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Substance Abuse and Psychosocial Factors in the Hepatitis C Population: Identifying Risk Factors in Disease Severity and Quality of Life

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A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctorate of Philosophy at Virginia Commonwealth University.

By

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Master of Science
Virginia Commonwealth University
2005

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Acknowledgment

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List of Abbreviations

ALT	Alanine Aminotransferase
APRI	Aspartate Aminotransferase to Platelet Ratio Index
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BSI	Brief Symptoms Inventory
CHC	Chronic Hepatitis C
COPE	COPE Questionnaire
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU	Intravenous Drug Users
QOL	Quality of Life
SF-36	Short Form-36 Questionnaire
SVR	Sustained Viral Response

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Abstract

SUBSTANCE ABUSE AND PSYCHOSOCIAL FACTORS IN THE HEPATITIS C POPULATION: IDENTIFYING RISK FACTORS IN DISEASE SEVERITY AND QUALITY OF LIFE

By Jill C. Clarida, M.S.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctorate of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2005

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Hepatitis C is the most common chronic blood-borne infection in the United States. Research has focused on contributing factors to the development and progression of liver disease, but few studies have considered nicotine use as a potential prognostic factor with CHC. Research has commonly found that CHC patients report with a diminished quality of life. Several factors have been proposed to account for a decrease in QOL; however, the mechanisms underlying the impairment in QOL have not yet been elicited. 76 CHC patients completed self-report measures on a variety of psychosocial variables and biochemical data for determining the patient's liver disease severity was obtained.

The findings revealed strong support for the deleterious effects of smoking cigarettes on liver disease symptomatology and it's progression. Smokers endorsed experiencing significantly more severe symptoms of fatigue, poor appetite, and headaches. The CHC smokers tended to present with higher scores on the Aspartate

Aminotransferase to platelet ratio index (APRI). The smokers' mean score is above the cut-off value of 1.50 that indicates a .88 predictive value for the presence of hepatic fibrosis. The level of cigarette consumption could also be a factor in the progression of liver disease. Individuals smoking more than one pack per day tended to report more severe symptoms of fatigue and a poorer appetite. Heavy smokers presented with an APRI mean score above the cut-off value of 2.00 that indicates a .93 negative predictive value for the presence of cirrhosis below the cut-off value.

General active coping moderated the relationship between liver disease severity and QOL. The results revealed that patients using more avoidant coping reported lower levels of QOL on the physical and mental component of the SF-36. Tobacco use moderated the relationship between liver disease severity and QOL. Interestingly, smokers reported a higher level of QOL compared to nonsmokers when experiencing more severe liver disease. CHC patients with higher levels of psychological distress reported lower QOL on both physical and mental functioning. Individuals smoking marijuana also tended to report lower levels of QOL on mental functioning. Information garnered from this study is aimed to help slow the progression of advanced liver disease in CHC patients in addition to improving their QOL.

Introduction

Increasing emphasis is placed on quality of life (QOL) issues in health care

practice and research today. In 1948, the World Health Organization made mention of the

importance of quality of life in defining health as "a state of complete physical, mental,

and social well-being, and not merely the absence of disease or infirmity." Quality of life

assessments have been used to measure changes in physical functioning, mental, and

social health in order to evaluate efficacy, cost effectiveness, and benefits of new

therapies. In recent years, quality of life variables such as physical functioning or the

extent to which health interferes with a variety of activities and mental health, including

general mood and psychological well-being, have become well established as important

outcomes in medical care. This has been especially true in the area of chronic diseases for

which there are no cures. Researchers have demonstrated that the ability to maintain well-

being in these different domains is essential to higher quality of life for individuals with

chronic illnesses such as cancer and AIDS (Ben-Zur, Gilbar, & Lev, 2001; Schlenk,

Erlen, Dunbar-Jacob et al., 1998).

Chronic hepatitis C (CHC) is one disease that has been receiving significant

attention in quality of life research. Research has found a diminished quality of life

across various stages of liver disease progression in CHC. Individuals with CHC

infection may have specific fears including abandonment, pain, death, and the exposure

of their drug use or unsafe sexual activity. Uncertainties of the outcome of the infection

can lead to anxiety and depression. For substance abusing patients, psychological distress

may lead them to increase substance use or relapse that will most often produce

additional stressors. These stressors combined together quite commonly result in diminished quality of life for CHC patients. CHC can have a serious impact on the individual's daily activities, well-being, social performance, and psychological status. For this reason, current research in the area of CHC has focused on the relationship between liver disease severity and quality of life outcomes (e.g. ability to continue daily activities and maintain a positive mood or affect) in assessing the effectiveness of therapeutic interventions, including immunotherapies. CHC patients commonly report diminished quality of life compared to the general population and patients with other chronic medical conditions (Bayliss, Gandek, & Bungay, 1998; Ware et al., 1999).

Millions of individuals infected with chronic hepatitis C (CHC) struggle daily with a life threatening medical illness. CHC is the most common cause of liver disease and the primary grounds for liver transplantation. In addition to the medical challenges of treating the chronically infected, CHC also presents many psychiatric concerns and challenges for health care professionals. The majority of CHC patients are battling with comorbid psychiatric and substance abuse disorders, which put them at risk for exacerbating their illness and decreasing the possibility of success in treatment; thus, the patient's quality of life is diminished in a number of ways. Research suggests that up to 20% of adults with severe mental illness are infected with hepatitis C (Rosenburg et al., 2001) In addition, a strong association has been found between CHC diagnosis and psychological distress (Davis, De-Nour, Shouval, & Melmed, 2001; Nagono, Nagase, Sudo, & Kubo, 2004; Obhari, Hall, & Anand, 2001).

Mental disturbances are frequently complicated by the high prevalence of substance abuse in the CHC population. Substance abuse is the prevailing risk factor in the etiology of HCV, with intravenous drug use accounting for the majority of new cases developing in the United States today (Fireman, 2003). Alcohol use in CHC has also received growing attention. Numerous studies provide evidence of an adverse effect of alcohol consumption on liver disease progression (Loguercio et al, 2000; Pessione et al., 1998; Poynard, Bedossa, & Opolon, 1997; Wiley et al., 1998). Research has repeatedly found a strong association between alcohol consumption and the progression of fibrosis, cirrhosis, hepatocellular carcinoma, and the risk of death.

Despite the attention given to alcohol consumption in the CHC population, few studies have considered nicotine use an independent prognostic factor in patients with CHC. However, as smoking is associated with increased mortality in the general population and it has been considered as a potential risk in other medical populations (e.g. coronary heart disease, HIV; Thun et al., 1997) it is reasonable to explore a connection between smoking and liver disease. Only in the 21st century did researchers start investigations into the effects of smoking on hepatitis C patients. The limited data suggest that smoking cigarettes may be independently related to increased risk of fibrosis, hepatic inflammation, and hepatic lesions (Hezode et al., 2003; Pessione et al. 2001).

Taking into account the context of psychological and substance use problems in the CHC population, the role of coping strategies is one important psychosocial factor that has been overlooked in the hepatitis C virus (HCV) literature. This is surprising given the extensive literature on the role coping processes play in the adjustment to a

chronic illness (DeGenova, Patton, Jurich & MacDermid, 1994; Elfstrom, Ryden, Kreuter, et al., 2005; Haythornthwaite, Meneffe, Heinberg, & Clark, 1998; Myaskovsky, Dew, Switzer et al., 2005; Namir, Wolcott, Fawzy et al., 1987; Smith & Wallston, 1992; Stanton, Collins, & Sworowski, 2001; Zautra et al., 1995). Studies examining coping styles among persons with other types of chronic medical conditions (e.g. HIV, rheumatoid arthritis) have found that individuals who use active coping strategies report less psychological distress, whereas avoidant coping is associated with higher levels of distress (DeGenova et al., 1994; Zautra et al., 1995). Additional study results suggest that perceived pain severity and quality of life are also associated with the patient's coping strategies (Haythornthwaite et al., 1998; Vosvick et al., 2003).

Considering the psychological complexities of most CHC patients and the concerns and challenges faced by medical professionals who treat these patients, further research is warranted to identify potential risk factors for liver disease progression and diminishment of a patient's quality of life. Despite suggestive studies, the specific mechanisms (e.g. coping strategies, psychological distress, substance use) that buffer or exacerbate the impact of liver disease severity on quality of life have been minimally addressed in the CHC literature. The present study served two purposes. The first aim of the study was to advance our understanding of the independent effects of tobacco use on liver disease progression. The other main goal of this study was to determine possible mechanisms for diminished quality of life found in CHC patients. This study explored alternative explanations regarding how psychological variables (e.g. coping strategies, psychological distress, substance use) may influence the relationship between liver

disease severity and quality of life. To investigate these relationships a number of self-report measures were administered to CHC patients seeking treatment at a Hepatology center. Participants completed questionnaires about their psychological distress, substance use, coping strategies, liver disease symptoms, and quality of life. In addition, physiological measures were examined to determine the participant's severity of liver disease progression. This study attempted to identify specific psychosocial variables as potential risk factors in the progression of liver disease and in diminishing quality of life.

Specifically, the present study tested the moderating effects of coping strategies in the CHC-quality of life relationship. Similarly, competing models assessing the moderating versus mediating effects of psychological distress and substance use in the CHC-quality of life relationship were also examined. The results of this study provide new information regarding the impact of these psychosocial factors on quality of life in the CHC population, potentially aiding in the advancement of treatment approaches and improving overall health outcome.

Review of Literature

In the ensuing literature review, Hepatitis C virus (HCV) is introduced as a major medical problem that is the epidemic at the opening of the 21st century. In the first section of the literature review, the description, etiology, epidemiology, and impact of HCV on society are presented. In addition, recent advancements in the treatment of CHC will be briefly discussed. Second, the review will focus on psychological considerations in the hepatitis C population. This section highlights comorbid psychopathology and substance use as risk factors for HCV transmission and for the progression of the disease. More specifically, this section focuses on the sparse hepatitis C literature that pertains to the potential impact of nicotine use on liver disease progression. Third, coping strategies will be described as an important psychosocial factor to consider in adjusting to CHC diagnosis. This section articulates the importance of examining coping strategies in the CHC population by exploring the literature pertaining to coping with other chronic medical illnesses. The fourth section reviews the surging literature pertaining to quality of life in the hepatitis C population. The fifth section discusses an omission in the literature pertaining to moderator and mediator relationships among psychological variables associated with quality of life in the CHC population. This section articulates the importance of expanding the range of research questions in this area to assess moderator and mediator models. Finally, hypotheses are stated along with a rationale for the present study.

Hepatitis C Virus: Description, Etiology, Epidemiology and Impact on Society

Description and Etiology. The hepatitis C virus (HCV) is an RNA virus that

belongs to the family flaviviridae (Lauer & Walker, 2001). This blood borne virus was

discovered in 1989 with a prior name of non-A, non-B hepatitis. HCV is spread primarily

by contact with blood and blood products including blood transfusions and shared

needles. Table 1 on page 8 presents individuals who are at high risk for acquiring HCV.

The hepatitis C virus enters the body through direct blood exposure and attacks cells in

the liver, where it multiples. This process causes inflammation in the liver and kills

healthy liver cells.

The majority of individuals infected with HCV develop chronic hepatitis C

(CHC). CHC is defined as inflammation of the liver caused by HCV that persists for

longer than six months (Achord, 2002). To understand the effects of CHC it is helpful to

examine the liver and its many functions. The liver plays an important role in metabolism

and it regulates the body's use of carbohydrates and sugars. In addition, the liver

produces albumin, a blood protein that regulates water balance in blood vessels and it

acts as a filter in detoxifying everything an individual eats, inhales or absorbs in the body

(Achord, 2002). CHC makes it difficult and sometimes impossible for the liver to carry

out its normal functions, resulting in serious complications.

Chronic hepatitis C can progress to fibrosis (scarring of the liver), cirrhosis

(advanced stage of scarring), liver failure, and liver cancer. Moreover, CHC can vary

greatly in disease course and outcome. At one end of the spectrum are patients who have

no signs or symptoms of liver disease. At the other end of the spectrum, there are many

patients with severe symptoms, who ultimately develop cirrhosis and end-stage liver

Table 1

High Risk Groups for Acquisition of HCV

1- Injection drug users, including those who used drugs briefly many years ago
2- Individuals who use cocaine, particularly with intranasal administration, using shared equipment
3- Individuals who had blood transfusions before June 1992, when sensitive tests for anti-HCV were introduced for blood screening
4- Individuals with multiple tattoos and body piercings
5- Individuals who have frequent exposure to blood products
6- Health care workers who suffer needle-stick accidents
7- Individuals with high-risk sexual behavior multiple sex partners and sexually transmitted diseases

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disease. If symptoms are present in early stages of the disease, they are usually mild and intermittent. They include flu-like symptoms like fatigue, nausea, poor appetite, and muscle and joint pain. When a patient develops cirrhosis or the patient has a severe form of the disease, symptoms become more prominent. In addition to the symptoms listed above, many patients complain of itchiness, fluid retention, and cognitive changes. The primary symptoms for liver disease are presented in Table 2 on page 10. Research suggests there are factors that may contribute to liver disease progression and symptom severity. These factors can be considered as being viral-related, host-related (e.g. age at time of infection), and consequences of external factors (e.g. alcohol consumption; Thomas, Astemborski, Rai, et al., 2000). Specific environmental factors will be discussed in detail later in this review.

Epidemiology and Impact on Society. When blood testing became available in 1992, HCV was found to be one of the most common chronic infections in the world. It is the most common chronic blood-borne infection in the United States (Alter, Kruszon-Moran, Nainan, et al., 1999). Hepatitis C infects nearly 100 million individuals worldwide and an estimated 4 million in the United States (Williams, 1999). Of the infected, 70-80% have chronic hepatitis C (CHC) (Alter, 1997). Chronic hepatitis C is the most common cause of liver disease and it is the primary grounds for liver transplantation. There has been a 5-fold increase in the number of patients with CHC who underwent liver transplantation annually between 1990 and 2000 (Kim, 2002). It is estimated that more than one third of liver transplant candidates have CHC. Clinical

Table 2

Common Symptoms of Chronic Hepatitis C

Without Cirrhosis:

    1- Fatigue
    2- Mild right upper quadrant discomfort or tenderness
    3- Nausea
    4- Poor appetite
    5- Muscle and joint pains

Additional Symptoms with Cirrhosis:

    1-Jaundice
    2-Muscle wasting
    3- Infections
    4- Itchiness
    5- variceal bleeding
    6- Fluid retention (e.g. stomach fluid, feet swelling)
    7- Mental changes (e.g. memory difficulties)

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studies have demonstrated that CHC patients are at risk to progress to cirrhosis, hepatocellular carcinoma (HCC), and decompensated liver disease, which may lead to liver transplantation or death. It is predicted that the number of annual deaths due to hepatitis C virus (HCV) related liver failure will rise from fewer than 9,000 in 2003 to more than 28,000 by 2008 (El-Serag & Mason, 1999). In addition to the negative effect on the chronically infected, the high prevalence of CHC also impacts our society in terms of a financial burden incurred in the health care system. Total direct health care costs associated with HCV are estimated to have exceeded one billion dollars in 1998 (Kim, 2002). A 4-fold increase in the cost of this illness is predicted between 1990 and 2015 (Kim, 2002).

Immunotherapy: Treatment of HCV

Given the significant impact of CHC on the society, the medical community has been working diligently to improve treatment. New combination therapies of interferon-alpha and ribavirin as well as the long-acting pegylated interferon immunotherapies have dramatically increased sustained viral responses (SVR) amongst CHC patients. Tangible improvements have been found with 54-56% of patients who complete a full course of combination therapy of peginterferon and ribavirin achieving a SVR with no recurrence of HCV (Fried, Shiffman et al., 2002). Moreover, studies show that CHC patients responding to antiviral treatment improve in health related quality of life outcomes compared to non-responders (Bernstein et al., 2002; Bonkovsky et al., 1999; Ware et al., 1999). However, a number of factors affect whether a patient with CHC will undergo a full course of treatment. Adverse side effects of interferon therapy are numerous.

Immunotherapies for CHC have been found to induce symptoms of depression, anxiety, and psychotic features in some patients (Bonaccorse et al, 2000; Gleason & Yates, 1999). Hence, the majority of people with comorbid psychiatric and substance abuse disorders have been deemed ineligible for the immunotherapy. Many have assumed that individuals with comorbid psychiatric illness would worsen in therapy, leading to poor treatment adherence and incomplete therapy (Goldsmith & Hauser, 2003). Furthermore, studies have found that patients abusing substances show a decreased response to interferon treatment. For example, Poynard, Bedossa, & Opolon (1997) determined that patients ingesting more than five alcoholic drinks per day are at greater risk for being a non-responder to interferon treatment.

Despite the remarkable advances in CHC immunotherapies, up to 50% of patients are unable to benefit from the therapies for a host of reasons. As discussed, psychiatric illness and substance use play a key role in decreased response rates in IFN therapies. It has been questioned as to whether these individuals are able to adhere to treatment protocols and if they should be deemed eligible for treatment. For this reason, research examining psychological concerns and challenges within the CHC population has expanded in recent years. Of the millions of CHC patients struggling with a life threatening illness, the majority are also diagnosed with comorbid psychiatric and substance abuse disorders. The next section highlights the prevalence of mental illness and substance use in this population and the impact these risk factors have on the progression of CHC.

Psychological Considerations

Cormorbid Psychopathology. High risk behaviors, such as the use of injection drugs and unprotected sex with high-risk partners are prevalent among individuals with severe mental illness which puts them at an increased potential to be exposed to pathogens (Straits-Troster, Sloan, & Dominitz, 2003). It is well noted in the literature that individuals with severe mental illness are at a higher risk for blood-borne infectious diseases, such as HIV and Hepatitis C, than those in the general population (Dinwiddie, Shicker, & Newman, 2003; Rosenburg et al., 2001). A multi-site study funded by the National Institute of Mental Health found that up to 20% of adults with severe mental illness are infected with hepatitis C, 11 times the overall United States population rate (Rosenburg et al., 2001). A study by Dinwiddie, Shicker, & Newman (2003) paralleled Rosenburg's study on a smaller scale reporting that 8.5% of a public-sector psychiatric hospital patients are infected with HCV. Moreover, the majority of the patients in the psychiatric hospital were unaware of their HCV condition. Few studies have explored the prevalence of specific psychiatric disorders amongst HCV patients. High comorbidity rates have been found with depression and anxiety disorders (Yates & Gleason, 1998). In a study looking at veteran affairs patients undergoing interferon treatment for HCV, 60% met criteria for a psychiatric diagnosis, with depression and posttraumatic stress disorder the most prevalent (Nguyen et al., 2002). Another study by Lehman et al. (2002) found a significant prevalence of psychopathology in a sample of HCV patients, 44% with depression, 38% anxiety, 21% PTSD, and 27% alcohol abuse.

Research has also found a strong association between CHC diagnosis and psychological distress (Davis, De-Nour, Shouval, & Melmed, 2001; Obhari, Hall, &

Anand, 2001). Davis and colleagues (2001) found a significant incidence of psychological distress amongst chronic hepatitis C patients. Patients with cirrhosis or severe liver disease ($\underline{M}$= 58.70, $\underline{SD}$ = 8.38) reported higher than average scores ($\underline{M}$= 53) on the global severity index (GSI) summed from the *Brief Symptoms Inventory* (BSI; Derogatis & Melisaratos, 1983 & 1993). Furthermore, even asymptomatic patients had a mean score of 55.2 ($\underline{SD}$= 8.4) on the GSI. Interestingly, psychological distress scores were not influenced by the histological severity of the liver disease. Simply stated, psychological distress was significantly pronounced even in asymptomatic patients suffering from chronic, uncomplicated liver disease. Another study by Obhrai et al. (2001) assessing psychological disturbances in patients with hepatitis C found similar results. Using the *Sickness Impact Profile* (Davis, Balart, Schiff, et al., 1994), they found that CHC patients had higher scores for psychological disturbances compared to healthy subjects and non-liver chronic diseases (e.g. diabetes mellitus, hypertension, coronary artery disease). More specifically, results indicate that CHC patients are more depressed and harbor greater feelings of anger and hostility compared to patients with other chronic diseases.

The literature also indicates that patients with psychological distress are at a particular risk for complications in the treatment of CHC. For a chance at a successful treatment, patients must be adherent with the immunotherapies. Immunotherapies for CHC frequently induce symptoms of severe psychological distress (Bonaccorse et al., 2000; Gleason & Yates, 1999). Most often, the onset of severe psychiatric symptoms results in premature discontinuation of the treatment regimen. Taking into account the

cormorbidity of psychiatric illness with CHC this poses a major problem and concern for hepatologists. Unfortunately to this date, there has been no determination of reliable risk factors to predict who will develop immunotherapy – induced psychiatric features, including depression and anxiety. Little is known regarding CHC among severely mentally ill patients. It is assumed that the course of the infection is worse due the lack of knowledge of infection and access to and compliance with health care. These facts highlight the importance of considering comorbid psychiatric illnesses in treating patients with CHC, ranging from screening for HCV in psychiatric settings to finding the correct treatment for patients on interferon with severe depressive symptoms.

Coupled with mental disorders is the high prevalence of substance abuse in the CHC population. It was noted before that mental illness is a major precipitant for individuals to partake in high-risk behaviors for the transmission of HCV. Substance abuse is the prevailing risk factor in the etiology of HCV, which also has profound implications in the treatment of this chronic illness.

Intravenous Drug Use. Intravenous drug use is considered the primary route of transmission for the virus and it accounts for the majority of the new cases developing in the United States today (Fireman, 2003). The hepatitis C infection has been detected in 50-80% of patients who are intravenous drug users (IDU's; Dieperink, Willenbring, Ho, 2000; Williams, 1999). HCV in IDUs is most commonly associated with a longer duration of injecting career and older age (Thomas et al., 1995; Thorpe et al., 2000). In addition, this subpopulation of HCV patients is the least likely to have awareness of infection and access to treatment because of adherence concerns. Experts report that

consequences of this lack of detection can be ominous, leading to end-stage liver disease and mortality (Straits-Troster, Sloan, & Dominitz, 2003). However, the minimal research data available on HCV amongst the IDU population suggests otherwise. A longitudinal study by Rai, Wilson, Astemborski et al. (2002) examined liver disease severity in 207 IDU men and women infected with hepatitis C. Liver biopsies were performed on each participant to determine severity of liver disease. Results suggest that fibrosis is uncommon in HCV-infected IDU's. These results are consistent with other cross-sectional studies of IDU's that show a low prevalence of cirrhosis in the first 20 years after HCV infection (Gordan, Bayati, & Silverman, 1998; Roudot-Thoraval, Bastie, Pawlotsky et al., 1997).

Collectively, the data indicates that in IDU's, HCV uncommonly causes cirrhosis within the first two decades of infection. However, the extent of liver disease observed in these studies may be underestimated due to many limitations of the studies. For instance, individuals who already died from liver failure would not be enrolled in longitudinal studies. Moreover, underestimation of liver disease could occur if individuals who died of other causes were more likely to have comorbid cirrhosis. Given these limitations in the sparse literature and the high prevalence of IDU's infected with HCV, further research is warranted in the investigation of illicit drug use and the progression of liver disease.

Alcohol. In recent years there has been a surge in the HCV literature pertaining to the effects of alcohol consumption on liver disease progression. A number of the studies provide supportive evidence that heavy drinking can worsen the course and outcome of a CHC patient (Loguercio et al., 2000; Pessione et al., 1998; Poynard, Bedossa, & Opolon,

1997; Wiley et al., 1998). The combination of HCV and heavy alcohol consumption can increase the progression of fibrosis, cirrhosis, hepatocellular carcinoma, and the risk of death. Poynard et al. developed the landmark study relating alcohol consumption to the progression of fibrosis in 1997. Poynard and co-researchers found that consuming more than 50 grams a day of alcohol was an independent factor associated with increased fibrosis progression. In addition, patients who drank more than 50 g a day had a 34% increased rate of fibrosis compared with non-drinkers. In a smaller study by Pessione et al. (1998) liver fibrosis is related to the age of the patient and the average daily alcohol consumption. This study provides evidence that even moderate drinking (one to two standard drinks a day) can be damaging with CHC infection. It has also been found that consumption of moderate to heavy amounts of alcohol is a risk factor in the development of cirrhosis in CHC patients. Probably the most well-known study showing the effects of heavy alcohol consumption on the development of cirrhosis in the CHC population is the 'Dionysos study' (Bellentani et al., 1999). Unlike many other studies in this area, this was a prospective study on the effects of alcohol consumption. It was found that CHC patients consuming more than 30 grams a day (3 standard drinks/day) were more likely to develop cirrhosis than the patients drinking less than 30 grams a day. More specifically, 32% of CHC patients drinking 30 grams a day developed cirrhosis compared to 10% of CHC patients with moderate alcohol consumption or less than 30 grams a day (1999).

A number of other large cohort studies report an increased risk of cirrhosis in CHC patients who consume moderate to heavy amounts of alcohol (Thomas et al., 2000; Harris et al., 2002). Research in Europe and Japan has recently provided supportive

evidence that excess alcohol consumption can predispose the CHC patient to the development of hepatocellular carcinoma (HCC; Bellentani et al., 1999; Ikeda et al., 1998; Roudot-Thoraval et al., 1997). In the Dionysos study, Bellentani and co-investigators (1999) found that heavy alcohol consumption is an independent factor in HCC development. Furthermore, Khan et al. (2000) determined that heavy alcohol consumption may also be a risk factor for clinical manifestations of variceal bleeding, ascites, and encephalopathy compared to a non-alcohol consumption group. Finally, in addition to the risk of the progression of liver disease, heavy alcohol consumption has also been found to be a relative contraindication to immunotherapies for HCV treatment. For example, in the study by Loguercio et al. (2000), inverse correlations were found between response to interferon treatment and level of alcohol consumption during therapy. As for the mechanism of the decreased response rate in CHC patients who consume alcohol, mixed results have left it undefined.

Taken together, recent studies demonstrate that heavy alcohol consumption can have devastating effects on liver disease progression among CHC patients and that even light to moderate intake can produce adverse effects. Nevertheless, Logeurcio and colleagues (2000) found that a considerable number of CHC patients on interferon therapy are continuing to drink alcohol, possibly because they do not feel they are consuming at dangerous levels. Unfortunately, there are insufficient data that there is any safe level of alcohol use when infected with HCV.

Tobacco Use. Although smoking is associated with increased mortality in the general population (Thun et al., 1997), few studies have considered smoking as an

independent prognostic factor in patients with CHC. In addition, there are no studies to date addressing the effect of smoking on CHC treatment. The possible occurrence of hepatotoxicity from smoking has just recently been considered in CHC research. Three studies to date have explored the effects of smoking as a risk factor to the progression of alcoholic cirrhosis (Corrao et al., 1994; Klatsky & Armstrong, 1992; Pessione et al., 2003). All conclude that smoking, independent of alcohol intake, is associated with an increased risk of cirrhosis in alcoholic patients. More specifically, Klatsky and Armstrong (1992) found that cigarette smokers of a pack or more per day are at greater risk to develop cirrhosis compared to lifelong nonsmokers. Beginning in the 1990's, Japanese researchers also began exploring the effects of smoking on the progression of hepatocellular carcinoma (HCC) in patients with hepatitis B (Chen et al., 1991; Mori et al., 2000; Yu et al., 1997). The researchers found moderate excess risk of HCC associated with cigarette smoking among patients with hepatitis B.

Only in the 21st century did researchers start investigations into the effects of smoking on hepatitis C patients. Mori and co-investigators (2000) started the new line of research by examining a small sample of Japanese patients on the independent and interaction effects of hepatitis C and lifestyle habits on developing HCC. Results showed for the first time that hepatitis C patients who had a history of cigarette smoking tended to be at greater risk for developing HCC compared to nonsmokers. In addition, a significant interaction was found for the risk of HCC development between CHC and a history of smoking. A similar community-based prospective study on Taiwanese men examined the effects of hepatitis C and nonviral cofactors to the development of HCC. There was no

significant association with HCC found for a history of cigarette smoking. However, when considered with a CHC diagnosis, cigarette smoking tended to interact additively to HCC development although it was not statistically significant.

Only four other studies from Europe and Asia have considered the implications of smoking behaviors on the progression of CHC or the prevention of further manifestations (El-Zayadi et al., 2002; Hezode et al., 2003; Pessione et al., 2001; Wang et al., 2002). A study by El-Zaydi and colleagues (2002) examined the hepatotoxicity effects of smoking on a small sample of men with hepatitis C. Researchers found that CHC patients who smoked heavily (2 or more packs a day) may be at risk for developing erythrocytosis (above normal total red blood cell count), which causes further liver injury in patients with CHC due to an overload of iron. Another study (Wang et al., 2002), investigated the role smoking tobacco may have on serum alanine aminotransferase (ALT), which is a protein enzyme used in the evaluation of hepatocellular damage and a surrogate marker of liver disease severity (2002). An association was found between elevated ALT levels and the consumption of cigarettes among CHC patients. More specifically, CHC patients are seven times more likely to have elevated ALT levels if they smoke one or more packs of cigarettes per day compared to nonsmokers. Two final analyses investigate the repercussions of smoking on the development of fibrosis in hepatitis C patients (Hezode et al., 2003; Pessione et al, 2001). The first study by Pessione et al. (2001) found that smoking is strongly correlated with other risk factors, including age, alcohol consumption, and a history of intravenous drug use. More importantly, this cross-sectional study concludes that smoking is independently related to an increased risk of

developing fibrosis and for the severity of hepatic lesions in patients with CHC. Hezode and co-researchers' prospective study (2003) did not find a significant relationship between smoking in general and hepatic fibrosis. However, it was determined that heavy tobacco consumption (greater than 15 cigarettes per day) is associated with more severe hepatic inflammation.

Taking these limited data together, the effect of smoking on the progression of CHC and the possible implications it has on antiviral therapies still remains unclear at this time. Furthermore, the majority of the research exploring the effects of smoking on CHC has taken place in Europe and Asia, which must be taken into consideration when generalizing to the CHC population in the United States. Pessione et al. (2003) note that studies are lacking in conclusive evidence that there is a direct negative relationship between smoking and progression of liver disease. Pessione and co-investigators state that researchers must eliminate other alternative hypotheses that may explain this relationship such as 1) similar effects found in the general population and 2) an indirect effect from the relationship between smoking and alcohol, considering studies usually find positive correlates between the amount of smoked tobacco and consumption of alcohol. However, there is supportive evidence of the hepatotoxicity of cigarette smoking that should be further investigated.

Coping Strategies

Taking into account the context of psychological and substance use problems in this population, the construct of coping strategies is one important psychosocial factor that has been overlooked in the HCV literature. An extensive literature on the role coping

processes play in the adjustment to a chronic illness can be informative (Stanton, Collins, & Sworowski, 2001). The experience of being diagnosed with hepatitis C can be extremely stressful; however, little research has examined how patients cope with these stressors. As found with individuals with human immunodeficiency virus (HIV) infection, CHC patients often estimate their infectious disease as fatal and stigmatizing, which can impact their quality of life and what coping strategies they employ (Kraus, Schafer, Csef et al., 2000). In contrast to HIV/AIDS, there has been minimal research examining coping strategies in the adjustment to having hepatitis C. To fully understand the literature related to coping with chronic illness it is important to consider the theoretical foundations to coping processes and strategies.

Lazarus and Folkman (1984) developed a theoretical framework for examining the stress and coping process. Coping is defined as "cognitive and behavioral efforts to manage (reduce, minimize, master, or tolerate) the internal and external demands of the person-environment transaction that is appraised as taxing or excluding the person's resources" (Folkman, Lazarus, Green, & Delongis, 1986a, p.572). This definition implies that coping is a dynamic process, which is different than Carver's (1989) idea of stable coping styles. Folkman et al. (1986b) stated there are three key features in the definition of coping. Folkman notes that coping first focuses on the process of coping. The second feature is that coping occurs with the context of a given situation and finally that no type of coping strategy is inherently considered good or bad. The term coping is employed whether or not the process has been adaptive, successful, or consistent (Lazarus, 1993).

Folkman and Lazarus (1986, 1993) emphasize that there are two major functions of coping: emotion-focused and problem-focused coping. Emotion-focused coping involves either changing the way a stress-inducing situation is attended to or altering the relational meaning of an event. Emotion-focused coping is most commonly used when an individual does not have control over the situation. Problem-focused coping involves changing a distressing person-environment transaction by operating on oneself or the environment. This type of coping is usually implemented when the individual has some control over the event. Lazarus (1993) highlights that people use strategies representing both forms of coping (emotion-focused and problem-focused) in every stressful situation.

More recently Carver (1994) has looked at coping as a means of functional strategies (i.e., active or avoidant coping). Carver et al. consider the distinction between problem-focused and emotion-focused coping an important one, but too simplistic. A study by Carver et al. (1989) attempted to develop a measure based on theory instead of empirically based evidence. This study determined that one cluster of strategies makes up what are theoretically known as adaptive coping strategies or "active coping strategies". These strategies include the following: active coping, planning, suppression of competing activities, restraint coping, positive reinterpretation and growth, and seeking out social support, both for instrumental and emotional reasons. The second cluster in the study was made up of strategies that theoretically are of more questionable value, which have been termed "avoidant/passive coping strategies". These strategies include the following: denial, behavioral disengagement, mental disengagement, focus on and venting of

emotions, and alcohol use. Coping refers to one's ability to appraise and respond to an illness or situation in an adaptive or maladaptive way (Gaynes & Drossman, 1999).

Transactional models of stress have emphasized coping as a process that can determine and/or influence appraisals of control (Haythornthwaite et al., 1998). Additionally, cognitive-behavioral models of pain propose that perceptions of control are critical factors in the relationship between pain and adaptation. For example, coping processes have repeatedly been implicated as influencing adjustment to chronic pain conditions. As Lazarus and Folkman (1984) have pointed out, the stress response is a dynamic one that includes not only events that happen to people and their interpretation of them, but also the many different ways in which people respond to those events and cope with them. Coping processes in this model are defined as the person's cognitive and behavioral efforts to manage the stress-producing aspects of the illness (Lazarus & Folkman, 1984).

Haythornthwaite et al. (1998) state that coping strategies are behavioral and cognitive activities intended to deal with or manage a specific stressor such as pain. Many studies (Geisser, Robinson, & Henson, 1994; Gil et al., 1993; Gil, Abraham, Phillips, & Williams, 1992; Thompson et al, 1992) examining coping processes and pain support Haythornthwaite et al.'s (1998) hypothesis that the ability to adapt to pain (i.e. health related stressor) relates highly to the individual's coping strategies. For example, research with sickle cell disease patients found that individuals reporting high levels of catastrophizing on the *Coping Strategies Questionnaire* (Rosenstiel & Keefe, 1983) are likely to report poorer adjustment to sickle cell disease, lower levels of physical activity,

and higher levels of hospitalization (Thompson et al., 1992; Gil, Abraham, Phillips, & Williams, 1992).

These researchers also mention that chronic pain is conceptualized as a stressor to which individuals show widely diverse adaptations, ranging in little disruption in daily life to total disability. For example, rheumatoid arthritis patients show varying levels of adjustment to pain and disability associated with this illness and coping processes that have been studied extensively in this population. The stress and coping model predicts that such variability in adjustment depends upon cognitive evaluations of physical symptoms as well as behavioral and cognitive coping strategies employed to manage the symptoms.

Specific coping strategies employed by liver disease patients have not been well studied. One cross-sectional study by Kraus et al (2000) investigated the relationship between coping styles and somatic variables (clinical, laboratory, and histological data) in patients with CHC. Coping styles were evaluated by the *Freiburg Questionnaire on Coping with Illness* (German version; Muthny, 1989) that includes both active and avoidant coping dimensions. The major finding of the study is that patients with recently diagnosed HCV have significantly lower scores for depression and anxiety and use more active coping strategies compared to patients with a longer time interval since the initial diagnosis. This suggests that the time since diagnosis with HCV influences the patient's emotional state and coping strategies. This indicates that patients with a longer period since initial diagnosis are more likely to use maladaptive coping styles. A thorough

review of the literature reveals that this is the only published study examining coping strategies in the CHC population.

Studies examining coping processes among persons with other types of chronic medical conditions may help illuminate the possible role of coping strategies in CHC patients. Research examining coping styles in the HIV-infected population has been growing in the past decade. From a psychosocial perspective, it has been documented that coping styles greatly influence the psychological impact of HIV infection. Early reports indicate that active coping strategies are related to less psychological distress, whereas avoidant coping is associated with higher emotional stress (DeGenova, Patton, Jurich, & MacDermid, 1994; Namir, Wolcott, Fawzy et al., 1987; Nicholson & Long, 1990; Wolf, Balson, Morse, et al., 1991) For example, DeGenova et al. (1994) explored coping processes in the HIV population by using the *Ways of Coping* questionnaire based on the work of Lazarus and Folkman (1984). They found that emotion-focused coping may increase depression and perceived illness symptoms for HIV patients. The results indicate that emotion-focused coping is related to more reporting of depressive and illness symptoms than is problem-focused coping.

HIV research has also found effective coping strategies to be related to a better quality of life and a reduction of risk-taking behaviors (e.g. substance use, unsafe sexual activity; Friedland, Renwick, & McColl, 1996; Folkman, Chesney, Pollack et al., 1992: Martin, 1993). Studies have shown that active coping is associated with better biochemical disease parameters (e.g. lymphocytes, Natural Killer cell count) and that a rapid progression of HIV disease is more likely in patients who use a passive or avoidant

coping style (Goodkin, Blaney, Feaster, et al., 1992; Solano, Costa, Salvati, et al., 1993). A recent example from the HIV literature determined that coping strategies are associated with reduced physical functioning, energy/fatigue, social functioning, and role functioning, all domains of quality of life (Vosvick et al., 2003). Vosvick and colleagues examined 142 men and women living with HIV/AIDS and had them complete the *Brief COPE* inventory (Carver, 1997) for measuring active and avoidant coping strategies and the *Short Form-36* questionnaire (Ware & Sherbourne, 1992) to measure quality of life outcomes. The researchers found that a greater use of maladaptive or avoidant coping strategies is associated with lower levels of quality of life. For example, a greater use of self-distraction, behavioral disengagement, and substance use coping strategies is associated with less energy and poorer social functioning. Additional results from the study suggest that perceived pain severity is also associated with diminished quality of life in HIV patients.

In the examination of other chronic pain populations it has been found that coping strategies are also associated with perceived pain severity. A study by Haythornthwaite et al. (1998) looking at 195 patients with chronic pain found that coping strategies predict perceived control over pain. Using the *Coping Strategies Questionnaire* (Rosensteil & Keefe, 1983), Haythornthwaite et al. (1998) found that self-statements and reinterpreting pain sensations predict greater perceptions of control over pain, whereas ignoring pain sensations predicted lower perceptions of control of pain. The researchers conclude that specific pain coping strategies are associated with a number of positive outcomes in patients with chronic pain conditions. Studies (Brown, Nicassio, & Walston,

1989; Parker et al., 1988; Revenson & Felton, 1989; Smith & Wallston, 1992; Zautra et al., 1995) examining the relationship between coping strategies and health status in a rheumatoid arthritis population have concluded that in general, self-blame, wishful thinking, praying, catastrophizing, and restricting activities are usually associated with poorer quality of life, whereas information-seeking, cognitive restructuring and active planning have been associated with better quality of life.

In general, studies examining pain coping strategies within chronic pain populations have found that individuals who catastrophize are more likely to exhibit poor adjustment to pain and poor health status. Also, research (Brown, Nicassio & Wallston, 1989; Smith, Wallston, Dwyer & Dowdy, 1997) with adult pain populations suggest that specific coping strategies, typically "avoidant/passive" strategies, such as restricting one's activities or assuming the worst, are associated with poorer health outcome (i.e. decreased physical functioning and increased psychological distress) (Walker, Smith, Garber, & Van Slyke, 1997). In addition, the research suggests that other strategies, typically "active" strategies, such as maintaining one's activities or using distraction to ignore pain, are associated with better health outcomes.

Quality of Life

Quality of life (QOL) outcomes have become a major interest for health care practice and research over the past decade. Specifically, an increasing emphasis is placed on quality of life factors in the CHC population. People suffering from CHC often experience a diminished quality of life. For example, individuals with CHC often report having to restrict their physical functioning and restrict their social activities. These

variables are measured by assessing an individual's level of social and psychological

functioning as well as physical and psychological aspects of performance (Chassany &

Bergmann, 1998).

Generic health QOL scales, such as the *Short Form-36* (SF-36; Ware &

Sherbourne, 1992), are designed to evaluate aspects of functional status and well-being

that is applicable to the general population. These types of scales are useful in comparing

CHC to other disease populations. Typical items to assess general health QOL include

asking the individual if he/she has had any difficulties with work or other regular

activities as a result of his/her physical health or emotional problems. Health QOL scales,

like the *SF-36*, are increasingly being used as outcome measures in clinical trials,

effectiveness research, and research on quality of care (Wilson & Cleary, 1995). While

the majority of research in this area has focused on the simple relationship between CHC

diagnosis and QOL variables, clinical investigation has begun to recognize the need to

determine the mechanisms underlying the impairment in QOL in the CHC population

(Cordoba, Flavia, Jacas et al., 2003).

A number of recent studies have documented the impact of CHC on quality of

life outcomes (Bonkovsky et al., 1999; Bernstein et al., 2002; Chong et al., 2003; Hauser

et al., 2004; Ware et al., 1999). Ware et al. (1999) determined that CHC patients,

independent of cirrhosis, report with a lower level of quality of life compared to the

general population. These results are consistent with other research findings concluding

that CHC patients experience decrements in health status, psychological well-being and

perceived health as his/her liver disease severity advances (Bayliss et al., 1998; Carithers,

Sugano, & Bayliss, 1996). The greatest differences in quality of life are found in the domains of role-physical functioning and perceived general health.

Similarly, studies detect that CHC patients report lower levels of QOL compared to other medical populations, including diabetes and hypertension (Gandek & Ware, 1993). The most pronounced differences are found on scales related to social functioning. This finding is consistent with the belief that CHC patients often times feel socially alienated from their environment and that the social stigma associated with an infectious disease additionally plays a role. A study attempted to identify a possible etiology for the impact of CHC on QOL. Rodger et al. (1999) hypothesized that the simple event of being diagnosed with HCV greatly impacts the individual's quality of life. Expectedly, individuals aware of their illness reported significantly lower levels of quality of life compared to HCV individuals who were unaware. Those individuals who were aware did not differ in demographics or severity of liver disease from those unaware. This strongly supports the assumption that there is an emotional impact of being diagnosed with an infectious disease that harbors great uncertainty. A recent study by Hauser et al. (2004) was the first to assess biopsychosocial predictors of health-related quality of life in patients with CHC. They determined that QOL in CHC is not defined by the severity of the liver disease, but it is instead related to psychiatric comorbidities, medical comorbidities, and disease-related worries (Hauser et al., 2004).

Research considering the benefits of immunotherapies in QOL has yielded promising results (Berstein et al., 2002; Bonkovsky et al., 1999; Ware et al., 1999). All three studies conclude that treatment yields improvements in QOL, specifically in

domains of vitality, social functioning, and health distress. This research suggests that when liver disease symptom severity improves or when patients perceive improvement in his/her health, quality of life improves as well.

As discovered in the QOL studies in CHC or other chronic illnesses, there are almost always psychosocial consequences. CHC patients often experience a diminished quality of life compared to the general population and even to patients with other chronic illnesses. CHC patients report having to restrict their social activities, are highly concerned about their health, and they experience severe symptoms of fatigue or lethargy. Few studies (Hauser et al., 2004; Rodger et al., 1999) have researched other possible reasons, besides the diagnosis of the disease, as to why individuals with CHC report lower levels of quality of life. Considering the complexity of the nature and treatment of CHC and typical traits or behaviors of those that are infected by it, a number of potential factors may affect the relationship between CHC diagnosis and quality of life as found in the study by Hauser et al. (2004). These factors may include a number of psychosocial variables, many of which that have been detailed in this manuscript, such as alcohol consumption, intravenous drug use, smoking, comorbid mental illness, or coping strategies. For example, research suggests that substance use and coping strategies are independently associated with quality of life (Bolliger et al., 2002; Mitra et al., 2004; Schmitz, Kruse, & Kugler, 2003; Smith & Larson, 2003; Strine et al., 2005; Vosvick, Koopman, Gore-Felton et al., 2003; Wilson, Parsons & Wakefield, 1999).

Research examining the effects of smoking on quality of life has produced two significant findings. First, the literature suggests that individuals smoking cigarettes

report a diminished quality of life compared to nonsmokers (Mitra et al., 2004; Schmitz, Kruse & Kugler, 2003; Strine et al., 2005. A recent study by Strine et al. (2005) found that current smokers reported a poorer quality of life compared to those who had never smoked cigarettes. In addition, they determined that smokers were more likely to consume alcohol and they tended to report more symptoms of depression and anxiety. Secondly, research is establishing that smoking reduction can improve an individual's quality of life (Bolliger et al., 2002; Mitra et al., 2004). Bolliger et al. (2002) found that individuals who reduced smoking consumption by at least 50% reported an improvement in quality of life outcomes. More specifically, successful reducers reported an improvement in general health, physical functioning, emotional well-being and energy level. Therefore, a more complex evaluation of QOL outcomes should be undertaken by including social and psychosocial factors, such as smoking cigarettes, along with HCV diagnosis and disease severity.

Moderator and Mediator Relationships between HCV and Quality of Life Outcomes: Consideration of Psychological Risk Factors

The bulk of the research indicates that hepatitis C is associated with an impairment in quality of life. More specifically, the research indicates a negative relationship between liver disease progression (i.e. disease severity) and quality of life. Simply stated, when a patient's liver disease severity increases, the patient's quality of life diminishes. Most research has focused on simple bivariate models relating CHC to quality of life. Considering the psychological complexities of most CHC patients and the literature's suggestion of a number of factors that may influence an individual's QOL besides disease severity/symptom severity, these simple bivariate relationships could be

affected by other mechanisms. More specifically, coping strategies could play an important role in altering the above mentioned relationship. Additionally, other psychosocial factors, such as psychological distress and substance use, may play a major role in altering the CHC-quality of life relationship. For example, a recent study by Smith and Larson (2003) assessed 570 substance-abusing clients from different detoxification centers and outpatient facilities on quality of life outcomes. Data support a strong association between substance abuse history and a diminished quality of life. The study found that substance abuse patients report significantly lower quality of life scores on the *SF-36* than patients about to undergo heart surgery and the general population. Moreover, the results indicate that physical functioning of adult substance abusers is similar to the levels for patients diagnosed with other chronic illness, but that mental functioning is much lower in this substance abusing population.

The possibility that specific mechanisms (e.g. coping strategies, psychological distress, substance use) buffer or exacerbate the impact of liver disease severity on quality of life has been minimally addressed in the CHC literature. Exploring the complex relationship between CHC severity and quality of life may require examining moderator and mediator variables. Holmbeck (1997) defines a moderator variable as "one that affects the relationship between two variables, so that the nature of the impact of the predictor on the criterion varies according to the level or value of the moderator." In other words, the moderator variable interacts with a predictor variable in such a way that it has an impact on the level of the dependent variable as well. A hypothesized moderator

relationship is presented in Figure 1 on page 35. This model depicts coping with illness strategies moderating the relationship between CHC severity and quality of life. Based on the literature just reviewed, a specific example of how coping strategies can moderate the relationship between CHC severity and quality of life is presented below to more fully elucidate these hypothesized relationships. Individuals using active coping (high active copers) strategies may report higher levels of quality of life independent of whether the individual has higher or lower liver disease severity. Second, individuals using avoidant coping (high avoidant copers) strategies may report lower levels of quality of life when the patient has more severe CHC, but not when individuals have a lower severity of CHC. Figures 2 and 3 on pages 36 and 37 respectively, illustrate the hypothesized moderator relationship in detail.

Another model for studying the relationship between CHC severity and quality of life is the competing mediator model. Holmbeck (1997) defines a mediator variable as specifying how, or the mechanism by which, a given effect occurs. In the words of Shadish and Sweeney (1991), "the independent variable causes the mediator which then causes the outcome." Simply stated, the mediator variable explains "why" a relationship exists between the predictor (CHC severity) and criterion (quality of life) variables. This relationship is presented in Figure 4 on page 38. This example of a mediator model illustrates the following: (1) variations in levels of CHC severity account for a significant portion of variations in the variable psychological distress, (2) variations in psychological distress account for a significant portion of variations in quality of life and (3) variations in CHC severity (i.e. path C) will not be significant when controlling for the
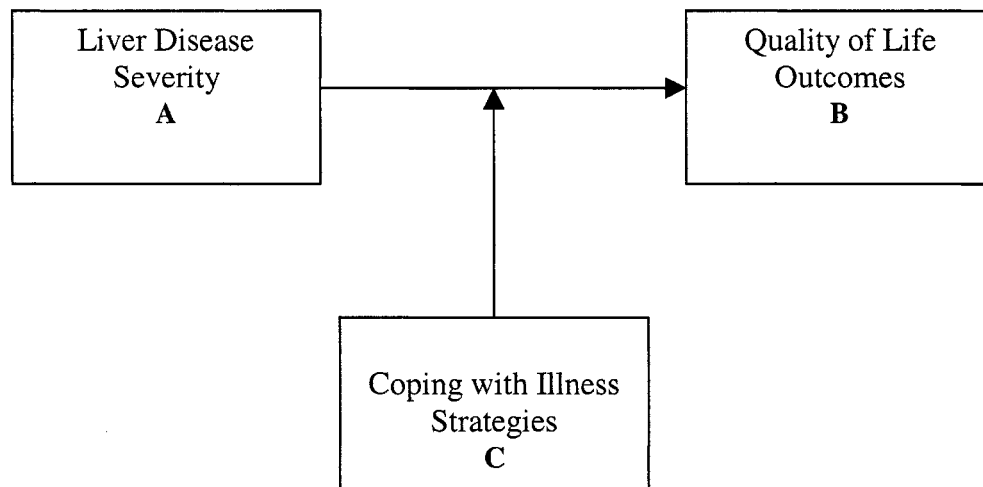
Figure 1. Coping as a Moderator in the Relationship between Liver Disease Severity and Quality of Life Outcomes
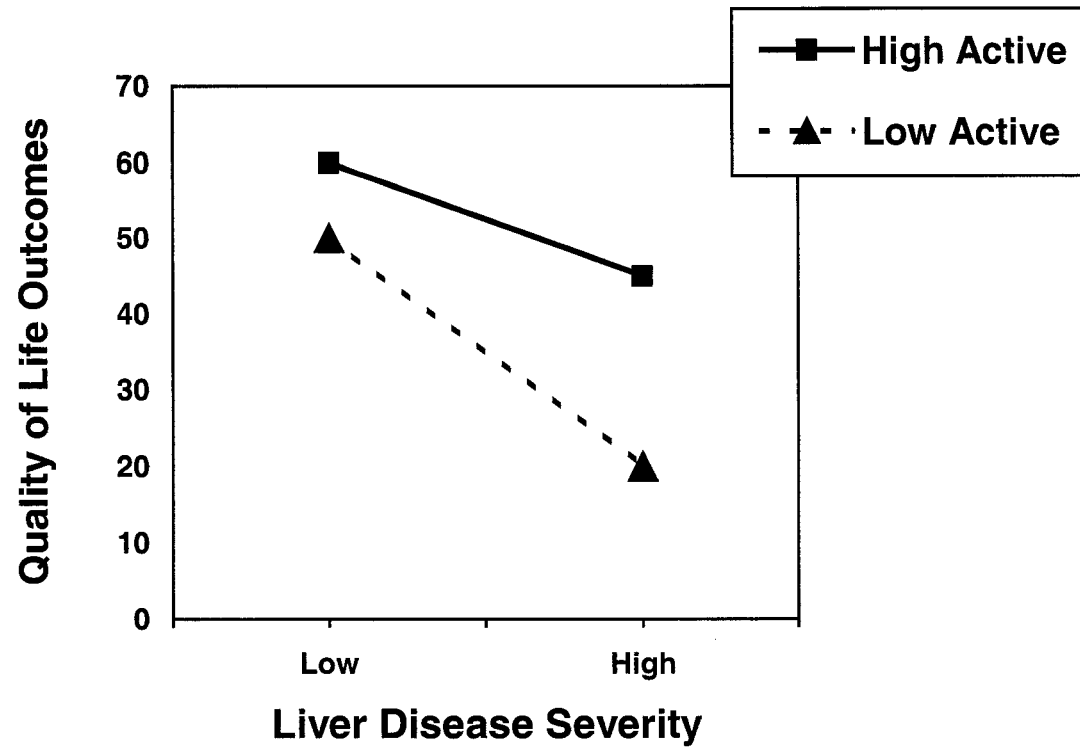
Figure 2. Moderation Model with Idealized Data: Active Coping Strategies (Illness) in the relationship between liver disease severity and quality of life outcomes
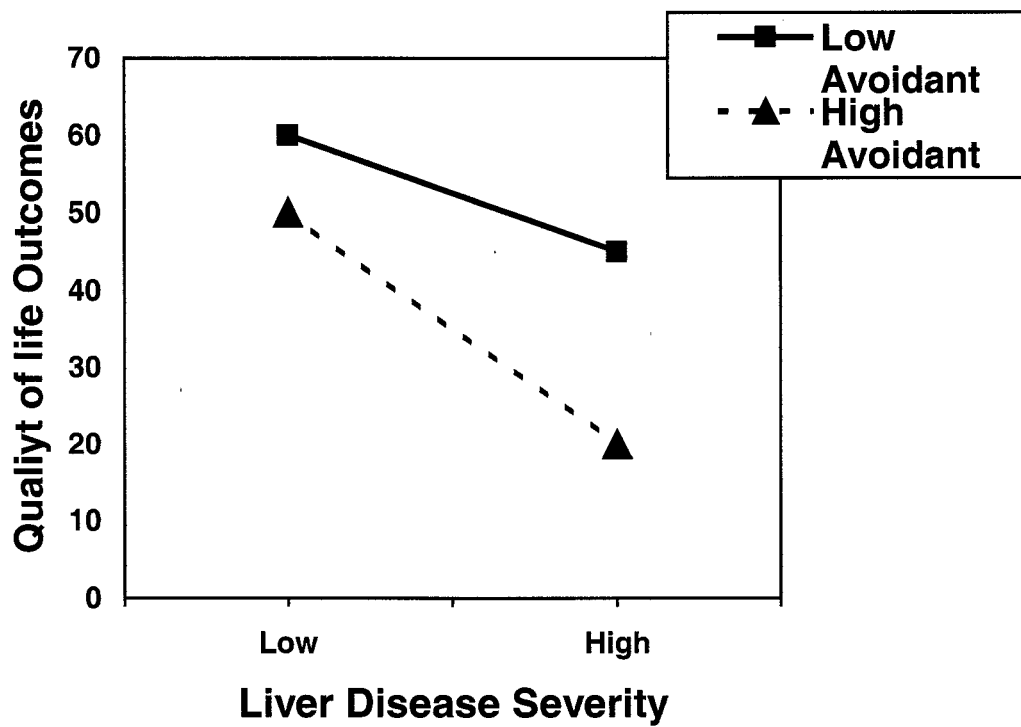
Figure 3. Moderation Model with Idealized Data: Avoidant Coping Strategies (Illness) in the Relationship between Liver Disease Severity and Quality of Life Outcomes
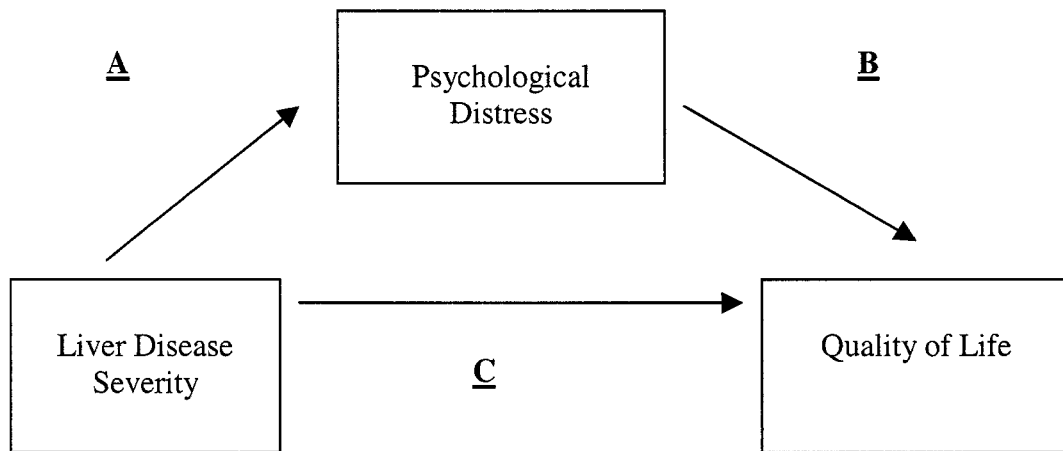
Figure 4. Mediator Model for Psychological Distress in the Relationship between Liver Disease Severity and Quality of Life Outcomes.

relationship between CHC severity and psychological distress (i.e. path A) and the relationship between psychological distress and quality of life (i.e. path B).

Several factors have been proposed to account for a poor quality of life among CHC patients, including low socioeconomic status, intravenous drug abuse, psychiatric comorbidities and the labeling effect of establishing the diagnosis of HCV infection (Foster, Goldin, & Thomas, 1998; Fontana, Moyer, Sonnad et al., 2001). However, the mechanisms underlying the impairment in quality of life have not yet been elucidated. There are no studies to date that have utilized the preliminary findings in the CHC literature for purposes of generating a more complex model for the relationship between CHC and quality of life outcomes.

Statement of the Problem

The principle goal of clinical care is shifting from taking care of the patient's

disease or illness to include a more holistic approach of improving patient outcomes-i.e.

quality of life. Consistent with this trend, there has been a recent expansion in the

hepatitis C literature examining the outcome variable Quality of Life (QOL). The

majority of these studies have examined a simple model whereby the diagnosis of

hepatitis C has been associated with a decrement in QOL outcome compared to other

chronic diseases and the general population (Berstein et al., 2002; Bonkovsky et al.,

1999; Gandek & Ware, 1993;Ware et al., 1999).

Another prominent area of research in hepatitis C has focused on the concerns and

challenges of comorbid psychiatric and substance abuse disorders within the population.

Studies indicate that up to 20% of adults with mental disorders are infected with hepatitis

C (Rosenburg et al., 2001). Moreover, a strong link has been found between CHC

diagnosis and severe psychological distress for the patient (Davis, De-Nour, Shouval, &

Melmed, 2001). Associated with mental disorders is the high prevalence of substance

abuse in the CHC population. The bulk of literature in this area examines the relationship

between substance abuse and hepatitis C disease progression (Hezode et al., 2003;

Pessione et al., 1998; Pessione et al., 2001; Poynard, Bedossa, & Opolon, 1997; Wang et

al., 2002). Research repeatedly confirms that alcohol use contributes to the development

and progression of liver disease in hepatitis C patients (Poynard, Bedossa, & Opolon,

1997; Wiley et al., 1998). Despite the attention given to alcohol consumption in the CHC

population, few studies have considered nicotine use a potentially independent prognostic

factor in patients with CHC. The limited data available suggests that smoking cigarettes may exacerbate hepatitis C symtomatology and progress the liver disease. (Hezode et al., 2003; Pessione et al., 2001).

Although the relationship between psychological distress, substance use and CHC diagnosis has been well established, the role of coping strategies in adjusting to CHC has been relatively neglected. Research in other areas of chronic illness support the idea that coping strategies play an important role in understanding the relationship between illness symptoms and quality of life outcomes (Stanton, Collins, & Sworowski, 2001). Cognitive-behavioral models of pain propose the moderation effect of coping strategies as a critical factor in the relationship between pain and adaptation (Geisser, Robinson, & Henson, 1994; Gil et al., 1993; Haythornthwaite et al., 1998). In general, the studies have found that individuals using more active or adaptive coping strategies report with a higher quality of life and better health outcomes compared to individuals using more avoidant or maladaptive coping strategies (Brown, Nicassio, & Wallston, 1989; Smith, Wallston, Dwyer, & Dowdy, 1997).

The HIV literature also provides supportive evidence for the need to study coping within the HCV population. It is well documented in the HIV literature that coping styles greatly influence the psychological and even biological impact of HIV infection (DeGenova, Patton, Jurich, & MaDermid, 1994; Goodkin, Blaney, Feaster, et al., 1992). HIV research has also found effective coping strategies to be related to a better quality of life and a reduction of risk-taking behaviors (Friedland, Renwick, & McColl, 1996; Folkman, Chesney, Pollack et al., 1992). In consideration of the fact that HIV and HCV

disease present areas that overlap at both psychosocial (e.g. death issues, psychiatric morbidity) and biological (involvement of the immune system, risk of cancer) levels, it seems warranted to extend analysis of coping strategies to patients with HCV infection.

Considering the psychological complexities of most CHC patients and the literature's suggestion of a number of factors that may influence an individual's quality of life besides disease severity, it seems likely that these simple bivariate relationships would be affected by other mechanisms. The investigation of potential moderator and mediator variables will expand the hepatitis C literature to provide potential answers to why specific relationships exist. In addition, these models can determine if specific relationships are buffered or exacerbated by other variables. To date there are no studies examining specific models of psychosocial moderator and/or mediator variables in these relationships.

The present study attempted to address these shortcomings in the hepatitis C literature. Given the sparse literature, the first aim of the study was to advance our understanding of the independent effects of tobacco use on liver disease progression. The second aim of the study was to determine possible mechanisms for diminished quality of life found in CHC patients. Specifically, the present study examined how psychological variables (e.g. coping strategies, psychological distress, substance use) may influence the relationship between liver disease severity and quality of life by testing competing moderator-mediator models. Research in this area provides new important information regarding the impact these psychological factors play on quality of life in the CHC

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population, potentially aiding in the advancement of treatment approaches and improving overall health outcomes.

In the present study, preliminary hypotheses replicated earlier studies reported in the literature (i.e. correlations between psychological distress and hepatitis C diagnosis, relationship between substance use and hepatitis C and correlations between hepatitis C and quality of life outcomes). The study's main hypotheses aimed to enhance our understanding of the relationship between psychological distress, substance use, hepatitis C, and quality of life outcome variables by testing competing moderators and mediators. These hypotheses were developed to fill the gap in the hepatitis C literature by studying more complex (i.e. moderator) relationships, expanding prior studies examining simple relationships among the aforementioned variables (i.e. correlations). In addition, the study aimed at advancing our understanding of the independent effects of smoking and alcohol on liver disease progression and quality of life outcomes. The presence of these more elaborate relationships were examined through the following hypotheses:

Preliminary Hypotheses

Hypothesis 1: Relationship between substance abuse and psychiatric comorbidity. Individuals reporting substance use and more severe levels of addiction (i.e., alcohol consumption, tobacco use) were predicted to report higher levels of psychological distress on the *Brief Symptoms Inventory*. This analysis sought to replicate earlier studies that have found significant relationships between substance abuse and psychiatric comorbidities.

Hypothesis 2: Relationship between substance abuse and coping skills.
Individuals reporting substance use and more severe levels of addiction (i.e., alcohol consumption, tobacco use) were predicted to report using more passive or avoidant coping strategies and fewer active coping strategies. In addition, individuals with no substance use were predicted to report using more active coping skill and fewer passive coping strategies. This analysis sought to replicate prior studies that have found significant relationships between substance use and coping skills.

Hypothesis 3: Relationship between substance abuse and hepatitis C progression.
Hepatitis C patients reporting substance use were expected to have more progressed liver disease and more severe liver disease symptomatology. Specifically, individuals reporting substance use were expected to have more severe liver disease symptomatology (e.g. severe ascites/edema, variceal bleeds, pain, fatigue) and worse biochemical liver function indicators. Past research suggests that alcohol consumption may be a risk factor in liver disease progression for CHC patients. However, few studies consider the influence alcohol has on liver disease symptomatology alone. Furthermore, there is sparse literature for the effects of nicotine use on CHC progression and symptomatology.

Hypothesis 4: Relationship between hepatitis C progression and quality of life outcomes. Hepatitis C patients with more severe liver disease symptomatology and more severe biochemical liver disease indicators were expected to score lower on measures of quality of life. Specifically, the hepatitis C patients with more severe liver disease were expected to have lower scores on the role-physical functioning and social functioning components of the *SF-36* measurement. It was anticipated that the hepatitis C patients

would score lower on both the physical and mental components of the *SF-36* compared to the general population. This analysis sought to replicate prior research that has found significant results when examining the relationship between hepatitis C and quality of life outcomes.

Primary Hypotheses

The main hypotheses in this study served two purposes. The first main hypothesis advances our understanding of the independent effects of tobacco use on liver disease progression and quality of life outcomes among patients with Hepatitis C. The other two main predictions offer explanations regarding how psychosocial variables (i.e. coping strategies, psychological distress, substance use) may influence the relationship between liver disease severity and quality of life outcome measures by considering competing moderator and mediator models.

Hypothesis 1: Tobacco use as a risk factor in the progression of hepatitis C

> *Hypothesis 1A:* It was hypothesized that tobacco use has an independent effect on liver disease progression. Specifically, it was predicted that smoking cigarettes would have an independent adverse effect, above and beyond the variance accounted for by alcohol intake and demographic variables (i.e., gender, ethnicity, age) on liver disease progression.
>
> *Hypothesis 1B:* It was hypothesized that tobacco use has an independent effect on quality of life outcomes among hepatitis C patients. More specifically, it was predicted that tobacco consumption would be related to lower levels of quality of life.

Hypothesis 2: The impact of coping strategies in the hepatitis C population. Coping as a moderator in the relationship between liver disease severity and quality of life outcomes

It was hypothesized that coping with illness strategies, measured by the situational *Brief COPE*, would moderate the relationship between liver disease severity and quality of life measures. More specifically, it was predicted that first, patients using active coping (high active copers) strategies (problem solving behaviors) would report higher quality of life when the individual presents with high levels of liver disease severity compared to individuals using low active coping strategies. Second, patients using avoidant or passive coping strategies (high passive copers) strategies (depressive coping, cognitive avoidance and dissimulation) were predicted to report lower quality of life outcomes when the individual had high levels of liver disease severity compared to individuals using low avoidant coping strategies. Figures 2 and 3 on pages 36 and 37 respectively, illustrate the moderator relationship in detail. The moderator model is presented fully in Figure 1 on page 35.

Hypothesis 3: The impact of psychological distress and substance use on quality of life outcomes. Competing moderator and mediation models

> *Hypothesis 3A: Moderator model-the impact of psychological distress on quality of life.* It was predicted that psychological distress would moderate the relationship between liver disease severity and quality of life outcome measures. More specifically, it was hypothesized that patients with high levels of psychological distress (i.e. depression, anxiety) would report lower levels of quality of life when the individual had high liver disease severity. Patients

reporting lower levels of psychological distress would report higher levels of quality of life when the individuals had high liver disease severity, but not at low levels of liver disease severity. Figures 5 and 6 on pages 48 and 49, respectively, illustrate the moderator relationship in detail.

Hypothesis 3B: Mediator model-impact of psychological distress on quality of life. In the competing model, it was predicted that the mediator (psychological distress) would explain why a relationship exists between the predictor variable of liver disease severity and the criterion variable of quality of life outcomes. This tested the idea that liver disease severity affects the patient's degree of psychological distress that in turn affects the individual's quality of life. It was hypothesized that higher psychological distress would affect quality of life outcomes negatively. The competing mediator model is presented in Figure 5 on page 48.

Hypothesis 3C: Moderator model- the impact of substance use on quality of life. It was predicted that substance use (alcohol intake, tobacco use) would moderate the relationship between liver disease severity and quality of life outcome measures. More specifically, it was hypothesized that patients with substance use would report lower levels of quality of life when the individual had high liver disease severity. Secondly, patients reporting no substance use would report higher levels of quality of life when the individuals had high levels of liver disease severity. Figures 7 and 8 on pages 50 and 51, respectively, illustrate the moderator relationship in detail.
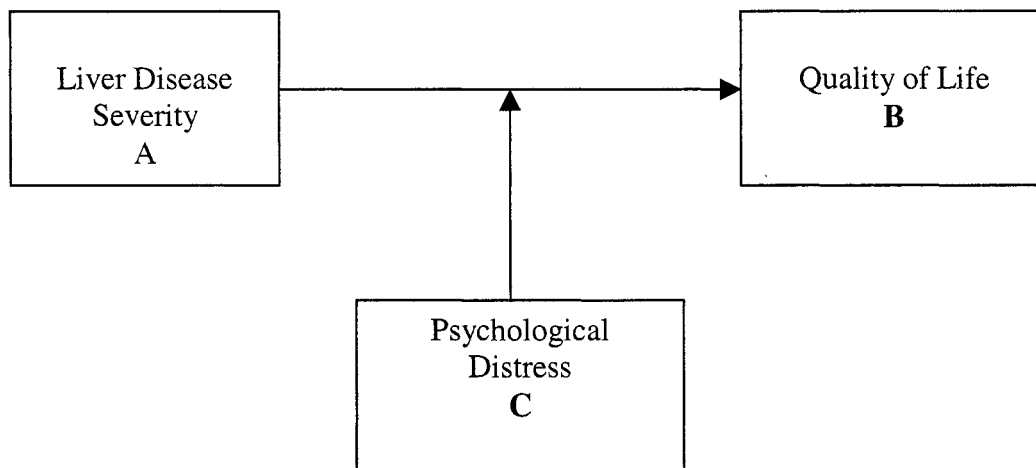
A) Psychological Distress as a Moderator
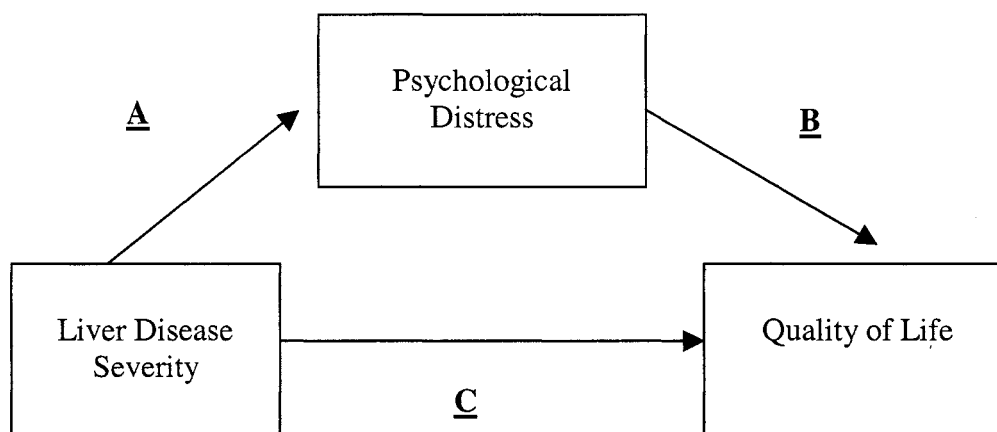
B) Alternative Model: Psychological Distress as a Mediator

Figure 5. Competing Models for Psychological Distress in the Relationship between Liver Disease Severity and Quality of Life Outcomes.
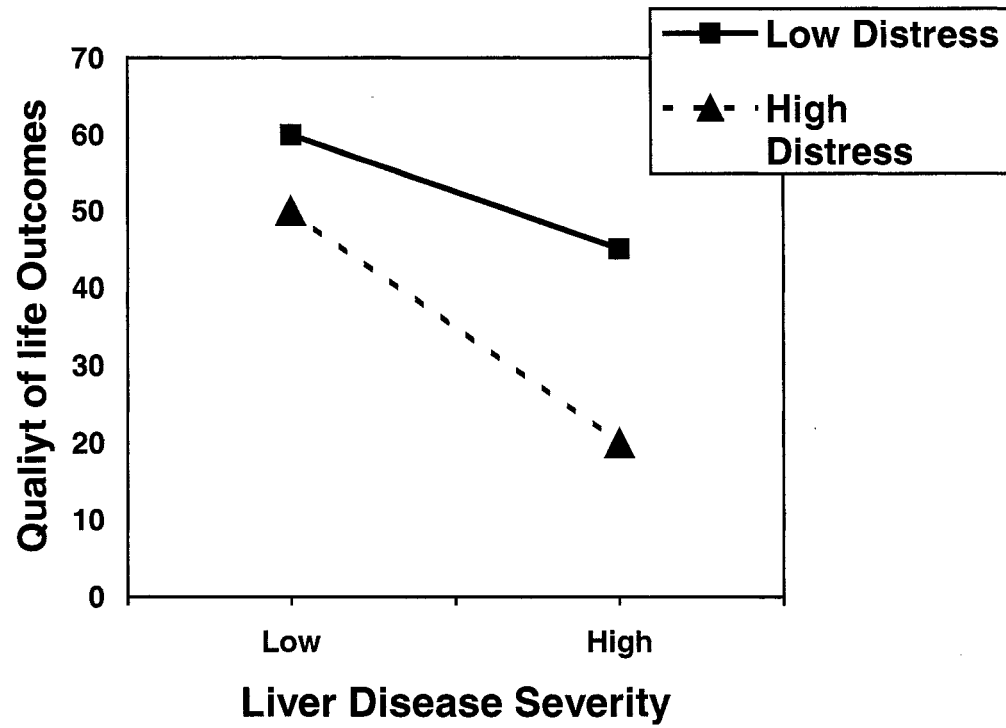
Figure 6. Moderation Model with Idealized Data: Psychological Distress in the relationship between liver disease severity and quality of life outcomes
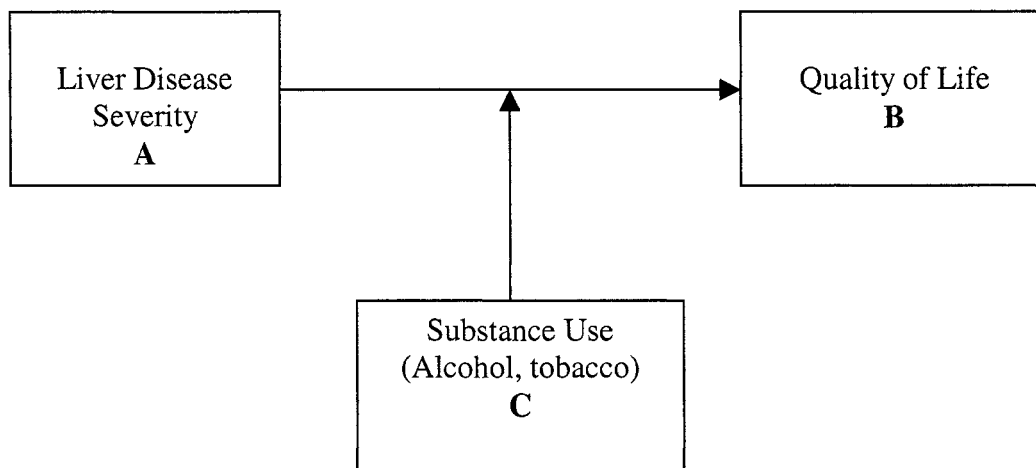
A) Substance Use as a Moderator
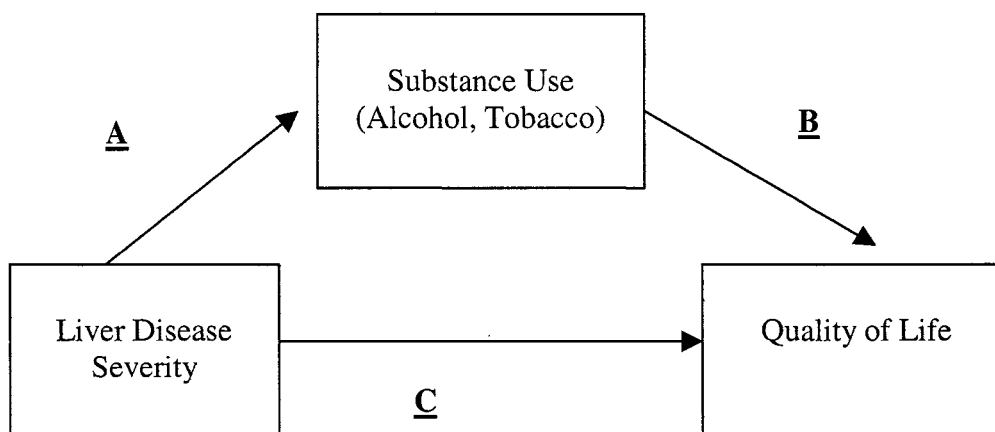
B) Alternative Model: Substance Use as a Mediator

Figure 7. Competing Models for Substance Use in the Relationship between Liver Disease Severity and Quality of Life Outcomes.
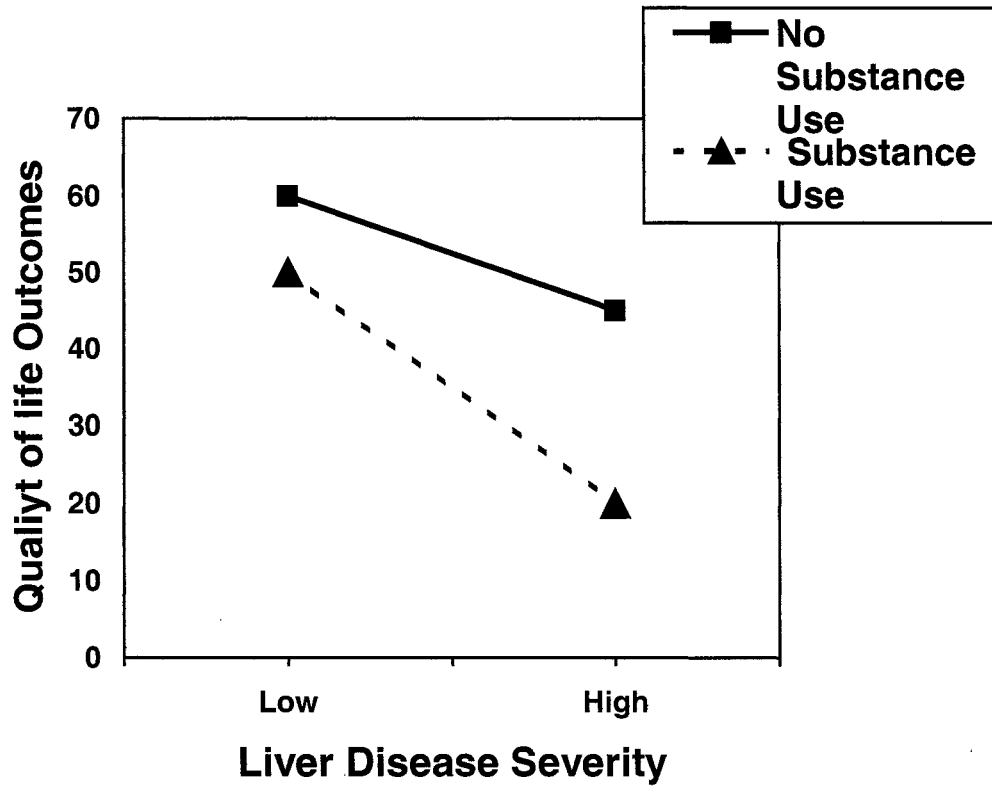
Figure 8. Moderation Model with Idealized Data: Substance Use in the relationship between liver disease severity and quality of life outcomes

Hypothesis 3D: Mediator model-impact of substance use on quality of life. In the competing model, it was predicted that the mediator (alcohol intake, tobacco consumption as independent mediators) would explain why a relationship exists between the predictor variable of liver disease severity and the criterion variable of quality of life outcomes. This tested the belief that liver disease severity affects the patient's use of alcohol or tobacco that in turn affects the individual's quality of life. It was hypothesized that substance use would affect quality of life outcomes negatively. The competing mediator model is presented in Figure 7 on page 50.

Methods

Participants

The participants were patients diagnosed with hepatitis C (HCV), who were seeking medical treatment at Virginia Commonwealth University Medical Center's Liver Center. To be included in the study, individuals had to have a documented antibody to HCV, indicating that he/she is positive for hepatitis C. Other inclusion criteria included: patients who are 18 years old or older, not actively psychotic, no obvious cognitive impairment, and posses the ability to give verbal and written consent to participate. Consent to participate in the study was obtained by having the individual read and sign the research subject information and consent form. The informed consent form is provided in Appendix A. There was no compensation offered to participate in this research study. This study received approval from the Virginia Commonwealth University Institutional Review Board.

One hundred and nineteen questionnaire packets were distributed to potential CHC participants between March 2004 and August 2004. In an effort to increase the response rate, participants who had not returned packets within one month of enrollment into the study were contacted by phone. Two individuals withdrew from the study because they reportedly felt uncomfortable with answering the questions in the packet. 41 participants did not return the questionnaire packets. Seventy-six packets were completed and returned to the investigator. This represents a response rate of 64%. One participant was excluded from the data analysis because of missing data.

Power Analysis

A power analysis for multiple regression analyses was conducted following the recommendations of Cohen and Cohen (1983) to estimate the number of research participants needed in the study. When alpha was set at .05, the desired power was set at .80, and a large effect size was estimated to be .40, the analysis revealed that 46 participants were needed to run multiple regression and correlation analyses for this study. Comparing to a range of effect sizes, when alpha and desired power were set the same and an effect size was estimated to be .30 and .20, the analysis revealed that 84 and 200 participants respectively, were needed to run the analyses for the study. With the study including 76 participants the desired power was obtained for data analyses if there was a large effect size.

Measures

Physiological Measures

Physiological measurements were recorded onto the Medical Record Abstract Form by chart extraction after the patient gave consent to participate in the study. The biochemical markers abstracted from the medical charts were used in combination to produce one liver disease severity index score as described below.

Medical Record Abstract Form. The medical status variables were collected on this form and included classification and date of liver disease diagnosis, current medication regimen, co-morbid medical conditions, and liver injury biochemical markers to determine the severity of liver disease. This form can be found in Appendix B on page 164. The biochemical markers included aspartate aminotransferase (AST), alanine

aminotransferase (ALT), platelet counts, bilirubin, and albumin. The significance of these biochemical liver tests, including normal ranges and the basis of abnormal scores is provided in Table 3 on page 56. Unfortunately to date, there are no standard, well-validated noninvasive tests that can accurately reflect the severity of liver disease progression in hepatitis C patients. Despite the mixed results in the literature, decreased platelet counts, increased ratio of aspartate to alanine aminotrasferase, and prolonged prothrombin time have found to be the best indicators of liver disease progression (Fontana and Lok, 2002). Recent progress has been made in developing an index score that combines these biochemical markers to more accurately predict liver disease severity (Wai et al., 2003).

One primary index score was used to determine the patient's severity of liver disease for patients with a diagnosis of hepatitis C in this study. The AST to platelet ratio index (APRI) was used in predicting severity of liver disease. The use of the APRI score follows the recommendations of Wai and colleagues (2003), who developed the noninvasive model for predicting liver disease severity. Wai et al.'s (2003) research found that this simple noninvasive index can predict significant fibrosis and cirrhosis in patients with hepatitis C. The researchers developed cut-off points that could predict the absence or presence of fibrosis and cirrhosis. For example, a cut-off score of 1.5 indicated that 88% of individuals above this score presented with significant fibrosis (e.g., positive predictive value of .88). In addition, a cut-off score of 2.0 indicated that 93% of individuals below this score did not present with cirrhosis (negative predictive value of .93). Simply stated, there is a likelihood of fibrosis in patients with APRI scores

Table 3

Significance of Biochemical Liver Tests adapted by Achord (2002)

Test (reference range)	Basis of Abnormal Scores
Aspartate Aminotransferase (AST) Alanine Amiotrasnferase (ALT) (0-40 IU/L)	These enzymes are made in the liver. Leakage from damaged tissue causes high levels that in turn causes injury to hepatic cells.
Platelet counts (150-300 10^9/L)	These are small cells in blood that function to initiate clotting. If there is a deficiency in platelets, blood clotting is slowed of fails to occur. This can result in unexpected bleeding.
Bilirubin (0.1 –1.0 mg/dL)	This is a yellow pigment metabolized by the liver that is the normal end product of hemoglobin breakdown. When it accumulates in tissues, it is recognized as jaundice.
Albumin (4.0-6.0 g/dL)	This is a protein produced only in the liver. It adds to the osmotic pressure in blood, which maintains water in the circulation. Decreased synthesis of albumin causes symptoms of fluid retention.

above 1.5 and there is a greater likelihood of cirrhosis in patients with APRI scores about

2.0. The APRI formula can be found in Table 4 on page 58.

Self-Report Measures

Participants completed self-report questionnaires about their physical symptoms,

psychological symptoms, substance use history, coping strategies, and quality of life.

Physical symptoms related to the participant's illness were measured with the liver

disease symptoms form. The *Brief Symptoms Inventory* was used in measuring the degree

of psychological distress of the participant. Substance use history (e.g. illicit substances,

alcohol consumption, nicotine use) was assessed with a number of brief measures.

Coping with illness strategies was measured with the situational *Brief*

COPE Scale. The *Short Form-36 version 2 (SF-36v2)* questionnaire was used to assess

the participant's quality of life outcomes.

Liver Disease Symptoms Form. The Liver Disease Symptoms Form is derived

from the symptoms form used in the VCU Medical Center Liver Center. The frequency

and bothersome indices are taken from a number of studies (Naliboff et al., 1999;

Thompson et al., 1997) assessing physical symptom severity in chronic medical

populations. A similar version of this form is used by the treatment team to monitor the

liver disease patient's symptoms during interferon treatment. This measure, found in

Appendix C, includes twelve typical physical complaints and symptoms associated with

liver disease. These symptoms include fatigue, nausea, poor appetite, headaches, pain

over the liver area, muscle/ joint aches and pains, infections, jaundice, itchiness,

abdominal fluid and/or feet swelling (e.g. ascites or edema), gastrointestinal bleeding

Table 4

The Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI)

Formula for APRI:

$$APRI = \frac{AST\ Level\ (/ULN)}{Platelet\ Count\ (10^9/L)} \times 100$$

(e.g. variceal bleeding), and mental changes (e.g. poor concentration, memory difficulties). For each of the twelve symptoms, individuals were asked to report the frequency and how bothersome (i.e. troublesome and/or disturbing) each symptom is for the individual. The first section of the questionnaire asks the individual to rate the frequency of each symptom from (0) not present to (4) occurs daily. The other section asks the individual to rate his/her bothersome level (i.e. how troublesome the symptom is in his/her life) for all twelve symptoms. The responses for this section range from (0) not bothersome to (4) extremely bothersome when occurs. From this information, total frequency scores, total bothersome scores, and total symptom severity scores can be calculated. In context of chronic pain, comparisons of these scales show strong reliability. For example, retrospective symptom severity ratings correlate $r= .8$ with the average of hourly severity of symptoms in pain over a 2 week period (Dancey et al., 1998).

Brief Symptoms Inventory. The *Brief Symptoms Inventory* (BSI; Derogatis & Melisaratos, 1983) is a 53-item measure in which respondents rate their level of distress during the past week. The BSI consists of nine subscales and three global indices of distress. The Global Severity Index (GSI) was used in the study considering it is the single best indicator of current psychological distress levels (Derogotis & Melisaratos, 1983). The GSI stability coefficient is .90, strongly indicating that the BSI is reliable over time.

Substance Use History Forms. Three brief questionnaires were used to assess the participant's substance use history. All three questionnaires have been derived from the

National Institute on Drug Abuse drug history form (NIDA, 1993). The *Brief Drug*

History Form assessed participant's current and past use of illicit substances, including

marijuana, cocaine, heroin, amphetamines, and hallucinogens. This form can be found in

Appendix D. The *Alcohol Use Questionnaire* measured the participant's current and past

use of alcohol. The form assesses the participant's alcohol use during the past six months.

If the participant was not currently using alcohol, he/she was asked to describe past

alcohol use. See Appendix E for a copy of this questionnaire. The final substance use

measure, the *Nicotine History Form,* assessed the participant's current and past nicotine

use. This measure can be found in Appendix F. It is noted that the Time Line Follow-

Back (TLFB) (Sobell & Sobell, 1992; Sobell et al., 1994) method, which is the most

widely used and accepted form for substance use history, was considered for use in the

study. However, interviewer-guided administration and the length of the assessment (30

minutes) made it unfeasible for this self-report questionnaire packet study. The three brief

substance use forms described above all have solid psychometrics and provide accurate

information for the purposes of these analyses.

    Alcohol Use Disorders Identification Test (AUDIT). The AUDIT (Saunders et al.,

1993) is a 10-item measure used to identify individuals "at risk" of developing alcohol

use disorders and it can be used in general to measure the severity of alcohol dependence.

The test is comprised of three questions that address symptoms associated with alcohol

dependence and four items that address harmful alcohol consumption behaviors. The

final three questions relate to consumption-based items, serving as an indicator for

hazardous alcohol consumption. The AUDIT has been exhaustively studied in terms of

its psychometric properties and it has been deemed psychometrically sound and suitable

for various populations (Kypri et al., 2002). See Appendix G for a copy of this scale.

Fagerstrom Test for Nicotine Dependence (FTND). The Fagerstrom Test for

Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is a 6-item

measure that has been widely used in measuring the severity of nicotine dependence. The

responses to the six questions are summed to compute a score ranging from 0 (least

dependent smoker) to 10 (most dependent smoker). The internal consistency of the scale

is .73 and test-retest reliability sits at r = .85 (Etter, Vu Duc, & Perneger, 1999). See

Appendix H for a copy of this scale and its scoring system.

Brief COPE Questionnaire (Situational Version). The Brief COPE Questionnaire-

Situational Version (Carver, 1997) is a 28-item scale in which respondents indicate how

frequently they use specific coping strategies in dealing with stressors in their life. More

specifically, the situational concurrent format was used for assessing how the patient is

coping with liver disease. The items represent the following coping strategy subscales

that have been combined to generate composite scores for Active coping strategies and

Avoidant coping: 1) Active coping: active coping, planning, positive reframing, and

acceptance 2) Avoidant coping: venting, denial, behavioral disengagement, self-

distraction, and self-blame. Responses are rated on a 4-point scale ranging from 0= *I*

usually don't do this at all to 3= *I usually do this a lot.* The Cronbach's alpha reliability

for the Brief COPE scales range from .50 to .90. The test-retest reliabilities for the Brief

COPE scales all met or exceeded the value of .50, which is regarded as minimally

acceptable (Nunnally, 1978; Nunnally & Bernstein, 1994). See Appendix I for a copy of this scale.

Short Form- 36 Version 2 Questionnaire. The Short Form-36 version 2 Questionnaire (SF-36v2; Ware, Kosinski, & Dewey, 2002) was used as a self-report measure of the individual's general health related quality of life. Relative to the standard SF-36, this version has improved the item wording, instructions, and response categories. The scale includes items that measure each of eight health concepts: 1) physical functioning; 2) role limitations because of physical health problems; 3) bodily pain; 4) social functioning; 5) general mental health (psychological distress and psychological well-being); 6) role limitations because of emotional problems; 7) vitality; and 8) general health perceptions. Responses to questions are based on a number of different rating scales. From this information, individual subscales, physical component summary scores and mental component summary scores can be calculated. The *SF-36* is scored from 0 to 100, with higher scores indicating better HRQOL. Median internal consistency and test-retest reliability for *SF-36* scales range from .76 to .95 (Ware, Kosinski, & Dewey, 2002). See Appendix J for a copy of this scale.

Demographic Questionnaire. A demographic questionnaire was used to assess participant characteristics including: age, gender, race/ethnicity, level of education, marital status, occupation, annual income, and liver disease diagnosis. See Appendix K for a copy of this questionnaire.

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Procedures

Participant recruitment

A convenience sample (i.e. volunteers recruited without randomization or stratification) of 126 patients from the VCU Medical Center Liver Center was recruited for this research project. Participants were recruited from the waiting room area and clinic exam rooms of the Liver Center located in the Gateway building and the waiting room of VCU Medical Center Consultation Liaison Psychiatry (e.g. patients under standard evaluation for liver transplantation) located in West Hospital by trained project staff. Inclusion criteria for this specific study was the following: age 18 or older, medical diagnosis of HCV, self-reported ability to read English, not actively psychotic, no obvious cognitive impairment, and ability to give verbal and written consent to participate.

Study procedures

Patients receiving medical care at the VCU Medical Center Liver Center were asked to participate in the study. The patients were approached by trained project staff in the waiting room areas or clinic exam rooms to inquire if the individual was interested in participating in the study. Participants who meet the inclusion criteria as described above were asked to participate in the study. There was no compensation for participation in this study. For those who were interested, the trained project staff reviewed the informed consent information and provided them with a packet of questionnaires to fill out. In addition, participants were given self-addressed stamped envelopes to return the packet to the research investigator. Patients who chose to participate and gave consent completed

the self-report measures included in the questionnaire packet study. The study consisted of a 5-minute informed consent discussion and written consent and a 20-35 minute period of completing self -report assessments. Participants had the option of completing the questionnaires in the waiting areas or completing the questionnaires at home.

Biochemical data for determining the liver disease severity index scores were obtained from the tests taken on the day of the interview or, if no tests were performed on that visit to the clinic, data was taken from the nearest previous visit. After the patient provided informed consent including consent for limited review of medical records data, the trained research assistant extracted selected medical information from the patient's chart located in the Liver Center and copied the information onto the medical record form. This procedure was approved by Dr. Shiffman, Section Head of Hepatology Department. To ensure confidentiality and minimize risks for the participant, medical record abstraction was not completed by Hepatologists or other treatment team staff at the center.

After completion of the self-report measures, participants were asked to read the final page of the packet, which debriefs them about the study. This form is located in Appendix L on page 185. The debriefing form also contained contact information to give the participants the opportunity to ask questions about the study. Once the packets were completed, all identifying information about the participant was removed from the packets to ensure confidentiality. All identifying information was deleted after lab values were obtained from chart abstraction, rendering data anonymous. The anonymous data was stored and entered into the database system. Confidentiality was protected and

maintained throughout the study. Specifically, participants were assigned a study number that was used on documents and databases. Electronic data files did not include identifiers. Information linking the patient identifiers to the study number was destroyed after medical record information was obtained. The informed consent information was kept in a locked cabinet but separate from the questionnaire packets. There was no identifying information with the packet that was also kept in a locked file cabinet under the supervision of the principal investigator.

Statistical Analyses for Research Hypotheses

Preliminary Hypotheses

> *Hypothesis 1:* Pearson correlations were conducted to determine if patients reporting higher levels of psychological distress report substance use (alcohol intake, tobacco use) and higher levels of addiction severity. Independent samples t-tests were also employed to determine group differences (i.e., smokers vs. nonsmokers, alcohol consumption vs. no alcohol consumption) for psychological distress.

> *Hypothesis 2:* Pearson correlations were conducted to determine if individuals reporting substance use (alcohol intake, tobacco use) and higher levels of addiction severity present higher use of general avoidant coping strategies and lower use of general active coping strategies. Independent samples t-tests were also employed to determine group differences (i.e., smokers vs. nonsmokers, alcohol consumption vs. no alcohol consumption) for coping strategies.

> *Hypothesis 3:* Pearson correlations were used to determine if patients reporting

substance use (alcohol consumption, tobacco use) and higher levels of addiction severity present with more progressed liver disease, as measured by the physiological liver disease markers and self-reported liver disease symptomatology severity. Independent samples t-tests were also used to determine group differences (i.e., smokers vs. nonsmokers, alcohol consumption vs. no alcohol consumption) for liver disease markers and liver disease symptoms. Furthermore, multivariate analyses of variance (MANOVA) were conducted to examine group differences in liver disease severity based on level of cigarette consumption. The three groups represented individuals smoking one or more packs per day, individuals smoking less than one pack per day, and nonsmokers.

Hypothesis 4: Pearson correlations were conducted to determine if patients presenting with more severe liver disease will report lower levels of quality of life. Analyses were run for role-physical functioning and social functioning scales of the *SF-36* to determine if there was a relationship between liver disease progression and these quality of life variables. In addition, analyses were run for the physical component summary and the mental component summary of the *SF-36* to determine the impact of liver disease severity on quality of life. Finally, separate one-sample t-tests were used to compare the means of the hepatitis population and the general population.

Primary Hypotheses

Hypothesis 1A: A hierarchical multiple regression analysis was conducted to determine if tobacco use has independent effects on liver disease severity. At step

1, demographic variables (gender, age) were entered into the model. This examined the main effects of the relationship between demographic variables and liver disease progression. The next step placed alcohol intake into the model to test for the main effects of alcohol on liver disease progression. Finally, tobacco use was placed into the model to test for the independent main effects of smoking on liver disease progression. This model considered the main effects of smoking tobacco on liver disease progression, above and beyond the variance accounted for by demographic variables and alcohol consumption.

Hypothesis 1B: A hierarchical multiple regression analysis was conducted to determine if tobacco use has independent effects on quality of life outcomes. At step 1, demographic variables (gender, age) were placed into the model. This examined the main effects of the relationship between demographic variables and quality of life. The next step placed alcohol intake into the model to test for the main effects of alcohol on quality of life outcomes. Finally, tobacco use was placed into the model to test for the independent main effects of smoking on quality of life. This model considered the main effects of smoking tobacco on quality of life outcomes, above and beyond the variance accounted for by demographic variables and alcohol consumption. In addition, independent samples t-tests and a MANOVA were used to examine group differences (i.e., smokers vs. nonsmokers; three groups based on level of nicotine consumption) for quality of life variables.

Hypothesis 2: A hierarchical multiple regression analysis was conducted to determine if coping with illness strategies moderated the relationship between the predictor variable liver disease severity and the criterion variable quality of life. At step 1, the predictor variable of liver disease severity was placed into the model. This examined the main effect of the relationship of the A→B path presented in Figure 1 on page 35. Next, the moderator variable coping with illness strategies (separate analyses for active coping strategies and passive coping strategies) was entered into the model to determine if it has a main effect on the criterion variable. This step examined the relationship of the A→ C path of the same figure. Finally, the product of both liver disease severity and coping with illness strategies was entered into the third and final equation (e.g., liver disease severity X coping strategies) with quality of life outcomes as the dependent variable to determine if there was an interaction effect. The interaction effect indicates that coping strategies (active and passive coping) interact with liver disease severity in such a way that it has an impact on the degree of quality of life.

Hypothesis 3A: A hierarchical multiple regression analysis was conducted to determine if psychological distress moderated the relationship between the predictor variable liver disease severity and the criterion variable quality of life. At step 1, the predictor variable of liver disease severity was placed into the model. This examined the main effect of the relationship of the A→B path presented in Figure 5 on page 47. In addition, the moderator variable psychological distress was entered into the model to determine if it has a main

effect on the criterion variable. This step examined the relationship of the A→ C path of the same figure. Finally, the product of both liver disease severity and psychological distress was entered into the final equation (e.g., liver disease severity X psychological distress) with quality of life as the dependent variable to determine if there was an interaction effect. As indicated above, the interaction effect indicates that psychological distress interacts with liver disease severity in such a way that it has an impact on the degree of quality of life.

Hypothesis 3B: For the competing mediator model, a hierarchical multiple regression analyses was conducted to determine if psychological distress mediates the relationship between liver disease severity and quality of life outcomes. A four-step procedure (Holmbeck, 1997; Baron and Kenny, 1986) utilizing multiple regression was used to test the mediation model. The procedure is outlined below. First, a relationship between the predictor (liver disease severity) and the outcome (quality of life) must be established. Secondly, the relationship between the mediator (psychological distress) and the outcome must be established. Next a relationship between the predictor and the mediator must be established. Finally, a relationship between the predictor and the outcome should be significantly reduced after controlling for the effects of the mediator. Correlation analyses were used for the first three criteria and multiple regression was used for the mediating model. Figure 5 represents this model and can be found on page 47. If the mediating model was significant, it indicated that psychological distress explains why a relationship exists between liver disease severity and quality of life.

Hypothesis 3C: A hierarchical multiple regression analysis was conducted to determine if substance use moderated the relationship between the predictor variable liver disease severity and the criterion variable quality of life outcomes. At step 1, the predictor variable of liver disease severity was placed into the model. This examined the main effect of the relationship of the A→B path presented in Figure 7 on page 50. In addition, the moderator variable substance use (separate analyses for alcohol, tobacco, and marijuana use) was entered into the model to determine if it has a main effect on the criterion variable. This step examined the relationship of the A→ C path of the same figure. Finally, the product of both liver disease severity and substance use was entered into the final equation (e.g., liver disease severity X substance use) with quality of life outcomes as the dependent variable to determine if there is an interaction effect. This effect indicates that substance use interacts with liver disease severity in such a way that it has an impact on the degree of quality of life.

Hypothesis 3D: For the competing mediator model, a hierarchical multiple regression analyses was conducted to determine if substance use (separate analyses for alcohol, tobacco and marijuana use) mediates the relationship between liver disease severity and quality of life. A four-step procedure (Holmbeck, 1997; Baron and Kenny, 1986) utilizing multiple regression was used to test the mediation model. First, a relationship between the predictor (liver disease severity) and the outcome (quality of life) must be established. Secondly, the relationship between the mediator (substance use) and the outcome must be

established. Next a relationship between the predictor and the mediator must be established. Finally, a relationship between the predictor (liver disease severity) and the outcome (quality of life) should be significantly reduced after controlling for the effects of the mediator (substance use). Correlation analyses were used for the first three criteria and multiple regression was used for the mediating model. Figure 7 represents this model and can be found on page 50. If the mediating model was significant, it indicated that substance use explains why a relationship exists between liver disease severity and quality of life.

Results

The analyses were conducted in three stages. First, descriptive statistics

presenting the demographic characteristics and normative data of the sample were

conducted. Next, the preliminary analyses were investigated to determine if relationships

found in the hepatitis C literature were represented in this sample. In addition, groups

were compared on specific measured variables using two group t-tests and multivariate

analyses of variance. Finally, the main analyses were conducted using multiple

regression to test moderator and mediator models.

Participant Characteristics

Demographic Information. The demographic characteristics for the 76 hepatitis C

participants included in all data analyses are summarized in Table 5 on page 73. The

sample consisted of 39 females (51.3%) and 37 males (48.7%). The majority (75%)

identified themselves as Caucasian, followed with 19.7% identifying as African

American, 2.6% Native American, 1.3% Asian/Pacific, and 1.3% as Other. Most

participants (59.2%) identified as being married or partnered, followed with 19.7%

divorced, 13.2% single, 3.9% cohabiting, 2.6% separated and 1.3% as widowed. 39.5%

of these participants had completed some college, 22.4% were high school graduates,

13.2% were college graduates, 9.2% had completed some high school, 6.6% had a

graduate/professional degree, 5.3% had less than an 8th grade education and 3.9% had

some graduate school training. The mean age of the sample was 50.58 years old ($\underline{SD}$ =

9.15), ranging from 21-73 years of age.

Table 5

Participant Demographics

Variable	Participants (76)
Gender	
Female	51.3% (39)
Male	48.7% (37)
Age (years)	
M	50.58
SD	9.15
Range	21-73
Ethnicity	
African-American	19.7% (15)
Asian/Pacific	1.3% (1)
Caucasian	75.0% (57)
Native American	2.6 % (2)
Other	1.3% (1)
Marital Status	
Married or Partnered	59.2% (45)
Divorced	19.7% (15)
Single	13.2% (10)
Co-habitating	3.9% (3)
Separated	2.6 % (2)
Widowed	1.3% (1)
Level of Education	
8th grade or less	5.3% (4)
Some high school	9.2% (7)
High school graduate/GED	22.4% (17)
Some college	39.5% (30)
College graduate	13.2% (10)
Some graduate school	3.9% (3)
Graduate/professional degree	6.6% (5)

Note. Number of participants for each category is given in parentheses.

There was a high prevalence of smoking cigarettes found in this hepatitis C sample. 51.3% of the sample were current smokers, 25% had quit smoking and 23.7% were nonsmokers. 23.7% of the sample endorsed drinking alcohol in the past six months. In addition, 22% of the chronic hepatitis C patients reported using marijuana in the past six months. With regard to other illicit substances, 52.6% reported trying cocaine and 3.9% were currently using the drug. 31.6% endorsed experimentation or use of heroin and 1.3% were current users. Substance use data can been found in Table 6 on page 75.

The demographic characteristics of the first group comparison (i.e., smokers versus nonsmokers) for preliminary hypothesis 3 and main hypothesis 1 are presented in Table 7 on page 76. Two cases were excluded from the analysis, one from missing data, and one as an outlier identified by Cook's distance measure D test. Of the 39 hepatitis C participants identifying themselves as smokers, 66.7% classified themselves as Caucasian, 23.1% as African-American, 5.1% as Native American, 2.6% as Asian American and 2.6% as Other. This group consisted of 22 females (56.4%) and 17 males (43.6%). The age range for these participants was from 21-71, with a mean age of 48.56 years ($\underline{SD}$= 8.69). 46.2% of the participants were married, 23.1% divorced, 15.4% single, 7.7% cohabiting, 5.1% separated, and 2.6% as widowed. 35.9% of these participants had completed some college, 33.3% were high school graduates, 10.3% had completed some high school or were college graduates, 7.7% had less than an 8th grade education, and 2.6% had a graduate or professional degree.

Of the 35 participants in the nonsmoker group, 85.7% identified themselves as Caucasian and 14.3% as African American. This group consisted of 17 females (48.6%)

Table 6

Substance Use History and Current Use

Variable	Participants (76)
Cigarette Use	
Current smokers	51.3% (39)
Quit smoking	25.0% (19)
Nonsmokers	23.7% (18)
Alcohol Use	
Ever used	96.1% (73)
Used in last 6 months	23.7% (18)
Marijuana	
Ever used	72.4% (55)
Used in last 6 months	22.4% (17)
Cocaine	
Ever used	52.6% (40)
Used in last 6 months	3.9% (3)
Heroin	
Ever used	31.6% (24)
Used in last 6 months	1.3% (1)

Note. Number of participants for each category is given in parentheses.

Table 7

First Group Comparison Demographics: Smokers vs. Nonsmokers

Variable	Group	
	Smokers(39)	Nonsmokers(35)
Gender		
Female	56.4% (22)	48.6% (17)
Male	43.6% (17)	51.4% (18)
Age (years)		
M	48.56	52.51
SD	8.69	9.48
Range	21-71	23-73
Ethnicity		
African-American	23.1%(9)	14.3%(5)
Asian/Pacific	2.6%(1)	-
Caucasian	66.7%(26)	85.7%(30)
Native American	5.1%(2)	-
Other	2.6% (1)	-
Marital Status		
Married or Partnered	46.2% (18)	71.4%(25)
Divorced	23.1% (9)	17.1% (6)
Single	15.4%(6)	11.4%(4)
Co-habitating	7.7%(3)	-
Separated	5.1% (2)	-
Widowed	2.6% (1)	-
Level of Education		
8th grade or less	7.7% (3)	2.9% (1)
Some high school	10.3% (4)	8.6% (3)
High school graduate/GED	33.3% (13)	11.4% (4)
Some college	35.9% (14)	42.9% (15)
College graduate	10.3% (4)	17.1% (6)
Some graduate school	-	5.7% (2)
Graduate/professional degree	2.6% (1)	11.4% (4)

Note. Number of participants for each category is given in parentheses.

and 18 males (51.4%). 42.9% of these participants had completed some college, 17.1%

were college graduates, 11.4% were high school graduates or had a graduate/professional

degree, 8.6% had completed some high school, 5.7% had completed some graduate

training, and 2.9% had less than an 8th grade education. Participants ranged in age from

23-73, with a mean age of 52.51 years ($\underline{SD}$ = 9.48). The majority (71.4%) of the

nonsmoking participants were married or partnered and 17.1% were divorced. Chi-

squared tests revealed no significant differences between the two groups on gender,

ethnicity, marital status, or level of education. An independent samples t-test revealed no

significant difference between the groups on age. In addition, no significant difference

was found between the groups on alcohol consumption.

The demographic characteristics of the second group comparison (i.e., level of

cigarette consumption) for preliminary hypothesis 3 and main hypothesis 1 are presented

in Table 8 on page 78. Two cases were excluded from the analysis, one from missing

data, and one as an outlier identified by Cook's distance measure D test. Of the 18

hepatitis C participants identifying themselves as smokers consuming one or more packs

of cigarettes per day, 77.8% classified themselves as Caucasian, 11.1% as Native

American, and 5.6% as African-American or Asian American. This group consisted of 7

females (38.9%) and 11 males (61.1%). The age range for these participants was from

33-64, with a mean age of 48.39 years ($\underline{SD}$= 6.60). 55.6% of the participants were

married, 22.2% divorced, and 5.6% as widowed. 38.9% of these participants had

completed some college, 27.8% were high school graduates, 11.1% were college

Table 8

Second Group Comparison Demographics: Dosage Effect

Variable	Group		
	1 or more packs (18)	less than 1 pack (21)	Nonsmokers (35)
Gender			
Female	38.9% (7)	71.4% (15)	48.6%(17)
Male	61.1% (11)	28.6% (6)	51.4%(18)
Age (years)			
M	48.39	48.71	52.51
SD	6.60	10.32	9.48
Range	33-64	21-71	23-73
Ethnicity			
African-American	5.6%(1)	38.1%(8)	14.3% (5)
Asian/Pacific	5.6%(1)	-	-
Caucasian	77.8%(14)	57.1%(12)	85.7%(30)
Native American	11.1%(2)	-	-
Other	-	4.8% (1)	-
Marital Status			
Married or Partnered	55.6%(10)	38.1%(8)	71.4%(25)
Divorced	22.2% (4)	23.8% (5)	17.1%(6)
Single	16.7%(3)	14.3%(3)	11.4%(4)
Co-habitating	-	14.3%(3)	-
Separated	-	9.5%(2)	-
Widowed	5.6% (1)		
Level of Education			
8th grade or less	11.1% (2)	4.8% (1)	2.9% (1)
Some high school	5.6% (1)	14.3% (3)	8.6% (3)
High school graduate/GED	27.8% (5)	38.1% (8)	11.4% (4)
Some college	38.9% (7)	33.3% (7)	42.9%(15)
College graduate	11.1% (2)	9.5% (2)	17.1% (6)
Some graduate school	-	-	5.7% (2)
Graduate/professional degree	5.6% (1)	-	11.4% (4)

Note. Number of participants for each category is given in parentheses.

graduates or had less than an 8th grade education, and 5.6% had completed some high school, or had a graduate/professional degree.

Of the 21 participants identifying themselves as smokers consuming less than one pack of cigarettes per day, 57.1% identified themselves as Caucasian, 38.1% as African American and 4.8% as Other. This group consisted of 15 females (71.4%) and 6 males (28.6%). 38.1% of these participants were high school graduates, 33.3% had completed some college, 14.3% had completed some high school, 9.5% were college graduates, and 4.8% had less than an 8th grade education. Participants ranged in age from 21-71, with a mean age of 48.71 years ($\underline{SD}$ = 10.32). 38.1% of the participants were married, 23.8% divorced, 14.3% cohabiting, and 9.5% were separated. As aforementioned, the demographics for the third comparison group, consisting of 35 hepatitis C nonsmoker, is presented in Table 7 on page 76. Chi-squared tests revealed no significant differences between the three groups on gender or level of education. However, Pearson Chi-Square tests did reveal a significant difference between the groups on ethnicity, $\underline{x}_(8)=19.45$, $\underline{p}<.05$ and marital status, $\underline{x}_(10)=18.85$, $\underline{p}<.05$. An analysis of variance revealed no significant difference between the groups on age. In addition, no significant difference was found between the groups on alcohol consumption.

Normative Data

Descriptive information on the measures, including Cronbach alpha reliability is found in Table 9. Means, standard deviations, and ranges for the measured variables are also presented in Table 9 on page 80 for the 76 participants. It is noted that two cases were excluded from the liver disease biochemical markers variables because of missing

Table 9

Alphas, Means, Standard Deviations, and Ranges of Measured Variables

Variable	α	Mean	SD	Sample Range	Normal/ Range Scores
ALT (Alanine Aminotransferase)		77.58	71.73	13-407	< 40
AST (Aspartate Aminotransferase)		71.01	65.54	15-403	< 40
Platelet Counts		173.09	89.30	43-414	>150
Bilirubin		.82	.73	.2-4.00	< 1.2
Albumin		4.34	4.14	2.2-39	3.5-4.5
APRI		1.52	2.11	.12-14.93	< 1.0
Liver Disease Symptoms Form					
Frequency Scores	.81	14.89	9.13	0 -35	0-48
Bothersome Scores	.82	13.29	8.8	0-36	0-48
Total Scores	.90	28.18	17.55	0 -71	0-96
FTND					
Total Sample	.83	1.97	2.81	0-9	0-10
Current Smokers		3.84	2.86	0-9	0-10
AUDIT	.86	2.14	4.16	0-21	0-40
Brief Symptoms Inventory					
Global Symptoms Index	.97	.73	.63	0 -3.04	0-4
Brief COPE					
Active Coping	.81	15.66	5.83	0-22	0-24
Avoidant Coping	.80	5.11	4.89	0 -22	0-24
Short Form-36 Total Score					
Physical component.	.93	42.33	12.26	14.7-61.7	0-100
Mental component	.95	42.17	14.00	7.8-65.8	0-100

data (1) or outlying data (1) as determined by the Cook's D test. The study's mean scores for the liver enzymes ALT (M=77.58, SD= 71.73) and AST (M=71.01, SD= 65.54) were both higher then the normal range of <40 IU/L. In addition, these mean score were found to be higher then mean scores of chronic hepatitis C patients without cirrhosis that had a ALT mean score of 66(SD=48) and a AST mean score of 45 (SD= 27, Cordoba et al., 2003). Conversely, the enzyme mean scores of this study are lower then the mean scores of chronic hepatitis C patients with cirrhosis that had a ALT mean score of 115 (SD= 64) and a AST mean score of 98 (SD= 64, Cordoba et al., 2003).

The liver disease biochemical markers bilirubin and albumin both had mean scores within the normal range. The bilirubin mean score of .82 (SD= .73) was within the normal range of <1.2. Similarly, the albumin mean score of 4.34 (SD= 4.14) was within the normal range of 3.5-4.5. Furthermore, the mean score of platelet counts (M=173.09, SD= 89.3) of this sample was also within the normal limits of >150. The APRI mean score of 1.52 (SD= 2.11) was found to be above the normal range of <1.0, which indicates the likely presence of fibrosis.

The most common liver disease symptoms found in this sample include fatigue (M=4.92, SD=1.51), muscle/joint aches or pains (M= 4.56, SD= 1.51), mental changes (M= 3.49, SD= 1.56), and headaches (M=2.74, SD= 1.42). This is consistent with the hepatitis C literature, which has found that fatigue is the most frequent and bothersome symptom reported in the hepatitis C population (Dwight et al., 2000, Obhrai, Hall, Anand, 2001). Individual symptoms mean scores associated with liver disease can be found in Table 10 on page 82.

Table 10

Means, Standard Deviations, and Ranges of Individual Liver Disease Symptoms

Symptom	Mean	SD	Sample Range	Range
1- Fatigue	4.95	2.85	0-8	0-8
2-Muscle/joint aches or pains	4.59	2.83	0-8	0-8
3-Mental changes	3.50	3.02	0-8	0-8
4-Headaches	2.74	2.74	0-8	0-8
5- Fluid Retention	2.53	2.89	0-8	0-8
5-Itchiness	2.45	2.76	0-8	0-8
7- Poor appetite	2.08	2.67	0-8	0-8

As aforementioned, 51.3% of this hepatitis C sample are current smokers. This percentage is significantly higher than the Center for Disease Control's 2004 estimate of a 20.7% prevalence of current smoking among adults in the United States. It is also a significantly higher percentage than is found in the general hospital inpatient population of 23% (Kouimtisidis et al., 2003). However, similar results have been found in the hepatitis C literature. A study by Hauser et al. (2004) found that 52.3% of chronic hepatitis C patients from an outpatient setting were current smokers. In our sample, the average FTND score for current smokers of 3.85 ($\underline{SD}$= 2.86) was lower than in other validation studies of this test, where the average FTND score ranged from 5 to 7 (Heatherton et al., 1991, Kozlowski et al., 1994). With regard to alcohol use, the mean score on the AUDIT was 2.14, which was well below the hazardous drinking cut off score of 8. 11% of these chronic hepatitis C patients scored above then cut off score to place them in the hazardous drinking range.

In regards to other psychological characteristics, the mean score from this study on the Brief Symptoms Inventory is higher than non-patient populations found in normative data investigations. The mean score on the Global Symptoms Index (GSI) was .73 ($\underline{SD}$ = .63), and higher than the mean .30 ($\underline{SD}$ = .31) found in a non-patient population (Derogatis & Melisaratos, 1993). The incidence of psychological distress was also found to be higher in this sample compared to the hepatitis C literature independent of the severity of the liver disease. This study's mean score on the GSI ($\underline{M}$= .73, $\underline{SD}$= .63) was higher than the mean score of .37 found amongst asymptomatic hepatitis C patients.

It was also found to be higher than chronic hepatitis C patients who had a mean score of .50 (Davis, De-Nour, Shouval, & Melmed, 2001).

For the Brief COPE scale, no normative data were available from earlier retrospective studies of individuals with hepatitis C. The mean on the Active coping strategies subscale in the present study was 15.66 ($\underline{SD}$ = 5.83). The mean of the Avoidant coping strategies subscale in the study was 5.18 ($\underline{SD}$ = 5.05). Compared to other medical population, this sample of hepatitis C patients reported using significantly less avoidant coping strategies compared to a sample of patients with HIV/AIDS ($\underline{M}$=10.79, $\underline{SD}$= 1.38, Vosvick et al., 2003).

Mean scores on quality of life measurements in the present study are below average compared to the general population. The mean score for the Physical component summary index was 42.33 ($\underline{SD}$ = 12.26), which is lower then the mean of 49.29 ($\underline{SD}$ = 8.66) found in the U.S. population (Ware, Kosinski, & Dewey, 2002). In addition, the mean score for the Mental component summary index was 42.17 ($\underline{SD}$= 14.00), which is significantly lower then the mean of 52.58 ($\underline{SD}$= 7.71) found in the U.S. population (Ware, Kosinski, & Dewey, 2002). Similar results have been found in the hepatitis C population. A study by Hauser (2004) examining QOL with a chronic hepatitis C sample found a mean score of 40.94 ($\underline{SD}$= 12.06) for the Physical component summary index and a mean score of 43.21 ($\underline{SD}$= 11.98) for the Mental component summary index.

Preliminary Hypotheses

The analyses of preliminary Hypothesis 1, Hypothesis 2, Hypothesis 3, and Hypothesis 4 incorporated the use of Pearson correlations and independent sample t-tests.

The correlations between all measured variables are presented in Table 11 on page 86. It is noted that point biserial correlations were used for the dichotomous variables (e.g., alcohol use, tobacco use). In addition, multivariate analyses of variance were conducted to examine group differences in liver disease severity.

Hypothesis 1: Relationship between substance abuse and psychiatric comorbidity. The first hypothesis explored the extent to which substance use (i.e. tobacco use, alcohol intake) and psychological distress was related. The correlations between tobacco use, tobacco dependence, alcohol dependence and psychological distress are presented in Table 11 on page 86. As predicted, participants who reported tobacco use also tended to report higher levels of psychological distress. A significant positive correlation was found between the tobacco use and the Global Severity Index (GSI) from the Brief Symptom Inventory ($r = .238$, $p < .05$). As anticipated, participants who reported more severe nicotine dependence also tended to report higher levels of psychological distress. A significant positive correlation was found between the Fagerstrom Test for Nicotine Dependence (FTND) and the GSI ($r = .323$, $p < .001$). An independent samples t-test determined that the mean of the GSI for smokers ($M = .88$, $SD = .70$) was significantly higher than the mean for nonsmokers ($M = .57$, $SD = .52$. $t(73) = 2.19$, $p < .05$). Furthermore, participants who reported more severe alcohol dependence also reported higher levels of psychological distress. A significant positive correlation was found between the Alcohol Use Disorders Identification Test (AUDIT) and the GSI ($r = .247$, $p < .05$). An independent samples t-test did not reveal a significant difference between the GSI means

Table 11

Zero-Order Correlations between Measured Variables

	Ast/platelet ratio	Total liver disease symptoms	Smoking	FTND	Alcohol	AUDIT	Active Coping COPE	Avoidant Coping COPE	GSI	Physical Component SF-36	Mental Component SF-36
Ast/platelet ratio	1.00										
Total liver disease symptoms	.302**	1.00									
Smoking	-.123	-.229*	1.00								
FTND	-.142*	.250*	-.684**	1.00							
Alcohol	-.137	-.056	-.131	-.005	1.00						
AUDIT	.170	.280*	-.273 *	.142	.608**	1.00					
Active Coping COPE	.230*	.311**	-.04	.064	-.077	-.015	1.00				
Avoidant Coping COPE	.138	.547**	-.126	.078	.060	.272*	.252*	1.00			
GSI	.104	.627**	-.238*	.323**	.071	.247*	.116	.751**	1.00		
Physical Component SF-36	-.417**	-.783**	.199	-.183	.165	-.151	-.262*	-.373**	-.501**	1.00	
Mental Component SF-36	-.128	-.687**	.093	-.193	.065	-.125	-.194	-.566**	-.693**	.538**	1.00

Note: Correlations for Smoking and Alcohol are point biserial correlations, *p<.05, **p<.01, ***p<.001

of participant who has consumed alcohol in the past six months compared to those who had not consumed alcohol in the past six months, $p > .05$.

Hypothesis 2: Relationship between substance abuse and coping skills. The second hypothesis examined the relationship between substance use (i.e. tobacco use, alcohol intake) and coping skills. The correlations between tobacco use, tobacco dependence, alcohol dependence and coping skills are presented in Table 11 on page 86. As predicted, participants who reported more severe alcohol dependence also tended to report using more avoidant coping strategies. Specifically, a significant positive correlation was found between the AUDIT score and the avoidant coping subscale of the Brief COPE ($r = .272$, $p < .05$). No other correlations were found to be significant. Likewise, independent samples t-tests did not reveal any significant differences between the smoking groups or alcohol groups when comparing the means of active and avoidant coping strategies.

Hypothesis 3: Relationship between substance abuse and hepatitis C progression. The third hypothesis assessed the extent to which substance abuse and hepatitis C progression was related. The correlations between tobacco use, tobacco dependence, alcohol dependence, biochemical liver disease markers and liver disease symptomatology are presented in Table 11 on page 86. As anticipated, a positive correlation between tobacco dependence and liver disease symptomatology was found, ($r = .250$, $p < .05$). Hepatitis C patients who reported more severe tobacco dependence also reported more severe liver disease symptoms. Likewise, a positive correlation between alcohol dependence and liver disease symptomatology was revealed, ($r = .280$, $p < .05$).

Participants who endorsed more severe alcohol dependence tended to report more severe

liver disease symptomatology. Other correlations were not found to be significant.

Independent samples t-tests revealed that smokers ($\underline{M}$= 32.23, $\underline{SD}$= 15.45)

reported experiencing more severe liver disease symptoms compared to nonsmokers ($\underline{M}$=

24.22, $\underline{SD}$= 19.01, $\underline{t}$(72)=1.99, $\underline{p}$<.05). More specifically, smokers endorsed experiencing

more severe symptoms of fatigue, poor appetite, and headaches compared to nonsmokers.

Table 12 on page 89 and Figure 9 on page 90 display these findings. No significant

differences were found with liver disease biochemical markers. These results are

presented in Table 13 on page 91 and displayed in Figure 10 on page 92. Although no

significant difference was found between the groups on the APRI score, smokers

($\underline{M}$=1.76, $\underline{SD}$= 2.57) tended to present with higher scores then nonsmokers ($\underline{M}$= 1.25,

$\underline{SD}$= 1.45). The mean score of smokers is above the higher cut-off value of 1.50 that

indicates a .88 positive predictive value for the presence of significant fibrosis (Wai et al.,

2003). Hence, these patients may be more likely to have fibrosis compared to the

nonsmoking group that has a mean below the cut off value. There were no significant

differences revealed with alcohol consumption.

Furthermore, multivariate analyses of variance were conducted to examine group

differences in liver disease severity. Participants were grouped based on level of cigarette

consumption. The three groups represented individuals smoking one or more packs of

cigarettes per day, individuals smoking less than one pack per day, and nonsmoker,

respectively. Two separate MANOVAS were run to compare the groups on liver disease

symptomatology variables and biochemical liver disease markers. Results from the

Table 12

Liver Disease Symptoms: Independent Samples T-Tests Comparing Smokers and Nonsmokers

Symptom	Mean Scores		Ranges	t-test (72)
	Smokers	Nonsmokers		
1- Fatigue	5.62 (2.63)	4.22 (2.93)	0-8, 0-6	2.15*, p<.05
2-Muscle/joint aches or pains	5.03 (2.67)	4.11 (2.97)	0-8, 0-8	1.39, p=.17
3-Mental changes	3.79 (2.95)	3.17 (3.10)	0-8, 0-8	.885, p=.38
4-Headaches	3.36 (2.66)	2.06 (2.70)	0-8, 0-8	2.09*, p<.05
5- Fluid Retention	2.92 (3.03)	2.09 (2.72)	0-8, 0-8	1.25, p=.22
5-Itchiness	2.44 (2.84)	2.46 (2.72)	0-8, 0-8	-.03, p=.97
7- Poor appetite	2.77 (2.83)	1.31 (2.29)	0-8, 0-8	2.14*, p<.05

Note: Standard Deviations for each group are given in parentheses.
     Range for smoking group given first, followed with range for nonsmoking group.
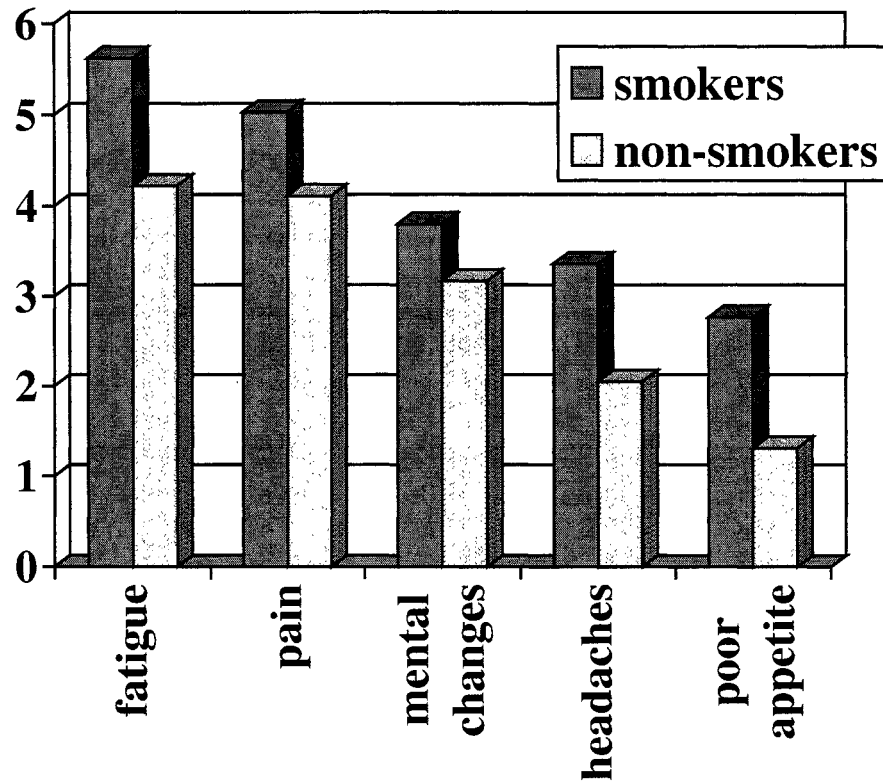
Figure 9. Liver Disease Symptoms: Group Means of Smokers and Nonsmokers

Table 13

Biochemical Markers: Independent Samples T-Tests Comparing Smokers and Nonsmokers

Biochemical Markers	Mean Scores		Ranges	t-test (72)
	Smokers	Nonsmokers		
1- AST Levels	75.95 (66.84)	65.51 (64.58)	17-403, 15-296	.681, p=.49
2-ALT Levels	83.38 (75.17)	71.11 (68.18)	13-407, 14-328	.732, p=.47
3-Platelet Counts	159.7 (88.69)	188.03 (88.84)	43-414, 49-353	-1.37, p=.18
4-Bilirubin	.86 (.81)	.77 (.63)	.30-3.4, .20-4.00	.577, p=.57
5- Albumin	4.70 (5.68)	3.94 (.61)	2.2-39, 2.2-4.90	.789, p=.43
6-APRI	1.76 (2.57)	1.25 (1.44)	.18-14.93, .12-4.8	1.05, p=.30

Note: Standard Deviations for each group are given in parentheses.
Range for smoking group given first, followed with range for nonsmoking group.
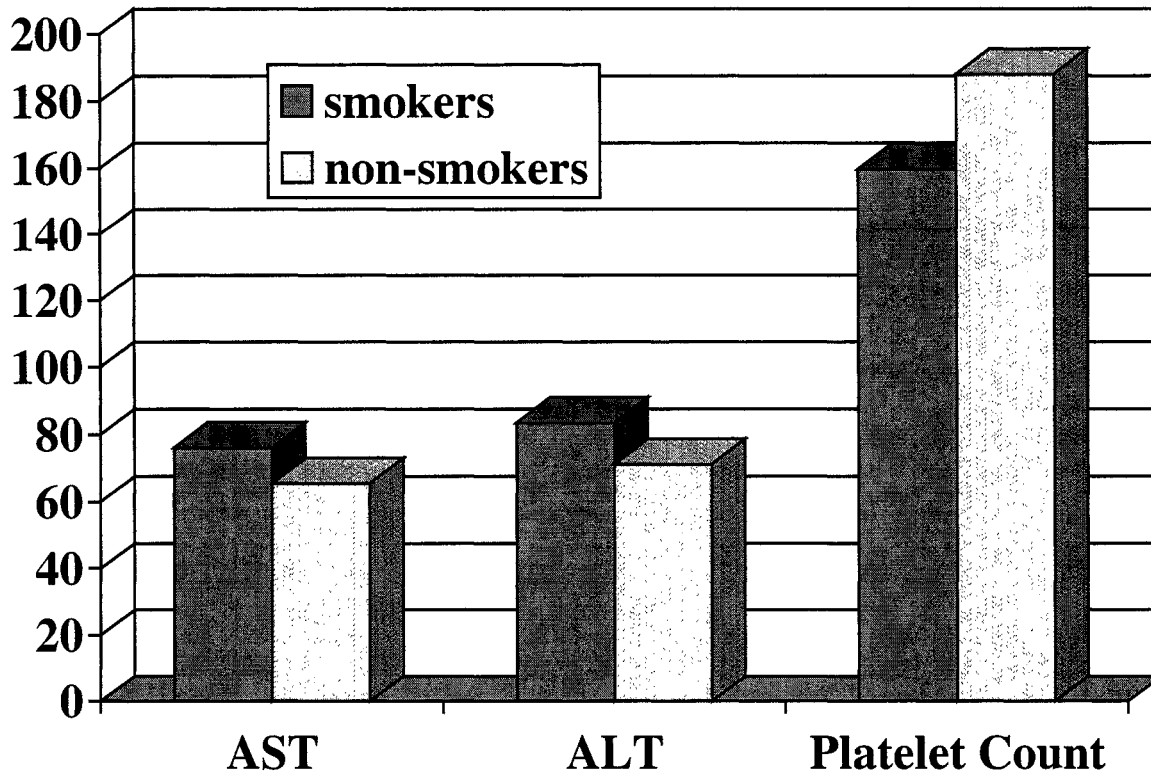
Figure 10. Biochemical Markers: Group Means of Smokers and Nonsmokers

analyses are presented in Table 14 on page 94 and Figures 11 and 12 on page 96 and 97,

respectively. No significant differences were found between the three groups; however,

group differences in fatigue scores and poor appetite scores are trending toward

significance. Although no significant difference was found between the groups on the

APRI score, smokers consuming more than 1 pack per day ($\underline{M}$= 2.17, $\underline{SD}$= 3.58) tended

to present with higher scores then smokers ($\underline{M}$=1.42, $\underline{SD}$= 1.16) consuming less than 1

pack per day and nonsmokers ($\underline{M}$= 1.25, $\underline{SD}$= 1.45). The mean scores of smokers

consuming less than 1 pack per day and nonsmokers are below the higher cut-off value of

2.00 that indicates a .93 negative predictive value for the presence of cirrhosis (Wai et al.,

2003). Hence, these patients may be less likely to have cirrhosis compared to the

smokers who consume more than 1 pack per day.

   Hypothesis 4: Relationship between Hepatitis C progression and quality of life

outcomes. The fourth hypothesis investigated the relationship between hepatitis C and

quality of life outcomes. The correlations between liver disease biochemical markers,

liver disease symptoms, and quality of life outcomes are presented in Table 11 on page

86. As predicted, participants who presented with more severe liver disease tended to

report lower levels of quality of life. A significant negative correlation was found

between liver disease severity as measured by the APRI and the physical component

score from the SF-36 ($\underline{r}$ = -.417, $\underline{p}$ <.001). Likewise, a significant negative correlation

was found between liver disease symptom severity and the physical component score of

the SF-36 ($\underline{r}$ = -.783, $\underline{p}$ <.001). As anticipated, a significant negative correlation was also

found between liver disease symptom severity and the mental component score of the SF-

Table 14

MANOVA's for Group Comparisons: Preliminary Hypothesis 3

Dependent Variable	Means	Ranges	F	p
Model 1. Liver Disease Symptoms				
Fatigue			2.84	065 ns
1 or more packs	6.11 (2.16)	0-8		
Less than 1 pack	5.19 (2.96)	0-8		
Nonsmoker	4.22 (2.93)	0-8		
Infection			.230	.795 ns
1 or more packs	1.28 (2.11)	0-6		
Less than 1 pack	.95 (1.75)	0-5		
Nonsmoker	.91 (1.90)	0-8		
Itchiness			.023	.977 ns
1 or more packs	2.33 (2.89)	0-8		
Less than 1 pack	2.52 (2.86)	0-8		
Nonsmoker	2.46 (2.72)	0-8		
Fluid Retention			1.48	.234 ns
1 or more packs	2.33 (3.16)	0-8		
Less than 1 pack	3.43 (2.89)	0-8		
Nonsmoker	2.09 (2.72)	0-8		
Mental Changes			.510	.603 ns
1 or more packs	4.06 (2.98)	0-8		
Less than 1 pack	3.57 (2.99)	0-8		
Nonsmoker	3.17 (3.10)	0-8		
Poor appetite			3.02	.055 ns
1 or more packs	3.00 (3.22)	0-8		
Less than 1 pack	2.57 (2.52)	0-8		
Nonsmoker	1.31 (2.29)	0-8		
Muscle/joint pain			1.03	.361 ns
1 or more packs	4.83 (2.79)	0-8		
Less than 1 pack	5.19 (2.62)	0-8		
Nonsmoker	4.11 (2.97)	0-8		

Note: ns= not significant. Standard Deviations for each group are given in parentheses

Table 14

Continues

Dependent Variable	Means	Ranges	F	p
Model 2. Biochemical Markers				
AST Levels			.713	.494 ns
1 or more packs	87.11 (90.98)	21-403		
Less than 1 pack	66.38 (35.27)	17-126		
Nonsmoker	65.51 (64.58)	15-296		
ALT Levels			2.38	.100 ns
1 or more packs	108.33 (95.71)	30-407		
Less than 1 pack	62.00 (43.71)	13-196		
Nonsmoker	71.11 (68.19)	14-328		
Platelet Counts			1.26	.291 ns
1 or more packs	172.06 (97.35)	43-414		
Less than 1 pack	149.09 (81.46)	52-294		
Nonsmoker	188.03 (88.85)	49-353		
Bilirubin			1.08	.347 ns
1 or more packs	.69 (.71)	.30-3.4		
Less than 1 pack	1.01 (2.9)	.3-2.9		
Nonsmoker	.77 (.64)	.2-4.00		
Albumin			1.79	.175 ns
1 or more packs	5.92 (8.28)	2.9-39		
Less than 1 pack	3.66 (.82)	2.2-4.7		
Nonsmoker	3.94 (.61)	2.2-4.9		
APRI			1.17	.316 ns
1 or more packs	2.17 (3.58)	.18-14.93		
Less than 1 pack	1.42 (1.16)	.25-4.05		
Nonsmoker	1.25 (1.43)	.12-4.80		

Note: ns= not significant. Standard Deviations for each group are given in parentheses.
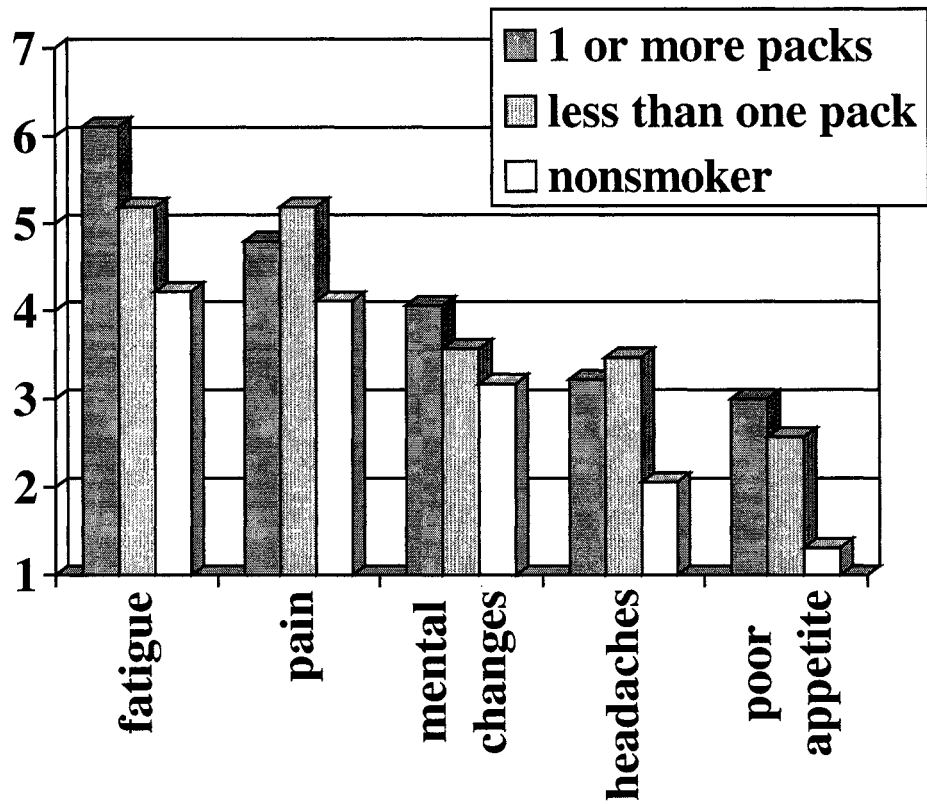
Figure 11. Liver Disease Symptoms: Means of Smoking Groups Based on Level of Cigarette Consumption.
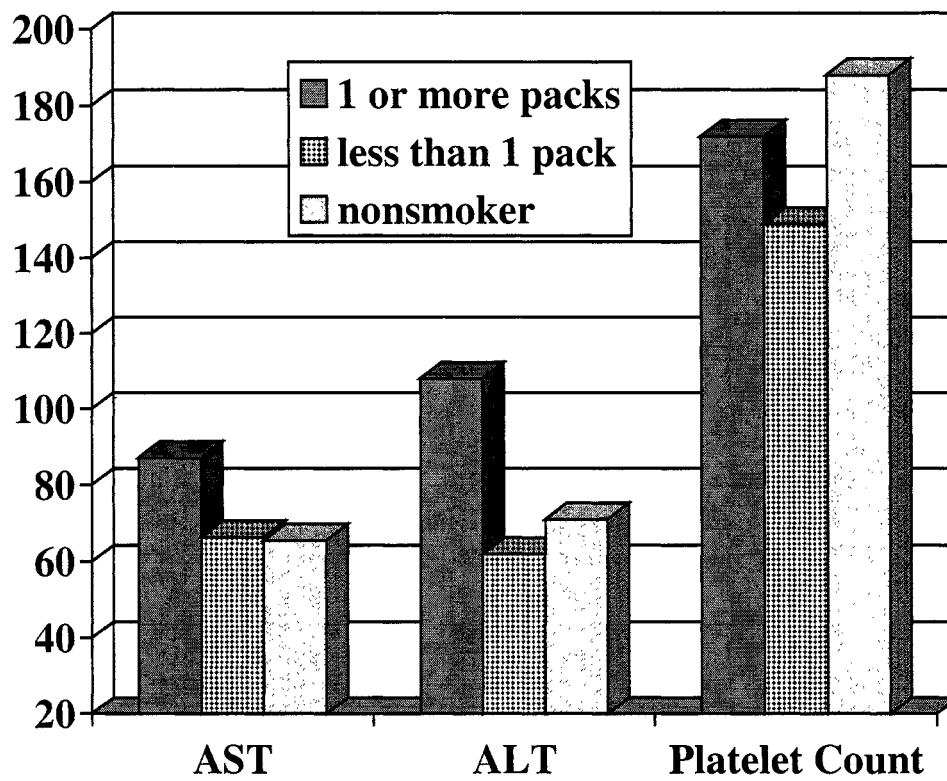
Figure 12. Biochemical Markers: Means of Smoking Groups Based on Level of Cigarette Consumption.

36 ($\underline{r}$ = -.687, $\underline{p}$ < .001). Significant correlations were also revealed between subscales of the SF-36. The role-physical functioning subscale was negative correlated with liver disease severity ($\underline{r}$=-.736, $\underline{p}$<.001). In addition, a negative correlation was found between liver disease severity and the social functioning subscale of the SF-36 ($\underline{r}$=-.703, $\underline{p}$<.001).

Finally, one-sample t-tests comparing the means of the hepatitis C sample and the general population found that patients with hepatitis C reported significantly lower levels of quality of life. The mean of the physical component score of the SF-36 for the hepatitis C sample ($\underline{M}$=42.33, $\underline{SD}$=12.26) was significantly lower than the mean for the general population ($\underline{M}$=49.29, $\underline{SD}$=9.33), $\underline{t}$(75)=-4.950, $\underline{p}$<.001. Similarly, the mean of the mental component score for the hepatitis C sample ($\underline{M}$=42.17, $\underline{SD}$= 13.99) was significantly lower than the mean for the general population ($\underline{M}$= 52.58, $\underline{SD}$=8.73), $\underline{t}$(75)=-6.48, $\underline{p}$<.001.

Main Hypotheses

Hypothesis 1: Tobacco use as a risk factor in the hepatitis C population

Hypothesis 1A: Tobacco use an independent factor in liver disease progression.
A hierarchical multiple regression analysis was employed to investigate the independent effects of tobacco use in predicting liver disease progression. The Cook's distance measure D was implemented to identify multivariate outliers. One participant was removed from the analysis with a value above 2.0, which was labeled as a potential outlier. Note that this was the only participant removed from all hierarchical multiple regression analyses due to being a potential outlier. Partial correlations for the variables are presented at each step of the analyses. This statistic provides information on the

unique contribution of each measured variable. The results of the analyses are displayed in Table 15 on page 100. The hierarchical multiple regression analysis did not reveal an independent main effect for tobacco use on liver disease progression, above and beyond the variance accounted for by demographic variables and alcohol consumption.

Hypothesis 1B: Tobacco use effects on quality of life. Hierarchical multiple regression analyses were employed to investigate the independent effects of tobacco use in predicting quality of life outcomes in the hepatitis sample. Four separate models were run. The first two models explored the main effect of tobacco use on the physical component score and mental component score of the SF-36, respectively. No main effects for tobacco use were found. The results from these analyses are presented in Table 15 on page 100. The other two models examined the main effect of tobacco use on two subscales of the SF-36, role-physical functioning and social functioning. Based on the literature, hepatitis C patients report the biggest decline of functioning in these two areas of QOL. A main effect for tobacco use, above and beyond the variance accounted for by demographic variables and alcohol consumption, was found on the social functioning subscale, $p<.05$. The results can be found in Table 15. No significant main effect for tobacco use was determined for the role-physical functioning subscale.

Furthermore, independent samples t-tests revealed that smokers ($\underline{M}$= 55.77, $\underline{SD}$= 32.80) reported experiencing a lower quality of life on the social functioning subscale of the SF-36 compared to nonsmokers ($\underline{M}$= 71.96, $\underline{SD}$= 28.47, $\underline{t}(74)$=-2.29, $\underline{p}<.05$). Table 16 on page 101 and Figure 13 on page 102 display these findings. Significant results were also found when comparing these two groups with the means from the general population

Table 15

Hierarchical Multiple Regression Models for the Prediction of Liver Disease and Quality of Life from Tobacco Use

Step and Variable	R	ΔR	ΔF	Overall F	Partial r
Model 1: Predicting Liver Disease Progression: APRI					
1. Age, Gender	.092	.092	3.6*		-.09, -.289*
2 Alcohol Use	.099	.007	.538		-.087
3. Smoking	.118	.018	1.44	$F(4,69)= 2.3$	-.143
Model 1: Predicting Quality of Life: Physical Component					
1. Age, Gender	.02	.02	.748		.07, .122
2. Alcohol Use	.056	.036	2.73		.191
3. Smoking	.103	.048	3.77	$F(4, 71) = 2.05$	.224
Model 2: Predicting Quality of Life: Mental Component					
1. Age, Gender	.074	.074	2.9		.24, -.11
2. Alcohol Use	.092	.019	1.48		.142
3. Smoking	.094	.002	.155	$F(4, 71)=1.85$	.047
Model 3: Predicting Quality of Life: Role-Physical Functioning					
1. Age, Gender	.002	.002	.085		.036, -.031
2. Alcohol Use	.045	.043	3.23		.207
3. Smoking	.071	.026	2.00	$F(4, 71)=1.36$	.167
Model 4: Predicting Quality of Life: Social Functioning					
1. Age, Gender	.056	.056	2.16		.182, .155
2. Alcohol Use	.096	.040	3.21		.207
3.Smoking	.144	.047	3.93*	$F(4, 71)=2.97*$	.229*

Note: The partial correlations signify the unique contribution of each variable.
*$p<.05$ **$p<.01$***$p<.001$

Table 16

Quality of Life: Independent Samples T-Test Comparing Smokers and Nonsmokers

Variable	Mean Scores		Ranges	t-test (74)
	Smokers	Nonsmokers		
1- Physical Comp.	39.90 (10.97)	44.90 (13.16)	18-56, 15-62	-1.81, p=.07
2-Mental Comp.	40.76 (14.79)	43.66 (13.45)	8-64, 12-66	-.901, p=.37
3-Role-Physical Functioning	52.56 (37.13)	63.51 (35.65)	0-100, 0-100	-1.32, p=.19
4-Social Functioning	55.77 (32.8)	71.96 (29.04)	0-100, 13-100	-2.29*, p<.05

Note: Standard Deviations for each group are given in parentheses.
Range for smoking group given first, followed with range for nonsmoking group.
  * p<.05
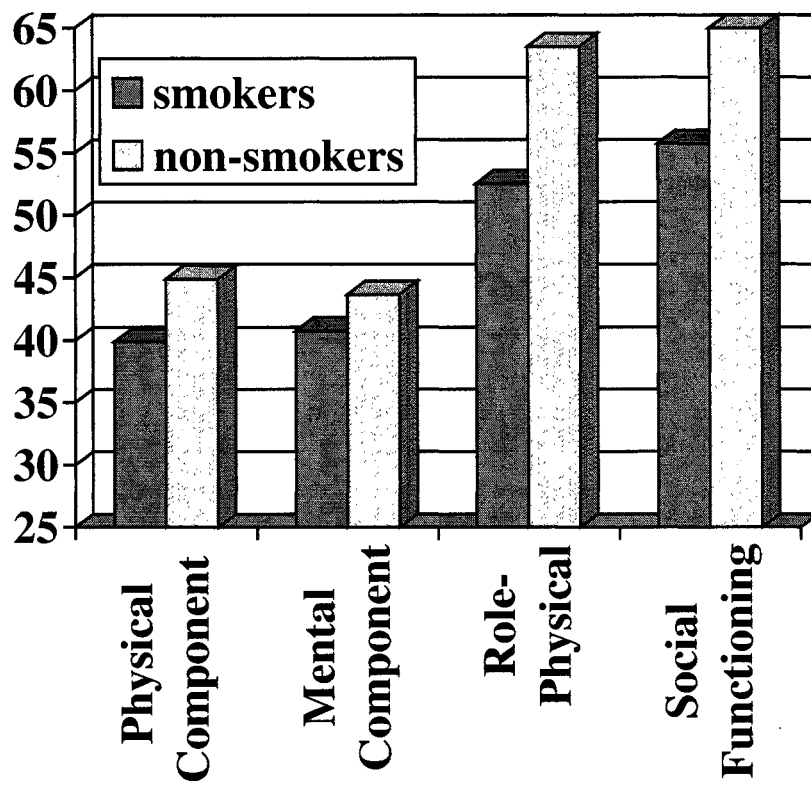
Figure 13. Quality of Life: Group Means of Smokers and Nonsmokers.

on quality of life variables. One sample t-tests determined that smokers ($\underline{M}$= 39.90, $\underline{SD}$= 10.98) reported experiencing a lower quality of life on the physical component score of the SF-36 compared to the general population ($\underline{M}$=49.29, $\underline{SD}$= 8.66), $\underline{t}$(38)=-5.34, $\underline{p}$<.001. Analyses also determined that smokers ($\underline{M}$= 40.76, $\underline{SD}$= 14.79) reported experiencing a lower quality of life on the mental component score of the SF-36 compared to the general population ($\underline{M}$=52.58, $\underline{SD}$= 7.71), $\underline{t}$(38)=-4.99, $\underline{p}$<.001. In addition, one sample t-test determined that nonsmokers reported experiencing a lower quality of life on both the physical ($\underline{M}$=44.9, $\underline{SD}$= 13.13) and mental ($\underline{M}$= 43.66, $\underline{SD}$= 13.14) component scores of the SF-36 compared to the general population, $\underline{t}$(36)= -2.034, $\underline{p}$<.05 and $\underline{t}$(36)= -4.13, $\underline{p}$<.001, respectively. Figure 14 on page 104 displays these findings.

Finally, multivariate analyses of variance were conducted to examine group differences in quality of life in regards to level of nicotine consumption. As before, the three groups represented individuals smoking one or more packs of cigarettes per day, individuals smoking less than one pack per day, and nonsmoker, respectively. One MANOVA was run to compare the groups on quality of life variables. Results from the analyses are presented in Table 17 on page 105 and Figure 15 on page 106. No significant differences were found between the three groups.

Hypothesis 2: The impact of coping strategies: Moderator model- coping strategies in the relationship between liver disease severity and quality of life outcomes

Hierarchical multiple regression analyses investigated the interactive effects of liver disease severity and coping strategies in predicting quality of life. Following the recommendations of Aiken and West (1991) the predictor and moderator variables
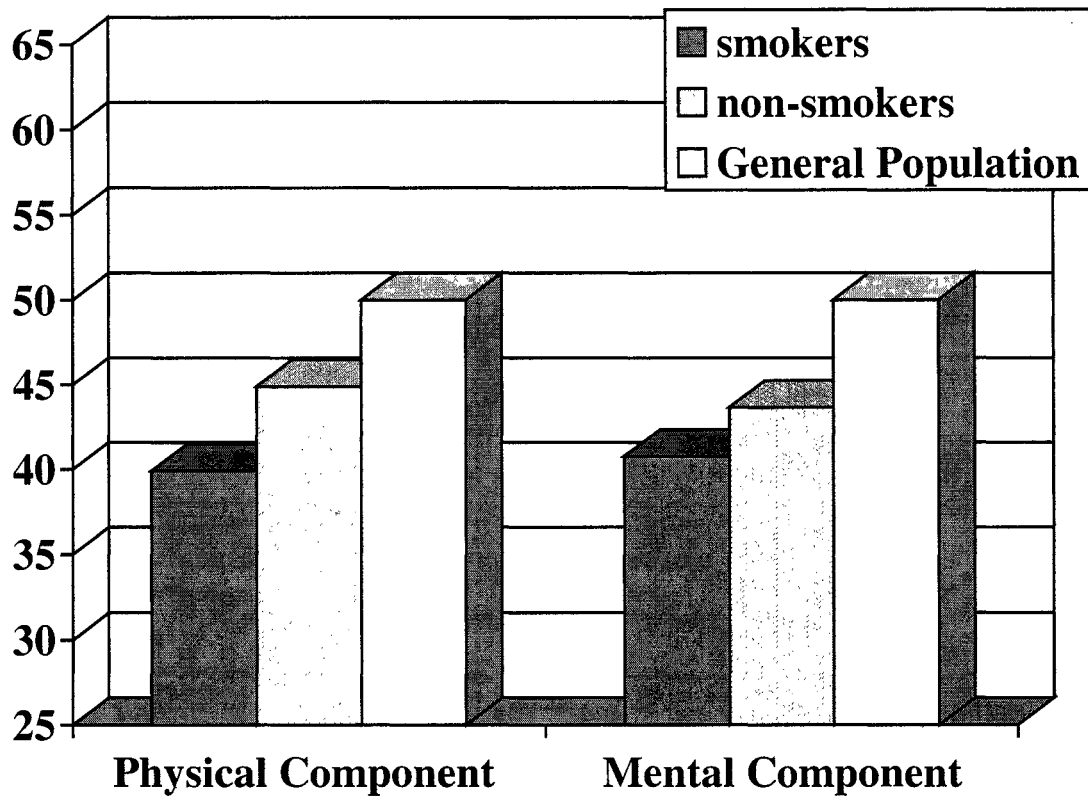
Figure 14. Quality of life: Sample Group Means Compared to the General Population.

Table 17

MANOVA's for Group Comparisons: Main Hypothesis 1B

Dependent Variable	Mean	Range	F	p
Model 1. Quality of Life				
Physical Component			1.61	.207 ns
1 or more packs	40.07 (9.85)	24-56		
Less than 1 pack	39.74 (12.10)	18-56		
Nonsmoker	44.73 (13.16)	15-62		
Mental Component			.403	.670 ns
1 or more packs	40.58 (16.65)	17-64		
Less than 1 pack	40.92 (13.41)	13-63		
Nonsmoker	43.39 (13.45)	12-66		
Role-Physical Functioning			.857	.428 ns
1 or more packs	52.78 (38.06)	0-100		
Less than 1 pack	52.38 (37.26)	6-100		
Nonsmoker	62.50 (35.65)	0-100		
Social Functioning			2.89	.062 ns
1 or more packs	59.72 (32.81)	0-100		
Less than 1 pack	52.38 (33.22)	0-100		
Nonsmoker	71.07 (29.04)	13-100		

Note. ns = not significant. Standard Deviations are given in parentheses.
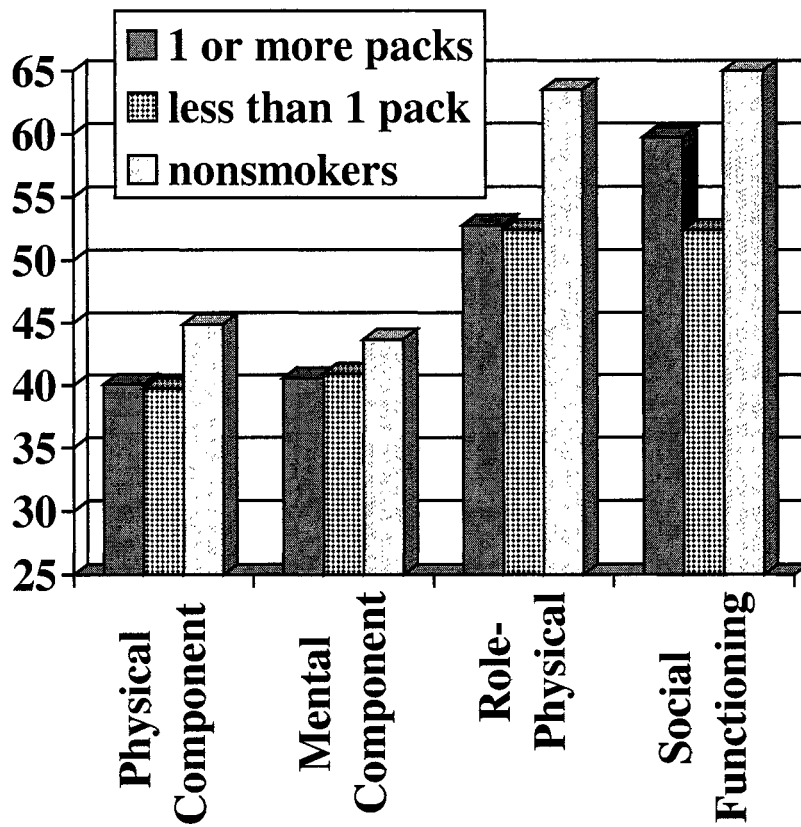
Figure 15. Quality of Life: Means of Smoking Groups Based on Level of Cigarette Consumption.

were centered to minimize problems with multicollinearity. In addition, the Cook's distance measure D was implemented to identify multivariate outliers. The outlier found to be above 2.0 was removed from the analyses. Four models of moderation were examined in the study. Analyses were conducted separately for the two coping strategies, active and avoidant coping and for the two quality of life outcomes, physical component of SF-36, and mental component of SF-36, respectively. The variables were entered hierarchically to follow theoretical conceptualizations. The order consisted of the following: (1) liver disease severity, (2) coping strategies (active and avoidant), and (3) the interaction between liver disease severity and coping strategies. Partial correlations for the variables are presented for the final step of the analyses. This statistic provides information on the unique contribution of each measure variable. The results from the analyses are presented in Table 18 on page 108.

The first model included liver disease severity along with active coping to predict the physical component score of the SF-36 quality of life outcomes measure. A main effect was found for liver disease severity for predicting the physical component of the SF-36. The main effect for liver disease severity suggests that individuals with more severe liver disease tended to report lower quality of life on the physical components of the SF-36 compared to individuals with less severe liver disease. Active coping was found to moderate the relationship between liver disease severity and the physical component of the SF-36. Hierarchical multiple regression analyses revealed a liver disease severity X active coping strategies interaction to predict the physical component of QOL, $p<.01$. The plots of the interaction revealed a strong negative relationship

Table 18

Hierarchical Multiple Regression Models for the Prediction of Quality of Life from Liver Disease Severity and Coping Strategies: Moderator Model

Step and Variable	R	ΔR	ΔF	Overall F	Partial r
Model 1: Active Coping Predicting Physical Component Quality of Life					
1. APRI	.17	.17	15.15***		-.71***
2. Active Coping	.20	.03	2.6		-.07
3. APRI X					
Active Coping	.30	.09	9.18**	F(3,70)= 9.78***	.44**
Model 2: Active Coping Predicting Mental Component Quality of Life					
1. APRI	.02	.02	1.2		-.27
2. Active Coping	.05	.03	2.12		-.12
3. APRI X					
Active Coping	.07	.03	2.03	F(3, 70)= 1.80	.24
Model 3: Avoidant Coping Predicting Physical Component of SF-36					
1. APRI	.17	.17	15.15***		-.40***
2. Avoidant Coping	.28	.10	9.97**		-.30**
3.APRI X					
Avoidant Coping	.28	.01	.87	F(3, 70)=9.27***	.10
Model 4: Avoidant Coping Predicting Mental Component of SF-36					
1. APRI	.02	.02	1.2		-.08
2. Avoidant Coping	.32	.31	32.12***		-.53***
3. APRI X					
Avoidant Coping	.33	.01	.95	F(3, 70)= 11.59***	-.10

Note: Partial Correlations are from the final step of the regression model. This signifies the unique contribution of each variable.

*p<.05**; p<.01; ***p<.001; APRI= AST to platelet count ratio index

between liver disease severity and the physical component of quality of life for individuals who use a low level of active coping. The interaction is displayed in Figure 16 on page 110. A negative relationship was also found for individuals who use high levels of active coping. In general, high active copers reported higher levels of quality of life compared to low active copers when experiencing more severe liver disease. Conversely, low active copers reported higher levels of quality of life compared to high active copers when experiencing less severe liver disease.

The second model included liver disease severity along with active coping to predict the mental component of the SF-36 QOL. No main effects or interactions were found in this model. The results from this analysis can be found in Table 18 on page 108. The third and fourth models included liver disease severity along with avoidant coping to predict two separate components of the SF-36 general quality of life outcomes measure, physical and mental components. Results for both models are displayed in Table 18. A main effect was found for avoidant coping strategies on both the physical and mental components of QOL, but no interactions were revealed. The main effect for avoidant coping strategies suggests that participants reporting higher levels of avoidant coping were also tending to report lower levels of quality of life on both the physical and mental components compared to individuals reporting lower levels of avoidant coping. Main effects are presented in Figure 17 and 18 on page 111 and 112, respectively. Avoidant coping was not found to moderate the relationship between liver disease severity and quality of life outcomes.
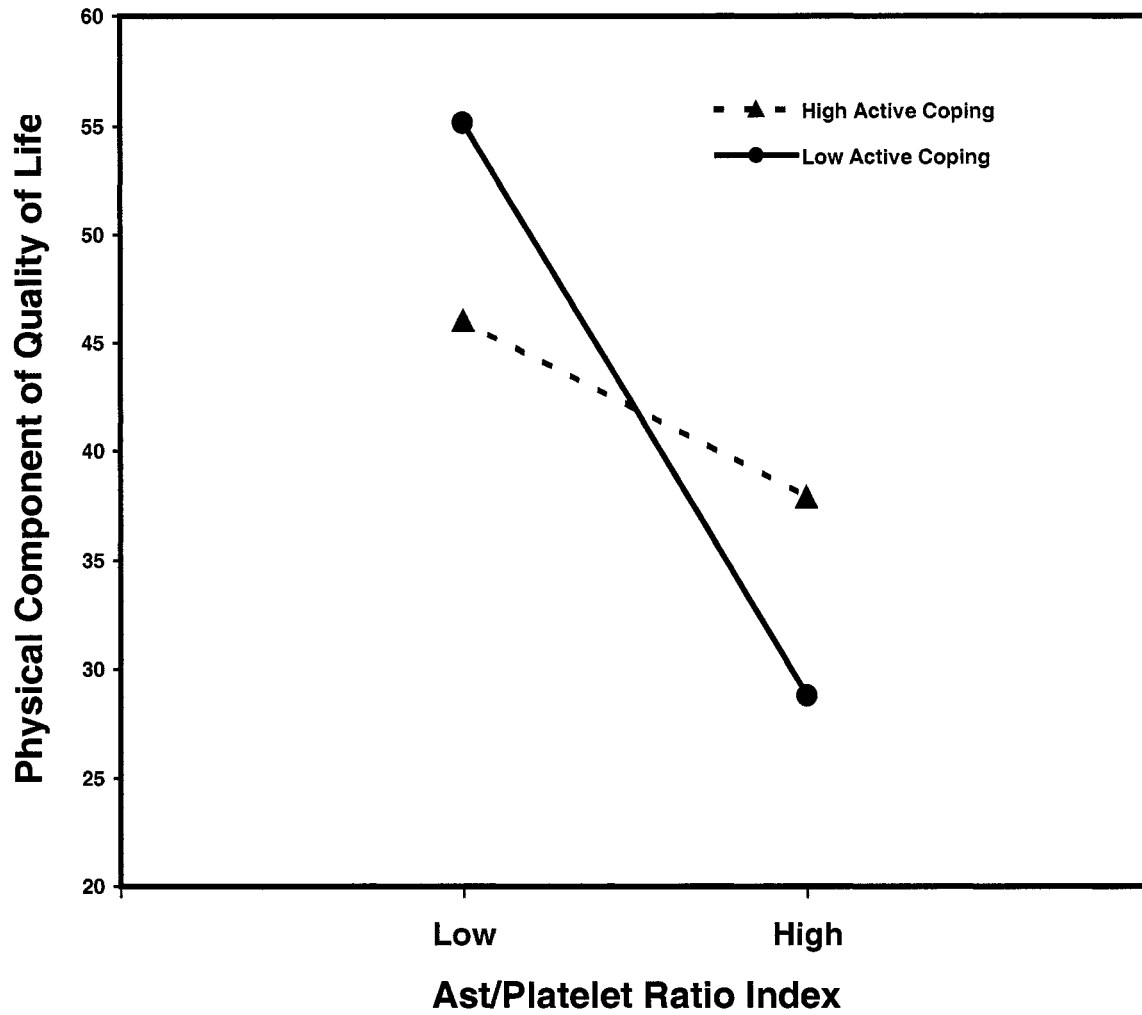
Figure 16. Moderation Model: Active Coping and Liver Disease Severity for Physical Component QOL
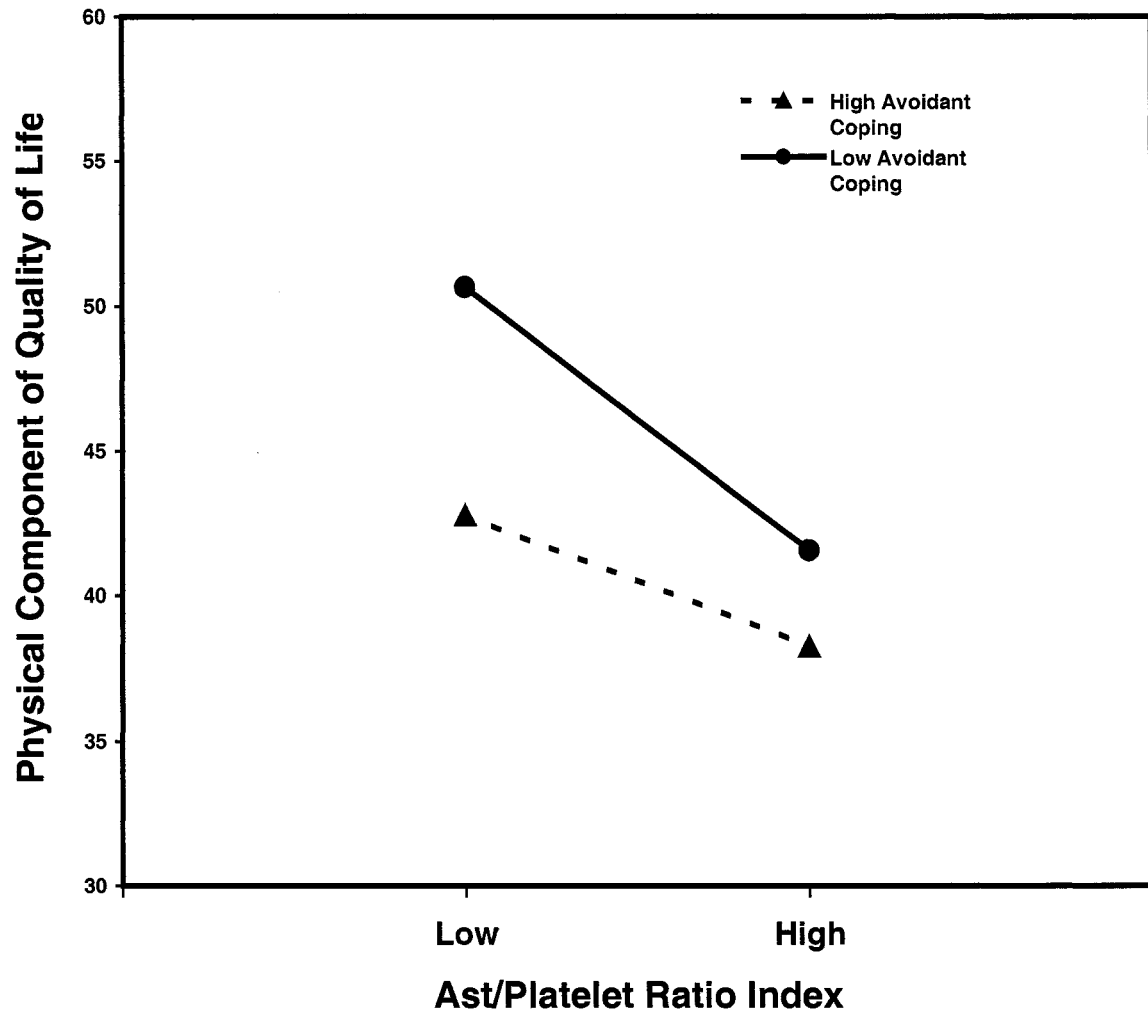
Figure 17. Main Effects for Avoidant Coping on Physical Component of QOL.
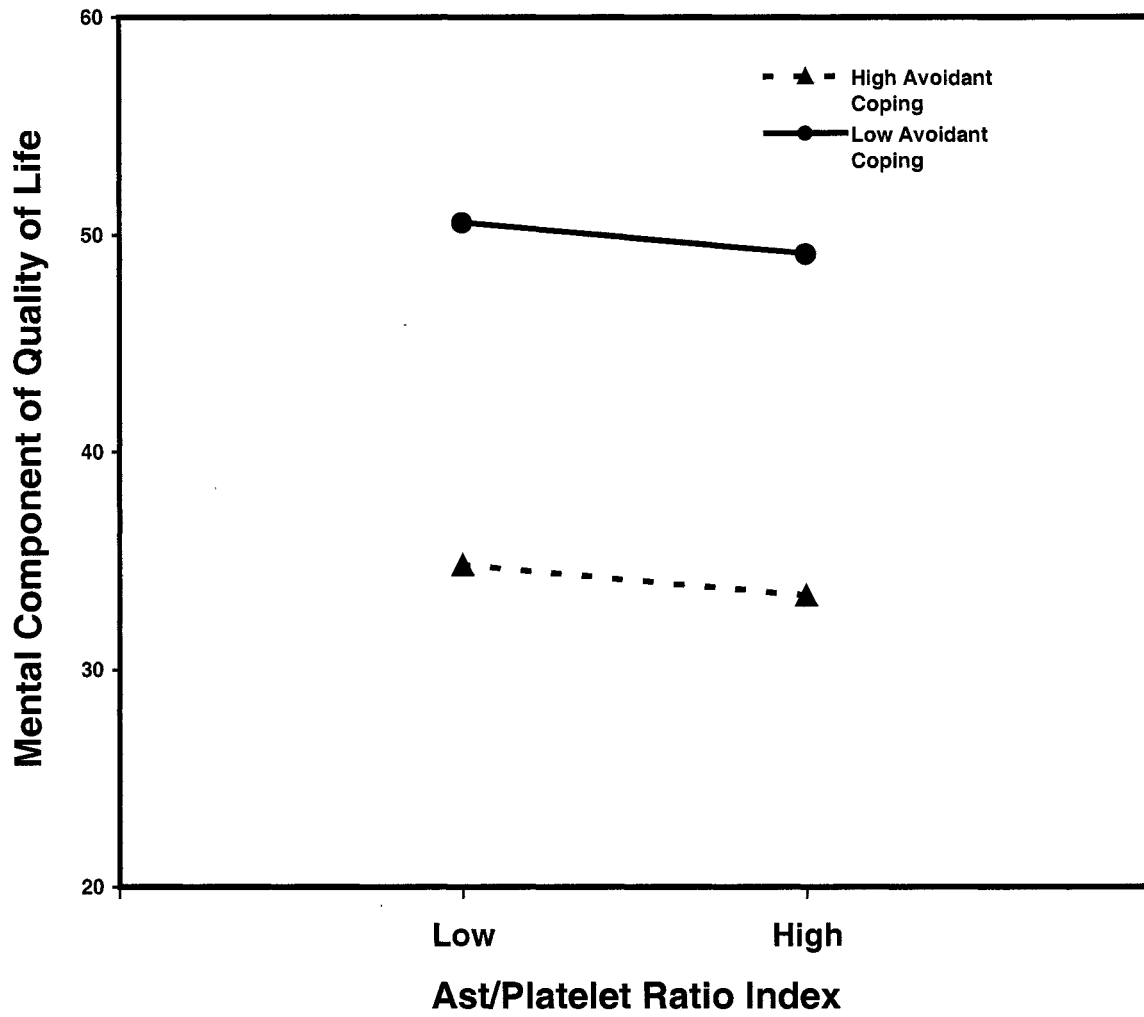
Figure 18. Main Effects for Avoidant Coping on Mental Component of QOL.

Hypothesis 3: The impact of psychosocial factors on quality of life: Competing moderator and mediator models

Hypothesis 3A: Moderator model-psychological distress in the relationship between liver disease severity and quality of life. Hierarchical multiple regression analyses were employed to investigate the interactive effects of psychological distress and liver disease severity in predicting quality of life outcomes. Following the recommendations of Aiken and West (1991) the predictor and moderator variables were centered to minimize problems with multicollinearity. In addition, the Cook's distance measure D was implemented to identify multivariate outliers. Outliers above 2.0 were removed from the analyses. One potential outlier was identified and removed from all analyses. Two models of moderation were examined. Analyses were conducted separately for the two main components of the SF-36, the physical and mental components, respectively. Partial correlations for the variables are presented for the final step of the analyses. This statistic provides information on the unique contribution of each measured variable.

The two models included liver disease severity along with psychological distress to predict the mental and physical components of the SF-36 QOL. A main effect was found for psychological distress on both the physical and mental components of QOL, but no interactions were revealed. As found in previous analyses, a main effect was also found for liver disease severity on the physical component of QOL. The results from this analysis can be found in Table 19 on page 114. The main effects for psychological

Table 19

Hierarchical Multiple Regression Models for the Prediction of Quality of Life from Liver Disease Severity and Psychological Distress: Moderator Model

Step and Variable	R	ΔR	ΔF	Overall F	Partial r
Model 1: Physical Component Quality of Life					
1. APRI	.38	.38	21.63***		-.08*
GSI					-.50***
2. APRI X					
GSI	.40	.02	1.87	F(3,69)= 15.22***	-.73
Model 2: Mental Component Quality of Life					
1. APRI	.48	.48	32.48***		.69
GSI					-.65***
2. APRI X					
GSI	.50	.02	2.31	F(3, 69)= 22.82***	.74

Note: Partial Correlations are from the final step of the regression model. This signifies the unique contribution of each variable.

*p<.05**; p<.01; ***p<.001;

APRI= AST to platelet count ratio index, GSI= Global Severity Index

distress suggests that participants reporting higher levels of psychological distress were also tending to report lower levels of quality of life on both the physical and mental components compared to individuals reporting lower levels of psychological distress. Main effects are presented in Figure 19 and 20 on page 116 and 117, respectively. Psychological distress was not found to moderate the relationship between liver disease severity and quality of life outcomes.

Hypothesis 3B: Mediator model- psychological distress in the relationship between liver disease severity and quality of life. A four-step procedure (Holmbeck, 1997; Baron and Kenny, 1986) utilizing multiple regression analyses was used to test the mediation model. The procedure is outlined below. First, a relationship between the predictor (liver disease severity) and the outcome (quality of life) must be established. Secondly, the relationship between mediator (psychological distress) and the outcome must be established. Next, a relationship between the predictor and the mediator must be established. Finally, the relationship between the predictor and the outcome should be significantly reduced after controlling for the effects of the mediator. Prior analyses in this study revealed that the first three criteria for the mediating model were not met. This is presented in Table 20 on page 118.

Hypothesis 3C: Moderator model-substance use in the relationship between liver disease severity and quality of life. Hierarchical multiple regression analyses were employed to investigate the interactive effects of substance use (i.e., tobacco use, alcohol consumption, marijuana use) and liver disease severity in predicting quality of life
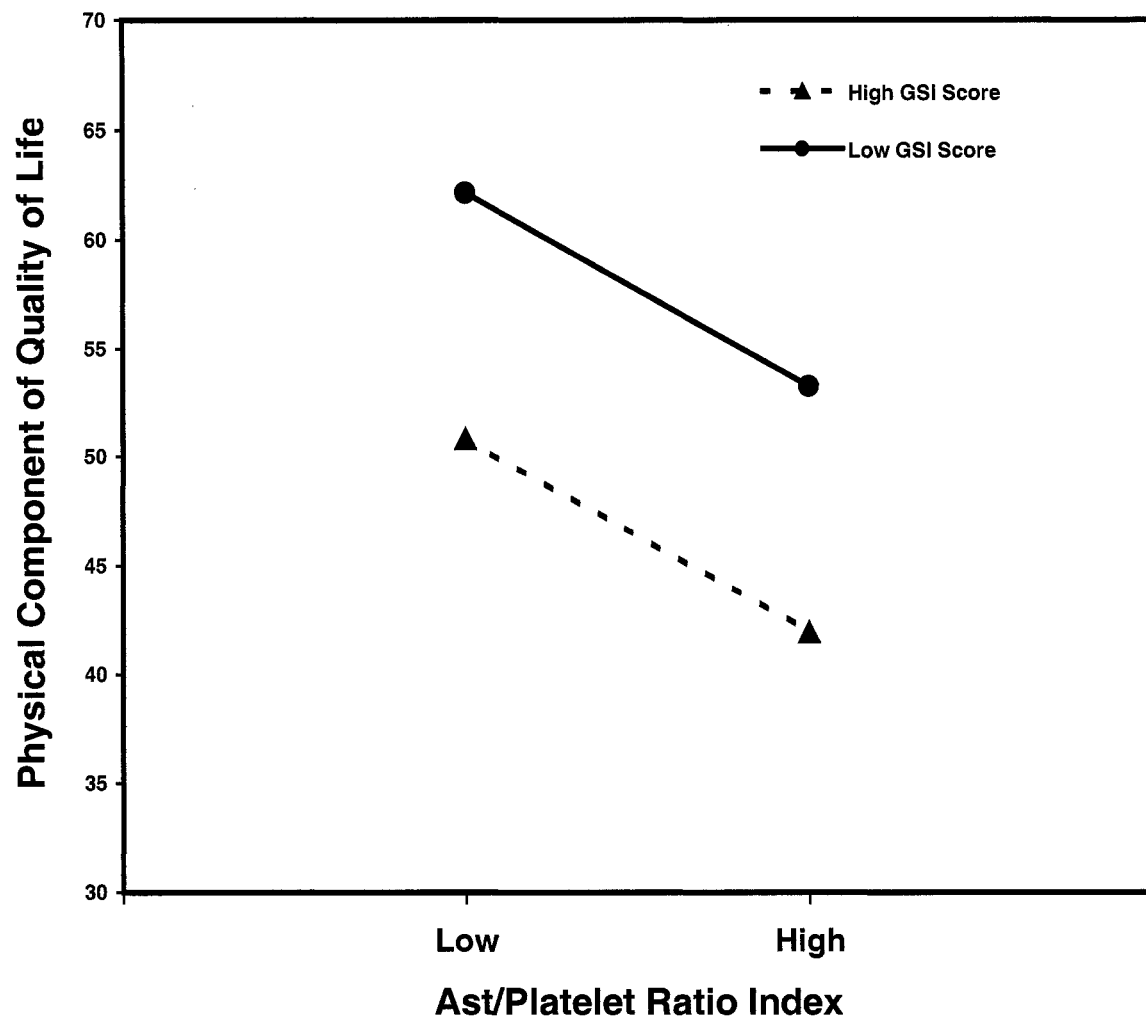
Figure 19. Main Effects for Psychological Distress on Physical Component of QOL.
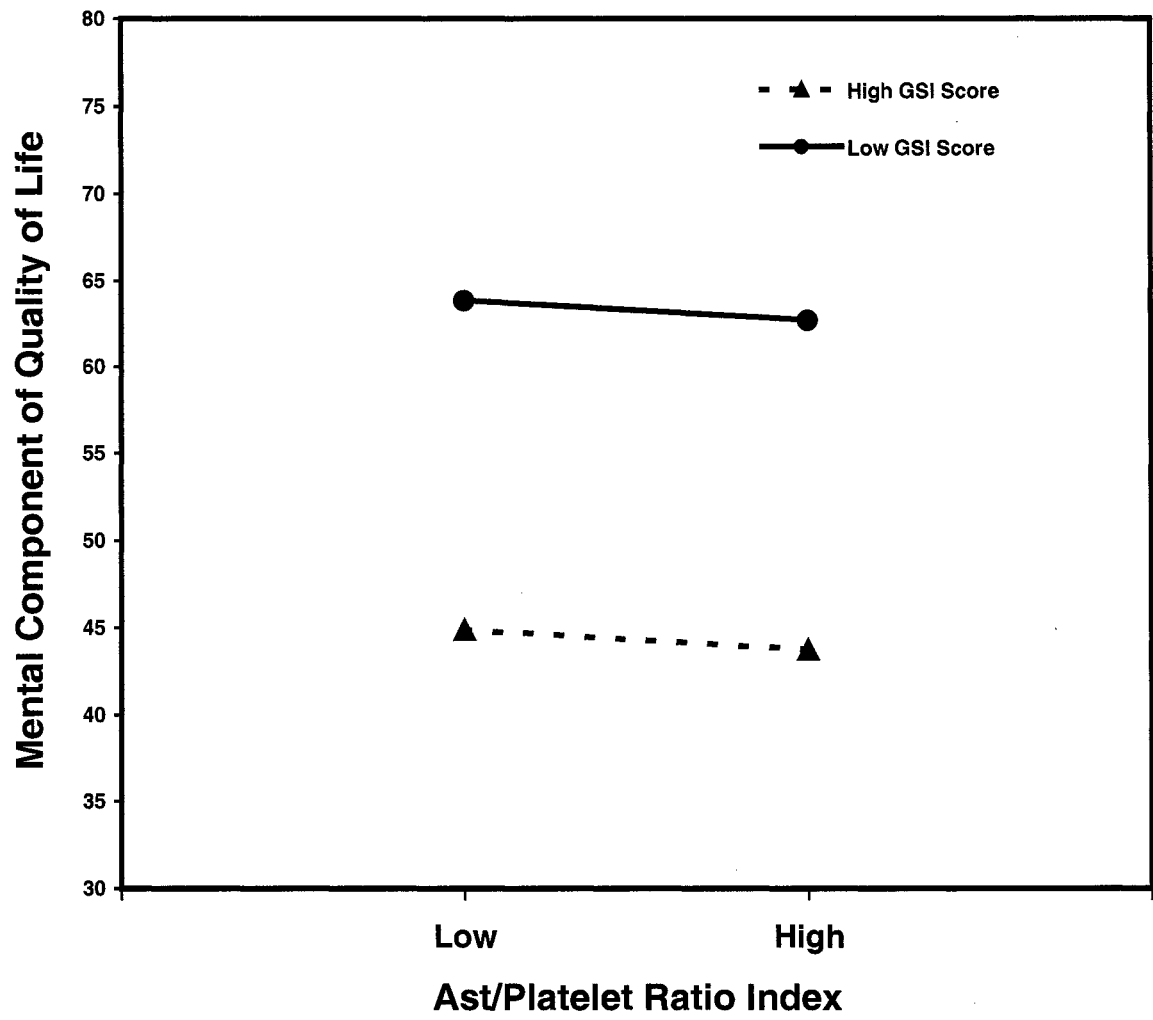
Figure 20. Main Effects for Psychological Distress on Mental Component of QOL.

Table 20

Mediator Models for Psychological Distress and Substance Use

IV	Possible Mediator	DV	IV→DV r	Med.→DV r	IV→Med. r	IV→DV partial r
APRI	GSI	Physical QOL	-.417**	-.501**	.104 ns (no mediation)	
APRI	GSI	Mental QOL	-.104 ns (no mediation)			
APRI	Tobacco Use	Physical QOL	-.417**	.199 ns (no mediation)		
APRI	Tobacco Use	Mental QOL	-.104 ns (no mediation)			
APRI	Alcohol Use	Physical QOL	-.417**	.165 ns (no mediation)		
APRI	Alcohol Use	Mental QOL	-.104 ns (no mediation)			
APRI	Marijuana Use	Physical QOL	-.417**	-.201 ns (no mediation)		
APRI	Marijuana Use	Mental QOL	-.104 ns (no mediation)			

Note: ns = not significant, * $p<.05$, ** $p< .01$, *** $p<001$. IV = Independent Variable, DV = Dependent Variable

r from prior analyses to determine if the first three criteria for mediation have been met.

partial r from hierarchical multiple regression analyses

outcomes. Following the recommendations of Aiken and West (1991) the predictor and moderator variables were centered to minimize problems with multicolinearity. In addition, the Cook's distance measure D was implemented to identify multivariate outliers. Outliers above 2.0 were removed from the analyses. One potential outlier was identified and removed from all analyses. Six models of moderation were examined. Analyses were conducted separately for the three substances (i.e. tobacco, alcohol, marijuana) and the two main components of the SF-36, the physical and mental components, respectively.

The first two models included liver disease severity along with tobacco use to predict the mental and physical components of the SF-36 QOL. No main effects were found for tobacco use; however, two interactions were revealed. The results from this analysis can be found in Table 21 on page 120. Hierarchical multiple regression analyses revealed a liver disease severity X tobacco use interaction to predict the physical component of QOL, $p<.001$. The plots of the interaction revealed a strong negative relationship between liver disease severity and the physical component of quality of life for individuals who were smokers. The interaction is displayed in Figure 21 on page 121. A negative relationship was also found for individuals who were nonsmokers. In general, smokers reported lower levels of quality of life compared to nonsmokers when experiencing less severe liver disease. Conversely, smokers reported a higher level of quality of life on the physical component compared to non-smokers when experiencing more severe liver disease.

Table 21

*Hierarchical Multiple Regression Models for the Prediction of Quality of Life
from Liver Disease Severity and Substance Use: Moderator Model*

Step and Variable	$\underline{R}$	$\Delta\underline{R}$	$\Delta\underline{F}$	Overall $\underline{F}$	Partial r
Model 1: Tobacco Use Predicting Physical Component of Quality of Life					
1. APRI					-.55***
Tobacco Use	.20	.20	8.65***		-.14
2. APRI X					
Tobacco Use	.35	.16	16.72***	F(3,70)=12.62***	.44***
Model 2: Tobacco Use Predicting Mental Component of Quality of Life					
1. APRI					-.27*
Tobacco Use	.02	.02	.817		-.06
2. APRI X					
Tobacco Use	.08	.06	4.35*	F(3,70)=2.02	.24*
Model 3: Alcohol Use Predicting Physical Component of Quality of Life					
1. APRI					.02
Alcohol Use	.19	.19	8.1**		.08
2.APRI X					
Alcohol Use	.21	.02	1.7	F(3, 70)=6.01**	-.15
Model 4: Alcohol Use Predicting Mental Component of Quality of Life					
1. APRI					.06
Alcohol Use	.02	.02	.68		.02
2. APRI X					
Alcohol Use	.03	.01	.68	F(3, 70)= .67	-.10

Note: Partial correlations are from the final step of the regression model. This signifies
the unique contribution of each variable.
*p<.05
**p<.01
***p<.001
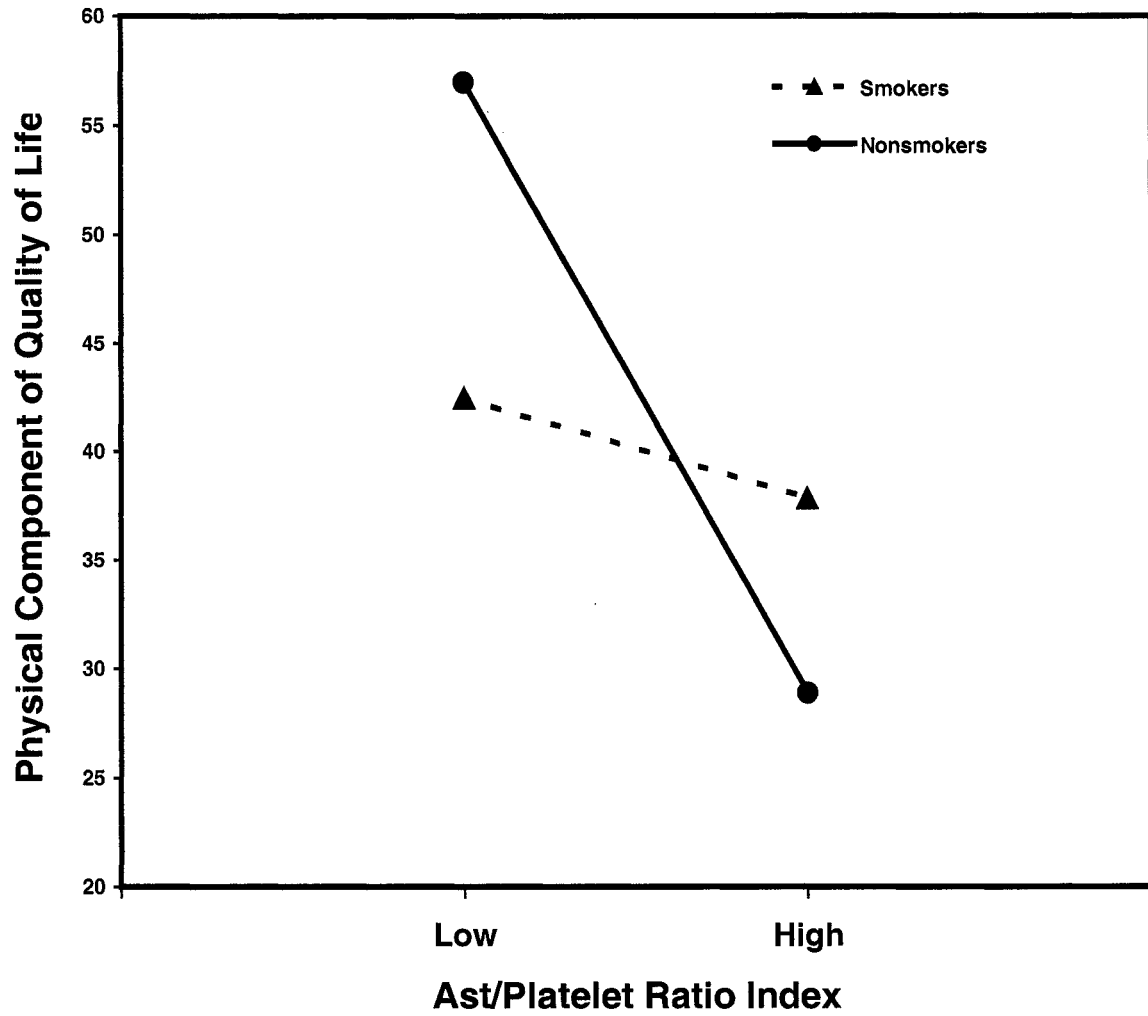
Figure 21. Moderation Model: Smoking and Liver Disease Severity on Physical
Component of QOL

Tobacco use was also found to moderate the relationship between liver disease severity and the mental component of quality of life outcomes. Hierarchical multiple regression analyses revealed a liver disease severity X tobacco use interaction to predict the mental component of QOL, $p<.05$. The plots of the interaction revealed a strong negative relationship between liver disease severity and the mental component of quality of life for individuals who were smokers. The interaction is displayed in Figure 22 on page 123. In general, smokers reported lower levels of the mental component of quality of life compared to nonsmokers when experiencing less severe liver disease. Conversely, smokers reported a higher level of quality of life on the mental component compared to nonsmokers when experiencing more severe liver disease.

The third and fourth models included liver disease severity along with alcohol consumption to predict the mental and physical components of the SF-36 QOL. The results from these analyses can be found in Table 21 on page 120. No main effects were indicated for alcohol consumption. In addition, alcohol consumption was not found to moderate the relationship between liver disease severity and quality of life outcomes.

The final two models included liver disease severity along with marijuana use to predict the mental and physical components of the SF-36 QOL. A main effect was found for marijuana use on the mental components of QOL, but no interactions were revealed. The results from this analysis can be found in Table 22 on page 124. The main effect for marijuana use suggests that those who reported using marijuana were also tending to report lower levels of quality of life on the mental component of quality of life compared to individuals who reported no use of marijuana. The main effect is presented in Figure

123
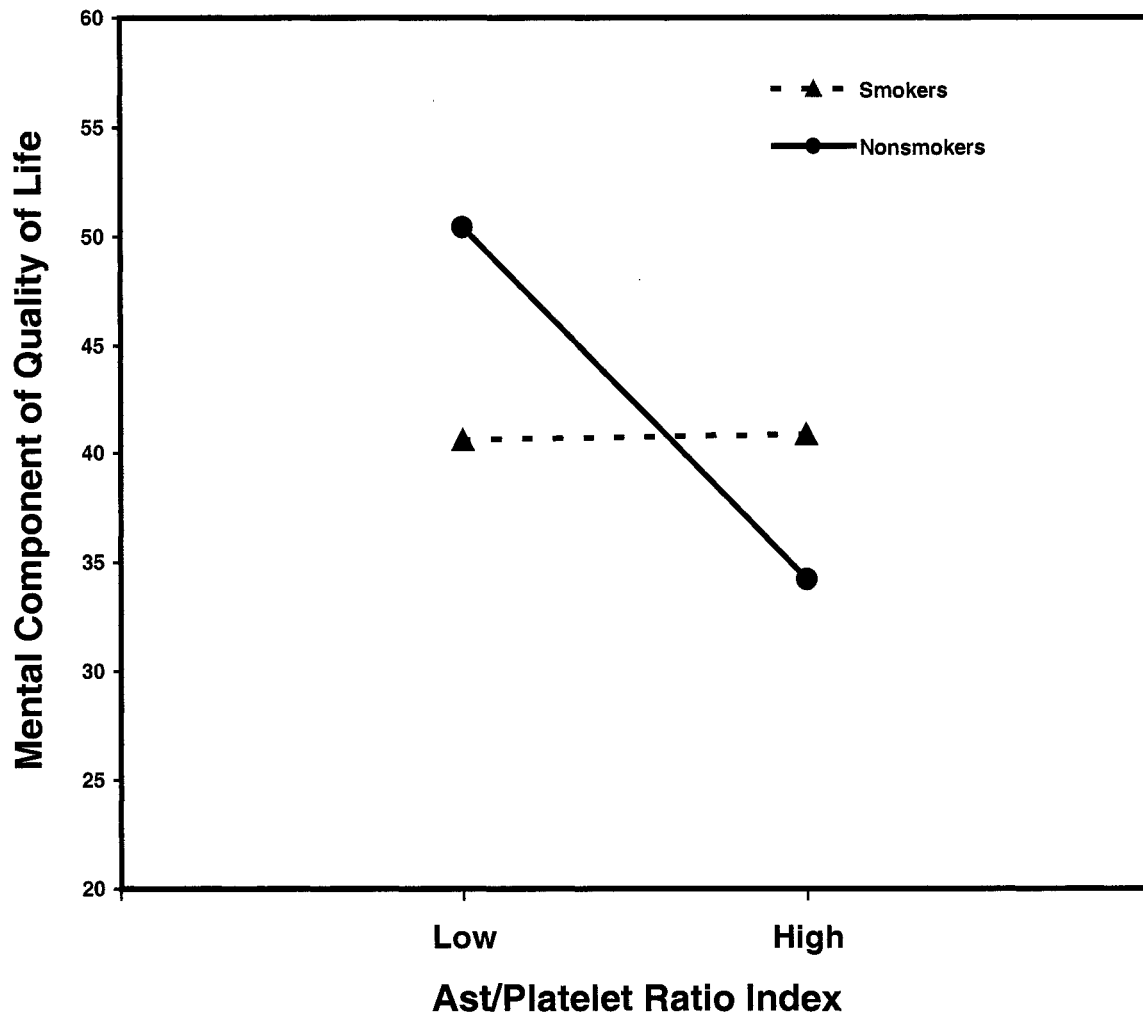
Figure 22. Moderation Model: Smoking and Liver Disease Severity on Mental Component of QOL

Table 22

Hierarchical Multiple Regression Models for the Prediction of Quality of Life from Liver Disease Severity and Marijuana Use: Moderator Model

Step and Variable	R	ΔR	ΔF	Overall F	Partial r
Model 1: Marijuana Use Predicting Physical Component of Quality of Life					
1. APRI					-.05
Marijuana Use	.21	.21	9.54***		-.21
2. APRI X					
Marijuana Use	.22	.004	.36	F(3,70)=6.42**	-.07
Model 2: Marijuana Use Predicting Mental Component of Quality of Life					
1. APRI					-.16
Marijuana Use	.13	.13	5.26**		-.35**
2. APRI X					
Marijuana Use	.15	.02	1.31	F(3,70)=3.96*	.14

Note: Partial correlations are from the final step of the regression model. This signifies the unique contribution of each variable.

*p<.05
**p<.01
***p<.001

23 on page 126. Marijuana use was not found to moderate the relationship between liver disease severity and quality of life outcomes.

Hypothesis 3D: Mediator model- substance use in the relationship between liver disease severity and quality of life outcomes. The four-step procedure (Holmbeck, 1997; Baron and Kenny, 1986) employing multiple regression analyses was used to test the mediation model. The procedure is outlined below. First, a relationship between the predictor (liver disease severity) and the outcome (quality of life) must be established. Second, the relationship between the mediator (substance use including tobacco, alcohol, and marijuana consumption) and the outcome must be revealed. Next, a relationship between the predictor and the mediator must be established. Finally, the relationship between the predictor and the outcome should be significantly reduced after controlling for the effects of the mediator. Prior analyses in this study indicated that the first three criteria for the mediating model for the cases were not met. These results are displayed in Table 20 on page 118.

Post Hoc Analyses- Coping Questionnaire

There have been arguments for and against the subscales used for the 2-factor structure of the COPE. Researchers have not agreed upon what scales go together to comprise the two factors of active coping and avoidant coping. The purpose of these analyses was to evaluate the psychometric properties of active and avoidant coping dimensions and to determine if the subscales used for analysis fit together properly. To answer these questions, intercorrelations were found between the subscales that should hypothetically fit together.
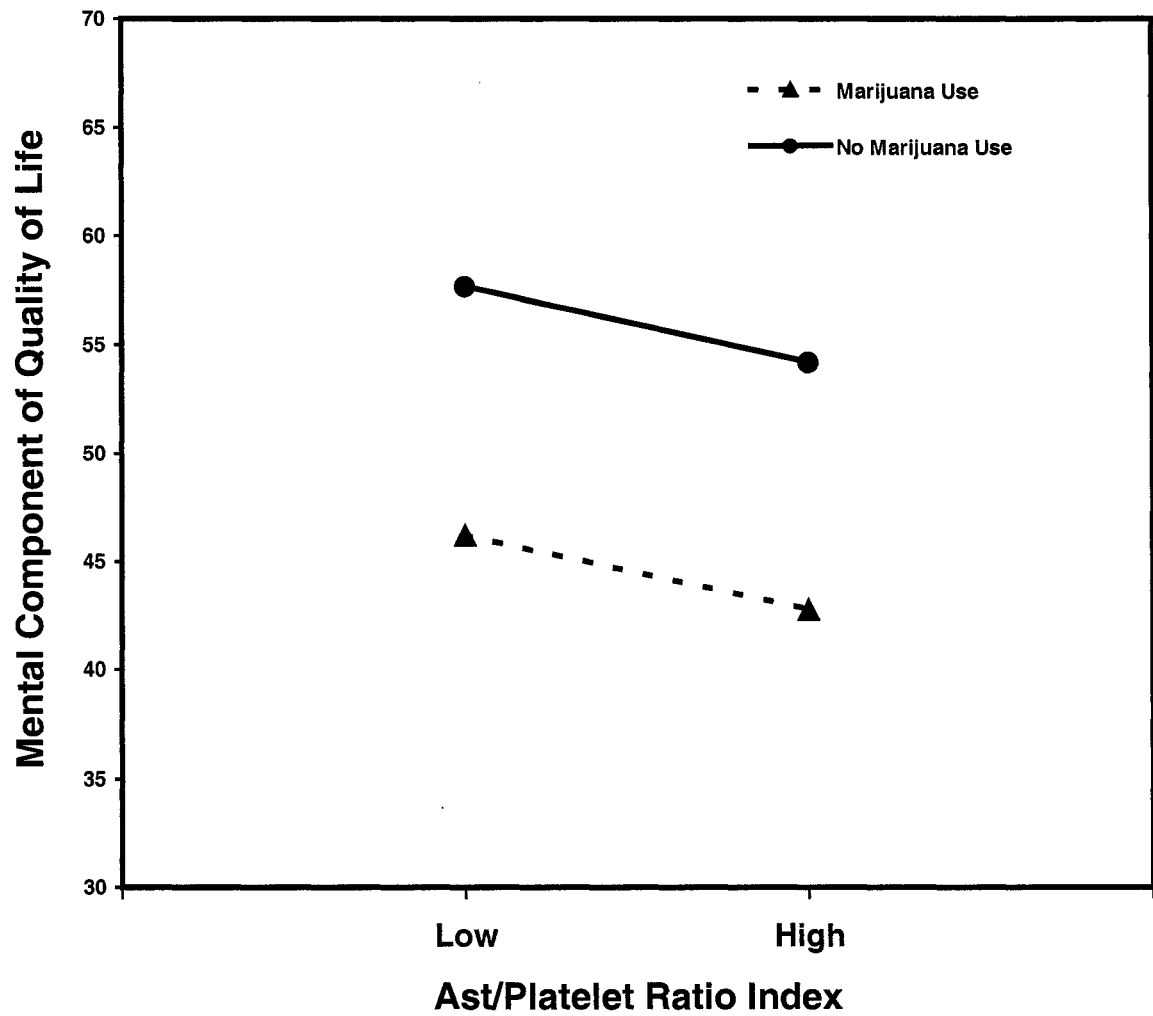
Figure 23. Main Effects for Marijuana Use on Mental Component of QOL

In regards to the COPE questionnaire, Carver (1997) determined two main clusters for the subscales, active and avoidant coping strategies. Carver explained that this measure assesses coping responses that seem potentially dysfunctional (i.e., avoidant coping strategies) as well as adaptive responses (i.e., active coping strategies). The active coping strategies (active coping, planning, positive reframing, and acceptance) were found to correlate significantly. The correlations can be found in Table 23 on page 128. Conversely, the avoidant coping strategy subscales (venting, denial, behavioral disengagement, self-distraction, and self-blame) did not all correlate strongly together. The self-distraction subscale was not significantly correlated with the behavioral disengagement subscale, $r=.115$, $p>.05$. In addition, the self-distraction subscale was positively correlated with all of the active coping subscales. These correlations ranged from .32- .4, all $p<.01$. The self-distraction scale focuses more explicitly on doing things to take one's mind off the stressor, in this case the patient's chronic illness. Individuals endorsing the use of this coping strategy reported turning to work or other activities, including watching TV, reading, daydreaming or shopping to take his/her mind off of the illness. This may be interpreted as the patient trying to function in spite of his/her chronic hepatitis C. In addition, the use of distraction techniques (i.e., watching TV, reading, visualization) to ignore pain or discomfort has been associated with better health outcomes (Walker, Smith, & Garber, 1997). For the above-mentioned reasons, the self-distraction subscale was removed from the avoidant coping scale. The new avoidant coping scale used in the analyses consisted of the venting, denial, behavioral disengagement, and self-blame subscales, respectively.

Table 23

Correlation Matrix for Intercorrelations of COPE Subscales for Active and Avoidant Coping Dimensions.

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1) Correlation Matrix 1: COPE Active Coping Subscales

	ACTIVE	PLANNING	POSITIVE	ACCEPT
ACTIVE	1.0000			
PLANNING	.6649**	1.0000		
POSITIVE	.4030**	.3515**	1.0000	
ACCEPT	.3554**	.3623**	.2877*	1.0000

Active= Active coping, Positive= Positive Reframing, Accept= Acceptance. **p<.01, *p<.05

2) Correlation Matrix 2: COPE Avoidant Coping Subscales with Self-Distraction

	VENTING	DENIAL	BEHAVIOR	SELF-B	SELF-D
VENTING	1.0000				
DENIAL	.414**	1.0000			
BEHAVIOR	.287*	.414**	1.0000		
SELF-B	.517**	.440**	.231*	1.0000	
SELF-D	.384**	.239*	.115	.315**	1.0000

Behavior= Behavioral Disengagement, Self-B= Self-Blame, Self-D= Self-Distraction. **p<.01, *p<.05

3) Correlation Matrix 3: Self-Distraction and Active Coping Subscales

	ACTIVE	PLANNING	POSITIVE	ACCEPT
SELF-D	.329**	.402**	.395**	.319**

Active= Active coping, Positive= Positive Reframing, Accept= Acceptance, Self-D= Self-distraction **p<.01

Discussion

The intent of the present study was twofold. The primary intent of this research was to advance our understanding of the independent effects of tobacco use on liver disease severity. Despite the strong association found between smoking cigarettes and its adverse effects in other medical populations, this is the first investigation in the United States to consider tobacco use a risk factor in the progression of liver disease in the hepatitis C population. The findings revealed strong support for the deleterious effects of smoking cigarettes on liver disease progression and liver disease symptomatology.

The other primary aim of this study was to determine possible mechanisms for the diminished quality of life that is found in the hepatitis C population. This is the first investigation of psychosocial factors as potential moderators and mediators for quality of life outcomes in CHC. This study examined the potential roles of coping strategies by testing moderator models of the relationships between liver disease severity and quality of life outcomes. The findings revealed that general active coping strategies moderated the relationship between liver disease severity and quality of life. The study explored other possible psychosocial factors, including psychological distress and substance use. Findings revealed that tobacco use moderated the relationship between liver disease severity and quality of life outcomes. Even though no moderation or mediation models were found for psychological distress, the variable did have a main effect on quality of life.

A summary of the research findings is presented, in addition to outlining the methodological limitations of the current study. To follow is a summary of the implications for researchers and health care professionals who work with hepatitis C patients. Finally, recommendations for future research directions are offered.

Replication of Earlier Studies

The present study first attempted to replicate the commonly found relationship between substance use and psychological distress. As hypothesized, a significant relationship was found between tobacco use and psychological distress. Smokers reported significantly higher levels of psychological distress compared to nonsmokers. This is consistent with the substance abuse literature examining the relation of tobacco use and psychiatric comorbidities (Lasser et al., 2000; Rohde et al., 2004; Upadhyaya et al., 2002). Research has found that up to 45% of cigarette smokers present with a mental disorder, most commonly meeting DSM-IV criteria for affective disorders and anxiety disorders (Lasser et al., 2000). Likewise, a significant positive relationship was observed between nicotine dependence and psychological distress. This result is concordant with findings in the literature that suggest that nicotine-dependent smokers are at an increased risk for psychiatric comorbidity (Breslau et al., 2004; John, Meye, Rumpf, & Hapke, 2004; Nelson & Wittchen, 1998). For example, Breslau et al (2004) found that pre-existing major depression and anxiety disorders predict an increased risk for nicotine dependence.

In addition, the present study found a significant positive relationship between alcohol dependence and psychological distress. This is in accordance with literature that identifies depression and anxiety as risk factors for alcohol use (Craig, 2004; Pagliaro & Pagliaro, 2004). Taken together, the data support the hypotheses that substance use and an increased level of dependence are associated with higher levels of psychological distress.

Next, as predicted by preliminary Hypothesis 2, it was found that individuals who report more severe alcohol dependence also report using more avoidant coping strategies. These findings are consistent with results from previous studies that explored the

relationship between alcohol use and coping styles (Johnson & Pandina, 2000). The study by Johnson and Pandina found that negative coping styles were strong predictors of problems with alcohol use.

Empirical evidence suggests that alcohol consumption contributes to the development and progression of liver disease in hepatitis C patients (Poynard, Bedossa, & Opolon, 1997; Wiley et al., 1998). The present results partially support previous research. As anticipated, individuals reporting more severe alcohol dependence, which includes heavier consumption, also reported with more severe liver disease symptomatology (e.g., fatigue, poor appetite, headaches, aches and pains). However, the results were not analogous to past research when considering the effects of alcohol on liver disease biochemical markers. Unlike previous studies (Loguercio et al., 2000; Pessione et al., 1998; Wiley et al., 1998) that found heavy alcohol consumption to be related to increased rates of fibrosis and cirrhosis, the present study did not determine a significant relationship between alcohol dependence and liver disease biochemical markers. It is believed that the results of this study do not support prior research findings due to limitations of the study, which are discussed in detail later in this section. Prior studies found that heavier drinkers tended to present with worse biochemical markers (Bellentani et al., 1999; Pessione et al., 1998; Thomas et al., 2000). The results from this study suggest that alcohol use independent of level of consumption was not related to more severe liver disease.

Tobacco Use and Hepatitis C

Tobacco Use and the Progression of Hepatitis C. With regard to the effects of tobacco use on the progression of liver disease, the present results partially support the hypotheses of this study. The results from this study suggest that smoking cigarettes and the level of consumption are related to more severe liver disease and liver disease

symptomatology. However, hierarchical multiple regression analyses did not reveal an independent main effect for tobacco use on liver disease progression, above and beyond the variance accounted for by demographic variables and alcohol consumption.

To date, there have been very few studies considering nicotine use a potential prognostic factor in patients with hepatitis C. This is surprising when considering the functions of the liver and the adverse effects of smoking cigarettes that have been found in various medical populations (Haustein et al., 2002; Kuper et al., 2002; Petty, 2002; Thun et al., 1997). The liver acts as a filter in detoxifying everything an individual consumes, including the thousands of chemicals found in cigarettes, over 50 of which have been identified as carcinogens (Kuper, Adami, & Boffetta, 2002).

The sparse literature available suggests that smoking cigarettes may exacerbate hepatitis C symptomatology and progress the liver disease (Hezode et al., 2003; Pessione et al., 2001). Based on the current literature review, this is the first study in the United States to consider the effects of nicotine use on liver disease progression in the hepatitis C population. As anticipated, a significant positive relationship was found between nicotine dependence and liver disease symptomatology. Participants reporting more severe nicotine dependence also tended to report with more severe liver disease symptomatology.

In addition, this study found that smokers reported experiencing more severe liver disease symptoms compared to nonsmokers. More specifically, smokers endorsed experiencing more severe symptoms of fatigue, poor appetite, and headaches compared to nonsmokers. This is an important finding given that fatigue is the most common and profound symptom reported by hepatitis C patients. Researchers have found that fatigue is not only the most prevalent symptom reported by hepatitis C patients (i.e., up to 97% experiencing this symptom), but that it is also the most disabling symptom (Barkuizen et

al., 1999; Jones, 2004; Lee et al., 1997). Fatigue related to chronic hepatitis C has been associated with decreased physical functioning, inability to work and premature discontinuation of IFN therapy (Cotler et al., 2000; Dwight et al., 2000). Currently, there is no widely accepted treatment for fatigue in the hepatitis C population because there is not a clear understanding of the etiology of this symptom (Hilsabeck, Hassanein, & Perry, 2005). Studies investigating possible predictors of fatigue in CHC have found that poor social functioning and psychological distress are highly related to this common symptom. Interestingly, smoking cigarettes is also highly correlated with poor social functioning and psychological distress (Mitra et al., 2004; Schmitz, Kruse & Kugler, 2003). In addition, several experiments have suggested that in some circumstances nicotine may produce analgesic effects (Pagliaro & Pagliaro, 2004). Furthermore, the initial psychostimulation of nicotine is followed by a marked reduction in muscle tone that typically leads to feelings of relaxation or possibly even fatigue. It is noted that other physiological effects of cigarette smoking include appetite suppression and headaches (Hoffman & Wynder, 1986; Jo, Talmage, & Role, 2002). This is consistent with the current study's findings that CHC smokers reported with a poorer appetite and headaches compared to CHC nonsmokers.

The smokers in this study also tended to present with higher scores on the APRI index compared to nonsmokers. Although not reaching statistical significance, the smokers' mean score is above the cut-off value of 1.50 that indicates a .88 positive predictive value for the presence of hepatic fibrosis. Hence, the results indicate that CHC patients who are smokers may be more likely to have fibrosis compared to the nonsmoking group. Also worthy of note, there appeared to be a trend in that the smoking group was presenting with worse liver disease biochemical markers (e.g., AST, ALT, platelet count) compared to the nonsmoking group.

It appears that the level of cigarette consumption could also be a factor in the progression of liver disease. While statistical signficance was not reached, the CHC patients smoking more than one pack per day presented with a mean score above the cut-off value of 2.00 that indicates a .93 negative predictive value for the presence of cirrhosis below the cut-off value. Hence, the results suggest that individuals smoking more than one pack of cigarettes per day may be more likely to have cirrhosis compared to smokers who consume less than one pack per day and compared to nonsmokers. Also trending toward significance, smokers who consumed more than one pack per day tended to present with worse ALT levels. This finding is in accordance with the study by Wang et al (2002), which found the prevalence of elevated ALT levels was about 3 times higher for those smoking one or more packs of cigarettes per day. Elevated ALT levels indicate more severe hepatic disease. In addition, patients with elevated ALT levels typically require more frequent hospital visits for biochemical tests, ultrasonography, and medical treatment (Wang et al., 2002). Furthermore, hepatocellular carcinoma is more likely to develop in patients with higher ALT levels. As mentioned by Wang et al (2002), one plausible explanation for the effect of cigarette smoking on hepatic injury is that the liver is a target organ for the chemicals in tobacco. It is also noted that the one or more pack per day smokers tended to report more severe fatigue and a poorer appetite.

Tobacco Use and Quality of Life. The literature suggests that individuals smoking cigarettes report a diminished quality of life compared to nonsmokers (Mitra et al., 2004; Schmitz, Kruse, & Kugler, 2003; Strine et al., 2005). A main effect for tobacco use, above and beyond the variance accounted for by demographic variables and alcohol consumption, was found on the social functioning subscale. More specifically, smokers tended to report that either their physical health or emotional problems negatively impact their social activity. This is consistent with prior studies that found social functioning to

be one of the biggest declines in quality of life compared to the general population (Croghan et al., 2005; Martinez et al., 2004). The smokers in this study reported experiencing significantly more problems with fatigue, which in turn could impair their social activity. Likewise, smokers also reported higher degrees of psychological distress compared to nonsmokers, which could also impact their social activity. Smokers many times present with depression and low esteem that can impair their social functioning (Martinez et al., 2004). Individuals tend to use smoking to manage negative moods such as anxiety and depression to help them relax and cope with stressful life events. Given the social stigma of infectious diseases like hepatitis C, it is possible that CHC smokers may use smoking to try and reduce their anxiety in social situations. Based on the literature, hepatitis C patients report one of the biggest functional declines in this area of QOL (Mitra et al., 2004; Schmitz, Kruse & Kugler, 2003).

The results partially supported past research when comparing smoking groups on quality of life outcomes. Results were trending toward significance (i.e., p= .07) when comparing smokers and nonsmokers on the physical component of quality of life. Smokers tended to report a lower quality of life on the physical component score compared to nonsmokers. One explanation for this finding could be that smokers tended to report more severe liver disease symptomatology compared to the nonsmokers in addition to worse biochemical markers that indicate more liver disease severity. In addition, a significant difference was found between the two groups on the social functioning subscale of the SF-36. Smokers tended to report poorer social functioning compared to nonsmokers.

Hepatitis C and Quality of Life Outcomes

The fourth preliminary hypothesis investigated the relationship between hepatitis C and quality of life outcomes. The results from this study are in accordance with

findings from prior research (Bonkovsky et al., 1999; Bernstein et al., 2002; Chong et al., 2003; Hauser et al., 2004; Ware et al., 1999). As predicted, hepatitis C patients who presented with more severe liver disease tended to report lower levels of quality of life, including the physical component score, the role-physical functioning subscale, and the social functioning subscale. Similarly, the participants who presented with more severe liver disease symptomatology tended to report lower levels of quality of life on both the physical and mental component score of the SF-36.

Another component of the present study was to examine group differences in quality of life. Group comparison studies in hepatitis C have generally found that hepatitis C patients report a lower quality of life compared to the general population and patients with other medical disorders (Gandek & Ware, 1993; Ware et al., 1999). The findings supported empirical evidence that individuals with hepatitis C experience a lower quality of life compared to the general population. These added findings support the need for continued use of quality of life outcome measures in clinical drug trials and treatment effectiveness research.

Quality of Life: Tests of Moderation and Mediation

To my knowledge, this is the first investigation of psychosocial factors as potential moderators and mediators of the relationships between liver disease severity and quality of life outcomes. Despite the large volumes of research in the area of quality of life, this study is the first to consider the role of different psychosocial factors as mechanisms in the relationship between liver disease severity and quality of life. It is advantageous to test alternative models as both provide substantially different explanations to why or how a particular relationship exists. More specifically, by testing for moderators it can identify groups that may be more or less vulnerable in certain conditions. In testing for potential mediators, one can determine why a variable has an

effect on the dependent variable. Identification of either model in the hepatitis C population would provide significant implications for treatment regimens.

General Coping Strategies. One of the most important findings in the present study is that general active coping strategies moderated the relationship between liver disease severity and the physical component of the SF-36 quality of life measurement. This finding supports the theoretical conceptualization of Carver's adaptive or active coping strategy approach (Carver, 1994; Gaynes & Drossman, 1999). Carver posited that there are adaptive and maladaptive ways of coping with an illness or a stressful situation. The theory suggests that the use of adaptive coping strategies (i.e. planning, positive reinterpretation and growth) in specific situations will result in better outcomes compared to individuals using more maladaptive coping resources. The present study has demonstrated that how an individual copes with stressors (i.e., illness) may be an important indication of whether he/she will experience a diminished quality of life. More specifically, the results indicate that active coping strategies are helpful in maintaining a higher quality of life when individuals are experiencing more severe liver disease. Moreover, the results also suggest that low active coping can lead to a diminished quality of life under chronic stress conditions (i.e., severe liver disease). These findings appear to extend the current hepatitis C research with regards to quality of life outcomes.

In regards to general avoidant coping strategies, no moderation or mediation models were found. However, a main effect was discovered for avoidant coping strategies and revealed that individuals using high avoidant coping reported lower levels of quality of life on both the physical and mental components compared to individuals

who use low avoidant coping. This finding posits that the use of avoidant coping strategies can be an etiological factor for a diminished quality of life. This result also supports Carver's (1994) adaptive and maladaptive coping theoretical conceptualization. Taken together with active coping findings, the results from this study suggest that coping strategies have a direct effect on quality of life outcomes.

Psychological Distress. Despite the fact that the results from this study did not support the moderation or mediation of psychological distress, the analyses do suggest that psychological distress has a direct effect on predicting quality of life outcomes. This study has ascertained that an individual's level of psychological distress is an important factor in the individual's overall quality of life. The data provides supportive evidence that individuals who report higher levels of psychological distress also report lower quality of life outcomes. More specifically, results from the current study found that individuals with higher levels of psychological distress reported lower quality of life outcomes on both physical and mental functioning compared to individuals who reported lower levels of psychological distress. These results support Hauser et al's (2004) finding that suggest that psychiatric comorbidity predicts poorer quality of life outcomes amongst hepatitis C patients.

Substance Use. Another important finding in the present study is that tobacco use moderated the relationship between liver disease severity on both the physical and mental component of the SF-36 quality of life measurement. More specifically, the results indicate that smokers reported lower levels of quality of life compared to nonsmokers when experiencing less severe liver disease. Interestingly, smokers reported a higher

level of quality of life compared to nonsmokers when experiencing more severe liver disease. In addition, the smokers had very little change in their perceived quality of life from low to high liver disease severity compared to the dramatic decline in quality of life reported by nonsmokers as their liver disease progressed.

One explanation for this result might be habituation or adjustment to the chronic illness by the smoking group. As found in this study, smokers tend to present with more psychological distress and more severe liver disease symptomatology than nonsmokers. Given this, smokers even with low liver disease severity may be experiencing more symptoms (e.g., fatigue, poor appetite, headaches) and more psychological distress, hence, leading to a poorer quality of life during the initial stages of the disease. This could be giving the smokers an opportunity to begin coping with the discomfort and physical incapacity of the illness (i.e. adjusting their goals in life to better fit with their declining health, increasing social support) as opposed to the nonsmoking group who has not had that window of time to adjust to their declining health, worsening symptoms and uncertain future. Using Lazarus and Folkman's framework (1984), the nonsmokers' primary appraisal of severe liver disease could be more threatening or harmful then the nonsmokers, which could lead to poorer functioning. The more an individual's central goals in life are threatened by a chronic disease, the more their apprasials, coping processes, and resources are challenged, which can lead to less positive adjustment (Stanton, Collins, & Sworowski, 2001). Another explanation could be that smoking is a protective factor for CHC patients with severe liver disease when considering quality of life outcomes. Simply stated, smoking could be used as an additional coping resource in dealing with this stressful life event (i.e., deteriorating health). It could also be a combination of habituation and the additional coping resource. These findings appear to

extend the current research in regards to tobacco use and quality of life outcomes in the hepatitis C population and pose important treatment implications for smoking cessation with this population.

With regards to other substance use, no moderation or mediation was found for alcohol consumption. Furthermore, alcohol consumption was not found to have a main effect on quality of life outcomes. On the other hand, the results from the study indicate a main effect for marijuana use on the mental component of QOL. This was the first study to consider marijuana use a risk factor in quality of life within the CHC population. The main effect for marijuana suggests that those using marijuana were also tended to report lower levels of quality of life on the mental component compared to individuals who reported no use of marijuana.

Limitations of the Study

The limitations of the present study relate to areas of sample size, measurement, and methodology. First, however, the majority of the findings from this study are consistent with the results from hepatitis C research and are considered to be generalizable to the hepatitis C population. It is believed that the sample size for both the multiple regression analyses and the group comparisons may have been too small to establish adequate statistical power. When estimating the needed sample size, 46 participants were needed for a large effect size. Perhaps the effect size was smaller and a larger sample size was needed to obtain adequate power for the statistical analyses. This could be one explanation as to why many analyses were trending toward significance, but did not reach the $p<.05$ level. In addition, Kazdin (2003) explains that small group sizes with less than 40 individuals are at risk for weak statistical power. The lack of differences found between the three group comparison (i.e., level of tobacco consumption groups) on measures of psychological distress and quality of life is surprising considering

increased tobacco use is often associated with depression, anxiety, and lower quality of life outcomes. It is believed that unequal group sizes and a low number in the one or more packs per day group could indicate there was insufficient power to determine differences between groups. Simply stated, the lack of power in the group comparisons could have led to Type II errors.

A second limitation involves the use of multiple self-report measures. This may have led to possible subject biases or distortions. There is a tendency for individuals to attempt to present themselves in a socially desirable fashion. For example, because the amounts of cigarette, alcohol, and other substance use consumption were self-reported, a bias toward underestimation might exist due to the social stigma associated with reporting these adverse lifestyle behaviors. More specifically, most hepatitis C patients have been advised to abstain from all alcohol use and many might have been fearful of admitting use and/or higher levels of consumption. Similarly, individuals may have attempted to report more socially approved coping strategies opposed to what he/she might actually use on a regular basis. With these considerations, the risk of subject bias is particularly salient.

Finally, the methodological drawbacks of the current study are expressed. While the moderator and mediator analyses indicated predictions of the dependent variable, the actual causal relations of the measured variables can not be inferred. Considering the findings are grounded on a retrospective approach, using correlational data inferences of causation can not be made. In addition, the research design in this study made between subject comparisons as opposed to within-person comparisons. As Tennen et al., (2000) posited the advantages of using a idiographic or with-in person approach in capturing proximal stressors, coping strategies, and adaptional outcomes allows for a closer

approximation to their actual occurrence. Furthermore, this approach would minimize recall error.

Implications

The results of the present study have important implications for the medical and mental health profressionals taking care of patients with CHC. It is important to identify how health care professionals can utilize the information found in this study in the hopes of providing education and recommendations to CHC patients and other medical staff for optimal health care services. As found in other medical populations, such as HIV, good health habits are necessary for the prevention of the progression of the disease and it may also give the patient a greater sense of control over their illness (Collins et al., 2001; Seeman & Seeman, 1983). Results from this study suggest that tobacco use could be a risk factor in liver disease progression and in liver disease symptomatology. Based on this study's findings, it is recommended that health care professionals advise their CHC patients to abstain or reduce tobacco consumption. Abstinence from smoking cigarettes could probably help in slowing the progression of liver disease and it may even minimize the need for health care services. Smoking cessation could also improve the CHC patient's quality of life during the initial stages of the liver disease with the possibility of minimizing liver disease symptoms including fatigue, poor appetite, and headaches. Interventions combining behavioral treatment and nicotine replacement thearpy have been found most beneficial for smoking cessation (DeLaune & Schmitz, 2004; Miller & Rollnick, 2002).

Findings from this study also indicated that other psychosocial variables could be risk factors for a diminished quality of life. Results indicated that maladaptive coping strategies were related to a lower quality of life and that active/adapative coping strategies were found to be a protective factor in maintaining a higher quality of life.

Mental health professionals can assist patients in altering their methods of coping (i.e. using more adapative coping strategies such as planning and acceptance), so that they are less likely to use venting, avoidance, self blame or other maladaptive strategies that are not useful in adjusting to a chronic illness and maintaining a higher quality of life. In addition, it is well-established that stress and the use of addictive substances are positively correlated (Grunberg, Faraday & Rahman, 2001). These new adapative coping resources can be good alternatives to use instead of abusing substances (e.g., tobacco use, alcohol consumption, marijuana use) to manage stress. Futhermore, mental health professionals can also work with CHC patients on reducing their psychological distress, which in turn could improve the patient's overall quality of life.

Despite the recent advancements of CHC medical treatments, there is still no cure for the primary disease process. For this reason, it is critical that we work with CHC patients to minimize or eliminate these risk factors, which can prevent further exacerbation of the course of the disease and optimize the individual's health status and quality of life. Even by simply educating our patients of these different risk factors, we are reducing the unawareness and uncertainity that fills many CHC patients' minds. More importantly, we are also reducing the chances of further progression of the patient's chronic illness and quite possibly saving lives.

Summary and Conclusions

Despite the limitations of the current study, there are several strengths of the study that provide a unique contribution to the hepatitis C literature. To start, this is the first study of its kind in the United States to examine the effects of tobacco use on the progression of liver disease in the hepatitis C population. This study shows a clear relationship between smoking cigarettes and liver disease progression. The mechanism by which smoking adversely affects the histological activity in CHC and how it may

cause certain liver disease symptoms is still yet to be determined. Based on the evidence from this study that support the deleterious role of smoking in CHC, it is recommended that CHC patients be advised to quit or reduce tobacco consumption.

In addition, this study tests alternative models of the relationships between liver disease severity, coping strategies, substance use, psychological distress, and quality of life outcomes, which has not been done before in the literature. More importantly, the present study provides preliminary evidence that coping strategies may play a role in the status of quality of life outcomes. The results suggest that quality of life outcomes may depend on the level of active coping an individual engages in. In addition, the study demonstrates extended evidence that maladaptive or passive coping strategies may lead to poor health outcomes. Furthermore, this study provides supportive evidence that psychological distress and substance use (tobacco use, marijuana use) are risk factors for a diminished quality of life in the hepatitis C population. Taken together, the results from this study also suggest that liver disease severity has a strong independent relationship with quality of life outcomes.

The present study poses interesting questions for future research directions. First, the prevalence of cigarette smoking is greater than double that of alcohol consumption (51.3% vs. 23.7%) in this study, but the effects of smoking on CHC patients is commonly overlooked in practice and research. Further study is needed to determine if cigarette smoking has similar effects to alcohol consumption, including an increase in viral replication and worsening histological progression (Wang et al., 2002). An accurate causal link between smoking and liver disease progression is still a major question in the hepatitis C literature. It is suggested that a prospective approach be taken in determining the causal relationship. Given that smoking was significantly related to fatigue symptoms, the proposed study should also consider the effects of smoking on liver

disease symptomatology. A long-term prospective study is warranted to study the combined effects of smoking and alcohol consumption on liver disease progression. In addition, statistical analyses should utilize structural equation modeling to examine reciprocal relationships between liver disease severity, liver disease symptomatology, coping strategies, substance use and quality of life. In addition to replicating this study with the updated methodology recommendations, future research may also want to address the effects of tobacco use on immunotherapy outcomes.

It is also recommended that researchers explore the effects of marijuana use on liver disease progression and quality of life outcomes in the CHC population. 22.4% of the partipants in this study reported using marijuana in the past six months. The prevalence of marijuana use in this study was over 5 times the national rate of 4% (Compton et al., 2004). This is understandable considering IV drug use is the primary route of transmission for the hepatitis C virus and a history of intravenous drug use is a good predictor of marijuana use (Fuler et al., 2004). Marijuana smoke contains similar levels of tar as tobacco smoke and it contains up to 50% more carcinogens (Moore et al., 2004; Pagliaro & Pagliaro, 2004). Studies examining the effects of marijuana use in other infectious disease populations like HIV have found that marijuana use has a negative impact on disease progression (Furler et al., 2004). Likewise, marijuana use has been associated with pulmonary aspergillosis, bacterial pheumonia, and reduced medication adherence (Furler et al., 2004). It is believed that the cognitive impairments (i.e., impairment of short-term memory, decreased attention span) demonstrated during acute marijuana intoxication could account for medication noncompliance (Kalant, 2004). Given this, researchers may also want to address the effects of marijuana use on immunotherapy outcomes. Furthermore, the effects of marijuana and tobacco appear to be additive (Kalant, 2004; Moore et al., 2004). The study by Moore et al. discovered that

individuals smoking both tobacco and marijuana had a greater prevalence of respiratory symptoms than those who smoked only tobacco. It appears worthwhile to examine the synergistic effects of marijuana and tobacco use on liver disease progression.

Finally, future research should continue to explore psychosocial variables as predictors of a diminished quality of life in CHC patients. In addition to the severity of the liver disease, this study has identified other possible risk factors, including coping styles, psychological distress and substance use, that may account for a CHC patient's diminished quality of life. Research is warranted to confirm the present study's findings. It is hoped that the information garnered from this research and that of future recommended studies will help to slow the progression of advanced liver disease in CHC patients in addition to improving the quality of life and refining treatment options for individuals suffering with hepatitis C.

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Appendix A

Informed Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Psychosocial Factors in Patients with Liver Disease
VCU IRB PROTOCAL NUMBER: 3575
INVESTIGATOR: Karen S. Ingersoll, Ph.D.

This consent form may contain information that you do not understand. Please ask the study staff to explain anything that you do not understand. You may take home an unsigned copy of this consent form and discuss this with family or friends before making your decision.

Purpose of the Study:
The purpose of this research study is to determine any group differences between chronic viral liver diseases, mild viral liver disease, and non-viral liver disease for mental health, substance use, and quality of life.

Description of Study:
This study will collect and compare psychosocial data (e.g. mental health, substance use, coping, quality of life) from five different liver disease classifications, mild, moderate and severe hepatitis C, cirrhosis, and non-viral liver disease. A maximum of 140 liver disease patients will participate in this study.

Procedures:
If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered. You will be asked to complete a set of questions about your health, alcohol and substance use, other lifestyle factors, and your feelings. You will be asked to fill out a number of paper and pencil measures. We will also gather some of your medical history from your medical chart. Completion of the assessment forms will take approximately 20-35 minutes.

Risks and Discomforts:
We may ask you some questions that may make you feel uneasy. You may refuse to answer any questions at any time. None of the information gathered in the study will effect your current or future medical care here at the VCU Medical Center.

Benefits:
This is not a treatment study, and you are not expected to receive any direct benefits from your participation in the study. However, your participation may help scientists learn more about liver disease patients and how to improve treatments for liver disease.

Compensation for Participation:
There is no compensation for participation in this study.

Alternative:
Your alternative is not to participate in this study.

Confidentiality:
Confidentiality of personal information gathered in connection with this study will be maintained in a manner consistent with federal and state laws and regulations. We will protect your confidentiality by assigning you an identification number. Private information collected during the study will be kept separate from your name. All information collected during the study will be stored in a locked cabinet and access to the information will be limited to study staff members only.

You should know that research data about you may be reviewed or copied by Virginia Commonwealth University for regulatory purposes. Absolute confidentiality cannot be guaranteed because of the need to give information to this party. Result of this research may be presented at meetings or in publications; however, identifiable personal information pertaining to participants will not be disclosed.

Compensation for Injury:
Virginia Commonwealth University and the VCU Medical Center have no plan for providing long-term care or compensation in the event that you suffer an injury as a result of your participation in this research study.

If you are injured or become ill as a result of your participation in this study, contact your primary investigator immediately. The primary investigator will arrange for short-term emergency care or referral if it is needed. Fees for such treatment may be billed to you or to appropriate third part insurance. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

Voluntary Participation and Withdrawal:
Your participation in this study is voluntary. You may decide to not participate in this study. If you do participate, you may freely withdraw from the study at any time. Your decision will not change your current or future medical care at this institution.

Questions:
In the future, you may have questions about your study participation. If you have any questions, contact:

Dr. Karen Ingersoll, Ph.D.
P.O. Box 980109
Virginia Commonwealth University
Richmond, VA 23298-0109
Phone: 804-828-7456

If you have any questions about your rights as a research participant, you may contact:

Office for Research Subjects Protection
Virginia Commonwealth University
1101 E. Marshall St., Room 1-023
P.O. Box 980568
Richmond, VA 23298
Phone: 804-828-0868

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions

Consent:
I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study.

I understand that I will receive a signed and dated copy of this consent form for my records.

_____

Participant's Name, printed

_____   _____

Participant's Signature   Date

_____   _____

Signature of Person Conducting Informed Consent   Date

_____   _____

Principal Investigator Signature   Date

Appendix B

Medical Record Abstract Form

1. **Participants Initials**_____

2. **Participants DOB:**   ____   ____   ____
                            mm   dd   yyyy

3. **Liver disease diagnosis**   **Date of Diagnosis (year):** _____

   ___ Hepatitis C (please circle) Mild   Moderate   Severe   Cirrhosis

   ___ Alcoholic Cirrhosis

   ___ Nonviral Liver Disease (Specify:_____)

   ___ Other _____

4. **Current Medication Regimen:**

   ____ **Aldactone**   ____ **Furosemide**   ___ **Lasix**   ___ **Lactulose** ____ **Nexium**

   ____ **Spironolactone** ____ **IFN Therapy** ___ **Antidepressant (specify_____)**

   **Please list other
   medications:**_____

5. **Co-Morbid Medical Conditions**

   ____ **Diabetes** ____ **Hypertension** ____ **GERD** _____ **Obesity** _____ **Chronic Pain**

   Please list other medical conditions:_____

6. **Biochemical Markers**

   Aspartate Aminotransferase (AST) (/ULN)   _____

   Alanine Aminotransferase (ALT) (/ULN)   _____

   Platelet counts   (10^9 / L)   _____

   Bilirubin (mg/dL)   _____

   Albumin (g/dL)   _____

Prothrombin time (seconds) _____

Grade of Hepatic Encephalopathy (please circle) none   grade 1 or 2   grade 3 or 4

Ascites (please circle)   none   mild   severe tense

_____

AST to platelet ratio index (APRI) _____

Appendix C

Liver Disease Symptoms Form

Please remember that there are no right or wrong answers to any of these questions. It is important that you think about each question and answer it truthfully to the best of your knowledge.

1. In the past 12 months, how often have you gone to the doctor's office specifically for liver disease symptoms
    (i.e. fatigue, infection, pain, abdominal fluid, mental changes, gastrointestinal bleeding, etc.)?

    1) ☐ Never   4) ☐   About once a month
    2) ☐ Once or twice   5) ☐   Several times a month
    3) ☐ Several times a year

For each of the symptoms listed below, please indicate the frequency and how bothersome (unpleasant) each symptom is for you.

Frequency Scores   Bothersome Scores
4- occurs daily   4-extremely bothersome when occurs
3- occurs several times a week   3-severely bothersome when occurs
2- occurs about once a week   2-moderately bothersome when occurs
1- occurs about once a month   1-slightly bothersome when occurs
0- not present   0- not bothersome

	Frequency Score (0-4)	Bothersome Score (0-4)
1- Fatigue	_____	_____
2- Infections	_____	_____
3- Jaundice (yellow skin/eyes)	_____	_____
4- Itchiness	_____	_____
5-Fluid Retention	_____	_____
6-Mental Changes (e.g. memory difficulties)	_____	_____
7- Gastrointestinal Bleeding	_____	_____
8- Nausea	_____	_____
9- Pain over the liver area	_____	_____
10- Poor Appetite	_____	_____
11- Headaches	_____	_____
12- Muscle/Joint aches or pains	_____	_____

Appendix D

Brief Drug History Form

Your honest answers will not affect your health care here at VCU Medical Center. Your name will not be associated with the answers to these questions in this packet.

Have Your Ever Tried?	Age when you first tried this drug	Have You Used in last 6 months?	If you used in the **past month**, how may days did you used in last **30 days** (0-30)
Alcohol (beer, wine, liquor) No Yes		No Yes	
Marijuana (reefer, pot, weed) No Yes		No Yes	
Cocaine or crack No Yes		No Yes	
Heroin No Yes		No Yes	
Heroin + cocaine (speed ball) No Yes		No Yes	
Amphetamines (speed, crank) No Yes		No Yes	

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Hallucinogens (LSD, Ecstasy) No Yes		No Yes	

Appendix E

Alcohol Use Questionnaire

Please use this form to help you answer the questions on the next page. As a guide, ONE standard drink is equal to each of the following:

BEER
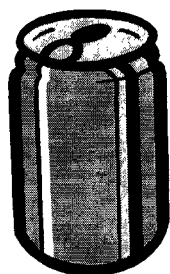
CAN, BOTTLE OR MUG
12 OZ
e.g. a 40's bottle = 3 drinks

LIQUOR
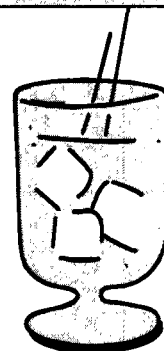
HI-BALL OR SHOT
1.5 OZ
e.g. rum, gin, vodka, whiskey

WINE

TABLE WINE
Red, White, Rose   5 OZ
Fortified Wine   3 OZ

WINE COOLER

CAN OR BOTTLE
12 OZ

Alcohol Use Questionnaire

Your honest answers will not affect your health care here at VCU Medical Center.

1. Circle the number below that best describes your usual drinking of alcohol during the **past six months.**

   1.   None
   2.   One drink per week
   3.   One to two drinks per week
   4.   Three to six drinks per week
   5.   One drink a day
   6.   Two drinks a day
   7.   More than two drinks a day

2. During the **last six months**, have you ever had more than 5 standard drinks in a single day?

   1. Yes
   2. No

3. If you answered yes, on how many days, during the **past six months,** did you have more than 5 standard drinks in a single day?

   _____ days

4. During the **last one month,** have you ever had more than 5 standard drinks in a single day?

   1.Yes
   2.No

5.If you answered yes, on how many days, during the **past one month,** did you have more than 5 standard drinks in a single day?

   _____ days

Appendix F

Nicotine History Form

Have you ever smoked cigarettes? YES   NO   (if you answered NO skip to the next page)

1. How old were you when you first smoked cigarettes?   _____

2. Did you ever smoke daily?   (please circle)   YES   NO

IF YES,

3. How old were you when you became a daily smoker?   _____years old

4. How many cigarettes do you smoke, on average, per day now?
                              (20 cigarettes per pack)_____

5. How many packs of cigarettes do you smoke per week?   _____ packs

6. How long have you smoked this amount (in years and in months)   ____ years &
                                                                   _____months

7. How many times have you quit smoking in the past?   _____

8. What was your longest quit period (in years and/or months?)   _____

9. When was the last time you quit smoking for at least 24 hours? _____   _____
                                                                   month   year

10. How long total have you stopped smoking in the past (in months)?   _____

11. At your heaviest use, how many cigarettes per day were you smoking?   _____

12. How long did you smoke at this heaviest use (in months)?   _____

13. What brand of cigarettes do you usually smoke?
    _____

14. Do you buy by the carton or the pack? Carton Pack
Both

15. What do you usually pay for cigarettes? $_____per pack $_____per
carton

Appendix G

Alcohol Use Disorders Identification Test

AUDIT

Please CIRCLE the answer that is correct for you during the <u>PAST YEAR (12 Months)</u>
1. How often do you have a drink containing alcohol?

| **Never** | **Monthly or less** | **2 to 4 times a month** | **2 to 3 times a week** | **4 or more times a week** |

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

| **1-2** | **3-4** | **5-6** | **7-9** | **10 or more** |

3. How often do you have six or more drinks on one occasion?

| **Never** | **Less than Monthly** | **Monthly** | **Weekly** | **Daily or almost daily** |

4. How often during the last year have you found that you were not able to stop drinking once you had started?

| **Never** | **Less than · Monthly** | **Monthly** | **Weekly** | **Daily or almost daily** |

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

| **Never** | **Less than Monthly** | **Monthly** | **Weekly** | **Daily or almost daily** |

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

| **Never** | **Less than Monthly** | **Monthly** | **Weekly** | **Daily or almost daily** |

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

| **Never** | **Less than Monthly** | **Monthly** | **Weekly** | **Daily or almost daily** |

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

| Never | Less than Monthly | Monthly | Weekly | Daily or almost daily |

9. Have you or someone else been injured as result of your drinking?

| No | Yes, but not in the past year | Yes, during the past year |

10. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

| No | Yes, but not in the past year | Yes, during the past year |

Appendix H

Fagerstrom Test For Nicotine Dependence

1) How soon after you wake up do you smoke your first cigarette?

   A. Within 5 minutes
   B. 6-30 minutes
   C. 31-60 minutes
   D. After 60 minutes

2) Do you find it difficult to refrain from smoking in places where it is forbidden e.g., in church, at the library, in cinema, etc.?

   A. Yes
   B. No

3) Which cigarette would you hate most to give up?

   A. The first one in the morning
   B. Any other

4) How many cigarettes in a day do you smoke?

   A. 10 or less
   B. 11-20
   C. 21-30
   D. 31 or more

5) Do you smoke more frequently during the first hours after waking than during the rest of the day?

   A. Yes

B. No

6) Do you smoke if you are so ill that you are in bed most of the day?

A. Yes
B. No

Appendix I

Brief Cope Questionnaire

We are interested in how patients respond to having liver disease. There are lots of ways to deal with having an illness. This questionnaire asks you to indicate what *YOU* generally do and feel, when dealing with your liver disease.

I usually don't do do this at all 1	I usually do this a little bit 2	I usually do this a medium amount 3	I usually do this a lot 4

1 2 3 4   1. I've been concentrating my efforts on doing something about the situation I'm in.

1 2 3 4   2. I've been saying to myself "this isn't real."

1 2 3 4   3. I've been saying things to let my unpleasant feelings escape.

1 2 3 4   4. I've been trying to come up with a strategy about what to do.

1 2 3 4   5. I've been criticizing myself.

1 2 3 4   6. I've been accepting the reality of the fact that it has happened.

1 2 3 4   7. I've been trying to see it in a different light, to make it seem more positive.

1 2 3 4   8. I've been using alcohol or other drugs to make myself feel better.

1 2 3 4   9. I've been giving up trying to deal with it.

1 2 3 4   10. I've been making jokes about it.

1 2 3 4   11. I've been trying to find comfort in my religion or spiritual beliefs.

1 2 3 4   12. I've been getting emotional support from others.

I usually don't do	I usually do	I usually do this	I usually do
do this at all	this a little bit	a medium amount	this a lot
1	2	3	4

1 2 3 4   13. I've been trying to get advice or help from other people about what to do.

1 2 3 4   14. I've been turning to work or other activities to take my mind off things.

1 2 3 4   15. I've been refusing to believe that it has happened.

1 2 3 4   16. I've been expressing my negative feelings.

1 2 3 4   17. I've been taking action to try to make the situation better.

1 2 3 4   18. I've been thinking hard about what steps to take.

1 2 3 4   19. I've been using alcohol or other drugs to help me get through it.

1 2 3 4   20. I've been giving up the attempt to cope.

1 2 3 4   21. I've been getting help and advice from other people

1 2 3 4   22. I've been praying or meditating.

1 2 3 4   23. I've been blaming myself for things that happened.

1 2 3 4   24. I've been making fun of the situation.

1 2 3 4   25. I've been getting comfort and understanding from someone.

1 2 3 4   26. I've been learning to live with it.

1 2 3 4   27. I've been looking for something good in what is happening.

1 2 3 4   28. I've been doing something to think about it less, such as going to the movies, watching TV, reading, daydreaming, sleeping, or shopping.

Appendix J

Short Form-36 Questionnaire

Quality of Life

Please circle the number that best describes your answer to each question. Circle only <u>one</u> response for each question.

1. In general, would you say your health is:

> Excellent........................ 1
> Very Good..................... 2
> Good............................ 3
> Fair............................. 4
> Poor............................. 5

2. Compared to one year ago, how would you rate your health in general <u>now</u>?

> Much better now than one year ago...................................... 1
> Somewhat better now than one year ago.............................. 2
> About the same as one year ago... 3
> Somewhat worse now than one year ago............................... 4
> Much worse than one year ago... 5

3. The following items are about activities you might do in a typical day. Does your health now
limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	Vigorous activities, such as running, lifting heavy objects, Participating in strenuous sport	1	2	3
b)	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c)	Lifting or carrying groceries	1	2	3

d)	Climbing several flights of stairs	1	2	3
e)	Climbing one flight of stairs	1	2	3
f)	Bending, kneeling, or stooping	1	2	3
g)	Walking more than a mile	1	2	3
h)	Walking several blocks	1	2	3
i)	Walking one block	1	2	3
j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other
regular daily activities <u>as a result of your physical health</u>?

		Yes	No
a)	Cut down on the amount of time you spent on work or other activities	1	2
b)	Accomplished less than you would like	1	2
c)	Were limited in the kind of work or other activities	1	2
d)	Had difficulty performing the work or activities (for example, it took extra time)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		Yes	No
a)	Cut down on the amount of time on work or on other activities	1	2
b)	Accomplished less than you'd like	1	2
c)	Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

7. How much <u>bodily</u> pain have you had during the past 4 weeks?

None	Very Mild	Mild	Moderate	Severe	Very Severe
1	2	3	4	5	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both
work outside the home and housework)?

Not at all	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1	2	3	4	5

9. These questions are about how you feel and how things have been with you during the
past 4 weeks. For each question, please give the one answer that comes closest to
what you are feeling. How much of the time during the past 4 weeks....

		All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a)	...did you feel full of pep?	1	2	3	4	5	6
b)	...have you been a very nervous person	1	2	3	4	5	6
c)	...have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5	6
d)	...have you felt calm and peaceful?	1	2	3	4	5	6
e)	...did you have a lot of energy?	1	2	3	4	5	6
f)	...have you felt downhearted and blue?	1	2	3	4	5	6
g)	...did you feel worn out?	1	2	3	4	5	6
h)	...have you been a happy person?	1	2	3	4	5	6
i)	...did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or
emotional problems interfered with your social activities (like visiting friends, relatives,
etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
a) I seem to get sick a little easier than other people.	1	2	3	4	5
b) I am as health as anybody I know.	1	2	3	4	5
c) I expect my health to get worse.	1	2	3	4	5
d) My health is excellent.	1	2	3	4	5

13. All things considered, how satisfied are you <u>at this time</u> with ......?

	Completely Satisfied	Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied	Completely Dissatisfied
a)your ability to function at work or as a homemaker or student?	1	2	3	4	5	6	7
b)your social life and relationships?	1	2	3	4	5	6	7
c)your life overall?	1	2	3	4	5	6	7

Appendix K

Demographic Questionnaire

1. Age: _____

2. What is your liver disease diagnosis? (please circle)

Hepatitis C   Alcoholic Cirrhosis   Autoimmune Hepatitis   Primary Sclerosing
                                                                 Cholangitis

Other(please specify):_____

3. Do you have any other medical conditions? If so, please list below...

_____

Note: Please circle your response.

4. Sex: Male   1   Female   2

5. Race/Ethnicity: (Which choice best describes you?)

Asian-American/ Pacific Islander...........................	1
African American/ Black...................................	2
Caucasian/ White/ European...............................	3
Hispanic..	4
Latino/Latina...	5
Native American..	6
Alaskan Native...	7
Other...	8
Specify:_____	

6. What is the highest grade or year of school that you have completed? (Circle one answer)

8th grade or less…….....………………..… 1
Some High School……………………..… 2
High School Graduate/ GED…………..… 3
Some College…………………………..… 4
College Graduate..…………………….… 5
Some Graduate School……………...….. 6
Graduate/Professional Degree……………... 7

7. What is your current marital status? Are you currently…..

Married or Partnered………………….… 1
Living Together……………………….... 2
Separated……………………………..… 3
Divorced……………………………….. 4
Widowed…………………………………5
Single, never Married……………….…… 6

Appendix L

Debriefing Form

This study had you complete a number of questionnaires, which looked at your liver disease symptoms. You reported how bothersome these symptoms are for you and we collected medical information on your liver disease. We also looked at your coping, substance use, and mental health. The purpose of this study was to look at the relationship between mental health, substance use, coping, liver disease symptoms, and quality of life across liver diseases.

We thought that patients with worse liver disease symptoms would have a lower quality of life compared to other patients. We also thought that the relationship between liver disease symptoms and quality of life was changed by mental health, substance use, and coping.

Research has found that liver disease patients have a poorer quality of life, but little research has looked at why this is true. Coping, mental health, and substance use, may impact quality of life for liver disease patients. The information from this study will improve our knowledge of these relationships.

If providing this information has made you feel distressed, we ask that you please let us know. We will help you find the right assistance. We will also provide you with a list of resources. If you have any questions or would like more information about the study please feel free to contact the investigator, Jill Clarida, The Department of Consultation Liaison Psychiatry, P.O. Box 980268, Richmond, VA 23298-0268 or by email at jclarida@vcu.edu

Vita

Jill Courtney Clarida was born on May 21, 1977, in Springfield, Illinois, and is an American citizen. She graduated from Springfield High School, Illinois in 1995. She received her Bachelor of Sciences in Psychology from the University of Dayton, Ohio in 1999, graduating Magna Cum Laude. She received her Master of Sciences in Clinical Psychology from Virginia Commonwealth University in 2003. She is currently at the University of North Carolina-Chapel Hill completing her internship to meet the requirements of a Ph.D. in Clinical Psychology. She is currently enrolled in the Clinical Psychology Ph.D. program at Virginia Commonwealth University.