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Comparison of blood culture results and clinical biochemistry laboratory parameters in geriatric patients with regards to infective agents

Geriatrik hastalarda kan kültürü sonuçları ile klinik biyokimya laboratuvar parametrelerinin enfeksiyon ajanlarına göre karşılaştırılması

Aslı Karadeniz [1], Mustafa Erinç Sitar [2], Belkız Öngen İpek [2]

[1] Maltepe University Faculty of Medicine Education and Research Hospital, Department of Infectious Diseases and Clinical Microbiology
[2] Maltepe University Faculty of Medicine Education and Research Hospital Central Laboratory Department of Biochemistry

ORCID ID of the author(s)

AK: 0000-0003-3799-1090
MES: 0000-0001-5114-8660
BÖİ: 0000-0002-2998-263X

Corresponding author / Sorumlu yazar:
Mustafa Erinç Sitar
Address / Adres: Maltepe Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Merkez Laboratuvar, Biyokimya Anabilim Dalı, Feyzullah Caddesi No: 39 34844, Maltepe, İstanbul, Türkiye
E-mail: merincsitar@gmail.com

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Abstract

Aim: Bacterial infections can cause life-threatening sepsis and should be identified and managed accurately, especially in the elderly. We aim to examine the relationships between positive blood cultures, Gram staining pattern and biochemistry parameters, in particular, procalcitonin (ProCT) levels.

Methods: This was a single center retrospective study, in which patients with positive blood cultures detected in Maltepe University Faculty of Medicine Research and Education Hospital were included. Two groups were formed according to age and evaluated with regards to bacterial Gram staining and biochemistry laboratory findings. Group 1 consisted of patients under 65 years of age (n=69) and Group 2 included those over 65 years of age (n=198).

Results: Two hundred and sixty-seven episodes of bacteremia (Gram-negative: 49.43%, Gram-positive bacteremia: 50.56%) were evaluated in two groups. CRP values, lymphocyte and thrombocyte counts, creatinine, AST, ALT, albumin, CRP/albumin ratio values were similar between two groups (P>0.05 for all), while leukocyte counts, neutrophil counts and BUN values were lower in group 1 (P=0.020, P=0.020 and P<0.001 respectively) and ProCT levels were lower in group 2 (P=0.049). ProCT values (independent of age) had significantly increased in patients with Gram-negative bacteremia (P<0.001 in both group 1 and 2).

Conclusion: ProCT measurement can be helpful as a distinguishing biomarker in different bloodstream infections, regardless of age.

Keywords: Bacteremia, Elderly, Procalcitonin

Öz

Amaç: Bakteriyel enfeksiyonlar yaşamı tehdit ederek sepsise neden olabilir ve özellikle yaşlılarda doğru bir şekilde tanı konmalı ve yönetilmelidir. Çalışmamızda kan kültürlerinde üreme olan hastaların, Gram boyama paterni ve biyokimya parametrelerinin, özellikle prokalsitonin (ProCT) seviyeleri temelinde incelenmesi amaçlanmıştır.

Yöntemler: Tek merkezli retrospektif bu çalışmada, Maltepe Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi'nde kan kültürü pozitif olan hastalar çalışmaya dahil edildi. Altmış beş yaş altı genç grup (n=69) ve 65 yaş üstü yaşlı grup (n=198), bakteriyel Gram boyama ve biyokimya laboratuvar bulgularına göre tanımlandı ve değerlendirildi.

Bulgular: 267 bakteriyemi epizodu (Gram negatif: %49,43 ve Gram pozitif: %50,56) iki ayrı yaş grubunda değerlendirildi. CRP değerleri, lenfosit ve trombosit sayıları, kreatinin, AST, ALT, albümin, CRP/albümin oranı değerleri iki grup arasında istatistiksel olarak anlamlı bulunmazken (P>0,05), lökosit sayıları (P=0,020), nötrofil sayıları (P=0,020) ve BUN değerleri (P<0,001) yaşlı grupta yüksek, ProCT seviyeleri ise düşük (P=0,049) olarak saptandı. ProCT değerleri (yaştan bağımsız olarak) Gram-negatif bakteriyemili hastalarda anlamlı olarak yüksek olarak ölçüldü (her iki grup için de P<0,001).

Sonuç: Prokalsitonin ölçümü, yaşa bakılmaksızın farklı kan dolaşımı enfeksiyonlarında ayırt edici bir biyobelirteç olarak yardımcı olabilir.

Anahtar kelimeler: Bakteriyemi, Yaşlı, Prokalsitonin

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Introduction

Imaging modalities and medical laboratory techniques are used to assist clinicians in diagnosis, after anamnesis and physical examination. Clinical laboratories are one of the key components in evidence-based medicine. They make a great contribution to medical decisions such as patient follow-up, visit frequency, definite diagnosis, length of hospital stay, discharge, surgery timing, emergency triage, risk assessment, prognostication, therapy, pharmaceutical dose arrangement and prediction of disease course in the general health system [1] . In our increasingly aging world population, due to low fertility and high longevity rates, the duty of laboratories in the health system will undoubtedly increase.

After entering the medical literature in the 1970s, Procalcitonin (ProCT) began to attract attention at an increasing speed [2]. Assicot et al. expressed the basis of clinical utility of ProCT and its substantial effect on bacterial septicemia in the early '90s, which was a pioneering research [3]. In today's modern world, ProCT is frequently used in the differentiation of infectious agents, noninfectious inflammatory states and monitoring antibacterial therapy [4,5]. As it is known, clinical courses of elderly patients are more uncertain than younger ones. Extraordinary symptoms related to infection may be described in cases of admission to the emergency room or the outpatient clinic, or the patients may not show any symptoms at all. Early diagnosis of the diseases, including sepsis, is of immense importance for the course of the disease. Interpretation of infection biomarkers (including ProCT), which are evaluated in the clinical diagnostic laboratories, may differ in elderly and young patients, just like clinical follow-up. Increased glucose intolerance, obesity, disability, sedentary lifestyle, polypharmacy, musculoskeletal comorbidities, absence or exclusion in reference interval studies, and/or unbalanced diet can be counted as the main reasons for this burden in elderly [6]. These changes in geriatric populations undoubtedly affect the laboratory test results directly, and the interpretation of the results indirectly. ProCT evaluation may provide valuable information at the onset of septicemia in differentiating Gram staining and fungal infections in non-geriatric patients [7]. As examples of studies on this subject, Charles et al., Yan et al. and Friend et al. concluded that ProCT levels were higher in Gram-negative bacteremia [7-9]. It can be stated that ProCT demonstrated encouraging results for pre-diagnosis of Gram-negative bacteremia [10]. Numerous studies have been found in current medical literature, including identification of the infectious agents and determination of clinical decision thresholds for ProCT. However, the scarcity of studies involving geriatric population and giving clear results is remarkable. When the problem regards the elderly, the scope changes significantly. It has low sensitivity for infection presence analysis (24%) and low discrimination rate in local infections in geriatrics [11,12]. In a study investigating the role of serum inflammatory markers in the diagnosis of sepsis, the positive predictive value of ProCT was 58 percent for elderly patients [13]. Based on previous information, this present study was planned to examine the relationships between length of hospital stay, invasive procedures, presence of a catheter, positive blood cultures, Gram staining pattern, C reactive protein (CRP), complete blood counts (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, albumin, and CRP/albumin ratio results. It was designed to compare the aforementioned parameters with ProCT results and its feasibility at the onset of infection.

Materials and methods

This retrospective observational data mining study was conducted by evaluation of laboratory information system and hospital information system of Istanbul Maltepe University Faculty of Medicine Research and Education Hospital, from June 2016 to December 2019. Patients with positive blood cultures, over 18 years of age, who were evaluated by infectious diseases specialists, were recruited for this current study. The study included two groups: The young group (Group 1, n=69, 34 males, 35 females) under 65 years of age and the geriatric group (Group 2, n=198, 105 females, 93 males) over 65 years of age (Figure 1). The Clinical Ethics Committee of Istanbul Maltepe University, Faculty of Medicine approved the study protocol (2019/900/37).

Phlebotomy procedure and blood analysis

After venipuncture, phlebotomies were performed, serum tubes were held in an upright position for at least 30 minutes and then centrifuged for at least 15 minutes at 2500 RPM. Serum ProCT, CRP, BUN, creatinine, AST, ALT, ferritin, and albumin levels were rapidly measured using Siemens Dimension RxL Max®(Germany), Roche Hitachi Modular e170® (Switzerland), Roche Cobas E411® (Switzerland) and Abbot Architect i1000SR® (United States of America) devices according to manufacturer's instructions. Whole blood tubes were gently inverted seven - eight times in room temperature and then complete blood count analysis was performed using Sysmex XT-1800® (Japan) and Sysmex XT-2000® (Japan) devices. At least two different levels of internal quality control materials were studied for each device and analytical parameter prior to measurements, and the results were followed according to Westgard rules [14]. In addition to internal quality control tests, periodic external quality tests were also studied for each analytical test and their suitability was documented. For culture analysis, blood samples were collected from patients during febrile episodes and/or in case of severe suspicion of bacteremia. At least two sets of blood samples were obtained from different peripheral veins and at least one of them was from a central venous catheter if the patient had one. BioMérieux BacT / ALERT 3D® (France) automatic blood culture system was used for blood cultures. Bacteremia was defined as the isolation of the bacteria from at least two or more bottles of blood cultures with associated signs and symptoms of systemic infection. Positive blood cultures were evaluated by Gram stain, and 5% sheep blood agar or MacConkey agar were used for incubation at 35 °C for 24 hours. Bacteria were identified using standard techniques of bacteriology. Recurrent results of patients with the same bacterial growth in repeating blood cultures were not included in this study. Blood culture examinations and measurements of infection biomarkers were performed independently of each other in different areas. Blood collection and all other analytical procedures were performed according to the requirements of

Istanbul Maltepe University Faculty of Medicine Education and Research Hospital Quality Management.

Statistical analysis

All statistical data analyses were done with Microsoft Excel 2010® (Microsoft Corporation, USA) and SPSS version 21.0® (SPSS Inc. Chicago, IL, USA). After determining the mean, median and standard deviations of the results, unpaired t-tests were used for comparing two groups (based on age and gram staining) because both groups consisted of separate patients [15]. Demographic data of the patients were presented numerically, and risk analyses were calculated as percentages. Chi square independence test was used to analyze categorical variables. $P<0.05$ was considered statistically significant.

Results

Among Group 1, the number of patients with Gram-negative and Gram-positive bacteremia were 38 and 31, respectively. In Group 2, these values were 94 and 104, respectively (Figure 1). To examine the relationship between age and Gram staining pattern, chi-square test was performed, which yielded insignificant results ($P=0.27$). In both age groups, *Enterobacteriaceae* species were found more frequently in terms of Gram-negative organisms grown in blood culture (Figure 1). *Staphylococcus* species were more frequent in laboratory data and culture analysis of patients with Gram-positive bacteremia. Among the staphylococcus spp., it is noteworthy that coagulase negative bacteria are detected in blood cultures more than others. CRP-values, lymphocyte and thrombocyte counts, creatinine, AST, ALT, albumin, CRP/albumin ratio values were similar between Groups 1 and 2 ($P>0.05$ for all, Table 1), while leukocyte counts, neutrophil counts and BUN values were lower in Group 1 ($P=0.020$, $P=0.020$ and $P<0.001$ respectively) and ProCT levels were lower in Group 2 ($P=0.049$) (Table 1). When patients younger than 65 years of age were compared according to Gram staining pattern, there was no difference in CRP values ($P=0.639$) and leukocyte count ($P=0.370$), while a statistically significant difference was detected in ProCT results ($P<0.001$, Table 2).

Table 1: Measured biochemical parameters of all patients and their comparison

Test parameter	Group 1 (<65 years of age)	Group 2 (≥65 years of age)	*P*-value
ProCT mean (SD) (ng/mL)	20.1 (32.8)	12.9 (23.4)	0.049*
CRP mean (SD) (mg/L)	15.1 (8.6)	12.6 (13.1)	0.187
Leukocyte count mean (SD) (per µL)	9,376 (6,592)	11,615 (6,915)	0.020*
Neutrophil count mean (SD) (per µL)	7,380 (5,593)	9,414 (6,492)	0.020*
Lymphocytes count mean (SD) (per µL)	1,379 (2,333)	1,297 (955)	0.685
Thrombocyte count mean (SD) (per µL)	183,742 (141,465)	201,959 (118,813)	0.299
BUN mean (SD) (mg/dL)	30.1 (24.8)	45.6 (34,3)	<0.001**
Creatinine mean (SD) (mg/dL)	2.1 (4.9)	1.7 (1.8)	0.331
AST mean (SD) (IU/L)	75 (97)	129 (434)	0.307
ALT mean (SD) (IU/L)	71 (106)	82 (181)	0.634
Albumin mean (SD) (g/dL)	2.54 (0.52)	2.53 (0.54)	0.893
CRP/Albumin ratio mean (SD)	6.4 (4.3)	5.3 (4.8)	0.094

Table 2: ProCT (Procalcitonin), CRP (C Reactive Protein) and leukocyte count results according to age groups and gram staining pattern of cases with bacteremia

Test parameter	Group 1 (<65 years of age)			Group 2 (≥65 years of age)		
	Patients with Gram negative bacteremia	Patients with Gram positive bacteremia	*P*-value	Patients with Gram negative bacteremia	Patients with Gram positive bacteremia	*P*-value
ProCT mean (SD) (ng/mL)	31.3 (37.8)	6.01 (16.87)	<0.001**	22.4 (29.8)	4.5 (9.8)	<0.001**
CRP mean (SD) (mg/L)	14.6 (7.9)	15.7 (9.4)	0.639	11.05 (8.08)	13.9 (16.3)	0.168
Leukocyte count mean (SD) (per µL)	8,742 (6,598)	10,173 (6,605)	0.370	12,117 (8075)	11,166 (5,686)	0.336

For gram staining patterns in the geriatric population, similar to that in the group below 65 years of age, there was a statistically significant difference between ProCT values ($P<0.001$), while CRP values ($P=0.168$) and leukocyte counts ($P=0.336$) were similar (Table 2). When ProCT values were evaluated independent of age, a significant increase was found in patients with Gram-negative bacteremia ($P<0.001$) (Table 3). However, in this age-independent evaluation, no significant difference was found between CRP ($P=0.431$), leukocyte count ($P=0.829$) and CRP / albumin ratio ($P=0.119$) according to gram staining pattern (Table 3). When ProCT results of patients with Gram-negative bacteremia were evaluated by age, there was no statistically significant difference between Groups 1 and 2 ($P=0.148$, Figure 2).

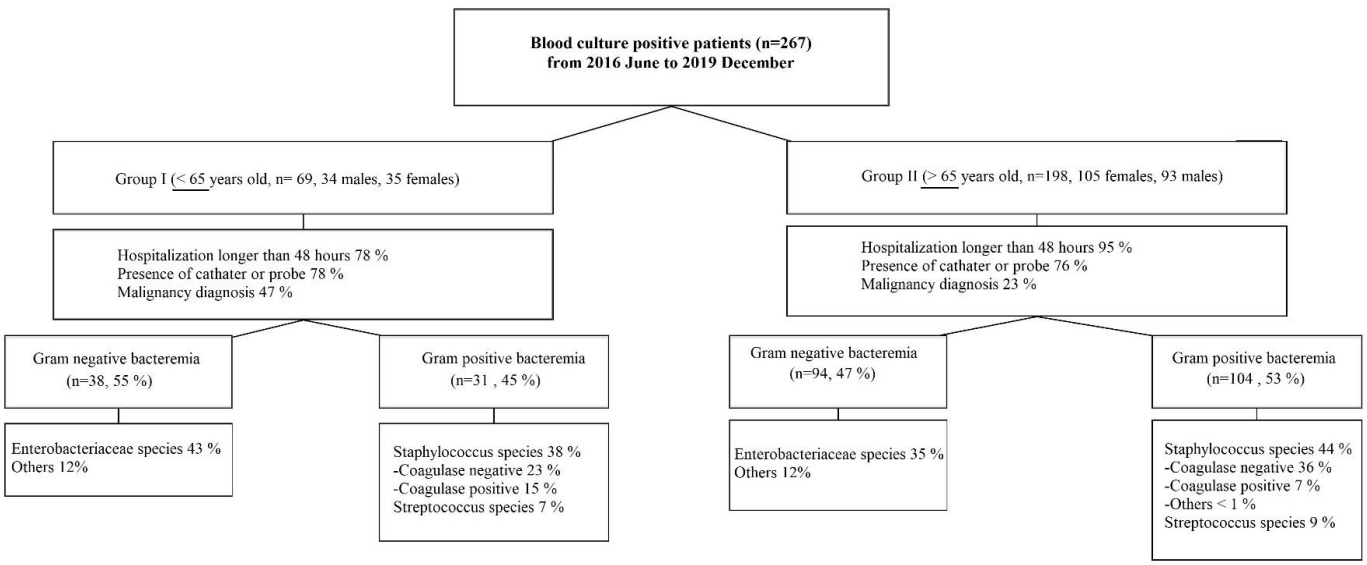

Figure 1: Blood culture results of both groups and their Gram staining distinctions

Table 3: ProCT (Procalcitonin), CRP (C reactive protein), leukocyte count, and CRP / albumin ratio results of all patients based on Gram staining pattern

Test parameter	Gram negative bacteremia (49.43 %)	Gram positive bacteremia (50.56 %)	*P*-value
ProCT mean (SD) (ng/mL)	25.1 (32.4)	4.9 (11.8)	<0.001**
CRP mean (SD) (mg/L)	13.9 (8.5)	12.6 (14.9)	0.431
Leukocyte count mean (SD) (per μL)	11,120 (7,768)	10,938 (5,899)	0.829
CRP / Albumin ratio mean (SD)	6.1 (4.3)	5.1 (5.1)	0.119

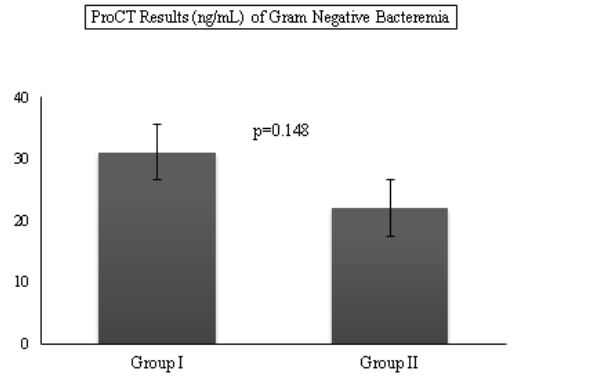

Figure 2: ProCT (Procalcitonin) results of two groups with Gram-negative bacteremia

Discussion

It is especially important to get an idea about the clinical course of elderly patients. Evaluation of blood culture results obtained during febrile periods in patients with a suspected serious infection is vital. Etiological agent variety can be challenging for the clinicians [16]. The time to start antibiotic treatment, the effectiveness of the dose administered, the type of the infective agent and the patient's response to treatment are the determining factors in the clinical course. In total, 267 episodes of bacteremia were evaluated in our study. Gram-negative bacteremia was identified in 49.43% (n=132), and Gram-positive bacteremia was identified in 50.56% (n=135) of these cases. There are different percentage rates for different patient groups in previous literature. One of the studies from our country revealed that 55.4% of 807 bacteremia episodes was caused by Gram-positive and 44.6% were caused by Gram-negative bacteria [17]. Daskalaki et al. [18] investigated bacteremia among renal transplant recipients, Prabhash et al. [19] studied infection in cancer patients and these studies confirmed that even if vastly different patient groups were included in the studies, bacterial growth outcomes were quite similar to our results.

In this current study, the fact that ProCT values were significantly higher in patients with Gram-negative bacteremia in both age groups was important. Li et al. evaluated ProCT levels in patients with sepsis and suspected sepsis, and found that ProCT levels were significantly increased in Gram-negative sepsis compared to Gram-positive or fungal sepsis [20]. Lin et al. [21] investigated ProCT levels in positive blood culture results in febrile patients with burn, and concluded that ProCT levels were significantly higher in Gram-negative infections. This finding is consistent with other relevant literature, as well [7,22]. However, the same findings could not be reached regarding CRP values and leukocyte counts. Liu et al. evaluated serum ProCT and CRP levels in patients with sepsis and found that serum ProCT levels were significantly elevated in Gram-negative sepsis compared to Gram-positive sepsis, but they did not detect a difference in CRP levels [23]. Bilgili et al. [24] evaluated septic patients with bacteremia in the intensive care unit to report significant differences in terms of CRP and ProCT in the Gram-negative group, but similar leukocyte levels. The fact that this result does not change by age should also be considered an important finding for the current literature. In Gram-negative bacteremia, which is more severe than Gram-positive bacteremia, higher ProCT values will enable clinicians to take early precautions. This parameter, which will contribute to the early detection of Gram-negative sepsis in intensive care units, will provide a chance for more effective and aggressive treatment to the patients. It will also provide valuable contributions during follow-up of patients' response to treatment, apart from CRP-values and leukocyte counts.

Limitations

This study had some notable restrictions. First, the number of young patients was lower and studies with larger cohorts are needed. This can be rationally explained, as the immune status of young individuals is stronger, and they rarely encounter comorbid diseases. Current study involved blood culture positivity encountered for about three and a half years. The number of patients that will be recruited for future studies can be increased, including the patient groups from different hospitals & regions. In addition, more comprehensive data can be obtained by increasing the biomarker diversity to be studied in clinical laboratories.

Conclusions

High serum ProCT values are highly valuable for Gram-negative bloodstream infections. It should always be kept in mind that physicians are advised to order less but effective laboratory tests for the elderly to avoid conflicting results. Even if there are some uncertainties, ProCT is an ideal marker, regardless of patient age.

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