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Regular paper

HIV infection and risk of heart failure: A meta-analysis and systematic review

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Background: Heart failure (HF) is commonly seen in patients with human immunodeficiency virus (HIV) infection. We aimed to evaluate the potential correlations of HIV infection and risk of HF, to provide evidence to the management of HIV and HF. Methods: We searched PubMed and other databases to identify prospective cohort studies on the risk of HIV infection and heart failure, we used Stata 13 software for Meta-analysis, and we calculated the hazard ratio (HR) values and 95% confidence interval (CI) values for the risks of HF in patients with and without HIV infections. Results: A total of five studies were included, with 8457 cases in the HIV-infection and 21917 cases in the non-HIV-infection group. Meta-analysis results showed that HIV infection can increase the risk of HF by 48% (HR=1.48, 95% CI1.31~1.67). Subgroups analyses by HIV-1 RNA viral load, CD4+ cell count, and study population also favored the overall results, and the research heterogeneity mainly come from the group of veterans in the research population. Conclusions: HIV infection is one of the risk factors for HF, which can increase the risk of heart failure, early preventions and interventions are needed for those populations.

Keywords: HIV, heart failure, AIDS, treatment; prevention

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Abbreviations: AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; 95% CI, 95% confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; WHO, World Health Organization

BACKGROUND

Acquired immunodeficiency syndrome (AIDS) is an acquired immunodeficiency syndrome caused by the human immunodeficiency virus (HIV). HIV destroys CD4+ T lymphocytes in a large amount, so that the body loses its immune function, causes a variety of opportunistic infections or tumors, and causes death (Jabłonowska *et al.*, 2021). Globally, there are at least 36.9 million HIV-infected people, and the trend is increasing year by year (Ashwitha *et al.*, 2021). It is reported that there were 36.9 million HIV respondents in the world in 2018, and 56.19% of the infected people received HIV antiretroviral therapy (ART) (Tabler *et al.*, 2021). HIV infection has been recognized by the World Health Organization (WHO) as an important public health event worldwide (Hurt *et al.*, 2017). The prevention and treatment of HIV is an important focus of current medical workers.

In recent years, the ART have successfully prolonged the life expectancy of HIV-infected persons, transitioning them from the field of terminal illness to the field of chronic diseases, and HIV-infected patients are becoming aging (Jackson-Best & Edwards, 2018). In high-income countries and developing countries, 55.12% of the deaths from HIV infections are related to non-HIV infections, especially cardiovascular diseases (37.10%), respectively (Cilliers *et al.*, 2019). Studies (Kanwugu & Adadi, 2021; Cotte *et al.*, 2021) have shown that 80% of cardiovascular diseases occur in low- and middle-income countries, and the risk of cardiovascular diseases for people with HIV infection is approximately 2.13 times that of the general population. Heart failure (HF) is a complex clinical syndrome that can lead to increased patient mortality and readmission (Czuczman *et al.*, 2021). It is one of the most important cardiovascular diseases, but non-cardiovascular diseases can also cause HF. In recent years, there have been a large number of epidemiological studies (Hsue & Waters, 2017; Hsue & Waters, 2019; Toribio *et al.*, 2019) on HIV infection and the risk of HF at home and abroad. It has been suspected that HF is related to HIV infection. However, the relationship between HIV infection and the risk of HF has not been fully elucidated. Therefore, it is necessary to conduct a meta-analysis and systematic review of prospective cohort studies on HIV infection and HF risk at home and abroad, to provide evidence-based evidence for the epidemiological study of HIV infection, and to provide insights into the prevention and treatment strategies for HIV-related HF.

METHODS

Literature search

We combined the subject word and free word to search the Cochrane Library, Embase, PubMed, China Biomedical Literature Database, China Knowledge Network, Wanfang Database, and Weipu Chinese Science and Technology Journal Database. The search time limit is until November 15, 2020. The search terms used included: HIV infection, acquired immunodeficiency syndrome, human immunodeficiency virus infection, and heart failure. We adjusted the search strategy according to each database, and combined subject words and free words for databases searching, and we carried out relevant search and traceability on the references of relevant important documents.

Table 1. The characteristics and NOS scores of included studies

Study	Area	HIV infection group	No-HIV infection group	Duration of follow-up(years)	Corrected factors	NOS score
Butt 2011	Pittsburgh, USA	2391	6095	7.5	Age, race, hepatitis C, body mass index, blood lipids, hypertension, diabetes, smoking, alcohol abuse, cocaine abuse, HIV-1 RNA virus load, CD4+ cell count, combined antiviral therapy	9
White 2015	Pittsburgh, USA	21850	45728	6.5	Age, gender, race, body mass index, high blood pressure, diabetes, lipid levels, statins, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking, alcohol abuse, cocaine abuse, hepatitis C	9
Freiberg 2017	Nashville, USA	31523	66492	8.5	Age, gender, race, high blood pressure, blood lipid level, lipid level, smoking, hydroxymethylglutaryl-CoA reductase inhibitor use, hepatitis C, renal function, body mass index, substance abuse, atrial fibrillation, severe Depression, HIV-1 RNA viral load, CD4+ cell count	8
Feinstein 2018	Chicago, USA	4640	4250	16.5	Age, gender, race, body mass index, high blood pressure, diabetes, hepatitis C, coronary heart disease, CD4+ cell count	9
Yen 2019	Taiwan, China	24153	96612	12	Age, gender, income level, place of residence, coronary heart disease, dyslipidemia, diabetes, chronic kidney disease, hypertension, malignant tumor, cerebrovascular disease, sleep apnea, hepatitis C	8

Literature inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were (1) Research population: People who mainly explored the risk of HIV infection and HF; (2) Exposure factor: HIV infection; (3) Control group: non-HIV infection; (4) Outcome indicators : The occurrence of HF; (5) study design: a publicly published prospective cohort study; (6) languages: Chinese and English; (7) the adjusted hazard ratio (HR) value and its 95% confidence interval (95% CI) could be obtained. The exclusion criteria of this study were (1) literature for which full text or data could not be extracted; (2) cross-sectional survey, case-control study, and review; (3) the study included other exposure factors and other outcome endpoints; (4) The patient had HF at the time of HIV infection.

Literature selection and quality evaluation

Two researchers independently screened the literature according to the established inclusion and exclusion criteria, and evaluated the literature quality according to the Newcastle-Ottawa Scale (NOS) (Stang, 2010), a non-randomized research quality evaluation tool. If there was a dispute between the two parties, it would be evaluated by a third-party researcher After confirming. The highest NOS score was 9 points, 0 to 3 points were rated as low quality, 4 to 6 points were rated as medium quality, and 7 to 9 points were rated as high quality.

Statistical methods

All data were checked by two authors, and Stata 13.0 software was used to conduct meta-analysis of the included literature data, and the corrected HR was used as the combined effect indicator. The heterogeneity analysis adopted Q test and I^2 statistics. If $P>0.10$ and $I^2<50\%$, it would be considered that there was no heterogeneity, and the fixed effects model was adopted; if $P\leq0.10$, $I^2\geq50\%$, then it was taken that there was heterogeneity among the studies, and the random effects model was adopted. In addition, we conducted subgroup analysis according to the HIV-1 RNA viral load, CD4+ cell count, and different populations. In this present meta-analysis, $P\leq0.05$ indicated that the difference between the groups was statistically significant.

RESULTS

Study selection

A total of 136 articles were obtained from the preliminary search of the literature, and five prospective cohort studies (Butt *et al.*, 2011; White *et al.*, 2015; Freiberg *et al.*, 2017; Feinstein *et al.*, 2018; Yen *et al.*, 2019) were finally included in the meta-analysis. The process of study selection was presented in Fig. 1.

Characteristics and quality assessment of included studies

Amongst the five included studies, a total of 303734 patients were enrolled, of which 84557 were exposed to HIV infection and 219177 were non-HIV infected patients, all of which were large-sample studies with long

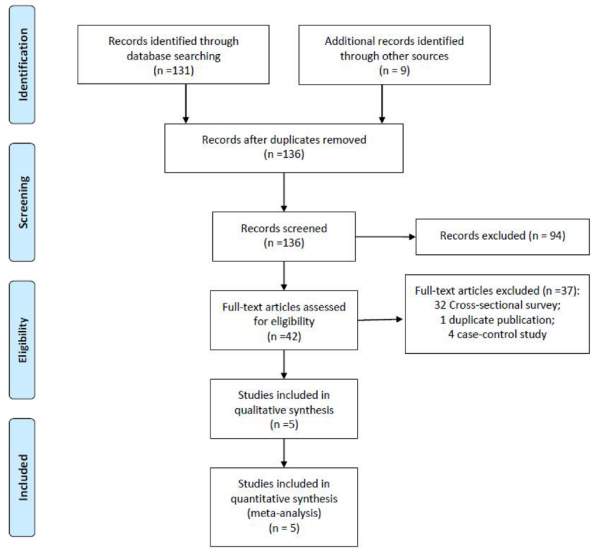

Figure 1. The flow chart of study selection

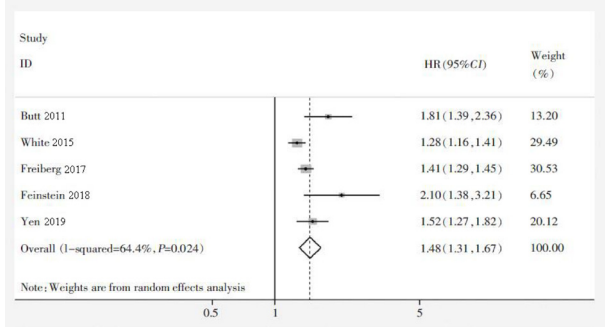

Figure 2. The Forest plot of HF risks between patients with HIV and no-HIV infection

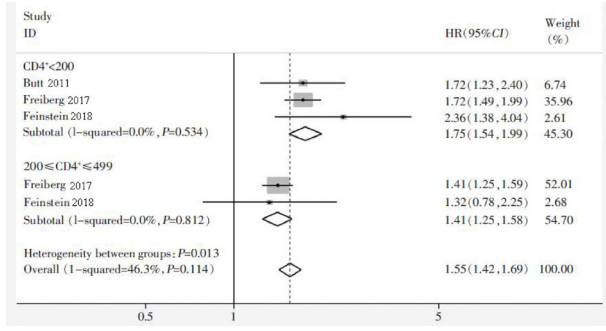

Figure 4. Forest plot of HF in HIV patients with different CD4+ cell count

follow-up of 6 to 17 years. The NOS score of three studies was 9 points, the NOS score of two studies was 8 points, and the quality evaluation results were all high-quality. The basic information and NOS scores of the included studies were shown in Table 1.

Meta analyses

The heterogeneity of the included studies was significant (I^2=64.4%, P=0.024), a random effects model was used for meta analysis. The results showed that HIV infection can increase the risk of HF by 48% compared with those people with no HIV infection (HR=1.48, 95 %CI:1.31~1.67, P<0.00, Fig. 2).

Subgroup analyses

The subgroup analysis was carried out according to the HIV-1 RNA viral load. As presented in Fig. 3, the results showed that when the HIV-1 RNA viral load was <500 copies/mL, the synthesized HR=1.62 (95% CI: 0.9 1~2.86) with no statistical difference (P=0.10). When HIV-1 RNA viral load was ≥500 copies/mL, the synthesized HR=1.79 (95% CI:1.21~2.64) with statistical difference (P=0.003).

We conducted subgroup analyses according to the CD4+ cell count. As shown in Fig. 4, the results showed that HR=1.75 in $CD4^+$ cell count <200 cells/mm^3 group (95% CI: 1.54~1.99) and HR=1.41 in the $CD4^+$ cell count ($200 \leq CD4^+ \leq 499$ pcs/mm^3) group (95% CI: 1.25~1.58) with statistical difference (all P<0.001).

In addition, we conducted a subgroup analysis according to the source of the study population. As presented in Fig. 5, the results showed that the HF risk of general population (HR=1.68, 95% CI: 1.25~2.26) was higher

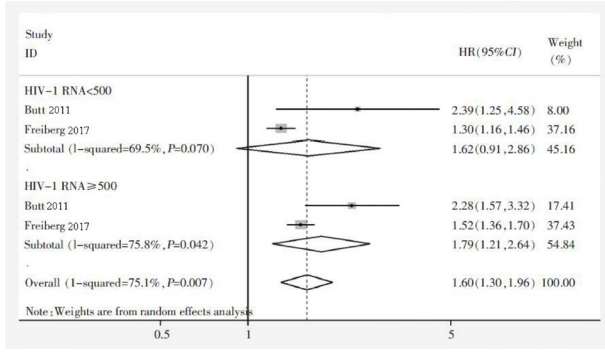

Figure 3. Forest plot of HF in HIV patients with different HIV-1 RNA viral load

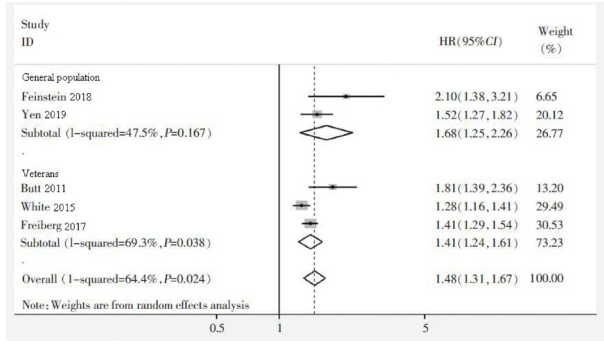

Figure 5. Forest plot of HF in HIV patients with different populations

than that of veterans (HR=1.41, 95% CI:1.24~1.61, all P<0.001).

DISCUSSIONS

HF is caused by abnormal changes in the structure and function of the heart due to a variety of reasons, leading to impaired ventricular systolic and diastolic function (Sinha & Feinstein, 2020). It is a serious or late stage of various heart diseases, and its clinical manifestations are dyspnea, fatigue, and fluid retention (Yen *et al.*, 2018). Among the many causes of HF, the most common cause is primary myocardial damage and abnormalities, but many non-cardiovascular diseases may also cause HF (Yen *et al.*, 2019). In recent years, the prevalence and mortality of HF have increased. Controlling HF risk factors and actively treating asymptomatic left ventricular systolic dysfunction can delay or even prevent the occurrence of HF (Sinha & Feinstein, 2021). Therefore, it is recommended to follow the HF guidelines for diagnosis and treatment, and to identify the cause of HF in patients and control risk factors, and take specific or targeted treatment as soon as possible, which will help improve the survival and quality of life of patients (Neilan *et al.*, 2020). With the effective ART and the prolonged lifespan of HIV-infected persons, HF becomes more chronic and insidious, making it more difficult to diagnose and treat HIV-infected comorbidities (Liu *et al.*, 2020). This study shows from an evidence-based perspective that HIV infection is a non-cardiovascular risk factor for HF, which can provide new ideas for the prevention and targeted treatment of HIV-related HF.

This study conducted a meta-analysis of the correlation between HIV infection and the risk of HF. The results showed that HIV infection can increase the risk of

HF by 48%. Therefore, HIV infection is one of the risk factors for HF. Research results (Niforatos *et al.*, 2020; Dash *et al.*, 2020; Conic *et al.*, 2020) show that the risk of HF in HIV patients is 1.50 times that of uninfected people, which is similar to the results of this meta-analysis. Previous study (Al-Kindi *et al.*, 2016) using case-control studies have shown that the risk of HF in HIV-infected patients is 1.64 times that of the control group, and the risk of HIV-related HF is the highest among young patients and women. At the same time, studies (Thiara *et al.*, 2015; Holloway *et al.*, 2013) have found that HIV infection can significantly increase the risk of HF-related readmissions. Therefore, the early alert of HF and interventions are needed for those patients with HIV infection.

At present, the mechanism by which HIV infection increases the risk of HF has not been fully elucidated. Studies (Diaz-Zamudio *et al.*, 2015; Ntusi *et al.*, 2016) believe that the pathophysiology of HIV-related HF is multifaceted. Increasing evidence (Savvoulidis *et al.*, 2019) indicates that HIV-related myocardial fibrosis and cardiac steatosis may be two important reasons for the high risk of HF in HIV-infected patients. Studies (Abelman *et al.*, 2019; Steverson *et al.*, 2017) have shown that compared with the control group, the contractile function of HIV-infected patients is significantly decreased, and the lipid level and fibrosis index in the myocardium are increased, and the lipid level in the myocardium is positively correlated with ART time and visceral fat mass. Myocardial fibrosis can reduce ventricular compliance and accelerate the progression of HF (Ng *et al.*, 2014). This may be an important cause of HIV-related HF. In addition, studies (Brozzi *et al.*, 2020; Moayedi & Walmsley, 2020) found that the myocardial lipid value of HIV-infected people was 47% morethan that of HIV-infected people. Animal experiments have shown that excessive lipids in cardiomyocytes can produce lipotoxic intermediates, cause cell apoptosis, and lead to the occurrence of HF. In addition, ART may be related to the increased risk of cardiovascular disease (Alvi *et al.*, 2019), but the research on the relationship between ART and HF development is limited, and further research is needed.

This study has certain limitations. First of all, this study only included published Chinese and English literature, and we did not search for other languages and gray literature. There may be incomplete literature collection. Secondly, among the 5 articles included, 4 are from the United States, which may have geographic limitations. In addition, the included studies have different corrections for confounding factors, and multiple confounding factors may have a certain influence on the results. However, our research has shortcomings. We will take into account the division of patients not only into VL<500 copies but also less and more than 10 log copies/ml, CD4 value less and more than 500/mm^3 and using Framingham Risk Score in a meta-analysis. Smoking, lipid levels, race, gender, HCV co-infection and use of cart were considered a breakdown by factors other than HIV infection itself. Therefore, the results of this meta-analysis need to be further verified by larger scale, more samples, multi-center, and high-quality researches.

CONCLUSIONS

In conclusion, the results of this meta-analysis have found that HIV infection can increase the risk of HF by 48%, indicating that HIV infection may be one of the risk factors for HF. Medical staff should pay attention to the HIV infection treatment and the prevention of HF risk factors recommended by the guidelines (Manmathan *et al.*, 2020; Janjua *et al.*, 2017). People who are already infected with HIV can choose to be screened for HF, and if appropriate, they should be screened for HIV in new-onset HF patients for early diagnosis and early treatment (Feinstein *et al.*, 2019). Furthermore, it is recommended to develop relevant tools to stratify the risk of HF among HIV-infected persons, screen out high-risk groups, and provide early intervention for the prevention and treatment of HF among HIV-infected persons.

Declarations

Ethical approval. This meta-analysis was approved by the institutional review board, the need for informed patient consent for inclusion was waived.

Availability of data and material. The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest. None

Funding. None

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