Presepsin and (1,3)-β-D-Glucan as a Tool for Predicting Candida Sepsis and Monitoring the Effectiveness of Treatment in Critically Ill Patients

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Abstract

Background: To improve the accuracy in invasive candidiasis diagnostics, a new biomarker panel has been developed and validated on a 165-patient cohort of critically ill adults.

Methods: The serum levels of inflammatory biomarkers, C-reactive protein, presepsin (PSEP), procalcitonin (PCT), and of panfungal (1,3)-β-D-glucan (BDG), were correlated with culture-confirmed candidemia or bacteremia in 58 or 107 patients, respectively. The diagnostic effect of the host and pathogen biomarkers was expressed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results: For invasive candidiasis, the best performing BDG exhibited 96.6% sensitivity, 97.2% specificity, 94.9% PPV and 98.1% NPV at a cut-off of 200 pg/mL ($P \leq 0.001$). PSEP exhibited 100% sensitivity and 100% NPV at a cut-off of 700 pg/mL. Furthermore, PSEP was more accurate for 28-day mortality prediction (AUC = 0.74) than PCT (AUC = 0.31; PCT cut-off 0.5 ng/mL). Finally, PSEP showed a significant serum decrease as early as 14 days after echinocandin therapy initiation ($P = 0.0012$).

Conclusions: At concentrations of BDG > 200 pg/mL and PSEP > 700 pg/mL, the probability of invasive candidiasis in critically ill adults is close to 100% defining a borderline between non-invasive superficial *Candida* colonization and invasive candidiasis.

Trial registration: The study was approved by the University Hospital Ostrava Ethics Committee for Multicenter Clinical Trials (no. 448/2018) and registered in ClinicalTrials.gov (ID: NCT03584594), date of registration June 28,2018.

Background

Critically ill patients are at high risk for hospital-acquired infections, with invasive candidiasis being most prevalent. Invasive candidiasis usually occurs after a longer ICU stay [1]. Over decades, non-albicans *Candida* species infections outranked *Candida albicans* infections in prevalence [2]. Candidemia remains associated with high mortality and treatment costs worldwide [3]. The 28-day ICU mortality is about 44% [4]. Indwelling devices including central venous catheters (CVCs) are of particular concern. Echinocandins are the drugs of choice and antifungal treatment should continue for at least 14 days after resolution of fungemia confirmed by blood cultures. Susceptibility testing is crucial for identification of resistance and managing transition to oral treatment. In persistent candidemia, echocardiography is necessary; ophthalmoscopy should be considered [5].

The dynamics of serum concentrations of the panfungal antigen 1,3-β-D-glucan (BDG) allows differentiation between bacterial and fungal infections. The clinical significance of elevated BDG concentrations in early stages of invasive candidiasis in critically ill patients is unclear, especially concerning laboratory BDG cut-offs [6]. Therefore, we analyzed the discriminative/predictive value of

serum BDG at various cut-offs for diagnosing *Candida* spp. colonization, catheter sepsis, invasive candidiasis (IC) and deep-seated candidiasis versus bacteremia.

We also evaluated the role of early inflammatory biomarkers: C-reactive protein (CRP), procalcitonin (PCT) and presepsin (PSEP). While the limitations of CRP are well known, PCT represents a useful biomarker at initial stages of bacterial infections, with higher concentrations in gram-negative compared to gram-positive and fungal infections but exhibiting very low concentrations (2–3 ng/L) in invasive candidiasis [7, 8]. PSEP, a soluble CD14, is highly accurate in predicting sepsis according to the Sepsis-3 criteria [9, 10], with a promising diagnostic accuracy in bacteremia and candidemia, including invasive candidiasis [11]. We analyzed the predictive values of combination of PSEP, PCT, CRP and BDG for diagnosing *Candida* sepsis and monitoring the efficacy of echinocandin therapy.

Methods

Study design, patient selection and outcome

This multicenter retrospective observational cohort study included patients aged > 18 years admitted to ICUs in three centers (University Hospital Ostrava, City Hospital Ostrava, Havířov Hospital) between January 2018 and December 2020. Their enrollment was based on clinical suspicion of sepsis according to the severity of organ dysfunction, represented by an increase in the Sequential Organ Failure Assessment Score (SOFA, sepsis-related) to 2 or more and confirmed IC in accordance with the EORTC/MSGERC consensus definitions [12]. The following data were collected: reason for ICU admission, age, sex, patient type (surgical, traumatic or medical), diabetes mellitus, CVC inserted for more than 48 h, hemodialysis, corticosteroid therapy, *Candida* colonization (i.e. one or more *Candida*-positive cultures from non-sterile sites), SOFA score [13, 14] and the Acute Physiology and Chronic Health Evaluation II score [15, 16].

The following serum biomarkers were determined: (a) BDG within 48 h before the time of the indexed blood culture (IBC) result; (b) PCT, CRP and PSEP within 24 h before IBC. We used different time windows due to various blood kinetics of the biomarkers [17, 18]. Kinetics data for PSEP are summarized in Additional file S1.

The time of the index culture corresponds to the first blood culture positivity for *Candida* spp. or bacteria detected by automated culture system BacT/ALERT (bioMérieux, France). Patients with cultures positive for *Candida* spp. and bacteria more than 48 h apart were excluded.

The significance of PSEP and BDG decline after 3, 14 and 28 days of echinocandin therapy was analyzed.

Samples And Laboratory

BDG, PSEP, PCT, CRP and creatinine levels were measured in accredited laboratories of the Public Health Institute in Ostrava and participating hospitals. BDG evaluation was performed with the Fungitell assay (Associates of Cape Cod, Inc., USA); PSEP and PCT were measured by a quantitative sandwich chemiluminescence immunoassay (Pathfast, Mitsubishi, Japan and ADVIA Centaur, BRAHMS PCT Assay, Siemens). CRP was measured by CRP Latex test (Beckman Coulter, USA).

Identification of *Candida* spp. and bacteria was performed by MALDI-TOF mass spectrometry (Bruker Daltonics, Germany).

Statistical analysis

Descriptive statistics (median, arithmetic mean, standard deviation, minimum and maximum values) and frequency table were used to characterize the study groups. Non- parametric two-sample Wilcoxon test, chi-square test and Fisher's exact test were used. Sensitivity, specificity, PPV, NPV and accuracy were calculated with 95% confidence intervals and the area under the receiver operating characteristic curve (AUC). The statistical tests were performed at a 5% significance level and $P < 0.05$ was considered statistically significant. The statistical software STATA version 13 was used for the analyses.

Results

Patient characteristics and outcome

A total of 165 patients who tested positive for candidemia (n = 58) or bacteremia (n = 107) were included in the study. Patients with mixed yeast and bacteria blood cultures were excluded as well as those with positive yeast cultures (except for sputum) within seven days before IBC, to minimize the effect of *Candida* colonization. In 17 out of 58 candidemia patients, consecutive measurements of biomarkers were performed at days 3, 14 and 28 after initiation of echinocandin therapy (Fig. 1). The baseline clinical characteristics of patients are summarized in Table 1. Presence of a CVC or peripherally inserted central catheter (PICC) was associated with candidemia more often than with bacteremia (100% vs. 69%, $P < 0.001$), similarly to administration of antibiotics (83% vs. 42%, $P < 0.001$). Candidemia developed later after hospital admission than bacteremia (23 vs. 13 days, $P < 0.001$) (Table 1).

Table 1
Patients characteristics (n = 165) and parameters at the time of infection

	Candidemia* **(n = 58; 35%)**	**Bacteremia**** **(n = 107; 65%)**	***P*-value**
Demographic			
Median age (IQR)	54 (46–72)	60 (46–72)	0.668[…]
Male gender	34 (58%)	76 (71%)	0.116[⊆]
Mortality rate	19 (33%)	24 (22%)	0.141[›]
Clinical type of patients	n (%)	n (%)	
Surgical	19 (33%)	25 (23%)	0.193[…]
Traumatic	2 (3%)	6 (6%)	0.714[›]
Medical	37 (64%)	76 (71%)	0.340[…]
Previous abdominal surgery	14 (24%)	13 (12%)	0.047[…]
Diabetes mellitus	1 (2%)	0 (0%)	0.352[›]
Inserted CVC or PICC	58 (100%)	74 (69%)	< 0.001[…]
Chronic renal disease	12 (21%)	12 (11%)	0.099[…]
Corticosteroid therapy	10 (17%)	14 (13%)	0.470[…]
Preceding antibiotic therapy	48 (83%)	45 (42%)	< 0.001[…]
Preceding antifungal therapy	6 (10%)	7 (6.5%)	0.387[…]
	median (IQR)	median (IQR)	
SOFA	3.5 (2–9)	6.0 (2–8)	0.191[⊆]
APACHE II	12.5 (8–18)	15.0 (10–21)	0.200[⊆]
Time from admission to candidemia or bacteremia, days	23.0 (18–30)	13 (10–18)	< 0.001[⊆]
Acute kidney injury stage (serum creatinine range)	n (%) 18 (31%)	n (%) 40 (33%)	
Stage 1 (110–170 µmol/L)	4 (22%)	16 (40%)	
Stage 2 (171–299 µmol/L)	11 (61%)	17 (43%)	0.362[…]

	Candidemia* (n = 58; 35%)	Bacteremia** (n = 107; 65%)	*P*-value
Stage 3 (300->440 µmol/L)	3 (17%)	7 (17%)	
Median serum creatinine, µmol/L (IQR)	274 (178–348)	180 (141–321)	0.217⊆
Values are shown as *n* (%), ⋯Pearson's chi-squared, ⊆ Mann-Whitney two-sample test, ›Fisher's exact test			
* *Candida albicans* (n = 24), *C. tropicalis* (n = 11), *C. krusei* (n = 7), *C. glabrata* (n = 6), *C. parapsilosis* (n = 4), *C. dubliniensis* (n = 1), *C. guilliermondii* (n = 1), *C. lusitaniae* (n = 1), *C. metapsilosis* (n = 1), *Saccharomyces cerevisiae* (n = 1), *Geotrichum clavatum* (n = 1)			
** coagulase-negative staphylococci (n = 39), *Enterococcus* spp. (n = 13), *Pseudomonas aeruginosa* (n = 10), *Klebsiella pneumoniae* (n = 9), *Escherichia* spp. (n = 6), *Acinetobacter* spp. (n = 5), *Propionibacterium acnes* (n = 4), *Enterobacter* spp. (n = 3), *Micrococcus luteus* (n = 3), *Staphylococcus aureus* (n = 3), *Stenotrophomonas maltophilia* (n = 3), *Streptococcus* spp. (n = 2), *Bacillus cereus* (n = 2), *Proteus penneri* (n = 1), *Serratia marcescens* (n = 1), *Actinomyces odontolyticus* (n = 1), *Burkholderia multivorans* (n = 1), *Corynebacterium* spp. (n = 1)			
CVC, central venous catheter; PICC, peripherally inserted central catheter; IQR, interquartile range			

Psep Exhibits The Highest Predictive Value For 28-day Mortality

Despite no significant difference in mortality rate between candidemia (33%) and bacteremia (22%) patients ($P = 0.141$) at 28 days after therapy initiation, two-sample Wilcoxon rank-sum test analysis with four biomarkers (CRP, PCT, PSEP and BDG) in comparison with SOFA score ($P = 0.012$) identified significant differences between candidemia and bacteremia patients (Additional file: Table ST1). PSEP significantly correlated with PCT. In case of invasive candidiasis, multivariable logistic regression showed that PSEP (AUC = 0.74) exhibited a significantly higher predictive value for mortality than PCT (AUC = 0.31) (P = 0.013) (Additional file: Table ST2). The sensitivity and specificity of PSEP vs. PCT predictive values were 81% and 69% vs. 68% and 23%, respectively.

Serum CRP, PCT, PSEP and BDG for differentiation between Candida **and bacterial sepsis**

CRP, PCT, PSEP and BDG serum levels were determined in blood culture-positive patients (candidemia n = 58, bacteremia n = 107) (Fig. 1). For bacterial species identified, see the legend to Table 1. Prediction and differential diagnosis are summarized in Table 2. As CRP at a cut-off of 5 mg/mL as well as **PSEP at a cut-off of 350 pg/mL** exhibited 100% positivity for both candidemia and bacterial sepsis patients, no discrimination between both groups is possible. Similarly, **PCT at a cut-off of 0.5 ng/L** does not discriminate between both groups ($P = 0.406$). By contrast, serum **PCT at a concentration cut-off of 3 ng/L** was moderately discriminative, exhibiting 76% positivity in candidemia and 56% positivity in bacteremia patients ($P = 0.012$), and so was **CRP at a cut-off of 130 mg/mL**, detecting 68% of bacteremia

patients and 38% of candidemia patients (P < 0.001). When analyzing single biomarker discriminative value, **BDG already at a cut-off 80 pg/mL** exhibited high discrimination between candidemia [58/58 (100%)] vs. bacteremia [19/107 (18%)] patients (*P* < 0.001). The median serum BDG concentration was significantly higher in the candidemia (1029 pg/mL) than in the bacteremia (35 pg/mL) group (*P* < 0.001). When the **BDG cut-off was increased to 200 pg/mL (or 220 pg/mL)**, the discrimination between candidemia and bacteremia groups continued to rise but the percentage of BDG-positive candidemia patients dropped from 100–97% (or 95%). Therefore, we tested whether combination of the serum biomarkers could achieve high discrimination without reducing sensitivity to candidemia.

Table 2
Prediction and differential diagnostics of *Candida* and bacteria sepsis using biomarkers at different cut-off values

Assessed biomarkers (recent cut-off)	**Candidemia n (%)**	**Bacteremia n (%)**	***P-value***
CRP (≧ 5 mg/mL)	58 (100%)	107 (100%)	0.999⋯
CRP (≧ 130 mg/mL)	22 (38%)	73 (68%)	< 0.001⋯
PCT (> 0.5 ng/l)	52 (90%)	91 (85%)	0.406⋯
PCT (< 3 ng/l) *	44 (76%)	60 (56%)	0.012⋯
PSEP (> 350 pg/mL)	58 (100%)	107 (100%)	0.999⊆
PSEP (> 700 pg/mL) **	58 (100%)	101 (94%)	0.091⊆
BDG (≧ 80 pg/mL)	58 (100%)	19 (18%)	< 0.001⊆
BDG (≧ 200 pg/mL)	56 (97%)	3 (3%)	< 0.001⋯
Median values (conc.)	Candidemia (IQR)	Bacteremia (IQR)	*P-value*
CRP (mg/L)	104 (78–150)	164 (101–234)	< 0.001[3,]
PCT (ng/L)	1.6 (0.90–2.80)	2.4 (1.03–8.54)	0.105[3,]
PSEP (pg/mL)	1784 (1203–3259)	1963 (1313–3524)	0.777[3,]
BDG (pg/mL)	1029 (500–1176)	35 (0–73)	< 0.001[3,]
Values are shown as *n* (%),⋯Pearson's chi-squared, ⊆Fisher's exact test, ›Mann-Whitney two-sample test			
Positivity of CRP, PCT, PSEP and BDG biomarkers was expressed relative to two or three preselected cut-offs in accordance with * and **.			
*Mostly the concentration of PCT in invasive candidiasis is very low, in the range of 2–3 ng/L [7, 8]; therefore, concentrations < 3 ng/mL were used as positive values for high probability of *Candida* sepsis.			
**Acute kidney injury stage 2 can affect the diagnostic accuracy of PSEP; usually, the median is close to 700 pg/mL [19] and the lowest concentrations of PSEP in fungal sepsis are usually close to 700 pg/mL [11]			
CRP, C-reactive protein; PCT, procalcitonin; PSEP, presepsin; BDG, 1,3-β-D-glucan; conc., concentration			

In summary, the best biomarkers of candidemia were BDG ≧ 200 pg/mL ($P < 0.001$), CRP ≧ 130 mg/L ($P < 0.001$), PCT < 3 ng/L ($P = 0.012$) and borderline discriminative PSEP > 700 pg/mL ($P = 0.091$). Sensitivity, specificity, PPV and NPV are shown in Table 3. The combination of PSEP having excellent sensitivity and

NPV with BDG having excellent specificity and PPV seems to be the most powerful laboratory approach to diagnosing invasive candidiasis.

Table 3
Comparison of biomarker cut-offs with the best diagnostic significance for invasive candidiasis

	CRP 130 mg/mL	PCT 0.5 ng/L	PCT 0–3 ng/L	PSEP > 700 pg/mL	BDG ≥ 200 pg/mL	BDG/PSEP*
Sensitivity (%)	**37.9**	**89.7**	**75.9**	**100**	**96.6**	**94.8**
95% CI	25.5–51.6	78.8–96.1	62.8–86.1	93.8–100	88.1–99.6	85.6–98.9
Specificity (%)	**31.8**	**15.0**	**43.9**	**5.6**	**97.2**	**100**
95% CI	23.1–41.5	8.8–23.1	34.3–53.9	2.1–11.8	92.0–99.4	96.6–100
PPV (%)	**23.2**	**36.4**	**42.3**	**36.5**	**94.9**	**100.0**
95% CI	15.1–32.9	28.5–44.8	32.7–52.4	29.0–44.5	85.9–98.9	93.5–100.0
NPV (%)	**48.6**	**72.7**	**77.0**	**100**	**98.1**	**97.3**
95% CI	36.4–60.8	49.8–89.3	64.5–86.8	54.1–100	93.4–99.8	92.2–99.4
AUC	**0.35**	**0.52**	**0.60**	**0.53**	**0.97**	**0.97**
95% CI	0.27–0.43	0.47–0.58	0.53–0.67	0.51–0.55	0.94–1.00	0.95–1.00

*BDG/PSEP - if both tests are positive, BDG ≥ 200pg/mL and PSEP > 700pg/mL

Because PSEP is excreted by the kidney, its level may be increased in the presence of renal dysfunction (and reduced by hemodialysis). Therefore, acute kidney injury (AKI) can affect the diagnostic accuracy of PSEP. The usually reported median is close to 700 pg/mL [19] and the lowest concentrations of PSEP in fungal sepsis are reported close to 700 pg/mL [11]. We found that 100% of candidemia patients without AKI tested positive for serum PSEP at a cut-off value of 350 pg/mL and 100% of those with stage 2 AKI (the KDIGO criteria [20]) at a cut-off value of 700 pg/mL, the latter predominating among our AKI patients (Tables 1 and 2). PSEP exhibited greater diagnostic accuracy than positive PCT (< 3 ng/L, 76%) and positive CRP (≥ 5 mg/mL, 100%).

To differentiate between *Candida* spp. colonization and sepsis, we analyzed serum BDG concentrations in patients with peripheral blood culture-confirmed candidemia relative to the time sequence of blood- versus catheter-culture *Candida* spp. positivity (Fig. 2). The *Candida* culture from catheters were performed within the interval +/- 3 days along IBC at the time of CVC and PICC replacement (Additional

file: Table ST3). Patients with catheter-related candidemia had significantly lower median BDG concentration (471 pg/mL, $P < 0.001$) than those with probable deep-seated candidiasis (1029 pg/mL) or catheter colonization confirmed following positive blood *Candida* culture (1203 pg/mL).

Monitoring Of Successful Echinocandin Therapy

Based on Additional file Table ST4, the most significant decrease was confirmed for PSEP (P = 0.0012) as early as 14 days after echinocandin therapy (Wilcoxon signed-rank test) (Fig. 3). By contrast, serum BDG and CRP concentrations decreased significantly as late as 28 days after echinocandin therapy initiation ($P = 0.0038$ and $P = 0.03$, respectively). PCT did not change over the 28-day period.

Proposal For The Use Of Results In Clinical Practice

Figure 4 provides a diagnostic algorithm for non-neutropenic and non-transplanted ICU patients at risk for invasive candidiasis and/or candidemia as an extension of a previously reported algorithm for ICU patients with suspected candidemia in sepsis of abdominal [26] and non-abdominal origin [4]. Our algorithm could accommodate both forms. The combination of PSEP and BDG could contribute to a many-fold increase (Table 3; SN = 94.8%, SP = 100%, PPV = 100%, NPV = 97.3% with AUC = 0.97) in the specificity of non-culture based methods in the early diagnosis of IC in the ICUs and may be helpful in cases of probable IC [12].

Discussion

PCT and PSEP in sepsis and sepsis-related mortality

According to the recent literature, PCT and PSEP are most accurate in diagnosing sepsis. The diagnostic accuracy of both PCT and PSEP in a systematic review and meta-analysis of 19 studies on the diagnostic value of PCT and PSEP for sepsis in critically ill adults is relatively similar, with AUC of 0.84 and 0.87, respectively [21]. A systematic review of 16 studies of 45,079 patients and 785 cases of candidemia versus bacteremia showed that PCT should not be used on its own as a tool discriminating between candidemia and bacteremia due to low reliability of PCT in guiding therapy [22]. PSEP exhibited better prognostic potential. There is a strong positive correlation between PSEP and SOFA scores [11], while PCT concentrations remain low to negative [7, 8]. Our results are consistent with the above reports. Furthermore, in our study, PSEP exhibited more significant predictive value in relation to IC mortality (AUC = 0.74 vs. AUC = 0.31) and showed better diagnostic performance in case of IC, when compared to PCT using both cut-offs, 350 pg/mL (58/58, 100%) and 700 pg/mL (58/58, 100%).

Nevertheless, the accuracy of sepsis diagnosis using PCT was reported significantly higher than PSEP when AKI is present [19]. Critically ill AKI patients mainly suffer from bacterial sepsis. In invasive candidiasis, however, PCT is rather negative and PSEP may fill this diagnostic gap [7, 11]. Because PSEP

levels can be a reliable indicator of sepsis in patients with non-injured or moderately injured kidney (Stage 1–2, Table 1), PSEP at a cut-off of 700 pg/mL seems to be optimal at AKI stages 1 and 2, as shown by our study and other reports [23]. This is also supported by a study of the diagnostic accuracy of PCT and PSEP for infectious diseases in AKI patients, suggesting the applicability of both biomarkers with different thresholds [24].

Prediction Values Of Biomarker Combination In Invasive Candidiasis

It is broadly accepted that the diagnosis of invasive *Candida* infections should rely on simultaneous detection of multiple biomarkers including early inflammatory ones (CRP, PCT and PSEP) and a highly specific one such as the panfungal antigen BDG [4, 25, 26]. We confirmed that existing bacterial colonization in candidemia patients had very little effect on false BDG positivity (0–224 pg/mL). ICU patients are very heterogeneous if we include patients after major abdominal surgery, with BDG > 100 pg/mL being associated with significantly increased SOFA scores and mortality from 13.7% (BDG ≤ 100 pg/mL) to 39.0% (> 100 pg/mL) [27]. Our results confirm the diagnostic value of BDG at serum concentrations > 250 pg/mL and particularly at borderline concentrations > 200 pg/mL in IC patients [26].

The role of BDG in predicting IC is essential as the early inflammatory biomarkers are not sufficiently specific to distinguish *Candida* from bacterial sepsis [21, 22]. Although our data suggest that CRP has great potential for distinguishing between candidemia and bacteremia at a cut-off of 130 mg/L (P = 0.005), its sensitivity and specificity for *Candida* sepsis are poor (67.2% and 66.9%, respectively; AUC = 0.67). Recent studies evaluating the ROC (i.e., AUC = 0.912) show that CRP in combination with other biomarkers increases the sensitivity or specificity for *Candida* sepsis [28]. Nevertheless, CRP is not appropriate for antifungal therapy, as compared with PCT to bacterial [29–31] and BDG to antifungal stewardship [32].

In the presence of risk factors for IC, the diagnosis of both bloodstream and deep-seated candidiasis requires combined tests [33]. The negative predictive value of BDG for IC is well evidenced [34, 35] and BDG was shown to impact on treatment decisions [36]. But in critically ill patients, the clinical significance of elevated BDG concentrations is still unclear [6], both because BDG is a panfungal antigen and because they are not know the differences in concentrations in the heterogeneous groups of IC patients (bloodstream candidiasis, *Candida* sepsis, deep-seated candidiasis). The analysis of samples from 58 patients with IC allows us to find statistically significant differences between the IC forms.

Psep, Monitoring And Prediction Of Successful Treatment

In contrast to a lack of evidence about the predictive value of PCT in the monitoring of the effect of antifungal or antibiotic therapy [22, 29, 31], we have shown the predictive value of serum PSEP concerning the success of echinocandin therapy of ICU patients with candidemia. The link between

decreased serum PSEP concentrations and successful therapy was statistically significant starting from 14 days after therapy initiation. This is 14 days earlier in comparison to BDG or CRP (Fig. 3). Our findings in 17 patients expand on a study of 7 patients by Bamba et al. demonstrating prompt PSEP decrease in successfully treated patients and continuous PSEP increase in poorly-responding ones [11]. Our PSEP results are important for predicting the success of echinocandin therapy, recommended as first-line treatment of candidemia, with de-escalation to fluconazole when clinical stability is achieved [33, 37].

Limitations

The main limitation of our study is its retrospective nature. In patients, only creatinine levels were evaluated, diuresis was not taken into account due to the retrospective nature of the study as diuresis over 6–12 hours is very difficult to determine retrospectively. Consequently, some measured values might be different from those present at the time of the index blood culture, although this affection was reduced by the fact that we mainly included patients who had underwent BDG, PSEP, PCT and CRP testing very close to the positive indexed blood culture. The elevation and decrease of PSEP levels are influenced by AKI of varying stages and subsequent dialysis, although it was significantly limited by the use of a PSEP concentration cut-off 700 pg/mL. In case of predicting the model response to echinocandin therapy, the study was limited by the small number of consecutive patients included.

Conclusion

Elevations of PSEP and BDG are a very powerful tool for differential diagnosis and determining the onset of invasive candidiasis in critically ill patients.

The use of PSEP and BDG could be helpful in the diagnostic workflow for critically ill patients with probable invasive candidiasis. Further studies are needed to understand whether this might significantly impact the involvement of PSEP and BDG in the diagnostic algorithm for non-neutropenic and non-transplanted ICU adults at risk for invasive candidiasis and/or candidemia.

Declarations

Ethics approval

Specific informed consent for this study was not necessary because of the retrospective nature of the analyses. The study, adhering to the Declaration of Helsinki, 2013 and Good Clinical Practice, was approved by the University Hospital Ostrava Ethics Committee for Multicenter Clinical Trials (no. 448/2018) and registered in ClinicalTrials.gov (ID: NCT03584594), date of registration June 28,2018.

Consent for publication Not applicable

Availability of data and material

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

Competing interest

The authors declare that they have no competing interests.

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Authors´contributions:

Conceptualisation**,** RD and MK; methodology, RD, MK, MR and NP; formal analysis, RD, MK, HS, ŠKP, RB, EK, MC and HT; investigation RD, MK and EK; data curration, MK, RD, HS, ŠKP and RB; writing-original draft preparation, RD and MK; writing-review and editing, RD, MK, MR, NP, VH and PH; supervision, MR

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Figures

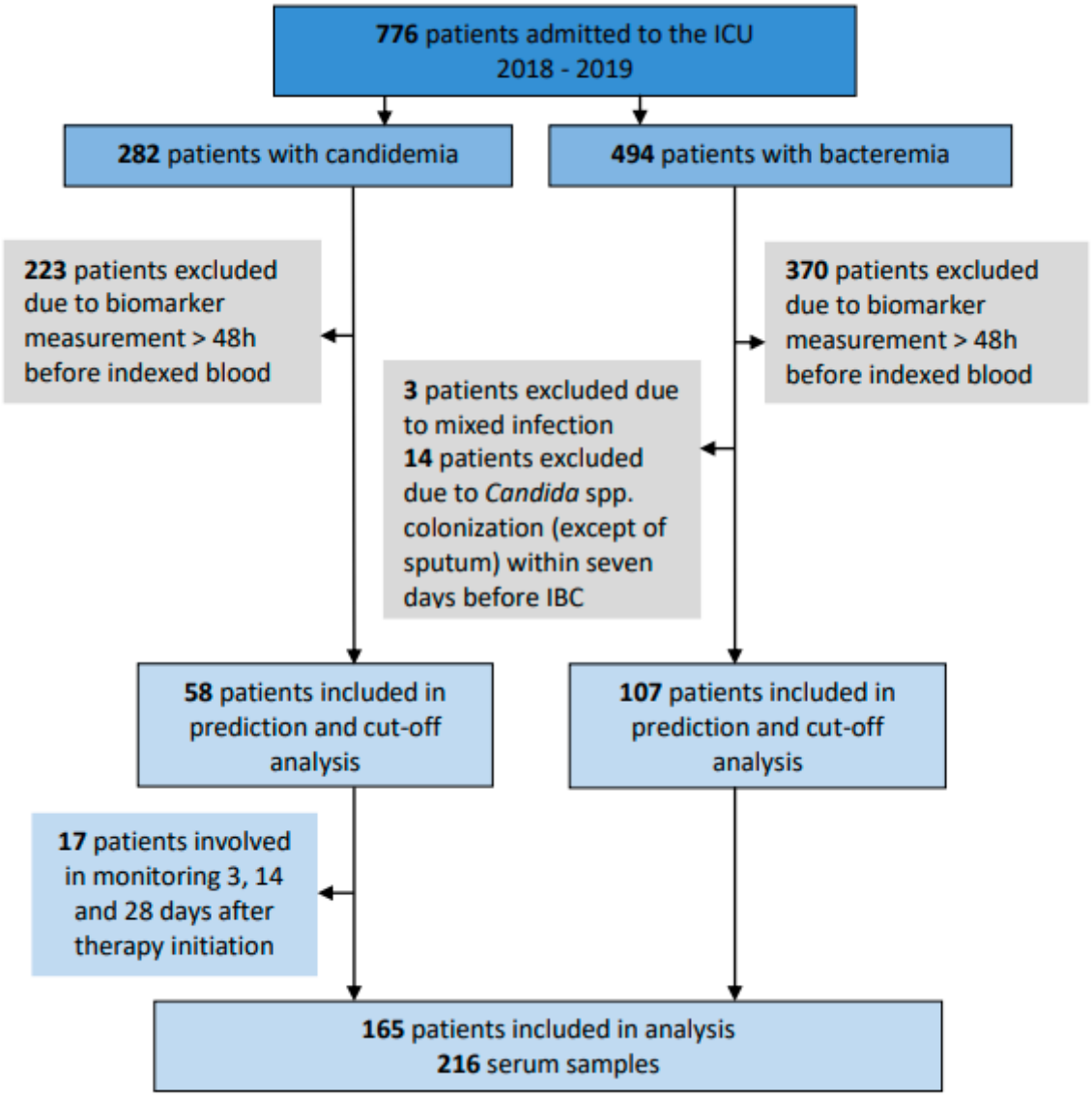

Figure 1

Flowchart of patients included in the analysis

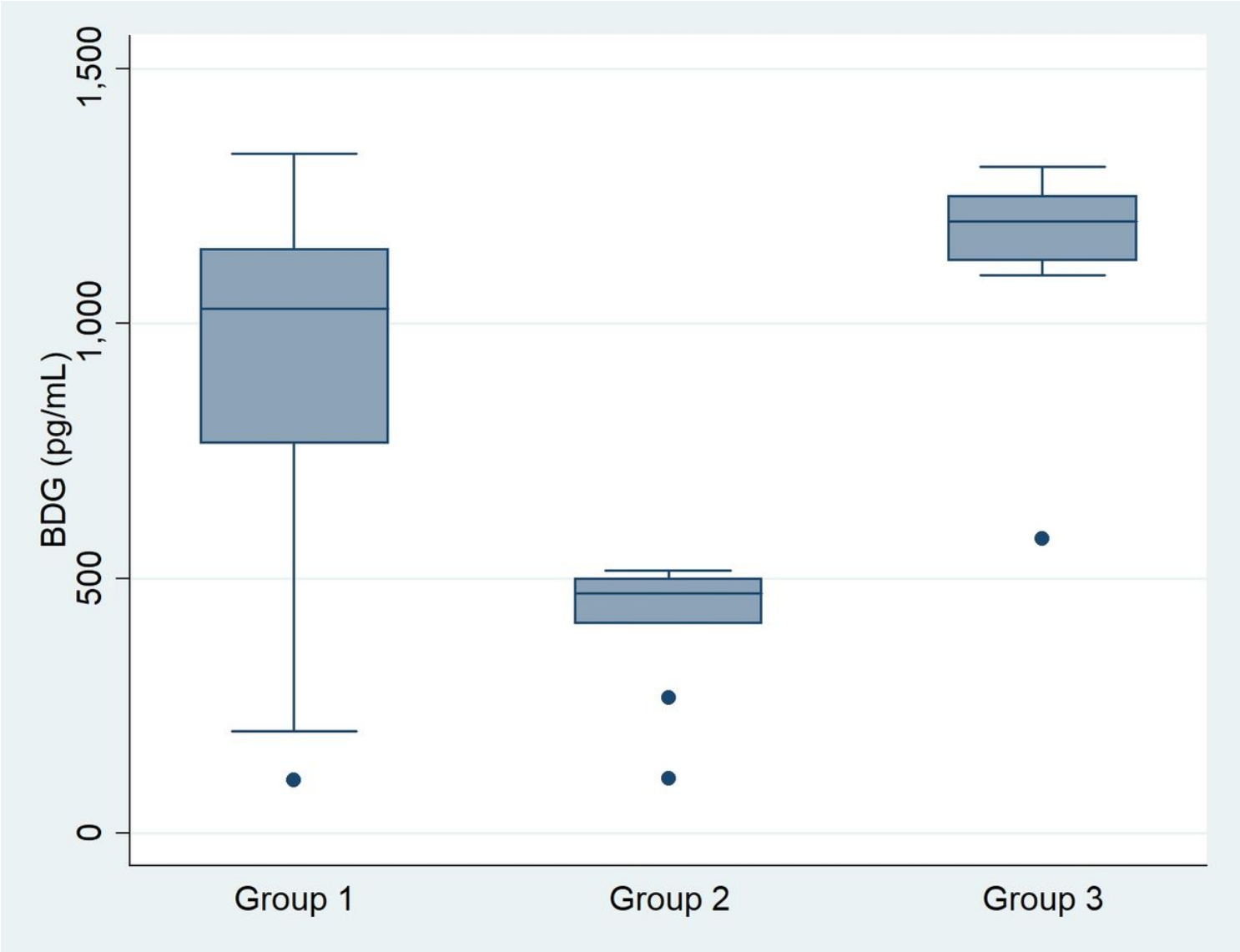

Figure 2

BDG relative to blood- versus catheter-cultures proved Candida (within the interval +/- 3 days around IBC). Legend: Group 1 Culture-confirmed candidemia in patients with non-colonized catheter (negative culture at day of IBC) – earlier state of invasion (1029 pg/mL), Group 2 Candidemia detected following culture-confirmed Candida-colonization of the catheter (catheter-related, culture set 1-3 day before candidemia) (471 pg/mL), Group 3 Catheter colonization was confirmed 1-3 days after the culture-proved candidemia (1203 pg/mL)

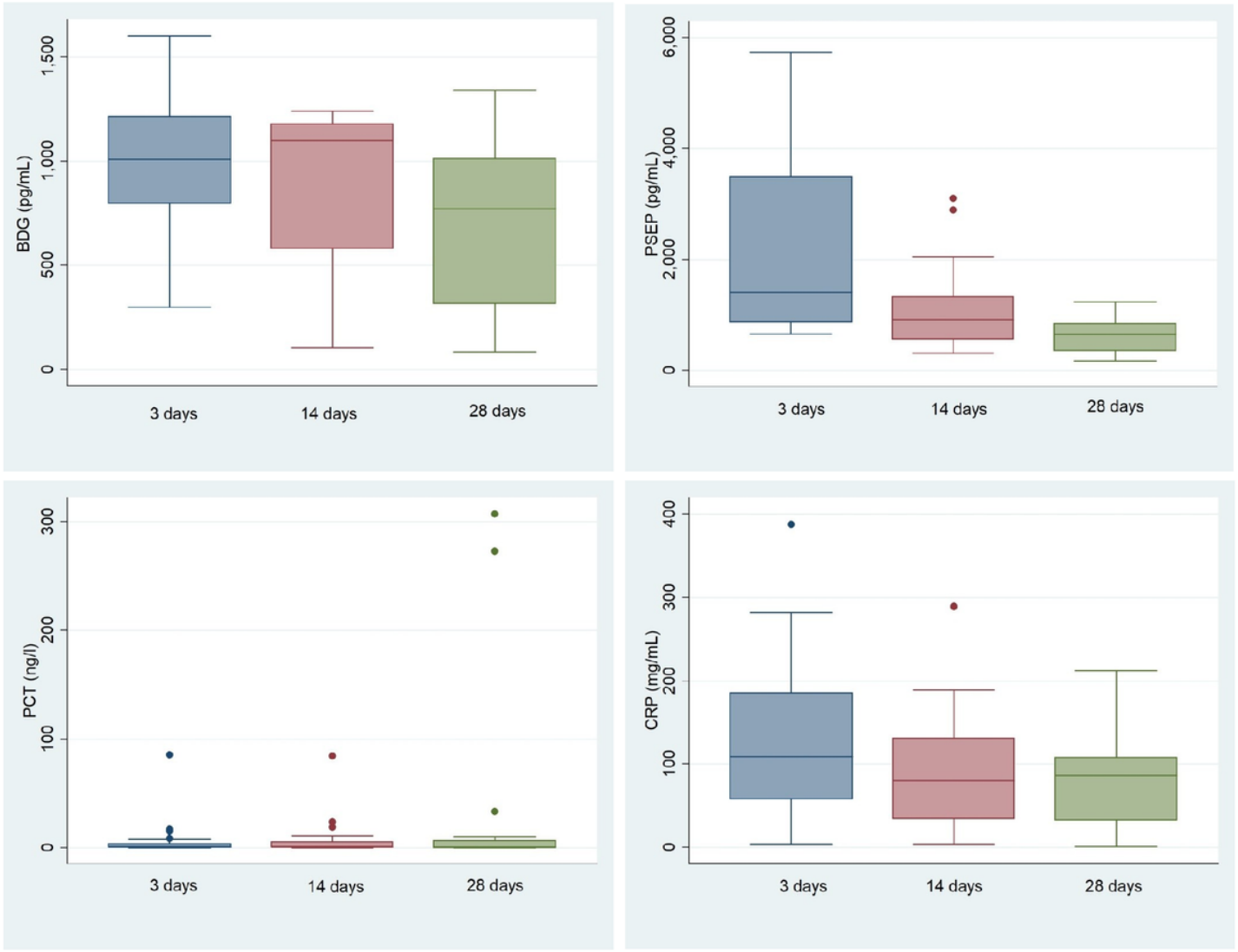

Figure 3

Changes in PCT, PSEP, CRP and 1,3-β-D-glucan within 3, 14 and 28 days of echinocandin therapy.

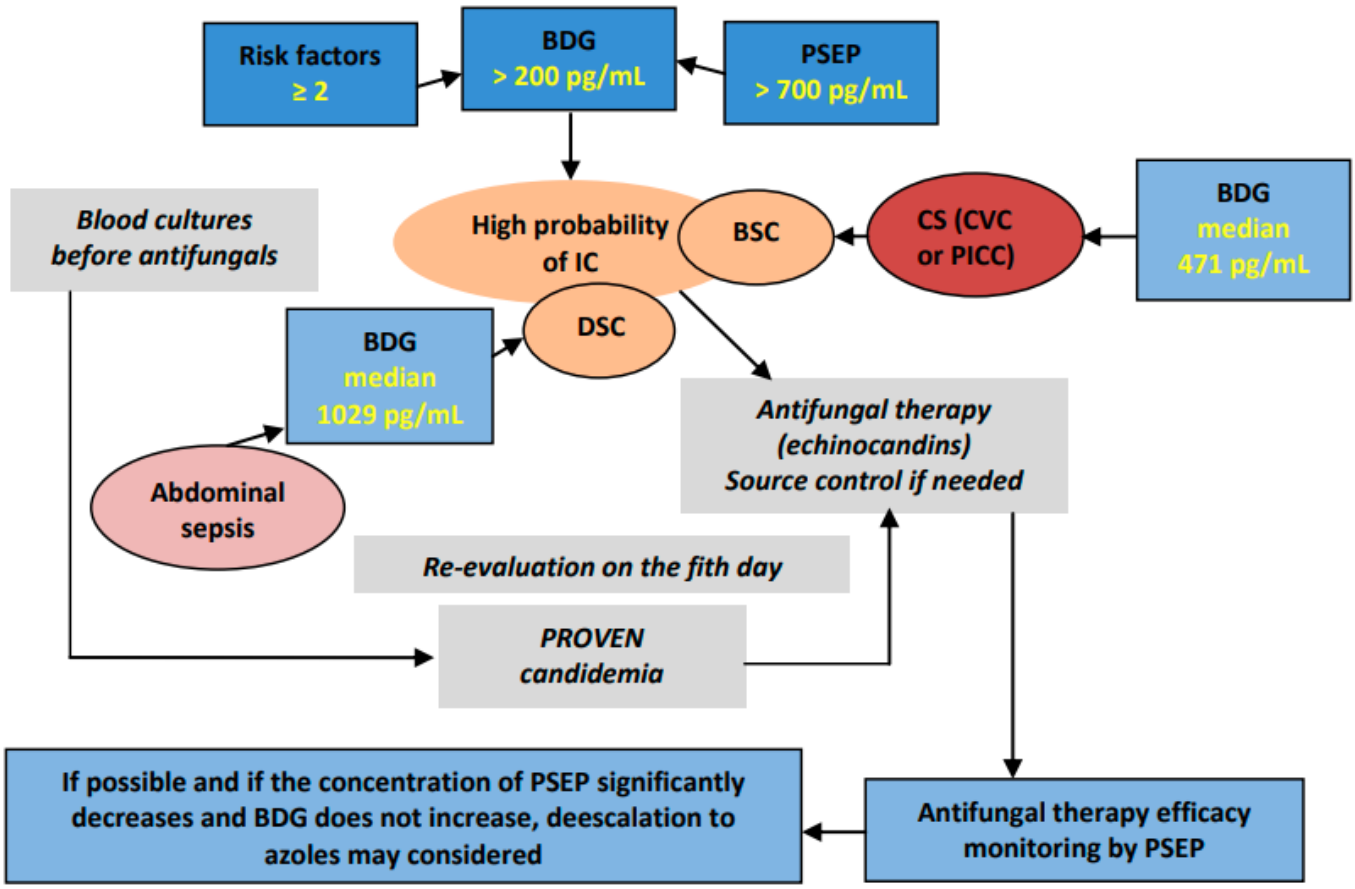

Figure 4

PSEP and BDG in a diagnostic algorithm in ICU patients at risk for invasive candidiasis. Legend: Risk factors: Broad spectrum antibiotics administered for at least 5 days, CVC or PICC, parenteral nutrition, chemotherapy for solid and hematological tumors (including steroids), hospitalization > 10 days within the preceding 3 months (including nursing homes / long-term care facilities), prior candidemia, Candida colonization at >1 site, transfer from ICU, dialysis. BDG, 1,3-β-D-glucan; PSEP, presepsin; BSC, blood stream candidiasis (candidemia); DSC, deep-seated candidiasis; CS, catheter sepsis; Abdominal sepsis: refers to anastomosis leak, postoperative abscess, repeated surgery for recurrent abdominal sepsis or infected pancreatitis.

Supplementary Files

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