PERFORMANCE OF MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE OF CANCER (MASCC) RISK INDEX SCORE FOR IDENTIFYING LOW RISK ADULT FEBRILE NEUTROPENIC CANCER PATIENTS

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CERTIFICATE

This is to certify that this dissertation on "PERFORMANCE OF MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE OF CANCER (MASCC) RISK INDEX SCORE FOR IDENTIFYING LOW RISK ADULT FEBRILE NEUTROPENIC CANCER PATIENTS" is a bonafide work done by **Dr. Suresh babu.M.C,** in the Department of Medical Oncology, College of Oncological sciences, Adyar, Chennai,, under my overall supervision and guidance, to my satisfaction.

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CONTENTS

Introduction

Febrile neutropenia (FN) represents one of the most common complications of chemotherapy in cancer patients[1]. Chemotherapy induced neutropenia remains a life threatening complication despite progress in our understanding and in the treatment of this event. Now days the accepted standard of care for such patients has been administration of empiric, broad spectrum antibiotics, and close monitoring for development of complications until fever resolution and neutropenia recovery. Though treatment of such patients can be done as in-patients in hospitals, not all febrile neutropenia patients require intensive treatment[2].

Many investigations have indicated 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. Over the past decade, several investigators have identified subsets of febrile neutropenic patients who are at low risk for the development of complications, including mortality. Several clinical studies involving neutropenic patients with predicted low risk have demonstrated the feasibility of newer approaches, such as outpatient therapy after early discharge from the hospital or outpatient therapy for the entire febrile episode, using parenteral, sequential (intravenous [IV] followed by oral), or oral antibiotic regimens[3].

Febrile Neutropenia can be defined   as a single oral temperature ≥ 38.3°C or 101°F or a temperature of ≥ 38°C or 100.4°F for at least 1 hour [5.] , With absolute neutrophil count (ANC) < 500 cells/mm^3 or an ANC < 1,000 cells/mm^3 with a predicted decline to < 500 cells/mm^3.

At least one-half of febrile neutropenic patients have a documented or occult infection. At least one-fifth of patients with neutrophil counts < 100 cells/mm3 have bacteremia. Fungi can be causes of secondary infection in neutropenic patients who have received broad-spectrum antibiotics and may also cause primary infections. The primary anatomic site of infection is the gastrointestinal tract, where mucosal damage from chemotherapy allows invasion of micro-organisms. Damage to the skin from invasive procedures, such as intravascular devices, similarly provides portals of entry for microbes.

The duration of neutropenia is also an important determinant of risk of infection. Patients with a low ANC and prolonged neutropenia (eg, > 10 days) are at further increased risk of infection [7].

Risk assessment is important in deciding whether febrile neutopenic patients can be treated as inpatients or outpatients and whether oral or intravenous antibiotics can be used. Historically, characteristics of low risk for serious medical complications include outpatient conventional chemotherapy for solid tumors, normal chest x-ray, hemodynamic stability, expected duration of neutropenia ≤ 7 days, normal kidney and liver function tests, early evidence of marrow recovery, malignancy in remission, and normal mental status.

Management of patients with febrile neutropenic fever is complex and involves careful consideration of multiple factors. At least one-half of neutropenic patients who become febrile have a documented or occult infection. The microbiology of infections has shifted, with more gram-positive infections, increased drug resistance, and previously less common organisms being seen more frequently. Risk assessment is needed to determine whether inpatient or outpatient treatment is indicated and whether intravenous or oral antibiotics can be used [7].

A thorough history is extremely important when evaluating patients for febrile neutropenia. The history should include the nature of the chemotherapy given, prior antibiotic prophylaxis, concomitant steroids or other immunosuppressive's, recent documented colonization or infection with susceptibilities, recent surgical procedures, and medication allergies.

In neutropenic patients, symptoms and signs of inflammation may be minimal or absent. The lack of inflammatory response can make detection of infection more difficult and requires close physical examination for more subtle signs and symptoms. There will likely be decreased erythema, induration, and purulence in response to bacterial infections (eg, a skin infection without typical features of cellulitis, a pulmonary infection without a clear infiltrate, meningitis that lacks cerebrospinal fluid pleocytosis, and urinary tract infections without pyuria). Careful evaluation of common sites of infections should include the mouth, pharynx, esophagus, lungs, perineum, eyes, skin, and vascular catheter access sites.

Laboratory studies include measurement of complete blood counts, serum creatinine levels, blood urea nitrogen, transaminase levels, and blood cultures. Blood cultures should be obtained from a peripheral vein and catheter if present. Depending on the clinical situation, other cultures can be obtained. Skin biopsies can also be obtained if indicated. If respiratory signs or symptoms are present, a chest x-ray can be performed[6].

There is a growing interest in designing risk-adapted strategies for the management of FN. The administration of parenteral, broad-spectrum empirical antibiotic therapy after the hospitalisation of patients with FN is the accepted standard of care.

This approach is effective (with an infection-related mortality rate of less than 10%) but is expensive and, when applied to all patients with FN, may represent a suboptimal use of resources. Over the past decade, the development of risk stratification models has allowed for the identification of low-risk patients with additional treatment strategies, such as initial hospitalisation followed by early discharge with parenteral or oral antibiotics (sequential therapy) and out-patient treatment with oral antimicrobials.

The most attractive option is out-patient treatment for the entire febrile episode, because of several advantages, including important repercussions on economic costs and quality of life as well as significant reduction in nosocomial super infections. Careful selection of patients at a low risk of developing complications, appropriate empirical regimens and the daily monitoring of patients

(for response and toxicity) are critical for the success of this approach. Expected duration of neutropenia (less than 10 days and under 60 years of age) and favourable social and economic environment, with access to prompt medical attention, are relevant prerequisites for considering this approach [11].

Epidemiology of infection is influenced not only by the severity and duration of neutropenia, but also by the intensity of chemotherapy, the use of prophylaxis and/or empirical antibiotic therapy, the use of central venous catheters, environmental factors and duration of the hospital stay, among others.

The detection of epidemiological shifts requires frequent monitoring and surveillance, particularly at centres treating large numbers of patients, as institutional differences can be substantial. For example, in recent years, some hospitals have experienced an increase of infections caused by multidrug-resistant gram-negative bacilli, such as *Acinetobacter* species or *Stenotrophomonas maltophilia*, and gram-positive cocci with increasing resistance to glycopeptides.Many reports have demonstrated the emergence gram-positive organisms in patients with neutropenia.

The practice of antimicrobial prophylaxis has been questioned repeatedly. Although oral prophylaxis against bacterial and fungal infections may decrease the risk of development of infections after bone marrow transplantation or chemotherapy, these practices also promote the emergence of drug-resistant strains (particularly fluoroquinolone-resistant *Escherichia coli* and fluconazole-resistant non-albicans *Candida* species). The use of fluoroquinolones for prophylaxis in high-risk patients with neutropenia has been also associated with the emergence of resistance among

Pseudomonas aeruginosa isolates (more than 20% at some institutions). The 2002 guidelines from the Infectious Diseases Society of America (IDSA) did not recommend the routine fluoroquinolone prophylaxis during neutropenia. However, this may be considered for high-risk patients in critical periods of time [11].

Several predictive models have indeed been developed to identify patients at low risk of complications. Two classification systems are notable, Talcott classification of risk groups and a scoring system proposed by the Multinational Association for Supportive Care in Cancer (MASCC) group. Both systems use serious medical complications as the endpoint for risk prediction. However, the sensitivity of the Talcott classification is limited (approximately 30%), and the misclassification rate is high. For example, many patients who do not have complications are not identified by the prediction rule. Also, when the classification system was used on patients discharged for home intravenous antibiotics after 2 days of inpatient observation, the complication rate was higher than anticipated, The so-called Multinational Association for Supportive Care in Cancer (MASCC) scoring system has been internationally validated under various clinical conditions and has been widely accepted. The use of the MASCC score also allows the selection of low-risk patients who can be safely treated with orally administered antibiotics and be, for at least some of them, successfully discharged early after a 24-h in-hospital observation[1,3].

Febrile neutropenic cancer patients will have different risk of developing a serious infection related complications. Although, there are no universally accepted criteria to recognise these patients, currently the most used model of prediction of

complications is the multinational association of supportive care (MASCC) index score[2].

This study was designed to validate MASCC index score in an attempt to accurately predict, on presentation with febrile neutropenia, which cancer patients are at low or high risk of developing serious medical complications during the episode.

Aims And Objectives

The primary objective of this study was to validate the performance of the Multinational Association for Supportive Care in Cancer (MASCC) risk index, in predicting the outcome of febrile neutropenia in adult cancer patients in the local health care setting of Cancer institute ,chennai.

The secondary objectives included the evaluation of the clinical outcome, infective aetiology and prognostic factors of febrile neutropenia in the local population.

Review of Literature

The Multinational Association for Supportive Care in Cancer (MASCC) Risk Index can be used to identify low-risk patients (score ≥21 points) for serious complications of febrile neutropenia (including death, intensive care unit admission, confusion, cardiac complications, respiratory failure, renal failure, hypotension, bleeding, and other serious medical complications). The score was developed to select patients for therapeutic strategies that could potentially be more convenient or cost-effective.

A prospective trial demonstrated that a modified MASCC score can identify patients with febrile neutropenia at low risk of complications as well. Here is review of literature of some studies who used different scores and tried to identify various prognostic markers in febrile neutropenia

M.Bykara et al, study was determine the clinical significance of lymphopenia and monocytopenia in terms of its duration and depth in patients with febrile neutropenia and MASCC scores parameters. Sixty-six patients with febrile neutropenia were prospectively analysed. Recurrent febrile neutropenia episodes were excluded in this trial. Twenty-four patients had solid tumours, 42 patients had lymphoma-leukaemia. Patients with MASCC-scores ≥ 21 evaluated as low-risk and the ones with their scores <21 were high-risk. Concluded the depth of monocytopenia and durations of lymphopenia and monocytopenia were the important parameter influencing antibiotic modification in febrile neutropenia.

Jean Klastersky, Marianne Paesmans, Edward B. Rubenstein et al did a study to develop an internationally validated scoring system to identify these patients. (756 patients), predictive factors were a burden of illness indicating absence of symptoms or mild symptoms (weight, 5; odds ratio [OR], 8.21; 95% confidence interval [CI], 4.15 to 16.38) or moderate symptoms (weight, 3; OR, 3.70; 95% CI,2.18 to 6.29); absence of hypotension (weight, 5; OR, 7.62; 95% CI, 2.91 to 19.89); absence of chronic obstructive pulmonary disease (weight, 4; OR, 5.35; 95%CI, 1.86 to 15.46); presence of solid tumor or absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07; 95% CI, 1.97 to 12.95); outpatient status (weight, 3; OR, 3.51; 95% CI,2.02 to 6.04); absence of dehydration (weight, 3; OR,3.81; 95% CI, 1.89 to 7.73); and age less than 60 years (weight, 2; OR, 2.45; 95% CI, 1.51 to 4.01). On the validation set, a Multinational Association for Supportive Care in Cancer risk-index score > 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%.The risk index accurately identifies patients at low risk for complications and may be used to select patients for testing therapeutic strategies that may be more convenient or cost-effective[3].

Almarie Uys et al, prospectively validated the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score in an attempt to accurately predict on presentation with febrile neutropenia those cancer patients who are at low or high-risk for development of serious medical complications during the episode. Of the 80 febrile neutropenic episodes, 58 were classified as low risk and 22 as high-risk patients. They correctly predicted 98.3% of low-risk patients and 86.3% of high-risk patients. This study had a positive predictive value of 98.3%and a negative

predictive value of 86.4% with both a sensitivity and specificity of 95%, concluded that MASCC risk index score correctly identifies low and high-risk patients at presentation with febrile neutropenia[4]

Marianne Paesmans et al did study to investigate the possible interaction between the MASCC score and bacteremic status and to assess whether, assuming that bacteremic status could be predicted at onset of febrile neutropenia, adding bacteremia as a covariate in a risk model would improve the accuracy of low-risk patients identification. Two consecutive multicentric observational studies were carried out from 1994 till 2005 involving 2,142 febrile neutropenic patients. The study data bases were retrospectively used for the present analysis a clinical prediction rule integrating the MASCC score and the bacteremic status was not helpful in improving the identification of low-risk patients[1.]

Edwin Pun Hui & Linda K. S. Leung et al validated the Multinational Association for Supportive Care in Cancer (MASCC) risk index, and compared it with the Talcott model and artificial neural network (ANN) in predicting the outcome of febrile neutropenia in a Chinese population. Total 227 patients were enrolled. Serious medical complications occurred in 22% of patients and 4% died. The positive predictive value of low risk prediction was 86% (95% CI=81–90%) for MASCC score≥21, 84% (79–89%) for Talcott model, and 85% (78–93%) for the best ANN model. The sensitivity, specificity, negative predictive value, and misclassification rate were 81%, 60%, 52%, and 24%, respectively, for MASCC score≥21; and 50%, 72%, 33%, and 44%, respectively, for Talcott model; and 84%, 60%, 58%, and 22%, respectively, for ANN model. In the low risk group identified by

MASCC score≥21 (70% of all patients)12.5% developed complications and 1.9% died, compared with 43.3%, and 9.0%, respectively, in the high risk group(p<0.0001).Concluded that MASCC risk index validated in a Chinese population demonstrated a better over all performance than the Talcott model and was equivalent to ANN model[5].

G.H. Lyman, J. Crawford et al designed a Risk Model for First-Cycle Febrile Neutropenia in Cancer Patients Receiving Systemic Chemotherapy in their study , Of 296 patients experiencing febrile neutropenia, 171 (58%) did so during cycle 1; use of prophylactic growth factors was reported in just 8.7% of patients. In their study according to excellent test performance characteristics, the risk model identified patients at increased risk for febrile neutropenia occurring during cycle 1 of chemotherapy for possible targeted prophylaxis with filgrastim or pegfilgrastim. Currently, this model in phase II of this ongoing registry study is being validated. Catherine Cordonnier, Raoul Herbrecht et al [8]studied the risk of Gram negative bacterial infections in febrile neutropenic patients and to develop a specific risk score. This prospective study included 513 consecutive febrile neutropenic, evaluable patients. Forty-five per cent of the patients were receiving prophylactic gut decontamination, and 6% were receiving prophylactic quinolones at the onset of febrile neutropenia. Data were collected from the onset of febrile neutropenia until 30 days later. Risk factors for Gram-negative bacterial infection were identified by comparing baseline characteristics of patients with and without Gram-negative bacterial infection. Independent risk factors in multivariate analysis were used to build a predictive score for Gram-negative bacterial. They concluded that their scoring system identifies patients with a high probability of Gram-negative bacterial

infection as those with a score 3. If confirmed in a validation set, this score could be considered in the choice of the first-line antibiotics in febrile neutropenic patients.

Rebecca B. Donohue and Glen Carbo et al[9] did retrospective study to Develop a neutropenia risk-assessment tool appropriate for the management of neutropenia and its complications in a small oncology practice. Study design was that ten relevant studies published in medical and nursing journals were identified using the Evidence-Based Utilization Framework to search the literature. Pertinent patient variables were extracted from the literature search and included a chemotherapy regimen with a ≥ 40% risk of development of febrile neutropenia, advanced age (≥ 70 years), and treated with combination chemotherapy, bone-marrow involvement and/or compromise, open wounds, prior occurrence of febrile neutropenia, a serum albumin level ≤ 3.5 g/dL, and a first-cycle absolute neutrophil count (ANC) ≤ 500/μL. Patients with one or more risk factors were considered to be at high risk for the development of neutropenia and were given growth-factor support with a colony-stimulating factor (CSF), as well as education about neutropenia and its complications, following a predetermined algorithm.

The neutropenia risk-assessment tool was developed based on these risk factors and neutropenia management guidelines published by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). Using the identified variables, a single-page risk-assessment tool was developed. They concluded that Use of this risk-assessment tool can help nursing staff and practitioners determine which patients are at high risk for chemotherapy-induced neutropenia. Proactive growth factor support in patients at high risk for

chemotherapy-induced neutropenia may be beneficial in decreasing life-threatening infections and hospitalizations and in helping deliver effective chemotherapy on time and at a planned dose.

Some studies have done for to know whether prophylaxis with antibiotics will reduce the risk of mortality in febrile neutropenia, like in study from M. Paul & A. Gafter-Gvili & A. Fraser[55] did meta analysis to evaluate whether antibiotic prophylaxis in neutropenic patients reduces mortality and incidence of infection and to assess related adverse events. Evaluated Ninety-five trials performed between 1973 and 2004 met inclusion criteria. Fifty-two trials addressed quinolone prophylaxis. Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment (relative risk, 0.67 [95% CI, 0.55 to 0.81]). All prophylactic antibiotics were associated with an increased risk for adverse events (relative risk, 1.69 [CI, 1.14 to 2.50]). Fluoroquinolone prophylaxis reduced the risk for all-cause mortality (relative risk, 0.52 [CI, 0.35 to 0.77]), as well as infection-related mortality, fever, clinically documented infections, and microbiologically documented infections. Fluoroquinolone prophylaxis increased the risk for harboring bacilli resistant to the specific drug after treatment and adverse events, but these results were not statistically significant (relative risks, 1.69 [CI, 0.73 to 3.92]) and 1.30 [CI, 0.61 to 2.76], respectively). Concluded that antibiotic prophylaxis for neutropenic patients undergoing cytotoxic therapy reduces mortality. Mortality was substantially reduced when analysis was limited to fluoroquinolones. Antibiotic prophylaxis, preferably with a fluoroquinolone, should be considered for neutropenic patients.

Whether early lymphopenia after cytotoxic therapy predicts development of complications was also seen in some of the studies.

Chul Won Choi, Hwa Jung Sung et al [12] in their prospective study, they intended to validate the feasibility of the day-5 lymphocyte count as a predictive factor for febrile neutropenia (FN) and define the characteristics of febrile neutropenia for their patients. In the results, they also confirmed that early lymphopenia was an independent risk factor for FN, and they also defined the incidence of FN (18%). Interpretations were proposed for these results.

An early lymphopenia could be a marker of the sensitivity of a patient to the hematologic toxicity of chemotherapeutic agents because chemotherapy induces lymphopenia before it induces neutropenia. Another possible interpretation was that lymphocytes may play a role in the restoration of normal hematopoiesis after cytotoxic chemotherapy. The decrease of lymphocyte counts result in a reduced production of cytokines, so this could interfere with the restoration of normal neutrophil counts. Early lymphocyte recovery was also associated with survival advantages in patients with multiple myeloma and non-Hodgkin's disease who have undergone autologous hematopoietic stem cell transplantation. Therefore, they proposed that early immune reconstitution may have a protective effect against residual disease progression.

Corticosteroid treatment is a well-recognized cause of lymphopenia ; however, all patients received dexamethasone or prednisone as part of

chemotherapy or as prevention of emesis or hypersensitivity. Therefore, it is unlikely that corticosteroid treatment has a major role in the correlation between lymphopenia and FN in their study.

JY Blay, F Chauvin, A Le Cesne[42] showed that Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia in their study Univariate and multivariate analyses of risk factors for FN were performed on a retrospective cohort of 112 consecutive patients treated with various chemotherapy regimens. Two independent risk factors were identified by the logistic regression and used to create a risk model for FN. The validity of the model was tested in three distinct groups of patients: two prospective groups of patients treated in two institutions (Centre Leon Berard [CLB] and Institut G. Roussy [IGR]) and the group of patients with intermediate- or high-grade non- Hodgkin's lymphoma (NHL) treated with the doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) regimen between 1988 and 1992 at their centre. Results were, Within the retrospective group, 23 of 47 (49%) patients with lymphocyte counts < or = 700/microL at day 5 after chemotherapy experienced FN compared with seven of 65 (11%) of other patients (P = .00002). The type of chemotherapy (high dose v others) was also significantly correlated to FN (48% v 11%, P = .0003). Age, performance status, the number of previous chemotherapy cycles, or polymorphonuclear leukocyte (PMN) counts, were not significantly correlated to the incidence of FN in univariate analyses. Two independent risk factors were identified in the logistic regression: day 5 lymphocyte counts (beta = 1.97 +/- 0.53) and the type of chemotherapy regimen (beta = 1.91 +/- 0.53). The calculated probability to experience FN in patients with none, one, and both of these risk factors was 4.3%,

24.0%, and 68.8%, respectively. The validity of this model was tested in the three groups of patients used as validation samples. The observed incidences of FN in the above defined risk subgroups were 3%, 19%, and 67%, respectively, within the CLB prospective series and 6%, 19%, and 75% within the IGR prospective series. In the ACVBP group, the incidence of FN was 33% and 72%, respectively, in patients from the intermediate- and high-risk groups. In the two prospective groups and in the ACVBP series, the observed numbers of FN in the different risk groups did not differ significantly from those calculated by the model (P = .89, P = .86, and P = .72 for these three groups, respectively. The conclusions in their study were Day 5 lymphocyte counts < or = 700/microL and the type of chemotherapy regimen enable oncologists to define subgroups of patients treated with chemotherapy as those with a high intermediate, and low risk of FN. These criteria could be used to select subjects in whom prophylactic measures for FN, in particular hematopoietic growth factors, should be proposed.

Malik A, Abbas Z, Karim M [44] did study of Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients and in their study they compared ofloxacin as an oral single agent with standard parenteral combination antibiotics for the management of neutropenic febrile patients in a prospective, randomised trial. Patients with severe neutropenia (absolute neutrophil count ≤0·5 × 109/l), fever above 38°C, and ability to take drugs by mouth were eligible for the study. After initial investigations, 60 patients were randomly assigned to oral ofloxacin 400 mg twice daily and 62 to parenteral combination antibiotic therapy (amikacin 15 mg/kg daily, plus, at various times in the trial, carbenicillin, cloxacillin, or piperacillin).

Patients were examined 72 h and 7 days after the start of treatment and when neutropenia resolved. 24 (40%) ofloxacin-treated and 26 (42%) combination-treated patients had pyrexia of unknown origin (PUO). In both treatment groups, the treatment success rate was higher for such patients than for those with clinically or microbiologically documented infections (92% vs 67% [p<0·05] for ofloxacin; 85% vs 64% for combination). There were no significant differences in success rates of ofloxacin and combination treatment for these subgroups or overall (77% *vs* 73%).

Patients with neutropenia for less than 1 week had better responses to both treatments than patients with longer-lasting neutropenia. There were 4 (7%) deaths in the ofloxacin group and 6 (10%) in the combination group. Both regimens were well tolerated. They conclude that oral single-agent ofloxacin is as effective as parenteral combination antibiotic therapy in neutropenic febrile patients, especially those expected to have short durations of neutropenia

M. Moreau1, J. Klastersky et al [13] did study and, in this study considered all haematological tumours and found a 35.4% of incidence of FN per chemotherapy cycle. The median neutrophil count at nadir (median 12th day) was 56/µl (range 0–8750). In the model, eight factors and an interaction were selected for inclusion: chemotherapy score, underlying disease, baseline monocyte count <150/µl, body surface ≤ 2 m^2, use of prophylactic antimicrobial agents, use of prophylactic CSF,bone marrow involvement, stem-cell transplantation and the interaction between the first cycle of a treatment line and the baseline hemoglobinemia.

Although chemotherapy is the most important determinant of the risk of neutropenia, they found that no study except the one published by their group attempted to develop a general scoring system to compare the aggressiveness of the different chemotherapy regimens. Up to now, the aggressiveness of chemotherapy has been studied either in terms of delivered dose intensity or of presence or not of a particularly aggressive drug in the regimen or as a simple comparison of different regimens, making difficult the comparisons between different studies. In their study, they used the same methodology as Lalami to score chemotherapy regimens according to their myelotoxicity with the objective to develop an easy and practical score, assessable before the start of the treatment.

Although the actual dose was not considered for other agents, they indirectly included it in the scoring system by taking the average toxicity score of the drugs included in the regimen. Although this agent's classification is not the result of a consensus, this methodology has the merit to be a widely applicable method of classification because it is not specific to particular chemotherapy regimens. In their study, the chemotherapy's score is one of the most important factors in the development of FN. Moreover, that score explained >30% of the variance of FN and was the highest among the nine factors of the model. The second most important factor in the model was the underlying disease; patients with AML or CML tumor have a risk to develop FN and almost nine times higher, respectively, than the myeloma. They did not find any other study reporting this finding, probably because most of them exclude tumors which could by themselves induce neutropenia, such as AML. The role of monocytopenia (measured on days 6–8) in the development of CIN has been already reported ; interestingly, their model showed that even a

baseline monocyte count <150/ll is an independent predictor of FN. An early anemia and in general an early drop of all hematopoietic cell counts after the chemotherapy has been reported in other studies as potential independent predictors of FN. They found the baseline haemoglobin level to be also predictor of FN as an interaction with number of cycle. Hemoglobinemia has probably no direct influence on FN, but might be reflecting only bone marrow depletion. As it is described in other studies, the first cycle of a new treatment is strongly associated with FN in our model. In their study, the variable was included as an interaction with haemoglobin levels in a general model that was already valid during the first cycle with an adjustment taking into account this characteristic Although older age is usually associated with a higher risk of FN in the literature , they found an opposite relation in their study in univariate analysis. Some other studies found the same relation in haematological and solid tumours. In their sample, this difference between younger and older age can only be explained by the higher proportion of stem-cell transplantation among younger patients. Anyway, age was not selected by the forward procedure in the final model. As found generally in the literature, body surface and bone marrow involvement are associated with FN and were selected in the final model. Although the administration of prophylactic antimicrobial agents is expected to reduce the occurrence of FN, they found an opposite result. It can be easily explained by the fact that the patients are not given these drugs randomly, but only when the risk of neutropenia is higher or on the basis of the medical indication. As some studies found that baseline and early lymphopenia (on day 5) might be associated with FN. They did not find an association between a low baseline lymphocyte count and FN, neither in univariate nor in multivariate analysis. In the development of this prediction rule, they did not include prophylactic antimicrobial agents administration and prophylactic CSF

administration, considering them as simple adjustment variables. They conclude that a score of15 (first cycles) and 10 (further cycles) gives the best results in term of sensitivity, specificity and predictive value and could be used as cut-offs to administer CSF, which would increase a little its use (absolute increase of 2% expected AML).

S Kelly and D Wheatle et al [14] said that there is good evidence to suggest that dose intensity is important when considering the effectiveness of adjuvant chemotherapy in patients with breast cancer. However, the development of chemotherapy-induced febrile neutropenia can lead to reduction in dose intensity and other treatment modifications, which may negatively affect patient outcomes. Febrile neutropenia can be prevented by the use of primary prophylactic treatment, notably with granulocyte colony-stimulating factors. This practice is supported by international guidelines, all of which recommend that primary prophylaxis with granulocyte colony-stimulating factors should be used with chemotherapy where the risk of febrile neutropenia is 20% or greater.

Essentially, two approaches are available for selecting a population of patients at low-risk. The first one is to rely on a set of predictive factors published in the literature or chosen on the basis of clinical expertise without analyzing the interaction between them but rather combining them empirically. The advantage of this approach is that the definition of low-risk may be changed very easily depending on the context of use and on the occurrence of new studies' results. The disadvantage is that it is very difficult to assess the performance of the definition in terms of sensitivity, specificity and positive and negative predictive values. The

following factors are often considered to delineate low-risk: absence of hemodynamic instability, absence of hypotension, no altered mental status, no respiratory failure, no renal failure, no abnormal hepatic tests, good clinical condition, an expected short duration of neutropenia, no acute leukaemia, no bone marrow or peripheral blood stem cell transplant, absence of chills, no abnormal chest X-ray, no cellulitis or signs of focal infection, no catheter-related infection, no need for intravenous supportive therapy [16].

This was the most frequently adopted methodology for the clinical trials which tested oral antibiotic regimens as an alternative for patients considered at low-risk. The second, more recent approach is to try to develop validated models integrating several factors in a well-defined way and considering their independent value or their interactions. Models have first to be developed and then tested on a separate patients population in order to be certain that they are well calibrated (predicted outcomes have to match observed outcomes) and reliably transportable in other settings (to other institutions for instance); alternatively, cross-validation techniques may be used. Their discrimination ability also has to be regularly monitored. Advantages are that such an assessment of low-risk is standardized and more objective and that the classification has known properties. The method is also more parsimonious with the use of independent only predictive factors. The predicted outcome is also more carefully defined. However, the development process is long; the need for validation should not be underestimated and the context of use has to be considered before introducing thin clinical practice.

As of now, for populations of adult patients, two popular scoring systems have been developed and validated: the Talcott model and the MASCC score. Both use the same endpoint: the occurrence of serious medical complications (and not the response to empiric treatment). The choice of this endpoint was stressed as a progress in the discussion of risk assessment, although the definition of a serious medical complication may appear somehow arbitrary. Indeed, the need to change empiric treatment does not necessarily mean that the clinical course of the patient will not be benign and is felt as less adequate in estimating the risk associated to groups of patients[16].

Materials And Methods

STUDY DESIGN

This single centre prospective and observational study was performed at department of medical oncology of cancer institute, Chennai .Total of 100 consecutive febrile neutropenia episodes studied from August 2010 to March 2011.Patient data was collected in separately designed proforma for the study.

PATIENT SELECTION

All consecutive febrile episodes occurring in patients meeting the following eligibility criteria were included: histologic diagnosis of malignancy, neutropenic febrile secondary to chemotherapy and/or radiotherapy, fever and age more than 18 years.

Neutropenia was defined as absolute neutrophil count (ANC) less than 500/µl, including polymorphonuclear leukocytes and band forms or ANC less than 1000/ µl expected to fall below 500/µl , within 24 hours. Fever was axillary temperature ≥38° C documented by the patient or the medical /nursing staff.

TREATMENT AND RISK ASSESSMENT

All patients underwent a detailed history taking and complete physical examination and were assessed by MASCC score in first 24 hours of study admission.

MASCC RISK SCORE

CHARACTERISTIC	RISK SCORE
Burden of illness	
No or Mild symptoms	03
Moderate symptoms	05
No Hypotension	05
No chronic obstructive pulmonary disease	04
Solid tumour or no previous fungal infection in hematologic tumour	04
Outpatient status	03
No dehydration	03
Aged <60 years	02

Patients with a score ≥21 were considered to be at low risk and less than that were considered to be at high risk.

All included patients were followed daily until discharge from hospital and those individuals that left the hospital kept as day care and received oral antibiotics were also followed.

Antibiotics were maintained until the ANC recovered to over 500/µl, and the patient had remained afebrile for 48 hours. Patient's clinical examination presence of mucositis, dehydration and any system involvement were documented.

DEFINING SERIOUS MEDICAL COMPLICATIONS

Serious medical complications were considered if the patient developed at least one of the following pre defined categories:

1. Antibiotic treatment change secondary to recurrence or persistent fever (unexplained fever higher than 38° C for ≥5 days, or fever higher than 39°C persisting after 72 hours of antibiotic therapy), development of a new clinical localisation of infection, clinical deterioration, serious adverse effects related to antibiotics, or bacterial sensitivity profile.

2. Clinical deterioration secondary to febrile neutropenic episode predefined as fallowing: presence of arterial hypotension (systolic blood pressure <90 mm Hg or need for medicine support to maintain blood pressure); respiratory failure (respiratory rate 24 breaths /min, arterial oxygen pressure less than 60 mm Hg while breathing room air ,or need for supplemental oxygen); confusion or altered mental status leading to diagnostic work up; renal failure (requiring investigation and/or treatment with parenteral fluids, dialysis ,or any other intervention; severe gastrointestinal disorder ;or sepsis.

3. Hospital readmission relate to neutropenic episode.

4. Dehydration requiring prolonged parenteral fluids replacement (>3 days).

5. Haemorrhage resulting in blood transfusion.

6. Platelet count <20,000/µl.

7. ECG changes and arrhythmias requiring urgent therapy.

8. Persistence of positive blood cultures or breakthrough bacteremia.

9. Intensive care unit admissions.

10. Death.

11. Other abnormalities judged serious and clinically significant by the investigator.

STATISTICAL ANALYSIS.

Descriptive statistics were used to express patient characteristics as frequencies. For calculation of sensitivity and specificity, a 2X2 table was used. The positive predictive value (PPV) was calculated for low risk patients predicted to have an uncomplicated recovery, and the negative predictive value (NPV) were calculated for high-risk patients who were predicted to indeed develop serious medical complications. Chi square test was used to identify significance individual parameters.

Observation
And Results

The total number of febrile neutropenia episodes studied was 100. Fallowing were the results observed.

Table 1 :   Distribution of cases according to sex.

SEX DISTRIBUTION (100 PATIENTS)	
MALE	46
FEMALE	54

Figure 1:   Distribution of cases according to sex.

SEX DISTRIBUTION
46
54
MALE
FEMALE
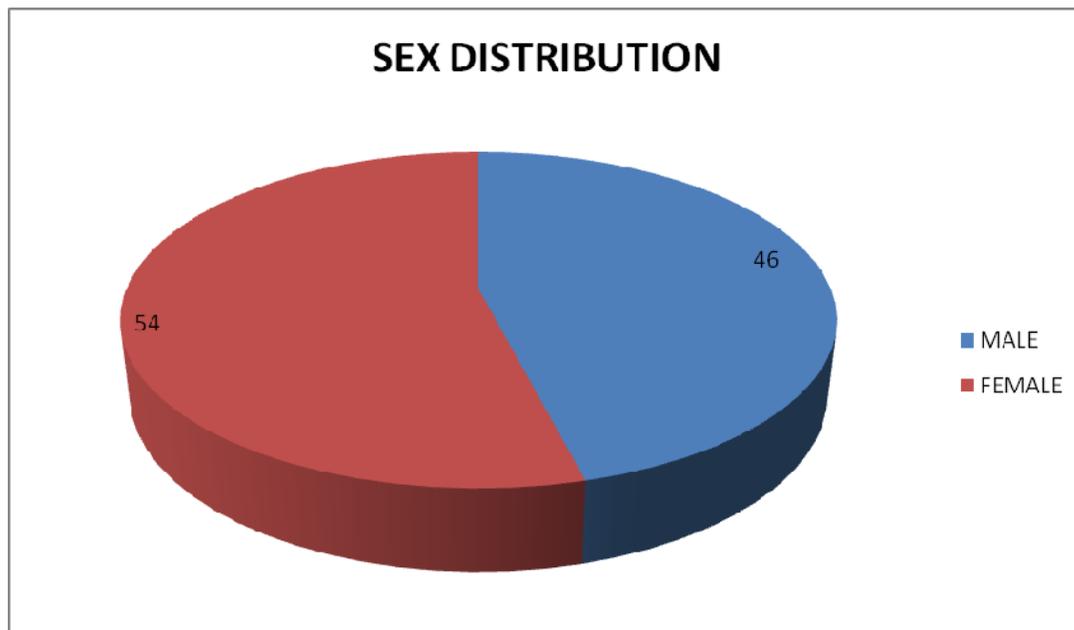
Table 2:   Age of the patients

AGE OF PATIENTS (MEDIAN AGE 39.5 YEARS)	
≤ 50 YEARS	75
> 50 YEARS	25

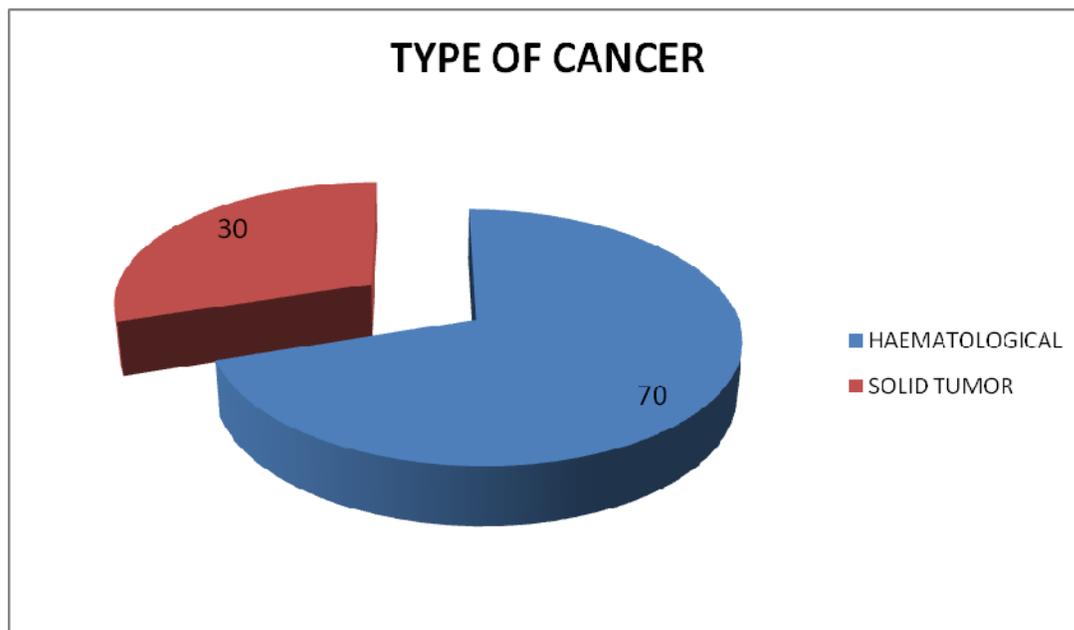**Figure 2:   Distribution of patients according to type of cancer.**

Table 3:   Total count and number of patients.

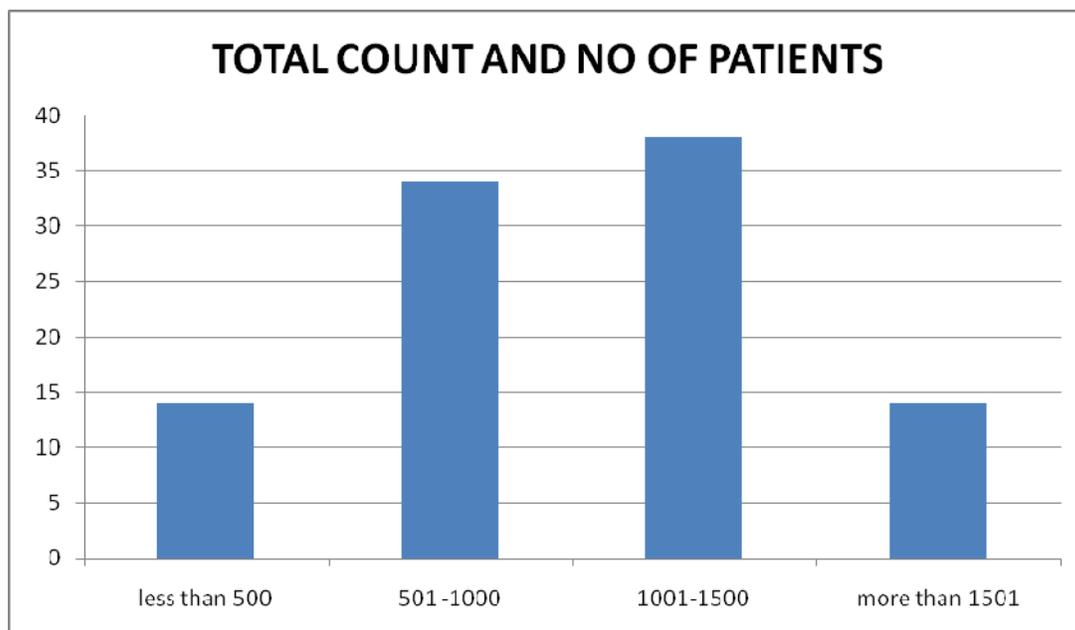| TOTAL COUNT	NO OF PATIENTS
≤ 500	14
501 – 1000	34
1001- 1500	38
MORE THAN 1501	14

Figure 4:   Total count and number of patients.

Table 4 :   Distribution of patients according to absolute neutrophil count (ANC).

ABSOLUTE NEUTROPHIL COUNT	NO OF PATIENTS
≤ 100	13
101 - 500	83
501 AND ABOVE	04

Figure 4 :   Distribution of patients according to absolute neutrophil count (ANC).
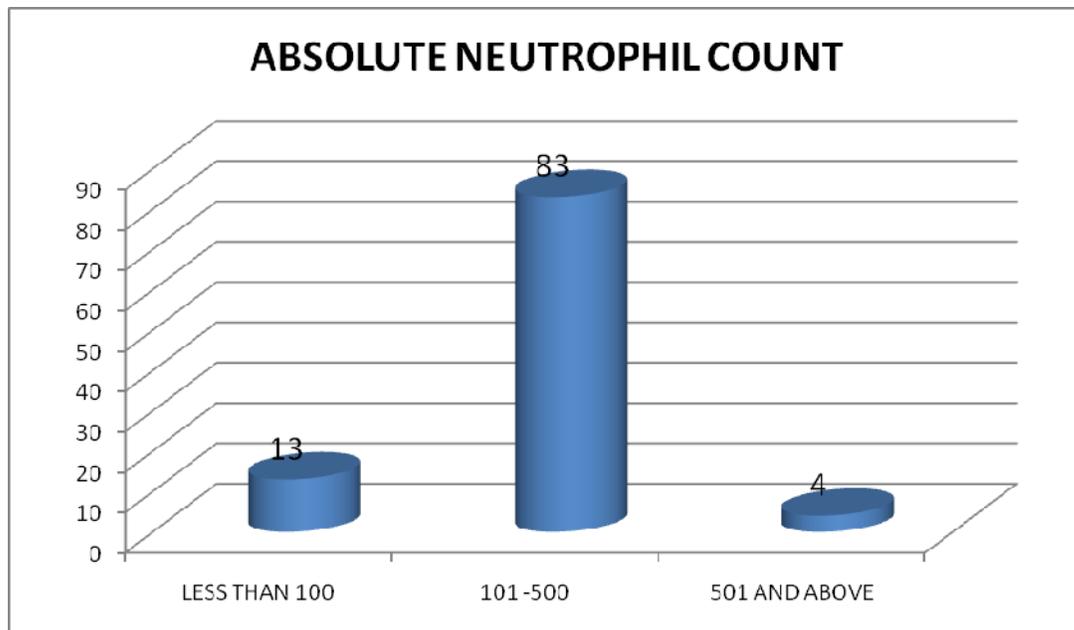
Table 5:   System involved during episode of febrile neutropenia (clinical).

SYSTEM INVOLVED (CLINICALLY)	NO OF PATIENTS
RESPIRATORY SYSTEM	44
GASTROINTESTINAL TRACT	15
ORAL CAVITY	01
URINARY TRACT	01
MULTI SYSTEM	05
NO IDENTIFIABLE FOCUS	34

Figure 5:   System involved during episode of febrile neutropenia (clinical).
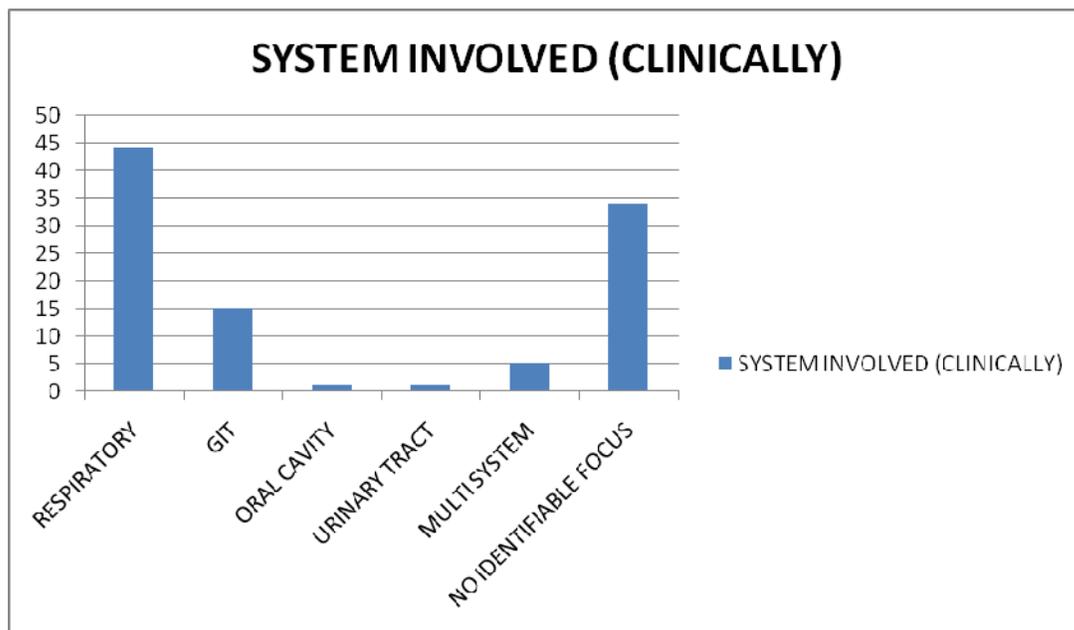
Table 6:   Number of patients with major complications.

MAJOR COMLICATIONS	NO OF PATIENTS
YES	32
NO	68

Figure 6:   No of patients with major complications.
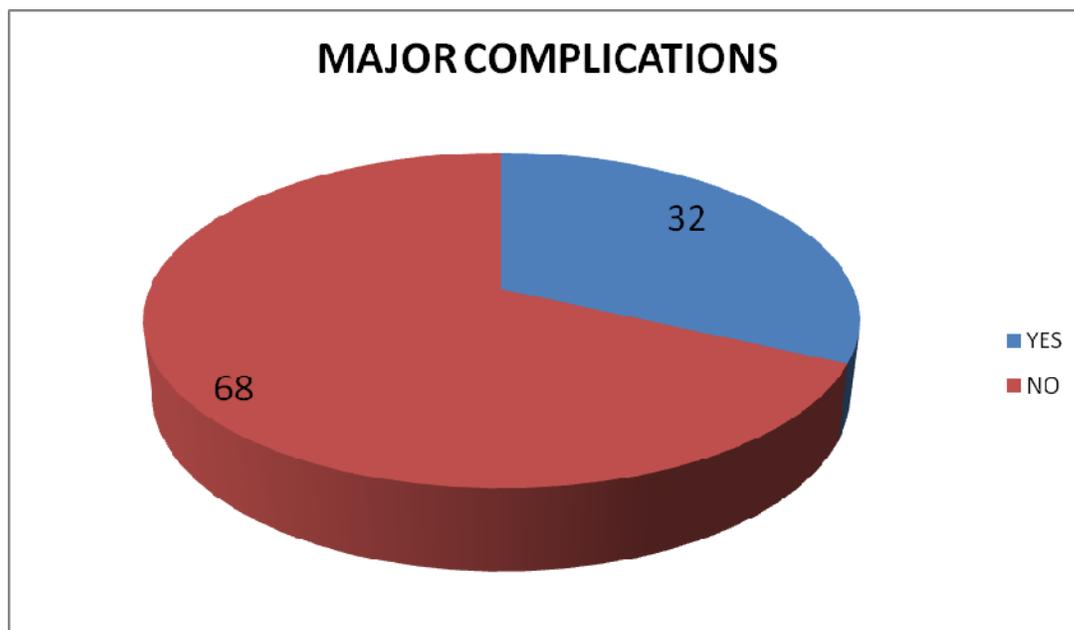
Among one hundred episodes thirty two were associated with major complications and sixty eight were not associated with any major complications. Total of thirty five episodes were categorised as low risk, of those only one patient developed major complication and sixty five were categorised as high risk and thirty one of them developed major complication.

Table 7 :   Number of patients who received G-CSF.

G- CSF GIVEN	NO OF PATIENTS
YES	77
NO	23

Table 8:   Sensitivity and Specificity of MASCC Risk Score.

MASCC RISK SCORE	NO OF PATIENTS	NO OF PATIENTS WHO HAD MAJOR COMPLICATION	SENSITIVITY	SPECIFICITY
≥ 21	35	01	50%	96%
< 21	65	31		

MASCC risk score had sensitivity of 50% and specificity of 96%. It also showed positive predictive value (PPV) and negative predictive value (NPV) of 97.7% and 47.7% respectively.

Table 9:   ANC and Major Complications

Absolute neutrophil count(ANC)	Total no of patients	No of patients who had major complications	Percentage of patients who had major complications	P value
< 100	13	10	76.9%	
101 - 500	83	21	25.3%	0.001
> 500	04	01	33.0%	

Patients who had low ANC were prone for more major complications than patients who had better ANC count. This was statistically significant (0.001).

Table 10 : Performance status (PS) and Major Complications

PS	Total no of patients	No of patients who had major complications	Percentage of patients who had major complications	P value
1	15	01	6.7%	
2	70	18	25.7%	0.0001
3	14	12	85.7%	
4	01	01	100%	

Patients who had poor PS at presentation were more prone to develop major complications subsequently, which was statistically significant (0.0001).

Table 11: Major Complications and No of patients.

MAJOR COMPLICATION	NO OF PATIENTS (32)
Bleeding severe enough to require blood transfusion	07
Platelet count less than 20000	05
Hypotension and sepsis	06
Patients requiring ICU admission	05
Respiratory failure and Hypotension	02
ECG changes and arrhythmias requiring urgent therapy	02
Platelet count less than 20000 and Patients requiring ICU admission	05

Total 32 among 100 episodes were associated with major complication, Bleeding severe enough to require transfusion was the Commonest Complication seen (07 patients), followed by hypotension and sepsis (06 patients). Platelet count less than 20,000, ICU admission was seen in 5 patients each. 5 patients had both platelet less than 20,000 and ICU admission. There were no any deaths.

Table 12: Culture Positivity and System involved.

System involved	Total no culture Positivity	Organisms isolated
Respiratory system (Sputum)	07	4 – Klebsiella 1 – Candida 1 – Candida & S.Aureus 1- Klebsiella & S.Aureus
Blood	02	1 – Klebsiella 1- S.Aureus
Urinary tract (Urine)	02	1- MDR Enterococcus 1- S.Aureus

There were 10 patients who had culture positivity as shown in Table 12 . Klebsiella was the commonest organism isolated from culture.

Discussion

In our study which had total of one hundred episodes of febrile neutropenia .Thirty was solid malignancy cases and seventy haematological. Total of thirty two patients had major complications. MASCC risk score had sensitivity of 50%, specificity of 96%, Positive predictive value and Negative predictive value were 97.7% and 47.7% respectively. Low Absolute neutrophil count and Poor Performance status were significant risk factors in our study. Respiratory system was the common system involved clinically in our study. Eleven patients had culture positivity, seven from respiratory system, two each from blood and urinary tract. Klebsiella was the commonest organism which was isolated.

The development of validated risk assessment tools will facilitate the identification of a group of low risk patients with febrile neutropenia at the onset of fever and the selection of newer therapeutic approaches including oral and/or outpatient therapeutic strategies for the "low risk" group.

Various studies using MASCC risk score index have reported various sensitivity, specificity, positive predictive value and negative predictive value.[2, 17, 18]

In study done at our centre as mentioned earlier we had one hundred episodes of febrile neutropenia which had 54 female and 46 male patients. 70% of were haematological malignancies and 30% were of solid malignancies. Total of 77 patients received growth factors.

Among hundred patients in our study, 32 patients developed major complications. Thirty five patients had MASCC risk score of 21 or more and classified as low risk among which only one patient had major complication (1/35). Total of sixty five patients had MASCC risk score of less than 21 and thirty one of them had major complications (31/65).

Jean Klastersky et[3] al validated this score in756 patients, Multinational Association for Supportive Care in Cancer risk-index score > 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%.Concluded that the risk index accurately identifies patients at low risk for complications and may be used to select patients for testing therapeutic strategies that may be more convenient or cost-effective[3].

Edwin Pun Hui & Linda K. S. Leung et al[5] studied 227consecutive patients. They compared MASCC risk score with Talcott model. Serious medical complications occurred in 22% of patients and 4% died. The positive predictive value of low risk prediction was 86% (95% CI=81–90%) for MASCC score≥21, sensitivity, specificity, negative predictive value were 81%,60% and 52%, respectively, for MASCC score≥21. They concluded that the MASCC risk index is prospectively validated in a Chinese population. It demonstrates a better overall performance than the Talcott model

In study reported from Inner H et al[18], where they studied total of 100 febrile neutropenia episodes occurring in 83 patients which included malignancies of solid tumours and lymphomas. They had around 90% of them being in low risk, of which 75 were treated with oral antibiotics. They had a positive predictive value of 96.7%% for MASCC index for identifying low risk patients.

They concluded that the MASCC risk index is both feasible and safe when used in standard clinical practice to guide the management of febrile neutropenia in patients with solid tumours and lymphomas. They also felt that patients predicted to have low risk can be managed safely with oral antibiotics and early hospital discharge.

Our study showed sensitivity of 50% and specificity of 96%, positive predictive value and negative predictive value of 97.7% and 47.7% respectively. There by among the patients who had low risk based on MASCC risk score only one patient had major complication (1/35). However the study had low negative predictive value as among sixty five patients who were categorised as high risk, only thirty one of them developed major complication.

B.L. repoport et al[19] from south Africa published their results in ASCO 2003, they collected data from 80 febrile neutropenic episodes prospectively (19 males and 61 females). Fifty six patients had solid tumours and twenty four haematological malignancies. Among which 22 patients were classified as high risk and only 10

developed complications. 58 patients who were categorised as low risk and 1 patient developed major complication. This study had 95% of positive predictive value in identifying low risk patient. Like in our study it had low negative predictive value as among 22 classified as high risk only 10 developed major complications.

Below is the table which compares different studies with our study. As we can see that almost al studies had high Positive Predictive Value (PPV) in identifying low risk patients.

	Sensitivity	Specificity	PPV	NPV
Our Study	50%	96%	97.7%	47.7%
Edwin et al[5]	81%	60%	86%	52%
Repport et al[19]			95%	
Inner H et al[18]			96.7%	
J Klastersky et al[3]	71%	68%	91%	

However some studies have failed to show impact of MASCC risk score in stratifying low risk patients.

J. Bajpai et al[20], in their study had total of 178 febrile neutropenia episodes (22 in solid tumors and 16 in hemato lymphoid malignancies).They concluded that the association between MASCC score and risk stratification could not be established.

Various studies have reported different rate and organisation in their culture positivity at their respective centre. In our study we had total of 11 (11) culture positivity among 100 episodes. Majority were sputum (7) culture sensitivity. Klebsiella was the commonest organism isolated.

In study from J. Bajpai et al had 59 episodes of culture positivity out of 178 episodes and E coli as the commonest organism that was isolated.

De Souza vienna et al in their study of 60 episodes of febrile neutropenia had 14 patients (26%), who had micro biologically documented infection, and gram negative pathogen was the main etiologic agent. Respiratory tract was the most common source as in our study.

In their study oral cavity and oropharynx was most common site of clinically documented infection. In our study Respiratory system was most common site of clinically documented infection (Table no. 5)

Different factors and parameters along with MASCC risk score were also associated with development of major complications.

In study from Escalante et al observed that patients with mucositis >grade 2 were associated with more possibility of developing major complications.

Though study from J Bajpai et al failed to show any impact of MASCC risk score, they found that mucositis, maximum temperature > 103 F, age high dose steroid were associated with major complications.

In our study the poor performance status and low absolute neutrophil count (ANC) were associated with major complications (p value of 0.0001 and 0.001 respectively), patients who had poor PS and low ANC were more likely to have more chance of developing major complications. There by patients with ANC less than 100 and PS 3 or 4 may need treatment as in patients.

Our study showed high positive predictive value for low risk patients. Patients with MASCC risk score of >21 are unlikely to develop major complications and they can be managed as day care patients.

Conclusion

- MASCC risk score had high specificity, positive predictive value and low sensitivity, negative predictive value for identification of low risk patients in our study.

- 11% of patients had microbiologically documented injection and Klebsiella was the commonest organism which was isolated

- Respiratory system was most common system involved clinically

- Poor performance status and low absolute neutrophil count were associated with major complications which was statistically significant

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PROFORMA

NAME - _____AGE - _____yrs ,_____SEX - M/F

OP NO-_____PS- _____

0	1	2	3	4

TYPE OF CANCR – SOLID/HEMATO_____ANTIBIOTIC PROPHYLAXIS – YES/NO

PREVIOUS FEBRILE NEUTROPENIA – YES/NO   TEMP -

DEHYDRATION – YES/NO   ORAL MUCOSITIES – YES / N

_____Grade

0	1	2	3	4

Total Count -

Less than 500	500 to 1000	1001 to 1500	1501 to 2000	2001 and more

ANC Count -

Less than 100	101 to 500	501 to 1000

MASCC Index score

Characteristic		
Burden of illness *No or mild symptoms *Moderate symptoms	5 3	
No hypotension	5	
No chronic obstructive Pulmonary disease	4	
Solid tumor or no previous fungal infection	4	
Outpatient status No dehydration	3 3	
Aged <60 years	2	
TOTAL		

Clinically documented infection   Yes/No

Respiratory tract	
Gastrointestinal tract	
Oral cavity and oropharynx	
CNS	
Sepsis	
Fever of unknown origin	

Microbiologically documented infection -   Yes/No

Bacterial	
Fungal	
Viral	
Others	

Bactremia without identifiable focus	
Catheter Related	
Urinary tract	
Respiratory tract	
Gastrointestinal tract	
Soft tissue infection	
Any other source	

Antibiotics given – Yes/No , If yes -   Oral/ IV

Name and Duration	Days -
Growth factor	Yes /No Days -

Major complications – Yes/No ,If yes then which of fallowing

Fever Duration	
Hypotension , Respiratory failure renal failure, severe GIT disorders or sepsis.	
Intensive care unit admission	
Dehydration requiring prolonged Parenteral fluids (3 days)	
Confusion or altered mental state.	
Persistence of positive blood culture or breakthrough bacteremia.	
Bleeding severe enough to require transfusion	
ECG changes and arrhythmias requiring urgent therapy.	
Platelet count less than 20000.	
Death	
Other complications	