Delta Neutrophil Index (DNI) as a Predictive and Prognostic factor for Candidemia patients: Matched Case-Control study

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Abstract

Background: Delayed antifungal therapy for candidemia leads to increased mortality. Discriminating bacterial infection from candidemia in systemic inflammatory response syndrome (SIRS) patients is very complex and difficult. Delta Neutrophil Index (DNI) is recently considered as a new factor which can distinguish infections from non-infections and reflect the severity of sepsis. We aimed to assess whether DNI can predict and provide a prognosis for candidemia in SIRS patients.

Methods: A matched case-control study was conducted from July 2016 to June 2017 at Kangdong Sacred Heart Hospital. Among patients with comorbidity of SIRS, those with candidemia were classified as the case group, while those with negative blood culture results were classified as the control group. The matching conditions included age, blood culture date, and SIRS onset location. To evaluate DNI as a predictive and prognostic factor for candidemia, multivariate logistic regression was performed.

Results: The 140 included patients were assigned to each group in a 1:1 ratio. DNI-D1 values measured on the blood culture date were higher in the case group (p <0.001). In the multivariate analyses, DNI_D1 (Odds ration□ORs□2.138, 95% confidential interval □CI□1.421-3.217, P <0.001) and Candida colonization were confirmed as predictive factors for candidemia. The cutoff value of DNI for predicting candidemia was 2.75%. The area under the curve for DNI value was 0.804 (95% CI, 0.719-0.890, p<0.001), with a sensitivity and specificity of 72.9% and 78.6%, respectively. Analysis of 14-day mortality was conducted for patients with candidemia. DNI_D1 and DNI_48, measured 2 days after the onset of candidemia, were both significantly high in the non-survivor group.

Conclusion: DNI was identified to be a predictive factor for candidemia in patients wit SIRS and a prognostic factor that predicts 14-day mortality in candidemia patients. DNI, along with clinical characteristics of patients, were useful in determining the occurrence of candidemia in patients with SIRS.

Background

The number of candidemia cases has been gradually increasing due to the development of various immunosuppressive treatments and invasive procedures. However, despite advances in medical science, candidemia still has a high mortality rate of 35–60% [1]. The foremost important factor to reduce candidemia-induced mortality rates is an early administration of appropriate antifungal therapy (AAT) [2]. If the administration of AAT is delayed, the mortality rate increases. For this reason, various markers and testing methods have been developed to predict candidemia to enable early-stage antifungal therapy [3–5]. However, there are cases in which these testing methods cannot be easily applied in actual treatment or are difficult to be commonly used. Moreover, studies reported varying degrees of sensitivity about the developed clinical scores or testing methods [3, 6]. Recently, several studies reported Delta Neutrophil Index (DNI) as a promising predictive and prognostic marker for sepsis [7–9]. Thus, we aimed to evaluate

DNI could be applied as a predictive marker of candidemia in patients with systemic inflammatory response syndrome (SIRS) and as a prognostic marker for patients with candidemia.

Methods

Study setting and patients

This study was performed at Kangdong Sacred Heart Hospital, a university-affiliated hospital with 640 beds, including 40 beds in three intensive care units (ICUs), located in Seoul, South Korea. This study was approved by the Institutional Review Board of Kangdong Sacred Heart Hospital (2019-04-003). Informed consent was not required by the board because of the retrospective design of the study. Between July 2016 and June 2018, we performed retrospective review of medical records and microbiology laboratory databases of patients. The case group included patients aged 20 years or older who developed candidemia during the study period. In cases of duplicated candidemia, only the initial candidemia episode was enrolled for the study. The matched control group included patients aged 20 years or older displaying SIRS during the same period with negative blood culture results. Case patients and control patients were matched at a 1:1 ratio, and the matching criteria are as follows: 1) blood culture procedure dates were within ± 3 days, 2) age ± 3 years, and 3) same patient location at the onset of SIRS (ICU vs. general ward). Patients with hematologic malignancy except lymphoma, neutropenia, and those who received granulocyte colony-stimulating factor were excluded in this study because these conditions may influence the hematologic parameters.

DNI measurement and other laboratory methods

The blood samples for DNI measurement were transferred to the laboratory department in EDTA tubes. The test for DNI was performed within one hour of blood sampling.

DNI is included as part of the routine complete blood count (CBS) test at our hospital. DNI was calculated using an automatic cell analyzer (ADVIA 2120 Hematology System, Siemens Healthcare Diagnostics, Forchheim, Germanty) [10]. This cell analyzer counts white blood cell (WBC) count in two independent channels, myeloperoxidase (MPO) and nuclear lobularity channels. The formula for calculating DNI is as follows: DNI (%)= (the neutrophil and the eosinophil subfractions measured in the MPO channel by a cytochemical MPO reaction)-(the polymorphonuclear neutrophil (PMN) subfraction measured in the nuclear lobularity channel by the reflected light beam). Blood cultures were ordered at the discretion of the primary physician because of signs and symptoms of SIRS. Each set of blood samples was inoculated into one aerobic and one anaerobic bottle and immediately loaded into a BacT/ALERT 3D microbial Detection System (bioMerieux, Inc., Durham, NC, USA). Candida species identification was done using the automated Vitek 2 Yeast Biochemical Crad (bio Merieux, Inc.).

Study variables and definitions

Clinical data were extracted from the patients' medical records and entered into a database. The following information was collected: leukocyte counts; C-reactive protein (CRP); procalcitonin; Candida score; site of infection; comorbidities; epidemiological setting at the time of performing blood culture; severity of illness; presence of severe sepsis or septic shock; and 14-day mortality. Severity of infection was assessed at the time of blood culture using Pitt bacteremia score [11]. Severity of comorbid conditions was assessed using McCabe classification [12].

Candidemia was defined as the minimum of one candida-positive blood culture obtained from patients with SIRS. The time of candidemia onset was defined as the time of sampling for the first positive blood culture. The time to positivity (TTP) was determined as the time interval between the start of incubation and the detection of yeast in blood, as documented using an automated monitoring system. Time to antifungal therapy (TAT) was described as the number of hours between the first blood culture sample obtained and the administration of antifungal agents. The clear-up period of candidemia was defined as the period of time required from the first blood culture that discovers candidemia until negative conversion of candidemia.

Candida colonization was considered unifocal when *Candida* species were isolated from one focus and multifocal when *Candida* species were isolated simultaneously from various non-contiguous foci. The Candida score (CS) for a cut-off value of 3 was as follows: total parenteral nutrition x1, plus surgery x 1, plus multifocal *Candida* colonization x 1, plus severe sepsis x 2 [3].

SIRS was defined based on two or more of the following conditions: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or PaCo2 <32 mmHg; and WBC >1200 cell/mm, <4000 cells/mm, or >10% immature forms. Severe sepsis was defined as one or more clinical signs of organ dysfunction. Severe sepsis, septic shock, and infection type were defined according to standardized criteria [13, 14]. Day 1 (D1) was defined as the first day of blood culture collection, with initial blood cultures collected within 24 hours of the onset of SIRS in study patients. DNI_D1 was defined as the DNI measured on the initial blood culture date, and DNI_48 was defined as the DNI measured 2-3 days after the blood culture was performed. The site of infection was determined by physicians based on clinical evaluation. Steroid use was defined as daily use of at least 20 mg of prednisone for at least 2 weeks. Patients with immunosuppression included those who had undergone immunosuppressive treatments (chemotherapy, radiation therapy, or immunosuppressive agent exposure).

Statistical analysis

Normally distributed continuous variables are reported as mean ± standard deviation (SD) and compared using a student's t-test. Non-normally distributed continuous variables are reported as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney U-test. Categorical variables are reported as percentages and compared using chi-squared tests or Fisher's exact test, as appropriate. To measure the sensitivity and specificity of DNI values at different cutoffs, a conventional receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to quantify the accuracy of DNI values as predictor and prognostic markers for candidemia. The cutoff

values were selected to maximize the sensitivity and specificity of the DNI values. An AUC of 0.5 was considered to be no better than expected by chance, whereas as a value of 1.0 signified a perfect marker. Using Spearman's method, the correlation between time of antifungal therapy and 14-day mortality and the correlations between other factors were analyzed.

Univariate and multivariate multiple logistic regression analyses were conducted to assess candidemia predictors and 14-day mortality prognostic factors. Variables with *p* values <0.05 in the univariate analyses and clinically significant factors were candidates for inclusion in the multivariate analysis. Odds ratios (ORs) were calculated at 95% confidence intervals (CIs). All reported *p*-values were two-tailed, and *p* <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 24 (IMB Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 140 patients participated in the study, and baseline clinical characteristics were summarized in Table 1. The mean age of the patients was 65.98±14.63, and there was no significant difference in age between the two groups. Matching technique was used, and there was no significant difference in the location of patients at the time of SIRS occurrence between the case and control groups. At the onset of SIRS for both groups, 27 patients (38.6%) were in the ICU and 43 patients (61.4%) were in the general ward.

The most common underlying disease was solid cancer, followed by neurological disorders and diabetes. The assessment of severity of co-morbidities using the McCabe classification showed a greater number of rapidly fatal cases in the case group (5.7% vs. 0%, *p*=0.007). There was also a clear difference in the cause of infection between the two groups (Table 1). The most common cause of candidemia in the case group was catheter related infection (CRI), which accounted for 48 out of the 70 cases (68.6%). CRIs were followed by primary bacteremia at 28.6% (20/70 cases). In contrast, the major cause of SIRS in the control group was pneumonia, which accounted for 42.9% (31/70) of the cases. However, the severity of infection assessed by the Pitt bacteremia score, severe sepsis, or septic shock yielded no statistically significant difference between the two groups (Table 1). To measure CSs, the presence of candida colonization, total parenteral nutrition (TPN), and receipt of surgery were examined. The proportion of patients with *Candida* colonization and the proportion of patients who underwent surgery while hospitalized appeared to be significantly higher in the case group than in the control group (Table 1). All patients were administered with antibiotics at the time of participation in this study. The 14-day mortality of all the patients was 10.7% (15/140), and was significantly higher in the case group (18.6% vs. 2.9%, *p*=0.005).

Comparison of DNI and other indicators as predictive markers of candidemia

To evaluate DNI effectivenss as a predictive factor for candidemia, DNI, CRP, Procalcitonin, leukocyte, and CS>3 were compared between the case and control groups (Table 2). DNI_D1 value was 3.5% (0.5-3.3) in the case group, which was significantly higher than the 1.3% (0.1-2.4) of the control group (p<0.001). The DNI_48 value was also significantly higher in the case group (2.0%) than the control group (1.0%) (p<0.001). Procalcitonin was also higher in the case group (Table 2). However, CS>3, which is a known predictive factor for candidemia, showed no significant difference between the two groups.

Multivariate analyses were conducted to determine independent predictive factors for candidemia in the case and control groups, and the results are summarized in Table 3. The factors, which were significantly different in the univariate analysis, “Candida Score>3” used for predicting candidemia, and clinically important factors exhibiting insignificant differences in univariate analysis were included in the multivariate analysis conducted in this study.

In the multivariate analyses, DNI_D1 (OR, 2.183, 95% CI, 1.421-3.217, p<0.001) and candida colonization (OR, 7.361, 95% CI, 1.717-31.553), p=0.007) were identified to be useful indices for predicting candidemia (Table 3).

Optimal cutoff value of DNI for predicting candidemia

To determine the DNI_D1 cutoff value for predicting candidemia, the ROC curve and AUC analyses were conducted (Fig. 1). The optimal cutoff value for predicting candidemia was found to be 2.75%, and the AUC of DNI_D1 was 0.804 (95% CI, 0.719-0.890, p<0.001). The sensitivity and specificity in predicting candidemia were 72.9% and 78.6%, respectively, with a cutoff DNI value of 2.75%, and the positive and negative predictive values were 77.3% and 74.3%, respectively. For DNI_D1 >2.75%, the OR for the presence of candidemia was 9.842 (95% CI, 4.562-21.402, p<0.001).

Factors associated with 14-day mortality in patients with candidemia

To determine prognosis factors for mortality of patients with candidemia, various factors were comparatively analyzed according to 14-day mortality. Among a total of 70 candidemia patients, 13 died within 14 days of candidemia onset. There was no difference in age, sex, or patient location at the time of candidemia onset (p=0.210) between the survivor and non-survivor groups. Underlying diseases and site of infection also yielded no significant differences between the survivor and non-survivor groups. The non-survivor group showed significantly higher Pitt bacteremia score than the survivor group (4.0□1.0-5.0□ vs 0.0 □0.0-2.0, p<0.001), and a higher septic shock rate (61.5% vs 7.5%, p=0.003). The percentage of patients showing a CS ≥3 was higher in the non-survivor group than the survivor group (46.2% vs. 19.3%, p=0.042). DNI_D1 and DNI_48 values were also significantly higher in the non-survivor group, measuring 7.4% (4.0-22.0) and 6.1% (2.1-14.4), respectively. TTP was 31.0 hours (26.5-53.0) in the non-survivor group, which was shorter than the 48.0 hours (34.0-72.0) of the survivor group, but there was no statistical significance (p=0.066).

In the case of TAT, the non-survivor group showed a significantly shorter period at 36hours (12.5-42.0) than the survivor group at 60hours (42.0-96.0), showing that antifungal therapies were administered earlier to the non-survivor group than the survivor group (p=0.013). As seen in Table 4, a significant difference was not found in TAT between the survivor and non-survivor groups in the multivariate analysis. However, antifungal therapy tended to be administered faster with earlier *Candida* detection from blood cultures (r=0.56 p=0.044). In addition, TAT and 14-day mortality showed an inverse correlation (r=-0.330, p=0.011).

The duration until negative conversion of candidemia also showed no difference between the survivor and non-survivor groups (Table 4).

Multivariate analysis also confirmed that DNI_D1 value (OR, 1.156, 95% CI, 1.039-1.287, p=0.008) and the occurrence of septic shock were reliable prognosis factors for 14-day mortality. The DNI_D1 cutoff value for predicting 14-day mortality was 3.95% and AUC was 0.769 (95% CI, 0.624-0.914, p=0.001).

Discussion

In this study, we confirmed DNI to be a predictive marker of candidemia in patients with SIRS and as a prognostic marker for patients with candidemia.

Candidemia is associated with one of the highest rates of mortality of any BSI [15]. To reduce the mortality of candidemia, AAT needs to be administered as early as possible. The initiation of antifungal therapy upon identification of the yeast from the blood culture as in the way currently applied, the treatment of candidemia must be delayed. However, avoiding delays in treatment of patients with candidemia is difficult. As those risk factors currently known to be associated with Candidemia are also used as the ones related to drug-resistant bacterial infection, they are not helpful in differentiating candidemia from bacterial infection in patients manifesting SIRS [16]. Various scoring systems and markers have been developed to distinguish candidemia, such as the CS or candida colonization index. [3–5]. However, their sensitivity for differentiating invasive Candida infection and colonization is only around 60% [6]. As such marker as B-D-glucan is generally not used by all hospitals, it has limits to its application. The administration of empirical antifungal therapy can be taken into consideration for patients suspected of sepsis, but it might cause problems like inappropriate administration of antifungal therapy and increased resistance

The DNI is a novel index reflecting a circulating fraction of immature granulocytes (IGs) [17, 18]. In previous studies, the DNI was identified as a factor that distinguishes conditions of infection from non-infection, and as a prognostic factor of severity in patients with sepsis [19–22]. Although studies on the differentiation between bacterial infection and noninfectious condition have been reported, there are no studies on invasive Candida infection, candidemia prediction, or candidemia prognosis assessment. DNI can be calculated automatically while measuring CBC. CBC is routinely and frequently evaluated in patients with SIRS at a substantially less cost than other laboratory markers. DNI can be easily calculated and reported without an additional cost. Using a sample collected from patients at the onset of SIRS in

our study, which included 70 patients with candidemia and 70 patients without candidemia, the DNI_D1 > 2.75% had a sensitivity of 72.9% and a specificity of 78.6% for predicting candidemia. In SIRS patients, Candida colonization was also identified as a predictor of candidemia, along with the DNI_D1. The cause of infection was mostly CRI or primary bacteremia in patients with candidemia. Among patients with suspected SIRS and sepsis, empirical antifungal therapy can be restrictively considered for patients with candida colonization with potential CRI or primary bacteremia due to the absence of clear infection site, with the application of DNI 2.75% as a cutoff value. In this study, the median detection time of candida was 48 hours (36–96). If preemptive antifungal therapy is administered only to the selected patients, it is possible to perform the early administration of antifungal therapy and even in a more economical way than to the administration of empirical antifungal agent to all patients. Based on previously conducted studies that reported the irrelevance of short-term administration of fluconazole in increasing the resistance of fluconazole in patients with candidemia [23, 24], preemptive antifungal therapy can be administered to patients with SIRS, Candida colonization, ambiguous primary infection sites, and increased DNI values.

DNI_D1 and DNI_48 were identified as independent predicting factors for 14-day mortality in patients with candidemia. Many patients in the non-survivor group were found to have comorbidity of septic shock. Although it is generally known that mortality can be reduced if antifungal therapy is administered earlier, this study found that the non-survivor group had earlier administration of antifungal therapy than the survivor group (36 hours (12.5–42.0) vs 60 hours (42.0–96.0)). TTP was also earlier in the non-survivor group than in the survivor group. As previously reported, the TTP of blood culture is associated with microbial burden in the blood. [25, 26]. In other words, shorter TTP indicates a larger amount of microbial burden in the blood. The shorter TTP (36 hours vs. 60 hours, p = 0.066) in the non-survivor group suggest greater Candida burden in the non-survivor group, thus leading to severe infection. In addition, the higher DNI values for the non-survivor group suggest that DNI reflects the severity of candidemia. As in the case of bacterial infection, increase of infection severity leads to increased DNI value [8, 19, 21].

To date, antifungal therapy for candidemia mostly begins when yeast is detected in the blood culture. This explains why antifungal therapy began earlier in the non-survivor group in this study. For the non-survivor group, the median TAT was 36 hours, and the median TTP was 31 hours, suggesting antifungal therapy was initiated after the detection of yeast from the blood culture. Earlier administration of antifungal therapy using DNI may increase the survival rate of candidemia patients, especially those with severe sepsis or septic shock.

Several limitations of our study should be mentioned. First, this study was performed at a single center and the results were analyzed retrospectively. There might be some selection bias although matching technique was applied. Second, the elevation of DNI is not specific for infection and may be observed in various other conditions, including hematologic malignancy, acute hemorrhage, chronic inflammatory diseases [18]. Third, this study classified patients with candidemia into the case group and patients without bacteremia into the control group. It is impossible to exclude the possibility that these selection criteria might contribute to differences in DNI values between the two groups. For these reasons, further

prospective analyses with a larger population are needed to confirm the DNI as a prediction and prognostic marker of candidemia.

Conclusion

In this study, DNI was confirmed as a predictive and prognosis factor for candidemia in patients with SIRS. Due to recent advancements in testing tools, DNI results can be obtained easily and quickly. Although prospective studies with a larger number of patients are needed, being able to screen high risk candidemia patients using DNI values and clinical characteristics of the patients (*Candida* colonization or site of infection) in real clinical settings may contribute to a decrease in candidemia mortality.

Abbreviations

AAT
Appropriate antifungal therapy
DNI
Delta neutrophil index
SIRS
Systemic inflammatory response syndrome
ICU
Intensive care units
IRB
Institutional Review Board
CBC
complete blood count
WBC
white blood cell
MPO
Myeloperoxidase
PMN
Polumorphomuclear neutrophil
CRP
C-reactive protein
TTP
time to positivity
TAT
time to antifungal therapy

Declarations

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on seasonal request.

Competing interests

Authors have disclosed no conflicts of interests.

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No

Authors' contributions

SY Park carried out screening and statistical analysis of the data and participated in design study and the writing of the manuscript. JS Lee participated in the study concept and design and interpretation of data. J Oh carried out screening and acquisition of data. JY Park participated the analysis and interpretation of data. All authors read and approved the final manuscript.

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Tables

Table 1. Clinical characteristics in 140 patients with and without candidemia

	With Candidemia N=70 (%)	Without Candidemia N=70 (%)	Total N=140 (%)	*p*
Age (mean ± SD)	67.04 ± 14.58	64.91 ± 14.71	65.98 ± 14.63	0.391
Sex				
Female	30 (42.9)	32 (45.7)	62 (44.3)	0.734
Male	40 (57.1)	38 (54.3)	78 (55.7)	
MaCabe classification				0.007
Non-fatal	13 (18.6)	27 (38.6)	40 (28.6)	
Ultimately fatal	53 (75.7)	43 (61.4)	96 (68.6)	
Rapidly fatal	4 (5.7)	0 (0.0)	4 (2.9)	
Immunosuppressant	7 (10.0)	1 (1.4)	8 (5.7)	0.063
Use of steroid	2 (2.9)	1 (1.4)	3 (2.1)	1.000
Underlying diseases				
Solid cancer	27 (38.6)	32 (45.7)	59 (42.1)	0.392
Neurologic diseases	32 (45.7)	20 (28.6)	52 (37.1)	0.036
Diabetes mellitus	22 (31.4)	22 (31.4)	44 (31.4)	1.000
Cardiovascular diseases	16 (22.9)	8 (11.4)	24 (17.1)	0.073
Chronic kidney disease	8 (11.4)	7 (10.0)	15 (10.7)	0.785
Chronic liver disease	7 (10.5)	8 (11.4)	15 (10.7)	1.000
Chronic lung diseases	2 (2.9)	5 (7.1)	7 (5.0)	0.245
Lymphoma	4 (5.7)	0 (0.0)	4 (2.9)	0.120
Solid organ transplantation	1 (1.4)	1 (1.4)	2 (1.4)	1.000
Site of infection				
Catheter related infection	48 (68.6)	0 (0.0)	48 (34.3)	<0.001
Pneumonia	0 (0.0)	31 (42.9)	31 (22.1)	<0.001
Primary bacteremia	20 (28.6)	0 (0.0)	20 (14.3)	<0.001
Intra-abdominal infection	1 (1.4)	12 (17.1)	13 (9.3)	0.002
Skin and soft tissue infection	0 (0.0)	13 (18.6)	13 (9.3)	< 0.001
Urinary tract infection	1 (1.4)	8 (11.4)	9 (6.4)	0.033
CNS infection	0 (0.0)	1 (1.4)	1 (0.7)	1.000
Noninfectious SIRS	0 (0.0)	5 (7.1)	5 (3.6)	0.058
Severity of infection				
Pitt bacteremia score (median, IQR)	0 (0.0-3.0)	0 (0.0-2.0)	0 (0.0-3.0)	0.561
Severe sepsis	9 (12.9)	5 (7.1)	14 (10.0)	0.485
Septic shock	18 (25.7)	17 (24.3)	35 (25.0)	
Total parenteral nutrition	25 (35.7)	17 (24.3)	42 (30.0)	0.140
Operation	20 (28.6)	37 (52.9)	57 (40.7)	0.003
Candia colonization	19 (27.1)	6 (8.6)	25 (17.9)	0.004

SD, standard deviation; IQR, interquartile ranges

Table 2 Comparison of delta neutrophil index with other laboratory markers for predicting candidemia

Laboratory marker	With Candidemia N=70 (%)	Without Candidemia N=70 (%)	Total N=140 (%)	*p*
DNI (median, IQR)	3.5 (2.3-5.4)	1.3 (0.1-2.4)	2.4 (0.9-4.0)	<0.001
DNI_48 (median, IQR)	2.0 (0.5-3.3)	1.0 (0.0-2.3)	1.3 (1.0-2.6)	0.004
Leukocytes, 10^3/uL (mean ± SD)	11087.6 ± 5898.8	9379.6 ± 3808.2	10079.1 ± 5216.5	0.081
CRP, mg/L (median, IQR)	82.0 (50.3-144)	66.8 (29.6-10.5.8)	74.5 (38.0-132.3)	0.249
Procalcitonin, mg/dL (median, IQR)	0.72 (0.29-1.91)	0.34 (0.18-0.66)	0.42 (0.19-1.43)	0.025
Candia Score ≥3	17 (24.3)	18 (25.7)	35 (25.0)	0.845

DNI, delta neutrophil index; IQR, interquartile ranges; SD, standard deviation; CRP, C-reactive protein

Table 3. Multivariate analyses for evaluating predictive factors of candidemia

	With Candidemia N=70 (%)	Without Candidemia N=70 (%)	ORs (95% CI)	*p*
DNI_D1, % (median, IQR)	3.5 (2.3-5.4)	1.3 (0.1-2.4)	2.138 (1.421-3.217)	<0.001
DNI_48, % (median, IQR)	2.0 (0.5-3.3)	1.0 (0.0-2.3)	0.913 (0.713-1.169)	0.471
Leukocytes, 10^3/uL (mean ± SD)	11087.6 ± 5898.8	9379.6 ± 3808.2	1.000 (1.000-1.000)	0.238
CRP (median, IQR)	82.0 (50.3-144)	66.8 (29.6-10.5.8)	1.001 (0.993-1.010)	0.729
Procalcitonin (median, IQR)	0.72 (0.29-1.91)	0.34 (0.18-0.66)	1.082 (0.775-10512)	0.643
McCabe classification Rapidly fatal	4 (5.7)	0 (0.0)	2.013 (0.574-7.055)	0.275
Operation	20 (28.6)	37 (52.9)	0.973 (0.330-2.872)	0.961
Candida colonization	19 (27.1)	6 (8.6)	7.361 (1.717-31.553)	0.007
Neurologic disease	32 (45.7)	20 (28.6)	1.683 (0.561-4.782)	0.367

DNI, delta neutrophil index; IQR, interquartile ranges; SD, standard deviation; CRP, C-reactive protein

Table 4 Comparison of prognostic factors of 14 day mortality in patients with candidemia between the survivor group and the non-survivor group

	Survivor N=57 (%)	Non-survivor N=13 (%)	*p*	Adjusted ORs (95% CI)	*p*
Age (mean ± SD)	65.81 ± 13.361	72.46 ± 18.715	0.959		
Sex					
Female	27 (47.4)	3 (23.1)	0.110		
Male	30 (57.1)	10 (76.9)			
Co-morbidities					
MaCabe classification			0.163		
Non-fatal	12 (21.2)	1 (7.7)			
Ultimately fatal	43 (75.4)	10 (76.9)			
Rapidly fatal	2 (3.5)	2 (15.4)			
Severity of infection					
Pitt bacteremia score (median, IQR)	0 (0.0-2.0)	4.0 (1.0-5.0)	<0.001	1.187 (0.890-1.584)	0.244
Septic shock	10 (17.5)	8 (61.5)	0.003	7.635 (1.159-50.290)	0.035
Candia colonization	15 (26.3)	4 (30.8)	0.739		
Candida score≥3	11 (19.3)	6 (46.2)	0.042	0.900 (0.225-3.609)	0.882
DNI_D1, %	3.4 (2.2-5.3)	7.4 (4.0-22.0)	0.002	1.156 (1.039-1.287)	0.008
DNI_48, %	2.0 (0.5-2.9)	6.1 (2.1-14.4)	0.015	1.226 (1.007-1.494)	0.043
Leukocytes, 10^3/uL (mean ± SD)	10831.58 ± 6010.190	10931 ± 7311.871	0.139		
CRP (median, IQR)	66.0 (39.0-145.0)	115.5 (84.2-136.0)	0.036	1.003 (0.996-1.009)	0.412
Procalcitonin (median, IQR)	0.47 (0.2-1.9)	1.0 (0.38-2.09)	0.303		
Time to positive, hours, (median, IQR)	48.0 (34.0-72.0)	31.0 (26.5-53.0)	0.066		
Time to antifungal therapy, hours (median, IQR)	60 (42.0-96.0)	36 (12.5-42.0)	0.013	0.968 (0.933-1.004)	0.079
Duration of Clear- up, days, (median, IQR)	5 (3.0-9.5)	4.5 (4.0-5.0)	0.638		

DNI, delta neutrophil index; IQR, interquartile ranges; SD, standard deviation; CRP, C-reactive protein

Figures

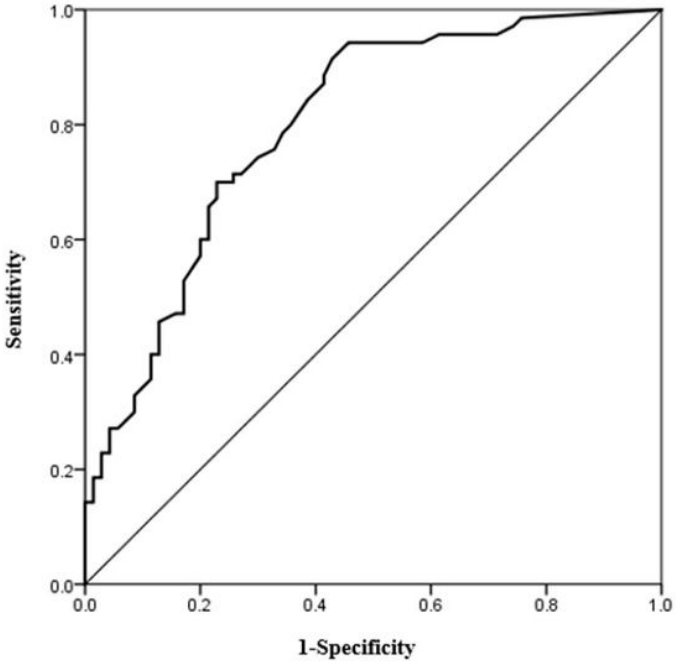

Figure 1

Receiver operating characteristics (ROC) curve to determine the cutoff value of delta neutrophil index (DNI) for predicting candidemia in patients with systemic inflammatory syndrome. Area under ROC was 0.804 (95% CU, 0.719-0.890)