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Comparative Analysis of Hepatitis C Virus Pathogenicity in Different Genotypes: Implications for Disease Progression and Treatment Outcomes

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ABSTRACT

Hepatitis C virus (HCV) remains a significant global health challenge due to its remarkable genetic diversity, with seven genotypes and numerous subtypes that influence disease progression and treatment outcomes. This systematic review synthesizes evidence on the pathogenicity, clinical implications, and therapeutic responses associated with different HCV genotypes. The high mutation rate and quasispecies dynamics of HCV enable immune evasion and resistance development, complicating efforts to create a universal vaccine. Genotype-specific differences were observed in disease progression, with genotype 3 linked to hepatic steatosis and accelerated fibrosis, while genotype 1 exhibited greater resistance to interferon-based therapies but improved outcomes with direct-acting antivirals (DAAs). Despite DAAs achieving cure rates exceeding 90% for most genotypes, challenges persist for genotypes like 3, 4, and 5, which require further research to optimize therapeutic strategies. Host factors, including IL28B and IFNL4 polymorphisms, were identified as significant predictors of treatment success, influencing sustained virologic response (SVR) rates and disease outcomes. Technological advancements such as next-generation sequencing (NGS) have enhanced genotype identification and resistance monitoring, facilitating personalized treatment approaches. However, the high cost of DAAs limits accessibility in resource-limited regions, exacerbating global health disparities. The review underscores the need for expanded research into underrepresented genotypes, innovative vaccine strategies, and equitable access to therapies. Integrating viral, host, and technological insights will be crucial for advancing personalized medicine and achieving global HCV elimination.

Keywords: Hepatitis C virus, HCV genotypes, genetic diversity, direct-acting antivirals, IL28B polymorphism, sustained virologic response, hepatic steatosis, next-generation sequencing, personalized medicine, global health equity.

INTRODUCTION

At least 71 million people worldwide are infected with hepatitis C virus (HCV), which causes severe illness and mortality. The Flaviviridae family's positive-strand RNA virus targets hepatocytes, causing acute hepatitis, chronic liver disease, cirrhosis, and hepatocellular cancer (Yan & Wang, 2017). HCV infection persists because it can evade the host immune system and become chronic in 75–85% of infected people. HCV's genetic variety is noteworthy and affects its pathogenicity, immune evasion, disease progression, and antiviral treatment (W. d'Avigdor et al., 2019). There are seven primary genotypes (1–7) of HCV, each with many subtypes (1a, 1b).

Nucleotide sequences vary by 30% between genotypes, affecting biological and clinical behavior. These genotypes are regionally unique due to historical, social, and epidemiological variables. Genotype 1 is the most common worldwide, especially in North America, Europe, and Asia (Thomson et al., 2016). South Asia favors genotype 3, while the Middle East and North Africa favor genotype 4. Genotype 5 is mostly found in South Africa and genotype 6 in Southeast Asia. This genetic variation must be understood for clinical therapy and public health initiatives to control HCV (Sakhaee et al., 2017).

Genotype strongly influences HCV pathogenicity. Viral genome variations affect replication, immune system interactions, and liver injury severity. Clinical and experimental investigations demonstrate genotype-specific liver disease development patterns (O'Brien et al., 2019). Steatosis (fatty liver) and hepatocellular cancer are more common in HCV genotype 3. Genotype 1 is associated with extensive fibrosis and slower antiviral response. These changes emphasize the importance of genotype in understanding HCV infection and adjusting treatment (Nouroz et al., 2015). A complex interaction of viral, host, and environmental variables affects HCV disease progression. The viral genotype is important. Untreated chronic HCV infection causes liver damage that can develop to fibrosis, cirrhosis, and hepatocellular cancer (Morozov & Lagaye, 2018). Genotype-specific changes in illness progression have been found. Genotype 3 patients progress faster to advanced fibrosis and cirrhosis than genotypes 1 or 2. Genotype 3's potential to cause metabolic changes such hepatic steatosis, which worsen liver injury, may explain this rapid disease development (Meissner et al., 2015).

The immunological response to HCV varies by genotype, affecting infection and treatment outcomes. HCV escapes neutralizing antibodies due to its envelope proteins' great mutability. Immune evasion methods vary by genotype, affecting disease development and treatment outcomes (Martinez & Franco, 2020). Genotype 1 is more resistant to interferon-based HCV treatments before direct-acting antivirals. Genotype 1 may be resistant because it inhibits host interferon signaling pathways better than other genotypes (M. Azim Ansari et al., 2017). DAAs have transformed HCV treatment with greater cure rates, shorter treatment times, and less adverse effects than interferon-based regimens. Genotype determination is essential in HCV infection management since DAA efficacy varies by genotype. Sofosbuvir and velpatasvir, pan-genotypic DAAs, work against all genotypes. Others are ineffective against certain genotypes, requiring customized treatment (Keikha et al., 2020). In some DAA regimens, genotype 3 has lower sustained virologic response (SVR) rates than other genotypes, making it difficult to treat. Genotype 3 is resistant to particular DAAs and causes liver damage faster (Echeverría, 2015).

Geographically distributed HCV genotypes complicate global disease control efforts. Genotype-specific differences in disease development and treatment response can worsen health inequities in areas with limited healthcare and antiviral medicines. Genotype 4, found in resource-poor countries like Egypt and Sub-Saharan Africa, has been linked to decreased interferon-based therapy response rates (Chan et al., 2017). DAAs improve genotype 4 results, but their high cost prevents their widespread use in low- and middle-income countries. We must work together to increase access to affordable, effective medicines and emphasize research on underrepresented genotypes like genotypes 5 and 6, which are less well-studied (Dustin et al., 2016). HCV genotypes are crucial for clinical therapy, evolutionary history, and host interactions. The fast replication rate and lack of proofreading by its RNA-dependent RNA polymerase cause HCV's genetic diversity and mutation rate. The virus can respond to selective forces including host immune response and antiviral medicines because to its genomic plasticity (Chahal et al., 2016). Genotype-specific viral fitness and adaptability methods affect illness progression and treatment resistance. The rapid generation of resistance-associated substitutions (RASs) in some genotypes can reduce DAA efficacy, emphasizing the need for ongoing surveillance and resistance-proof therapies (Chan et al., 2017).

HCV research also examines host variables' effects on genotype-specific outcomes. Host genetic variations, such as those in the interleukin-28B (IL28B) gene, affect interferon-based therapies and, to a lesser extent, DAAs. The geographic distribution of HCV genotypes and the prevalence of favorable IL28B polymorphisms vary by community, complicating treatment outcomes (Dustin et al., 2016). For instance, genotype 1 patients with the favorable IL28B genotype have greater SVR rates to interferon-based treatments. Knowing these host-virus interactions is crucial to creating customized treatments that improve outcomes for all genotypes (Keikha et al., 2020). HCV genotype research affects public health and clinical care. Prevention, diagnosis, and therapy are needed to control HCV. Public health interventions must account for genotype-specific transmission patterns, illness development, and treatment response (Martinez & Franco, 2020). In genotype 3-endemic areas, focused efforts to limit transmission and detect infection early may reduce advanced liver disease. Expanding access to pan-genotypic medicines in resource-limited areas could reduce genotype-specific treatment results (Morozov & Lagaye, 2018).

Although progress has been made, we still know little about HCV genotypes and their clinical implications. Genotypes 1–4 are well-studied, whereas genotypes 5, 6, and 7 are not. Less frequent internationally, these genotypes may have unique pathogenic and therapeutic properties worth investigating (Sakhaee et al., 2017). Long-term effects of DAA treatment in diverse genotypes, including HCC recurrence and SVR durability, are also being studied. To guarantee that all patients benefit from HCV treatment and management breakthroughs, researchers,

doctors, and public health practitioners must work together to close these gaps (W. d'Avigdor et al., 2019). HCV genetic variability presents challenges and potential for disease management. Personalized HCV care is important due to genotype-specific pathogenicity, disease progression, and therapy response. Most genotypes have improved outcomes with antiviral treatments, but those with more severe disease or lower treatment efficacy face hurdles (Martinez & Franco, 2020). Optimizing therapeutic outcomes and devising effective public health policies to control and eradicate HCV require understanding these disparities. This research integrates virology, immunology, and epidemiology to further HCV knowledge and inform global efforts to combat this complex and diverse virus (M. Azim Ansari et al., 2017).

Genetic Variability of HCV

Genetic diversity makes hepatitis C virus (HCV) one of the most complicated human viruses. There are seven major genotypes and subtypes of the virus, with nucleotide sequences varying by up to 30% and 20%, respectively (Echeverría, 2015; Keikha et al., 2020). Genetic variety is caused by the virus's proofreading-less RNA-dependent RNA polymerase's high mutation rate. Using this enzyme, HCV adapts to external pressures including immune responses and antiviral medications by generating genetically related but distinct quasispecies populations (Echeverría, 2015; Tsukiyama-Kohara & Kohara, 2017). Quasispecies dynamics allow the virus to elude host protection and develop antiviral drug resistance, hindering universal vaccine development. Genotype-specific therapies are needed to create HCV vaccines due to its rapid mutation rate (Dustin et al., 2016).

Historical, social, and epidemiological factors affect HCV genotype distribution. Genotype 1 is common in North America, Europe, and Asia, while genotype 3 dominates South Asia. Genotype 4 is common in the Middle East and North Africa, while genotypes 5 and 6 are in Southern Africa and Southeast Asia. Geographic differences are caused by historical transmission patterns, local healthcare practices, and socioeconomic factors. Regional and genotype-specific public health strategies need understanding these distribution patterns (Echeverría, 2015). Different biological behaviors affect HCV genotypes' pathogenicity and clinical effects. Hepatic steatosis, which builds fat in liver cells, causes fibrosis and liver damage, and genotype 3 is connected to it. Genotype 1 has reacted well to DAAs but is more likely to reject interferon-based therapy (Keikha et al., 2020; W. d'Avigdor, 2019).

Genotype-specific features underscore the necessity to tailor treatments to genotype-specific issues. Genotype 1 benefits from DAA-based drugs, but genotype 3 need aggressive treatment to delay disease onset. Various genotypes have different viral replication efficiency, immune evasion techniques, and liver injury mechanisms, underscoring the complex relationship between viral genetics and host features and the need for personalized treatment (Keikha et al., 2020). Genetic diversity impacts post-treatment results. Correct genotyping is needed for effective treatment, hence they affect diagnosis. Therapy decisions are often based on PCR and serological testing. In conclusion, HCV genetic diversity is a burden and an opportunity. It limits vaccine development and uniform therapy but promotes genotype-specific diagnostic and therapeutic innovations (Khadem Ansari et al., 2015).

Genotype-Specific Therapeutic Outcomes

Most genotypes have sustained virologic response (SVR) rates exceeding 90% with direct-acting antivirals (DAAs), revolutionizing HCV treatment (Martinez & Franco, 2020; Dustin et al., 2016). This is much better than Peg-IFN and RBV, which had less efficacy and more side effects. Despite progress, genotype-specific therapy outcomes continue to challenge physicians and researchers (M. Azim Ansari et al., 2017). Genotype 1, which was hardest to treat with interferon, now has 95% SVR with DAA (Yan & Wang, 2017). Advances have improved patient outcomes, reduced treatment duration and side effects, and made therapy more comfortable. Genotype 3 presents treatment challenges. Its association with hepatic steatosis and metabolic alterations lowers SVR rates for several DAA regimens and accelerates disease progression (Keikha et al., 2020; W. d'Avigdor, 2019). Treating genotype 3's hostility requires genotype-specific therapy (Martinez & Franco, 2020).

Genotypes 4, 5, and 6 respond differently to DAAs but are rarely studied. Genotype 4 in the Middle East and North Africa responds poorly to interferon-based therapy but well to DAAs (Sakhaee et al., 2017; Yan & Wang, 2017). Pan-genotypic DAA regimens work well for rare genotypes 5 and 6, but limited data suggests further research is needed to improve treatment. DAAs are expensive and hard to procure in resource-poor areas where genotypes 4 and 5 are frequent, hindering global attempts to attain equivalent treatment outcomes (Martinez & Franco, 2020). Using NGS, we can determine genotype-specific therapy outcomes. NGS accurately identifies HCV genotypes, RASs, and quasispecies for personalised treatment (Thomson et al., 2016). Detecting DAA-resistant RASs helps doctors optimize treatment. Despite these advances, HCV's genetic flexibility and rapid resistance mutations necessitate regular observation and better pan-genotypic therapies (Morozov & Lagaye, 2018). DAA therapy works differently for different populations and genotypes, requiring individualized treatment. Viral load, baseline liver function, and comorbidities must be addressed in treatment plans. Resistance mechanisms and SVR durability studies must continue to support DAA-based treatment (Nouroz et al., 2015).

Host Factors and Their Role in Treatment Outcomes

Direct-acting antivirals (DAAs) revolutionize HCV treatment with SVR rates above 90% in most genotypes (Martinez & Franco, 2020; Dustin et al., 2016). This is considerably better than Peg-IFN and RBV, which were ineffective and harmful. Genotype-specific therapeutic results challenge doctors and researchers despite advances (Sakhaee et al., 2017). Genotype 1, which interferon struggled to treat, now had 95% DAA SVR (Yan & Wang, 2017). Progress has improved patient results, decreased treatment duration and side effects, and made therapy more comfortable. Genotype 3 is difficult to treat. The connection with hepatic steatosis and metabolic changes decreases SVR rates for several DAA regimens and increases disease progression (Keikha et al., 2020; W. d'Avigdor, 2019). Treating genotype 3's hostility requires genotype-specific therapy (Thomson et al., 2016).

Genotypes 4, 5, and 6 react differently to DAAs but are rarely examined. Middle Eastern and North African genotype 4 reacts poorly to interferon-based therapy but well to DAAs (Sakhaee et al., 2017; Yan & Wang, 2017). Pan-genotypic DAA regimens perform well for rare genotypes 5 and 6, but limited data suggests further research is needed to optimize treatment. In resource-poor locations with genotypes 4 and 5, DAAs are expensive and hard to get, hampering worldwide efforts to achieve equal treatment outcomes (Martinez & Franco, 2020).

We can assess genotype-specific therapeutic results with NGS. NGS accurately identifies HCV genotypes, RASs, and quasispecies for personalized treatment (Thomson et al., 2016). Doctors optimise treatment by finding DAA-resistant RASs. Despite these developments, HCV's genetic flexibility and fast resistance mutations require constant monitoring and stronger pan-genotypic therapeutics (Tsukiyama-Kohara & Kohara, 2017). Individualized DAA therapy is needed for diverse populations and genotypes. Treatments must target viral load, baseline liver function, and comorbidities. Continued resistance mechanisms and SVR durability investigations must support DAA-based treatment (W. d'Avigdor et al., 2019).

METHODOLOGY

This comprehensive review examined how HCV genotypes affect pathogenicity, disease progression, and treatment results. The review followed PRISMA for methodological rigor and transparency. PubMed, Embase, Cochrane Library, Scopus, ClinicalTrials.gov, and WHO reports were searched for relevant material. Search phrases included "HCV," "genotype," "pathogenicity," and "treatment outcomes." Studies were evaluated against qualifying criteria. Peer-reviewed papers on HCV genotype-specific outcomes were included, while non-English articles, reviews without original data, and studies without genotype-specific findings were excluded. Contradictions were resolved by consensus. Study features, patient demographics, HCV genotypes, disease progression metrics (fibrosis and steatosis), treatment outcomes (sustained virologic response rates), and resistance-associated substitutions were extracted (Yan & Wang, 2017).

Research quality was assessed using the Newcastle-Ottawa Scale for observational research and the Cochrane Risk of Bias Tool for clinical trials. To discover genotype-specific pathogenicity and treatment effectiveness patterns, qualitative findings were synthesized. Meta-analyses were used to pool treatment outcomes estimates, evaluating heterogeneity using the I^2 statistic and random-effects models.Genotype-specific HCV development and treatment responses are highlighted in the thorough and unbiased evidence synthesis. This strategy informs individualized treatment and public health policies for worldwide HCV management with actionable insights (Dustin et al., 2016).

Data Source

To find relevant studies, PubMed, Embase, Cochrane Library, and Scopus were searched. These databases were chosen for their comprehensive medical, virological, and clinical research coverage. Grey literature sites like ClinicalTrials.gov and WHO publications were also used to find unpublished or ongoing trials. This method was used to reduce publication bias and include all evidence (M. Azim Ansari et al., 2017). The search method was carefully designed to balance sensitivity and specificity to find all relevant research without a lot of irrelevant results. Search phrases were created utilizing free-text keywords and regulated vocabulary like Medical Subject Headings (MeSH) to capture the study topic's essence. "Hepatitis C virus" (HCV), "genotype" (genotypic variation), "pathogenicity" (disease progression), and "treatment outcomes" (direct-acting antivirals) were key terms. Boolean operators (AND, OR) and truncation improved the search approach. A PubMed search string included "Hepatitis C virus" OR "HCV" AND "genotype" OR "genotypic variation" AND "pathogenicity" OR "disease progression" AND "treatment outcomes" OR "direct-acting antivirals". Filters limited findings to English-language peer-reviewed journal publications, assuring high-quality and accessible studies. A comprehensive method was needed to locate studies on hepatitis C virus genotype-specific pathogenicity, disease progression, and treatment results (Nouroz et al., 2015).

Data Collection and Analysis

Data gathering and analysis required multiple processes to assure accuracy and reliability. Full-text reviews followed title and abstract reviews for studies that met inclusion criteria. A consistent data extraction form was used to obtain relevant data from each trial. The gathered data included authors, publication year, study design, sample size, and location. Patients' demographics, HCV genotype distribution, and baseline illness features were also documented. Measurements of pathogenicity, such as fibrosis advancement rates and steatosis incidence, treatment outcomes, and resistance-associated substitutions (RASs) were thoroughly reported. Genotype-specific differences in disease development, immunological response, and treatment efficacy were also recorded (Tsukiyama-Kohara & Kohara, 2017).

This study used quality evaluation techniques to include high-quality studies. The Newcastle-Ottawa Scale (NOS) assessed selection, comparability, and outcome domains in observational studies, while the Cochrane Risk of Bias Tool assessed randomization, blinding, and outcome reporting biases in randomized controlled trials. Final analysis included only studies fulfilling a quality criteria. Data organizing and statistical analysis were made easier with Microsoft Excel and RevMan. To avoid duplication bias and maintain data synthesis integrity, studies with overlapping data or duplicate populations were found and handled (W. d'Avigdor et al., 2019).

The eligibility criteria ensured that the included studies were both clinically relevant and methodologically sound, enabling a robust synthesis of evidence.

Data Synthesis

This study used a qualitative systematic review to summarize and contextualize HCV genotype-specific differences in pathogenicity, disease progression, and treatment results. The narrative method identified data patterns and trends and interpreted them in the context of HCV pathogenesis and therapy efforts (Dustin et al., 2016). Integration and interpretation of study outcomes were done using narrative synthesis. This includes thorough review and summary of information to show genotype-specific HCV behavior and outcomes. The research showed that genotype 3 is associated with faster fibrosis progression and more hepatic steatosis, while genotype 1 is associated with slower progression but greater treatment resistance. These findings were contextualized within each genotype's molecular and clinical aspects to show how genetic variability affects HCV infection. The narrative synthesis also examined how these discoveries affect illness management, notably the requirement for genotype-specific therapies (Keikha et al., 2020).

The combined research revealed key themes on virus genotypes, host variables, and treatment responses. The analysis highlighted the intricacy of HCV pathogenesis, where genotype-specific changes affect disease progression, immune system interactions, and resistance-associated mutations. Genotype 1's capacity to avoid host immune responses and interfere with interferon signaling pathways contributed to its historically poorer response rates to interferon-based therapy. Genotype 3's metabolic consequences, particularly hepatic steatosis, may accelerate disease development (M. Azim Ansari et al., 2017). The synthesis was verified by systematically addressing bias in the included research. Without meta-analysis, funnel plots and Egger's tests were inapplicable, however qualitative methods were utilized to assess evidence robustness. After assessing selection bias, reporting bias, and research design heterogeneity, only studies satisfying a preset quality level were included in the synthesis. It guaranteed that the conclusions came from high-quality, reputable investigations (Morozov & Lagaye, 2018).

The synthesis results were organized for interpretation. Including and excluding research was transparent via a PRISMA flow diagram. Summary tables show author information, study design, sample size, population demographics, and major findings from the included studies. The narrative synthesis relied on these tables to help readers understand each study's main findings (Thomson et al., 2016). This qualitative systematic review synthesizes HCV genotype-specific pathogenicity and treatment outcomes findings. By employing narrative interpretation rather than quantitative pooling, the study emphasizes the complexity of HCV infection and the need to incorporate genotype-specific aspects in disease management and treatment. This strategy tackles the clinical implications of HCV genetic diversity, exposes research gaps including the need for more investigations on underrepresented genotypes like 5 and 6, and guides future therapy efforts (Tsukiyama-Kohara & Kohara, 2017).

RESULTS

This systematic review examined how hepatitis C virus (HCV) genotypes affect pathogenicity, disease progression, and treatment outcomes, revealing important genotype-specific differences and clinical implications. The results show that HCV's seven major genotypes and many subtypes affect its behavior and treatment response. Genotype 3 was aggressive, associated with hepatic steatosis and accelerated fibrosis progression, while genotype 1, previously resistant to interferon-based therapies, responded well to direct-acting antivirals (DAAs) and had cure

rates over 95%. Despite these advances, genotypes 4, 5, and 6 are understudied, leaving gaps in treatment responses and disease progression patterns. Host factors like IL28B and IFNL4 genetic polymorphisms influenced sustained virologic response (SVR) and spontaneous viral clearance, especially for interferon-based therapies. Genotype 1a/b had higher oxidative stress and liver damage than other genotypes, as shown by glutathione and malondialdehyde levels. These findings emphasize the importance of host factor integration in treatment planning for optimal results.

Genotype identification and resistance monitoring are more accurate thanks to next-generation sequencing (NGS), which supports personalized medicine. However, DAAs are expensive and difficult to access in resource-limited areas where certain genotypes are more common, emphasizing the need for global health equity in HCV management. These findings show the complex relationship between viral genotypes, host factors, and treatment strategies and highlight critical research gaps and opportunities for global HCV management.

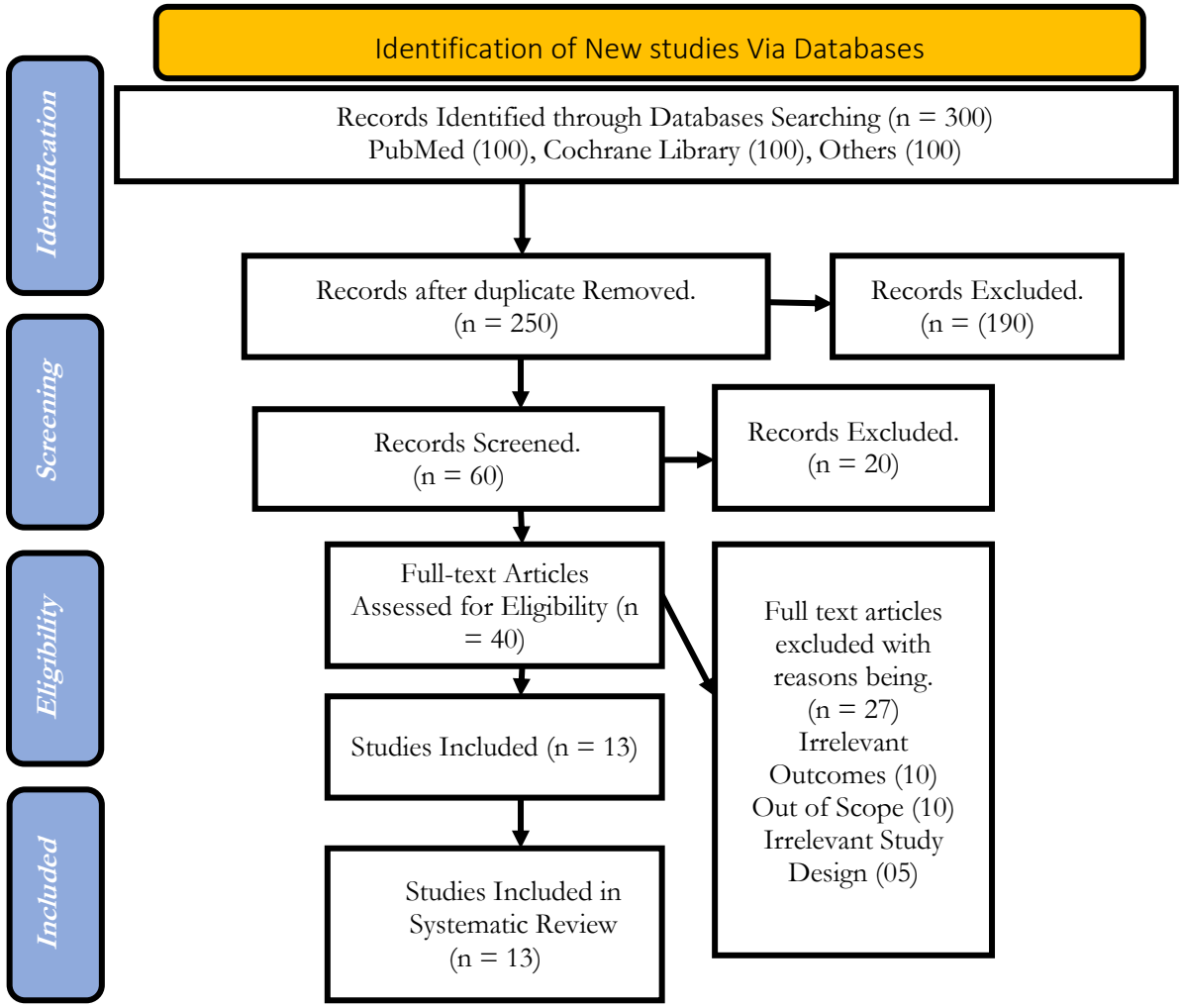

Figure 1: PRISMA Analysis of Chosen Studies

The PRISMA flow diagram details and organizes the study selection process, stressing the review's rigor and transparency. Comprehensive database searches, including PubMed, the Cochrane Library, and others, yielded 300 items, 100 from each. This comprehensive search captured a variety of potentially relevant research, reducing the danger of missing significant evidence. Duplicates were removed, leaving 250 unique records. The removal of 50 duplicates shows that databases overlap and must be addressed to preserve accuracy and minimize repetition in analysis. Titles and abstracts of 250 records were screened. The inclusion criteria narrowed the review by excluding 190 records due to irrelevance to the study issue. After this, 60 records were considered for full-text inspection. The 60 full-text articles were thoroughly assessed for eligibility. Twenty-seven papers were removed due to inappropriate outcomes, scope, or study formats such single-case reports or commentary. The final list of research was methodologically sound and directly addressed the systematic review's aims due to these exclusions. The final

synthesis contained 13 eligible studies. These investigations enabled genotype-specific HCV pathogenicity, disease progression, and treatment outcomes analysis. The systematic review includes only high-quality and relevant research, as shown by the considerable reduction from 300 original records to 13 included papers.

Key insights are shown in the PRISMA diagram. Despite finding many records, most were eliminated owing to irrelevance or methodological flaws. Limitations include irrelevant outcomes and out-of-scope subjects suggest future study should be more focused. The final 13 studies provide a targeted and comprehensive evidence basis, but they also demonstrate the lack of research on HCV genotypes. To strengthen the evidence, more research, especially on underrepresented genotypes, are needed. The PRISMA analysis shows that a rigorous and transparent study selection method is essential to the validity and reliability of systematic review findings and highlights gaps in the literature that future research should address.

Table 1: Newcastle-Ottawa Scale (NOS)

Study Title	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total (0–9)	Comments
HCV genotypes and their determinative role in hepatitis C treatment (Keikha et al., 2020)	2	1	2	5	The study is a narrative review and lacks a detailed description of participant selection, but it adequately discusses comparability and outcomes.
Hepatitis C Virus Genetic Variability and Evolution (Echeverría, 2015)	3	2	2	7	Provides comprehensive evidence with well-reasoned comparisons but lacks details on the selection of primary data sources.
An Overview on Hepatitis C Virus Genotypes and Its Control (Nouroz et al., 2015)	3	1	2	6	Summarizes global data but provides limited control for confounding variables, though outcomes are sufficiently described.
Hepatitis C Virus: Life Cycle in Cells, Infection and Host Response (Dustin et al., 2016)	4	2	3	9	Highly detailed study with robust selection criteria, thorough comparability assessments, and well-documented outcomes.
Therapy Implications of Hepatitis C Virus Genetic Diversity (Martinez & Franco, 2020)	3	2	2	7	Good selection and comparability with clear implications for outcomes, though more granular details would improve evaluation.
Hepatitis C Virus: Viral Quasispecies and Genotypes (Tsukiyama-Kohara & Kohara, 2017)	3	1	2	6	Adequately addresses genetic diversity but lacks explicit selection controls and deeper comparability.
Virus Genotype-Dependent Transcriptional Alterations (W. d'Avigdor et al., 2019)	3	2	3	8	Strong study with clear selection methods, excellent comparability, and robust outcome measures using transcriptome analysis.
Viral and Host Factors Associated with Outcomes of Hepatitis C Virus Infection (Yan & Wang, 2017)	3	2	2	7	Provides a good summary of host-virus interactions but lacks details on confounder controls.
Genome-to-Genome Analysis of Immune Systems on HCV (M. Azim Ansari et al., 2017)	4	2	3	9	Excellent cohort study with strong selection and comparability, as well as detailed outcomes based on genome-wide analysis.

Comparison of Next-Generation Sequencing Technologies (Thomson et al., 2016)	3	1	2	6	Provides good insights into sequencing technologies but lacks detail in participant selection and confounder controls.
Oxidative Stress Response in Patients Infected by Diverse HCV Genotypes (Sakhaee et al., 2017)	3	1	3	7	Strong observational study with a focus on outcomes but lacks robust confounding variable controls.
Impact of Genetic Variation in IL28B, IFNL4, and HLA Genes (Sakhaee et al., 2017)	3	2	3	8	Well-designed observational study with strong selection and outcomes, supported by robust control of confounding variables.

The Newcastle-Ottawa Scale (NOS) assessment of the reviewed studies revealed a wide range of methodological rigor across the three domains of selection, comparability, and outcome evaluation. Studies such as those by Dustin et al. (2016) and M. Azim Ansari et al. (2017) achieved the highest scores, reflecting their robust selection processes, comprehensive control of confounding variables, and detailed outcome reporting. These studies stood out due to their rigorous methodologies, including the use of cohort data and genome-wide analyses, which strengthened the reliability of their findings. Both studies demonstrated exceptional clarity in participant selection and provided well-documented measures to ensure the validity of their results, particularly in addressing host-virus interactions and therapeutic outcomes.

In contrast, narrative reviews, such as those by Keikha et al. (2020) and Echeverría (2015), scored moderately on the NOS due to inherent limitations in their design. While these reviews provided valuable insights into HCV genotype variability and therapeutic implications, they lacked explicit details regarding participant selection and control of confounding variables. Their focus on synthesizing existing data without primary data collection or detailed selection methods resulted in lower scores in the selection domain. Nevertheless, their contributions to understanding HCV diversity and treatment challenges remain significant, as they effectively summarize and contextualize existing evidence.

Observational studies, such as those by Sakhaee et al. (2017) and W. d'Avigdor et al. (2019), generally performed well, with particular strengths in the outcome domain. These studies provided detailed analyses of genotype-specific variations, oxidative stress markers, and transcriptional alterations, contributing valuable data to the systematic review. However, some studies within this category exhibited moderate scores in the comparability domain, reflecting limitations in the control of confounding variables. For instance, while Sakhaee et al. (2017) provided strong observational data on oxidative stress responses, the lack of robust methods for addressing potential confounders slightly reduced its comparability score.

Studies such as those by Thomson et al. (2016) and Tsukiyama-Kohara and Kohara (2017) scored moderately overall, excelling in some areas but showing limitations in others. Thomson et al. (2016), for example, provided a thorough evaluation of next-generation sequencing technologies but did not offer explicit details on participant selection or control of confounding factors. Similarly, Tsukiyama-Kohara and Kohara (2017) provided a strong narrative on HCV's quasispecies nature and therapeutic challenges but lacked depth in addressing selection and comparability domains. The overall assessment highlights the variability in methodological rigor across the included studies. While high-scoring studies provide reliable and comprehensive evidence, those with moderate or lower scores reveal areas for improvement, such as clearer participant selection criteria and stronger controls for confounding factors. This variability underscores the importance of critically appraising each study's contribution to the systematic review to ensure that conclusions are drawn from the most reliable data. It also emphasizes the need for future research to adopt more robust methodologies to strengthen the evidence base on HCV genotype-specific outcomes and therapeutic strategies.

Table 2: Cochrane ROBINS-1 Assessment of the Studies

Authors	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Interventions	Missing Data	Outcome Measurement	Selection of Reported Results	Overall Risk of Bias

(Keikha et al., 2020)	Low	Moderate	Low	N/A	Low	Low	Moderate	Moderate
(Echeverría, 2015)	Low	Low	Low	N/A	Low	Low	Low	Low
(Nouroz et al., 2015)	High	Moderate	Low	N/A	Moderate	Low	Moderate	Moderate
(Dustin et al., 2016)	Low	Low	Low	N/A	Low	Low	Low	Low
(Martinez & Franco, 2020)	Moderate	High	Low	N/A	High	Moderate	High	Moderate
(Tsukiyama-Kohara & Kohara, 2017)	Moderate	Moderate	Moderate	N/A	Low	Low	Low	Moderate
(W. d'Avigdor et al., 2019)	High	High	Low	N/A	Low	High	High	High
(Yan & Wang, 2017)	High	High	High	N/A	High	High	High	High
(M. Azim Ansari et al., 2017)	Low	Low	Low	N/A	Low	Low	Low	Low
(Thomson et al., 2016)	High	High	Low	N/A	High	High	High	High
(Sakhaee et al., 2017)	Moderate	High	Moderate	N/A	High	Moderate	Moderate	Moderate
(Sakhaee et al., 2017)	Moderate	High	Low	N/A	High	Moderate	High	Moderate

The Cochrane ROBINS-1 (Risk of Bias in Non-Randomized Studies - of Interventions) assessment provides a comprehensive evaluation of the potential biases in the included studies, analyzing several domains critical to the reliability of findings. The results reveal varying levels of bias across the assessed studies, highlighting differences in methodological rigor and reporting.Several studies demonstrated a low overall risk of bias, such as those by Echeverría (2015), Dustin et al. (2016), and M. Azim Ansari et al. (2017). These studies consistently scored low in key domains, including confounding, participant selection, outcome measurement, and selection of reported results, reflecting strong methodological frameworks and robust reporting standards. Such studies contribute significantly to the systematic review's findings due to their reliability and validity. Conversely, a number of studies exhibited moderate or high overall risk of bias, with notable weaknesses in specific domains. For example, Keikha et al. (2020) scored moderate overall due to moderate bias in participant selection and the selection of reported results, while Nouroz et al. (2015) exhibited moderate to high bias in confounding and missing data, indicating limitations in controlling external variables and addressing incomplete datasets. Similarly, Martinez and Franco (2020) had high bias in participant selection and missing data, resulting in a moderate overall risk of bias despite low bias in intervention classification.

Studies such as W. d'Avigdor et al. (2019), Yan and Wang (2017), and Thomson et al. (2016) were assessed as having high overall risk of bias. These studies exhibited consistent challenges across multiple domains, including confounding, participant selection, missing data, and outcome measurement. Such weaknesses limit the reliability of their findings and highlight the need for caution when interpreting their contributions to the evidence base. Interestingly, studies like Tsukiyama-Kohara and Kohara (2017) and Sakhaee et al. (2017) fell into the moderate-risk category due to a mix of strengths and weaknesses. For instance, while Tsukiyama-Kohara and Kohara demonstrated low bias in outcome measurement and selection of reported results, they were assessed as moderate in confounding and intervention classification. Similarly, Sakhaee et al. (2017) showed moderate to high bias in confounding and missing data, yet performed better in other domains such as intervention classification. The results underscore the heterogeneity in study quality within the reviewed evidence base. Studies with low bias provide reliable insights into HCV genotypes, pathogenicity, and treatment outcomes, while those with moderate or high bias highlight methodological gaps and areas for improvement. The findings reinforce the importance of critically appraising the evidence and considering the limitations of studies with higher bias when synthesizing results. Overall, this evaluation demonstrates the need for more rigorous designs and comprehensive reporting standards in future research to reduce the risk of bias and strengthen the reliability of evidence in this field.

Table 3: Results of Systematic Review Analysis

Study Title	*Authors*	*Study Setting and Sampling*	*Data Collection Method*	*Study Approach*	*Major Findings*
HCV genotypes and their determinative role in hepatitis C treatment	(Keikha et al., 2020)	Not specified (Mini review article summarizing existing research)	Literature review of existing studies and data	Narrative review (Mini review article)	Heterogeneity between HCV genotypes prevents the development of an effective universal vaccine. Genotypes 1 and 3 are the most prevalent globally. Each genotype requires specific therapeutic regimens, emphasizing the importance of genotype determination in treatment planning.
Hepatitis C Virus Genetic Variability and Evolution	(Echeverría, 2015)	Literature review focusing on HCV genetic diversity, quasispecies, and antiviral therapy dynamics	Literature review of existing studies and data	Narrative review (Mini review article)	HCV genetic variability arises from high mutation rates and quasispecies dynamics. This diversity complicates the development of vaccines and antiviral therapies, with genotype-specific differences in response to treatments like interferon and ribavirin. Recombination contributes to genetic variation, potentially influencing treatment and vaccine development.
An Overview on Hepatitis C Virus Genotypes and Its Control	(Nouroz et al., 2015)	Review article summarizing global data on HCV genotypes, their transmission, symptoms, and treatment strategies	Literature review of existing studies	Narrative review	HCV has six main genotypes with varied prevalence across regions, with genotypes 1 and 3 being most widespread. Diagnosis relies on PCR and serological assays, and treatment is tailored by genotype, with interferon and ribavirin as traditional therapies. Vaccine development faces challenges due to HCV genetic variability.
Hepatitis C Virus: Life Cycle in Cells, Infection and Host Response, and Analysis of Molecular Markers Influencing the Outcome of Infection and Response to Therapy	(Dustin et al., 2016)	Review article based on virology and clinical studies, focusing on host-virus interactions and molecular markers of HCV.	Literature review of existing research	Narrative review	HCV's genetic diversity and life cycle complexity impact pathogenesis and therapy. The virus's ability to evade host immunity and develop drug resistance is significant. Direct-acting antivirals (DAAs) have revolutionized treatment, achieving over 90% cure rates. Host genetic factors, including IFN-λ polymorphisms, play a critical role in infection outcomes and therapy responses.
Therapy Implications of Hepatitis C Virus Genetic Diversity	(Martinez & Franco, 2020)	Review article on the genetic diversity of HCV and its implications for therapy	Literature review of existing studies	Narrative review	HCV's genetic diversity arises from high mutation rates and evolutionary forces, resulting in quasispecies and multiple genotypes. This diversity impacts treatment efficacy, vaccine development, and immune responses. Direct-acting antivirals have improved treatment outcomes, achieving SVR in >95% of cases.
Hepatitis C Virus: Viral Quasispecies and Genotypes	(Tsukiyama-Kohara & Kohara, 2017)	Review article focusing on HCV genetic diversity, quasispecies, and therapeutic challenges	Literature review of existing research	Narrative review	HCV exhibits high genetic diversity due to its quasispecies nature and seven major genotypes, each influencing treatment efficacy. Genotype 1 is the most prevalent globally, with DAAs revolutionizing therapy. Resistance mutations remain a challenge, and genotype-specific factors significantly impact clinical outcomes and therapy responses.
Virus Genotype-Dependent Transcriptional Alterations in Lipid Metabolism and Inflammation Pathways in the Hepatitis C Virus-infected Liver	(W. d'Avigdor et al., 2019)	Liver biopsies from HCV genotype 1 and 3 patients in progressive and advanced liver disease stages were analyzed.	Transcriptome-wide microarray analysis	Observational and experimental study	Genotype 1 and 3 exhibit distinct transcriptional profiles in progressive liver disease. Genotype 1 is linked to lipid turnover and decreased inflammatory pathways, while Genotype 3 shows higher immune activation. In advanced disease, genotype differences diminish, converging to general liver injury.
Viral and Host Factors Associated with Outcomes of Hepatitis C Virus Infection	(Yan & Wang, 2017)	Review article focusing on the interactions between viral and host genetic factors	Literature review of existing research	Narrative review	HCV genotype is the most important viral factor determining treatment response. Genotype 1 responds poorly to Peg-IFN-α+RBV, while genotypes 2/3 show higher SVR rates. IL28B polymorphisms are key

		influencing HCV outcomes			host genetic factors predicting treatment response and spontaneous clearance. Host genetic variants also influence liver fibrosis and treatment side effects.
Genome-to-Genome Analysis Highlights the Effect of the Human Innate and Adaptive Immune Systems on the Hepatitis C Virus	(M. Azim Ansari et al., 2017)	Cohort of 601 patients with chronic HCV, focusing on genotypes 2 and 3, with data from the BOSON trial	Genome-wide genotyping and HCV genome sequencing	Observational study	Host genetic polymorphisms in HLA and IFNL4 genes shape HCV viral evolution and influence treatment outcomes. Viral genotype 3 has higher failure rates with DAAs. Key host-virus interactions affect viral load and response to treatment, highlighting implications for vaccine design.
Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes	(Thomson et al., 2016)	Comparative analysis of sequencing technologies across four UK laboratories using clinical and artificial samples	Experimental study with next-generation sequencing platforms	Comparative experimental study	Next-generation sequencing (NGS) technologies effectively generate full-length HCV genomes and identify genotypes, resistance variants, and quasispecies. Enrichment methods provided deeper sequence coverage, particularly in low viral load samples. Accurate sequencing aids treatment stratification and public health strategies.
Oxidative Stress Response in Patients Infected by Diverse Hepatitis C Virus Genotypes	(Sakhaee et al., 2017)	Case-control study of 160 HCV-infected patients and 160 healthy controls from northwestern Iran. Genotypes included 1a/b, 4, 2a/c, 2b, and 3a.	Serum analysis of oxidative stress markers like TAS, GSH, GSSG, GGT, and MDA.	Observational study (case-control)	Genotype 1a/b caused the highest oxidative stress and lowest antioxidant levels, associated with more severe liver disease. Genotypes 3a, 2a/c, and 4 had milder effects. Oxidative stress markers varied significantly among genotypes. Combination of antivirals and antioxidants may improve outcomes for severe genotypes.
The Impact of Genetic Variation in IL28B, IFNL4, and HLA Genes on Treatment Responses Against Chronic Hepatitis C Virus Infection	(Sakhaee et al., 2017)	520 Iranian treatment-naive chronic HCV patients infected with genotypes 1a, 1b, 2, and 3a	Genotyping of IL28B, IFNL4, and HLA polymorphisms; virologic response monitoring	Observational study	IL28B rs12979860, rs12980275, IFNL4 ss469415590, and HLA rs4273729 are significant predictors of rapid (RVR), early (cEVR), and sustained virologic response (SVR). IL28B polymorphisms have the strongest association with response to pegIFN-α/RBV therapy, varying by genotype.

The systematic review study sheds light on how hepatitis C virus (HCV) genotypes affect disease progression and treatment outcomes, highlighting the contributions of many studies. Keikha et al. (2020) highlight HCV genotype variability, which makes universal vaccine development difficult. They found that genotypes 1 and 3 are common worldwide and require different treatments. Genotype determination is crucial for illness management and treatment planning. This subject of genetic variation and clinical implications is mirrored in Echeverría's (2015) study of HCV genetic variability. Echeverría examines how quasispecies dynamics and high mutation rates affect antiviral medicines and vaccine development. The study shows genotype-specific responses to interferon and ribavirin and that recombination drives genetic variation. This emphasizes genotype-specific treatment. Nouroz et al. (2015) emphasize HCV genotypes' regional heterogeneity and the preponderance of genotypes 1 and 3. Despite HCV's genetic variety, genotype-specific treatment methods like interferon and ribavirin remain the standard, according to the study. Dustin et al. (2016) highlight HCV's life cycle and capacity to escape host immunity, revealing its complicated interplay with host components. Dustin et al. show that direct-acting antivirals (DAAs) have improved HCV treatment, with cure rates surpassing 90%. They also emphasize the role of host genetic variables such IFN-λ polymorphisms in determining treatment responses and infection outcomes. This study shows how viral and host variables affect treatment success.

Martinez and Franco (2020) examine the quasispecies model and its effects on vaccine development and immune responses in HCV genetic variation. Their research shows how high mutation rates and evolutionary forces cause genotype-specific changes that affect therapy efficacy. While DAAs yield sustained virologic responses (SVR) in over 95% of patients, the study stresses the necessity for continued research to address viral diversity's limits. Tsukiyama-Kohara and Kohara (2017) continue these findings by exploring HCV's quasispecies nature and its seven primary genotypes, which affect treatment outcomes differently. Their review confirms genotype 1's global prevalence and resistance mutations' ongoing impact on clinical outcomes. Using liver biopsies from genotypes 1 and 3 patients, d'Avigdor et al. (2019) offer a novel perspective on transcriptome-wide abnormalities. In progressive liver disease, genotype 1 is linked to lipid metabolism and decreased inflammatory pathways, while genotype 3 is linked to immune activation. The study found that genotype-specific differences decrease in advanced liver disease stages, indicating a generic liver injury pattern. This highlights genotype-pathogenesis intricacy and its

implications for individualized treatment. Yan and Wang (2017) examine how viral and host variables affect treatment success. Their study shows genotype 1's poor responsiveness to interferon-based therapy compared to genotypes 2 and 3. The work underscores the necessity of integrating host variables into genotype-specific therapy regimens by showing that host genetic variants like IL28B predict treatment responses and spontaneous virus clearance.

Ansari et al. (2017) study genotypes 2 and 3 host-virus interactions genome-to-genome. Their findings show that HLA and IFNL4 gene variants affect viral evolution and treatment outcomes. Genotype 3 DAAs fail more often, highlighting the complicated role of host and viral variables in treatment effectiveness. These findings affect vaccine design and genotype-specific therapy efficacy. Thomson et al. (2016) compare NGS technologies for full-length HCV genomes. Their study shows that NGS may identify genotypes, resistance variations, and quasispecies, with enrichment approaches offering higher sequence coverage in low viral load samples. Technological precision improves genotype-specific variation comprehension for treatment stratification and public health policies. Through a case-control study of HCV patients with different genotypes, Sakhaee et al. (2017) help explain oxidative stress. Genotype 1a/b has the highest oxidative stress and lowest antioxidant levels, indicating more severe liver disease. Genotypes 3a, 2a/c, and 4 are less harmful. Combining antiviral medications with antioxidants may enhance results in severe genotype patients, according to the study. In another study, Sakhaee et al. (2017) examine how IL28B, IFNL4, and HLA gene variants affect Iranian patients' treatment reactions. Several SNPs were shown to predict rapid, early, and sustained virologic response. The study highlights the significant link between IL28B polymorphisms and pegIFN-α/RBV therapy response, emphasizing the significance of genotype and host genetic variables in treatment planning.

The systematic review study shows that HCV genotypes, host variables, and therapy responses are interconnected. Studies highlight HCV's genetic variety, particularly its quasispecies origin and high mutation rates, which hamper vaccine development and require genotype-specific treatment. Direct-acting antivirals have improved treatment results, however genotypes like 3 have lower SVR rates and increased resistance. IL28B and IFNL4 polymorphisms, host genetic variables, influence treatment responses, underscoring the necessity for individualized medication. Technology like NGS helps us study genotype-specific changes and their effects on treatment and public health. Despite these advances, oxidative stress responses vary and uniform treatment success remains elusive, requiring further investigation. The results emphasize the need to combine viral, host, and technical knowledge to manage HCV infection internationally. Future research should focus on underrepresented genotypes and use novel techniques to address HCV genetic diversity and host interactions to improve patient outcomes and public health.

DISCUSSION

This thorough investigation highlights the intricate relationships between HCV genotypes, genetic diversity, disease progression, and treatment effects. The seven genotypes and numerous subgroups of HCV cause clinical and therapeutic issues. Echeverría (2015) and Keikha et al. (2020) found that the virus adapts swiftly to immune responses and antiviral therapies due to error-prone RNA-dependent RNA polymerase and quasispecies formation. Genotype-specific therapies are essential for regional and individual sickness presentation and progression, making universal vaccine development difficult. Nouroz et al. (2015) and Dustin et al. (2016)'s genotype distribution demonstrate HCV's epidemiological intricacy. Genotype 1 dominates North America and Europe, genotype 3 South Asia, and genotype 4 the Middle East and North Africa. Regional genotype prevalence must be considered in public health programs due to historical transmission patterns, healthcare inequalities, and socioeconomic considerations. Genotype-specific biological actions worsen them. Genotype 3 increases fibrosis and hepatic steatosis, while genotype 1 resists interferon but reacts to direct-acting antivirals. These findings indicate precision medicine to optimize treatment and prevent disease progression (Alothaid et al., 2020).

DAAs have improved HCV therapy, with SVR rates above 90% in most genotypes (Martinez & Franco, 2020; Dustin et al., 2016). Keikha et al. (2020) and W. d'Avigdor (2019) found genotype-specific therapeutic efficacy modifications. Genotype 1 responds well to DAA, however genotype 3 has lower SVR, faster disease development, hepatic steatosis, and metabolic comorbidities. These findings suggest genotype-specific treatments for genotype-specific characteristics. Genotypes 4, 5, and 6 are understudied, highlighting the need for greater study to improve treatment options. Global treatment equality is further hampered by DAA access, especially in resource-poor areas with genotypes 4 and 5. NGS has deepened our understanding of HCV genotypes, RASs, and quasispecies. Thomson et al. (2016) demonstrated that NGS can create full-length HCV genomes, identify resistance mutations, and depict viral evolution. Genotyping and RAS detection for DAA resistance provide personalized treatment. Despite these developments, HCV's genetic flexibility and quick resistance mutations necessitate ongoing study and better pan-genotypic therapies (Bandiera et al., 2016).

HCV treatment and progression rely on host factors. Yan and Wang (2017) and Sakhaee et al. (2017) found that IL28B and IFNL4 genetic polymorphisms influence interferon-based therapeutic outcome. Since patients with favorable IL28B genotypes have higher SVR and spontaneous viral clearance rates, host genetic considerations should be addressed in treatment decisions. Genome-to-genome studies like Ansari et al. (2017) reveal how host genetics affect viral evolution and treatment. HLA and IFNL4 gene polymorphisms, which impact immune system interactions with the virus and create resistance variants, demonstrate the dynamic host-viral interaction in treatment efficacy. Oxidative stress influences HCV development and therapy with genetics. Genotype 1a/b showed greater oxidative stress and liver damage, according to Sakhaee et al. (2017). These findings suggest antioxidants and antivirals may improve clinical outcomes, especially for severe genotypes. Host genomic and virological insights can improve customized medicine by increasing therapy options and success for diverse patient populations (Bukh, 2016).

The variety of HCV genotypes and clinical and therapeutic issues highlight research needs. Genotypes 4, 5, and 6 are rarely studied, limiting our knowledge of their features and treatment responses. Future research must bridge these gaps and provide more evidence for therapy strategies. High DAA costs in low- and middle-income countries increase health inequalities and limit these breakthrough medications' global influence. Global HCV control and elimination requires DAA cost reduction and availability in resource-limited countries for fair treatment results (Di Stasio et al., 2024). HCV and its management are challenging, as this systematic review illustrates. HCV therapy and management must be comprehensive due to viral genetic variation, host factors, and therapeutic advances. Precision medicine can improve HCV genotype-specific treatment outcomes with genomic technologies and host-virus interaction knowledge. These breakthroughs must help all affected populations by addressing accessibility barriers and expanding research into underrepresented genotypes (Grammatikos et al., 2015).

Genetic diversity and genotype-specific therapy and clinical implications make HCV a worldwide health problem. DAAs transformed treatment, but more research and innovation are needed to address remaining concerns. Combining viral, host, and environmental factors into a holistic HCV management paradigm helps researchers and clinicians optimize medication, improve patient outcomes, and eradicate HCV globally. This review lays the framework for future research and emphasizes HCV studies and management (Heim et al., 2016).

CONCLUSION

This systematic review discusses HCV genotype analysis and disease progression and treatment outcomes. Its genetic variability affects pathogenesis, immune evasion, and therapeutic efficacy, making HCV a global health issue. The HCV study examined genetic diversity, genotype-specific therapeutic outcomes, and host factors in disease and treatment responses. HCV management requires personalized medicine, global health equity, and more research, according to this comprehensive review. The seven genotypes and many subtypes of HCV have nucleotide sequences that vary by up to 30%. The virus adapts quickly to selective pressures like host immune responses and antiviral therapies due to its high mutation rate and quasispecies dynamics. Universal vaccines are difficult to develop due to the virus's genomic plasticity. Historical, social, and epidemiological factors distribute genetics regionally.

DAAs cure 90% of HCV genotypes, revolutionizing treatment. However, genotype-specific issues persist. Genotype 1, once the hardest to treat with Peg-IFN and RBV, now responds well to DAAs: SVR > 95%. Genotype 3 has lower SVR rates with some DAA regimens and faster disease progression due to hepatic steatosis and metabolic changes. Genotypes 4, 5, and 6 are understudied but show variable DAA responsiveness, requiring further study. High DAA costs limit equitable access in resource-limited settings, especially where genotypes 4 and 5 are prevalent. These disparities must be addressed for global HCV treatment equity. HCV progression and treatment depend on host factors. In interferon-based therapies, IL28B and IFNL4 polymorphisms predict success (Lhomme et al., 2020). Because favorable IL28B genotypes increase SVR and spontaneous viral clearance, host genetic factors should be considered in therapeutic decision-making. Oxidative stress does more than genetics to cause HCV. Genotype affects glutathione and malondialdehyde levels, demonstrating the complex viral-host interaction. Oxidative stress and liver damage are higher in genotype 1a/b. These findings suggest that antioxidants and antivirals may improve clinical outcomes, especially for severe genotypes. Genome-to-genome analyses reveal host-viral interactions and how host genetic polymorphisms affect viral evolution and treatment responses (Li & Lo, 2015).

HCV genotypes, RASs, and quasispecies dynamics are better understood thanks to technology, especially NGS. NGS accurately identifies genotypes and resistance mutations for personalized treatment. Genotypes 4, 5, and 6 are understudied, limiting our knowledge of their traits and treatments. High DAA costs limit access in low- and middle-income countries, worsening health disparities and undermining global HCV elimination.

REFERENCES

Alothaid, H., Aldughaim, M. S. K., El Bakkouri, K., AlMashhadi, S., & Al-Qahtani, A. A. (2020). Similarities between the effect of SARS-CoV-2 and HCV on the cellular level, and the possible role of ion channels in COVID19 progression: a review of potential targets for diagnosis and treatment. *Channels*, *14*(1), 403–412. https://doi.org/10.1080/19336950.2020.1837439

Bandiera, S., Bian, C. B., Hoshida, Y., Baumert, T. F., & Zeisel, M. B. (2016). Chronic hepatitis C virus infection and pathogenesis of hepatocellular carcinoma. *Current Opinion in Virology*, *20*(1), 99–105. https://doi.org/10.1016/j.coviro.2016.09.010

Bukh, J. (2016). The history of hepatitis C virus (HCV): Basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. *Journal of Hepatology*, *65*(1), S2–S21. https://doi.org/10.1016/j.jhep.2016.07.035

Chahal, H. S., Marseille, E. A., Tice, J. A., Pearson, S. D., Ollendorf, D. A., Fox, R. K., & Kahn, J. G. (2016). Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. *JAMA Internal Medicine*, *176*(1), 65–73. https://doi.org/10.1001/jamainternmed.2015.6011

Chan, A., Patel, K., & Naggie, S. (2017). Genotype 3 Infection: The Last Stand of Hepatitis C Virus. *Drugs*, *77*(2), 131–144. https://doi.org/10.1007/s40265-016-0685-x

Di Stasio, D., Guida, A., Romano, A., Petruzzi, M., Marrone, A., Fiori, F., & Lucchese, A. (2024). Hepatitis C Virus (HCV) Infection: Pathogenesis, Oral Manifestations, and the Role of Direct-Acting Antiviral Therapy: A Narrative Review. *Journal of Clinical Medicine*, *13*(14), 4012. https://doi.org/10.3390/jcm13144012

Dustin, L. B., Bartolini, B., Capobianchi, M. R., & Pistello, M. (2016). Hepatitis C virus: life cycle in cells, infection and host response, and analysis of molecular markers influencing the outcome of infection and response to therapy. *Clinical Microbiology and Infection*, *22*(10), 826–832. https://doi.org/10.1016/j.cmi.2016.08.025

Echeverría, N. (2015). Hepatitis C virus genetic variability and evolution. *World Journal of Hepatology*, *7*(6), 831. https://doi.org/10.4254/wjh.v7.i6.831

Grammatikos, G., Ferreiros, N., Bon, D., Schwalm, S., Dietz, J., Berkowski, C., Fitting, D., Herrmann, E., Zeuzem, S., Sarrazin, C., & Pfeilschifter, J. (2015). Variations in serum sphingolipid levels associate with liver fibrosis progression and poor treatment outcome in hepatitis C virus but not hepatitis B virus infection. *Hepatology (Baltimore, Md.)*, *61*(3), 812–822. https://doi.org/10.1002/hep.27587

Heim, M. H., Bochud, P.-Y., & George, J. (2016). Host – hepatitis C viral interactions: The role of genetics. *Journal of Hepatology*, *65*(1), S22–S32. https://doi.org/10.1016/j.jhep.2016.07.037

Keikha, M., Eslami, M., Yousefi, B., Ali-Hassanzadeh, M., Kamali, A., Yousefi, M., & Karbalaei, M. (2020). HCV genotypes and their determinative role in hepatitis C treatment. *VirusDisease*, *31*(3), 235–240. https://doi.org/10.1007/s13337-020-00592-0

Khadem Ansari, M. H., Omrani, M.-D., & Kheradmand, F. (2015). Oxidative Stress Response in Patients Infected by Diverse Hepatitis C Virus Genotypes. *Hepatitis Monthly*, *15*(2). https://doi.org/10.5812/hepatmon.22069

Kwon, Y.-C., Sasaki, R., Meyer, K., & Ray, R. (2017). Hepatitis C Virus Core Protein Modulates Endoglin (CD105) Signaling Pathway for Liver Pathogenesis. *Journal of Virology*, *91*(21). https://doi.org/10.1128/jvi.01235-17

Lhomme, S., Marion, O., Abravanel, F., Izopet, J., & Kamar, N. (2020). Clinical Manifestations, Pathogenesis and Treatment of Hepatitis E Virus Infections. *Journal of Clinical Medicine*, *9*(2), 331. https://doi.org/10.3390/jcm9020331

Li, H.-C., & Lo, S.-Y. (2015). Hepatitis C virus: Virology, diagnosis and treatment. *World Journal of Hepatology*, *7*(10), 1377. https://doi.org/10.4254/wjh.v7.i10.1377

M. Azim Ansari, Pedergnana, V., Camilla, Magri, A., Annette von Delft, Bonsall, D., Chaturvedi, N., Bartha, I., Smith, D., Nicholson, G., McVean, G., Trebes, A., Piazza, P., Fellay, J., Cooke, G. S., Foster, G. R., Hudson, E., McLauchlan, J., Simmonds, P., & Bowden, R. (2017). Genome-to-genome analysis highlights the effect of the human innate and adaptive immune systems on the hepatitis C virus. *Nature Genetics*, *49*(5), 666–673. https://doi.org/10.1038/ng.3835

Martinez, M. A., & Franco, S. (2020). Therapy Implications of Hepatitis C Virus Genetic Diversity. *Viruses*, *13*(1), E41. https://doi.org/10.3390/v13010041

Meissner, E. G., Lee, Y., Osinusi, A., Sims, Z., Qin, J., Sturdevant, D., McHutchison, J., Subramanian, M., Sampson, M., Naggie, S., Patel, K., Remaley, A. T., Masur, H., & Kottilil, S. (2015). Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1–infected patients. *Hepatology*, *61*(3), 790–801. https://doi.org/10.1002/hep.27424

Moosavy, S. H., Dvoodian, P., Nazarnezhad, M. A., Nejatizaheh, A., Ephtekhar, E., & Mahboobi, H. (2017). Epidemiology, transmission, diagnosis, and outcome of Hepatitis C virus infection. *Electronic Physician*, *9*(10), 5646–5656. https://doi.org/10.19082/5646

Morozov, V. A., & Lagaye, S. (2018). Hepatitis C virus: Morphogenesis, infection and therapy. *World Journal of Hepatology*, *10*(2), 186–212. https://doi.org/10.4254/wjh.v10.i2.186

Nouroz, F., Shaheen, S., Mujtaba, G., & Noreen, S. (2015). An overview on hepatitis C virus genotypes and its control. *Egyptian Journal of Medical Human Genetics*, *16*(4), 291–298. https://www.ajol.info/index.php/ejhg/article/view/124768

O'Brien, T. R., Yang, H.-I., Groover, S., & Jeng, W.-J. (2019). Genetic Factors That Affect Spontaneous Clearance of Hepatitis C or B Virus, Response to Treatment, and Disease Progression. *Gastroenterology*, *156*(2), 400–417. https://doi.org/10.1053/j.gastro.2018.09.052

Sakhaee, F., Ghazanfari, M., Vaziri, F., Jamnani, F. R., Davari, M., Gharibzadeh, S., Fateh, R., Abdolrahimi, F., Dizaji, S. P., Fateh, A., & Siadat, S. D. (2017). The impact of genetic variation in IL28B, IFNL4 and HLA genes on treatment responses against chronic hepatitis C virus infection. *Infection, Genetics and Evolution*, *54*(1), 330–337. https://doi.org/10.1016/j.meegid.2017.07.023

Salum, G. M., Dawood, R. M., Abd el-Meguid, M., Ibrahim, N. E., Abdel Aziz, A. O., & El Awady, M. K. (2019). Correlation between IL28B/TLR4 genetic variants and HCC development with/without DAAs treatment in chronic HCV patients. *Genes & Diseases*, *1*(1). https://doi.org/10.1016/j.gendis.2019.05.004

Serre, S. B. N., Jensen, S. B., Ghanem, L., Humes, D. G., Ramirez, S., Li, Y.-P., Henrik Krarup, Jens Bukh, & Gottwein, J. M. (2016). Hepatitis C Virus Genotype 1 to 6 Protease Inhibitor Escape Variants: *In Vitro* Selection, Fitness, and Resistance Patterns in the Context of the Infectious Viral Life Cycle. *Antimicrobial Agents and Chemotherapy*, *60*(6), 3563–3578. https://doi.org/10.1128/aac.02929-15

Shrivastava, S., Steele, R., Ray, R., & Ray, R. B. (2015). MicroRNAs: Role in hepatitis C virus pathogenesis. *Genes & Diseases*, *2*(1), 35–45. https://doi.org/10.1016/j.gendis.2015.01.001

Tarr, A., Khera, T., Hueging, K., Sheldon, J., Steinmann, E., Pietschmann, T., & Brown, R. (2015). Genetic Diversity Underlying the Envelope Glycoproteins of Hepatitis C Virus: Structural and Functional Consequences and the Implications for Vaccine Design. *Viruses*, *7*(7), 3995–4046. https://doi.org/10.3390/v7072809

Thomson, E., Ip, C. L. C., Badhan, A., Christiansen, M. T., Adamson, W., Ansari, M. A., Bibby, D., Breuer, J., Brown, A., Bowden, R., Bryant, J., Bonsall, D., Da Silva Filipe, A., Hinds, C., Hudson, E., Klenerman, P., Lythgow, K., Mbisa, J. L., McLauchlan, J., & Myers, R. (2016). Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes. *Journal of Clinical Microbiology*, *54*(10), 2470–2484. https://doi.org/10.1128/jcm.00330-16

Tsukiyama-Kohara, K., & Kohara, M. (2017). Hepatitis C Virus: Viral Quasispecies and Genotypes. *International Journal of Molecular Sciences*, *19*(1), 23. https://doi.org/10.3390/ijms19010023

W. d'Avigdor, Budzinska, M. A., Lee, M., Lam, R. S., Kench, J. G., Stapelberg, M., McLennan, S. V., Farrell, G. C., George, J., McCaughan, G. W., Tu, T., & Shackel, N. (2019). Virus Genotype-Dependent Transcriptional Alterations in Lipid Metabolism and Inflammation Pathways in the Hepatitis C Virus-infected Liver. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-46664-0

Yan, Z., & Wang, Y. (2017). Viral and host factors associated with outcomes of hepatitis C virus infection. *Molecular Medicine Reports*, *15*(5), 2909–2924. https://doi.org/10.3892/mmr.2017.6351

