Diagnostic value of EBV-DNA in CSF for PCNSL in AIDS patients with focal brain lesions
A meta-analysis of diagnostic test

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Abstract

Background: Epstein-Barr virus (EBV) infection plays a crucial role in the progression of acquired immunodeficiency syndrome related primary central nervous system lymphoma (AR-PCNSL). This study aimed at evaluating the diagnostic value of cerebrospinal spinal fluid (CSF) EBV-deoxyribonucleic acid (DNA) for PCNSL in patients with infection of human immunodeficiency (HIV) virus through a meta-analysis of diagnostic test.

Methods: A systematic search in PubMed, Embase, Web of Science, Wanfang, Chinese Biomedical Database and Chinese National Knowledge Infrastructure was conducted before May 10, 2022. Heterogeneity among the studies was assessed using Q test and I^2 statistics. Publication bias was assessed using the Deek's funnel plot asymmetry test. Statistical analyses were performed using Stata 16.0 software. The pooled sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratios (DOR) and 95% confidence intervals (CI) were caculated to evaluate the diagnostic value. A symmetric receiver operating characteristic (SROC) curve and the area under the SROC curve (AUC) were constructed to evaluate the test-performance.

Results: Twelve studies were included in the final analyses, with a total of 141 patients with AR-PCNSL and 590 controls. The pooled diagnostic values were sensitivity of 0.83 (95% CI: 0.73–0.90), specificity of 0.95 (95%CI: 0.89–0.98), PLR of 17.8 (95%CI: 6.8–46.1), NLR of 0.17 (95%CI: 0.10–0.30), DOR of 102 (95%CI: 28–379), and AUC of 0.94 (95%CI: 0.91–0.96).

Conclusion: In summary the overall diagnostic value of CSF EBV-DNA is very high and it can be a reliable diagnostic biomarker for AR-PCNSL.

Abbreviations: AIDS = acquired immunodeficiency syndrome, AR-PCNSL = acquired immunodeficiency syndrome related primary central nervous system lymphoma, AUC = area under the SROC curve, CI = confidence interval, CSF = cerebrospinal spinal fluid, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus, FBL = focal brain lesion, HARRT = highly active antiretroviral therapy, HIV = human immunodeficiency virus, NLR = negative likelihood ratios, PCR = polymerase chain reaction, PLR = positive likelihood ratios, QUADAS-2 = quality assessment of diagnostic accuracy studies, SROC = symmetric receiver operating characteristic.

Keywords: diagnosis, Epstein-Barr virus, HIV/AIDS, meta-analysis, PCNSL, PCR

1. Introduction

Focal brain lesion (FBL) disease in patients with acquired immunodeficiency syndrome (AIDS) may be caused by various opportunistic pathogens or malignancies, including toxoplasma gondii, JC virus (JCV), cytomegalovirus, and primary central nervous system lymphoma (PCNSL), among which PCNSL is 1 of the most prevalent and major cause of morbidity and mortality. Distinguishing PCNSL from other infectious FBL diseases in human immunodeficiency virus (HIV)-infected patients is extremely significant for treatment decision making because their treatment strategies vary greatly. Histological examination of brain biopsy or resection surgery specimen is the gold standard for diagnosing PCNSL. However, its use may be limited by its invasiveness, high rate of complications,[1] and few survival benefit.[2] Early and minimally invasive diagnosis of FBL in HIV-infected patients remains a challenging clinical problem. Despite some radiographic examinations, such as

computed tomography, magnetic resonance, and thallium-201 (201Tl) single-photon emission computed tomography are regularly used for its preoperative differential diagnoses. Generally, these imaging methods are insufficient for accurate diagnosis.

The strict association between acquired immunodeficiency syndrome related primary central nervous system lymphoma (AR-PCNSL) and Epstein-Barr virus (EBV) infection suggests that EBV deoxyribonucleic acid (DNA) in the cerebrospinal spinal fluid (CSF) might serve as a remarkable diagnostic marker, which can reduce the time for diagnosis and allow a minimally invasive approach. In fact, the detection of EBV-DNA in the CSF by polymerase chain reaction (PCR) has a relatively high sensitivity and specificity for AR-PCNSL in many studies.[3–6] However, the diagnostic ability from different studies varies, which may be affected by limitations such as small sample size and inter- and intraobserver variations. Considering the limitations of single center studies, we conducted this meta-analysis based on more study samples and rigorous statistics, aiming to more accurately evaluate the diagnostic efficiency of CSF EBV-DNA for PCNSL in patients with HIV infection.

2. Materials and methods

2.1. Literature search

A systematic search was conducted for relevant articles published in PubMed, Embase, Web of Science, Wanfang, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Database (CBD) from inception to May 10, 2022.

The following keywords were used: Epstein-Barr virus, EBV, PCR, DNA, primary central nervous system lymphoma, PCNSL, and PCL. The language was restricted in English and Chinese. This research was approved by the ethics committee of Beijing Diantan Hospital.

2.2. Selection criteria

Studies that met the following criteria were included: All the AR-PCNSL patients must be diagnosed through the gold standard (histological examination); Studies that provided diagnostic value of CSF EBV-DNA for PCNSL; Studies that presented sufficient data to allow calculation of the diagnostic value (true positive, false positive, false negative, and true negative). Duplicate publications, studies with duplicate patients data, studies without qualified data, and other types of research such as letters, reviews, case reports, and editorials were excluded.

2.3. Data extraction

For each study included in this meta-analysis, the following information was extracted: the first author, year of publication, region, sample size (separately for PCNSL and control individuals), and 4 main data (true positive, false positive, false negative, true negative). Data of non-histologically diagnosed PCNSL,[7] CNS involved system non-Hodgkin lymphoma[7] or system non-Hodgkin lymphoma without CNS involved[4,8,9] were removed from this research. During the study selection process, 2 review authors (DX and LT) independently extracted the information, and cross
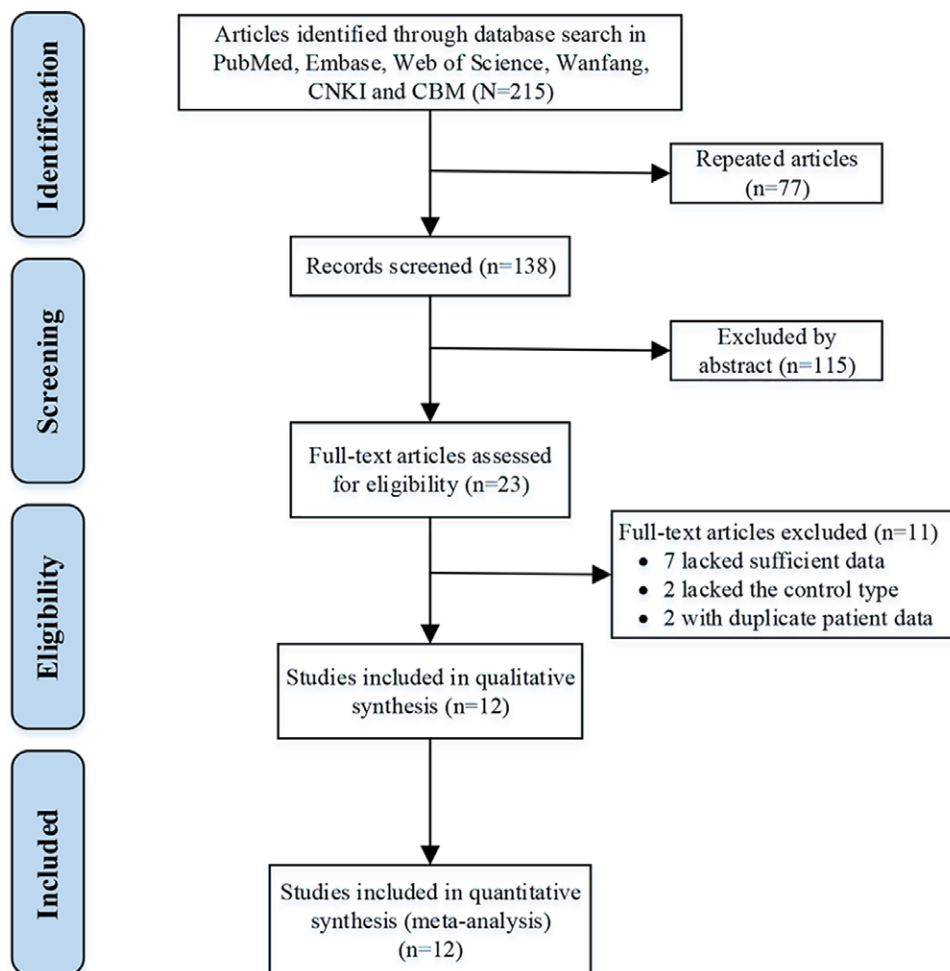

Figure 1. Flow diagram of studies selection process.

checked the data. Discrepancies were discussed and arbitrated by a third author (FE) to achieve consensus.

2.4. Quality evaluation

Two researchers independently assessed the methodological quality of each included study using the revised quality assessment of diagnostic accuracy studies (QUADAS-2) criteria. Four key domains (patient selection, index test, reference standard, and flow and timing) were evaluated in terms of risk of bias ("high", "unclear" or "low") based on the answers to relevant questions. In addition, the first 3 domains (patient selection, index test, and reference standard) were assessed for concerns about applicability.[10] Any disputes were settled by a third investigator.

2.5. Statistical analysis

Stata 16.0 software (Stata Corp, College Station, TX) was used to perform all the statistical analyses. Heterogeneity among studies was assessed using the Q test and I^2 statistic. An $I^2 > 50\%$ and $P < .1$ indicated the existence of heterogeneity.[11] Publication bias was assessed based on Deek's funnel plot asymmetry test. The bivariate mixed-effects regression model developed by van Houwelingen[12] was used to calculate the pooled sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic odds ratio and their 95% confidence intervals (CI). A symmetric receiver operating characteristic (SROC) curve was constructed for the overall analysis. The area under the SROC curve (AUC) was calculated to evaluate the accuracy of the test. We also conducted a subgroup analysis based on the PCR method and highly active antiretroviral therapy (HARRT) therapy using univariate meta-regression. Taking the year 1996[13] as the boundary, we divide all studies into 2 subgroups: the pre-HARRT era and the post-HARRT era. Finally, a Fagan plots diagram was constructed to show the relationship between prior probability, likelihood ratio, and posterior test probability. $P < .05$ was considered to be statistically significant.

Graphs were produced by MIDAS module for the STATA and QUADAS-2 module for RevMan 5.4.

3. Results

3.1. Study selection and characteristics

The selection flow of the literature search was presented in Figure 1. The initial search yielded 215 records. 77 duplicate records were removed, and 115 were excluded after reviewing their titles and abstracts. With further work on full-text screening of the remaining 23 articles, we removed 11 records for the following reasons: 7 lacked sufficient data, 2 lacked a control cohort and 2 had duplicated patient data.[14,15] Finally, 12 articles[3–9,16–20] were included in the ultimate meta-analysis. A search of the reference lists of the identified articles and previous systematic reviews[21] did not identify any more relevant articles.

In Table 1, we summarized the characteristics of the 12 studies included in this meta-analysis. Across the 12 studies, the publication year ranged from 1995 to 2013. Most studies (8 of 12) were conducted in Europe, while 2 in the USA and 2 in Japan, involving 141 PCNSL patients and 590 control patients. The sample size of patients with AR-PCNSL in different studies varied from 2 to 36. The control cohort included patients with toxoplasmosis, progressive multifocal leukoencephalopathy, cytomegalovirus encephalitis, cryptococcal meningitis, tuberculoma, neurosyphilis, HIV encephalitis and other AIDS-associated neurological disorders. A qualitative method of nest PCR or general PCR was applied in 10 of the 12 included studies to detect EBV-DNA in CSF, while the other 2 used a quantitative assay of real-time (RT) PCR. Participants from 7 studies were in the pre-HARRT era, while the other 5 were in the post-HARRT era. The sensitivity of CSF EBV-DNA for diagnosing PCNSL ranged from 62.5% to 100.0%, and the specificity ranged from 76.2% to 100.0%.
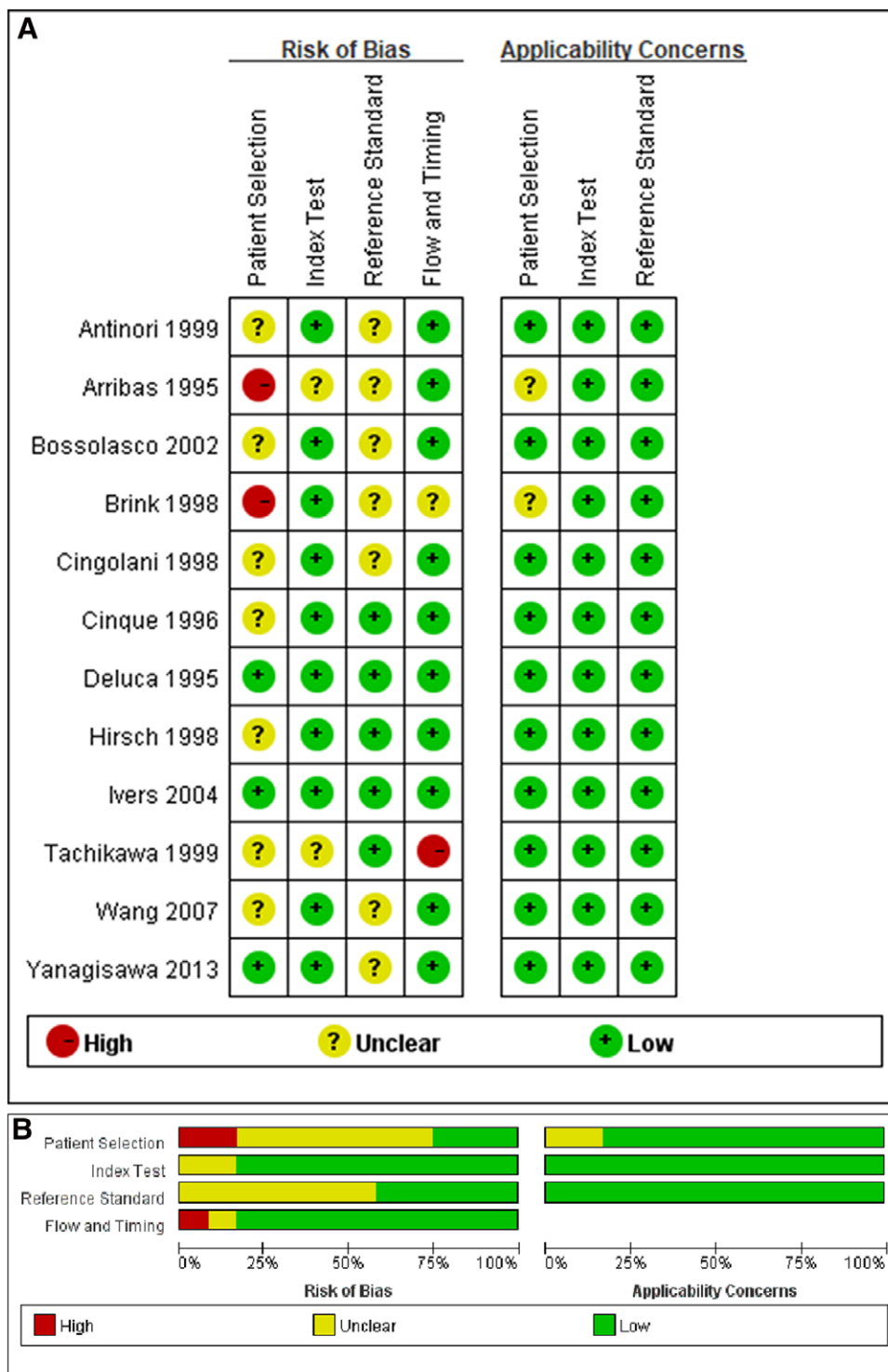
3.2. Quality assessment

The methodological quality of the included studies using QUADAS-2 criteria is summarized in Figure 2 (the risk of bias

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Table 1

Characteristics and diagnostic performance of CSF EBV-DNA in PCNSL patients from the included studies.

NO	Author[ref]	Year	Region	Sample size PCNSL	Sample size Others	Study design	Analytic method	Amplified Gene	TP	FP	TN	FN	Sensitivity	Specificity
1	Arribas[16]	1995	USA	6	16	Retrospective	PCR	BamHI-W and EBNA1	5	1	15	1	0.833	0.938
2	Yanagisawa[9]	2013	Japan	8	63	Retrospective	RT-PCR	BNRF1	5	13	50	3	0.625	0.794
3	Tachikawa[3]	1999	Japan	5	12	Retrospective	nested PCR	EBNA1	5	0	12	0	1.000	1.000
4	Hirsch[17]	1998	Switzerland	9	18	Retrospective	nested PCR	EBNA1	6	0	18	3	0.667	1.000
5	Deluca[4]	1995	Italy	8	26	Prospective	nested PCR	EBNA1	7	0	26	1	0.875	1.000
6	Bossolasco[7]	2002	Italy	13	16	Retrospective	RT-PCR	LMP-1	9	2	14	4	0.692	0.875
7	Brink[5]	1998	UK	7	96	Prospective	nested PCR	NA	7	9	87	0	1.000	0.906
8	Wang[8]	2007	UK	4	60	Retrospective	nested PCR	EBNA1	3	7	53	1	0.750	0.883
9	Ivers[18]	2004	USA	2	21	Retrospective	PCR	BamH1W	2	5	16	0	1.000	0.762
10	Antinori[14]	1999	Italy	13	18	Prospective	nested PCR	EBNA1	11	0	18	2	0.846	1.000
11	Cinque[6]	1996	Italy	36	183	Prospective and Retrospective	nested PCR	EBNA1	35	3	180	1	0.972	0.984
12	Cingolani[20]	1998	Italy	30	61	Prospective	nested PCR	EBNA1	24	0	61	6	0.800	1.000

CSF = cerebrospinal spinal fluid, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus, FN = false negative, FP = false positive, PCNSL = primary central nervous system lymphoma, TN = true negative, TP = true positive.

Figure 2. Methodological quality of the included studies using the QUADAS-2 checklist. (A) Risk of bias and applicability concerns summary. (B) Risk of bias and applicability concerns graph. QUADAS-2 = quality assessment of diagnostic accuracy studies.

and applicability concerns summary [A] and graph [B]). The overall quality of the available literature is moderate. Sample selection was heterogeneous for several reasons. First, the control patients varied from separate studies, including patients without mass effect such as HIV encephalopathy, CNS vasculitis, various types of encephalitis, retinitis, and AIDS dementia. And not all patients in the control group were histologically diagnosed. In addition, many patients underwent biopsy diagnosis only after the absence of clinical or radiologic response to

the 2-week empiric therapy, resulting in an increased incidence of PCNSL in these patients.

3.3. Heterogeneity and publication bias

Heterogeneity test among studies with an $I^2 = 20\%$ and $Q = 2.49(P = .144)$ indicated the absence of heterogeneity, which was also visualized in the Galbraith graph and bivariate boxplot (Figure S1, Supplemental Digital Content, http://links.lww.com/

MD/H923), A and B. Nevertheless, we identified publication bias by Deeks' regression test of asymmetry (P < .001, Figure S2, Supplemental Digital Content, http://links.lww.com/MD/H924).

3.4. Pooled diagnostic values

The fixed effect model was used to pool the sensitivity and specificity because the I^2 values were no more than 50%. The overall pooled sensitivity and specificity were 0.83 (95%CI: 0.73–0.90) and 0.95 (95%CI: 0.89–0.98) (Fig. 3). The pooled PLR was 17.8 (95%CI: 6.8–46.1), NLR was 0.17 (95%CI: 0.10–0.30), and diagnostic odds ratios was 102 (95%CI: 28–379). The overall SROC curve with an AUC of 0.94 (95%CI: 0.91–0.96) was presented in Figure 4. In Fagan plots diagram (Fig. 5), the prior probability was 20%, the post-test probability was 82% for PLR, and 4% for NLR. Scatter matrix of the likelihood ratio (Fig. 6) showed that the integrated LRP and LRN of the pooled studies fell into the first quadrant (LRP > 10, LRN > 0.1).

3.5. Subgroup analyses

Subgroup analyses based on the PCR method and HARRT therapy were performed (Fig. 7), which showed that both factors were sources of heterogeneity in this meta-analysis. The sensitivity and specificity with the use of qualitative method (nest PCR) were 0.89 (95%CI: 0.81–0.97) and 0.97 (95%CI: 0.94–1.00) while the sensitivity and specificity with the use of quantitative method (real-time PCR) were 0.67 (95%CI: 0.44–0.90) and 0.84 (95%CI: 0.59–1.00) independently. The sensitivity and specificity of pre-HARRT era were 0.89 (95%CI: 0.81–0.97) and 0.98 (95%CI: 0.96–1.00) while the sensitivity and specificity of post-HARRT era were 0.76 (95%CI: 0.61–0.92) and 0.87 (95%CI: 0.77–0.97) independently.

4. Discussion

Patients with HIV infection have a significantly increased risk of PCNSL, which is 3600 times higher than that of the general population.[22] With the advent of the HARRT era, the incidence of AIDS-related tumors including AR-PCNSL has decreased. However, it remains 1 of the most common AIDS-related malignancies, with a prevalence of 20.6% in HIV-positive patients with FBL.[23] EBV infection plays a crucial role in the progression of AR-PCNSL. EBV is a gamma herpesvirus that infects more than 90% of the world's population as a latent asymptomatic infection of B-lymphocytes. In immunosuppressed hosts, EBV-infected lymphocytes may proliferate without regulation, resulting in malignant lymphomas.[24] The most likely etiology is that the ineffective immunoregulation of EBV induced oncogenic protein expression, subsequent loss of apoptosis and increased proliferation of lymphocytes, and ultimately resulted in malignant lymphomas. Nevertheless, there is no difference in the plasma viral load between AR-PCNSL patients and the control groups.[7] However, the detection of EBV-DNA in the CSF of HIV-infected individuals has been reported as a reliable marker for diagnosing AR-PCNSL in numerous studies.[3–6] In this study, a meta-analysis was conducted to assess the diagnostic significance of CSF EBV-DNA in patients with AR-PCNSL. Our meta-analysis showed that the sensitivity and specificity of EBV-DNA detection in CSF could be as high as 0.83 (0.73–0.90) and 0.95 (0.89-0.98) for PCNSL diagnosis, with an AUC of 0.94, indicating a very high level of overall accuracy. The scatter matrix of the likelihood ratio showed that a positive CSF EBV-DNA detection is very supportive for PCNSL, and negative results do not exclude PCNSL.

Although the pathomechanism leading to the development of AR-PCNSL is unclear, it is well established that there is a strong association between EBV infection and AR-PCNSL. All of these studies showed that CSF examination for EBV-DNA is a recommended diagnostic test for PCNSL. Nonetheless, some factors can influence the accuracy of this test. With the advent of new PCR technology, EBV-DNA load can be tested quantitatively. In 2 of the included studies, the real-time PCR assay was used to detect EBV-DNA quantitatively with a cutoff of 100 and 200 copies/mL independently. Unexpectedly, in our subgroup analysis according to the method of EBV detection, the sensitivity and specificity of studies with the
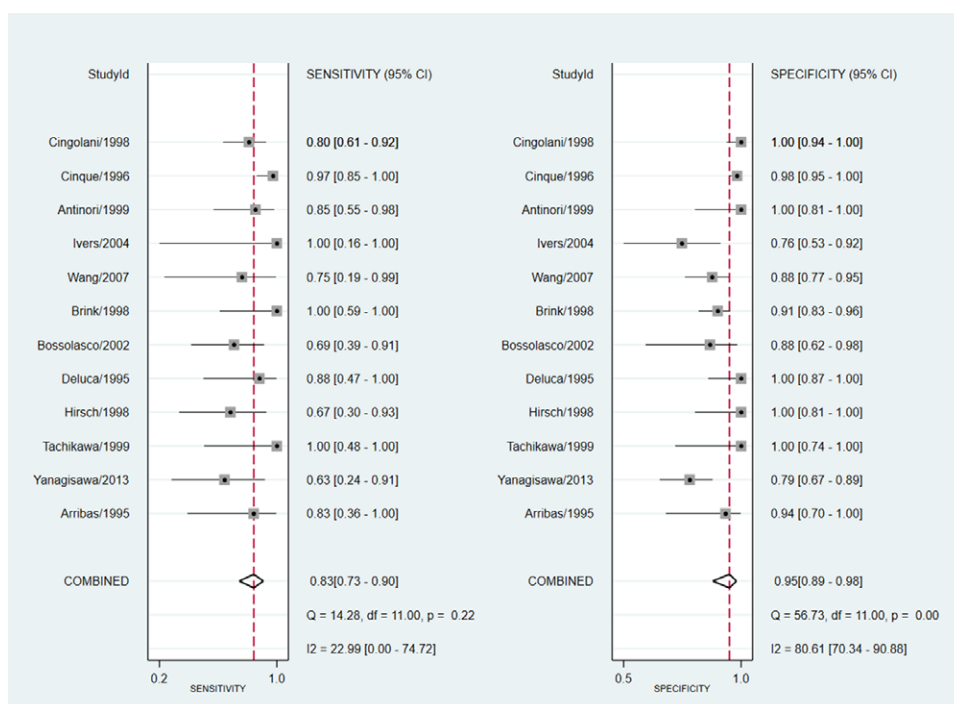
Figure 3. Forest plot of pooled sensitivity and specificity of CSF EBV-DNA for AR-PCNSL. AR-PCNSL = acquired immunodeficiency syndrome related primary central nervous system lymphoma, CSF = cerebrospinal spinal fluid, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus.
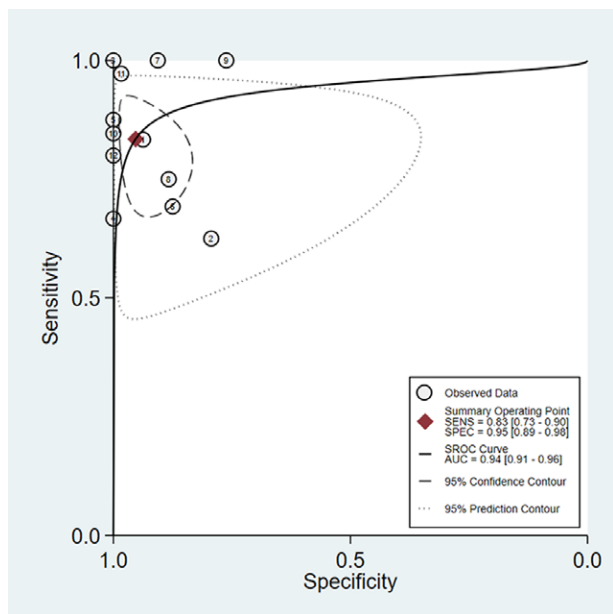
Figure 4. Symmetric receiver operator characteristic curve with 95% confidence contour and 95% prediction contour for the pooled accuracy of CSF EBV-DNA for AR-PCNSL. AR-PCNSL = acquired immunodeficiency syndrome related primary central nervous system lymphoma, CSF = cerebrospinal spinal fluid, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus.

quantitative method were lower than those with the qualitative method ($P = .02$ and $P = .15$ respectedly). Decreasing cutoff value will increase its sensitivity, but the specificity will be worse at the same time. Corcoran[25] found that using a cutoff of 10,000 copies/mL can increase the specificity and positive predictive value (PPV) for diagnosing PCNSL compared with qualitative EBV-DNA detection. HARRT, another factor that can influence the accuracy of the test, was found in our study to decrease both sensitivity ($P = .02$) and specificity ($P < .001$), which was similar to the previous studies.[18,26] One of the reasons for this decline seems to be the lower incidence of PCNSL in the post-HAART era compared to that in the pre-HAART era. The use of ganciclovir is also associated with lower or undetectable EBV-DNA load in the CSF of patients with AR-PCNSL. In a study, EBV-DNA load was found to be significantly lower for ganciclovir-treated patients, compared with untreated patients (median value, 2.15 vs 4.16 log copies/mL).[27] We did not analyze this factor in the present study, as none of the 12 included articles mentioned the treatment of ganciclovir neither in the PCNSL patients or the control cohort.

To the best of our knowledge, this is the first meta-analysis to cover the largest sample size pooled from rigorously screened studies to evaluate the diagnostic value of CSF EBV-DNA in patients with AR-PCNSL. However, these results should be noted due to certain limitations. First, publication bias and the complicated control types in this study may contribute to heterogeneity and then affect the accuracy of the pooled results. Second, most of the included populations were Italian, which could lead to population selection bias. Third, nucleic acid extraction techniques, DNA primers, and amplification technologies vary across different research centers, including the inconsistent cutoff values. Therefore, a prospective and multi-centered research should be conducted to further evaluate the diagnostic value of CSF EBV-DNA in AR-PCNSL.

5. Conclusion

The detection of EBV-DNA from the CSF by PCR is an extremely sensitive and specific diagnostic method for AR-PCNSL as a possible alternative to brain biopsy, and should be routinely evaluated in HIV-FBL patients before their empiric anti-Toxoplasma therapy. A positive CSF EBV-DNA detection is very supportive for AR-PCNSL, and negative results do not exclude PCNSL. In summary, this meta-analysis indicated that CSF EBV-DNA is a reliable diagnostic biomarker for AR-PCNSL.
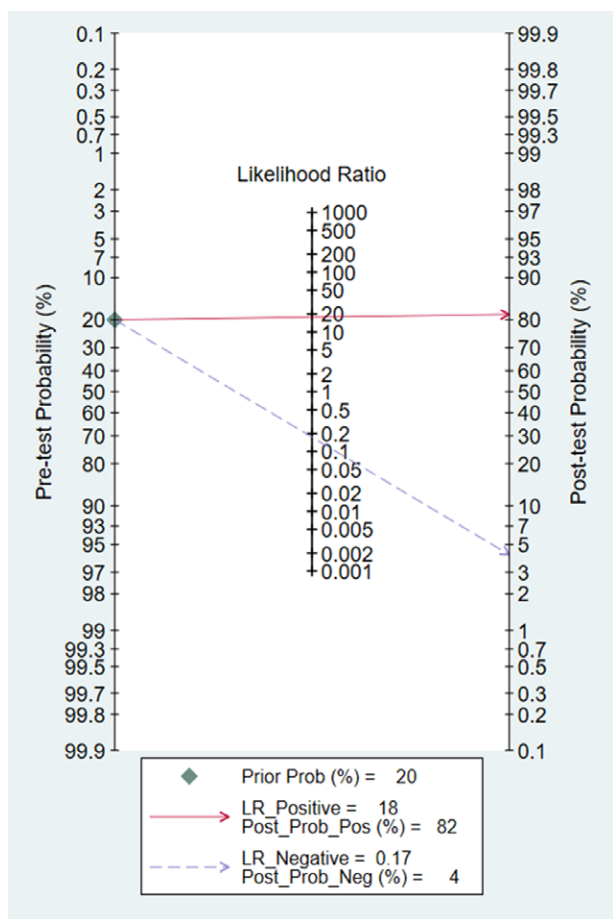
Figure 5. Fagan plots diagram of the overall diagnostic value of CSF EBV-DNA for AR-PCNSL. AR-PCNSL = acquired immunodeficiency syndrome related primary central nervous system lymphoma, CSF = cerebrospinal spinal fluid, DNA = deoxyribonucleic acid, EBV = Epstein-Barr virus.
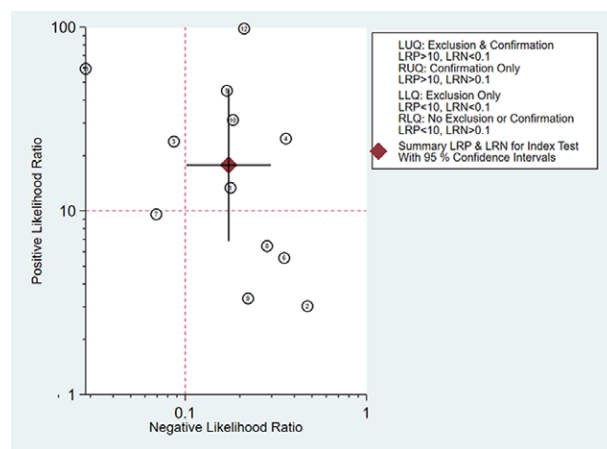
Figure 6. Scatter matrix of the likelihood ratio.
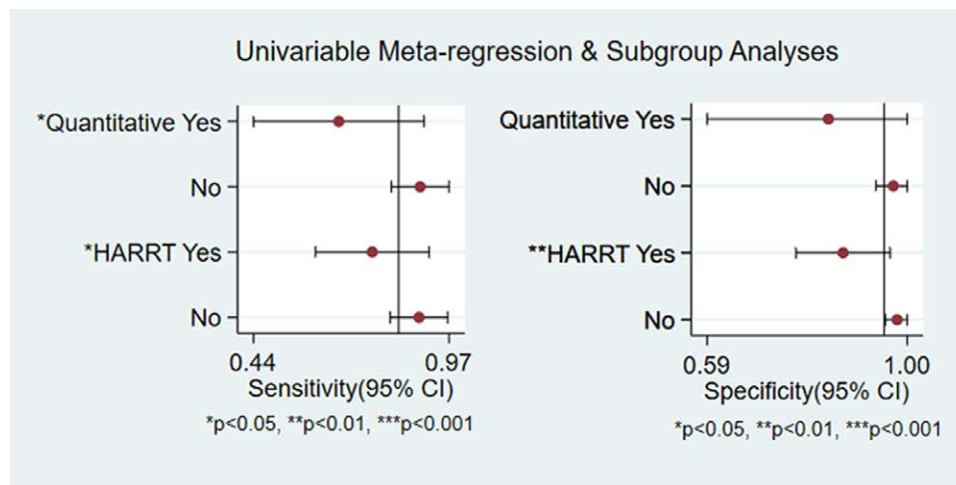
Figure 7. Subgroup analyses based on the PCR method and the therapy of HARRT. HARRT = highly active antiretroviral therapy.

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