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# Diagnostic performance of mycological tests for invasive pulmonary aspergillosis in non-haematological patients: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Increasing numbers of patients with non-haematological diseases are infected with invasive pulmonary aspergillosis (IPA), with a high mortality reported which is mainly due to delayed diagnosis. The diagnostic capability of mycological tests for IPA including galactomannan test, (1,3)-β-D-glucan test, lateral flow assay, lateral flow device and PCR for the non-haematological patients remains unknown. This protocol aims to conduct a systematic review and meta-analysis of the diagnostic performance of mycological tests to facilitate the early diagnosis and treatments of IPA in non-haematological diseases.

**Methods and analysis** Database including PubMed, CENTRAL and EMBASE will be searched from 2002 until the publication of results. Cohort or cross-sectional studies that assessing the diagnostic capability of mycological tests for IPA in patients with non-haematological diseases will be included. The true-positive, false-positive, true-negative and false-negative of each test will be extracted and pooled in bivariate random-effects model, by which the sensitivity and specificity will be calculated with 95% CI. The second outcomes will include positive (negative) likelihood ratio, area under the receiver operating characteristic curve and diagnostic OR will also be computed in the bivariate model. When applicable, subgroup analysis will be performed with several prespecified covariates to explore potential sources of heterogeneity. Factors that may impact the diagnostic effects of mycological tests will be examined by sensitivity analysis. The risk of bias will be appraised by the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2).

**Ethics and dissemination** This protocol is not involved with ethics approval, and the results will be peer-reviewed and disseminated on a recognised journal.

**PROSPERO registration number** CRD42021241820.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis will incorporate all studies on the diagnostic sensitivity and specificity of current mycological tests (eg, galactomannan, (1,3)-β-D-glucan, lateral flow assay, lateral flow device and PCR) in non-haematological patients.
⇒ The evidence of results of this study will be assessed by the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2).
⇒ Different subgroup analysis and sensitivity analysis will be conducted.
⇒ Outcomes from studies using different reference standards will unable to be compared with each other.
⇒ For aspergillus PCR assay, only commercialised PCR will be addressed due to the low quality and standards of manufacture for home-brew PCR.

## INTRODUCTION

Invasive pulmonary aspergillosis (IPA), characterised by the attack of aspergillus hyphae on lung tissue, is the most frequent invasive fungal infection in immunocompromised patients with haematological malignancies or allogenic stem cell transplantation with high mortality rates.[1] Recently, patients with non-haematological diseases such as solid malignancy, chronic obstructive pulmonary disease (COPD) and live cirrhosis, etc, have been increasingly found to be infected with IPA, with reported incidence ranging from 3.6% to 16.5%.[2–4] The prognosis of IPA patients from non-haematology units is as poor as that of the haematology;[5–7] therefore, the early diagnosis and timely treatment are essential to improve prognosis and reduce mortality for this patient population.[8]

Compared with the haematological patients, the diagnosis of IPA in non-haematological patients is often overlooked.[9] For non-haematological patients, the clinical symptoms and images of IPA, such as persistent febrile neutropenia, halo sign and air-crescent sign, are not typical as in haematological patients.[10] The version 2019 of European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), which is the newest update of diagnostic criteria of IPA, has recognised

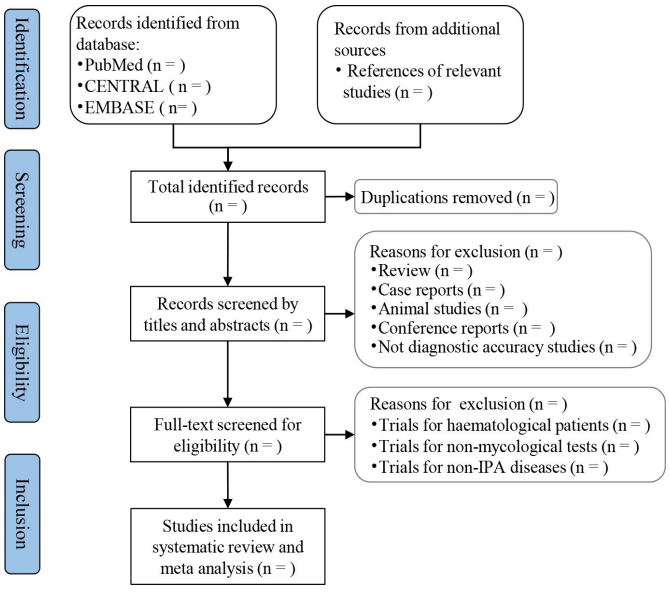


**Figure 1** Flow diagram of literature selection. IPA, invasive pulmonary aspergillosis.

the increasing occurrence of IPA in non-haematological and has included some non-haematological diseases as host factors such as chronic granulomatous disease.[11] Importantly, the non-haematological patients infected with IPA are often featured with non-neutropenia, and the pathogenesis of aspergillus tends to be airway invasion rather than angioinvasion, which causes a different clinical picture and performance of laboratory tests from that in haematological patients.[12–14] For example, the serum galactomannan (GM) test has a lower diagnostic yield in non-haematological patients than those in haematological patients (66.7% vs 23.1%).[15 16]

Mycological tests of aspergillosis, including GM test, (1,3)-β-D-glucan (BDG) test, lateral flow assay (LFA), lateral flow device (LFD) and PCR,[11 17] have been emerged and widely used in diagnosing suspected IPA in clinical practice. Due to the non-specific clinical signs of IPA, mycological tests are the key evidence to establish the diagnosis of IPA to prompt early initiation of antifungal therapy.[1] However, the diagnostic capability of these mycological tests for non-haematological patients remains unclear. Current available studies generally had small sample sizes, and the diagnostic yields of tests varied. For example, the sensitivities of the serum tests of GM, BDG and PCR range from 11% to 80% which increase to 44%–90% when tested in bronchoalveolar lavage (BAL) fluid for the non-haematological patients.[18–23] Recent novel tests such as LFD and LFA appear to have better results, with sensitivities of 77%–94% and specificities of 81%–92% in patients with non-haematological diseases.[24 25] Moreover, the EORTC/MSG definitions have been recognised as diagnostic standards for IPA; however, other reference criteria including AspICU algorithm and Bulpa definition have been used,[26 27] which may impact the diagnostic yields for mycological tests. Therefore, we will perform a systematic review and meta-analysis of mycological tests in non-haematology patients based on rigorous methodology, aiming to summarise diagnostic recommendations to facilitate the diagnosis of IPA in this population.

## METHOD

This systematic review and meta-analysis will be reported in adherence to the items of Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P).[28] The information about method of this review also has been registered on PROSPERO with registration number CRD42021241820.

### Search methods for identification of studies

We will search PubMed, CENTRAL and EMBASE for appropriate literatures. A search strategy with medical and subject headings and text words as search fields, using the keywords 'IPA', 'invasive fungal disease' and 'diagnosis', will be created. We will restrict the language of publication to English, and the year of publication will be from 2002 onwards, in which the first version of EORTC/MSG definition was published. In addition, we will check for suitable literatures from references of other pertinent reviews. The search strategy for PubMed is presented in online supplemental file 1.

### Selection of studies

The retrieved documents will be imported into Endnote X9 (Clarivate Analytics US, Philadelphia), and the duplications will be removed. The remaining literatures will be first screened by reviewers (ML and GC) independently according to the previous defined Participaants, Intervention, Control, Outtcomes, and Study dessigns (PICOS) criteria based on information of the titles and abstracts. The full text screening will be carried out to obtain the final eligible studies by two reviewers (WX and TM) simultaneously. Discussion with senior reviewers (JF and BM) will be managed to solve the discrepancy of reviewers. The screening process of studies will be shown in figure 1.

### Inclusion and exclusion criteria

Generally, we will include studies assessing the diagnostic effect of mycological tests for IPA in non-haematology patients. Studies that do not report the sensitivity and specificity of diagnostic tests will be excluded. We will also exclude studies that investigating on other invasive fungal diseases (eg, invasive candidiasis disease and invasive cryptococcosis disease).

### Type of studies

The eligible designs of studies will be case-control and cohort study.[29] Case reports and other observational studies without non-IPA groups will be ineligible. We will also exclude literatures that do not provide details of the study designs.

### Participants

Patients with non-haematological diseases will be eligible. Studies that only include or include more than 49% of

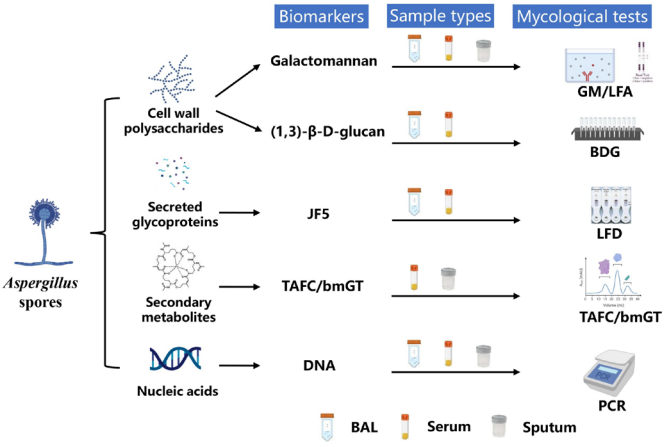


**Figure 2** Mycological tests using differents sample types for the diagnosis of invasive pulmonary aspergillosis. BAL, bronchoalveolar lavage fluid; GM, galactomannan; BDG, (1,3)-β-D-glucan; LFA, lateral flow assay; LFD, lateral flow device; TAFC/bmGT, triacetylfusarinine C or bis(methylthio) gliotoxin.

patients with haematological diseases such as haematological malignancy or haematopoietic stem cell transplantation will be excluded.[30] Patients with neutropenia and solid organ transplantation (SOT) as typical IPA host factors will also be excluded. The eligible underlying diseases will be as follows: solid organ malignancy, rheumatological disease, diabetes mellitus, respiratory disease, liver disease, cardiovascular disease, HIV infection, influenza or COVID-19.

## Index tests

The eligible mycological tests will include:

1. GM test (eg, Platelia Aspergillus Ag, Bio-Rad Laboratories, California, USA).
2. BDG test (eg, Fungitell kit, Associates of Cape Cod, East Falmouth, Massachusetts, USA; β-Glucan Test, FUJIFILM Wako Pure Chemical, Tokyo, Japan; Fungitec G-MK, Seikagaku, Tokyo, Japan; β-Glucan Test; Maruha, Tokyo, Japan).
3. LFA (sōna Aspergillus Galactomannan LFA, IMMY, Norman, Oklahoma, USA).
4. LFD (eg, Aspergillus-specific LFD, OLM Diagnostics, Newcastle upon Tyne, UK; Aspergillus-specific LFD, ISCA Diagnostics, Truro, Cornwall, UK).
5. Aspergillus PCR test, as the quality and standards of manufacture of home-brew PCR assay are low, only commercialised PCR will be included (eg, artus Aspergillus diff. RG PCR Kit, QIAGEN, Hilden, Germany; Multiplex real-time PCR kit, AsperGenius, Maastricht, the Netherlands; Aspergillus spp ELITe MGB Kit, The ELITechGroup, Puteaux, France; MycAssay Aspergillus Kit, Myconostica, UK).
6. Triacetylfusarinine C or bis(methylthio)gliotoxin (liquid chromatography tandem mass spectrometry (LC-MS/MS) method).
7. Aspergillus-specific IgG test (eg, *Aspergillus fumigatus* IgG ELISA kits, Immunolab GmbH, Kassel, Germany).

Other biomarkers aiming to diagnose the IPA will also be included. Samples used to detect aspergillosis biomarkers such as serum, sputum and BAL fluid are all eligible (figure 2). Except a single mycological test, combination of tests such as BAL PCR plus GM test, serum GM test and BDG test, or BAL GM test plus serum GM are all in the scope of this review.[23 31]

## Reference standards

Definitions of the EORTC/MSG with its modifications will be used as reference standards.[11 32 33] The patients will be classified as 'proven', 'probable', 'possible' or 'no IPA' based on the standards. For the possible IPA, evidence of fungal infection on the autopsy is usually absent, and prophylactic antifungals are not given in the clinical management of these patients.[34] Patients with proven or probable IPA will be classified as IPA case group, while those with possible IPA and no IPA will be classified as no IPA group. Also, studies that excluding possible IPA group will be analysed separately. Additionally, studies using other reference standards include AspICU classification for patients in ICU, definition of Bulpa *et al* for COPD, The International Society for Heart and Lung Transplantation (ISHLT) definition for cardiothoracic transplant recipients, ECMM/ISHAM (The European Confederation for Medical Mycology and the International Society for Human and Animal Mycology) consensus criteria for COVID-19, definition of Schauwvlieghe *et al* and Verweij *et al* for patients with influenza in ICU will be also included in this review.[26 27 35–38] The criteria of IPA are all listed in online supplemental file 2 with a precise description. To avoid the bias introduced by different reference standards, studies will be included in meta-analysis separately based on the criteria of IPA used. For those tests that are not qualitative, we do not preset thresholds in order to explore the multifaceted diagnostic performance of the tests.

## Collection and management of data

Two reviewers (CX and LD) will extract the data with a predesigned form. The information extracted will include basic characteristics of the studies (ie, year of publication, study design, recruitment of patient, underlying disease and department, reference standard with its details of modifications, administration of antifungal drugs and incorporation of mycological tests to reference standard) and the diagnostic accuracy of mycological tests against the reference standard (ie, sensitivity and specificity; true-positive, false-positive, false-negative, true-negative and false-negative). When applicable, the cut-off values of the index tests will also be extracted.

## Outcomes of the review

The primary outcomes of this review will be the sensitivity and specificity of single mycological tests or a combination of several tests, and the secondary outcomes were positive (negative) likelihood ratio (LR), area under the

receiver operating characteristic (AUROC) curve and diagnostic OR (DOR).

### Strategy for data synthesis

Data of diagnostic accuracy of index tests per study will be pooled using bivariate random-effects model to calculate the sensitivity and specificity.[39] The forest plots and summary receiver operating characteristics curves will be plotted. Other pooled diagnostic effect including positive (negative) LR, AUROC and DOR can also be calculated in that model. The magnitude of heterogeneity will be evaluated by I-squared and the Cochran Q test. Also, a p value <0.05 in Deek's regression test means the publication bias of result. The Stata software v16.0 (StataCorp, College Station, Texas) will be used to perform all the analysis with the midas set of commands.

### Subgroup analysis

To examine the heterogeneity of the sensitivity and specificity, several covariates will be used in the bivariate random-effects model assuming that no interaction exists among the covariates. If necessary, posthoc analyses will be performed where possible. The current prespecified covariates are as follows:

1. Version 2008 versus 2002 of EORTC/MSG categories. As the newly published 2020 version of the EORTC/MSG categories is used by a few studies, we are unable to explore its impact on the heterogeneity.
2. Modified versus unmodified EORTC/MSG criteria.
3. Prospective versus retrospective enrolment of patients.
4. Case control versus cohort.
5. The reference incorporating the index test versus those not incorporating.
6. The use of antifungal prophylaxis (yes vs no), including itraconazole, amphotericin B, posaconazole, etc.
7. Patients admitted in ICU versus general wards.

### Sensitivity analysis

Sensitivity analysis will be performed according to the characteristics of studies.[40] We will exclude studies with a high risk of methodological bias to observe changes of the combined diagnostic accuracy, and we speculate that mycological tests in studies with methodological bias have a higher diagnostic effect. As the division of IPA may introduce bias on the results,[41] patients classified as possible IPA will be left out of the analysis or grouped into IPA case group. For the tests that are reported with several diagnostic results from different techniques, we will use the best results for meta-analysis and the least satisfactory results for sensitivity analysis.

### Risk of bias assessment

The risk of bias will be assessed with the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2). The tool covers four domains of patient selection, index test, reference standard, and flow and timing, each of which will be judged as 'yes', 'no' or 'unclear' depending on whether the designs of studies meet the requirements of the question. If all questions are 'yes', then the domain is at '"low risk of bias'. If at least one question is 'no', then the domain has a 'high risk of bias'; otherwise the domain has an 'unclear' risk of bias. The results of the assessment will be presented graphically.

### Patient and public involvement

Patients will not be directly involved in this review as the data will be extracted from studies.

## DISCUSSION

The diagnostic frame for IPA is composed of host factors, clinical characteristics and mycological tests.[11] With the merits of rapidity and well-tolerant procedure, mycological tests of aspergillosis are indispensable and crucial for the screening and diagnosis of IPA. Mycological tests including GM, BDG, LFA, LFD and PCR, showing different diagnostic performance, are recommended for diagnosing IPA in haematological patients by EORTC/MSG.[11] The occurrence of IPA has been increasingly reported in non-haematological diseases; however, the diagnostic capability of above mycological examinations cannot be generalised to this patient population with distinct immune status.[42]

Most of the haematological patients infected with aspergillosis have profound neutropenia, for which the clinical manifestations are usually notable, and diagnostic yield of the mycological tests are already established.[43] In non-haematological wards, underlying diseases predisposing to IPA infection include respiratory diseases such as COPD, idiopathic pulmonary fibrosis, lung cancer, influenza, liver cirrhosis, HIV infection and other critical ill diseases.[15 37 44–46] Patients with these diseases usually suffer from excessive environmental exposure of aspergillosis, immunodysfunction caused by the use of steroid, antibiotics and immunosuppressive therapy, and immune derangement condition due to critical ill diseases.[5 43 46 47] The absence of neutropenia and airway invasion of aspergillosis are the essential pathogenesis for these patients population.[48] Different pathogenesis of haematological and non-haematological patients contributes to varied clinical features and diagnostic performance of mycological tests.[8] The absent classical clinical symptoms and host factors of IPA as in haematological diseases protract the diagnosis of IPA and lead to a high mortality in non-haematological patients.[46] Thus, the diagnostic capability of mycological tests for IPA is urgently needed to be established in patients with non-haematological diseases.

Four previous reviews summarised the accuracy of mycological tests in diagnosing IPA in non-haematology patients.[30 49–51] In these reviews, it is well accepted that the clinical signs of IPA in non-haematological patients are less typical than that in haematological patients, and the commonly used mycological tests for diagnosing IPA in haematological patients show different diagnostic accuracy in non-haematological patients (eg, BAL GM, with a sensitivity of 71% for haematological patients while dropping to 22% for non-haematological patients). Two of

these reviews consistently agreed that GM in BAL exhibits better sensitivity comparing with in serum and other mycological tests.[30 49] The other two reviews concluded that single test yields unsatisfactory diagnostic capability, while a combination of several tests may improve the diagnostic performance.[50 51] However, critical information such as sensitivity and specificity of tests was not systematically evaluated. Further, most of reviews did not take comprehensive literature retrievals, and the risk of bias of included studies was not assessed.[49–51] There is one study by Bassetti *et al* that conducted a systematic review on current evidence of diagnostic performance of GM, BDG, PCR and radiology for IPA in non-haematological and non-SOT patients, while the patients included were from ICU only, and there was a moderate risk of bias.[30]

Therefore, it is necessary to conduct a meta-analysis and systematic review of the studies that test the diagnostic yield of IPA for non-haematological patients to facilitate the awareness of these mycological tests in this population. The study results will elucidate the diagnostic performance of each test to direct their different use in clinical practice in this broad patient population.

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**Contributors** JF and BM conceived the study topic and design. WX, CX, LD and TM developed the search strategy. ML and GC written the registry protocol and submitted it on the PROSPERO. ML and GC drafted the manuscript. JF and YL refined the protocol, and all the authors (JF, ML, GC, CX, WX, LD, BM, YL and TM) approved the final protocol and manuscript.

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