ASSESSING THE FREQUENCY OF CYTOPENIAS IN PATIENTS WITH HEPATITIS C THERAPY: AN ANALYTICAL DESCRIPTIVE OBSERVATIONAL STUDY

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ABSTRACT

OBJECTIVES

This study aimed to determine the frequency of cytopenias among patients receiving hepatitis C therapy and to examine their relationship with different treatment regimens

METHODOLOGY

This analytical descriptive observational study was conducted over six months (May-October 2024) at the Department of Medicine and Gastroenterology, Lady Reading Hospital, Peshawar. A total of 113 patients aged 20-70 years with chronic hepatitis C receiving antiviral therapy were included using consecutive sampling. Data were collected at the 12-week follow-up. Hematological parameters and sustained virological response (SVR) were assessed. Data were analyzed using SPSS version 25. Chi-square test, Cramer's V, and multivariate logistic regression were applied. A p-value ≤0.05 was considered statistically significant.

RESULTS

The mean age of participants was 40.1 ± 9.0 years, with a male predominance (55.8%). The overall SVR rate was 80.5%, with the highest response observed in patients treated with sofosbuvir/velpatasvir (90.8%; 95% CI: 82.1-96.2). Cytopenias were observed in a considerable proportion of patients, with anemia being the most common (23.9%; 95% CI: 16.1-31.7), followed by Thrombocytopenia (9.7%), leukopenia (8.8%), and pancytopenia (6.2%).

A statistically significant association was found between treatment regimen and cytopenias ($p < 0.001$), with a strong effect size for anemia (Cramer's V = 0.768). Multivariate analysis identified treatment regimen as the only independent predictor of anemia. Patients receiving sofosbuvir/velpatasvir had significantly lower odds of anemia than those receiving conventional therapy (AOR = 0.006; 95% CI: 0.001-0.054; $p < 0.001$).

CONCLUSION

Direct-acting antiviral therapy, particularly sofosbuvir/velpatasvir, is associated with high virological response and a lower frequency of cytopenias. However, given the observational design, findings should be interpreted cautiously. Further multicenter studies are recommended.

KEYWORDS: *Hepatitis C, Direct-acting antivirals, Ribavirin, Cytopenias, SVR.*

INTRODUCTION

Hepatitis C virus is one of the major health concerns among bloodborne viral infections, affecting approximately 71 million people worldwide, with a prevalence of 2.8%.[1] The burden of HCV has been reported to be higher in low-and middle-income countries. Cytopenias, a deficiency of mature blood cells resulting in anemia, leukopenia, and Thrombocytopenia, are major complications associated with HCV infection, especially during antiviral therapy.[2] Thrombocytopenia, affecting up to 37% of HCV patients, is the first abnormality detected in routine laboratory tests, way before diagnosis of cirrhosis.[3] The risk is reportedly associated with disease progression and is affected by interferon-based antiviral treatment.[4] As the burden of HCV in Asia is significantly higher, prevalence in Egypt, India, and Pakistan is among the highest worldwide.[5] The second-highest burden of HCV disease is reported in Pakistan, with a prevalence of 4.5% to 8.2%. The overall prevalence of Thrombocytopenia is reported to be 23.5%-37% in HCV patients.[6] Risk is higher in patients with prolonged illness and associated comorbidities, including thalassemia, end-stage renal disease patients who are dialysis dependent, with a prevalence of 32%-46% Cytopenias continue to be a major clinical dilemma among the health care providers in the high-

burden, low and middle-income nations such as Pakistan.[7] The severity of Cytopenias influences the treatment advancements of HCV, leading to a high rate of morbidity and antiviral therapy discontinuation.[8] The need for area-based data on the frequency, determinants, and risk factors of cytopenias in patients receiving antiviral therapy for HCV is important for mapping prevention strategies, improving patient management, reducing morbidity, and enhancing treatment outcomes. Routine hematologic tests will assist health professionals in tracking and identifying patients at risk, managing treatment regimens, and allocating resources.[9] This study aims to assess the frequency of cytopenias in patients on hepatitis C therapy after a 12-week follow-up visit at Lady Reading Hospital in Peshawar (LRH).

METHODOLOGY

This analytical cross-sectional study was conducted at the Department of Medicine and Gastroenterology, Lady Reading Hospital (LRH), Peshawar. Ethical approval was obtained from the Institutional Review Board of LRH (ERC#156/LRH/MTI). The study was carried out over a period of six months from 20th May 2024 to November 2024. Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki. A total of 113 adult patients diagnosed with chronic hepatitis C and receiving antiviral therapy were included in the study. A consecutive non-probability sampling technique was used to recruit eligible participants who had attended the medical or gastroenterology outpatient or inpatient departments after completing 12 weeks of hepatitis C treatment. Consecutive, non-probability sampling technique was used. The sample size was calculated using the WHO sample size formula for proportion estimation: $\mathbf{n = Z^2 \times p \times (1-p) / d^2}$
where Z = 1.96 at a 95% confidence level, p = 0.32 (expected prevalence of anemia among patients with hepatitis C based on previous regional studies) and d = 0.08 (margin of error).[10] The calculated sample size was approximately 113 participants, and all eligible patients meeting the inclusion criteria during the study period were included in the final analysis. These included patients aged 20-70 years who had confirmed hepatitis C infection and were under antiviral therapy using direct-acting antivirals (DAAs) or a conventional regimen. The study excluded patients with an acute case of hepatitis C infection, fulminant hepatitis, cytopenias that had been previously diagnosed before treatment, hematological malignancies, myeloproliferative disorders, multiple myeloma, decompensated chronic liver disease, liver transplant patients, or hepatocellular carcinoma. Data were collected using a pre-structured questionnaire consisting of three sections. The first section recorded demographic characteristics, including age, gender, residence, socioeconomic status, and occupation. The second section included clinical variables such as hepatitis C infection duration, treatment regimen, and sustained virological response (SVR). The third section included laboratory investigations, including complete blood count (hemoglobin, white blood cell count, and platelet count), liver function tests (ALT and AST), and HCV RNA PCR results. Cytopenias were defined using standardized laboratory criteria. Anemia was defined according to World Health Organization thresholds as hemoglobin <12 g/dL in females and <13 g/dL in males, while leukopenia and Thrombocytopenia were defined as white blood cell count <4.0 $\times 10^9$/L and platelet count <150 $\times 10^9$/L respectively, based on established hematological reference ranges. Pancytopenia was defined as a simultaneous reduction in all three cell lines.[11] The 12-week follow-up visit was conducted to obtain blood samples from eligible patients. This time point was selected as it corresponds to the standard assessment of sustained virological response (SVR12) and allows evaluation of early hematological adverse effects of antiviral therapy. Sustained virological response (SVR) was established by demonstrating HCV RNA levels below the limit of detection in qualitative and quantitative PCR analysis following therapy. This study was conducted and reported in accordance with the STROBE guidelines. All collected data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 25. The quantitative variables, including age, the period of hepatitis C infection, the period of therapy, and the laboratory measures, were reported as the mean ± standard deviation. Categorical variables included gender, residence, treatment regimen, and the presence of cytopenias (anemia, leukopenia, Thrombocytopenia, and pancytopenia), and were also expressed as frequencies and percentages. Associations between treatment regimens and study outcomes, including SVR and cytopenias, were evaluated using the Chi-square test. The strength of association was assessed using Cramer's V. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 113 patients receiving hepatitis C antiviral therapy were included in the final analysis. The mean age of participants was 40.1 ± 9.0 years (95% CI: 38.4-41.8), indicating a predominantly middle-aged population. There was a slight male predominance, with 63 (55.8%) males and 50 (44.2%) females. Most participants resided in urban areas (69.0%), and over

half belonged to the moderate socioeconomic class (51.3%). The mean duration of hepatitis C infection was 29.6 ± 10.1 months, while the mean duration of therapy was 12.3 ± 1.3 weeks. A statistically significant association was observed between treatment regimen and sustained virological response (SVR) ($\chi^2 = 23.31$, $p < 0.001$). Patients receiving SOF/VEL achieved the highest SVR rate (90.8%; 95% CI: 82.1-96.2), followed by SOF+RBV (72.0%; 95% CI: 50.6-87.9), whereas conventional therapy demonstrated the lowest response (33.3%; 95% CI: 9.9-65.1). The effect size was moderate (Cramer's V = 0.454), indicating a clinically meaningful association between treatment regimen and virological response. At the 12-week follow-up, hematological parameters revealed a mean hemoglobin level of 11.36 ± 1.64 g/dL (95% CI: 11.06-11.67). The mean white blood cell count was 4.91 ± 1.38 $\times 10^9$/L (95% CI: 4.65-5.16), while the mean platelet count was 169.96 ± 52.96 $\times 10^9$/L (95% CI: 160.09-179.83). Biochemical assessment showed a mean ALT level of 49.18 ± 24.59 IU/L (95% CI: 44.59-53.76) and a mean AST level of 39.98 ± 17.83 IU/L (95% CI: 36.66–43.31). Cytopenias were observed in a notable proportion of patients. Anemia was the most frequent abnormality (23.9%; 95% CI: 16.1-31.7), followed by Thrombocytopenia (9.7%; 95% CI: 4.2-15.2), leukopenia (8.8%; 95% CI: 3.6-14.0), and pancytopenia (6.2%; 95% CI: 1.8-10.6). There was a statistically significant association between treatment regimen and cytopenias. Anemia was most prevalent among patients receiving SOF+RBV (64.0%) and conventional therapy (83.3%), while it was rare in the SOF/VEL group (1.3%) ($\chi^2 = 66.73$, $p < 0.001$). The effect size was strong (Cramer's V = 0.768), indicating a substantial clinical difference across treatment groups. Similarly, leukopenia was highest in the conventional therapy group (50.0%), followed by SOF+RBV (8.0%) and SOF/VEL (2.6%) ($\chi^2 = 28.86$, $p < 0.001$). Thrombocytopenia was more frequent in SOF+RBV (20.0%) and conventional therapy (25.0%) compared to SOF/VEL (3.9%) ($\chi^2 = 9.08$, $p = 0.011$). Pancytopenia was observed only in RBV-containing and conventional regimens, further highlighting the improved hematological safety profile of SOF/VEL. To address potential confounding, multivariate logistic regression analysis was performed. The overall model was statistically significant ($\chi^2 = 74.78$, $p < 0.001$) and demonstrated good fit (Hosmer–Lemeshow test $p = 0.946$). The model explained 72.6% of the variance (Nagelkerke $R^2 = 0.726$) and correctly classified 90.3% of cases. Treatment regimen emerged as the only independent predictor of anemia. Patients receiving SOF/VEL had significantly lower odds of developing anemia than those receiving conventional therapy (AOR = 0.006; 95% CI: 0.001-0.054; $p < 0.001$), indicating a strong protective effect. Although SOF+RBV was associated with increased odds of anemia (AOR = 4.10; 95% CI: 0.61-27.60), this association did not reach statistical significance ($p = 0.147$). Other variables, including age, gender, duration of hepatitis C infection, and duration of therapy, were not significantly associated with anemia.

Table 1: Demographic Characteristics of Patients (n = 113)

Variable	Category	Frequency (%) / Mean ± SD
Age (years)	-	40.1 ± 9.0
Duration of Hepatitis C (months)	-	29.6 ± 10.1
Duration of Therapy (weeks)	-	12.3 ± 1.3
Gender	Male	63 (55.8%)
	Female	50 (44.2%)
Residence	Urban	78 (69.0%)
	Rural	35 (31.0%)
Socioeconomic Status	Low	43 (38.1%)
	Moderate	58 (51.3%)
	High	12 (10.6%)
Occupation	Laborer	41 (36.3%)
	Housewife	26 (23.0%)

Table 2: Association between Treatment Regimen and SVR (n = 113)

Treatment Regimen	SVR Yes n(%)	SVR No n (%)	Total	χ^2	P-value	Cramer's V
SOF/VEL	69 (90.8%)	7 (9.2%)	76	23.31	<0.001	0.454
SOF+RBV	18 (72.0%)	7 (28.0 %)	25			
Conventional	4 (33.3%)	8 (66.7%)	12			

Table 3: Laboratory Parameters at 12-week followup (n=113)

Parameter	Mean ± SD	Minimum	Maximum	95% CI
Hemoglobin (g/dL)	11.36 ± 1.64	7.50	15.00	11.06–11.67
WBC ($\times 10^9$/L)	4.91 ± 1.38	2.00	8.34	4.65–5.16
Platelets ($\times 10^9$/L)	169.96 ± 52.96	57	322	160.09–179.83
ALT (IU/L)	49.18 ± 24.59	10	113	44.59–53.76
AST (IU/L)	39.98 ± 17.83	10	95	36.66–43.31

Table 4: Overall Frequency of Cytopenias (n = 113)

Cytopenia	Frequency (n)	%age	95% CI
Anemia	27	23.9	16.131.7
Leukopenia	10	8.8	3.6–14.0
Thrombocytopenia	11	9.7	4.2–15.2
Pancytopenia	7	6.2	1.8–10.6

Table 5: Frequency of Cytopenias by Treatment Regimen (n = 113)

Cytopenia	SOF/VEL (n=76)	SOF+RBV (n=25)	Conventional (n=12)	χ^2	p-value	Cramer's V
Anemia	1 (1.3%)	16 (64.0%)	10 (83.3%)	66.73	<0.001	0.768
Leukopenia	2 (2.6%)	2 (8.0%)	6 (50.0%)	28.86	<0.001	0.505
Thrombocytopenia	3 (3.9%)	5 (20.0%)	3 (25.0%)	9.08	0.011	0.283
Pancytopenia	0 (0%)	6 (24.0%)	1 (8.3%)	18.75	<0.001	0.407

Table 6: Multivariate Logistic Regression for Predictors of Anemia

Variable	AOR	95% CI	p-value
Age	1.01	0.93–1.10	0.810
Gender	0.33	0.07–1.55	0.161
Duration HCV	1.02	0.94–1.10	0.700
Duration Therapy	0.69	0.43–1.11	0.123
SOF+RBV vs Conventional	4.10	0.61–27.60	0.147
SOF/VEL vs Conventional	0.006	0.001–0.054	<0.001

DISCUSSION

This study evaluated the frequency of cytopenias and treatment outcomes among patients receiving hepatitis C antiviral therapy in a tertiary care setting. The findings demonstrate that direct-acting antiviral (DAA) regimens, particularly sofosbuvir/velpatasvir (SOF/VEL), are associated with significantly higher sustained virological response (SVR) rates and a markedly lower incidence of hematological complications compared to ribavirin-containing and conventional therapies. The overall SVR rate observed in this study (80.5%) is consistent with real-world data from low- and middle-income countries, although slightly lower than the >90% rates reported in controlled clinical trials. Patients treated with SOF/VEL achieved the highest SVR (90.8%), consistent with recent studies demonstrating the high efficacy of pan-genotypic DAA regimens across diverse populations. A multicenter study by Mushtaq et al. reported SVR rates exceeding 90% with SOF/VEL in genotype 3 patients, supporting the effectiveness observed in our cohort.[12] Similarly, a large meta-analysis published in the Journal of Hepatology confirmed superior virological outcomes with interferon-free DAA regimens compared to older therapies.[13] A key finding of this study is the significant association between treatment regimen and cytopenias, with a particularly strong effect size observed for anemia (Cramer's V = 0.768). The strong effect size indicates a clinically meaningful difference, suggesting that the treatment regimen is a major determinant of hematological toxicity. This indicates a substantial clinical impact of treatment choice on hematological outcomes. Patients receiving ribavirin-containing regimens demonstrated markedly higher rates of anemia, consistent with the well-established mechanism of ribavirin-induced hemolysis. Ribavirin accumulates in erythrocytes, leading to oxidative membrane damage and premature red cell destruction. Previous clinical and pharmacological studies have consistently demonstrated this mechanism and its association with treatment-related anemia.[14] In contrast, the SOF/VEL regimen demonstrated a significantly lower frequency of cytopenias, particularly anemia (1.3%), highlighting its favorable safety profile. This finding is strongly supported by contemporary evidence, including a systematic review by Zoratti et al., which concluded that pangenotypic DAA regimens are associated with minimal hematological toxicity.[15] The markedly reduced odds of anemia observed in our multivariate analysis (AOR = 0.006) further emphasize the protective effect of SOF/VEL, even after adjusting for potential confounders. Leukopenia and Thrombocytopenia were also more prevalent among patients receiving conventional or ribavirin-containing regimens. These findings are consistent with previous reports indicating bone marrow suppression associated with interferon-based therapies. A recent study by Xia H et al. (2020) demonstrated similar trends, with significantly higher rates of cytopenias in patients treated with older antiviral regimens compared with those treated with modern DAAs.[16] The variability observed across treatment groups in our study may also be influenced by baseline disease severity, nutritional status, and liver function, factors that were not fully adjusted in this analysis. The multivariate logistic regression analysis identified treatment regimen as the only independent predictor of anemia, whereas demographic and clinical variables such as age, gender, and disease duration were not significantly associated. This finding underscores the dominant role of pharmacological factors over patient-related characteristics in determining hematological toxicity during hepatitis C treatment. Similar observations have been reported in recent real-world studies evaluating predictors of adverse effects in DAA-treated patients.[17,18] Nevertheless, this study provides important real-world evidence from a high-burden setting, highlighting both the efficacy and safety advantages of modern DAA regimens. The findings support current global recommendations favoring ribavirin-sparing regimens and emphasize the need for routine hematological monitoring, particularly in patients receiving ribavirin or older therapies.[19,20]

LIMITATIONS

It was conducted in a single tertiary care center, which may limit the generalizability of findings. Baseline hematological parameters and liver disease severity (e.g., fibrosis stage, cirrhosis status) were not included in the regression model, potentially confounding the observed associations. The relatively small sample size in the conventional therapy group may have affected the precision of estimates. Additionally, longer follow-up beyond 12 weeks would be valuable to assess late-onset hematological complications.

CONCLUSIONS

Direct-acting antiviral regimens, particularly sofosbuvir/velpatasvir, are associated with higher sustained virological response rates and a lower frequency of cytopenias compared to ribavirin-containing and conventional therapies. The treatment regimen emerged as the primary determinant of hematological outcomes. However, given the observational design and limited adjustment for confounders, these findings should be interpreted with caution. Further multicenter studies with larger sample sizes and comprehensive clinical data are recommended to validate these results.

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AUTHORS CONTRIBUTION

Shadman Ahmad Jan - *Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Critical Revision; Final Approval*

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The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.