Original Article

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Hyperhomocysteinemia in Patients with Chronic Viral Hepatitis C

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ABSTRACT

Objective: To determine the incidence of hyperhomocysteinemia among patients with chronic hepatitis C virus (HCV).

Methodology: A descriptive cross-sectional, descriptive study was conducted at Department of Medicine, Liaquat University Hospital Hyderabad from May to October 2023. Patients aged 20 to 60 years, both genders, who were known case of viral hepatitis C for duration of more than six months were enrolled. 2 ml venous blood sample was collected from each patients using sterilized disposable syringes and sent to the laboratory for serum homocysteine analysis and hyperhomocysteinemia was defined as serum homocysteine level >15 µmol/L. Data were collected and entered in a pre-designed proforma attached at the end of dissertation.

Results: A total of 121 patients were enrolled with a male preponderance (73.1%) and overall median age of 41 years. Hyperhomocysteinemia was observed in 66.9% patients with chronic Hepatitis C. None of the effect modifiers were observed to have a significant impact on the outcome variable i.e. presence of hyperhomocysteinemia (p->0.05).

Conclusion: Hyperhomocysteinemia was found to be highly prevalent among patients with chronic hepatitis C, indicating it as a common metabolic abnormality in this population. This underscores the importance of routine homocysteine level screening to facilitate early detection and timely intervention, thereby potentially reducing the risk of subsequent complications.

Keywords: Hepatitis C, hyperhomocysteinemia, hepatic inflammation, viral hepatitis, liver fibrosis, liver cirrhosis

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Introduction

Hepatitis C Virus (HCV) represents a major global health challenge, as it can progress to chronic viral hepatitis and more fatal conditions like cirrhosis, liver failure, and hepatic cancer, making it a significant contributor to global mortality, with particular reference to resource limited nations.[1,2] Even though nearly 15–45% of recent HCV infections resolve spontaneously within half a year, a majority of HCV infections (55-85%) progress to chronic form of HCV infection, and even following successful treatment, likelihood of reinfection still persists.[3] During 2019, around 58 million global population was projected to suffer from chronic viral infection with hepatic C and it is projected that around 20–25% of patients with chronic viral hepatitis are likely to develop cirrhosis within next 2.5 to 3 decades.[4,5] The growing disease burden calls for the exploration of sensitive prognostic markers to predict disease progression in individuals who are chronically infected with HCV.

Hyperhomocysteinemia has been noted to contribute to the development as well as progression of various systemic conditions including hepatic, cardiovascular, and renal diseases, making it a significant biochemical

indicator of increased risk of these conditions.[6,7] It is a non-coded amino acid, which is a derivative of methionine metabolic activity and is regulated through remethylation and transsulfuration pathways. Circulating homocysteine concentrations may elevate on disruption of these pathways. [8] Chronic viral hepatitis C may contribute to this imbalance of remethylation and trans-sulfuration pathways due to persistent inflammation, hepatocellular injury, and impaired methylation capacity.[9,10]

Additionally it has been evident that moderate elevations in homocysteine levels are strongly linked to a higher likelihood of developing deep vein thrombosis and experiencing recurrent venous thromboembolism. Hence the portal vein thrombosis (PVT) is recognized as a serious and common complication in patients with liver cirrhosis.[11,12] One proposed mechanism is that homocysteine exerts a damaging effect on vascular endothelial cells and the coagulation process, resulting in reduced nitric oxide (NO), platelet aggregation raised and a state of increased blood coagulability.[11] Although, the relationship between chronic HCV infection and hyperhomocysteinemia is not well established, particularly regarding its prevalence. Therefore, this study aims to determine the frequency of hyperhomocysteinemia in patients with chronic hepatitis C, which may help guide early management strategies to prevent further complications such as portal vein thrombosis and fibrosis.

Methodology

This cross-sectional, descriptive study was conducted in the Department of Medicine, Liaquat University Hospital, Hyderabad, over a period of six months from May to October 2023. Patients of either gender, aged 20–60 years, with a known diagnosis of chronic viral hepatitis C for more than six months were included. Patients were excluded if they had a history of alcohol consumption, were on anti-HCV therapy, corticosteroids, or immunosuppressive therapy, had known hematological disorders (e.g., leukemia, lymphoma), chronic renal failure, were pregnant or lactating, were on vitamin/mineral supplements, or had received a blood transfusion. Exclusion criteria were confirmed through relevant medical records and consultant-provided diagnosis cards. A non-probability consecutive sampling technique was used. Based on a reported prevalence of hyperhomocysteinemia in chronic viral hepatitis C of 91.35%, with a 6% margin of error, a sample size of 84 patients with chronic viral hepatitis C was calculated. After obtaining approval from the Research and Evaluation Unit, CPSP, and informed consent from eligible participants, 2 cc venous blood samples were collected by the principal investigator using sterilized disposable syringes and sent to the laboratory for serum homocysteine analysis. All specimens were evaluated by a senior pathologist with more than three years of clinical laboratory experience. Hyperhomocysteinemia was diagnosed according to predefined cut-off values, while potential effect modifiers, including hypertension, smoking, obesity, diabetes mellitus, vitamin B12 deficiency, folic acid deficiency, anemia, and educational status, were also assessed. Hyperhomocysteinemia was considered when serum homocysteine >15 μmol/L. Data were recorded on a pre-designed proforma, and all study expenses were borne by the researcher. Data were analyzed using SPSS version 24.0. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were computed for quantitative variables. Stratification was performed for potential effect modifiers, followed by post-stratification chi-square tests for categorical data. A p-value of ≤ 0.05 was considered statistically significant.

Results

The present study enrolled a total of 121 patients, with the majority of participants were male (57.0%) and resided in urban areas (77.7%). Over half (54.5%) had only primary education, while 20.7% had completed matriculation, and smaller proportions had secondary (11.6%) or intermediate education (13.2%). Common comorbidities included hypertension (36.4%), obesity (28.9%), diabetes mellitus (27.3%), anemia (19.0%), folic acid deficiency (12.4%), and vitamin B12 deficiency (7.4%). A history of smoking was reported by 64.5% of participants. Hyperhomocysteinemia was present in 66.9% of cases. The mean age was 39.7 ± 11.0 years, with a median of 41 years (range 21–58 years). The mean duration of complaints was 10.7 ± 2.9 months, and mean homocysteine levels were 17.6 ± 4.3 μmol/L. Table I

Hyperhomocysteinemia was observed in a significant proportion of the study population, affecting 66.9% of the participants. Figure 1

Based on stratification analysis there was no statistically significant associations between hyperhomocysteinemia and any of the assessed demographic or clinical variables ($p>0.05$). In the patients aged 20–40 years, 46.9% had hyperhomocysteinemia compared to 53.1% in the 41–60 years group ($p=0.444$). Males had a higher proportion

without hyperhomocysteinemia (70.0%) compared to females (30.0%), with a borderline significance (p=0.052). Most participants resided in urban areas in both groups (76.5% vs. 80.0%, p=0.817). Educational background, diabetes mellitus, hypertension, obesity, smoking status, and disease duration showed no significant differences between groups. Table II.

Table:1. Clinical and demographic characteristics of the patients. (n=121)

Variables	Frequency	Percentage
Gender		
Male	69	57.0%
Female	52	43.0%
Residential Status		
Urban	94	77.7%
Rural	27	22.3%
Educational background		
Primary	66	54.5%
Secondary	14	11.6%
Metric	25	20.7%
Intermediate	16	13.2%
Co-morbidities		
HTN	44	36.4%
DM	33	27.3%
Obesity	35	28.9%
B12 Deficiency	9	7.4%
Folic Acid Deficiency	15	12.4%
Anemia	23	19.0%
Smoking History		
Yes	78	64.5%
No	43	35.5%
Variable	Mean (SD)	Median (IQR)
Age (Years)	39.7 (11.0)	41.0 (30.0-49.0)
Duration of complaints (months)	10.7 (2.9)	11.0 (8.0 –13.0)
Homocysteine levels (µmol/L)	17.6 (4.3)	17.9 (13.5 –21.1)

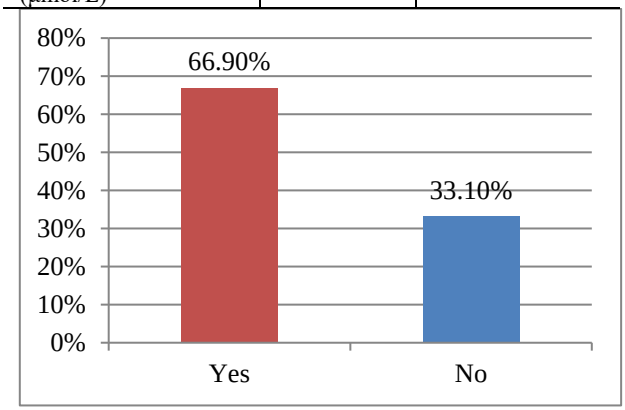

Figure 1. Frequency of Hyperhomocysteinemia.

Table II: Stratification of various parameters on the basis of hyperhomocysteinemia.

Variable		Hyperhomocysteinemia		p-value
		Yes	No	
Age (years)	20-40	38 (46.9)	22 (55.0)	0.444
	41-60	43 (53.1)	18 (45.0)	
Gender	Male	41 (50.6)	28 (70.0)	0.052
	Female	40 (49.4)	12 (30.0)	
Residence	Urban	62 (76.5)	32 (80.0)	0.817
	Rural	19 (23.5)	8 (20.0)	
Education	Primary	44 (54.3)	22 (55.0)	0.791
	Secondary	11 (13.6)	3 (7.5)	
	Matric	16 (19.8)	9 (22.5)	
	Intermediate	10 (12.3)	6 (15.0)	
DM	Yes	22 (27.2)	11 (27.5)	1.000
	No	59 (72.8)	29 (72.5)	
HTN	Yes	30 (37.0)	14 (35.0)	0.844
	No	51 (63.0)	26 (65.0)	
Obesity	Yes	24 (29.6)	11 (27.5)	0.835
	No	57 (70.4)	29 (72.5)	
Smoking	Yes	29 (35.8)	14 (35.0)	1.000
	No	52 (64.2)	26 (65.0)	
Disease duration (months)	6-10	41 (50.6)	19 (47.5)	0.747
	11-15	40 (49.4)	21 (52.5)	

Discussion

Chronic HCV infection represents a significant burden of morbidity and mortality around the world, with a risk of progression to more severe complications including cirrhosis and hepatocellular carcinoma.[13,14] In Pakistan, earlier research on HCV prevalence and its regional distribution highlighted the growing burden of HCV, aiming to help developing more effectively tailored presentation and management techniques. However, the results are inconsistent across the studies.[15] In the present study, the prevalence of hyperhomocysteinemia was evaluated among patients with chronic viral hepatitis C, with a mean age of 39.7 ± 11.0 years and study population comprised predominantly males (57.0%) and a majority residing in urban areas (77.7%). Our demographic patterns also consistent with the findings of Siqueira et al[16] where they reported a predominance of male participants (52.3%) in their study. In line with the present study, Dashjamts G et al[17] reported a mean participant age of 40.7 ± 11.1 years; however, in contrast to our findings, they observed a lower proportion of men (22.9%, n=51) and a higher proportion of women (77.1%, n=171). This gender difference may be due to variations in population characteristics, regional factors, or healthcare-seeking behaviors.

In this study, the most common comorbidity was hypertension (36.4%), followed by obesity (28.9%), diabetes mellitus (27.3%), anemia (19.0%), folic acid deficiency (12.4%), and vitamin B12 deficiency (7.4%), while 43 patients (35.5%) were smokers. Consistent with these findings, Hsu et al[18] also reported hypertension as the most frequent comorbidity, followed by diabetes.

However, Hudson et al[19] reported differing results, identifying depression (26.1%) as the most common comorbidity, followed by diabetes (11.3%).

In this study, hyperhomocysteinemia (>15 µmol/L) was observed in 66.9% (n=81) patients, with median homocysteine level of 17.9 µmol/L. These findings are much higher than those reported in the study of Herrero et al[20] where 27% of patients were detected with hyperhomocysteinemia. On the other hand, in the study of Mustafa et al[21] Hyperhomocysteinemia (91.35%) was much higher than that of ours. These findings highlight the significant variability across studies, possibly due differences in geographical location and study design. According to another previous study by Ventura P et al[22] reported that the prevalence of hyperhomocysteinemia in the liver cirrhosis group was 40.9%, which was significantly higher (all $p < 0.01$) compared to the control group (12%), chronic active hepatitis group (14.7%), and fatty liver group (25%). Moreover, its frequency increased progressively with the severity of liver disease, as reflected by Child–Pugh classification: 22.2% in Child A, 50% in Child B, and 58.3% in Child C.[22]

In this study, hyperhomocysteinemia was more frequent in patients aged 41–60 years (53.1%) compared to those aged 20–40 years (46.9%), though the difference was not statistically significant (p = 0.444). Males showed a higher proportion without hyperhomocysteinemia (70%) than females (30%), with a borderline p-value (p = 0.052). Most participants resided in urban areas, with similar distribution of hyperhomocysteinemia between urban (76.5%) and rural (23.5%) residents (p = 0.817).

Educational status, diabetes mellitus, hypertension, obesity, smoking, and disease duration also showed no significant association with hyperhomocysteinemia (all p > 0.05). Partially overlapping with our findings, a meta-analysis conducted by Yang et al[23] reported that hyperhomocysteinemia was more frequent in those age above 65 (35.2%), and frequency decreased with age as 22.7% in age range 45–65, and in 17.9% of the patients aged below 45. Similar to our study, hyperhomocysteinemia in men (34.8%) was two-fold higher as compared to women (18.7%). However, unlike our results, Hyperhomocysteinemia was more common in rural residents (28.1%) than the urban population (26.5%). Additionally, they found statistically significant heterogeneity across all variables (p<0.01). Overall, our age and sex patterns differ from large population meta-analyses conducted by Yang et al[23] which shows increasing hyperhomocysteinemia with age and higher prevalence in men. This discrepancy may reflect differences between our chronic HCV clinical cohort and general population samples, limited sample size and cohort-specific factors such as folate/B12 status, MTHFR genotype, HCV genotype, and liver disease severity. However, HCV-specific studies on age- and sex-stratified prevalence are limited.[24] Therefore; our findings contribute valuable insights to the limited literature on the distribution of hyperhomocysteinemia in the chronic HCV population. However, this study has several limitations, most notably the relatively small sample size, which may restrict the generalizability of the results. Hence, future large-scale studies are warranted to validate these findings and to explore more in-depth correlations between hyperhomocysteinemia and adverse complications of chronic hepatitis C, particularly among patients with chronic liver disease.

Conclusion

Hyperhomocysteinemia observed to be highly prevalent (66.9%) among patients with chronic hepatitis C, highlighting it as a common metabolic abnormality in this population. It emerges as a significant concern in the realm of chronic Hepatitis C, potentially compounding the existing health risks associated with HCV infection, highlighting the need for routine screening of homocysteine levels in chronic hepatitis C patients, regardless of clinical or demographic profile, to enable early identification and timely management, potentially reducing the risk of complications such as portal vein thrombosis and liver fibrosis.

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