Risk Index for Predicting Complications and Prognosis in Thai Patients with Neutropenia and Fever

METHEE CHAYAKULKEEREE, MD*,
VISANU THAMLIKITKUL, MD*

Abstract

Background : New strategies in the treatment of febrile neutropenic patients have been proposed during the past decade. It is more and more widely accepted that febrile neutropenic patients are a heterogeneous population and they have varying risks for complications and death. However, most of the data have been collected from patients in Western countries. The purpose of the study was to identify types of infection and etiologic organisms in febrile neutropenic patients at Siriraj Hospital, Thailand, and also to develop a prediction model in order to identify patients who are expected to have a favorable outcome or a low-risk subset.

Method : The medical records of chemotherapy-induced neutropenic patients with fever hospitalized at Siriraj Hospital, Thailand, from January 1999 to December 2000 were analyzed. Data included patient characteristics, epidemiological data and the potential factors at the onset of fever for predicting patient outcome. A scoring system for predicting patients with favorable outcome was developed. The scoring system developed from this study was compared with a previously used scoring system.

Results : Of 220 patients with 267 febrile neutropenic episodes, 71.8 per cent had hematologic malignancies and 28.2 per cent had solid tumors. Bacteremia was found in 61 episodes (22.8%) and gram negative bacilli were the most common causative organism in bacteremia (88.6%). Overall mortality was 17.7 per cent. Multivariate analysis revealed that the factors predicting outcome were burden of illness, control of cancer, duration of neutropenia and dehydration. The scoring system developed from this set of data revealed that a score $\geq$ 16 identified patients with a favorable outcome with a specificity of 90.2 per cent, sensitivity of 76.6 per cent and positive predictive value of 85.4 per cent.

Conclusion : The causative organisms of bacterial infections in febrile neutropenic patients in Thailand are still gram negative bacteria. The locally developed risk index has a fair accuracy to identify patients with favorable outcome and may be used to identify patients suitable for less aggressive treatment strategies.

Key word : Agranulocytosis, Neutropenia, Febrile Neutropenia, Prognosis

CHAYAKULKEEREE M & THAMLIKITKUL V
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* Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Chemotherapy-induced neutropenia in cancer and hematologic malignancy patients is almost always associated with infections[1]. This complication usually limits effective chemotherapeutic treatment in those patients. Neutropenic patients presenting with fever are usually treated empirically with broad-spectrum antimicrobials[2]. Despite such prompt treatment, the complications and mortality rate in febrile neutropenic patients remain high. In a large series, the mortality reported ranged from 4 per cent to 30 per cent of episodes[3-5]. In 1997, the Infectious Diseases Society of America (IDSA) developed guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever[6]. The guideline recommendation is to treat all patients with a homogeneous regimen. In most of the febrile neutropenic episodes, the causative organisms were unknown and bacteremia was identified in only 22 per cent-32 per cent of the patients in most reports[5,7-12]. Over the past decade, there has been a clear shift in the infecting organisms from gram negative bacilli to gram positive cocci in the United States and Europe, and currently 60 per cent-70 per cent of the episodes of bacteremia are due to gram positive cocci[13,14].

Recent investigations suggest that neutropenic patients with fever are a heterogeneous population, with subsets with varying risks regarding response to initial therapy, development of serious medical complications and mortality. An increased understanding of febrile neutropenia over the past decade has given clinicians the ability to identify patients with expected favorable outcome or, in other words, these patients with a lower risk of serious medical complications or mortality. Talcott et al have developed a clinical prediction classifying patients into four risk groups. They suggested that neutropenic patients with controlled cancer and no serious comorbidity who develop fever in an outpatient setting are at low risk, with an expected rate of serious medical complications of less than 5 per cent[15]. The ability to differentiate reliably between favorable and unfavorable outcome subsets was further developed by the Multinational Association for Supportive Care in Cancer (MASCC) by using a scoring system. The characteristics used in the MASCC scoring system were burden of illness, no hypotension, no chronic obstructive pulmonary disease, solid tumor or no previous fungal infection, no dehydration, outpatient status and age less than 60 years. A score ≥ 21 can identify low-risk patients with a positive predictive value of 91 per cent, specificity of 68 per cent and sensitivity of 71 per cent[16].

Because of the changing situation and new knowledge concerning febrile neutropenia, it has now become possible to evaluate not only the nature of empirical antibiotic therapy for such patients, but

also the setting in which such therapy is delivered (17-19). Many studies have shown that patients in a low-risk subset can be treated safely with oral antibiotics and/or as an outpatient(20-26).

Although several studies in the United States and Europe have been performed to investigate the causative organism and outcome in febrile neutropenic patients, data in developing countries is lacking. Kanitsap et al reviewed 147 patients with hematologic malignancy with 64 episodes of febrile neutropenia at Siriraj Hospital, Thailand, from January to June 1998. They found that 22 per cent of the patients had bacteremia and the most common causative pathogens identified from blood were gram negative bacilli which accounted for 18 per cent of all episodes of febrile neutropenia (82% of all bacteremia). However, this study did not identify the potential factors for predicting favorable outcome(12).

The purpose of this study was to identify the types of infection and etiologic organisms in febrile neutropenic patients and also to develop a prediction model to identify patients who are expected to have favorable outcome or a low-risk subset.

MATERIAL AND METHOD

Patients

Patients with febrile neutropenic episodes who were admitted to Siriraj Hospital, Thailand from January 1999 to December 2000 were included in the study. All of the patients' records which were coded for agranulocytosis (D70) using ICD-10 were reviewed. Patients who met the following eligibility criteria were included in the analysis : neutropenia (absolute neutrophil count < 500/ μl) that was related to chemotherapy for hematologic malignancy or solid tumor, temperature greater than 38°C and age older than 12 years. Patients who received antibiotics for treating febrile neutropenic episodes concurrently with chemotherapeutic agents, and patients who died within 24 hours of admission were excluded.

Data extraction

The following data were extracted from the patients' medical records; patient's age, gender, underlying cancer, ECOG (Eastern Cooperative Oncology Group) performance status, number of courses and regimens of chemotherapeutic agents, use of growth factors and antibiotic prophylaxis, onset of fever at presentation, duration since the first day of the last episode of chemotherapy to hospitalization, duration of neutropenia, temperature, blood pressure, pulse rate and respiratory rate. Laboratory data included total leukocyte count, absolute neutrophil count, absolute monocyte count, absolute phagocyte count, platelets, hemoglobin, blood urea nitrogen, creatinine, electrolytes, alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, albumin, globulin and chest radiograph. Microbiological results and susceptibility profiles were also recorded for further analysis.

Operational definitions

Control of cancer

Control of cancer was assessed using the diagnostic information available in the medical records. For patients with leukemia, uncontrolled cancer was defined as the absence of documented complete remission. For patients with lymphoma or solid tumors, uncontrolled cancer was defined as either development of new lesions, ≥ 25 per cent enlargement of a measurable lesion while receiving chemotherapy or other evidence of treatment failure such as progressive cancer symptoms.

Burden of illness

Burden of illness was categorized into three groups. No or mild symptoms included patients who had no or minimal clinical signs and symptoms. Moderate symptoms included patients who had moderate clinical signs and symptoms with stable vital signs. Severe symptoms and moribund included patients who arrived bed-bound with clinical sepsis or who had unstable vital signs and needed close monitoring or intensive care.

Occurrence of fever

Occurrence of fever was categorized into outpatient or inpatient. The inpatient setting was defined as a patient who developed fever during his/her hospitalization or within 72 hours of discharge.

Co-morbidity

Co-morbidity was defined as significant blood loss requiring blood transfusion, respiratory failure needing intubation, altered mental state, presence of mucositis, presence of superficial fungal infection, diarrhea, abdominal pain, nausea/vomiting, central intravenous catheter insertion, dehydration requiring intravenous treatment, suspected spinal cord compression, severe pre-existing cardiac diseases, chronic pulmonary diseases, diabetes, history of surgery within 6 weeks, previous febrile neutropenia, previous inva-

sive fungal infection, previous antifungal treatment within the last 6 months, previous antibiotic treatment within 7 days and other serious diseases.

Dehydration

Dehydration was defined as volume depletion, i.e. combined sodium and water deficit. Signs of volume depletion included one or more of the followings; reduced skin turgor, dry oral mucous membrane, decreased axillary sweating, postural hypotension, hypotension.

Classification of fever

Fever was classified into fever of unknown origin (FUO), clinically documented infection and microbiologically documented infection.

Outcome measure

Patients' final outcomes were categorized using the parameters of survival, serious complications, modification of initial treatment, relapse of fever within 5 days of resolution, and the time taken for the fever to resolve after starting antibiotics

Patients were classified into two groups according to the outcome :

- Favorable outcome : Patients whose fever resolved within 5 days of starting treatment and without serious medical complications.
- Unfavorable outcome : Death from any causes or development of serious medical complications or modification of initial antibiotic treatment or relapse of fever after resolution or fever not yet resolved after 5 days of treatment.

Statistical analysis

The data were analyzed using descriptive statistics. Student's *t*-test or Mann-whitney U test, Chi-square test or Fisher's exact test were used for univariate analysis. A multiple logistic regression model was used for multivariate analysis. All statistical tests were two-sided and $p < 0.05$ was considered significant. Based on the logistic model, a prediction score was calculated for each patient. Patients with scores higher than the threshold constituted the group with favorable outcome. The sensitivity, specificity, positive predictive value and negative predictive value

Table 1. Causative organisms isolated from the patients.

Organisms	All culture (N)	%	Blood cultures (N)	%
Gram negative bacteria	86	87.8	54	88.6
Escherichia coli	25	25.5	16	26.3
Pseudomonas aeruginosa	24	24.5	17	27.9
Klebsiella spp	13	13.2	10	16.4
Nonfermentative gram negative rod	6	6.1	3	4.9
Enterobacter spp	5	5.1	2	3.3
Salmonella group D	3	3.1	2	3.3
Aeromonas spp	2	2.1	1	1.6
Proteus spp	2	2.1	0	0
Vibrio cholera non O1 non O139	2	2.1	2	3.3
Salmonella group B	1	1.0	1	1.6
Morganella morganii	1	1.0	0	0
Vibrio fluvialis	1	1.0	0	0
Moraxella catarrhalis	1	1.0	0	0
Gram positive bacteria	12	12.2	7	11.4
Streptococcus spp	4	4.0	3	4.9
Enterococcus spp	2	2.1	0	0
MSSA	2	2.1	2	3.3
MRSA	1	1.0	0	0
Coagulase Negative *Staphylococcus*	1	1.0	1	1.6
Corynebacterium spp	1	1.0	0	0
Bacillus spp	1	1.0	1	1.6
Total	98	100	61	100

of the system were computed. The data set in the present study was used to validate the scoring system developed by the Multinational Association for Supportive Care in Cancer Risk Index[16]. The sensitivity, specificity, positive predictive value and negative predictive value of both sets were also compared.

RESULTS

The medical records of 433 episodes coded as D70 (agranulocytosis) during the 2 years from January 1999 to December 2000 were identified. 344 episodes met the criteria for febrile neutropenia. 77 episodes were excluded because of inadequate data (56 episodes), concurrent chemotherapy and antimicrobials (14 episodes) and death within 24 hours (7 episodes). Therefore, there were 267 episodes from 220 patients suitable for analysis.

Out of 267 episodes, 98.5 per cent of the cases were hospitalized on medical wards and 1.5 per cent were in the department of Surgery, Obstetrics & Gynecology, Orthopaedic Surgery and Radiation Therapy.

99 patients (45%) were male. Mean age was 44.7 years (SD = 18, range 13-91). 158 patients (71.8%) had hematologic malignancies, of which acute leukemia (101 patients or 45.9%) and lymphoma (42 patients or 19.1%) were the most common underlying diseases. The other 62 patients (28.2%) had solid tumors, 17 patients (7.7%) had breast cancer and 16 patients (7.3%) had sarcoma. 75 patients (28.1%) received growth factors and 6 patients (2.2%) received antibiotic prophylaxis.

The source of infection was unknown in 139 episodes (52.1%) and this group was classified as FUO, whereas, 38 episodes (14.2%) were classified as clinically documented infection, and 90 episodes (33.7%) which had culture proven data were classified as microbiologically documented infection. The common sites of infection of patients with clinically documented infection were lung (42.1%), perineum (21.1%) and soft tissue (18.4%). Most of the patients with microbiologically documented infection were classified as primary bacteremia (55.6%), whereas, urinary tract (17.8%) and soft tissue (10%) were the second and third most common source of infection.

There were 94 clinical specimens taken from patients with 267 episodes that had a positive culture (35.2%). 61 culture-positive specimens (22.8%) were taken from blood. There were 4 episodes that had 2 positive culture specimens. Two episodes had a positive culture with same organisms from pus and blood specimens, one was *Escherichia coli* and another was *Vibrio cholerae*. *Streptococcus* spp was found in blood and urine from a patient. One patient with osteomyelitis had *Escherichia coli* in pus and group B streptococcus in blood. The other culture-positive specimens were urine (6%), pus (3.7%), sputum (1.5%), stool (0.4%), synovial fluid (0.4%) and urethral swab (0.4%).

98 organisms grew from the clinical specimens as shown in Table 1. Most of the causative organisms were gram negative bacteria that accounted for 86 specimens (87.8 %). Gram positive bacteria were found in 12.2 per cent. 8 episodes had polymicrobial infections. Two sets of blood grew two organisms each (*Escherichia coli* & *Klebsiella* spp, and *Aeromonas* spp & *Klebsiella* spp). One patient grew *Streptococcus* spp from blood culture and *Escherichia coli* from pus simultaneously as mentioned previously. Three pus specimens grew dual organisms which were *Escherichia coli* & *Pseudomonas aeruginosa*, nonfermentative gram negative rods & *Pseudomonas aeruginosa*,and *Klebsiella* spp & *Enterococcus* spp. One urethral swab grew *Corynebacterium* spp & *Enterobacter* spp and one urine culture grew *Escherichia coli* & *Enterobacter* spp.

The antimicrobial drugs given to the patients are shown in Table 2. The most commonly used antimicrobial regimen was ceftazidime plus amikacin which was prescribed in 204 episodes (76.4%).

Out of 267 episodes, 159 episodes met the criteria for high-risk or unfavorable outcome and 108 episodes met the criteria for low-risk or favorable

Table 2. Antibiotics given to the patients with febrile neutropenia.

Antibiotic	Frequency of prescription	%
Amikacin	242	44.4
Ceftazidime	239	43.9
Metronidazole	17	3.1
Cefepime	11	2.0
Clindamycin	8	1.5
Cloxacillin	7	1.3
Ceftriaxone	5	0.9
Ciprofloxacin	4	0.7
Imipenem	4	0.7
Netilmicin	3	0.6
Ampicillin	1	0.2
Gentamicin	1	0.2
Cefpirome	1	0.2
Amoxicillin/clavulanate	1	0.2
Meropenem	1	0.2

outcome. The mortality rate in 220 neutropenic patients with fever was 17.7 per cent. The cause of death was due to infection in 97.4 per cent. Antimicrobial treatments were modified in 92 episodes (34.5%) because of poor response to treatment. Common complications that occurred during treatment of 267 episodes were hypotension (10.1%), respiratory failure (10.1%), serious bleeding (4.9%) and alteration of consciousness (4.1%).

Of 228 episodes in which patients survived, 17 (7.5%) episodes relapsed, 117 (51.3%) episodes subsided within 5 days and 111 (48.7%) episodes still had fever for more than 5 days. All of these episodes and the patients who died during treatment were classified as unfavorable outcome.

Potential factors for predicting outcome of febrile neutropenic patients were analyzed by univariate analysis. The factors shown in Table 3 were observed to be statistically significant. Multivariate analysis revealed only 4 independent factors that had a statistically significant association with poorer outcome in the patients as shown in Table 4. They were burden of illness, control of cancer, duration of neutropenia and dehydration.

Table 3. Univariate analysis of potential factors for predicting outcome in febrile neutropenic patients.

Factors	Outcome				P
	Unfavorable N = 159	%	Favorable N = 108	%	
Male	83	52.2	38	35.2	0.009
Mean age (SD), year	44.7 (16.7)		45.0 (19.2)		0.875
Underlying diseases					
Acute leukemia	95	59.7	41	38.0	< 0.001
Chronic leukemia	5	3.1	3	2.8	
Myeloma	5	3.1	1	0.9	
Lymphoma	26	16.4	21	19.4	
Other hematologic malignancies	0	0	1	0.9	
Breast cancer	10	6.3	8	7.4	
Lung cancer	4	2.5	5	4.6	
Sarcoma	1	0.6	17	15.7	
Other solid tumors	13	8.2	11	10.2	
Uncontrolled cancer	143	89.9	48	44.9	< 0.001
Number of courses of chemotherapy, median (interquatile range)	3 (5)		3 (3)		
Number of regimens of chemotherapy, median (interquatile range)	2 (1)		2 (1)		
Burden of illness					
No or mild	19	11.9	79	69.4	< 0.001
Moderate	85	53.5	31	28.7	
Severe	55	34.6	2	1.9	
ECOG performance status					
0	0	0	1	0.9	< 0.001
1	21	13.2	68	63	
2	52	32.7	29	26.9	
3	43	27.0	9	8.3	
4	43	27.0	1	0.9	
Use of growth factor	42	26.4	33	30.6	0.548
Use of antibiotic prophylaxis	6	3.8	0	0	0.084
Mean duration from first day of last course of chemotherapy (SD), days	11.5 (13.7)		7.6 (6.6)		0.017
Mean duration of neutropenia (SD), days	11 (6.3)		8.3 (4.6)		< 0.001
Onset of fever at presentation					
≤ 24 h	87	54.7	36	33.3	0.006
> 24-48 h	32	20.1	28	25.9	
> 48-72 h	19	11.9	23	21.3	
> 72 h	21	13.2	21	19.4	
Occurrence of fever in hospital	82	51.6	34	31.5	0.002
Temperature ≥ 39°C	83	52.2	48	44.4	0.263
Systolic blood pressure < 90 mmHg	17	10.7	1	0.9	0.004

Table 3. Univariate analysis of potential factors for predicting outcome in febrile neutropenic patients (Continue).

Factors	Outcome				P
	Unfavorable N = 159	%	Favorable N = 108	%	
Diastolic blood pressure<60 mmHg	21	13.2	1	0.9	0.001
Pulse rate ≥ 120/min	66	41.5	27	25	0.008
Respiratory rate > 20/min	58	36.5	21	19.4	0.004
Significant blood loss	58	36.5	9	8.3	< 0.002
Respiratory failure	10	6.3	0	0	0.007
Altered mental state	27	17.0	5	4.6	0.004
Mucositis	57	36.1	16	14.8	< 0.001
Superficial fungal infection	44	27.8	16	14.8	0.019
Diarrhea	46	28.9	12	11.1	0.001
Abdominal pain	28	17.6	7	6.5	0.014
Nausea/vomiting	29	18.2	13	12.0	0.232
Diarrhea	46	28.9	12	11.1	0.001
Central intravenous catheter insertion	8	5.0	1	0.9	0.088
Dehydration	66	41.5	7	6.5	0.001
Spinal cord compression	3	1.9	0	0	0.275
Underlying heart diseases	2	1.3	0	0	0.516
Underlying pulmonary diseases	1	0.6	3	2.8	0.307
Diabetes mellitus	10	6.3	6	5.6	1
Surgery within 6 weeks	7	4.4	5	4.6	1
Previous febrile neutropenia	73	47.7	25	23.6	< 0.001
Previous fugal infection	1	0.6	5	4.7	0.042
Antifungal treatment within 6 months	12	7.7	6	5.6	0.668
Antibiotic treatment within 7 days	36	22.6	13	12.0	0.042
Co-morbid diseases	7	4.4	3	2.8	0.774
Hemoglobin < 8 g/dl	79	49.7	42	38.9	0.107
Median leucocytes (interquartile range), /μl	600 (630)		750 (662.5)		0.037
Median absolute neutrophils (interquartile range), /μl	92 (227)		145 (272.5)		0.057
Median absolute monocytes (interquartile range), /μl	34 (71)		65.5 (109.5)		< 0.001
Median absolute polymorphonuclear leukocytes (interquatile range), /μl	202 (336)		289 (377.5)		0.005
Median platelets (interquatile range), /μl	32,000 (58,000)		68,500 (111,500)		< 0.001
Blood Urea Nitrogen ≥ 20 mg/dl	43	27.2	13	12.5	0.007
Creatinine ≥ 2 mg/dl	6	3.8	6	5.7	0.551
Sodium ≥ 150 mmol/L	1	0.6	0	0	1
Potassium < 3.5 mmol/L	68	43.3	38	36.9	0.368
Bicarbonate < 24 mmol/L	77	49.0	57	55.3	0.386
Alanine Transaminase ≥ 74 U/L	28	21.9	5	7.6	0.021
Aspartate Transaminase ≥ 80 U/L	30	23.4	10 1	5.2	0.244
Alkaline phosphatase ≥ 117 U/L	56	43.8	20	31.7	0.151
Bilirubin ≥ 2 mg/dl	29	22.8	4	6.5	0.010
Albumin < 2.5 mg/dl	25	18.0	6	8.7	0.118
Globulin ≥ 3.5 mg/dl	45	33.8	15	23.8	0.209
Abnormal chest radiograph	115	72.8	90	84.9	0.030
Classification of fever					
Fever of unknown origin	68	42.8	71	65.7	0.001
Clinically documented infection	26	16.4	14	13.0	
Microbiologically documented infection	65	40.9	23	21.3	
Antimicrobial susceptibility	56	90.4	21	95.5	0.632

The MASCC scoring system was used to validate this set of data and examine the trade-offs between sensitivity, specificity, positive and negative predictive values[16]. When using the threshold scores of 21 and 22, the sensitivity, specificity, positive predictive value and negative predictive value was 88.8 per cent and 78.5 per cent, 45.5 per cent and 75 per cent, 52.8 per cent and 68.3 per cent, and 85.5 per

Table 4. Factors associated with the outcomes from the multivariate analysis.

Factors	OR (95% CI)	P
Burden of illness : moderate	3.94 (1.78, 8.73)	0.001
Burden of illness : severe	18.59 (3.55, 97.49)	0.001
Controlled cancer	0.21 (0.09, 0.50)	< 0.001
Duration of neutropenia for 1 additional day	1.17 (1.08, 1.26)	< 0.001
No dehydration	0.17 (0.05, 0.55)	0.003

Table 5. The scoring system developed from local data.

Characteristic	Weight
Burden of illness : no or mild symptoms	8
Burden of illness : moderate symptoms	4
Controlled cancer	5
Expected time of neutropenia (day) : 0-3	8
Expected time of neutropenia (day) : 4-10	4
Expected time of neutropenia (day) : 11-15	2
No dehydration	5

cent and 83.6 per cent respectively. A scoring system was also developed from this data set in order to identify the low-risk subgroup. The factors that were statistically significant in the multivariate model were used to create the scoring system as shown in Table 5. Then the sensitivity, specificity, positive and negative predictive values of this scoring system were also examined as shown in Table 6.

The MASCC scoring system was compared to the scoring system developed from this data set as determined by the area under the Receiver Operating Characteristic (ROC) curves as shown in Fig. 1. The scoring system locally developed had an area under the curve of 0.908 (95% CI 0.870-0.945), whereas, that of the MASCC scoring system was 0.803 (95% CI 0.748-0.858).

DISCUSSION

Although previous studies have demonstrated a shift of pathogenic bacteria in febrile neutropenic patients from gram negative organisms to gram positive organisms, the data observed in the present study did not show that shift. Gram negative bacteria remained the core organisms and were isolated in 87.8 per cent of microbiologically documented infections in febrile neutropenic patients in Siriraj Hospital. Prior sets of data from Siriraj Hospital and the Royal Army Hospital, Thailand, also failed to demonstrate a shift from gram negative to gram positive bacteria[12,27]. The increased use of central intravenous catheters may be responsible for the increase in gram positive pathogens found in Western countries. Only 9 patients in the present study had a central intravenous catheter in place.

In 267 episodes of febrile neutropenia, 61 episodes had a positive blood culture (22.8%) and 50 episodes of these were classified as primary bacteremia. This observation did not differ from the previous study in the same hospital which reported bacteremia in 22 per cent[12]. Other studies have also reported bacteremia in febrile neutropenic patients ranging from 22 per cent to 32 per cent[5,7-12]. Among gram negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* were the most common causative organisms in both bacteremia and overall infections, followed by *Klebsiella pneumoniae*. Most organisms were susceptible to antimicrobials prescribed by the physicians. The most common antimicrobials prescribed for treating febrile neutropenic patients were ceftazidime and amikacin which were active to all isolates of gram negative bacteria. So, the extended-spectrum beta-lactamase (ESBL) producing organism was not the main problem. Only 7 episodes (11.4%) found gram positive bacteria in blood cultures. *Streptococcus* spp and methicillin-sensitive *Staphylocoous aureus* (MSSA) were the most common causes of gram positive bacteremia in 3 and 2 episodes respectively. Thus, the most appropriate antimicrobials for treating febrile neutropenia should cover mainly gram negative bacteria including *Pseudomonas aeruginosa*. Although there is controversy concerning the use of vancomycin for the initial treatment in febrile neutropenic patients, the data from the present study indicated that vancomycin is not necessary for initial

Table 6. Clinical prediction performance of the locally developed scoring system.

Score	Sensitivity	Specificity	PPV*	NPV**
12	91.6	64.3	65.8	91.1
13	82.2	81.8	77.2	86.0
14	81.3	83.9	79.1	85.7
15	76.6	89.5	84.5	83.7
16	76.6	90.2	85.4	83.8
17	60.7	95.8	91.5	76.5

* PPV = Positive Predictive Value
** NPV = Negative Predictive Value

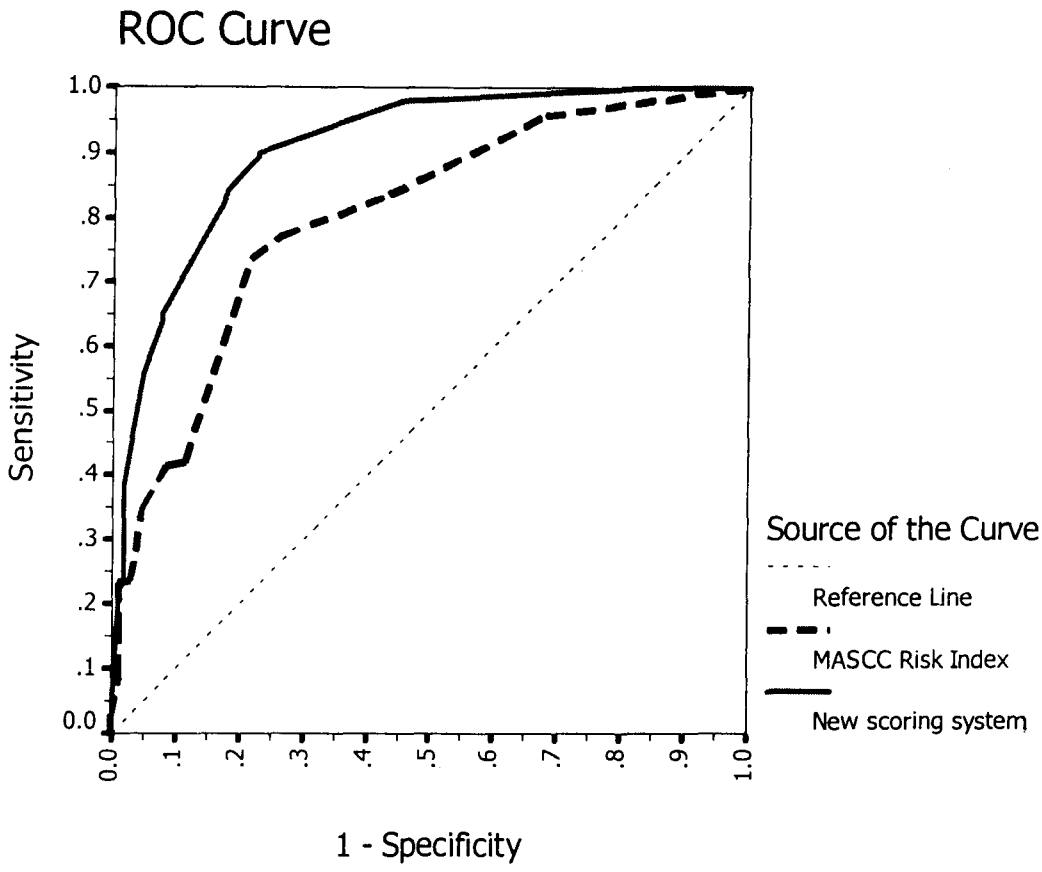

Fig. 1. Receiver Operating Characteristic (ROC) curves for the MASCC Scoring System and the locally developed scoring system using local data.

empirical treatment but it could be considered in some specific patients with an increased risk for acquiring methicillin-resistant *Staphylococcus aureus* (MRSA)[28].

Appropriate treatments may vary for febrile neutropenic patients who are at substantially different risk. There is general acceptance that febrile neutropenic patients comprise a heterogeneous popu-

lation. The identification of these low-risk patients has led to changes in treatment regimens, including changes in antimicrobial therapy, mode of antibiotic administration and treatment setting. Several clinical trials have demonstrated the safety and efficacy of oral antibiotics for low-risk patients[24-26]. Talcott et al demonstrated the factors defining the high-risk subgroup include in-patient status, or outpatient status with serious concurrent co-morbidity or patients with uncontrolled cancer[15]. By using the scoring system, Klastersky et al demonstrated that weighting of the potential risk factors led to more precise identification of a low-risk subgroup. With a threshold score of 21, the prediction had sensitivity of 71 per cent, specificity of 68 per cent, positive predictive value of 99 per cent and negative predictive value of 36 per cent for patients with favorable outcome or low-risk subgroups[16].

Despite many studies which have demonstrated the ability of the scoring system to differentiate low-risk subgroup patients and have led to the development of new guidelines[29], data from developing countries with different epidemiological and socioeconomic backgrounds is lacking. The MASCC scoring system was used to validate this data set and the authors found that for a threshold score of 21, the sensitivity, specificity, positive predictive value and negative predictive value was 88.8 per cent, 45.5 per cent, 52.8 per cent and 85.5 per cent respectively. When using a threshold score of 22, the specificity became higher (75%). Therefore, if the MASCC scoring system is to be used in Thai patients, the threshold score of 22 is more accurate in predicting the outcome.

A scoring system to identify the low-risk subgroup was developed using the data from Thai patients. It was found that a threshold score of 16 had a low misclassification rate with a sensitivity of 76.6 per cent, specificity of 90.2 per cent, positive predictive value of 85.5 per cent and negative predictive value of 83.8 per cent in predicting a favorable outcome. Looking at the ROC curve, the locally developed scoring system had an area under the curve greater than that of the MASCC scoring system and, is therefore, more accurate in predicting patient outcome.

Among the factors expected to be predictors for unfavorable outcome (underlying diseases, duration of neutropenia and co-morbidity), only the duration of neutropenia was included in the model. Underlying disease was shown to be statistically significant in the univariate analysis but was not in the multivariate model. This was due to the fact that patients with hematologic malignacies usually had a longer duration of neutropenia because of poor bone marrow recovery. Thus, duration of neutropenia was an independent risk factor for predicting patient outcome. Co-morbidity did not show a significant difference between the groups because of the small number of patients.

In conclusion, this retrospective study revealed that the epidemiology of causative organism in febrile neutropenic patients is different from Western countries. A locally developed scoring system with a threshold score of 16 can identify a low-risk subgroup accurately. However, the locally developed scoring system needs to be validated on another set of data collected during different periods and the data prospectively collected before it can be adopted for use in clinical practice.

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ดัชนีปัจจัยเสี่ยงต่อการเกิดภาวะแทรกซ้อนและการพยากรณ์โรคในผู้ป่วยไทยที่มีเม็ดเลือดขาวในเลือดต่ำและมีไข้

เมธี ชยะกุลคีรี, พบ, วิษณุ ธรรมลิขิตกุล, พบ**

บทนำ : แนวทางการรักษาผู้ป่วยที่มีเม็ดเลือดขาวในเลือดต่ำและมีไข้ได้เปลี่ยนแปลงไปในปัจจุบัน การศึกษาในต่างประเทศพบว่าระบาดวิทยาของเชื้อก่อโรคได้เปลี่ยนจากเชื้อแบคทีเรียกรัมลบเป็นเชื้อแบคทีเรียกรัมบวก และผู้ป่วยกลุ่มนี้มีลักษณะทางคลินิกแตกต่างกันมากและมีการพยากรณ์โรคที่หลากหลายจนมีการศึกษาปัจจัยที่ช่วยในการทำนายการพยากรณ์โรค แต่ยังไม่เคยมีการศึกษาถึงปัจจัยดังกล่าวในคนไทย

วัตถุประสงค์ : เพื่อศึกษาระบาดวิทยาของเชื้อก่อโรคและปัจจัยที่ช่วยทำนายการพยากรณ์โรคในผู้ป่วยไทยที่มีเม็ดเลือดขาวในเลือดต่ำและมีไข้

วิธีการศึกษา : เก็บข้อมูลที่เกี่ยวข้องจากเวชระเบียนผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชที่ได้รับการวินิจฉัยว่ามีภาวะเม็ดเลือดขาวในเลือดต่ำจากยาเคมีบำบัดและมีไข้ ระหว่างเดือนมกราคม พ.ศ. 2542 ถึงเดือน ธันวาคม พ.ศ. 2543

ผลการศึกษา : ผู้ป่วย 220 คนมีเม็ดเลือดขาวในเลือดต่ำและมีไข้จำนวน 267 ครั้ง โดยเป็นผู้ป่วยโรคมะเร็งเม็ดเลือดร้อยละ 71.8 และผู้ป่วยโรคมะเร็งอื่นร้อยละ 28.2, มีการติดเชื้อในกระแสโลหิตร้อยละ 22.8 โดยพบเป็นแบคทีเรียกรัมลบร้อยละ 88.6, อัตราตายรวมร้อยละ 17.7 และปัจจัยที่มีผลต่อการพยากรณ์โรคได้แก่ ความรุนแรงของการเจ็บป่วย, การตอบสนองของการรักษาด้วยเคมีบำบัด, ระยะเวลาของภาวะเม็ดเลือดขาวต่ำและภาวะขาดน้ำ ระบบคะแนนที่สร้างขึ้นโดยใช้เกณฑ์แบ่งที่ 16 คะแนนสามารถคาดคะเนผู้ป่วยที่มีการพยากรณ์โรคดีได้ โดยมีความจำเพาะร้อยละ 90.2, ความไวร้อยละ 76.6 และคุณค่าการพยากรณ์ (positive predictive value) ร้อยละ 85.4

สรุป : เชื้อก่อโรคส่วนมากในผู้ป่วยไทยที่มีเม็ดเลือดขาวในเลือดต่ำและมีไข้ ยังคงเป็นเชื้อกรัมลบ ปัจจัยพยากรณ์โรคโดยใช้ระบบคะแนน สามารถคาดคะเนการพยากรณ์โรคได้ดีและอาจนำไปสู่การพัฒนาแนวทางการรักษาที่ดีขึ้น

คำสำคัญ : อะแกรนูโลซัยโตสิส, เม็ดเลือดขาวในเลือดต่ำ, ไข้, พยากรณ์โรค

เมธี ชยะกุลคีรี, วิษณุ ธรรมลิขิตกุล
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* สาขาวิชาโรคติดเชื้อและอายุรศาสตร์เขตร้อน, ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700