AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 38, Number 9, 2022

DOI: 10.1089/aid.2021.0155

The Impact of Frailty on All-Cause Mortality in Patients with HIV Infection: A Systematic Review and Meta-Analysis

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Abstract

The aim of this study was to conduct a systematic review and meta-analysis of cohort studies that have examined the association between frailty and all-cause mortality in patients with HIV infection. We searched Embase, Medline through the Ovid interface, PubMed, Cochrane Library, and Web of Science to identify potential studies. Cohort studies of death outcomes in HIV patients under debilitating conditions were included and other ineligible or inadequate data were excluded. Data related to all-cause mortality in patients with HIV were extracted. The quality of the included studies was assessed using the Newcastle–Ottawa Scale for cohort studies. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were pooled to estimate the association between frailty and all-cause mortality using Stata, version 12.0. We identified 845 unduplicated citations. Of these, six cohort studies were eligible for inclusion in the review after applying our inclusion and exclusion criteria. Pooled results demonstrated that patients with HIV experiencing frailty were at an increased risk of all-cause mortality (pooled HR = 2.69, 95% CI = 1.83–3.97, $p < .001$) compared with those without frailty. Frailty was significantly associated with an increased risk of all-cause mortality among patients with HIV, indicating that frailty is an important predictor of adverse clinical outcomes. Therefore, more attention should be paid to screen patients with HIV for frailty and adopt appropriate interventions and personalized treatment plans to prevent the occurrence of adverse events. However, these results need to be validated in further prospective cohort studies in ethnically or geographically diverse populations.

Keywords: frailty, HIV, all-cause mortality

Introduction

The epidemic caused by HIV was first recognized in the United States in the early 1980s. Shortly after, HIV was identified worldwide. According to the report of the Joint United Nations Programme on AIDS, there were nearly 37,700,000 people living with HIV (PLHIV), 680,000 AIDS-related deaths, and 1,500,000 new HIV infections worldwide in 2020. AIDS is a chronic disease that seriously affects public health around the world. Mortality caused by AIDS is significantly higher than that from other sexually transmitted diseases.[1]

Frailty is characterized by a decline in functioning across multiple physiological systems and is accompanied by increased vulnerability to stressors.[2,3] It is associated with increased mortality, hospitalization, falls, and admission to long-term care.[2] The association between frailty and mortality has been confirmed in many studies across various

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settings and subpopulations.[4–8] Frailty can occur in adults at any age, but is more prevalent in older adults.[9]

The life expectancy of PLHIV has dramatically improved with effective and well-tolerated antiretroviral therapy.[10] As a result, the number of older HIV-infected adults is increasing significantly worldwide. In the United States, over 50% of HIV-infected individuals are aged 50 years or older. By the year 2030, an estimated 70% of those with HIV will be over the age of 50. These figures are similar to estimates for other developed nations.[11,12]

As the number of older adults with HIV increases, this population is at an increased risk of frailty.[13] A study reported a high prevalence of frailty of 15.2% in an older HIV-infected population.[14] Moreover, the prevalence of comorbidities, multimorbidities, and frailty is higher in PLHIV than in the general population at all ages, and the gap between the two populations widens with age.[15–17] Therefore, frailty assessment is necessary for patients with HIV.

Several studies have found that frailty in older adults is a predictor of all-cause mortality in patients with HIV.[18–22] However, some studies did not find any significant relationship between frailty and all-cause mortality.[23] Given the observed contradictory relationship between frailty and all-cause mortality in patients with HIV among the reported studies, there is a need for a meta-analysis to synthesize the pooled risk effect and determine whether frailty is a predictor of all-cause mortality.

This study aimed to perform a systematic review and meta-analysis to investigate the impact of frailty on all-cause mortality in patients with HIV.

Methods

Search strategy

A systematic literature search was conducted in five electronic databases, Ovid, Embase, Cochrane Library, PubMed, and Web of Science, on January 24, 2022. The search strategy was tailored according to the database. We used a combination of key words, such as mortality (mortality*), OR death (death*), OR survival (survival*), frailty (frailty*), and (human immunodeficiency virus * or AIDS or HIV), as well as MeSH terms. We also used the subject terms and truncation symbols in our search. Detailed search strategies are provided in Supplementary Data.

Selection procedure

All records were extracted using the EndNote reference management software. Duplicates were detected and deleted. The literature screening was conducted independently by two researchers. Two researchers screened the titles and abstracts to identify potentially relevant studies. The potentially relevant studies were assessed by reading the full texts to determine eligibility for inclusion. Any doubt was resolved through consultation with a third reviewer.

We included all original articles that met the following criteria: (1) studies reporting the association of frailty with all-cause mortality in patients with HIV, (2) cohort studies, and (3) studies reporting clear diagnostic criteria for frailty. The exclusion criteria were as follows: (1) reviews; (2) conference abstracts; and (3) studies written in languages other than English.

Data extraction

A standardized form was used by two researchers to extract data from the included studies. The following information was extracted from each study: the first author, publication year, country of origin, study design, sample size, age of patients, proportion of men, diagnostic criteria for frailty, duration of follow-up, and primary endpoint (all-cause mortality).

We sent an email to the author when the potential studies did not provide hazard ratios (HRs) and 95% confidence intervals (CIs) about the association of frailty with all-cause mortality in HIV patients.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies. The details of NOS cover three broad criteria, including representativeness of study groups, comparability of study groups, and quality of the outcome assessment. Studies were scored none, one, two, or three stars for the internal validity of representativeness.

The maximum NOS score was 9. The study quality was considered high when the NOS score was ≥7.

Statistical analyses

The meta-analysis was performed using STATA 12. We reported the results of the meta-analyses—obtained after pooling individual study estimates with a fixed effects model and random effects model—as HRs with 95% CIs. The degree of heterogeneity between the studies was assessed using the I^2 index, with percentages of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.

A random effects model was used when I^2 was over 50%; otherwise, the fixed effects model was applied. To assess publication bias, a funnel plot was created by plotting the natural logarithm of the HR against the inverse of the standard error. The symmetry of funnel plots was visually inspected and statistically checked using the Begg and Egger tests.

Results

Search results

Our literature search identified 1,069 publications. After removing duplicates, 748 titles and abstracts were screened. The full texts of 27 articles were read and evaluated in detail. Finally, six articles were included in the systematic review and meta-analysis. The reasons for exclusion are explained in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart, as shown in Figure 1.

Study characteristics

Six articles, including five retrospective cohort studies and one prospective cohort study, were included in the pooled analysis (Table 1). Studies were mainly conducted in America, while one study was conducted in The Netherlands. The average age of participants in the samples ranged from 42.6 to 54.4 years. The proportion of men was between 0% and 97.4%.

Regarding frailty, there were four studies evaluating frailty based on the Fried frailty phenotype (FFP), one study used the Fried frailty index (FFI), and one study applied the

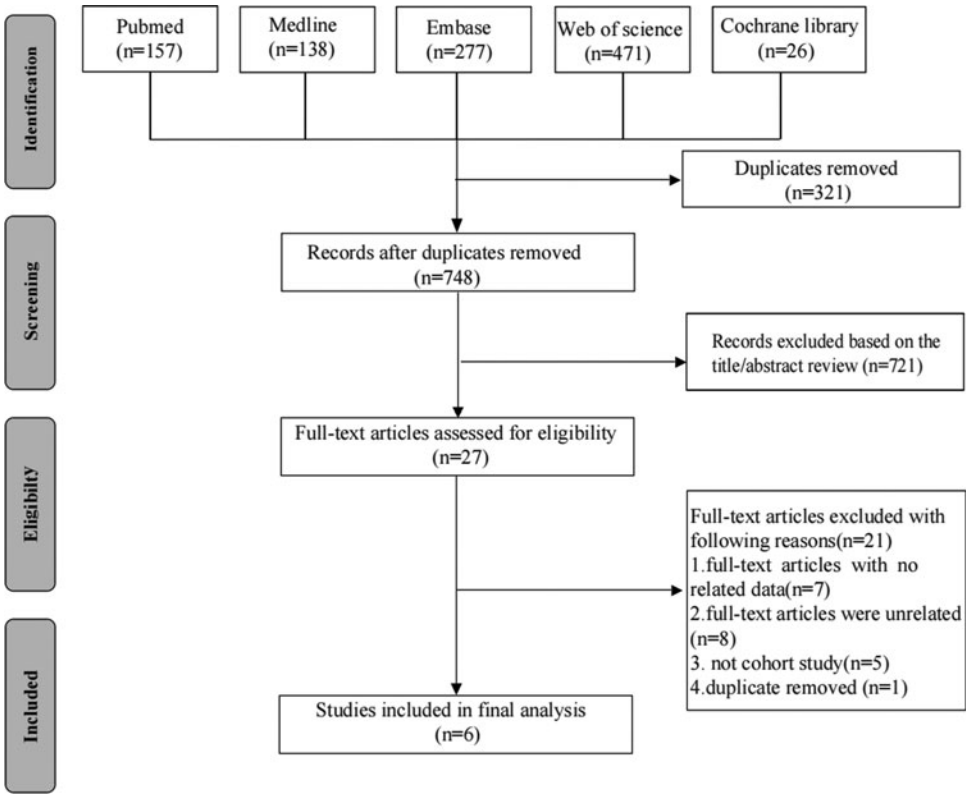

FIG. 1. The flowchart of study selection.

adapted survey-based frailty-related phenotype (aFRP). The follow-up period of the included studies ranged from 3 to 10 years. Two of the studies had a sample size of <1,000 and four studies had a sample size of >1,000, of which one had a sample size of >3,000.

Influence of frailty on all-cause mortality

The meta-analysis demonstrated that frailty was significantly associated with increased risk of mortality in patients with HIV, with a pooled HR of 2.69 (95% CI = 1.83–3.97, $p < .001$) (Fig. 2), and heterogeneity was reasonably acceptable with I^2 of 56.6% (95% CI = 0%–83%). The results were also consistent in the subgroup analysis according to the frailty assessment tools, sample number, and follow-up period (Figs. 3–6).

Frailty was associated with an increased mortality risk in the group with frailty defined by FFP, with a pooled HR of 3.57 (95% CI = 1.95–6.53, $p < .001$). When frailty was defined by aFRP, the pooled HR was 1.83 (95% CI = 1.27–2.64, $p = .001$). When frailty was defined by FFI, the pooled HR was 2.35 (95% CI = 1.68–3.28, $p < .001$). Frailty was associated with an increased mortality risk of 1.13- and 2.88-fold in patients with HIV in studies with follow-up periods ≥5 and <5 years, respectively.

Risk of bias assessment—publication bias

To explore publication bias, we conducted funnel plots, the Begg test, and the Egger test. There was no significant publication bias among the studies according to the Begg test ($p = .707$) and Egger test ($p = .381$).

Discussion

In the present meta-analysis of six studies with 7,370 patients, we investigated the role of frailty in predicting mortality in patients with HIV and found that frailty was significantly associated with mortality. These results further support the utility of frailty in predicting adverse clinical outcomes among patients with HIV infection.

These results have been confirmed in several original studies. Pelloquin *et al.* prospectively collected the electronic health records of 359 patients. At the 8-year follow-up, frailty/prefrailty, as assessed by the Fried frailty phenotype, was associated with an increased risk of all-cause mortality compared with nonfrail patients with HIV.[18] In another study of 3,472 patients with HIV, multivariable models demonstrated that the aFRP and prefrailty were significantly associated with 75% and 44% increased risk for 5-year all-cause mortality, respectively.

Frailty has also been associated with increased hospitalization.[21] This association was also observed in AIDS deaths. Gustafson *et al.* also reported significantly increased AIDS deaths (by 1.35-fold) in patients with frailty, defined by an FFI of 3–5, in comparison with those with an FFI of 0–2.[22] The change in frailty is another important indicator for predicting adverse outcomes in patients with HIV. Kelly *et al.* used Fried's frailty criteria to assess frailty and found that an increased frailty score from baseline to week 48 was associated with a higher risk of mortality.[23]

Although current evidence indicates an inner association between frailty and an increased risk of mortality among patients with HIV, the precise underlying mechanisms remain unclear. We hypothesized the following mechanisms.[24] Previous evidence has demonstrated that frail patients are at

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Study design	Male, %	Mean age, years	Sample size	Country	Definition of frailty	Follow-up, years	NOS
Pelloquin *et al.*[18]	Retrospective cohort study	84.2	52.27	155	America	Patient was defined as frail, meeting ≥3 domains of FFP (weak handgrip strength, exhaustion, slow gait speed, low physical activity, and unintentional weight loss)	7.9	7
Verheij *et al.*[18]	Prospective cohort study	86.4	54.42	283	The Netherlands	Patient was defined as frail, meeting ≥3 domains of FFP (weak handgrip strength, exhaustion, slow gait speed, low physical activity, and unintentional weight loss)	4	8
Kelly *et al.*[19]	Prospective cohort study	81	51	1,016	America	Patient was defined as frail, meeting ≥3 domains of FFP (weak handgrip strength, exhaustion, slow gait speed, low physical activity, and unintentional weight loss)	4	8
Piggott *et al.*[20]	Prospective cohort study	63.4	48.7	1,059	America	Patient was defined as frail, meeting ≥3 domains of FFP (weak handgrip strength, exhaustion, slow gait speed, low physical activity, and unintentional weight loss)	3	8
Akgün *et al.*[21]	Prospective cohort study	97.4	49.2	3,472	America	Patient was defined as frail, meeting ≥3 domains of aFRP (physical shrinking, exhaustion, slowness, and decreased physical activity)	10	8
Gustafson *et al.*[22]	Prospective cohort study	0	42.6	1,385	America	The FFI was defined according to well-described criteria. The patient was classified as frail if she exhibited three or more of five characteristics: (1) impaired mobility, (2) reduced grip strength, (3) physical exhaustion, (4) unintentional weight loss, and (5) low physical activity	10	8

aFRP, adapted survey-based frailty-related phenotype; FFI, Fried frailty index; FFP, Fried frailty phenotype; HR, hazard ratio; NOS, Newcastle–Ottawa Scale.

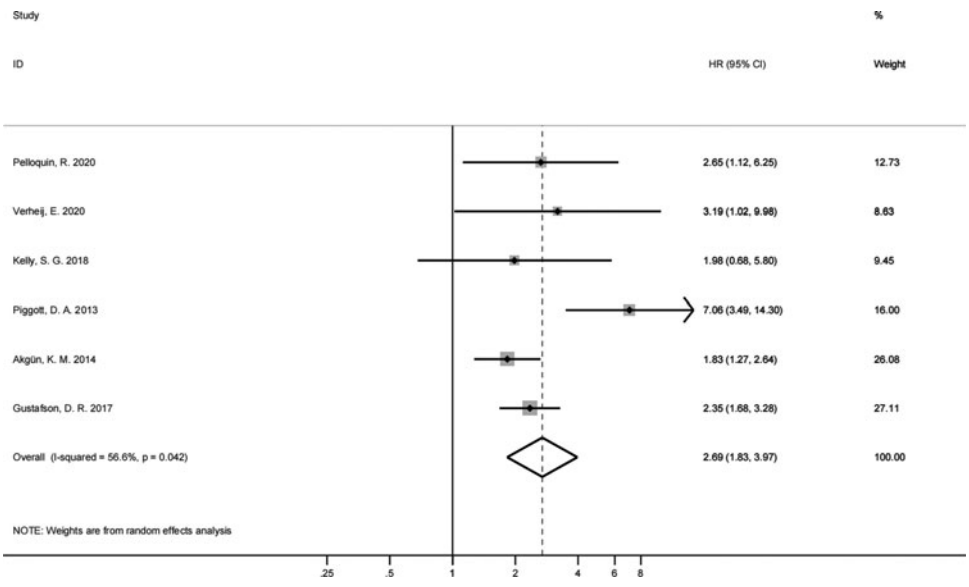

FIG. 2. Forest plot showing the pooled weighted frequency of mortality in patients with HIV. CI, confidence interval; HR, hazard ratio.

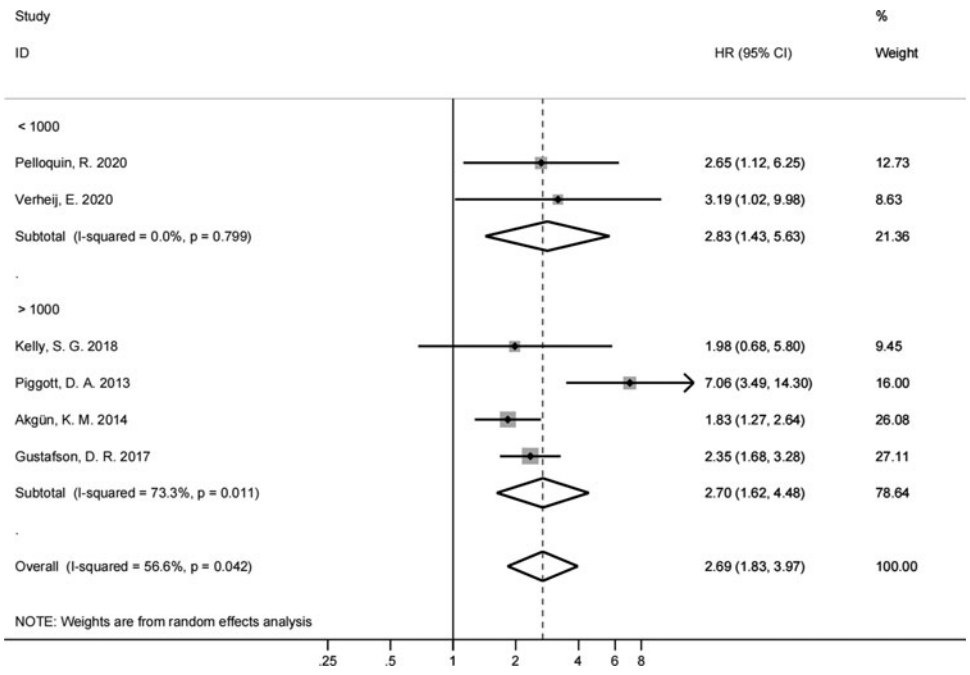

FIG. 3. Subgroup analysis according to the sample number.

high risk of cardiovascular diseases, metabolic diseases, pulmonary dysfunction, or renal dysfunction.[25–28] Therefore, it is likely that frail patients with HIV have an increased risk of subclinical organ damage when compared with those who are not frail, leading to more adverse clinical outcomes.[25]

Frailty has also been associated with increased plasma levels of the innate immune activation marker, sCD163, and oxidative stress.[29,30] Furthermore, frailty may accelerate aging. Sánchez-Conde *et al.* investigated the association between DNA methylation and frailty in an HIV-infected population and found that frail patients with HIV were significantly associated with a higher predicted biological age when compared with those without frailty.[31]

The subgroup analysis demonstrated that frailty (according to frailty definitions such as FFP, FFI, and aFRP) was associated with an increased risk of mortality in patients infected with HIV, which further strengthens the need to focus on frail patients with HIV. Some parameters of frailty have also been reported as important predictors of adverse outcomes in patients with HIV.

Pelloquin *et al.* found that a 0.1 m/s decrease in gait speed in a 400-m walk test among patients with HIV was significantly associated with mortality, after adjusting for smoking, sex, or physical activity.[18] Moreover, handgrip is a critical risk indicator of fractures in patients with HIV infection.[32] In contrast, frailty is closely related to sarcopenia, which is

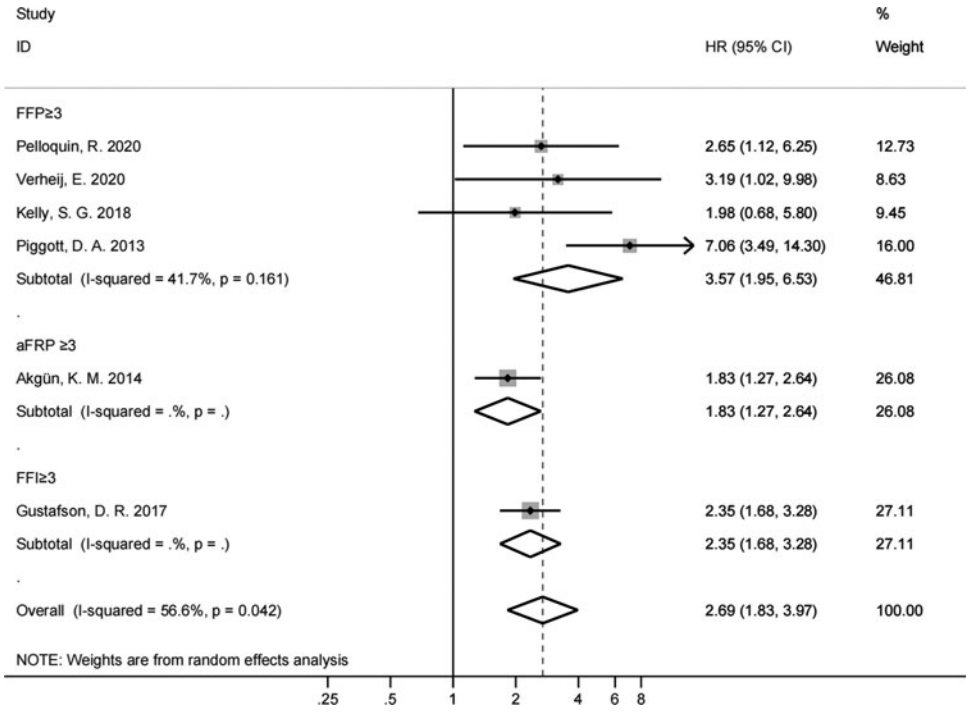

FIG. 4. Subgroup analysis according to the frailty assessment tools. aFRP, adapted survey-based frailty-related phenotype; FFI, Fried frailty index; FFP, Fried frailty phenotype.

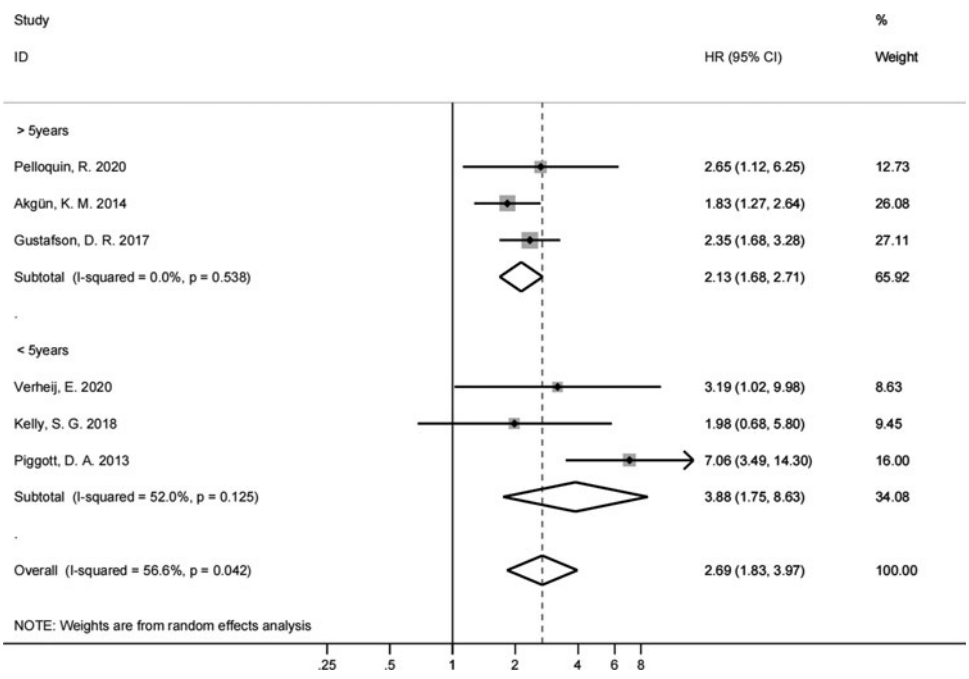

FIG. 5. Subgroup analysis according to the follow-up period.

characterized by loss of skeletal muscle and decreased physical function.[33] de Almeida *et al.* included 101 patients with HIV, aged over 50 years, and found that 12% of patients had sarcopenia, as evaluated by DXA.[34]

Meanwhile, patients with sarcopenia were associated with an increased risk of low hip bone mineral density and a high prevalence of morphometric vertebral fractures compared with those without sarcopenia.[34]

The present study is the first systematic review and meta-analysis to summarize the available evidence on the association between frailty and all-cause mortality among patients with HIV according to the Meta-analysis Of Observational Studies in Epidemiology guidelines. The results confirmed the negative effect of frailty on mortality among patients with HIV by conducting subgroup analyses according to frailty assessment tools, sample number, and follow-up period.

Furthermore, screening factors that increase the risk of frailty was helpful for preventing adverse outcomes in HIV patients. McMillan *et al.* demonstrated that HIV patients with hepatitis C virus coinfection, cirrhosis, metabolic syndrome, lung disease, and polypharmacy were associated with increased risk of frailty.[35] In addition, hypothyroidism, arthritis, and tobacco use were associated with 2.55-, 2.54-, and 1.79-fold risk of frailty, respectively.[36] Therefore, more attention should be paid to screening for frailty in HIV patients with comorbidities.

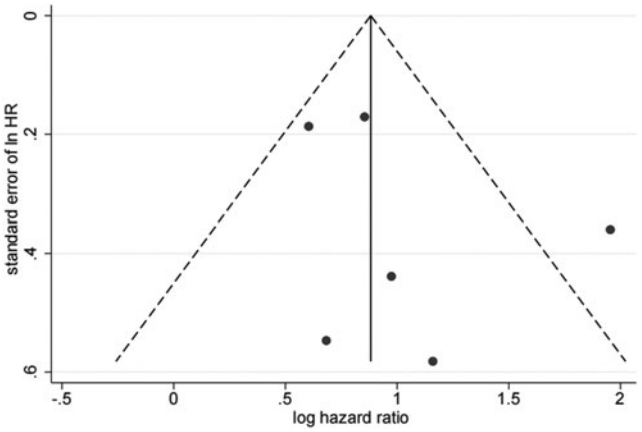

FIG. 6. Funnel plot with pseudo 95% confidence limits.

However, there are several limitations to this systematic review. First, although the systematic search included five electronic databases, only six studies were included in our final analysis, which may weaken the reliability of our results. Second, the frailty assessment tools in the included studies varied, which may have induced high heterogeneity. Fortunately, the heterogeneity was reasonably acceptable. We also performed subgroup analyses according to the frailty assessment tools to explore the source of heterogeneity.

Therefore, although an association was observed between frailty and negative health outcomes in patients with HIV, we believe that more research is required to further validate the role of frailty in prediction of relevant clinical outcomes in this population. In addition, the participants in the included studies are from high-income countries, which may limit the application of the result for low- and middle-income countries, therefore studies from low- and middle-income countries are needed to assess the impact of frailty on all-cause mortality in patients with HIV infection.

Conclusions

Frailty was significantly associated with an increased risk of all-cause mortality among patients with HIV. This finding indicated that frailty may be an important predictor of adverse clinical outcomes.

Therefore, more attention should be paid to screening for frailty in patients with HIV and adopting appropriate interventions and personalized treatment plans to prevent the occurrence of adverse events.

Authors' Contributions

S.L. was involved in conceptualization, methodology, data curation, formal analysis, writing—original draft, and writing—review and editing. Q.Y. was involved in methodology, conceptualization, and writing—review and editing. Y.J. was involved in conceptualization, methodology, writing—review and editing, and supervision. M.X. and J.Z. were involved in methodology and literature screening. Y.W. was involved in writing—review and editing, and supervision. R.D. was involved in data extraction and analysis. C.W. was involved in methodology, data extraction and analysis, and writing—review and editing. Z.Y. was involved in writing—review and editing.

Author Disclosure Statement

The authors report no conflicts of interest.

Funding Information

The work was supported, in part, by the West China Nursing Discipline Development Special Fund Project, Sichuan University (HXHL19035).

Supplementary Material

Supplementary Data

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