Comparison of CISNE and MASCC Score in Predicting Complications on Post Chemotherapy Febrile Neutropenia

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ABSTRACT

Background: *Febrile neutropenia (FN) is an oncologic emergency which commonly occurrs in patients who undergo chemotherapy, with a mortality rate of 12.5%. Risk stratification in FN plays an important role in increasing the accuracy of therapy. This study aims to compare the performance between CISNE score and MASCC score in predicting complications on post-chemotherapy FN in solid and hematologic malignancy.* ***Methods:*** *This is a retrospective cohort study on FN patients undergoing inpatient treatment at Cipto Mangunkusumo Hospital between July 2015 and December 2019. Basic demographic and clinical data were collected from medical records. Subjects were grouped based on the CISNE and MASCC score, and complications during hospitalization were recorded. Predictive performance of each score was analyzed and compared using area of under curve.* ***Results:*** *CISNE score showed a better performance both in solid malignancy with AUC of CISNE score (0.80 CI 95% 0.73-0.88, p = 0.00) compared to AUC of MASCC score (0.68; 95% CI 0.59 – 0,78, p = 0.00) and in hematologic malignancy with AUC of CISNE score (0.85; 95% CI 0.77 - 0.93, p = 0.00) and AUC MASCC score (0.65 ; 95% CI 0.54 - 0.76, p = 0.007).* ***Conclusion:*** *CISNE score showed a better performance compared to MASCC score in predicting in-hospital complication in both solid and hematologic malignancy with cut-off point of 2.*

Keywords: *CISNE, MASCC score, oncology, infectious disease.*

INTRODUCTION

Febrile neutropenia (FN) is an oncologic emergency that occurs in 20 cases per 1000 patients who undergo chemotherapy. FN is a life-threatening condition with a 12.5% mortality rate.[1,2] Risk stratification in FN plays an important role in determining therapy thus reducing complications. The Infectious Diseases Society of America (IDSA) recommends using Multinational Association for Supportive Care in Cancer (MASCC) scores to differentiate between low-risk and high-risk patients and to select the appropriate antibiotics.[3–5] Despite the routine use of MASCC scores in daily practice, researches has shown that serious complications still occur in 15–42% of low-risk patients.[3,4,6] Therefore, a new scoring system, the Clinical Index of Stable Febrile Neutropenia (CISNE), was developed to better predict such complications. However, several studies have been conducted to assess

the performances of CISNE scores, and the results remain controversial.[2,7–9] Further study comparing CISNE score with MASCC score based on tumor type is still needed to assess the role of each score in predicting complications and therefore reducing mortality.

METHODS

Study Design and Participant

This is a retrospective cohort study to assess the performances of CISNE and MASCC scores in predicting complications in FN patients with solid and hematological malignancy. We collected data from medical records of patients with chemotherapy-induced FN who were undergoing inpatient treatment in Cipto Mangunkusumo General Hospital from January 2015 to December 2019. Inclusion criteria included the following: above 18 years of age, fulfilling the diagnostic criteria of FN, and receiving appropriate antibiotics based on IDSA guideline. The exclusion criteria were acute leukemia, incomplete medical records, and FN unrelated to chemotherapy. This study was approved by The Faculty of Medicine Universitas Indonesia Ethics Committee (Number: KET-368/UN2.F1/ETIK/PPM.00.02/2020)

Study Definition

Febrile neutropenia was defined as temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l that occurred after patients had received chemotherapy.[4] Patient were screen using the diagnosis entered in the medical resume. Each component of CISNE and MASCC score were assessed based on the record from the day of admission as assessed by the emergency department physician in charge. Documented infection were determined using clinical judgement of attending clinicians.

Sample Size and Data Collection

Sample size was calculated using the formula for comparative area of under curve study (AUC) for solid and hematologic malignancy, using known AUC index of 0.65 and 0.7 respectively, with a 95% confidence level, and 5% prediction error, thus a sample size of 95 for solid malignancy group and 73 subjects of hematologic malignancy group were determined.[10]

Outcome Measurement

Complications were defined as occurrence of hypotension or shock, respiratory or heart failure, acute kidney injury, disseminated intravascular coagulation, decreased of consciousness, major bleeding in need of transfusion, ICU admission, or death during hospitalization that was stated in the medical records.[2]

Statistical Analysis

Baseline characteristics were presented in numerical and categorical data with percentages and medians with interquartile range. CISNE and MASCC scores were analyzed using the area under the receiver operating characteristic (AUROC). We used the Liu method in determining the cut-off point and the DeLong method in comparing the AUROC between the CISNE and MASCC score. Diagnostic study of each score was calculated based on the 2x2 table.

RESULTS

A total of 729 records were found, 561 records were excluded and 95 cases of FN due to chemotherapy in solid malignancy patients and 73 cases of FN due to chemotherapy in hematologic malignancy were included in the study. In the solid malignancy group, we found 46.32% cases of FN that had resulted from chemotherapy treatment of a head and neck tumor, and in the hematologic malignancy group, we found 87.67% cases of FN in patients with non-Hodgkin's lymphoma who underwent chemotherapy. Febrile neutropenia was found in 39.88% of patients after the first cycle of chemotherapy. We found that 55.36% of FN patients had been admitted with a secondary infection, and 51.5% of that group were diagnosed with pneumonia. **Table 1** shows demographic data and clinical characteristics based on the type of malignancy.

Table 1. Demographic and Clinical Characteristics

Characteristics	Solid Malignancy (n=95)	Hematologic Malignancy (n=73)
Gender		
- Female, n (%)	50 (52.7)	31 (42.4)
- Male, n (%)	45 (47.3)	42 (57.6)
Mean age (SD)	47.1 (14.9)	48,3 (15.6)
Type of Solid Malignancy (n=95)		
- Head and neck, n (%)	44 (46.32)	
- Lung, n (%)	2 (2.11)	
- Breast, n (%)	12 (12.63)	
- Gastrointestinal, n (%)	4 (4.21)	
- Genitourinary, n (%)	6 (6.32)	
- Bone and soft tissue, n (%)	17 (17.89)	
- Gynecologic, n (%)	9 (9.47)	
- Thymus, n (%)	1 (1.05)	
Type of Hematologic Malignancy (n=73)		
- Non Hodgkin Lymphoma, n (%)		64 (87.67)
- Hodgkin Lymphoma, n (%)		3 (4.11)
- Myeloma, n (%)		4 (5.48)
- Chronic Leukemia, n (%)		2 (2.74)
Documented infection		
- With documented infection, n (%)	51 (53.7)	42 (58.2)
- Without documented infection, n (%)	44 (46.3)	31 (41.8)
Type of infection		
- Pneumonia , n (%)	25 (49.0)	23 (54.8)
- Urinary tract infection , n (%)	3 (5.1)	2 (4.7)
- Gastrointestinal infection, n (%)	16 (31.3)	9 (21.5)
- Skin and soft tissue infection, n (%)	5 (9.8)	4 (9.5)
- Upper respiratory tract infection (%)	2 (3.9)	4 (9.5)
Median neutrophil count (IQR)	216 (362.5)	201 (495)

Complications during admission were found in 45.83% of patients, 83.1% of patients with complications were diagnosed as septicemia. **Figure 1** shows the number of complications occurred on study subjects in both groups. Mortality during treatment was found in 21.4% subjects hospitalized with febrile neutropenia.

The CISNE scores were effective in predicting complications in febrile neutropenia resulting from chemotherapy treatment of a solid tumor with an AUROC of 0.80 (CI 95% 0.73-0.88; p = 0.00), whereas the MASCC scores with an AUROC of 0.68 (CI 95% 0.59–0.78; p = 0.00). Therefore, CISNE scores were found to be significantly better at predicting complications than MASCC scores in solid tumor. CISNE scores are also effective at predicting complications in febrile neutropenia resulting from chemotherapy in hematologic malignancies with an AUROC of 0.85 (CI 95% 0.77–0.93; p = 0.00), whereas MASCC scores with an AUROC of 0.65 (CI 95% 0.54–0.77; p = 0.007). **Figure 2** and **3** shows AUC for each score in solid and hematologic malignancy.

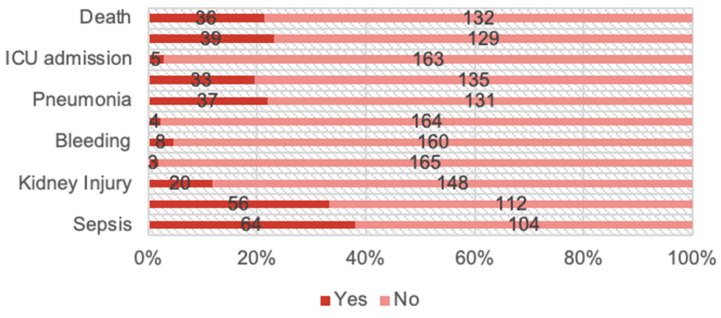

Figure 1. Complication found in subjects

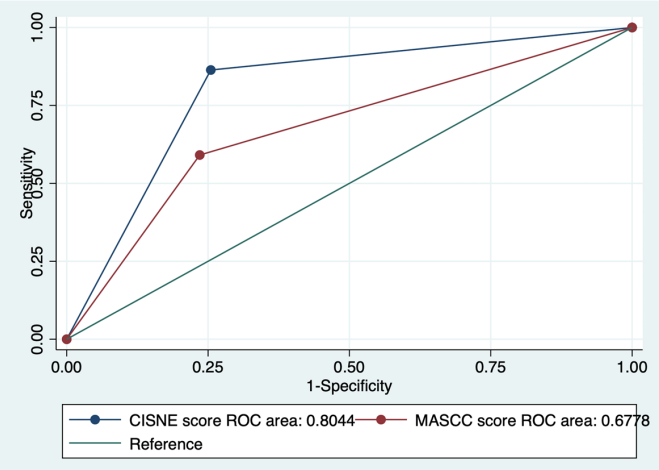

Figure 2. Comparison of Area Under Curver between CISNE and MASCC Score as Predictors of Complication in Patients with Febrile Neutropenia After Solid Tumor Chemotherapy

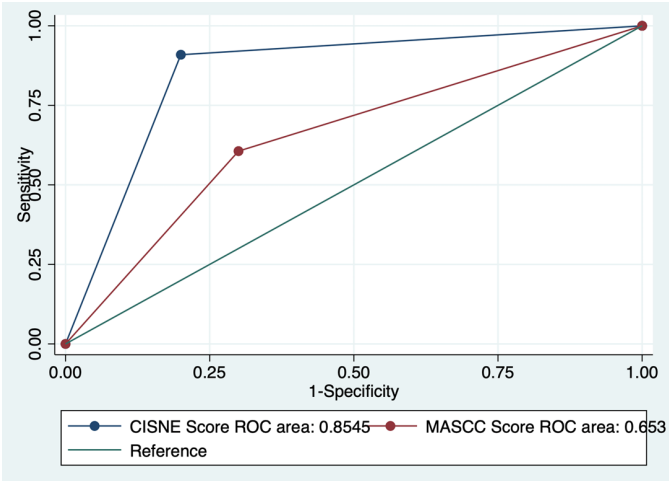

Figure 3. Comparison of Area Under Curver between CISNE and MASCC score as predictors of complication in patients with febrile neutropenia after hematologic malignancy chemotherapy

Table 2. Descriptive statistics for CISNE and MASCC for predicting complication of FN

Risk tool	Sensitivity	Specificity	PPV	NPV	+LR	-LR
Solid tumor						
CISNE	74.5 (60.4-85.7)	86.4 (72.6-94.8)	86.4 (72.6-94.8)	74.5 (60.4-85.7)	5.46 (2.55-11.69)	0.30 (0.18-0.48)
MASCC	68.4 (51.3-82.5)	68.4 (54.8-80.1)	59.1 (43.2-73.7)	76.5 (62.5-87.2)	2.17 (1.4-3.36)	0.46 (0.28-0.76)
Hematologic malignancy						
CISNE	78.9 (62.7-90.4)	91.4 (76.9-98.2)	90.9 (75.7-98.1)	80.0 (64.4-90.9)	9.21 (3.08-27.52)	0.23 (0.12-0.43)
MASCC	62.5 (43.7-78.9)	68.3 (51.9-81.9)	60.6 (42.1-77.1)	70.0 (53.5-83.4)	1.97 (1.17-3.33)	0.55 (0.34-0.90)

DISCUSSION

Febrile neutropenia was a known complication of chemotherapy that increases the risk of hospitalization, increase healthcare cost and increase risk of mortality. Neutrophil plays an important role in the defence against extracellular bacteria and fungal infection, therefore patients who were neutropenic had an increased risk of secondary infection.[11]

Risk stratification in febrile neutropenia had a pivotal role, especially in the emergency department, where better tools in predicting complications can help physicians to make important clinical decisions such as admitting to ICU or giving a broad-spectrum antibiotics as well as safely sending the patients home when their condition is stable enough.

MASCC score were introduced in 2000 and continued to be one of the risk stratification tools recommended to use in febrile neutropenia, despite its poor performance.[3,6] The CISNE score was published in 2015, firstly developed in clinically stable patient with febrile neutropenia in solid malignancy, then studied in different clinical settings and showed a better performance compared to MASCC score.[9]

We aimed to compare the performance of CISNE and MASCC score in predicting complications in patients with FN due to chemotherapy in solid and hematologic malignancy. Studies assessing the performance of CISNE score in hematologic malignancy is still limited, as the CISNE score was originally developed in a solid tumor population, and the previous studies were done in mostly solid malignancy with only one study involving hematologic malignancy.[2,8,12] The incidence of neutropenia in hematologic malignancy and solid tumors displays different characteristics; for instance, neutropenia periods are longer, and positive culture results are more often found in patients with hematologic malignancy.[16] In our study, there were no significant differences between the characteristics of patients with solid tumors and hematologic malignancy subjects.

This study analyses the performance of CISNE scores compared with MASCC scores in predicting complications in FN patients with solid and hematologic malignancies after chemotherapy. In patients with solid malignancies, CISNE scores performed well, with an AUROC of 0.80. Two previous studies have analyzed the performance of CISNE scores in patients with solid malignancies. Research by Koppaka et al.[12] also showed that CISNE scores had an AUROC of 0.846, whereas in Moon et al.[13], CISNE scores had an AUROC of only 0.66. In our study, the population of solid malignancies was dominated by head–neck malignancies, whereas previous studies showed head–neck malignancies in only 5% of populations. These findings showed a difference in the prevalence of tumors in our study location, because as the national referral hospital we received many end-stage cancer patients with different types of tumor distribution.[17,18] The dominancy of head and neck malignancies may also affect the number of mucositis found in our study (28 cases) which may cause the increase in CISNE score.

Previous studies gathered subjects from the emergency wings and outpatient clinic, whereas in our study, subjects were recruited from FN patients who were hospitalized. The CISNE score in study by Bayonas et al.[2] was divided into three groups: low, moderate, and high risk, with a sensitivity of 80.1% and a specificity of 75.6%. Koppaka et al. used the cut-off point 2 to divide patients into low risk and high risk groups with a sensitivity of 80.6% and specificity of 72.8%, a positive predictive value of 35.2%, and a negative predictive value of 95.3%.

We conducted an analysis to assess the cut-off point. With cut-off point of 1, the sensitivity of CISNE score in solid malignancy was 78.9% with specificity 91.4%, while cut-off point of 2 showed a sensitivity of 88.9% with specificity 80.4% specificity, therefore, we suggest using cut-off point of 2 for CISNE score as it gives a better performance in predicting complications.

This is the first study to analyze the effectiveness of CISNE scores in predicting complications of FN after chemotherapy in patients with hematologic malignancy. The analysis showed that the CISNE scores perform well, with an AUROC of 0.91. Previous research by Mohindra et al.[27] was not specific to hematologic malignancy, but this group also

conducted a subgroup analysis of the hematologic malignancy population and obtained an AUROC of 0.67.

There was a significant difference between the performances of the CISNE and MASCC scores in predicting complications in patients with FN that had resulted from hematologic malignancy chemotherapy. These results showed that CISNE scores are effective in predicting complications in febrile neutropenia patients, both in those with solid and hematologic malignancies. These differences between CISNE and MASCC scores may result from different score components. CISNE scores assess patient conditions with ECOG performance, whereas MASCC scores assess patients' burden of disease. The use of ECOG performance can give a more objective assessment compared to the burden of disease, which is highly dependent on clinician assessment. These objective assessments resulted in less misclassification of patients.[6]

In hematologic malignancy subjects, 87.67% of patients had non-Hodgkin's lymphoma. We excluded patients with acute leukemia because febrile neutropenia in acute leukemia patients, according to the IDSA guidelines, are in the high-risk category, regardless of their MASCC scores. Aplasia in patients with acute leukemia is influenced by many factors, including those associated with the disease (e.g., leukocyte function defects, or humoral immunity deficiencies); patient-dependent factors (e.g., age, comorbidities, or malnutrition); or the effects of chemotherapy (e.g., prolonged aplasia due to high-intensity chemotherapy, bacterial colonization due to aplasia, recurrent antibiotic use, or central catheter–related infection) therefore we exclude acute leukemia in our study.[19]

By the time of FN diagnosis, 55.36% subjects had documented infections, a greater number than in previous studies, which recorded an infection rate around 30% in FN patients.[20] In subjects with documented infection, 51.5% had pneumonia, a common comorbidity in neutropenic patients. Vehreschild et al.[21] showed that 36.4% of the neutropenic patients in their study had pneumonia. In addition to pneumonia, some subjects also displayed gastrointestinal infection in the form of acute gastroenteritis and diarrhea. These conditions in neutropenic patients are also known as neutropenic enterocolitis, which displays an incidence estimated around 5.6%. Such infections can occur as a direct result of taxane-class chemotherapy, which can damage the mucosal surface. In addition, they may be caused by an invasion of translocated bacteria.[22]

Complications was found in 45.83% of subjects, a greater prevalence than previous studies. For example, in an experiment by Ahn et al.,[26] complications occurred in 20.8% of subjects, and in Coyne et al.,[14] complications occurred in 25.7% of subjects. This difference might occur because of the different settings from which subjects were recruited. Coyne et al. and Ahn et al. recruit subjects from the emergency wing triage so that clinically stable patients were included in the subject, whereas in this study, we did not include outpatient data. This was also illustrated in the percentage of subjects classified in the low-risk category by both MASCC and CISNE scores. In this study, based on MASCC scores, 58.3% of participants were included in the low-risk category. These results differed from those found by Ahn et al., in which 89.1% of subjects were at low risk; by Coyne et al., in which 73.5% of subjects were at low risk; and by Bayonas et al.,[2] in which 86% of patients were at low risk. The population in this study showed a higher prevalence of complications. In those who appeared to have complications, 83.1% was diagnosed as sepsis and 72.7% underwent shock. This is clearly higher than a previous study that estimated the prevalence of this sepsis in FN patient ranges from 7 to 45%.[24]

Our study showed that the use of CISNE scores to substitute MASCC scores in risk classification of FN patients, both solid and hematologic malignancies, can reduce misclassifications. Further research on the role of CISNE scores in the selection of antibiotic therapy may be needed. We found that re-classification of CISNE scores into two groups (low risk and high risk) with a cut-off point of 2 was more effective in predicting complications, thus aiding clinicians in determining patient therapy.

The limitations of this study are the relatively small sample size and the use of secondary

data obtained from medical records, whereby some subjective score components did not have standard parameters.

CONCLUSION

Our study showed that the performance of CISNE scores in predicting complications in patients with FN caused by chemotherapy in both solid and hematologic malignancies was better than MASCC scores, with a cut-off point of 2. Therefore, in choosing a risk-stratification score to anticipate such complications, the CISNE score should be chosen over an MASCC score.

REFERENCES

1. Schelenz S, Giles D, Abdallah S. Epidemiology, management and economic impact of febrile neutropenia in oncology patients receiving routine care at a regional UK cancer centre. Ann Oncol. 2012;23(7):1889–93.
2. Carmona-Bayonas A, Jiménez-Fonseca P, Echaburu JV, 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. Journal of Clinical Oncology. 2015;33(5):465–70.
3. Klastersky J, Paesmans M, Rubenstein EB, et al. The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. JCO. 2000;18(16):3038–51.
4. Klastersky, J N J, Rolston, K, Rapoport, B, Maschmeyer, G, Appro, M, Herrstedt, J. Management of febrile neutropaenia: ESMO clinical practice guidelines ESMO. Ann Oncol. 27(5):111–8.
5. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):e56–93.
6. Bitar RA. Utility of the multinational association for supportive care in cancer (MASCC) risk index score as a criterion for nonadmission in febrile neutropenic patients with solid tumors. Perm J. 2015;19(3):37–47.
7. Ahn S, Rice TW, Yeung SCJ, Cooksley T. Comparison of the MASCC and CISNE scores for identifying low-risk neutropenic fever patients: analysis of data from three emergency departments of cancer centers in three continents. Support Care Cancer. 2018;26(5):1465–70.
8. Moon H, Choi YJ, Sim SH. Validation of the clinical index of stable febrile neutropenia (CISNE) model in febrile neutropenia patients visiting the emergency department. Can it guide emergency physicians to a reasonable decision on outpatient vs. inpatient treatment? PLoS One. 2018;13(12):e0210019.
9. Zheng B, Toarta C, Cheng W, Taljaard M, Reaume N, Perry JJ. Accuracy of the Multinational Association of Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores for predicting serious complications in adult patients with febrile neutropenia: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology. 2020;149:102922.
10. Blume JD. Bounding sample size projections for the area under a ROC curve. J Stat Plan Inference. 2009;139(1):711–21.
11. Justiz Vaillant AA, Zito PM. Neutropenia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507702/
12. Koppaka D, Kuntegowdanahalli LC, Lokanath D, et al. Assessment and comparison of CISNE model versus MASCC model in clinically stable febrile neutropenia patients. Annals of Oncology. 2018;29:ix129.
13. Moon H, Choi YJ, Sim SH. Validation of the Clinical Index of Stable Febrile Neutropenia (CISNE) model in febrile neutropenia patients visiting the emergency department. Can it guide emergency physicians to a reasonable decision on outpatient vs. inpatient treatment? PLoS ONE. 2018;13(12):1–12.
14. Coyne CJ, Le V, Brennan JJ, et al. Application of the MASCC and CISNE risk-stratification scores to identify low-risk febrile neutropenic patients in the emergency department. Ann Emerg Med. 2017;69(6):755–64.
15. Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela J, et al. Performance of the clinical index of stable febrile neutropenia (CISNE) in different types of infections and tumors. Clin Transl Oncol. 2017;19(3):386–95.
16. Al-Ahwal MS, Johar I, Al-Sayws, Fatih. Febrile neutropenia comparison between solid tumours and hematological malignancies. Pan Arab Medical Journal. 2005;2(4):4–7.
17. Hassan BAR, Yusoff ZBM, Othman SB. A close look at neutropenia among cancer patients — Risk factor and management. Updates on Cancer Treatment. 2015 Oct 28.
18. Budiana ING, Febiani M. Febrile neutropenia pada pasien pascakemoterapi. Indonesian Journal of Cancer. 2017;11(2):77–82.
19. Hansen BA, Wendelbo Ø, Bruserud Ø, Hemsing AL, Mosevoll KA, Reikvam H. Febrile neutropenia in acute leukemia. Epidemiology, etiology, pathophysiology and treatment. Mediterr J Hematol Infect Dis. 2019;12(1).
20. Punnapuzha S, Edemobi PK, Elmoheen A. Febrile neutropenia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Dec 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541102/
21. Vehreschild JJ. Pneumonia and lung infiltrates in

neutropenic patients: Many stones unturned. Annals ATS. 2013;10(5):493–5.
22. Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. World J Gastroenterol. 2017;23(1):42–7.
23. Cancer NCC for. Diagnosis of neutropenic sepsis [Internet]. Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients. National Institute for Health and Clinical Excellence (UK); 2012 [cited 2020 Jul 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK373673/
24. Kochanek M, Schalk E, von Bergwelt-Baildon M, et al. Management of sepsis in neutropenic cancer patients: 2018 guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol. 2019;98(5):1051–69.
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.
26. Ahn S, Rice TW, Yeung SCJ, Cooksley T. Comparison of the MASCC and CISNE scores for identifying low-risk neutropenic fever patients: analysis of data from three emergency departments of cancer centers in three continents. Support Care Cancer. 2018;26(5):1465–70.
27. Mohindra R, Mathew R, Yadav S, Aggarwal P. CISNE versus MASCC: Identifying low risk febrile neutropenic patients. The American Journal of Emergency Medicine. 2019 Nov 30.