Time to and differential time to blood culture positivity for assessing catheter-related yeast fungaemia: A longitudinal, 7-year study in a single university hospital

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Time to and differential time to blood culture positivity for assessing catheter-related yeast fungaemia: A longitudinal, 7-year study in a single university hospital

Running title: TTP, DTTP and CVC- related yeast fungaemia

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Statement of Authors contributions

MGM, SV, SH and NG participated in data analysis.

MGM, SB and AA wrote the manuscript.

BB, JLD and BD made practical comment on the results and statistics

All the authors read the manuscript and agreed with the final version.

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Abstract:

Background: Time to positivity (TTP) and differential time to positivity (DTTP) between central and peripheral blood cultures are commonly used for bacteraemia to evaluate the likelihood of central venous catheter (CVC) related bloodstream infection. Few studies have addressed these approaches to yeast fungaemia.

Objectives: This study aimed to evaluate TTP and DTTP to assess CVC-related yeast fungaemia (CVC-RYF).

Patients/Methods: We retrospectively analysed the results from 105 adult patients with incident fungaemia, with CVC removed and cultured, collected from 2010 to 2017. The bottles were incubated in a BioMérieux BacT/ALERT 3D and kept for at least 5 days.

Results: Of the 105 patients included, most were oncology patients (85.7%) and had of long-term CVC (79.6%); 32 (30.5%) had a culture positive CVC (defined as CVC-RYF) with the same species as in blood culture and 69.5% had culture negative CVC (defined as non-CVC-RYF, NCVC-RYF). *Candida albicans* represented 46% of the episodes. The median TTP was statistically different between CVC-RYF or NCVC-RYF [16.8h interquartile range (IQR) [9.7–28.6] *vs*. 29.4h [IQR 20.7–41.3]; p = 0.001]. A TTP <10h had the best positive likelihood ratio (21.5) for CVC-RYF, although the sensitivity was only 28%. DTTP was available for 52 patients. A DTTP >5h had a sensitivity of 100% and a specificity of 71% for CVC-RYF. **Conclusions:** Since the median TTP was 17h and the most performing DTTP >5h, these delays are too long to take a decision in the same operational day. More rapid methods for detecting infected catheters should be tested to avoid unnecessary CVC withdrawal.

Keywords: Blood cultures, central venous catheter, yeast fungaemia, candidaemia, diagnosis, time to positivity, differential time to positivity

INTRODUCTION

Central venous catheters (CVCs) significantly increase the risk of candidaemia, and inversely, candidaemia is often associated with intravascular catheters.[1] Indeed, the increased incidence in candidaemia has paralleled the increased use in a variety of indwelling catheters. CVCs are present in at least 80% of cancer patients with candidaemia, for which the source of infection can be clinically related to the catheter.[2,3] As a consequence, most guidelines for candidaemia management recommend removal of existing intravascular catheters, if feasible.[4-7] Although the recommendation is strong, the evidence is of low-quality, and various authors have recommended a re-consideration of CVC removal on an individual basis.[4-8] Practically, one must consider the possible deleterious consequence of CVC removal, especially in patients who require long-term CVC for cancer treatment or parenteral nutrition. This scenario is even more complicated to manage when the catheter's infection is not subsequently confirmed.

To incriminate a CVC as a source of bacteremia, time to positivity (TTP) and differential time to positivity (DTTP) have been extensively studied and are routinely used for decision making.[9-11] Few similar analyses have been performed for CVC-related candidaemia but with controversial results and no definitive thresholds.[2,12,13] In parallel, TTP has also been evaluated to identify yeast species as soon as the blood culture is positive.[14-17] We, therefore, used our comprehensive database on yeast-positive blood culture episodes collected over 7 years in our institution to analyse the usefulness of TTP and DTTP to predict CVC-related yeast fungaemia (CVC-RYF).

MATERIALS AND METHODS

Study design and data collection

We enrolled all ≥15-year-old patients for whom at least one blood culture (BC) bottle was positive for yeast between October 1st, 2010 and September 30th, 2017 through the records of the Department of Microbiology of Saint-Louis Hospital. This hospital is a 550-bed tertiary university hospital located in Paris, France, with more than two-thirds of its activity dedicated to haematology or oncology patients. Burn patients were excluded as these were analysed separately because all the removed catheter tips were culture-negative for *Candida* spp. suggesting that CVC is not the source of candidaemia whereas candidaemia was always concomitant with *Candida* carriage of the skin.[18]

The clinical data collected were age, gender, underlying conditions, hospitalization in

intensive care unit (ICU) at the time of positive BC, antifungal preexposure defined as administration of systemic antifungal drugs for at least 5 days within 30 days prior to fungaemia (whatever dosage and duration), and outcome at day 30 after the first positive BC as described elsewhere.[19] Because of the retrospective design of the study and the multiple regimens of antifungal drugs prescribed in haematology, it was not possible to reliably collect more data on type, dose, and duration of the antifungal drugs.

The type of CVCs, its duration, and the reason for removing it were collected from the Anesthesiology Department. The CVCs were divided into short-term (mainly from ICU) and long-term CVC.

Microbiological methods

Nurses were instructed to draw 10 ml of blood into each aerobe and anaerobe bottles and to send the inoculated bottles to the microbiology laboratory without delay. Bottles were incubated (BioMérieux BacT/ALERT 3D, Marcy l'Etoile, France) for at least 5 days or until positivity. When the BC was detected as positive, and the Gram stain demonstrated the presence of yeasts, a fresh mount with KOH 15% was done to observe the morphology of the yeast and a subculture was performed in BBL CHROMagar Candida Medium plate (Hardy Laboratories, Santa Monica, CA, USA). Identification was confirmed using the API ID 32C (bioMérieux, Marcy l'Etoile, France) from October 2010 to the end of 2011, then the Biomerieux MALDI-TOF system (VITEK-MS) (bioMérieux, Marcy l'Etoile, France) from January 2013 to September 2017. For the uncommon fungal species [i.e. not for *Candida albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. krusei* (syn. *Pichia kudriavzevii*), and *Cryptococcus* spp.], identification was confirmed by molecular analysis at the National Reference Centre for Invasive Mycoses and Antifungals at Institut Pasteur, Paris, France, as described elsewhere.[19]

After CVC removal, the catheter tip and/or the chamber of the implantable venous access port system were cultured using a quantitative method.[20] Briefly, tip and/or chamber were immersed in 1 mL of sterile water and vortexed for 1 min. Then, 50 µL were plated on a blood and chocolate agar Petri dishes. The plate was then incubated at 35°C (±2°C) with 5% (± 1%) CO_2 for 24h. CVC culture was considered negative (CVC-negative) if there was no growth observed after 5 days of culture. A CVC was considered positive (CVC-positive) if either the tip, the chamber, or both grew at least one yeast colony.

Definition of CVC-related yeast fungaemia

The date of fungaemia was the date of blood sampling. Paired bottles were defined as respectively drawn through CVC and percutaneously within less than 30 min. TTP is routinely recorded by the BacT/Alert system as the time recorded until growth detection after recording the BC bottle in the incubation cabinet. DTTP is defined as the difference in TPP recorded for paired bottles (DTTP = TTP percutaneously – TTP CVC). When multiple positive BC were available for a given patient, only the first was considered for TPP analysis and only the first paired bottles for DTTP, since this was the first information available for the clinicians.

Patients with CVC removed and cultured at the time of fungemia were divided into two groups: (i) CVC-related yeast fungemia (CVC-RYF) when the same yeast species was recovered from at least one BC and from the CVC culture; (ii) non-CVC-related yeast fungemia (NCVC-RYF) when a yeast species was recovered from at least one BC, and the CVC culture was negative or yielded a different species.[12] This definition of CVC-RYF was adapted from the definition proposed by Bouza et al. except we considered for TTP calculation the patients with a positive BC drawn through CVC and not only the patient with a positive peripheral BC.[12]

Statistical analysis

Patients with CVC-RYF and NCVC-RYF were compared. Quantitative variables were reported as medians and interquartile ranges (IQR) or means ± standard deviations. Chi^2, Kruskal Wallis and Mann-Whitney tests were used for quantitative variables (TTP and DTTP). The Area Under a Receiver Operating Characteristic (ROC) Curve (AUC) was calculated to detect the best cut-off values for predicting CVC-RYF using TTP or DDTP values. A p-value <0.05 was considered significant. Prism 7 (GraphPad Software, La Jolla, CA, USA) was used for statistical analyses and graphs.

Ethics statement

The present study is a retrospective analysis of the data collected as part of our usual procedure for standard diagnostics with no additional sampling for the patients and no impact on management. This study was registered with our hospital review committee (reference number: 2018000000077). Because this was a retrospective observational study, it does not require the application for specific informed consent according to French law.

RESULTS

Selection of patients

Over the 7 years, 249 episodes of fungaemia were recorded in 240 patients. The presence of CVC was noted in 203/240 (85%) patients. The patients with CVC were more often oncology patients (p = 0.01, Supplemental Table S1). We excluded 98 patients because of: lack of CVC culture (n = 65), lack of BC through the CVC (n = 24), co-infection with bacteria (n = 17) or mixed yeasts infection (n = 3) (Figure 1). Finally, a total of 105 patients with CVC removed and cultured were selected for further analysis (Supplemental Table S1) The 98 patients excluded were not statistically different except that they had a less frequent antifungal pre-exposure (p = 0.01) than the selected patients. No recurrent episode for these 105 remaining patients was observed (Supplemental Table S1).

Yeast identification and patient characteristics (Table 1)

The 105 patients were divided into NCVC-RYF (n = 73, 69.5%) and CVC-RYF (n = 32, 30.5%) based on the CVC culture results. The only significant difference between the two groups was the percentage of negative CVC culture when a preexposure to antifungal drugs was recorded [NCVC-RYF 22/73 (30%) *vs*. CVC-RYF 2/32 (6%); p = 0.007].

The main species involved were *C. albicans* (46%), *C. parapsilosis* (19%), *C. glabrata* (15%), and *C. tropicalis* (9%), with no statistical difference between NCVC-RYF and CVC-RYF. Only four non-*Candida* species were identified (Table 1), representing less than 4% (4/105) of the total. Out of the 32 culture-positive CVCs, 24/32 (75%) grew $>10^3$ CFU/mL and 8/32 (25%) grew $>10^2$ CFU/mL without difference in the species distribution or the CVC features (short-term *vs*. long-term CVC) according to the number of colonies and were therefore not subsequently differentiated.

Most of the CVCs were long-term [82/105; 78%; median duration time: 68 days [IQR: 22-157], and were more frequent in onco-hematology patients. These long-term CVCs were including totally implantable venous access port system (n = 44), tunnelled cuffed catheter (n = 32), and peripheral insertion central catheter (n = 6). The long-term central venous access catheters were not more frequent in CVC-RYFs than in NCVC-RYFs (Table 1). In contrast, the 23 short-term CVCs were more frequent in ICU patients (21/23; 91.3%) with a median duration time of 10 days [IQR: 6–14]. The motive for removal and culture was always a suspicion of infection. Only 30.5% (32/105) of the tested CVCs were culture-positive, with no statistical difference between long and

short-term CVCs (data not shown). The median delay between the date of blood sampling of the first positive BC and the date of CVC removal was 3 days [IQR 2-3] and 2 [IQR 1-3] for NCVC-RYFs and CVC-RYFs respectively (p = 0.08).

TTP according to CVC or non-CVC related yeast-fungaemia

Considering all species, the median TTP of the first bottle collected from CVC was statistically shorter in the CVC-RYF group (16.8h [IQR 9.7-28.6]) compared to the NCVC-RYF group: median (29.4h [IQR 20.7–41.3], p = 0.0001, Figure 2). When analysing TTP regarding the *Candida* species, a significant shorter TPP was only observed in *C. albicans* with a median of 12.9h [10.0–22.7] *vs*. 32.3h [24.4–41.0]) for CVC-RYF and NCVC-RYF, respectively (p = 0.0001, Figure 2). A trend towards shorter TTPs in the CVC-RYF *vs*. NCVC-RYF was observed for *C. tropicalis* (p = 0.09) and *C. glabrata* (p = 0.17). No difference was observed for *C. parapsilosis* (p = 0.86). The TTP distribution was not statistically different (Kruskal Wallis test; p = 0.9) between patients who died compared with the patients alive at 30 days (Table 1). The median TTP values were not statistically different (p = 0.9) when comparing NCVC-RYF patients with (median TTP = 32h) or without (median TTP = 31h) pre-exposition with antifungal agent.

Using TPP as a predictor of CVC-RYF, we obtained an AUC of 0.73 [Confidence Interval 95% (CI95%) 0.62 to 0.85, p = 0.0001] when considering all yeast species (Figure 3). A threshold of <10h provided the best positive likelihood ratio (21.6), but the sensitivity was only 28.1% (Table 2). When restricting the analyses to *C. albicans* (Figure 3), the AUC was improved (0.84 [CI95% 0.69 to 1.00], p = 0.0002). A threshold of <15h was associated with a high positive likelihood ratio (30.5), with a sensitivity of 61% (Supplemental Table S2).

Among the 105 patients included in the study, 65 (62%) had a peripheral positive BC. When restricted the TTP analysis to these patients, the rate of infected CVC increased from 30.5% (32/105) to 33.8% (22/65), which is not statistically significant, p = 0.6. The median TTP was 11.75h [IQR 8.5-20.4] for CVC-RYF (*vs*. 16.8h [IQR 9.7-28.6] for the 105 patients) and 29.3h [IQR 22.7-43.2] (*vs*. 29.4h [IQR 20.7–41.3] for the 105 patients) for NCVC-RYF (p <0.0001). Out of the 40 patients with no positive peripheral BC recorded, 24 (60%) had a peripheral negative BC, and 16 (40%) did not have any peripheral BC performed.

DTTP according to CVC or non-CVC related yeast fungaemia

DTTP was available for 52/105 (49.5%) patients, including 32 NCVC-RYF and 20 CVC-

RYF. The median DTTP was significantly higher for CVC-RYF (18.8h [IQR 15.0–22.7]) than for NCVC-RYF (-0.4h [IQR -5.1–4.8]) patients, p <0.0001). Calculation by species was not possible given the low number of positive pairs.

The AUC was 0.86 ([CI95% 0.74 to 0.98], p <0.0001) for the diagnosis of CVC-RYF without difference between *C. albicans* and non-*albicans Candida* spp. (Figure 4). The sensitivity was 100% in the first 5h, which is translated in a null negative likelihood ratio, although the specificity did not exceed 71% and the positive likelihood ratio was never >5 (Table 3).

DISCUSSION

When analysing 105 patients with CVC withdrawn and cultured, and using a strict definition of infected CVC (i.e., positive or negative CVC culture), a TTP <10h had the best likelihood ratio (21.6), although the sensitivity was only 28.1% for identifying CVC-RYF. A DTTP between 1 and 5h presented 100% specificity but a low positive likelihood ratio (LOR<4). Our observation stands for a population of oncology patients (86%) with mainly long-term central venous access catheter (78%). *Candida albicans* represented 46% of the episodes followed by *C. parapsilosis* (19%). We nevertheless kept the term of fungaemia, acknowledging that only 4 were not *Candida* species.

Comparison of TTP results with previous reports is difficult because of numerous differences in the studies design, inclusion of children or only adults, different underlying diseases, single or multiple centres recruitment, number of long-term or short-term CVCs included, culture method used for testing CVC tips, variable definitions of CVC infection with probable criteria added, and various *Candida* spp. considered). Also, the small number of fungaemia and the even smaller number of CVC-RYF add to the heterogeneity. The number of analysed episodes of CVC-RYF rarely reach more than 100 [22 in[14], 64 in[2], 108 in[12], and 105 in[13]] compared to 105 in our study, which precludes subset analyses. Here the method used for CVC testing was different from the one used by other authors.[2,12] Moreover, we analysed the TTP for patients with negative or no peripheral BC in contrast to Bouza et al.[12] and Ben-Ami et al.[2] who included only patients with at least one positive peripheral BC. When excluding patients with no positive peripheral BC, the TTP decreased to 11.75h [IQR 8.5-20.4] *vs*. 16.8h [IQR 9.7-28.6] for CVC-RYF. This probably results from the higher fungal load when both peripheral and central bottles are positive. However, to exclude patients without peripheral positive BC does not correspond to onco-haematology patients with long-term CVC for who peripheral BC is not

obtained because of practical or comfort reasons. Additionally, there is no recommendation to consider peripheral and central yeast fungaemia differently.[4-8]

Taking all these limitations into account, our best TTP cut-off of 10h is different from other proposals. Ben-Ami et al. suggest a TTP cut-off of 30h (100% sensitive and 51.4% specific) for CVC-related candidaemia with an AUC of 0.76, close to our observation (0.73).[2] Bouza et al.[12] found TTP to be significantly shorter in peripheral blood culture in adults with catheter-related candidaemia compared to adults with non CVC-related candidaemia (29.8 *vs*. 36.8h, p <0.03), which we confirmed even if the figures were slightly different (16.8 *vs*. 29.4h, p = 0.001), and the best TTP cut-off for the prediction of catheter-related candidaemia in adults to be <55h.[12] Only two patients in that study had long-term CVCs (tunnelled-CVC). However, even the 10h cut-off that we proposed is too long to be clinically relevant when the goal is withdrawing the CVC as soon as possible. Indeed, the median TTP of the first bottle collected through the CVC was around 17h in the present study, corresponding to a median of two operational days for catheter removal after blood sampling (Figure 2). Waiting further could be deleterious for the patients.[23] When restricting to *C. albicans*, the AUC improved as the positive likelihood ratio for TTP with the threshold of <15h, but this is a formal observation as long as the species is identified at least 24h after BC positivity. Species identification could be achieved much faster using PCR-based identification tests,[24] matrix-assisted laser desorption ionization time-of-flight mass spectrometry,[25] or peptide nucleic acid fluorescence in situ hybridization.[26]

TTP can, however, be used for other purposes than diagnosing CVC-RYF. For instance, shorter TTPs was shown associated with mortality.[27] In contrast, other authors found an association between long TTP and mortality.[28] We did not observe any significant difference between the median TTP and the global mortality at day 30 (here 30%), acknowledging that underlying diseases and patient management could prevail in the crude mortality over infected CVC. While it has been previously associated with the number of positive BCs,[12] we did not find such an association.

TTP can also be used for presumptive species identification since *C. glabrata* growth rate is lower than that of other *Candida* spp. and is known for its decreased susceptibility to azoles.[15-17] However, the current recommendations for the initial treatment of candidaemia is candin whatever the species is,[4-6] which limits the clinical utility of TPP for identification.

For DTTP, Park et al. found an overall sensitivity and specificity of a DTTP of >2h for diagnosing CVC-RYF of 85% (CI95%: 74% to 93%) and 82% (CI9586% 66% to 92%),

respectively, when studying 99 pairs, 47 with definite, 14 with probable, and 38 with non CVC-related candidaemia.[12] The authors concluded that a DTTP of >2h was the optimal cut-off, except for CVC infection caused by *C. glabrata*. Other authors found this threshold accepted for bacteraemia would have a sensitivity of 94% but a specificity of 40%.[11] We did not observe major differences between 2 and 5h for the DTTP performance, with specificity not exceeding 71% and positive likelihood ratio <4. An analysis by species was not performed because of the small number of pairs for each *Candida* species.

A noticeable point is the low yield of positive catheter culture. Only 30% (32/105) of tested CVCs were positive in culture with the method used.[20] In the literature, the rate of definite infected CVCs is variable: from 20.3%[2] to 44.8%[13] or 56%[12]. Part of these differences could come from the methods used, either semiquantitative (with a threshold of >15 CFU per catheter segment),[22] or quantitative (>10^2 CFU per catheter segment),[20] although both are equivalent for bacteria[29] and knowing that both are usually accepted.[9] Despite these differences, these observations suggest that CVCs could not be the main source of infection, even though they are present in >80% of patients with candidaemia. On the other hand, some authors even suggest that a positive culture tip is not always linked to candidemia,[30] which can interfere with the definition of CVC-RYF. If the CVC is mostly not the source of infection in the cases categorized as CVC-RYF, this could explain why the patients' survival is not impacted by CVC removal.[8] Another explanation for the lack of benefit of CVC removal could be that dissemination has already occurred when the CVC is withdrawn. This raises the question of systematic early removal of CVC in the management of candidaemia since some authors did not report differences,[8] knowing that patients who cannot tolerate CVC removal have often a worse prognosis. Nevertheless, CVC removal has to be evaluated on an individual basis, knowing that the consensus recommendation is CVC withdrawal if possible as soon as a BC is positive for *Candida* species.[6,9,21] In our study, the removal of long-term CVCs was scheduled by the anaesthesiologist as soon as possible after the BC result in considering the availability of a surgery room for this removal.

The low yield of CVC culture can also be due to the consequence of previous antifungal drugs prescription, and we indeed observed a higher percentage of antifungal drugs preexposure in the group of culture-negative CVC ($p = 0.007$). This is obviously an important factor to consider when antifungal prophylaxis is increasing in haematology patients. However, the delay between the day of sampling of the first positive BC and CVC removal was short (median 2-3 days) and not statistically different between NCVC-RYF and CVC-RYF suggesting that an antifungal

treatment between the clinical suspicion and the removal of the CVC may not impact the CVC culture. The low yield of CVC culture could be also due to non optimal culture method. For instance, the length of sonication is rarely controled. In this study, positive CVC culture yielded yeast CFU count above 10^2 CFU/mL and was then strongly suggestive of CVC-RYF.[31,32] Lower tresholds could be considered.

We must acknowledge some limitations in our study. The volume of blood collected was not controlled, whereas it is well known that the volume collected from CVC is usually higher than via peripheral venipuncture.[33] The time between blood sampling and BC loading into the incubator was not controlled, knowing that delays tend to shorten TTP.[34] The population studied was mostly (86%) oncology patients thereby restricting our findings to this population. One can also argue the choice of analysing the first BC when multiple BCs were available instead of the BC with the shortest TTP.[12] Our choice was clearly to look for a means to provide, as quickly as possible, information useful for the clinicians and to stick to routine practice.

In conclusion, a TTP <10 h and a DTTP between 2 and 5h could be relevant for incriminating a CVC during yeast fungaemia in oncology patients. However, even the shortest DTTP of 2h as proposed by others[13] means waiting longer than the already prolonged incubation time required for a BC to become positive for *Candida* spp. with the potential risk of maintaining an infected CVC. Clearly, rapid molecular-based methods are needed to speed the detection process[35] and to safely reduce the unnecessary removal of uninfected CVC, acknowledging that these new methods should be evaluated in real-world clinical settings.[36]

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Table 1: Main characteristics of the 105 patients selected for the central venous catheter (CVC)-related yeast fungaemia study.

	Patients with CVC culture n = 105	**Non-CVC-related yeast fungaemia n = 73**	**CVC-related yeast fungaemia n = 32**
Age median (years) [range]	56 [15-91]	53 [15-82]	63 [18-91]
Sex ratio M/F	1.9	1.8	2
Underlying condition, n (%)			
Oncology	90 (86)	63 (86)	27 (84)
Acute leukaemia	36 (40)	28 (44)	8 (29.6)
Chronic lymphoproliferative disorders	32 (36)	27 (43)	5 (18.5)
Solid tumour	22 (24)	8 (13)	14 (52)
No malignancy	5 (4)	3 (4)	2 (6)
Solid organ transplantation	4 (80)	2 (67)	2 (100)
HIV positivity	1 (20)	1 (33)	0
Not specified	10 (10)	7 (10)	3 (9)
ICU, n (%)	39 (37)	29 (40)	10 (33)
Antifungal pre-exposure, n (%)	24 (23)	22 (30) [a]	2 (6) [a]
Recent surgery, n (%)	21 (20)	12 (16)	9 (28)
Long-term central venous access catheter, n (%)	82 (78)	55 (75)	27 (84)
Median number of positive BCs/patient [IQR]	2 [1-5]	2 [1-4]	4 [2-5]
Mortality within 30 days, n (%)	30/103 (29) 2 LFU	20/73 (27)	10/30 (33) 2 LFU
Yeast species n (%)			
Candida albicans	48 (46)	35 (48)	13 (41)
C. parapsilosis	20 (19)	15 (21)	5 (16)

C. glabrata	16 (15)	9 (12)	7 (22)
C. tropicalis	9 (9)	6 (8)	3 (9)
C. lusitaniae	2 (2)	1 (1)	1 (3)
Others [b]	10 (10)	7 (10)	3 (9)

CVC: Central Venous Catheter, M/F: Male/Female Ratio, HIV: Human Immuno-deficiency Virus, ICU: Intensive Care Unit, BC: Blood Culture. LFU: Lost of Follow Up

[a] p=0.007 (Chi^2 test) between non CVC-related fungaemia and CVC-related fungaemia

[b] Others: only one episode per yeast species*: Candida dubliniensis*, *Candida fabianii*, *Candida inconspicua*, *Candida kefyr (Kluveromyces marxianus)*, *Candida krusei*, *Candida palmioleophila*, *Geotrichum clavatum*, *Rhodotorula mucilaginosa*, *Saccharomyces cerevisiae*, *Trichosporon inkin.*

Table 2: Performance of the different cut-offs for TTP to predict CVC-related candida infection

Cut-off (time in hours)	Sensitivity % [95% CI]	Specificity % [95% CI]	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value (%)	Negative predictive value (%)
<5	9.4 [2 -25]	98.7 [92 -99]	7.2	0.9	75.0	71.8
<10	28.1 [13 -46]	98.7 [92 -99]	21.6	0.7	90.0	76.3
<15	46.9 [29 -65]	90.7 [81 -96]	5.0	0.6	68.2	80.0
<20	59.4 [40 -76]	80.0 [69 -88]	3.0	0.5	55.9	82.2
<25	71.9 [53 -86]	66.7 [54 -77]	2.2	0.4	47.9	84.7
<30	75.0 [56 -88]	49.3 [37 -61]	1.5	0.5	38.7	82.2
<35	78.1 [60 -90]	34.7 [24 -46]	1.2	0.6	33.8	78.8

<40	90.6 [74 -98]	28.0 [18 -39]	1.3	0.3	34.9	87.5
<45	90.6 [74 -98]	18.7 [11 -30]	1.1	0.5	32.2	82.4
<50	93.8 [79-99]	13.3 [6 -23]	1.1	0.5	31.6	83.3
<55	93.8 [79 -99]	9.3 [3 -18]	1.0	0.7	30.6	77.8

TTP: time to positivity, DTTP: differential time to positivity; CI: confidence interval

Table 3: Performance of the different DTTP cut-off values and their validity to predict catheter-related *Candida* infection

Cut-off (time in hours)	Sensitivity % [95% CI]	Specificity % [95% CI]	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value (%)	Negative predictive value (%)
>1	100.0 [80 -100]	61.5 [40 -79]	2.6	0.0	63.0	100.0
>2	100.0 [80 -100]	69.2 [48-85]	3.2	0.0	68.0	100.0
>3	100.0 [80 -100]	70.8 [50 -87]	3.4	0.0	70.8	100.0
>4	100.0 [80 -100]	70.8 [52 -88]	3.4	0.0	70.8	100.0
>5	100.0 [80 -100]	70.8 [53 -90]	3.4	0.0	70.8	100.0
>6	94.1 [71 -99]	75.0 [56 -91]	3.8	0.1	72.7	94.7
>10	82.4 [56 -96]	79.2 [60 -93]	4.0	0.2	73.7	86.4
>15	76.5 [43 -90]	79.2 [60 -93]	3.7	0.3	72.2	82.6
>18	60.0 [37 -84]	87.5 [65 -95]	4.8	0.5	75.0	77.8

DTTP: differential time to positivity

Legends to Figures:

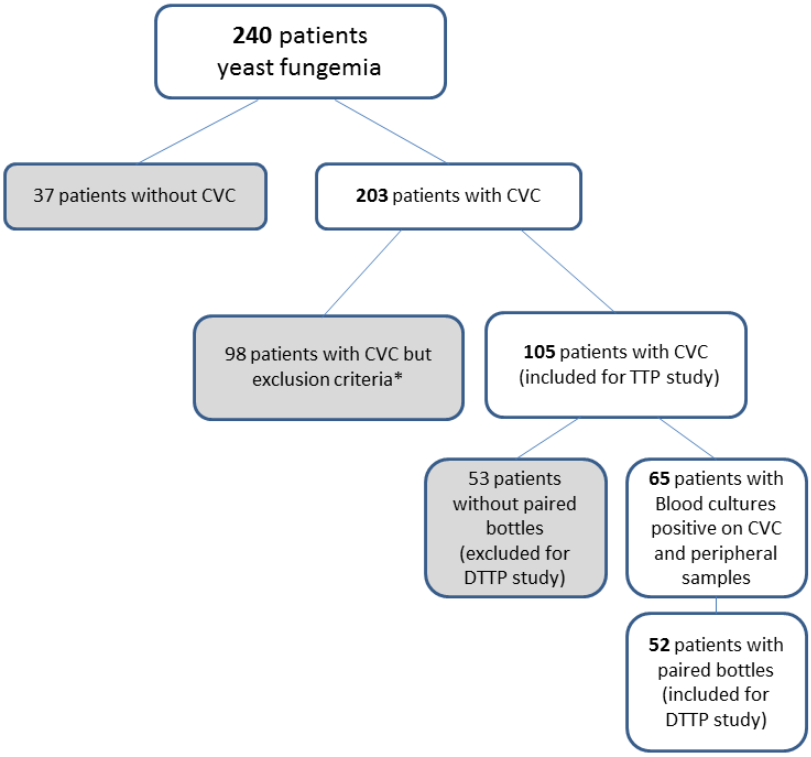
Figure 1: Flow Chart of the study proces

TTP: time to positivity, DTTP: differential time to positivity. Paired bottles collected within 30 minutes. *Exclusion criteria: lack of CVC Culture, lack of Blood Culture through CVC, co-infection with bacteria, mixed yeasts infection.

Figure 2: Comparisons of time to positivity (TTP) between positive (CVC+) and negative (CVC-) central venous catheter for all yeast cultured and according to the four more frequent *Candida* spp. (*: p = 0.0001). Data presented in scatter dot-plot with the median line and the interquartile range.

Figure 3: Receiver operating characteristic (ROC) curve analysis of time to positivity (TTP) for all yeasts (blue line; AUC = 0.73), *C. albicans* (green line; AUC = 0.84), and non-*albicans Candida* spp. (pink line; AUC = 0.64).

Figure 4: Receiver operating characteristic (ROC) curve analysis of differential time to positivity (DTTP) for all yeasts (blue line; AUC = 0.86), *C. albicans* (green line; AUC = 0.84), non-*albicans Candida* spp. (pink line; AUC =0.90).



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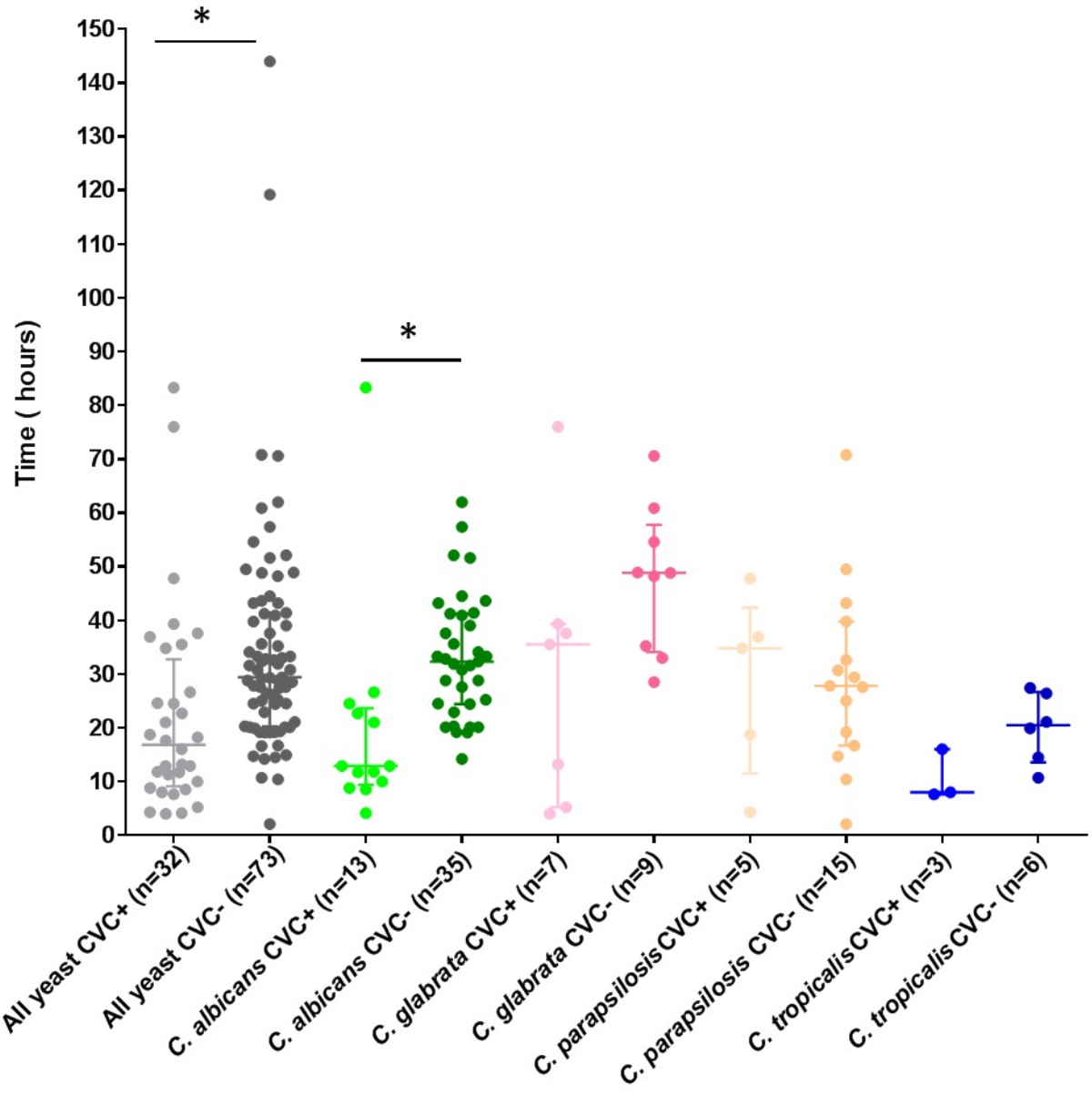

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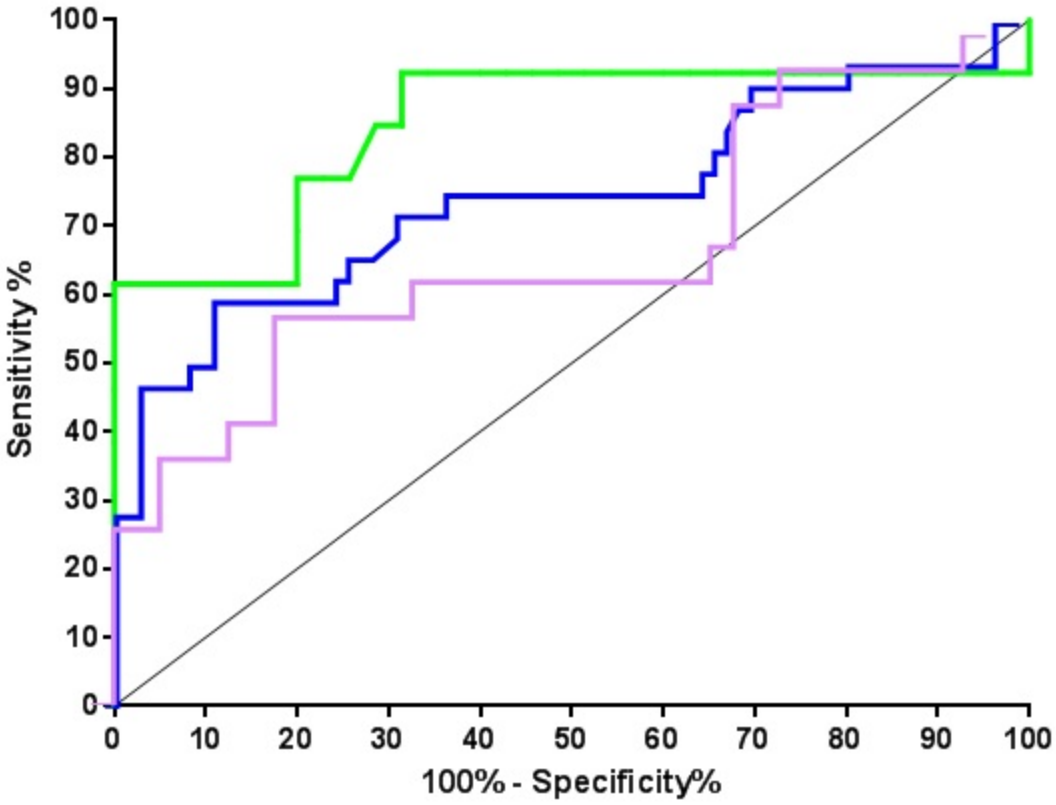

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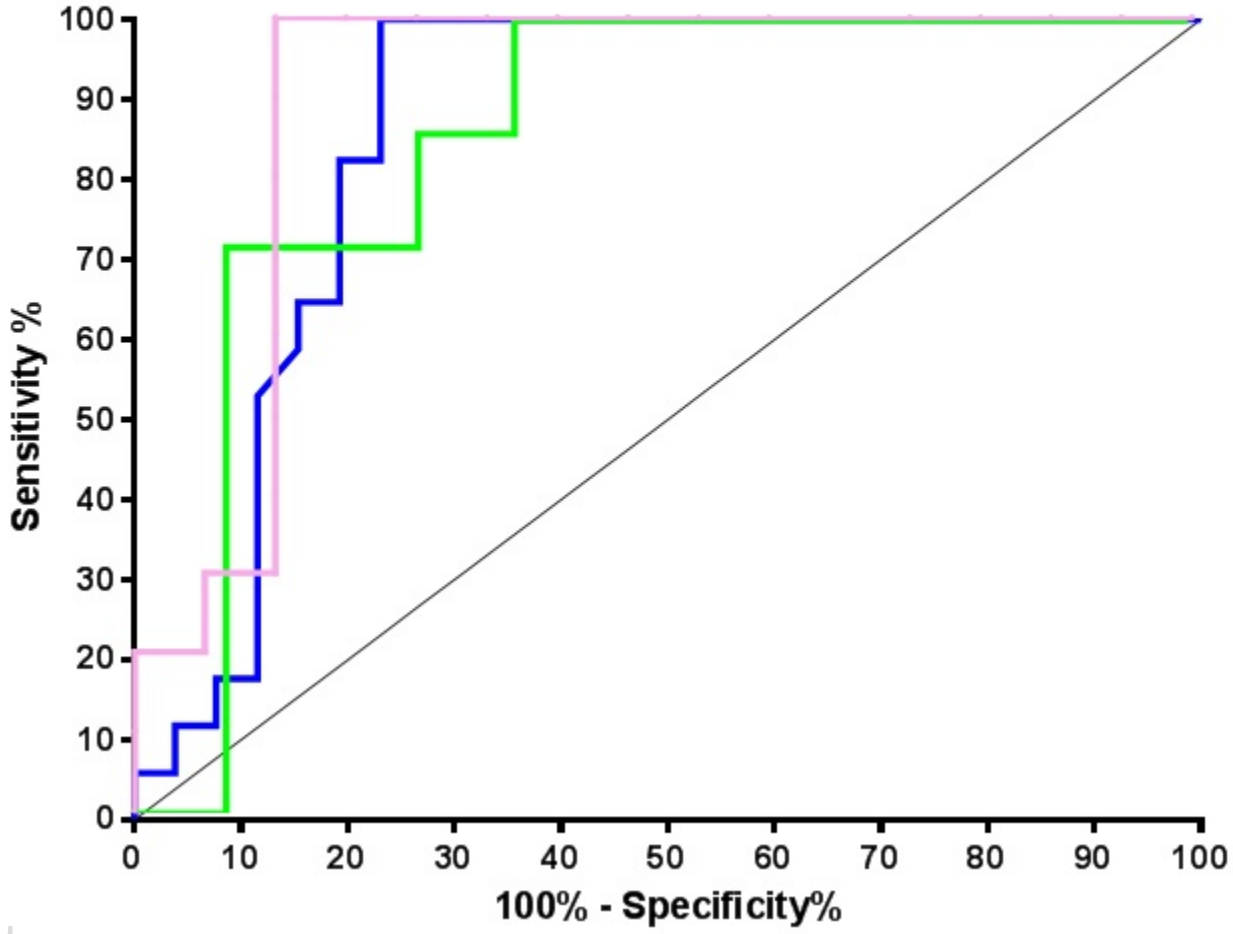

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