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Scoring Systems Identifying the Low-Risk Febrile Neutropenia Patients in the Emergency Department: Usefulness of MASCC, CISNE and qSOFA

Acil Serviste Düşük Riskli Febril Nötropeni Hastalarını Tanımada Skorlama Sistemleri: MASCC, CISNE ve qSOFA Skorunun Kullanılabilirliği

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ABSTRACT

Objective: *We aimed to investigate the effectiveness of quick Sequential Organ Failure Assessment (qSOFA), Multinational Association for Supportive Care in Cancer (MASCC), and Clinical Index of Stable Febrile Neutropenia (CISNE) scores in identifying the low-risk febrile neutropenia (FN) patients among patients with chemotherapy-associated neutropenia in the emergency department setting.*

Material and Method: *The risk scores of the patients were calculated and divided into low-risk and high-risk categories according to the guidelines. Serious complications and 30-day mortality were recorded. Patients who survived and did not develop any serious complications were defined as low-risk FN.*

Results: *The median age of the patients was 63 years, and 56.3% were male. Of all patients, 50.6% had hematological malignancy. Blood culture positivity was detected in 31% of the patients. Of all patients, 51 (58.6%) were low-risk FN. The complication rate in patients was 40.2%, while the mortality rate was 25.3%. When evaluated according to the risk scores, 69 (79.3%) patients with qSOFA, 40 (46%) patients with MASCC and 7 (8.1%) patients with CISNE were classified as low-risk. The qSOFA score had the highest sensitivity with 96.08%, MASCC had the highest PPV with 85%, and the CISNE score had the highest specificity with 88.89% in patients with low-risk febrile neutropenia.*

Conclusion: *MASCC, CISNE and qSOFA scores have reasonable discriminating power in identifying low-risk neutropenia patients. The combined use of scoring systems with the clinical gestalt and communication with oncologists will further increase the percentage of the recognized low-risk neutropenic patients in the emergency department.*

Keywords:
CISNE
Emergency department
Febrile neutropenia
MASCC
qSOFA,

ÖZET

Amaç: *Acil servis ortamında qSOFA (quick Sequential Organ Failure Assessment), MASCC (Multinational Association for Supportive Care in Cancer) ve CISNE (Clinical Index of Stable Febrile Neutropenia) skorlarının düşük riskli febril nötropeni (FN) hastalarının belirlemedeki etkinliğini ve kullanılabilirliğini araştırmayı amaçladık.*

Gereç ve Yöntem: *Hastaların risk skorları hesaplanarak kılavuzlara göre düşük riskli ve yüksek riskli kategorilerine ayrıldı. Ciddi komplikasyonlar ve 30 günlük mortalite kaydedildi. Hayatta kalan veya ciddi komplikasyon gelişmeyen hastalar düşük riskli FN olarak tanımlandı.*

Bulgular: *Hastaların ortanca yaşı 63 yıl olup, %56,3'ü erkekti. Tüm hastaların %50,6'sında hematolojik malignite vardı. Hastaların %31'inde kan kültürü pozitifliği saptandı. Tüm hastaların 51'i (%58,6) düşük riskli FN idi. Hastalarda komplikasyon oranı %40,2 ve mortalite oranı ise %25,3 idi. Risk skorlarına göre değerlendirildiğinde qSOFA skoruna, MASCC skoruna ve CİSNE skoruna göre sırası ile 69 (%79,3), 40 (%46) ve 7 (%8,1) hasta düşük riskli olarak sınıflandırıldı. Düşük riskli febril nötropenili hastalarında qSOFA skoru %96,08 ile en yüksek duyarlılığa, MASCC %85 ile en yüksek PPV'ye ve CISNE skoru %88,89 ile en yüksek özgüllüğe sahipti.*

Sonuç: *MASCC, CISNE ve qSOFA skorlarının düşük riskli nötropeni hastalarını belirlemede makul bir ayırt edici gücü vardır. Skorlama sistemlerinin klinik tecrübe ve onkologlarla iletişim ile birlikte kullanılması, acil serviste düşük riskli nötropeni hastalarının tanınırlılığının yüzdesini daha da artıracaktır.*

Anahtar Kelimeler:
CISNE
Acil Servis
Febril nötropeni
MASCC
qSOFA

INTRODUCTION

Febrile neutropenia (FN) is an important and life-threatening oncological emergency that requires hospitalization and broad-spectrum antibiotic treatment (1). Infectious Diseases Society of America (IDSA) defined FN: Oral temperature measurement higher than >38.3 C° in a single measurement or persistence at >38° C for at least one hour. Absolute neutrophil count <500 cells/microL, or anticipate this decrease within 48 hours (2). Its mortality is 5-11%, and this rate increases up to 18% in the presence of bacteremia (3). However, not all patients with FN need to be hospitalized. The studies have shown that outpatient treatment of low-risk groups with broad-spectrum oral antibiotics can be followed as it is both safe

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and cost effective (4-7).

Accordingly, risk stratification methods for outpatient treatments have been developed. In 2000, the on-set of clinical instability, age, and comorbidity decided by Multinational Association for Supportive Care in Cancer (MASCC) was approved (8). In 2015, the Clinical Index of Stable Febrile Neutropenia (CISNE) score, which has been used in solid malignancies and is currently under evaluation in hematological malignancies, was developed. The CISNE score is based on clinical instability, laboratory data, and comorbid conditions (9). In addition, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) 2016 described a simpler method called "quick SOFA (qSOFA)" for the prediction of early mortality in sepsis. qSOFA consisted of the following three elements: Respiratory rate ≥22/min, Change in mental status, and Systolic blood pressure ≤100 mmHg (10).

In our study, we aimed to investigate the effectiveness of qSOFA, MASCC and CISNE scores in identifying the low-risk FN patients among patients with chemotherapy-associated FN in the emergency department (ED) setting.

MATERIAL AND METHOD

Study design

This single-centered retrospective study was performed at the ED of university hospital which has 60,000 ED applications annually. Data were collected from hospital database between January 01, 2017, and January 01, 2020. The ethics committee approval was obtained (Date: February 14, 2020 and no: 26547).

Study protocol and selection of patients

Files of 102 patients with neutropenia were scanned. Fifteen patients were excluded from the study due to the absence of fever, diagnosis of acute leucosis, and unrelated chemotherapy. The IDSA criteria were used for diagnosis of chemotherapy-associated FN. Total of 87 patients who met criteria for FN were included in the study. Basic characteristics of the patients such as age, gender, type of malignancy, and outcomes were recorded.

The risk scores of the patients were calculated at the ED admission. The risk scores divided into low and high-risk categories according to the guidelines. Zero and 1 points were considered as low risk, and 2 and 3 points were considered as high risk for the qSOFA score. MASSC score ≥21 points was consid-ered as low risk and score <21 was high risk. CISNE scores were divided into 3 categories: CISNE I was considered as low risk (0 points), CISNE II as medium risk (1-2 points), and CISNE III as high risk (3 points). In the calculations, CISNE score 0 and 1 was accepted as low risk and ≥2 as high risk.

Patient who had one of any complications or died in 30 day of admission accepted as high-risk FN. Seri-ous complications were altered mental status, respiratory failure, organ failure, hypotension, arrhythmias that require intervention, and intensive care unit admission. Patients who survived or did not develop any serious complications were defined as low risk FN.

Statistical analysis

Statistical analysis was performed with the IBM SPSS statistics 21 software program for Windows (IBM Corp. Armonk, NY: USA. Released 2012). Frequency (n, %), median, minimum-maximum (min-max) values, and Chi-square test were used in the analysis of the data. In low-risk prediction analysis, standard sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated. In addition, qSOFA, MASCC and CISNE scores were measured with the area under the receiver operating characteristic curve (AUROC). P value <0,05 was accepted as statistically significant.

RESULTS

The median age of the patients was 63 years, and 56.3% were male. Of all patients, 50.6% had hematological malignancy. Blood culture positivity was detected in 31% of the patients. Of all patients, 51 (58.6%) were low-risk FN. The complication rate in patients was 40.2%, while the mortality rate was 25.3%. When evaluated according to the risk scores, 69 (79.3%) patients with qSOFA, 40 (46%) patients with MASCC and 7 (8.1%) patients with CISNE were classified as low risk (Table 1).

Table 1: Demographic characteristics of the patients

Age, median (min-max)	63 (28-79)
Gender, n (%)	
Male	49 (56.3)
Female	38 (43.7)
Tumor Type, n (%)	
Solid	43 (49.4)
Hematologic	44 (50.6)
Bacteremia, n (%)	27 (31)
Risk Classification and Categories, n (%)	
qSOFA	
Low-risk (0-1)	69 (79.3)
High-risk (2-3)	18 (20.7)
MASCC	
Low-risk ≥21	40 (46)
High-risk <21	47 (54)
CISNE	
Low-risk (0-1)	18 (20.7)
High-risk (≥2)	69 (70.3)
Outcome, n (%)	
Complication	35 (40.2)
Mortality	22 (25.3)

qSOFA: quick Sequential Organ Failure Assessment, MASCC: Multinational Association for Supportive Care in Cancer, CISNE: Clinical Index of Stable Febrile Neutropenia

When the risk categories were compared in cases of complications and mortality, qSOFA and MASCC scores were found to be significantly different in both, while the CISNE score was found to be significantly different only in the case of complications (Table 2).

While the qSOFA score had the highest sensitivity with 96.08% (86.54%-99.52%), MASCC had the highest PPV with 85% (72.69%-92.35%), and the CISNE score had the highest specificity with 88.89% (73.94%-96.89%) in

Table 2: Comparison of risk categories for complications and mortality.

	None, n (%)	Yes, n (%)	p
Complication	52 (58.8)	35 (40.2)	
qSOFA, low-risk (0-1)	50 (96.2)	19 (54.3)	<0.001
qSOFA, high-risk (2-3)	2 (3.8)	16 (45.7)	
MASCC, low-risk (≥21)	35 (67.3)	5 (14.3)	<0.001
MASC, high-risk <21	17 (32.7)	30 (85.7)	
CISNE, low-risk (0-1)	15 (28.8)	3 (8.6)	0.030
CISNE, high-risk (≥2)	37 (91.4)	32 (71.2)	
Mortality	65 (74.7)	22 (25.3)	
qSOFA, low-risk (0-1)	58 (89.2)	11 (50)	<0.001
qSOFA, high-risk (2-3)	7 (10.8)	11 (50)	
MASCC, low-risk (≥21)	36 (55.4)	4 (18.2)	0.003
MASCC, high-risk (<21)	29 (44.6)	18 (81.8)	
CISNE, low-risk (0-1)	14 (21.5)	4 (18.2)	1
CISNE, high-risk (≥2)	51 (78.5)	18 (81.8)	

qSOFA: quick Sequential Organ Failure Assessment, MASCC: State Association for Supportive Care in Cancer, CISNE: Clinical Index of Stable Febrile Neutropenia

Table 3: Analysis of scoring systems in identifying low-risk febril neutropenia patients.

	Sensitivity	Specificity	PPV	NPV	LR +	LR-
qSOFA	96.08 (86.54-99.52)	44.44 (27.94-61.90)	71.01 (64.54-76.74)	88.89 (66.21-97.03)	1.73 (1.28-2.33)	0.09 (0.02-0.37)
MASCC	66.67 (52.08-79.24)	83.33 (67.19-93.63)	85.00 (72.69-92.35)	63.83 (53.82-72.76)	4.00 (1.88-8.52)	0.40 (0.26-0.61)
CISNE	27.45 (15..9-41.77)	88.89 (73.94-96.89)	77.78 (55.64-90.74)	46.38 (41.34-51.48)	2.47 (0.89-6.89)	0.82 (0.67-1.01)

qSOFA: quick Sequential Organ Failure Assessment, MASCC: Multinational Association for Supportive Care in Cancer, CISNE: Clinical Index of Stable Febrile Neutropenia, PPV: positive predictive value, NPV: negative predictive value, LR +: positive likelihood ratio, LR-: negative likelihood ratio

Table 4: AUROC values of risk scores in patients with low-risk febrile neutropenia.

	AUROC	95% CI	p
Complication			
qSOFA	0.762	0.652-0.872	<0.001
MASCC	0.857	0.776-0.938	<0.001
CISNE	0.752	0.647-0.857	<0.001
Mortality			
qSOFA	0.695	0.553-0.837	0.006
MASCC	0.747	0.634-0.859	0.001
CISNE	0.686	0.540-0.833	0.009

qSOFA: quick Sequential Organ Failure Assessment, MASCC: Multinational Association for Supportive Care in Cancer, CISNE: Clinical Index of Stable Febrile Neutropenia, AUROC: the area under the receiver operating characteristic curve, CI: confidence interval

patients with low risk FN (Table 3).

In general, MASCC score (AUC for complication 0.857, 95% CI 0.776-0.938 and AUC for mortality 0.747, 95% CI 0.634-0.859) had higher discriminable power for low-risk patients than qSOFA and CISNE scores (Table 4).

DISCUSSION

Nowadays, the number of cancer patients requiring emergency room admissions due to complications are gradually increasing; they constitute 2-5% of emergency room admissions (11,12). Since the patients' length of stay in the ED for hospitalization is increasing, early recognition and outpatient treatment for patients with FN will be beneficial. In our study, although the qSOFA, MASCC and CISNE scores have different sensitivity, specificity, PPV and NPV values in identifying low-risk FN patients, have an overall reasonable discriminating power.

The qSOFA is a scoring system with a performance equivalent to Sequential Organ Failure Assessment (SOFA) score in predicting prognosis of patients with sepsis. In addition, the low number of criteria provides ease of use in the ED (13). Studies have shown that qSOFA helps in making a fast and accurate decision in predicting the poor prognosis of patients with FN (14).

In studies conducted with FN patients in intensive care, the AUC value was found to be 0.651 (95% CI 0.513-0.789), which is lower than MASCC, and it was found to be an important predictor in terms of mortality and length of stay in intensive care (15,16). However, to the best of our knowledge, there are no studies that identify low-risk FN patients with qSOFA. In our study, the sensitivity of qSOFA score in low-risk FN patients was 96.08%, which was higher than that of others. However, its specificity was lower than that of others with 44.44% and indicating that it will be more beneficial to use it with others rather then using it alone.

The MASCC score was originally developed to identify low-risk patients and has been used for over 20 years. Studies have reported the sensitivity of MASCC score to be over 90% and specificity to be around 50-60%. However, the AUROC of MASCC score was found high in the identification of low-risk FN (8,15,17-20). In our study, although the sensitivity of qSOFA score and the specificity of CISNE score were higher than the MASCC score, the AUROC value of the MASCC score was the highest in identifying low-risk FN patients. The difference between sensitivity and specificity of the MASCC score is relatively lower than that of others, making this score valuable in identifying low-risk FN patients.

On the other hand, CISNE score was developed for the prediction of major complications in patients with solid tumors. The specificity of CISNE score was found over 90%, and its sensitivity was found to be around 10-30% in studies performed to identify low-risk FN patients. In addition, the specificity for identifying low risk was found to be over 90% in patients with hematological malignancies (17-20). In our study in which hematological malignancies were equal, the high specificity of the CISNE score was 97.14% in identifying low-risk FN patients. This scoring system is valuable in emergency room conditions.

The limitations of our study included it being a single-center study, retrospective nature and small number of patients.

CONCLUSION

As a result, MASCC, CISNE and qSOFA scores have reasonable discriminating power in identifying low-risk FN patients. The combined use of scoring systems with the clinical gestalt and communication with oncologists will further increase the percentage of the recognized low-risk FN patients in the ED. In addition, we think that the increase in the percentage of patients to be treated in an outpatient setting with the correct diagnosis will be beneficial in preventing the ED crowd and decreasing unnecessary hospitalizations and complications that may develop during the waiting period.

Conflict Interest: The authors declare that there are no conflicts of interest.
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