Evaluation of the FilmArray Meningitis/Encephalitis Panel for Diagnosis of Infectious Meningitis and Encephalitis

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Research

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Abstract

Background: Infectious Meningitis/Encephalitis (M/E) is caused by pathogens. The FilmArray M/E panel can quickly detect 14 kinds of pathogens and facilitate diagnosis for patients with M/E. This study aimed to perform a evaluation of the sensitivity and specificity of the FilmArray M/E panel compared with classic method of diagnosing M/E.

Methods: Relevant studies published before August 15, 2021, were identified by searching Web of Science, PubMed, Cochrane Library, and Embase, using keywords Meningitis, Encephalitis, and FilmArray M/E panel. After the initial screening, EndNoteX9 was used to manage the studies and extract data. The quality of the study was based mainly on the quality evaluation standard of diagnostic tests recommended by Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Meta-DiSc 1.4 statistical software was used to determine the sensitivity, specificity, 95% confidence interval (CI), diagnostic odds ratio (DOR), positive likelihood ratios (PLR) and negative likelihood ratios (NLR) of each group of data, and summary receiver operating characteristic curve (SROC). All P values were two sided, and P <0.05 was considered statistically significant.

Results: A total of 269 studies were retrieved, and 16 full-text studies were identified. The sensitivity of all the full-text studies was 0.93 (95% CI: 0.91–0.95) and the specificity 0.98 (95% CI: 0.98–0.98).

Conclusions: Compared with the gold standard, the FilmArray M/E panel had a sensitivity of 0.93 and a specificity of 0.98 to 16 pathogens. Further studies are needed to determine whether the FilmArray M/E panel can be used as a clinical standard for the diagnosis of M/E.

Introduction

Generally speaking, infectious meningitis and encephalitis almost have no difference. Meningitis/encephalitis (M/E) is caused by infection by pathogens such as viruses and bacteria. These pathogens may also be fungi, parasites, and so on. Patients with meningitis/encephalitis have high mortality and morbidity. M/E is prone to some serious sequelae such as epilepsy, audio-visual disorder, limb dyskinesia, and so forth, and may even be life-threatening. Primary bacterial pathogens are responsible for more than 80% of community-acquired acute bacterial meningitis, such as Haemophilus influenzae, Neisseria meningitidis, Listeria monocytogenes, Lancefield Group B streptococci, and Streptococcus pneumoniae. However, meningitis caused by the virus is usually benign with no sequelae in patients with normal immunity. It has been reported that the main pathogens detected in patients with viral M/E are enterovirus and Human herpesvirus 6. Because of the different types of pathogens, the treatment of meningitis and encephalitis is quite different. In the past, the method of diagnosing M/E was inefficient and the accuracy was not high. Hence, a more complete method for diagnosing M/E was urgently needed.

The FilmArray M/E plate is a multi-molecular panel approved by the FDA in 2015 for the rapid detection of 14 pathogens, including bacteria (Escherichia coli K1, H. influenzae, N. meningitidis, L. monocytogenes, S. pneumoniae, and Streptococcus agalactiae), viruses (cytomegalovirus [CMV], enterovirus [EV], herpes simplex virus 1 [HSV-1], herpes simplex virus 2 [HSV-2], human herpesvirus 6 [HHV-6], varicella-zoster virus [VZV] and
human parechovirus [HPeV]) and fungi (Cryptococcus neoformans/Cryptococcus gattii). A comparison of the FilmArray M/E panel with the classic cerebrospinal fluid (CSF) culture revealed that the price of the FilmArray M/E panel for every patient was similar. The test could produce results in an hour. A multi-center clinical trial supporting the FDA's multivariate analysis reported that the positive agreement between the M/E panel and the conventional methods was 84.4%, and the negative agreement was >99.9%. A large number of studies showed that the panel detected multiple samples. This study aimed to further evaluate the M/E panel using CSF specimens known to be positive for bacterial, viral, or fungal targets represented by the multiplex analysis of the FilmArray M/E panel. Several studies on the detection of bacteria, fungi, and viruses in the FilmArray M/E panel were included. The detection results were further evaluated by analyzing the data of the FilmArray M/E panel.

Methods

Electronic searches

Relevant studies published before August 15, 2021, were identified by searching Web of Science, PubMed, Cochrane Library, and Embase. The authors used the keywords Meningitis, Encephalitis, FilmArray M/E panel and the related synonyms searched in Medical Subject Headings terms (MeSH) and EMTREE terms. Also, relevant references in the retrieved studies were searched to identify other potentially relevant studies. Further, studies in all languages were included and managed in the analysis.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) clinical samples were tested using the M/E panel; (2) other commonly used diagnostic methods were employed to analyze the samples and compared with the results of the FilmArray M/E panel; and (3) the 2 × 2 table was extracted based on the experimental results, and the specificity and sensitivity were calculated.

The exclusion criteria were as follows: (1) unsatisfactory data; (2) duplicate studies; and (3) reviews, lectures, abstracts, or review studies.

Data extraction

EndNoteX9 was used to manage the studies and extract data after the preliminary screening. Data extracted included country, author, literature year, sample source, study design type, sample type, gold standard, true positive, false positive, true negative, and false negative.

Quality assessment

The methodological quality of each study was assessed using the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Two investigators independently evaluated the risk of bias in each study according to the QUADAS. Total risk of bias in every study was assessed with “Yes,” “Unclear,” and “No.” Discrepancies were resolved by discussion to get a consensus assessment. In the case of persistent disagreement, an adjudicator was consulted.

Statistical analysis
The Meta-DiSc 1.4 software was used to analyze the data from reconstructed 2 × 2 tables: sensitivity, specificity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), 95% confidence interval (95% CI), and diagnostic odds ratio (DOR). A bivariate mixed model was adjusted to obtain a summary receiver operating characteristic (SROC) curve by summarizing the joint distribution of sensitivity and specificity with the Moses linear model, and the corresponding area under the curve (AUC) was calculated as a global measurement of test performance\textsuperscript{14,15}. To avoid empty cells in 2 × 2 tables, “0.5” was used to replace the cell “0”. Statistical tests were generally two sided, and therefore only \( P \) values < 0.05 were considered statistically significant.

Results

Search results

A total of 269 studies were retrieved and 129 studies were excluded due to duplication. Of the remaining 140 studies, 31 were excluded after browsing the titles and abstracts and 92 (66 insufficient information, 13 letter, 1 Meta-analysis and systematic review, 4 review and 8 case reports) were excluded after screening the full-text. Eventually, 16 studies and in total 17 datasets were selected for full-text review and evaluation\textsuperscript{2–4,16–25}. The elaborated process of this literature search is presented in S1 Fig.

Study characteristics

Among the 16 studies till July 15, 2021, 15,057 samples with no age restriction were included. The "total" in Table 1 represents the overall datum (including bacterial, viruses, and fungi) of each study. Bacteria, viruses, and fungi were used as subgroups to extract data for each article. Eventually, 16 studies had bacterial data, 10 had viruses’ data, and 7 had fungi data. In addition, a study could only extract the total data. The characteristics of these studies are presented in Table 1.

Risk-of-bias assessment

A summary of the risk of bias assessment results are shown in Table 2. Each of the 11 components according to QUADAS-2 criteria was graded as “yes”, “unclear” or “no”, which meant “low risk of bias”, “uncertain of bias” and “high risk of bias” respectively, based on the methods reported in each study.

Diagnostic accuracy of FilmArray for infectious meningitis and encephalitis

Pooled sensitivity and specificity of FilmArray in meningitis and encephalitis are shown in Fig. 1(A and B). Among the 16 included studies, sensitivity ranged from 0.52 to 1.00 (pooled 0.93, 95% CI 0.91–0.95), and specificity ranged from 0.35 to 1.00 (pooled 0.98, 95% CI 0.98–0.98). Additionally, pooled parameters including PLR (20.98, 95% CI 7.42–59.36), NLR (0.09, 95% CI 0.04–0.21), and DOR (286.21, 95% CI 64.99–1260.37) were calculated (Fig. 1(C and D), Fig. 2). Reflected by \( I^2 \) statistics of the indices (84.1% for sensitivity and 95.2% for specificity), there existed heterogeneity in diagnostic performance between studies. An SROC curve displaying sensitivity against 1 − specificity from individual study was plotted for FilmArray in meningitis and encephalitis, with an AUC of 0.9765 (Fig. 3), suggesting high overall diagnostic accuracy of FilmArray in detection and evaluation of meningitis and encephalitis. No publication bias was found in this research \( [P = 0.391 \ (p > 0.05)] \) (Fig. 4).
Diagnostic accuracy of FilmArray in infectious meningitis and encephalitis for bacteria

Among the 16 included studies, the pooled sensitivity (0.92, 95% CI 0.87–0.96) and specificity (0.99, 95% CI 0.99–0.99) in diagnosing meningitis and encephalitis for bacteria are displayed in Fig. 5(A and B).

Diagnostic accuracy of FilmArray in meningitis and encephalitis for viruses

Among the 10 included studies, the pooled sensitivity (0.96, 95% CI 0.94–0.98) and specificity (0.99, 95% CI 0.99–1.00) in diagnosing meningitis and encephalitis for viruses are displayed in Fig. 6(A and B).

Diagnostic accuracy of FilmArray in infectious meningitis and encephalitis for fungi

Among the 7 included studies, the pooled sensitivity (0.91, 95% CI 0.59–1.00) and specificity (1.00, 95% CI 1.00–1.00) in diagnosing meningitis and encephalitis for fungi are displayed in Fig. 7(A and B).

Discussion

The use of the FilmArray M/E panel started in October 2015. The 14 pathogens detected in CSF included 6 bacteria, 7 viruses, and 1 yeast9. In the present study, 269 published studies were searched and 16 were extracted after screening. The data were analyzed to evaluate the accuracy of the FilmArray M/E panel. The whole data displayed that the sensitivity was 0.93; specificity was 0.98; PLR was 20.98; NLR was 0.09; DOR was 286.21; and SROC AUC was 0.9765. The FilmArray M/E panel had sensitivity to bacteria, viruses, and fungi of 0.92, 0.96, and 0.91, with specificity of 0.99, 0.99, and 1.00, respectively. PLR was greater than 10 and NLR was 0.13, which was close to 0.1. The DOR indicated that the probability of correct diagnosis was 148.89 times that of diagnostic errors. The AUC in the SROC curve was closer to 1, and the SROC curve was closer to the upper left corner. These findings indicated that the overall diagnostic accuracy of the FilmArray M/E panel was high. In addition, viruses, bacteria, and fungi had high sensitivity and specificity. The data on fungi was insufficient; hence, the specificity was shown as 1. In addition, the coefficient of bias P = 0.391 > 0.05, indicating that the probability for publication bias was subtle.

A total of 16 studies were retrieved, and 15057 samples were detected using the FilmArray M/E panel. The definite diagnosis of bacterial meningitis has historically been based on culture, with a sensitivity of ≤ 80%. Compared with the gold standard, 26336 true negatives plus true positives and 367 false positives plus false negatives accounted for 99% and 1% of the total sample size, respectively. Among these, 10021 true positives plus true negatives of bacteria accounted for about 99%, while 91 false positives plus false negatives accounted for about 1%. A total of 6204 true positives and true negatives of viruses accounted for about 99%, while 74 false positives and false negatives of viruses accounted for 1%. Further, 2502 true positives and true negatives of fungi accounted for 99%, while 8 false positives and false negative for fungi accounted for about 1%.
Another study can be used for comparison, which is “Evaluation of the BioFire FilmArray M/E panel for the detection of bacteria and yeast in Chinese children.” A total of 223 patients were detected, and 68 CSF samples met the inclusion criteria. The mean age of the patients was 2.76 years (from 3 days to 12 years), and the male–female ratio was 2.09 (46:22). The present study focused mainly on younger patients. In this paper, the ability of the FilmArray M/E panel in the diagnosis of bacterial and fungal meningitis has been demonstrated through the study of children in China. However, in our paper, we analyzed the data of virus, bacteria and fungi in detail and comprehensively, and analyzed the situation of patients of all ages.

This meta-analysis had several limitations. First, no virus comparison results were used. Second, the sample size was small, affecting the statistical certainty of the sensitivity and specificity calculations of the FilmArray M/E panel. The other study entitled “Diagnostic test accuracy of the BioFire® FilmArray® ME panel: a systematic review and meta-analysis,” screened 3059 patients. The gold standard for this study was consistent with that used in the present analysis. It concentrated on the analysis of specificity and sensitivity. Moreover, its sensitivity and specificity were both > 90%. The high accuracy estimates pointed out that the FilmArray M/E panel could be a very useful adjunct tool for the diagnosis of meningitis/encephalitis.

This clinical evaluation had a few restrictions. First, only 13 studies met the inclusion criteria, leading to a small sample size and limiting the extrapolation of the results. In addition, despite collecting all relevant studies, it was still difficult to ensure that no data were missed. Furthermore, the use of different diagnostic criteria led to the heterogeneity among the selected studies. This analysis can be further improved by accumulating clinical data in the future.

In summary, the FilmArray M/E panel is a method with high sensitivity and specificity when used for the diagnosis of meningitis and encephalitis. It is a rapid, sensitive, and specific detection method valuable for the clinical diagnosis of meningitis and encephalitis.

**Conclusion**

The FilmArray M/E panel is a tool with high diagnostic performance. However, more research is needed to explore its effects.

**Abbreviations**

M/E: Meningitis/Encephalitis; CSF: Classic cerebrospinal fluid; *E. coli* K1: *Escherichia coli* K1; *S. pneumoniae*; *Streptococcus pneumoniae*; *C. neoformans/C. gattii*; *Cryptococcus neoformans/Cryptococcus gattii*; *H. influenzae*; *Haemophilus influenzae*; *S. agalactiae*; *Streptococcus agalactiae*; *N. meningitidis*; *Neisseria meningitidis*; *L. monocytogenes*; *Listeria monocytogenes*. QUADAS: Quality Assessment of Diagnostic Accuracy Studies; NLR: Negative likelihood ratio; PLR: Positive likelihood ratio; CI: Confidence interval; DOR: Diagnostic odds ratio; SROC: Summary receiver operating characteristic; AUC: Area under the curve;

**Declarations**

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article and its supplementary information files.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Tables**

Table 1. Characteristics of the included studies
| Authors       | Year | Study Design   | Geographic distribution of strains | Source of strains        | Ref. method(s)                                      | TP  | FP  | FN  | TN  |
|--------------|------|---------------|-----------------------------------|--------------------------|-----------------------------------------------------|-----|-----|-----|-----|
| Arora        | 2017 | Prospective   | America                           | 62 samples from clinical | CSF culture                                         | 5   | 4   | 0   | 53  |
| Blaschke     | 2018 | Retrospective | America                           | 145 samples from clinical| CSF culture                                         | 38  | 0   | 1   | 106 |
| Leber        | 2016 | Prospective   | America                           | 1560 samples from clinical| CSF bacterial culture                                | 98  | 39  | 6   | 1451|
| Lee          | 2019 | Prospective   | Taiwan, China                     | 42 samples from clinical | Microbiological cultures                             | 6   | 10  | 0   | 26  |
| Lopez-Amor   | 2019 | Prospective   | Spain                             | 21 samples from clinical | Microbiological cultures                             | 7   | 4   | 1   | 9   |
| Radmard      | 2019 | Retrospective | Italy                             | 63 samples from clinical | conventional microbiological procedures/CMR          | 36  | 0   | 6   | 108 |
| Piccirilli    | 2018 | Retrospective | America                           | 658 samples from clinical| culture                                              | 31  | 1   | 15  | 658 |
| Lumley       | 2018 | Prospective   | England                           | 345 samples in the clinical microbiology laboratory | bacterial culture                                   | 0   | 9   | 0   | 336 |
| Lee          | 2018 | Retrospective | Singapore                         | 28 Clinical samples     | Culture and/or PCR                                   | 28  | 0   | 12  | 12  |
| Messacar     | 2016 | Retrospective | America                           | 138 samples from clinical| CSF samples                                          | 0   | 16  | 0   | 12  |
| Graf         | 2017 | Retrospective | America                           | 67 samples from clinical| lab-developed (LDT) real time PCR and bacterial culture | 0   | 16  | 0   | 12  |
| Du           | 2019 | Retrospective | China                             | 68 samples from clinical| routine culture                                      | 0   | 5   | 0   | 5   |
| Hanson       | 2016 | Retrospective | America                           | 342 samples from clinical| Microbiological cultures                             | 0   | 14  | 0   | 66  |
| Johan        | 2021 | Prospective   | Sweden                            | 4199 samples from clinical| in-house real-time PCR                                | 0   | 6   | 0   | 6   |
| Susanne      | 2020 | Retrospective | Germany                           | 4623 samples from clinical| bacterial culture and real-time PCR                  | 0   | 5   | 0   | 5   |
| Tam(a)       | 2020 | Retrospective | America                           | 1348 samples from clinical| CSF CrAg testing                                     | 0   | 0   | 1   | 6   |

**Note:** The table includes columns for authors, year, study design, geographic distribution of strains, source of strains, reference method(s), true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values.
Twenty-six de-identified residual CSF samples and two human-contrived CSF positive controls that have been previously tested by CSF culture and/or target specific polymerase chain reaction (PCR) tests were included in this study. The two human-contrived CSF positive controls were prepared from commercially-available NATtrol ME controls (ZeptoMetrix Corp., Franklin, MA, USA). The first positive control was comprised of cytomegalovirus, echovirus type 11, human herpesvirus 6, herpes simplex virus 2, varicella zoster virus, human parechovirus and Cryptococcus gattii. The second positive control was comprised of Escherichia coli K1, Streptococcus pneumoniae, Streptococcus agalactiae, Neisseria meningitidis, Haemophilus influenzae, Listeriamonocyctogenes and herpes simplex virus 1.

CSF culture for bacteria, Xpert EV for EV virus, Multicode-RTx HSV RT-PCR for HSV virus.

This article can only extract the total data, not the subgroups.

Abbreviations

TP: true positive  FP: false positive  FN: false negative  PN: true negative  PCR: Polymerase chain reaction

| Study            | Year | QUADAS-2 |
|------------------|------|----------|
| Arora17          | 2017 | Y Y UC Y Y Y Y Y Y Y Y |
| Blaschke18       | 2018 | Y N Y UC Y UC Y Y Y Y Y Y |
| Leber22          | 2016 | Y Y N N UC Y Y Y Y Y Y |
| Lee23            | 2019 | UC UC UC Y UC Y Y Y Y Y Y |
| Lopez-Amor25     | 2019 | Y Y UC Y UC Y Y Y Y Y Y |
| Radmard29        | 2019 | N N Y N UC Y N N N UC |
| Piccirilli28     | 2018 | UC N Y N UC Y N UC N N Y |
| Lumley26         | 2018 | Y UC Y UC Y Y Y Y Y Y Y Y |
| Lee23            | 2019 | UC N Y UC Y Y Y Y Y Y Y Y |
| Du19             | 2016 | Y N Y N UC Y Y Y Y Y Y N N |
| Messacar27       | 2017 | UC N Y N Y Y Y Y Y N Y |
| Graf20           | 2016 | UC Y Y N UC Y Y Y Y Y Y Y Y |
| Johan21          | 2021 | Y UC UC UC UC Y UC Y N N UC |
| Susanne10        | 2020 | Y UC Y UC UC Y UC Y Y Y N Y |
| Tam              | 2020 | Y UC Y UC UC Y UC Y Y Y Y Y Y |

Note: Y=Yes; N=No; UC=Unclear

Figures
Figure 1

Forest plots of sensitivity(A), specificity(B), PLR(C) and NLR(D) of FilmArray M/E panel.

Figure 2

Forest plots of sensitivity(A), specificity(B), PLR(C) and NLR(D) of FilmArray M/E panel.
Forest plots of DOR of FilmArray M/E panel.

Figure 3

Summary receiver operating characteristic of FilmArray M/E panel.
Figure 4

Deeks’ funnel plot asymmetry test to assess publication bias in estimates of diagnostic odds ratio for FilmArray M/E panel detection of meningitis and encephalitis.

Figure 5

Forest plots of sensitivity(A) and specificity(B) of FilmArray M/E panel for bacteria.
Figure 6

Forest plots of sensitivity (A) and specificity (B) of FilmArray M/E panel for viruses.

Figure 7

Forest plots of sensitivity (A) and specificity (B) of FilmArray M/E panel for viruses.
Forest plots of sensitivity (A) and specificity (B) of FilmArray M/E panel for fungi.

**Supplementary Files**

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- S2Text.Checklist.doc