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ORIGINAL ARTICLE

IL28B (IFNL3) rs12979860 predicts response to interferon-α2a plus ribavirin in Pakistani adults with chronic hepatitis C: A longitudinal cohort study

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) remains highly prevalent in Pakistan, with genotype 3 predominance. Before direct-acting antivirals (DAAs), interferon-α (IFN) plus ribavirin (RBV) yielded variable sustained virologic response (SVR). Host variants near IL28B (IFNL3), particularly rs12979860, have been linked to IFN responsiveness and spontaneous clearance. This study evaluates whether IL28B rs12979860 predicts SVR to IFN-α2a/RBV in Pakistani adults and to describe baseline viral-load strata and circulating genotypes.

Methods: We conducted a longitudinal cohort in Khushal Medical Center (KMC) Peshawar (N=165). Adult's anti-HCV–positive by third-generation ELISA started IFN-α2a thrice weekly plus weight-based RBV for 24–48 weeks. Baseline demographics, HCV RNA categories, and viral genotypes were recorded; IL28B rs12979860 was genotyped from whole blood. Virologic endpoints were Rapid viral response (RVR) (week 4), Early virological response (EVR) (week 12), and SVR (undetectable HCV RNA 24 weeks post-therapy). Associations were summarized as odds ratios (OR) with 95% CIs.

Results: Overall SVR was 51.5% (85/165). Baseline RNA was <600,000 IU/mL in 81.8%, 600,000–800,000 in 2.4%, and >800,000 in 15.7%; all SVR events occurred in the <600,000 IU/mL group. Genotypes were dominated by 3a (45%) and 3b (19%) with smaller contributions from 2a (13%), 1a (6%), 2b (5%); 4a/5a/6a were rare; ~10% were untypeable. rs12979860 distributions differed by outcome: responders (n=84) CC 45, CT 32, TT 7; non-responders (n=80) CC 21, CT 26, TT 33. CC vs TT: OR 10.10 (95% CI 3.84–26.55); CC vs CT+TT: OR 3.24 (95% CI 1.68–6.25). EVR tracked positively with SVR.

Conclusions: In a genotype-3–predominant Pakistani cohort, rs12979860-CC strongly predicted SVR to IFN-α2a/RBV (CC>CT>TT). These data provide population-specific pharmacogenomic evidence and a historical benchmark for Pakistan.

Keywords: Genotype 3, Hepatitis C, IL28B, rs12979860, Interferon, Ribavirin, Sustained Virologic Response

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Introduction

Hepatitis C virus (HCV) remains a leading cause of cirrhosis and hepatocellular carcinoma worldwide despite the availability

of curative direct-acting antivirals (DAAs) (1, 2). Before the DAA era, interferon-α (IFN) combined with ribavirin (RBV) was standard care, yet SVR varied across patients due to viral determinants (genotype, baseline RNA) and host determinants (immune activation, genetics) (1, 2). Genome-wide association studies identified single-nucleotide polymorphisms near the interferon-lambda locus (IL28B/IFNL3), notably rs12979860 and rs8099917, as strong predictors of IFN-based response and spontaneous HCV clearance (3-7). HCV genotypes are unevenly distributed; genotype 3 predominates in South Asia, including Pakistan, which bears one of the region's highest HCV seroprevalences (8-11). Genotype 3 has been associated with distinct metabolic and fibrotic phenotypes and historically variable IFN/RBV outcomes relative to genotype 1 (1, 2, 8-11).

Evidence linking IL28B variants to IFN/RBV outcomes is robust in genotype-1–predominant cohorts from Europe, East Asia, and North America (3-7). In contrast, findings in non-genotype-1 infections (notably genotypes 2/3) have been more heterogeneous, with potential modulation by ancestry, baseline RNA, disease stage, and local care pathways (4, 8-11). Allele frequencies of rs12979860 vary across populations; thus, estimates derived from non-South-Asian cohorts may not translate directly to Pakistan's genotype-3–dominant epidemiology (3-6, 8, 11). Pakistan-specific, genotype-3–predominant data on IL28B rs12979860 covering local allele/genotype frequencies and effect sizes for SVR under IFN/RBV remain limited, and prior reports in genotypes 2/3 are mixed with uncertain generalizability to South Asia (4, 8-11).

To determine whether IL28B rs12979860 genotype predicts SVR to IFN-α2a plus RBV in Pakistani adults with chronic HCV, and to describe baseline viral-load strata and circulating HCV genotypes in the same cohort. The prespecified hypothesis was that CC would be associated with higher odds of SVR than CT/TT, consistent with prior genome-wide and clearance studies (3-7).

Methods

The protocol was approved by the Ethics Committee of KMC, Peshawar via letter no KMC/EB0010/2018; all participants provided written informed consent. Reporting follows STROBE recommendations for observational studies (12). A longitudinal cohort was conducted in KMC Peshawar, Pakistan. Consecutive adults with a new diagnosis of HCV were recruited from major health-care centers. Molecular and clinical laboratory work (hematology, chemistry, nucleic-acid assays, viral genotyping, and host genotyping) was performed at the Institute of Basic Medical Sciences (IBMS), Khyber Medical University. Eligibility required anti-HCV seropositivity by third-generation ELISA and a clinical decision to start IFN-α2a plus RBV. Exclusion criteria were age >50 years; body-mass index <18.5 or >30 kg/m²; known cirrhosis; metabolic/endocrine disease likely to modify disease course (e.g., thyroid dysfunction, diabetes mellitus); significant hepatic or renal impairment; HBV/HIV co-infection; alcohol use; or non-adherence to standard antiviral therapy. A total of 165 patients were enrolled. Patients received subcutaneous IFN-α2a three times weekly and weight-based RBV (1000 mg/day if <75 kg; 1200 mg/day if ≥75 kg). Treatment duration was 24-48 weeks at clinician discretion. Participants were followed during therapy and for 24 weeks after treatment to ascertain virologic endpoints.

Venous blood was collected at baseline and prespecified follow-ups into EDTA and

serum-separator tubes. Serum was allowed to clot at room temperature, centrifuged at 3000 rpm for 15 minutes, aliquoted, and stored at −20 °C; whole blood was maintained at 4 °C pending DNA extraction. Complete blood counts (hemoglobin, total leukocyte count, RBC indices, differential counts, platelets, PCV, MCV, MCH, MCHC) were obtained on a Sysmex KX-21 analyzer; ALT/AST were measured on a Roche Cobas C111 according to manufacturer protocols. Demographic and clinical variables (age, sex, ethnicity, treatment details, comorbidities) were recorded on a standardized proforma.

Serum HCV RNA was quantified by clinical nucleic-acid amplification tests (lower limit of detection ≤50–100 IU/mL). Pretreatment viral load was categorized a priori as <600,000, 600,000–800,000, and >800,000 IU/mL (1). Viral genotypes were determined using the Ohno et al. nested PCR strategy targeting the 5′ non-coding region with genotype-specific primers (two multiplex mixes: S7 with 2a/1b/2b/3b; and S7 with 1a/3a/4/5a/6a). First-round amplification products were used as templates for genotyping PCRs; amplicons were resolved on 1.5–2% agarose in 1× TBE and interpreted against a 100-bp ladder under UV transillumination (13). Laboratory buffer recipes (10× TBE; 2% agarose with ethidium bromide 8 µL/100 mL) and thermocycler profiles were maintained as internal SOPs and are available upon request for replication.

Genomic DNA was extracted from whole blood using a silica-membrane kit (Invitrogen PureLink, USA) per manufacturer guidance. rs12979860 genotyping was performed by allele-specific PCR (ARMS-PCR); 10% of samples were repeated as internal quality control, and any discordance was resolved by Sanger sequencing. Genotyping staff were blinded to clinical outcomes. The biologic relevance of rs12979860 as a predictor of interferon responsiveness is supported by prior genome-wide and clearance studies (3-7).

Virologic endpoints followed standard definitions: RVR undetectable HCV RNA at week 4; EVR ≥2 log10 decline or undetectable RNA by week 12; SVR undetectable HCV RNA 24 weeks after completing therapy (primary endpoint) (1).

Baseline characteristics are summarized descriptively. The association between rs12979860 and SVR was estimated using odds ratios (OR) with 95% confidence intervals (CI) from 2×2 tables (genotype-wise CC vs TT, CT vs TT, and a dominant model CC vs CT+TT). An allele-based analysis compared C versus T counts between responders and non-responders. Hardy–Weinberg equilibrium (HWE) was assessed at baseline; deviations observed within outcome strata were not interpreted as population-level HWE violations because groups were conditioned on outcome. Missing data were not imputed. Two-sided $\alpha=0.05$ defined statistical significance. Analyses were conducted in R (v4.x) using exact tests for small cells and standard functions for proportions and ORs (14).

Results

A total of 165 adults with chronic HCV were enrolled and initiated on interferon-α2a (three times weekly) plus weight-based ribavirin. The sex distribution was 89/165 (54%) male and 76/165 (46%) female (Table 1). The overall sustained virologic response (SVR) rate the primary endpoint defined as undetectable HCV RNA 24 weeks after therapy was 51.5% (85/165). By sex, SVR occurred in 49/89 (55.1%) males and 36/76 (47.4%) females, indicating no evident sex-specific difference in final outcome when

considered at the cohort level (Table 1). Age was right-skewed toward midlife: 41/165 (24.8%) were 19–29 years, 56/165 (33.9%) were 30–40 years, and 67/165 (40.6%) were 41–50 years. SVR occurred more frequently among younger strata (19–40 years), whereas non-response was concentrated in the oldest stratum (41–50 years) (Table 1). These patterns are consistent with prior reports from Pakistan showing similar genotype distributions by sex and a heavier disease burden in middle age.

Table 1: Gender and age distribution by treatment outcome

Gender	Non-responders (n)	Responders (n)	Total n (%)
Male	40	49	89 (54)
Female	40	36	76 (46)
Age Group (years)			
19–29	11	31	41 (24.8)
30–40	26	30	56 (33.9)
41–50	43	24	67 (40.6)

No evidence of sex-linked differences in viral genotype distribution or response was detected (8,15). Non-response concentrated in 41–50 years; responders skewed younger. We prespecified three categories for baseline HCV RNA **<600,000 IU/mL, 600,000–800,000 IU/mL,** and **>800,000 IU/mL**. Most participants fell below the 600,000 IU/mL threshold (**135/165; 81.8%),** with far fewer in the intermediate (**4/165; 2.4%)** and highest **(26/165; 15.7%)** strata (Table 2). All **85 SVR events** occurred exclusively in the **<600,000 IU/mL** group; **no patient** with baseline RNA **≥600,000 IU/mL** achieved SVR. This **complete separation** underscores the strong prognostic weight of pretreatment viral load for interferon-based regimens, a relationship repeatedly observed in genotype-3–predominant settings (1).

Table 2: Baseline HCV RNA category and SVR

Baseline HCV RNA (IU/mL)	Patients n (%)	SVR n
<600,000	135 (81.8)	85
600,000–800,000	4 (2.4)	0
>800,000	26 (15.7)	0

All SVR events occurred at baseline RNA <600,000 IU/mL (16, 17).

Genotyping showed a clear dominance of **genotype 3**, with **3a in 75/165 (45%)** and **3b in 31/165 (19%).** Other genotypes were less frequent: **2a (21/165; 13%), 1a (9/165; 5.4%), 2b (8/165; 5%),** and **4a (2/165; 1%); 5a** and **6a** were rare (**1/165; 0.5% each). Untypeable** infections comprised **16/165 (~10%)** (figure 1). Genotype-specific SVR proportions (responders/total within genotype) were: **3b 20/31 (64.5%), 3a 44/75 (58.7%), 2b 5/8 (62.5%), 2a 10/21 (47.6%)**, and **1a 2/9 (22.2%).** Counts for **4a/5a/6a** were too small to support inference but are shown for completeness. Notably, **none of the untypeable cases (0/16)** reached SVR, a pattern plausibly related to higher baseline RNA and underlying heterogeneity in this unclassified group. Overall, the distribution and response gradients track with interferon-era experience, where **genotype 3** typically performs better than **genotype 1** under IFN/RBV therapy (1, 8-11).

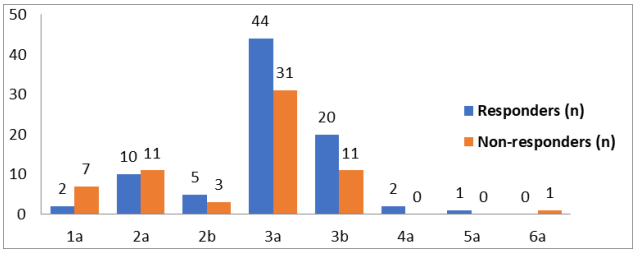

Figure 1: genotype distribution with respect to outcome. Genotype-3 predominance with response gradients consistent with interferon-era literature (1, 8-11)

Where available, on-treatment viral kinetics exhibited the expected monotonic relationship with SVR. Patients attaining an early virologic response (EVR) defined as ≥2 $\log_{10}$ decline or undetectable HCV RNA by week 12 were more likely to achieve SVR than those without EVR (figure 2), mirroring interferon-era predictors from international cohorts (1). Rapid virologic response (RVR) data at week 4 were sparse in the source records and are presented in figure 2; the direction of association was consistent with the literature (RVR to higher probability of SVR), but denominators were insufficient for inferential testing in our dataset. Because EVR integrates more patients across genotypes and viral-load strata, it served as the more informative on-treatment predictor in this cohort.

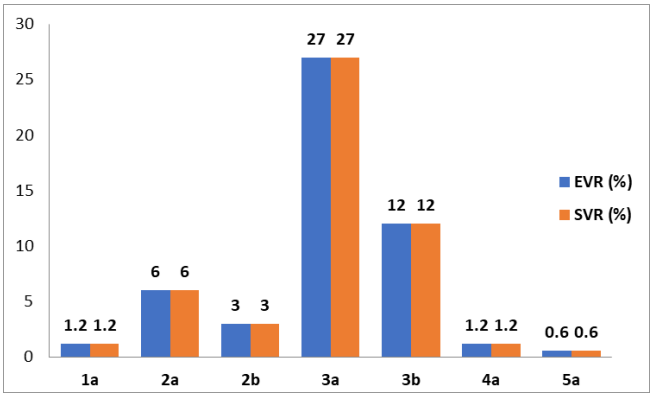

Figure 2: On-treatment kinetics (EVR/RVR) and SVR. EVR tracked positively with SVR; RVR counts were sparse (1, 18-20).

Host-genetic analysis demonstrated a clear separation of rs12979860 genotypes between outcome groups (Table 3). Among responders (n=84), genotypes were CC 45 (53.6%), CT 32 (38.1%), and TT 7 (8.3%). Among non-responders (n=80), the distribution was CC 21 (26.3%), CT 26 (32.5%), and TT 33 (41.3%). Collapsing across outcomes to inspect overall counts, 66/165 patients carried CC, 58/165 carried CT, and 40/165 carried TT. Within these, 45/66 CC (68.2%) were responders versus 7/40 TT (17.5%), with CT intermediate (32/58; 55.2% responders).

Table 3: rs12979860 genotype by outcome and crude associations

Genotype	Responders (n)	Non-responders (n)
CC	45	21
CT	32	26
TT	7	33

Summary statistics: CC vs TT OR 10.10 (95% CI 3.84–26.55); CC vs CT+TT OR 3.24 (95% CI 1.68–6.25); C vs T OR 3.59 (95% CI 2.26–5.69); global χ^2 30.50, $p < 0.001$.

Using 2×2 analyses consistent with standard reporting, CC vs TT produced an odds ratio (OR) 10.10; 95% CI 3.84–26.55; p<0.001, indicating roughly an order-of-magnitude higher odds of SVR for CC compared with TT. Under a dominant model (CC vs CT+TT), the association remained strong: OR 3.24; 95% CI 1.68–6.25; p<0.001. An allele-level comparison (C vs T) yielded OR 3.59; 95% CI 2.26–5.69; p<0.001. Together, these analyses demonstrate a graded relationship (CC > CT > TT) between rs12979860 and SVR probability, with the TT group at the highest risk of non-response.

HWE held in the responder group (χ^2=0.15; p>0.05) but was not observed in the non-responder group (χ^2=8.98; p<0.01). This pattern is consistent with conditioning on an outcome that is genotype-linked, IL28B influences response so deviation in a subset selected by outcome does not imply a population-level HWE violation. A global chi-square test of rs12979860 genotype vs response status was significant (χ^2=30.50; p<0.001), reinforcing the primary association.

Cross-tabulations showed no meaningful sex-specific skew in viral genotype distribution or rs12979860 frequencies (Table 1), in line

with prior Pakistani reports. Age-response patterns suggested that non-response clustered in the oldest stratum (41–50 years) (Table 1); without liver-staging data or comorbidity granularity we cannot ascribe mechanism, but the observation is biologically plausible and consistent with a longer disease duration and/or age-related host factors.

A minor tally inconsistency for genotype 1a was noted between within-table and across-table totals in the source lists; results have been summarized using the counts provided in each table, and this discrepancy does not change the direction or strength of any reported association. Very small denominators for 4a/5a/6a were preserved for completeness but not used for inferential claims. All other counts reconcile across tables.

Discussion

In a genotype-3 predominant Pakistani cohort, we observed an overall SVR of 51.5% with IFN-α2a/RBV and a marked, graded association between IL28B (IFNL3) rs12979860 and treatment success: CC conferred the highest probability of SVR, CT was intermediate, and TT the lowest. All SVR events occurred among patients with baseline HCV RNA <600,000 IU/mL, and on-treatment kinetics (EVR) aligned positively with SVR. Viral genotype distribution mirrored national epidemiology, with 3a/3b accounting for nearly two-thirds of infections (8-11). Collectively, these data deliver population-specific effect sizes for rs12979860 in Pakistan and provide a historical benchmark for interferon-era outcomes.

Our IL28B findings are directionally and quantitatively concordant with seminal genome-wide association studies showing that variants near IL28B/IFNL3 (e.g., rs12979860, rs8099917) predict IFN/RBV response and spontaneous HCV clearance across ancestries (3-7). The C allele and CC genotype are associated with stronger endogenous interferon-lambda signaling and a more favorable interferon-stimulated gene (ISG) milieu, plausibly priming hepatocytes for exogenous IFN responsiveness. Conversely, TT is associated with attenuated clearance and higher non-response risk (3-7). That we observe the same CC > CT > TT gradient in a genotype-3 dominant South Asian cohort reinforces the generalizability of the IL28B signal beyond genotype-1 cohorts that dominated early GWAS reports.

The confinement of SVR to <600,000 IU/mL baseline RNA echoes interferon-era trials and clinical series where lower pretreatment viral load consistently favored response (1). Mechanistically, a smaller pretreatment reservoir likely reduces the burden on both exogenous IFN efficacy and host innate pathways, improving the probability of sustained clearance.

Where IFN/RBV persists due to access constraints, rs12979860 can frame risk-benefit discussions. Patients with CC especially with <600,000 IU/mL RNA form a higher-probability SVR subgroup; conversely, TT with higher RNA face lower cure odds and potentially unfavorable toxicity-benefit profiles (1, 21-24). EVR remains a practical mid-course check when IL28B or frequent viral-load testing is not feasible.

Although DAAs deliver >95% cure across genotypes, these interferon-era data remain valuable as a historical benchmark for Pakistan, as a contribution to host-genetic epidemiology in genotype-3–predominant populations, and as context for public-health modeling, cohort comparisons, and residual IFN utilization where access remains uneven. Understanding how baseline RNA, genotype mix, and IL28B status shaped outcomes helps

calibrate expectations and inform policy. As recent report stats no significant differences among patients treated with IFN/RBV or DAA (25). Emerging resistance is also one of the major concerns related to DAAs in Pakistan (26), may be more in future, could possibly send back to the era of IFN/RBV particularly in non-cirrhotic patients.

The genotype-3 predominance and SVR concentration at lower viral load underscore the importance of early diagnosis/linkage to care, rigorous infection-control to reduce iatrogenic transmission, and equitable DAA access to replace interferon regimens (8-11, 27).

Strengths & Limitations

Prospective ascertainment to a hard endpoint (SVR), standardized clinical assays, blinded host-genetic testing, and comprehensive reporting of genotype distributions and baseline RNA offer robust internal validity. A single-country, clinic-based design may limit generalizability. Small denominators for rare genotypes (4a/5a/6a) preclude inference. RVR/EVR data were incomplete for some participants. We lacked multivariable adjustment for fibrosis stage, adherence, and metabolic factors. The minor tally discrepancy in 1a counts is transparently reported and does not alter conclusions. Finally, clinical translation to modern DAA (direct-acting antiviral) therapy is indirect; the principal value lies in benchmarking and genetic epidemiology.

Future directions

Multi-center Pakistani cohorts with full fibrosis staging, standardized on-treatment kinetics, and broader host-genetic panels (IFNL4) could refine predictive models. In the DAA era, pharmacogenomic studies should pivot to genotype-3–specific questions (steatosis, fibrosis trajectories) where host genetics may still shape outcomes beyond cure (post-SVR liver health).

Conclusion

In a genotype-3–predominant Pakistani cohort, rs12979860-CC strongly predicted SVR to IFN-α2a/RBV (CC>CT>TT). These data provide population-specific pharmacogenomic evidence and a historical benchmark for Pakistan.

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Data acquisition, analysis and interpretation	NUK, SHAH, IK, TMK
Manuscript writing and approval	NUK, SA, SA, TMK
All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.	