Thiol/Disulphide markers and multinational association for supportive care in cancer risk score in febrile neutropenia

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Abstract

Introduction: This study aims to determine the use of thiol/disulphide homeostasis parameters together with procalcitonin (PCT), C-reactive protein (CRP) and Multinational Association for Supportive Care in Cancer (MASCC) risk scoring system for the prediction of prognosis and mortality in the patients with febrile neutropenia presenting to the emergency department. Material and methods: The study was carried out prospectively on 53 patients with febrile neutropenia and 51 healthy subjects presenting to the emergency department. Thiol/disulphide homeostasis parameters, which are oxidative stress markers, were measured through a new method developed by Erel and Neşelioğlu. PCT and CRP were also measured. Patients were grouped in to high-risk and low-risk groups in terms of prognosis and mortality through MASCC scores. Results: Mean values of disulphide/native thiol, CRP and PCT were found to be significantly higher in the patients having febrile neutropenia ($p=0.029$, $p<0.001$ and $p<0.001$, respectively). Mean values of disulphide/native thiol, CRP and PCT were found to be significantly higher in the high-risk patients ($p=0.038$, $p=0.004$, and $p=0.002$, respectively). Conclusion: The use of thiol/disulphide homeostasis parameters, PCT and CRP together with the MASCC system may be used for the prediction of the prognosis in the patients with febrile neutropenia.

What is already known about this topic?

Despite the widespread use of CRP and PCT as inflammatory markers and their occasionally inconsistent results, PCT has become prominent as a diagnostic and prognostic marker in the recent studies on febrile neutropenic patients with systemic infections.

What does this article add?

We observed that thiol/disulphide homeostasis parameters are significantly different amongst different prognostic groups of febrile neutropenia.

INTRODUCTION

Febrile neutropenia is a well-known complication of chemotherapy and it is one of the most frequent oncologic emergencies treated by emergency physicians [1]. Neutropenia often develops due to both the toxic effect of chemotherapy and the spread of malign cells into the bone marrow preventing the growth of hematopoietic cells. Neutrophils play an important role against infectious agents thus neutropenic patients become more susceptible to infections [2]. Invasive infections and the conditions that cause sterile tissue damage may lead to an increase in the systemic inflammation together with inflammatory mediators and high fever. High fever in the patients with malignancy can result from the malignant cell lysis or mucosal damage induced by chemotherapy apart from the infections [3].

It is quite important to diagnose and treat serious infections resulting in morbidity and mortality in febrile neutropenia in the early phase. On the other hand, insufficient clinical and microbiological data in these patients cause serious problems in the diagnosis of the disease [4, 5]. It is hard to distinguish the infected patients from the non-infected ones through the use of simple inflammation parameters in febrile neutropenia, thus reliable biomarkers are necessary for the early prediction of the complications [3, 6]. Certain biological markers were suggested for this purpose and their relationship with the risk assessments was studied. The accuracy and predictive values of these markers were generally evaluated by small-scale, single-center clinical and laboratory studies and different results were obtained [7-9].

The mediators released due to oxidative stress are known to cause numerous systemic diseases accompanied by inflammation. Thiol/disulphide homeostasis parameters have been used for the detection of oxidative stress, and they have been measured in a one-sided way since 1979. Today, these parameters can be measured both separately and collectively by means of a new method developed by Erel and Neselioglu [10-13]. Moreover, PCT and CRP are the biochemical markers released in infection and inflammation [14, 15].

Researchers have tried to develop prognostic models for many years in order to classify patients with febrile neutropenia to foresee severe complications and risks that may occur. In 2000, the MASCC risk scoring index was published so as to make risk classification and especially to identify the ambulant patients at low risk [16, 17].

This study aims to determine whether it is beneficial to use thiol/disulphide homeostasis parameters, PCT and CRP together with the MASCC risk scoring system for the prediction of prognosis and mortality in the patients with febrile neutropenia presenting to the emergency department.

METHODS

This is a prospective and single-center observational study. The study was conducted in an urban training and research hospital's emergency department with approximately 150000 patient visits per year. Patients were screened and were included in the study if they were over the age of 18, underwent chemotherapy within the last 7 days due to malignancy and were febrile at the time of presentation. According to Infection Disease Society Of America guidelines, fever is defined as a single oral temperature measurement of $>38.3°C$ or a temperature of $>38.0°C$ sustained over a 1 hour period. Patients were than excluded if they did not have neutropenia. The cases with an Absolute Neutrophil Count (ANC) of 500 cells/mm^3 or an ANC that is expected to decrease to 500 cells/mm^3 during the next 48 hours have been included in the category of febrile neutropenia [18]. The patients who had another condition that may change oxidative stress parameters(degenerative disease, diabetes mellitus, cardiovascular disease, acute renal failure, cerebrovascular disease, and chronic liver disease apart from the malignancy) were also excluded from the study. Control group included the healthy volunteers.

Written informed consents of both patients and subjects in control group were obtained before their inclusion in the study.

The researchers recorded demographic features (age, gender) chief complaints, medical history of disease and drugs, and signs and symptoms at the time of admission to the emergency department the standardized study forms.

Blood samples were drawn from all patients at the time of admission in order to analyze the blood culture, complete blood count, biochemical markers, thiol/disulphide homeostasis parameters (thiol, disulphide, native thiol, disulphide/native thiol, disulphide/total thiol, native thiol/total thiol), CRP and PCT levels.

After we collected venous blood samples for the measurement of thiol/disulphide homeostasis parameters, centrifuged them at 1500 rpm for ten minutes, and we separated the serum. We stored the serum samples at -80°C until the collection of all samples.Then we sent the serum samples to the biochemistry laboratory at Ataturk Training and Research Hospital, Ankara, Turkey subsequent to the completion of the sample collection process.

The laboratory staff measured the native thiol and total thiol by means of a new and fully automatic system, and they calculated the disulphide and ratios of disulphide/native thiol, disulphide/total thiol and native thiol/total thiol [10]. PCT (Roche Cobas 6000 Japan) and CRP (Siemens BNII, Germany) were also measured in the same laboratory.

MASCC risk scores (Table 1) of the patients were calculated at the time of admission. Patients whose MASCC score was [?] 21 points were classified as a low-risk group while the patients that have MASCC score $<$ 21 points were categorized as a high-risk group [18,19]. The patient group was compared with the control group in terms of thiol, disulphide, disulphide/native thiol, disulphide/ total thiol, native thiol/total thiol, CRP and PCT values. Moreover, the patient group was divided sub-groups: patients who had mortality within 28 days and patients who survived over 28 days, high-risk patients and low-risk patients according to MASCC scores and the patients who had a positive or a negative blood culture. These groups were compared to each other in terms of thiol, disulphide, disulphide/native thiol, disulphide/total thiol, native thiol/total thiol, CRP and PCT values.

The results were presented as mean +- SD. Univariate statistical analyses were performed by using a chi-square test for categorical variables and Student-t-test for continuous variables. P $<$0.05 was accepted to be statistically significant.

RESULTS

Fifty three patients were included in the study, 32 of these 53 patients were male, and mean age was 62.62+-12.80. Control group had 51 volunteers, 23 of these 51 volunteers were male and mean age was 60.25+-6.86. There was no statistically significant difference between the patient group and the control group in terms of age and gender (p = 0.245 and p = 0.169, respectively).

When the treatment group and the control group were compared according to thiol/disulphide homeostasis, PCT and CRP parameters, mean values of disulphide/native thiol, PCT and CRP were found to be significantly higher in the patient group in comparison with the control group (p=0.029, p$<$0.001 and p$<$0.001, respectively) while mean values of disulphide, native thiol, total thiol and native thiol/total thiol were detected to be significantly lower in the same group (p=0.001, p$<$0.001, p$<$0.001 and p=0.046, respectively). There was no significant difference between the treatment group and control group in terms of the mean value of disulphide/total thiol (p = 0.057). The thiol/disulphide homeostasis, PCT and CRP parameters of the treatment group and control group are given in Table 2.

When patients who survived more than 28 days were compared with patients with mortality in terms of thiol/disulphide homeostasis, PCT and CRP parameters, mean values of disulphide/native thiol, disulphide/total thiol and PCT were found to be significantly higher in dying patients in comparison with surviving patients (p=0.007,p=0.012 and p=0.018, respectively), while mean values of native thiol, total thiol and native thiol/total thiol were detected to be significantly lower in the same group (p=0.002, p=0.006 and p=0.007, respectively). There was no significant difference between patients who died and surviving ones in terms of mean values of disulphide and CRP (p = 0.073 and p = 0.115, respectively). The comparison of results of mean thiol/disulphide homeostasis parameters, PCT and CRP levels in surviving and dying patients are given in Table 3.

When high-risk patients according to MASCC score were compared with low-risk patients in terms of thiol/disulphide homeostasis, CRP and procalcitonin parameters, mean values of disulphide/native thiol, PCT and CRP were found to be significantly higher in high-risk patients (p=0.038, p=0.004 and p=0.002, respectively) while mean values of native thiol and total thiol were detected to be significantly lower (p=0.012 and p=0.018, respectively). There was no significant difference between the high-risk and low-risk patients in terms of mean values of disulphide, disulphide/total thiol and native thiol/total thiol (p = 0.497, p = 0.070 and p = 0.058, respectively).Comparisons of thiol/disulphide homeostasis, PCT and CRP parameters according to MASCC score are given in table 4.

When the patient group was divided in to two groups according to the blood culture results, PCT and

CRP values were seen to be significantly higher in the sub-group with positive blood culture ($p = 0.034$ and $p = 0.027$, respectively) while no significant difference was recorded between the sub-groups in terms of native thiol, disulphide, total thiol, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol values. The comparison of the thiol/disulphide homeostasis, PCT, and CRP parameters in the patients with positive and negative blood cultures is given in Table 5.

DISCUSSION

In diseases where inflammation is at the forefront, there is an increase in the production of proinflammatory cytokines associated with the increase of oxidative stress mediators. Thiol/disulphide homeostasis is also one of the oxidative stress markers [12, 20]. The impaired thiol/disulphide balance plays a role in the formation of most inflammatory diseases such as diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, chronic renal failure, cancer, Alzheimer's disease and Parkinson's disease [21]. PCT is a specific marker that is used in the diagnosis of inflammatory and infectious cases, and it is released from c cells [22, 23]. High PCT levels are associated with the severity of the infection and they can also be used to monitor the patients with severe infections, sepsis and multiple organ dysfunction syndrome (MODS). For all the reasons stated above, PCT is considered to be a reliable marker in the differential diagnosis of bacterial and non-bacterial inflammation [15, 24]. CRP is a biochemical marker that is secreted as an acute phase reactant after the cytokines are released in almost all microbial infections and inflammatory conditions [14].

Despite the widespread use of CRP and PCT as inflammatory markers and their occasionally inconsistent results, PCT has become prominent as a diagnostic and prognostic marker in the recent studies on febrile neutropenic patients with systemic infections [25]. A meta-analysis performed by Wu et al. has evaluated the possibility of using CRP and PCT for the early diagnosis in the febrile neutropenic patients with severe infections [26]. Despite PCT and CRP, the severity of the infection and the risk of mortality still cannot be predicted accurately. Therefore, new biomarkers are being searched [27, 28].

In the study conducted by Wenneras et al., PCT and CRP values were found to be above the normal range in all febrile neutropenic patients with proven or unproven infections and severe inflammation. PCT values were measured to be higher in infected patients as the strongest parameter. CRP was again recorded to be slightly higher in infected patients [3]. Similarly, in the study carried out by Ruokonen et al., PCT values measured in the patients with infections or with bacteremia were found to be higher than in patients with fewer of unknown origin in neutropenic patients [29]. The data of our study also provided similar results in febrile neutropenic patients in terms of PCT and CRP. In our study, disulphide/native thiol ratio was found to be higher in the patients with febrile neutropenia when compared to the control group, while the disulphide, native thiol, total thiol and native thiol/total thiol values were measured to be lower.No difference was recorded between the two groups in terms of disulphide/total thiol ratio.

Mortality rates in the patients with febrile neutropenia were found to be at different rates ranging from 4% to 24% in the literature [30-32]. The mortality rate in our study was approximately 25%. In the literature, Massaro et al. reported that PCT was not a good marker for predicting mortality [33-35], although there are some studies that have indicated that PCT may show short-term mortality when used as an early prognostic biomarker in oncologic emergencies. In certain studies on febrile neutropenia, CRP has been shown to have no significance in predicting the mortality [27, 28]. In another study, the relationship between mortality and CRP was found to be stronger in the patients with the febrile neutropenic disease, especially bacteremia, than in those who died from non-infectious causes [36]. In our study, disulphide/native thiol, disulphide/total thiol, and PCT values were measured to be higher in dying patients while the mean values of native thiol, total thiol, and native thiol/total thiol were recorded to be lower in the same group. There was no difference between dying and surviving patients in terms of disulphide and CRP values. PCT values were found to be compatible with the studies in the literature in terms of predicting the mortality. High values of disulphide/native thiol, disulphide/total thiol and low values of native thiol, total thiol and native thiol/total thiol may be used as valuable markers for the prediction of mortality in febrile neutropenia together with PCT.

Risk classifications are used for deciding which patients will have outpatient treatment, and to prevent serious complications infebrile neutropenic patients, [37, 38]. The MASCC score is a risk management-based scoring system with sensitivityof 71% and positive predictive value of 91%, which has been shown to be reliable in numerous studies for the management of febrile neutropenia and is widely used in clinical practices. Early discharge and outpatient treatment of the low-risk patients in febrile neutropenia according to MASCC score increase the quality of life and decrease nosocomial infections. MASCC score has been shown to be a cost-effective and safe method that can be used for identifying the patients with low risk [16, 17, 39]. Although there have been many studies in the literature showing the relationship between MASCC and PCT and CRP, there is no study that compares MASCC with thiol/disulphide homeostasis parameters. Combariza et al reported that the combination of MASCC risk score and mean CRP value successfully diagnosed the high mortality risk in the patients with neutropenic fever within the first 5 days [40]. Uys et al. indicated in their study that PCT and CRP values were significantly associated with the risk classification (strongest correlation) in the low-risk and high-risk patients according to MASCC risk score [41]. In the study carried out by Ahn et al., the combination of high-risk MASCC score and PCT elevation was found to be a strong predictor for the detection of bacteremia and septic shock [42]. PCT and CRP levels were found to be high in our study in high-risk patients according to MASCC risk score, which is compatible with the literature. In addition to the literature, high-risk patients were found to have high levels of disulphide/native thiol, while native thiol and total thiol levels were lower. There was no difference between disulphide, disulphide/total thiol and native thiol/total thiol values between high-risk and low-risk patients according to the MASCC risk score. Although there are different studies investigating the correlation between MASCC and PCT and CRP, our study is the first research indicating the correlation between thiol/disulphide homeostasis and MASCC risk score.

Although the majority of febrile neutropenic episodes are thought to result from a bacterial infection, it is difficult to determine the cause of febrile neutropenia because of the relatively poor diagnostic performance of the blood cultures [43]. In a study carried out by Viscoli et al., The frequency of bacteremia in febrile neutropenia was detected to be 29% [44]. In the literature, there are also the studies showing high PCT and CRP levels in the patients with positive blood cultures [45-47]. In our study, PCT and CRP values were found to be high in the patients with positive culture results, which is similar to the data in the literature. There was no significant relationship between thiol/disulphide homeostasis parameters and culture results.

To the best of our knowledge our study is the first research analyzing the relationship between thiol/disulphide homeostasis parameters and PCT and CRP and the MASSC scoring system in the patients diagnosed with febrile neutropenia. We observed that thiol/disulphide homeostasis parameters are significantly different amongst different prognostic groups of febrile neutropenia and we believe that with further studies these markers may be used in the prognostic evaluation of febrile neutropenic patients presenting to the emergency department.

References

1. Adelberg DE, Bishop MR. Emergencies related to cancer chemotherapy and hematopoietic stem cell transplantation. Emerg Med Clin North Am.2009;27:311-31
2. Bodey GP, Buckley, M, Sathe YS, Freireich EJ. (1966) Quantative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328-40
3. Wenneras C, Hagberg L, Andersson R, Hynsjo L, Lindahl A, Okroj M, Blom AM, Johansson P, Andreasson B, Gottfries J et al. Distinct Inflammatory Mediator Patterns Characterize Infectious and Sterile Systemic Inflammation in Febrile Neutropenic Hematology Patients, Open Access, www.plosone.org, March 2014, 9 (3), e92319
4. Bille J. Laboratory diagnosis of infections in febrile neutropenic or immunocompromised patients. Int J Antimicrob Agents.2000;16(2):87-9
5. Mulinde J, Joshi M. The diagnostic and therapeutic approach to lower respiratory tract infections in the neutropenic patient. J Antimicrob Chemother.1998;41(suppl D):51-5
6. Juutialinen A, Hamalainen S, Pulkki K Kuittinen T, Nousiainen T, Koivula I. Biomarkers for bac-

teremia and severe sepsis in hematological patients with neutropenic fever: multivariate logistic regression analysis and factor analysis. Leuk Lymphoma, 2011;52:2349-55
7. Buyukberber N, Buyukberber S, Sevinc A, Camci C. Cytokine concentrations are not predictive of bacteremia in febrile neutropenic patients. Med Oncol.2009;26:55-61doi:10.1007/s12032-008-9081-z
8. Persson L, Engervall P, Magnuson A, Vikerfors T, Soderquist B, Hansson LO, Tidefelt U. Use of inflammatory markers for early detection of bacteraemia in patients with febrile neutropenia. Scand J Infect Dis 2004;36:365-71.doi:10.1080/00365540410020217
9. Kern WV, Heiss M, Steinbach G. Prediction of gram-negative bacteraemia in patients with cancer and febrile neutropenia by means of IL-8 levels in serum: targeting empirical monotherapy versus combination therapy. Clin Infect Dis.2001;32:832-35.doi:10.1086/319207
10. Erel O, Neselioglu S (2014) A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 47:326–332
11. Wasterlain CG, Fujikawa DG, Penix L, Sankar R (1993) Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 34:37–53
12. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: The role of antioxidant therapy. Toxicology 2003;189(1-2):75-88
13. Ellman G, Lysko H. A precise method for the determination of whole blood and plasma sulfhydryl groups. Anal Biochem. 1979;93:98–102
14. Sudhoff T, Giagounidis A, Karthaus M, Serum and plasma parameters in clinical evaluation of neutropenic fever Antibiot Chemother, 2000,50;10-19
15. Carrol ED, Thomson AP, Hart CA. Procalcitonin as a marker of sepsis. Int J Antimicrob Agents.2002;20(1):1-9
16. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J. The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol, 2000, 18(16):3038-51
17. Carmona-Bayonas A, Jimenez-Fonseca B, Virizuela Echaburu J, Antonio M, Font C, Boisca M, Ramchandani A, Martinez J, Hernando Cubero J, Espinosa J et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. J Clin Onc,2015 33(5):465-71
18. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR .Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America, e56 d CID 2011:52 (15 February)
19. De Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F; Management of febrile neutropenia: ESMO clinical practice guidelines. Ann Oncol,2000,21(suppl 5):252-56,doi:10.1093/annonc/mdq196
20. LeGrand A, Fermor B, Fink C, Pisetsky DS, Weinberg JB, Vail TP, Guilak F. Interleukin-1, tumor necrosis factor alpha, and interleukin-17 synergistically up-regulate nitric oxide and prostaglandin E2 production in explants of human osteoarthritic knee menisci. Arthritis Rheum 2001;44(9):2078-83
21. Groitl B, Jakob U. Thiol-based redox switches. Biochim Biophys Acta 2014;1844:1335–1343
22. Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogesang H, Junker U, Jager L, Reinhart K. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro.J Lab Clin Med,1999,134;49-55
23. Meisner M, Muller V, Khakpour Z, Toegel E, Redl H. Induction of procalcitonin and proinflammatory cytokines in an anhepatic baboon endotoxin shock model.Shock,2003,19:187-90
24. Meisner M. Pathobiochemistry and clinical use of procalcitonin. Clin Chim Acta.2002;323(1-2):17-29
25. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection, 2008,36(5):396-407.doi:10.1007/s15010-008-7374-y
26. Wu CW, Wu JY, Chen CK, Huang SL, Hsu SC, Lee MT, Chang SS, Lee CC. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with

febrile neutropenia? A systematic review and meta-analysis. Support Care Cancer,2015;23:2863-72
27. Luz Fiusa MM, Costa Lima C, de Souza GR, Vigorito AC, Penteado Aranha FJ, Lorand-Metze I, Annichino-Bizzacchi JM, de Souza CA, De Paula EV. A high angiopoetin2/angiopoetin1 ratio is associated with a high risk of septic shock in patients with febrile neutropenia. Crit Care 2013;17:R169
28. Alves BE, Montalvao SA, Aranha FJ Siegl TF, Souza CA, Lorand-Metze I, Annichino-Bizzacchi JM, De Paula EV. Imbalances in serum angiopoetin concentrations are early predictors of septic shock development in patients with post chemotherapy febrile neutropenia. BMC Infect Dis 2010;10:143
29. Ruokonen E, Nousiainen T, Pulkki K, Takala J. Procalcitonin concentrations in patients with neutropenic fever. Eur J Clin Microbiol Infect Dis,1999,18(4);283-85
30. Dulisse B, Li X, Gayle JA, Barron RL, Ernst FR, Rothman KJ, Legg JC, Kaye JA. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia. J Med Econ.2013;16 (6):720-35. doi: 10.3111/13696998.2013.782034
31. Yetkin F, Senol E, Yalcın S, Haznedar R. The Evaluation of Procalcitonin as a Diagnostic and Prognostic Marker of Bacterial Infections in Febrile Neutropenic Patients. Klimik Dergisi 2011;24(1):24-30
32. Coyne JC,BS Le Vivian, Brennan JJ, Castillo EM, Shatsky RA, Ferran K, Brodine S, Vilke GM . Application of the MASCC and CISNE Risk-Stratification Scores to Identify Low-Risk Febrile Neutropenic Patients in the Emergency Department. Annals of Emergency Medicine,Volume 69,No:6:June 2017
33. Rast AC, Kutz A, Felder S, Faessler L, Steiner D, Laukemann S, Haubitz S, Huber A, Buergi U, Conca A. Procalcitonin Improves the Glasgow Prognostic Scale for Outcome Prediction in Emergency Patients with Cancer: a Cohort Study, Dis Markers, 2015, E Pub
34. Sedef AM, Köse F, Mertsoylu H, Ozyılkan O. Procalcitonin as a biomarker for infection related mortality in cancer patients. Curr Opin Support Pall Care,2015;9:168-73
35. Massaro KSR, Macedo R, de Castro BS, Dulley F, Oliveira MS, Yasuda MA, Levin AS, Costa SF. Risk factor for death in hematopoietic stem cell transplantation: are biomarkers useful to forsee the prognosis in this population of patients? Infection 2014,42:1023-32
36. Ortega M, Rovira M, Almela M, de la Bellacasa JP, Carreras E, Mensa J . Measurement of C-reactive protein in adults with febrile neutropenia after hematopoietic cell transplantation. Bone Marrow Transplantation 2004;33:741-44
37. Ahn S, Lee YS, Lee JL, Lim KS, Yoon SC. A new prognostic model for chemotherapy-induced febrile neutropenia. Int J Clin Oncol.2016:21:46-52
38. Ha YE, Song JH, Kang WK, Peck KR, Chung DR, Kang CI, Joung MK, Joo EJ, Shon KM. Clinical factors predicting bacteremia in low-risk febrile neutropenia after anti-cancer chemotherapy. Support Care Cancer.2011;19:1761-67
39. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, Herrstedt J. Management of febrile neutropenia : ESMO Clinical Practice Guidelines. Ann Oncol. 2016:27;111-118
40. Combariza JF, Lombana M, Pino EL, Arango M. C-reactive protein and the MASCC risk index identify high-risk patients with febrile neutropenia and hematologic neoplasms. Support Care Cancer 2015, 23:1009-13
41. Uys A, Rapoport BL, Fickl H, Meyer PW, Anderson R. Prediction of outcome in cancer patients with febrile neutropenia: comparison of the Multinational Association of Supportive Care in Cancer risk-index score with procalcitonin C-reactive protein, serum amyloid A, and interleukins-1β,-6,-8 and 10 European Journal of Cancer Care,2007;16:475-483
42. Ahn S, Lee YS, Lim KS, Lee JL. Adding procalcitonin to the MASCC risk-index score could improve risk stratification of patients with febrile neutropenia. Support Care Cancer, 2013,21:2303-08
43. Klastersky J,Ameye L, Maertens J, Georgala A, Muanza F, Aoun M, Ferrant A, Rapoport B, Rolston K, Paesmans M. Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents.2007:30 (suppl 1):51-9
44. Viscoli C, Cometta A, Kern WV, Bock R, Paesmans M, Crokaert F, Glauser MP, Calandra T . Piperaccilin-tazobactam monotherapy in high risk febrile neutropenic cancer patients. Clin Microbiol Infect 2006;12:212-16

45. Rintala E, Irjala K, Nikoskelainen J. Value of measurement of C-reactive protein in febrile patients with hematological malignancies. Eur J Clin Microbiol Infect Dis 1992;11:973-78
46. Kern WV. Risk assessment and treatment of low risk patients with febrile neutropenia. Clin Infect Dis 2006;42:533-40
47. Prat C,Sancho MJ, Dominguez J, Xicoy B, Gimenez M, Ferra C, Blanco S, Lacoma A, Ribera JM, Ausina V. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leukemia and Lymphoma, 2008 September;49(9):1752-61

Tables

Table 1. The Multinational Association for Supportive Care in Cancer (MASCC) Score

Characteristics of MASCC Score	Weight (points)
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age < 60 years	2

Table 2. Comparison of the patient group and the control group in terms of mean Thiol/disulphide homeostasis parameters, CRP+ and PCT++ levels

	Patient group(n=53)	**Control group(n=51)**	**P value**
Νατιε Τηιολ (μμολ/Λ)	258.27 ± 81.36	429.13 ± 50.82	<0.001
Τοταλ Τηιολ (μμολ/Λ)	289.82 ± 79.84	471.61 ± 53.33	0.001
Δισυλπηιδε (μμολ/Λ)	15.61 ± 9.31	21.29 ± 7.39	0.001
Disulphide/native thiol	0.071 ± 0.065	0.050 ± 0.018	0.029
Disulphide/total thiol	0.057 ± 0.041	0.045 ± 0.015	0.057
Native thiol/total thiol	0.884 ± 0.084	0.909 ± 0.030	0.046
CRP (mg/L)	144.58 ± 101.29	4.00 ± 1.28	< 0.001
PCT (ng/ml)	12.82 ± 12.64	5.76 ± 2.33	<0.001

+: C Reactive Protein

++: Procalcitonin

Table 3. Comparison of thiol/disulphide homeostasis parameters, CRP+ and PCT++ levels insurviving and dying patients

	Death(n=11)	**Survival (n=42)**	**P value**
Νατιε Τηιολ (μμολ/Λ)	224.71 ± 80.86	293.13 ± 67.00	0.002
Τοταλ Τηιολ (μμολ/Λ)	261.04 ± 80.77	319.70 ± 68.20	0.006
Δισυλπηιδε (μμολ/Λ)	17.85 ± 10.44	13.29 ± 7.47	0.073
Disulphide/native thiol	0.095 ± 0.081	0.046 ± 0.029	0.007
Disulphide/total thiol	0.071 ± 0.050	0.042 ± 0.024	0.012
Native thiol/total thiol	0.854 ± 0.101	0.915 ± 0.047	0.007

	Death(n=11)	Survival (n=42)	P value
CRP (mg/L)	166.08 ± 115.20	122.26 ± 80.76	0.115
PCT (ng/ml)	20.31 ± 32.83	3.92 ± 8.96	0.018

+: C Reactive Protein

++: Procalcitonin

Table 4. Comparison of Thiol/disulphide homeostasis, CRP+ and PCT++ parameters according to MASCC§ score

	High Risk(n=40)	Low Risk(n=13)	P value
Νατιε Τηιολ (μμολ/Λ)	241.89 ± 77.23	308.68 ± 75.19	0.012
Τοταλ Τηιολ (μμολ/Λ)	274.51 ± 75.76	336.93 ± 76.06	0.018
Δισυλπηιδε (μμολ/Λ)	16.09 ± 9.54	14.12 ± 8.73	0.497
Disulphide/native thiol	0.079 ± 0.071	0.047 ± 0.033	0.038
Disulphide/total thiol	0.062 ± 0.044	0.042 ± 0.028	0.070
Native thiol/total thiol	0.874 ± 0.090	0.915 ± 0.054	0.058
CRP (mg/L)	163.34 ± 104.08	86.85 ± 66.87	0.004
PCT (ng/ml)	15.95 ± 28.35	0.92 ± 1.78	0.002

+: C Reactive Protein

++: Procalcitonin

§: The Multinational Association for Supportive Care in Cancer

Table 5. The comparison of the thiol/disulphide homeostasis, CRP+ and PCT++ parameters in the patients with positive and negative blood cultures

Laboratory markers	Negative blood culture n=17	Positive blood culture n=36	P value
CRP (mg/L)	191.23 + 110.52	122.55 + 90.02	0.034
PCT (ng/ml)	27.80 + 38.16	4.93 + 11.02	0,027
Νατιε Τηιολ(μμολ/Λ)	245.39 + 98.88	264.36 + 72.42	0,486
Δισυλπηιδε (μμολ/Λ)	13.92 + 8.40	16.41 + 9.71	0.346
Τοταλ Τηιολ (μμολ/Λ)	273.23 + 94.60	297.65 + 72.00	0,355
Disulphide/native thiol	0.074 + 0.081	0.070+0.058	0,863
Disulphide/total thiol	0.059+0.047	0.056 + 0.039	0,806
Native thiol/total thiol	0.881 + 0.095	0.885 + 0.080	0,880

+: C Reactive Protein

++: Procalcitonin