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Article

Validation of the FENCE Risk Groups for Prediction of Febrile Neutropenia With First-Cycle Chemotherapy

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Abstract

Background: The FEbrile Neutropenia after ChEmotherapy (FENCE) score was developed to estimate the risk of febrile neutropenia (FN) at first cycle of chemotherapy but has not been externally validated. We aimed to validate the FENCE score based on its risk groups in patients treated at a comprehensive cancer center. **Methods:** We conducted a retrospective study of treatment-naïve adult patients with solid tumors and diffuse large B-cell lymphoma who received first-cycle chemotherapy between January and November 2019. Patients were followed until the second cycle of chemotherapy to identify any FN events (neutrophil count $<0.5 \times 10^9$/L with fever $\geq 38.2^{\circ}$C). The FENCE score was determined and patients classified as low, intermediate, high, and very high risk. The discriminatory ability of classifying patients into FENCE risk groups was calculated as the area under the receiver operating characteristics curve and incidence rate ratios within each FENCE risk group. **Results:** FN was documented during the first cycle of chemotherapy in 45 of the 918 patients included (5%). The area under the receiver operating characteristics curve was 0.66 (95% confidence interval [CI] = 0.58 to 0.73). Compared with the low-risk group (n = 285), the incidence rate ratio of developing FN was 1.58 (95% CI = 0.54 to 5.21), 3.16 (95% CI = 1.09 to 10.25), and 3.93 (95% CI = 1.46 to 12.27) in the intermediate (n = 293), high (n = 162), and very high (n = 178) risk groups, respectively. **Conclusions:** In this study, classifying patients into FENCE risk groups demonstrated moderate discriminatory ability for predicting FN. Further validation in multicenter studies is necessary to determine its generalizability.

Febrile neutropenia (FN) induced by chemotherapy is an oncological emergency and a major cause of morbidity and mortality in patients with cancer (1). Furthermore, FN may result in chemotherapy delays, chemotherapy dose reductions, and treatment discontinuation, all of which may reduce the effectiveness of treatment and compromise survival outcomes (2).

The occurrence of FN ranges from 10% to 50% in patients with solid tumors and up to 80% in those with hematological malignancies (3). Given the increased health-care costs associated with granulocyte colony-stimulating factors (G-CSF), it is neither practical nor clinically appropriate to be used for all patients. Current guidelines recommend primary prophylaxis with G-CSF starting at the first cycle of chemotherapy if the incidence of FN is at least 20% with a chemotherapy regimen or if the patient has specific risk factors associated with an increased risk of FN, such as older age, substantial comorbidities, poor performance status, and advanced disease status (4-6). However, there is no clear guidance in terms of how to determine the specific risk for FN based on the underlying risk factors. Thus, a risk prediction model that predicts FN over the course of chemotherapy cycles may provide more personalized insight and cost-effective treatment plans taking into consideration patients' specific risk factors.

Prognostic risk assessment scores such as the Multinational Association for Supportive Care in Cancer index and Clinical Index of Stable Febrile Neutropenia are used to identify low- and high-risk patients with FN for serious complications and help to determine treatment setting accordingly (7,8). Although the guidelines recommend considering treatment and a patient's specific risk factors to identify the risk of FN, few prediction models and scores have been developed to stratify patients and identify those at high risk for developing FN. Nevertheless, due to various study designs, relatively small sample size, and diverse chemotherapy regimens

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and cancer types in those studies, conclusive results were limited, and the guidelines did not provide recommendations regarding what to use (9-13).

Recently, Aagaard et al. (14) developed a risk score for predicting FN at the first cycle of chemotherapy for treatment-naïve patients with solid cancers and diffuse large B-cell lymphoma (DLBCL). The FEbrile Neutropenia after ChEmotherapy (FENCE) score determines the patient's risk for developing FN based on pretherapy risk factors, including sex, age, cancer type, disease stage, albumin, bilirubin, estimated glomerular filtration rate, infection before chemotherapy, number of chemotherapy drugs, and type of chemotherapy. Quintiles of the derived FENCE score were used to define 4 risk categories: low, intermediate, high, and very high. The discriminatory ability of the score as assessed by Harrell's C-statistic in the validation cohort was 0.79 (95% confidence interval [CI] = 0.75 to 0.82). The authors concluded that the FENCE score reliably predicted the risk of FN during the first cycle of chemotherapy and may be useful for personalizing patient management.

Despite the large sample size included in the development and validation of the FENCE score and its reported good discriminatory ability, the data were based on 1 institution and the score has not been validated externally in any other institute. External validation is necessary to assess a model's reproducibility and generalizability in clinical practice. Therefore, we aimed to conduct this study to validate the FENCE score for predicting FN based on its risk groups in patients with solid tumors and DLBCL treated at a comprehensive cancer center.

Methods

This was a retrospective study conducted at King Hussein Cancer Center (KHCC), a 350-bed comprehensive teaching center located in Amman, Jordan. KHCC is a leading hospital in the Middle East region that treats all types of cancer, with an estimated 3500 new cases of adult and pediatric patients per year. It is accredited by the Joint Commission International as a disease-specific cancer center. The study was approved by the KHCC institutional review board (study # 20 KHCC188) with a waiver of consent due to the retrospective nature of the study.

The hospital's cancer registry was used to identify all treatment-naive adult patients (≥18 years) with solid tumors and DLBCL who received their first cycle of chemotherapy between January 2019 and November 2019. We excluded patients who were on more than 1 chemotherapy regimen simultaneously (ie, alternating chemotherapy regimens), patients who received concurrent weekly radiotherapy with platinum-based chemotherapy, patients who had undergone hematopoietic stem cell transplantations, and those who received chemotherapy as part of an investigational study or compassionate protocol.

The electronic medical records were used to extract the patients' baseline characteristics and demographics as well as the items needed for the FENCE score calculation, which included age, sex, planned length of cycle, cancer type, disease stage, albumin, total bilirubin, estimated glomerular filtration rate, infection before chemotherapy, and the number and types of chemotherapy per regimen. In addition, we recorded the use of G-CSF and antibiotics as primary prophylaxis with the first cycle of chemotherapy.

The FENCE score was calculated by adding the coefficients for each item, as described by Aagaard et al. (14). The patients' risk for developing FN at the first cycle was determined based on the calculated FENCE score. Subsequently, the scores were used to classify patients to one of the following FENCE groups: low risk (score ≤16), intermediate risk (scores 17-35), high risk (scores 36-52), and very high risk (scores ≥53) for developing FN (14).

The patients' electronic medical records were reviewed from the start of the first cycle of chemotherapy to the time of the second cycle to identify any visits to the emergency department or hospital admissions for the management of FN, defined as neutrophil count less than 0.5×10^9/L with fever of at least 38.2°C (4-6). Though our definition for FN differed from that used in the original study by Aagaard et al. (14) (blood culture or death within 3 days of neutrophil count $<0.5 \times 10^9$/L or a leucocyte count $\leq 2.0 \times 10^9$/L), which was considered as a wide definition, the authors reported that the discriminatory ability of the score was similar between the wide and narrow (ie, documented fever and neutropenia) definition of FN and recommended to validate their results using the narrow definition that is consistent with the guidelines (5,14). Thus, we used the narrow definition as used in our center and more commonly used in clinical practice (4-6). For patients who developed FN, we recorded the outcomes of FN, including hospital admission and mortality, as well as chemotherapy dose reduction and dose delay in the second cycle.

Statistical Analysis

Continuous data were presented as median and interquartile range, and nominal data were presented as numbers and percentages. The discriminatory ability of classifying patients into FENCE risk groups was calculated as the area under the receiver operating characteristics curve (AUROCC) and incidence rate ratios, with their corresponding 95% confidence intervals within each FENCE risk group. The receiver operating characteristics curve is a plot of a sensitivity (y coordinate) vs 1 − specificity (x coordinate) within each risk group. A sensitivity analysis was performed to test the score performance when excluding patients who received G-CSF. All analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

During the study period, a total of 1023 chemotherapy-naïve patients received their first cycle of chemotherapy. We excluded 92 patients who received weekly radiotherapy with platinum-based chemotherapy, 7 patients on investigational chemotherapy, and 6 patients receiving alternating chemotherapy regimens. Therefore, we included 918 patients with solid tumors and DLBCL who received their first cycle of various types of chemotherapy regimens. Table 1 outlines the characteristics of the patients who were included in the study.

Among the enrolled patients, 45 (5%) developed FN, of whom the majority (n = 40, 89%) required hospitalization while the remaining were treated in the emergency department. All patients were discharged from the hospital, except for 1 patient who died in the intensive care unit. Following the episode of FN, 11 (24%) patients had dose reduction in their second cycle of chemotherapy, and 12 (27%) patients had delays in their second cycle.

Patients were classified in each risk group as follows: low risk (n = 285, 31%), intermediate risk (n = 293, 32%), high risk (n = 162, 18%), and very high risk (n = 178, 19%). Among the patients who developed FN, 6 (13%) were classified as low risk based on the FENCE score, 11 (24%) were classified as intermediate risk, 12 (27%) were classified as high risk, and 16 (36%) were classified as very high risk for developing FN at the first cycle of chemotherapy (Figure 1). Among the patients who received

Table 1. Characteristics of the patients (n = 918) who developed FN and those who did not[a]

Characteristics	FN (n = 45)	No FN (n = 873)
Sex, No. (%)		
Male	16 (36)	313 (36)
Female	29 (64)	560 (64)
Median age (IQR), y	55 (45-63)	55 (44-63)
Cancer type, No. (%)		
Breast	21 (48)	389 (45)
Lymphoma (DLBCL)	8 (18)	28 (3)
Small cell lung	4 (9)	24 (2)
Prostate	2 (4)	13 (2)
Non-small cell lung	2 (4)	71 (8)
Colorectal	1 (2)	151 (17)
Cervical or endometrial	1 (2)	18 (2)
Bladder	1 (2)	25 (3)
Head and neck	0 (0)	12 (1)
Gastric	0 (0)	49 (6)
Ovarian	0 (0)	26 (3)
Other	5 (11)	67 (8)
Disease stage, No. (%)		
Adjuvant or Ann Arbor I	8 (18)	203 (23)
Neoadjuvant or concomitant or Ann Arbor II	14 (31)	353 (41)
Locally advanced or disseminated or Ann Arbor III+	23 (51)	317 (36)
Albumin[b], No. (%)		
<Normal	11 (24)	98 (11)
Normal (3.4-4.8 g/dL)	31 (68)	736 (84)
>Normal	3 (8)	39 (5)
Bilirubin[b,c], No. (%)		
<5 mmol/L	13 (29)	362 (41)
5-25 mmol/L	31 (69)	495 (57)
>25 mmol/L	1 (2)	13 (2)
Estimated glomerular filtration rate (CKD-EPI)[b], No. (%)		
<60 mL/min	6 (13)	50 (6)
60-90 mL/min	13 (29)	206 (23)
>90 mL/min	26 (58)	617 (71)
Infection before chemotherapy[b,d], No. (%)		
Yes	8 (18)	41 (5)
No	37 (82)	832 (95)
Chemotherapy drugs, No. (%)		
1	1 (2)	63 (7)
2	25 (56)	625 (72)
3	11 (24)	157 (18)
4	8 (18)	28 (3)
Platinum, No. (%)		
Yes	14 (31)	415 (48)
No	31 (69)	458 (52)
Nonplatinum alkylating agents, No. (%)		
Yes	24 (53)	384 (44)
No	21 (47)	489 (56)
Taxanes, No. (%)		
Yes	9 (20)	133 (15)
No	36 (80)	740 (85)
Topoisomerase inhibitors, No. (%)		
Yes	34 (76)	464 (53)
No	11 (24)	409 (47)
Antimetabolites, No. (%)		
Yes	5 (11)	374 (43)
No	40 (89)	499 (57)
Vinca alkaloids, No. (%)		
Yes	8 (18)	29 (3)
No	37 (82)	844 (97)
Other chemotherapy and targeted therapy[e], No. (%)		
Yes	16 (36)	62 (7)
No	29 (64)	811 (93)
Radiotherapy[f], No. (%)		
Yes	4 (9)	48 (6)
No	41 (91)	825 (94)
Prophylaxis G-CSF, No. (%)		
Yes	3 (7)	41 (5)
No	42 (93)	832 (95)
Prophylactic antibiotics, No. (%)		
Yes	0 (0)	4 (0.5)
No	45 (100)	869 (99.5)
FENCE risk group, No. (%)		
Low (score ≤16)	6 (13)	279 (32)
Intermediate (score 17-35)	11 (24)	282 (32)
High (score 36-52)	12 (27)	150 (17)
Very high (score ≥53)	16 (36)	162 (19)

[a]The column percentages represent the proportion of patients based on the total number of patients who developed or did not develop FN in each category. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DLBCL = diffuse large B-cell lymphoma; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factors; IQR = interquartile range.
[b]Assessed closest to and up to 90 days before baseline.
[c]Bilirubin levels were missing in 3 patients in the no-FN group.
[d]Infection before chemotherapy: infection within the last 90 days, where a blood culture was sampled.
[e]Other chemotherapy and targeted therapy: bleomycin, mitomycin, pertuzumab, rituximab, and trastuzumab.
[f]Radiotherapy: concurrent radiotherapy during cycle.

prophylactic G-CSF (n = 44, 5%), 15 (34%) were classified as low risk, 15 (34%) were classified as intermediate risk, 9 (21%) were classified as high risk, and 5 (11%) were classified as very high risk. The AUROCC was 0.66 (95% CI = 0.58 to 0.73) (Figure 2). When excluding patients who were on G-CSF, sensitivity analysis resulted in an AUROCC of 0.65 (95% CI = 0.58 to 0.73).

The incidence rate ratio per point increase in FENCE score was 1.59 (95% CI = 1.21 to 2.08). Compared with those at low risk, the incidence rate ratio of developing FN was 1.58 (95% CI = 0.54 to 5.21), 3.16 (95% CI = 1.09 to 10.25), and 3.93 (95% CI = 1.46 to 12.27) in the intermediate, high, and very high risk groups, respectively.

Discussion

In this study, we validated classifying patients into risk groups according to the FENCE score for the development of FN at the first chemotherapy cycle among treatment-naive adult patients with solid tumors and DLBCL. Such classification demonstrated moderate discriminatory ability for predicting FN. Our findings were consistent with Aagaard et al. (14), who reported good discriminatory ability for the FENCE score in predicting FN in both the derivation and validation cohorts (14).

The rate of FN reported in our study (5%) was consistent with what was reported by Aagaard et al. (14). The relatively infrequent occurrence of FN following the first chemotherapy cycle may be related to the underreporting of FN cases and the type of patients included, where the majority had solid tumors

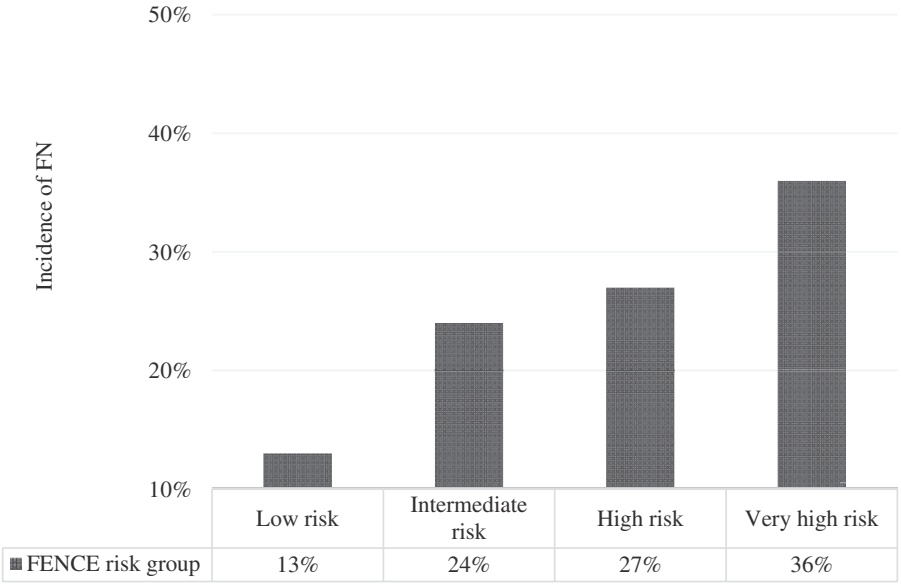

Figure 1. Proportion of patients within each risk group with febrile neutropenia (FN).

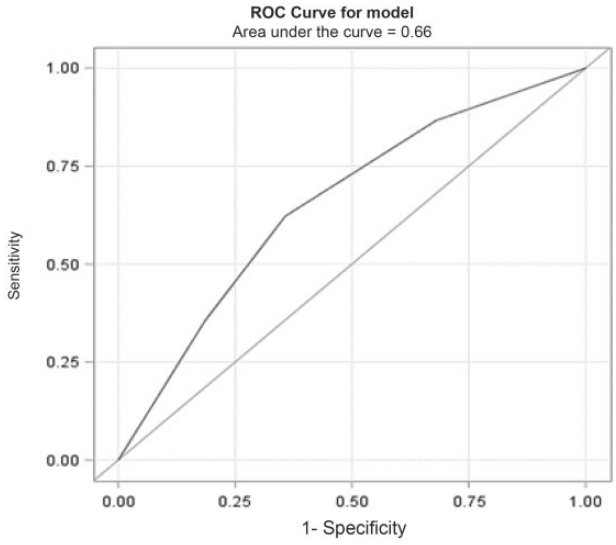

Figure 2. Receiver operating characteristic (ROC) curve for prediction of febrile neutropenia based on FEbrile Neutropenia after ChEmotherapy risk groups. Area under the ROC curve = 0.66 (95% confidence interval = 0.58 to 0.73).

and normal renal and hepatic function, were aged a median of 65 years, and were receiving less myelosuppressive chemotherapy regimens than those used in hematological malignancies. However, this small number of FN may reduce the ability of the study to accurately assess the model's performance, which may potentially limit its generalizability and reproducibility.

Though the overall incidence of FN was less than 20% in all FENCE risk groups, we had a number of patients who received G-CSF. This likely represents prescribers' clinical judgment for the addition of G-CSF prophylaxis based on the presence of other risk factors suggested by the guidelines, such as older age, performance status, comorbidities, and disease characteristics (5,6). This highlights the importance of developing risk prediction models that can aid in determining an individual's risk of developing FN objectively and the necessary supportive care that should be provided.

Although we included the same patient population reported by Aagaard et al. (14), there were some differences in the patients' baseline characteristics between the 2 studies. First, the population in this study was younger at baseline (median 55 years, interquartile range = 44-63) than in the original study (median 66 years, interquartile range 55-72). This may result in discrepancies in FENCE risk group performance because, notably, age older than 65 years is considered a risk factor for developing FN (5,15). Second, breast cancer was diagnosed in the majority of our patients who developed FN, followed by DLBCL, whereas ovarian and small cell and non-small cell lung cancer were the most common cancer types, according to Aagaard et al. (14). Third, FN was most commonly reported in patients on topoisomerase inhibitors, followed by non-platinum alkylating drugs and platinum agents in this study. However, platinum agents were the most common drugs producing FN, followed by topoisomerase inhibitors and taxanes in the Aagaard et al. (14) study.

The performance of the FENCE risk groups might have been influenced by the following limitations. First, information on chemotherapy regimens such as chemotherapy dose and intensity were not included as risk factors in the FENCE risk score. Second, there is variability in terms of how targeted therapy is handled in the score. For example, a chemotherapy regimen containing a targeted therapy such as cetuximab, bevacizumab, or trastuzumab would be considered as "other chemotherapy" when calculating the final risk group. However, if a regimen contains more than 1 targeted therapy (ie, trastuzumab- pertuzumab) that is not listed among the suggested regimens in the FENCE score, then it would be considered as only 1 drug when calculating the score. In addition, the score does not incorporate poor performance status and fragility of patients, which have been described as risk factors of FN (16). Other studies have also shown that the prevalence of FN increases in a linear fashion with the number of comorbidities per patient as accounted in the Charlson Comorbidity Index (eg, congestive heart failure, cardiovascular disease, dementia, chronic pulmonary disease, diabetes) (11,17). Although the univariate analysis by Aagaard et al. (14) demonstrated an increase in FN incidence with higher Charlson Comorbidity Index score, body surface area, abnormal hemoglobin, and lymphocyte and platelets counts, these risk factors were not statistically significant in the

multivariable logistic regression and therefore were not included in the final model.

Former studies addressing FN prediction models generally had less diversity. Some studies focused on a single cancer type such as non-Hodgkin's lymphoma and breast cancer (18), whereas others have focused on elderly patients with breast, lung, colorectal, and prostate cancer (11). Power issues were found in some prospective studies due to small sample size limiting the number of patients' specific risk factors included (12,19). Furthermore, the definition of FN was not specified in some articles (15), whereas others have considered and adjusted different risk factors and few models have been validated independently (18). A partial validation by Jenkins et al. (20) was performed to a FN risk model in patients with breast cancer using an independent dataset; however, the model accuracy was limited. This heterogeneity in patient populations, treatment regimens, study designs, and analytical methods make it difficult to compare between studies (15).

To our knowledge, this is the first study to externally validate the FENCE model according to its risk groups, with a relatively large sample size, variety of tumors, and more current treatment regimens compared with those used in previous modeling efforts. Other strengths of this study include the use of objective criteria for FN prediction, which increases the likelihood of reproducibility.

The major limitations are primarily related to the retrospective nature of the study with all the limitations of retrospective data sets, which may be associated with underreporting of FN cases, being conducted in a single center, and including patients over 1 year instead of a longer duration. Secondly, because our aim was to externally validate the risk groups, we did not analyze risk factors for FN other than those presented in the original study, such as delivered chemotherapy dose intensity, comorbidities, bone marrow involvement, and performance status. Lastly, we were unable to analyze the impact of prophylactic antibiotics and immunomodulatory effect of corticosteroids due to expected low usage among selected patients in this study.

The FENCE score is practical to implement because it relies on objective characteristics that can be easily obtained from patients' medical records. Given its discriminatory ability, applying the score in clinical practice may guide physicians to identify patients who are most likely to benefit from prophylactic measures such as G-CSF and antibiotics to decrease the risk of FN and the resulted complications. Given its limitations, however, addressing additional risk factors in a larger cohort of patients may improve the model's discrimination and provide a better contribution to the field.

Classifying patients based on the FENCE risk groups demonstrated moderate discriminatory ability for predicting FN at first chemotherapy cycle in patients with solid tumors and DLBCL. However, given its limitations, further prospective validation in large multicenter studies is needed to determine its generalizability and performance when used in clinical practice.

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Data Availability

The data underlying this article are available in the article.

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