

CD4/CD8 ratio can predict the risk of septicemia in HIV infection

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Research

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Abstract

Objectives There are few reports about the effect of CD4/CD8 ratio on the infection of HIV with sepsis. Here we analyze the correlation between the baseline CD4 / CD8 ratio and the pathogenic spectrum of AIDS patients with sepsis and the effect on the prognosis. **Methods** A retrospective analysis study(May 2010 to June 2017) was carried out using routinely collected data from HIV with sepsis at Chengdu Public Health Clinical Center. The values of clinical data, CD4/CD8 ratio and pathogenic spectrum were evaluated in the study. **Results** Among 322 positive blood culture HIV patients with septicemia, 208 (64.60%) were fungal infection, 64 (19.90%) were gram-negative bacterial infection, 47 (14.60%) were Gram-positive bacterial infection, and 3 (0.90%) were fungal and bacterial infection. Among the fungal infections, Cryptococcus was found in 152 cases (73.08%), followed by cyanobacteria marneffeii in 53 cases (25.48%) and Candida in 3 cases (1.44%); Salmonella in 38 cases (59.38%) and Escherichia coli in 17 cases (26.56%); Staphylococcus in 28 cases (59.58%) were positive. When the CD4 / CD8 ratio ≤ 0.3 , the risk of sepsis infection was significantly higher than that of CD4 / CD8 > 0.3 . The lower the ratio of CD4 / CD8 (< 0.1), the higher the risk ($\chi^2 = 188.968, P = 0.00$). When the ratio of CD4 / CD8 was less than or equal to 0.3, the incidence of fungal infection was significantly increased (67.14%), and the incidence of gram-negative bacterial infection (18.02%) was significantly higher than that of Gram-positive bacterial infection (13.78%), ($\chi^2 = 283.277, P = 0.00$); when the ratio of CD4 / CD8 was greater than or equal to 0.3, the incidence of septicemia was significantly reduced, and there was no significant difference between the original spectrum of infection ($\chi^2 = 1.750, P = 0.42$) 286 patients (88.82%) were discharged after treatment, 36 patients (11.18%) died after treatment. **Conclusions** In Chengdu of China, the main pathogens of septicemia in AIDS patients are fungi, including Cryptococcus and cyanobacteria marneffeii, next are bacteria containing Salmonella and Staphylococcus. The lower the ratio of CD4 / CD8, the higher the risk of infection with sepsis, the higher the risk of multiple infection, and the higher the mortality. Therefore, we think that CD4 / CD8 ratio is an important risk factor for HIV infection with septicemia. We should pay more attention to role of the CD4 / CD8 ratio in clinical work, and it may help us predicting progress of HIV disease.

Introduction

AIDS is an infectious disease caused by HIV infection, and it also be called acquired immune deficiency syndrome. HIV virus in the body infects immune cells, especially CD4 + T lymphocytes, which can activate and induce cell death, leading to progressive decrease of CD4 + T lymphocytes. CD4 cell count which is used a measure of human immune function decreased, leading to HIV patients with lower immune function, thus prone to opportunistic infection and tumor. However, HIV infection does not destroy all T cell subsets, and CD8 + T cells (cytotoxic T cells) may have obvious activation and expansion. Therefore, more and more scholars begin to pay attention to cd8 T cell count and CD4 / CD8 ratio in HIV patients. The purpose of this study is to analyze the correlation between CD4 / CD8 ratio and the distribution of pathogenic spectrum of AIDS patients with sepsis and its influence on the prognosis of patients, to provide further reference for the diagnosis and treatment of such diseases.

Materials And Methods

322 HIV/AIDS subjects were included in a retrospective case-control study. Data was obtained from histories of HIV/AIDS patients who were hospitalized at the Chengdu public health clinical center in the period from May 2010–June 2017. Blood culture tests were carried out according to aseptic operation principle before antibiotic treatment in all patients after admission. The Peripheral blood samples were collected to used to obtain the CD4 cell absolute count and CD8 cell absolute count by FACS 2 Calibur flow cytometry (BD, Co.Ltd ,USA). SPSS 26.0 was used for statistical analysis and Nonparametric Test was used, $P < 0.05$ was considered statistically significant.

Results

Among 322 AIDS patients with septicemia, 267 were male, 55 were female; the youngest was 2 years old, the oldest was 79 years old, the median age was 39 years old; 229 (71.10%) were heterosexual, 71 (22.00%) were same-sex, 10 (3.10%) were drug addicts, 3 (0.90%) were blood transfusion, 1 (0.30%) was mother infant, and 8 (2.50%) were other unknown causes(see table1).

Pathogenic spectrum analysis Among 322 AIDS patients with septicemia, 208 (64.60%) were fungal, 64 (19.90%) were gram-negative, 47 (14.60%) were gram-positive, and 3 (0.90%) were fungal and bacterial. Among the fungal infections, *Cryptococcus neoformans* was 152 (73.08%), followed by *Cyanobacteria marneffeii* 53 (25.48%) and *Candida* 3 (1.44%); Gram-negative bacteria were mainly *Salmonella* in 38 cases (59.38%) and *Escherichia coli* in 17 cases (26.56%), followed by 3 cases (4.68%) of *Pseudomonas aeruginosa* and 6 cases (9.38%) of other rare bacteria (*Klebsiella pneumoniae*, *Citrobacter freundii* and *Francisella tularensis* and so on); 28 cases (59.58%) of Gram-positive bacteria were *Staphylococcus*, then there were 4 cases of *Rhodococcus* (8.51%), 6 cases of *Corynebacterium* (12.76%), 4 cases of *Streptococcus* (8.51%), 5 cases of rare bacteria (*Bacillus subtilis*, *Nocardia asteroides*, *Cellulomonas*, etc.) (10.64%).

Correlation analysis between CD4 / CD8 ratio and pathogenic spectrum of AIDS patients with sepsis 8 out of 322 AIDS patients with sepsis had data lossing. Among the other 314 patients, 69.11% (217 / 314cases) had a CD4 / CD8 ratio ≤ 0.1 ; the ratio of CD4 / CD8 > 0.1 and ≤ 0.3 accounted for 21.02 (66 / 314 cases); the ratio of CD4 / CD8 > 0.3 accounted for 9.87% (31 / 314 cases).When the CD4 / CD8 ratio ≤ 0.3 , the risk of sepsis infection was significantly higher than that of CD4 / CD8 ratio > 0.3 . The lower the CD4 / CD8 ratio (< 0.1), the higher the risk ($\chi^2 = 188.968$, $P = 0.00$). When the CD4 / CD8 ratio was less than or equal to 0.3, the incidence of fungal infection increased significantly (67.14%), and the incidence of gram-negative bacterial infection (18.02%) was significantly higher than that of Gram-positive bacterial infection (13.78%), ($\chi^2 = 283.277$, $P = 0.00$); When the CD4 / CD8 ratio was more than 0.3, the incidence of sepsis was significantly reduced, and there was no significant difference between the pathogenic spectrum of infection ($\chi^2 = 1.750$, $P = 0.42$)(see table3).In this study, the CD4 / CD8 ratio in patients with fungus and bacteria was ≤ 0.1 , suggesting that the lower the ratio of CD4 / CD8 in patients, the higher the probability of multiple infection in patients.

Prognosis analysis Among 322 AIDS patients with septicemia, 286 (88.82%) were discharged from the hospital after anti-viral, anti-infective and symptomatic treatment, 36 (11.18%) died after active treatment. In the dead patients, the CD4 / CD8 ratio was absent in 2 cases. It was found that 97.06% (33 / 34) of the dead patients with CD4 / CD8 ratio ≤ 0.3 and 61.76% (21 / 34) of the dead patients with CD4 / CD8 ratio ≤ 0.1 (see table 2). Therefore, we consider that when the CD4 / CD8 ratio ≤ 0.3 , the mortality of AIDS patients with sepsis increased significantly. The lower the ratio of CD4 / CD8, the higher the mortality.

Discussion

Our study revealed a correlation between baseline CD4 / CD8 ratio and HIV associated sepsis. We observed that the lower the CD4 / CD8 ratio, the higher the risk of septicemia for AIDS patients. After HIV enters the body, CD8 T cells will be more reactive before the CD4-T cells are reduced, resulting in a lower CD4 / CD8 ratio [1]. The replication of HIV virus in vivo leads to the decrease of CD4 T cells and the decrease of CD4/CD8 ratio. As for the study of CD4/CD8 ratio, the prevailing view is that the inversion of CD4/CD8 ratio is an indicator of immunosenescence and is associated with increased morbidity and mortality, also it could affect the immune reaction to

pathogens during their primary infection [2–4]. In HIV negative patients, the lower the CD4 / CD8 ratio, the higher the incidence of chronic diseases (such as diabetes) and malignant tumors [5]; and it can also predict the morbidity and mortality in older people [6–7]. For HIV positive patients, starting early combination antiretroviral therapy (cART) is recommended to reduce the duration of high viremia exposure and prevent HIV-related diseases and mortality. Also it can increase CD4 T cell counts [8], promote immune reconstitution and restore CD4 / CD8 ratio (≥ 1) [9]. The later the cART is started, the less likely it is to normalize the CD4 / CD8 ratio [10]. However, Mutoh, Y et al. found that even after long-term successful cART treatment, the CD4 cell count, CD4 percentage and CD4 / CD8 ratio of HIV patients with long-term viral load inhibition were difficult to recover to the level of healthy people [11]. Therefore, it is confirmed that the CD4 / CD8 ratio is an indicator of immune system attenuation, but it has not been reported in HIV patients with sepsis.

In our study, we found that there was a significant positive correlation between HIV infection with sepsis and the CD4 / CD8 ratio. When the ratio of CD4 / CD8 ≤ 0.3 , the risk of sepsis infection was significantly higher than that of CD4 / CD8 > 0.3 . The lower the CD4 / CD8 ratio (< 0.1), the higher the risk of infection. After the occurrence of septicemia, the prognosis of most patients was improved significantly after timely and effective treatment. When the ratio of CD4 / CD8 ≤ 0.3 , the mortality of AIDS patients with sepsis increased significantly. And the lower the ratio of CD4 / CD8, the higher the mortality. In addition, it has been reported that the risk of non-AIDS is higher when the ratio of CD4 / CD8 is less than 0.45 [12]. Therefore, our study showed that when the ratio of CD4 / CD8 ≤ 0.3 , the risk of sepsis infection and death in HIV patients will increase. The ratio of CD4 / CD8 can be used as a biomarker to predict the risk and prognosis of sepsis infection in HIV patients.

At the same time, we also found that in HIV patients with septicemia, when the ratio of CD4 / CD8 \leq 0.3, the patients were mainly infected by fungi, followed by gram-negative bacteria and Gram-positive bacteria. When the ratio of CD4/CD8 was more than 0.3, the infection of septicemia was significantly reduced, and there was no significant difference between the original spectrum of infection. *Cryptococcus neoformans* and *cyanobacteria marneffeii* were the main fungal infections; and the infection of Gram-negative bacteria was mainly *Salmonella* and *Escherichia coli*; *Staphylococcus* was the main Gram-positive bacteria. Remarkably, when the CD4/CD8 ratio \leq 0.1, the probability of multiple infection increased significantly. This is consistent with some studies which showed that HIV-infected patients with preoperative CD4 count \leq 200 cells/ μ L or CD4/CD8 ratio \leq 0.15 had overall higher postoperative sepsis morbidity[13]. These findings will help us to strengthen the awareness and vigilance of such diseases and accelerate the diagnosis and treatment of patients when we find patients with similar clinical characteristics in clinical work.

In conclusion, our study is the first to reveal the clinical significance of CD4 / CD8 ratio in HIV patients with sepsis. The lower the CD4 / CD8 ratio, the higher the risk of sepsis. When the CD4 / CD8 ratio \leq 0.1, the risk of multiple infections and the mortality increased. Therefore, our data shows that the CD4 / CD8 ratio is an important risk factor for HIV infection with sepsis, which suggests that we should pay attention to the effect of CD4 / CD8 ratio on sepsis infection. These findings may have a positive effect on the clinical diagnosis and treatment of HIV with sepsis.

Declarations

Ethics And Consent Statements

The study was approved by the Ethics Committee of *Public Health Clinical Center of Chengdu*.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

Authors' contributions

ZY, CL, ZR, WY, WZ collected and provided the data. ZY, ZP extracted data and cleaned data. ZY, ZP analyzed the data. ZY, ZP were major contributors in writing the manuscript. ZY and ZP were the first co-authors. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline Characteristics

Category	Median	Frequency(%)
Sex		
Male		267(82.90%)
Female		55(17.10%)
Age(2-79years)	39	
Opportunistic infection		
Fungus		208(64.60%)
Gram-positive bacteria		47(14.60%)
Gram-negative bacteria		64(19.90%)
Fungus+Bacteria		3(0.90%)
Infection Pathway		
Mother-baby		1(0.30%)
Heterosexual		229(71.10%)
Homosexual		71(22.00%)
Injecting drug		10(3.10%)
Blood transfusion		3(0.90%)
Others		8(2.50%)
Prognosis		
Cured		286(88.82%)
Dead		36(11.18%)

Table2 relationship between CD4/CD8 Ratio and prognosis

	prognosis	
CD4/CD8 Ratio	Cured(6data missing)	Dead(2 data missing)
≤0.1	197(70.36%)	21(61.76%)
≤0.3	249(88.93%)	33(97.06%)
>0.3	31(11.07%)	1(2.94%)

Table3 CD4/CD8 Ratio and pathogenic spectrum analysis

CD4/CD8 Ratio	fungus	Gram-positive bacteria	Gram-negative bacteria	Fungus+Bacteria	<i>P</i> values
$\leq 0.3(\leq 0.1)$	190(153)	39(25)	51(36)	3(3)	0.00
>0.3	13	8	10	0	0.42
<i>P</i>values					0.00