References / Literature Review and Grading

Can risk stratification tools be utilized to safely discharge low-risk febrile neutropenic patients from the emergency department? **(11/10/2021)**

1. Baugh CW, Faridi MK, Mueller EL, Camargo CA Jr, Pallin DJ. Near-universal hospitalization of US emergency department patients with cancer and febrile neutropenia. PLoS One. 2019;14(5):e0216835. Published 2019 May 23. doi:10.1371/journal.pone.0216835

2. Mueller EL, Jacob SA, Cochrane AR, Carroll AE, Bennett WE Jr. Variation in hospital admission from the emergency department for children with cancer: A Pediatric Health Information System study. Pediatr Blood Cancer. 2020;67(6):e28140.

3. Bavle A, Grimes A, Zhao S, et al. Cost-effectiveness and Improved Parent and Provider Satisfaction With Outpatient Management of Pediatric Oncology Patients, With Low-risk Fever and Neutropenia. J Pediatr Hematol Oncol. 2018;40(7):e415-e420.

4. 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. *J Clin Oncol*. 2000;18(16):3038-3051. doi:10.1200/JCO.2000.18.16.3038

5. Carmona-Bayonas A, Gómez J, González-Billalabeitia E, et al. Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. Br J Cancer. 2011;105(5):612-617. doi:10.1038/bjc.2011.284

6. Cooksley T, Campbell G, Al-Sayed T, LaMola L, Berman R. A novel approach to improving ambulatory outpatient management of low risk febrile neutropenia: an Enhanced Supportive Care (ESC) clinic. Support Care Cancer. 2018;26(9):2937-2940. doi:10.1007/s00520-018-4194-1

7. García de Guadiana-Romualdo L, Cerezuela-Fuentes P, Español-Morales I, et al. Prognostic value of procalcitonin and lipopolysaccharide binding protein in cancer patients with chemotherapy-associated febrile neutropenia presenting to an emergency department. Biochem Med (Zagreb). 2019;29(1):010702.

8. Gunderson CC, Erickson BK, Wilkinson-Ryan I, et al. Prospective Evaluation of Multinational Association of Supportive Care in Cancer Risk Index Score for Gynecologic Oncology Patients With Febrile Neutropenia. Am J Clin Oncol. 2019;42(2):138-142. doi:10.1097/COC.0000000000000498

9. Kim M, Ahn S, Kim WY, et al. Predictive performance of the quick Sequential Organ Failure Assessment score as a screening tool for sepsis, mortality, and intensive care unit admission in patients with febrile neutropenia. Support Care Cancer. 2017;25(5):1557-1562.

10. Marshall W, Campbell G, Knight T, Al-Sayed T, Cooksley T. Emergency Ambulatory Management of Low-Risk Febrile Neutropenia: Multinational Association for Supportive Care in Cancer Fits-Real-World Experience From a UK Cancer Center. J Emerg Med. 2020;58(3):444-448.

11. Nguyen M, Jacobson T, Torres J, Wann A. Potential reduction of hospital stay length with outpatient management of low-risk febrile neutropenia in a regional cancer center [published online ahead of print, 2021 Feb 26]. Cancer Rep (Hoboken). 2021;e1345. doi:10.1002/cnr2.1345
12. Taj M, Nadeem M, Maqsood S, Shah T, Farzana T, Shamsi TS. Validation of MASCC Score for Risk Stratification in Patients of Hematological Disorders with Febrile Neutropenia. Indian J Hematol Blood Transfus. 2017;33(3):355-360.

13. Ying FLM, Ping MCY, Tong M, et al. A cohort study on protocol-based nurse-led out-patient management of post-chemotherapy low-risk febrile neutropenia. Support Care Cancer. 2018;26(9):3039-3045.

14. Baugh CW, Wang TJ, Caterino JM, et al. Emergency Department Management of Patients With Febrile Neutropenia: Guideline Concordant or Overly Aggressive?. Acad Emerg Med. 2017;24(1):83-91. doi:10.1111/acem.13079

15. Jansma B, Vakkalanka P, Talan DA, Negaard B, Faine BA. Guideline adherence for the management of emergency department patients with febrile neutropenia and no infection source: Is there room for improvement?. J Oncol Pharm Pract. 2020;26(6):1382-1389. doi:10.1177/1078155219896396

16. Ahn S, Rice TW, Yeung SJ, 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):1465-1470.

17. 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):755-764.

18. 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.

19. 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. Crit Rev Oncol Hematol. 2020;149:102922.

20. Haeusler GM, Gaynor L, Teh B, et al. Home-based care of low-risk febrile neutropenia in children-an implementation study in a tertiary paediatric hospital. Support Care Cancer. 2021;29(3):1609-1617.

21. Haeusler GM, Thursky KA, Slavin MA, et al. Risk stratification in children with cancer and febrile neutropenia: A national, prospective, multicentre validation of nine clinical decision rules. EClinicalMedicine. 2020;18:100220. Published 2020 Jan 7. doi:10.1016/j.eclinm.2019.11.013

22. Haeusler GM, Thursky KA, Mechinaud F, et al. Predicting Infectious ComplicatioNs in Children with Cancer: an external validation study. Br J Cancer. 2017;117(2):171-178.

23. Janssens KP, Valete COS, Silva ARAD, Ferman SE. Evaluation of risk stratification strategies in pediatric patients with febrile neutropenia [published online ahead of print, 2020 Jun 4]. J Pediatr (Rio J). 2020;S0021-7557(20)30181-9. doi:10.1016/j.jped.2020.05.002

24. Paolino J, Mariani J, Lucas A, et al. Outcomes of a clinical pathway for primary outpatient management of pediatric patients with low-risk febrile neutropenia. Pediatr Blood Cancer. 2019;66(7):e27679.

25. Ding S, Ma J, Song X, et al. Diagnostic Accuracy of Procalcitonin, Neutrophil-to-Lymphocyte Ratio, and C-Reactive Protein in Detection of Bacterial Infections and Prediction of Outcome in Nonneutropenic Febrile Patients with Lung Malignancy. J Oncol. 2020;2020:2192378.

26. García de Guadiana-Romualdo L, Jiménez-Santos E, Cerezuela-Fuentes P, et al. Analyzing the capability of PSP, PCT and sCD25 to support the diagnosis of infection in cancer patients with febrile neutropenia. Clin Chem Lab Med. 2019;57(4):540-548. doi:10.1515/cclm-2018-0154

27. Kelly RS, Lasky-Su J, Yeung SJ, et al. Integrative omics to detect bacteremia in patients with febrile neutropenia. PLoS One. 2018;13(5):e0197049. Published 2018 May 16. doi:10.1371/journal.pone.0197049

Literature Review and Grading

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Table. Summary of the Findings

Publication	Grade	Quality	Comments
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. Crit Rev Oncol Hematol. 2020;149:102922.	A	Good	Meta-analysis - Pooled sensitivity and specificity for MASCC < 21 was 55.6 % (95 % CI: 46.2 %-64.5%) and 86.0 % (95 % CI: 81.3 %-89.7 %), respectively. Pooled sensitivity and specificity for CISNE ≥ 3 was 78.9 % (95 % CI: 65.3 %-88.1 %) and 64.9 % (95 % CI: 49.6 %-77.7 %), respectively. Pooled sensitivity and specificity for CISNE ≥ 1 was 96.7 % (95 % CI: 93.6 %-98.3 %) and 22.2 % (95 % CI: 15.6 %-30.4 %), respectively. The CISNE score had higher sensitivity and may be more useful than the MASCC score in the acute setting.

Haeusler GM, Thursky KA, Slavin MA, et al. Risk stratification in children with cancer and febrile neutropenia: A national, prospective, multicentre validation of nine clinical decision rules. EClinicalMedicine. 2020;18:100220.	C	Good	This was a prospective, observational study of 858 febrile neutropenia episodes in 462 patients from 8 hospitals assessing 9 clinical decision rules. PICNICC was 90.9% sensitive and 20.8% specific. SPOG-AE was 75.8% sensitive and 47.9% specific. Hakim et al was 29.3% sensitive and 83.8% specific. Alexander et al. was 69.7% sensitive and 44.6% specific. Klaassen et al. was 87.4% sensitive and 27.6% specific. SPOG-bact was 90.9% sensitive and 17.6% specific. Ammann et al. was 92.9% sensitive and 18.9% specific. Baorto et al. was 89.9% sensitive and 19.4% specific. Rackoff et al. was 27.3% sensitive and 82.9% specific.
García de Guadiana-Romualdo L, Jiménez-Santos E, Cerezuela-Fuentes P, et al. Analyzing the capability of PSP, PCT and sCD25 to support the diagnosis of infection in cancer patients with febrile neutropenia. Clin Chem Lab Med. 2019;57(4):540-548.	C	Good	Prospective study evaluating three biomarkers: PCT, PSP and sCD25 in the identify infection in patients with febrile neutropenia. PCT was the biomarker with the highest diagnostic accuracy for infection (AUC: 0.901), whereas PSP and sCD25 showed a similar performance, with AUCs of 0.751 and 0.730, respectively.
García de Guadiana-Romualdo L, Cerezuela-Fuentes P, Español-Morales I, et al. Prognostic value of procalcitonin and lipopolysaccharide binding protein in cancer patients with chemotherapy-associated febrile neutropenia presenting to an emergency department. Biochem Med (Zagreb). 2019;29(1):010702.	C	Good	This was a prospective, observational study of consecutive ED patients with febrile neutropenia (n=111 patients). MASCC ≥ 21 was 75% sensitive and 86% specific with a PPV of 53% and an NPV of 94%.

Kelly RS, Lasky-Su J, Yeung SJ, et al. Integrative omics to detect bacteremia in patients with febrile neutropenia. PLoS One. 2018;13(5):e0197049.	C	Good	Prospective study evaluating metabolomics/transcriptomics to detect bacteremia in FN patients. A 5-predictor metabolomic model had an area under the receiver operating characteristic curve of 0.991 (95%CI: 0.972,1.000), 100% sensitivity, and 96% specificity for identifying bacteremia.
Mohindra R, Mathew R, Yadav S, Aggarwal P. CISNE versus MASCC: Identifying low risk febrile neutropenic patients. Am J Emerg Med. 2020;38(11):2259-2263.	C	Good	Retrospective cohort study comparing the MASCC and the CISNE Score. Results suggest that the CISNE <1 score is more sensitive than the MASCC >21 score.
Haeusler GM, Gaynor L, Teh B, et al. Home-based care of low-risk febrile neutropenia in children-an implementation study in a tertiary paediatric hospital. Support Care Cancer. 2021;29(3):1609-1617.	C	Adequate	This was a prospective study of low-risk pediatric patients with febrile neutropenia (n=132 patients), of whom 44 were discharged home. Low risk was assessed using a novel clinical decision tool assessing chemotherapy, hemoglobin, white blood cells, and platelets. Among those discharged home, 13.6% were readmitted with none requiring ICU admission. Among those admitted, 2.3% required ICU admission. There were no deaths.
Gunderson CC, Erickson BK, Wilkinson-Ryan I, et al. Prospective Evaluation of Multinational Association of Supportive Care in Cancer Risk Index Score for Gynecologic Oncology Patients With Febrile Neutropenia. Am J Clin Oncol. 2019;42(2):138-142.	C	Adequate	This was a prospective observational study (n=31 patients) at four institutions of patients with gynecologic cancer and febrile neutropenia. Of patients who were low risk as defined by a MASCC ≥ 21 (n=18 patients), 17% had positive urine or blood cultures, but none required ICU admission and there were no deaths.

Ying FLM, Ping MCY, Tong M, et al. A cohort study on protocol-based nurse-led out-patient management of post-chemotherapy low-risk febrile neutropenia. Support Care Cancer. 2018;26(9):3039-3045.	C	Poor	Prospective cohort study. Only 38 patients were enrolled. Majority were female with breast cancer (97%). Two patients required hospitalization due to persistent fever. The success rate of the out-patient program was not significantly different from the historical in-patient cohort (94.9 versus 97.4%, p = 0.053) including no deaths in the outpatient group.
Ahn S, Rice TW, Yeung SJ, 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):1465-1470.	D	Good	This was a retrospective study (n=571 patients) at three institutions comparing CISNE and MASCC for identifying low-risk patients with febrile neutropenia. CISNE was 12.4% sensitive and 96.6% specific with a PPV of 93.3% and an NPV of 22.5%. MASCC was 93.4% sensitive and 26.9% specific with a PPV of 82.9% and an NPV of 51.6%.
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):755-764.	D	Good	This was a retrospective study (n=230 patients) at two institutions comparing CISNE and MASCC for identifying low-risk patients with febrile neutropenia. CISNE was 98.3% sensitive and 30.4% specific with a PPV of 98.1% and an NPV of 32.8%. MASCC was 54.2% sensitive and 83.0% specific with a PPV of 84.0% and an NPV of 52.5%.
Ding S, Ma J, Song X, et al. Diagnostic Accuracy of Procalcitonin, Neutrophil-to-Lymphocyte Ratio, and C-Reactive Protein in Detection of Bacterial Infections and Prediction of Outcome in Nonneutropenic Febrile Patients with Lung Malignancy. J Oncol. 2020;2020:2192378.	D	Good	Retrospective analysis comparing several biomarkers. Inflammatory markers such as PCT, CRP, WBC, and NEU levels and NLR were significantly higher in patients with bacterial infections than in those with TF ($p < 0.0001$). However, PCT level was the best predictor of bacterial infections, with an area under the curve (AUC) of 0.874, followed by CRP level (AUC = 0.855) and NLR (AUC = 0.792) ($p < 0.0001$). Additionally, PCT level was

			significantly elevated in patients with bacterial infections with progressive disease after radiotherapy and chemotherapy ($p < 0.01$)
Haeusler GM, Thursky KA, Mechinaud F, et al. Predicting Infectious ComplicatioNs in Children with Cancer: an external validation study. Br J Cancer. 2017;117(2):171-178.	D	Good	This was a retrospective study of 650 pediatric patients with cancer and febrile neutropenia. The PICNICC rule was 78.4% sensitive, 39.8% specific, with a PPV of 28.6% and an NPV of 85.7%.
Jansma B, Vakkalanka P, Talan DA, Negaard B, Faine BA. Guideline adherence for the management of emergency department patients with febrile neutropenia and no infection source: Is there room for improvement?. J Oncol Pharm Pract. 2020;26(6):1382-1389.	D	Good	Retrospective cohort study including 237 patients using the MASCC score to risk stratify into low-risk and high-risk groups. 96.8% of high-risk patients and 0.4% of low-risk patients. 96.8% of high-risk patients were admitted and 0.4% of low-risk patients were discharged. Low-risk patients were almost universally admitted. There were 4 deaths (4.4%) in the low risk MASCC group.
Kim M, Ahn S, Kim WY, et al. Predictive performance of the quick Sequential Organ Failure Assessment score as a screening tool for sepsis, mortality, and intensive care unit admission in patients with febrile neutropenia. Support Care Cancer. 2017;25(5):1557-1562.	D	Good	Retrospective cohort study - 615 patients, 100 developed sepsis, 20 died, and 38 were admitted to ICUs. AUCs of the qSOFA score were poor predictors for sepsis [0.678, 95% CI (0.614–0.741)] and 28-day mortality [0.651, 95% CI (0.513–0.789)] and fair predictors for ICU admission [0.715, 95% CI (0.618–0.811)]. SIRS showed the smallest AUCs among the three scores, and MASCC was the most accurate score in predicting all three outcomes
Marshall W, Campbell G, Knight T, Al-Sayed T, Cooksley T. Emergency Ambulatory Management of	D	Good	Retrospective cohort of 100 consecutive low-risk febrile neutropenic patients presenting to a single center. Utilized the MASCC score. No patients

Low-Risk Febrile Neutropenia: Multinational Association for Supportive Care in Cancer Fits-Real-World Experience From a UK Cancer Center. J Emerg Med. 2020;58(3):444-448.			developed serious complications. Eight (8%; 95% CI 4.1-15.0%) patients had a 7-day readmission.
Paolino J, Mariani J, Lucas A, et al. Outcomes of a clinical pathway for primary outpatient management of pediatric patients with low-risk febrile neutropenia. Pediatr Blood Cancer. 2019;66(7):e27679.`	D	Good	Retrospective cohort study evaluating 169 cases of FN. Sixty-seven (40%) in the outpatient setting (41 episodes, 24%), the rest in a step-down/observation unit (26 episodes, 15%). There were no intensive care unit admissions or deaths among the low-risk patients. Of those identified as low risk, seven patients (10%) required subsequent hospitalization during the follow-up period, two for inadequate oral intake, two for persistent fevers, one for cellulitis, one for seizure unrelated to the febrile episode, and one for a positive blood culture.
Baugh CW, Wang TJ, Caterino JM, et al. Emergency Department Management of Patients With Febrile Neutropenia: Guideline Concordant or Overly Aggressive?. Acad Emerg Med. 2017;24(1):83-91.	D	Adequate	This was a retrospective study (n=173 patients) of patients with low-risk febrile neutropenia (defined as a MASCC score of ≥ 21). Of those deemed low risk (n=44 patients), 2.2% had a positive blood culture, but no patients had sepsis-induced hypotension or died within 30 days.
Cooksley T, Campbell G, Al-Sayed T, LaMola L, Berman R. A novel approach to improving ambulatory outpatient management of low risk febrile neutropenia: an Enhanced Supportive Care (ESC) clinic. Support Care Cancer. 2018;26(9):2937-2940.	D	Adequate	This was a retrospective study of low-risk patients with febrile neutropenia (n=68 patients) defined as a MASCC score ≥ 21 and an Early Warning Score ≤ 3. 8.8% were readmitted within 7 days, but none required critical care admission and there were no deaths within 30 days.

Nguyen M, Jacobson T, Torres J, Wann A. Potential reduction of hospital stay length with outpatient management of low-risk febrile neutropenia in a regional cancer center [published online ahead of print, 2021 Feb 26]. Cancer Rep (Hoboken). 2021;e1345.	D	Adequate	Retrospective cohort study on a small number of patients from 1 January 2016, and 31 December 2018 utilizing MASCC score. Over ½ of patients were breast cancer with over 70% female. There were no adverse outcomes in the low-risk group.
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.	D	Poor	Retrospective cohort study comparing the MASCC and CISNE scores in solid tumor patients from 2010 to 2016. CISNE broken into 3 groups (0, 1-2, 3 or greater)CISNE I stratum had significantly lower sensitivity (0.22 vs. 0.95 of MASCC low risk) but higher specificity (0.91 vs. 0.17) to predict zero occurrence of the primary outcome.
Taj M, Nadeem M, Maqsood S, Shah T, Farzana T, Shamsi TS. Validation of MASCC Score for Risk Stratification in Patients of Hematological Disorders with Febrile Neutropenia. Indian J Hematol Blood Transfus. 2017;33(3):355-360.	D	Poor	Retrospective cohort study. 226 febrile neutropenia patients in total. 132(58.4 %) categorized as low-risk; 94(41.5 %) as high-risk patients according to MASCC risk index score. In low-risk group 123(93 %) had uncomplicated infection while 9(7 %) had complicated infections. There was no mortality documented in the low-risk group while eight patients died in the high-risk group.
Janssens KP, Valete COS, Silva ARAD, Ferman SE. Evaluation of risk stratification strategies in pediatric patients with febrile neutropenia [published online ahead of print, 2020 Jun 4]. J Pediatr (Rio J). 2020;S0021-7557(20)30181-9.	D	Poor	Retrospective cohort study including 118 pediatric patients (199 episodes of FN). Utilized less common, pediatric specific risk stratification tools. Many patients were included multiple times in the study. The Rackoff score was considered most appropriate with a NPV of 100% (1.0).