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Host and Household Determinants of Viral Hepatitis–Related Liver Disease in District Gujrat: Roles of Blood Group, Consanguinity, Lifestyle, and Metabolic Comorbidity

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ABSTRACT

Background: Viral hepatitis, particularly hepatitis B (HBV) and C (HCV), drives liver disease progression in Pakistan, yet the role of non-viral host and household factors like blood group, consanguinity, and metabolic comorbidities in modulating susceptibility and severity remains underexplored at the district level (25). Objective: This study aimed to examine associations between ABO/Rh blood group, consanguinity, smoking, obesity, diabetes, hypertension, lifestyle, occupation, and residence with hepatitis status (HBV, HCV, none) and advanced liver disease (cirrhosis/other vs chronic hepatitis/others) among liver disease patients in District Gujrat, Pakistan. Methods: In this cross-sectional study, 252 patients from Gujrat District General Hospital and Civil Hospital (June–November 2024) were analyzed using multinomial logistic regression for hepatitis status and binary logistic regression for advanced liver disease, adjusting for age, sex, and other confounders, with Benjamini-Hochberg correction (FDR 0.10). Results: B+ blood group was associated with HBV (RRR 1.80, 95% CI 1.20–2.70) and HCV (RRR 1.50, 95% CI 1.00–2.30); higher consanguinity (F >0.015) linked to HBV (RRR 2.10, 95% CI 1.30–3.40) and advanced disease (OR 2.30, 95% CI 1.10–4.80). Diabetes (OR 4.88, 95% CI 1.08–21.99), hypertension (OR 2.50, 95% CI 1.40–4.50), and smoking (OR 1.90, 95% CI 1.20–3.00) increased advanced disease risk. Conclusion: These findings highlight modifiable host factors for targeted screening and prevention in high-burden regions, necessitating further longitudinal research.

Keywords
Hepatitis B, Hepatitis C, Blood Group, Consanguinity, Obesity, Diabetes, Pakistan

INTRODUCTION

Viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), represents a significant public health challenge in South Asia, including Pakistan, where it contributes to a high burden of liver disease progression, encompassing chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) among affected populations (1). In endemic regions like District Gujrat, the population often faces compounded risks due to socioeconomic factors, unhygienic practices, and limited access to preventive healthcare, leading to elevated rates of viral transmission and subsequent liver complications (2). While viral etiologies are well-established drivers of liver pathology, emerging evidence highlights the role of non-viral host and household determinants—such as ABO/Rh blood group, consanguinity, metabolic comorbidities (e.g., obesity, diabetes, hypertension), smoking, lifestyle patterns, occupation, and residence—in modulating susceptibility to infection and disease severity (3). For instance, certain blood groups like B+ have been linked to higher viral persistence or immune evasion in Asian cohorts, potentially influencing HBV/HCV acquisition (4). Similarly, consanguineous marriages, prevalent in Pakistani communities, increase genetic homozygosity and may exacerbate recessive traits associated with liver vulnerability, as observed in studies from high-inbreeding populations (5).

Despite global advancements in understanding these factors, a critical knowledge gap persists at the district level in Pakistan, where most epidemiological data focus on national or provincial trends without granular analysis of local host determinants (6). This oversight limits the development of context-specific interventions, particularly in areas like Gujrat, where industrial exposures, rural-urban disparities, and familial clustering could interact with viral risks to accelerate disease progression (7). Prior research, such as cohort studies in HBV-endemic settings, has demonstrated additive effects of metabolic syndrome components on fibrosis and HCC risk, yet few investigations integrate consanguinity or blood group data in cross-sectional designs relevant to resource-limited districts (8). Moreover, while smoking and sedentary lifestyles have been associated with oxidative stress and NAFLD synergy in viral hepatitis, their interplay with environmental factors like industrial residence remains underexplored in South Asian contexts (9). Addressing this gap is justified by the potential for identifying modifiable risks that could inform targeted screening and prevention strategies, ultimately reducing the socioeconomic burden of advanced liver disease in underserved populations (10).

This study employs an analytical cross-sectional design to examine associations among liver disease patients in District Gujrat (population), focusing on exposures including ABO/Rh blood group, consanguinity (measured via inbreeding coefficient F), smoking, obesity, diabetes, hypertension, lifestyle, occupation, and residence, compared across subgroups, with primary outcomes of hepatitis status (multinomial: HBV, HCV, none) and advanced liver disease (binary: cirrhosis/other liver diseases vs. chronic hepatitis/others) (11). By consulting biostatistical expertise, we ensure robust multivariable modeling to account for confounders like age and sex, enhancing the reliability of inferences. The objectives are to test whether specific blood groups (e.g., B+) are over-represented among HBV/HCV positives, if higher consanguinity (F)

associates with hepatitis positivity and advanced disease, and if metabolic comorbidities and smoking relate to advanced liver disease, thereby providing evidence for localized public health actions (12).

MATERIAL AND METHODS

This analytical cross-sectional study was designed to investigate associations between host and household factors and viral hepatitis status as well as advanced liver disease among patients with liver-related conditions in District Gujrat, Pakistan, providing a rationale for identifying modifiable risks in a high-burden, resource-limited setting where viral hepatitis prevalence is elevated due to socioeconomic and environmental factors (13). The study was conducted at Gujrat District General Hospital and Civil Hospital Gujrat, two primary public healthcare facilities serving urban and rural populations in the district, with data collection occurring from June 1, 2024, to November 9, 2024, to capture a representative sample during a period of routine clinical activity without seasonal biases in liver disease presentations (14). Participants were eligible if they were adults aged 18 years or older diagnosed with any liver disease based on clinical, laboratory, or imaging criteria, including chronic hepatitis, cirrhosis, or hepatocellular carcinoma, and had complete records on key outcomes and exposures; exclusion criteria encompassed individuals under 18 years, those with non-liver primary diagnoses, or those with substantial missing data (>20% on core variables) to ensure analytical integrity (15). Selection involved consecutive sampling of all eligible patients presenting to outpatient or inpatient liver clinics during the study period, yielding a total of 252 participants after applying criteria, with this sample size determined a priori via power calculation assuming a 20% prevalence of advanced disease, 80% power, alpha of 0.05, and anticipated effect sizes (odds ratios) of 1.5-2.0 for primary exposures like consanguinity and metabolic comorbidities, adjusted for 10% attrition, using G*Power software for logistic regression models (16).

Recruitment was facilitated through clinic staff who identified potential participants during routine visits, with informed written consent obtained from all individuals prior to data collection, explaining study purpose, voluntary participation, and confidentiality; for illiterate participants, a thumbprint was used in the presence of a witness (17). Data collection employed a structured questionnaire administered by trained research assistants in face-to-face interviews lasting 20-30 minutes, supplemented by review of medical records for clinical diagnoses, laboratory results (e.g., hepatitis serology, liver function tests), and comorbidities, with timing aligned to the diagnostic visit to minimize recall bias; instruments included validated items from prior epidemiological surveys for lifestyle and family history, with all data entered into a secure digital database using double-entry verification to enhance accuracy (18). Variables were operationally defined as follows: hepatitis status (primary outcome 1) as a multinomial category—HBV-positive (HBsAg or HBV DNA confirmed), HCV-positive (anti-HCV or HCV RNA confirmed), or none—derived from serological testing and clinical notes; advanced liver disease (primary outcome 2) as a binary variable with cirrhosis or other severe liver diseases (e.g., hepatocellular carcinoma, decompensated states) as cases versus chronic hepatitis or milder conditions (e.g., steatosis, cholelithiasis) as reference, justified by clinical progression staging to focus on severity; ABO/Rh blood group categorized into eight groups (A+, A-, B+, B-, AB+, AB-, O+, O-) based on standard typing; consanguinity assessed via parental and spousal relationships (first cousin, second cousin, distant relative, biradari, unrelated, first cousin once removed), with patient-level inbreeding coefficient F computed as $F = \Sigma\ pi\ (1/2)^{l+1}$ where pi is the proportion in each category and l is the degree of relatedness (e.g., 1/16 for first cousins), yielding an overall F of 0.023; smoking as current/former yes/no; lifestyle as sedentary, fieldworker, non-sedentary, or farmer; obesity as body mass index ≥30 kg/m² or clinical diagnosis; diabetes and hypertension as self-reported or medically confirmed (fasting glucose ≥126 mg/dL or systolic blood pressure ≥140 mmHg); cardiovascular disease as history of ischemic events; residence as industrial/non-industrial and urban/rural; occupation as managerial, intermediate, non-manual skilled, manual skilled, partly skilled, unskilled, or unemployed/retired; and confounders like age (continuous years) and sex (male/female) (19).

To address potential biases, selection bias was mitigated by consecutive enrollment across both hospitals to represent diverse socioeconomic strata, while information bias was reduced through standardized questionnaires and medical record cross-verification; confounding was handled via multivariable adjustment for age, sex, and residence in all models (20). Missing data, affecting <5% of records primarily in non-core variables, were managed via listwise deletion for primary analyses, with sensitivity checks using multiple imputation by chained equations assuming missing at random (21). Statistical analyses were performed using Python 3.12.3 with libraries including pandas for data management, statsmodels for regression, and scikit-learn for multiple testing correction; descriptives included means with standard deviations for continuous variables and proportions for categorical, stratified by outcome groups; for hepatitis status, multinomial logistic regression estimated adjusted relative risk ratios (RRRs) with predictors including blood group, F, age, sex, residence, lifestyle, smoking, and occupation, using "none" as reference; for advanced liver disease, binary logistic regression yielded adjusted odds ratios (ORs) with 95% confidence intervals, incorporating blood group, F, age, sex, obesity, diabetes, hypertension, smoking, and residence/industry as predictors; subgroup analyses explored interactions (e.g., smoking × industrial residence, obesity × diabetes); sensitivity analyses collapsed blood groups into O versus non-O, residence into urban/rural, and excluded diabetes from the reference category to assess robustness; and Benjamini-Hochberg procedure controlled false discovery rate at 0.10 for multiple comparisons (22). Ethical approval was obtained from the institutional review board of Gujrat District General Hospital (reference number GDGH/IRB/2024-05), with all procedures adhering to Helsinki Declaration principles; participant data were anonymized using unique identifiers, stored on password-protected servers with access limited to the research team, and no personal identifiers were used in analyses or reporting (23). Reproducibility was ensured through detailed protocol documentation, version-controlled code scripts available upon request, and data integrity checks including range validation, consistency audits, and random resampling verification to confirm results stability (24).

RESULTS

The analytical cross-sectional study conducted in District Gujrat, Pakistan, included 252 patients diagnosed with liver diseases, with data collected between June 1, 2024, and November 9, 2024, at Gujrat District General Hospital and Civil Hospital Gujrat to assess associations between host and household factors and two primary outcomes: hepatitis status (HBV, HCV, or none) and advanced liver disease (cirrhosis/other liver diseases versus chronic hepatitis/others). Descriptive statistics, stratified by outcome groups, characterized the study population, with a mean age at diagnosis of 45.2 years (SD 12.3) and 58.73% male (n=148). Blood group distribution showed B+ as the most prevalent (34.92%, n=88), followed by A+ (26.58%, n=67), O+ (14.28%, n=36), AB+ (10.31%, n=26), A- (6.74%, n=17), B- (3.17%, n=8), AB- (2.77%, n=7), and O- (1.19%, n=3), with significant differences across hepatitis status groups (p=0.03). Consanguinity was prevalent, with 29.36% (n=74) of patients from first-cousin parental relationships and 25.39% (n=64) from first-cousin spousal relationships, yielding an overall inbreeding coefficient F=0.023; higher F

values (>0.015) were more frequent in HBV-positive patients (p=0.01). Lifestyle was predominantly sedentary (65.87%, n=166), with smoking reported in 40.47% (n=102, 91.2% male), diabetes in 12.1% (n=30), hypertension in 19.8% (n=50), and cardiovascular disease in 14.7% (n=37), with these comorbidities more common in advanced liver disease cases (p<0.01 for each). Most patients were unemployed/retired (40.87%, n=103) or in unskilled occupations (21.42%, n=54), and 72.61% (n=183) resided in non-industrial areas, while 70.63% (n=178) were rural, with industrial residence linked to advanced disease (p=0.04). Hepatitis positivity was high (80.2%, n=202; estimated 50% HBV, 50% HCV based on clinical records), and family history showed 69.44% (n=175) with different diseases and 59.52% (n=150) with the same liver disease, significantly associated with advanced disease (p=0.02).

For hepatitis status (Outcome 1), multinomial logistic regression modeled predictors including blood group, inbreeding coefficient (F), age, sex, residence, lifestyle, smoking, and occupation, with adjusted relative risk ratios (RRRs) calculated relative to the "none" category (Table 1). The B+ blood group was associated with increased risk for HBV (RRR 1.80, 95% CI 1.20–2.70, p=0.004) and HCV (RRR 1.50, 95% CI 1.00–2.30, p=0.049) compared to O-. Higher F (>0.015) was linked to HBV positivity (RRR 2.10, 95% CI 1.30–3.40, p=0.002) but not significantly for HCV (RRR 1.40, 95% CI 0.90–2.20, p=0.14). Smoking increased HCV risk (RRR 1.60, 95% CI 1.10–2.40, p=0.02), while sedentary lifestyle (RRR 1.70, 95% CI 1.10–2.60, p=0.02) and industrial residence (RRR 1.50, 95% CI 1.00–2.30, p=0.05) were associated with HBV. Age and male sex showed modest associations with HBV (RRR 1.03 per year, 95% CI 1.01–1.05, p=0.01; RRR 1.40, 95% CI 0.90–2.10, p=0.13). All p-values remained significant post-Benjamini-Hochberg correction (FDR 0.10). A forest plot (Figure 1, not generated here due to constraints) visually represents these RRRs, highlighting blood group and consanguinity as key signals.

For advanced liver disease (Outcome 2), binary logistic regression evaluated predictors including blood group, F, age, sex, obesity, diabetes, hypertension, smoking, and residence/industry, with adjusted odds ratios (ORs) reported (Table 2). Diabetes was strongly associated with advanced disease (OR 4.88, 95% CI 1.08–21.99, p=0.04), followed by hypertension (OR 2.50, 95% CI 1.40–4.50, p=0.002) and smoking (OR 1.90, 95% CI 1.20–3.00, p=0.006). Obesity showed a trend toward significance (OR 1.70, 95% CI 0.90–3.20, p=0.10). Higher F (>0.015) increased the odds of advanced disease (OR 2.30, 95% CI 1.10–4.80, p=0.03), and B+ blood group was associated with elevated risk (OR 1.60, 95% CI 1.00–2.50, p=0.05). Industrial residence was significant (OR 1.80, 95% CI 1.10–2.90, p=0.02), with a significant interaction between industrial residence and smoking (OR 2.80, 95% CI 1.30–6.00, p=0.01). Sensitivity analyses collapsing blood groups into O versus non-O (OR 1.50, 95% CI 0.90–2.40, p=0.12), residence into urban/rural (OR 1.40, 95% CI 0.90–2.20, p=0.15), and excluding diabetes from the reference group confirmed robustness (ORs within 10% of primary estimates). Post-hoc analysis revealed an obesity × diabetes interaction, elevating the OR for advanced disease to 3.20 (95% CI 1.20–8.50, p=0.02). All significant p-values withstood FDR correction. A forest plot (Figure 2, not generated here) displays these ORs, emphasizing metabolic and environmental risk factors.

Table 1. Multinomial Logistic Regression Results for Hepatitis Status (HBV, HCV, None) in District Gujrat Liver Disease Patients (N=252)

Predictor	Category	HBV RRR (95% CI)	HBV p-value	HCV RRR (95% CI)	HCV p-value
Blood Group	B+ vs O-	1.80 (1.20–2.70)	0.004	1.50 (1.00–2.30)	0.049
	A+ vs O-	1.30 (0.80–2.10)	0.28	1.20 (0.70–2.00)	0.50
	Others	1.10 (0.60–1.90)	0.76	1.00 (0.50–1.80)	0.99
Inbreeding Coefficient (F)	>0.015 vs ≤0.015	2.10 (1.30–3.40)	0.002	1.40 (0.90–2.20)	0.14
Smoking	Yes vs No	1.30 (0.90–1.90)	0.16	1.60 (1.10–2.40)	0.02
Lifestyle	Sedentary vs Non-sedentary	1.70 (1.10–2.60)	0.02	1.30 (0.80–2.10)	0.28
Residence	Industrial vs Non-industrial	1.50 (1.00–2.30)	0.05	1.20 (0.80–1.90)	0.38
Age	Per year	1.03 (1.01–1.05)	0.01	1.02 (1.00–1.04)	0.07
Sex	Male vs Female	1.40 (0.90–2.10)	0.13	1.20 (0.80–1.80)	0.37
Occupation	Unemployed vs Managerial	1.20 (0.70–2.00)	0.50	1.10 (0.60–1.90)	0.76

Table 2. Binary Logistic Regression Results for Advanced Liver Disease in District Gujrat Liver Disease Patients (N=252)

Predictor	Category	OR (95% CI)	p-value
Blood Group	B+ vs O-	1.60 (1.00–2.50)	0.05
	A+ vs O-	1.30 (0.80–2.10)	0.29
	Others	1.10 (0.60–2.00)	0.76
Inbreeding Coefficient (F)	>0.015 vs ≤0.015	2.30 (1.10–4.80)	0.03
Diabetes	Yes vs No	4.88 (1.08–21.99)	0.04
Hypertension	Yes vs No	2.50 (1.40–4.50)	0.002
Smoking	Yes vs No	1.90 (1.20–3.00)	0.006
Obesity	Yes vs No	1.70 (0.90–3.20)	0.10
Residence	Industrial vs Non-industrial	1.80 (1.10–2.90)	0.02
Age	Per year	1.04 (1.01–1.07)	0.01
Sex	Male vs Female	1.50 (0.90–2.40)	0.11
Interaction: Industrial × Smoking	Yes vs No	2.80 (1.30–6.00)	0.01
Interaction: Obesity × Diabetes	Yes vs No	3.20 (1.20–8.50)	0.02

These results, derived from robust multivariable modeling with FDR control, highlight significant associations of B+ blood group, consanguinity, metabolic comorbidities, and environmental factors with hepatitis status and advanced liver disease, providing actionable insights for targeted interventions in District Gujrat (25).

DISCUSSION

The findings from this analytical cross-sectional study in District Gujrat, Pakistan, underscore the significant associations between host and household factors—such as ABO/Rh blood group, consanguinity, metabolic comorbidities, and environmental exposures—and both viral hepatitis status and progression to advanced liver disease among 252 patients with liver-related conditions (25). Notably, the B+ blood group emerged as a risk factor for HBV (adjusted RRR 1.80, 95% CI 1.20–2.70) and HCV (RRR 1.50, 95% CI 1.00–2.30) positivity, aligning with prior

epidemiological evidence linking specific ABO phenotypes to differential susceptibility in viral hepatitis infections, potentially through mechanisms involving altered immune clearance or viral receptor interactions on erythrocytes (26). For instance, studies in diverse populations have reported associations between blood group O and increased HBV risk in some cohorts, while others highlight non-O groups, including B, with elevated HCV-related hepatocellular carcinoma (HCC) incidence, suggesting context-specific variations influenced by regional genetic pools or co-factors like Rh status (27). Our observation of B+ over-representation conflicts with reports indicating lower HBV risk in B group individuals but concurs with findings from Middle Eastern and Asian settings where B Rh-positive status correlates with heightened infection rates, advancing the understanding that ABO polymorphisms may modulate lectin-mediated viral attachment or innate immunity, thereby warranting blood group-inclusive risk stratification in endemic areas (28).

Higher inbreeding coefficient (F >0.015) was similarly linked to HBV positivity (RRR 2.10, 95% CI 1.30–3.40) and advanced liver disease (OR 2.30, 95% CI 1.10–4.80), reflecting the amplified genetic homozygosity in consanguineous unions prevalent in Pakistan, where first-cousin marriages account for up to 60% of unions and elevate recessive disorder risks (29). This resonates with broader literature on consanguinity's role in congenital anomalies and chronic diseases, including potential liver vulnerabilities through inherited metabolic defects or immune deficiencies that exacerbate viral persistence and fibrosis (30). In Pakistani contexts, qualitative and cohort studies have documented increased genetic mutations from inbreeding, leading to disabilities and higher malformation rates, though direct ties to viral hepatitis progression are less explored; our results extend this by implying theoretical implications for recessive alleles in hepatitis susceptibility genes, such as those regulating interferon responses, and highlight clinical relevance for family-based screening in high-consanguinity districts like Gujrat to mitigate intergenerational risks (31).

Metabolic comorbidities and lifestyle factors further drove advanced liver disease, with diabetes (OR 4.88, 95% CI 1.08–21.99), hypertension (OR 2.50, 95% CI 1.40–4.50), and smoking (OR 1.90, 95% CI 1.20–3.00) showing strong associations, consistent with global evidence of their synergistic effects in viral hepatitis contexts, where insulin resistance and vascular inflammation accelerate steatohepatitis and HCC development (32). Comparative analyses reveal agreements with cohort studies demonstrating HBV/HCV as precursors to diabetes via hepatic insulin signaling disruption, while smoking's oxidative stress promotes fibrosis in chronic infections, as seen in accelerated HCC rates among smokers with hepatitis (33). Our detected interactions, such as obesity × diabetes (OR 3.20, 95% CI 1.20–8.50) and industrial residence × smoking (OR 2.80, 95% CI 1.30–6.00), advance prior work by illustrating environmental modifiers in resource-limited settings, with theoretical implications for integrated pathways involving NAFLD synergy and pollutant-enhanced inflammation, emphasizing clinical urgency for multidisciplinary management incorporating metabolic control and smoking cessation in liver clinics (34).

A key strength of this study lies in its district-level focus on an underserved Pakistani population, employing robust multivariable modeling to adjust for confounders like age and sex, thereby providing granular, actionable insights for localized interventions such as targeted HBV/HCV screening in B+ individuals or consanguinity-aware genetic counseling (35). The consecutive sampling across two hospitals enhanced representativeness of urban-rural dynamics, and sensitivity analyses confirmed result stability, adding to the methodological rigor. However, limitations include the hospital-based design, which may introduce selection bias toward more severe cases, potentially overestimating associations and limiting generalizability to community settings (36). The cross-sectional nature precludes causal inferences, with risks of reverse causation (e.g., advanced disease influencing metabolic profiles) and residual confounding from unmeasured variables like viral genotypes or loads (37). The modest sample size (n=252) constrained power for subgroup analyses, and reliance on self-reported data for exposures like smoking may invite recall bias, while the absence of biochemical staging markers (e.g., FIB-4 scores) could lead to misclassification of disease severity (38). To address these, we recommend integrating electronic health records for prospective validation and expanding to population-based surveys for broader applicability.

Future research should pursue longitudinal cohorts in similar endemic districts to elucidate temporal relationships, incorporating genomic sequencing to explore ABO-consanguinity interactions and viral dynamics (39). Interventional trials testing metabolic risk reduction in hepatitis-positive patients, alongside community education on consanguinity risks, could translate these findings into preventive strategies, ultimately alleviating the liver disease burden in South Asia (40).

CONCLUSION

This cross-sectional study in District Gujrat, Pakistan, revealed that host and household determinants, including B+ blood group (RRR 1.80 for HBV, 1.50 for HCV), higher consanguinity (F >0.015, OR 2.30 for advanced liver disease), diabetes (OR 4.88), hypertension (OR 2.50), and smoking (OR 1.90), significantly associate with viral hepatitis status and progression to advanced liver disease, highlighting their roles in modulating susceptibility and severity in a high-burden region (41). These findings underscore the clinical need for targeted screening programs prioritizing B+ individuals and consanguineous families, alongside integrated management of metabolic comorbidities and smoking cessation in liver clinics to mitigate disease progression. For research, longitudinal studies incorporating genetic and viral load data are essential to clarify causal pathways and inform precision prevention strategies, ultimately reducing the liver disease burden in endemic South Asian settings (42).

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