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Evaluation of risk assessment tools and infectious aetiology in cancer patients with fever and neutropaenia in Hong Kong

Key Messages

1. A total of 227 cancer patients who developed fever and neutropaenia after chemotherapy were prospectively evaluated according to the Talcott and the Multinational Association of Supportive Care in Cancer (MASCC) risk models.
2. The positive predictive value (PPV) of low-risk prediction by the Talcott model was 84%. The sensitivity (SE), specificity (SP), negative predictive value (NPV) and misclassification rate (MR) were 50%, 72%, 33% and 44%, respectively.
3. The MASCC score of ≥21 identified low-risk patients with a PPV of 86%, SE of 81%, SP of 60%, NPV of 52% and MR of 24%. Of the 160 (70%) low-risk patients, 12.5% developed complications and 1.9% died. In contrast, of the 67 (30%) high-risk patients, 43.3% developed complications and 9% died (P<0.0001).
4. The MASCC risk index was superior to the Talcott risk model in terms of a higher discriminative power for identifying low-risk patients.
5. An infective aetiology was microbiologically documented in 21% of the 227 patients. Gram-negative bacteria were more commonly implicated than Gram-positive bacteria (58% vs 31%).

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Introduction

Neutropaenic fever remains a common life-threatening complication of cancer chemotherapy, and standard management entails hospitalisation and administration of empirical broad-spectrum intravenous antibiotics. Febrile neutropaenic cancer patients form a heterogeneous population with variable risks for infection-related morbidity and mortality. Worldwide, this has led clinicians to consider more selective, risk-adapted management approaches, including shorter antibiotic courses, earlier hospital discharge, oral antibiotic treatment, and/or outpatient supervision. The development of risk-adapted approaches depends on the availability of universally accepted and validated clinical prediction rules to identify these low-risk patients.

Talcott et al[1] were the first to develop a clinical prediction rule based on clinical features at the onset of febrile neutropaenia. Patients were classified into four groups. Groups I, II, and III represented high-risk patients, namely inpatients, patients with comorbidities, and patients with uncontrolled cancer, respectively. Group IV represented low-risk patients that consisted of outpatients with febrile neutropaenia, having controlled cancers and no comorbidities. This model has been validated in a subsequent prospective study.[2]

To further improve the Talcott model, the Multinational Association of Supportive Care in Cancer (MASCC) developed a scoring system based on seven independent prognostic factors, derived from a multiple logistic regression model.[3] Patients with a score of ≥21 were regarded as low risk. This risk-predicting tool has been validated in prospective studies in other patient populations.[4,5] However, none of these risk-predicting tools has been validated in cancer patients in the local health care setting.

Objectives

The primary objective was to validate the Talcott risk model and the MASCC risk index for predicting the outcome of cancer patients with febrile neutropaenia in the local health care setting. Secondary objectives included evaluation of clinical outcomes and infective aetiologies of cancer patients with febrile neutropaenia in Hong Kong.

Methods

Settings and subjects

This prospective, observational cohort study of consecutive cancer patients with febrile neutropaenia was approved by the institutional review board of the Prince of Wales Hospital. All subjects gave written informed consent prior to enrolment. All patients were hospitalised and the clinical management of the febrile episodes was at the discretion of the attending physicians. Cancer patients aged ≥16 years who presented with chemotherapy-induced neutropaenia (absolute neutrophil count of <500 cells/mm^3 or <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3) and fever (≥38°C on two occasions more than 1 hour apart or ≥38.3°C on a single occasion) were included. Only the first febrile episode occurring in any given patient during the study period was counted.

Study instruments

Baseline admission data were collected when they were inpatients. Outcomes were evaluated after discharge by an investigator blinded to the baseline data.

Main outcome measures and statistical methods

Final outcome was defined as (1) fever resolution for 5 consecutive days without a serious medical complication, with modification of the initial antibiotic treatment allowed (good outcome), or (2) occurrence of a serious medical complication, or death before fever resolution (poor outcome).

A 2x2 table was used for the calculation of positive predictive value (PPV) and negative predictive value (NPV), sensitivity and specificity. Patients predicted to be at low risk and with uncomplicated recoveries represented true positives. The PPV was calculated for low-risk patients predicted to have uncomplicated recoveries, and the NPV was calculated for high-risk patients predicted to develop serious medical complications including death. The sensitivity was calculated for patients with good outcomes who were identified as having a low risk. The specificity was calculated for patients with poor outcome who were identified to be at high risk. The misclassification rate was calculated for the falsely predicted high- and low-risk patients. The Chi squared test was used to compare the outcomes of low- and high-risk groups. All P values were two sided. Statistical analysis was performed using SAS version 8.0 (SAS Institute, Cary [NC], USA). The receiver operating characteristic curve was constructed with SPSS 16.0 (SPSS Inc, Chicago [IL], USA).

Sample size

In the original MASCC publication,[3] the PPV of the MASCC risk index was validated in a set of 383 patients and found to be 91%. It was 87% in a recent prospective validation study of 663 patients in a multicentre, multinational setting.[4] In our study, the PPV was postulated to be around 85%, and the sample size was calculated with a 95% confidence interval (CI) for the PPV when the lower bound exceeds 80%. Interim analyses were planned at the end of 12 and 24 months. The accrual was closed when the result of the second interim analysis at 24 months confirmed the lower boundary of the 95% CI for PPV exceeded 80%.

Results

Patient characteristics

Between October 2005 and February 2008, 108 men and 119 women were recruited. Their median age was 51 (range, 16-88) years. About 61.2% of the patients were outpatients, with an Eastern Cooperative Oncology Group performance status of 0 (39.2%) or 1 (42.3%) at the onset of febrile neutropaenia. Of the 227 patients, 53.3% had a solid tumour, 26.4% had a lymphoma, and the remaining 20.3% had leukaemia. Only 11 (4.9%) of the patients had used prophylactic granulocyte colony stimulating factor; 29 (12.8%) of the patients had used prophylactic antibiotics; and 52 (22.9%) of the patients had an implanted central venous catheter.

Validation of risk models

According to the Talcott risk model, 101 (45%) of the patients were classified as low risk (Table 1). Of them, 14 (13.9%) developed serious medical complications and 2 (2%) died. In contrast, 126 (55%) of the patients were classified as high risk. Of these, 35 (27.8%) developed complications and 7 (5.6%) died. The PPV was 84% (95% CI, 79-89%). The sensitivity, specificity, NPV and misclassification rate were 50%, 72%, 33% and 44%, respectively (Table 2).

Table 1. Patient outcomes according to the Talcott risk model and the Multinational Association of Supportive Care in Cancer (MASCC) risk index

Risk model	Good outcome	Poor outcome		Total No. (%) of patients
	Resolution without complication	Resolution with complications	Death before fever resolution	
Talcott risk model*				
No. (%) of low-risk patients	85 (84.1)	14 (13.9)	2 (2)	101 (45)
No. (%) of high-risk patients	84 (66.7)	35 (27.8)	7 (5.6)	126 (55)
Total No. (%) of patients	169 (74)	49 (22)	9 (4)	227 (100)
MASCC risk index†				
No. (%) of low-risk patients	137 (85.6)	20 (12.5)	3 (1.9)	160 (70)
No. (%) of high-risk patients	32 (47.7)	29 (43.3)	6 (9.0)	67 (30)
Total No. (%) of patients	169 (74)	49 (22)	9 (4)	227 (100)

* P=0.0027, Chi squared test
† P<0.0001, Chi squared test

Table 2. Clinical risk prediction rules of the Talcott risk model and the Multinational Association of Supportive Care in Cancer (MASCC) risk index

Parameter	Talcott model in MASCC validation set[3] (n=383)	MASCC score of ≥21 in MASCC validation set[3] (n=383)	Talcott model in current study (n=227)	MASCC score of ≥21 in current study (n=227)
Patients at low risk (%)	26	63	45	70
Sensitivity (%)	30	71	50	81
Specificity (%)	90	68	72	60
Positive predictive value (%)	93	91	84	86
Negative predictive value (%)	23	36	33	52
Misclassification rate (%)	59	30	44	24
Death rate among low-risk patients (%)	3	1.6	2.0	1.9

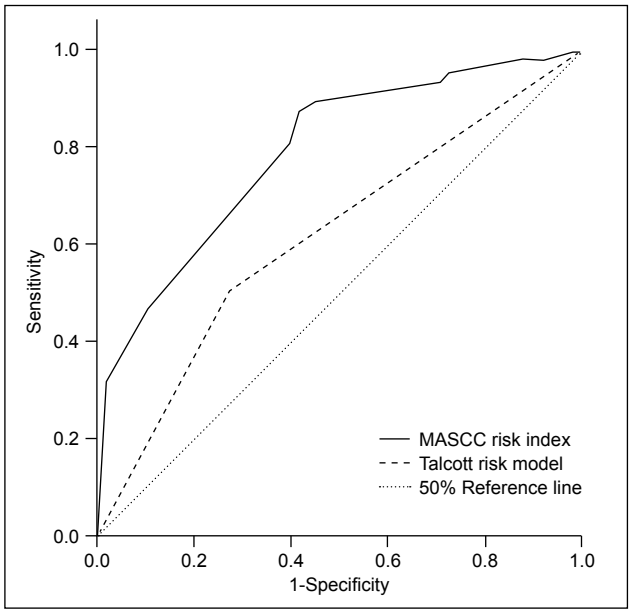

Fig. Receiver operating characteristic (ROC) curves for the Multinational Association of Supportive Care in Cancer (MASCC) risk index and the Talcott risk model

The area under the ROC curves for MASCC risk index is 0.79 (95% CI, 0.73-0.86) and that for the Talcott risk model is 0.61 (95% CI, 0.53-0.70)

Using the MASCC risk index, a score of ≥21 identified 160 (70%) of the patients as low risk with a PPV of 86% (95% CI, 81-90%). The sensitivity, specificity, NPV and misclassification rate were 81%, 60%, 52% and 24%, respectively (Table 2). Of the 160 (70%) low-risk patients, 20 (12.5%) developed serious medical complications and 3 (1.9%) died. Of the 67 (30%) high-risk patients, 29 (43.3%) had complications and 6 (9%) died (Table 1).

The receiver operating characteristic curves for the MASCC risk index and the Talcott risk model are shown in the Figure.

Clinical outcomes

Complete resolution of fever without a complication was noted in 169 (74%) of the patients, whereas 49 (22%) developed serious complications and 9 (4%) died before fever resolution. The most frequent serious medical complications were hypotension (23%), respiratory failure (12%) and arrhythmias or electrocardiographic changes (10%).

Infective aetiology

Among the febrile neutropaenic episodes of these 227 patients, only 47 (21%) had microbiologically documented infection, 169 (74%) had clinically documented infection, and 11 (5%) were classified as having an unknown fever. Table 3 summarises the clinically identified sites of infection. Most of the microorganisms were cultured from the blood (48%), followed by sputum (23%), urine (17%) and wounds (6%). Gram-negative organisms (58%) were more commonly implicated than Gram-positive organisms (31%). Polymicrobial infections accounted for 11%. Bacteraemias were more commonly due to Gram-negative than Gram-positive organisms (57% vs 35%).

Discussion

The ideal risk assessment tool should have a high PPV, high sensitivity and specificity but a low misclassification rate. In the clinical management of neutropaenic fever, false-positive predictions are disastrous, whereas false-negative ones are unpleasant. The optimal threshold for a given rule should take into account the relative seriousness of adverse sequelae associated with false-positive and false-negative errors. The misclassification rate is of secondary importance compared to the PPV. The misclassification rate is the sum of both the false-positive and false-negative rates and gives equal weight to both results. As patient safety remains our top priority, we are more concerned about the false-positive rate (low-risk patients who developed poor outcome) than the false-negative rate (high-risk patients who developed good outcome). Another parameter used to decide whether a risk assessment tool is safe is the mortality rate in the low-risk group. In this study, mortality rates among the low-risk patients in both the Talcott risk model and MASCC risk index were low (2.0% and 1.9%).

In this study, the MASCC risk index (with a score of ≥21) appeared superior to the Talcott risk model with a similar PPV (86% vs 84%), a higher sensitivity (81% vs 50%), a higher NPV (52% vs 33%) and a lower misclassification rate (24% vs 44%). Moreover, it

Table 3. Microbiological diagnoses in the 227 patients with febrile neutropaenia

Site of infection	No. of microbiologically documented infection	No. of clinically documented infection	No. of unknown infection	Total No. (%)
Fever of unknown origin	2	48	1	51 (22)
Upper respiratory tract	3	27		30 (13)
Bronchopneumonia	17	23	-	40 (18)
Urinary tract	8	5	-	13 (6)
Catheter	1	1	-	2 (1)
Cholangitis	1	-	-	1 (0.4)
Enterocolitis	2	9	-	11 (5)
Mucositis	6	34	-	40 (18)
Perianal abscess	1	2	-	3 (1.35)
Cellulitis	4	14	-	18 (8)
Dental abscess	-	3	-	3 (1.3)
Others	2	2	-	4 (2)
Unknown	-	1	10	11 (5)
Total No. (%)	47 (21)	169 (74)	11 (5)	227 (100)

identified a higher proportion of low-risk patients (70% vs 45%).

A higher proportion of bacteraemias were caused by Gram-positive than Gram-negative organisms in western series. Nonetheless, Gram-negative bacteria remained the predominant microorganisms we isolated. This may be due to the relatively low percentage of our patients receiving prophylactic antibiotics (12.8%), as compared to 35% in the MASCC study.[3] The use of prophylactic antibiotic agents is known to decrease the proportion of Gram-negative bacteraemias in febrile neutropaenic patents.

Conclusions

We have validated the two risk assessment tools in a prospective observational cohort of local cancer patients. The MASCC risk index was superior to the Talcott risk model in terms of a higher discriminative power for identifying low-risk patients. Further studies should be carried out to assess the feasibility of simplified management strategies in low-risk patients, such as the use of oral antibiotics and/or outpatient management. The risk assessment tools also identified a high-risk group with a morbidity of 43% and mortality of 9%. Future management strategies should be directed to the high-risk group in order to improve overall treatment outcomes in febrile neutropaenic cancer patients.

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