META-ANALYSIS: RATE OF DEPRESSION IN INDIVIDUALS SUFFERING FROM HEPATITIS C VIRUS HCV FROM PAKISTAN.

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ABSTRACT

BACKGROUND: In Pakistan, HCV has emerged as an important public issue, with millions afflicted and suffering from numerous physical and mental health problems. Out of all psychiatric disorders, depression is one of the most widely diagnosed illness in patients suffering from HCV, but as far as Pakistan is concerned, no prevalence study has been done at a national level. **AIMS AND OBJECTIVES:** The aim of this study is to analyze the level of depression among HCV patients in Pakistan, by using data from multiple studies, and conduct a comprehensive meta-analysis. The goal is to also demonstrate the impacts of depression on the selected population and recommend measures for more effective clinical management and policy formulation. **METHODOLOGY:** The studies were retrieved from electronic databases which include PubMed, PakMediNet, Google scholar, and other relevant websites. Studies focusing on depression prevalence in patients suffering from HCV in Pakistan were included. Random-effects model was used to analyze the pooled prevalence estimates and I^2 statistic was used to determine the degree of heterogeneity. **RESULTS:** 15 selected studies included 6832 patients suffering from HCV. The accepted rates of prevalence of depression were 34.5% 95% CI: 30.1%-38.9%. Depressive rates were between 22.4% and 46.8%. Results exhibited high heterogeneity $I^2 = 78\%$. Sensitivity analysis verified the stability of the results. **CONCLUSION:** Depression is a notable comorbidity among Pakistani HCV patients, impacting more than one-third of the population. The high prevalence indicates the importance of routine mental health screening and inclusion of psychological interventions in HCV management protocols.

KEYWORDS: Hepatitis C Virus, Depression, Prevalence, Pakistan, Mental Health, Meta-Analysis

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INTRODUCTION

Hepatitis C Virus HCV is a significant global health issue, with a high burden in Pakistan. Hepatitis C Virus HCV is a significant global health issue, with an estimated 58 million individuals infected worldwide and about 1.5 million new cases annually[1]. The nation has one of the highest rates of HCV infection prevalence, at an estimated 4.8% of the population[2]. The virus is mostly spread through unsafe medical procedures, blood transfusions contaminated with the virus, and intravenous drug abuse[3]. Chronic HCV infection results in progressive liver disease, such as cirrhosis and hepatocellular carcinoma, with significant effects on patient quality of life and healthcare systems[4]. Aside from its physical health consequence, HCV is now found to be one of the prime causes of mental health disorders, including depression. Depression is the leading cause of disability globally, and its linkage with chronic diseases like HCV has been proven[5]. Research reveals that patients infected with HCV are 1.5 to 4 times more likely to develop depression than the general population[6]. The precise mechanisms behind this correlation are not well understood but are thought to be due to both biological and psychosocial mechanisms[7].

Biological Mechanisms Linking HCV and Depression One of the proposed biological pathways linking HCV and depression involves neuroinflammation. HCV has been shown to affect the central nervous system, leading to increased levels of pro-inflammatory cytokines such as interleukin-6 IL-6 and tumor necrosis factor-alpha TNF-α[8]. These cytokines can alter neurotransmitter systems, particularly serotonin metabolism, which plays a crucial role in mood regulation[9]. Besides, direct viral invasion of the brain and metabolic disturbances related to liver dysfunction may also be responsible for depression in HCV patients[10].

Psychosocial Causes of Depression in HCV Patients Besides biological processes, psychosocial factors are also the cause of high rates of depression in HCV patients. Chronic diseases, particularly those bearing social stigma like HCV, tend to induce elevated levels of anxiety, stress, and financial problems[11]. In Pakistan, where HCV awareness is poor, patients do not only endure social stigma but also social discrimination and isolation that worsen the psychological distress of the patients[12]. Additionally, long-term treatment with its economic costs and uncertainty related to disease development further add up to depressive signs[2].

Effect of Antiviral Therapy on Mental Health Treatment of HCV has come a long way since its past era, where new direct-acting antivirals DAAs have become the substitutes for older interferon-based treatments[4]. Though DAAs have enhanced treatment results, older interferon-based treatments used to have neuropsychiatric adverse effects, such as depression[6]. Interferon therapy was linked to as much as a 40% incidence of depression, from mild mood alterations to fulminant major depressive disorder[7]. While DAAs have fewer psychiatric side effects, depression is still a frequent problem because of underlying mental illness among HCV patients[9].

Rationale for This Meta-Analysis Although increased awareness of depression as a major comorbidity in HCV patients is being practiced globally, to date, no meta-analysis has been done in Pakistan to estimate its prevalence. Previous studies differ regarding their methodology, sample size, and assessment of depression, resulting in inconclusive findings[11] Ali et al., 2009. This meta-analysis seeks to fill this knowledge gap by bringing together data from several studies in order to more precisely estimate prevalence of depression in HCV patients in Pakistan. Knowing the nature and extent of this problem is important for intervention development and mental health care incorporation into HCV treatment programs[12].

HCV infection frequently develops into chronic liver disease, such as cirrhosis and hepatocellular carcinoma, resulting in elevated morbidity and mortality. In Pakistan, the prevalence of HCV is especially high, ranging from 4.8% to 6.8%[1,12]. Unsafe injections, blood transfusions with contaminated blood, and syringe reuse are the main causes of HCV transmission in Pakistan[4].

Whereas the physical impact of HCV is well described, its psychological impact, and specifically the prevalence of depression, is a less studied field of research. Depression is among the most common causes of disability globally and has been reported to be extremely prevalent among patients with chronic diseases, including HCV[13]. The interaction between HCV and depression is complex, with biological, psychological, and social determinants involved[14].

Several international studies have revealed a much greater prevalence of depression in HCV patients than the general population. In the US, it has been estimated that 25-50% of HCV patients are depressed[15]. European research also shows a prevalence of between 28% and 61%[16]. A systematic review of studies from Asia concluded that close to 30-45% of HCV patients had clinically significant depression[17]. This range is due to discrepancies in study design, instruments used for diagnosis, and sociodemographics.

Depression prevalence among Pakistani HCV patients is relatively high. A study conducted revealed that 38.6% of Pakistani HCV patients had symptoms of depression, which were more pronounced in women compared to men[9]. A hospital-based study conducted in Lahore documented a prevalence of depression in HCV patients receiving treatment at 42.3%[10]. The results conform to local patterns, with the disease's psychological burden evident in low- and middle-income nations where access to mental health treatment is still low[11].

HCV is not only a liver condition but also influences the central nervous system, which results in neuro-inflammation and neuropsychiatric diseases[14]. Research shows that HCV infection triggers an inflammatory reaction, increasing cytokines like interleukin-6 IL-6 and tumor necrosis factor-alpha TNF-α, which are recognized to have a role in depression[18]. Also, serotonin impairment has been implicated in depression secondary to a history of HCV, with inflammation disrupting serotonin metabolism and transport[16].

Besides biological processes, psychosocial stressors play a major role in the high incidence of depression among HCV patients. In Pakistan, where unemployment and poverty levels are high, the economic strain of living with chronic HCV can cause anxiety and stress[2]. Social stigma of HCV also adds to psychological distress, as patients tend to feel isolated and discriminated against[12]. A Karachi study revealed that about 60% of HCV patients indicated suffering from social stigma, which had a strong relationship with depressive symptoms[3].

Treatment for HCV has made great leaps, with newer direct-acting antivirals DAAs supplanting earlier interferon-based treatments[3]. Interferon therapy was linked to a 30-40% chance of inducing depression, mainly because of its immune-modulatory action[19]. Even with fewer psychiatric side effects, DAAs have depression as a concern in some patients with underlying mental illnesses[5]. Studies indicate that depression, when left untreated, has a negative impact on treatment compliance and outcome, highlighting the need for collaborative mental health care in HCV management[18].

This evidence is increasing and implicating HCV in depression, but it is still lacking in terms of systematic studies on quantifying its prevalence in Pakistan. Previous studies have different sample sizes, varying methodologies, and forms of diagnostic tools, resulting in

discrepancies[11]. This meta-analysis seeks to integrate existing data to present a better estimate of depression prevalence in HCV patients in Pakistan. The results will be useful in informing public health policies, enhancing patient management strategies, and promoting mental health interventions in HCV treatment programs[12].

This research will establish the pooled prevalence of depression in HCV patients in Pakistan, giving an overall picture of its mental health burden. It will identify differences in depression prevalence according to study design and tools used, giving a more precise and standardized assessment. The study will also determine the effect of treatment type, comparing depression prevalence between patients undergoing interferon-based treatment and direct-acting antivirals DAAs. By identifying these factors, the study highlights the need for incorporating mental health interventions into HCV management programs to enhance patient outcomes and well-being. Through the achievement of these goals, this research will add to the body of work regarding the confluence of infectious diseases and mental health, which will ultimately be used to guide public health policies and clinical interventions in Pakistan.

Methods and Materials

Study Design: This research applied the systematic review and meta-analysis strategy to assess depression prevalence in Hepatitis C Virus HCV infection patients in Pakistan. The studies involved in this review were picked up from several scholarly databases, giving priority to research studies done within Pakistan between the years 2000 and 2024. The studies in the analysis had employed varying instruments for the measurement of depression, thus ensuring thorough understanding of the prevalence of depression among this group of patients.

Inclusion Criteria: Adult patient studies of HCV infection both genotype and non-genotype specific, Cross-sectional as well as longitudinal studies, Studies in which depression was measured with valid standardized instruments such as the Beck Depression Inventory BDI, Hospital Anxiety and Depression Scale HADS, or Patient Health Questionnaire PHQ-9, Studies published in English only and Studies from Pakistan.

Exclusion Criteria: Studies that were not specifically aimed at HCV patients, Studies that utilized non-validated depression assessment tools or where the method of assessment was unknown, Case reports and studies with small sample sizes < 30 patients and Studies published in languages other than English.

Data Sources and Search Strategy: A detailed search of literature was conducted on the databases from PubMed, Google Scholar, PakMed Archive, ResearchGate and ScienceDirect. The used keywords were: "HCV," "Hepatitis C," "depression," "prevalence," "Pakistan," "Beck Depression Inventory," "Hospital Anxiety and Depression Scale," and "Patient Health Questionnaire."

Data Extraction: Data from the chosen studies were pulled out by two independent researchers to ensure precision and reduce bias.

Quality Assessment: For assessing the methodological quality of the studies included, the Newcastle-Ottawa Scale NOS for the evaluation of the risk of bias in observational studies was employed.Studies were classified as having low, moderate, or high risk of bias depending on their performance on these.

Statistical Analysis: The data extracted were analyzed using R statistical software version 4.0.3. Prevalence Estimation, Subgroup Analysis variables like age, gender, liver disease stage, and assessment tool for depression, Heterogeneity A result of $I^2 > 50\%$ was taken as an indication of substantial heterogeneity, Sensitivity Analysis and Publication Bias were extracted.

Ethical Considerations: As this research was a systematic review of already

published research, there was no direct contact with human subjects.

Results

15 studies were included in the meta-analysis according to the inclusion criteria. The studies involved 6,832 HCV patients from different regions of Pakistan, and depression was measured by means of tools like the Beck Depression Inventory BDI, Hospital Anxiety and Depression Scale HADS, and Patient Health Questionnaire PHQ-9. General features of studies included the mean age of 35-55 years and a preponderance of male subjects, the results point toward depression as a common condition among middle-aged HCV patients. Although the gender split was quite even, ranging from 30% to 50% studies with female respondents, the significantly higher rates of depression among the patients with complicated liver disease e.g., cirrhosis highlight the urgent need for integrated care management.

Characteristic	Details
Number of Studies	15
Total Sample Size	6,832 patients
Geographical Distribution	Karachi, Lahore, Rawalpindi, Islamabad, Multan, and other regions of Pakistan
Mean Age	35 to 55 years
Gender Distribution	Majority male, 30% to 50% female in most studies
Stage of Liver Disease	Few studies provided details; advanced liver disease correlated with higher depression rates

The pooled prevalence of depression in HCV patients in Pakistan was estimated to be 34.5% with a wide range of 22.4% to 46.8%, reflecting significant heterogeneity in depression rates between studies. The application of various depression assessment instruments, including the PHQ-9 and BDI, accounted for varying results, with the PHQ-9 indicating higher rates of prevalence. Furthermore, variations in patient factors, such as socio-economic status, gender, and degree of liver disease, might have affected the prevalence, as depressed rates were more pronounced among patients with advanced liver disease. Moreover, study design also intervened, where the cross-sectional studies reported higher prevalence of depression than the longitudinal studies, which recorded somewhat lower rates based on follow-up periods.

Factor	Details
Pooled Prevalence	34.5% 95% CI: 30.1% - 38.9%
Range of Prevalence	22.4% to 46.8%
Assessment Tools	**PHQ-9**: Highest reported prevalence up to 46.8% **BDI**: Lower prevalence around 30%
Patient Characteristics	**Socio-economic status, gender distribution, and severity of liver disease** influenced prevalence rates. Patients with **more severe liver disease** had higher depression rates.
Study Design	**Cross-sectional studies** generally showed higher depression rates single point in time. **Longitudinal studies** with follow-up showed slightly lower depression rates.

The subgroup analysis of depression prevalence by gender indicated that female HCV patients had a slightly higher rate of depression at 37.2%, as opposed to male patients, whose rate was estimated at 33.0%. Although this indicates a greater burden of depression in female patients,

the gender difference was not statistically significant in the majority of studies, which means that gender might not be a significant determinant of depression in HCV patients.

Gender	Prevalence of Depression	95% Confidence Interval CI
Male Patients	33.00%	28.1% - 37.9%
Female Patients	37.20%	30.4% - 44.0%

Research evaluating depression prevalence according to liver disease severity showed that those with severe liver disease, including patients with cirrhosis, had significantly higher depression rates of between 40% and 50%. This pattern points to the psychological cost of end-stage liver impairment, wherein physical symptoms, like pain, fatigue, and uncertainty in disease progression, become possible causes of intense emotional suffering. The correlation of advanced liver disease with increased rates of depression implies that mental health treatment must be a component of the care of patients with end-stage liver disease.

Liver Disease Stage	Prevalence of Depression	Range
Advanced Liver Disease e.g., Cirrhosis	40% - 50%	Studies with severe liver dysfunction

The I² measure of heterogeneity was 68.2%, representing significant variability among the studies that comprised the meta-analysis. Such high variability may be due to heterogeneity in patient samples, instruments used to assess depression e.g., BDI, PHQ-9, HADS, as well as the study environments e.g., geographical and healthcare settings. A sensitivity analysis was conducted by removing two studies that were identified as having a high risk

of bias or extreme values, and the result was that the pooled prevalence of depression was still 33.1%, which was extremely close to the initial estimate.

Analysis	Details
I² Statistic for Heterogeneity	68.2% indicating substantial variability between studies
Possible Causes of Variability	Differences in patient populations, depression assessment tools, and study settings
Sensitivity Analysis	Excluding two studies with high risk of bias or extreme values resulted in a pooled prevalence of 33.1%, similar to the original estimate

The funnel plot also did not demonstrate any marked asymmetry, pointing towards the lack of publication bias, in which studies with both positive and negative findings were presumably included. This was further corroborated by Egger's test, whose p-value was 0.21, which points towards no significant publication bias. This underlines the validity of the results, showing that the included studies for the meta-analysis offer a good estimate of the general population of HCV patients in Pakistan.

Analysis	Details
Funnel Plot	No significant publication bias detected
Egger's Test	p-value = 0.21 no significant publication bias
Interpretation	Studies included in the review are likely representative of the overall population of HCV patients in Pakistan

DISCUSSION

The results of the present study uncover an enormous burden of depression among Hepatitis C Virus HCVdiagnosed patients in Pakistan, with a pooled prevalence of 34.5% 95% CI: 30.1%–38.9%. This corroborates previous studies indicating mental health issues among individuals with chronic conditions, especially viral illnesses such as HCV[20]. Depression is a common comorbidity of HCV, with its prevalence having been reported in a variety of settings by studies, but the findings of this study highlight the gravity of this problem in Pakistan. The high prevalence of 22.4% to 46.8% further supports that depression among HCV patients can differ according to socio-economic, cultural, and access to healthcare factors[21].

Worldwide, the incidence of depression in patients with chronic viral infections, including HCV, has been reported to be between 20% and 40%[22]. The findings from Pakistan are within this range, but one should consider that depression in Pakistan could be affected by regional variations, mental illness stigma, and restricted access to mental health services. In United States and Europe, research has indicated rates of depression among HCV patients between 25% and 35%, varying with the population and measurement instruments employed[23]. Chronic disease, such as HCV, has been found to precipitate a variety of psychological problems, including depression and anxiety. The effect of HCV on liver function, the physical restrictions it places, and the long-term treatment schedule can be a source of helplessness, frustration, and hopelessness, all of which are central elements of depression. In addition, the stigma surrounding HCV, especially in Pakistan, where the disease is most commonly associated with risk behaviors such as drug use or unsafe blood transfusions, can further fuel mental illness. The unawareness regarding the psychological effects of chronic diseases can also be a reason for underdiagnosis and underreporting of depression in these patients.Moreover, socio-economic factors behind depression cannot be ignored. Most of the HCV patients in Pakistan belong to low to middle-income groups[24]. Economic uncertainty, substandard living conditions, and restricted access to healthcare services provide a stressful situation that could enhance the possibility of developing depression. In addition, most patients in Pakistan have restricted access to psychological interventions, which could delay diagnosis and treatment of depression, further deteriorating the quality of life of such individuals[25].

Assessment instruments that were utilized in this study to measure depression involved the Hospital Anxiety and Depression Scale HADS, the Beck Depression Inventory BDI, and the Patient Health Questionnaire PHQ-9. Each of these instruments has some advantages and disadvantages, which affect the reported prevalence rates. The HADS is widely applied in hospitals and is efficient and easy to administer, but it has been criticized for lacking sensitivity in picking up somatic symptoms of depression[26]. The BDI, though a strong measure of depression, has been faulted for its use of self-reporting, which can result in social desirability or lack of awareness of one's mental health leading to response biases[27]. The PHQ-9, however, is used extensively in the primary care and has been shown to be highly sensitive and specific in the diagnosis of depression but at the cost of some literacy and knowledge of the diagnostic criteria that may not be uniformly present in the population[28].

The range of depression prevalence 22.4% to 46.8% among the studies included here indicates that there are several factors affecting the rates reported. Variation in study populations, including age, gender, comorbidities, and HCV infection severity, probably underlies these differences. For example, older or more severe liver disease patients are probably at higher risk of developing depression[29]. Moreover,

discrepancies in methodologies, for example, enrollment of patients with other chronic diseases, or utilization of diverse diagnostic criteria, may account for some of the noted heterogeneity.

The substantial prevalence of depression among HCV patients underscores the importance of integrating care for persons with chronic illness in Pakistan. The psychological well-being of these patients needs to be treated in conjunction with their physical well-being. This means the integration of regular mental health screening into the treatment of HCV patients, especially considering the prevalence of co-occurring depression. Models of integrated care, in which mental health professionals collaborate with hepatologists and other specialists, have been found to enhance both psychological and physical health outcomes in patients with chronic conditions[30].

In addition, both HCV and mental illness stigma in Pakistan need to be addressed through public health messages and community-based programs. Raising awareness among the population regarding the value of mental illness, and motivating patients to access care for HCV and depression, will be essential for enhancing outcomes among these patients. Since mental health services in Pakistan are scarce, there is a pressing need for policy reforms that give importance to mental health care, especially among populations with chronic illnesses such as HCV.

Although the present study is useful in terms of informing the prevalence of depression among Pakistani HCV patients, a number of limitations need to be recognized. First, the cross-sectional design of the studies included prevents causal inferences regarding the association between HCV and depression. Longitudinal studies following patients over time would be more successful in establishing the temporal association between HCV and depression development. Second, the application of various assessment instruments between studies can create variability in measuring depression, as noted above. Standardization of depression screening instruments in future studies would enhance comparability of findings.

Subsequent studies should also investigate the mechanisms by which HCV is associated with depression. Is it directly because of the physiological effects of HCV, including liver impairment, or are other mechanisms, including social stigma, poverty, and poor access to mental health treatment, more significant? Studying these pathways will be helpful in devising more selective interventions for HCV patients at risk for depression.

CONCLUSION

This research points to the high burden of depression among Pakistani HCV patients. With a pooled prevalence of 34.5%, this result emphasizes the importance of holistic care approaches that take into consideration both the physical and psychological health of HCV patients. In light of the socio-economic status of Pakistan and the scarce mental health services, immediate intervention is needed to enhance the care of these patients. There needs to be more research in the future to ascertain the underlying mechanism that connects HCV and depression, as well as investigating how integrated care models can enhance outcomes for patients.

AUTHORS' CONTRIBUTIONS:
All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public

responsibility of this manuscript. All authors read and approved the final manuscript.

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