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Diagnostic performance of micropthalmia transcription factor for melanoma: a systematic review and meta-analysis

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Abstract. – BACKGROUND AND AIM: The diagnosis of melanoma is still a clinical challenge, many studies reported that micropthalmia transcription factor (MITF) plays a role in diagnosing melanoma, but with considerable inconsistent results. The present work aimed to summarize the overall performance of MITF in diagnosing melanoma.

METHODS: A systematic literature search was performed in Pubmed and Embase for studies regarding the usefulness of MITF to diagnose melanoma. Data were retrieved and pooled sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio were determined. The post-test probability was performed to evaluate clinical usefulness. A summary receiver operator characteristic curve and the area under the curve were used to summarize the overall diagnostic accuracy.

RESULTS: Nine studies with 1,299 subjects (651 melanomas and 648 non-melanomas) were included for present meta-analysis. The pooled sensitivity and specificity of MITF for diagnosing melanoma were 0.84 (95% CI: 0.81-0.87) and 0.96 (95% CI: 0.95-0.98), respectively. The positive likelihood ratio was 17.73 (95% CI: 10.85-28.99), negative likelihood ratio was 0.18 (95% CI: 0.10-0.32) and diagnostic odds ratio was 221.56 (95% CI: 66.16-741.96). In a setting of 20% prevalence of melanoma, the probability of melanoma would be 92% if the MITF test was positive, and the probability of melanoma would be 1% if it was negative. The area under the summary receiver operator characteristic curve was 0.99.

CONCLUSIONS: MITF may play a valuable role in the diagnosis of melanoma with a high specificity. Nevertheless, the results of MITF should be interpreted with the combination of other test results and clinical findings.

Key Words:
Micropthalmia transcription factor, Melanoma, Diagnosis, Meta-analysis.

Introduction

Melanoma is an important public health burden in the worldwide with increasing caution, and in United States, the incidence of melanoma has been increasing faster than that of any other kinds of cancer[1,2]. Recent studies reported that melanoma is now the fifth most common cancer in the United States, and it is estimated that 76,250 melanoma patients were newly diagnosed in 2012[3]. In addition, melanoma incidence may be underestimated because many superficial and in-situ melanomas in outpatient settings are not reported[4]. Although melanoma accounts for less than 5% of all skin cancers, it is responsible for the majority of skin cancer-related mortality[5]. According to surveillance, epidemiology and end results data, there were an estimated 9,180 deaths attributed to melanoma in 2012, and the mortality of melanoma continues to rise[3]. Growing studies suggest that early detection of malignant melanoma remains the key factor in lowering mortality from this cancer[6].

The diagnosis of melanoma remains a clinical challenge. The standard method to diagnose melanoma is by biopsy followed by histopathological examination, however, the commonly used markers for melanoma (S100, HMB45, Melan-A and Tyrosinase A, etc) are not satisfied in all cases, and it is reported that none of these markers is entirely sensitive for the diagnosis of even typical melanomas[7]. This situation is even worse in desmoplastic melanomas, which are typically negative for common specific melanoma markers[8]. Thus, the search for reliable melanoma markers continues. Microphthalmia transcription factor (MITF) is an important nuclear transcription regulator protein and a com-

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ponent of the signal transduction pathway for the development and differentiation of melanocytes[9]. When malignant melanoma occurs, MITF appears to be critical in tumor cell survival and it is the only nuclear melanocytic marker, thus, plays a role in diagnosing MITF[10,11]. The application of MITF as a marker in the diagnosis of melanoma has been extensively studied, but the results are not universally accepted. The present study aimed to summarize the overall diagnostic accuracy of MITF for melanoma.

Methods

Data Sources

We performed systematic literature search in Pubmed and Embase databases for relevant studies that reported diagnostic accuracy data of MITF for melanoma (Up to October 2013). The following search terms were used: "microphthalmia transcription factor *or* MITF" in combination with "melanoma" in combination with "sensitivity *or* specificity" The search was restricted to human subjects. Although no language restrictions were imposed initially, for the full-text review and final analysis, our study only permitted articles published in the English language. We also reviewed the relevant references listed in the searched papers to identify potential related articles.

Study Selection

A study was included in present meta-analysis if it fulfilled the following criteria: (1) It was a diagnostic report, and there were a case group and control group; (2) Original publication; (3) True-positive (TP), false-positive (FP), false negative (FN), and true negative (TN) results of the diagnostic tests were reported or could be calculated; and (4) The article should be written in English. The studies with populations fewer than 20 were excluded in order to avoid selection bias. Conference abstracts were excluded because of the limited data provided. Two authors (JS and QQL) independently screened the articles for inclusion. Disagreements between authors were resolved by consensus.

Data Extraction and Quality Assessment

The data was extracted independently by two of the reviewers (JS and QQL) using a pre-designed form. For each study, the following information was recorded: first author, year of publication, country of origin, method of MITF assay, and data for two-by-two tables and so on. The methodological quality of included studies was estimated by using the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) Tool[12]. This is an evidence-based score tool to quality assessment intended for use in meta-analysis of diagnostic accuracy studies. A quality index is generated, with a maximum value of 14. Discrepancies between the extracted data were resolved by team discussion.

Statistical Analysis

First, the heterogeneity among included studies was evaluated by the I^2 test, $I^2 \geq 50\%$ indicated substantial heterogeneity, then the random-effects model was chosen to synthesize the data; Otherwise, the fixed-model was chosen. The pooled sensitivity and specificity, positive and negative likelihood ratios (PLR and NLR, respectively), and diagnostic odds ratio (DOR) with their 95% confidence intervals (95% CIs) were calculated. The Fagan's nomogram was used to calculate the posttest probability. We also constructed summary receiver operating characteristic (SROC) curve to summarize the study results and calculate the respective area under the SROC curve (AUC) and Q value, where sensitivity was equal to specificity, on the SROC curve[13]. Since publication bias is a concern in meta-analyses of diagnostic studies, we tested for it using Deeks' funnel plots[14]. All meta-analyses were performed using two statistical software programs: Meta-DiSc 1.4 for Windows (XI, Cochrane Colloquium, Barcelona, Spain) and Stata (version 12.0, Stata Corporation, College Station, TX, USA). All statistical tests were two-sided, and significance was set at $p < 0.05$.

Results

Clinical Characteristics of Included Studies

After a systematic literature search and selection, nine reports met the inclusion criteria and were selected for the meta-analysis[15-23]. Flow diagram was shown in Figure 1. Studies were excluded for primarily the following reasons: they were not diagnostic works (no control groups), or they did not report sufficient data to construct a 2 ×2 table.

The characteristics of included melanoma patients were shown in Table I. There were 1,299 subjects, containing 651 melanomas and 648 non-melanomas. The diagnosis of melanoma was

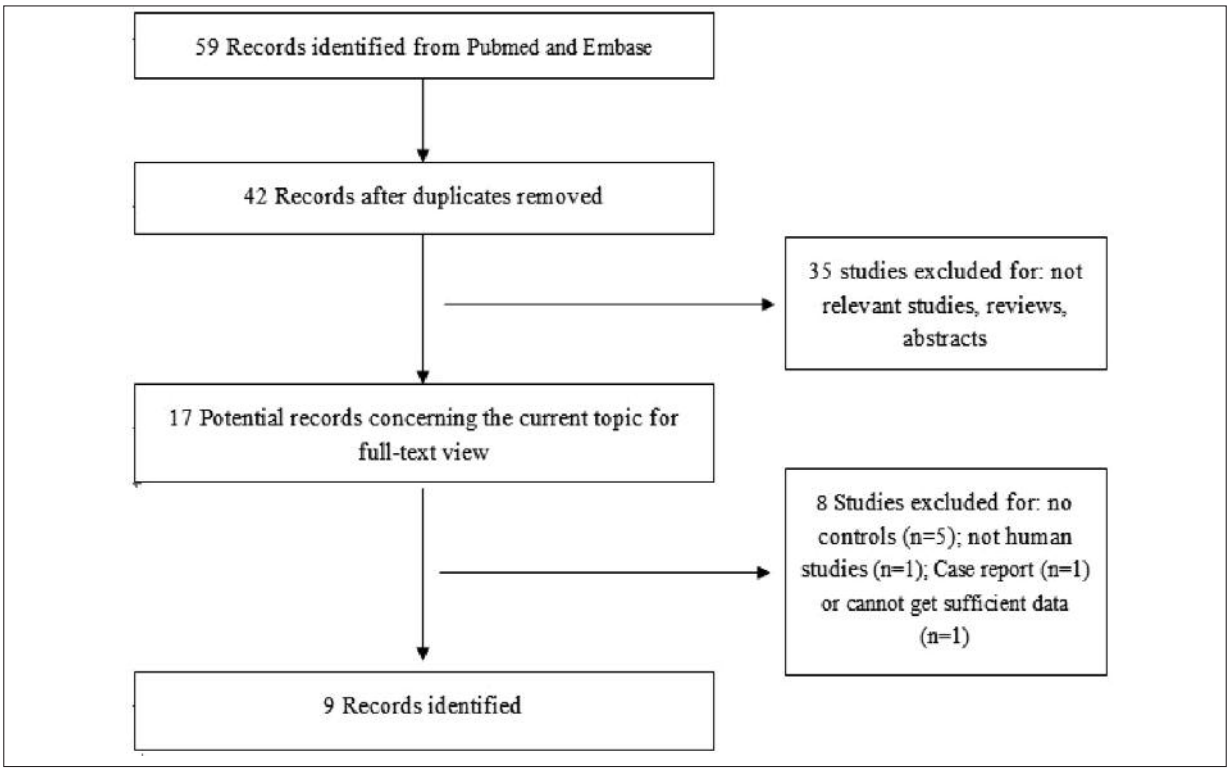

Figure 1. Flow diagram of study selection process.

based on histopathological results, findings as gold standard. Of included studies, seven used the immunohistochemistry method for MITF detection in tissue samples, and the immunocytochemistry method was used in the other two studies in cytological samples[18,20]. The subjects distribution and methodological quality assessment for the included nine studies were shown in Table II. Eight studies included in our meta-analysis showed high quality with QUADAS scores ≥ 9, suggesting the reliability of our findings.

Data Synthesis and Meta-Analysis

The heterogeneity analysis showed I^2 of 92.1% for sensitivity, 58.7% for specificity, 17.2% for PLR, 85.3% for NLR, and 69.3% for DOR, represented a significant heterogeneity, thus, the random effects model was selected for data synthesis in this meta-analysis.

The pooled sensitivity of MITF was 0.84 (95% CI, 0.81-0.87) (Figure 2, Left) and the pooled specificity was 0.96 (95% CI, 0.95-0.98) (Figure 2, Right). The PLR was 17.73 (95% CI, 10.85-28.99), the NLR was 0.18 (95% CI, 0.10-0.32), and the DOR was 221.56 (95% CI, 66.16-741.96). The SROC curve shows an overall summary of tests, which illustrates the relationship between sensitivity and specificity. As shown in Figure 3, the AUC was 0.99 and the Q value was 0.95, indicating a high diagnostic accuracy. Figure 4 shows the Fagan's nomogram for likelihood ratios, and the results indicated that the MITF for detection melanoma increased the post-probability to 92% when the results were positive and reduced the post-probability to 1% when the results were negative.

Of the nine studies, seven identified MITF in tissue samples, two tested MITF in cytological samples. The pooled sensitivity, specificity, PLR, NLR, and DOR for the tissue samples were listed as follows: 0.82 (95% CI 0.78-0.85), 0.96 (95% CI 0.94-0.98), 16.85 (95% CI 9.62-29.51), 0.24 (95% CI 0.14-0.40), 124.41 (95% CI 38.75-399.43), the AUC was 0.98. These results suggest that tissue sample is a reliable matrix for diagnostic usefulness of MITF in melanoma. Since there were only two studies used cytological samples, we can't make a sub-group analysis based on cytological samples.

Evaluation of Publication Bias

Our meta-analysis used Deeks' funnel plot asymmetry test to evaluate the final included studies for potential publication bias (Figure 5).

Table I. Clinical summary of include melanoma patients.

Author (Ref)	Year	Country	Melanoma cases	Melanoma diagnosis standard	Specimen	Melanoma assay method	Melanoma patients details
King R	1999	USA	76	Histopathology	Tissue	Immunohistochemistry	Melanomas in situ (n=19), conventional melanomas (n=50), metastatic melanoma (n=7)
Dorvault CC	2001	USA	44	Histopathology	Cell blocks	Immunohistochemistry	Melanomas (n=44, including 3 patients with spindle-cell melanoma)
King R	2011	USA	58	Histopathology	Tissue	Immunohistochemistry	Melanomas in situ (n=5), superficial spreading melanomas (n=24), lentigo maligna melanomas (n=11), nodular melanomas (n=4), desmoplastic neurotropic melanomas (n=14)
Koch MB	2001	USA	20	Histopathology	Tissue	Immunocytochemistry	Desmoplastic/spindle cellmelanoma (n=20)
Miettinen M	2001	USA	297	Histopathology	Tissue	Immunohistochemistry	Conventional melanomas (n=266), desmoplastic melanomas (n=30), melanoma with rhabdoid features (n=1)
Sheffield MV	2002	USA	40	Histopathology	Cell blocks	Immunocytochemistry	Melanomas (n=40, including 2 patients with spindle-cell melanoma)
Xu X	2002	USA	30	Histopathology	Tissue	Immunohistochemistry	Desmoplastic melanomas (n=8), spindle-cell melanomas (n=8), epithelioid melanomas (n=14)
Granter SR	2002	USA	36	Histopathology	Tissue	Immunohistochemistry	Conventional melanomas (n=36)
Buonaccorsi JN	2013	USA	50	Histopathology	Tissue	Immunohistochemistry	Melanomas in situ (n=50)

Table II. Patients distribution between case and control group.

Author (Ref)	Case	Control	TP	FP	FN	TN	QUADAS
King R[15]	76	60	76	0	0	60	8
Dorvault CC[16]	44	37	44	0	0	37	9
King R[17]	58	53	45	0	13	53	10
Koch MB[18]	20	42	11	3	9	39	9
Miettinen M[19]	297	260	236	13	61	247	10
Sheffield MV[20]	40	32	40	1	0	31	10
Xu X[21]	30	42	17	0	13	42	9
Granter SR[22]	36	102	29	6	7	96	11
Buonaccorsi JN[23]	50	20	50	0	0	20	11

The slope coefficient was associated with a *p* value of 0.25 suggesting symmetry in the data and a low likelihood of publication bias.

Discussion

Melanoma remains a public health problem in the worldwide and to make an early detection of a melanoma is a major concern for clinicians[6,24]. MITF has been used to diagnose melanoma for many years and many studies have investigated the diagnostic performance of MITF for melanoma, but with considerable inconsistent results. Our work summarized the overall diagnostic accuracy of MITF for melanoma and our results suggested that MITF may be function as a useful biomarker for melanoma.

The pooled sensitivity and specificity for MITF diagnosing melanoma were 0.84 and 0.96, respectively, with a high specificity for the confirmation of melanoma. DOR is defined as the ratio of the odds of a true positive to the odds of a false positive, it is a single indicator of diagnostic accuracy that combines the data from sensitivity and specificity into a single number. The value of a DOR ranges from 0 to infinity, with higher values indicating higher accuracy. In our meta-analysis, the mean DOR was 221.56, indicating that MITF assay seemed to be valuable in the diagnosis of melanoma. Since the DOR is not easy to interpret and use in clinical practice, likelihood ratios are considered more clinically meaningful, we also presented both PLR and NLR as our measures of diagnostic accuracy. The value of pooled PLR higher than 10 indicates that the positive result of the given test is useful for the confirmation of presence of melanoma, while the value of pooled NLR lower than 0.1 indicates that the negative result is useful for the exclusion of the disease. In present meta-analysis, a PLR value of 17.73 suggests that patients with melanoma have about 18-fold higher chance of being MITF assay-positive compared with pa-

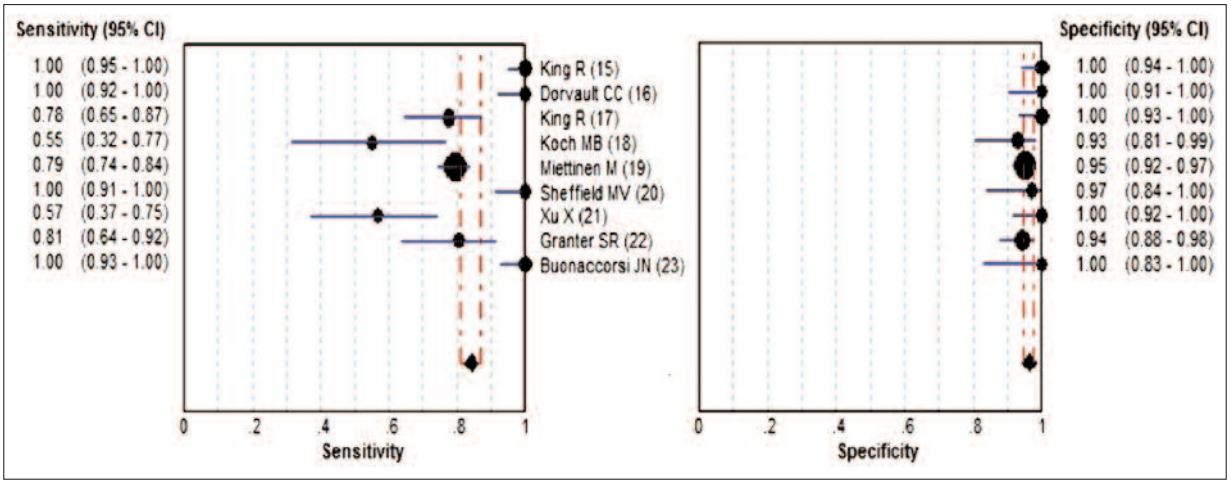

Figure 2. Forest plot of sensitivity and specificity of MITF for the diagnosis of melanoma. The point estimates of sensitivity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

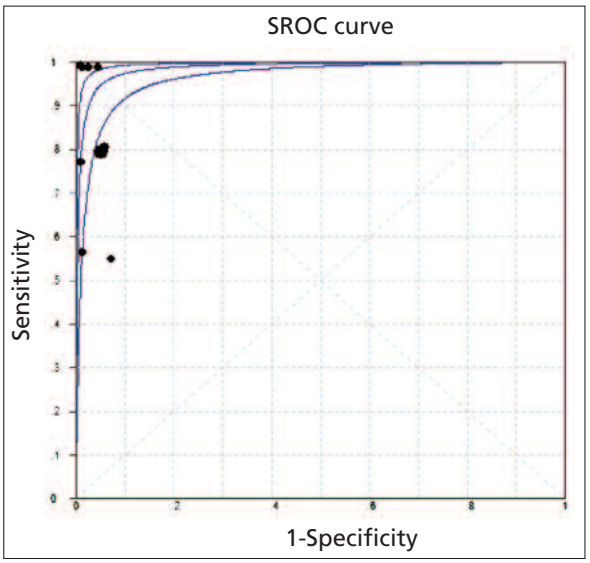

Figure 3. SROC curve of MITF for the diagnosis of melanoma. The size of each solid circle represents the size of each study in the meta-analysis. The regression SROC curve indicates the overall diagnostic accuracy.

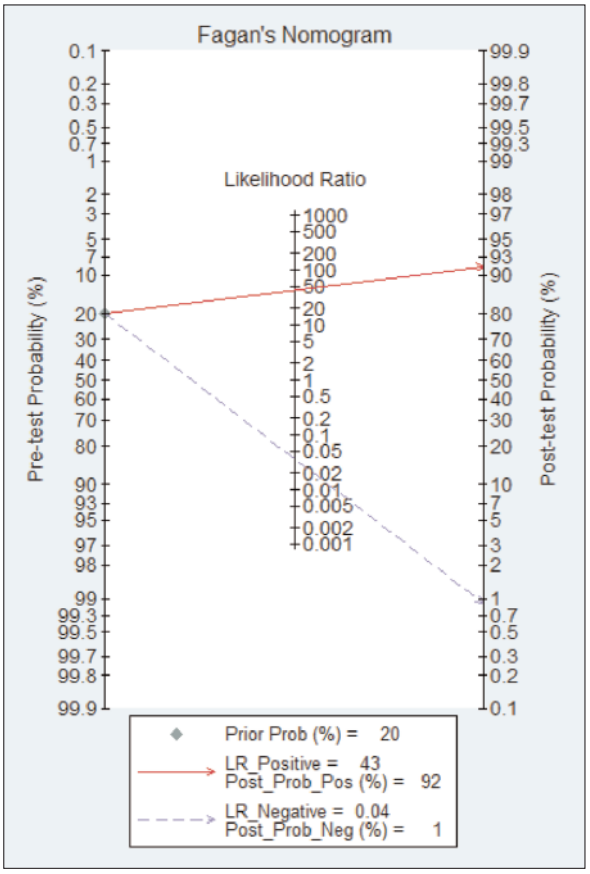

Figure 4. Fagan's nomogram for likelihood ratios and the probability for MITF in the diagnosis of melanoma.

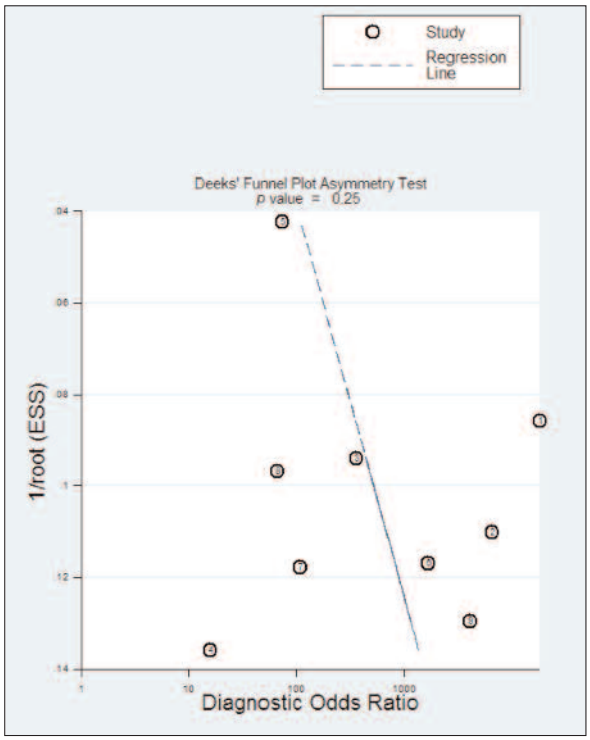

Figure 5. Linear regression test of funnel plot asymmetry. The statistically non-significant p value of 0.25 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

tients without melanoma. On the other hand, NLR was found to be 0.18 in the present meta-analysis. It means if the MITF assay result was negative, the probability that this patient has melanoma is 18%, which is not low enough to rule out melanoma.

The SROC curve presents a global summary of test performance, and shows the trade-off between sensitivity and specificity. Our results of analysis based on SROC curve showed the maximum joint sensitivity and specificity was 0.95, the AUC was 0.99, suggesting the level of overall accuracy was relative high. In clinical practice, whether MITF assay is appropriate as a diagnostic test depends ultimately on the predictive values in the intended setting. Fagan's nomogram showed that in a setting of 20% prevalence of melanoma, the probability of melanoma would be less than 1% if the MITF test was negative and the probability of melanoma would be more than 92% if the MITF test was positive, which is very helpful for the diagnosis of melanoma. Consider for the results from most included studies had similar findings with high diagnostic accuracy, and the numbers of include studies were lim-

ited, QUADAS scores were not used to perform a meta-regression to assess the influence of study quality on the accuracy of MITF in the diagnosis of melanoma. For the same consideration, no exploration was made of whether or not study design, such as blinded and prospective design, cross-sectional, consecutive/random, affect the diagnostic accuracy of MITF.

There are several points that should be addressed when explain and apply the results of MITF test. First, we noticed that the sensitivity of MITF for spindle cell and desmoplastic melanomas was low, as reported by Granter et al[26], only 5 of 21 spindle cell and desmoplastic melanomas were reactive for MITF. Such result means that the reactivity of MITF to melanoma may be tumor-subtype specific, further work is needed to further define sensitivity, specificity, and the utility of MITF as a melanoma marker[19]. We admit that the application of MITF for melanoma diagnosis remains to be controversial, and we suggest that the results of MITF test should be interpreted with the combination of other test results and clinical findings[19,23]. Second, although we carried out a comprehensive literature search, only nine reports were included in present meta-analysis, the sample sizes of several included studies were rather small and they may not have adequate ability to assess the diagnostic accuracy. In addition, we included only English-language articles, this may be cause language bias, and this meta-analysis limited to published studies that may miss some of the gray literature.

Conclusions

To our best knowledge, this is the first meta-analysis to summarize the diagnostic performance of MITF for melanoma. Taken together, the evidence from current meta-analysis suggests that MITF plays a role in the diagnosis of melanoma. Further studies are needed to confirm our findings.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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