Virologica Sinica (2018) 33:227–233
https://doi.org/10.1007/s12250-018-0028-z

www.virosin.org
www.springer.com/12250

RESEARCH ARTICLE

Evaluation of Epstein-Barr Virus Salivary Shedding in HIV/AIDS Patients and HAART Use: A Retrospective Cohort Study

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Received: 25 October 2017 / Accepted: 9 March 2018 / Published online: 13 April 2018

Abstract

Little data is available on the evaluation of the occurrence rates of Epstein-Barr virus (EBV) in saliva and relationship with highly active antiretroviral therapy (HAART) use in HIV/AIDS patients in China. We conducted a retrospective cohort study of EBV serological tests for HIV/AIDS patients who were treated in the hospitals for infectious diseases in Wuxi and Shanghai, China from May 2016 to April 2017. The EBV-seropositive samples were identified by ELISA. EBV-specific primers and probes were used for the quantitative detection of viral DNA from saliva via quantitative real-time polymerase chain reaction. CD4 cell counts of the HIV/AIDS patients were detected by a flow cytometry. A total of 372 HIV/AIDS patients were ultimately selected and categorized for this retrospective cohort study. For EBV IgG and IgM, the HIV/AIDS HAART use (H) and non-HAART use (NH) groups had significantly higher seropositive rates than the HIV-negative control group. The HIV/AIDS (NH) group had the highest seropositive rate (IgG, 94.27%; IgM, 68.98%) and the highest incidence of EBV reactivation or infection. For salivary EBV DNA-positive rates and quantities, the HIV/AIDS (H) (73.69%) and the HIV/AIDS (NH) (100%) groups showed significantly higher values than the HIV-negative control group (35.79%, > twofold). Further, the salivary EBV DNA-negative population had significantly higher CD4 cell counts than the EBV DNA-positive population in the HIV/AIDS (H) group and the HIV/AIDS (NH) groups. Thus, HAART use is beneficial in decreasing the EBV salivary shedding in HIV/AIDS patients and indirectly decreases EBV transmission risk.

Keywords Epstein-Barr virus (EBV) · Human immunodeficiency virus (HIV) · Saliva · HIV/AIDS · Highly active antiretroviral therapy (HAART)

Introduction

The Epstein-Barr virus (EBV) is a universal, opportunistic, infectious virus that establishes lifelong persistent infection in the oral cavity and is intermittently shed in the saliva (Guidry *et al.* 2017). Nearly 95% of people worldwide are infected by this virus (de-The *et al.* 1975). EBV infection is often acquired during infancy and childhood through oral secretions, intimate contact, or the exchange of saliva from an infected person. Many people can carry and periodically spread the virus throughout their lives. Blood can also

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serve as a source of transmission of the virus; however, this occurrence is rare (Hanley *et al.* 2009).

EBV can infect B lymphocytes and establish viral latency (Guidry *et al.* 2017; Hanley *et al.* 2009). EBV infection is strongly associated with several malignancies of both B cell and epithelial cell origins, especially in the immunodeficient population. Approximately 200,000 new patients with EBV-associated malignancies are reported annually worldwide (Cohen *et al.* 2011). EBV as a nasopharyngeal pathogen has been classified as a human carcinogen (Group 1) by the International Agency for Research on Cancer (Shin *et al.* 2016). Considering that many infection-related cancers are preventable, particularly those associated with HIV-1, hepatitis B virus (HBV), hepatitis C virus, and liver fluke infection, such chronic infections are responsible for 17%–28% of the overall cancer incidence or mortality in China, Japan and Korea (Shin *et al.* 2016). Infant immunization with the HBV vaccine has significantly decreased the incidence of chronic HBV hepatitis; however, vaccines for important infectious agents, such as EBV, still warrant further investigation.

EBV prevalence is age-specific, occurring primarily in children under 10 years old in China. Only 19.22% and 20.62% of children were found to be antibody-negative in the North and in the South of China, respectively (Xiong *et al.* 2014), and only 37% of university students in America were antibody-negative (Balfour *et al.* 2013). Thus, young people are at risk for EBV primary infection. Relatively, these vulnerable people have a higher risk of contact with HIV/AIDS patients in social activities. Therefore, this study aimed to investigate the risk of EBV shedding in HIV/AIDS patients and how preventive measures affect EBV transmission and disease progression.

The goal of this study was to investigate the positive rate of EBV co-infection with HIV. As persistent infection with EBV is the first step of EBV-associated malignancies and EBV transmission (Shin *et al.* 2016), there is a need for a better understanding of the relationship between HIV therapy and EBV infection. Therefore, we conducted a retrospective study to analyze EBV serological features and the salivary DNA quantity status in different populations to provide evidence and serve as a reference for the prevention and treatment of EBV infection or reactivation.

Materials and Methods

Study Design, Participants, and Inclusion Criteria

This retrospective cohort study included HIV-infected patients who were treated in hospitals for infectious diseases in Wuxi and Shanghai, China from May 2016 to April 2017. The HIV/AIDS patients had clear disease histories recorded in the Hospital Information System (HIS) database, including gender, HIV confirmation date, CD4 counts, viral load, diagnosis date, inspection reports, HAART status, HAART initiation date, duration of HAART, sexual orientation, and complications. The HIV-negative controls were recruited from people who received daily health physical examinations and had clear basic information in the HIS database. The patients with detailed personal information, good treatment adherence, were not undergoing HAART, and had qualified samples were all included in this study.

Sample Collection

EDTA-anticoagulated plasma and non-stimulated whole saliva from the patients were collected by following the Biological Specimen Bank work-flow and were stored separately in − 80 °C until use. The detailed clinical information of these samples was recorded.

Measurement of Serum EBV-Specific IgG and IgM, Saliva EBV DNA Quantity and Blood CD4 Cell Counts

Plasma samples for EBV-specific IgG and IgM measurements were analyzed using commercial ELISA products (Medell, China). The procedures were conducted according to the manufacturer's instructions. EBV DNA was extracted from 200 μL of saliva using the MiniBEST Viral RNA/DNA Extraction Kit Ver.4.0 (Takara, China) following the manufacturer's instructions. EBV DNA and HIV RNA were detected with the appropriate primers and probes as described previously (Vargas-Meneses *et al.* 2015). Quantitative real-time PCR (qRT-PCR) was performed using the Premix Ex Taq^{TM} (Probe qPCR) and One Step PrimeScript RT-PCR Kit (Perfect Real Time) (Takara, China). Blood CD4 cell counts were analyzed by the Flow Cytometry Counter in the local hospitals' laboratories of Wuxi and Shanghai.

Statistical Analysis

The data were analyzed by GraphPad Prism 5.0. The final data are presented as the mean ± standard deviation (SD). Comparisons between two groups were analyzed by Student's *t*-test and the Mann-Whitney U test and comparisons among more than three groups were analyzed by one-way ANOVA with Newman-Keuls multiple comparison analysis. The P values < 0.05 were considered statistically significant.

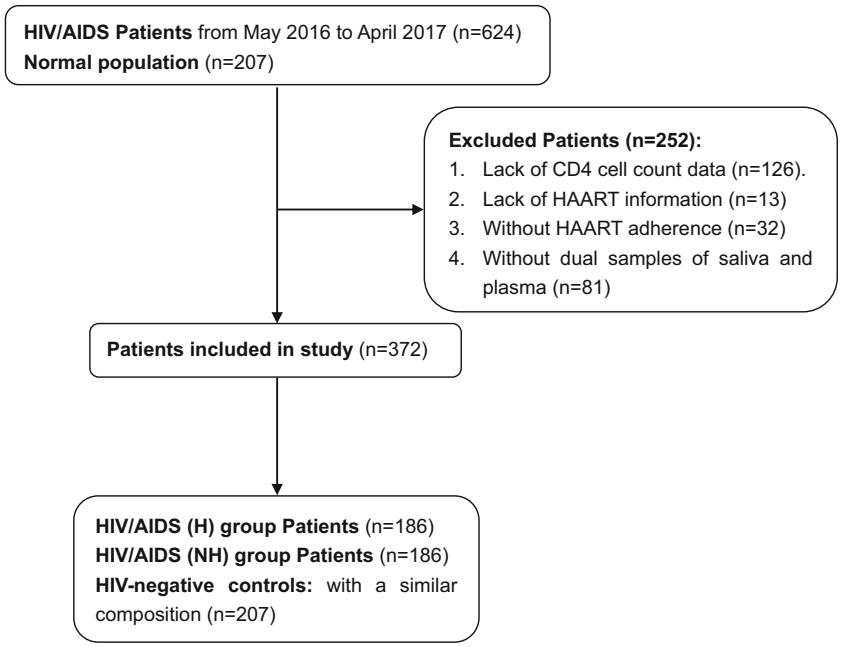

Fig. 1 Study profile.

Results

Participant Characteristics

EBV usually establishes lifelong persistent infection and latency; 50% of children under 5 years of age are infected, and up to 90% of adults acquire the infection. Therefore, the age proportion in each group is important for the analysis of EBV primary infection or reactivation (Cohen *et al.* 2011; Porter *et al.* 1969). From May 2016 to April 2017, 831 patients were evaluated, and 252 patients were excluded based on the exclusion criteria. Among the evaluated patients, 186 were enrolled in the HIV/AIDS HAART use (H) group, 186 were enrolled in the HIV/AIDS non-HAART use (NH) group, and 207 were enrolled in the HIV-negative control group (Fig. 1). No differences were observed in the average age ($P = 0.291$, analyzed by Mann–Whitney U test), gender, marital status, or infection route between the HIV/AIDS (H) and the HIV/AIDS (NH) groups (Table 1).

Seroprevalence of EBV

We analyzed the seroprevalence of EBV in the HIV/AIDS patients and the HIV-negative controls. For EBV IgG and IgM, we observed a significantly higher proportion of patients positive for EBV IgG in the HIV/AIDS (H) and HIV/AIDS (NH) groups than in the HIV-negative control group (Fig. 2A). However, EBV IgM displayed a significantly higher positive rate in the HIV/AIDS (NH) group than in the HIV/AIDS (H) group (68.98% ± 2.80% vs. 52.68% ± 6.07%, $P < 0.001$), but both HIV/AIDS (H) and (NH) groups showed significantly higher values than the HIV-negative control group (68.98% ± 2.80% and 52.68% ± 6.07% vs. 46.69% ± 2.40%, $P < 0.001$, respectively). An EBV IgG-positive result represents past infection and an IgM-positive result represents EBV primary infection or reactivation, according to a previous study (Fourcade *et al.* 2017). Notably, the HIV/AIDS (NH) group's IgM/IgG ratio (0.74 ± 0.03) was significantly higher than that of the HIV/AIDS (H) group (0.59 ± 0.02, $P < 0.001$) and the HIV-negative control groups (0.57 ± 0.03, $P < 0.001$) (Fig. 2B).

Salivary EBV DNA

To test whether EBV salivary shedding, which can increase the risk of transmission, was significantly higher in the HIV/AIDS (NH) group than in the HIV-negative controls, salivary EBV DNA was detected by qRT-PCR. Surprisingly, the salivary EBV DNA-positive rate was 100% in the HIV/AIDS (NH) group. The HIV/AIDS (H) group (76.83% ± 0.15%) had a relatively higher EBV DNA-positive rate than the HIV-negative control group (35.37% ± 0.31%). The EBV DNA-positive rate was nearly twofold higher in the HIV/AIDS groups than in the HIV-negative control group (Fig. 3A). Moreover, the HIV/AIDS groups had a significantly higher viral load of EBV

Table 1 Basic characteristics of the HIV/AIDS patients in this study.

Groups	HIV/AIDS (H)	HIV/AIDS (NH)	HIV-negative controls
Number of patients	186	186	207
Age (years)			
18–24	30	27	31
25–34	53	48	57
35–44	36	45	44
45–54	31	33	35
≥ 55	36	33	40
Mean age	38	34	37
Gender			
Male (%)	121 (65)	140 (75)	145 (74)
Female (%)	65 (35)	46 (25)	52 (26)
CD4 counts, cell/μL			
< 100 (%)	28 (15)	89 (48)	–
≥ 100 (%)	158 (85)	97 (52)	–
Median CD4 count	385	257	–
Viral load of HIV < 150 copies/mL (%)	125 (67)	0 (0)	–

"–" Means no data.

(≥ 100,000 copies/mL in saliva) when compared to the HIV-negative control group (Fig. 3B).

CD4 Cell Counts and Viral Load of HIV in HIV/AIDS Groups

The results revealed that HIV infection could increase the salivary viral positive rate and viral load of EBV. In contrast, HIV infection can increase the risk of acquiring HBV, with risk being inversely associated with CD4 counts (Liu *et al.* 2018; Kelly *et al.* 2018). The correlation between acquiring EBV infection and CD4 counts or HAART use in HIV-infected patients was poorly understood. Subsequently, we further investigated whether higher CD4 counts can reduce the risk of EBV primary infection or reactivation. HAART use has been demonstrated to help CD4 immune reconstitution in HIV/AIDS patients (Yao *et al.* 2013); in particular, HAART use in HIV/AIDS patients is likely critical for decreasing the risk for complications. We also analyzed the CD4 cell counts and viral load of HIV in the HIS database of EBV-negative and -positive HIV/AIDS patients and found that higher CD4 cell counts were observed in the EBV-negative HAART use group ($P < 0.001$) (Fig. 4). Among the HIV-positive patients, 67% had a HIV viral load under the detection limit after more than 6 months of HAART use, which was correlated with the EBV-negative rate (Table 1).

Discussion

Several clinical studies have proven that EBV seroprevalence displays a wide range of values in different countries, ranging from 17.5% to 90% (Ammatuna *et al.* 2001; de Franca *et al.* 2012; Fourcade *et al.* 2017; Scaggiante *et al.* 2016). The EBV shedding rate is highest in the non-suppressed HIV population (Scaggiante *et al.* 2016). However, we need to know the role of HAART use in reducing EBV shedding for the population of people living with HIV/AIDS, as well as its relationship with CD4 reconstruction.

We observed that there were high levels of IgM and a high IgM/IgG ratio in the HIV/AIDS (NH) group. A high proportion of HIV/AIDS patients were EBV-seropositive (Fig. 2A, 2B). A relatively lower proportion of the HIV-negative patients were EBV-negative. Therefore, HIV-positive populations have a high risk for EBV infection and reactivation outcomes.

EBV primary infections in children are usually asymptomatic, tend to exhibit very mild symptoms, or exhibit symptoms that are similar to that of other viral infections (Xiong *et al.* 2014). However, EBV primary infection in adolescents or young adults can result in nearly 50% of patients acquiring mononucleosis (Balfour *et al.* 2013; Cao *et al.* 2017). Most adolescents and young adults eagerly participate in social activities, so they have a high risk of contact with the higher-risk population. In recent years, the patients that had higher HIV infection rates were under 30 years old and were homosexuals (Table 1), while this age was relatively younger than that of individuals diagnosed during 2009–2010 (Shen *et al.* 2013).

Data on EBV-associated co-infection outcomes are limited. Dual infection with Hepatitis B and EBV may cause severe acute hepatitis with HBV chronicity (Rao *et al.* 2017). Acute HIV co-infection patients can present with an acute febrile mononucleosis-like illness, with mononucleosis as an alternative criterion in the differential diagnosis of acute HIV syndrome (Choi and Graber 2014; Grimes *et al.* 2016). Considering that both HIV and EBV are transmitted by intimate contact, these adolescents or young adults with EBV acute infection will have increased susceptibility to HIV-1 infection of peripheral blood lymphocytes (Moriuchi M and Moriuchi H 2003). Taken together, adolescents and young adults co-infected with HIV and EBV are in danger of developing acute HIV syndrome. To reduce the transmission risk of HIV and EBV, adolescents and young adults should avoid intimate contact or practice safe sexual activities.

Evaluating the EBV-positive rate in saliva and its relationship with HAART use in people living with HIV/AIDS can help prevent EBV infection-related transmission risk and malignant carcinomas. HAART can help decrease the

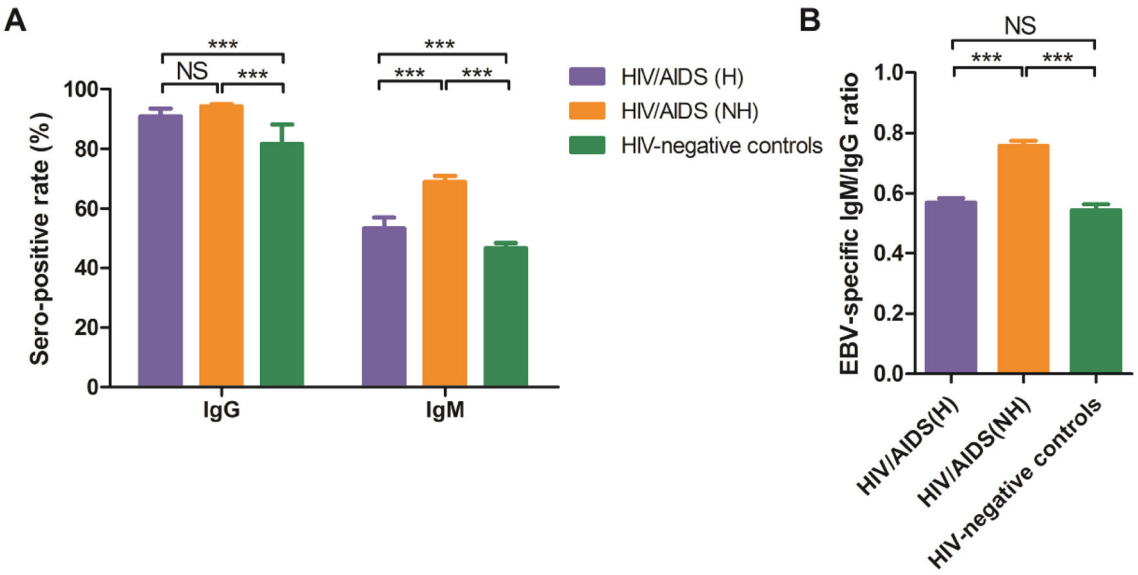

Fig. 2 EBV serological analysis. **A** The proportions of EBV-specific IgG and IgM in the three groups. **B** The EBV-specific IgM/IgG ratio. HAART use information was collected from the hospital database. The data shown are the mean ± SD (HIV/AIDS, n = 186/group; HIV-negative controls, n = 207), and each experiment was performed in duplicate. NS, not statistically significant, $***P < 0.001$.

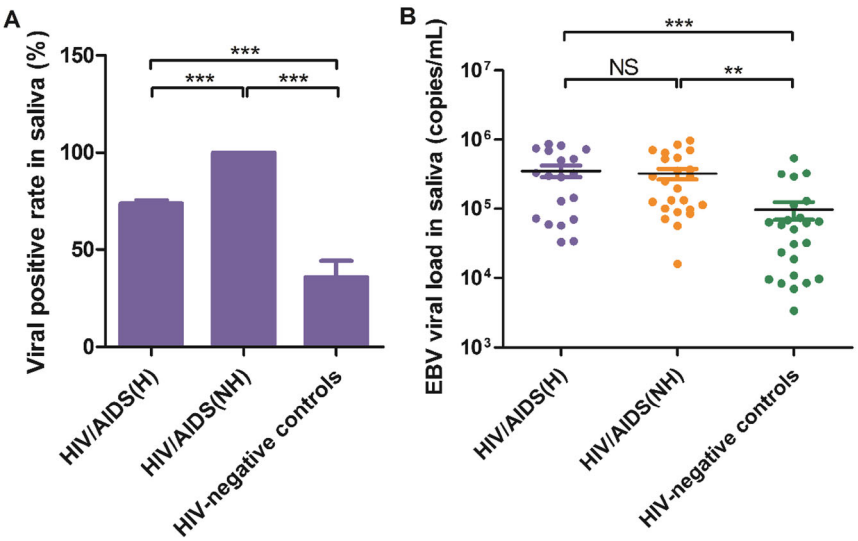

Fig. 3 EBV in saliva. **A** The proportion of the EBV DNA-positive rate among the three groups. **B** The viral quantity distribution among the three groups. The data shown are mean ± SD (HIV/AIDS, n = 186/group; HIV-negative controls, n = 207) and each experiment was performed in duplicate. The data in the figure are representative of the analysis results. NS, not statistically significant, $**P < 0.01$; $***P < 0.001$.

prevalence of EBV opportunistic diseases (Amornthatree *et al.* 2012; Chakraborty *et al.* 2010). We compared the salivary EBV DNA of patients undergoing HAART and those who do not; we concluded that HAART could play a pivotal role in indirectly decreasing the possibility of EBV co-infection with HIV or promoting EBV immune clearance in saliva. According to our results (Fig. 3), the salivary EBV DNA-positive rate reached 100% in the HIV/AIDS (NH) group, but the IgM seroprevalence was lower. One reason may be a newly infected population that had an undetectable IgM titer or an IgM titer under the detection limit of the EBV-specific IgM reagent, skewing the observed IgM levels. A second reason is that the immunodeficient population has damaged humoral immunity as we found some individuals with lower HIV IgG in plasma (data not shown). In this study, we determined that EBV has a higher primary infectious or reactivity rate in saliva in the HIV/AIDS population, with a nearly twofold higher salivary EBV DNA rate. This population can infect more individuals through intimate contact during social activities. According to the specific psychological and social characteristics of the HIV/AIDS population, under the stress of stigma, some wish that more individuals were infected with HIV, so more agents will probably spread to the HIV-negative population (Burnham *et al.* 2016; Molina and Ramirez-Valles 2013). Therefore, understanding the

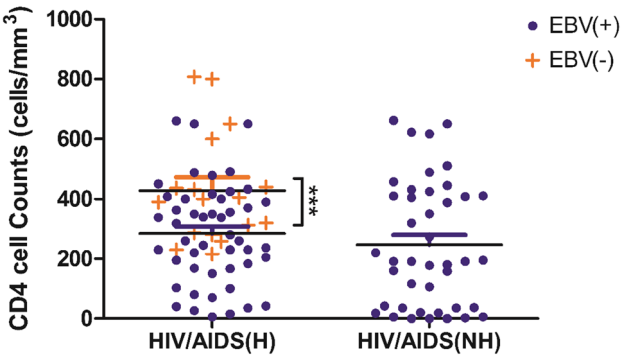

Fig. 4 CD4 cell counts in EBV DNA-positive and -negative groups. CD4 cell counts of HIV/AIDS patients were determined by flow cytometry. The reports were kept in the hospital database. The data are representative of the analysis results. Statistical significance was measured by a two-way ANOVA and a two-tailed unpaired Student's *t* test. ***$P < 0.001$.

co-infectious state of HIV/AIDS individuals can provide a theoretical basis for the prevention of opportunistic agent transmission or co-infection in this special cohort.

The overall HIV morbidity and mortality rates have been sharply decreasing worldwide due to the global implementation of HAART, while HIV infection is now recognized as a chronic disease rather than a deadly one (Sun *et al.* 2017). Ever since China established national HIV prevention and treatment programs, the mortality of AIDS has decreased significantly (Wu *et al.* 2015; Zhang *et al.* 2011). Since the financial resources allocated to HIV/AIDS are increasing, the HAART eligibility criteria keep changing accordingly. In 2008, antiretroviral therapy (ART) was recommended to be initiated at $\leq$ 350 cells/μL instead of at $\leq$ 200 cells/μL (WHO 2014). In 2013, the recommended eligibility for ART began at CD4 cell counts $\leq$ 500/μL (Zhang *et al.* 2011). In this study, HAART had been started immediately with good adherence in the HIV infectious patients. The lifesaving benefits of HAART for HIV patients will serve as a significant catalyst for decreased mortality based on the global experience (Wu *et al.* 2015). However, disease progression and prevalence are positively associated with late HIV diagnosis (Dai *et al.* 2015; Shen *et al.* 2013). The drugs for HIV cocktail therapy are limited, and the side effects are usually serious, thereby limiting the adherence to some extent. Both of these factors weaken the effect of HAART among the HIV-positive population (Mocroft *et al.* 2013; Wang *et al.* 2015). According to our previous study, in individuals with good adherence to HAART, CD4 cell counts increased and achieved immune reconstruction (Sun *et al.* 2017). In this study, we also found CD4 cell counts increased in the HIV/AIDS patients undergoing HAART (Table 1).

In conclusion, HIV infection can enhance the risk of EBV shedding in saliva, with risk being inversely associated with CD4 cell counts. Therefore, HAART use plays an important role in decreasing the risk of HIV and EBV transmission.

Acknowledgements We thank Yanping Guo and Xiaojuan Yang from the Department of Medical Instruments of Wuxi Fifth People's Hospital Affiliated to Jiangnan University for the purchase of reagents. This work was supported by the Grant of Wuxi Technology Bureau Scientific and Technology Project (CSE31N1607), the Wuxi Key Medical Talents Program (ZDRC024), Shanghai Pujiang Program (15PJ1407300), the Wuxi Medical Development Discipline Program (FZXK006, MS201702), the Significant Program from Wuxi Health and Family Planning Commission (z201603), the National High Technology Research and Development Program of China (2014AA021403), the National Natural Science Foundation of China (81571977, 81701550) and the Project from Shanghai Municipal Commission of Health and Family Planning (15GWZK0103).

Author Contributions HZL, LHH and YY conceived the study. YY, YR, RFC, YJJ, JYY, JW and JH carried out the experiments and formal analysis. YR, RFC, JYS, JYY, YWQ, LYH and HP carried out the investigation. YY and YR wrote the paper. HZL and LHH checked and finalized the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Animal and Human Rights Statement The study project was submitted to and approved by the Fifth People's Hospital of Wuxi, Affiliated to Jiangnan University Ethics Committee and the Shanghai Public Health Clinical Center Ethics Committee. The Ethics Committee authorized this study, which was performed with written informed-consent files by patients and was anonymous.

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