Predicting Chemotherapy-Induced Febrile Neutropenia Outcomes in Adult Cancer Patients: An Evidence-Based Prognostic Model

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Abstract

Aims: This thesis explored and examined the clinical factors associated with the outcomes of chemotherapy-induced febrile neutropenia for adult cancer patients and confirms the independent predictive value of these factors. Established as predictors, the factors were used to formulate a multivariable prognostic model to stratify patients according to their risk groupings (high- or low-risk) for adverse outcomes for febrile neutropenia. Newly developed models underwent preliminary validation for their performance as prognostic models for febrile neutropenia outcomes.

Background: Accuracy in risk stratification for cancer patients presenting with chemotherapy-induced febrile neutropenia is of critical importance. Serious morbidity may result when treatment is tailored according to misclassified levels of risk. New predictors and prediction tools used for risk stratification have been reported in the recent years. A systematic review was conducted on this topic as part of the thesis and the findings showed a lack of conclusive information on predictive values for some factors identified as predictors, and limitations in prognostic research studies' methodologies which affect the internal and external validity of the risk prediction tools.

Methods: Clinical factors identified through the systematic review contributed to the candidate factors investigated. Additional factors were also included based on other primary studies not included in the systematic review. A retrospective review of patients' medical records was conducted. Tests of association using

univariate analysis were conducted on these variables. Significant variables were tested and adjusted for confounders in a multivariate logistic regression analysis to formulate a multivariable tool for risk stratification of patients presenting with febrile neutropenia.

Results: Predictive values for some variables were re-established while some variables failed to demonstrate their predictive values in a univariate analysis. After statistically adjusting to the current factors used in existing prognostic models, a new risk prediction tool was developed predict the risk of adverse outcomes. This tool has been subjected to preliminary validation that confirmed its potential utility. Limitations of the study included single-centre data and the small sample size.

Conclusions: Application of a risk prediction tool has its benefits and limitations. However, enhancement of the methodological rigor and comprehensiveness of reporting of results in prognosis research needs to be emphasised for clarity in interpretation and implementation of the studies' findings. Despite the promising initial validation of the tool developed in this thesis, further extensive validation and evaluation of the tool's performance are needed to show the true impact of the tool on clinical practice.

List of abbreviations

ANC   -Absolute neutrophil count

APC   - Absolute phagocyte count

BW   - Backward Wald

CBC   - Complete blood cell

CCF   - Congestive cardiac failure

CDI   - Clinically documented infection

CIN   - Chemotherapy-induced neutropenia

COPD   - Chronic obstructive pulmonary disease

CSF   - (Granulocyte) colony stimulating factor

EBHC   - Evidence-based healthcare

EBM   - Evidence-based medicine

ECOG   - Eastern Cooperative Oncology Group

FN   - Febrile neutropenia

IDSA   - Infectious Diseases Society of America

IHD   - Ischaemic heart disease

IPD   - Individual patient data

JBI   - Joanna Briggs Institute

LB   - Literature-based (selected predictors)

MAStARI   - Meta Analysis of Statistics, Assessment and Review Instrument

MDI   - Microbiologically documented infection

MoAbs   - Monoclonal antibodies

OR   - Odds ratio

PUO   - Pyrexia of unknown origin

ROC   - Receiver operating characteristic

WBC   - White blood cell

Declaration

I certify that this thesis contains is a record of original work and contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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1 Introduction to the thesis

1.1 Clinical context

Neutropenia as a consequence of systemic cancer treatment is the most common and potentially serious haematological complication of chemotherapy cancer patients.[1] Neutropenia of this aetiology is commonly known as chemotherapy-induced-neutropenia (CIN).[2] Between 20% to more than 70% cancer patients undergoing chemotherapy experience some degree of neutropenia depending on the chemotherapy regimen, doses and cycles administered.[3] For each episode of CIN, cancer patients are highly susceptible to different types of infection that could lead to life-threatening medical complications. The risk of infection ranges between 10% to 50% for patients with solid tumours and more than 80% for haematological malignancies.[2, 4]

The first sign of suspected infection in patients with CIN is the presence of fever. This clinical syndrome is often identified as chemotherapy-induced febrile neutropenia or in short, febrile neutropenia (FN). Febrile neutropenia is defined as a single oral temperature measurement of $\geq$38.3°C or a single temperature of $\geq$38.0°C sustained over a period of an hour in patients with an absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours.[5] In the presence of FN, this condition is often classified as a medical emergency requiring immediate medical consult.[6]

The suppressed immune response against infection in these patients makes them vulnerable to sudden acute deterioration in medical condition if not treated promptly.[7] Hence, the medical management necessitates immediate clinical evaluation, prompt diagnostic tests to be performed followed by initiation of empirical antimicrobial therapy without delay.[8] Conventional practice also requires patients to be admitted to the hospital for observation of medical complications.[6]

1.2 Clinical impact of chemotherapy-induced febrile neutropenia

Patients who develop CIN and fever experience substantial risk of infection-related mortality and morbidity.[5] Although mortality from FN has improved steadily over the years, it remains significant.[9] General mortality rates ranging from 3% to 24% have been reported for FN,[10, 11] whereas in-patient case fatality ranges from 6.8% to 10.6%.[12-14] Besides being at risk of life-threatening infection, patients also experience physical symptoms with fatigue as the most common symptom reported during neutropenia.[15] At the same time, some of the other side-effects of chemotherapy such as mouth sores and generalised pain are also experienced by these patients .[16] In addition, social, cognitive and emotional functioning of patients are also affected when precautions to minimise the risk of infection are enforced.

A unique type of psychological stress triggered by protective isolation has been documented.[17] Frequent clinic visits for blood tests and medical reviews can disrupt patients' routines and activities.[18] As a consequence, patients' quality of

life is affected.[19, 20] The impact of CIN and fever goes beyond physical and psychological effects. Despite advances in preventive measures, FN continues to be a major cause of inferior clinical outcomes for cancer patients and extensive utilisation of healthcare resources.[13]

Neutropenia and its complications can compromise optimal cancer treatment that leads to inferior clinical outcomes for patients. Adjustment for subsequent cycles of cancer treatment is often necessary when patients develop severe neutropenia (ANC <500/mm³) or FN.[2] Modifications can be made by either dose reduction or treatment interruption by delaying subsequent treatment.[21] Altering chemotherapy treatment regimen is known to compromise disease control and overall survival, especially for treatment with curative intent.[21] It has been well documented that dose reduction or unplanned interruptions of treatment cycles have a serious effect on local tumor control, tumor cell re-growth and development of resistant tumor cells.[22]

Poorer outcomes such as incomplete disease response and reduced survival have been reported in patients with lymphoma, breast, lung and ovarian cancer when their treatment was adjusted.[23, 24] Apart from the negative consequences related to dose attenuation, FN remains a unique challenge because of its significant risk of developing medical complications and associated morbidities such as invasive pulmonary aspergillosis,[13] thromboembolism[25] and organ dysfunction.[2, 13]

1.3 Economic implications of chemotherapy-induced febrile neutropenia

The economic burden of FN has been reported in a few published reports.[13, 14, 26-30] Findings of these studies confirmed that FN episodes are resource intensive. The main drivers of FN-related costs include the recurrent episodes of hospitalisation, increased utilisation of high-cost antimicrobial therapies, additional blood tests and diagnostic procedures.[14]

A gradual increase in the cost of hospitalisation and care of patients with FN has been observed in several published studies over the last decade.[12, 13]

Conducted almost a decade ago, two large studies of FN cancer patients in the United States of America (USA) showed a mean hospitalisation cost of $13,372 (Year1999 US dollars)[12] and $19,110 (Year 2000 US dollars)[13]. A more recent published report indicated that the costs associated with FN in the USA amounted to US$9, 628 ±12,517 per patient-month(mean±SD).[30] In summary the financial burden of FN for patients, healthcare providers and policymakers is significant and it remains a constant clinical issue in every healthcare organisation providing cancer care.

1.4 Evolving practice in the management of febrile neutropenia

A long series of efforts have led to a changed approach to the syndrome of FN. While strategies for prevention of CIN and its complications remain clinical priorities, a major development in the management of patients with FN has been established.[31] The requirement for patients presenting with FN to be

hospitalised for observation and intravenous antibiotics has been revolutionised.[32] It is currently recognised that out-patient or home-based therapy for a sub-group of patients with FN is feasible, safe and effective.[33-35]

This practice arose from the clinical observation that patients differ in their risk of adverse outcomes for FN episodes.[10, 36] They may present with similar characteristics, but differ in response to treatment and clinical outcomes associated with a FN episode.[4, 31] The similar characteristics include fever and low ANC post chemotherapy; but the prognosis for each episode of FN varies among individual patients depending on the duration of neutropenia, type of infection and existing medical conditions.[13, 37, 38]

Based on previous studies, as many as two thirds of FN patients remained stable and recovered from FN without requiring escalation to more intensive therapy.[10, 36] These patients are known as the low-risk group with favourable outcomes of FN. Approximately 85% to 98% of these patients experience resolution of FN without medical complications or mortality.[39, 40] Because of their lower probability of developing serious medical complications, it has been proposed that they could be candidates for a new concept in care delivery for FN, that being an ambulatory care model.[41, 42] Patients are prescribed anti-microbial therapy and they are either discharged on the same day or admitted as in-patients with plans for early discharge from hospital.[42-44]

The remaining FN patients (being the high-risk group) have an increased risk of clinical deterioration and mortality.[36] Although the percentage of FN patients

categorised as high-risk is small (15% to 27%), 70% to 90% of these patients are at risk of developing serious medical complication requiring further intervention.[39, 40] In the presence of bacteraemia, their prognosis is worse with a mortality rate of 28% as compared with 2% for patients in the low-risk group.[31] Causes of mortality were mainly infection and septicaemia.[11, 31] Because of the high-risk profile, an increased intensity for medical surveillance and therapeutic approach may be indicated.[11] Early detection and escalation of therapy in addition to continuous improvement in the risk assessment may possibly modify the outcomes of these patients.[31]

Approaching the management of FN based on risk stratification and tailoring therapy according to risk of complications as compared with conventional in-patient therapy has been investigated for its potential benefits.[45] The approach to streamline the management of FN patients has been endorsed in international recommendations and this is based on the increasing evidence demonstrating its advantages and positive outcomes.[34, 35, 46-48]

From the perspective of patients and family, this model of care shortens the length of hospital stay and minimises the risk of nosocomial infection.[49] Streamlining or de-escalation of initial empirical coverage of antimicrobial therapy reduces the risk of toxicity of prolonged or intensive antimicrobial therapy that may lead to multi-drug resistance micro-organisms while in the hospital.[50] The advantages of ambulatory care also include potential cost savings and improved utilisation of healthcare resource as evident from recent cost-analysis studies.[34, 41, 44] Cost savings as large as one-third of current

treatment costs exist for each episode of FN being treated in the out-patient setting as compared with hospitalised care.[51]

1.5 Prognostic factors and prognostic models

A prognostic factor, also known as prognostic marker, prognostic variable or predictor,[52] is described as a variable that identifies patients with different risks and predicts the outcomes of a clinical condition or disease regardless of therapy.[53] Used either individually or in combination, candidate factors are derived from clinical features or patient characteristics such as age, gender, stage of disease, or size of tumour, comorbidity and other more complex variables such as genetic biomarkers and other laboratory tests.[52]

When multiple prognostic factors or predictors are used in combination they formulate prognostic models,[54] also known as risk prediction models, risk index scores, and clinical prediction rules. One of the many benefits of a prognostic model is its utility in the process of clinical decision-making.[54] They are used to assess and calculate risks of an individual experiencing a specific outcome of interest and group these patients according to different levels of risk.[54] In the context of patients with FN, the change in practice for the management of FN patients has sparked increased interest to explore and establish factors which could be useful in assessing risk and predicting the outcomes of individual patients for each FN episode and tailor treatment accordingly.[55-61]

1.6 Prognostic factors and models for risk stratification of febrile neutropenia patients

The outcomes of FN are generally dependent on many factors. They include patient's characteristics,[62] type of cancer and the treatment administered,[3] type of micro-organisms in the presence of bacteraemia[37] and many others[38]. Patient-related factors that have been identified and associated with FN patients at risk of adverse outcomes include; advanced age, poor performance status, presence of comorbidities[10] and abnormal clinical signs such as hypotension and tachycardia[10, 59]. In addition, variables such as cytokine concentrations have been gaining the interest of many clinicians for risk assessment strategies for FN patients.[63]

Two of the more established models for risk stratification of FN patients which were statistically derived and have been validated are the Talcott model[64] and Multinational Association Supportive Care for Cancer (MASCC) risk scoring system[10]. The Talcott model categorised FN patients into four risk groups based on the assessment of a pre-set clinical criteria at the onset of fever. These criteria include disease status, concurrent co-morbidities and location of patient.[64]

A subsequent model, which is the MASCC risk–index score was developed using seven independent predictors with assigned individual integer weights. A risk score of more than 21 (based on the sum of assigned integer weights to the respective predictors) categorised patients to the low-risk group.[10] Both models have undergone the validation process which reported different levels of

accuracy for the performance of the respective risk models. The Talcott model had a sensitivity of 30%[36] as compared with the MASCC risk-index score of 71%[10]. In contrast, the Talcott model reported a higher specificity than the MASCC model (90% versus 68%).[10, 36] Such discrepancy has been one of the challenges faced by clinicians who have attempted to adopt the practice of risk stratification for FN patients.

Of primary concern is the possibility of patients receiving sub-optimal care during the episodes of FN due to incorrect risk classification. There have been incidences of low-risk FN categorised cases that failed out-patient care and required hospital admission for persistence fever and deterioration of clinical condition.[65-67] Although these events are uncommon and often salvageable, there are reports indicating increased mortality or requirement for transfer to intensive care units for ventilator and haemodynamic support.[47, 65, 68] Because of the clinical safety issue and the perceived lack of comprehensive medical surveillance for out-patients as compared with hospitalised patients, ambulatory care or home-based therapy was less adopted into mainstream of clinical practice.[66]

1.7 Current state of prognostic factors and models for risk stratification of febrile neutropenia patients

Following the pioneering work of Talcott and colleagues,[36] there has been an emergence of prognostic factors and a proliferation of prognostic models in relation to FN outcomes.[11, 69-71] In spite of the increasing number of studies, there does not appear to be an increase in the overall quality of evidence for some

of the prognostic factors or resolution of issues related to the specificity of prognostic models.[72] This may be attributed to the following reasons. Firstly, the predictive value of some of the identified prognostic factors remains controversial[10, 73] which results in uncertainty among clinicians as to which factors are more relevant and perform better as prognostic factors.

Secondly, the identified predictors were mostly based on single studies that have limitations to the reliability of their predictions due to inadequately reported methodologies, small sample sizes and the confounding factors associated with descriptive study designs.[74, 75] Lastly, the validity of prognostic factors used in current models may no longer be relevant as they may already have been replaced by newer and more advanced approaches to supportive care such as new prophylactic anti-fungal therapies,[76] improvements for the detection of bacteraemia using multiplex blood PCR,[77] and new biomarkers for predicting bacteraemia, sepsis and septic shock[78-81]. These developments are not always reflected in the updates of existing predictive models.

Other challenges faced by model users revolve around the performance (prediction accuracy) of current prognostic models for FN outcomes. Some of the performance related limitations include inadequate validation; misclassification in the low-risk group that could compromise patient safety[68, 82]and limited discriminatory ability when used among subgroups of cancer patients[11, 67] The crux of the issue remains in the accuracy of risk assessment and classification of neutropenic cancer patients at presentation of fever.

1.8 Optimal prognostic model for risk stratification of febrile neutropenia patients

There is a growing need to identify up-to-date predictors with strong predictive values for the development of more robust tools that can be implemented as part of care. Such an instrument would also take into consideration the complexity of patients' illness, the practice environment of the clinical areas and scarcity of resources as well as an increased emphasis on patients' preferences in clinical decision making. In addition to accuracy, characteristics for clinical applicability of the model such as practicality, reproducibility and time efficiency must be taken into consideration when developing a new model.[83]

1.9 Significance of the research

With the increasing numbers of studies which identify new prognostic factors for risk stratification of patients with FN; this thesis firstly reports on current knowledge for factors which are predictive of levels of risk for adult FN patients through a systematic review. The significance of the review is that it offers new insights on the predictive value of current prognostic factors and potential new factors. This is followed by the development of a prognostic model based on advances in knowledge from secondary evidence and a primary research study. It comprises of three major phases: a systematic review, model development using retrospectively collected data and preliminary validation of the model.

1.10 Structure of the thesis

In addition to the chapters for introduction and background, the major phases of this thesis are presented in three chapters (chapter 3, 4 and 5). Within each chapter, significant points in relation to the specific work of model development are highlighted.

Chapter 1: Introduction to the context of the thesis.

Chapter 2: Background which describes the current evidence for prognostic factors and models for adult patients with FN.

Chapter 3: A systematic review of published literature which provides a wider evidence-based assessment of the best available evidence for prognostic factors to risk stratify adult cancer patients at the onset of febrile neutropenia associated with myelosuppressive chemotherapy. Methodology and results of the review are presented.

Chapter 4: The conduct of a primary cohort study to test the validity of the current prognostic factors (based on the findings of the systematic review) and to establish new prognostic factors in a clinical cohort.

Chapter 5: Development and preliminary validation of a prognostic model for risk stratification of adult cancer patients presenting with FN.

Chapter 6: This section provides a summary of the entire study and the implications of the research on clinical practice. Recommendations for further research in the area of prognostic research either for factors or model development and strategies for translating research evidence into practice are discussed. A final conclusion of the thesis is provided.

2   Background

2.1   Introduction to the chapter

The chapter provides a more in-depth discussion on neutropenia, a major adverse effect and serious clinical issue faced by many patients undergoing myelosuppressive cancer chemotherapy. The chapter is divided into sub-sections beginning with an overview of neutropenia, followed by challenges in the management of chemotherapy-induced febrile neutropenia. Finally, risk assessment and stratification of neutropenic patients presenting with fever will be explored in greater depth in the remaining portion of this chapter.

2.2   Neutrophils and the body immune system

White blood cells, also known as leukocytes, form about 7000 cells per microliter of blood and make up about 1% of the total volume of the blood in a healthy human body.[84] There are two major groups of leukocytes: granulocytes and agranulocytes. The major characteristic that differentiates the two groups is the presence or absence of granules in the cytoplasm.[85] The granulocyte group consists of neutrophils, basophils and eosinophils, while the agranulocytes group consists of lymphocytes, monocytes and macrophages.[85] In general they make up the body's cell-based immune response system for fighting infections.[85]

Neutrophils, which are also known as polymorphonuclear leukocytes or PMNs, play an essential role in the human immune system. Being the most abundant cells, constituting approximately 50% to 70% of the total leukocyte count, their life span ranges between 8 hours to 5 days in circulation.[84] The primary function

of neutrophils is as the first line of defence against infection, in particular bacterial and fungal infections.[86] During the acute inflammatory phase of infection or injury, neutrophils are activated through chemical signals by the immune system. These cells migrate to the affected area via the blood vessels within 30 minutes and initiate an acute inflammatory response at the cellular level.[86] Non-host cells which invade tissue or the vascular system are directly killed through the process chemotaxis, bactericidal activities and phagocytosis.[86]

The other major contribution of white blood cells to the immune system is made by lymphocytes. Made up of T-lymphocyte and B-lymphocyte cells, their functions differ. T-lymphocyte cells regulate the function of other immune cells and directly respond to infected cells and tumours.[87] Conversely the B-lymphocyte cells produce antibodies targeted at bacteria, viruses and other unfamiliar materials in the body.[88]

The number of neutrophils present in the blood is measured in terms of Absolute Neutrophil Count (ANC).[89] An ANC is obtained by the multiplication of the number of total White Blood Cells (WBCs) by the percentage of neutrophils plus the band forms of neutrophils.[89] The result of this calculation is usually found in a complete blood count report presented as cells per mm^3 of blood. In some laboratories, this test is performed using modern instruments, which provide the measurement of ANC.

However, in the event that the number of WBCs is extremely low, instrument generated readings have been found to lack sensitivity and are unable to report an accurate ANC reading.[90] In these circumstances, neutrophils are often counted manually under the microscope with the results specified as 'manual count' in the laboratory reports.[91] An abnormally high level of neutrophils in the bloodstream is known as neutrophilia while a low level of neutrophils is often called neutropenia.

2.3   Grades of neutropenia

Neutropenia is defined as a reduction of circulating neutrophils in the bloodstream.[92] In a healthy adult, the lower limit of the reference value for neutrophil counts varies slightly between laboratories. However, the National Cancer Institute (NCI) has established a neutrophil count of 1500 cells/mm^3 as the acceptable threshold for minimum count for commencement or continuation of chemotherapy treatment in many therapeutic clinical trials. A neutrophil count less than 1500 cells/mm^3 has become the commonly accepted definition of neutropenia. According to the NCI Common Terminology Criteria for Adverse Events (version 3.0),[93] the grades of severity of neutropenia are described in Table 2.1.

Table 2.1 National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE) for Neutrophils[93]

Grade 1   <LLN – 1500 cells/mm^3

Grade 2   <1500 – 1000 cells/mm^3

Grade 3   <1000 – 500 cells/mm^3

Grade 4   <500 cells/mm^3

Grade 5 Death

(LLN =lower limit of normal)

Profound neutropenia is sometimes used to refer to an extremely low ANC (<100mm³/L) and these patients are vulnerable to more than one type or source of infection especially when they remain in this state for a prolonged period of time.[94] Conversely, defects in the quality of circulating neutrophils that impair phagocytosis and the killing of pathogens is known as functional neutropenia.[5] This form of neutropenia usually happens to patients with haematological malignancy. These patients are considered to be at risk of infection despite a normal ANC reading.[5]

In general, the decrease or absence in the number of circulating neutrophils increases patients' susceptibility to infection. When a patient is in a neutropenic state, the immune system is not able to mount a normal inflammatory response at the onset of infection.[95] As a result, the physiological response of abscess or pus formation is diminished.[95] The impaired phagocytic function of available circulating neutrophils allows further invasion and multiplication of micro-organism(s) in the body to an extent where it overwhelms the immune system and becomes fulminant.[95]

2.4   Chemotherapy-induced neutropenia

The causes of neutropenia are classified according to broad aetiologies: congenital and acquired. While congenital related neutropenia is rare, acquired neutropenia is related to infection, nutritional deficiency, autoimmune disorders and drugs.[96] Numerous types of drugs have been associated with neutropenia and the categories with the highest risk include anti-thyroid medications, procainamides and macrolides.[97] Other categories of drugs that

create a risk of neutropenia include analgesics, anti-inflammatory agents, anti-psychotics, anti-depressants, hypoglycemic agents and anti-platelet agents.[97] The mechanisms by which these classes of drugs cause neutropenia can be immune-mediated mechanisms, a direct harmful effects on the stem cells, or a composite of mechanisms.[96] However, anti-neoplastic agents universally known as cytotoxic chemotherapy are the most common cause of drug induced neutropenia in cancer patients.[2]

Chemotherapy is often described as a form of cancer treatment that involves systemic administration of anti-neoplastic agents. It has been a cornerstone of cancer therapy either as a mainstay or an adjunct to other treatment modalities. Although the mechanism of cell destruction differs with each anti-neoplastic agent, the general principle of chemotherapy involves impairing rapidly dividing cancer cells by irreparably damaging their DNA and inducing cell death.[98] Organs which have normal cell cycles involving rapid cell division such as gastrointestinal tract, skin, hair follicles and bone marrow are not spared. As a result, patients experience side-effects of treatment such as mucositis, diarrhoea, pigmentation, alopecia and bone marrow suppression.[99]

All rapidly dividing blood cells in the bone marrow are affected when exposed to anti-neoplastic agents and this is often known as myelosuppression. The onset of myelosuppression of white blood cells and neutrophils in particular is estimated to occur between three to seven days following chemotherapy. It continues for approximately a week until it reaches the lowest point (nadir) before returning back to normal levels again. During this period, patients with

CIN are at a heightened risk of multiple types of infections including gram-negative, gram-positive, viral and fungal organisms.[13, 50]

2.5 Challenges in the management of chemotherapy-induced febrile neutropenia

For many years, the clinical approach to the management of FN has been one that required immediate medical attention.[100] Although the management of FN has evolved to a more targeted approach, the recommendation for immediate medical assessment, diagnostic evaluation and initiation of empirical antibiotic therapy at presentation of fever is still applicable.[31, 101] This approach remains critical because of the difficulty in diagnosing infection in these patients due to their suppressed immune response.[100] Presence of fever may not be the most reliable indicator of an infection or as a trigger point for clinicians to initiate therapeutic interventions for patients with neutropenia.[5]

Some cancer patients may experience hypothermia, especially those who are receiving corticosteroids as part of their chemotherapy regimen and in such cases, fever may be masked.[102] In addition, clinical signs and symptoms for normal inflammatory response such as dysuria, sputum production and purulence, presence of exudates at infection site(s), and to some extent heat and swelling, are also blunted in these patients.[95] Hence, clinicians are required to be constantly vigilant for other symptoms suggestive of infection, including the presence of chills, rigors, hypotension, tachycardia and altered mental state.[5]

Recognition of patients' disease and characteristics of chemotherapy regimen in association with potential serious infection helps clinicians to be more astute in managing FN according to individual's medical condition. However, achieving this standard is often not straightforward, especially when the challenge is to distinguish the aetiology of fever due to infection from other causes of fever such as drugs and/or medical interventions in individual patients.[94, 103, 104] The lack of rapid and accurate diagnostic tools for infection adds to the challenge of managing the FN patient. Furthermore, fever associated with infection may lead to rapid clinical deterioration and life-threatening sepsis and these patients are at increased risk of mortality; potentially within a short span of hours.[105]

The need for immediate intervention in the presence of fever for neutropenic patients was based on research conducted in the 1970s.[106] It was reported that more than half of these patients with infection died from bacteraemia within 48 to 72 hours of fever onset.[106] The high rates of mortality were attributable to a gram-negative strain of bacteraemia and a delay in commencing antibiotic therapy.[106] Patients with FN therefore have a small window of opportunity to commence treatment and for treatment to take effect. Due to the clinical variations among patients with FN, clinical judgment is needed for decision making on empirical antimicrobial therapy for patients with neutropenia who present with nonspecific symptoms of infection or appear clinically unwell, even in the absence of fever.[5, 107]

In summary, the current standard approach for the management of FN includes prevention of neutropenia and its complications,[31] assessment of risk for complications at presentation of fever,[5] followed by a risk-based approach to determine the type of antimicrobial therapy, the appropriate venue of treatment and duration of therapy.[5, 31]

2.6 Chemotherapy-induced neutropenia and febrile neutropenia – risk factors and preventive measures

Different strategies have been developed over time to minimise the incidence of neutropenia and its associated severe clinical consequences such as FN, infection, sepsis and death.[38] Significant effort has been focused on risk assessment and targeted pharmacological intervention to minimise the risk of patients developing CIN, FN and subsequent complications.[2, 3, 108, 109] Although the primary interest of this thesis is to explore factors predictive of adverse outcomes of FN episodes, knowledge of factors associated with CIN and preventive measures aids in the overall positioning of this thesis. Moreover, the outcomes of each phase of neutropenia are inter-linked and have a direct influence on the overall clinical outcomes of patients who present with FN.

A number of studies have established factors that predict the development of CIN, FN and FN-related adverse outcomes. A summary of these factors is found in Figure 2.1.

CIN

- Older age, female gender, poor performance status, albumin level <3.5g/dl, bone marrow involvement, high LDH, low lymphocyte counts (Day 5), high-risk chemotherapy regimen, use of etoposide and high-dose cyclophosphamide, absence of GSF,high TNF receptor level, nitrogen ind level <0.891, increased baseline billirubin, lower baseline blood counts, higher planned dose of epirubicin, doxoribicin or docetaxel , depth of nadir

FN

- Older age, female gender, malnurition, poor performance status, leukemia, lypmphoma, lung cancer, presence of comorbidites, bone marrow involvement, advanced disease or uncontrolled cancer, high LDH (lymphoma), grade 4 neutropenia at first cycle or at any cycle of (neo)adjuvant chemotherapy, intensity of chemotherapy regimen, extensive previous chemotherapy, use of anthracycline, etoposide and high-dose cyclophosphamide, concurrent or previous radiotherapy, absence of CSF use, open wounds, tissue infection

Abbreviation: CIN- chemotherapy-induced neutropenia; FN- febrile neutropenia; CSF- colony stimulating factor /myeloid growth factor; LDH – lactic dehydrogenase; TNF – tumour necrosis factor; COPD – chronic obstructive pulmonary disease; ANC – absolute neutrophil count

Figure 2.1 Risk factors /Predictors for CIN[110-112] and FN and its complications[112-114] from published studies

A comparison of the factors that predict the development of CIN and FIN reveals that there are many factors which are concomitant in their association with the occurrence of neutropenia and its complications. Some of the factors which identify patients at risk of CIN have been incorporated into clinical guidelines for targeted use of colony stimulating factors (CSFs)[114, 115] and antimicrobial prophylaxis[35].

2.6.1 Use of colony-stimulating factors in patients with neutropenia

Colony stimulating factors stimulate the production of white blood cells and accelerate neutrophil recovery.[116] As a consequence, duration of neutropenia

is shortened which indirectly decreases the risk of infection in patients with neutropenia.[116] The benefits of this strategy were demonstrated in a meta-analysis of 17 randomised control trials which showed a 46% decrease in risk of FN (RR= 0.54; 95% CI, 0.43 to 0.67, p<0.001) and a 45% reduction in infection-related mortality with primary prophylactic CSFs as compared with controls (RR= 0.55; 95% CI, 0.33 to 0.90, p=0 .018).[109]

When CSFs were used as part of therapy for patients with FN, the findings of a Cochrane systematic review showed favourable results as compared with patients without CSFs.[117] They reported a decrease in prolonged neutropenia (25% versus 45%; OR=0.32; 95% CI, 0.23-0.46, p<0.00001), decreased prolonged hospitalisation (23% versus 32%;OR=0.63; 95% CI, 0.49-0.82, p<0.0006) and marginally less infection-related mortality (3.1% versus 5.7%; OR=0.51; 95% CI, 0.26-1.00, p=0.05).[117] However, there was no significant difference in overall mortality (r=0.68; 95% CI, 0.43-1.06, p=0.10).[117]

According to one of the guidelines on the use of CSFs in adult cancer patients undergoing chemotherapy, CSFs prophylaxis is recommended only to specific groups of patient.[114] They include: i) patients receiving chemotherapy regimen with high risk (> 20%) for FN; ii) patients with risk factors that may increase their overall risk of FN who are receiving a chemotherapy regimen with an intermediate risk for FN (10 - 20%), iii) patients on dose-dense or dose-intense chemotherapy established to have survival benefits and iv) patients who experienced a previous episode of FN.[114]

Patients who do not meet these criteria do not receive CSFs and therefore remain at risk of FN and its associated complications. Even with a secondary prophylaxis approach for subsequent cycles of chemotherapy, most of the complications which could have been minimised or prevented may have already occurred in the first cycle.[2] Selective use of CSFs particularly at the initial cycles of chemotherapy also has an impact on the risk of hospitalisation for FN.[118]

This was demonstrated in a study involving non-Hodgkin lymphoma patients which reported that the lack of early use of CSFs administration is associated with hospitalisation for FN (OR 1.99, 95% CI, 1.02-3.87, p=0.041).[118] In another study, the use of CSFs as part of the treatment regimen was not only significant in reducing neutropenia incidences but also reducing infectious complications, antibiotics requirements, and length of hospitalisation in a group of elderly patients with non- Hodgkin lymphoma.[119] Finally, it is noteworthy that there remains a proportion of neutropenic patients who develop FN despite the use of CSFs for primary prophylaxis[114] or secondary prophylaxis[120].

2.6.2 Use of antimicrobial prophylaxis in patients with neutropenia

The effectiveness of oral prophylactic antibiotics to decrease incidences of bacteraemia and infection related mortality in cancer patients during episodes of neutropenia has been proven in a systematic review.[121] Pooled analysis showed a significant decrease in the incidence of gram-negative bacteraemia (pooled OR 0.39; 95% CI, 0.24–0.62) without an increase in gram-positive

bacteraemia.[121] In addition, infection-related mortality related to bacteria was also decreased with the use of antibiotic prophylaxis (pooled OR 0.49; 95% CI 0.27–0.88).[121]

In another meta-analysis, antibiotic prophylaxis showed a significant reduction in the risk of all-cause mortality in patients with neutropenia (relative risk, 0.67; 95% CI, 0.55 to 0.81) as compared with placebo or no prophylaxis.[122] Secondary outcomes also demonstrated a reduction in infection-related mortality (relative risk, 0.58; 95% CI, 0.55 to 0.81), fever (relative risk, 0.79; 95% CI, 0.75 to 0.82), gram-negative infections (relative risk, 0.39; 95% CI, 0.32 to 0.46), gram-positive infections (relative risk, 0.42; 95%CI, 0.35 to 0.50), and bacteraemia (relative risk, 0.52; 95% CI, 0.46 to 0.59).[122] In terms of choice of drugs, oral fluoroquinolones was a preferred option for prophylaxis as compared with trimethoprim-sulfamethoxazole (TMP-SMZ) because of their broad anti-microbial spectrum, systemic bactericidal activity and good tolerability[121, 123].

However, the association between antimicrobial resistance and the use of fluoroquinolones[124-126] resulting in potential costs and consequences of resistance has also been a cause for concern among clinicians[127, 128]. In view of the current evidence of benefits and constraints of the use of prophylactic antimicrobial, it has been suggested that anti-bacterial prophylaxis should be considered for cancer patients with expected prolonged duration (> 7 days) and profound neutropenia (ANC <100 cells/mm^3) if they are managed as out-patients,[35] those who are undergoing out-patient stem cell transplantation, or those with bone marrow failure undergoing palliative care.[129]

2.7   Factors predictive of febrile neutropenia outcomes

In the 1960s a ground breaking study documented two very important factors which profoundly influenced the outcome of cancer patients with CIN and infection.[130] These factors were the depth and duration of neutropenia. In this seminal paper, three major findings were highlighted: 1) there is a proportional inverse relationship between incidence of infection and the level of circulating neutrophils; 2) the risk of developing infection increases with the duration of neutropenia and; 3) leukemic patients with relapsed disease fare worse during infection episodes.[130] Since then, a substantive volume of research has been performed to investigate clinical factors with potential predictive value for outcomes of FN. These predictors are discussed in the following section under the subheadings: patient-related factors, disease-related factors and treatment-related factors.

2.7.1 Patient-related factors

Age

The association of age with risk of neutropenia and its complication has been one of the most extensively explored factors. Younger age (< 60 years) has been associated with low-risk and was predictive of favourable outcomes of FN (OR 2.45; 95%CI, 1.51-4.01, p<0.001),[10] and older age (> 60 years) was one of the predictors for gram-negative bacteraemia (OR 1.81; 95%CI,1.31-2.49, p<0.001)[73]. The significance of age in prognostication in FN was also highlighted in the study by Hann et al.[131] The study compared the demographic characteristics of children (<18 years) and adult patients with FN with regard to infection type and outcomes.[131]

Clear differences were reported for clinically documented infections; overall success rate of treatment; time to defervescence and mortality from infection. Children less frequently presented with a defined site of infection (32% versus 41%, p<0.0001) and they experienced a significantly higher success rate for the initial empirical therapy regimen (58% versus 49%, p<0.001) based on the intention-to-treat analysis.[131] The adult group took an extra day to recover as compared with children (3 days versus 4 days, p<0.001), and a major difference was observed for mortality rate with 3% for children versus 10% for adults (p<0.0001). In general, children performed significantly better than adults in most outcomes measured.[131] In another study, one of the characteristics significantly associated with increased risk of hospitalisation for FN was being aged 65 years and above(Hazard Ratio, 1.79; 95% CI, 1.35–2.37, p<0.001).[132]

Lastly, the older age group has also been associated with longer duration of hospitalisation for neutropenic infections,[133] experiencing greater toxicity from treatment as compared with patients who are younger (OR 1.68; 95%CI, 1.25-2.26, p<0.0001)[134] and having 1.12 odds of mortality when hospitalised for FN as compared with patients who were younger (95%CI, 1.04-1.22, p=0.006)[13]. In spite of these studies' findings, a prospective study which evaluated patients with haematological malignancies who developed FN reported no significant difference in infection rates and outcome for patients who were elderly compared with those who were younger adults.[135]

Comorbidities

In the practice of medicine, comorbidity describes one or more disorder(s) that are present concomitantly in the patient, they may be unrelated to the primary disease or condition, or the effect of additional disorder(s).[136] Mucositis and diarrhoea associated with chemotherapy are common comorbidities that increase the risk of fever and infection for neutropenic patients.[68, 137] Malik et al[138] reported that FN patients who present with shock syndromme had clinical characteristics such as presence of diarrhoea ($p<0.01$), altered mental status ($p<0.01$) and bleeding ($p=0.02$). Although some of the comorbidities related to chemotherapy may be self-limiting, a minority of them could cause deterioration in FN patients.

One comorbidity which could cause deterioration is chemotherapy-induced mucosal injury, which usually involves the oral cavity and gastrointestinal tract.[139, 140] Compromise of the mucosa barrier, which serves as an important mechanical defence, can contribute to local invasion by colonising micro-organisms that could lead to systemic infection.[141] Grade III or IV mucositis has been reported as a major risk factor for the development of early post-stem cell transplantation febrile neutropenia,[137] while neutropenic enterocolitis, as a result of chemotherapy-induced mucosal injury, has been associated with mortality rates of 50% or higher.[140] Hence in the presence these conditions, it is not unusual for neutropenic patients to be at risk of infection and fever.[139, 142]

With regards to the number of comorbidities, a study on risk of hospitalisation for FN patients with non-Hodgkin lymphoma demonstrated that the presence of at

least one comorbid condition increased the likelihood of hospitalisation.[132] The importance of the number of comorbidities as a prognostic factor for the outcomes of FN was further emphasised by the increasing trend of risk of mortality in hospitalised FN patients from 2.6% to 10.3% to 21.4% in association with those without any major comorbidity, patients with one comorbidity and those with more than one comorbidity, respectively.[13]

Although the presence of comorbidity (non-specific condition) has been utilised for risk stratification of neutropenia patients who developed fever,[5, 36] specific conditions such as chronic bronchitis (OR 4.45; 95%CI, 1.95-10.17, $p<0.0001$), chronic heart failure (OR 6.47; 95%CI, 1.60-26.15, $p=0.009$), stomatitis (grade >2) (OR 2.59; 95%CI, 1.15-5.81, $p=0.02$) and stress hyperglycaemia (OR 3.06; 95%CI, 1.43-6.54, $p=0.004$) have been associated with medical complications in the already identified low-risk group of FN patients.[68]

In a multivariate logistic regression analysis of in-patient FN patients for risk of mortality, medical conditions including congestive heart failure (OR 1.27; 95% CI, 1.12-1.45, $p<0.0001$), lung disease (OR 3.94; 95% CI, 3.64-4.26, $p<0.0001$), liver disease (OR 2.89; 95% CI, 2.48-3.37, $p<0.0001$), renal disease (OR 3.16; 95% CI, 2.89-3.46, $p<0.0001$), cerebrovascular disease (OR 3.26; 95% CI, 2.64-4.02, $p<0.0001$) and pulmonary embolism (OR 1.94; 95% CI, 1.44-2.60, $p<0.0001$) were found to be significant predictors.[13] Lastly, the absence of chronic obstructive pulmonary disease (COPD) was associated with low-risk of FN adverse outcomes [OR 5.35; 95%CI,1.86-15.46, $p=0.002$].[10]

Previous febrile neutropenia episode

The risk of neutropenia in relation to the phase or cycle of therapy has provided some pertinent information to initiate preventive measures for subsequent cycles of chemotherapy.[3] The study conducted by Crawford and his team showed that more than half of all neutropenic related events which include severe (ANC <500 cells/mm^{3}) and/or FN occurred during the first cycle of chemotherapy.[3] The proportion for the first cycle neutropenic related events ranged from 50% to 75% as compared with an incidence of 44% to 75% for the three subsequent cycles combined.[3]

Furthermore, patients who experienced one episode of FN are at high risk of subsequent episodes especially after the occurrence of severe and prolonged neutropenia.[132] Information pertaining to this factor could be used to assess patients' risk of recurrent episodes of FN, response to treatment, types of micro-organisms from previous episode[5] and whether CSFs administration was initiated[120]. All these events could influence the outcomes of FN although the outcomes of each episode of FN are also dependent on other factors. Given the role of previous episode of FN as a predictor or surrogate marker for the outcomes of FN has yet to be determined, it is timely to explore its significance in the present primary study.

2.7.2 Disease-related factors

Type of underlying disease

It has been established that patients with haematological malignancies are recognised as being at high-risk of medical complications from FN as

compared to patients with solid tumours.[5] It is assumed that the underlying disease process and the intensity of the treatment; both influence the degree and duration of neutropenia.[5] In addition, malignant diseases involving the bone marrow such as acute leukaemias not only present with abnormal levels of blood cells (very high or very low white cell) but also defects in cell functions.[5] From the start, these patients are already at risk of infection.[5] Chemotherapy administered to these patients further reduces the white blood cells in the body resulting in prolonged and profound neutropenia that may lead to increased risk for severe infection.[5]

Consistent with these findings, in-patient mortality rates were reported to be significantly higher in patients with leukaemia (14.3%), as compared with lymphomas (8.9%) and solid tumours(8%).[13] This was based on an analysis of databases from 115 USA medical centres for adult cancer patients hospitalised for FN between 1995 and 2000.[13]

Bone marrow involvement / uncontrolled cancer

Patients with advanced malignant disease or disease which has not been controlled with treatment have been shown to not only be at risk of serious neutropenic complications and hospitalisation for FN[143] but also at risk of mortality from bacteraemia in the presence of FN (OR4.3; 95 %CI, 1.5–12.7)[144]. Uncontrolled malignant disease was one of the factors associated with a high-risk of developing medical complications in FN patients in the study conducted by Talcott et al.[64]

Similar principles to those held for bone marrow disease are applicable for malignant disease with bone marrow involvement, commonly seen in patients with lymphoma.[145] In a prospective study of patients with non-Hodgkin lymphoma, presence of disease in the bone marrow was one of the predictors which was significant for severe neutropenia and FN.[146] The presence of disease in the marrow indicates impaired bone marrow function which suggests that there will be slower recovery of neutrophils depending on the degree of involvement.[146] However, the sensitivity of this bone marrow involvement in predicting the outcomes of FN has not been validated and it is not one of the covariates included in existing models.

2.7.3 Treatment–related factors

Types and dose of anti-neoplastic drugs

Chemotherapy regimen as one of the primary determinants of the risk of neutropenia has been well-established.[114] Some chemotherapy regimens induce more myelotoxicity than others. For example, treatments which have high risks of FN include anthracycline and platinum-based regimens.[3, 147] Furthermore, the addition of taxanes to commonly used regimens for many solid tumours often results in grade 4 neutropenia and has been shown to increase FN rates of more than 20%.[148, 149]

Within the same or similar regimens, the dose also play a critical role in the risk of neutropenia and FN.[38, 147] However, it may be difficult to determine the actual risk of specific chemotherapy regimens, especially when treatment regimens are numerous and are applied in different combinations. Furthermore, even

within the same or similar regimens the rates of myelosuppression and associated complications have been found to be reported inconsistently and to vary greatly.[150]

A newer group of cancer therapies known for their increased risk of infection are monoclonal antibodies (MoAbs).[151] The introduction of MoAbs to improve efficacy of treatment for patients with lymphomas, chronic lymphocytic leukaemia, breast, lung, colorectal and head and neck cancers has added new infectious disease challenges to the management of FN patients.[151] These therapies are directed against specific surface markers on B-cells and T-cells. This promotes cancer cells destruction, but also leads to depletion of these cells in the body. Although MoAbs generally have good toxicity profiles, myelosuppression is increased and they are associated with a high incidences of grade 3 and 4 neutropenia.[151] Profound and prolonged immunosuppression increases patients' susceptibility to opportunistic and non-opportunistic infections which may result in increased infection-related mortality.[151, 152]

Along with the types and doses of anti-neoplastic agents used, chemotherapy intensity is the other important determinant of the risk of neutropenia – as well as the severity and duration of neutropenia.[112, 153, 154] As previously mentioned, severity or depth of neutropenia has been associated with increased risk of bacteraemia,[73, 155] and gram-negative type during FN[73]. Furthermore, both of these conditions have been associated with poorer outcomes for FN.[13]

With regards to duration of neutropenia, FN patients were reported to have a less favourable outcome, as duration of neutropenia increased by one additional day (OR 1.17; 95% CI, 1.08-1.26, p<0.001).[143]Duration of neutropenia of four days or more from the onset of fever (OR 2.52; 95%CI, 1.21-5.25, p=0.014) is an independent predictor for poor prognosis of FN for patients triaged at the emergency department.[59] The association of increased duration of neutropenia with less favourable outcomes may be related to the increased risk of developing bacteraemia as reported by Pagano et al. (OR 3.01; 95% CI, 1.7-9.5; p= 0.03).[156]

The role of expected or estimated duration of neutropenia has been used as a basis for several clinical decisions. These include selection of the low-risk patient group for oral therapy and out-patient management, commencement of prophylactic therapy and adjustment to dose or intensity of cancer treatment. However, this factor is usually derived from an estimate based on the chemotherapy regimen, and studies have reported different cut-off of days (ranging from 4 to 10 days) as prolonged neutropenia.[5, 59] For this factor to be included in a prognostic model it may result in some degree of discrepancy and lack reliability when applied in different settings.

2.7.4 Febrile episode-related factors

Clinical state of patient with neutropenia presenting with fever

In the late 1990s some of the pragmatic exclusion criteria for prediction of low-risk complications during FN included: presence of shock, respiratory insufficiency, being on intravenous supportive therapy, haemodynamically

instability and neurological or mental changes.[157, 158] Subsequent studies to identify predictors of the outcome of FN reported more specific, measurable clinical factors such as temperature, pulse rate, respiration rate and blood pressure.[10, 59, 73, 74]

These clinical characteristics reflect the physiological state of neutropenic patients presenting with fever. Abnormal vital signs such as high temperature (OR 1.81; 95%CI, 1.43-2.30, $p<0.001$),[73] hypotension (OR 1.66; 95%CI, 1.11-2.47, $p=0.01$),[73] abnormal respiration rate (OR 3.61; 95%CI,1.44-9.08, $p=0.006$),[59] and presence of dehydration ($p=0.003$)[143] have been established as predictors for adverse outcomes of FN episodes.

Lastly, in a multivariate logistic regression analysis for hospitalised patients with FN, hypotension (OR 2.12; 95% CI, 1.85-2.42, $p<0.0001$) and hypovolemia (OR 1.52; 95% CI, 1.38-1.66, $p<0.0001$) were significantly associated with risk of mortality.[13]

Performance status

Performance status is a measure of functional status and general wellbeing of cancer patients in a quantifiable manner.[159] This measure is often used to determine the eligibility of cancer patients for treatment, dose-adjustment and an evaluation of quality of life in randomized controlled trials for cancer.[159] There are various scoring systems available for the assessment of performance status; commonly used systems include the Eastern Cooperative Oncology Group (ECOG) score[160] and the Karnofsky scoring system[161].

Poor performance status has been identified as a significant risk factor for CIN, FN and reduced dose-intensity for cancer patients.[162] In addition, this factor (poor Karnofsky score <70) was reported to be a significant predictor of early death in adult cancer patients with bloodstream infections (OR 3.2, 95% CI, 1.13-9.35, p<0.05)[69] and failure for out-patient treatment of low-risk FN patients (p=0.029).[45] For FN patients who were apparently stable at the onset, performance status (ECOG >2) was one of six factors predictive of deterioration in patients with solid tumours undergoing out-patient treatment for FN.[68]

Additional confirmation of the role of this factor for prognosis of FN was demonstrated in a recent study by Ahn et al,[40] who showed that for the prediction of bacteraemia occurring in the low-risk group, poor performance status was among the three factors that were statistically significant.[40] It is evident from current studies that performance status has a role to play in the prognostication of several outcome measures related to neutropenia and its complications. However, in the context of predictive significance of the outcomes of FN, performance status failed to achieve statistical significance in a multivariate analysis after adjusted for other factors.[10] Because of its clinical applicability the relationship of this factor to the outcome of FN would need further exploration.

Infection

Bacteraemia is a common complication in patients with FN, occurring in 29% of patients in one study.[163] For haematological malignancies and solid tumours, the ratio of patients with bacteraemia was 2.7:1 respectively.[37] Febrile

neutropenia patients' complications were significantly higher in the presence of bacteraemia with a mortality rate of 10% as compared with 4% for FN patients without bacteraemia (p<0.001).[37] In patients with complex bacteraemia who presented with a clinical site of infection, the observed mortality rate was higher than for those without a clinical site infection (12% versus 8%, p=0.07) while polymicrobial bacteraemias was associated with an overall complication rate of 35%, including a mortality of 13%.[37]

In terms of microbiological characteristics, gram-negative micro-organism infections were associated with an overall complication rate of 40% and a mortality rate of 18% (p<0.001), while the complication and mortality rate associated with gram-positive micro-organism infections were a lot lower (25% and 5%, p<0.001) respectively.[37] For specific micro-organisms, mortality rate was the highest when the infection was caused by *Pseudomonas aeruginosa* (31%) followed by *Escherichia coli* (18%) and *Klebsiella pneumoniae* (10%).[37] There was a significant reduction in mortality rate when the infection was related to *coagulase-negative staphylococci* (5%) and 4% for streptococcal bacteraemias.[37] Some of the sites of infection including mucositis, lower respiratory infections, skin/soft tissue and the presence of a vascular access device were more commonly associated with complications in FN patients.[37]

That the epidemiological data for infection in FN patients supports the establishment of the presence of infection as a predictor of the outcome of FN is discussed as follows. The use of central venous catheter, which is a type of vascular access device, was associated with bacteraemia in patients with

haematological malignancies and FN in two studies (OR 6.14; 95% CI, 1.3-12.3, p=0.0)[156], OR 3.36; 95% CI, 1.46-7.72, p <0.01)[58]. The use of vascular access devices, in particular intravascular catheters, has been associated with the risk of bloodstream infection either as potential portals of entry for micro-organisms through the fluid infusion pathway or colonisation of the external surface of the catheter.[164]

The presence of lung infection has been repeatedly associated with medical complications (OR 6.003; 95% CI, 1.825-19.741, p=0.003),[71] septic shock (OR 5, p=0.043),[165] and infection-related mortality in FN patients with bacteraemia (OR4.4; 95% CI, 1.9–10,p=0.0004)[144]. Lastly, a multivariate logistic regression analysis reported that the following are independent risk factors for in-patient mortality for FN; gram-negative sepsis (OR 4.92; 95% CI, 4.5-5.39, p<0.0001), invasive aspergillosis (OR 3.48; 95% CI, 2.7-4.48, p<0.0001), invasive candidiasis (OR 2.55; 95% CI, 1.94-3.34, p<0.0001), pneumonia (OR 2.23; 95% CI, 2.04-2.45, p<0.0001) and gram-positive sepsis (OR 2.29; 95% CI, 2.01-2.6, p<0.0001).[13]

Despite this evidence, the predictive value of this factor has been brought into question by a study which found that knowledge of the bacteraemia status in FN patients did not alter their prognosis.[73] With the research findings of this study highlighting controversies surrounding this factor, one of the aims of this thesis is to explore the significance of the role of infection status and the type of infection(s) which potentially affect the clinical outcomes and influence therapeutic options for FN management.

Location of patients at the onset of febrile neutropenia

Patient's location as a predictive factor to distinguish the level of risk and prognosis of FN outcomes has been used as a covariate in two prognostic models for FN outcomes.[10, 64] A possible reason for location's relevance is the tendency for post-chemotherapy neutropenic cancer patients who remain in the hospital to be those who are undergoing complex chemotherapy or are unwell due to side-effects of chemotherapy or existing co-morbidities that need further medical attention.[64]

This is in contrast with patients already discharged from the hospital or being managed as out-patients for cancer treatment, who are commonly categorised as clinically stable or receiving less complicated chemotherapy regimens.[64] While location could be a reliable indicator of patient's general well-being before the onset of fever, a recent study by Park et al[11] reported a differing explanation. The development of fever in neutropenic patients who were not in-patients was significantly associated with serious medical complication (OR 2.742; 95% CI, 1.451-5.115, p=0.003).[11]

Nonetheless, with medical indications aside, the decision to hospitalise cancer patients is multi-factorial; depending on institution policies as well as clinician and patient preferences.[45, 166] Hence, this factor may not necessarily be a sensitive marker for risk assessment for the outcomes of FN episodes among cancer patients.

2.7.5 Diagnostic / Laboratory markers

At presentation of fever, post chemotherapy patients undergo blood tests, which include a complete blood cell (CBC) with differential leukocyte count, measurement of serum levels of creatinine and blood urea nitrogen, electrolytes and hepatic enzymes.[5] The CBC helps to ascertain the level of white blood cells, neutrophils as well as platelet and haemoglobin levels which are expected to be affected by chemotherapy. Aseptic work up which encompasses blood cultures and other microbiology tests as indicated by presenting symptoms is also performed.[5] The culture(s) results provide information on the type of micro-organisms that caused the infection and are used to guide antimicrobial therapy. Some results of the laboratory tests have been shown to be associated with the outcomes of FN and they are discussed in the following sections.

Absolute neutrophil count (ANC)

The association of severe infectious episodes with ANC levels was well established in the study by Bodey et al.[155] In the same study, the risk of developing severe infection was not related to the magnitude of the decrease of ANC but the final neutrophil count.[155] The findings of the study were supported by subsequent studies (discussed below) that showed that ANC levels are a predictor for incidence of neutropenia, FN and hospitalisation and outcomes related to the FN episode. The severity of the first-cycle ANC reduction was reported to be a strong predictor for neutropenia, potential dose reduction and treatment delay in subsequent cycles (p=0.0001 to 0.004).[167] Baseline ANC less than 1500 cells/mm^3 (HR 1.98; 95% CI, 1.28–3.06, p=0.001) was associated with increased risk of hospitalisation for FN.[132]

The significance of ANC levels as predictors for bacteraemia (OR 2.55; 95%CI,1.90-3.42, p<0.001) and gram-negative bacteraemia (OR 3.38; 95%CI,2.15-5.30, p<0.001) in FN patients was reported in the study by Paesman et al.[73] In addition, severe neutropenia (ANC <100 cells/mm^3) was the only independent factor associated with out-patient treatment failure for low-risk FN patients (OR 17.9; 95% CI,1.59-200, p=0.04)[46] and the recovery of ANC has been associated with favourable outcomes of FN (OR 17.3; 95% CI, 5.298-56.56, p<0.001)[11].

Although significant emphasis has been placed on ANC levels, it is has been reported that ANC at the onset of FN was not predictive of FN outcomes.[11] In another study of infection episodes in breast cancer patients treated with anthracycline-based chemotherapy, the number of chemotherapy courses but neither age, baseline neutrophil count or chemotherapy regimen were associated with occurrence of infection.[57] In fact, ANC level was shown to be the least sensitive indicator of bone marrow recovery.[168] A rising monocyte count (another type of white blood cell) and increasing absolute phagocyte count (APC) have been shown to be more sensitive and earlier predictors of impending recovery of neutropenia in paediatric patients with FN.[168]

Monocytes and lymphocytes

Monocytes and lymphocytes are types of the white blood cells. Between them they form the majority of the lymphatic function of the immune system. Monocytes appear to have an important role in the development of neutrophils in cancer chemotherapy.[169] A decrease in monocyte levels was

suggested to cause a decrease in the production of granulocyte-colony stimulating factor and induces neutropenia.[169] As such, early reduction of monocytes (<150 cells/mm^3) after chemotherapy on Day 6 and Day 8 may be a predictor for Grade 3 or 4 neutropenia and it was recommended that its predictive significance be tested in a prospective study.[169] The other study which tested the predictive potential of serious medical complications related to FN episodes was conducted by Carmona-Bayonas et al.[68] Monocytes <200mm^3 (OR 2.29, 95% CI, 1.04-5.07, p=0.04) was a significant factor associated with medical complications for patients with solid tumour and lymphoma who were categorised as stable at clinical presentation of FN.[68]

Lymphocyte counts were the other blood marker studied for an association with the risk of FN after chemotherapy. The independent factors were: Day 5 lymphocyte counts (< 700 cells/mm^3) (OR7.17; 95% CI, 2.52-20.35, p=0.0001) and high-risk chemotherapy regimen (OR 6.75; 95% CI, 2.37-19.19, p=0.0003).[170] Similar findings were reported in another study for lymphocyte counts and its association with incidence of FN and early mortality after chemotherapy. Only the baseline count had an independent prognostic value for FN. However, baseline count did not have an independent prognostic value for early mortality in multivariate analysis.[171]

Given the persistent emergence of newly reported laboratory indicators across the published literature, a primary research study is indicated to investigate possible associations between the levels of ANC, monocyte and lymphocyte

counts with the outcomes of FN with emphasis on their trends and measurement timings in adult patients.

Platelets levels

Thrombocytopenia has shown to be associated with bacteraemia in febrile granulocytopenic cancer patients (OR 0.51; 95% CI, 0.38-0.72, p< 0.001).[172] In the presence of FN, this factor has been shown to be predictive of poor prognosis (OR 3.41; 95%CI,1.69-6.89, p=0.001)[59] and subsequent development of medical complication (OR 4.982; 95%CI, 2.00-12.40, p=0.00)[173]. Although thrombocytopenia has been frequently reported in critically ill patients with sepsis syndrome,[174] the biology explaining its relationship underpinning its predictive role in the prognosis of FN remains unclear.

It is noteworthy that the aetiology of thrombocytopenia during the period of FN could be related to either severe infection with impending sepsis[174] or part of the concomitant side-effect of cancer treatment[175]. Despite having been a recurring feature for neutropenia events and complications, thrombocytopenia is not included in current risk prediction models. Given the evidence of a role for thrombocytopenia, additional investigation to establish its value in risk stratification of FN patients at different time points of treatment cycle is needed.

Other conventional laboratory variables

Laboratory abnormalities are generally indicators of organ dysfunctions although additional tests would be required to investigate and confirm the cause. Several biochemical parameters have been analysed for prognostic

significance for outcomes of FN. Serum creatinine levels of >1.2 mg/dL were associated with significant risk of failure of out-patient treatment for FN patients with haematological malignancies (OR 7.97; 95%CI, 2.19-28.95, p=0.002).[47] Another study reported a similar relationship between serum creatinine and albumin with regards to time taken to defervescence for FN.[176] Abnormal levels of serum creatinine (> 1.5mg/dL, p=0.04) and serum albumin (< 3.0g/dL, p=0.004)are associated with longer duration for recovery.[176]

Other abnormal laboratory tests such as abnormal hepatic function (alkaline phosphatase, p=0.022; bilirubin, p=0.007) and renal function (p<0.001) were shown to be major independent risk factors for neutropenic complications.[38] For patients admitted to the hospital for FN, abnormal baseline electrolytes, mainly hypokalaemia, hypomagnesaemia and hyponatremia had a negative impact on the outcome of the admission.[177] Most of these laboratory tests are routine test prior to chemotherapy; however they have not been studied for their predictive value for the outcomes of FN.

Low albumin level is associated with malnutrition, which may correlate with weight loss and potentially impaired immunological function.[178] Because malnutrition is a common problem in cancer patients and it has serious implications for recovery of from illness,[179] albumin level will be explored for its prognostic impact on the outcomes of FN patients in the primary cohort study of this thesis. Levels of creatinine which reflect the function of the kidneys will also be included in the primary study to determine if it has any association on the outcomes of FN episode.

Inflammatory markers

C-reactive protein (CRP) as a marker of inflammation was widely used by clinicians in the diagnosis of sepsis in non-neutropenic patients, especially in the acute care settings.[180] The utility of the marker has also been studied extensively in adult patients with FN.[181, 182] In the study by Povoa et al[182] elevation of CRP concentrations was found in septic and critically ill FN patients. In addition, CRP was one of the predictive markers used in adjunct with other clinical factors in the identification of bacteraemia in low-risk FN patients[183] and has been associated with FN patients who are at risk of developing serious medical complications[173].

However, the predictive value of this marker in FN patients has been controversial. Studies which evaluated the significance of CRP level as a prognostic marker in patients with FN reported it to be either less sensitive[184] or comparable[185] with another inflammatory marker (procalcitonin). Given the limitations of CRP in its specificity for the identification of sepsis and bacterial infection, other markers of infection have been proposed and studied.[186-188]

2.8 Summary of prognostic factors for the risk stratification of patients with febrile neutropenia

In summary, factors which are predictive of the outcomes of FN patients including mortality have been derived from findings of primary studies as well as the consensus of clinicians who have extensive experience in the management of patients with neutropenia. Overall, the outcomes of FN are greatly influenced by a combination of factors and a robust prognostic model is

needed to profile FN patients' risks accurately, with minimal misclassification rate. The emergence of inflammatory markers as prognostic markers may add value to the performance of current models although further validation would be required.

2.9   Prognostic models for risk stratification of patients with febrile neutropenia

Multivariable models consisting of prognostic factors are commonly used for risk assessment of neutropenic patients presenting with fever. They guide clinical decision-making for the type of antibiotic therapy (oral or intravenous), geographical location for treatment (out-patient or in-patient) and the duration of antibiotic therapy.[5] It is recommended in current clinical practice guidelines for the management of patients with FN that the assessment of risk for complications of adverse outcomes related to FN should be performed at presentation of fever.[5, 189]

Patients with FN categorised as high-risk require hospital admission for intravenous antibiotics and medical surveillance for clinical deterioration if they are not already in-patients. In contrast, low-risk patients may be candidates for oral antibiotics as out-patients after a brief period of observation or early discharge from hospital.[5] Two of the more established models for risk stratification of FN patients which were statistically derived and have been validated are: the Talcott model[64] and the Multinational Association Supportive Care for Cancer (MASCC) risk scoring system.[10]

2.9.1 Talcott model

The first generation of risk stratification models was developed in the late 1980s. A study by Talcott et al[64] investigated a broad range of clinical characteristics of neutropenic patients presenting with fever who were at risk of significant adverse outcomes. Based on a review of medical records of patients admitted with neutropenia between 1984 to 1985, the retrospective study looked at 281 patients.[64] The sample was well distributed across haematological malignancies (leukaemias and lymphomas) and solid tumours. However, not all patients had CIN with 8 of the sample identified as having newly diagnosed acute leukaemia.[64] Factors included in the analysis were those that could be assessed within 24 hours of admission.[64]

The outcome of the analysis was the categorisation of patients into four risk groupings based on the three main criteria: disease status (controlled or uncontrolled cancer); concurrent co-morbidities (other than fever and neutropenia) and location of patient (in-patient or out-patient).[64]Group I, II and III were accorded high-risk with more frequent incidence of medical complications while Group IV is categorised as low-risk with minimal likelihood of clinical deterioration during FN.[64] The characteristics of each group were described as follow: group I was pre-existing in-patients at the onset of fever; group II included out-patients with significant comorbidity, group III were out-patients with uncontrolled malignant disease and lastly group IV were out-patients with controlled disease and without comorbidity.[64]

The Talcott risk stratification model was not only simple to apply but also thought to have reasonable predictive validity in its categorisation of patients into the high- and low-risk groupings. This was demonstrated in the prospective study conducted to validate the model performance.[36] With a sample size of 444 cancer patients with FN across two hospitals the model reported 90% for sensitivity; 30% specificity, 23% negative predictive value (NPV) and 93% positive predictive value (PPV).[36] Among the low-risk group, there were 3 deaths (3%).[36]

Although being shown to be reliable for stratifying FN patients to the low-risk of complications, the model was less effective when used to select patients who were low-risk for home-based therapy.[32] Among 30 patients who were discharged after two days, 30% (9 patients) were readmitted either for treatment for medical complications or for prolonged fever with no mortality reported.[32]

Consequently a list of exclusion criteria was proposed for the prediction of FN patients with low-risk of complications, including patients who have; undergone allogeneic stem cell transplantation, with renal failure, presented with shock, respiratory insufficiency, on intravenous therapy, with human-immunodeficiency virus, existing infection(s), and at risk of mortality within 48 hours.[190] Another study added the following clinical symptoms to the list; haemodynamically unstable, abdominal pain, nausea and/or vomiting, diarrhoea, altered mental changes and liver insufficiency.[158] However, these criteria were not validated and some of the criteria were limited in their ability

to be assessed at clinical settings as they were not entirely objective in their measurements.

2.9.2 MASCC risk-index score

Following the pioneering work of Talcott and colleagues (1988) another model was developed to improve on the Talcott model. Known as the Multinational Association for Supportive Care in Cancer (MASCC) risk-index scoring system, the objective of this model was to establish a more accurate method of assessment of FN patients.[10] The model was developed to identify patients who are at low-risk of developing serious medical complications during the FN episode.[10]

These patients were defined as those with high probability of fever resolution without risk of clinical deterioration.[10] A multicentre prospective study was conducted involving more than 1,110 patients with FN.[10] The definitive aim of this study was to develop a risk prediction tool suitable for the selection of patients who might be eligible for new ambulatory therapeutic intervention(s) other than the standard practice for FN.[10]

The risk score was derived using multiple logistic regression to select seven independent factors with assigned individual integer weights. The maximum score is 26 and a score of > 21 (based on the sum of assigned integer weights to the respective factors) categorises patients to the low-risk group.[10] Validation of the model showed a sensitivity of 71%; specificity of 68%, NPV of 36% and PPV of

91%.[10] Based on these results, it appears that the MASCC risk score performed better than the Talcott model with an improved sensitivity (71% versus 30%), lower global misclassification rate (30% versus 59%) and increased rate of identification of low-risk FN patients (63% versus 26%).[10, 36]

Subsequently there have been numerous studies performed to validate further attributes of the MASCC risk-index score. One of the studies, performed prospectively to categorise FN patients according to their level of risk of adverse outcomes, reported both sensitivity and specificity of 95%, NPV of 86% and PPV of 98%.[39] The other validation study was conducted on a group of haematology patients.[41] The MASCC risk score was used to identify FN patients with low-risk for medical complications suitable for early discharge from the hospital.[41] Of the 279 episodes of FN, 38% had a MASCC score of > 21 (low-risk) but as many as 15% of patients experienced subsequent clinical deterioration requiring re-admission.[41] The performance of the MASCC score model in this particular study was reported as 58% for sensitivity; 87% for specificity and 84% for PPV, 64% for NPV and an overall rate of misclassification of 28%.[41]

2.9.3 Risk model for patients with haematology malignancies

Park and his colleagues developed a risk stratification system for FN patients with haematological malignancies.[11] The basis for a new risk model specifically for this group of patients was related to the clinical course of infection which differs from patients with solid tumour.[11] The progression of infection for FN patients with haemtological malignancies is typically more rapid and severe[191]

and hence, a model to identify FN patients with high-risk of clinical deterioration was deemed more relevant.[11] A total of 259 episodes of FN in 137 patients were evaluated for the baseline characteristics and the outcomes of each FN episode. Prognostic factors that were statistically significant from multivariate analysis included: recovery of neutropenia, low levels of serum albumin and bicarbonate; elevated levels of CRP (Day 0 and 5th day) and respiratory tract infection.[11]

However, some of the study findings were incongruent with predictors reported in previous studies. For example, "out-patient"; the development of fever outside the hospital, was found to be significantly associated with serious complications in the univariate analysis of the study (OR 2.742, p=0.003).[11]Although it failed to achieve significance in the multivariate analysis in the study, the same factor was associated with the low-risk group of FN patients in the Talcott model[64] and MASCC risk score[10].

Additional factors such as ANC level at onset of fever, duration of neutropenia and history of neutropenia were not statistically significant in association with the development of complications.[11] This again is contrary to what had been previously reported.[59, 183] However, a new predictor, late onset of fever, was shown to be positively related to a favourable outcome in hospitalised patients.[11] The differences in the findings may be attributed to the sample population since one was mainly concentrated on haematological malignancies[11] while the other models consisted of patients with different cancer diagnosis[10, 64]

2.9.4 Summary of the prognostic models

Based on these risk models, it is evident that some predictors are common across models, and there are also different predictors used in varied combinations across respective models. Although some of these predictors have demonstrated their roles in predicting the outcome measures, the strength of association of each of the predictors in association with the outcome measures remains questionable. In reality the clinical outcomes of FN are influenced by many of the existing predictors. However, the predictive value of current individual predictors can be challenged by newly identified ones particularly if the end point improves the accuracy of current risk models or increases the robustness of existing models.

2.10 Current state of evidence

More than two decades have passed since the development of the first risk model for stratification of FN patients.[64] The proliferation of new prognostic factors continues, with increasing numbers of primary studies reporting new variables with potential predictive value for the risk assessment and stratification of individual cancer patients' FN episodes. In spite of the growing number of studies, some of the issues related to predictors have not been addressed. The predictive value of some of the identified predictors remained controversial being based on single studies,[10, 73]of which some were underpowered.[11, 74, 75]This has led to uncertainty among clinicians about which factors are more relevant and better predictors.[11, 68, 69, 192]

The other challenge faced by users revolves around the performance (prediction accuracy) of current prognostic models for FN outcomes. Some of the limitations include absence of or inadequate validation, misclassification in the low-risk group that could compromise patient safety[11, 68, 82], and limited discriminatory ability when used among certain subgroups of cancer patients.[11, 67] Apart from the MASCC risk score and Talcott model, there have not been reports of validation studies for the other tools. Misclassification compromises patients' safety, and there is no consensus on the acceptable level of misclassification in the management of FN.

As the management of FN patients continues to evolve, there is a genuine need for a robust evidence-based prognostic model to assist clinicians in deciding on type of therapy, frequency of monitoring and setting of care. Given the lack of consensus on current factors in addition to the development of additional prognostic factors and laboratory markers[193-195] as well as the changing patterns of sites of cancer care,[196, 197] a more detailed examination of prognostic factors for FN patients is needed. A systematic review was undertaken to identify the current available evidence on clinical factors, and evaluate their association with the outcomes of FN episode. The details of the review are discussed in the following chapter.

3   Systematic Review of Prognostic factors for Febrile Neutropenia Outcomes in Adult Cancer Patients

3.1   Introduction to the chapter

This chapter provides an overview of evidence-based practice and its utility in healthcare practice. This is followed by an introduction to systematic reviewing and a discussion of the different types of reviews; as well as the important elements of this methodology in relation to the review of prognostic studies. Subsequent sections describe the details of the systematic review undertaken to identify the best available evidence for prognostic factors of the outcomes of chemotherapy-induced febrile neutropenia. The methodologies, quality assessment, analysis of secondary data and the findings of the review are described in the respective sections.

3.2   Evidence-based practice

Evidence-based practice (EBP) is described as a unified approach in clinical decision making through the integration of current best available evidence with healthcare expertise and patient values.[198] In the field of health care, shared-decision making where both clinicians and patients participate actively in deciding on therapeutic and diagnostic interventions, EBP provides the basis for an adequately informed decision making process.[199] Evidence-based practice does not only assess the quality of evidence but also considers other aspects such as risk and benefits of the intervention or no intervention.[200, 201] The

main challenge faced by busy healthcare practitioners is the management of massive amount of information available from medical literature.[202]

Given the lack of time and capacity to find, read, organize and interpret the study results, what is needed is to have information presented in concise manner to facilitate daily practice.[202] However, the information should be based on more than the findings of a single study. This requires a systematic approach to reviewing international literature, followed by the presentation of a synthesis of the literature on the identified topic, from an *a-priori* protocol.[203] The ultimate aim of EBP is to achieve better quality, effective and efficient delivery of healthcare through the utilisation of current evidence to support healthcare practitioners in making clinical decisions.[204]

Clinical evidence informs practice but does not routinely replace individual clinical acumen and neither of these will achieve its purpose if applied without consideration of the context and patient's preferences.[205] In recent years, the EBP movement has gathered momentum of wider adoption extending to other areas of healthcare such as nursing[206] and allied health[207]. The effect of this expanding ripple is evident in the embrace of EBP among healthcare leaders, policy makers, legislators and consumers.[208, 209] The term evidence-based healthcare (EBHC) is now used frequently to reflect the integration of EBP in multidisciplinary practices among healthcare providers and users.

3.3 Barriers of evidence-based healthcare adoption

The concepts and ideas of EBHC have become a part of daily practice at the point of care, although there remain barriers in the uptake of EBHC. These can be attributed to constraints in access to clinical evidence;[210] the notion of EBHC being prescriptive, and the perception of it being a strategy to cut the cost of healthcare[211]. To address the first issue, having recognised the need for healthcare practitioners to have easy access to evidence, there are now a plethora of evidence-based centres and governmental agencies that provide free access to sources of systematic reviews. Among them include Agency for Healthcare Research and Quality (www.ahrq.gov) and Bandolier (http://www.medicine.ox.ac.uk/bandolier/). Additional sources which require subscription include Cochrane Library (www.CochraneLibrary.com), Joanna Briggs Institute (http://www.joannabriggslibrary.org/jbilibrary/index.php/jbisrir) and BMJ Clinical Evidence (www.ClinicalEvidence.com).

Additionally, EBHC has been perceived to be restricted to randomised control trials (RCTs) and meta-analyses, excluding other types of evidence.[205] This argument can be refuted by acknowledging that the generation of evidence can be and is achieved using diverse methods, of which RCTS is but one. Indeed, according to Pearson et al,[212] research, discourse (or narrative) and experience are recognised as valid means of evidence or knowledge generation to answer a question on specific health related topic.[212] As such, sources of evidence for healthcare can range from clinical trials, non-experimental, observational studies, clinical expertise and opinion, patients or clients' experience, and from the local context of care.[213]

3.4   The Joanna Briggs Institute model of evidence-based healthcare

There are several international not-for-profit organizations championing EBHC and they include the Joanna Briggs Institute (JBI), the Cochrane Collaboration and the Campbell Collaboration. The Cochrane Collaborations' emphasis is on the systematic review of effects of healthcare interventions (therapeutic and non-therapeutic) that are mainly based on the analysis of randomised control trials.[214] Comparably, the focus of Campbell Collaboration is also on effects but in the aspect of social interventions related to education, crime and justice, social welfare and international development.[215]

Unlike these two EBHC collaborations that focus mainly on effectiveness the JBI model is unique and distinctive as it acknowledges the importance of a pluralistic and inclusive conceptualisation of what constitutes evidence for practice.[198] The JBI model argues that this holistic approach is necessary to address the increasingly diverse and complex needs of healthcare delivery. In addition to conducting reviews on effectiveness, the JBI model also utilises other types of quantitative, qualitative, textual and economic data to systematically review and synthesise evidence to inform policy and practice.[212]

The JBI model of EHBC was established in 2005 by Professor Alan Pearson and colleagues.[198] The concept of EBHC for this model considers the integration of four factors when making a clinical decision. These are: i) best available evidence, ii) the context of care delivery, iii) client preference and iv) professional judgment of the clinicians.[198] The aim of the JBI model is to facilitate

and promote EBHC across the world with the intention of contributing to improved global health. These outcomes are achieved through local and international collaborative programs of activity for the translation, implementation and evaluation of evidence.[198]

3.4.1 Framework of the Joanna Briggs Institute model

The conceptual model of EBHC, as defined by the JBI model, is comprised of four major components. There are: i) generation of healthcare evidence, ii) synthesis of evidence, iii) transfer of evidence and iv) utilisation of evidence.[198] Each of the components is not a stand-alone but works in a continuous cyclical process incorporating various essential elements.

Evidence generation

The JBI model recognizes the importance of a pluralistic approach to the concept of evidence. The term "evidence" is reflected as the basis of belief through confirmation and validation of the truth.[198] In this model, the generation of evidence or knowledge relies on the assessment of global healthcare needs through research, experience and discourse. The methods of generation are linked to the purpose and nature of activities that seek to determine the feasibility, appropriateness, meaningfulness and effectiveness in all aspect of healthcare delivery.(Figure 3.1) The guiding principle is to generate evidence or knowledge on the effectiveness of an intervention / activity and to ensure that when it is applied within the context or situation, it is feasible and meaningful to the specific settings, populations, or cultures to address the identified healthcare issue.[198]

Evidence synthesis

Evidence synthesis is conceptualised to consist of the following elements: theory, methodology and systematic review.[198] In general, evidence synthesis involves the examination and evaluation of primary research evidence to aid in decision making concerning healthcare issues. The first two conceptual elements aid in the science of evidence synthesis while the operationalisation of methods for synthesis is through the process of systematic review.[198] Systematic review is accorded the highest level of evidence within each domain of evidence in the JBI EBHC model.

Figure 3.1 JBI Model of Evidence-Based Healthcare[198]

Evidence transfer

Evidence transfer is another important component of the process of EBHC. It is

described as methods of communicating evidence generated from

synthesised findings (knowledge) to individual healthcare professionals and

other healthcare related systems worldwide. This encompasses the

development of strategies to disseminate evidence in the most succinct and

easily accessible manner accommodating the context and needs of respective users of evidence. For evidence to reach users, the most cost-effective processes for the transfer/ delivery of information include: continuing education, training, organisational and team systems. The methods used in JBI for evidence transfer include the development of Evidence Summaries and Best Practice Information Sheets.

Evidence utilisation

The final step of EBHC in the JBI model relates to the practical utilisation of evidence – that is implementing evidence to improve and change practice / systems. Evidence utilisation is underpinned by three elements which are: practice change; embedding evidence to influence organizational and system change; and lastly the evaluation of the utility of evidence in its impact on healthcare delivery, system, and outcomes.[198] The first element is mostly targeted at the individual practitioner level while the second and third elements focus on organisational and system levels. The challenge for this component is the effectiveness of implementation strategies to affect the intended degree of practice change at all levels to positively impact the overall healthcare practice worldwide.[198]

3.5   Systematic review

Systematic reviews provide a rigorous and robust method of reviewing literature.[202] The significant benefit of systematic review is the generation of evidence from a body of literature rather than a single study's findings.[203] An overall result based on multiple studies of the same intervention or topic of

interest and outcomes can be established; although, some of the results for individual studies may be contentious.[203] This approach provides a more explicit overview of a body of literature in addition to minimising the effect of poor quality studies on the overall findings.[216]

As such, systematic review findings are regarded as the best available evidence for a given topic of interest and in the hierarchy of evidence they are considered the highest quality.[198] Besides generating evidence, systematic reviews also highlight the quality and rigour of published primary studies on the specific area of research. In most cases, this approach provides an assessment of the methodological quality and risk of bias which exist in respective types of primary studies, which inadvertently limit evidence-based practice.[216, 217]

The conduct of the systematic review adheres to a set of procedures which build on the elements of transparency, objectivity and reproducibility.[218] It encompasses the analysis and review of empirical evidence in an objective and methodical manner. The undertaking of a systematic review is a complex process involving a series of steps. Each step requires strictly adhering to the *a priori* methods, and they are explicitly defined to facilitate the important elements of a systematic review, but also reduce the risk of bias.

The steps of a systematic review include the following key characteristics: i) clearly stated objectives of a specific topic or research question; ii) pre-defined inclusion criteria for studies; iii) a systematic, comprehensive and exhaustive approach to the search and identification of all eligible studies; iv)

standardized tools for critical appraisal and synthesis of evidence and lastly, v) presentation of synthesized findings and recommendations.[219, 220] These strategies are implemented with the aim to produce more objective, reliable evidence to inform clinical practice and policymaking. The process of a systematic review is illustrated in Figure 3.2:

TOPIC
- Identify research question(s) and set clear objectives
- Develop a protocol: peer-reviewed and approved by the Institute

SEARCH
- Comprehensive search strategy of international literatures; published & unpublisehd
- Assess literatures for suitability according to inclusion criteria

APPRAISAL
- Retrieval and assessment of literatures for applicability of the review
- Critical appraisal of the included literatures using standardized tools (2 independent reviewers)

ANALYSIS & SYNTHESIS
- Extract data from the included literatures
- Analyse and synthesis of evidence according to respective methodologies

RESULTS
- Reporting of review results and findings
- Develop recommendations for practice and indications for future research

Figure 3.2 Overview of the JBI process for systematic review[221]

3.6   Scope of review for factors associated with febrile neutropenia outcomes

Evidence based healthcare has evolved dramatically in a relatively short period of time. In the context of prognostic factors and models, healthcare practitioners are increasingly aware of the importance of evidence-based approaches in this area of research and adopting these tools arising from such research to guide their decision making.[219, 220, 222-225] Numerous prognostic factors predictive of the outcomes of FN in adult cancer patients have been identified over the years.

These prognostic factors aid in the classification of FN patients into different groupings according to their risk levels which therapy can be tailored.[11, 71, 137] As the number of prognostic factors for this group of patients continue to proliferate across primary studies, some with conflicting results, the challenge remains to establish the best available evidence of these prognostic factors in predicting the outcomes of adult cancer patients experiencing FN.

At the commencement of this systematic review, there were no existing published systematic reviews on this topic although there were literature reviews. One such literature review reported on clinical and laboratory characteristics predicting FN cancer patients with low-risk of developing medical complication hence available for early discharge.[192] The review included both children and adult populations with diverse underlying malignant disease and a big variation in age groups. The findings included predictors such as general clinical condition of patient, status of the malignant disease, the function of the bone marrow, signs of infection and social factors.[192]

Subsequently, two other reviews addressed topics such as predictors of CIN and development of FN and its complications.[110, 111] However, inferences in these literature reviews are made mostly based on the expert opinions and they reflect the author's views on the given subject.[226] As they are highly susceptible to biases, they are usually not perceived as evidence-based. In addition, the choice of included articles for the reviews is highly subjective to the author(s) preference, and the process of literature searching and selection are not described.[226]

Additional, critical information on methodologies such as searches strategies used, inclusion and exclusion criteria and the assessment of study quality are not explicitly stated.[226] Furthermore, the reviewers in a literature review are not obliged to provide a clear description of the process and conduct of the review of which both are vital in the quality assessment of a review.[227]

Two recent and significant systematic reviews and meta-analyses related to FN and outcomes in the paediatric group of patients were published by others since the commencing this project. One of them looked at the discriminatory performance of risk prediction rules in FN episodes[228] and the other looked at the value of initial biomarkers in predicting adverse outcomes in FN episodes.[81] Both reviews were unable to draw any firm conclusions on the effectiveness of current prediction tools or the predictive value of biomarkers in the FN episodes. Because both reviews were conducted for children and young people with cancer the findings are not applicable for adult cancer patients with FN. As such, the systematic review reported in the present chapter is a unique contribution to knowledge as it reports on the compiled evidence for clinical factors and their overall predictive values in association to the low- and high-risk group of adult cancer patients with FN.

3.7 Challenges associated with systematic review of prognostic factors

Methods developed for prognostic factor research have remained less advanced as compared with clinical trials.[229] This has resulted in a great deal of ambiguity in the study findings, their interpretation, and the synthesis of

combined results.[229] Systematic reviews conducted for various medical conditions have further highlighted poor methodologies utilised for primary studies, poor reporting and inconsistency and/or conflicting findings.[230-232] Despite much effort being made to improve the methods of primary studies over the years, there has been little or no improvements in study quality as demonstrated in the most recent review of prognostic studies by Mallett et al. in 2010.[217] In short, the poor quality of primary research on prognostic variables may add to the complexity of performing a good quality systematic review which could compromise the results of a secondary analysis.[52]

As compared with systematic reviews and meta-analysis of effectiveness of healthcare interventions that are based on RCTs, the methodological principles for systematic reviews on studies of prognostic variables are neither well-developed nor standardized.[229] Having acknowledged the need for an appropriate methodology for this type of review, additional work is required to clarify other elements of the review process faced by reviewers in a synthesis of prognostic studies. As in all systematic reviews, a comprehensive search to identify all relevant studies is considered compulsory to minimise risk of bias.

In spite of this ideal benchmark, there are no optimal or effective search strategies for literature on prognostic studies that offer good sensitivity or specificity.[229] This problem is augmented by publication bias, which has been shown to be more prevalent for the types of study designs associated with prognostic studies (i.e. epidemiological studies as compared with randomised trials).[233]

3.8   Meta-analysis of individual patient data

To improve the conduct of systematic review for prognostic studies, it has been suggested that reviewers should not merely rely on information extracted from published literature which are subjected to biases.[234] Where possible, a method known as meta-analysis of individual patients data (IPD) is a recommended approach as an alternative to the aggregate data from individual study publications.[235] This method has been termed the "gold-standard" for systematic review and has its advantages and disadvantages.[235]

The use of IPD in prognostic study reviews avoids the biases of published aggregate data though a detailed and exploratory analysis of raw data from each study and hence improves the quality of data for the synthesis of evidence.[235] Some of the common issues such as variability in cut-off points for continuous data, heterogeneity in outcomes assessed, unavailability or imprecise estimates and other statistical findings of interest can be overcome easily.[236] As a result, a more reliable and clinically useful evidence-base review of prognostic factors and research can be generated.[237]

Conversely, disadvantages of using IPD also exist. The suggested methodology requires a considerable amount of resources to carry out a review of this nature in terms of time, and labour costs. [235]Furthermore, this method does not resolve the issue of publication bias or poor methodological reporting of systematic review findings.[235] The other pertinent issue with IPD is the unavailability of raw data of individual patients and regulations governing data sharing and protection.[52]

In summary, the approach selected for the conduct of this systematic review is supported by fundamental principles linking evidence generation to translation of evidence into practice in improving healthcare and its related outcomes. As such, the systematic review undertaken within this thesis adheres to the JBI methodological framework. The details of the review are discussed in the following paragraphs.

3.9   Systematic Review Protocol

3.9.1 Statement of the review question

What is the best available evidence for prognostic factors applied in risk stratification according to the outcomes of chemotherapy-induced febrile neutropenia in adult cancer patients?

3.9.2 Objectives of the review

The objective of the review was to critically examine and synthesise the best available evidence for prognostic factors for risk stratification in adult cancer patients, at the onset of FN associated with myelosuppressive chemotherapy.

3.9.3 Review Questions:

1. What are the prognostic factors that stratify adult cancer patients at the onset of chemotherapy-induced FN to a high-risk group?

2. What are the prognostic factors that stratify adult cancer patients at the onset of chemotherapy-induced FN to a low-risk group?

3.9.4 Inclusion criteria

Types of participants

At the protocol stage of this review, the stipulated age for participants of interest was adults aged 18 years or above. However, the reviewer decided to consider studies that included patients of age 15 years and above, as there are

minimal differences in the physiology and medical treatment between the two groups except for adjustment of drug dosages, and this allowed for greater flexibility in managing data from papers where the age groups were wider than initially stated in the protocol.

Other criteria included; patients with a diagnosis of cancer regardless of stage and status of the disease, who had sought medical treatment at healthcare institutions as in-patients or out-patients for febrile neutropenia induced by myelosuppressive chemotherapy (not longer than four weeks from the last cycle of chemotherapy). Patients who were treated with high dose chemotherapy or undergoing haematopoietic stem cell transplantation were also included.

Focus of interest

The focus of this systematic review was the current available prognostic factors and their predictive value for categorising cancer patients with chemotherapy-induced febrile neutropenia at presentation of fever into high- and low-risk for adverse outcomes. In this review, the prognostic factors of interest were variables or characteristics that would predict FN cancer patients to be in either the high-risk group with unfavourable outcomes or the low-risk group with favourable outcomes. The outcomes were measured with end-points as listed below:

i) **High-risk group:** defined as factors associated with the following end-points:

    a. Bacteraemia

    b. Gram-negative bacteraemia

c. Sepsis

d. Severe sepsis

e. Septic shock

f. Death

g. Other serious medical complications:[10]

- Hypotension (systolic blood pressure < 90mmHg) or requiring vasopressor to sustain blood pressure

- Respiratory failure needing mechanical ventilation

- Admission to Intensive Care Unit (ICU)

- Disseminated intravascular coagulation

- Confusion or altered mental state

- Congestive cardiac failure as ascertained on chest x-ray, necessitating treatment

- Bleeding requiring blood product transfusion

- Arrhythmia or electrocardiogram changes requiring treatment

- Renal failure requiring investigation, treatment and intervention

- Any other complications determined to be serious and clinically significant by the investigator.

ii) **Low-risk group:** defined as factors associated with the following end-points:

a. duration of neutropenia expected to resolve within seven days, with no active medical co-morbidity with normal hepatic and renal function[5]

b. absence of fever for five consecutive days without development of serious medical complication, regardless of modifications of the initial antibiotic treatment.[10]

In the context of this review, the emphasis was on the prognostic variables (clinical and laboratory) assessed within the first 24 hours from onset of febrile neutropenia for the prediction of high and low-risk group allocation. The duration of follow-up required was a minimum of five days. The timing and accuracy of patients' information at the point of assessment are important because factors with significant predictive value at the onset of fever could have different significances or be invalid at a later period, e.g.at 72 hours of FN.

In this review, bacteraemia and gram-negative bacteraemia have been used as surrogates for high-risk of adverse outcomes. Although this does have disadvantages since not all incidences of bacteraemia are associated with increased risk of severe complications such as sepsis or shock. By categorising patients with bacteraemia or gram-negative bacteraemia as belonging to the high-risk group it is plausible that the specificity and positive predictive value of either of these two factors may be altered. However, studies have shown that FN patients with bacteraemia or blood stream infection, in particular the gram-negative strains, may be associated with a higher risk of adverse outcomes and tend to fare worse than FN patients with unexplained fever.[37, 101, 238] As such, neutropenic cancer patients with bacteraemia do have an incremental risk of unfavourable outcomes in the event of a febrile episode.

Types of studies

The review considered any experimental study design including randomised control trials, non-randomised controlled trials, quasi-experimental studies, cohort studies, case control studies, case-cohort studies and case series that examined prognostic factors for risk assessment of chemotherapy-induced febrile neutropenia for adult cancer patients at the presentation of fever or within 24 hours from onset. Both retrospective and prospective studies that reported sufficient data for prognostic factor analysis and matched the review's outcomes were also included.

Types of outcomes

The primary outcome of interest in this review was to identify the prognostic factors used to categorise patients with chemotherapy-induced FN into the high- and low-risk group. This review was guided by the following definitions:

a. **Fever** - a single oral temperature measurement of $\geq$38.3°C (101°F) or a temperature of $\geq$38.0°C (100.4°F) sustained over a one-hour period.[5]

b. **Neutropenia** - ANC of <1000 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 within 48 hours.[5]

c. **Bacteraemia** - the presence of microorganism/ pathogens in the bloodstream as documented by positive blood culture(s) (after contamination is excluded).[239]

d. **Sepsis –** presence of infection in combination with systemic inflammatory response to infection, as evident by two or more of the following conditions: a) temperature >38°C or <36°C; b) heart rate>90beats/min; c) respiratory rate>20 breaths per minute or PaCO2 <32 mmHg; and d)

white blood cell count >12,000/mm³,<4,000/mm³, or >10% immature (band) forms[240]

e. **Severe sepsis -** presence of sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.[240]

f. **Septic shock -** sepsis-induced hypotension (despite adequate fluid resuscitation and inotropic or vasopressor agents) in the presence of severe sepsis.[240]

3.9.5 Search strategy

Prior to undertaking the systematic review on this topic, a preliminary search of the Cochrane Library, Joanna Briggs Institute Library of Systematic Reviews, MEDLINE and the Database of Abstracts of Reviews of Effects (DARE) was performed to establish that no previous systematic reviews had been published on this topic. None were found specific to the criteria in this systematic review.

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised. An initial limited search of MEDLINE using identified keywords was followed by the analysis of the free text and keywords contained in the title and abstract, and of the index terms used to describe articles. A second search using all identified keywords and index terms was undertaken across all included databases. To accommodate the differences in search features between databases, the search strategy was modified as

required. The third step included a search for additional studies from the reference lists of relevant reports and articles.

Only studies published in English were included in this review. Published reviews identified through the screening search that addressed prognostic factors related to FN outcomes were retrieved to examine the included primary studies with relevance to the objectives and criteria that could be included for this systematic review. Hand searches, reference list scans and citation indices were also performed for further relevant articles.

Electronic databases searched from their respective inception date up to December 2011 included:

1. MEDLINE

2. EMBASE

3. CINAHL

4. Cochrane Central Register of Controlled Trials (CENTRAL)

5. Web of Science

6. Science-Direct

7. Scopus

8. Mednar

The key words used in combination to generate database search strategies were:

Prognostic, predictive, factor, marker, variable, fever, febrile, neutropenia, granulocytopenia, immunosuppressed, chemotherapy, outcome, mortality, bacteraemia, sepsis.

The detailed search terms used for each database are available in Appendix I.

3.9.6 Method of the review

Assessment of methodological quality

Studies that matched the review's objectives and inclusion criteria were retrieved and subject to independent assessment by two reviewers (Yee Mei and Dora Lang). An agreement had been established between both reviewers for criteria considered vital for the assessment of quality for review of prognostic factor studies prior to undertaking the independent evaluation of study quality. The quality of studies was assessed for internal and external validity.

The domains of appraisal included: representativeness and generalisation of study population; clearly defined and appropriately measured prognostic factors and outcomes; whether potential confounders were addressed; loss to follow-up and appropriate statistical analysis undertaken for the study design.[111] The standardised critical appraisal tool from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument for cohort studies (JBI-MAStARI) was used (Appendix II). Disagreements about critical appraisal were resolved by consensus of both reviewers, a third reviewer (Craig Lockwood) was consulted when required.

Data collection

Data was extracted from individual included studies using the data extraction tool from JBI-MAStARI for experimental and non-experimental studies with minor modification based on the characteristics of prognostic studies (Appendix III). The data extracted included the publication details, study methods, setting, patient population, age, sample size, duration of follow up, prognostic variables in univariate analysis and multivariate analysis, and the results reported as Odds Ratio (OR), 95% Confidence Interval (CI).

Data synthesis

The methods and processes for meta-analysis were based upon the nature of the data (dichotomous data for the outcomes of interest in this review). Within the options for meta-analysis of dichotomous data, a fixed effects model was applied using OR. Odds ratios were chosen as there was no statistical imperative to select relative risks as a preferred method of reporting. If fixed effect models were compromised by statistical heterogeneity, a random effects model would have been utilised as a test of heterogeneity; however, there was no confounding by statistically significant levels of heterogeneity.

The significance of factors from each included study was identified from the reported multivariate regression, and the ORs and CIs reported for these factors were extracted. Study results were pooled in statistical meta-analysis using Review Manager 5.1. Results were displayed in a Forest Plot and log Odds Ratio (lg OR) with 95% Standard Error used to report the predictive value for each factor. The Odds Ratios were analysed using a log odds approach as scales across studies become symmetric when subject to a log odd procedure,

(values for odds ratios range from zero to infinity where one (1) represents no effect, resulting in a non-symmetric scale.[241]

Statistical heterogeneity was assessed using the I^2 value. An I^2 value greater than 50% with a $P<0.05$ was considered evidence of substantial heterogeneity.[242] None of the included meta-analyses reported in this systematic review exceed these criteria as such there was no statistically significant heterogeneity. Where statistical pooling was not possible the findings have been presented in narrative form.

3.9.7 Results of the systematic review

Description of studies

The comprehensive database searches were performed and a total of 2256 studies were retrieved. Duplicates of 217 studies were removed, and titles and abstracts of 2039 studies were screened. Of these, 2005 were excluded. Thirty-four studies were retrieved for detailed analysis of the full text. Twenty were excluded after detailed full text examination as they did not meet inclusion criteria. Fourteen studies were assessed for methodological quality with seven studies included in the final review (Figure 3.3).
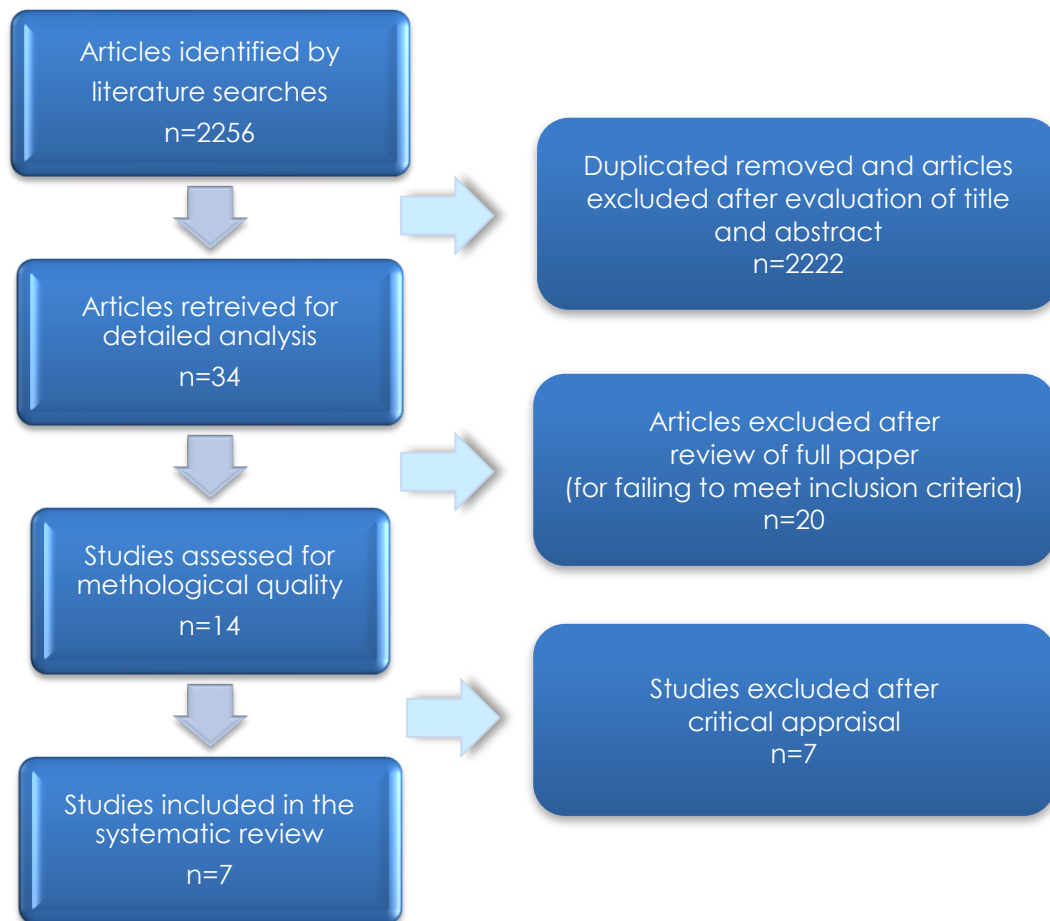
Figure 3.3 Identification and selection of studies

Description of included studies

In the seven included studies, there were two factors identified that could be combined in meta-analysis while the remaining findings (factors) lacked repetition studies suitable for combining in statistical analysis. The included studies comprised of four prospective[10, 58, 73, 165] and three retrospective[59, 74, 173] cohort studies. Three studies analysed data according to repetitive episodes of FN[58, 59, 173] while the remainder was analysed by study population. A table was used to summarise the characteristics of the included studies and can be found in Appendix IV.

The total number of patients included in the studies was 3747, with each study ranging from 20 to 2142 patients. The patients were aged 15 years and above, and they comprised of a wide mix of patients with solid tumour, haematological malignancies and patients undergoing haematopoietic stem cell transplantation. All patients received some form of myelosuppressive chemotherapy regimen. Two studies included patients with acute leukaemia[74, 165] and the other five studies were comprised of mixed groups of cancer patients.[10, 58, 59, 73, 173]

The included studies were conducted in a large range of countries including: Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Italy, Korea, Pakistan, Singapore, Spain, South Africa, Sweden, Sweden, Switzerland, The Netherlands, Tunisia, and United States of America. Patients were either admitted to the in-patient setting, received treatment as an out-patient or at the emergency department.

The end-points measured across the included studies were diverse. Only one study looked at factors identifying low-risk.[10] Four other studies concentrated on identifying factors predictive of high-risk. The remaining two studies looked at factors predictive of bacteraemia and gram-negative bacteraemia in FN cancer patients. The following were used as end-point measures for the prognostic factors identified as high-risk with complicated FN: bacteraemia and gram-negative bacteraemia, development of serious medical complications and infection-related mortality. For the low-risk group: fever resolution for five consecutive days (with or without modification of antibiotic therapy) without

development of serious medical complications was used. In terms of follow up, the duration ranged from five days up to 30 days mortality.

Description of excluded studies

Many studies were excluded because the patient selection criteria were unclear. For example, patients with neutropenic fever due to uncontrolled disease and not related to chemotherapy were included in the study by Talcott et al.[64] Other studies were excluded due to assessment of prognostic factors occurring after 24 hours or after patients were categorised as low-risk group (from initial assessment)[40, 68, 82, 183] or specifically cancer patients with confirmed bacteraemia[69]. Others were excluded because results were reported with only *p*-values[243, 244] and some were not primary studies. Studies that included paediatric and adult patients in which a separate analysis was not performed were also excluded. The studies' characteristics and reasons for exclusion are reported in Appendix V.

Methodological quality

An assessment of the methodological quality of each study was performed independently by two reviewers against the Joanna Briggs Institute critical appraisal instruments. For each of the criteria a "Y" (Yes) was assigned if the criteria were met. If the stated criterion was not met, an "N" was assigned. In the presence of insufficient information to determine if a particular criterion was met, a "U" (Unclear) was assigned. To be considered a "Y", the studies must have demonstrated complete description regarding the process and outcome of each criterion while the "U" was assigned when the reviewers were not able to clearly identify the particular aspect of method addressed in the questions

due to unclear or inadequate reporting. The score were summed up to give an overall score assessing the quality of the studies.

Seven included cohort studies varied in quality ranging from poor to moderate quality although majority of studies achieved above more than 50% of scores as reflected in Table 3.1. All were categorised as level III evidence according to the Joanna Briggs Institute levels of evidence (Appendix VI).All included studies applied univariate statistical analysis methods to identify the significance of prognostic factors followed by the application of multivariate logistic regression to adjust for confounding factors. All results with *p*-values equal to or less than 0.05 were considered significant for analysis.

Limitations of the included studies stemmed from important aspects of prognostic studies not having been adequately addressed. They included: inconsistent FN definitions for inclusion criteria of patients in the primary studies, lack of clear reporting on methods of assessment, confounding factors and strategies to deal with them, details relating to patient drop-out and loss of follow up and, questionable statistical analysis due to selective reporting. Among the seven included studies, there were four different definitions of neutropenia[10, 74, 165, 173] and three of fever[10, 74, 173]. However, all definitions were clinically similar, inclusive and matched the inclusion criteria of the review.

The lack of clear or inadequate reporting on independent assessment of outcomes in FN patients[74, 165] can increase the risk of bias of the factors reported in the respective studies, therefore every attempt (including

contacting authors) was made to facilitate accurate assessment of internal validity. Additional limitations were also noted in the study design and sample size, the assessment of prognostic factors investigated and types of outcome measured. Of the included studies, only one study applied prognostic factors identified from its study to develop a clinical prediction model.[10] Variables considered as candidate predictors were chosen according to physician judgment or published reports.[10]

Table 3.1 Results for the critical appraisal of included studies using the JBI-MAStARI critical appraisal instrument

Comparable Cohort / Case Control Studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Klastersky, J, Paesmans, M, Rubenstein, EB, Boyer, M, Elting, L, Feld, R, Gallagher, J, Herrstedt, J, Rapoport, B, Rolston, K, Talcott, J, 2000	Y	Y	U	Y	Y	Y	U	Y	Y
Ahn, S., Lee, Y. S., Chun, Y. H., Kwon, I. H., Kim, W., Lim, K. S., Kim, T. W., Lee, K. H., 2011	Y	Y	U	Y	Y	Y	U	Y	Y
Jin, J., Lee, Y. M., Ding, Y., Koh, L. P., Lim, S. E., Lim, R., Tambyah, P. A., Hsu, L. Y., 2010	Y	Y	U	Y	Y	Y	U	Y	U
Moon, J. M. & Chun, B. J., 2009	Y	Y	U	Y	Y	Y	U	Y	Y
Ramzi, J., Mohamed, Z., Yosr, B., Karima, K., Raihane, B., Lamia, A., Hela, B. A., Zaher, B., Balkis, M., 2007	Y	Y	U	Y	Y	Y	U	Y	U
Paesmans, M., Klastersky, J., Maertens, J., Georgala, A., Muanza, F., Aoun, M., Ferrant, A., Rapoport, B., Rolston, K., Ameye, L., 2011	Y	Y	U	U	Y	Y	U	Y	Y
Yoo, J-H., Choi, S.M., Lee, D-G., Choi, J-H., Shin, W-S., Min, W-S. & Kim, C-C, 2005	Y	Y	U	U	Y	Y	U	Y	Y
% 'yes' responses	100.0	100.0	0.0	71.43	100.0	100.0	0.0	100.0	71.43

This table shows the results of critical appraisal for the included studies (listed in the first column)
Refer to, Appendix II for questions 1-9 in the relevant MAStARI critical appraisal instrument
Y= yes; U= unclear
Q1, Q2, Q3 – Study population representativeness (inclusion and exclusion criteria)
Q4 – Confounding factors identified and addressed
Q5, Q8 – Outcomes criteria relevant and standardised in assessment
Q6, Q7 – Follow-up duration sufficient
Q9 – Appropriate statistical techniques

3.9.8 Review findings

An overview of the prognostic factors predictive of risk stratification of FN patients is presented in Table 3.2. The review findings were categorised into five main groupings which include: patient-related factors, disease-related factors, treatment-related factors, FN-episode-related factors and laboratory markers.

A total of 22 factors were identified in this review. Prognostic factors reported in more than one (included) study were hypotension[73, 74] and thrombocytopenia (platelet <50,000/mm³)[59, 173]. Given the homogeneity of the outcomes measured and patient populations of the respective studies, meta-analysis was performed for these two factors.

Other prognostic factors, where pooling of data was not possible due to lack of homogeneous samples across studies and inconsistencies in the analysis of data between studies, are presented in narrative form. It was not possible to undertake subgroup analysis for primary studies due to data for mixed patient groups not being reported separately (e.g. solid tumour and haematological malignancy data were combined).[10, 58, 59, 73, 173]

Table 3.2 Summary of Clinical Factors Predictive of High- and Low-risk from the Included Studies according to Sub-groups

Primary Studies	Individual Factors	Subgroups	Categories
Paesmans et al.[73] Klastersky et al.[10]	Age$\geq$ 60 yrs; Age <60 yrs	Age	Patient-related factors
Klastersky et al.[10]	Absence of COPD	Comorbidities	
Yoo et al.[74]	Previous fungal infection Invasive fungal infection		
Klastersky et al.[10]	No history of fungal infection		
Paesmans et al.[73]	Haematological malignancy	Underlying disease	Disease-related factors
Klastersky et al.[10]	Solid tumour		
Paesmans et al.[73]	No adjuvant or neo-adjuvant cancer treatment	Treatment indication	Treatment-related factors
Paesmans et al.[73]	No administration of prophylaxis	Antimicrobial prophylaxis	
Jin et al.[58]	Presence of central venous catheter	Vascular access device	
Yoo et al.[74]	Median days to fever	Days to onset of fever	
	Total febrile days	Total febrile days	
Ahn et al.[59]	Neutropenia duration*		
Paesmans et al.[73]	Temperature $\geq$39ºC	Clinical presentation and vital signs	FN episode-related factors
Ahn et al.[59]	Tachypnoea		
Yoo et al.[74], Paesmans et al.[73]	Hypotension		
Paesmans et al,[73] Klastersky et al.[10]	Burden of illness: -severe signs / moribund -moderate symptoms -mild symptoms		
Klastersky et al.[10]	Absence of dehydration Absence of hypotension		
Paesmans et al.[73]	In-patient	Geographical location at onset of fever	
Klastersky et al.[10]	Out-patient		
Moon et al.[173]	Pulmonary infiltration	Presence of infection site	
Yoo et al.[74]	Pneumonia		
Jeddi et al.[165]	Pulmonary infection		
Ahn et al.[59], Moon et al.[173]	Thrombocytopenia	Platelets count at fever onset	Laboratory markers
Paesmans et al.[73]	Absolute Neutrophil Counts: -0 uL -1-99 uL	ANC at fever onset	
Yoo et al.[74]	Recovery from neutropenia		

Duration of neutropenia $\geq$ 4 days (from the onset of febrile episode)

3.9.9 Patient-related factors

Table 3.3 Patient–related factors predictive of FN outcomes

Patient-related factors	Primary studies	Predictors	Multivariate Odds ratios (95% CI)
Age	Paesmans et al.[73]	Age$\geq$ 60 yrs;	1.81, [1.31-2.49],p<0.001
	Klastersky et al.[10]	Age <60 yrs (low-risk)	2.45, [1.51-4.01],p<0.001
Comorbidities	Klastersky et al.[10]	Absence of COPD (low –risk)	5.35, [1.86-15.46],p=0.002
		No history of fungal infection (low-risk)	5.07, [1.97-13.04],p=0.0008
	Yoo et al.[74]	Previous fungal infection	82.5, [3.00-2268.57],p=0.0091
		Invasive fungal infection	5.7, [2.80-88.03],p=0.0017

COPD – Chronic obstructive pulmonary disease
Factors not listed as low-risk are otherwise high-risk

Age

Older age (age $\geq$ 60 years) emerged as an independent prognostic factor for

gram-negative bacteraemia while younger age (age <60 years) was

independent predictive factors of favourable outcome. (Table 3.3)

Comorbidities

Comorbidities which were independent prognostic factors for FN outcomes in

the review findings included absence of COPD and fungal infection (absent,

previous or concurrent). Absence of COPD and fungal infection were

predictive of low-risk for developing serious medical complications among FN

patients. In contrast, presence of fungal infection or having been previously

diagnosed with fungal infection has been associated with cancer patients at

high-risk of developing adverse outcomes during the period of FN. (Table 3.3)

3.9.10   Disease-related factors

Table 3.4 Disease-related factors predictive of FN outcomes

Disease-related factors	Primary studies	Predictors	Multivariate Odds ratios (95% CI)
Underlying disease	Paesmans et al.[73]	Haematological malignancy	1.38, [1.06-1.80],p=0.02
	Klastersky et al.[10]	Solid tumour (low-risk)	5.07, [1.97-12.95],p<0.001

Factors not listed as low-risk are otherwise high-risk

Underlying disease

In multivariate analysis, a solid tumour was one of the factors predictive of FN patients with low-risk with favourable outcomes while the diagnosis of haematological malignancy was predictive of FN patients with high-risk with unfavourable outcomes. (Table 3.4)

3.9.11   Treatment-related factors

Table 3.5 Disease-related factors predictive of FN outcomes (high-risk)

Treatment-related factors	Primary studies	Predictors	Multivariate Odds ratios (95% CI)
Treatment indication	Paesmans et al.[73]	No adjuvant or neo-adjuvant cancer treatment	2.021, [1.34-3.06],p<0.001[a] 3.80, [1.63-8.86,p=0.002[n]
Prophylaxis therapy		Absence of prophylactic antibiotic	1.45, [1.04-2.01],p=0.03[n]
Vascular access device	Jin et al.[58]	Presence of central venous catheter	3.36, [1.46-7.72], p<0.01
Duration of fever onset and total days to defervescence	Yoo et al.[74]	Median days to fever	1.03, [0.88-1.20],p=0.7124[t]
		Total febrile days	1.03, [0.95-1.11],p=0.4737[t]
	Ahn et al.[59]	Neutropenia duration**	2.52, [1.21-5.25], p=0.014

[a]bacteraemia as end-point
[n]gram-negative bacteraemia as endpoint
** duration of neutropenia $\geq$ 4 days
[t] not statistically significant

Treatment indication

With regards to factors associated with bacteraemia and gram-negative bacteraemia, cancer patients who were not undergoing adjuvant or neo-adjuvant cancer treatment were at risk of infection which may lead to

unfavourable outcomes (microbiologically documented) as indicated in Table 3.5.

Prophylactic antibiotic

The odds of cancer patients who were not prescribed antibiotic prophylaxis was 1.45 higher in developing gram-negative bacteraemia during FN compared with patients who were receiving prophylactic antibiotic and FN patients with gram-negative bacteraemia are at risk of unfavourable outcomes.(Table 3.5)

Vascular access device

Neutropenic patients were reported to be at increased risk of bacteraemia which may lead to sepsis during the period of FN, if they have a central venous catheter which was inserted for chemotherapy. (Table 3.5)

Duration of neutropenia, to onset of fever and total febrile days

In the study conducted by Yoo et al[74], two factors appeared to be predictive of FN patients with high-risk for infection-related mortality through univariate analysis. These were: median days to fever and total febrile days.[74] The group of patients who died was recorded to have longer duration of fever (median febrile days=10 versus 5; p=0.001) as compared with patients who survived.[74] However, both factors failed to achieve statistical significance in multivariate analysis. (Table 3.5)

In terms of duration of neutropenia, Ahn et al[59] reported that patients who experienced neutropenia for longer than four days from onset of fever were categorised as high-risk of developing serious medical complications during FN. (Table 3.5)

3.9.12 Febrile neutropenia episode-related factors

Table 3.6 Febrile neutropenia episode-related factors predictive of FN outcomes

FN Episode-related factors	Primary studies	Predictors	Multivariate Odds ratios (95% CI)
Clinical presentation and vital signs	Paesmans et al.[73]	Temperature ≥39°Cl	1.81 [1.43-2.30],p<0.001
	Ahn et al.[59]	Tachypnoea*	3.61 [1.44-9.08],p=0.006
	Yoo et al.[74], Paesmans et al.[73]	Hypotension	1.59, [0.31-8.25],p=0.5783 1.66, [1.11-2.47], p=0.01]
	Klastersky et al.[10]	No hypotension (low-risk)	7.62, [2.91-19.89],p<0.001
	Paesmans et al.[73]	Burden of illness: -severe signs/ moribund	1.97, [1.43-2.71],p<0.001ᵃ 2.44, [1.60-3.73],p<0.001ⁿ
		-moderate symptoms	1.44, [1.13-1.83],p=0.00ᵃ 1.30,[0.90-1.86],p=0.16ⁿ
	Klastersky et al.[10]	Burden of illness: -no/mild symptoms -moderate symptoms (low-risk)	8.21, [4.15-16.38],p<0.001 3.70, [2.18-6.29],p<0.001
		No dehydration (low-risk)	3.81, [1.89-7.73],p<0.001
Location at onset of fever	Paesmans et al.[73]	In-patient	2.07, [1.61-2.68], p<0.001
	Klastersky et al.[10]	Out-patient (low-risk)	3.51, [2.02-6.04],p<0.001
Presence of infection site	Moon et al.[173]	Pulmonary infiltration	30.167, [7.281-124.99],p<0.001
	Yoo et al.[74]	Pneumonia	1.30, [0.27-6.26],p=0.7435
	Jeddi et al.[165]	Pulmonary infection	5, [1.052-23.764]; p=0.043

ᵃbacteraemia as end-point
ⁿgram-negative bacteraemia as endpoint
*Respiration rate >24 breaths/min
Factors not listed as low-risk are otherwise high-risk

Clinical presentation and vital signs

At fever presentation, the majority of the abnormal clinical signs and symptoms were associated with high-risk of adverse outcomes in cancer patients with neutropenia. High fever, tachypnoea, hypotension and moderate to severe

clinical symptoms were predictive of unfavourable outcomes of FN patients. In contrast, absence of hypotension, adequate hydration and displaying no or mild to moderate clinical symptoms were associated with low-risk of deterioration in clinical condition. (Table 3.6)

For the same factor "burden of illness", severe signs or moribund and moderate symptoms were predictive of FN patients at risk of bacteraemia and gram-negative bacteraemia in the study conducted by Paesmans et al.[73]An overlap of factor (moderate symptoms) was noted between the two studies although the outcomes associated with this factor were bacteraemia (high-risk) and low-risk of FN outcomes. (Table 3.6)

Two studies that reported the same factor (hypotension) were pooled together,[73, 74] and the meta-analysis showed that hypotension is statistically significant as a prognostic factor for FN patients with high-risk as shown in Figures 3.4 and 3.5. Performed using a fixed effect model with a total of 1143 patients, there was no heterogeneity detected in the analysis for bacteraemia or gram-negative bacteraemia.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Paesman 2011	0.5068	0.1962	94.8%	1.66 [1.13, 2.44]	
Yoo 2004	0.4637	0.8342	5.2%	1.59 [0.31, 8.16]	
Total (95% CI)			100.0%	1.66 [1.14, 2.41]	
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%					
Test for overall effect: Z = 2.64 (P = 0.008)					
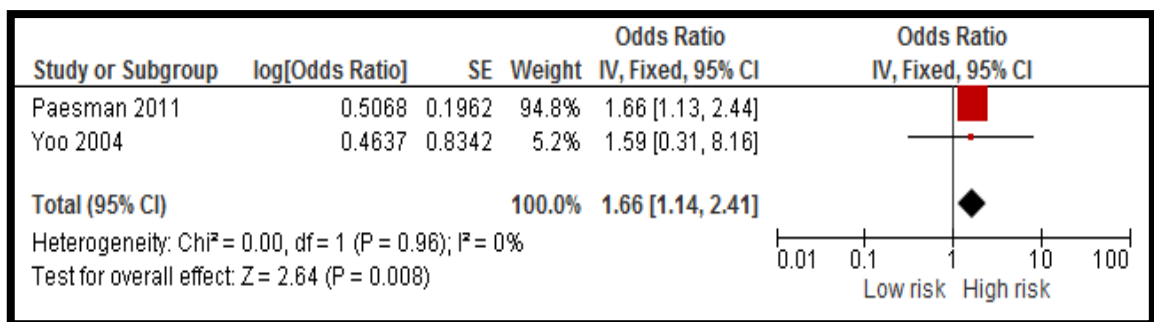
Fixed – Fixed effects model; SE – Standard error; CI- Confidence interval

Figure 3.4 Meta-analysis for hypotension as a prognostic factor for high-risk patient with bacteraemia
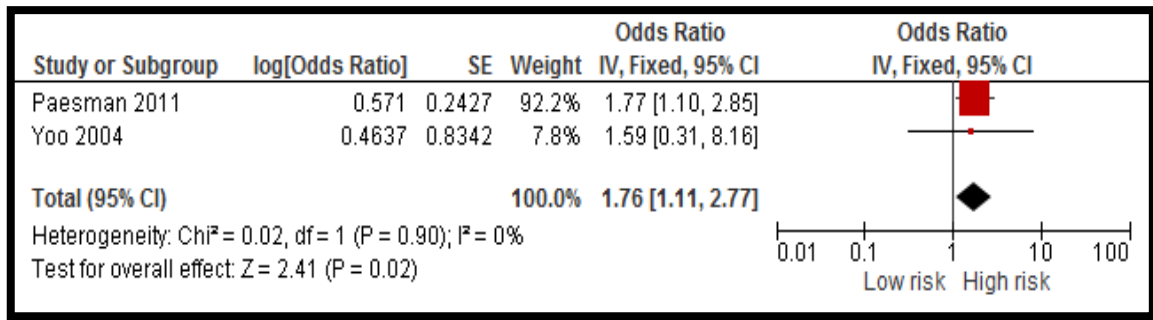
Fixed – Fixed effects model; SE – Standard error; CI- Confidence interval

Figure 3.5 Meta-analysis for hypotension as a prognostic factor for high-risk FN patients with gram-negative bacteraemia

Location of patient at onset of fever

The review findings confirmed that in-patient status is predictive of high-risk while being out-patient is predictive of low-risk. (Table 3.6) Both factors are shown to be statistically significant in prognostication of FN outcomes.

Pulmonary infection

Three factors, which are related to the respiratory system, were identified in the review findings as predictors of unfavourable outcomes for FN patients. They include: presence of pulmonary infiltration, pneumonia or pulmonary infection. (Table 3.6)Presence of pulmonary infiltration in chest radiograph was reported to be an independent factor for the prediction of FN with complications in the study conducted by Moon et al.[173] This cohort study included an analysis of 193 episodes among 168 cancer patients who presented to the emergency department with chemotherapy-induced febrile neutropenia.

In a retrospective observational study involving 284 FN patients with acute leukaemia conducted by Yoo et al[74], the presence of pneumonia was identified as a prognostic factor for infection-related mortality through

univariate analysis (OR 8.09; 95%CI,3.46-18.90, p<0.001) but this factor failed to show statistical significance when adjusted for the simultaneous effect of other variables in the multivariate analysis.[74]

In another primary study, an analysis of 110 episodes of acute leukaemia reported the presence of pulmonary infection as a statistically significant prognostic factor for septic shock[165](Table 3.6). Although both studies were homogeneous in terms of patient populations and prognostic factors identified (pneumonia and pulmonary infection), statistical pooling was not possible due to the differences in methods of analysis across studies.

3.9.13   Laboratory markers

Table 3.7 Laboratory markers predictive of FN outcomes

Laboratory markers	Primary studies	Predictors	Multivariate Odds ratios (95% CI)
Absolute neutrophil count at onset of fever	Paesmans et al.[73]	ANC level -0 cells/mm^3 -1-99 cells/mm^3	2.55,[1.90-3.42],p<0.001[a] 3.38,[2.15-5.30,p<0.001[n] 1.80,[1.31-2.48],p<0.001[a] 1.96, [1.20-3.22],p<0.001[n]
	Yoo et al.[74]	Recovery of neutropenia (low-risk)	0.01, [.001-0.031],p=0.7128
Low platelet count at onset of fever	Ahn et al.[59]	Thrombocytopenia	4.982, [2.00-12.048], p=0.001
	Moon et al.[173]		3.41, [1.69-6.89], p=0.001

[a]bacteraemia as end-point
[n]gram-negative bacteraemia as endpoint
Factors not listed as low-risk are otherwise high-risk

Absolute neutrophil count at onset of fever

A laboratory variable that was found to be statistically significantly associated with unfavourable outcomes of FN was low ANC levels. In the study by Paesmans et al[73], an ANC level of 0cells/mm^{3}and between 1-99 cells/mm^{3}were

associated with unfavourable FN outcomes. In contrast, the recovery from neutropenia appeared to be a protective factor for infection-related mortality although it was not statistically significant in the multivariate analysis[74] (Table 3.7).

Platelet count at onset of fever

Meta-analyses of two studies[59, 173] with a total of 514 patients (588 episodes) identified thrombocytopenia as a factor predictive of high-risk group of FN patients. (Table 3.7) Using a fixed effect model it showed a pooled effect size that was statistically significant for this factor as shown in Figure 3.6. There was no significant heterogeneity detected between the two studies.
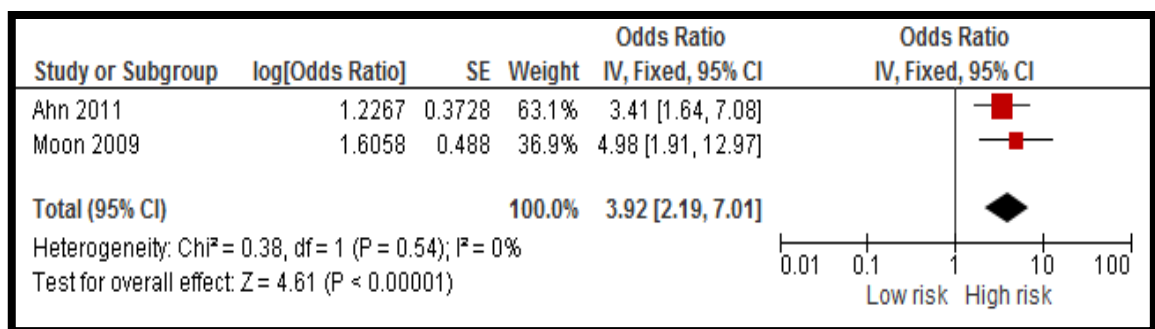
Fixed – Fixed effects model; SE – Standard error; CI- Confidence interval

Figure 3.6 Meta-analysis for thrombocytopenia (platelets <50,000/mm³) as a prognostic factor for high-risk patients

3.9.14   Factors summarised according to the odd ratios

Clinical factors reported with point estimates of ORs above five and statistically significant in association with FN patients with low-risk and high-risk of adverse outcomes are reported in Table 3.8 and Table 3.9.

Table 3.8 ORs above 5 (Factors associated with low-risk)

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI), p value
Klastersky et al.[10]	Burden of illness: -mild symptoms	8.21, (4.15-16.38), p<0.001
	Absence of hypotension	7.62, (2.91-19.89),p<0.001
	Absence of COPD	5.35, (1.86-15.46), p=0.002
	Solid tumour /no previous fungal infection	5.07, (1.97-12.95),p<0.001

Table 3.9 ORs above 5 (Factors associated with high-risk)

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI), p value
Yoo et al.[74]	Previous fungal infection	82.5, (3.0-2268.57), p=0.0091
	Invasive fungal infection	15.7, (2.80-88.03),p=0.0017
Moon et al.[173]	Pulmonary infiltration	30.167(7.281-124.99),p<0.001
Jeddi et al.[165]	Pulmonary infection	5, (1.052-23.764),p=0.043

Although these factors have considerably high point estimates and significant p-values, they also have wide confidence interval (range from 1.05 to 2268.57). The moderate to extreme wide range of CIs is attributed to studies that included small sample size and low events rates of intended outcomes measured. As a consequence, these factors lack precision in their magnitude of association with the measured outcomes, thus making it difficult for clinicians to draw conclusions in relation to their prognostic values.

Table 3.10 ORs above 2 (Factors associated with low-risk)

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI) p value
Klastersky et al.[10]	Absence of dehydration	3.81, [1.89-7.73],p<0.001
	Burden of illness: moderate symptoms	3.70, [2.18-6.29], p<0.001
	Out-patient	3.51, [2.02-6.04],p<0.001
	Age < 60 years	2.45, [1.51-4.01],p<0.001

Table 3.11 ORs above 2 (Factors associated with high-risk)

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI), p value
Ahn et al.[59]	Tachypnoea*	3.61, [1.44-9.08], p=0.006
	Duration neutropenia $\geq$ 4 days	2.52, [1.21-5.25], p=0.014
Jin et al.[58]	Presence of central venous catheter	3.36, [1.46-7.72], p<0.01
Paesmans et al.[73]	Burden of illness: severe signs / moribund	2.44, [1.60-3.73], p<0.001
	Absolute Neutrophil Counts: 0 uL	2.55,[1.90-3.42], p<0.001[a] 3.38, [2.15-5.30], p<0.001[n]
	In-patient	2.07, [1.61-2.68], p<0.001
	No adjuvant or neo-adjuvant cancer treatment	2.02,[1.34-3.06]; p<0.001[a] 3.80,[1.63-8.86], p=0.002[n]

[a]bacteraemia as end-point
[n]Gram-negative bacteraemia as endpoint
Respiration rate $\geq$24b/min

The group of prognostic factors for low-risk with ORs above two and statistically significant p-values are presented in Table 3.10 and Table 3.11. The CIs for these factors were narrower as compared to those factors reported in the previous paragraph. They ranged from 1.44 to 9.08, which is suggestive of an improved estimate of precision of the prognostic power of these factors. However, each of these factors was only reported in single studies.

Table 3.12 OR above 1 (Factors associated with high-risk)

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI, p value)
Paesmans et al.[73]	Absolute Neutrophil Counts: 1-99u/L	1.80, [1.31-2.48], p<0.001[a] 1.96, [1.20-3.22], p=0.008[n]
	Temperature ≥39ºC	1.81, [1.43-2.30], p<0.001
	Burden of illness: -moderate symptoms	1.44, [1.13-1.831], p=0.003[a]
	Age ≥ 60 years	1.81, [1.31-2.49], p<0.001[n]
	Absence of prophylaxis administration	1.45, [1.04-2.01], p=0.03[n]
	Haematological malignancy	1.38, [1.06-1.80], p=0.02[a]

[a]bacteraemia as end-point
[n]Gram-negative bacteraemia as endpoint

Lastly, prognostic factors with ORs above one which were statistically significantly associated with unfavourable outcomes are detailed in Table 3.12.Generally these factors had narrow confidence intervals ranging from 1.04 to 3.22, indicating a better estimation of the prognostic power for the respective factors.

Table 3.13 Factors with OR not statistically significant

Studies	Individual Factors	Multivariate analysis (ORs, 95% CI, p value)
Yoo et al.[74]	Pneumonia	1.30, [0.27-6.29], p=0.7435
	Total febrile days	1.03, [0.95-1.11], p=0.4737
	Median days to fever	1.30, [0.88-1.20], p=0.7124
	Recovery from neutropenia	0.01, [0.001-0.031], p=0.7128
Paesmans et al.[73]	Burden of illness: - moderate symptoms	1.30, [0.90-1.86], p=0.16[n]

[n]gram-negative bacteraemia as endpoint

There were also five other prognostic factors that failed to achieve statistical significance in the multivariate analysis (Table 3.13). All these factors had CIs crossing the point of no effect. The first four factors were reported in one single study of which the sample size of patients studied was underpowered and therefore unable to detect a true effect.[74] The prognostic factor, burden of illness -'presence of moderate symptoms with gram-negative bacteraemia', was reported to be not statistically significant and this could be related to insufficient number of patients who developed the outcome measured.[73] Although these factors were not statistically significant, it does not mean that they are not important as candidate factors in future, larger prognostic studies investigating similar outcome measures.

3.9.15 Summary of the review findings

Despite the overall limitations highlighted in the included studies, some of the prognostic factors reported in this review are consistent with previous literature reviews[31, 110, 192] and the Infectious Disease Society of America (IDSA) clinical practice guidelines.[5] For example, age of patients, clinical condition at presentation, presence or absence of co-morbidities, infections (especially of respiratory and fungal aetiologies), duration and severity of neutropenia. Prognostic factors found to be statistically significant in the systematic review component of the thesis (thrombocytopenia, presence of central venous catheter and duration and severity of neutropenia) were not included in any of the current prognostic models for FN outcomes. Possible reasons for the exclusion could be related to lack of availability of information such as duration and total febrile days at the point of care when needed.

3.9.16   Discussion

The systematic review has identified a weak to modest association for most factors which in current research studies have been reported to be of prognostic relevance for both high- and low-risk groups of cancer patients with FN.[5] Therefore, caution is advised with the interpretation of the review findings because of relatively poor methodological quality of primary studies.

Patient-related factors

As older age is often generally correlated with increased prevalence of chronic disease[245] this could explain why age was not specifically highlighted as a major predictor for risk stratification of FN patients in the guideline[5]. Although older age is independently associated with increased risk of neutropenia, FN and its complication,[132] this factor has been suggested to be less relevant than major comorbidities that accompany increasing age.[13, 147]

The findings of the systematic review on current or previous invasive fungal infection and absence of chronic lung disease in association with the outcome of FN were congruent with the factors specified in the clinical practice guidelines for the use of anti-microbial agents in neutropenia cancer patients.[5] Absence of chronic obstructive pulmonary disease (COPD) was used as a specific comorbidity in the MASCC risk-index model to identify low-risk FN patients.[10] Although it is unclear why COPD and no other chronic conditions were identified as one of the prognostic factors for FN outcomes in that study,[10] it is well-established that infection in particularly lower respiratory infections are linked with the occurrence of exacerbations of COPD.[246] When this happens,

patients may develop acute respiratory failure, potentially requiring mechanical ventilation support and admission to the intensive care unit.[247]

However, due to the limited evidence, and being the only study that reported this factor (absence of COPD) to be prognostic for FN outcomes, the contention is whether the absence of COPD should be replaced with another factor, i.e. other chronic illness(es)that may have an influence on the clinical severity of febrile episode. Presence of comorbidity in general is perhaps a more clinically relevant factor to be considered in the aging population of patients with cancer, although this warrants further investigation.

Disease-related factors

In many studies, the diagnosis of haematological malignancy has been associated with increased risk of infection, length of hospitalisation and mortality, as compared with solid tumours.[243, 248, 249] In the clinical practice guidelines by Infectious Diseases Society of America (IDSA), patients receiving induction chemotherapy for Acute Myelogenous Leukaemia (AML) or undergoing allogeneic haematopoietic cell transplantation with high-dose chemotherapy are automatically placed in the high-risk group due to the associated prolonged and severe neutropenia.[5]

In the same guidelines however, patients undergoing autologous haematopoietic cell transplantation and patients with acute leukaemia receiving consolidation treatment do not fall into the high-risk group.[5] Using tumour type as a prognostic factor is very much related to the association

between disease and neutropenia; it acts as a surrogate measure for the intensity of the cancer treatment that patients receive.

However, a recently published study by Klastersky et al[37] reported no statistically significant difference in the infection-related mortality rate between patients with solid tumour and haematological malignancies. This implies that the type of malignancy may not be a strong predictor for FN outcomes as compared with the status of the malignancy as reported in several primary studies.[64, 146] The first study to document that acute leukaemia patients with relapsed disease have a poorer outcome in the presence of infection was that by Bodey et al.[155]

Other studies reported early mortality for neutropenic cancer patients with uncontrolled disease in the presence of bacteraemia.[69, 144] Furthermore, in the Talcott risk assessment model, disease status strongly distinguished patients with high-risk (uncontrolled cancer) despite being out-patient at the onset of fever, versus low-risk (controlled disease).[36] This indicates that disease status may be a better prognostic factor in the risk assessment for FN patients even though clinically it is more challenging for physicians to obtain this information accurately as the evaluation of disease status for cancer patients is not performed regularly.

Treatment-related factors

i)No adjuvant or neo-adjuvant cancer treatment

Adjuvant therapy is cancer treatment administered in addition to primary therapy to improve disease-specific symptoms and overall survival while neo-

adjuvant therapy is administered before primary therapy commonly with the aim to reduce the size of tumour, both therapies are of curative intent.[250] Therefore, cancer patients who are not receiving either of these treatments are generally undergoing chemotherapy for disease-control. The inference that could be made for this factor found to be a predictive characteristic to stratify FN patients to the high-risk group is inter-related with the factor, disease status. As mentioned in the explanation under the section (disease-related factor), patients with relapsed disease or disease in the refractory stage are more susceptible to infection[155] and early mortality when they have bacteraemia[69, 144] and these patients are likely to be at risk of adverse outcomes during FN.

ii) Absence of prophylactic antibiotic

The use of antibiotic prophylaxis for neutropenic patients has been reported to reduce the incidence of bacterial infections (especially gram-negative)[123] and mortality. The effect of prophylaxis appears to be greater with quinolone use, as reported in a meta-analysis by Gafter-Gvilli.[122] Absence of prophylaxis with norfloxacin (a quinolone based antibiotic) was also reported to be a factor associated with increasing mortality in FN patients with bacteraemia.[144]

However, prophylaxis antibiotic prescription has not been a standard practice internationally and it is still dependent on clinicians' preference and institutional policies. Given the inconsistency in practice, it is therefore not practical to incorporate this variable as a predictive factor for FN patients although absence of prophylaxis could denote that these patients are more susceptible

to acquiring gram-negative types of infection(s)[251] and given the virulence of this types of infection, FN patients are at increased risk of sepsis and mortality[37].

iii) Presence of vascular access device(s)

There has been an increased use of long term indwelling central venous catheter (CVC) or other vascular access devices as part of the management of cancer patients.[102] Cancer patients requiring a CVC are predominantly patients with haematological malignancy who have regular blood tests, multiple blood product transfusions, parenteral nutrition and administration of chemotherapy (anthracyclines).[252]

However, the extensive use of CVCs has resulted in an increased risk of infection including catheter-related blood stream infection (CRBSI) and other complications such as septic thrombophlebitis and bacterial endocarditis.[253] The difference with CRBSI in cancer patients as compared with other ill patients is that signs and symptoms such as inflammation or purulence may not be present in neutropenic patients, hence the difficulty in clinical evaluation at the point of risk assessment.[95] Because the presence of a CVC in cancer patients increases their risk of infection, including this variable as a prognostic factor for risk assessment has merit.[254]

iv) Duration of neutropenia, to onset of fever and total febrile days

Attempts have been made to derive a method to calculate duration of neutropenia (days) for patients undergoing chemotherapy. Even at present, this factor has been mainly estimations made by clinicians based on clinical

experience.[5] Studies which have explored methods to predict duration of CIN in FN patients based on regimen-specific risk factors have been limited to solid tumour patients and standard chemotherapy regimens.[255, 256] With the increased utilisation of new chemotherapy regimens for cancer treatment, the estimation for expected duration of neutropenia proves to be even more challenging. Current practice is still very much based on existing drug information and clinical judgment as no reliable tools or formula have been developed to accommodate all cancer treatment regimens thus far.

As the importance of this factor as a prognostic factor for FN outcomes has been stressed repeatedly,[10, 59, 64] there is an immediate need for a model that accurately predicts the expected duration of neutropenia for all chemotherapy regimens and dose(s). Until then, information for this factor remains retrospective and, as a prognostic factor, it is not clinically useful.[257]

Very few studies have explored duration of neutropenia before the onset of fever and total febrile days in association with the outcomes of FN. One study reported that patients with granulocytopenia which ranged from 1 to 5 days (OR, 1.53, 95% CI, 1.17-1.99, p=0.01), 6 to 15 days (OR, 3.53, 95% CI, 3.06-4.06, p=0.01) and $\geq$ 16 days (OR, 5.37, 95%CI, 4.66-6.17, p=0.01) were at risk of bacteraemia.[172] A similar trend has also been observed for FN patients with total febrile days; this being that the longer the patient is febrile there is an associated increase in adverse outcomes.[59] In short, the longer patients remain in a neutropenic state, the more their risk of bacteraemia increases; particularly

for the development of invasive aspergillosis, and these conditions are known to lead to medical complications during FN.[5]

Febrile neutropenia episode-related factors

i) Clinical presentation and vital signs

Cancer patients experiencing FN have their vital signs and overall clinical condition assessed at triage on presentation with a fever. Vital signs such as maximum temperature, blood pressure, heart rate, respiration rate and patients' general condition are critical components that reflect episode-specific clinical features of patients at that point of time. These measurements are objective, easily accessible and they are immediate indications suggestive of the degree of severity of illness.

Cancer patients who are immunocompromised presenting with an increased heart rate, respiration rate or abnormal blood pressure reading are commonly admitted to the hospital for treatment and further investigation even in the absence of fever. However, the utility of clinical presentation and vital signs as predictors for the outcome of FN has been debated as these clinical features are generic and abnormal vital signs could be linked with a variety of aetiologies such as dehydration resulting in hypotension[258] or tachypnoea and tachycardia with or without fever associated with pulmonary embolism[259].

The other concern is the reliability of predictors that necessitate a subjective individual clinician led assessment for each FN patient.[260] Without a tested and validated scale to base the assessment of "burden of illness" (degree of

symptoms) of patients presenting with FN on, the assessment is subjected to risk of rater reliability and variability of interpretations by clinicians. This concern has been raised in the subsequent studies using the MASCC risk index score and it needs to be addressed.[5, 260]

ii) Location of patients at the onset of fever

The location of patients at the onset of fever (inpatient / outpatient) is not useful as a predictor because of several limitations. Firstly, this factor is a surrogate measure of risk, with the assumption that patients who develop FN when they are out of hospital, are perceived to be less sick or serious.[64] However, this factor is easily influenced by many external factors such as practice variability, organizational structure and policies and lastly the preferences of patients. Based on these grounds, this factor may not be suitable as a predictor and other more relevant factors could be considered in the assessment of patients and categorisation of their level of risk.

iv) Respiratory abnormalities

The characteristics of infections frequently associated with adverse outcomes in FN patients include mainly respiratory infections (source) andgram-negative, fungal or polymicrobial (micro-organisms).[37]FN patients with clinically or microbiologically proven infection are rated as moderate to high risk compared to those with fever of unknown source.[11, 37] These findings are congruent with the prognostic factors identified in this review, presence of pulmonary infiltration[173], pulmonary infection[165] and invasive fungal infection[74], which have been associated with high-risk of adverse outcomes in FN patients.

However, time and tests (laboratory or imaging) are needed to confirm the diagnosis of these infections. Under these circumstances, the clinical applicability of these factors for risk assessment of FN patients at the onset of fever may be limited due to the unavailability of test results at the point of assessment.

Laboratory markers

i) ANC at presentation of fever

Besides clinical characteristics, laboratory variables such as ANCs and platelet levels at presentation of fever have been identified as significant predictors for outcomes of FN episodes in this review. The degree of neutropenia has also been associated with severity of clinical condition of FN patients and types of anticipated infection(s) they may be likely to have.[5] In addition, neutrophil recovery has been recognised as important determinant for discontinuation or modification of antibiotics.[5] However, it has been suggested that a single reading of ANC would not be a sensitive predictor for infection episodes[57] or for the outcomes of FN.

Conversely, information on the nadir and trend of ANC levels (with a rising trend reflecting the recovery of white blood cells and the function of the bone marrow in general) may improve the utility of ANC as a prognostic factor.[168] Nonetheless, despite its established role in the outcomes of FN episode, ANC level is not a common predictor included in current prognostic models or stratification tools for FN outcomes. The utility of a single reading of ANC as compared with the pattern of ANC levels may require further investigation.

ii) Platelet count at presentation of fever

Thrombocytopenia has been associated with mortality in severely ill patients in the presence of sepsis[261] although the relationship between low platelet levels with sepsis and mortality remains unclear. Furthermore, a majority of cancer patients who undergo myelosuppressive chemotherapy experience some degree of thrombocytopenia; hence the applicability of this factor in relation to the outcomes of FN requires further primary research to establish its predictive significance.

A recent study reported pre-chemotherapy thrombocytopenia to be statistically significantly associated with the risk of serious complications.[11] As such, a pre-chemotherapy platelet level could be investigated for its prognostic value in the risk assessment of FN patients, given that the value represents the condition of the bone marrow and is not induced by chemotherapy.

3.9.17   Limitations of the review

This review has identified limitations across the included primary studies that are similar to those reported in other reviews of prognostic factors studies.[52, 229, 236]There isa lack of uniformity in definitions for inclusion criteria and outcome measurements, poor methodological quality, lack of clarity in reporting of analyses, measurements methods and definition of prognostic variables identified. The definitions for inclusion criteria were similar across included studies but with some modifications of definitions between studies resulting in important differences between patients in the study populations.[59, 173]

The outcomes measured for the high-risk group were diverse and ranged from medical complications to bacteraemia and infection-related mortality.[73, 74, 173] The variability of outcome measures could mask the true predictive value of the respective identified prognostic factors especially among subgroups of patients with different outcome measurements. Furthermore, the methodological quality of the included studies was not high for cohort study designs.

In this review, only observational studies were included, and they are often regarded as having less validity in the results as compared with results of randomised control trials.[262] However, this was inevitable because prognostic factor study designs are predominantly observational (cohort and case-control)[263]. This study design is known for its limitations which include risk of population bias and, when conducted retrospectively, missing important data that could affect the analysis. Studies which provide incomplete and inadequate information on the clinical factors, demographics characteristics, statistical analyses performed and criteria and adjustment made to the set of variables caused additional difficulty in the interpretation of the studies' findings.[73, 74]

Limitations in this review also include: restriction to English language for published articles, the inability to retrieve full text articles of some studies that appeared to contain relevant data based on the abstracts, and risk of publication bias.

3.9.18   Conclusions to the systematic review

The role of risk stratification of chemotherapy-induced FN patients continues to evolve as the practice of risk-based therapy has proven to be beneficial to patients, clinicians and health care organisations.[15, 50, 51] Despite the limitations, this systematic review has highlighted additional factors (thrombocytopenia and the presence of central venous catheter) which may enhance the discriminative ability and performance of existing prognostic models.

However, the dynamic aspects of prognostic model development, validation and utilisation have not been addressed adequately thus far. Given the findings of this review, current models should be reviewed and revised or a new model developed which is reliable and accurate across cancer types. A robust and well-validated prognostic model is the key to enhancing patient safety in the risk-based management of cancer patients with chemotherapy-induced FN and to improving the utilisation of prognostic models in clinical practice.

3.9.19   Implications for practice

This review has provided a synthesis of the best available evidence for the prognostic factors used in assessing the risk of FN cancer patients. The newly identified factors are not only clinically relevant but they are also easily applied in the clinical setting. Current risk assessment practice for FN patients may even be enhanced with the additional prognostic information.

3.9.20   Implications for research

There has been a significant increase in interest in prognostic factor studies and the development of prognostic models for the management of FN. However, the research base to inform this development remains inadequate, and unclear on many important aspects of methodology and outcome reporting. A three-pronged approach is proposed.

In the area of prognostic factor research studies, high quality primary studies are needed to produce strong evidence-based results. To achieve this, primary researchers must work collaboratively to improve the rigour of these studies. A multi-site study with prior agreement on the inclusion criteria, variables assessed, methodological design, analyses and reporting of outcomes is needed to ensure consistency so as to allow subsequent pooling of data for meta-analysis.[52]. These measures should be taken to overcome the current barriers faced by reviewers for prognostic factor studies.

Future studies are needed to examine the quality of prognostic factors which are both statistically and clinically significant. This is in addition to exploring other variables such as blood markers that could improve the robustness of current prognostic models. Given the heterogeneity of FN cancer patients, a separate prognostic model for haematological malignancy patients could be explored. The study should include prognostic factors reported in this review (for example duration of neutropenia, severity of neutropenia, thrombocytopenia, and presence of CVC) because these are some of the factors that are more significant to patients with haematology malignancy. Additional prognostic

factors such as co-morbidities, presence of complex infection and performance status of patients could be explored to improve on the clarity of operational definitions of these variables and to establish their significance in the risk assessment for FN patients.

Lastly, the importance of validating prognostic models before they are adopted into daily clinical practice cannot be emphasised enough. In addition to internal validation, these models should also be externally validated for generalisability and evaluated with respect to their calibration and discriminative ability.[264] It has been suggested that the usefulness of these models depends on characteristics such as accuracy in discriminative ability, clinical reliability and effectiveness when applied to a similar group of patients from a different setting from the derivation sample population.[265]

4 Primary Study to Establish Candidate Factors for the Prognosis of Febrile Neutropenia

4.1 Introduction to the chapter

This chapter reports on the second part of the thesis which was the conduct of a primary cohort study focusing on the assessment of prognostic factors for febrile neutropenia. The chapter introduces the principles and methods of prognostic factors research with discussion on the recommended characteristics of predictors, methodological principles and methods specifically for this type of study. This is followed by the detailed description of the primary study which entails the testing and identification of predictors, the study's methodologies and reporting of research findings. Description on the elements of model development will be explored and discussed in the next chapter (chapter 5) of the thesis.

4.2 Prognosis and its utility in decision making

Prognosis is an estimation of the future outcomes of a medical condition or the likelihood of a disease onset over a period of time.[266] It is central to medical practice and plays an integral role in the management of patients in relation to diagnosis, treatment planning and screening.[267, 268] Examples include the use of the Notthingham Prognostic Index to guide decision making on adjuvant therapy for women diagnosed with early breast cancer[223] and the use of a decision-analytic model when deciding between surgery and medical follow-up in patients presenting with primary hyperparathyroidism.[269]

Besides being recognised for its integral role in clinical practice, prognosis has also been incorporated into the practice of other healthcare professionals. In nursing practice, risk assessments are frequently performed using risk scores or prediction models to estimate the likelihood occurrence of deep vein thrombosis[270] and pressure ulcers[271]. Among the allied healthcare professions, the use of predictive models is common in rehabilitation medicine particularly for whiplash injury[272] and musculoskeletal disorders.[273]

Besides healthcare providers, prediction of the course and outcome of disease processes aids health policy makers in determining resource allocation for screening initiatives, choice of therapeutic interventions and evaluation of healthcare policies.[274] Prognostic information can also be used in the process of "shared clinical decision making" between clinicians and patients through objective communication of risks and benefits. [275] In short, prognostic information provides a more holistic approach to clinical decision making and its utility has been well-documented [276] However, it is important to note that prognostic information is not intended to replace the clinical reasoning and expertise of healthcare professionals, but instead it should complement decision making by providing a quantifiable and objective estimate of the probability of the outcome of interest occurring that is supported by scientific evidence.[277]

4.3   Single versus multiple predictors in prognostication

Prediction or prognosis can be made based on a single or multiple factors which have been established as having a predictive role in the outcome of a

clinical condition or disease.[53] These factors are commonly known as prognostic factors, prognostic variables, prognostic determinants, prognostic markers, predictors or molecular markers.[52, 268] In many diseases, factors derived from patient demographics, clinical history, physical assessment, disease and treatment related characteristics and test results are the basic predictors commonly used in clinical practice.[278]

Some of the less common predictors may also include psychosocial and behavioural characteristics[279], physical environment and social indicators[268]. Through primary research, factors are examined and evaluated for their relationship with the outcome of interest.[277] Once established, predictors are used to modify interventions to improve outcomes and measure treatment response. In addition, when multiple predictors have been identified they may be assembled to build prognostic models.[268]

The utility of a single predictor versus multiple predictors in prognostication depends on the predictive strength the single predictor for the outcome measure. A single marker such as C-reactive protein (CRP) level taken on the day of discharge of patients with ischemic stroke was found to be the strongest independent marker of adverse outcome (Hazard Ratio 7.42, 95% CI 2.75 to 20.03; P=0.0001).[280] In contrast, microvessel density (MVD) was found to be a significant predictor with weak predictive value in a meta-analysis of 87 published studies in women with breast cancer.[281] The review findings reported a relative risk (RR) of 1.99 for relapse-free survival (95% CI, 1.33–2.98) and RR of 1.54 for overall survival (95% CI, 1.01–2.33).

These examples illustrate that a single predictor with weak predictive value may not be sufficient for accurate prediction especially among a group of patients of differing age-group, disease status and other clinical factors to be considered. Given the variability of patients' characteristics, conditions and treatment, multiple predictors are more in favour for prognostication as compared with a single predictor.[83] This is evident in the increasing numbers of multivariable models being developed and used by the majority of healthcare professionals[282-284] either in the form of risk prediction rules or prognostic models or risk scores.[285, 286]

4.4   Types of prognostic studies

Over the years, the study of prognosis has gained increased interest among clinicians, scientist and policy makers.[275] Given the array of potential and actual uses of prognostic factors and models and their impact on healthcare practice, research and policymaking, it is not surprising to observe a steep increase in this area of research.[287] In the year 1995, more than 6000 articles were published for prognostic models and a two-fold increase was noted a decade later.[288]

With the proliferation of prognosis research, it is important to differentiate the different types of prognosis research with corresponding study designs and methodologies. A framework of four inter-related prognosis research themes has been developed recently and they include:[275]

- Exploration of the natural and clinical course of health related conditions (fundamental prognosis research)[275]

- Identification of factors associated with prognosis (prognostic factor research)[268]

- Development, validation and impact analysis of statistical prediction models (prognostic model research)[54]

- Utilisation of prognostic information to tailor therapy according risk groupings (stratified medicine research)[289]

Each theme has a different aim but in general they seek to understand and improve future outcomes of patients with a medical condition or disease through evidence generation and translation from clinical research to clinical practice.[275] Evidence generated from these studies not only leads to improvements in the understanding of disease pathways with opportunities to change disease course by modification of the factor(s),[268]but also provides a more objective and evidence-based estimate of probabilities for disease onset or the outcome of a medical condition.[54]

Given the potential utility of prognostic factors both in patient care and clinical research, high quality prognostic research to identify and establish their predictive values is essential. Different stages of prognostic studies are recommended with the initial stage being to identify or explore factor(s) in association with prognosis. The following section describes the steps and stages recommended for prognostic model development.

4.5 Prognostic factors and model development

Guidelines for the development of prognostic model, describe three major steps as detailed below.[264, 282, 285, 286, 290] (Figure. 4.1):
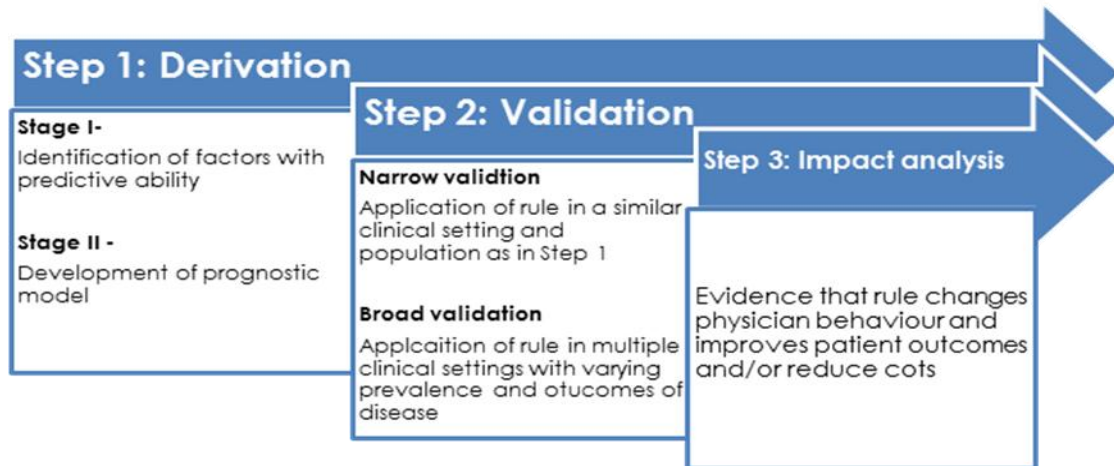
Figure 4.1 Steps in the development of a multivariable prognostic model
(adapted from the Users' Guide to the Medical Literature XXII: How to use articles about Clinical Decision Rules, JAMA 2002, 284(1):79-84)[290]

Step 1: This step is known as the development or derivation phase and involves two stages. The first stage involves the identification and evaluation of factors that might be useful as predictors and each predictor is assigned relative weights. The second stage is the development of a multivariable model based on the selected predictors.[291]

Step 2: This step is known as the validation phase. It involves testing the performance of the predictive model (i.e. calibration and discrimination) and this can be performed in two ways. A narrow validation entails testing the model in a similar clinical setting and population of the development group while broad validation includes applying the rule in a group of participants selected from various other institutions using additional inclusion criteria.[265, 278]

Step 3: The final step encompasses primary studies to quantify the utility of the prognostic model in its impact on clinical decision making, quality of healthcare and other health related outcome measured. Also known as impact analysis this phase can be performed in a similar manner (narrow and broad) as described in Step II.[278]

4.6   Quality of prognostic studies

The majority of the prognosis research has focused on the identification of candidate predictors and the development of new models with minimal studies on validation and impact analysis.[288] Despite the large number of prognosis research being reported, this type of study continues to fall short of the quality and standards demanded of other fields such as research on therapeutic interventions and novel diagnostic technologies.[275] Increasingly, severe limitations in the existing studies on prognosis have been highlighted in the literature.[217]

Systematic reviews on different types of prognostic factors[292-294], across a variety of clinical specialties and diseases including cancer[295], cardiovascular disease[296, 297] and musculoskeletal disorders[298, 299] have reported that the included studies in these reviews were methodologically poor[232].

When primary studies were critically examined, a high proportion of them were found to have flaws in the choice of study design[232, 300], inappropriate statistical methods for data analysis[301] and poor reporting of results[236, 302]. As a result, some of the findings remained inconsistent and unreliable, which further limits the

value and potential application of factors in clinical practice.[229, 277, 287, 303] This is evident in the gap that exists between the potential benefits and the actual impact of prognosis research on health practice.[286] Given the importance of study design limitations to the value and application of prognostic factor research, a more in-depth discussion specific to the design and reporting of prognostic studies is presented in the following sections.

4.6.1 Study design: prospective compared with retrospective designs

Applying the appropriate study design for prognosis research studies has remained a challenge. A large majority of prognostic factor research is retrospective, without a prior hypotheses nor guided by a pre-set research protocol.[287] The recommended study design to answer prognostic questions is a well-defined cohort study, preferably prospective with a protocol established prior to the commencement of the study.[232, 268, 278, 287] A prospective study design for prognostic factor studies is one that selects a group of patients with a similar condition, at the same stage of their disease so as to represent the population of interest.[278, 287] Identified as the "inception cohort", these patients are followed for a specific length of time to explore the differences in values of the prognostic factors in association with the outcome of interest.[287]

The advantage of a prospective design is that it enables criteria for inclusion and exclusion of sample population to be pre-defined with clear consistent definitions and measurement methods of predictors. Furthermore, the assessment of outcomes of interest are fixed at specific points with intermittent

quality checks of data.[304] Application of these criteria for well-designed prospective studies should reduce incorrect or incomplete data recording; unclear identification of sample population and inconsistent measurement of information from candidate predictors and outcomes all of which are potential issues associated with retrospective studies.[268] As such, a well-designed prospective study reduces the risk of selection bias and false positive results for candidate predictors.[268]

However, retrospective cohort studies are still favoured because of the their simplicity and practicality.[305] Indeed, a carefully designed and executed retrospective cohort study is a valuable tool to perform prognostic factor research in settings where time and resources are limited.[305] A major advantage is that the sample population of interest is easily searched and data is often available through electronic patient records or existing hospital information systems.[305] Trade-offs include lack of standardisation of measurements for predictors and outcomes measured; unavailability of data for predictors or outcome of interest and unknown completeness of the cohort or follow-up duration.[268, 287] Rigorously designed retrospective studies should be considered for exploration of prognostic factors before committing to resource intensive and lengthy prospective studies, especially given the utility and cost effectiveness of the retrospective study design.[268]

When the outcome of interest is relatively rare a case-control design is recommended for prognostic factor research.[278] However, the limitations of using this study design are highlighted in its retrospective assessment of

predictors' information and the inability to estimate the absolute risks due to the unknown size of the population the cases and controls were drawn from.[278] In view of its limitations, nested case-control or case-cohort studies are other alternatives.[278, 306]

4.6.2 Selection of candidate variables

The other important consideration in prognostic factor research is the candidate variables to be studies for their association with the outcome of interest. While no consensus exits with regards to the best method for selecting variables to be studied, the conventional way has been based on clinical expert knowledge and existing evidence arising from primary research.[236] Irrespective of selection method, there are key characteristics of variables that need to be considered when including them for study. Firstly, variables should be clearly defined, reproducible and should have standardised measurement methods.[278] Secondly, the reliability of the variables is of utmost importance.

Variable reliability can be compromised by exposure to potential observer and / or biological effects.[83] These could compromise the predictive stability of any given variable and cause the ensuing model to be less reliable.[83] Observer variability involves subjective interpretation by the assessor or user which could cause inconsistencies.[83] Biological variability relates to potential influences of other factors affecting the reproducibility of the results measured, for example single blood pressure measurement is known to be unreliable.[274] Last, other considerations for choice of predictors include the availability at the time of use,

applicability in daily practice, costs involved and reasonable degree of precision.[274]

4.6.3 Choice of appropriate outcome measures

The majority of prognosis studies involve mortality as the single important outcome measure. Other common outcomes include either specific events such as disease onset or other quantifiable indices such as time to disease progression and quality of life.[278] Due to the implications, the choice of the most appropriate outcome(s) for prognostic factor research cannot be over-emphasised. The outcome(s) chosen for the study determine the length of follow up required for the study, and influences the performance of the ensuing prediction model. Also, there needs to be consistency in the definition and application of the outcome measure, since drift will result in a difference in the outcome of interest and when applied to application and validation studies might lead to overestimation or underestimation of risk.[307]

In terms of assessment and measurement of outcomes, characteristics that are similar to those used to select candidate variables apply. Methods of measurement of outcome should be clearly defined prior to the commencement of study, with assessment of outcomes being unbiased and with a sufficient follow-up period of patients.[278]

Outcomes selected for prognostic research should primarily be meaningful to the patients or individuals and should include treatment response,

complications, remission of disease or quality of life.[83] If surrogate outcomes are used, they must be closely related to the intended outcomes measures, otherwise, it will be inaccurate to generalise the findings. [274] In most studies, composite end-points are used as a method to increase sample size and power for statistical analyses for the study. A composite end point may be a combination of mortality with the development of adverse events such as organ failure, relapse of disease, treatment failure and others. [274]

4.6.4 Sample size and events in analysis – some limitations

The planning of a prognostic study also includes an estimation of sample size and more importantly the number of events of the intended outcome measures.[217] Specifically for prognostic studies, the number of events is emphasised because a low number of events per variable (EPV) create biases for the regression coefficients that may lead to increasing chance of overestimation and underestimation of the true effect for candidate variables.[308]

As demonstrated in the study conducted by Peduzzi and colleagues,[309] a recommended EPV value of 10 or greater was considered the ideal to reduce the risk of false positive finding of predictors and over-fitting of model.[83, 285, 308, 309] However, these are the two common limitations for prognostic studies as reported in a recent review. It highlighted 77% of the included studies lacked clear sample size justification and about 30% had lesser than 10 events per variable studied.[217]

4.6.5 Reporting of results

A lack of clarity and insufficient information provided in the reporting of results have been the two main issues that limit the ability of others to evaluate and replicate the research with the objective of applying the findings into practice.[287] To improve on the quality of prognostic studies, transparency of reporting is needed in order to allow the introduction of new predictors in to clinical practice, facilitate the conduct of systematic reviews and meta-analyses on the subject and promote the utilisation of evidence from prognostic studies.[268]

A substantial amount of work to strengthen and improve the conduct and reporting of prognosis research has been published in recent years. Significant developments in methodologies for the conduct of primary studies and systematic review of prognosis research have been achieved.[268, 287, 310]These advances have the potential to generate a more reliable evidence-base recommendations to be used in different translational pathways and improve the conversion of clinical and health research outcomes into clinical practice improvements.[268]

4.7 Primary Study: Design and Methods

4.7.1 Justification for primary study

When a validation study of a prediction model shows that the model has only limited predictive value, attempts are made to develop new models. Some of the validation studies for models predictive of FN outcomes for adult cancer patients were reported to have low sensitivity or specificity in their identification of patients at risk of adverse events.[32, 41, 68, 311] Other validation studies reported newly identified predictors without achieving much of a consensus on predictors.[68, 157, 243] The consequence of this is a proliferation of prediction models measuring the same outcomes[11, 143] and in many cases the models are of inferior quality in performance, being based on a smaller sample size.[288] As a result, clinicians have difficulty in deciding which rule to adopt for clinical practice, and the necessary testing of each rule within their context of practice prior to implementation is not feasible.[288]

In the previous chapter, a systematic review of the international literature identified new predictors that were not present in previous models. These predictors which include thrombocytopenia, presence of central venous catheter and duration and severity of neutropenia could represent a possible extension of existing models.[312] In addition, some of the predictors from the review findings had wide confidence intervals, weak odds ratios for their association and lack precision of point estimates.[312] These predictors were thoroughly re-evaluated for their predictive ability in the present primary study.

As such the primary cohort study for the thesis involved re-estimation and validation of the strength of each predictor identified from the review; in addition to other factors reported from medical literatures with the aim to derive a new logistic regression model for the prognosis of adult cancer patients presenting with FN. On this basis, the approach taken is supported by findings from the review of international literature, and congruent with accepted processes for establishing and validating clinical prediction models.

4.7.2 Purpose of the study

The primary cohort study involved two parts and its purposes were to evaluate the independent association of identified candidate variables (based on literatures and findings of the systematic review) with the outcome of FN and to develop a prognostic model for risk stratification of adult cancer patients presenting with FN.

4.7.3 Study questions:

i) What are the candidate variables independently associated with the outcomes of adult cancer patients experiencing chemotherapy-induced febrile neutropenia?

ii) What are the candidate predictors for the development of a prognostic model for risk stratification of adult cancer patients presenting with FN?

4.7.4 Site of study

The primary study was conducted at the Royal Adelaide Hospital, the largest accredited tertiary public teaching hospital in South Australia. The hospital has over 600 beds at the North Terrace campus within which the comprehensive cancer centre is situated. Developed in the 1980s, the cancer centre provides the full range of cancer related services including allogeneic stem cell transplantation and it is known for teaching and research excellence for cancer care. Apart from patients from Adelaide, the cancer services are also extended to those within the outreach borders such as Port Pirie, Broken Hill, Darwin and Alice Springs through their Outreach programs.

4.7.5 Study design

In medical research, randomised control trials (RCTs) have been known as the gold standard to answer a therapeutic related question and in testing hypotheses. Although this study design has been well-documented for its advantages, RCTs are not suitable for certain research questions such as studies of prognosis and risk factors.[278] Furthermore, well-conducted observational studies, particularly cohort or case-control designs, are equally valuable and their results can be comparable to those of RCTs.[262] Cohort study designs have been recognised as the most suited designs for prognostic studies.

This study design is best described as the study of a group of individuals selected based on the presence of one or more similar characteristics, and the exposures and outcomes that are being researched.[263] A prospective cohort study requires exposures of these individuals to be defined at baseline; the

cohort is then followed forward in time for the outcome of interest. [263] In contrast, a historical or retrospective cohort study involves looking at exposures and outcomes in the past and determines the exposures which existed before the development of the outcomes.[263]

A cohort study design was chosen for this study as this design is recommended for prognostic studies. (Section 4.6.1) A retrospective cohort method based on reviews of the medical records of patients was the most appropriate design for the primary study reported in this thesis. This design is practical and addressed the research questions within available resources. Furthermore, the intention of the primary research was to test the predictors and validate the newly identified ones for model development.

As such, the retrospective design facilitates a rapid evaluation of putative prognostic predictors and will be informative for the design of subsequent resource-intensive prospective validation studies. The availability of electronic laboratory and diagnostic imaging records at the site of research facilitated the conduct of data collection and minimised the incidence of missing data. Data required from each predictor was operationally defined prior to the commencement of the study and all predictors are measured in an objective manner.

4.7.6 Sampling

Convenience sampling was used for the study. A list was generated for patients who were admitted to the participating healthcare facility. The list included all patients who received treatment at the in-patient with the following admission diagnosis during the period from June 2004 to June 2012.

- febrile

- febrile neutropenia

- febrile illness

- febrile illness of unknown cause

- febrile post chemotherapy

- febrile neutropenia with infections

- acute febrile illness

- febrile for investigation

- febrile low neutrophils

- febrile with confusion

- febrile sepsis

- presumed febrile neutropenia

- febrile neutropenia / transplantation

This list was used to identify candidate cases for medical records retrieval. Patients' data from the medical records were checked against the inclusion and exclusion criteria set for the study and when there was a match, these cases were selected. Where the same patient had multiple admissions for FN

episodes, data from the second episodes was also collected. However, only data from the first of the two selected episodes was utilised for analysis in this phase of the study.

4.7.7 Study population

The sample population included all adult cancer patients of aged 18 years and above, who received treatment for chemotherapy-induced febrile neutropenia at the Royal Adelaide Hospital. The sample population also included patients with solid or haematological malignancies who had received chemotherapy as part of their cancer treatment. According to the standard protocol of the hospital, patients with febrile neutropenia were admitted to the hospital at the onset of fever and they were treated with an appropriate initial empiric antibiotic regimen as recommended by the Infectious Disease Society of America guideline.[5]

4.7.8 Sample size

In developing a regression model predictive of high-risk for adverse events in patients with febrile neutropenia, power analysis estimation of sample size was calculated based on the statistical calculator for multiple regression.[313] The calculator provides a minimum required sample size for a multiple regression study, given the desired probability level, the number of predictor to be studied, the anticipated effect size and desired statistical power level.

- Anticipated effect size (f^2): 0.35 (by convention this is termed large effect size)[314]

- Desired statistical power level: 0.8[314]

- Number of predictors: 35

- Probability level: 0.05 (also known as the p-value, alpha level, or type I error rate, by convention this value should be less than or equal to 0.05 to claim statistical significance.

- Minimum required sample size: 103

4.7.9 Operational definitions for variables

Candidate variables with predictive values for the outcome of febrile neutropenia included in the study were obtained from the findings of the systematic review[312], existing literature of predictors[59] and prediction models for febrile neutropenia outcomes in cancer patients post chemotherapy[11]. A total of 19 factors identified from the review and additional 16 factors based on existing literature formed the list of factors to be tested for the primary study.(Table 4.1)

Table 4.1Candidate variables included in the primary study

Candidate variables	Sources
1) Age, 2) Chronic obstructive pulmonary, 3) Previous fungal infection , 4) Current fungal infection, 5) Type of tumour, 6) Indications of cancer treatment, 7) Prophylaxis antibiotics, 8) presence of central venous devices, 9) Median days to fever, 10) Total febrile days, 11) Temperature, 12) Systolic blood pressure, 13) Diastolic blood pressure, 14) Respiration rate, 15) Hydration status, 16) Geographical location of patient at the onset of FN, 17)Pulmonary infection/abnormal chest radiograph, 18) Absolute neutrophil count, 19) Platelet count.	Systematic review findings[312]
1)Gender, 2) Ischemic heart disease/congestive cardiac failure, 3) Diabetes mellitus, 4) Hypertension, 5) Previous febrile neutropenia episode, 6) Prophylactic CSF, 7) ECOG performance status, 8) Pulse rate, 9) Presence of infection site, 10) Mucositis, 11) White blood count, 12) Albumin level, 13) Creatinine level at FN, 14)C-reactive protein, 15) Monocytes, 16) Lymphocytes level.	Primary studies and prediction models[11, 13, 64, 82, 168, 172, 173, 315]

Accordingly the definitions are as follow:

Comorbidities – the presence of concurrent medical condition(s) as documented in patient's medical records

Days to fever – the number of days from chemotherapy administration to the onset of fever. (Duration of neutropenia could not be determined as the onset of neutropenia which is captured by the measurement of blood test for ANC was not performed on a daily basis) Instead data was collected for the duration from the most recent cycle of chemotherapy to the onset of fever)

ECOG performance status –based on assessment of performed and explicitly documented in the nursing charts at the onset of fever

Geographical location – the site where patient develops fever during neutropenia

GCSF prophylaxis - administration of growth factor prior to the onset of FN

Hydration status - documentation of clinical findings: dry oral mucosa, tachycardia, orthostatic falls in blood pressure, decreased skin turgor, dry mucous membranes, irritability, decreased peripheral perfusion with a delay in capillary refill between two and three seconds[316]

Presence of infection site – presence of visible soft-tissues wound, exudate, ulceration or fissure, local pain, swelling, erythema, local pain or tenderness[95] Infection was considered to be related directly to neutropenia if it occurred during neutropenia and before recovery of ANC (1000/mm^3)

Previous fungal infection - history of fungal infection in the last six months

Total febrile days – duration taken to defervescence from the onset of fever.

Tumour types - the diagnosis of patients which is documented in their medical records by their physicians. Disease was assigned to haematological malignancies or lymphomas or solid tumours.

The variables considered as potential prognostic factors are listed in Table 4.2; all were measured at the time of presentation with fever. All continuous variables were categorized on the basis of clinical significance according to published reports.

Table 4.2 Variables and their categories

Variables tested for Predictive Values	Categories
Patient-related	
• Age	Years (<60 years; $\geq$60 years)
• Gender	Male, Female
Comorbidity	
• Ischemic heart disease /congestive heart failure	No; Yes
• Diabetes mellitus	No; Yes
• Hypertension	No; Yes
• Chronic obstructive pulmonary disease	No; Yes
• Previous febrile neutropenia episode	No; Yes
• Previous fungal infection	No; Yes
• Anti-fungal therapy within 6 months	No; Yes
Underlying cancer	Haematological tumour, Lymphoma, Solid tumour
Treatment-related	
• Treatment indication	Adjuvant; Non-adjuvant
• Prophylactic growth factor	No, Yes
• Antimicrobial prophylaxis	No; Yes
• Central venous devices	No; Yes
• Duration from recent treatment to FN onset	<7days; 7-14days; >14 days
• Duration from onset of FN to defervescence	<7days; 7-14days; >14 days
Clinical condition at presentation	
• Temperature	<39^{0}C;$\geq$39^{0}C
• Pulse rate	<120beats/min; $\geq$120/min
• Systolic blood pressure	<90mmHg; $\geq$90mmHg
• Diastolic blood pressure	<60mmHg; $\geq$60mmHg
• Respiration rate	<24breaths/min; $\geq$24/min
• Dehydration requiring IV therapy	No; Yes
• ECOG performance status	0-2, 3-4
• Geographical setting at FN onset	In-patient; Out-patient
• Presence of infection site	No; Yes
• Mucositis	No; Yes
• Abnormality on chest X-ray	No, Yes
Laboratory results (Serum)	
At baseline	
• Platelet count	<50K x10^9/L; $\geq$50K x10^9/L
Range: 150-350 x 10^9/L [317]	
• Albumin level	<35 g/L ; 35-50 g/L
Range: 35-50 g/L[317]	
At presentation of febrile neutropenia	
• White cell count	<0.5 x10^9/L; $\geq$0.5 to <1 x10^9/L; $\geq$1 x10^9/L
Range: 4-11 x 10^9/L [317]	
• Absolute neutrophil count	Low (<500/mm³) ; high (>500/mm³)
Range:1800-7500/mm³[317]	
• Platelet count	<50K x10^9/L; $\geq$50K x10^9/L
• Range:150K – 400Kx109/L[317]	
• Albumin level	<35 g/L ; 35-50 g/L
• Creatinine	<50 µmol/L; 50-110µmol/L; >110 µmol/L
Range: 50-110 µmol/L[317]	
• C-reactive protein	1- 3 mg/L (range)[317]
• Monocytes	0.2- 0.8 x10^9/L (range)[317]
• Lymphocytes	1- 3.5 x 10^9/L (range)[317]

4.7.10   Outcomes

The dependent variable of interest as the final outcome of the patient were categorised as unfavourable or favourable. Unfavourable outcome corresponds to the group of febrile neutropenic patients with high-risk of adverse events while the favourable outcome category is associated with febrile neutropenic patients with low-risk of adverse events. The outcomes selected for this study are not only relevant to patients, but also to healthcare providers and organizations. In the febrile neutropenia episodes, the most important outcome measure is mortality.

Ideally this measures the mortality rate which is directly related to the febrile neutropenia episodes. However, ambiguities in medical records documentation and the difficulty of distinguishing between infection and underlying uncontrolled disease for specific cause-of-death impede accurate extraction of data. In view of these difficulties, overall mortality has been used as one of the relevant measure of outcome instead.

Other outcome measures for the study were mainly secondary indicators measured at an intermediate time point of the febrile neutropenia episode. These indicators generally reflect the clinical course of the medical condition. High-risk patients could experience clinical deterioration and presenting signs and symptoms of serious complications any time during the period of febrile neutropenia.[10] Fever resolution was used as an indicator for recovery although in some practices, recovery of ANC remains the determinant for hospital discharge for most patients.[189] Fever resolution for five consecutive days as a

measure of favourable outcome reflects the complete recovery of possible or probable infection; however, these patients are susceptible to recurrent infections as long as the ANC remains abnormally low.[318]

The outcomes selected for the study are also similar with the ones considered by the previous literature.[10] The decision to have the same outcomes was made as part of the effort to improve and standardise the individual studies, with the long-term aim of pooling data together from each study to generate evidence-based results.[52] The outcomes are defined as follow:

Unfavourable outcome is defined as development of at least of one serious medical complication followed by fever resolution for ≥5 consecutive days; but will also include cases where mortality occurred before resolution of fever for 5 consecutive days.[10]

Serious medical complications may include: hypotension (systolic blood pressure < 90mmHg) or requiring vasopressor to sustain blood pressure; respiratory failure (pulse oximetry reading of < 94% while breathing in room air) or needing mechanical ventilation; admission to Intensive Care Unit (ICU); disseminated intravascular coagulation (DIC); confusion or altered mental state; congestive cardiac failure as ascertained on chest x-ray, necessitating treatment; bleeding requiring blood product transfusion; arrhythmia or electrocardiogram changes requiring treatment; renal failure requiring investigation, treatment and intervention and any other complications as determined to be serious and clinically significant by the investigator.[10]

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Favourable outcome is defined as resolution of fever for 5 consecutive days without the development of serious medical complications, (modifications of the initial antibiotic treatment permitted).[10]

Infection status and febrile neutropenia episodes were classified into one of the three groups:

MDI - Microbiologically documented infection[5]

CDI - Clinically documented infection as defined as positive physical or diagnostic (radiological) findings compatible with an underlying infection, but with no evidence of positive reports on microbiological results[5]

PUO - Pyrexia of unknown origin as defined as no positive signs or clinical evidence of infection, nor microbiologically positive for cause of infection[5]

4.7.11 Data extraction and management

Patients' medical records were retrieved using patient's identifiers (hospital registration number). A randomly selected febrile neutropenia episode recorded for the patient was screened for the following eligibility criteria.

Inclusion criteria:
i) Diagnosis of malignancy confirmed and treatment with myelosuppressive chemotherapy

ii) Presence of fever as defined by a single oral temperature measure of 38.3ºC or an oral temperature of 38ºC lasting for more than an hour[5]

iii) Presence of neutropenia as defined by an absolute neutrophil count of <500 cells/mm³ or a count of <1000 cells/mm³ with an expected decline within the next 48-72 hours[5]

iv) Has received chemotherapy (within 4 weeks) prior to the febrile neutropenia episode, and

v) Has follow-up data on outcomes from the onset of FN up to 30-days of treatment or discharged from the hospital

Exclusion criteria:

i) Patients who experience fever and neutropenia from the underlying malignant disease which are not related to the adverse effect of chemotherapy.

ii) Patients who experience febrile neutropenia from chemotherapy treatment for non-malignant disease.

iii) Retrospective data from the medical records of patients recruited for clinical trials involving febrile neutropenia management and outcomes was not included.

All identifiers for each case were removed and replaced by an assigned case number / code and only the case numbers / codes were used for data entry, analysis and report writing. Information on patients' demographics, clinical parameters, laboratory and microbiological data were extracted along with clinical outcomes from medical records and all the relevant charts and

databases (e.g. patient's in-patient / out-patient notes, medical progress notes, discharge notes, blood test results, radiological tests results, medication or chemotherapy charts, nursing charts). Data was extracted and documented manually on paper by the author herself. (Appendix VII) This step was put in place so that the hard copy could serves as a backup document in case of computer / technical malfunction.

For data checking, a pilot test was undertaken based on the first 10 cases extracted. These data underwent a preliminary data check and analysis to ensure that the data extraction template was capturing the relevant data, that the data collection process was feasible and appropriate for the nature of the data and that the data collected was congruent with the analytic methods. Minor changes were made to the data extraction form because the pilot test indicated that procalcitonin and lactate were not routinely tested for and recorded in febrile neutropenic patients in the RAH, hence lack of availability of data.

These were replaced with monocyte and lymphocyte counts. These two parameter were selected based on studies that have demonstrated both monocyte and lymphocyte counts to be independent risk factors for FN in adult[169] and paediatric population[319] and both test results are available in the complete blood count report. The changed was agreeable with supervisors and ethics approval was sought and granted for the minor amendments made to the study.

Data extracted was keyed into a spread sheet using the programme MS Excel with codes assigned to each variable. Retrieval and entering of data were performed by the researcher in accordance with ethical treatment of research data, and the policy requirements of the RAH Medical Records Office. Access to data was limited to the researcher and approved individuals. The physical copy of the case assignment number and data collection were kept locked at all times at the researcher's personal work station while de-identified cases' data in the computer were password protected.

All documents with patients' information will be kept with strict adherence to security and confidentiality for a total of 15 years from the date of publication of the research study. After this period, physical documents of research data will be shredded and disposed according to the material disposal guidelines. In short, the author is overall responsible for all matters pertaining to data management and security.

4.7.12   Statistical analysis

Data was analysed based on the first recorded FN episode for the present study occurring in a patient, using the Statistical Package for Social Sciences (SPSS) version 21.0 (Chicago, IL).Descriptive analysis was performed for patient baseline characteristics data and presented in frequency tabulations for categorical variables, where applicable mean and range were reported for continuous variables. All continuous variables were subsequently categorised according to the standard clinical cut-off points and published reports.[320]

Candidate variables were firstly examined for their individual relationship with the outcomes of interest using univariate analysis.

All covariates were assessed for missing values. Variables with more than 10% missing data were not included for regression analysis because it could lead to incorrect association being established. Missing values of more than 10% were observed for variables: CRP, monocytes and lymphocytes. Estimated odds ratios (ORs) with confidence intervals (CIs) and the statistical significance of results as reflected by the p-value of less than 0.05 were reported. Relevant interaction terms were also considered and multicolinearity was assessed. From univariate analysis, variables with p-values less 0.05 for the null hypothesis of no effect were considered for multivariate logistic regression analysis for prognostic model development. All p-values were two-sided. A backward and forward Wald regression analysis was later used for model development is reported in the chapter 5.

4.7.13   Ethics and Human Subject Issues

The study was approved by the institutional review board from the Royal Adelaide Hospital and the University of Adelaide's Human Research Ethics Committees. A waiver for patients consent was approved by both committees due to the minimal risk profile associated with a retrospective review of patients' medical records, which has no impact to therapeutic interventions and provision of care.

Furthermore, the research study involved no contact with participants even for cases with missing data. In relation to privacy and confidentially, the measures were implemented to protect patients' privacy (using de-identifiers for data analysis and reporting) and confidentially of data. All handling of data was performed by the researcher personally according to the work-flow of Medical Record Office in RAH.

4.8   Results

4.8.1 Patient characteristics

Table 4.3 Demographics of sample population

DEMOGRAPHICS	No. of Patients(n=166)	%
Age (mean/ median) years	53.3 / 56.5	
• Range	19-85	
• <60	99	60
• >60	67	40
Gender:		
• Male	98	59
• Female	68	41
Co-morbidity		
• IHD/ CCF	7	4
• Diabetes	16	10
• Hypertension	42	25
• COPD	12	7
Previous fungal infection	4	2
Anti-fungal therapy	4	2
Previous febrile neutropenia episode	22	13
Underlying disease:		
• Acute leukaemia	57	34
• Chronic leukaemia	12	7
• Myeloma	17	10
• Hodgkin's Lymphoma	3	2
• Non-Hodgkin Lymphoma	29	18
• Breast cancer	18	11
• Colon cancer	3	2
• Lung cancer	9	5
• Other solid tumour	18	11
Treatment indication		
• Adjuvant or neo-adjuvant	12	7.5
• First line	92	55
• Second (subsequent) line	40	24
• Myeloablative:	12	7.5
o Autologous	(7)	
o Allogeneic (Sibling)	(3)	
o Allogeneic (unrelated donor)	(2)	
• Palliative	10	6
Prophylactic CSF administration	98	59
Antimicrobial prophylaxis	68	41
Geographical setting at onset of FN		
• In-patient	50	30
• Out-patient	116	70
Days to FN onset*		
Mean: 10.3 days		
• <7days	19	11
• 7-14days	129	78
• >14days	18	11
Total febrile days		
Mean: 6.4days		
• <7days	107	65
• 7-14days	42	25
• >14days	15	9
Missing data: n=2		

COPD -Chronic obstructive pulmonary disease IHD – ischaemic heart disease
CCF – congestive cardiac failure*Days from most recent treatment to FN onset

Data was extracted from a total of 166 patients' medical records. Baseline characteristics are summarised in Table 4.3. The median age of patients was 56.5 years (range 19 to 85 years). There were more patients who were in the younger age group as compared with the older age group with a ratio of 1:1.5. The sample was made up of 98 (59%) male patients and 68 (41%) female patients. The most prevalent comorbidity for this cohort of patients was hypertension, followed by diabetes mellitus, COPD and ischaemic heart disease. Only a few patients had a history of fungal infection (2%) and were receiving anti-fungal therapy at the time of FN (2%). Only 13% of the patients had history of FN.

There were 86 (52%) cases with haematological cancer diagnoses; 48 (29%) cases of solid tumours and 32 (19%) cases of lymphoma. The distribution of cases was slightly dissimilar with previous studies in particular the present study consisted of more patients with haematological patients and less patients with solid tumours.[10, 64] Acute leukaemia was the most common haematological malignancy while chronic leukaemia and myeloma accounted for the remainder of cases classified as haematological malignancies in this study. Breast cancer (n=18; 11%) was the most common cancer among the solid tumour group, followed by lung cancer (n=9) and colon cancer (n=3). There were about 10 times more patients with non-Hodgkin (n=29) than with Hodgkin lymphoma (n=3).

All patients were treated with chemotherapy; the majority of them underwent first line treatment, followed by second or subsequent lines of treatment. A

minority of patients received adjuvant / neo-adjuvant treatment (7.5%) or myeloablative chemotherapy for stem cell transplantation (7.5%). Only a few patients (6%) received treatment for palliative intent. In terms of prophylactic measures, slightly more than half of these patients (59%) received CSFs to improve neutrophil count recovery while 41% were prescribed antimicrobial prophylaxis. The majority of the patients were out-patients when fever occurred (70%) which reflected the current trend of moving towards ambulatory care for cancer patients.[321, 322](Table 4.3)

Duration to the onset of fever from the most recent treatment and total febrile days were categorised into three groups respectively. The median duration for fever onset time from most recent chemotherapy was 10.3 days with more than three quarter of patients falling into the (7-14 days) category. The mean duration for time taken for recovery from fever was 6.4 days and 64.5% of patients were in this group (less than 7 days). (Table 4.3)

4.8.2 Outcome measures

Table 4.4 Outcome measures for primary cohort study

Outcomes	No. of Patients (n=166)	%
Serious medical complications	47	28
• Hypotension	(30)	
• Hypoxia	(23)	
• Atrial fibrillation	(9)	
• Congestive cardiac failure	(3)	
• Acute renal failure	(10)	
# a patient may have multiple complications		
• Death	7	4
○ FN related	(6)	
○ Others	(1)	
Infection status		
• Clinically documented infection (CDI)	21	13
• Microbiologically documented infection (MDI)	58	35
• Pyrexia of unknown origin (PUO)	87	52
Culture result (from MDI)		
• Gram-negative	13	22
• Gram-positive	24	41
• Fungal	10	17
• Viral	5	9
• Poly-microbial	6	10

Hypotension- (SBP <90mmHg) or requiring vasopressor to sustain BP
Hypoxia- pulse oximetry of <94% at room air

Of the 166 patients, 28.3% developed medical complications related to the FN episode. The most common complications included hypotension and hypoxia, followed by acute renal failure, atrial fibrillation and congestive heart failure. Mortality rate was 4% (n=7). The leading cause of death was septic shock with multi-organ failure for six patients, and the other patient opted for palliative care when his clinical condition deteriorated after contracting pneumocystis (carinii) jiroveci pneumonia (PCP). Some patients experienced two or multiple complications simultaneously. (Table 4.4)

With regards to infection status, pyrexia of unknown origin (PUO) was the most common group identified as compared with patients with microbiologically documented infection (MDI) and patients with clinically documented

infection (CDI). Among the 58 patients with MDI, 22% were gram-negative bacteria with Pseudomonas aeruginosa and Escherichia coli being the main bacteria. The incidence of gram-positive infection was almost double that of gram-negative infections with 41%; with *Streptococcus* and *Coagulase-Negative Staphylococci (CoNS)* being the more common bacteria. Fungal infection accounted for 17% of the patients with MDI while viral infection was the least frequent among the infections reported (9%). About 10% of patients with MDI were reported to have poly-microbial infection. (Table 4.4)

4.8.3 Patient-related factors

Table 4.5 Patient-related factors and febrile neutropenia outcomes

Patient-related factors	No Complication n, (%)	With Complication n, (%)	OR	C.I (95%)	p-value
Age			2.083	1.05-4.134	0.036
• < 60	77 (78)	22 (22)			
• ≥ 60	42 (63)	25 (37)			
Gender			0.511	0.248-1.051	0.068
• Male	65 (66)	33 (34)			
• Female	54 (79)	14 (21)			
Co-morbidity					
IHD /CCF			1.960	0.422-9.114	0.391
• Yes	4 (57)	3 (43)			
• No	115 (72)	44 (28)			
Diabetes mellitus			2.846	1.00-8.098	0.05
• Yes	8 (50)	8 (50)			
• No	111 (74)	39 (26)			
Hypertension			1.597	0.756-3.376	0.22
• Yes	27 (64)	15 (36)			
• No	92 (74)	32 (26)			
COPD			3.990	1.198-13.285	0.024
• Yes	5 (42)	7 (58)			
• No	114 (74)	40 (26)			
Medical history					
Previous febrile neutropenia episode			0.522	0.167-1.633	0.264
• Yes	18 (82)	4 (18)			
• No	101 (70)	43 (30)			
Previous fungal infection			8.045	0.815-79.409	0.074
• Yes	1 (25)	3 (75)			
• No	118 (73)	44 (27)			
Anti-fungal therapy			8.045	0.815-79.409	0.074
• Yes	1 (25)	3 (75)			
• No	118 (73)	44 (27)			

COPD -Chronic Obstructive Pulmonary Disease
p value is significant <0.05 for ORs

Age

Of the total of 99 patients who were under the age of 60 years, 22% developed medical complications associated with FN episode. The percentage increased by 15 percentage points for patients who were age 60 years and above. Between the two age groups, patients in the older age group were 2.08 (95%CI 1.05-4.134) more likely to experience complication as compared to patients who were in the younger age group. The relationship between age and complication from FN was statistically significant (p=0.036). (Table 4.5)

Gender

Among the male patients, 34% of them developed medical complications when they experienced FN. The incidence of complications for the female patients was 13 percentage points less than the male patients. However, the differences in the complications were not statistically significant (p = 0.068). (Table 4.5)

Comorbidities

Comorbidities studied were common chronic diseases. They included heart disease, diabetes, hypertension and COPD. Among them, only two diseases showed statistical significant relationships with the outcome measure. Diabetes mellitus demonstrated an odds ratio of 2.846 with borderline p-value (95%CI 1.00-8.098; p=0.05) and COPD showed a larger odds ratio reading of 3.990 (95%CI 1.198-13.285, p=0.024). The remaining chronic diseases were not shown to have any relationship with the outcome measure as their respective p-values were not statistically significant. (Table 4.5)

Previous medical history

Additional factors such as previous febrile neutropenia episode and history of fungal infection or current anti-fungal therapy were shown to have no relationship with the outcome measure as their respective p-values were not statistically significant. (Table 4.5)

4.8.4 Disease-related factors

Table 4.6 Disease-related factors and febrile neutropenia outcomes

Disease-related factors	No Complication n, (%)	With Complication n, (%)	OR	C.I (95%)	p-value
Underlying disease			1.061	0.506-20225	0.0876
• Haematological malignancies	60 (70)	26 (30)			
• Lymphoma	25 (78)	7 (22)			
• Solid tumours	34 (71)	14 (29)			

p value is significant < 0.05 for ORs

Underlying disease

The study sample consisted mainly of patients with haematological malignancies (n=86) and 30% of them developed medical complications from FN. Patients with lymphoma (n=32) experienced approximately 22% of complications while 29% of the group of patients with solid tumours (n=48) developed complications. However, this factor (underlying disease) was not associated with the outcome measure and the difference in percentages of complication was not statistically significant (p=0.0876). (Table 4.6)

4.8.5 Treatment-related factors

Table 4.7 Treatment-related factors and febrile neutropenia outcomes

Treatment-related factors	No Complication n, (%)	With Complication n, (%)	OR	C.I (95%)	p-value
Treatment indication			4.685	0.588-37.353	0.145
• Adjuvant	11 (92)	1 (8)			
• Non-adjuvant	108 (70)	46 (30)			
Prophylactic growth factor			1.032	0.519-2.052	0.929
• Yes	70 (71)	28 (29)			
• No	49 (72)	19 (28)			
Antimicrobial prophylaxis			1.237	0.625-2.448	0.541
• Yes	47 (69)	21 (31)			
• No	72 (73)	26 (27)			
Central venous catheter			1.373	0.695-2.712	0.362
• Yes	59 (69)	27 (31)			
• No	60 (75)	20 (25)			
Days to FN onset			0.997	0.908-1.096	0.955
• <7days	12 (63)	7 (37)			
• 7-14days	94 (73)	35 (27)			
• >14days	13 (72)	5 (28)			
Total febrile days			1.100	1.035-1.169	0.002
• <7days	87 (81)	20 (19)			
• 7-14days	22 (52)	20 (48)			
• >14days	8 (53)	7 (47)			
Missing data: n=2					

p value is significant < 0.05 for ORs
The first category of each covariate is used as the reference category

Treatment indication

This factor was categorised into two groups. A small per cent of patients (8%) who received treatment under the adjuvant setting developed complication, while in contrast, 30% of patients who were undergoing treatment under the non-adjuvant settings (which includes first or subsequent lines, myeloablative and palliative care) experienced complications However, the difference between the two groups was not statistically significant (p=0.145), although the odds ratio was of a substantial value. (Table 4.7)

Prophylactic use of growth factors

The use of growth factor prophylaxis to facilitate neutrophil recovery was not shown to improve the incidence of complication related to FN. Patients who

received and those who were without prophylactic growth factor were noted to have similar percentages of complications, 29% and 28% respectively. The difference between the two groups was not statistically significant (p=0.929). (Table 4.7)

Prophylactic antimicrobial therapy

The administration of prophylactic antimicrobial therapy to reduce the risk of bacteraemia from gram negative micro-organisms did not improve patients' risk of developing complication during FN. Among the 68 patients who were prescribed with antimicrobial therapy, 69% of them did not experience complication while 31% did. Patients who did not receive antimicrobial prophylaxis were noted to have a lower incidence of complications (27%) as compared to patients who were prescribed with the therapy. However, the difference between the two groups was not statistically significant (p=0.541). (Table 4.7)

Vascular access device

At the onset of fever 86 neutropenic patients (52%) had some form of vascular access device. About a third of these patients developed complications. In contrast, in patients without a central venous device the incidence of complication was less than patients with the device (25% vs 31%, respectively). However, the difference between the two groups was not statistically significant (p=0.36). (Table 4.7)

Days to onset of fever

Duration to the onset of FN from most recent chemotherapy treatment was also studied for its relationship with the outcome measure. Categorised into three groups, there were more patients who developed fever between 7-14 days (n=129), followed by the group with less than seven days (n=19) and last the group with more than 14 days before onset of fever (n=18). Patients who developed fever within a short period of time from recent cancer treatment (less than 7 days) had the highest percentages of complications (37%) as compared with the other two groups. Despite the differences highlighted between the groups, they were not statistically significant (p=0.955). (Table 4.7)

Total febrile days

Of the six factors under the treatment-related category, this is the only factor which demonstrated statistical significance for its association with the outcome measure. Categorised into three groups, the majority of the patients with FN took less than 7 days to defervescence (n=107). This group of patients also experienced the lowest complication rates (19%). Between the three groups, patients who experienced prolonged FN (>7 days) were noted to have approximately twice the incidence of developing complications. The differences between groups were statistically significant with an odds ratio of 1.1 (95% CI 1.035-1.169, p=0.002). (Table 4.7)

4.8.6 Febrile episode-related factors

Table 4.8 Febrile episode-related factors and febrile neutropenia outcomes

FN episode-related factors	No Complication n, (%)	With Complication n, (%)	OR	C.I (95%)	p-value
Temperature (max)			2.461	1.075-5.634	0.033
• <39^{0}Cel	103 (75)	34 (25)			
• ≥39^{0}Cel	16 (55)	13 (45)			
Pulse rate			3.147	1.295-7.651	0.011
• <120/min	107 (76)	34 (24)			
• ≥120/min	12 (50)	12 (50)			
Missing data: n= 1					
Systolic Blood Pressure			12.00	2.444-58.922	0.002
• <90mmHg	2 (17)	8 (83)			
• ≥90mmHg	117 (75)	39 (25)			
Diastolic Blood Pressure			0.357	0.166-0.766	0.008
• <60mmHg	20 (54)	17 (46)			
• ≥60mmHg	99 (77)	30 (23)			
Respiration rate			2.341	0.743-7.377	0.146
• <24/min	112 (73)	41 (27)			
• ≥24/min	7 (54)	6 (46)			
De-hydration			4.208	1.828-9.691	0.001
• Yes	13 (45)	16 (55)			
• No	106 (77)	31 (23)			
ECOG performance status			3.459	1.478-8.093	0.004
• 0-2	106 (76)	33 (24)			
• 3-4	13 (48)	14 (52)			
Location at FN onset			1.477	0.720-3.027	0.287
• In-patient	33 (66)	17 (36)			
• Out-patient	86 (74)	30 (26)			
Presence of infection site			4.301	2.055-9.003	<0.0001
• Yes	45 (57)	34 (43)			
• No	74 (85)	13(15)			
Mucositis			1.239	0.602-2.547	0.560
• Yes	35 (69)	16 (31)			
• No	84 (73)	31 (27)			
Abnormal CXR			6.094	2.592-14.33	<0.0001
• Yes	11 (38)	18 (62)			
• No	108 (79)	29 (21)			

p value is significant < 0.05 for ORs
The first category of each covariate is used as the reference category

Body temperature

This factor was categorised into two categories: maximum temperature of less than 39^{0}C (lower) and equal to or greater than39^{0}C (higher). There were about five times more patients with the lower temperature (n=137) than those with higher temperature (n=29). Within the group, patients with lower temperature readings, only a quarter of them developed complication (25%). The rate of complication increased to 45% when FN patients reported with a higher

maximum body temperature. The association of this factor with the outcome measure was confirmed with a statistically significant *p*-value of 0.033 (OR=2.461, 95%CI 1.075-5.634). (Table 4.8)

Pulse rate

The majority of the patients had pulse rates less than 120beats per minute (n=141) while 24 patients presented with pulse rate of 120beats per minute and above. The rate of complication was twice that for patients in the lower pulse rate group. Patients with an abnormally high pulse rate (≥120b/min) are 3.147 times more likely to develop serious medical complication from FN as compared with the group of patients with a lower pulse rate. The difference is statistically significant (95% CI 1.295-7.651, p =0.011). (Table 4.8)

Blood pressure

Both systolic and diastolic blood pressure readings were statistically significant in their association to the outcome measure. Overall, 83% of patients who developed complications presented with low systolic reading, compared while only 25% had normal reading (OR=12, 95% CI 2.444-58.922, p=0.002). (Table 4.8) Patients with FN presenting with low diastolic pressure reading (<60mmHg) were reported to be associated with higher incidence of complications as compared with patients who have higher diastolic pressure reading (≥60mmHg)(46% versus 23%).(Table 4.8)

Respiration rate

Patients with tachypnoea (≥24/min) experienced a higher rate of complication (46%) as compared to those who had normal limits of respiration rate (27%). However, the difference observed was not statistically significant. (Table 4.8)

Dehydration

Patients who presented with signs of dehydration were 4.301 times (95% CI 1.828-9.691,p=0.001) more likely to experience medical complication compared to those who were sufficiently hydrated. The complication rate doubled between the two groups; with 55% of patients who were dehydrated at the onset of fever, developing complications compared to 23% of those who were well hydrated. This factor is independently associated with the outcome measure as demonstrated by the statistically significant p-value.(Table 4.8)

ECOG performance status

Patients with FN who presented with higher ECOG scores (3-4) for performance status were 3.459 times (95% CI 1.478-8.093,p=0.004) more likely to experience medical complication as compared to those who continued to be ambulatory and performed self-care activities. Patients with lower ECOG scores (0-2) were noted to experience less complication during FN and this factor demonstrated a statistically significant relationship with the outcome measure. (Table 4.8)

Location at onset of FN

Patients who developed FN while they were still hospitalised (36%) were shown to have a higher rate of complication as compared to those who were at home at the onset of fever (26%). However, the observed difference was not

statistically significant; hence this factor was not independently associated with the outcome measure. (Table 4.8)

Presence of infection site

The presence of an infection site in patients made them 4.301 times (95% CI 2.055-9.003,p<0.0001) more likely to experience complication during FN than patients without any source of infection. Complication rate was more than double for patients who had a visible or likely source of infection (43%) and the association of this independent variable with the outcome is confirmed by the statistically significant p-value. (Table 4.8

Mucositis

Mucositis has not been shown to be associated with the outcome of interest based on the non- statistically significant p-value of 0.560. (Table 4.8)

Abnormal chest radiograph

Patients who presented with abnormal chest radiograph were 6.094 times (95% CI 2.592-14.326,p<0.0001) more likely to develop complication with a rate as high as 63%, as compared to patients with normal radiograph readings of the chest (21%). With a statistically significant p- value, the association of this factor with the outcome measure has been confirmed. (Table 4.8)

4.8.7 Laboratory results

Table 4.9 Laboratory results and febrile neutropenia outcomes

Laboratory results	No Complication n, (%)	With Complication n, (%)	OR	C.I (95%)	p-value
Platelet level at baseline			1.400	0.485-4.041	0.534
• <50K	17 (77)	5 (23)			
• ≥50K	102 (71)	42 (29)			
Albumin level at baseline			1.495	0.247-1.495	0.247
• <35	64 (75)	21 (25)			
• 35-55 (normal range)	53 (67)	26 (33)			
Missing data: n=2					
White cell count at onset of FN			0.980	0.613-1.567	0.934
• <0.5 x10⁹/L	64 (70)	28 (30)			
• ≥0.5 to <1 x10⁹/L	39 (78)	11 (22)			
• ≥1 x10⁹/L	15 (56)	8 (44)			
Missing data: n=1					
Absolute neutrophil count at onset of FN			1.595	0.545-4.669	0.394
• Low (<0.5 x10⁹/L)	109 (73)	41 (27)			
• High (≥0.5 x10⁹/L	10 (63)	6 (37)			
Platelet level at onset of FN			0.852	0.433-1.679	0.644
• <50K	51 (70)	22 (30)			
• ≥50K	68 (73)	25 (27)			
Albumin level at onset of FN			1.242	0.589-2.621	0.569
• <35	38 (75)	13 (25)			
• 35-55 (normal range)	80 (70)	34 (30)			
Missing data: n=1					
Creatinine level at onset of FN			5.842	2.258-15.11	<0.0001
• <50	21 (81)	5 (19)			
• 50-110 (normal range)	92 (76)	29 (24)			
• >110	6 (32)	13 (68)			

p value is significant < 0.05 for ORs
The first category of each covariate is used as the reference category

Platelet levels at baseline and onset of fever

Platelet levels checked at the commencement of chemotherapy and at the onset of FN were not statistically significant in their association with the outcome measure. (Table 4.9)

Albumin level baseline and onset of FN

Albumin levels checked at two time points did not show independent association with the outcome measure with the p-values of 0.247 and 0.569 respectively. (Table 4.9)

White cell count at the onset of FN

Between the sub-groups of white cell count at the onset of FN, the group of patients with the highest count ($\geq$1 x10^9/L) and the lowest count (<0.5 x10^9/L) had higher rates of complications (44%) and (30%) respectively. However, the differences observed were not significant with the p-value above 0.05. (Table 4.9)

Absolute neutrophil count at the onset of FN

Patients with lower ANC (<0.5 X 10^9/L) at the onset of fever were noted to develop less complication compared with patients who presented with higher ANC ($\geq$0.5 X 10^9/L). However, the results were not statistically significant (p = 0.394). (Table 4.9)

Creatinine level at the onset of FN

Categorised into three groups, renal impairment (creatinine >110) occurred in 19 patients (11%). Complication rates were two to three times higher for patients with creatinine levels above the normal range (68%) as compared with patients with normal (24%) and subnormal creatinine levels (19%). Patients presented with renal impairment were noted to be 5.842 times (95% CI 2.258-15.111,p<0.0001) more likely to experience complications as compared to

those with normal or below normal creatinine levels. This factor showed an independent association with the outcome measure (p< 0.001).(Table 4.9)

4.8.8 Summary of the results

The present study established 11 factors as being independently associated with the outcomes for adult patients experiencing FN episodes. Seven predictors were based on episode-specific clinical features of patients presenting with fever and they include: body temperature, heart rate, blood pressure, hydration status, ECOG performance status, presence of infection site and abnormal chest radiograph result.

Older age group, presence of COPD and DM were predictors which reflect patient's general well-being based on comorbidity. The remaining predictors were creatinine level checked at the onset of fever, and duration taken for patients with FN to defervescence. Creatinine level which indicates kidney function is crucial for optimal administration of antimicrobial therapy while duration for defervescence is usually a prospective estimation based on types of regime and underlying diagnosis of patients.

4.8.9 Discussion

Overall the percentage of patients with FN who developed medical complications (28%) in this cohort study was higher than previous studies, which range between 15%[10] to 18%[59]. This could be related to the distribution of younger age group in the study by Klastersky et al[10] which was 70.6% while the

present study comprised of 60% of patients with age younger than 60 years. In spite of the higher percentages of complications, mortality rate was reported as 4% for the present study, similar trend to with the previous studies which range between 3.8%[59] to 5%[10].

In terms of infection status, the results from the present study were similar with the previous study[11] of which majority of FN patients would present with pyrexia of unknown origin (PUO), followed by microbiologically documented infection (MDI) with a positive blood culture and lastly clinically documented infection (CDI). The epidemiology and micro-organism of the present study were also reflecting similar trend of pathogens, with gram-positive infection being the most predominant pathogens, followed by gram-negative and polymicrobial bacteraemias as reported in the a few studies.[37, 251, 323] Significant changes in the pattern of infectious micro-organisms in cancer patients have emerged during the past decade. Among blood culture isolates from FN patients, gram-positive pathogens have become prevalent and this could be attributable to a few reasons.[323]

Firstly, the increased use of prophylactic antimicrobial therapy has been associated with a lower incidence of gram-negative bacteraemia in FN patients.[324] Secondly, increased intensity of combination cancer treatment is associated with more damage to the mucosal barriers which is associated with an increased gram-positive infections from resident oral flora.[137] Lastly, there are more cancer patients indicated for implantable intravascular access devices

given the complexity of treatment requiring multiple intravenous accesses, and these devices are known for a major source of infection.[325, 326]

The present study established a positive association of11 factors and invalidated others.for the outcomes of patients with chemotherapy-induced febrile neutropenia. Candidate variables and predictors are discussed in the following section.

Patient-related factors

The primary study indicated that older age is associated with increased risk of developing adverse outcomes in patients with FN. The result concurs with the finding of the systematic review as reported in Chapter 3. Being younger than 60 years was a predictor of favourable outcome in the MASCC risk-index model predictive of low-risk group of FN patients.[10] In the context of neutropenia and FN, older age has been shown to unequivocally increases risk of not only neutropenia but also the associated complications[327, 328] but also FN[329]. Furthermore, age is also an important surrogate for other covariates. The relative contribution of age as a predictor in a multivariable model may help adjust for covariates such as chronic diseases which are prevalent in the elderly patients.

Among the comorbidities included in the present study, COPD and DM were the only factors that showed a positive association with the outcome measure. Similar to the older age group, the absence of COPD is also a predictor for FN patients with low-risk of complications in the MASCC risk-index model.[10] The

presence of DM, which demonstrated a borderline association with unfavourable outcomes in FN patients in the present study, may be relevant as reported in its association with increased length of stay for FN in a univariate analysis. However, DM failed to achieve statistical significant at multivariate logistic regression analysis for in-patient mortality and was not a common predictor for FN outcomes in other primary studies.[13]

As opposed to utilising a specific comorbidity as in the case of the MASCC model, Talcott and his team included presence of serious comorbidity as one of the predictors in their risk prediction model.[36] It is apparent that the presence of comorbid condition(s) plays an important role in prognostication of patients with FN. One of the reasons may be related to the significant number of patients with FN reported with major comorbid conditions, and as many as 19.1% have two or more major comorbidities.[13]

In addition, it has been established that the number of major comorbid conditions correlates with a significant increase in the risk of in-patient mortality for patients with FN.[13] Comparing patients with one major comorbidity and those with two or more major comorbidities, the incidence of mortality was 10.3% and 21.4% respectively.[13] In contrast, in-patients without comorbidity the incidence of mortality was on average 2.6% .[13]

Only COPD has been verified repeatedly as a predictor based on the finding of the systematic review[330] and primary study. For other comorbidities there is no documented evidence to indicate if one comorbid conditions has a stronger

predictive ability over another. In contrast to the finding of the systematic review,[330] the candidate variables of previous fungal infection and anti-fungal therapy were reported not to be independently associated with the outcomes of FN in the present primary study. This could be attributed to the small number of patients with fungal infection in the present study. Absence of previous fungal infection was one of the predictors in the MASCC risk score and it was suggested that this predictor may be a surrogate marker for FN patient with expected prolonged neutropenia or for relapsed or uncontrolled leukaemia.[72]

The value of fungal infection as a predictor is and has been questioned. Firstly invasive fungal infection in FN patients is difficult to diagnose and the lack of available information at the point of assessment for FN patient reduces its clinical applicability as a predictor.[331] Secondly this type of infection is not prevalent in all patients with FN[332] the exception is prolonged neutropenia which is mainly related to patients with haematological malignancies.[333] As such, fungal infection is limited in its generalisability when applied to FN patients with solid tumours. Finally the practice of prophylactic anti-fungal therapy for patients who are at risk of contracting fungal infection may change the epidemiology and clinical outcomes for patients[334] which may minimise its significance as a predictor.

Previous febrile neutropenia episodes was studied for its potential predictive ability given its potential ability to extrapolate the risk of subsequent FN episodes.[120] In addition, information such as site of infection(s) and type of pathogen from previous FN episode outcomes may be helpful for treatment

plan. However, this variable has not been shown to be to statistically significant to the outcome of FN in the present study. Although this factor is suggested to be relevant in terms of therapeutic approach for FN patients, the present study provided insight that it was not predictive FN patients' outcome.

Disease-related factors

Underlying disease was not independently associated with the outcome of interest in the present study. However, solid tumour was a predictor of favourable outcome in the MASCC risk score[10] while haematological malignancy was a predictor for bacteraemia in FN patients[73], as reported in the systematic review[330]. In spite of these differences in findings, the underlying disease of FN patients has often been used as a surrogate indicator in clinical practice to estimate the duration and severity of neutropenia.[5]

The basis of this is related to the treatment directed at respective cancer diagnoses and aims of treatment, which are typically related to the dose and intensity of treatment administered.[24, 335] While it is clinically acceptable to extrapolate the duration and severity of neutropenia based on underlying tumours,[5] the status and degree of bone marrow involvement would be a better indicator for estimation of neutropenia duration and recovery of FN.

This is based on the fact that the bone marrow is the source of blood cells and production.[64, 146] The challenge for this factor as a predictor in a model for FN outcomes remains in the unavailability of information at the point of risk stratification. Unless there is a marker which reflect the condition of the bone

marrow specifically for disease status without requiring an invasive bone marrow procedure or diagnostic imaging, the factor would be of limited utility at this point of time.

Treatment-related factors

Among the six factors under this category only one factor was identified as a predictor in the primary study. When the duration of FN exceeded seven days the risk of developing medical complications was observed to be greater and statistically significant. The result corresponds with the finding from the systematic review.[330] Two of the included studies in the review reported longer duration to defervescence for FN is associated with poor prognosis[59] but failed to be statistically significant in association with infection-related mortality when analysed in a multivariate analysis[74].

Although the predictive ability for this factor has been confirmed in the present cohort study, it is not a suitable predictor. Clinical information for this factor is unavailable at real-time (onset of FN) but only retrospectively after the recovery or response to treatment is documented, hence it is of little value in the prognostic model.

Another common variable pertaining to treatment and neutropenic patients is the interval between the chemotherapy treatment and the onset of fever. A short duration to the onset of fever has been shown to be statistically significant in its association with risk of adverse outcomes for FN patients.[36, 74] In contrast to the duration to defervescence, the number of days to the onset of fever can

be calculated and the information is readily available for application, hence it is suitable as a predictor.[278] However, the factor was not-statistically significant in this primary study.

The remaining candidate variables that are treatment related and not independently associated with the outcomes of FN are treatment indication, prophylactic therapy and presence of central venous devices. However, of the four variables, receiving no adjuvant therapy (treatment indication)[73], absence of prophylactic antimicrobial therapy[73] and presence of vascular access device[58] have been established as predictors for bacteraemia in the systematic review[330.] The difference in the findings from the systematic review and this primary study may be attributable to the limited sample size of this cohort study as compared to the included studies from the systematic review. This is evident in the wide confidence interval generated from univariate analysis for the variable treatment indication in the cohort study. The limitation of small sample size may also result in the instability of coefficient estimates when the recommended number of event per variable is infringed upon.[217]

Febrile episode-related factors
Of the 11 candidate variables associated with FN episode, eight were independently associated with the outcomes of FN. They include the vital signs (maximum temperature, blood pressure and heart rate) and clinical presentation (hydration status) of patients at the point of medical triage. Variables from the cohort study which differed in their predictive ability from the

findings from the systematic review were respiration rate and geographical setting of patients at the onset of FN.

Additional information of ECOG performance status and presence of infection site, particularly abnormal chest radiograph results, were also shown to be independently associated with the outcomes of FN in the univariate analysis. There are several advantages of episode-specific clinical features; the information is available at the time of patient presentation to clinicians, and that they are standardised objective measurements that are easily reproducible. These elements are vital in promoting accurate assessment when the model is applied.[278]

Laboratory measurements

The use of laboratory results has increasing clinical utility for the prognosis and monitoring of response to treatment in the management of patients with FN. From the cohort study, data was collected for two laboratory measurements performed at two time points, once prior to the commencement of chemotherapy and at the onset of fever. The remaining ones were mainly tested on fever presentation. Among the five laboratory tests, abnormally high level of serum creatinine was the only variable shown to be independently associated with the adverse outcome of FN.

An important and fairly reliable indicator of renal function is plasma creatinine. Elevated levels of the variable signify impaired function specifically damage to functioning nephrons.[336] Two of the common causes of impaired renal function

include dehydration and presence of an infection.[336] These conditions are critical when present in patients with FN and necessitate prompt treatment hence an elevated serum creatinine is a valuable predictor. However, this laboratory result may not be immediately available at the point of triage; although it may only be available a few hours after, depending on the policy of the respective healthcare institution.

Data for platelet counts were collected at two time points – one at the commencement of chemotherapy and another at the presentation of fever. Thrombocytopenia at the onset of fever in patients with neutropenia was reported as a significant predictor for the high-risk group in a meta-analysis from the systematic review.[330]. However, the aetiology of thrombocytopenia was unclear. As a predictor for FN patients at risk of adverse outcome, platelet levels at both time points (at the commencement of chemotherapy and the onset of FN) were studied for their relationship with the outcome measure in the cohort study. In the present study, this variable failed to demonstrate an independent relationship with the outcome measure for both time points in the cohort study. The variance observed between the present study and reported literature may be explained by the small number of FN patients with thrombocytopenia who experienced complications as compared with those who did not.

4.8.10　Limitations of the primary cohort study

One limitation of this study was that the results of the study may not be representative of other institutions because it was conducted in a single healthcare institution; hence the generalisability may be restricted. Although a larger sample size may have improved the confidence intervals of some factors (particularly for those with limited numbers of occurrence) the sampling of data was stopped at Year 2004 to minimise potential heterogeneity of the sample population in terms of of patients' medical records, some of the laboratory values had treatment approach for FN patients. Finally, as the study was a retrospective review more than 10% of missing data which prevented the analysis of these variables.

4.8.11　Conclusion

Heterogeneity in the outcomes of FN requires treatment to be tailored according to patients' level of risk. Risk assessment and stratification using multivariable prognostic models rely very much on the predictive ability of the clinical and laboratory variables after adjusting for other predictors. The evidence-based approach in the identification of new candidate variables, coupled with re-validating the predictive ability of known variables in a primary study provided a more robust method for the selection of predictors for the derivation of a new prognostic model for the outcomes of patients experiencing FN.

5 Prognostic Model Development

5.1 Introduction to the chapter

This chapter opens with an overview of the importance of prognostic models and how they are being utilised in medical settings. An outline of methodological characteristics and recommendations for prognostic model development are discussed in the subsequent sections. Details on the methods used to develop a new prognostic model that is predictive of the outcomes of febrile neutropenia in adult cancer patients are then presented.

5.2 Prognostic models – an overview

Prognostic models are instruments that provide an estimated probability of the individual person with a given health state experiencing the outcome of interest within a specified time.[83] Such models are also commonly known as risk prediction tools or rules, risk scores, predictive models, clinical prediction rules and risk-score indexes.[54] These models are usually made up of a combination of multiple predictors used to assess and calculate risks of a patient or a healthy person experiencing a specific outcome or disease.[54] Prognostic models play an important role in improving the quality of healthcare at different stages. At clinical practice settings, the utility of prognostic models has been recognised as enhancing decision-making among medical personnel.[276] This ties in with the progressive transformation towards stratified medicine.[337, 338, 339,340, 341]

Traditionally prognostication in medicine relied mainly on clinical acumen, experience of clinicians[267] and intuition[342]. It has been reported that intuitive decision-making occurs more frequently under conditions of uncertainty in clinical practice.[342] These traditional methods of prognostication not only result in inconsistency and disparity, especially with less experienced clinicians, they are also prone to errors and biases.[342]

The inherent advantage of incorporating prognostic models into clinical decision making processes lies in the systematic, reproducible and evidence-based methods used in deriving the estimated outcome probabilities for individual patients.[83] Prognosis that is derived using prognostic models, is more objective, consistent and accurate as compared with traditional practice methods.[267] This notion is supported by studies which reported better accuracy of several prognostic models over clinical judgment alone.[276, 343, 344]

With the current movement towards stratified medicine and evidence-based healthcare, where clinical decision making is informed by current best available evidence, the use of objective tools such as prognostic models is preferred over unstructured clinical judgment.[276, 345] An example of evidence-based decision making that incorporates the use of a prognostic model in clinical practice is the Nottingham Prognostic Index.[223] A prognostic score was derived from multiple factors such as the grade of tumour, number of lymph nodes involved and the size of tumour. It reflects the survival probability of a woman with newly diagnosed breast cancer, [223]and treatment can be tailored based on the score.[223]

5.3 Characteristics of good prognostic models

The underlying principle of a good prognostic model lies in the performance of the tool to inform decision-making when applied in the clinical setting.[346] In addition to being valid and reliable, a good prognostic model also needs to be practical and generalisable.[347] Although there are several measures of model performance there is no consensus on which measure is most clinically useful. However, the accuracy of the model is often described by two components; discrimination and calibration.[346] Discrimination demonstrates how well the model distinguishes individuals who develop the outcome of interest from those who do not.[348] Calibration deals with the model's ability to estimate correctly the risk of probability of a future event of interest. It measures the precision of the predicted probabilities as compared to the actual observed outcome.[348]

To achieve these attributes of discrimination and calibration, two essential steps for model development must be performed. The first step of model development involves the identification and testing of candidate predictors for their individual predictive ability with the outcome of interest. Details of this part of model development which include study design, sample size and events per variable, development of *a priori* study aims and outcomes, statistical methods and the reporting of findings have been presented in chapter four. The other essential step in model development lies in the appropriate application of a regression analysis. The necessary process for deriving a regression model is the subject of the following sections of this chapter.

5.4   Building a multivariable prognostic model

Testing and confirming the predictive ability of the candidate variables are the initial steps of model development. Once a set of candidate variables are established as predictors, the next step uses the analysis of candidate predictors in combination to derive a prognostic model. The steps of this section include i) selection of candidate predictors to be included in the final model, ii) handling of continuous data, iii) the statistical approach to be utilised in model derivation, iv) measurement of model performance or predictive accuracy and v) internal validation.[291]

5.4.1 Selection of candidate predictors

For a prognostic model based on multiple predictors, the candidate predictors need to be tested in multivariate analysis so that each predictor included in the final model is mutually adjusted for the other predictors in the final model.[83] Depending on the selection method used, not all candidate predictors will be incorporated into the final model.[83] Although various methods of predictor selection exist, there is no consensus on which are the most suitable methods; certain considerations and concerns should be addressed as follows.

In addition to the characteristics of candidate variables discussed in chapter four (section 4.6.2), other considerations for potential predictors include testing for correlation and interaction with other predictors.[348] If they are found to be highly correlated, they may be excluded as they add minimal independent information as a predictor.[349]

Candidate predictors which are well established in the literature and have clinical credibility should also be considered, although they may not be significant in univariate analysis.[350] Such candidate predictors are in addition to those selected based on their statistical significance in an univariable analysis of the candidate variable-outcome association.[291] Conditional selection of candidate predictors based only on univariable tests and *p-values* could eliminate candidate predictors which may have been by chance not prognostic in the specific sample population.[217]

5.4.2 Data quality and handling

The quality of data is evaluated by measurement accuracy, whether there are missing values and, for prospective studies, whether assessors have been blinded to prevent bias.[83] Predictors with potential measurement inconsistencies both between clinicians and across study institutions may not be suitable as candidate predictors as they are likely to produce a different predictive ability of the model when applied in other areas [291] Missing values are usually resolved using modern statistical techniques such as multiple imputation.[351] However, if missing values exceed 5% of the data for any given predictor, it is advised to exclude such data from analysis because they lead to loss of statistical power and inaccurate estimates of the predictive ability of the derived model.[291]

Predictors are defined by continuous, categorical or binary data. The methods used to handle different types of data are important; this is especially true for predictors that are characterised by continuous data. This is because the

coefficient values for included variables affect the final model performance.[352] Furthermore, dichotomising continuous data into categories causes loss of pertinent information and statistical power in addition to increasing the prevalence of different cut-points for the same predictor in similar studies.[353]

Despite these limitations, dichotomisation of continuous data is widespread in model development.[217] A systematic review of methods used in studies to develop prognostic models reported only one study among 47 articles included in the review maintained data for continuous variables in their original format at analysis.[217] A common explanation for the practice of dichotomisation of data lies in the simplicity of data analysis, easy interpretation of results and application in the clinical settings.[352]

5.4.3 Approach to final model derivation

Two broad approaches that are commonly reported for the derivation of a final model are the full model approach that is inclusive of all identified predictors and the application of a predictor selection strategy.[83] In the full model approach, predictors are pre-selected and regardless of their predictive ability, they are fitted into a final model without further manipulation in predictor selection. This method has been suggested to minimise predictor selection bias and overfitting.[349]

In this respect a selection bias relates to the overestimation of a regression coefficient because the corresponding predictor is more likely to be statistically

significant if its estimated effect is large.[291] This happens when predictors are chosen based on conventional statistical significance level and results in overfitting.[291] Overfitting is described as a model too closely fitting the data from which it is derived, which may result in an increased prediction inaccuracy when the model is applied to an independent data set.[291] Furthermore, the full model may be impractical for clinical application, especially when the final model consists of many predictors.[291]

An alternative is to select promising candidate predictors based on clinical credibility and those which are already well established in the literature.[217] This method is recommended to reduce the potential biases that stem from selection methods based on pre-determined p-values for inclusion and exclusion of variables (discussed above, section 5.4.1).[291] The selection of candidate predictors for multivariate analysis is then based on a combination of clinical and statistical significance which include information from the published literature and investigator's choice.[350, 354]

The other approach is the use of statistical methods to select predictors for the multivariate analyses. Depending on the specific method used, the broad principle involves the assessment of candidate predictors and, based on their predictive contribution to the model, their removal or inclusion.[83] One method is backward elimination, this starts with a set of all candidate predictors in the multivariate mode. A pre-defined nominal significance level for exclusion of predictor(s) is set to guide the sequence of testing to either remove or include candidate predictors in the final model.[83]

On the other hand, the forward selection approach involves selecting the best candidate predictors based on their statistical significance without simultaneously considering the effects of all candidate predictors.[83] While both methods have their advantages and limitations, the backward elimination is preferred to the forward selection method as the former considers a wider range of possible best models without missing predictors which are potentially important or correlated.[355]

Another consideration for using a statistical method for the selection of predictors is the cut-off level for significance, as it has an important effect on the number of variables selected. Often statistical significance values for example $p<0.05$ or $p<0.01$ are chosen and this produces models with fewer predictors because of the stricter level of significance.[83] In contrast, models based on less stringent levels ($p< 0.20$ or $p<0.25$) will yield a model that has an increased number of predictors. Greater stringency with respect to statistical significance may lead to discarding potentially important predictors while a reduced stringency increases the possibility of selecting less relevant predictors.[83]

Nonetheless, the issue of "overfitted" models is not avoided by either the full or selective methods for model derivation; especially when applied to small data sets and predictors with borderline significance. Although selecting a 1% ($p=0.01$) level of significance is less susceptible to causing overfitting and selection bias, it is common for prognostic data sets to include a mixture of

predictors with different levels of significance.[83] Regardless of the methods or

level of significance used for the selection of predictors, it is recommended that

subsequent validation of the models be performed to assess the likelihood of

the final model having missed important predictors and being overfitted;

resulting in instability when it is eventually utilised.[356, 357]

5.4.4 Assessment of model performance

Once the prognostic model is finalised, the predictive performance of the

model is evaluated to establish its accuracy. This is done using estimates of

sensitivity, specificity, predictive values and the area under the receiver

operating characteristic (ROC) curve as indices of discrimination. Sensitivity

describes the ability of the prognostic model to reliably identify FN patients as

being at risk of adverse outcomes when they are at risk of adverse outcomes,

while specificity refers to the ability of the model to avoid the misclassification of

those FN patients who are not at risk of adverse outcomes as being at risk.[358]

Positive predictive value is the proportion of FN patients with positive prediction

of high-risk that truly belongs to the high-risk group. Conversely, NPV is the

proportion of FN patients not stratified to the high-risk group who are ultimately

not high-risk.[359] In terms of prognostic model accuracy, a high sensitivity and

specificity is preferred, although it is rarely possible as both are inversely

proportional, and as one component increases the other will likely decrease.[360]

The area under the receiver operating characteristic (ROC) curve which

represents the overall accuracy of a model's performance provides a

graphical illustration of the best "cut-off" value for both the highest sensitivity

and the highest specificity.[346] For a ROC plot, the closer the curve is towards the

upper left corner the greater the discriminatory ability of the model (i.e. the

true-positive rate is high and the false-positive rate is low).[346]
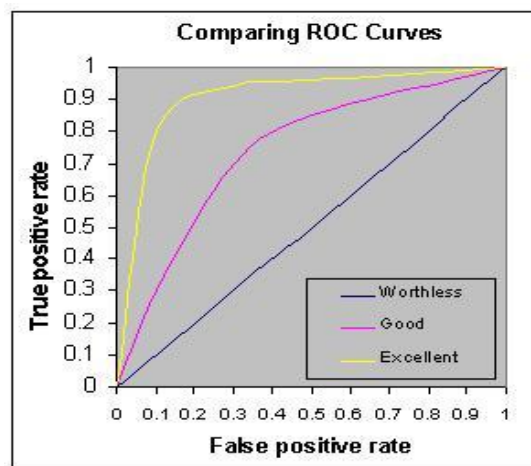
The graph above shows three ROC curves representing excellent, good and worthless tests plotted on the same graph. The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease in question. Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of .5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

- .90-1 = excellent (A)
- .80-.90 = good (B)
- .70-.80 = fair (C)
- .60-.70 = poor (D)
- .50-.60 = fail (F)

Figure 5.1 Example and explanation of the area under the receiving operator characteristic curves[361]

Measured quantitatively, the maximum value for the area under the ROC curve

is 1.0 indicating a perfect discrimination (100% sensitive and 100% specific),

while a value of 0.5 indicates no discriminative ability, as illustrated in Figure

5.1.[346]The final step of model development involves evaluating the clinical utility

and its potential impact on clinical outcomes.[286, 362] However, it is not part of the present study.

5.4.5 Model validation

Before models are adopted into clinical practice is it highly recommended that they be subjected to both internal and external validation.[264, 265] This is because the model derived from the inception cohort of the sample population needs to demonstrate similar validity and reliability when evaluated against a new independent data set to be considered generalisable.[265] One reason for this is that model performance tends to be more optimistic against the original data set as compared with a new but similar cohort of individuals.[265]

The incongruence of model performance may be attributed to various statistical or clinical factors. Predictions generated from the model may not be reproducible because of the limitations in the design or modeling methods used in the primary study for model development – for example if the model was originally overfitted or missing an important predictor.[265] The performance of the model when tested in a new group of patients may also be compromised by differences in the patient characteristics, setting, healthcare system and methods of measurement between the inception cohort and validation cohort of patients.[265]

Different types of validation exist. These include internal validation, temporal validation and external validation.[265] Internal validation involves only the

original sample population used for the study.[265] No new group of patients is involved but the original dataset is split into two parts; one set is used for model development (often known as training set or inception cohort) while the second part is used to assess the model's predictive accuracy.[265] Internal validation is advocated to estimate the extent of overfitting and optimism in model performance.[265] This approach often yields better performance results because of the similarity between the training set and validation set. To reduce the similarity that arises from the "data-splitting" approach, non-random splitting method is preferred.

Temporal validation applies the same principle of "data-splitting" as described in internal validation but on subsequent patients from the same centre. The emphasis of this method is that the evaluation is performed prospectively, independent of the original dataset and inception cohort.[265] External validation examines the generalisability of the model, examining the performance of the model in a new dataset from similar patient population in a different centre.[265]

5.4.6 Barriers to prognostic model implementation

The number of prognostic models published in the last decade has sharply increased, even within the same clinical disorder or disease.[222, 303] However, very few of these models are externally validated, yet alone used in clinical practice.[303] This is evidenced by the small proportion of validation studies and the minimal number of reports confirming the clinical impact of models among an increasing number of papers on prognosis studies[363]. In the management of traumatic brain injury there have been 102 risk prediction models developed

since early 1990s.[303] However, only five studies reported external validation and none has been widely implemented in clinical practice.[303]

Model validation provides pertinent information for clinicians to assess and verify the performance and generalisability of models, which is an essential step before adoption of a model in a clinical setting.[265, 288, 363]Although not the only factor influencing the uptake and implementation of prognostic models, validation studies are more likely to increase clinicians' confidence in incorporating prognostic models into their practice.[265] This is especially true for validation studies conducted over multiple-sites that demonstrate adequate reliability and validity of a particular model.[364]

In addition, this may address clinicians' concern of medico-legal consequences in the event of misclassification based on model predictions and decisions.[365, 366] Other factors that may improve utilisation include practical issues such as the availability of information in routine care for easy application, hassle free assessment format, cost effectiveness and time-efficiency.[286]

5.5 Results:

5.5.1 Development of a prognostic model for febrile neutropenic outcomes

The following sections describe the details of the model development of a

prognostic model for adult patients presenting with FN.

Selection of candidate predictors and methods utilised for model derivation

After completing the univariate analysis (chapter 4), the full model approach

and automated predictor selection methods were used for the selection of

candidate predictors to derive the final model. Multivariate logistic regressions

were used to generate the full model (all-variable), forward selection,

backward elimination model, model with statically significant p-values of <0.05

and a literature-based (non-statistically significant) selected predictors model.

An area under the operating ROC curve was performed to select the two best

models. (Figure 5.2)
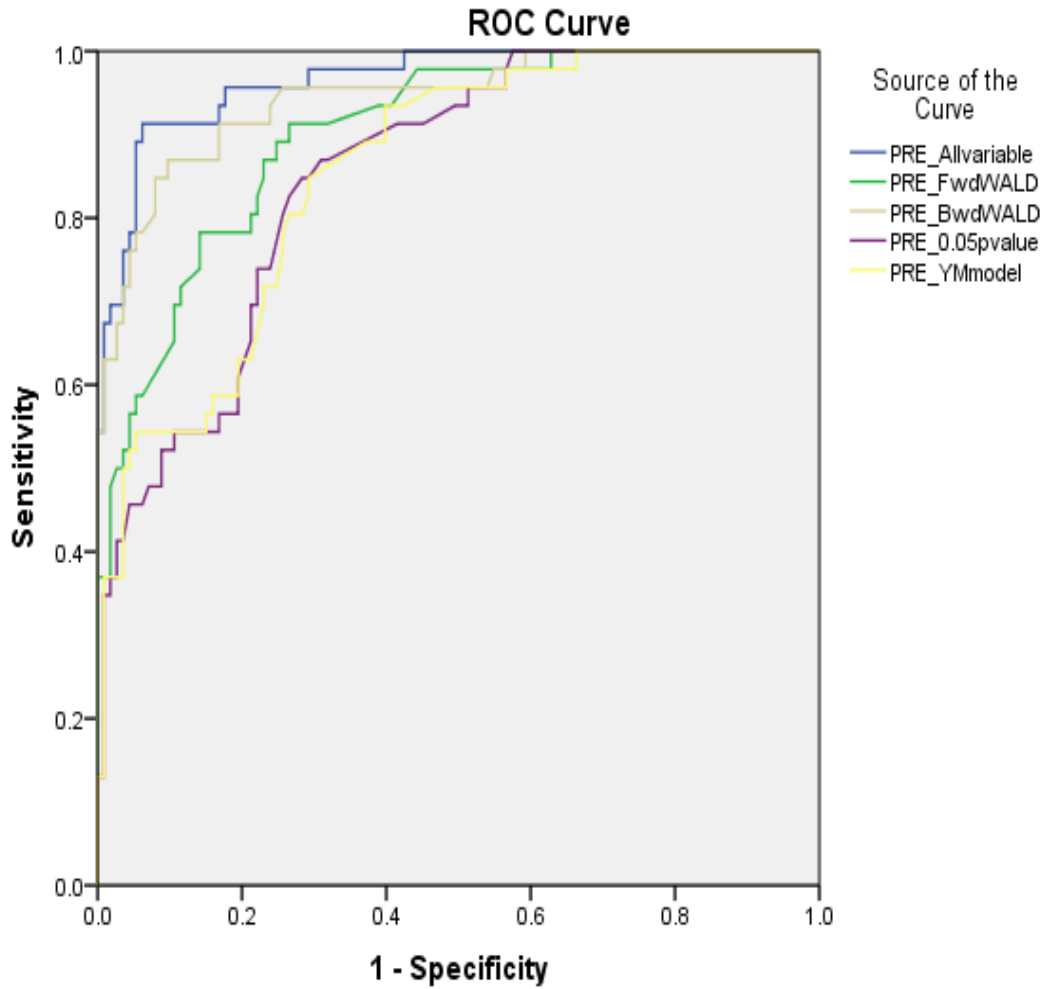
ROC Curve

*YM model refers to the LB model

Figure 5.2The area under the receiver operating characteristic curve for 5 models generated from multivariate logistic regression

The full model showed the highest area under the ROC which was 0.965 (95% CI, 0.938-0.992, p<0.0001). However, the general scientific principle of parsimony inferred that complex models are not as reasonable descriptions of reality as simpler models.[285] Furthermore, smaller models may be applied more easily in clinical practice and are less prone to overfitting.[285] Hence, the backward elimination model (AUC 0.944, 95% CI, 0.904-0.983, p<0.0001) and literature-based selected predictors model (AUC 0.854, 95% CI, 0.793-0.914, p<0.0001) were preferred as they gave the next best area under the ROCs. (Table 5.1)

Table 5.1The area under the receiver operating characteristic curve for 5 models generated from multivariate logistic regression

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PRE_Allvariable	.965	.014	.000	.938	.992
PRE_FwdWALD	.902	.025	.000	.853	.951
PRE_BwdWALD	.944	.020	.000	.904	.983
PRE_0.05pvalue	.851	.031	.000	.791	.911
PRE_YMmodel	.854	.031	.000	.793	.914

All variable –all predictors included model
FwdWALD – Forward WALD model
BwdWALD – Backward WALD elimination model
0.05 value – Predictors with p-value ≤0.05 model
YM - literature-based selected predictors model
PRE- predicted probability

Backward WALD elimination model (BW model)

A total of 15 prognostic factors were selected for the backward WALD elimination model after adjustment for confounders. They include age, gender, comorbidity (COPD), use of prophylactic antibiotic, presence of vascular access device, total febrile days, body temperature, blood pressure, pulse rate, presence of infection site, white cell count, platelet count, creatinine level and abnormal finding of chest radiograph at onset of fever. The β coefficient estimates of the independent variables of the model are listed in the table. (Table 5.2)

Table 5.2 Backward WALD elimination prognostic model for chemotherapy-induced febrile neutropenia in adult cancer patients

Variables	Coefficient	S.E.	OR	95% CI for OR
Age	2.157	0.827	8.648	1.710-43.743
Gender	-2.292	0.804	0.101	0.021-0.488
COPD	3.330	1.340	27.932	2.022-385-763
Antibiotic prophylaxis	2.277	0.995	9.747	1.387-68.48
Temperature	2.694	1.020	14.794	2.005-109.177
Systolic blood pressure	5.094	1.830	163.068	4.517-5887.04
Diastolic blood pressure	-2.403	0.855	0.090	0.017-0.484
Pulse rate	3.529	1.159	34.079	3.513-330.625
White blood cell				
WBC2 Cat(1)	-2.130	0.939	0.119	0.019-0.748
WBC2 Cat(2)	5.137	1.388	170.205	11.198-2587.1
Platelet count Cat(1)	-2.729	0.978	0.065	0.010-0.444
Creatinine level				
Cr Cat(1)	-0.474	1.000	0.622	0.088-4.423
Cr Cat (2)	2.642	1.601	14.035	0.609-323.281
Total febrile days				
DDay2 Cat (1)	2.587	0.834	13.290	2.593-68.10
DDay2 Cat (2)	2.162	1.063	8.689	1.082-69.755
Presence of infection site	3.107	0.919	22.345	3.686-135.454
Presence of VAD	3.018	1.068	20.449	2.522-165.796
Abnormal CXR	2.174	0.850	8.792	1.661-46.546
Constant	-19.368	4.748	0.00	

COPD- Chronic obstructive pulmonary disease;
WCC- white blood count at onset of fever;
Cr – creatinine at onset of fever;
DDays2 – total febrile days
VAD – vascular access device
CXR-chest x-ray

A prognostic score was derived from the predictors and associated coefficients of the BW model. The formula is presented as follows:

$$8 * AgeCAT + 10 * (1- GenderMale1\_Fem2) + 28 * COPD + 10 * AbxBactprop + 15 * TempCat + 163 * SBPCat + 11 * (1 - DBPCat) + 34 * PRCat + 8 * (1 -WCC2\_2) + 170 * WCC2\_3 + 15 * (1 - Plt2Cat) + 2 * (1 - Cr2corrCat\_2) + 14 * Cr2corrCat\_3 + 13 * DDay2Cat\_2 + 9 * DDay2Cat\_3 + 22 * PInfectionSite + 20 * CVC + 9 * AbN\_CXR$$

The optimal cut-off score for this model was at 344 to predict high-risk for FN patients. The sensitivity, specificity, NPV, PPV of this model is 95.7%, 59.5%, 97.2% and 48.4% respectively. The area under the ROC curve was reported as 0.776.

Literature-based predictors model (LB model)

A simplified version of the model was derived based on literature selected predictors. A total 12 predictors were chosen based on clinical applicability and the availability of information at medical consultation. The model is presented in Table 5.3 along with the β coefficient estimates of the independent variables of the model .The prognostic score can be obtained from the following formula:

2 * AgeCAT + 1 * Deh2O + 2 * TempCat + 14 * SBPCat + 1 * (1 - DBPCat) + 4 * PRCat + 1 * Cr2corrCat_2 + 4 * Cr2corrCat_3 + 5 * PInfectionSite + 3 * AbN_CXR + 2 * ECOG_34 + 2 * GCSFNo1Yes2 + 4 * COPD

The optimal cut-off score to estimate high-risk FN patients was 45,with predictive sensitivity (82%), specificity (69.7%), NPV (91.2%) and PPV (51.4%). The area under the ROC curve was reported as 0.762.

Table 5.3Literature-based (LB) model for chemotherapy-induced febrile neutropenia in adult cancer patients

Variables	Coefficient	S.E.	OR	95% CI for OR
Age	0.486	0.511	1.626	0.597-4.431
COPD	1.422	0.793	4.145	0.876-19.607
Prophylactic CSF	0.539	0.492	1.715	0.654-4.501
Temperature	0.518	0.597	1.678	0.521-5.411
Systolic blood pressure	2.635	1.155	13.941	1.45-134.04
Diastolic blood pressure	-0.378	0.541	0.685	0.237-1.981
Pulse rate	1.385	0.703	3.996	1.008-15.833
ECOG performance status	0.413	0.611	1.512	0.457-5.005
Dehydration	0.344	0.638	1.411	0.404-4.924
Presence of infection site	1.681	0.531	5.369	1.895-15.210
Abnormal CXR	0.950	0.561	2.586	0.861-7.771
Creatinine level				
Creatinine Cat(1)	0.289	0.718	1.335	0.327-5.451
Creatinine Cat (2)	1.500	0.967	4.484	0.674-29.814
Constant	-8.982	2.058	0.00	

COPD- Chronic obstructive pulmonary disease
CSF – colony stimulating factor
CXR-chest x-ray
Cr – creatinine at onset of fever

5.5.2 Preliminary validation of BW and LB models

Assessment of the performance of both models was undertaken using data from FN patients from the same cohort as the inception sample, but taken at the time of a subsequent FN event. The use of same cohort but with different event sequence is similar to the internal validation of which the purpose was to estimate the extent of overfitting and optimism in the model performance. True positives and negatives in addition to false positives and negatives were calculated for the BW model and LB model to compare the agreement between the actual outcome frequencies and the estimated probability of the outcome provided by the respective models. The demographics of the patients are summarised and listed in Table 5.4.

Table 5.4 Demographics for cancer patients experiencing second episode of febrile neutropenia

DEMOGRAPHICS	No. of Patients (n=67)	%
Age (mean/ median) years	48.3/50	
• Range	20-75	
• <60	46	69
• ≥60	21	31
Gender:		
• Male	41	61
• Female	26	39
Co-morbidity		
• IHD/ CCF	1	1
• Diabetes	4	6
• Hypertension	7	10
• Chronic obstructive pulmonary disease	1	4
Previous fungal infection	7	10
Anti-fungal therapy	8	12
Previous febrile neutropenia episode	59	88
Underlying disease:		
• Haematological malignancies	56	84
• Lymphomas	7	10
• Solid tumours	5	6
Treatment indication		
• Adjuvant or neo-adjuvant	1	1
• First line	38	57
• Second (subsequent) line	13	19
• Myeloablative	13	19
• Palliative	2	3
Prophylactic growth factor administration	52	78
Antimicrobial prophylaxis	46	69
Geographical setting at onset of FN		
• In-patient	17	25
• Out-patient	50	75
Days from most recent treatment to FN onset		
Mean: 10.4 days		
• <7days	4	6
• 7-14days	60	90
• >14days	3	4
Total febrile days		
Mean: 6.6days		
• <7days	41	61
• 7-14days	21	31
• >14days	5	7

There were 67 patients in total and the demographics for variables such as age, gender, comorbidities, treatment indications, geographical location of patients and both measures of durations did not differ greatly from the inception cohort (Chapter 4, section 4.8). Increased numbers of patients were seen for variables including previous fungal infection, anti-fungal therapy and prophylactic therapies. There was a higher percentage of patients with haematological malignancies as compared with the inception cohort. Based on the calculated true and false negatives and positives for both models, the predictive values were indicated as follow (Table 5.5):

Table 5.5 Results from preliminary internal validation of BW and LB models

Prognostic models for FN outcomes	Sensitivity(%)	Specificity(%)	NPV(%)	PPV(%)
BW model	65.2	50	73.3	40.5
LB model	56.5	61.4	73	43.3

BW model– backward WALD-elimination model
LB model - Literature-based selected predictors model
NPV - Negative Predictive Value
PPV - Positive Predictive Value

5.6   DISCUSSION

In the present study, the aim was to develop a prognostic model to predict the risk of adverse outcomes in FN patients based on admission characteristics that could be assessed easily and objectively within the first few hours after the onset of fever. As a result, two prognostic models were derived. These were a backward WALD elimination model (BW model) and a literature-based selected predictors model (LB model). Overall most of the predictors utilised have clinical and biological plausibility and have previously been part of routine patient assessment in the clinical setting.

5.6.1 Backward WALD elimination model and literature-based selected predictors model

The two models have fairly comparable predictors. Both models are comprised of predictors from each category (patient-related, treatment-related, episode-related and diagnostic/laboratory markers) (Chapter 2, section 2.7). Older age, presence of COPD, high temperature, hypotension, and dehydration were already established predictors in the MASCC risk score[10] and are repeated in the models derived from the present study.

Between the two models, the LB model was considered to be the most practical for clinical application. The LB model was comprised of fewer prognostic factors as compared with the BW model and all predictors can be promptly assessed and are interpretable to clinicians. Therefore, unfamiliarity with the measurements would not be a concern when the model is applied in the clinical setting. Furthermore, most of these predictors have been recognised for their significance

in other prediction model studies of risk and associated outcomes of febrile neutropenia patients.

Laboratory parameters which have not yet been widely used for prognosis for patient with FN until recently are gaining increased interest.[78, 367, 368] The models developed in the present study are congruent with the current trend of incorporating laboratory parameters as predictors. White cell count, platelet count and level of creatinine at presentation of fever have been selected into the BW model as predictors. However, the only laboratory parameter selected for the LB model (based on clinical importance) was creatinine level at fever onset.

Although creatinine level has not been adequately studied as a predictor for FN outcomes in previous studies, there is a general consensus that renal function plays a critical role in drug administration which includes anti-microbial therapy. An abnormal creatinine level may result in sub-optimal dosing or withholding renal toxic type of antibiotic administration for FN patients.[369] This could compromise the response and recovery of patients.[370]

Neither model had a predictor selected from the disease-related category, although the type of malignancy (haematology) has been reported as prognostic risk factor for bacteraemia.[73] This could infer that the importance of the underlying disease as a predictor may have been adjusted by other predictors in the model; such as the use of vascular access device. The use of vascular access device is typically associated with patients with haematological malignancies because of

their need for regular blood tests and the complexity of their treatment requiring multiple intravenous infusions simultaneously.

The LB model was developed due to the moderately large number of predictors in the BW model. Consequently an attempt was made to reduce the number of predictors from15 to 12. The selection was made based on the predictors' documented relevance in the literature and practical reasons; although most of the predictors were not statistically significant after adjusting for confounders in the LB model. Performance status (ECOG) and hydration status were selected for the LB model over presence of vascular access device and total days of fever. While vascular access device has been frequently associated with patients with haematological malignancies, more patients with solid tumour are requiring similar device due to the increasing complexity of cancer treatments. In turn, this may lead to increased rates of bacteraemia and complications for patients with solid tumour, especially during FN.[371]

"Total days of fever" was statistically significant in univariate and multivariate analysis for the backward model. However, it was omitted from the LB model because information for this predictor remains a clinical estimation (only available in retrospect) and it has been found to be unreliable and inconsistent. Furthermore, although duration of neutropenia is directly related to the aggressiveness of the chemotherapy regimen, it is a continuous outcome.[255] Nonetheless, when some of the predictors in the BW model were replaced or removed to derive a model with fewer predictors (LB model) the model's apparent discriminative ability was decreased. (AUC 0.944 to 0.854).

The reduction of the number of predictors also affected the sensitivity, specificity and predictive values of both models when they underwent preliminary testing. Considering that the main objective was to select FN patients with high-risk of adverse outcomes, NPV with the good percentage of sensitivity is preferred. Based on this assumption, the BW model, which has the highest sensitivity and NPV as compared with the LB model, should be the model of choice. This is a measure to ensure that a minimal number of FN patients with high-risk of adverse events are misclassified as being at low risk.

However, when both models underwent preliminary testing on a small sample of patients similar to the inception cohort, the performance of the models was shown to be comparable. Given the LB model has fewer predictors, that the predicors have higher clinical applicability, and that it performed almost as well as the BW model, the LB model is a better choice than the BW model for the clinical setting. While the preliminary validation results of the BW and LB models were less favourable, there was a higher percentage of patients with haematological malignancies as compared with the inception cohort, which may have negatively affected the performance of the models.

5.6.2 Comparison between the prognostic models

Models developed from the present study demonstrated increased sensitivity compared to the Talcott model and increased NPV compared to both the Talcott model and the MASCC risk-index score. (Table 5.6) While the Talcott model[64] and MASCC risk-index score[10] were designed to identify FN patients with low-risk of developing adverse outcomes, and therefore potential eligibility for early

discharge and out-patient therapy, the models from the present study were interested in the identification of the high-risk group of FN patients for early identification of clinical deterioration as optimising the management of patients could improve outcome of FN episode.

Table 5.6 Preliminary internal validation for backward WALD (BW) and literature-based (LB) models

Prognostic models for FN outcomes	Sensitivity(%)	Specificity(%)	NPV(%)	PPV(%)
*BW model	65.2	50	73.3	40.5
*LB model	56.5	61.4	73	43.3
Talcott et al[36]	30	90	23	93
MASCC risk-index[10]	71	68	36	91

BW model– backward WALD -elimination model
LB model - Literature-based selected predictors model
NPV - Negative Predictive Value
PPV - Positive Predictive Value
*preliminary tested

Similar to the inception cohort for the Talcott model and MASCC risk-index score, the present study also included a heterogeneous group of cancer patients with FN with the aim of developing a prognostic model generalisable to the cancer patient population at large. However, some clinicians have raised issues with this approach based on the contention that patients with haematological malignancy have a different clinical course for FN, hence the prognostic models developed based solid and haematological tumour patients would be less applicable to the latter group.[11, 176]

While this concept is applicable to some situations, such as patients with acute leukaemia undergoing induction therapy or allogeneic stem cell transplantation,[5] validation studies have shown that the MASCC risk-index score is applicable for patients with haematological malignancies.[47, 243] However, when the predictors for the four models derived from multi-cancer groups of patients (Talcott model,

MASCC risk-index, BW and LB model) were compared with those from models restricted to haematological diseases, distinct differences were noted. (Table 5.7)

In particular, laboratory markers were included in the models developed specifically for patients with haematological diseases while the earlier models with mixed group patients (Talcott model and MASCC risk-index) did not include any laboratory markers. Due to the variable frequency of measurement encountered in practice for some of the predictors i.e. daily white cell count before FN onset and digestive tract sterilisation[176] these variable may not be practical in terms of clinical utility.

Moreover, both models for FN patients with haematological malignancies have not been internally or externally validated. The inference that can be made from the observation is patients with haematological diseases may have specific characteristics that justify adaption or discovery of new predictors targeted at unique issues faced by this group of patients during FN episode.

Within the models developed from a mixed group of cancer patients (Talcott model, MASCC risk-index, BW and LB model) similarity among the predictors from these models were observed. The differences between the current models and models developed in the present study lies in the laboratory test(s) in the new models. The LB model was developed based on clinical features and diagnostic criteria for sepsis[372] which may assist in the early assessment at the point of triage for characteristics of sepsis for FN patients, especially for FN patients with high-risk.[105]

Table 5.7 Current prognostic models for outcomes of febrile neutropenia in adult cancer patients

Prognostic models	Aim of study	Sample population	Predictors in models	External Validation
Talcott et al[64]	Clinical identification of a low-risk sub-group of FN patients	261 patients -solid tumours (42%) -haematology malignancies (40%) -lymphomas (18%)	Geographical location of patient at fever onset Comorbidity Malignant disease status	Multiple sites
Klastersky et al[10]	To develop an internationally validated scoring system to identify low risk chemotherapy-induced FN cancer patients	756 patients -solid tumours (41%) -haematology malignancies (39%) -lymphomas (20%)	Burden of illness(no/mild symptoms) Burden of illness(moderate symptoms) No of hypotension No of COPD Solid tumour/No previous fungal infection No dehydration Out-patient status Age < 60 years	Multiple sites
Nakagawa et al[176]	To develop a score-index to risk stratify FN patients with haematopoietic diseases	354 patients -acute leukaemias (42.9%) -lymphomas (15.5%) -myelodysplastic syndromme (19.5%) -multiple myelomas(10.7%) -others (11.3%)	Age Type of haematopoietic disease White cell count at onset of fever Daily fluctuation in white cell count before FN onset Prophylactic treatment with anti-mycotic agents Sterilisation of digestive tract Urine albumin level Creatinine level C-reactive protein value	Not validated
Park et al[11]	To identify prognostic factors of chemotherapy-induced FN cancer patients with haematological disease	137 patients, 259 episodes -haematology malignancies (68.7%) -lymphomas (31.3%)	Recovery of neutropenia Low serum albumin level (<3.3g/dL) Low serum bicarbonate level (<21 mmol/L) High CRP ($\geq$20 mg/L) High CRP on 5th day of treatment (>100 mg/L) Respiratory tract infection	Not validated
*Backward WALD elimination (BW)	To develop an evidence-based prognostic model for risk stratification of adult cancer patients presenting with chemotherapy-induced FN	166 patients -solid tumour (28.9%) -haematological malignancies (51.8%) -lymphomas (19.3%)	Age Gender Chronic obstructive pulmonary disease Antibiotic prophylaxis Temperature Systolic blood pressure Diastolic blood pressure Pulse rate White blood count Platelet count Creatinine level at onset Total febrile days Presence of infection site Presence of VAD Abnormal chest radiograph	Not validated*
*Literature based (LB)			Age Chronic obstructive pulmonary disease Prophylactic CSF Temperature Systolic blood pressure Diastolic blood pressure Pulse rate ECOG performance status Dehydration Creatinine level at onset Presence of infection site Abnormal chest radiograph	Not validated

*Preliminary internal validation has been performed (section 5.7)

5.6.3 Limitations

The application of the prognostic models derived from the present study should take into consideration the following limitations. The outcome of the present study is limited by its study design that relied on a retrospective cohort. Being based on a single centre limits the generalisability of the models derived, although the study was underpinned by an evidence-based review for the identification of prognostic factors.

The present study was also limited by its sample size and the number of FN patients who developed medical complications in inception cohort was small. As a result low positive and high negative predictive values were seen in the BW and LB models.[309] Therefore, the selection of candidate variables, degree of coefficients and the accuracy of both the BW and LB models' performance requires careful interpretation. The other limitation also included the validation of the two models (BW and LB) based on the same cohort of patients but at a different event sequence. Similar to internal validation, this approach often reports better performance results of the model because of the similarity arises from the same cohort of patients. In any case, all newly developed prognostic models should undergo independent validation before being considered for clinical application. Further external validations would provide necessary information that can be used to update or adjust the prognostic model of choice.[288]

5.7   Conclusions

Early assessment and accurate prediction of outcomes through the use of prognostic models provides a baseline risk profile for individual neutropenic patients presenting with fever. With the newly developed prognostic model which emphasised predictor sensitive to the early detection of sepsis, adverse outcomes of FN could be averted with vigilant monitoring and prompt initiation of aggressive therapeutic interventions.

5.7.1 Implications for practice

The importance for newly developed prognostic models to undergo independent validation before being considered for clinical application cannot be over-emphasised. While the use of prognostic models has been shown to augment clinical decision-making and improve utilisation of healthcare resources, they should be approached with care and not directly applied for treatment decisions without other considerations. The validity and applicability of prognostic models are affected by various factors including the infrastructure and clinical expertise of the site where care is provided.

Categorisation of patients into the low-risk group cannot by default be considered absolute; and vigilant observation and rapid access to appropriate medical care at all times remain fundamental in the management of FN patients. On the other hand, identification of FN patients with high-risk group of adverse outcomes is only the first step in potentially altering the outcomes of these patients through close medical surveillance and early interventions. However, this is not the same as prevention, particularly when most of the

predictors included in the models are not modifiable factors. Therefore further assessment of modifiable risk factors for neutropenia and FN could be incorporated into the overall management of FN patients and improve the outcomes of these patients.

5.7.2 Future research

Given the infancy of the newly developed evidence-based prognostic models for adult FN patients from the current study, additional work will be required to validate, recalibrate with new clinical and laboratory information, and revalidate in an independent cohort of patients. Other approaches to improve the prediction of the models for FN patients would include rapid diagnostic tests for bacteraemia status, and broad identification of bloodstream pathogens in combination with inflammatory markers. Continuous work in prognostic research with the aim to provide accurate and useful probabilistic assessments of risk for future events should be undertaken with collaboration between clinician-scientists, biostatisticians and patients. This may lead to changes in clinical practice patterns and the integration of prognostic models into beside practice in a timely manner.

6 Discussion and Conclusion

6.1 Introduction to the chapter

This chapter presents a general discussion of the overall thesis. To introduce the chapter, current indications and practice of risk stratification in management of FN patients will be reviewed. A summary of the systematic review, prognostic factors identification and the development of the prognostic model are presented. This is followed by a discussion on the implications for clinical practice and strategies for the translation of the research evidence to clinical practice. Recommendations for further research in the areas of risk stratification and model development for the management of adult cancer patients presenting with chemotherapy-induced febrile neutropenia are also discussed.

6.2 Review of current approach to risk stratification and management of patients with febrile neutropenia

Over the past decades, substantial progress has been observed in the treatment and overall management of patients with FN. The previous practice of admitting all FN patients to in-patient and keeping them until defervescence of fever has evolved to increasing acceptance of stratified medicine based on risk groupings.[5] Guidelines have been developed and updated not only for the management of neutropenic cancer patients in terms of antimicrobial agents and prophylactic therapy recommendations,[5, 114] but also the out-patient care for patients with FN categorised as low-risk[35]. While optimistic results have been published for out-patient based therapy for FN patients stratified to the low-risk group[67, 373] the focus has begun to shift to exploring the benefits of risk-based therapy for FN patients stratified to the high-risk group.[31]

Early identification and diagnosis of sepsis may improve the outcomes and mortality rates of FN episodes from this clinically important prognostic factors.[374] This is especially so given that FN patients with attenuated classical inflammatory response may experience sudden acute deterioration across the sepsis continuum without a window of opportunity for treatment to take effect. Furthermore delay in initiating resuscitative measures has been associated with inferior outcomes.[374] In patients with deteriorating clinical condition, the key to successful resuscitation is the simultaneous identification and treatment of impending life-threatening physiological abnormalities as soon as possible after onset of the symptoms.[374]

Given that mortality rates for patients with haematological malignancy with severe sepsis range from 36% to 45% and 37% in patients with solid tumours,[375] the importance of early identification of these patients through risk stratification using a prognostic model cannot be over-emphasised. The current model for high-risk identification that is most often utilised for both groups of cancer patients with FN is the MASCC risk-index score. However, this tools was developed originally for the identification of low-risk FN patients.[10] The development in this best practice project of the literature-based (LB) model, a novel prognostic model based on current and updated predictors but designed to identify FN patients at high risk of adverse outcomes, is therefore timely.

Best practice aims to achieve meaningful clinical outcomes through the use of robust prognostic models for individualised therapy according to their level of

risk. This thesis reports on the development of a prognostic model that provides the best predictive validity and reliability of developing serious medical complications in adult neutropenic patients presenting with fever. The process of prognostic model development undertaken over the course of this project and the outcomes achieved has implications for the future of this area of proficiency.

6.3   Summary of the studies

6.3.1 Systematic review of prognostic factors for febrile neutropenia outcomes

A systematic review was undertaken to examine and synthesise the best available evidence for clinical variables and their overall predictive values in association to the low- and high-risk grouping of adult cancer patients presenting with febrile neutropenia. The findings of the systematic review presented in chapter 3 demonstrated that there were potentially important predictors not included in existing indices for the risk stratification of FN patients.

New predictors were identified and conflicting findings between the same predictor were also highlighted. However, the independent influences of the new predictors, when adjusted for other predictors in multivariable models were not well established and hence warrant additional confirmation. The review also reported that the predictor "burden of illness" has subjective characteristics which could impede accurate assessment. Substantial variations in data analysis, outcome measures and reporting from the included primary studies that limited the findings of the review were also highlighted. Therefore, a

re-examination of prognostic factors and their predictive values was warranted and this formed the basis for the primary research presented in chapter 4.

6.3.2 Primary study for prognostic factors associated with febrile neutropenia outcomes

The findings of the systematic review provided the candidate variables to be studied to establish their association with the outcomes of FN. Additional pre-defined clinical and laboratory variables based on literature reports were also included. Patients' information was collected from 166 medical records and analysed. The results showed that particular candidate variables were consistent with published research in their predictive roles, and these included age, presence of COPD, total febrile days, temperature, heart rate, systolic & diastolic blood pressure, hydration status, presence of infection site, abnormal chest radiographs and creatinine level at presentation of fever.

The remaining candidate variables failed to show independent association with the outcomes of FN (chapter 4, section 4.8). Additional laboratory markers which could enhance the discriminative ability and performance of existing prognostic models were also established as candidate predictors. The next step of the project was to review the predictors in current prognostic models and utilising the newly established predictors, develop a new model for risk stratification of FN patients. The aim was to include predictors with easily assessable information, which were objective in their measurement and practical when applied in clinical settings with increased attention to patient's clinical condition at the onset of fever.

6.3.3 Development of a new prognostic model for febrile neutropenia outcomes

Candidate predictors identified from the cohort study (chapter 4) were analysed in combination to adjust for confounding effects between predictors. As expected, not all candidate predictors were included in the final model. The logistic regression method was applied for model derivation. Statistical modeling and literature-based selection of predictors were applied to generate the final model. Five models were generated. Based on the area under the ROC readings and consideration for clinical applicability, the BW (Backward WALD) and LB (Literature Based) models were preferred.

A preliminary testing of both newly developed prognostic models was undertaken which demonstrated reasonable and comparable performance between both models. Given the preliminary results of the predicted performance, the LB model which has fewer predictors all of which are objectively measured, may be a better choice of prognostic model for application in practice settings as it is likely to have better clinical applicability.

6.4   Implications for clinical practice

6.4.1 The literature-based prognostic model for febrile neutropenia outcomes

One of the major features of the newly developed LB prognostic model that distinguished it from previous prognostic models for FN outcomes was that it met the criteria recommended for predictor selection. The use of well-defined and clinically relevant predictors, similar to the criteria for sepsis detection,

reinforced early assessment of cancer patients for complications related to FN episodes.

As mentioned in section 6.2, early initiation of therapeutic interventions in these patients may lead to better clinical outcomes. Furthermore, the inclusion of predictors that are based on uncomplicated and unambiguous measurements (LB model) could facilitate the assessment of risk for this group of patients to be undertaken by nursing personnel with advanced practice qualifications who are licensed to initiate therapy.

Addressing the increasing importance of incorporating risk stratification based on evidence-based developed prognostic model is the first step to embracing change in practice. The aim of the adoption of prognostic model into clinical practice is to compliment decision making which otherwise relies primarily on clinical judgment.

These implications for practice have arisen from the findings of the systematic review and primary study component of this thesis, and should be considered by health systems and services where patients with febrile neutropenia are treated and they include:

- Consider using the LB model as it is based on criteria derived from evidence of relevance and applicability for detection of risk of adverse outcomes.

- Early intervention based on the LB model can be recommended for patients at high risk, and may result in improved clinical outcomes arising from increased rates of detection.

- Systematic clinical risk stratification may allow health service providers to better target health care resources and interventions, while avoiding unnecessary treatments for those at low risk of adverse outcomes.

- Prognostic models should be incorporated in to routine clinical practice to enhance clinical decision making, and supplement clinical assessment.

6.5 Implications for synthesis science

6.5.1 Improvement in the conduct and reporting of prognostic research

For the present study the systematic review presented in Chapter 3, highlighted several limitations on the conduct of prognostic research studies. The review highlighted methodological limitations which included inadequate sample size, unclear definitions and measurements for predictor and poor reporting of results which compromised the review findings and compromised the utility for practice recommendations.[330] These findings were also consistent with the recent systematic review on methods in studies for the development of prognostic models in cancer.[217]

The use of systematic reviews and meta-analyses to address issues such as small sample size and lack of precision through the pooling of data from multiple studies is often not successful due to individual studies being poorly designed and reported, which limits the synthesis of evidence to narrative summary.[287] These limitations also affect the reliability and clinical applicability of the prognosis derived from models generated from these studies.[217, 347] Unless primary studies improve in their methods of research, additional similar studies are not likely to address the uncertainty of current evidence. As a result, the systematic review of prognostic research studies will continue to be of limited benefit for evidence generation.

Prognostic research is an area of increasing importance in the health sciences and efforts to improve the conduct of prognostic research has been reported in recent years.[54, 268] Many of the recommendations across the series of publications by the PROGRESS(prognostic research strategy) group have addressed issues which include study design,[268] sample size to meet the recommended events per variable[308] and guide for reporting of results[236].

Future studies should build upon the work of the PROGRESS group to increase the quality of study design reporting within the context of prospectively pooled analysis for a clinical question. It is through collective effort to conduct high quality primary studies with carefully considered study protocol and consistency in methodologies across studies that good-quality evidence can be achieved through prognostic studies.[54, 268]

6.5.2 Improvement in methodology for the systematic review of prognostic studies

The systematic review in chapter 3 also identified the unavailability of generic methods to appraise the quality of prognostic studies. Although there have been numerous different criteria and checklists derived over the years, there is little empirical evidence or consensus to support review criteria pertinent to prognostic studies.[229] This results in inconsistencies in the conduct and reporting of systematic reviews for prognostic variables and models,[299] and limits the impact of systematic review in the resolution of the existing uncertainty surrounding evidence generated from prognostic studies.

Given the importance of systematic reviews for identifying and reliably providing an overall assessment of the topic of focus, there is an immediate need to improve the methods for conducting systematic reviews of prognostic studies. Areas of focus include better indexing and more sensitive search strategies, criteria to assess important potential biases and methodological quality assessment in addition to reporting of synthesised findings.[299]

An alternative approach to overcome limitations encountered when undertaking conventional methods of systematic reviews with or without meta-analyses has been proposed for prognostic studies. This is systematic review using individual patient data (IPD).[287] The use of IPD for systematic reviews addresses issues related to data extraction due to selective reporting of results, publication bias and incomplete statistical and clinical information.

As highlighted in chapter 3, a systematic review based on IPD has several advantages. Specifically for prognostic studies, the availability of estimates (not summarised statistics) for standardised statistical analysis and adjustment across studies for variables is often very useful when primary studies lack clarity in reporting.[52] In addition, systematic review using IPD allows researchers to assess the overall characteristics of sample populations with potential subgroup analysis.[52] Nonetheless this approach also has its limitations.

For this method of review, data for primary studies has to be meticulously recorded and made available for reviewers. Extensive collaboration between researchers and reviewers is essential particularly in open data sharing, and it is extremely resource intensive.[235] Conversely, as mentioned previously (chapter 4, section 4.6.4) it is important to achieve the sample size recommended for events per variable specifically for prognostic studies,[308] and systematic review based on IPD may facilitate this goal being consistently met through increasing the availability of large data sets for analysis. As a consequence biased selection of candidate variables and imprecise regression estimates resulting in inaccurate predictions would be minimised.[217]

The following recommendations have been developed on the basis of the methodological issues that arose during the planning and conduct of the systematic review presented in this thesis. Further methodological development that investigates these three points would assist in advancing the science of systematic review, promoting international standardisation of methods and

reporting, and therefore advance the conduct of systematic reviews particular to the field of prognostic studies.

- International acceptance that systematic reviews provide an appropriate and robust framework for the identification of risk factors, and prognostic model development.

- The quality and consistency of systematic reviews in this field would be enhanced by development of appraisal and extraction instruments specific to prognostic methods of synthesis.

- Further work should be undertaken to develop the process of individual patient data meta-analysis and to understand its application to prognostic reviews.

6.6   Implications for research

6.6.1 Risk-targeted interventions for management of febrile neutropenia

Risk assessment and stratification based on individual patients' prognosis is only one of the steps to enhance the overall care of FN patients. The significance of accurate categorisation of FN patients to different risk groupings would be better appreciated if the intended outcomes such as decreased in morbidity, mortality, shortened length of stay, improved utilisation of antimicrobial therapy, optimal use of healthcare resources, improved or sustained patient's quality of life throughout cancer treatment are achieved. While the practice of risk-

based therapy for low-risk group of FN patients has gained recognition given the documented benefits, the management of high-risk group of FN patients has yet to be formalised in some practice settings.

Considering current deficiencies in clinical practice a more definitive and targeted approach is needed for the management of high-risk FN patients. Because optimal time of admission to the intensive care unit influences the outcome[376], there is a need to review traditional admission criteria which include the presence of organ failure(s) and/or irreversible hypotension. Although controlled trials may be required to demonstrate effectiveness and benefit of risk-based treatment of high-risk FN patients, it is plausible that timely admission for close surveillance for high-risk group of FN patients would improve their outcomes.[376] Therefore, a well-established protocol in managing FN patients with high-risk of adverse outcomes would provide clear indicators for escalation of therapy in a timely manner.

6.6.2 Validation of newly developed prognostic model for febrile neutropenic outcomes

The newly developed prognostic model (LB) with updated objective predictors focusing on indicators for sepsis provides clinicians an alternative risk stratification tool for FN patients. Because all the predictors are well known among clinicians managing cancer patients, the model would be easy to implement with minimal concern for inconsistency in assessment. However, a good prognostic model is required to produce reasonable and reliable classification of patients into designated risk groups at repeated assessments.[265]

Therefore, validation studies are required to establish the validity and reliability of the new prognostic model prior to implementing it at the clinical setting.[264] The process of validation provides an insight in to the model's predictive performance and pertinent information on potential deficiencies of the model such as overfitting, or under / over estimation of predictors. [83, 364] If the new model is shown to perform less well in the different sample population, adjustment or adaptation based upon new data should be considered.[377] Updating of a model may involve simple recalibration or model revision with additional new predictors which is more complex and extensive.[288, 378]

6.6.3 Comparative studies and impact analysis

Comparative studies to evaluate the performance of the new model with established models such as the MASCC risk score or existing prognostic models for FN would provide users with useful information for deciding on which model to choose for implementation in their practice. An additional step for the development of models includes evaluation of model adoption. This step is known as impact analysis and involves studies of clinicians' practice behaviour patterns, patient outcomes and cost effectiveness as compared with these characteristics in clinicians who are not using the model.[362]

Impact analysis adds to the understanding of utility as well as the barriers to model implementation within specific practice settings. However, impact analysis should only be attempted once the quality of prognostic research with respect to the assessment of potential predictors and model development

along with clear guidelines for recalibration / enhancement of existing models is improved.

6.6.4 Heterogeneity in patient characteristics

It has been acknowledged that FN patients are not homogenous in their outcomes when they experience FN.[64] Subsequent studies have also highlighted heterogeneity in the characteristics of cancer patients with differing underlying diagnosis[176, 191] as well as the outcomes of FN among patients with bacteraemia versus those without.[4] Because of this heterogeneity in outcome and prognosis, and to improve the performance of prognostic models, further research and exploration of prognostic models for specific subgroups of cancer patients with FN would be worthwhile.

The implications for research highlighted in section 6.6 of this chapter were developed both from the gaps in current literature, and from the experience of conducting the primary study reported in this thesis. On this basis, future research should:

- Seek to investigate and identify the range of appropriate clinical pathways for FN patients with high-risk of developing adverse outcomes.

- Include validation studies that address wider cultural understandings of the LB model, including its predictive validity among diverse populations and heterogeneous groups of patients.

- Seek to evaluate comparative validity against existing models in order to further test validity, reliability, and to develop the predictive sensitivity and specificity across patient populations.

6.7   Conclusion

This thesis reported on the complete development and validation of a new evidence–based prognostic model for patients with febrile neutropenia. The model predicts patients who are at risk of developing adverse outcomes during FN episodes and may be used to guide therapeutic interventions. The thesis also argues for the increasingly important role of prognostic research in the practice of evidence-based clinical decision-making. However, application of prognostic models has its limitations, and systematic reviews provide a comprehensive picture of both the strength and magnitude of the evidence, as well as the gaps in the current evidence base.

Prognostic research literature is characterised by methodological flaws and this impacts on the credibility and adoption of current models in clinical practice. Enhancement in the methodological rigor and comprehensiveness in reporting of results in prognostic research studies needs to be addressed for clarity in interpretation and implementation of the studies' findings. Methods of validation of tool's performance are needed to show true impact of the tool in treatment recommendations or adoptions in policy decisions.

This thesis has generated new knowledge based on the review of current primary studies on prognostic factors for the outcomes of FN patients, and from it, a new evidence-based prognostic model was developed to stratify FN patients according to their risk groupings. Through the review, which highlighted the current state of evidence in prognostic research, a series of practice and research implications have been generated to advance the current knowledge base and guide future prognostic research.

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Appendix I: Detailed search terms used for each database for systematic review

Medline: (265)

1. prognostic[mh]

2. prognos$[tiab]

3. predict[mh]

4. predict$[tiab]

5. risk[mh]

6. risk assessment[tiab]

7. factor[mh]

8. factor$[tiab]

9. marker[mh]

10. marker$[tiab]

11. variable$[tiab][tw]

12. #1 OR #2

13. #3 OR #4

14. #5 OR #6

15. #7 OR #8 OR #9 OR #10 OR #11

16. #12 OR #13 OR #14 OR #15

17. fever[mh]

18. febrile[tiab][tw]

19. neutropeni*[tiab] OR granulocytopeni*[tiab] OR immunosuppress*[tw]

20. (#16) AND (#17 OR #18) AND #19

21. chemotherapy[mh]

22. chemotherapy[tiab]

23. #20 AND (#21 OR #22)

24. outcome$[tw]

25. mortality[tw]

26. bacteremi*[tw]

27. sepsi*[tw]

28. #24 OR #25 OR #26 OR #27

29. #28 AND #23

Science Direct: (492)

(**prognos* OR predict* OR risk**) AND (**factor OR marker OR variable**) AND (**chemotherapy-induced neutropenia**) AND fever AND(**outcome OR bacteremia OR mortality OR sepsis**) AND adult AND NOT child* AND EXCLUDE(**cid, "271153,272553","Critical Reviews in Oncology/Hematology,Blood Reviews"**) AND EXCLUDE(**topics, "g-csf,gm-csf,growth factor"**) [*All Sources(Medicine and Dentistry)*]

Scopus: (483)

((TITLE-ABS-KEY("risk factors" OR prognos* OR predict* AND factor OR variable OR marker)) AND (TITLE-ABS-KEY("Chemotherapy" AND "fever" AND "granulocytopenia" OR "neutropenia"))) AND (TITLE-ABS-KEY("outcome" OR "sepsis" OR "bacteremia")) AND (EXCLUDE(DOCTYPE, "le") OR EXCLUDE(DOCTYPE, "ed")) AND (EXCLUDE(SUBJAREA, "BIOC") OR EXCLUDE(SUBJAREA, "ENVI") OR EXCLUDE(SUBJAREA, "PHYS") OR EXCLUDE(SUBJAREA, "VETE")) AND (EXCLUDE(LANGUAGE, "French") OR EXCLUDE(LANGUAGE, "Spanish") OR EXCLUDE(LANGUAGE, "German") OR EXCLUDE(LANGUAGE, "Japanese"))

Mednar (421)

"prognostic factor" OR "predictive marker" AND "chemotherapy-induced febrile neutropenia" AND "outcome"

Web of Science (21)

#1. Topic=(Prognos*) OR Topic=(Predict*) OR Topic=(risk assessment)

#2. Topic=(factor) OR Topic=(marker) OR Topic=(variable)

#3. Topic=(fever) OR Topic=(febrile)

#4. Topic=(chemotherapy) OR Topic=(cytotoxic agent)

#5. Topic=(outcome) OR Topic=(mortality) OR Topic=(bacteremia) OR Topic=(sepsis)

#6. Topic=(neutropeni*) OR Topic=(granulocytopeni*) OR Topic=(immunosuppresed)

#7. #6 AND #5 AND #4 AND #3 AND #2 AND #1

#8. #6 AND #5 AND #4 AND #3 AND #2 AND #1
Refined by: Web of Science Categories=(ONCOLOGY OR HEMATOLOGY OR INFECTIOUS DISEASES OR TRANSPLANTATION OR HEALTH CARE SCIENCES SERVICES OR CRITICAL CARE MEDICINE OR PHARMACOLOGY PHARMACY OR MEDICINE GENERAL INTERNAL OR EMERGENCY MEDICINE) AND Document Type=(ARTICLE OR PROCEEDINGS PAPER) AND Languages=(ENGLISH) AND Subject Areas=(ONCOLOGY OR GENERAL INTERNAL MEDICINE OR HEMATOLOGY OR MICROBIOLOGY OR EMERGENCY MEDICINE OR HEALTH CARE SCIENCES SERVICES OR NURSING OR INFECTIOUS DISEASES OR TRANSPLANTATION OR PHARMACOLOGY PHARMACY) AND Subject Areas=(ONCOLOGY OR GENERAL INTERNAL MEDICINE OR HEMATOLOGY OR EMERGENCY MEDICINE OR HEALTH CARE SCIENCES SERVICES OR NURSING OR INFECTIOUS DISEASES OR TRANSPLANTATION OR PHARMACOLOGY PHARMACY)

#9. Topic=(adult) NOT Topic=(child*)

#10. #8 AND #9

Embase (350)

1. prog* OR predict*

2. factor OR 'marker'/exp OR mrker OR variable

3. 'fever'/exp OR fever OR febrile

4. 'neutropenic fever'/exp OR 'neutropenic fever'

5. 'granulocytopenia'/exp OR granulocytopenia

6. 'chemotherapy'/exp OR chemotherapy

7. outcome OR 'mortality'/exp OR mortality OR 'bacteremia'/exp OR bacteremia OR 'sepsis'/exp OR sepsis

8 . #1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7

9. #8 AND ('clinical article'/de OR 'clinical protocol'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'drug dose comparison'/de OR 'feasibility study'/de OR 'human'/de OR 'major clinical study'/de OR 'model'/de OR 'multicenter study'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'pilot study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND ('advanced cancer'/de OR 'bone marrow suppression'/de OR 'febrile neutropenia'/de OR 'fever'/de OR 'infection'/de OR 'leukopenia'/de OR 'neutropenia'/de OR 'sepsis'/de OR 'side effect'/de)

10. 'adult'/exp OR adult

11. #9 AND #10

CINAHL (70)

1. TX Prognos* OR TX predict* OR TX risk

2. TX factor OR TX marker OR TX variable

3. TX fever OR TX febrile

4. TX neutropen* OR TX granulocytopen* OR TX immunosuppresed

5. TX chemotherap* OR TX antineoplastic agent OR TX antineoplastic drug

6. TX outcome OR TX bacteremia OR TX mortality AND TX sepsis

7. #1 AND #2

8. #3 AND #4

9. #5 AND #8

10. #9 AND #7

11. #10 AND #6

12. #10 AND #6Limiters - Human; Language: English; Age Groups: Adolescent: 13-18 years, Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over

Central (154)

#1 (Prognos*) or (Predict) or (Risk)

#2 (febrile) or (fever) and (neutropenia) or (leukopenia) or (granulocytopenia)

#3 (chemotherapy) or (cytotoxic therapy) or (cancer treatment)

#4 (#2 AND #3)

#5 (Outcome*) or (Bacteremia) or (Mortality) or (Sepsis)

#6 (#4) 2910

#7 (#6 AND #5)

#8 (Factor) or (marker) or (variable) in Trials

#9 (#1 AND #8)

#10 (#9 AND #4 AND #5)

Appendix II: Critical Appraisal Tools

From the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument cohort studies (JBI-MAStARI)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _ Date _

Author _ Year _ _ _ _ _ _ _ Record Number _ _ _ _ _ _ _

		Yes	No	Unclear	Not Applicable
1.	Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2.	Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3.	Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4.	Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5.	Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6.	Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7.	Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

_____

_____

_____

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

		Yes	No	Unclear	Not Applicable
1.	Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2.	Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3.	Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4.	Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5.	If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6.	Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7.	Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐   Exclude ☐   Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix III: MAStARI Data Extraction Instrument (Adapted)

JBI Data Extraction Form for Experimental / Observational Studies (Modified)

Title..
....

Reviewer...Date:...

Author...Year:...

Journal...Record Number..............................

Country...

Study Method:

RCT ☐ Quasi-RCT ☐ Longitudinal ☐ Observational ☐

Retrospective ☐ Prospective ☐ Others ☐

Participants:

Setting..Population......................................Age.........................

Sample size:

No. of participants..No. of episodes...

Duration of follow-up...

Authors Conclusions:

_____
_____
_____

Reviewers Conclusions:

_____
_____
_____

Results:

SN	Prognostic Variables	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	p value	OR	95% CI	p value

Appendix IV: Characteristics of the Included Studies

Study ID	Study Objectives	Study Design	Setting	Population	Prognostic factors Reported (Multivariate analysis)
Ramzi(2007)[165]	To identify biological predictive factors for septic shock and mortality in neutropenia patients with leukemic and bacteraemia	Prospective cohort	Single centre In-patients	Age: 21-53yrs; Median: 41 20 patients, 110 episodes de novo Acute leukaemia	Pulmonary infection [OR 5; 95%CI,1.052-23.764; p=0.043] Serum lactate >3mmol/l [OR 10; 95%CI, 2.1856-45.7534; p=0.003]
Moon (2009)[173]	To identify simple independent factors that can predict patients who develop subsequent complications after chemotherapy-induced neutropenic fever	Retrospective cohort	Single academic tertiary care centre at ED	Age ≥18yrs; Mean:53 168 patients, 192 FN episodes Solid tumour & haematology malignancies	Platelets<50,000cells/mm³ [OR 4.982; 95%CI, 2.00-12.408; p=0.001] Pulmonary infiltration [OR 30.167; 95%CI,7.281-124.99; p<0.001] CRP >10mg/dL [OR 2.719; 95%CI,1.111-6.651; p=0.028]
Ahn (2011)[59]	To identify factors predictive of poor prognosis in cancer patients with chemotherapy-induced FN at the time of admission	Retrospective cohort	Single medical centre at ED	Age:15-83yrs; Mean:52.9 346 patients, 396 FN episodes Solid tumour & haematology malignancies	Respiration rate ≥24/min [OR 3.61; 95%CI,1.44-9.08; p=0.006] Thrombocytopenia [OR 3.41; 95%CI,1.69-6.89; p=0.001] CRP ≥9mg/dL [OR 3.23; 95%CI,1.62-6.45; p=0.001] Duration neutropenia ≥4days [OR 2.52; 95%CI,1.21-5.25; p=0.014] MASCC <21 [OR 23.2; 95%CI,10.48-51.37; p=0.000]
Jin (2010)[58]	To audit compliance with the new protocol with regards to the initial management of FN, to describe the epidemiology & clinical outcomes of FN	Prospective cohort	In-patient Single centre	Age:19-80yrs; Median:53 31 patients,178 FN episodes Solid tumour & haematology malignancies	Presence of a central line [OR 3.36, 95% CI,1.46-7.72, p<0.01] High-risk FN [OR 2.78; 95%CI,1.24-6.23; p=0.01]
Yoo (2005)[74]	To identify the prognostic factors influencing infection-associated mortality in patients with acute leukaemia	Retrospective cohort	Single centre Haematopoietic Stem Cell Transplant Centre	Age:15-68yrs; Median:32.5 284 patients Acute leukaemia	Episodes of hypotension [OR1.59;95%CI, 0.31-8.25; p=0.5783] Pneumonia [OR1.30;95%CI, 0.27-6.29; p=0.7435] Previous fungal infection [OR 82.5; 95%CI,3.0-2268.57; p=0.0091] Invasive fungal infection [OR 5.7; 95%CI,2.80-88.03; p=0.0017] Recover from neutropenia [OR 0.01; 95%CI,0.001-0.031; p=0.7128] Days to fever [OR1.30;95%CI, 0.88-1.20; p=0.7124] Total febrile days [OR1.03;95%CI, 0.95-1.11; p=0.4737]
Klastersky (2000)[10]	To develop an internationally validated scoring system to identify low risk febrile neutropenia cancer patients	Prospective cohort	In-patients & out-patient 20 institutions from 15 countries	Age:16-91yrs; Median:52 756 patients Solid tumour, haematology malignancies & bone marrow transplantation	Burden of illness(no/mild symptoms) [OR 8.21; 95%CI,4.15-16.38; p<0.001] Burden of illness(moderate symptoms) [OR 3.70; 95%CI,2.18-6.29; p<0.001] No of hypotension [OR 7.62; 95%CI,2.91-19.89; p<0.001] No of COPD [OR 5.35; 95%CI,1.86-15.46; p=0.002] Solid tumour/No previous fungal infection [OR 5.07; 95%CI,1.97-12.95 p<0.001] No dehydration [OR 3.81; 95%CI,1.89-7.73; p<0.001] Out-patient status [OR 3.51; 95%CI,2.02-6.04; p<0.001] Age < 60 yrs [OR 2.45; 95%CI,1.51-4.01; p<0.001]
Paesmans (2011)[73]	To explore the ability to predict bacteraemia at the time of treatment initiation	Prospective cohort	Multicentre 32 institutions from 15 countries	Age: 16-85yrs 2142 patients Solid tumour, haematology malignancies & bone marrow transplantation	*Bacteraemia* ANC (0/uL) [OR 2.55; 95%CI,1.90-3.42; p<0.001] ANC (1-99/uL) [OR 1.80; 95%CI,1.31-2.48; p<0.001] No adjuvant or neoadjuvant treatment [OR 2.02; 95%CI,1.34-3.06; p<0.001] Burden of illness(severe signs/moribound)[OR 1.97; 95%CI,1.43-2.71; p<0.001] Burden of illness (moderate symptoms) [OR 1.44; 95%CI,1.13-1.831; p=0.003] Hypotension [OR 1.66; 95%CI,1.11-2.47; p=0.01] In-patient [OR 2.07; 95%CI,1.61-2.68; p<0.001] Temperature ≥39°Cel [OR 1.81; 95%CI,1.43-2.30; p<0.001] Haematological malignancy [OR 1.38; 95%CI,1.06-1.80; p=0.02] *Gram negative bacteraemia* ANC (0/uL) [OR 3.38; 95%CI,2.15-5.30; p<0.001] ANC (1-99/uL) [OR 1.96; 95%CI,1.20-3.22; p=0.008] No adjuvant or neoadjuvant treatment [OR 3.80; 95%CI,1.63-8.86; p=0.002] Burden of illness(severe signs/moribound)[OR 2.44; 95%CI,1.60-3.73; p<0.001] Burden of illness (moderate symptoms) [OR 1.30; 95%CI,0.90-1.86; p=0.16] Hypotension [OR 1.77; 95%CI,1.10-2.87; p=0.02] Talcott score I, I or III [OR 2.60; 95%CI,1.54-4.39; p<0.001] Age ≥ 60years [OR 1.81; 95%CI,1.31-2.49; p<0.001] No administration of prophylaxis [OR 1.45; 95%CI,1.04-2.01; p=0.03]

Appendix V: Characteristics and reasons for exclusion of studies

1. Ha Y, Song J-H, Kang W, Peck K, Chung D, Kang C-I, et al. Clinical factors predicting bacteremia in low-risk febrile neutropenia after anti-cancer chemotherapy. Support Care Cancer. 2011;19(11):1761-7.
Reasons for exclusion: Study sample was not at similar point in the course of illness

2. Ahn S, Lee Y-S, Chun YH, Lim KS, Kim W, Lee J-L. Predictive factors of bacteraemia in low-risk patients with febrile neutropenia. Emergency Medicine Journal. 2011.
Reasons for exclusion: Study sample was not at similar point in the course of illness

3. Leong DCS, Kinlay S, Ackland S, Bonaventura A, Stewart JF. Low-risk febrile neutropenia in a medical oncology unit. Aust N Z J Med. 1997;27(4):403-7.
Reasons for exclusion: Unclearly defined factors and incongruent reporting

4. Lanoix JP, Pluquet E, Lescure FX, Bentayeb H, Lecuyer E, Boutemy M, et al. Bacterial infection profiles in lung cancer patients with febrile neutropenia. BMC Infect Dis. 2011;11:183.
Reasons for exclusion: Multivariate analysis reported only in p-value, unable to extract data as information provided was insufficient to calculate OR.

5. Lal A, Bhurgri Y, Rizvi N, Virwani M, Memon RU, Saeed W, et al. Factors influencing in-hospital length of stay and mortality in cancer patients suffering from febrile neutropenia. Asian Pac J Cancer Prev. 2008;9(2):303-8.
Reasons for exclusion: Unclear study design and outcomes measured

6. Baskaran N, Gan G, Adeeba K. Applying the Multinational Association for Supportive Care in Cancer risk scoring in predicting outcome of febrile neutropenia patients in a cohort of patients. Ann Hematol. 2008;87(7):563-9.
Reasons for exclusion: Analyses reported only p-value for uni and multivariate, unable to extract data as information provided was insufficient to calculate OR.

7. Carmona-Bayonas A, Gomez J, Gonzalez-Billalabeitia E, Canteras M, Navarrete A, Gonzalvez ML, et al. Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. Br J Cancer. 2011;105(5):612-7.
Reasons for exclusion: Study sample was not at similar point in the course of illness

Appendix VI: The Joanna Briggs Institute Level of Evidence

JBI Levels of Evidence	Effectiveness	No. of Included Studies	Citation
I	Meta-analysis (with homogeneity) of experimental studies (e.g. Randomised Controlled Trials (RCT) with concealed randomisation) OR One or more large experimental studies with narrow confidence intervals	0	
II	One or more smaller RCTs with wider confidence intervals OR Quasi-experimental studies (without randomisation)	0	
III	Cohort studies (with control group) Case-controlled Observational studies (without control group)	7	Jeddi(2007)[165] Moon(2009)[173] Ahn (2011)[59] Jin(2010)[58] Yoo (2005)[74] Paesmans(2011)[73] Klastersky(2000) [10]
IV	Expert opinion, or physiology bench research, OR consensus	0	

Name:_____
MRN:_____Index:_____

Variables		Information (Description)			Date of FN:		
1	Age / Gender	DOB:		Age:	years		Male / Female
2	Cancer type						
3	Co-morbidities						
4	Chemotherapy type	RDI / Adjuvant or Neo adjuvant / Myeloablative / 1st Line tx / 2nd (subsequent) line tx / Palliative					
5	Disease status	Controlled / Not controlled		Regime:			
	Type of tspt: Autologous / Allogeneic, related / unrelated			Date of last tx:			
6	Duration (fever onset to ctx)			days			
7	Duration (neutropenia to fever)			days			
8	Location at fever onset	In-pt (1) / Out-pt (2)					
9	Performance status (PS)	Karnosky/ ECOG					
10	Presence of infection	Yes (1) / No (2)		Antibiotics / Famciclovir Norflox Bactrim		Antifungal / Fluconazole Itraconazole Posaconazole Voriconazole	Growth factor GCSF
11	Prophylaxis	Yes (1) / No (2)					
12	Previous FN	Yes (1) / No (2)					

Vital Signs | | | | | **Presenting Symptoms** | |

13	Temperature (peak)		CVC Yes / No	CVC site	
14	Blood Pressure		Mucositis Yes / No	GIT	
15	Heart Rate		GCS	Resp	□ Previous FI
16	Respiration Rate		SpO2	Abscess	
17	Hydration status	Dehydrated / Not dehydrated / Not stated		OTHERS	

Laboratory Tests

18	ANC	(Day 1)	nadir at Day__		@ fever onset	Tim / Tazo / Genta
19	Platelet	(Day 1)			@ fever onset	
20	Haemoglobin	(Day 1)			@ fever onset	
21	Creatinine level				@ fever onset	
22	Albumin level				@ fever onset	
23	C-reactive protein				@ fever onset	
24	Procalcitonin				@ fever onset	
25	Lactate				@ fever onset	

OUTCOME(S):		Afebrile on:		CDI / MDI / RDI / PUO	
27	If MDI -	Types of Micro-organisms:	BC on (	): NAD /	
28	If RDI -	CXR on (	): NAD /		
29	EVENTS:				