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META-ANALYSIS

Host Immune Recognition, Pattern Recognition Receptor Signaling, and Antigen Presentation Pathways Initiating Chronic Host–Pathogen Interactions

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ABSTRACT

Background: The spread of chronic viral diseases like Hepatitis B (HBV) and Human Immunodeficiency Virus (HIV) became a significant health issue in the world. Pattern recognition receptor (PRR) signaling, antigen presentation pathways (APP), and host immune recognition (HIR) were the key pathways of host immune response that were often dysregulated to allow viral persistence. This study aimed at synthesizing available literature on the dysregulation of PRR signaling, HIR and APP pathways in the development and persistence of chronic HBV and HIV infections. **Methods:** This study was performed according to PRISMA 2020 guidelines. Research was conducted in PubMed, Scopus, Web of Science, and Google Scholar from August 2014 to September 2024. Those studies included that involved PRR (e.g. TLRs), HIR (e.g. T cell subsets), and APP (e.g. dendritic cell function) interactions in the chronic HBV and HIV. Non-English articles, reviews, and studies without quantitative data were excluded. Statistical analyses were performed using MetaAnalysisOnline tool. The risk of bias was assessed using appropriate tools, and the certainty of evidence was evaluated using the GRADE framework. **Results:** The analysis of twelve studies revealed downregulation of TLR7 (SMD: -1.92, 95% CI: -3.19 to -0.66) and reduction of $CD3^+$ T cells (SMD: -1.95, 95% CI: -3.36 to -0.55) in patient cohorts versus controls, whereas TLR2, TLR4, $CD4^+$, $CD8^+$ T, and dendritic cell markers showed no statistically association. Overall risk of bias was evaluated to be moderate, whereas the certainty of evidence was low. **Conclusion:** Chronic infections were characterized by parallel dysfunctions across PRR signaling, adaptive HIR, and APP.

Keywords: Viral Infection, Hepatitis B, HIV, Pattern Recognition Receptor, T Lymphocytes, Antigen Presentations, Immune Evasions, Meta-Analysis, Systematic Review.

INTRODUCTION

The initiation and persistence of chronic viral infections, including the ones caused by Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV), represented a significant global health burden [1-3]. These chronic infections were characterized by a complicated dynamic in which the pathogens have developed advanced means to evade the host immune response [4]. The key processes involved were initial recognition and response phase, which was managed by the host immune recognition (HIR) pathways, pattern recognition receptor (PRR) signaling, and antigen presentation pathways (APP) [5-7]. These systems played a central role in triggering both innate and adaptive immunity and its failure was a critical variable in the acquisition of chronicity, allowing pathogens to evade and find a permanent residence in the host.

The immunopathogenesis of chronic HBV and HIV was driven by a combination of particular abnormalities in PRR (such as Toll-like receptors 2/4/7 (TLR)) signaling, HIR (such as T Lymphocytes dynamics ($CD3^+/4^+/8^+$)), and APP (such as dendritic cell development and function) [8,9]. Early innate cytokine production was hampered by impaired TLR signaling in HBV, which in turn prevented effective dendritic cell maturation; these defected antigen-presenting cells then enhanced the dysfunctional HIR that appeared as altered T cells responses [10]. These pathways had been identified as potential targets of therapeutic interventions to restore immune dysregulation. The exploration of these pathways provided a model that could account for the heterogeneity in disease outcome and the variable efficacy of treatments in various individuals and viral pathogens.

Although many studies have examined individual constituents of these pathways in particular viral settings, the synthesized analysis to compare and contrast these mechanisms had not been done in major chronic viral infections (HBV and HIV). The current evidence was fragmented due to different study designs and disease settings, and biomarkers assessed, which resulted in inconsistent findings. A logical synthesis was needed to bring the findings on the diagnostic, prognostic, and therapeutic relevance of the critical biomarkers. The rationale behind this review was to elucidate the associations and indicate gaps in the existing knowledge. Because of the heterogeneity and the lack of methodological limitations in the published literature, additional rigorous studies were needed to determine a final justification of clinical translation.

The purpose of this systematic review and meta-analysis was to critically evaluate the role of pattern recognition receptor signalling, host immune recognition and antigen presentation pathways in the development and persistence of chronic hepatitis B virus and human immunodeficiency virus infections. The review specifically focused on Toll-like receptor expression, T lymphocyte subset changes and dendritic-cell-related antigen presentation markers to identify common patterns of immune dysfunction and highlight gaps for future research.

METHODOLOGY

Study Design and Reporting Standards: The approach of systematic review and meta-analysis were based on PRISMA guidelines [11].

Inclusion and Exclusion Criteria: Those studies were included that were original research articles, such as observational (cross-sectional, cohort) or interventional clinical investigations, examining the role of PRR signaling, HIR, and APP in human chronic infections (i.e., HBV and HIV). Only articles published in English were considered. Studies were excluded if they were non-primary research including reviews and editorials, or if they did not report quantitative measurements, or if the full text was unavailable.

Data Sources: The authors selected research from August 2014 to September 2025 by using databases i.e., PubMed, Scopus, Web of Science, and Cochrane Library.

Search strategy: The search strategy involved a combination of free-text keywords that are related to chronic viral infections and MeSH terms, immune pathways, and specific pathogens. Core search terms included: "chronic viral infection," "persistent infection," "Hepatitis B," "HIV," "pattern recognition receptors," "Toll-like receptors," "TLR," "immune exhaustion," "T Lymphocytes," "antigen presentation," "dendritic cells," "immune evasion," "biomarker," "dysregulation," and "immunopathogenesis." Boolean operators (AND, OR) were applied while searching, and the reference lists of included studies were manually screened to identify additional eligible articles.

Study Selection: The title and abstract of studies were reviewed independently by two researchers until proper inclusion requirement met. The reviewers settled their selection differences either through group agreement or expert consultation.

Data Extraction: Two independent reviewers performed data extraction, which included information about study design, confounding variables, outcome measures, and key results. The reviewers either achieved consensus or consulted a third person to settle any differences between their findings. When necessary, corresponding authors were contacted for missing or clarifying data.

Outcome Measures: The primary outcome of this review was to evaluate the role of PRR signaling (TLR), HIR (T Lymphocytes dynamics) and APP (dendritic cell function) pathways in the development and persistence of chronic HBV and HIV infections. The secondary outcomes included assessment of Toll-like receptor expression, T lymphocyte subset changes, dendritic-cell-related antigen presentation markers, and their association with viral persistence and disease progression.

Quality Assessment: Risks of bias among the included studies were assessed through the NOS for observational studies and case-control studies, JBI critical appraisal checklist for cross-sectional studies and custom domain-based qualitative framework for experimental studies [12,13]. The level of evidence was determined based on the GRADE approach.

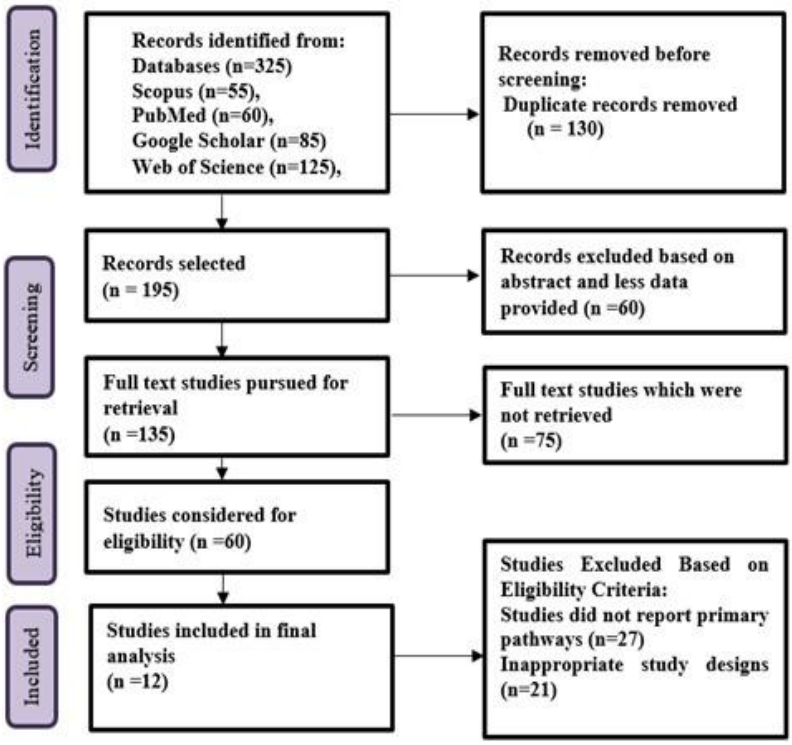

Figure 1: Figure 1: PRISMA Flow Diagram for selection of studies. The flowchart was designed in accordance with the PRISMA guidelines 2020, displaying study identification, screening, assessment eligibility, and final selection in the systematic review.

Statistical Assessment: The statistical analysis and forest plots were generated in MetaAnalysisOnline Tool [14]. The mean and standard deviation were calculated using standard protocols where researchers had reported data in the form of medians and interquartile ranges. As a measure of heterogeneity, the I^2 value was used and considered as low <50%, moderate 50–75%, high >75%**.** In study design, populations, or measurement methods that could not be statistically pooled because of heterogeneity, a narrative synthesis was offered in a more structured format. The measures of immune pathway dysregulation (such as TLR expression, T Lymphocytes dynamics, and dendritic cell function) were correlated with clinical and virological outcomes (such as viral load, disease progression). The sensitivity analysis was performed for eligible studies.

RESULTS

The study demonstrated the role of PRR signaling, HIR and APP pathways in the development and persistence of chronic HBV and HIV infections. Initially, 325 research articles were selected from the four databases searched and other sources. After removing duplicates, the number was reduced to 195 records. Title and abstract screening excluded a further 60 studies. The remaining 135 articles were then screened for eligibility, and 75 were excluded due to unavailability of full-texts. Forty-eight additional articles were excluded because they did not contain stratified data, and included reviews, case reports, or were not in English. Finally, 12 studies that met the inclusion criteria were included in this schematic review. The PRISMA flow diagram presented in Figure 1 illustrates the selection process.

Table I provided a structured overview summarizing the characteristics and key findings of the twelve included studies, illustrating the role of PRR signaling (TLR), HIR (T Lymphocytes dynamics) and APP (Dendritic cell function) pathways in the development and persistence of chronic HBV and HIV infections.

Table I: Characteristics of Included Studies and Role of Pattern Recognition Receptor Signaling, Human Immune Recognition, and Antigen Presentation Pathways in HBV and HIV

Author & Year	Disease Context	Key Biomolecule Investigated	Study Design & Model(s)	Sample Size / Population Characteristics	Biomolecule Levels Mean ± SD (%)	Key Findings
Dey et al., 2022 [15]	Chronic HBV	TLR2, TLR4 via flow cytometry	Observational cross-sectional study	CHB patients = 15, HC = 19	CHB (TLR2 = 75 ± 4; TLR4 = 75 ± 3) HC (TLR2 = 90 ± 3; TLR4 = 90 ± 2)	In individuals with CHB, monocyte expression of TLR2 and TLR4 was found to be significantly reduced, correlating with broader functional impairment.
Kalita et al., 2024 [16]	HBV	TLR7 via qRT-PCR, IHC	Observational cross-sectional study	72 HBV+ pregnant women, 23 HC	HBV (TLR7= -9 ± 60) HC (TLR7= 140 ± 48)	TLR7 expression downregulated in placentas of HBV+ mothers, especially in cord blood HBV DNA+ cases.
Lu et al., 2014 [17]	Chronic HBV	TLR2, TLR4 via flow cytometry	Observational cross-sectional study	35 HBV patients, 30 HC	HBV (TLR2 = 2.67 ± 2.89; TLR4 =53.94 ± 16.21) HC (TLR2 =2.60 ± 1.70; TLR4 =45.34 ± 24.46)	TLR2 and TLR4 expression on DCs increased with disease progression. TLR2 correlated positively with HBsAg.
Kalita et al., 2023 [18]	HBV	TLR-7 via qRT-PCR	Observational cross-sectional study	HBsAg-positive pregnant women=53, Healthy pregnant women=22	HBV (TLR7= -14 ± 50); HC (TLR7=104 ± 150)	TLR-7 expression was significantly downregulated in HBsAg+ women compared to healthy controls.
Dou et al., 2025 [19/]	HBV-related acute chronic liver failure	Peripheral blood T lymphocyte subsets ($CD3^+$, $CD4^+$) via Fluorescence immunoassay	Retrospective case-control study	HBV =40, Healthy controls=40	HBV ($CD3^+$= 32.6±3.8, $CD4^+$= 21.5±2.1); HC ($CD3^+$= 46.9±4.5, $CD4^+$= 31.3±2.6)	$CD3^+$ and $CD4^+$ percentages were significantly lower in HBV related acute chronic liver failure vs. controls.
Wang et al., 2021 [20]	HBV-related acute chronic liver failure	Peripheral T lymphocytes ($CD3^+$, $CD4^+$, $CD8^+$) via flow cytometry	Prospective case-control study	HBV- ACLF =97, Healthy controls=23	HBV ($CD3^+$= 32.40±19.09, $CD4^+$= 58.69±14.19, $CD8^+$= 36.08±12.50); HC ($CD3^+$= 50.38±13.87, $CD4^+$= 50.75±9.45, $CD8^+$= 39.17±6.65)	$CD3^+$ cells decreased and $CD4^+$ increased in HBV-ACLF. $CD8^+$ not significantly changed.
Ko et al., 2020 [21]	Chronic HBV	T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$) via flow cytometry	Cross-sectional Study	N=26	$CD3^+$=44.5 ± 14.0, $CD4^+$=11.4 ± 6.2, $CD8^+$=8.6 ± 5.9	Serum vitamin D3 levels were significantly associated with CD8+ T-cell counts in chronic HBV patients, with CD8+ T-cells identified as a key immune parameter linked to HBV DNA viral load in multivariate analysis.
Wang et al., 2023 [22]	HBV-related Liver Cirrhosis	T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$) via flow cytometry	Retrospective cohort	Patients=84, Healthy controls=70	Patients ($CD3^+$=57.20 ± 6.18, $CD4^+$=31.37 ± 5.53, $CD8^+$=23.97 ± 7.08); HC ($CD3^+$= 67.23 ± 6.74, $CD4^+$= 42.53 ± 5.16, $CD8^+$= 21.35 ± 6.24)	$CD3^+$ and $CD4^+$ decreased, while $CD8^+$ increased in HBV related Liver cirrhosis.

Cardinaud et al., 2017 [23]	HIV	DC-SIGN via ELISpot	Experimental study	MDDCs from 4 HLA-A*02+ donors	DC-SIGN= 200±150	PRR triggering (DC-SIGN) reduces HIV replication but enhances infected DC ability to stimulate HIV-specific CTLs.
Gutierrez-Martinez et al., 2023 [24]	HIV	Siglec-1 (CD169) on Dendritic cells via STED imaging	Experimental study	PBMCs from 3 donors	mDC= 24.8±23.3	DC maturation induces Siglec-1 nanoclustering. It enhances HIV-1 capture avidity and promotes trafficking to virus-containing compartments.
Bertram et al., 2019 [25]	HIV	Epidermal CD11c$^+$ DCs via flow cytometry, RNAseq, immunofluorescence	Experimental study	75 healthy donors (abdominal, anogenital tissues)	Epidermal CD11c$^+$ DCs=15 ± 10	Identified CD11c+ epidermal DCs in anogenital tissues preferentially bind and uptake HIV, and efficiently transmit virus to CD4+ T cells.
Rhodes et al., 2021 [26]	HIV	Langerin+ cDC2 via flow cytometry, RNAseq, RNAscope	Experimental study	52 donors (abdominal tissue)	Langerin$^+$ cDC2=1 ± 0.5	Langerin+ cDC2 efficiently uptake HIV, express high CCR5, become productively infected, and transmit HIV to CD4+ T cells.

CHB = Chronic Hepatitis B; HBV = Hepatitis B Virus; TLR = Toll-Like Receptor; HBsAg = Hepatitis B Surface Antigen; qRT-PCR = Quantitative Reverse Transcription Polymerase Chain Reaction; IHC = Immunohistochemistry; HC = Healthy Control; CD8 T = CD8+ T Lymphocyte; DAA treatment = Direct-Acting Antiviral treatment; ELISpot = Enzyme-Linked Immunospot Assay; DC = Dendritic Cell; HIV = Human Immunodeficiency Virus; mMDDCs = Monocyte-Derived Mature Dendritic Cells; iMDDCs = Monocyte-Derived Immature Dendritic Cells; HLA = Human Leukocyte Antigen; DC = Dendritic cell; PBMCs = Peripheral Blood Mononuclear Cells

The pathway-specific immune changes of chronic HBV and HIV among the included studies were evaluated. In the case of PRR signaling, the studies showed that there was a down-regulation of the major Toll-like Receptors (TLRs 2/4/7) expression in persistent HBV, which was linked to a reduction in cytokine production and an elevation of viral antigens. In case of HIR, there was a consistent reduction in peripheral CD3$^+$ and CD4$^+$ T-cell percentages with changes in disease stages of HBV. In the case of APP in HIV, particular subsets of dendritic cells (e.g., CD11c$^+$, Langerin$^+$ cDC2) and receptors (DC-SIGN, Siglec-1) were found to mediate viral capture, infection and trans-infection of T cells.

Two random-effects model studies (n=50 experimental and n=49 controls) revealed no statistically significant difference between the means of TLR2 expression among the cohorts. The standardized mean difference (SMD) was summed up to be -2.05 (95% CI: -6.21-2.11). The level of heterogeneity was found to be high (I^2 = 97%, p < 0.01) implying that the magnitude and direction of the effect sizes were vastly inconsistent among the studies (**Figure 2**).

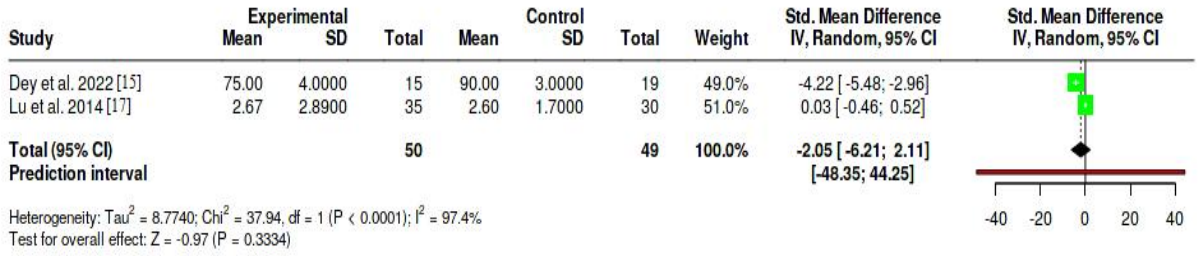

Figure 2: Forest plot comparing Pattern Recognition Receptor TLR2 expression between chronic HBV patients and healthy controls.

The meta-analysis of two studies (n=50 experimental, n=49 control) on TLR4 expression showed that there was no statistically significant difference between the groups with a summarized SMD of -2.69 (95% CI: -8.86 to 3.49). The heterogeneity of the analysis was also very high (I^2 = 98%, p<0.01) as shown in **Figure 3.**

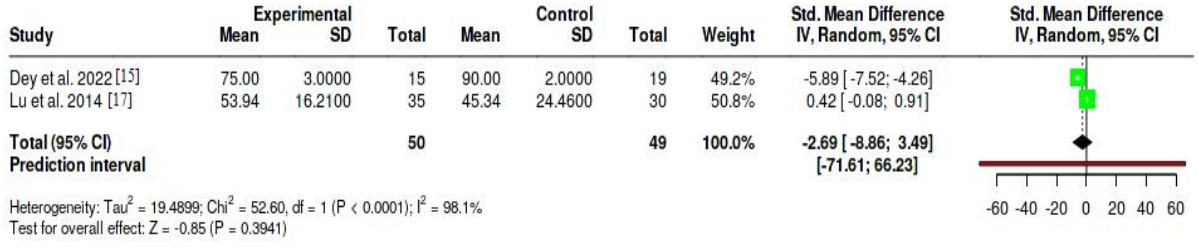

Figure 3: Forest plot comparing Pattern Recognition Receptor TLR4 expression between chronic HBV patients and healthy controls.

The pooled analysis of two-studies (n=125 experimental, n=45 control) on TLR7 expression showed a statistically significant decrease in the experimental group. The summarized SMD was -1.92 (95% CI: -3.19 to -0.66, p<0.05). There was still a high heterogeneity (I^2 = 89.8%, p<0.01) in this analysis (**Figure 4**).

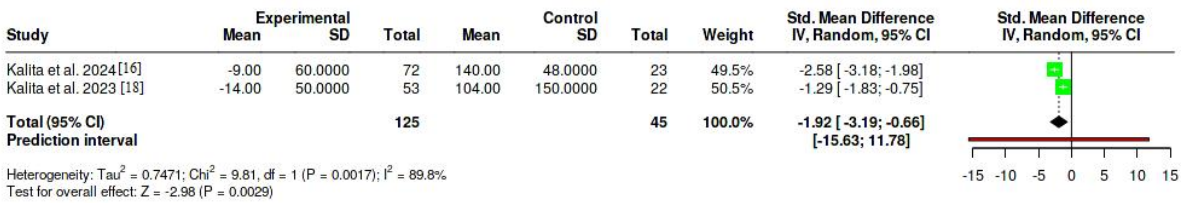

Figure 4: Forest plot comparing Pattern Recognition Receptor TLR7 expression between HBV patients and healthy controls.

The synthesis of three studies (n=221 experimental, n=133 control) of $CD3^+$ T cell levels revealed that there was a statistically significant reduction in the levels of the experimental group (**Figure 5**). The summarized SMD was -1.95 (95% CI: -3.36 to -0.55, p<0.05). These results were found to be highly heterogeneous (I^2 = 94%, p<0.01).

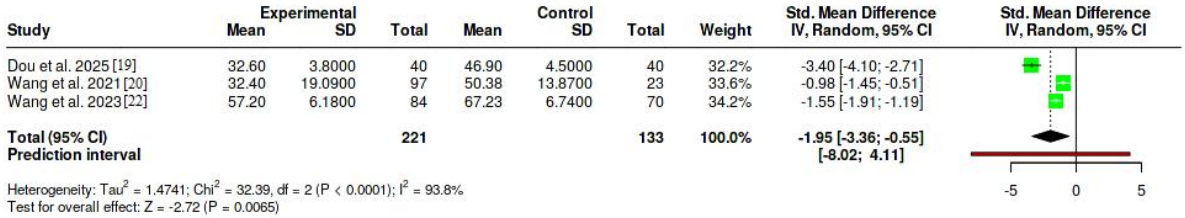

Figure 5: Forest plot comparing CD3+ T cell levels between patients of HBV- related acute chronic liver failure and healthy controls.

In the case of the $CD4^+$ T cells levels, the meta-analysis of three studies (n=221 experiment, n=133 control) do not show a statistically significant cohort difference with the summarized SMD of -1.85 (95% CI: -4.50 to 0.81). The heterogeneity was very high (I^2 = 98%, p<0.01) as shown in **Figure 6**.

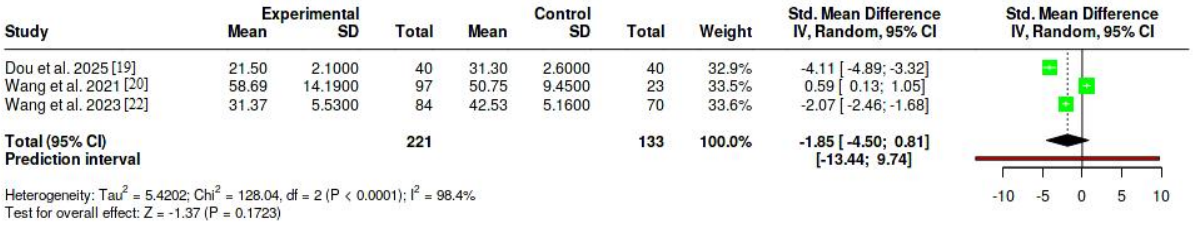

Figure 6: Forest plot comparing CD4+ T cell levels between patients of HBV- related acute chronic liver failure and healthy controls.

The analysis of two studies (n=181 experimental, n=93 control) of the $CD8^+$ T cell levels revealed no statistically significant difference, with the summary SMD of 0.08 (95% CI: -0.55 to 0.72). The degree of heterogeneity was I^2 = 81%, p=0.02 (**Figure 7**).

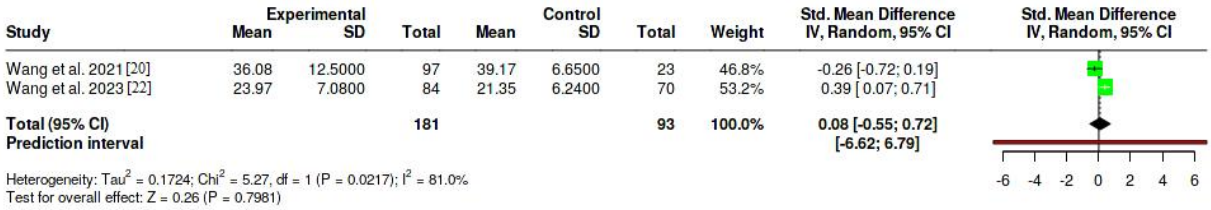

Figure 7: Forest plot comparing CD8+ T cell levels between patients of HBV- related acute chronic liver failure and healthy controls.

A meta-analysis of four studies (n=134 total **samples**) on different dendritic cell markers found no statistically significant overall effect, with summarized raw mean of 11.97 (95% CI: -0.90 to 24.84). It was found that the analysis was heterogeneous (I^2 = 98%, p<0.01), as suggested by **Figure 8**.

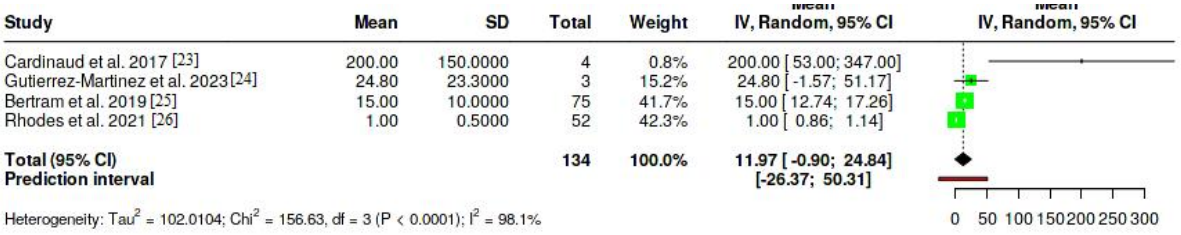

Figure 8: Forest plot presenting antigen presentation on dendritic cells in HIV using in-vitro models.

The study by Ko et al., 2020 [21] was excluded from the meta-analysis due to its single-group design, which lacked a comparator control group necessary for calculating effect sizes. The impact of individual studies on the aggregated effect size was evaluated using the leave-one-out sensitivity analysis. The robustness of our findings was confirmed by the fact that eliminating any one study did not substantially change the overall results.

Table II presents the results of the JBI Critical Appraisal checklist, which was used to determine the risk of bias for the cross sectional studies. The overall level of risk of bias was moderate in most studies, primarily because of the small sample sizes and unequal group sizes, clinic-based recruitment, and lack of adjustment for confounding variables and partial statistical control. Exposure and outcome measurements, however,

were mostly considered to be low risk due to the use of validated laboratory methods like flow cytometry, qRT-PCR and immunohistochemistry. Overall, risk of bias varied across study designs. The overall GRADE certainty of evidence was low.

Table II: Risk of Bias for Cross-Sectional Studies using JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Study	Sample selection	Exposure measurement	Outcome measurement	Confounding	Statistical analysis	Overall RoB
Dey et al., 2022 [15]	Moderate – small sample	Low – validated flow cytometry	Low – standardized assays	Moderate – limited adjustment	Low – appropriate tests	Moderate
Kalita et al., 2024 [16]	Moderate – unequal groups	Low – qRT-PCR/IHC validated	Low – blinded lab assays	Moderate – pregnancy confounders	Low – appropriate comparisons	Moderate
Lu et al., 2014 [17]	Moderate – clinic-based recruitment	Low – established flow cytometry	Low – objective measurements	Moderate – disease stage effects	Low – correlation analyses	Moderate
Kalita et al., 2023 [18]	Moderate – small control group	Low – standardized qRT-PCR	Low – objective outcome	Moderate – limited covariates	Low – appropriate statistics	Moderate
Ko et al., 2020 [21]	High – very small sample	Low – flow cytometry validated	Low – laboratory outcomes	Moderate – partial adjustment	Moderate – multivariate limits	Moderate–High

Foot notes: Green-color represents low risk of bias. Yellow-color represents moderate risk of bias. Dark orange color represents moderate-high risk of bias. Red-color represents moderate-high risk of bias

Table III presents the risk of bias of the case-control studies, which was assessed with the Newcastle–Ottawa Scale. In both studies, the study group was well defined and exposure assessment was conducted in a standardised manner in the laboratory. But there were some issues regarding control selection and comparability, especially because the controls were hospital-based, and the number of controls was small and there was limited matching. The overall score for the two studies were moderate risk of bias for Dou et al., 202519, and low-to-moderate risk of bias for Wang et al., 2021 [20].

Table III: Risk of bias for Case-control Studies using Newcastle–Ottawa Scale (NOS) – Case-Control

Study	Case definition	Control selection	Comparability	Exposure ascertainment	Statistical analysis	Overall RoB
Dou et al., 2025 [19]	Low – clear ACLF criteria	Moderate – hospital controls	Moderate – limited matching	Low – standardized assays	Low – appropriate tests	**Moderate**
Wang et al., 2021 [20]	Low – defined ACLF severity	Moderate – small control group	Low – multivariable adjustment	Low – flow cytometry	Low – robust modelling	**Low–Moderate**

Foot notes: Green-color represents low risk of bias. Yellow-color represents moderate risk of bias. Dark orange color represents moderate-high risk of bias.

The Newcastle–Ottawa Scale was used to evaluate the risk of bias in the cohort study shown in **Table IV**. The study by Wang et al., 2023[22] was clearly defined with a standardize measurement of exposure and objective assessment of the outcome. But moderate concerns were raised on the adequacy of confounding controls and follow-up data were compiled because of limited co-variate adjustment and retrospective data collection. The overall level of risk of bias for the study was moderate.

Table IV: Risk of bias for Cohort Studies using Newcastle–Ottawa Scale (NOS) – Cohort Studies

Study	Cohort selection	Exposure measurement	Outcome assessment	Confounding control	Follow-up adequacy	Overall RoB
Wang et al., 2023 [22]	Low – defined cirrhosis cohort	Low – standardized flow cytometry	Low – objective immune markers	Moderate – limited covariates	Moderate – retrospective data	**Moderate**

Foot notes: Green-color represents low risk of bias. Yellow-color represents moderate risk of bias.

The risk of bias for experimental in vitro and ex vivo human studies was assessed using a custom domain-based qualitative framework, as shown in **Table V**. Most studies had appropriate experimental controls, validated outcome measurements and transparent reporting. However, some concerns were noted due to limited donor numbers, restricted biological material selection and moderate replication limitations. Overall, Bertram et al., 2019[25] and Rhodes et al., 2021[26] showed low risk of bias, Cardinaud et al., 2017[23] showed moderate risk, and Gutierrez-Martinez et al., 2023[24] showed moderate-to-high risk.

Table V: Risk of bias for Experimental in vitro / ex vivo human studies using Custom domain-based qualitative framework

Study	Biological material selection	Experimental controls	Replication	Outcome measurement	Reporting bias	Overall RoB
Cardinaud et al., 2017 [23]	Moderate – limited donors	Low – appropriate controls	Moderate – limited donors	Low – ELISpot validated	Low – transparent reporting	Moderate
Gutierrez-Martinez et al., 2023 [24]	High – 3 donors only	Low – strong experimental design	Moderate – technical replicates	Low – STED imaging	Low – comprehensive reporting	Moderate–High
Bertram et	Low – large	Low – robust	Low – multiple	Low – multi-	Low – detailed	Low

al., 2019 [25]	donor pool	controls	replicates	modal validation	reporting	
Rhodes et al., 2021 [26]	Low – well-characterized donors	Low – strong comparators	Low – replicated experiments	Low – RNAseq + flow	Low – transparent analysis	Low

Foot notes: Green-color represents low risk of bias. Yellow-color represents moderate risk of bias. Dark orange color represents moderate-high risk of bias. Red-color represents moderate-high risk of bias

DISCUSSION

This study indicated that chronic HBV and HIV infections were linked to a dysregulation of PRR signaling, HIR and APP. The PRR markers that had significant differences between HBV patients and healthy controls were TLR7, which was lower in HBV patients, indicating a defective innate viral sensing mechanism. TLR2 and TLR4 did not reveal any statistically significant pooled differences, though, with the high degree of study heterogeneity. $CD3^+$ T cells were significantly depleted in HBV related disease while there was no significant pooled differences for the levels of $CD4^+$ and $CD8^+$ T cells. For APP, dendritic-cell related markers in HIV studies exhibited functional involvement in viral capture, antigen presentation and trans-infection, but the pooled estimate was not statistically significant, and was highly heterogeneous.

The synthesized evidence of this review revealed association of chronic viral infections with dysregulations in PRR signaling, HIR, and APP. In HBV, the transcription of TLR2/4/7 in innate immune cells was decreased and this was correlated with viral persistence and insufficient cytokine production [27,28]. However, HIR showed a marked and persistent decrease in HBV disease at various stages of $CD3^+$ and $CD4^+$ T lymphocytes in the periphery [29-31]. Furthermore, it was discovered that certain subsets of dendritic cells, namely Langerin+ cDC2, and receptors, such as DC-SIGN and Siglec-1 were implicated in APP. These receptors facilitated viral capture and trans-infection of T cells [32,33].

These results were aligned with previous studies which found immune exhaustion and innate sensing defects as hallmarks of chronic infection [34]. Analysis of the current study confirmed the notion of chronicity as not only a failure to respond, but rather as an active process of immune reprogramming [35,36]. Mechanistically, the identification of certain pathways to which the downregulation of TLRs was linked (e.g. activation of β-catenin) added new dimensions to previous descriptive studies [37,38] which remained descriptive. Similarly, the decreased number of peripheral $CD3^+$ T cells and the non-significant increase in $CD4^+$ and $CD8^+$ T cells, plus the dysregulated dendritic-cell markers, corroborated previous studies showing long-term exposure to antigens could lead to significant changes in immune-cell composition and function [39,40]. These results indicated that PRR, HIR and APP dysfunctions were mutually connected and involved in the immunopathogenesis of chronic HBV and HIV. The high heterogeneity seen in most of the pooled analyses, however, suggested that these immune changes were dependent on the stage of the disease, source of the samples, study design, type of assay and the characteristics of the populations

The limitations can be seen as the number of studies included was small, and thus the estimates from the pooled studies were less powerful. The review was limited to published studies in English. Some biomarkers of the immune system were not included in two or three studies, which restricted the conclusions drawn. Only a few studies evaluated HBV longitudinally and therefore causal interpretation of the immunologic changes that occurred before or after viral persistence was not possible. Different measurement techniques were also used such as flow cytometry, qRT-PCR, immunohistochemistry, ELISpot, STED imaging and RNA sequencing. Several studies also included peripheral blood immune parameters, which may not integrate the immune activity in the primary sites of viral replication and/or immune interaction in the tissues.

Bigger, better and longitudinal cohorts should be used in future to clarify the role of PRR signaling, subsets of T cells and functions of dendritic cells in acute infection through to chronic persistence. To enhance comparability between studies, there is a need for standardized immune assays, and a need for uniform reporting of quantitative data. Further studies should also be stratified according to disease stage, viral load, disease treatment and clinical outcome. The immune-restorative therapeutics (PRR agonists, checkpoint-modulating and dendritic-cell based therapies) may also be explored in interventional studies to assess their efficacy in enhancing viral control in the context of antiviral therapy.

CONCLUSION

This study identified a link between chronic HBV and HIV infections and dysregulation of pattern recognition receptor (PRR) signaling pathways, host immune recognition and antigen presentation pathways. The levels of TLR7 and CD3+ T cells were significantly decreased, whereas the levels of TLR2, TLR4, CD4+, CD8+ and dendritic-cell markers had high heterogeneity with non-significant pooled results. The results indicated a type of chronic viral persistence associated with the dysfunction of both innate and adaptive immunity mechanisms. Small sample size and methodological variation and cross-sectional designs, however, restricted the conclusions drawn. Larger and more longitudinal studies should be conducted to clarify cause and effect and to inform immune-restorative therapeutic strategies.

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Conflict of Interest

None

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Use of Artificial Intelligence

The corresponding author declared that no other artificial intelligence or AI-assisted tools were used anywhere in this manuscript.

Authors' Contribution

EA, FA: Conceptualization, protocol design, literature search strategy formulation, drafting the manuscript, and final approval. MA: Study screening (title/abstract and full-text), data extraction, statistical analysis (meta-analysis execution), drafting the methodology, and final approval. EA: Study screening (title/abstract and full-text), data extraction, risk of bias/quality assessment, revising the manuscript critically, and final approval. FA, MA: Risk of bias/quality assessment, acting as the third reviewer for screening disagreements, data interpretation, critical revision of the manuscript for intellectual content, and final approval.

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