Herpes Zoster and Frailty in Older Adults: a Systematic Review

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ABSTRACT

Background

Herpes zoster (HZ) and its complications, postherpetic neuralgia (PHN), are common in adults, particularly the frail. Frailty may affect infection outcomes and vaccine efficacy. This study evaluated the association between frailty and HZ/PHN risk, and examined vaccine uptake, immunogenicity, and efficacy in frail versus non-frail individuals.

Methods

We systematically reviewed PubMed/MEDLINE, the Cochrane Library, Embase, and grey literature for studies published from January 2015 to January 2025. Eligible studies included observational and randomized controlled trials evaluating frailty in adults aged ≥50 years and reporting HZ incidence, severity, PHN, or vaccination. Two reviewers independently selected studies, extracted data using a standardized form, and assessed quality using JBI tools. Due to heterogeneity, data were synthesized narratively.

Results

Eight studies met the inclusion criteria, with a sample size exceeding 15,000 participants. Two studies identified an association between frailty and an increased incidence of HZ, while two others indicated an elevated risk of PHN among frail individuals. One study highlighted low vaccine uptake in a frail Italian cohort. Three studies assessed the immunogenicity of the zoster vaccine, suggesting that although absolute immune responses may be diminished in frail individuals, relative responses are often maintained. A pooled analysis of recombinant zoster vaccine trials demonstrated consistently high efficacy (exceeding 90%) across all frailty levels.

Conclusions

Frailty may increase vulnerability to HZ and PHN. Routine frailty assessment may improve vaccine uptake and prevention. Further longitudinal studies using standardized frailty measures are needed to understand the causal pathways and optimize care.

Key words: herpes zoster, shingles, varicella zoster virus, herpes zoster vaccine, postherpetic neuralgia, frailty, middle-aged adults, older adults, frail elderly, aged

INTRODUCTION

Herpes zoster(HZ), commonly known as shingles, arises from the reactivation of latent varicella-zoster virus(VZV) within sensory nerve ganglia.[1–3] This reactivation produces a painful dermatomal rash and, in some cases, evolves into postherpetic neuralgia (PHN), a chronic neuropathic pain condition that can severely impair the quality of life of older adults.[2–5] The lifetime risk of developing HZ is estimated to be approximately one in four individuals, increasing sharply with advancing age and approaching 50% among those aged ≥80 years.[1,6]

The heightened vulnerability of older adults to HZ is largely attributed to immunosenescence, a gradual decline in immune competence associated with aging.[1,7] However, beyond chronological age, frailty has emerged as an equally important determinant of health outcomes in older adults.[8] Frailty is a multifaceted condition that increases vulnerability to adverse outcomes, modifies the course of infection, elevates systemic inflammation, and diminishes vaccine efficacy.[1,2]

Although frailty and HZ share overlapping biological underpinnings, particularly those related to immune dysregulation and chronic inflammation, the extent and clinical significance of this association remain poorly defined.[3,9] Previous studies have varied considerably in terms of design, frailty operationalization, and outcome measures, limiting the capacity to derive coherent conclusions or clinical guidance.

This systematic review was designed to synthesize the current evidence on the relationship between frailty and HZ in older adults. Specifically, this study examined whether frailty is associated with an increased risk of HZ and its primary complication, PHN, and whether it influences vaccine uptake, immunogenicity, and effectiveness. By consolidating available data and methodological approaches, this review aims to clarify how frailty intersects with infectious vulnerability

in the aging population, and highlight key gaps informing future preventive strategies.

METHODS

Study Design & Protocol Registration

This systematic review was conducted following a protocol developed a priori and registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number:CRD420251019302). The protocol specified the review objectives, eligibility criteria, search strategy, methods for study selection, data extraction, quality assessment, and data synthesis approach. No deviations from the original protocol were observed during the review process. The methodology adheres to the Cochrane Handbook for Systematic Reviews of Interventions and follows PRISMA2020 reporting guidelines.

Eligibility Criteria

We included studies that met the following inclusion criteria:

- Study Design: Observational studies (cohort, case-control, or cross-sectional) and randomized controlled trials (RCTs).
- Population: Adults aged ≥50 years. This threshold acknowledges that aging develops gradually and often before the conventional cutoff of 60 years used in public policies. Adults in their fifties occupy a transitional period shaped by changes in health, work, and family roles, making this group relevant for studies on the effects of frailty.[10,11]
- Exposure: Individuals classified as frail using psychometrically validated frailty instruments that demonstrated reliability, predictive validity, and adherence to their original assessment protocols (e.g., Fried Frailty Phenotype, Clinical Frailty Scale, Frailty Index, FRAIL Scale).
- Comparator: Individuals without frailty or classified as pre-frail.
- Outcomes: At least one predefined clinical outcome related to herpes zoster incidence, severity, frailty progression, or vaccine response was assessed.

We excluded studies that lacked clear definitions of frailty or herpes zoster, did not report relevant outcomes, were not peer-reviewed, or involved overlapping populations with larger trials. Additionally, we excluded case reports, case series, reviews, study protocols, letters to the editor, editorials, guidelines, and conference abstracts.

Rationale for Outcome Selection

The selection of primary and secondary outcomes for this review was based on clinical relevance and empirical evidence, indicating a dynamic and potentially bidirectional relationship between frailty and HZ. The aim was to capture the susceptibility to HZ among frail adults aged ≥50 years and the clinical course, complications, and immunological responses that might differentiate this group from their non-frail counterparts.

The primary outcomes were defined as follows:

1. The incidence of herpes zoster;
2. Disease severity and complications (particularly the development of postherpetic neuralgia and need for hospitalization); and
3. Progression or exacerbation of frailty after HZ infection.

The secondary outcomes were as follows:

1. Uptake of herpes zoster vaccination among frail versus non-frails; and
2. Immunogenicity and efficacy/effectiveness of vaccination on frailty status.

All outcomes were pre-specified and selected according to the Cochrane methodological standards to minimize selective outcome reporting bias and ensure that the review would address clinically meaningful endpoints across the continuum of frailty and zoster-related vulnerability.

Information Sources & Search Strategy

We systematically searched PubMed/MEDLINE, Cochrane Library, and Embase from January 1, 2015, to January 1, 2025. Google Scholar was used to identify grey literature and additional relevant studies. A combination of free-text keywords was used to capture relevant studies on frailty, herpes zoster, and older adults. Boolean operators (AND, OR) were applied to refine the search, and truncation was used to account for variations in the terminology. The search terms included:(frailty OR fragile OR fragility OR frail* OR "frailty index" OR "frailty syndrome" OR "frailty phenotype" OR "physical frailty")AND("herpes zoster" OR "herpes-zoster" OR shingles OR shingle* OR "postherpetic neuralgia" OR "zoster" OR "varicella-zoster virus" OR VZV OR HZ) AND("aged" OR elder* OR geriatric OR "older adults" OR "older individuals" OR "senior citizens" OR ageing OR aging). The full search strategies for each database are provided in Supplementary Material, Appendix S1. Only studies published in English were included.

Study Selection Process

All records were imported into EndNote X9 (https://www.endnote.com) for reference management and deduplication screening. Two reviewers (H.P. and M.P.D.) independently screened the titles and abstracts to assess eligibility, followed by a full-text review of the potentially eligible studies. Discrepancies were resolved by consensus or consultation with a third reviewer (M.K.A.). The study selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction

Data extraction was performed independently and in duplicate by two reviewers (H.P. and M.P.D.) using a standardized pilot-tested form (Supplementary Material: Appendix S2). The extracted data included study characteristics (author, year, country, design), population demographics (age, sex distribution), frailty assessment method and classification,

zoster-related outcomes (e.g., incidence, complications, vaccination response), and key findings and conclusions. Disagreements were resolved by consensus or by consulting a third reviewer (M.K.A.).

Quality Assessment of Included Studies

The methodological quality and risk of bias of the included studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools (University of Adelaide, South Australia; https://jbi.global), appropriate for each study design. Two reviewers (H.P. and M.P.D.) independently appraised the included studies. Any disagreements were resolved through discussion. The results of the quality assessment are provided in Supplementary Material Tables S1, S2, and S3.

Data Synthesis

A meta-analysis was not possible because of the high variability in frailty definitions and outcome measures. The findings were synthesized narratively through thematic analysis, adhering to Cochrane's guidelines for non-meta-analytical synthesis. The results were categorized into conceptual domains to discern consistent patterns and variations in the evidence base.

Ethics Considerations

This study did not involve human participants or the collection of primary data; therefore, it did not require ethical approval.

RESULTS

Study Selection

Database searches yielded 265 records: PubMed/MEDLINE (n = 90), Embase (n = 156), and Cochrane Library (n = 19). After the removal of 56 duplicates, 209 titles and abstracts were screened, of which 187 were excluded. Twenty-two full texts were reviewed, of which eight met the eligibility criteria. Exclusions were due to the absence of frailty assessment (n = 10), non-English full text (n = 1), methodological design (n = 1), or lack of relevant outcomes (n = 2). The PRISMA flowchart depicts the study selection process (Figure 1).

Study Characteristics & Frailty Measurement

Of the eight included studies, six were cohort studies, one was cross-sectional, and one was a multicenter randomized controlled trial. The studies were primarily conducted in North America, Europe, and South Korea. Frailty was assessed using validated tools, including the Fried Frailty Phenotype, Frailty Index, modified Frailty Index, Johns Hopkins ACG Frailty Indicator, Korean Frailty Questionnaire, and SELFY-MPI. Table 1 summarizes the study designs, sample characteristics, frailty prevalence, and outcomes.

Quality Assessment

The methodological quality of the included studies was evaluated using the JBI critical appraisal tools tailored to

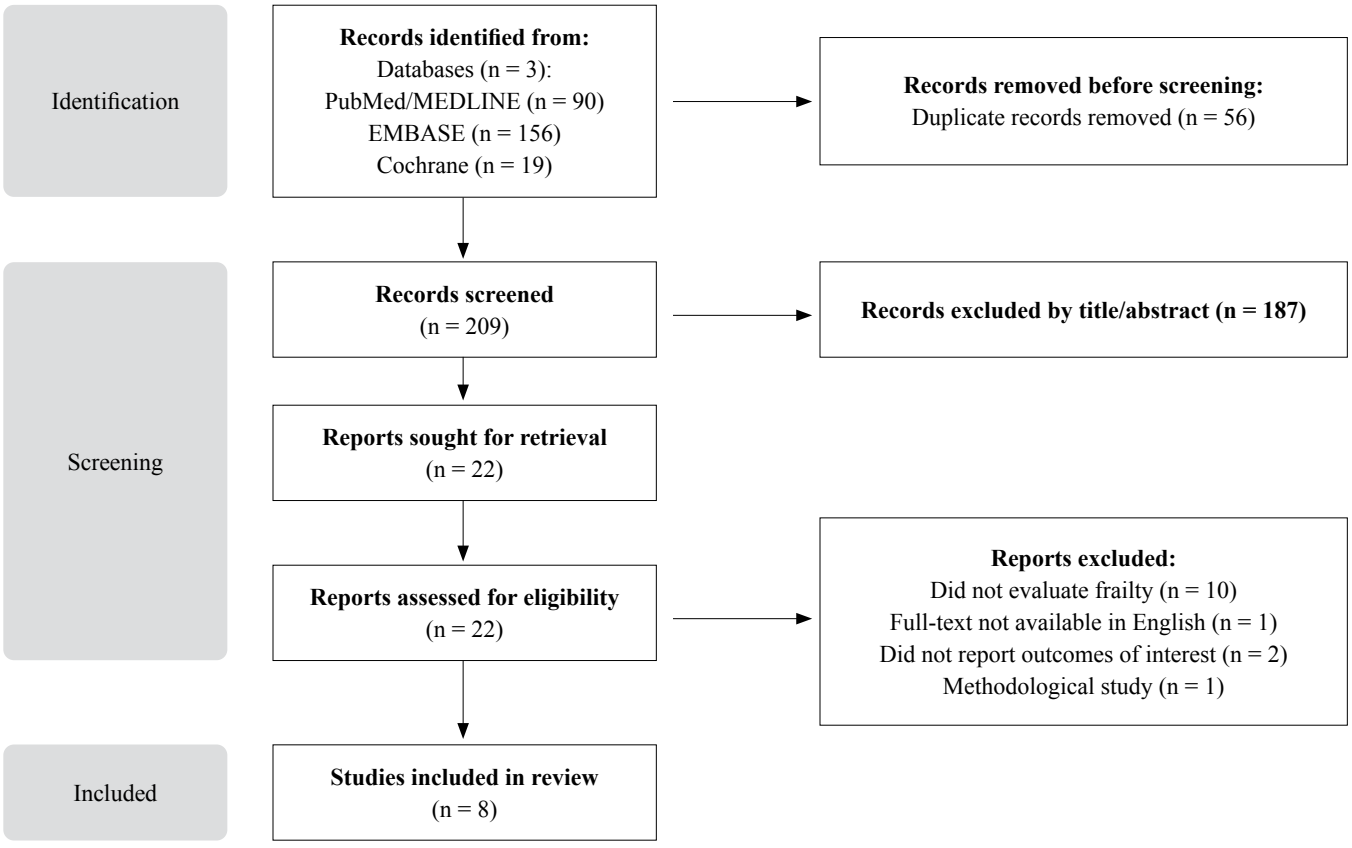

FIGURE 1. Identification of studies via databases and registers

TABLE 1.
Summary of the included studies on herpes zoster and frailty

Author/Year	*Study Type*	*Location*	*Sample Size (N)*	*Female (%)*	*Age (range)*	*Frailty Measure*	*Frail (%)*	*Non-Frail/ Pre-Frail (%)*	*Outcome*
Wang[15] 2016	Cohort	United States	N=633 N=481	100% 100%	73.9 (70-79)	FFP FFP	72 (11.4%) 69 (17.8%)	127 (20.1%) 318(66.1%)	HZ prevalence
Buchan[19] 2021	Cohort	Canada	N=162.507	60.7%	ND (≥65)	JHACG-FI	20.298 (12.5%)	142.209 (87.5%)	PHN incidence
An[14] 2024	Cohort	Republic of Korea	N=351	60.6%	ND (≥60)	mFI	73 (20.8%)	278 (79.2%)	HZ prevalence PHN incidence
Verschoor[12] 2017	Cohort	Canada	N=187 NHR N=50 CDS	NHR 81% CDS 64%	NHR 89 (80-102) CDS 68 (60-75)	FI	NA	NA	Immune response
Veronese[16] 2022	Cross-sectional	Italy	N=319 N=8 (VZV vaccinated)	58% NA	77.5 ± 7.6 (NA)	SELFY-MPI	106 (33.2%) 2 (25%)	213 (66.8%) 6 (75%)	Vaccine uptake
Lelic[13] 2016	Cohort	Canada	190 NHR 50 CDS	NHR 81% CDS 64%	NHR 89 (80-102) CDS 68 (60-75)	FI	NA	NA	Immune response
Curran[22] 2020	RCT	Multicenter	26.976 13.487(RZV)	58.1% 58%	68.8 (50- ≥80) 68.8 (50-96)	FI	3.037 (11.3%) 1.449 (10.7%)	23.808 (88.2%) 11.283 (89.3%)	Vaccine efficacy Immune response
Choi[21] 2019	Cohort	Republic of Korea	69	50.72%	73 (69-79)	KFQ	2 (2.9%)	67 (97.1%)	Immune response

NHR = nursing home residents; CDS = community-dwelling seniors; NRE = non-robust elderly; PHN = postherpetic neuralgia; NA = not available; FFP = Fried Frailty Phenotype; JHACG-FI = Johns Hopkins Adjusted Clinical Groups frailty index; FI = frailty index; SELFY-MPI = Selfy Multidimensional Prognostic Index; PFI = prospective frailty index; KFQ = Korean frail questionnaire; mFI = modified frailty index; RCT = randomized controlled trial; VZV = varicella-zoster virus.

each study design, as detailed in Supplementary Material Tables S1, S2, and S3.

- Cohort Studies (n=6): All cohort studies clearly defined their exposure and outcome measures and reported appropriate follow-up periods. However, two studies, Verschoor *et al*.[12] and Lelic *et al*.,[13] included groups that were not directly comparable at baseline, such as institutionalized versus community-dwelling older adults. This introduced a potential selection bias and limited the external validity. Additionally, strategies to address loss to follow-up were generally unclear across studies. Although An *et al*.[14] employed appropriate longitudinal methods, they did not fully adjust for potential confounders, which may have compromised their internal validity. Wang *et al*.[15] also did not adjust for key confounders, which could potentially affect the robustness of the findings.
- Cross-Sectional Study (n=1): The cross-sectional study clearly defined its inclusion criteria and utilized appropriate statistical analysis in its design. Nevertheless, some limitations were identified: Veronese *et al*. relied on a relatively small and specific sample, limiting generalizability.[16] Despite these issues, this cross-sectional study met the minimum methodological quality criteria for inclusion.
- Randomized Controlled Trial (n=1): One RCT clearly defined its inclusion and exclusion criteria and utilized appropriate statistical analyses. Although allocation concealment was not clearly reported, all other methodological quality criteria were satisfied, justifying the inclusion of this study in the review.

KEY FINDINGS

Association Between Frailty & Herpes Zoster

HZ appears to have a bidirectional relationship with frailty. Individuals who develop HZ may experience a decline in functional status and quality of life, potentially progressing toward frailty.[17] Conversely, frail individuals are at an increased risk of developing active VZV infection.[18] In a

retrospective cohort study of 351 older adults with HZ, 20.8% were classified as frail[14]; however, the absence of a non-HZ comparator group limits the inference of excess frailty prevalence. In a prospective cohort of community-dwelling women aged 70–79 years, frailty was slightly more frequent among those with positive anti-VZV serology (11.9% vs. 9.4%).[15] Collectively, these findings suggest that HZ may contribute to subsequent functional decline, although evidence supporting frailty as a precursor to HZ remains limited.

Frailty & Risk of Postherpetic Neuralgia

Frailty appears to heighten the vulnerability to PHN following HZ. PHN affects 10–15% of individuals with HZ and up to 30% of those aged >70 years.[9] Although this increased risk is often attributed to age-related frailty, it remains uncertain whether frailty independently contributes to PHN beyond its association with HZ. Current evidence suggests a possible direct relationship, but the data remain limited.

``Two studies have specifically examined this association. In a large population-based cohort of 162,507 adults aged ≥65 years in Ontario, Canada, frailty (measured using the Johns Hopkins ACG Frailty Indicator) was associated with a higher incidence of PHN (18.6% in frail individuals vs. 13.6% in non-frail individuals).[19] Similarly, a retrospective study by An *et al*.[14] reported that frailty, as quantified by the modified Frailty Index, significantly increased the risk of PHN within six months of HZ diagnosis (adjusted OR 2.46; 95% CI 1.21–4.98). Although causal inference remains limited, frailty has consistently emerged as a marker of increased PHN susceptibility.

Frailty & Vaccination Coverage

Vaccination uptake against HZ remains suboptimal in older adults. In Canada, only 36.3% of individuals aged ≥65 years have received the HZ vaccine.[20] Low coverage is attributed to a perceived lack of necessity, reported by nearly 40% of older adults, and vaccine cost, cited by approximately 12%. The limited integration of HZ vaccination into public immunization programs has further contributed to low uptake, although accessibility is gradually improving.

In a cross-sectional study of 319 Italian adults (mean age, 77.5 years), the frailty prevalence reached 33.2%, yet only 2.5% reported receiving the HZ vaccine.[14] Vaccine uptake did not differ significantly across frailty tertiles, suggesting that factors beyond frailty status, such as access, awareness, and cost, may influence vaccination behaviour. Conversely, pneumococcal vaccination was more common among frail individuals, highlighting the differing perceptions or policy-related drivers of vaccines.

Frailty & Immune Response to Vaccination

Four studies assessed the immunological response to HZ vaccination in frail populations. Nursing home residents (who exhibited higher frailty scores and multimorbidity) had lower baseline VZV-specific cell-mediated immunity (measured by IFN-γ spot-forming cells) and reduced absolute immune responses after live-attenuated vaccination than community-dwelling older adults.[13] However, fold increases in the immune response were similar between frail and non-frail individuals, indicating preserved relative responsiveness despite lower baseline immunity. Chronic conditions, rather than frailty alone, were more strongly associated with reduced immune response.[13]

Other studies have reinforced this pattern. No direct association was observed between frailty and immunogenicity (measured by IFN-γ spot-forming cells) following live-attenuated zoster vaccination in community-based cohorts, although congestive heart failure and other comorbidities predicted lower antibody response.[12] In a South Korean cohort with a low frailty prevalence (2.9%), significant increases in VZV-specific IgG and T-cell (quantified by the VZV-specific IFN-γ ELISPOT assay) responses were observed following vaccination in all frailty strata.[21]

A pooled analysis of two phase III randomized trials involving 26,976 participants evaluated the efficacy of the recombinant zoster vaccine (RZV).[22] High response rates were observed one month after the second dose: 98.0%, 97.9%, and 95.7% among non-frail, pre-frail, and frail individuals, respectively, with sustained anti-gE antibody levels for up to 36 months.[22]

These findings indicate that although frailty may attenuate baseline immunity and absolute response to vaccination, proportional immunogenicity is largely maintained. Chronic comorbidities have a more pronounced effect on vaccine-induced immunity than frailty alone.

Vaccine Effectiveness in Frail Individuals

Aligned with the preserved proportional immune responsiveness observed across frailty strata, clinical outcomes reinforce the vaccine's relevance in this population. Curran *et al*.[22] reported that RZV prevented incident HZ with efficacy exceeding 90% in frail adults, closely paralleling rates in non-frail and pre-frail participants. Importantly, RZV substantially reduced the overall burden of HZ illness, with a greater absolute reduction observed among frail individuals than among non-frail participants. The vaccine demonstrated a consistent safety profile across frailty categories. Rates of any solicited adverse effects, which were predominantly mild and transient symptoms such as arm pain, fatigue, and myalgias, decreased with increasing frailty: 87.3% in non-frail participants, 83.4% in pre-frail participants, and 73.5% in frail participants. Serious adverse events were uncommon and occurred at similar or lower frequencies in the vaccinated groups (17.4%, 14.1%, and 15.3% across the same categories). These findings indicate that frail older adults achieve meaningful protection without evidence of increased safety risk.

DISCUSSION

This systematic review aimed to evaluate the association between frailty and HZ in older adults, focusing on HZ incidence, risk of complications, and vaccine responses. Some

studies suggest a potential bidirectional relationship between frailty and HZ; however, methodological heterogeneity, particularly in frailty assessment and outcome definitions, and limited longitudinal data hinder definitive conclusions. While frailty may independently increase susceptibility to HZ and its complications, individuals who develop HZ may experience declines in functional status and quality of life, potentially contributing to frailty progression.

Currently, the literature lacks a systematic integration of frailty into HZ risk stratification models, highlighting a significant gap. To address this, Andrew *et al*.[23] developed the Clinical Trial Frailty Index (CT-FI), a reliable and practical tool based on baseline medical history and patient-reported outcomes. The CT-FI facilitates frailty assessment in clinical trials without significantly increasing participant burden, especially in a population often underrepresented despite an elevated need for protection.[23]

Frailty is Associated with HZ

First, it is important to acknowledge the existing gap in the literature concerning estimates of frailty prevalence among patients diagnosed with HZ. An *et al*.[14] is the sole reference addressing this issue, indicating that 20.8% of the individuals were frail. Nonetheless, frail older adults seem to experience higher HZ incidence rates than their non-frail counterparts. For instance, in the context of a zoster vaccine RCT, Curran *et al*.[22] reported an HZ incidence of 0.3% among frail individuals, in contrast to 0.1% among non-frail individuals.

The existing literature broadly supports the role of immunosenescence in HZ pathogenesis; however, few studies have dissected frailty-specific mechanisms. Frailty is associated with chronic inflammation, reduced T-cell function, and impaired viral surveillance, all of which are plausible contributors to VZV reactivation. Despite this, a significant portion of earlier studies often merges the concepts of aging and frailty, failing to recognize their unique biological differences. For instance, although age is a well-established HZ risk factor, the added vulnerability conferred by frailty remains underexplored.

The current review underscores a critical gap in our understanding of the interplay between frailty and HZ. While existing studies hint at frailty exacerbating HZ risk, methodological limitations, homogenous samples, and comorbidity adjustment prevent definitive conclusions about frailty's independent contribution. It is also likely that the association runs in both directions, such that HZ contributes to the deficit accumulation that causes and defines frailty. This complexity highlights the need for larger, well-controlled, longitudinal studies with robust frailty measurements as both exposure and outcome.[24]

Frailty & PHN Development

Frailty emerged as a potential predictor of PHN, with frail individuals experiencing higher rates (e.g., 18.6% vs. 13.6% in non-frail individuals; Buchan *et al*.[19]). This aligns with evidence linking frailty to prolonged pain syndromes resulting from neuroinflammatory dysregulation and delayed tissue repair.[25,26] Although PHN has traditionally been attributed to age-related neuronal vulnerability, emerging data suggest that systemic inflammation and immune dysfunction, both characteristic features of frailty, may also shape susceptibility to sustained neuropathic pain.[27–29] Studies outside this review,[25,26] and Pansarasa *et al*.,[30] further indicate that frail adults often exhibit amplified pro-inflammatory responses, a biological profile that could plausibly increase the risk of PHN. Still, these mechanisms remain speculative when considered specifically within the PHN pathway.

It is relevant to consider whether the observed association operates only through a higher incidence of HZ in frail individuals or whether, among those who develop HZ, frailty independently increases the likelihood of PHN. The limited available evidence tends to support this second possibility. However, interpretation is constrained by methodological inconsistencies. Definitions of PHN varied substantially across studies, particularly with respect to pain duration thresholds, and most analyses relied on retrospective data. An *et al*., for instance, used an mFI but did not include baseline immune metrics,[14] which limits causal inference.

Even with these constraints, the consistency in direction of the association across studies strengthens the rationale for incorporating frailty assessment into PHN risk stratification frameworks, particularly in clinical settings where early identification of higher-risk groups may support more anticipatory management strategies.

Vaccine Response in Frail Populations

Our findings suggest a complex interplay, particularly regarding vaccine response, where frail individuals demonstrate a seemingly preserved yet attenuated immune response to HZ vaccination,[12,13,21] ultimately achieving high efficacy with RZV across varying frailty levels.[22] This highlights a nuanced picture that warrants further exploration beyond the simple assumption of impaired vaccine effectiveness in frail older adults.

Limited studies specifically examining HZ vaccine immunogenicity in frail individuals indicate a trend in which absolute antibody titers and cell-mediated immunity may be reduced compared to those in robust individuals.[13] However, the immune response or fold change from baseline appeared to be maintained.[13] This observation aligns with the findings for other vaccines, such as influenza, where frail individuals achieved similar humoral immune responses and seroprotection rates compared to robust individuals, suggesting that frailty may not necessarily blunt the protective immune response to all vaccines.[31] Notably, the presence of chronic comorbidities, particularly congestive heart failure, seems to exert a more substantial negative influence on achieving a clinically significant antibody response than frailty status.[12] This underscores the importance of considering a multifactorial assessment of health status beyond frailty when evaluating vaccine response in older adults.

While our review points towards preserved relative immunogenicity and high RZV efficacy in frail individuals,

the current evidence base presents several limitations. The heterogeneity in frailty assessment tools across studies makes direct comparisons challenging and potentially obscures subtle differences in vaccine responses across the frailty spectrum. Future research should prioritize the standardization of frailty assessments, and correlate these measures with a comprehensive panel of humoral and cellular immune outcomes following vaccination. This will provide a more detailed understanding of the qualitative and quantitative aspects of vaccine-induced immunity in frail individuals, and refine strategies for protecting this vulnerable population.

The finding of high RZV efficacy (>90%) across all frailty strata, despite potentially lower absolute immunogenicity, as demonstrated by Curran *et al*.,[22] offers a significant advancement in understanding this problem. This suggests that the threshold of the immune response required for clinical protection against HZ may be attainable, even in frail individuals receiving RZV. However, the durability of this protection, and whether the attenuated absolute immune responses observed in frail individuals might lead to a more rapid waning of vaccine-induced immunity over longer follow-up periods, remains unanswered. Future studies with extended follow-up and detailed longitudinal immunomonitoring of frail vaccine recipients are essential to address this critical knowledge gap and inform optimal revaccination strategies for this population.

Direction of Association

It is important to consider the direction of the association: Does a history of HZ contribute to the development of frailty, leading to deficit accumulation, or are individuals who are already frail more susceptible to developing HZ infection? Both scenarios are plausible. The reactivation of VZV, which causes HZ, affects individuals by hindering their ability to regain their previous health status and quality of life, both of which are closely tied to frailty. Similarly, frailty induces physiological and immunological changes that may promote the reactivation of VZV. In individuals who are already frail, this acute infection can have a more severe impact, including a higher incidence of complications, such as PHN.

Limitations & Strengths

This review has several methodological limitations. First, the predominance of observational studies, including one cross-sectional and six cohort studies, limits causal interpretation. Only two studies evaluated frailty as a primary exposure variable, while others used it as a secondary variable. Only one study was an RCT. Frailty assessment varied across studies, with some using validated instruments such as FFP and FI, while others used SELFY-MPI, KFQ, mFI, and JHACG-FI, complicating result comparison. Second, geographic representation was mainly limited to North American and European populations, which affected the generalizability of the findings. Third, outcome measurements showed inconsistencies, particularly in postherpetic neuralgia assessment, with varying pain-duration thresholds. Finally, most studies inadequately adjusted for potential confounders, including comorbidities, vaccination history, and immunosuppressive therapy history.

Despite these limitations, this review has several notable strengths. The methodology followed the PRISMA guidelines, with dual independent screening and quality assessment using Joanna Briggs Institute tools. Protocol registration in PROSPERO minimizes reporting bias. This review provides the first comprehensive analysis of frailty and HZ outcomes, offering clinical insights into vulnerable populations. Focusing on clinical manifestations and immunological parameters provides a perspective on the frailty-HZ relationship. Vaccine-specific findings demonstrate that meaningful immune protection is achievable despite frailty-related immunosenescence, particularly regarding the efficacy of the recombinant zoster vaccine in frail older adults. This review identified knowledge gaps for future research, especially regarding standardized frailty assessments and longitudinal designs, with immediate implications for clinical practice and vaccination strategies in frail older adults.

CONCLUSIONS

This review identifies frailty as a plausible modifier of HZ risk, complications, and vaccine response, although the evidence remains preliminary owing to methodological inconsistencies. Key contributions include: 1) frailty may exacerbate HZ susceptibility independent of age, 2) PHN risk appears elevated in frail adults, warranting early intervention, and 3) RZV efficacy is preserved across grades of frailty. Combining all three could build support for a strategy advocating for the prioritized use of RZV in frail older adults, or at least for public health and vaccine program messaging around the particular importance of vaccination for people who are frail or at risk of becoming frail. Clinically, integrating frailty screening into HZ prevention programs could optimize outcomes for vulnerable, older adults. Future research should prioritize longitudinal designs with standardized frailty metrics, mechanistic studies linking frailty to VZV-specific immunity, and trials evaluating adjuvanted vaccines in advanced frailty. Addressing these gaps holds significant public health relevance as the aging global population confronts increasing burdens of frailty-associated infectious diseases.

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CONFLICT OF INTEREST DISCLOSURES

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SUPPLEMENTARY MATERIALS

Supplemental material linked to the online version of the paper (https://doi.org/10.5770/cgj.29.916):

- **Appendix S1:** Search Strategies for Frailty and Herpes Zoster Across Databases
- **Appendix S2:** Data Extraction Form
- **Table S1:** Joanna Briggs Institute 8-item Critical Appraisal Checklist for Cohort Studies
- **Table S2:** Joanna Briggs Institute 8-item Critical Appraisal Checklist for Analytical Cross-Sectional Studies
- **Table S3:** Joanna Briggs Institute Checklist for RCTs

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