A Comprehensive Evaluation of the Bruker Biotyper MS and Vitek MS Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry Systems for Identification of Yeasts, Part of the National China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study, 2012 to 2013

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Among the 2,683 yeast isolates representing 41 different species (25 *Candida* and *Candida*-related species and 16 non-*Candida* yeast species) collected in the National China Hospital Invasive Fungal Surveillance Net (CHIF-NET) program (2012 to 2013), the Bruker Biotyper MS matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) system exhibited significantly higher accuracy rates than the Vitek MS system for identification of all yeast isolates (98.8% versus 95.4%, $P < 0.001$ by Pearson's chi-square test) and for all *Candida* and *Candida*-related species isolates (99.4% versus 95.5%, $P < 0.001$).

Invasive fungal infections are associated with high mortality and morbidity rates, especially in immunocompromised and critically ill patients (1–3). Although the most important causes of opportunistic mycoses are *Candida* species, especially *Candida albicans*, the incidence of invasive fungal infections due to non-*albicans Candida* species is increasing, especially in China (4–8).

The National China Hospital Invasive Fungal Surveillance Net (CHIF-NET) program is a nationwide, multicenter surveillance network established in July 2009 to provide updated information on the epidemiology of invasive fungal infections in China (9). The continual expansion of the CHIF-NET program has led to a dramatic increase in the number of laboratories submitting isolates. Therefore, an accurate, time-saving, cost-effective, and user-friendly yeast identification method is needed to replace the high-cost and labor-intensive sequence-based methods used by the central laboratory.

Several studies have reported that matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is an accurate, rapid, and inexpensive method for identification of clinically relevant yeasts (10, 11). In our previous study, we evaluated the performance of the Vitek MS system (bioMérieux, France) for identifying yeast isolates collected as part of the CHIF-NET program in 2011 (12). In the present study, we further systematically compared the performance of the Bruker Biotyper MS (Bruker Daltonics GmbH, Germany) and the Vitek MS systems for the identification of a large number of clinically relevant yeast isolates collected through the CHIF-NET program (2012 to 2013).

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The 2,683 yeast isolates analyzed in this study were all derived from patients with invasive candidiasis from 48 clinical microbiology laboratories of hospitals situated in 24 provinces across China during the period August 2012 to July 2013. The majority of the nonduplicate isolates were obtained from blood (44.2%), followed by ascitic fluid (18.2%), intravascular catheters (7.6%), pus

(7.3%), and cerebrospinal fluid (5.9%) (see Table S1 in the supplemental material). The isolates were inoculated onto CHROMagar *Candida* medium (CHROMagar, Paris, France), incubated for 48 h at 35°C, and then simultaneously identified using the Vitek MS and Bruker Biotyper MS systems.

For the Vitek MS v.2.0 system, proteins were extracted as recommended by the manufacturer. Briefly, a small portion of a single colony was directly spotted onto a target plate and covered with 0.5 μ l of formic acid (bioMérieux). All mass profiles were analyzed using the Vitek MS database (MS-ID v.2.0 knowledge base clinical use). For the Bruker Biotyper MS system, pure yeast isolates (each from a single colony), were directly smeared onto the target plate (Bruker Daltonics GmbH) and overlaid with 1 μ l of 70% formic acid (Sigma-Aldrich). Each spectrum was analyzed by Bruker Biotyper MS v.3.1 software and compared to the available database (DB 5627). For *Cryptococcus* species, besides the direct “on-plate testing” method, an additional protein extraction procedure was performed as recommended by the manufacturer.

For internal transcribed spacer (ITS) sequencing, universal

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TABLE 1 Isolates with misidentification and no identification results by Vitek MS (database v.2.0) and Bruker Biotyper MALDI-TOF MS (database v.3.1) systems

Identification results by gene sequencing for the ITS ^a region	No. of isolates	Identification results by the Vitek MS system (no. of isolates) (confidence value) ^b	Identification results by the Bruker Biotyper MS system (no. of isolates) (score value) ^c	Inclusion in the currently available database: Vitek MS/Bruker Biotyper MS systems
<i>Candida</i> and <i>Candida</i> -related species				
<i>C. albicans</i>	1,051	No identification (1)		Yes/yes
<i>C. catenulata</i>	1	<i>C. parapsilosis sensu stricto</i> (1) (99.9%)		Yes/yes
<i>C. famata</i>	1		No identification (1)	Yes/no
<i>C. fermentati</i> (<i>Pichia caribbica</i>)	3	<i>C. guilliermondii</i> (2) (both 99.9%) No identification (1)	No identification (2) <i>C. metapsilosis</i> (1) (1.838)	No/no
<i>Meyerozyma guilliermondii</i> (<i>C. guilliermondii</i>)	53	No identification (1)		Yes/yes
<i>C. inconspicua</i> (<i>Pichia cactophila</i>)	3	<i>C. intermedia</i> (3) (all 99.9%)	(<i>Pichia cactophila</i>)	Yes/yes
<i>C. intermedia</i>	12	No identification (3)		Yes/yes
<i>Clavispora lusitaniae</i> (<i>C. lusitaniae</i>)	12	No identification (1)		Yes/yes
<i>C. metapsilosis</i>	53	No identification (26) <i>Cryptococcus laurentii</i> (17) (all 99.9%) <i>C. parapsilosis sensu stricto</i> (10) (all 99.9%)		No/yes
<i>C. nivariensis</i>	6	No identification (3) <i>C. famata</i> (1) (99.9%) <i>C. sphaerica</i> (1) (99.9%) <i>C. glabrata sensu stricto</i> (1) (99.9%)		No/yes
<i>C. orthopsilosis</i>	12	No identification (7) <i>C. parapsilosis sensu stricto</i> (5) (all 99.9%)		No/yes
<i>C. parapsilosis sensu stricto</i>	459		No identification (1)	Yes/yes
<i>C. tropicalis</i>	412	No identification (5)	No identification (1)	Yes/yes
<i>Lodderomyces elongisporus</i>	12	No identification (9) <i>C. pelliculosa</i> (2) (both 99.9%) <i>Cryptococcus laurentii</i> (1) (99.9%)		No/yes
<i>Pichia fabianii</i>	7	No identification (7)	No identification (7)	No/no
<i>Pichia jadinii</i>	1	No identification (1)	No identification (1)	No/no
<i>Pichia jadinii</i>	1	No identification (1)	No identification (1)	No/no
<i>Pichia kluyveri</i>	1	<i>Stephanoascus ciferrii</i> (1) (99.9%)		No/yes
<i>Pichia manshurica</i>	1	No identification (1)	No identification (1)	No/yes
Non- <i>Candida</i> species				
<i>Aureobasidium pullulans</i>	1	No identification (1)	No identification (1)	No/yes
<i>Cryptococcus gattii</i>	2	<i>Cryptococcus neoformans</i> (2) (both 99.9%)	No identification (2)	No/yes
<i>C. neoformans</i> var. <i>neoformans</i>	10		No identification (1)	Yes/yes
<i>C. neoformans</i> var. <i>grubii</i>	176	No identification (6)		Yes/yes
<i>Kodamaea ohmeri</i>	9		<i>M. guilliermondii</i> (9) (1.734–1.985)	Yes/no
<i>Rhodosporidium fluviale</i>	1	No identification (1)	No identification (1)	No/no
<i>Trichosporon asteroides</i>	1	<i>Trichosporon asahii</i> (1) (99.9%)	No identification (1)	Yes/no
<i>Trichosporon jirovecii</i>	1	No identification (1)	No identification (1)	No/no
<i>Trichosporon montevidense</i>	1	No identification (1)	No identification (1)	No/no

^a ITS, internal transcribed spacer.^b For spots with confidence values of <99.9% were considered to be no (unacceptable) identifications.^c Identification scores of <1.7 were considered to be no (unreliable) identifications indicates identical results with those identified by ITS sequencing methods.

primers ITS1 and ITS2 were used to amplify the ITS1 region, and primers ITS3 and ITS4 were used for the ITS2 regions (13, 14). The sequences determined were compared to the reference data available in two databases: GenBank, searched by using the nucleotide BLAST tool (blast.ncbi.nlm.nih.gov), and the CBS (Centraalbureau voor Schimmelcultures) yeast database (www.cbs.knaw.nl). The results were considered acceptable if homology with other entries in the databases was >99.5% (15).

On the basis of previous studies and to minimize the costs associated with ITS sequencing (12, 16), the reference (or “gold”) standard for this study was a combination of both MALDI-TOF MS systems and ITS sequencing (an integrated gold standard).

Briefly, an isolate was considered correctly identified if the two MALDI-TOF MS systems yielded similar results (and with an acceptable confidence value of 99.9% for the Vitek MS system and an identification score of ≥ 1.700 for the Bruker Biotyper MS system) (17). Thus, ITS sequencing was performed on (i) all isolates with unacceptable confidence values (<99.9% for the Vitek MS system) and confidence scores (<1.700 for the Bruker Biotyper MS system), (ii) isolates with discordant identification results between the two MALDI-TOF MS systems (irrespective of the confidence values or scores), and finally (iii) all isolates with “no identification” results for one or both MALDI-TOF systems. In addition, ITS sequencing was performed on all *Cryptococcus* spe-

FIG 1 Summary of performance of yeast identification by two MALDI-TOF MS systems, the Vitek MS and Bruker Biotyper MS systems (3, 15, 16, 19–23), compared to that of the ITS sequencing method. In the studies by Hamprecht et al. (21), Pence et al. (22), and Deak et al. (23), the preparation method used for MALDI-TOF MS analysis was the direct on-plate smear method. In the present study, the identification results were interpreted based on the direct on-plate smear method for all yeast isolates except that for *Cryptococcus* species the results were interpreted based on the in-tube protein extraction method. In other studies, in-tube protein extraction was used. The currently available databases for the two systems (the Vitek MS system v.2.0 knowledge base clinical use and the Bruker Biotyper MS system DB 5627 v.3.1) were applied.

cies isolates regardless of the identification score values (Bruker Biotyper MS system) or confidence values (Vitek MS system).

The 2,683 isolates submitted to the central laboratory comprised 25 *Candida* and *Candida*-related species (*Pichia* species and *Lodderomyces elongisporus*) (2,445 isolates, 91.1%), three *Cryptococcus* species (189 isolates, 7.0%), and 13 other yeast species (49 isolates, 1.8%), as confirmed by our integrated reference identification strategy. Using our integrated reference strategy, ITS sequencing was performed on 348 isolates (13.0%), including 189 (7.0%) isolates of *Cryptococcus* species, and 159 (5.9%) isolates of other yeasts.

Among the 2,683 isolates studied, identical results with acceptable confidence values (99.9% for the Vitek MS system) and identification scores (≥ 1.700 for the Bruker Biotyper MS system) were obtained for 2,529 (94.3%) isolates. In addition, among these isolates, 0.9% (25/2,683) and 3.8% (102/2,683) isolates belonged to species that were not listed in the Bruker Biotyper MS v.3.1 or Vitek MS v.2.0 MALDI-TOF MS database ($P < 0.001$ by Pearson's chi-square test), respectively. Using the integrated reference method as the standard, the Vitek MS system accurately identified 95.4% of the isolates (2,559/2,683), misidentified 48 isolates (1.8%, 48/2,683), and was unable (no identification) to identify 76 isolates (2.8%, 76/2,683) (Table 1; see also Table S2 in the supplemental material). The Bruker Biotyper MS system accurately identified 98.8% (2,651/2,683) of the isolates, misidentified 10 isolates (0.4%), and yielded a no identification result for 22 (0.8%) isolates (see Table S2 in the supplemental material). The Bruker Biotyper MS system exhibited significantly higher accuracy rates than the Vitek MS system for overall identification of yeast isolates (98.8% versus 95.4%; $P < 0.001$ by Pearson's chi-square test) and for all *Candida* and *Candida*-related species (99.4% versus 95.5%; $P < 0.001$). However, there was no significant difference in the identification accuracy for non-*Candida* or *Candida*-related yeasts between the two systems (92.8% for the Bruker Biotyper MS versus 94.5% for the Vitek MS; $P = 0.451$). In this study, no *Candida dubliniensis* was identified, which is not surprising as this

organism rarely causes invasive candidiasis or candidemia (4, 5, 18); all of the isolates in the present study were obtained from patients with invasive candidiasis or candidemia.

Eight previous studies, in addition to the present one compared the performance of the Vitek versus the Bruker Biotyper MS MALDI-TOF MS systems for yeast identification, using the currently available databases (Fig. 1) (3, 15, 16, 19–23). Three of these studies used the direct smearing method, while the others used “in-tube” extraction for sample preparation for MALDI-TOF MS analysis. Compared to those for ITS sequencing, the accuracy levels for yeast identification in these eight studies ranged from 76.5% to 96.2% for the Vitek MS system and from 89.8% to 98.8% for the Bruker Biotyper MS system. In comparison to previous studies, our study tested the largest number of yeast isolates and had the third most diverse number of yeast species (Fig. 1). Our findings on the performance of MALDI-TOF MS systems in the identification of yeasts are in agreement with findings from other parts of the world.

In the present study, none of the two MALDI-TOF MS systems could differentiate between *Meyerozyma caribbica* and *Meyerozyma guilliermondii* among the *M. guilliermondii* complex isolates (15). *M. guilliermondii*, which was the predominant species among our *M. guilliermondii* complex isolates, is frequently associated with candidemia (24). The misidentification rate for *M. guilliermondii* isolates was significantly higher using the Vitek MS system than the Bruker Biotyper MS system (1.8% versus 0.5%; $P < 0.0001$).

The Bruker Biotyper MS system performed poorly (41.8%, 79/189) in the identification of *Cryptococcus* species using the direct on-plate testing method. However, the identification accuracy reached 98.4% (186/189) when the recommended protein extraction method was used. This is because of the organism's carbohydrate-rich cell walls, making protein extraction more difficult with the direct on-plate testing method. The three *Cryptococcus* species not identifiable by the Bruker Biotyper MS system using the recommended method for protein extraction, included two *Crypto-*

Coccidioides immitis and one *Cryptococcus neoformans* var. *neoformans* isolates. A recent study by Posteraro et al. has demonstrated that the Bruker Biotyper MS system is able to discriminate not only *C. neoformans* from *C. gattii* but also *C. neoformans* var. *neoformans* from *Cryptococcus neoformans* var. *grubii* and the AD hybrids, using an in-house database (25).

In summary, we found that both the Vitek MS and the Bruker Biotyper MS MALDI-TOF MS systems performed well for the routine laboratory identification of commonly encountered yeast species in the CHIF-NET central laboratory and in other reference mycological laboratories where there are a large number of isolates to be tested. However, the Bruker Biotyper MALDI-TOF MS system performed better than the Vitek MS system, given the higher accuracy levels in the overall identification of yeasts and specifically for *Candida* species.

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