

# Humoral Cytokine Levels in Patients with Herpes Zoster: A Meta-Analysis

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**Background:** The neurocutaneous disease caused by the reactivation of varicella-zoster virus (VZV) is called herpes zoster (HZ). The virus remains in the spinal cord back root after the chickenpox disappears. Diminished immune function can reactivate VZV, causing severe neuropathic pain that can last for months or even years, leading to postherpetic neuralgia (PHN), which severely affects the patient's quality of life. Much literature compares various cytokine levels in the body fluids HZ and PHN patients; however, no studies comprehensively evaluate them.

**Methods:** The Cochrane Library, PubMed, Web of Science, and Medline were screened for studies on cytokine levels in body fluids of HZ and PHN patients in the English language. Healthy individuals were selected as the control group, and the standardized mean difference (SMD) between the case and control groups was imputed using a fixed-effects or random-effects model and expressed as a 95% confidence interval (CI). The Newcastle-Ottawa Scale (NOS) was used to assess article quality.

**Results:** This meta-analysis included 13 articles with 1373 participants. Compared with the control group, the HZ group had significantly higher levels of interleukin (IL)-4, IL-6, IL-10, Hcy, and C-reactive protein (CRP), whereas the levels of CD3+ T and CD4+ T lymphocytes were reduced. Additionally, PHN patients had significantly higher levels of IL-6 and IL-1 $\beta$  compared with the control group.

**Conclusion:** This meta-analysis provides compelling evidence that CRP, Hcy, IL-1 $\beta$ , IL-4, IL-6, IL-8, and IL-10 are associated with the genesis and development of HZ and PHN. These markers can be used to improve the diagnosis and treatment of these diseases. Furthermore, for making the results more convincing, it is necessary to harmonize sample acquisition techniques and analytical methods and also require larger, more rigorously designed studies with broader subgroups and sex/age-matched controls.

**Keywords:** herpes zoster, varicella-zoster virus, neurocutaneous disease, postherpetic neuralgia, biomarker

## Introduction

Herpes zoster (HZ) is a disease characterized by skin blisters and nerve pain. When the immune system is compromised, latent varicella-zoster virus (VZV) reactivates in the back root ganglia of the spinal nerve. Age and immunosuppression are the main risk factors of HZ. Approximately one-third of people are at risk for HZ in their lifetime, and nearly half of people  $\geq 85$  years old develop HZ.<sup>1,2</sup> Zoster-related pain can be classified into acute HZ neuralgia (AHN; within 1 month after the rash) or subacute (SHN; within 3 months after the rash) HZ neuralgia, and postherpetic neuralgia (PHN; more than three months after the rash).<sup>3</sup> The main symptom of PHN is severe and persistent pain, mostly in HZ-infected areas such as the chest, abdomen, face, or neck. The pain can be described as a stabbing, burning, tingling, or electric shock sensation and is often unbearable in severity.<sup>4,5</sup>

The etiopathogenesis of HZ is not well known; however, several studies have indicated that it may be associated with immune system dysfunction,<sup>6</sup> impaired oxidative status,<sup>7</sup> and neuroinflammatory response.<sup>8</sup> These factors can be determined using biomarkers, such as CRP, interleukins, lymphocytes, and antioxidant factors. Impaired immune function is closely related to the onset and progression of HZ.<sup>9</sup> Lymphocytes crucially modulate viral infections, and their depletion is associated with viral reactivation.<sup>10</sup> Oxidative stress and inflammation cause tissue damage, and redox

regulation is involved in activating or inhibiting the inflammatory response during cellular stress.<sup>11</sup> Pathogen invasion disrupts the body's redox state, causing oxidative stress and promoting inflammation of skin cells, blood, and the central nervous system (CNS).<sup>12</sup> However, the body's natural antioxidants can counteract the damage caused by oxidative stress-related factors.<sup>13</sup> Inflammation depletes antioxidants as they are consumed for the elimination of excess free radicals.<sup>14</sup> C-reactive proteins (CRP) are biomarkers of systemic inflammation<sup>15</sup> and modulate inflammation development and enhance the prevalence of chronic inflammatory and cardiovascular diseases.<sup>16</sup> The relative stability of proinflammatory and anti-inflammatory cytokines contributes to the homeostasis of the inflammatory system, and their dysregulation can lead to PHN. Increased pro-inflammatory cytokine levels such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF) have been associated with immune response in infants, elevated blood pressure, and target organ damage.<sup>17</sup> Furthermore, anti-inflammatory factors such as IL-4 and IL-10 reduce the generation of pro-inflammatory factors and mitigate the inflammatory reaction.<sup>18</sup>

Currently, the treatment of HZ is based on medication and surgery, which mainly includes antiviral drugs, nutritive nerve drugs and painkillers, etc. Surgical treatments include nerve blocks, implantation of epidural analgesic pumps and radiofrequency ablation, etc. In recent years, many studies have suggested that the use of the HZ vaccine also has an impact on HZ. In recent years, the number of people vaccinated against shingles has also been expanding, but its effectiveness is still the subject of much controversy. In conclusion, the treatment and management of HZ remains a worldwide challenge.

Although some studies have emphasized the alterations in cytokine during HZ and PHN, the outcomes have varied, which may be because of the variations in patient characteristics, samples, or specific assays used. Therefore, a systematic approach to analyzing these studies is required. This meta-analysis aimed to provide a systematic and quantitative assessment of the existing data on cytokines in HZ and PHN.

## Materials and Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the Cochrane Handbook for Systematic Reviews and Meta-Analyses<sup>19</sup> and has been registered in PROSPERO (Registration number: CRD42023464039).

## Data Sources and Search Strategy

Two investigators independently searched the Cochrane Library, PubMed, Web of Science, and MEDLINE databases. The search strategy included a combination of keywords and Medical Subject Headings (MeSH): herpes zoster OR shingles OR postherpetic neuralgia) AND (inflammation OR inflammations OR innate inflammatory response OR innate inflammatory responses OR cytokine OR biomarker OR chemokine) AND (cohort studies OR case-control studies OR comparative study OR risk factors OR cohort OR compared OR groups OR case-control OR multivariate).

## Selection Criteria

Inclusion criteria: 1) Studies that assessed the cytokine levels in body fluids of HZ or PHN diagnosed patients, 2) were in English language, and 3) 5 or more cases were included.

Exclusion criteria: 1) Studies lacking valid data, 2) were performed on animals, 3) were meta-analyses, case reports, letters, reviews, meeting abstracts, and posters, 4) lacked full text, and 5) included controls with any other disease were excluded.

## Data Extraction and Quality Assessment

Two authors screened the data independently according to a predetermined spreadsheet. The acquired data included study information (article title, year of publication, study design), participant characteristics (number of participants, age, proportion of females), sample characteristics (sample type and method of analysis), biomarkers measured, and the mean and standard deviation (SD) of the biomarkers examined.

The Newcastle-Ottawa Scale was used to measure each study's quality. Quality assessment criteria included: (1) selection of cases and controls: A. definition of cases; B. representativeness of these cases; C. selection of control

systems; D. comparability of cases and controls; (2) comparability: comparability of cases and controls based on design or analysis; (3) exposure: A. determination of exposure status; B. same determination method for case and control groups; C. non-response rate. Table 1 indicates the evaluated results. The star allocation range for each parameter was from 0 (lowest) to 9 (highest). Studies with a score of  $\geq 7$  were considered high-quality studies, while others were classified as medium-quality.<sup>20</sup>

## Data Synthesis and Analysis

All data were converted to mean and standard deviation.<sup>33,34</sup> All variables were analyzed with a standardized mean difference (SMD) and 95% confidence intervals (CI). Cochran's Q test was performed to gauge heterogeneity, whereas to identify the degree of consistency,  $I^2$  statistic was carried out:  $I^2 > 75\%$  = high,  $> 50\%$  = moderate, and  $< 25\%$  = low inconsistency. Using a random-effects model, the size of the combined effect was estimated when heterogeneity was  $> 50\%$ ; otherwise, a fixed-effects model was used.<sup>35</sup> A two-tailed  $p$ -value  $< 0.05$  was considered statistically significant. A full assessment of publication bias was not performed because of the small number of studies in each comparison ( $< 10$ ). All statistical analyses were performed using Review Manager 5.4.1.

## Results

### Literature Search

Figure 1 indicates the detailed search information. In total, 1720 documents were acquired from the Cochrane Library, PubMed, Web of Science, and Medline. All searchable articles were included in the EndNote database for searching. Finally, 13 studies that met the selection criteria were selected.

### Study Characteristics

Table 2 lists basic information about the included studies. A total of 13 articles, which comprised 1373 contributors, were included in this study. All studies compared the levels of cytokines between HZ or PHN patients and control individuals. Of these 13 studies, 8 directly compared HZ patients with control groups, 1 categorized HZ patients into severe and mild groups based on clinical manifestations, 1 grouped HZ patients into groups with a duration of  $< 7$  and  $> 7$  days, 1 divided HZ patients into pre- and post-treatment groups, 2 directly compared PHN patients with control groups, and 1 categorized PHN patients into severe and mild groups based on pain scores.

Each study's levels of cytokines were assessed. The samples included peripheral venous blood, blister fluid, and cerebrospinal fluid, and the detection methods used were ELISA (Enzyme-Linked Immunosorbent Assay), FACS (Fluorescence-Activated Cell Sorting), and CBA (Cytometric Bead Array).

### Quality Assessments and Risk of Bias

The quality scores of the included studies ranged from 7 to 9, reflecting the robustness of the different research approaches. Three studies, two by Marjan Khazan et al.<sup>7,27</sup> and one by Tuba Oskay et al.,<sup>30</sup> scored the highest with 9 points, indicating that they had good quality methods and low risk of bias. Seven studies had a high-quality score of 8, indicating representative cases, appropriate selection and definition of controls, good comparability between cases and controls, and sound and reliable study methodology and data analysis. Three other remaining studies scored 7 because of the minor flaws in the selection of controls or comparability based on design or analyses (Table 2).

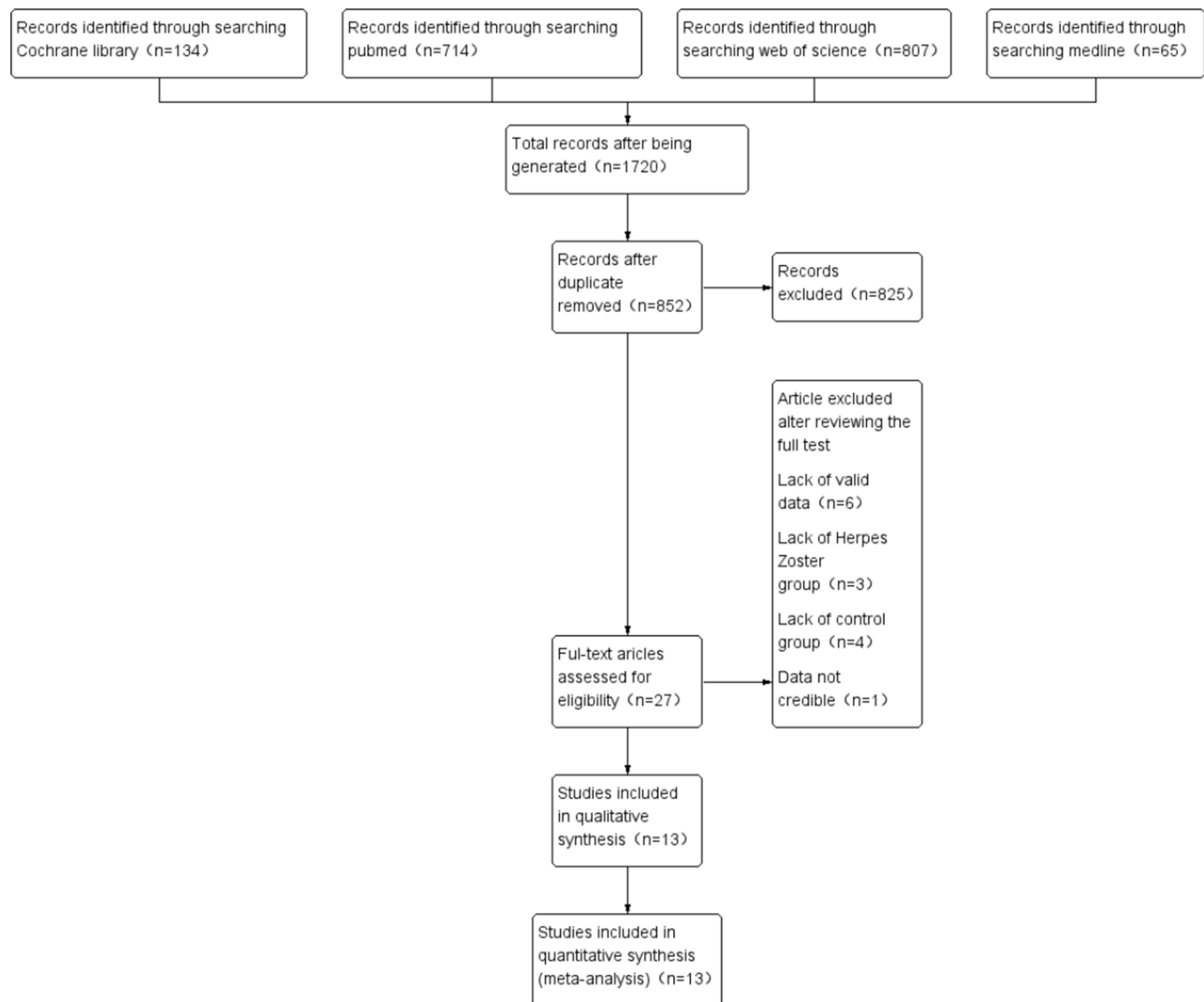
### Comparison of Cytokine Levels in Patients with HZ CRP

Sufficient data was acquired from 4 comparative groups comprising 457 participants, which indicated a significant difference in CRP levels between the HZ group and the control group. The CRP levels in HZ patients were significantly higher than in the control group (SMD = 4.48; 95% CI: 1.38 to 7.59;  $p = 0.005$ ; Figure 2A). Furthermore, there was significant heterogeneity within the groups ( $I^2 = 99\%$ ;  $p < 0.00001$ ), which was resolved after excluding the studies by Wei et al.,<sup>26</sup> and Oskay et al.<sup>30</sup> However, the effect size remained significant (SMD = 1.52, 95% CI: 1.12 to 1.92,  $p < 0.00001$ ).

**Table I** Quality Assessments and Risk of Bias of Observational Studies

Author	Selection				Comparability		Exposure		Total
	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non Response Rate	
Zak-Prelich et al, 2003 <sup>21</sup>	*	*	*	*	*	*	*	*	8
Zhu et al, 2009 <sup>22</sup>	*	*	*	*	*	*	*	*	8
Zhang et al, 2011 <sup>23</sup>	*	*	*	*	*	*	*	*	8
Zajkowska et al, 2016 <sup>24</sup>	*	*		*	*	*	*	*	7
Zhao et al, 2017 <sup>25</sup>	*	*	*	*	*	*	*	*	8
Wei et al, 2017 <sup>26</sup>	*	*	*	*	*	*	*	*	8
Khazan et al, 2018 <sup>7</sup>	*	*	*	*	**	*	*	*	9
Khazan et al, 2020 <sup>27</sup>	*	*	*	*	**	*	*	*	9
Fukuyasu et al, 2021 <sup>28</sup>	*	*		*	**	*	*	*	8
Yang et al, 2021 <sup>29</sup>	*	*	*	*	*	*	*	*	8
Oskay et al, 2022 <sup>30</sup>	*	*	*	*	**	*	*	*	9
Lin et al, 2023 <sup>31</sup>	*	*		*	**	*	*	*	7
Yuan et al, 2023 <sup>32</sup>	*	*	*		*	*	*	*	7

**Notes:** NOS evaluates the quality of the literature using the semi-quantitative principle of the star system, with the exception of comparability, which can be rated at a maximum of 2 stars, and the rest of the entries, which can be rated at a maximum of 1 star out of a total of 9 stars, with higher scores suggesting a higher quality of the study. \*:1 star, \*\*:2 star.



**Figure 1** PRISMA flow diagram.

#### IL-4

The IL-4 levels were also extracted from four control groups, totaling 196 individuals. The pooled effect sizes showed that IL-4 levels significantly differed between the HZ group and the control group (SMD = 5.28; 95% CI: 3.01 to 7.55;  $p < 0.00001$ ; **Figure 2B**). The subgroup was highly heterogeneous ( $I^2 = 93\%$ ;  $p < 0.00001$ ), and the sensitivity analysis could not resolve the heterogeneity.

#### IL-6

A total of 201 samples were included in the three comparison, and the fixed-effects model revealed a significant difference in IL-6 levels between the HZ and other groups, with HZ patients indicating higher IL-6 levels (SMD = 0.92; 95% CI: 0.63 to 1.22;  $p < 0.00001$ ; **Figure 2C**). The combined data were homogeneous ( $I^2 = 0\%$ ;  $p = 0.38$ ).

#### IL-8

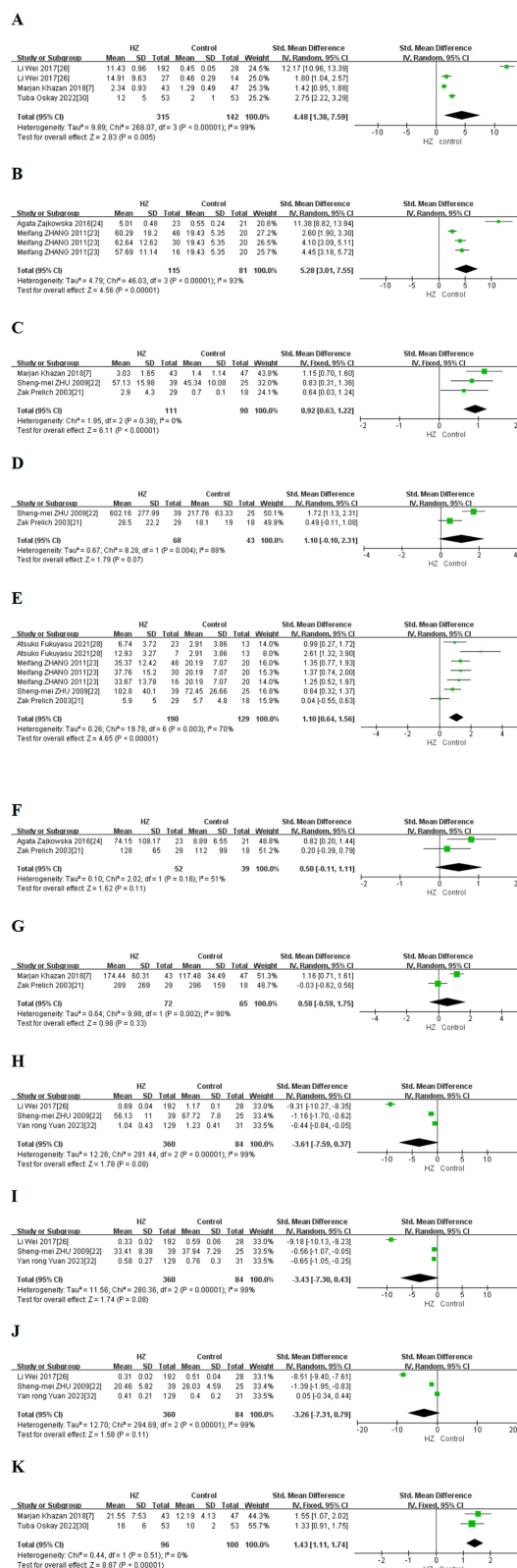
Two studies with 111 participants reported IL-8 levels, and no significant differences were observed in IL-8 levels between HZ patients and controls (SMD = 1.10; 95% CI: -0.10 to 2.31;  $p = 0.07$ ; **Figure 2D**). Moreover, high levels of heterogeneity were detected ( $I^2 = 88\%$ ;  $p = 0.004$ ), and sensitivity analysis could not resolve this heterogeneity.

**Table 2** Basic Information About the Included Studies

Author	Year	Study Design	N	Study Groups	Age	Female	Type of Sample	Diagnostic criteria	Analytical Method	Assessed Biomarkers
Zak-Prelich et al, <sup>21</sup>	2003	Case control	47	HZ (n=29)	49	18 (62.1%)	Peripheral venous blood	Clinical diagnosis	ELISA	IL-6, IL-8, IL-10, IL-12, IL-18
				ctrl (n=18)	46	12 (66.7%)				
Zhu et al, <sup>22</sup>	2009	Case control	74	PHN (n=10)	67±5	6 (60%)	Peripheral venous blood	Clinical diagnosis	FACS, CBA	IL-6, IL-1β, IL-8, IL-10, TNF-α, CD3+T, CD4+T, CD8+T
				HZ (n=39)	65±6	15 (38.5%)				
				ctrl (n=25)	63±7	8 (32%)				
ZHANG et al, <sup>23</sup>	2011	Case control	112	HZ (n=46)	55.67±19.78	21 (45.7%)	Pimple fluid	Clinical diagnosis	FACS	IL-4, IL-10
				ctrl (n=20)	53.52±16.32	9 (45%)				
				HZ≤7days (n=30)	NA	NA				
				HZ>7days (n=16)	NA	NA				
Zajkowska et al, <sup>24</sup>	2016	Case control	44	HZ (n=23)	66.5	13 (56.5%)	Peripheral venous blood	Clinical diagnosis	ELISA	IL-17, IL-23, IL-21, IL-4, IL-12
				ctrl (n=21)	63.8	10 (47.6%)				
Zhao et al, <sup>25</sup>	2017	Case control	78	PHN (n=50)	67.1 ± 9.2	23 (46.0%)	Cerebrospinal fluid	Clinical diagnosis	ELISA	IL-1β, IL-8, TNF-α
				ctrl (n=28)	61.4 ± 8.1	15 (53.6%)				
Wei et al, <sup>26</sup>	2017	Case control	261	HZ1 (n=192)	57.69±14.39	94 (48.96%)	Peripheral venous blood	ICD-10 code B02 (Zoster)	ELISA, FACS	CD3+T, CD4+T, CD8+T, CRP
				ctrl1 (n=28)	55.75±9.78	15 (53.57%)				
				HZ2 (n=27)	67.74 ± 7.43	12 (44.4%)				
				ctrl2 (n=14)	57.29 ± 5.08	6 (42.86%)				
Khazan et al, <sup>7</sup>	2018	Case control	90	HZ (n=43)	65.70±9.72	28 (65.11%)	Peripheral venous blood	ICD-10 code B02 (Zoster)	ELISA	TPC
				ctrl (n=47)	62.87±9.31	29 (61.70%)				
Fukuyasu et al, <sup>28</sup>	2021	Case control	43	mHZ (n=23)	64±7.7	NA	Peripheral venous blood	Committee on Guideline for Treatment of Japan Society of Pain Clinicians	ELISA	IL-10
				SHZ (n=7)	73±11					
				ctrl (n=13)	NA					

Khazan et al, <sup>27</sup>	2020	Case control	90	HZ (n=43)	65.70±9.72	28 (65.11%)	Peripheral venous blood	ICD-10 code B02 (Zoster)	ELISA	IDO, IL-18, IL-6, ferritin, CRP, Hcy, MLT
				ctrl (n=47)	62.87±9.31	29 (61.70%)				
Yang et al, <sup>29</sup>	2021	Case control	108	PRHZ (n=30)	NA	NA	Peripheral venous blood	Clinical diagnosis	ELISA	GAPDH, mtATP8, mtND4, Plasma concentration of MBP, Plasma concentration of S100B
				ARHZ (n=41)						
				ctrl (n=37)						
Oskay et al, <sup>30</sup>	2022	Case control	106	HZ (n=53)	70.1±8.0	31 (58.5%)	Peripheral venous blood	Clinical diagnosis	ELISA	UA, Tbil, ALB, Hcy, CRP, vitamin D
				ctrl (n=53)	67.7±9.5	31 (58.5%)				
Lin et al, <sup>31</sup>	2023	Case control	160	mPHN (n=40)	68.3 ± 10.1	23 (57.5%)	Peripheral venous blood	Clinical diagnosis	ELISA	IL-6, IL-10, TNF- $\alpha$
				sPHN (n=40)	70.3 ± 8.4	22 (55%)				
				ctrl (n=80)	69.5 ± 9.2	44 (55%)				
Yuan et al, <sup>32</sup>	2023	Case control	160	HZ (n=129)	59.9±14.7	66 (51.2%)	Peripheral venous blood	S2k guideline on the management of herpes zoster - part 1: diagnosis	FACS	CD3+T, CD4+T, CD8+T
				ctrl (n=31)	58.6±19.4	11 (35.5%)				

**Abbreviations:** HZ, Herpes Zoster; mHZ, mild Herpes Zoster; sHZ, serious Herpes Zoster; PRHZ, Presenting Rash Herpes Zoster; ARHZ, After Rash Healing Herpes Zoster; ctrl, control; PHN, postherpetic neuralgia; IL, interleukin; TNF-A, tumor necrosis factor-alpha; IDO, Indoleamine 2,3-dioxygenase; UA, uric acid; Hcy, homocysteine; MLT, melatonin; Tbil, total bilirubin; CRP, C-reactive protein; ALB, albumin; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; mtATP8, mitochondrially encoded ATP synthase 8; mtND4, mitochondrially encoded NADH dehydrogenase 4; ELISA, Enzyme-Linked Immunosorbent Assay; FACS, Fluorescence Activated Cell Sorting; CBA, Cytometric Bead Array.



**Figure 2** Forest plot of differences in each cytokine between HZ patients and controls. (A) CRP; (B) IL-4; (C) IL-6; (D) IL-8; (E) IL-10; (F) IL-12; (G) IL-18; (H) CD3<sup>+</sup>T cell; (I) CD4<sup>+</sup>T cell; (J) CD8<sup>+</sup>T cell; (K) Hcy.



## IL-10

A study of 319 individuals comprising seven comparisons and random-effects meta-analysis indicated significant differences in IL-10 levels between the case and control groups. The HZ patients had significantly higher IL-10 levels than healthy individuals (SMD = 1.10; 95% CI: 0.64 to 1.56;  $p < 0.00001$ ; Figure 2E). To resolve high heterogeneity ( $I^2 = 70\%$ ;  $p = 0.003$ ), the study by Zak Prelich et al<sup>21</sup> was excluded (heterogeneity after removal  $I^2 = 31\%$ ;  $p = 0.20$ ), and the effect size remained significant (SMD = 1.24; 95% CI: 0.90 to 1.58;  $p < 0.00001$ ).

## IL-12

Random effects modeling in two studies showed no significant difference in IL-12 levels between HZ patients and controls (SMD = 0.50; 95% CI: -0.11 to 2.31;  $p = 0.11$ ; Figure 2F). Furthermore, moderate levels of heterogeneity were detected ( $I^2 = 51\%$ ;  $p = 0.16$ ), which was not resolved by the sensitivity analysis.

## IL-18

Two studies comprising 111 individuals assessed IL-18 levels, and the results indicated no significant difference in IL-18 levels between the two groups (SMD = 0.58; 95% CI: -0.59 to 1.75;  $p = 0.33$ ; Figure 2G). Additionally, a high degree of heterogeneity was found ( $I^2 = 90\%$ ;  $p = 0.002$ ) but could not be resolved by sensitivity analysis.

## CD3<sup>+</sup>T Cells

Data were extracted from three comparisons with a sample size of 444 cases. The random effects model indicated no significant differences in the levels of CD3<sup>+</sup> T cells between HZ patients and controls. (SMD = -3.16; 95% CI: -7.59 to 0.37;  $p = 0.08$ ; Figure 2H). However, this result had high heterogeneity ( $I^2 = 99\%$ ;  $p < 0.00001$ ), which was resolved by excluding the study by Wei et al.<sup>26</sup> After resolving the heterogeneity, the CD3<sup>+</sup>T cell concentration was found to be lower in the HZ patients than in the controls (SMD = -0.78; 95% CI: -1.47 to -0.08;  $p = 0.03$ ).

## CD4<sup>+</sup>T Cell

The pooled results of samples from the three control groups showed that the CD4<sup>+</sup> T cell levels in the HZ group were not comparable to the control group (SMD = -3.43; 95% CI: -7.30 to 0.43;  $p = 0.08$ ; Figure 2I). However, this result had high heterogeneity ( $I^2 = 99\%$ ,  $p < 0.00001$ ), which was addressed by excluding Wei et al.<sup>26</sup> The CD4<sup>+</sup> T cell concentration in the HZ group was significantly reduced compared to the control group after resolving the heterogeneity (SMD = -0.62, 95% CI: -0.93 to -0.03,  $p = 0.0001$ ).

## CD8<sup>+</sup>T Cell

A study of three control groups revealed no significant differences in CD8<sup>+</sup> cell levels in body fluids between patients and healthy individuals (SMD = -3.26; 95% CI: -7.31 to 0.79;  $p = 0.11$ ; Figure 2J). However, this result had a high degree of heterogeneity, which could not be resolved ( $I^2 = 99\%$ ;  $p < 0.00001$ ).

## HCY

Fixed-effects modeling obtained from 196 samples showed that Hcy concentrations were significantly higher in the HZ patients than the control group (SMD = 1.43; 95% CI: 1.11 to 1.74;  $p < 0.00001$ ; Figure 2K), and the merged data are homogeneous ( $I^2 = 0\%$ ;  $p = 0.51$ ).

## Comparison of Cytokine Levels in Patients with PHN

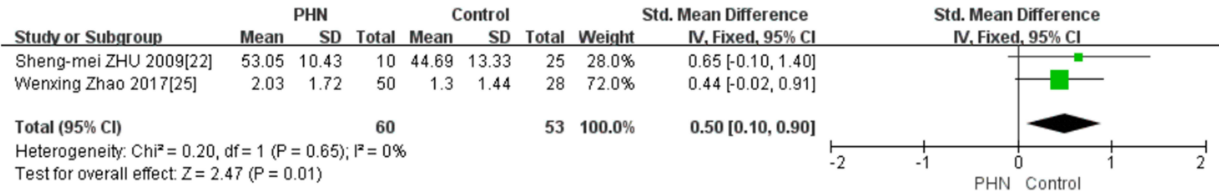
### IL-1 $\beta$

IL-1 $\beta$  levels were extracted from two control groups, including 113 participants. The fixed-effects modeling revealed substantially higher IL-1 $\beta$  concentrations in the PHN group than the control group (SMD = 0.50; 95% CI: 0.10 to 0.90;  $p = 0.01$ ; Figure 3A), and the heterogeneity was almost non-existent ( $I^2 = 0\%$ ;  $p = 0.65$ ).

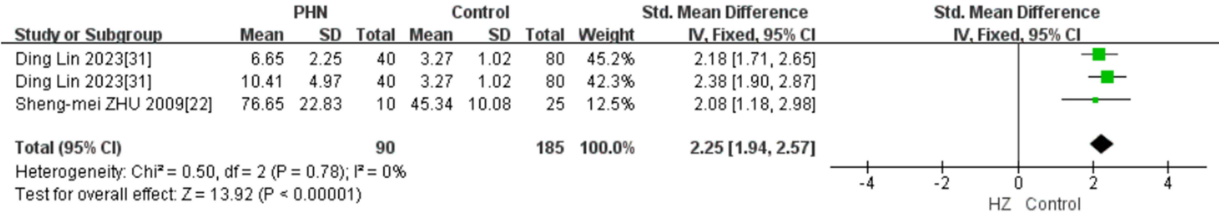
### IL-6

A fixed-effects meta-analysis of 3 contrasting groups comprising 275 participants showed that IL-6 concentrations were significantly higher in the PHN group compared to the control group (SMD = 2.25; 95% CI: 1.94 to 2.57;  $p < 0.00001$ ; Figure 3B). The combined data were homogeneous ( $I^2 = 0\%$ ;  $p = 0.78$ ).

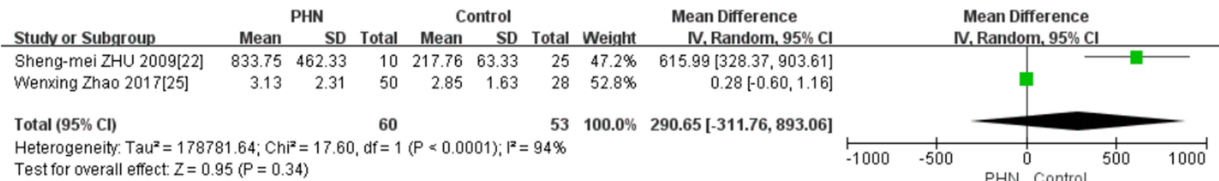
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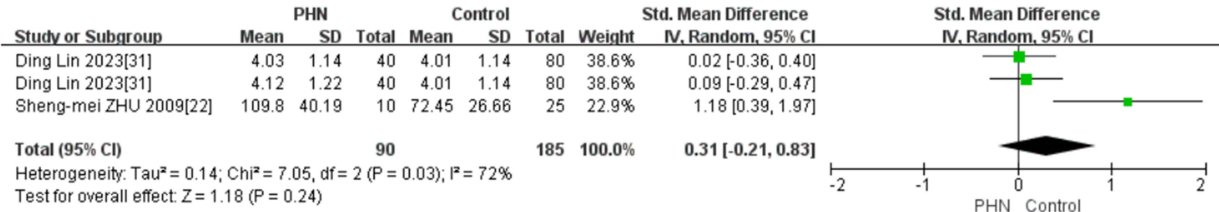
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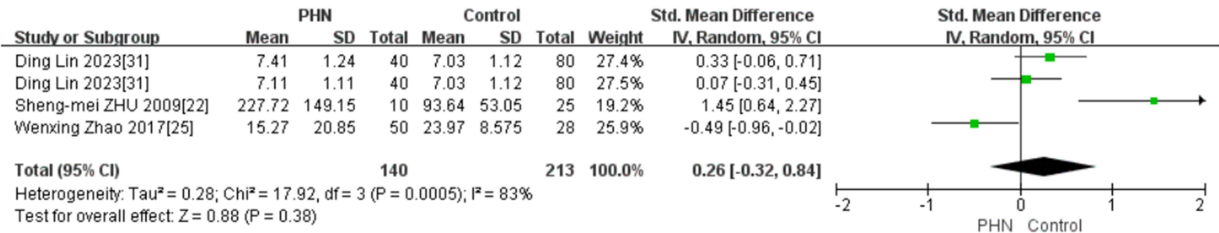


Figure 3 Forest plot of differences in each cytokine between PHN patients and controls. (A) IL-1β; (B) IL-6; (C) IL-8; (D) IL-10; (E) TNF-α.

## IL-8

Two comparisons, including 113 participants, performed a random-effects meta-analysis to assess the levels of IL-8 levels and revealed that its levels in body fluids were the same in both groups (SMD = 290.65; 95% CI: -311.76 to 893.06;  $p = 0.34$ ; Figure 3C). However, the high heterogeneity could not be resolved by sensitivity analysis ( $I^2 = 94\%$ ;  $p < 0.0001$ ).

## IL-10

A three-group comparison of 275 samples provided data indicating that the PHN group had the same IL-10 concentration as the control group (SMD = 0.31; 95% CI: -0.21 to 0.83;  $p = 0.24$ ; Figure 3D). The heterogeneity for this result was moderate ( $I^2 = 72\%$ ;  $p = 0.03$ ) and could not be resolved through sensitivity analysis.

## TNF- $\alpha$

From 4 sets of comparisons, the levels of TNF- $\alpha$  in the body fluids obtained from 113 participants were assessed, which showed that TNF- $\alpha$  levels were similar between PHN patients and healthy individuals (SMD = 0.26; 95% CI: -0.32 to 0.84;  $p = 0.38$ ; Figure 3E). The heterogeneity for this result was high ( $I^2 = 83\%$ ;  $p = 0.0005$ ) and could not be resolved by sensitivity analysis.

## Results of Individual Studies

Xin Yang et al<sup>29</sup> found that during the occurrence of HZ and after its cure, the HZ group had significantly higher levels of GAPDH, mtATP8, mtND4, and plasma concentration of MBP and S100B compared to the control group. Furthermore, according to Marjan Khazan et al,<sup>7,27</sup> compared to controls, the HZ group had significantly higher levels of IDO and ferritin and lower levels of MLT and TPC. These differences were statistically significant. Zajkowska et al<sup>24</sup> also found that HZ patients had higher levels of IL-17, IL-21, and IL-23 compared to healthy individuals. Additionally, Tuba Oskay et al<sup>30</sup> indicated that the HZ group had significantly lower levels of UA, Tbil, and albumin than the control group. These differences were also statistically significant.

## Discussion

The reactivation of the primary VZV infection causes shingles. After the original infection, the virus may remain latent in the dorsal root or cranial ganglia, and its reactivation causes characteristic nerve pain and blister-like rash.<sup>36</sup> Several underlying mechanisms, including immune suppression, pro-inflammatory and anti-inflammatory factors dysregulation, and imbalanced oxidative stress and antioxidant levels, have been associated with VZV reinfection. Assessing the patient's cytokines alterations can provide preliminary insights into the pathogenesis of HZ. Different assays and sample types often affect cytokine expression, leading to inconsistent results. Meta-analysis integrates information, removes the effects of confounding factors, and provides reliable outcomes. Furthermore, different stages and disease severity can alter cytokine levels differently. Therefore, this investigation analyzed all the subgroups.

Neuroinflammation is a complex biological process that has an essential role in various neurological conditions and increases the secretion of various inflammatory mediators.<sup>37</sup> Here, HZ patients indicated significantly higher CRP, IL-4, IL-6, and IL-10 levels than controls. IL-6 is an early tissue damage marker associated with chronic inflammatory and immune-mediated diseases.<sup>38,39</sup> Moreover, it is essentially associated with abnormal pain perception and hyperalgesia following peripheral nerve injury in rodents.<sup>40</sup> Furthermore, enhanced IL-6 transcription and expression are observed on the surface of herpes viruses infected newborn skin.<sup>41</sup> However, the pathological role of IL-6 in virus-induced inflammatory diseases remains unknown. IL-10 inhibits macrophage-specific immune function, potentiates immune induction, inhibits inflammatory cytokine release from macrophages, and diminishes the expression of adhesion molecules, thus playing an essential role in immune-mediated processes in humans. The source of IL-10 in HZ patients is still unclear, and regulatory T cells have been suspected as one of its sources.<sup>42</sup> Furthermore, studies suggest that IL-10 gene polymorphisms may be associated with susceptibility to HZ.<sup>43</sup> IL-4 is produced by Th2, eosinophils, and mast cells and has a wide range of biological effects. Excessive IL-4 production is associated with inflammation and autoimmune disorders.<sup>44</sup> Under inflammatory conditions, acute-phase proteins are stimulated and produced by pro-inflammatory

cytokines such as IL-6. CRP is an important acute-phase protein marker and is significantly elevated, especially in infectious and inflammatory diseases. The elevated levels of pro-inflammatory cytokines accompanied by an increase in anti-inflammatory cytokines and CRP stimulation by pro-inflammatory cytokines might explain the observed results.<sup>45,46</sup>

Elevated levels of Hcy may act as a potential factor that enhances oxidative stress and alters inflammatory status, causing endothelial dysfunction and promoting chronic inflammation development.<sup>47–49</sup> Additionally, Hcy is not only a pro-inflammatory factor but also an anti-inflammatory factor. Furthermore, its high levels are closely associated with vitamin B12 and folate deficiencies, which are major cofactors in Hcy metabolism and are influenced by dietary intake.<sup>50</sup> The elevated Hcy levels in HZ patients may result from oxidative stress, inflammatory reactions, and deficiency in folate, vitamin B12, or both.

Studies have shown that in the pathogenesis of HZ, the body's defense primarily relies on cellular immune responses, and the function of T lymphocyte subsets is crucial for maintaining normal immune function.<sup>32</sup> The literature has confirmed the presence of cellular immune abnormalities in HZ patients, particularly specific cellular immune suppression. The number of specific T cells against VZV gradually decreases as the age increases.<sup>51,52</sup> CD3<sup>+</sup> T cells are markers of mature T cells in peripheral blood, while CD4<sup>+</sup> T cells help activate B and cytotoxic T cells and induce their antibody production to activate macrophages. Studies have shown that a significant decrease in CD3<sup>+</sup>T and CD4<sup>+</sup>T cells in peripheral blood leads to severe impairment of autoimmune function,<sup>53</sup> consistent with the results of this study.

Complications occur in 5–30% of people with HZ, and PHN is the most common of these complications. PHN is defined as pain that persists for > 3 months after HZ onset and is usually accompanied by sensory deficits and sensory irregularities that can be disabling or even fatal as the disease progresses.<sup>54</sup> PHN pathogenesis is complex and may result from a combination of factors such as nerve injury, immune activation, and genetic predisposition, all of which may cause chronic pain onset and persistence. VZV predominantly infects sensory nerve fibers, leading to inflammation and neuronal impairment. This damage sensitizes the nerves, promoting the transmission of painful signals, even after the virus has been removed from the body.<sup>55–57</sup> Immune activation also produces inflammatory molecules that injure nerve cells and cause persistent pain. Furthermore, chronic inflammation alters how the CNS processes pain signals; in the case of HZ lesions, the pain persists even after the lesions have healed.<sup>57–59</sup> In addition, genetic factors are also critically associated with pathogenesis, and several researches have indicated specific genetic variants associated with an elevated risk of PHN, suggesting a genetic predisposition to the condition.<sup>60–62</sup>

When cells are damaged, infected, or invaded, and inflammation occurs, monocytes, macrophages, and other non-immune cells, such as fibroblasts and endothelial cells, release a cytokine called interleukin-1 beta (IL-1 $\beta$ ). Recent literature has revealed that injured dorsal root ganglion (DRG) neurons also express IL-1 $\beta$ .<sup>63</sup> Its expression increases in peripheral nerves after compression injury and in the CNS microglia and astrocytes after trauma.<sup>64,65</sup> Furthermore, IL-1 $\beta$  promotes the production of neuropeptide substance P and prostaglandin E2 (PGE2) in many neurons and glial cells.<sup>63,66</sup> It can also inhibit glutamate clearance between synapses by glial cells.<sup>67</sup> Additionally, an *in-vivo* study suggested that IL-1 $\beta$  is involved in neurodevelopment.<sup>68</sup> In conclusion, the onset and progression of PHN may be closely associated with IL-1 $\beta$ , as evidenced by this meta-analysis.

This investigation also suggests distinct discrepancies in IL-6 levels between PHN patients and healthy individuals. Previous studies have found increased IL-6 and its receptor expression in spinal cord tissue following peripheral nerve injury. An animal study showed that injection of IL-6 into normal rats inhibited their response to thermal and mechanical stimuli. Even with the preserved pain response to mechanical stimuli, IL-6 injection could suppress pain response to heat stimuli. Thus, IL-6 is an important factor in persistent pain caused by peripheral and CNS injuries.<sup>69,70</sup>

The above studies suggest these cytokines may be used for HZ and PHN diagnosis and prognosis. Although there is substantial heterogeneity among the included research, sensitivity analyses can effectively verify the results. The main sources of heterogeneity are classification criteria, sample type, analytical techniques, and possible individual differences in the included research. For the classification criteria, among the 13 included articles, Atsuko Fukuyasu et al<sup>28</sup> followed the criteria of the Committee on Guideline for Treatment of Japan Society of Pain Clinicians,<sup>71</sup> Li Wei et al<sup>26</sup> and Marjan Khazan et al<sup>7</sup> used the ICD-10 code B02 (Zoster) criteria, and Yanrong Yuan et al<sup>32</sup> used the S2k guideline on the management of HZ-part 1: diagnosis.<sup>72</sup> Patients were clinically diagnosed in the remaining 9 articles without specifying which diagnostic criteria were used. Previously, it has been indicated that different types and levels of cytokines are

found in different body fluids.<sup>73</sup> In this literature, one study<sup>23</sup> used blister fluid as a sample, and another<sup>25</sup> used cerebrospinal fluid. Since different analysis techniques can result in different cytokine levels,<sup>74</sup> ELISA for quantitative analysis of large samples, FACS for multi-parameter analysis and cell sorting at the single-cell level, and CBA for quantitative analysis of multiple cytokines or markers were used in the included studies.

This meta-analysis showed no significant differences in IL-8, IL-12, IL-18, and CD8+ T cell levels between the HZ and healthy cohort or that of IL-8, IL-10, and TNF- $\alpha$  between the PHN and healthy cohort.

The study by Wenxing Zhao et al<sup>25</sup> used cerebrospinal fluid rather than peripheral venous blood as samples, which may explain the inconsistency in the results of TNF- $\alpha$  and IL-8 with other studies. ShenMei Zhu et al<sup>22</sup> used different analytical methods, which may be the reason for the higher heterogeneity and inability to resolve it through sensitivity analysis in the comparison of IL-8 and CD8+ T cells in the HZ group. The data from the study of Zak Prelich et al<sup>21</sup> had a large standard deviation for IL-8, IL-10, IL-12, and IL-18, indicating significant individual differences in the included study samples, which may have resulted in insignificant differences in these cytokines between the HZ and controls groups. Therefore, the data of these studies should be interpreted carefully. Among the reported studies, Ding Lin et al<sup>31</sup> found no significant difference in IL-10 levels between PHN and control groups, which is inconsistent with the studies of ShenMei Zhu et al<sup>22</sup> and Wei Chen et al<sup>75</sup> and the reason for the difference may be due to the use of different analytical methods. Yanrong Yuan et al<sup>32</sup> reported that CD8+ T cells did not show a remarkable difference between the two groups, which may be because 129 patients were included in the case group while only 31 patients were included in the control group, causing an insufficient statistical test.

Furthermore, the study by Zak Prelich et al<sup>21</sup> included younger subjects, with an average age of 49 years in the case group and 46 in the control group. The literature reported by Xin Yang<sup>29</sup> did not specify the age of the included cases, and the same samples were used in the two Khazan et al articles;<sup>7,27</sup> no independent validation was performed, which might have caused biased results. In one study,<sup>28</sup> the queue size involved was relatively small, with 30 patients in the case group and only 7 in the control group. This would affect the credibility of the obtained cytokine levels and cause an inability to conduct statistical tests. The included researchers did not group diseases for most studies, which we believe is flawed.

## Limitation

1) There was a significant degree of heterogeneity in some of the included studies, and while sensitivity analyses can address this in some cases, the impact of heterogeneity on the reliability and utility of the results must be carefully assessed and considered. 2) The comprehensive analysis of publication bias was impossible because of the relatively small number of studies included in each comparison. Although tools such as funnel plots or Egger regression tests are commonly used to assess publication bias in such cases, these tests are often considered unreliable or insignificant for < 10 studies. Therefore, there is a possibility of publication bias in this meta-analysis. 3) Due to insufficient relevant data, the association between the above cytokines and disease severity or subgroup analyses was performed. 4) Non-English and other gray literature were excluded.

## Conclusions

This meta-analysis provides compelling evidence that CRP, Hcy, IL-1 $\beta$ , IL-4, IL-6, IL-8, and IL-10 are associated with the genesis and development of HZ and PHN. These markers can be used to improve the diagnosis and treatment of these diseases. Furthermore, for making the results more convincing, it is necessary to harmonize sample acquisition techniques and analytical methods and also require larger, more rigorously designed studies with broader subgroups and sex/age-matched controls.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.



## Disclosure

The authors report no conflicts of interest in this work.

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