text{-}H}(A_i) < 0.05$ to select attributes and then excluded those attributes unique to the Cirrhosis group listed in **Table I**. Twenty attributes were selected, including 6 Depression attributes (2 of them describe insomnia), 3 Anxiety attributes (1 of them describes insomnia) and 11 Insomnia attributes satisfied this criterion (**Table II**). We found a major difference between the "cirrhosis-driven" attributes and the "chronic-driven" attributes that the "chronic-driven" attributes are mainly Insomnia related while none of the "cirrhosis-driven" attributes is related to Insomnia.

D. Correlation between TCM attributes and psychiatric attributes

For each pair of a psychiatric attribute A_i and a TCM attribute B_i, we calculated their mutual-information $\mathrm{I}(A_i, B_i)$ to measure the mutual dependence between them. Because both A_i and B_i are discrete attributes, the mutual-information value $\mathrm{I}(A_i, B_i)$ is defined as follows:

$$\mathrm{I}(A_i, B_i) = \sum_{x \in A_i} \sum_{y \in B_i} p(x,y) \log \left(\frac{p(x,y)}{p(x)p(y)} \right) \tag{2}$$

where $p(x,y) = P(A_i = x, B_i = y)$ is the joint probability distribution function of A_i and B_i, and $p(x) = P(A_i = x)$ and $p(y) = P(B_i = y)$ are the marginal probability distribution functions of A_i and B_i, respectively. Higher mutual-

TABLE II. TWENTY ATTRIBUTES WERE IDENTIFIED AS THE "CHRONIC-DRIVEN" ATTRIBUTES. IN THE ***SEVERITY*** COLUMN, "+"/"–" INDICATES THAT THE CORRESPONDING ATTRIBUTE IS MORE/LESS SEVERE IN THE CHRONIC GROUP THAN IN THE HEALTHY GROUP. FOUR INSOMNIA ATTRIBUTES (SLEEP_1 ~ SLEEP_4) ARE OBJECTIVE FACTS AND THUS THEIR VALUES DO NOT REPRESENT THE SEVERITY.

Attribute	Chronic *vs.* Healthy		
	$p_{CN\text{-}H}$	$FDR_{CN\text{-}H}$	$S_{CN\text{-}H}$
DEP_4 (insomnia, early)	0.009	0.019	+
DEP_5 (insomnia, middle)	0.002	0.006	+
DEP_14 (genital symptoms)	0.000	0.000	+
DEP_22 (obsessional and compulsive symptoms)	0.000	0.001	-
DEP_23 (helplessness)	0.000	0.000	+
DEP_24 (hopelessness)	0.003	0.006	+
ANX_2 (tension)	0.000	0.001	-
ANX_3 (fears)	0.002	0.006	-
ANX_4 (insomnia)	0.003	0.006	+
SLEEP_1 (bed time)	0.000	0.000	N/A
SLEEP_2 (time taken to fall asleep)	0.000	0.000	N/A
SLEEP_3 (getting up time)	0.000	0.000	N/A
SLEEP_4 (hours of sleep per night)	0.000	0.000	N/A
SLEEP_5 (cannot get to sleep within 30 minutes)	0.000	0.000	+
SLEEP_6 (wake up in the middle of the night or early morning)	0.000	0.000	+
SLEEP_7 (have to get up to use the bathroom)	0.000	0.000	+
SLEEP_10 (feel too cold)	0.000	0.000	-
SLEEP_14 (other reasons)	0.000	0.000	-
SLEEP_15 (self rating of sleep quality)	0.000	0.000	+
SLEEP_18 (have problem to keep up enthusiasm)	0.003	0.006	+

information normally indicates higher mutual dependence, and vice versa.

To identify significant pairs of A_i and B_i, we need to calculate the p-value of $\mathrm{I}(A_i, B_i)$. To generate the null distribution of mutual-information, we randomly shuffled the samples between two groups and calculated a large number of permutation controls $\mathrm{I}\left(A_i^{(k)}, B_i^{(k)}\right)$ (k = 1…100000) to form the empirical null distribution. Then the p-value of an $\mathrm{I}(A_i, B_i)$ was calculated as the proportion of permuted mutual-information that beyond the observed mutual-information:

$$p = \mathrm{P}\left(\mathrm{I}(A_i, B_i) < \mathrm{I}\left(A_i^{(k)}, B_i^{(k)}\right)\right)_{k=1\ldots100000} \quad (3)$$

Among all 2622 pairs (46 TCM attributes × 57 psychiatric attributes), 476 were selected if $p < 0.05$; 289 were selected if $p < 0.01$; 225 were selected if $p < 0.005$; and 131 were selected if $p < 0.001$. Here, we only focused on the 131 pairs with $p < 0.001$, which included 22 pairs between TCM attributes and "cirrhosis-driven" attributes (**Table I**), and 39 pairs between TCM attributes and "chronic-driven" attributes. These are illustrated in **Fig.1** and **Fig.2**, respectively. In both figures, we set the edge width proportional to its corresponding mutual-information so the thicker the edge the higher its mutual-information. Fifteen TCM attributes were significantly correlated to at least one "cirrhosis-driven" attribute, and also 16 TCM attributes were significantly correlated to at least one "chronic-driven" attribute. Ten TCM attributes were shared by **Fig.1** and **2**.

IV. DISCUSSION

Our analyses identified several psychiatric attributes with significantly higher severity only in liver cirrhosis patients, and many others significantly associated with general chronic diseases. Our findings indicate that patients with liver cirrhosis tend to have more severe issues in the Depression and Anxiety categories while Insomnia issues were common issues experienced by patients with chronic diseases. In particular, seven psychiatric attributes in the Depression and Anxiety categories were significantly more severe in the Cirrhosis group than in the Non-cirrhosis and Healthy groups: feeling of guilt, suicide, somatic symptoms (general), loss of weight, intellectual, depressed mood and genitourinary symptoms. Below we focus our discussions on the nutrition factors that may underlie the observed associations between liver cirrhosis and some of those psychiatric attributes, which help explain previous research findings that certain nutrition supplements could assist treating patients with liver cirrhosis.

A. Trace element deficiency underscores the cirrhosis-driven attributes

Trace elements are widely known to be very essential in maintaining health. Human body requires several key trace elements: chromium, copper, fluoride, iron, iodine, manganese, molybdenum, selenium and zinc. Among them, zinc and selenium have been particularly proved to be highly related to cirrhosis. Patients with liver cirrhosis are usually found to have notably lower concentration of zinc and selenium in their serum and liver tissue. Both the deficiency of zinc and selenium were reported to be involved in the pathogenesis of chronic liver disease [36]. A number of researches suggested that cirrhosis can lead to both zinc deficiency [37-39] and selenium deficiency [39-41], which can result in general emotional issues, weight loss and genitourinary symptoms. It was demonstrated that zinc and selenium supplementation may be beneficial in treating and preventing liver cirrhosis [42-47].

Zinc is one of the most important trace elements in human body. Zinc has been found in more than 100 enzymes and is

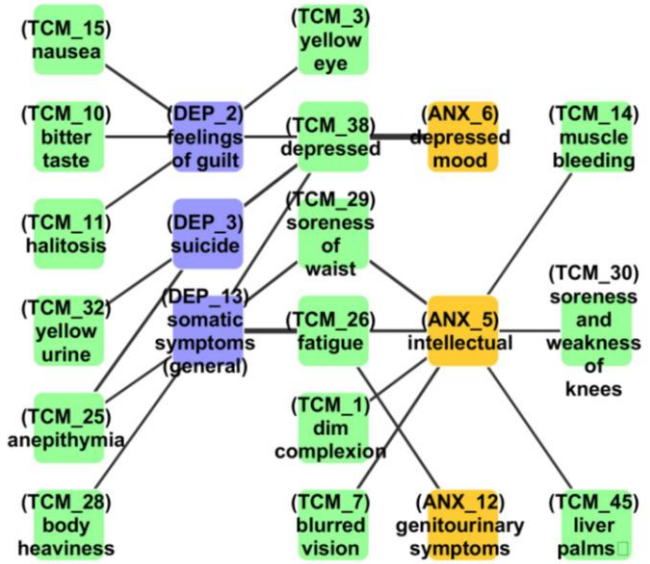

Fig. 2. Significantly correlated TCM attributes (green) and identified "cirrhosis-driven" psychiatric attributes (blue for the Depression attributes and orange for the Anxiety attributes). The thickness of the edges is proportional to the mutual-information of their connected attributes.

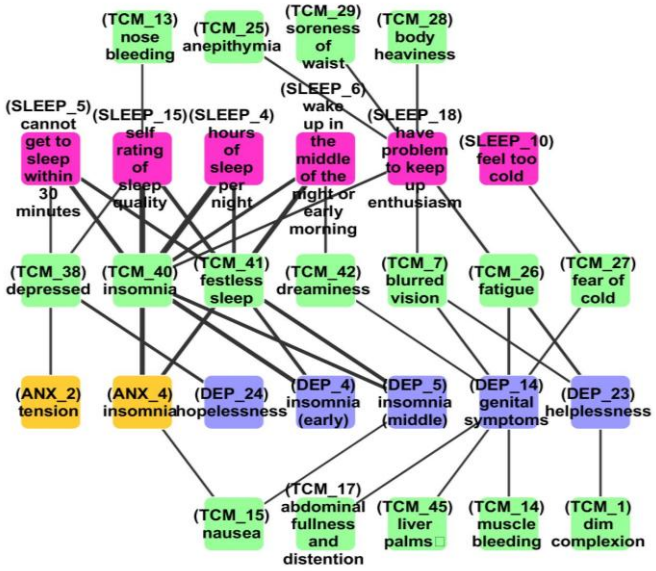

Fig. 1. Significanlty correlated TCM attributes (green) and identified "chronic-driven" psychiatric attributes (blue for the Depression attributes, orange for the Anxiety attributes and pink for the Insomnia attributes). The thickness of the edges is proportional to the mutual-information of their connected attributes.

essential for DNA, RNA and protein synthesis. About 10% of human proteins (2800) potentially bind zinc [48]. Zinc deficiency can result in poor appetite, mental lethargy, growth retardation, hypogonadism in males, taste abnormalities, emotional disorders, weight loss and death [37, 49]. Selenium is also an essential trace element for humans though it is toxic when taken in excess. Similar to zinc, selenium has both structural and enzymic roles, such as being a constituent of selenoprotein and the catalyst for the production of active thyroid hormone [50]. Selenium deficiency can result in cardiomyopathy, muscular weakness [51], low sperm motility and miscarriage [50].

Both zinc and selenium deficiency will lead to serious psychological and mental issues. They have been reported to play critical roles in human's nervous system, and therefore can be closely related to psychological and mental issues. More over, it was suggested that zinc was involved in attention-deficit/hyperactivity problems in children [52]. Zinc deficiency can cause depression and anxiety [53-56]. Low selenium intake is associated with mood status [57]. It was demonstrated that zinc deficiency can precipitate hepatic encephalopathy, a brain function disease that occurs since the liver fails to remove the toxic substance remained in blood [46]. Zinc supplementation can help preventing hepatic encephalopathy by activating glutamine synthetase to remove toxic substance harmful to brain functions from blood. In addition, selenium deficiency plays a potential role in suicide behavior [58, 59]. In our study, patients with liver cirrhosis had significantly higher suicide risk than both patients with non-cirrhosis diseases (p = 0.002, FDR = 0.007) and healthy participants (p = 0.001, FDR = 0.002).

In our study, patients with liver cirrhosis suffered significantly more severe loss of weight than patients with non-cirrhosis chronic diseases (p = 0.009, FDR = 0.031) and healthy participants (p = 0.007, FDR = 0.016) while the difference between the Non-cirrhosis group and the Healthy group is fairly mild (p = 0.986, FDR = 1). This echoes a finding reported early that patients with liver cirrhosis experienced weight loss regardless of age, sex, schooling and income [60]. Unintentional weight loss is usually due to malnutrition, and one of the most common reasons is impaired intake. Impaired intake is often associated with dysfunctions of taste, such as ageusia (completely lack of taste), hypogeusia (the decrease in taste sensitivity) or dysgeusia (distorted sense of taste).

Zinc deficiency can also lead to weight loss. Zinc deficiency has been broadly known to be responsible for ageusia, hypogeusia and dysgeusia, in many different ways. Firstly, it is known that zinc is an important cofactor for alkaline phosphatase as well as a component of a parotid salivary protein. The former performs as the most abundant enzyme in taste bud membranes and the latter is vital in the development and maintenance of taste buds [61]. It was also reported that zinc interacts with carbonic anhydrase VI, which influences gustin concentration and the production of taste buds [62]. Another study suggested that zinc treatment can help elevating calcium concentration in the saliva [62], and taste buds rely on calcium receptors to work properly [61]. It is possible that patients with liver cirrhosis in general experience more severe zinc deficiency, which leads to taste dysfunctions and poor appetite, and eventually results in loss of weight.

We identified genitourinary symptoms in the Anxiety category as a significant "cirrhosis-driven" attribute, which was more severe in the Cirrhosis group than in the Non-cirrhosis group (p = 0, FDR = 0) and the Healthy group (p = 0, FDR = 0). Zinc deficiency was reported in many researches to be responsible for genitourinary systems. For males, it was suggested that zinc is essential for the complete development

and maturation of sperm [63]. It was also demonstrated with an experiment that most zinc (Zn^{65}) in testis was associated with the seminiferous elements and transported from the testis through the sperm transport system by products from the testis [64, 65]. For females, it was reported that zinc deficiency in pregnancy could lead to serious outcomes, such as infertility, pregnancy wastage, congenital abnormities, pregnancy induced hypertension, placental abruption, premature rupture of membranes, still births and low birth weight [66].

B. Vitamin D deficiency links liver cirrhosis and suicide risk

Besides the selenium deficiency mentioned above, vitamin D deficiency can be another a significant link between suicide risk and liver cirrhosis. Low serum vitamin D level was reported to be related to severe fibrosis, including liver cirrhosis [67-69]. It was also suggested that patients with alcoholic cirrhosis are more likely to have low serum vitamin D level than those with other cirrhosis diseases (e.g. biliary), and such vitamin D deficiency in cirrhosis relates to liver dysfunction [68]. On the other hand, vitamin D deficiency can lead to higher suicide risk. For example, it was suggested that vitamin D plays a potential role in reducing suicide risk [70]. Also, a recent research declared that low vitamin D status is correlated to a higher propensity for suicide in U.S. military personnel [71]. It is possible that liver cirrhosis patients have higher suicide risk partially due to low vitamin D level. Our findings suggest another avenue to investigate the relationship between vitamin D deficiency and prevalence and severity of liver cirrhosis and responses to therapy.

V. CONCLUSION

In this paper, we examined the various aspects of depression, anxiety and insomnia on a group of patients with liver cirrhosis in comparison with a set of patients with non-cirrhosis chronic diseases and healthy participants. We demonstrated that some of the Depression and Anxiety attributes are more significantly associated with liver cirrhosis rather than other chronic diseases, while the Insomnia attributes are in general more likely to be driven by the common characteristics of general chronic diseases. Based on the results of previous studies, we discussed some of our findings about several psychiatric attributes found significantly associated with liver cirrhosis. We further suggested that liver cirrhosis has its uniqueness in affecting human's emotions, and special therapeutic plans should be designed to better treat these patients.

Another major contribution in this project is that both the "cirrhosis-driven" and the "chronic-driven" psychiatric attributes were demonstrated to be highly correlated to the "four diagnostic methods" – the most common diagnosis methodology applied today in TCM. These interesting correlations can potentially build bridges between Western Medicine and Traditional Chinese Medicine, and suggest a new direction to treat liver cirrhosis. More profound researches based on our findings can focus on designing more advanced diagnosis and prognosis methods for liver cirrhosis by monitoring both psychiatric attributes and the TCM attributes. We expect such researches could lead to better treatments for severe chronic diseases by taking advantages of both Western and Traditional Chinese Medicine, and eventually benefits millions of patients.

TABLE III. FOUR DIAGNOSTIC METHODS ATTRIBUTES IN ENGLISH AND CHINESE. EACH ATTRIBUTE IS RATED IN THE RANGE OF 0-3 ACCORDING TO THE SEVERITY.

No.	Attribute (English)		Attribute (Chinese)	
1	dim complexion		面晦黯	
2	sallow complexion		面萎黄	
3	yellow eye		目黄	
4	yellow skin		身黄	
5	dizziness		头晕	
6	dry eye		两目干涩	
7	blurred vision		视物模糊	
8	tinnitus		耳鸣	
9	thirst		口干	
10	bitter taste		口苦	
11	halitosis		口臭	
12	gum bleeding		齿龈衄	
13	nose bleeding		鼻衄	
14	muscle bleeding		肌衄	
15	nausea		恶心	
16	belching		嗳气	
17	abdominal fullness and distention		脘腹胀满	
18	hypochondrium pain	stabbing pain	胁肋痛	刺痛
19		distending pain		胀痛
20		dull pain		隐痛
21		burning pain		灼痛
22		scurrying pain		窜痛
23		stuffy pain		闷痛
24		hypochondrium discomfort		胁肋不适
25	anepithymia		纳差	
26	fatigue		乏力	
27	fear of cold		畏寒肢冷	
28	body heaviness		肢体困重	
29	soreness of waist		腰疼	
30	soreness and weakness of knees		膝疼软	
31	leg swelling		下肢水肿	
32	yellow urine		尿黄	
33	constipation		便秘	
34	loose stool		便溏	
35	dysphoria with feverish sensation in chest, palms and soles		五心烦热	
36	spontaneous sweating		自汗	
37	night sweating		盗汗	
38	depressed		抑郁	
39	dysphoria		烦躁易怒	
40	insomnia		失眠	
41	festless sleep		易醒	
42	dreaminess		多梦	
43	itching		皮肤痒	
44	spider angiomas		蜘蛛痣数量	
45	liver palms		肝掌	
46	varicose abdominal veins		腹壁脉络曲张	

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