
# AN INVESTIGATION INTO THE RELATIONSHIP BETWEEN THE SYSTEMIC INFLAMMATORY RESPONSE AND SURVIVAL: A GLASGOW INFLAMMATION OUTCOME STUDY

**by**

**MICHAEL J. PROCTOR**

**MBChB, MRCS (Glas)**

**SUBMITTED IN THE FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MEDICAL DOCTORATE (MD)**

**To**

**THE UNIVERSITY OF GLASGOW**

**FROM RESEARCH CONDUCTED IN THE UNIVERSITY DEPARTMENT OF SURGERY, GLASGOW ROYAL INFIRMARY, FACULTY OF MEDICINE, UNIVERSITY OF GLASGOW**

**ABSTRACT**

Inflammation has been shown to play an integral role in a number of different disease processes. There is evidence that measurements of the systemic immune/inflammatory response are associated with mortality in patients with certain malignancies, as well as those with atherosclerotic disease. A variety of readily available inflammation-based prognostic scores, combining serum constituents of the systemic immune/inflammatory response, have been suggested for use in these patient groups. However, it is unclear whether systemic inflammation-based scores are universally associated with mortality across all tumour types and whether this relationship persists in atherosclerotic conditions including cardiovascular and cerebrovascular disease. The optimal constituents of such a score are also still to be determined. The present thesis further examines these topics with specific reference to:

1. The relationship between the presence of cancer, an inflammation-based prognostic score and biochemical parameters in a large group of unselected patients.

2. The relationship between an inflammation-based prognostic score and cancer survival in patients with malignancies at a number of different sites.

3. A comparison of commonly available inflammation-based prognostic scores in patients with cancer.

4. The prognostic value of a derived neutrophil to lymphocyte ratio, commonly available in patients with cancer undergoing chemotherapy.

5. The optimal serum constituents of the systemic inflammation-based Glasgow Prognostic Score (optimised) in patients with cancer.

6. The optimal constituents and prognostic value of a systemic inflammation-based score for predicting cardiovascular, cerebrovascular and all-cause mortality.

**TABLE OF CONTENTS**

**LIST OF TABLES**

## LIST OF FIGURES

**ACKNOWLEDGEMENTS**

I am sincerely grateful for the assistance provided by the following individuals, each of whom has offered their expertise, encouragement and guidance throughout the period of research working towards this thesis:

| | |
|---|---|
| Professor Donald McMillan | University Department of Surgery<br>Glasgow Royal Infirmary |
| Professor Paul Horgan | University Department of Surgery<br>Glasgow Royal Infirmary |
| Dr David Morrison | University Department of Cancer Surveillance<br>Institute of Health and Wellbeing |
| Dr Dinesh Talwar | Department of Biochemistry<br>Glasgow Royal Infirmary |

## DECLARATION

The work presented in this thesis was undertaken during a period of research between 2009 and 2011 in the University Departments of Surgery and Public Health at Glasgow Royal Infirmary. The introduction (Chapter 1) and literature search (Chapter 2) were written prior to the start of data collection and these sections are therefore based on current knowledge at the time (December 2009). Individual chapters contain more recent references as the study progressed and the knowledge base grew. The work has been completed whilst working as a Speciality Registrar in General Surgery in the South East of Scotland deanery. The study was approved by the Research Ethics Committee, North Glasgow NHS Trust. I declare the work presented in this thesis was solely undertaken by me with the exception of the following:

- Writing of the computer code used to extract biochemical variables (Chapters 2-7) and pathological details (Chapter 2) for patients from the North of Glasgow biochemical and pathological database was performed with assistance from Mr Stephen Balmer, laboratory information management and technology, NHS Greater Glasgow and Clyde.

- Writing of the computer code used to extract haematological variables (Chapters 4-7) for patients from the North of Glasgow haematological database was performed with assistance from Mr Colin Fletcher, consultant clinical scientist, Greater Glasgow and Clyde.

- Extraction of cancer follow-up data from the Scottish Cancer Registry (Chapter 3-7) was performed with assistance from Mr Billy Sloan.

- Extraction of all-cause follow-up data from Information Services Division for Scotland (ISD) datasets was performed with assistance from ISD, NHS National Services Scotland, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB.

Word Count: 51,477

**PUBLICATIONS**

1. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study.
   Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC.
   *BJC* 2010; **103**: 870-876.

2. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study.
   Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC.
   *BJC* 2011; **104**: 160-161.

3. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study.
   Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC.
   *Eur J Cancer* 2011; **47:** 2633-41.

4. A derived Neutrophil to Lymphocyte Ratio (dNLR) predicts survival in patients with cancer.
   Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ.
   *BJC* 2012. **107**: 695-9.

5. Optimisation of the systemic inflammation-based Glasgow prognostic score: a Glasgow Inflammation Outcome Study.
   Proctor MJ, Horgan PG, Talwar D, Fletcher CD, Morrison DS, McMillan DC.
   *Cancer* 2013. **119**. 2325-32.

6. Systemic inflammation predicts all-cause mortality. A Glasgow Inflammation Outcome Study.
   Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS.
   Submitted to Plos One.

**PRESENTATIONS**

1. The relationship between the systemic inflammatory response and tumour type in a large hospital based cohort.
   The Association of Surgeons of Great Britain and Ireland, Glasgow, 2009 (Poster)

2. The relationship between deprivation and the systemic inflammatory response in cancer: a large hospital based cohort study.
   The Association of Surgeons of Great Britain and Ireland, Glasgow, 2009 (Oral)

3. Inflammation-based prognostic score are predictive of outcome in patients with cancer.
   The Association of Surgeons of Great Britain and Ireland, Bournemouth 2011 (Oral)

**DEDICATION**

To my father John, my mother Helen and my sister Lucy for their love and support through thick and thin.

# 1.0. INTRODUCTION

## 1.1. THE IMMUNE/INFLAMMATORY RESPONSE

### 1.1.1. The Local Immune/Inflammatory Response

The immune/inflammatory response, as a reaction to injury, infection, inflammatory conditions or malignancy, occurs at both a local and systemic level. The local immune/inflammatory reaction is characterised by the four clinical signs of inflammation; erythema, heat, swelling and pain. Erythema and increased tissue temperature occur as a result of mast cell degradation and cytokine mediated vasodilatation. Similarly, swelling occurs as a result of cytokine mediated increased capillary permeability and subsequent accumulation of extravascular exudate and inflammatory cells. During the local immune/inflammatory response, pain evoking proinflammatory mediators are also released [Chandrasoma and Taylor, 2005]. The local immune/inflammatory response, through complex immunological processes detailed below, can in turn initiate a global, systemic immune/inflammatory response.

### 1.1.2. The Innate Immune System

Immunity can be broadly divided into the innate, humoral and adaptive systems [Abbas et al., 2005]. It is however worth noting that these definitions are arbitrary as the processes involved are interrelated and the distinctions between each system blurred at both the local and systemic levels (Figure 1.1). The innate immune system is a non-specific, first line defence against insult or attack and aims to promote clearance of pathogens, wound healing and tissue repair. Cells of the innate immune system have germline encoded recognition with the ability to detect non-self and are therefore integral in local and systemic

inflammatory processes [Janeway and Medzhitov, 2002]. At a local level, activation of the complement system stimulates mast cell release of histamine and protease, resulting in clinical signs of local inflammation [Reid and Porter, 1981; Galli et al., 1993]. As illustrated in Figure 1.1, phagocytic cells initiate inflammatory pathways by releasing pro-inflammatory cytokines and activating the complement system, termed the humoral response [Laskin and Pendino, 1995; Koj, 1996].

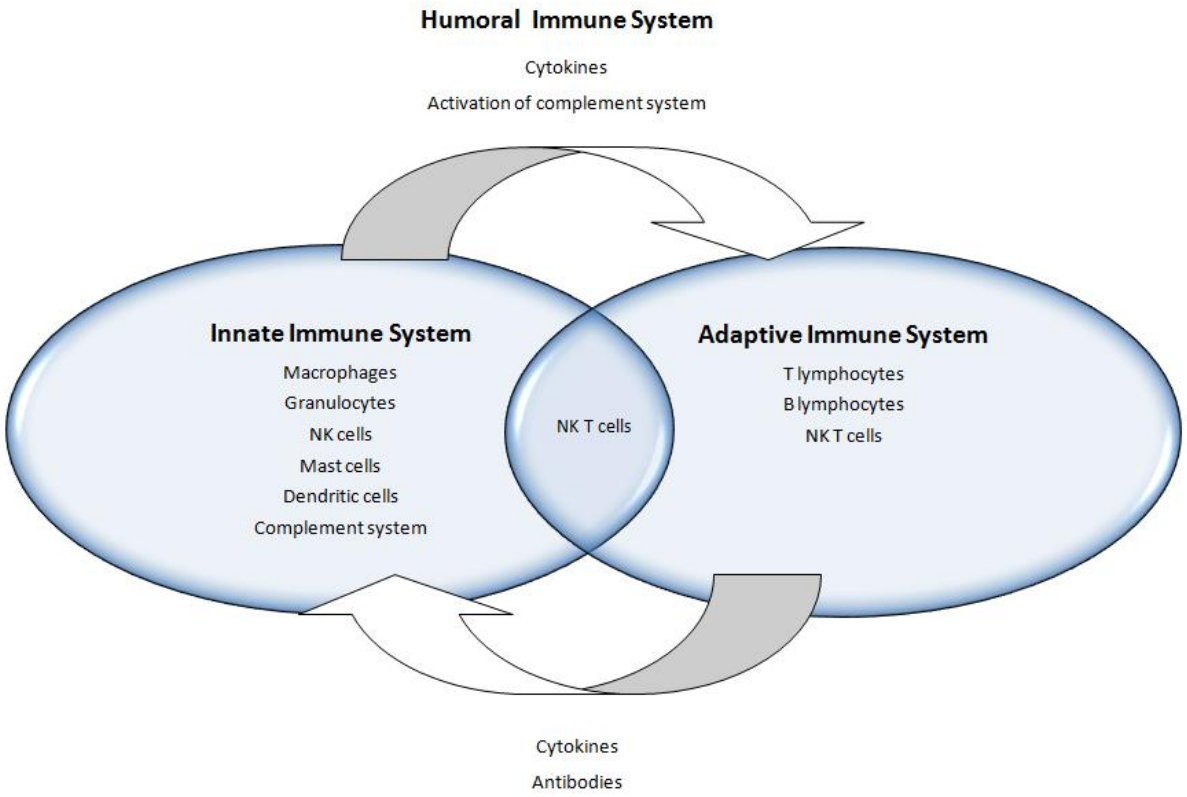



**Figure 1.1. Interactions between the innate, humoral and adaptive immune systems [de Visser and Coussens, 2005]**

### 1.1.3. The Humoral Immune System

The humoral system refers to the non-cellular components of the immune system found in extracellular fluid, in particular the serum. It is normally initiated by the innate immune-based local inflammatory response and triggers a cascade of immunological

processes that help link and co-ordinate the innate and adaptive immune/inflammatory responses (Figure 1.1). It is composed of a number of blood based proteins including antibodies, constituents of the complement pathway, cytokines and opsonins that promote pathogen cell lysis and phagocytosis [Janeway et al., 2001]. Indeed, following tissue damage from infection, chemical injury, trauma, malignancy or immune based destruction, a wide variety of growth factors including colony stimulating, as well as a variety of chemotactic cytokines that attract monocytes and stimulate them to transform into macrophages, are released. As well as the recruitment of innate and adaptive immune cells and promotion of pathogen death, humoral immunity also helps to drive the resulting systemic immune/inflammatory response [Baumann and Gauldie, 1994; Janeway and Medzhitov, 2002].

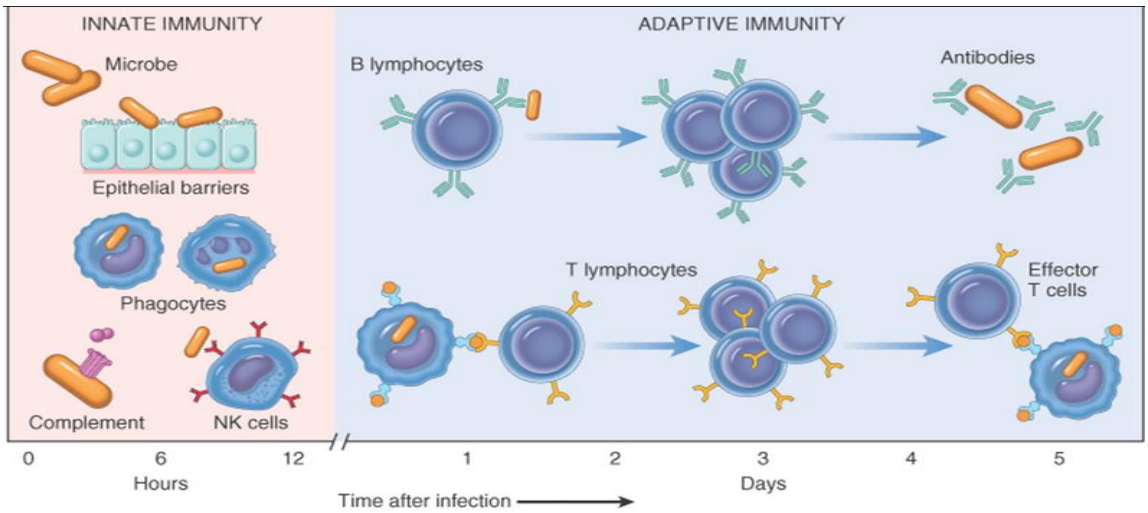



**Figure 1.2. The temporal relationship between the innate and adaptive immune system [Abbas et al., 2005]**

### 1.1.4. The Adaptive Immune System

The adaptive immune system is predominantly composed of lymphocytes, and through the recognition of foreign antigens, aims to develop immunological memory and

speed the elimination of future pathogen attacks [Janeway and Medzhitov, 2002]. The adaptive immune system can be classified as antibody mediated (part of the humoral response) or cell mediated, although many of the processes are interrelated. As illustrated in Figure 1.2, the antibody mediated response relies on phagocytic cells of the innate immune system, such as macrophages and neutrophils, as well as dendritic cells and B-lymphocytes, to present non-self peptides to T-lymphocytes and produce circulating antibodies [Unanue, 2002]. Cell mediated immunity results in antigen-specific cytotoxic T-lymphocytes recognition and phagocytosis of previously exposed pathogens [Herberman and Holden, 1978; Santoni et al., 1979].

### 1.1.5. The Systemic Immune/Inflammatory Response

Following a local immune/inflammatory reaction, and activation of the innate, humoral and adaptive immune systems, circulating pro-inflammatory mediator can result in a subsequent systemic immune/inflammatory response. Indeed, a correlation has been demonstrated between local cytokine production and systemic inflammation in patients with a variety of inflammatory processes [Vernooy et al., 2002; Grigoryev et al., 2008]. While the immune system aims to promote healing and prevent further injury by destroying harmful or infectious agents, the systemic immune/inflammatory response, also referred to as the acute phase reaction, can influence neuroendocrine, haematopoietic, metabolic and hepatic regulation with a number of associated negative physiological outcomes (Table 1.1.) [Baumann and Gauldie, 1994; Koj, 1996]. As part of the systemic immune/inflammatory response, circulating serum constituents of the fore-mentioned innate, humoral and adaptive immune systems, as well as a number of other physiological markers are altered. The systemic immune/inflammatory response has often been overlooked during the study of inflammation, disease pathogenesis and progression, however it is becoming increasingly

evident that this process is closely associated with outcome. This thesis will therefore concentrate on the systemic, opposed to the local immune/inflammatory response.

**Table 1.1. The acute phase phenomena**

| |
|---|
| Neuroendocrine |
| Fever, somnolence, and anorexia |
| Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol |
| Increased secretion of arginine vasopressin |
| Decreased production of insulin-like growth factor I |
| Increased adrenal secretion of catecholamines |
| Hematopoietic changes |
| Anaemia of chronic disease |
| Leukocytosis |
| Thrombocytosis |
| Metabolic changes |
| Loss of muscle and negative nitrogen balance |
| Decreased gluconeogenesis |
| Cachexia and osteoporosis |
| Increased hepatic lipogenesis |
| Increased lipolysis in adipose tissue and decreased lipoprotein lipase activity in muscle and adipose tissue |
| Hepatic changes |
| Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase-1 |
| Decreased phosphoenolpyruvate carboxykinase activity |
| Changes in non-protein plasma constituent |
| Hypozincemia, hypoferremia, and hypercupremia |
| Increased plasma retinol and glutathione concentrations |

[Gabay and Kushner, 1999]

### 1.1.6. Acute Phase Proteins

During the systemic immune/inflammatory response, as a result of physiological changes in protein metabolism and distribution, serum protein levels fluctuate [Fleck, 1989]. Acute phase protein have been defined as those demonstrating a plasma concentration change of at least 25% during an immune/inflammatory reaction [Kushner, 1982]. There are around forty acute phase proteins and these can be positive, (increasing in concentration) or negative (reducing in concentration) [Gabay and Kushner, 1999]. Immunomodulating cytokines, including IL-1, IL-6, IL8 and tumour necrosis factor α, are released from activated cells of

the innate immune system and, under glucocorticoid and growth factor regulatory control, act predominantly on the liver to synthesise positive acute phase proteins [Balkwill and Burke, 1989; Kulkarni and Karlsson, 1993; Wigmore et al., 1997], some of which have immunological roles and function as part of the humoral immune system.

As shown in Figure 1.3, the majority of acute phase proteins are positive and increase in serum concentration during an immune/inflammatory response. Examples of positive proteins include those of the complement system (C3, C4 and factor B), the coagulation and fibrinolytic system (fibrinogen, plasminogen, urokinase and protein S), antiproteases (α1-

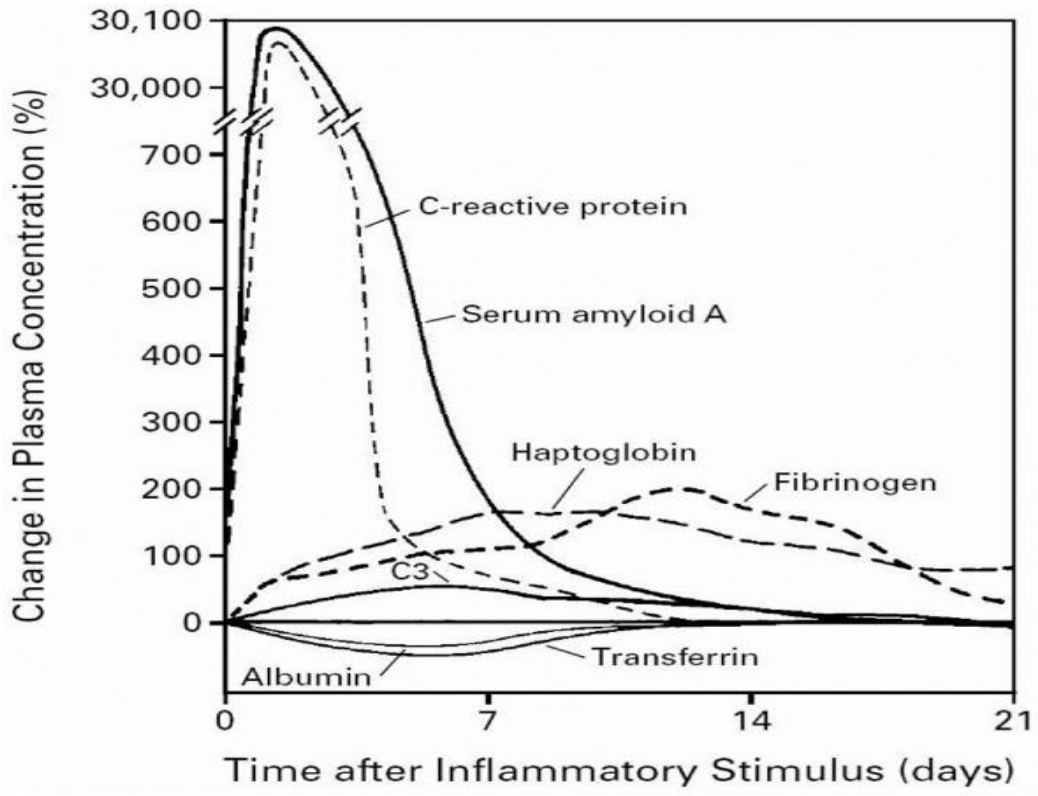



**Figure 1.3. The temporal relationship of acute phase proteins [Gabay and Kushner, 1999]**

Antichymotrypsin and α1-Protease inhibitor), transport proteins (Haptoglobin) as well as many others including C-reactive protein and serum amyloid A [Gabay and Kushner, 1999]. Examples of negative proteins include albumin, transferrin, alpha-fetoprotein and insulin-like growth factor I [Gabay and Kushner, 1999].

In 1930, C-reactive protein was the first acute phase protein to be discovered [Tillett and Francis, 1930] and is now one of the most readily available markers of the systemic immune/inflammatory response. C-reactive protein belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins. It predominantly binds to phosphocholine residues found in necrotic and apoptotic cell walls [Thompson et al., 1999] but has also been shown to have an affinity for extrinsic ligands on bacterial, fungal and parasitic microorganism [Du Clos, 1996]. Binding of these ligands results in the aggregation and precipitation of such structures, initiation of the complement system and subsequent opsonisation and phagocytosis [Mold et al., 1999].

C-reactive protein is currently one of the most commonly used markers of systemic inflammation in clinical practice with the median concentration of C-reactive protein having been found to be 0.8mg/l in healthy individuals. It is also of interest that 90% of healthy people have a concentration of less than 3.0mg/l and 99% a concentration of less than 10mg/l [Shine et al., 1981]. As illustrated in Figure 1.3, serum concentrations peak around 48 hours following insult with a half life of around 19 hours [Vigushin et al., 1993]. It is also known to be one of the most sensitive acute phase proteins and can vary in magnitude by up to 1000 times [Gabay and Kushner, 1999]. C-reactive protein levels in the general population tend to be stable with no seasonal change and only minor yearly variations [Macy et al., 1997; Pepys and Hirschfield, 2003]. However, C-reactive protein concentrations are known to vary across

a number of parameters including body mass index (BMI) [Ford, 1999] and smoking [Wong et al., 2001].

Serum albumin is also commonly sampled in clinical practice and is known to reduce in serum concentration during the acute phase response [Ritchie et al., 1999; McMillan et al., 2001]. Serum albumin is produced in the liver and accounts for the majority of hepatic protein synthesis [Williams and Scott, 1998] with serum levels being influenced by inflammatory cytokine regulation of hepatic production, as well as protein degradation and redistribution [Goldwasser and Feldman, 1997]. A number of conditions, including sepsis, malignancy and chronic disease, can result in increased vascular permeability, albumin redistribution into extra-vascular tissues and subsequent reduction in serum albumin levels [Fleck et al., 1985]. Factors known to influence serum albumin levels include gender [Ritchie et al., 1999], daily activity, muscle mass [Baumgartner et al., 1996] and smoking [Salive et al., 1992].

### 1.1.7. Liver Function Tests, Calcium and Inflammation

Commonly sampled serum biochemical parameters also affected during the systemic immune/inflammatory response include liver function tests and serum calcium levels. A number of liver function tests have been shown to be associated with an inflammation associated C-reactive protein rise [Kerner et al., 2005; Cheung et al., 2008] and alkaline phosphatase has been associated with altered levels of other acute phase proteins including albumin [Blayney et al., 2008]. Similarly, gamma-glutamyl transferase, thought to be an early marker of oxidative stress, has been associated with raised C-reactive protein levels [Lee and Jacobs, 2005]. Bilirubin, known to have endogenous antioxidant properties, has been found to have lower serum concentrations in the presence of an active leukocytosis

[Stocker et al., 1987; Greabu et al., 2001]. There is also evidence that liver function tests are altered as part of the systemic immune/inflammatory response in conditions including lung and gastrointestinal cancer [Brown et al., 2007; Roxburgh et al., 2009a]. Furthermore, it has been suggested that the systemic immune/inflammatory response and C-reactive protein have an effect on cellular calcium metabolism [Foldes-Filep et al., 1992].

### 1.1.8. The Chronic Systemic Immune/Inflammatory Response

If the precipitating factor leading to an acute phase response is persistent, this process can be prolonged and a chronic systemic immune/inflammatory state will occur [Gabay and Kushner, 1999]. Examples of chronic local immune/inflammatory conditions that may lead to a chronic systemic immune/inflammatory response include atherosclerotic lesions [Ross, 1999], chronic infection [Cassell, 1998; Moutsopoulos and Madianos, 2006], chronic pancreatitis [Nair et al., 2007] and malignancy [Rakoff-Nahoum, 2006]. This ongoing process is sometimes referred to as the "Systemic Inflammatory Response" that, in part, involves alterations of the pre-mentioned circulating constituents of the immune system and associated serum biochemical variables. It is this phenomenon and its associations with outcome, predominantly in cancer but also in artheriosclerotic disease, that will be focused on in this thesis.

## 1.2. INFLAMMATION AND CANCER

### 1.2.1. Cancer Incidence

In 2008, it was estimated that there were 12.4 million new cancer cases diagnosed worldwide. Traditionally cancer has been a disease of Western, high income countries, however, this is changing. As shown in Figure 1.4, over half of all newly detected cancers are now occurring in developing countries [Boyle and Levin, 2008].

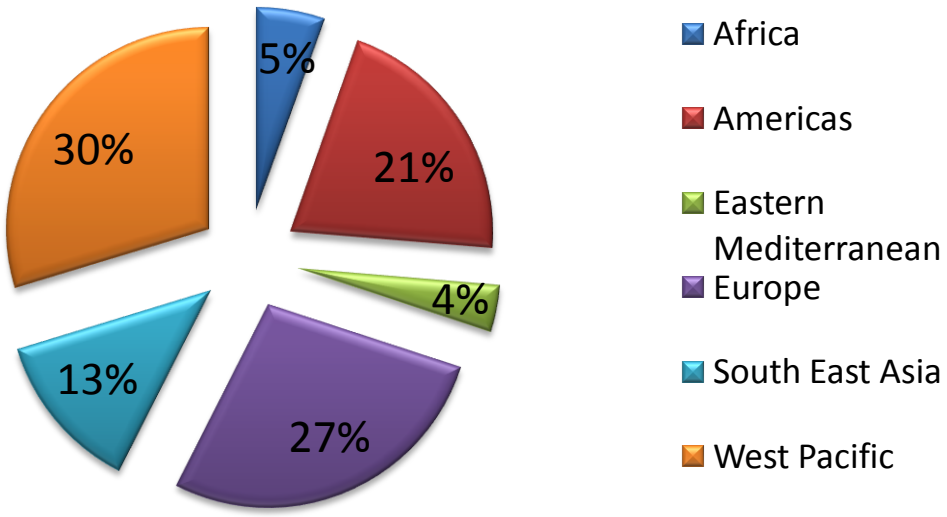



**Figure 1.4. Worldwide cancer incidence by region in 2008 [Boyle and Levin, 2008]**

With a growing global population and increasing life expectancy, the current incidence figures are set to rise to at least 20 million by 2030 [Boyle and Levin, 2008]. This is expected to be a global phenomenon with a projected increase in European regions from 4.1 million cases per annum in 2008 to at least 5.5 million per annum in 2030 [Boyle and Levin, 2008]. In the United Kingdom cancer incidence has also risen by approximately 25% between 1975 and 2004. As a consequence, more than one in three people will develop

cancer during their lifetime [Cancer Research UK, 2008] with similar projected increases in the number of cases forecasted [Moller et al., 2007].

Worldwide, lung cancer is the most commonly diagnosed tumour with approximately one million new cases in 2002. The incidence of lung cancer varies from approximately 2 per 100 000 in African women to 61 per 100 000 in North American men [Kamangar et al., 2006], a difference largely attributable to cigarette smoking [Ezzati and Lopez, 2003]. Colon cancer is approximately 25 times more common in developed countries, a difference partially attributable to differences in meat, fat and fibre consumption [Trock et al., 1990; Willett et al., 1990]. Female breast cancer is also more common in developed populations, a difference possibly due to an older population and increasing detection since the introduction of screening [Alberg and Singh, 2001].

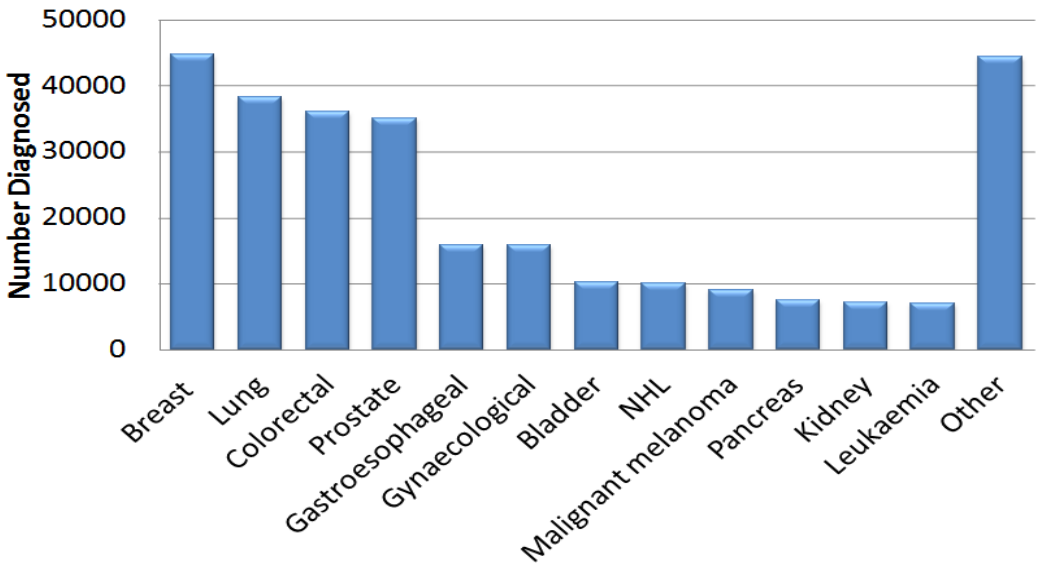



**Figure 1.5. Number of cancers diagnosed in the UK per year. [Cancer Research UK, 2008]**

Of the 280 000 new cancers diagnosed each year in the United Kingdom (Figure 1.5), the majority occur in people over 60 years of age [Cancer Research UK, 2008]. During 2004

the commonest cancers diagnosed in males were prostate (34 986), lung (22 495), colorectal (19 657), gastroesophageal (10 100) and bladder (7168). During the same time period, in females, the most commonly diagnosed malignancies were breast (44 335) followed by colorectal (16 452), lung (15 818), gynaecological (15 779) and gastroesophageal (5732).

### 1.2.2. Cancer Mortality

Worldwide, in 2008 there were an estimated 7.6 million deaths attributed to cancer with projected figures to reach at least 12.9 million by 2030 [Boyle and Levin, 2008]. Survival from common cancers including breast, colorectal and prostate, is generally better for those diagnosed in developed countries of western Europe, North America and Australia, when compared to less developed areas including eastern Europe, Algeria and Brazil [Coleman et al., 2008].

In the United Kingdom cancer is the leading cause of death and responsible for approximately thirty percent of all mortality, equating to around 150,000 deaths per year [Cancer Research UK, 2007]. Most deaths occur in males and those over the age of 75 with an increased mortality rate in the socioeconomically deprived [Coleman et al., 2004]. The commonest cancers responsible for death are lung, bowel, breast and prostate with the relative five year survival of these, and other common cancers illustrated in Figure 1.6.

In recent decades there have been improvements of approximately ten percent in cancer mortality rates with these changes largely affecting people under the age of 75 with cancers of the stomach, lung, bladder, bowel and cervix [Cancer Research UK, 2006]. These improvements are likely due to better detection and treatment modalities, however, with increasing population age a rise of 40% in cancer deaths is expected by 2025 [Olsen et al.,

2008]. This clearly has significant financial implications and will require a greater proportion of annual healthcare spending [Bosanquet and Sikora, 2004; Boyle and Levin, 2008].

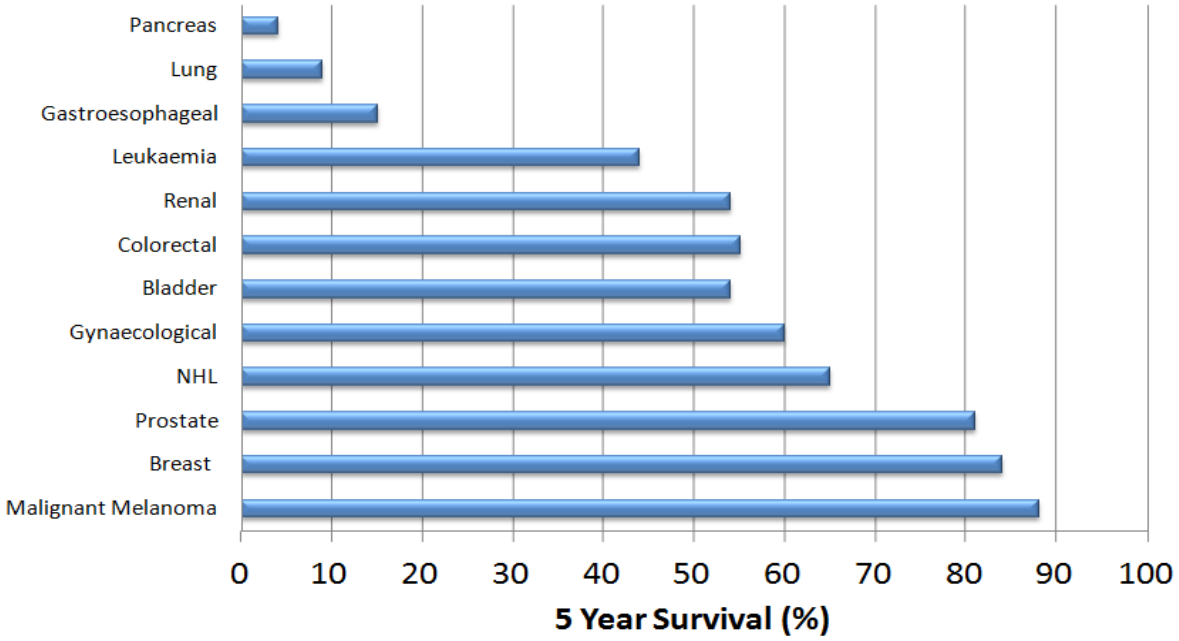



**Figure 1.6. Relative 5 year survival in common tumour types in the UK. [Cancer Research UK, 2007]**

### 1.2.3. Patient Demographics and Cancer Survival

A number of patient based factors are known to be related to survival in patients with cancer. Increasing age is associated with reduced survival when adjusted for other known factors in the majority of cancers [Sant et al., 2003; Lam et al., 2007]. In part, this may be explained by inadequate staging and fewer treatment options in the elderly [de Rijke et al., 1996; Fentiman, 1996]. There are however certain tumour types, specifically lung, breast and prostate, that do not conform to this pattern with some evidence that older patients have an improved survival [Romano and Mark, 1992; Merrill and Bird, 2002; Chia et al., 2004; Mathew et al., 2004].

Male gender is also associated with reduced survival in variety of tumour types that can affect both sexes. For example, male gender tends to be associated with a poorer outcome in patients with colorectal and lung cancer, as well as chronic lymphocytic leukaemia [Romano and Mark, 1992; Diehl et al., 1999; Wichmann et al., 2001; McArdle et al., 2003; Sant et al., 2003; Visbal et al., 2004].

Furthermore, increasing socioeconomic deprivation has been associated with reduced survival in a number of different tumour types including lung, breast, colorectal, bladder, prostate, uterine and cervical, independent of other prognostic factors [Schrijvers et al., 1995; Coleman et al., 2004]. In population studies, deprivation has traditionally been measured by the Carstairs index [Sloggett and Joshi, 1998], a postcode based score derived from a number of socioeconomic factors including car ownership, household crowding, head of household social class and male unemployment [Carstairs and Morris, 1991]. Currently, the recommended measurement of deprivation in Scotland is the (SIMD). Similarly it categorises post code areas, however, a more detailed measurement of 37 indicators across seven domains including income, employment, education, housing, health, crime and geological area is used [Bishop et al., 2004]. Scotland is divided into 6,505 data zones with these ranked from 1 (least deprived) to 6,505 (most deprived). These data zones have further been divided into quintiles of the Scottish population, with the present body of work using quintiles that range from 1 (least deprived) to 5 (most deprived). As can be seen in Figure 1.7, an increasing SIMD score has been shown to be associated with an increased cancer incidence as well as an increased cancer associated mortality in the Scottish population [The Scottish Government, 2008].

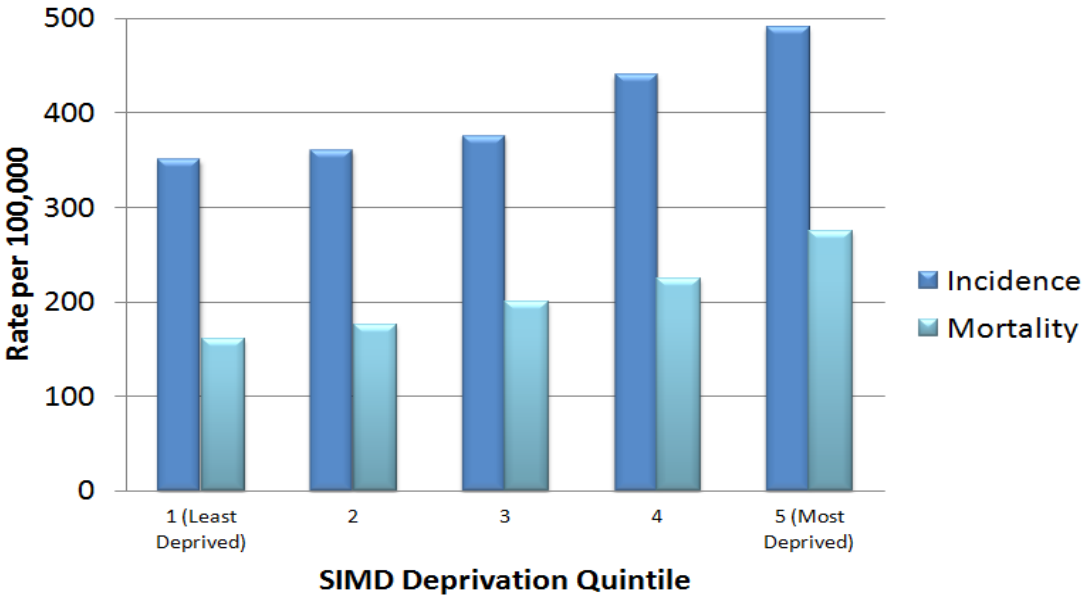



**Figure 1.7. Malignant neoplasm age-standardised incidence and mortality by SIMD Quintiles [The Scottish Government, 2008]**

### 1.2.4. Inherited Genetic Mutations and Carcinogenesis

The development of malignancy is a multi-step process depending on the inheritance or development of deoxyribonucleic acid (DNA) mutations that result in the interruption of tumour suppression or activation of pro-oncogenic pathways at a cellular level [Kinzler and Vogelstein, 1996]. Genetic mutations ultimately result in the development of several cellular characteristics, including invasion and the potential to metastasise, that are required for malignant transformation [Hanahan and Weinberg, 2000].

It has long been accepted that cancer has a genetic basis with a variety of tumours noted to have potentially hereditary patterns [Easton, 1994]. In twin studies it has been estimated that genetic predispositions are a contributing factor in approximately 28% of gastric, 35% of colorectal, 27% of breast and 42% of prostate cancers [Lichtenstein et al., 2000]. A number of genes have been identified as increasing cancer risk including BRCA1 and 2 in breast cancer, APC, MSH2, MLH1 in colon cancer and MET in renal cell cancer.

### 1.2.5. Acquired Genetic Mutations and Carcinogenesis

DNA mutations, whether they result in the activation of oncogenes or the loss of tumour suppressor genes, can occur as a consequence of point mutations, insertions or deletions of base pairs, gain or loss of entire chromosomes, translocations and gene amplifications [Lengauer et al., 1998]. Acquired mutations are thought to be responsible for the majority of DNA mutations and can be secondary to oxidative stress or radiation [Lichtenstein et al., 2000; Hemminki and Jiang, 2002]. Oxidative stress can occur as the result of contact with a number of carcinogens including those found in food [Wong et al., 2001; Straif et al., 2006; Baan et al., 2007], cigarette smoke [Wogan et al., 2004] and other chemical compounds [Baan et al., 2008].

### 1.2.6. Inflammation and Carcinogenesis

There is growing evidence that a local inflammatory microenvironment encourages the development of malignancy with an increased prevalence of cancer in tissues experiencing chronic inflammation [Balkwill and Coussens, 2004; Vakkila and Lotze, 2004; Lu et al., 2006]. Continued immune/inflammatory stimuli secondary to chemical irritation [Whitcomb, 2004], infection [Pagano et al., 2004] or immunological disorders [Itzkowitz and Yio, 2004] can result in the release of a variety tumour promoting cytokines [Lin and Karin, 2007]. Increased tissue turnover, loss of tissue architecture and oxidative stress can result in DNA damage with subsequent risk of neoplastic transformation and eventual cancer development [Shacter and Weitzman, 2002; Balkwill et al., 2005; Colotta et al., 2009].

Globally, approximately 17% of all cancers are attributed to infectious aetiology [Kuper et al., 2000; Parkin, 2006]. For example, chronic viral hepatitis has been implicated in the pathogenesis of the majority of hepatocellular cancers [Kew, 1998] and the human

papilloma virus has been clearly associated with the development of cervical cancer [Bosch et al., 2002].

Non-infective, autoimmune inflammatory conditions also predispose individuals to the development of neoplasia. Colorectal cancer incidence increases by approximately 10 fold in patients with chronic inflammatory conditions of the colon, such as ulcerative colitis [Itzkowitz and Yio, 2004]. Fibrotic and inflammatory lung conditions, including idiopathic pulmonary fibrosis and systemic sclerosis, have also been shown to increase risk the of developing cancer [Daniels and Jett, 2005]. Similarly, patients with systemic lupus erythematosus (SLE) have a higher incidence of cervical dysplasia [Blumenfeld et al., 1994].

### 1.2.7. Inflammation and Cancer Progression

It has been suggested that essential alterations in cell physiology, including self sufficiency in growth, sustained angiogenesis and the potential for tissue invasion and metastasis, are essential if tumours are to succeed in malignant growth [Hanahan and Weinberg, 2000; Colotta et al., 2009]. It is becoming clear, as detailed in Figure 1.8, that the oncogenic process of tumour development and progression is influenced by the interaction of surrounding non-malignant cells [Hanahan and Weinberg, 2000; Coussens and Werb, 2002] and it is therefore of interest that certain malignant tumours may consist of over 90% stromal and inflammatory cells [Mesker et al., 2007]. Moreover, this is consistent with growing evidence that suggests a pro-inflammatory tumour microenvironment is vital for the progression of malignancy [Balkwill and Coussens, 2004; Mantovani et al., 2008; DeNardo et al., 2008].

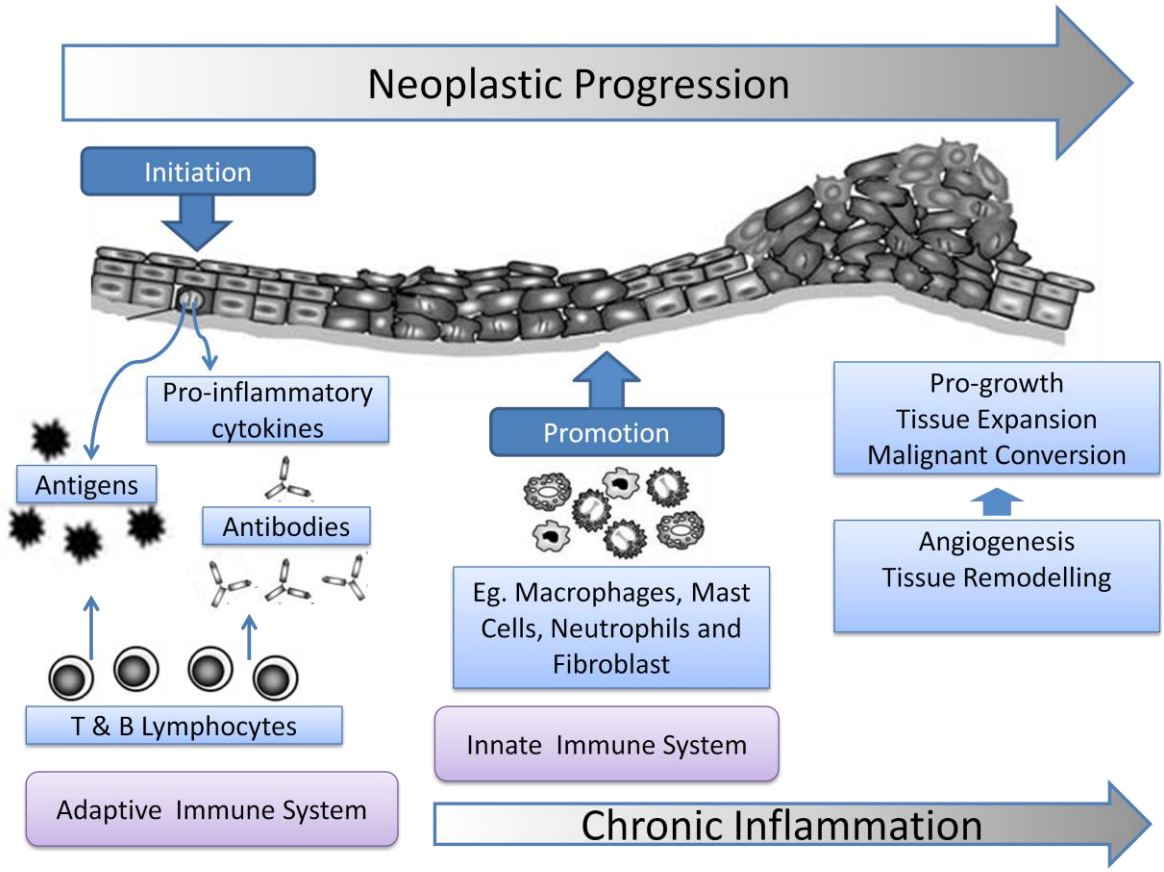



**Figure 1.8. Inflammation, carcinogenesis and neoplastic progression [de Visser et al., 2006]**

To achieve malignant growth, cancer cells hijack normal immunological and physiological processes to aid angiogenesis and stromal tissue development. For example, infiltrating cells belonging to the innate immune system, including neutrophils, macrophages and mast cells will increase the angiogenic potential of a tumour and allow it to lay down a supportive connective tissue framework [Hanahan and Folkman, 1996; Jackson et al., 1997; Imada et al., 2000; Benitez-Bribiesca et al., 2001; Kalluri and Zeisberg, 2006; Joyce and Pollard, 2009].

Tumour Associated Macrophages (TAMs) are the predominant tumour leukocyte infiltrate and have been implicated in both the destruction of tumour cells as well as the promotion, in part by cytokine production, of cancer progression and metastasis [Jonjic et al.,

1992; Mantovani et al., 2002; Pollard, 2004]. Macrophages have also been shown to have an atrophic, remodelling role that contributes to tumour progression and cancer cell survival by increasing the proliferative potential, increasing cancer cell motility, intravasation and invasiveness as well as increasing angiogenesis, mediating immunosuppression and promoting extracellular matrix formation [Mantovani et al., 2002; Lewis and Pollard, 2006; Nardin and Abastado, 2008]. While it remains a controversial issue, there is some corresponding evidence that TAMs are associated with reduced survival in certain tumour types [Leek et al., 1996; Bingle et al., 2002].

While there is evidence that a number of local inflammatory cells can promote tumour progression, conversely, an abundance of tumour margin lymphocytes has been associated with an improved outcome [Jass et al., 1987]. Indeed, this lymphocytic infiltrate has been, in colorectal, hepatocellular and gastroesophageal cancer, shown to correlate with improved survival [Ma et al., 1994; Wada et al., 1998; Ohashi et al., 2000; Canna et al., 2005]. This is clearly a complex relationship as low intertumoral T regulatory cells, in the presence of high cytotoxic T cells (CD8+), have also been associated with improved survival [Gao et al., 2007]. Moreover, it has been suggested that the inverse relationship between cytotoxic T cell infiltrate and survival may be due to the inhibition of micrometastasis [Chiba et al., 2004] and tumour induced modulation, at the lymph node level, may inhibit or down regulate the action of cytotoxic T-cells and therefore increase the potential for distal spread [Cochran et al., 2006].

Neutrophils produce cytotoxic substances, including proteinases, to defend the host from microorganism attack and promote healing [Smith, 1994]. They can also produce cytokines to drive the immune/inflammatory response with evidence to show that tumour associated neutrophils can play an active part in tumour angiogenesis and proliferation

[Nathan, 2006; Tazzyman et al., 2009]. Neutrophilia is also known to occur as a result of cancer related production of myeloid growth factor, granulocyte colony stimulating factor and cytokine production [Ulich et al., 1987; Lord et al., 1989].

Platelets are also influenced by malignancy and can be activated by direct contact with tumour cells or via release of tumour based cytokines [Zucchella et al., 1989; Grignani et al., 1989]. They have been shown to play a multifactorial role in angiogenesis, the pro-coagulopathy observed in malignancy as well as tumour progression [Poggi et al., 1988; Sierko and Wojtukiewicz, 2004].

### 1.2.8. Cancer Stage and Indicators of Survival

Cancer staging is important as it currently helps identify those patients who will benefit from potentially curative interventions such as resectional surgery or oncological therapy. It also provides an indication of prognosis and guides the requirement for surveillance following treatment. The most commonly used staging system for malignant tumours is the TNM classification (Table 1.2) which is recommended by the Union for International Cancer Control (UICC), Cancer Research UK as well as the American Joint

**Table 1.2. Tumour Node Metastasis classification**

| Primary Tumour | |
|---|---|
| T0 | No evidence of malignant tumour |
| Tis | Carcinoma in situ (preinvasive) |
| T1-T4 | Size and/or extent of primary tumour |
| Regional Lymph Nodes | |
| N0 | No regional lymph node involvement |
| N1-3 | Degree of regional lymph node involvement (number and location) |
| Distant Metastasis | |
| M0 | No distant metastasis |
| M1 | Distant metastasis present |

[National Cancer Institute, 2009]

Committee on Cancer (AJCC). TNM is based on the extent of the primary tumour (T), spread to the local lymph nodes (N) and the presence of distal metastasis (M) [Sobin and Wittekind, 2002]. It can be calculated by clinical means, including examination and radiological investigations, objective assessment of resected pathological specimens or a combination of these techniques. A shortened TNM classification comprising five stages (0-IV) is also commonly used, but differs in detail depending on the specific tumour type (Table 1.3). In colorectal cancer, this broadly corresponds to the Dukes classification where the more advanced the tumour, the shorter the expected survival [National Institute for Health and Care Excellence, 2009]. While the TNM system is used in the majority of tumour types, some central nervous system and haematological cancers do not comply and different systems are used.

**Table 1.3. Tumour stage classification**

| | |
|---|---|
| Stage 0 | Carcinoma in situ |
| Stage I-III | Higher number indicates more extensive disease. Larger tumour size and/or spread of the cancer beyond the organ in which it first developed to nearby lymph nodes and/or tissue or organs adjacent to the location of the primary tumour. |
| Stage IV | Distal metastasis |

[National Cancer Institute, 2009]

While being considered the gold standard for staging prognosis, the TNM based classification has potential pitfalls. It is clear that staging by clinical and radiological means may be open to a certain amount of subjective judgment and it has been shown that computerised tomography may provide different results from resected pathological specimens [Schlomer et al., 2006]. There are also concerns that inadequate pathological assessment, with regards to number of lymph nodes examined, may result in under staging and not effectively identify individuals who would benefit from adjuvant therapy [Tepper et

al., 2001; Joseph et al., 2003; Swanson et al., 2003]. These issues have compounded worries that while this system may be adequate for those at the extremes of the stage spectrum (I or IV), those in the middle may be getting inaccurately staged and under or over treated.

A number of other tumour related, pathological features are associated with outcome and survival in a variety of tumour types. Tumour differentiation, as detailed in Table 1.4, is a measure of how abnormal tumour cells appears and a reflection of how rapidly a tumour is likely to grow and disseminate. Tumour differentiation has been associated with outcome in the majority of neoplastic malignancies including gastroesophageal [Khan et al., 2004], breast [Bloom and Richardson, 1957], pancreatic [Lim et al., 2003] and colorectal [Mori et al., 2006] cancers.

**Table 1.4. Grade of differentiation classification**

| | |
|---|---|
| Grade 1 | Well differentiated (low grade) |
| Grade 2 | Moderately differentiated (intermediate grade) |
| Grade 3 | Poorly differentiated (high grade) |
| Grade 4 | Undifferentiated (high grade) |

[National Cancer Institute, 2009]

While these methods are clearly important and provide a wealth of information regarding tumour status, they do little to estimate the host response to the malignant process. Performance status can be used as a potential indicator of host response and aims to measure physical function and gauge how malignancy impacts on a patient's daily life. The Eastern Cooperative Oncology Group (ECOG) performance status score is a 5 point system that ranges from 0 (no symptoms/restriction to activity) to 5 (death) and is commonly used when making decisions as to whether a patient is fit enough to receive chemotherapy [Oken et al.,

1982]. There have however been concerns that these subjective measures of patient function have been shown to have significant inter-observer variability [Ando et al., 2001]. As performance status is a measure of host function, and therefore a surrogate marker of cancer cachexia and muscle mass, it is also of no surprise that an association between the host systemic immune/inflammatory response and performance status has been demonstrated [Brown et al., 2007].

Taken together, it is therefore expected that there is increasing interest in the "seed and soil" hypothesis that suggests patient outcome depends not only on tumour characteristics but also on the host immunological response to a malignant process [Fidler and Poste, 2008]. It therefore stands that a measure of the pre-mentioned host immune/inflammatory response may offer a useful adjunct in the risk stratification of patients with cancer.

## 1.3. INFLAMMATION AND ATHEROSCLEROSIS

### 1.3.1. Cerebrovascular and Cardiovascular Atherosclerotic Disease and Mortality

According to the World Health Organisation, cardiovascular and cerebrovascular disease are responsible for the majority of mortality worldwide. In 2004, ischaemic heart disease was responsible for approximately 7.2 million deaths, thus accounting for over 12 percent of all deaths worldwide. The World Health organisation predict that this will increase to approximately 23 million by 2030 and concerns have been raised that cardiovascular disease may become the most common cause of death in the 21st century [Sporn, 1996; Hansson, 2005]. Similarly, cerebrovascular disease was responsible for approximately 10 percent of all deaths worldwide in 2004 with this figure set to increase [Mathers et al., 2004]. In high income countries this pattern persisted with approximately 16 percent of deaths being attributable to ischaemic heart disease and 9 percent as a result of cerebrovascular disease [Mathers et al., 2004]. These reported death rates are consistent with those published for the UK with approximately one third of all deaths being due to circulatory disease [Office for National Statistics, 2008; McNiven D, 2010].

### 1.3.2. Atherosclerotic Disease and Inflammation

The link between atherosclerotic disease and inflammation is well recognised and has been shown to be independent of other arteriopathic risk factors including smoking and obesity [Kuller et al., 1996; Tracy, 1998; Ross, 1999; Williams et al., 2004]. While the relationship between inflammation, C-reactive protein and atherosclerotic disease is not entirely clear, arterial wall lipoprotein retention and the subsequent formation of fatty streaks has been implicated [Ross, 1999; Pepys and Hirschfield, 2003]. Once established, fatty streaks can encourage fibrous plaque formation, which in turn can rupture, precipitate

thrombus and result in a cardiac event [Ross, 1999]. Atherosclerotic vessel wall inflammatory infiltrate has been found to have increased levels of a number of inflammatory cells including lymphocytes and dendritic cells [Galkina and Ley, 2009]. Macrophages have also been implicated and, as illustrated in Figure 1.9, have been found to oxidise low density lipoproteins and drive an immune/inflammatory response [Jonasson et al., 1986; Berliner et al., 1990]. Neutrophils and platelets are similarly involved in atherosclerotic disease and have been shown to have a pro-inflammatory role with the subsequent propagation of atheromatous plaque and potential rupture [Ross, 1993; Massberg et al., 2002; Kraaijeveld et al., 2007; von Hundelshausen and Weber, 2007; Zernecke et al., 2008]. These activated cells of the immune system involved in atheroma development also produce inflammatory

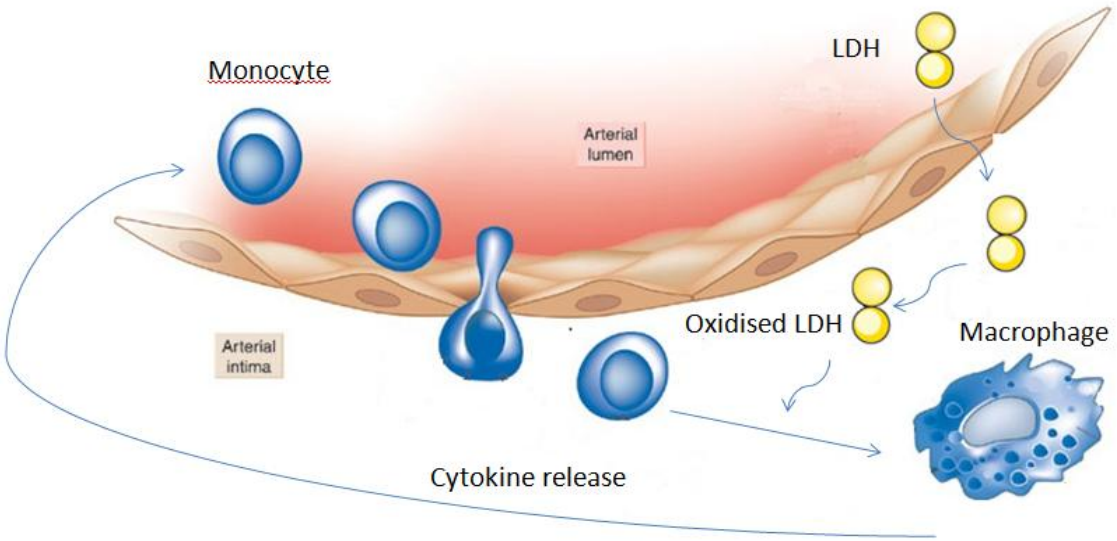



**Figure 1.9. Low density lipoprotein, inflammation and atherosclerotic vessel wall infiltrate [Barter et al., 2004]**

cytokines including IL-1 and IL-6, and as a consequence, acute phase reactants including C-reactive protein from the liver [Hansson et al., 1989; Clinton and Libby, 1992; Frostegard et

al., 1999]. As a result, both IL-6 and C-reactive protein levels have been shown to be elevated in patients with unstable angina and myocardial infarction [Liuzzo et al., 1994; Lindahl et al., 2000; Danesh et al., 2008]. Traditionally, C-reactive protein levels of 10mg/l or less have been regarded as clinically unimportant, however smaller rises have since been classed as abnormal in those at risk, or with a history of ischaemic heart disease [Haverkate et al., 1997; Gabay and Kushner, 1999]. It is likely that these small rises reflect the local inflammatory process in the artery, however, it is also possible that they represent inflammation at a distal site [Hansson, 2005]. It is also of interest that albumin, a negative acute phase protein, can reduce platelet adhesion and has an anti-oxidant effect that helps clearance of reactive oxygen species that are pathogenic in ischaemic heart disease [Halliwell and Gutteridge, 1990; Porcellati et al., 1995].

### 1.3.3. Risk Stratification in Cardiovascular and Cerebrovascular Disease

A strategy that assists in the identification of those at increased risk can help individualise treatment and ensure that appropriate therapies are received by those who will benefit [Alderman, 1993]. The optimal prognostic tool would be of low financial cost, openly available and easily interpreted with a high sensitivity and specificity [Parikh and Vasan, 2007].

The extensively validated Framingham Risk Score can be used to calculate the probability of an individual having a major cardiac event and the requirement for therapy [Kannel et al., 1976; Anderson et al., 1991; Brindle et al., 2003; Greenland et al., 2010]. It includes gender, total cholesterol, HDL cholesterol, smoking status as well as systolic blood pressure and is recommended by European and American cardiac societies [Wood et al., 1998; Grundy et al., 1999].

A similar score, the CHADS2, is used in the risk stratification for future cerebrovascular events in patients with atrial fibrillation. It looks at the presence of congestive heart failure, hypertension, age, diabetes and a history of prior cerebrovascular events and indicates the requirement for anticoagulation therapy [Gage et al., 2004].

As inflammation is pathologically related to atherosclerotic disease, C-reactive protein as a measure of the systemic immune/inflammatory response, is currently recommended by the American Heart Association for cardiovascular screening and statin management [Greenland et al., 2010]. It therefore stands that that other simple, easily obtainable measures of the systemic immune/inflammatory response may also predict outcome in patients with cardiovascular and cerebrovascular disease.

## 1.4. SERUM MARKERS OF SYSTEMIC INFLAMMATION AND MORTALITY

### 1.4.1. C-reactive Protein

A number of markers of the systemic immune/inflammatory response have been associated with all-cause mortality. In 274,515 incidentally sampled patients, Marsik and co-workers, demonstrated that a raised baseline serum C-reactive protein concentration was associated with mortality from cancer, cardiovascular and cerebrovascular disease [Marsik et al., 2008]. This study was noted to be particularly robust as patient cause of death was confirmed by a post mortem in approximately 35% of cases. Also, when 22,962 patients with subacute C-reactive protein measurements (<10mg/l) were studied, high sensitivity measurements were found to have additional value to the traditional thresholds (>10mg/l), when predicting all-cause mortality [Currie et al., 2008].

Serum C-reactive protein levels have also been associated with both the risk of developing cancer and a reduced survival in patients with cancer. In a cohort of 22,887 patients, a baseline elevated C-reactive protein level was associated with a greater risk of developing colorectal cancer, with similar studies demonstrating comparative findings for lung cancer [Erlinger et al., 2004; Allin et al., 2009]. Elevated levels of C-reactive protein have also been associated with survival in a number of malignancies including colorectal [Nozoe et al., 1998], oesophageal [Guillem and Triboulet, 2005; Crumley et al., 2006a], pancreatic [Falconer et al., 1995; Jamieson et al., 2005], ovarian [Hefler et al., 2008], endometrial [Schmid et al., 2007], cervical [Polterauer et al., 2007], breast [Albuquerque et al., 1995], renal cell [Casamassima et al., 2005; Komai et al., 2007] and hepatocellular [Hashimoto et al., 2005; Nagaoka et al., 2007] cancer.

Correlations between C-reactive protein concentrations and atherosclerotic disease have also been found. Koenig and co-workers demonstrated, in 936 healthy men, that a raised C-reactive protein was independently associated with an increased risk of developing cardiovascular disease [Koenig et al., 1999]. Also, meta-analysis of 1953 coronary events demonstrated a relative risk of 2.0 for the development of future coronary events if a patient's C-reactive protein was in the top tertile (>2.4mg/l Vs <1mg/l) [Danesh et al., 2000]. Moreover, many other studies have shown similar associations with a raised C-reactive protein, in patients with unstable angina or myocardial infarction, and future cardiac events and death [Liuzzo et al., 1994; Ridker et al., 2000; Ridker et al., 2001; Danesh et al., 2004].

In patients with cerebrovascular disease, C-reactive protein has been found to have prognostic value in both identifying patients at risk of developing the condition, as well as those who are likely to die as a result. In a cohort of 7901 healthy Japanese men, those with raised C-reactive protein measurements were more likely to have a cerebrovascular event, as well as die from all-cause mortality [Makita et al., 2009]. Similar associations between a raised C-reactive protein and cerebrovascular related mortality have been noted in other studies [Di Napoli et al., 2001; den Hertog et al., 2009].

### 1.4.2. Albumin

Hypoalbuminaemia has been shown, in 7735 randomly enrolled men, to be associated with an increased risk of all-cause mortality independent of other risk factors [Phillips et al., 1989]. Similarly, hypoalbuminaemia was found to be a risk factor associated with all-cause mortality in the American National Health and Nutrition Examination Survey (NHANES) longitudinal follow-up survey [Gillum and Makuc, 1992] as well as in other large cohorts [Goldwasser and Feldman, 1997; Grimm et al., 2009; Desai et al., 2009].

Hypoalbuminaemia has also long been associated with reduced survival in patients with a variety of cancers [Phillips et al., 1989; Lam et al., 2007; Penel et al., 2008]. A number of studies have demonstrated a link between hypoalbuminaemia and survival in lung cancer. These include work carried out by Maeda and co-workers demonstrating this relationship in 261 patients with advanced Non-small Cell Lung Cancer (NSCLC) [Maeda et al., 2000] as well as a number of other studies with similar results [Hespanhol et al., 1995; Maestu et al., 1997; Tas et al., 1999]. In 1367 patients undergoing surgical treatment for colorectal cancer, hypoalbuminaemia was shown to be independently associated with a reduced survival [Sun et al., 2009] with comparable results being found in other operable and palliative cohorts [Heys et al., 1998; Schindl et al., 2005; Cengiz et al., 2006]. This association, between hypoalbuminaemia and reduced survival, has been shown to persist in a number of solid organ malignancies including gastric [Lien et al., 2004; Alici et al., 2006; Onate-Ocana et al., 2007], oesophageal [Di Fiore et al., 2007; Wang et al., 2009], hepatocellular cancer [Nagaoka et al., 2007; Takahashi et al., 2008; Choi et al., 2008], pancreatic [Siddiqui et al., 2007], ovarian [Gupta et al., 2009] and breast cancer [Wyld et al., 2003; Lis et al., 2003]. Similar studies have also shown this association to occur in haematological malignancies including, Non-Hodgkin's Lymphoma [Alici et al., 2003].

Serum albumin is also known to be associated with cardiovascular mortality in unselected patients and in those with pre-existing renal disease [Goldwasser and Feldman, 1997; Grimm et al., 2009]. Similarly, hypoalbuminaemia has been shown to be associated with an increased risk of death from cardiovascular disease independent of other risk factors [Phillips et al., 1989]. These findings were further confirmed in the American National Health and Nutrition Examination Survey (NHANES) [Gillum and Makuc, 1992] with several other studies also demonstrated this relationship [Kuller et al., 1991; Corti et al.,

1996; Weijenberg et al., 1997]. Hypoalbuminaemia has also been shown, after controlling for stroke risk factors, to predict cerebrovascular incidence as well as mortality in subjects of NHANES epidemiological follow-up study [Gillum et al., 1994].

### 1.4.3. Liver Function Tests and Calcium

Liver function tests have similarly been associated with outcome and survival. Bilirubin, a potential antioxidant, has been associated with a reduction in the incidence of coronary artery disease [Schwertner et al., 1994]. Higher levels of bilirubin, in approximately 10 000 unselected patients, has been linked with improved all-cause, cancer and cardiovascular survival [Temme et al., 2001]. Conversely, an elevated alkaline phosphatase has been associated with a reduced survival in patients with kidney disease, cardiovascular disease and in the general population [Blayney et al., 2008; Tonelli et al., 2009]. Furthermore, it is of interest that γ-glutamyl transferase (GGT) and serum calcium have also been reported to predict cancer and non-cancer outcomes [Leifsson and Ahren, 1996; Kazemi-Shirazi et al., 2007].

### 1.4.4. White Cell Count

A white blood cell count has likewise been shown to have prognostic value in previously health individuals. When 2011 men were followed up for an average of thirteen years, their initial white cell count corrected for lifestyle risk factors, was shown to predict all-cause mortality [de Labry et al., 1990]. In addition, a study of 13,555 individuals demonstrated positive correlation between white cell count and all-cause mortality, as well as risk of stroke and cardiovascular disease [Gillum et al., 2005] with a number of other studies demonstrating similar relationships [Tamakoshi et al., 2007].

In cancer cohorts, an elevated white cell count has been shown to have prognostic significance in a range of advanced malignancy including lung [Tibaldi et al., 2008], colorectal [Kohne et al., 2002], pancreatic [Engelken et al., 2003] and other gastrointestinal cancers [O'Gorman et al., 2000]. While these reported associations between a white count and mortality in both cancer and non-cancer groups is of interest, it remains to be seen whether a particular cell type, for example neutrophils, are predominantly responsible for this relationship.

### 1.4.5. Neutrophil Count

Elevated neutrophil counts have been associated with a reduced survival in renal cell and Non-Small Cell Lung cancer [Donskov, 2007; Teramukai et al., 2009]. In addition, the NHANES epidemiological follow-up study of approximately 5000 patients demonstrated a link between neutrophil count and all-cause and cardiovascular mortality [Gillum et al., 2005].

### 1.4.6. Lymphocyte Count

Conversely, a raised lymphocytes count seems to be of prognostic benefit and in elderly populations, lymphocytosis has been shown to reduce all-cause mortality [Bender et al., 1986; Izaks et al., 2003; Lukito et al., 2004]. Similarly, an increased lymphocyte count has been associated with an improved survival in patients with metastatic renal cell [Fumagalli et al., 2003], pancreatic cancer [Fogar et al., 2006] and sarcoma [Ray-Coquard et al., 2009]. The prognostic value of a low lymphocyte count has also been studied in patients with cardiac disease and congestive heart failure and has been found to be associated with increased mortality [Acanfora et al., 2001].

### 1.4.7. Platelet Count

Thrombocytosis, in patients with renal disease, has been shown to be associated with presence of coronary artery disease [Sokunbi et al., 1994]. It has also been linked with both tumour stage [Ito et al., 2006] and prognosis in renal cell carcinoma [O'Keefe et al., 2002; Erdemir et al., 2007] with similar associations in colon [Abbasciano et al., 1995] and lung cancer [Teramukai et al., 2009].

## 2.0. SUMMARY AND AIMS

### 2.1. SUMMARY

Local inflammation occurs as a response to injury, infection, autoimmune conditions or malignancy. Through complex pathways involving the innate, humoral and adaptive immune systems, the local immune/inflammatory reaction can result in a systemic immune/inflammatory response. As well as exhibiting clinical manifestations including pyrexia, anorexia and cachexia, the systemic response is also associated with alterations in a number of serum markers of inflammation. These include components of the innate and adaptive immune systems, for example the constituents of a differential white cell count and acute phase reactants such as C-reactive protein, as well as other biochemical parameters including albumin and liver function tests.

Worldwide, approximately 12.4 million new cases of cancer are diagnosed each year with 7.6 million people dying as a result. In the United Kingdom, around one in three people will develop cancer during their lifetime with breast, followed by lung and colorectal malignancies being the most common. Increasing age, male gender and socioeconomic deprivation have been shown to be associated with a reduced survival in the majority of malignancies. Deoxyribonucleic acid (DNA) mutations that result in the interruption of tumour suppression or the activation of pro-oncogenic pathways can occur secondary to a genetic predisposition. However, the majority of genetic mutations are acquired and it is recognised that a local inflammatory microenvironments can lead to DNA damage, neoplastic transformation and cancer development. It has also been shown that cancer progression, and subsequent metastasis, is dependent on complex interactions with the inflammatory tumour microenvironment involving the innate, humoral and adaptive immune systems. The Tumour

Node Metastasis (TNM) staging system utilises evidence of local invasion and distal tumour spread in the risk stratification of patients with cancer. It is however recognised that this system may be open to an element of subjectivity and therefore, there is increasing interest in the study of the host immune/inflammatory response in predicting outcome in patients with malignancy.

Cardiovascular and cerebrovascular atherosclerotic disease is responsible for approximately a third of all deaths in the United Kingdom. Atherosclerotic plaques have a significant inflammatory cell infiltrate and clear relationship between inflammation and vascular disease has been established. Patient risk stratification tools, such as the Framingham Score and CHADS2, are composed of a variety of risk factors including patient age, high density lipoproteins and systolic blood pressure. These scores can be used to individualise therapies in patients with cardiovascular or cerebrovascular disease and help ensure that treatment is received by those who will benefit. Similarly, C-reactive protein as a measure of the systemic immune/inflammatory response, is recommended in the assessment of patients with cardiovascular disease. This therefore raises the possibility that other, widely available serum markers of inflammation may also predict outcome.

A number of commonly sampled serum markers of the systemic immune/inflammatory response have been associated with cancer, cardiovascular, cerebrovascular and all-cause mortality. Serum C-reactive protein levels have been widely studied and shown to be predictive of outcome in a variety of cancers including colorectal, gastroesophageal and pancreatic, with similar associations demonstrated in patients with cardiovascular and cerebrovascular disease. Comparative associations with survival in similar cohorts have been reported when other serum inflammatory markers including

albumin, liver function tests and the constituents of a differential white cell count have been studied.

There has therefore been increasing interest in systemic inflammation-based scores that combine these commonly sampled markers of the systemic immune/inflammatory response and whether they can be used to predict outcome in patients with a range of diseases. A variety of scores have been suggested including the Glasgow Prognostic Score (GPS), the modified Glasgow Prognostic Score, the Neutrophil Lymphocyte Ratio (NLR), the Platelet Lymphocyte Ratio (PLR) and the Prognostic Nutritional Index (PNI). There has however been little work to investigate directly the effect that the presence of cancer has on these markers of systemic inflammation and whether their relationship with survival is a universal phenomenon in all tumour types. It is also unclear as to the optimal constituents of such an inflammation-based prognostic score and whether these would differ for cancer, atherosclerotic disease or all-cause mortality.

**2.2. AIMS**

To investigate the areas detailed above, in a single cohort of incidentally sampled patients, studies were carried out:

1. To explore the relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters.
2. To investigate whether an inflammation-based prognostic score can predict cancer survival independent of tumour site and assess any derangement of associated biological parameters.
3. To compare the previously suggested inflammation-based prognostic scores in patients with cancer with regard to their universal utility and predictive value.

4. To investigate whether an inflammation-based score using variables available in large oncological data sets, specifically a white cell and neutrophil count, can be used to predict cancer survival.
5. To investigate the optimal constituents of an inflammation-based prognostic score for use in patients with cancer.
6. To explore whether a similar inflammation-based score can be used to predict cardiovascular, cerebrovascular and all-cause mortality.

## 3.0. SYSTEMIC INFLAMMATION-BASED PROGNOSTIC SCORES

### 3.1. ABSTRACT

**Introduction:** As disease associated inflammation is increasingly recognised as a key determinant of prognosis in patients with cancer, cardiovascular disease and stroke, there has been significant interest in measurements of the systemic immune/inflammatory response in an attempt to help predict patient outcome.

**Methods:** A systematic review was carried out looking at all published literature between September 1999 and September 2009 in the Pubmed database. The following search term were entered ("glasgow prognostic score" OR "modified glasgow prognostic score" OR "neutrophil lymphocyte ratio" OR "neutrophil to lymphocyte ratio" OR "platelet lymphocyte ratio" OR "platelet to lymphocyte ratio" OR "prognostic index" OR "prognostic nutritional index" AND (survival OR mortality)).

**Results:** 1095 studies were returned in the pubmed search but only 31 investigated the relationship between inflammation-based scores and mortality. The majority of these (n=19) investigated the prognostic value of the Glasgow Prognostic Score (GPS/mGPS).

**Conclusion:** The results indicate that good evidence exists demonstrating an association between inflammation-based scores and mortality in certain cancer types as well as cardiovascular disease. It is however unclear as to whether this is a universal phenomenon in all cancers and whether these scores could be utilised in patients with other atherosclerotic conditions such as cerebrovascular disease.

## 3.2. INTRODUCTION

As disease associated inflammation is increasingly recognised as a key determinant of prognosis in patients with cancer, cardiovascular disease and stroke, there has been significant interest in measurements of the systemic immune/inflammatory response in an attempt to help predict patient outcome. Furthermore, it has been suggested that an optimal biomarker should have a standardised assay, be universally available in clinical practice and financially viable for widespread use [Paoletti et al., 2004]. While single measures of commonly sampled parameters, such as an isolated C-reactive protein, white cell count or albumin, have been shown to have prognostic significance there has been a move towards combining these markers in order to create inflammation-based prognostic scores with improved sensitivity and specificity. Inflammation-based scores that quantify the systemic immune/inflammatory response associated with a disease process have the potential to provide important prognostic information and allow the risk stratification of patients. It is also recognised that the optimal constituents of a score may change depending on the clinical situation. For example, in patients entering large chemotherapeutic trials that routinely record only a differential white cell count, a score consisting of these constituents would be optimal. It is with all this in mind that the main focus of this thesis will be on systemic inflammation-based scores that utilise commonly sampled markers of inflammation including C-reactive protein, liver function tests and the constituents of a differential white cell count.

On review of the current literature, it is evident that there are a number of regularly studied inflammation-based prognostic scores that incorporate multiple, routinely available, markers of the systemic immune/inflammatory response and have been shown to be associated with mortality. The Glasgow Prognostic Score (GPS, Table 2.1), a combination of acute phase proteins namely C-reactive protein and albumin using standard thresholds (C-

reactive protein >10mg/L, albumin <35g/L) has been shown to have prognostic value in certain cancers [Forrest et al., 2003; McMillan et al., 2007]. The GPS was subsequently refined to form the modified Glasgow Prognostic Score (mGPS Table 2.1) [McMillan et al., 2007] when, in patients with primary operable colorectal cancer, hypoalbuminaemia alone was found to have similar prognostic value as a GPS of 0. Several studies have reported the mGPS to have independent prognostic value in patients with a number of different cancers in a variety of clinical scenarios [McMillan, 2009]. Other commonly sampled markers of the systemic immune/inflammatory response have also been combined to form inflammation-based prognostic scores associated with survival in patients with cancer, atherosclerotic disease and all-cause mortality (Table 3.1). These include the Neutrophil Lymphocyte Ratio (NLR), a combination of circulating neutrophil and lymphocyte counts, the Platelet Lymphocyte Ratio (PLR), a combination of circulating platelet and lymphocyte counts, the Prognostic Index (PI), a combination of C-reactive protein and white cell count and finally, Onodera's Prognostic Nutritional Index (PNI), a combination of albumin and lymphocyte count.

The aim of the present Chapter was to examine the relationship between inflammation-based prognostic scores and survival in cancer and non-cancer cohorts.

**Table 3.1. Systemic Inflammation-Based Prognostic Scores**.

| The Glasgow Prognostic Score | Score |
|---|---|
| C-reactive protein ≤10 mg/l and albumin ≥35 g/l | 0 |
| C-reactive protein ≤10 mg/l and albumin <35 g/l | 1 |
| C-reactive protein >10 mg/l and albumin ≥35 g/l | 1 |
| C-reactive protein >10 mg/l and albumin <35 g/l | 2 |
| The modified Glasgow Prognostic Score | |
| C-reactive protein ≤10 mg/l and albumin ≥35 g/l | 0 |
| C-reactive protein ≤10 mg/l and albumin <35 g/l | 0 |
| C-reactive protein >10 mg/l and albumin ≥35 g/l | 1 |
| C-reactive protein >10 mg/l and albumin <35 g/l | 2 |
| Neutrophil Lymphocyte Ratio | |
| Neutrophil count:lymphocyte count <5:1 | 0 |
| Neutrophil count:lymphocyte count ≥5:1 | 1 |
| Platelet Lymphocyte Ratio | |
| Platelet count:lymphocyte count <150:1 | 0 |
| Platelet count:lymphocyte count 150–300:1 | 1 |
| Platelet count:lymphocyte count >300:1 | 2 |
| Prognostic Nutritional Index | |
| Albumin (g/l) + 5 × total lymphocyte count $\times 10^9$/l ≥45 | 0 |
| Albumin (g/l) + 5 × total lymphocyte count $\times 10^9$/l <45 | 1 |

## 3.3. MATERIALS AND METHODS

A systematic review was carried out looking at all published literature between September 1999 and September 2009 in the Pubmed database. The following search term were entered ("glasgow prognostic score" OR "modified glasgow prognostic score" OR "neutrophil lymphocyte ratio" OR "neutrophil to lymphocyte ratio" OR "platelet lymphocyte ratio" OR "platelet to lymphocyte ratio" OR "prognostic index" OR "prognostic nutritional index" AND (survival OR mortality)) and 1095 results were returned.

Abstracts were searched to identify appropriate citations with subsequent paper acquisition for those manuscripts included. Only papers in English, or those that had been translated into English were included. Only original articles were considered with all reviews being excluded. Multiple papers from the same cohort were included if the comparative findings differed. Any scores including variables other than commonly available serum markers of inflammation were excluded. Only those articles with death as a primary or secondary endpoint were considered and only those reporting disease specific or overall survival were included. Overall survival was preferentially reported, otherwise disease free survival noted. If only "survival" was mentioned then this was taken to be overall survival. Articles that grouped other events with survival (i.e. Major Adverse Cardiac Events) were disregarded. Only studies using multivariate statistical model analysis or relative survival to control for confounding factors (including age and gender) were included. As tumour stage is a major predictor of survival in patients with cancer, only papers correcting for this were included. Hazard ratios, probability values and, where available, 95% confidence intervals were included. Categorical Hazard Ratios (HR) were included where available, otherwise single continuous variables were presented. If tertile or quartile based results were presented then, where available, the HR from the first to the last were presented. HRs were shortened

to two decimal places and P-values to 3 decimal places. In patients with malignancy, where stated in the original paper, the stage of disease was reported. Where stage was not absolutely stated but could be accurately defined from the text/tables then stage is marked * to show implied. If stage could not be accurately identified then this was marked as "stage not defined." Patients with resectional/operable tumours were taken to be stage I-III and denoted with a * unless otherwise stated (excluding ovarian). Each paper's main conclusion or details of original findings were noted. If a score was independent to other factors this was noted. If other factors in a multivariate model did not retain statistical significance then a score was stated to be a superior measure.

### 3.4. RESULTS - Table 3.2 Systemic review of inflammation-based prognostic scores

| Reference | Site | N | Score | Threshold | HR (95% CI) | P-value | Stage | Survival | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Breast | | | | | | | | | |
| [Al Murri et al., 2006] | - | 96 | GPS | 0/1/2 | 2.26 (1.45-3.52) | <0.001 | IV | Cancer | GPS independent of palliative chemotherapy and radiotherapy |
| Gynaecological | | | | | | | | | |
| [Sharma et al., 2008] | Ovarian | 154 | GPS | 0/1/2 | Not Stated | <0.05 | III-IV | Overall | Treated with systemic chemotherapy with or with-out surgery<br>GPS superior to performance status |
| [Cho et al., 2009a] | Ovarian | 192 | NLR | >2.60 | 6.05 (1.77-20.71) | 0.004 | I-IV | Overall | Treated with surgery<br>NLR Independent of cell type and grade of tumour |
| Gastroesophageal | | | | | | | | | |
| [Nozoe et al., 2002] | Oesophageal | 258 | PNI | >46 | 1.80 (1.16-2.81) | 0.009 | I-IV | Cancer | Treated with surgery<br>PNI independent to lymphatic and vascular invasion |
| [Crumley et al., 2006b] | Gastro-oesophageal | 258 | GPS | 0/1/2 | 1.51 (1.22-1.86) | <0.001 | I-IV | Cancer | Treated with palliative intent<br>GPS independent of palliative adjuvant therapy |
| [Han-Geurts et al., 2006] | Oesophageal | 400 | PNI | Per single unit increase | - | ns | I-III* | Overall | Treated with resection with or without neoadjuvant therapy<br>PNI not independently significant |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| [Crumley et al., 2008] | Gastro-oesophageal | 65 | GPS | 0/1/2 | 1.65<br>(1.10-2.47) | <0.05 | III-IV | Cancer | Treated with palliative chemotherapy<br>GPS superior to ECOG-Performance Status |
| [Kobayashi et al., 2008] | Oesophageal | 48 | GPS | 1-2/0 | 0.17<br>(0.06-0.52) | 0.002 | I-III | Cancer | Treated with surgery and neoadjuvant chemoradiotherapy<br>GPS independent of lymphatic and venous invasion |
| Renal | | | | | | | | | |
| [Ramsey et al., 2007] | - | 119 | GPS | 0/1/2 | 2.93<br>(1.88-4.55) | <0.001 | IV | Cancer | Treated with immunotherapy<br>GPS independent of MSKCC and MRCCPS scores |
| Ramsey et al., 2008] | - | 23 | GPS | 0/1-2 | 2.23<br>(1.09-4.57) | 0.029 | IV | Cancer | Treated with immunotherapy<br>GPS superior to interleukin 6 |
| Colorectal | | | | | | | | | |
| [Read et al., 2006] | Colorectal | 48 | mGPS | 0/1/2 | 2.27<br>(1.09-4.73) | 0.028 | IV | Overall | Treated with palliative therapy with or without previous therapies<br>mGPS independent of performance status, nutritional assessment tool (PGSGA) and LFTs |
| [McMillan et al., 2007] | Colorectal | 123 | mGPS | 0/1/2 | 1.74<br>(1.20-2.51) | <0.001 | II | Cancer | Treated with resection with or without adjuvant therapy<br>mGPS superior to tumour site and delivery of adjuvant therapy |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| [Leitch et al., 2007] | Colorectal | 149 Primary Operable | mGPS | 0/1/2 | 2.08 (1.32-3.28) | 0.002 | I-III | Overall | Treated with colorectal resection, or palliative procedure or chemotherapy or radiotherapy<br>mGPS superior to NLR, deprivation and independent to constituents of the differential white cell count |
| | | | NLR | >5 | - | ns | | | |
| | | 84 Hepatic Mets | mGPS | 0/1/2 | 1.44 (1.01-2.04) | 0.043 | IV | Cancer | |
| | | | NLR | >5 | - | ns | | | |
| [Ishizuka et al., 2007] | Colorectal | 315 | GPS | 1-2/0 | 0.17 (0.04-0.73) | 0.018 | I-IV | Overall | Treated only with surgery with-out adjuvant therapy<br>GPS superior to tumour markers (CEA, CA19-9, CA72-4) |
| [Halazun et al., 2008] | Colorectal | 440 | NLR | >5 | 2.28 (1.65-3.13) | <0.001 | IV | Overall | Treated with colonic surgery then liver surgery and adjuvant chemotherapy<br>NLR superior to positive margin and tumour number |
| [Leung et al., 2008] | Colorectal | 53 | mGPS | 0/1/2 | 2.12 (1.34-3.35) | 0.001 | IV | Cancer | Treated with chemotherapy or supportive care<br>mGPS independent of lipid-soluble antioxidant vitamins |
| [Crozier et al., 2009] | Colorectal | 188 | mGPS | 0/1/2 | 2.22 (1.06-4.74) | 0.039 | II | Cancer | Treated with surgery with or without neoadjuvant chemotherapy.<br>mGPS superior to presentation (emergency/elective), deprivation and adjuvant therapy |
| [Neal et al., 2009] | Colorectal | 174 | NLR | >5 | - | ns | IV | Overall | Treated with resection of liver metastasis with or without chemotherapy<br>NLR not independently significant |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| [Kishi et al., 2009] | Colorectal | 290 | NLR | >5 | 2.00<br>(1.30-3.30) | 0.005 | IV | Overall | Colorectal with liver metastasis with chemotherapy with or without resection<br>NLR independent to number and size of metastasis, history of previous treatment and positive margins |
| [Roxburgh et al., 2009a] | Colorectal | 244 | mGPS | 0/1/2 | 2.34<br>(1.65-3.31) | <0.001 | I-III | Cancer | Treated with surgery without or without adjuvant therapy<br>mGPS independent of high risk pathological Petersen's Index |
| [Roxburgh et al., 2009b] | Colorectal | 287 | mGPS | 0/1/2 | 2.56<br>(1.66-4.25) | <0.001 | I-III | Cancer | Treated with surgery without or without adjuvant therapy<br>mGPS superior to nodes sampled, adjuvant therapy and Jass criteria and independent to Klintrup criteria |
| [Ishizuka et al., 2009] | Colorectal | 112 | mGPS | 0/1/2 | 6.07<br>(1.63-22.68) | 0.007 | II-IV | Cancer | Treated with surgery then palliative chemotherapy<br>mGPS superior to liver function tests (AST, ALT, GGT) and tumour markers (CEA, CA19-9, CA 72-4) |
| [Roxburgh et al., 2009c] | colon | 245 | mGPS | 0/1/2 | 1.56<br>(1.03-2.38) | 0.038 | I-III | Cancer | Treated with surgery with or without adjuvant therapy<br>mGPS superior to adjuvant therapy and independent to Klintrup criteria |
| | rectum | 140 | | | 1.76<br>(1.00-3.10) | 0.033 | | | |
| Hepatocellular | | | | | | | | | |
| [Glen et al., 2006] | Pancreatic | 187 | GPS | 0/1/2 | 1.72<br>(1.40-2.11) | <0.001 | III-IV | Overall | Treated with or without palliative bypass<br>GPS superior to bilirubin |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| [Clark et al., 2007] | Pancreatic | 44 | NLR | >5 | - | ns | NS | Overall | Treated with surgery<br>NLR not independently significant |
| [Gomez et al., 2008a] | HCC | 96 | NLR | >5 | - | ns | NS | Overall | Treated with surgery<br>NLR not independently significant |
| [Smith et al., 2009] | Pancreatic | 110 | NLR | Per single unit increase | - | ns | NS | Overall | Treated with surgery with or without adjuvant therapy<br>PLR superior to NLR, positive margin, differentiation and independent of lymph node ratio |
| | | | PLR | Per single unit increase | 1.00<br>(1.00-1.01) | <0.001 | | | |
| [Halazun et al., 2009] | HCC | 150 | NLR | >5 | 6.10<br>(2.29-16.29) | <0.001 | NS | Overall | Treated with liver transplant with or without adjuvant therapy<br>NLR superior to, tumour grade, vascular invasion and independent to AFP |
| Lung | | | | | | | | | |
| [Forrest et al., 2005] | NSCLC | 101 | GPS | 0/1/2 | 2.32<br>(1.52-3.54) | <0.001 | III-IV | Overall | Treated with or without palliative chemotherapy or radiotherapy<br>GPS independent of treatment |
| [Sarraf et al., 2009] | NSCLC | 177 | NLR | Per single unit increase | 1.10<br>(1.03-1.17) | 0.005 | I-IV | Overall | Treated with surgery<br>NLR independent to total white cell count |
| [Teramukai et al., 2009] | NSCLC | 388 | NLR | >4.74 | 1.56<br>(1.09-2.24) | 0.011 | IIIb-IV | Overall | Treated with palliative chemotherapy<br>NLR independent to smoking history and ECOG performance status |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cardiovascular | | | | | | | | |
| [Duffy et al., 2006] | CVD | 1046 | NLR | Tertile 1 vs 3 | 1.60 (1.00-2.55) | 0.048 | Overall | Patients undergoing PCA |
| [Gibson et al., 2007] | CVD | 1938 | NLR | Per single unit increase | 1.09 (1.03-1.16) | 0.004 | Overall | Patients undergoing elective CABG |
| [Nunez et al., 2008] | CVD | 470 | NLR | Quintile 1 vs 5 | 4.2 (1.72-10.21) | 0.002 | Overall | Patients with STEMI |
| [Papa et al., 2008] | CVD | 422 | NLR | >2.42 | 8.13 (1.42-46.57) | 0.0186 | Cardiac | Consecutive patients with stable coronary artery disease |
| [Tamhane et al., 2008] | CVD | 2833 | NLR | Tertile 1 vs 3 | 3.88 (3.19-8.06) | <0.001 | Overall | Patients admitted with ACS |
| [Poludasu et al., 2009] | CVD | 372 | NLR | >3.5 | 2.11 (1.11-4.02) | 0.023 | Overall | Patients treated with PCI |

## 3.5. DISCUSSION

The results of the current chapter show that the presence of a systemic immune/inflammatory response, as evidenced by a number of inflammation-based scores, can predict mortality in both cancer and cardiovascular disease. A number of different scores, that all incorporate multiple, routinely available, markers of the systemic immune/inflammatory response have been suggested for use. These include the Glasgow Prognostic Score (GPS and mGPS), Neutrophil Lymphocyte ratio (NLR), Platelet Lymphocyte Ratio (PLR) and Onodera's Prognostic Nutritional Index (PNI).

The majority of studies (n=31) to date (September 2009) have investigated the relationship between inflammation-based scores and cancer. Over half of these (n=18) include patients with malignancies of the alimentary tract including colorectal and gastroesophageal cancer. However, there is also good evidence that inflammation-based scores have a predictive role in pancreatic, hepatobiliary, renal and ovarian cancers. Of these scores the Glasgow Prognostic Score (GPS/mGPS) is the most widely validated with 19 studies all showing a statistically significant association with mortality. The NLR has also been extensively investigated in a variety of tumour types with varying associations with mortality demonstrated. The PLR and PNI have only been included in one study each but, never the less, have also been reported to be to be associated with mortality. Indeed, it is likely that, while some scores may be more sensitive than others, they are essentially measuring the same process. There have been six studies looking at cardiovascular disease, all of which have demonstrated a positive correlation between the NLR and mortality.

This chapter has detailed evidence demonstrating that inflammation-based scores have predictive value in certain cancer types as well as cardiovascular disease. It is however unclear whether this is a universal phenomenon in all cancers and if these scores could be

utilised in patients with other atherosclerotic conditions such as cerebrovascular disease. The optimal constituents of an inflammation-based score for use in cancer and non-cancer cohorts is yet to be determined.

# 4.0. THE RELATIONSHIP BETWEEN THE PRESENCE AND SITE OF CANCER, AN INFLAMMATION-BASED PROGNOSTIC SCORE AND BIOCHEMICAL PARAMETERS

## 4.1. ABSTRACT

**Introduction:** Biochemical parameters, such as C-reactive protein and liver function tests, have been associated with mortality. The aim of the present chapter was to examine the relationship between the presence and site of cancer, an inflammation-based prognostic score (mGPS) and biochemical parameters.

**Methods:** Patients (n=223,303) who had a single incidental sample taken for C-reactive protein, albumin, calcium and serum liver function tests where available, between 2000 and 2008 were studied. Those with a pathological diagnosis of cancer (n=22,715) were also identified.

**Results:** The strongest associations (Spearman's correlation $\geq$ 0.3) in both the non-cancer and cancer groups were found between albumin, C-reactive protein and Alk phos, AST and ALT, AST and GGT and ALT and GGT (all $p<0.001$). On multivariate analysis, age, deprivation, C-reactive protein, albumin, adjusted calcium, Alk phos and GGT were associated with the presence of cancer (all $p<0.01$). When cancer diagnoses were ranked from those with the lowest proportion of mGPS 1 or 2 to those with the highest, the percentage of cases with a mGPS of 1 or 2 ranged from 21% in breast cancer to 68% in pulmonary cancer.

**Conclusion:** The results indicate that the systemic inflammatory response is increased by the presence of cancer. There is a striking parallel between the proportions of cases with a mGPS of 1 or 2 and reported survival rates in these tumours.

## 4.2. INTRODUCTION

In the West of Scotland there has been a longstanding interest in the role of the systemic immune/inflammatory response in determining outcome in cancer [McMillan, 2008; McMillan, 2009; Roxburgh and McMillan, 2010]. Although, as detailed in Chapter 1, it is recognised that the development of cancer has a genetic basis, there is increasing evidence that host immune/inflammatory responses play a pivotal role in the development and progression of cancer [Balkwill and Mantovani, 2001; Coussens and Werb, 2002; Mantovani et al., 2008; Colotta et al., 2009; McDonald et al., 2009]. This is consistent with the hypothesis that chronic exposure to inflammatory processes, either through infection, social conditions or lifestyle, enhances the ageing process [Finch and Crimmins, 2004].

As has also been detailed in Chapter 1, the presence of a systemic immune/inflammatory response as evidenced by an elevated C-reactive protein concentration sampled incidentally in a large hospital based cohort, was associated with a shorter duration of cancer and non-cancer survival [Marsik et al., 2008]. Goldwasser and Feldman, amongst others, have reported a similar relationship in a systematic review of the prognostic value of albumin [Goldwasser and Feldman, 1997]. These acute phase proteins, produced exclusively in the liver, have been shown to be a major factor in the progressive nutritional and functional decline of patients with cancer [McMillan, 2008]. Also, C-reactive protein and albumin concentrations have been combined to form the modified Glasgow Prognostic Score (mGPS) and have been reported to be independently associated with reduced survival in patients with a variety of cancers as detailed in Table 3.2 [McMillan, 2009; Roxburgh and McMillan, 2010].

It is also of interest that liver function tests such as bilirubin [Temme et al., 2001], alkaline phosphatase [Tonelli et al., 2009] and γ-glutamyl transferase [Kazemi-Shirazi et al.,

2007] as well as serum calcium [Leifsson and Ahren, 1996], have also been reported to predict cancer and non-cancer outcome (Chapter 1.). There is also some evidence that liver function tests are altered as part of the systemic immune/inflammatory response in patients with lung and gastrointestinal cancer [Brown et al., 2007; Roxburgh et al., 2009a].

The aim of the present Chapter was to examine the effect of cancer on markers of systemic inflammation induced by the liver (mGPS) and on these variables (bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, γ-glutamyl transferase and adjusted calcium).

## 4.3. MATERIALS AND METHODS

This cohort includes patients who have had a single sample taken for C-reactive protein, albumin and calcium between the 1st of January 2000 and the 1st of November 2008 in the North of Glasgow. The samples were taken incidentally and if more than one set of measurements were available for a given patient, only the initial set was used. Where available, serum liver function tests, including bilirubin and alkaline phosphatase (Alk phos) were recorded. Patients were excluded if they did not have a complete set of identifying details (name, gender, date of birth and hospital number). The limit of detection of C-reactive protein was a concentration of less than 5mg/L. The mGPS was constructed, using C-reactive protein and albumin, as follows; patients with both an elevated C-reactive protein (>10 mg/L) and low albumin (<35 g/L) were allocated a score of 2; patients in whom only C-reactive protein was elevated (>10 mg/L) were allocated a score of 1 and those with a normal C-reactive protein were allocated a score of 0 [McMillan et al., 2007]. The rationale and basis of the mGPS has been previously described [McMillan, 2008]. Serum C-reactive protein, albumin and liver function tests, including bilirubin, Alk phos, AST, ALT and GGT, as well as calcium adjusted for albumin [Ashby et al., 1986], were classified in accordance

with the NHS Greater Glasgow and Clyde biochemistry laboratory reference ranges. These analytes were measured using identical standard operating procedures on identical automated platforms using reagents from the same manufacturer (Abbot Diagnostics). Analysis was carried out in three linked laboratories in the North of Glasgow which take part in external quality assurance schemes for routine biochemical analysis. All samples were refrigerated, as stable for a number of days in these conditions, and analysed within 6 hours.

All patient records fulfilling these criteria were then cross referenced with the local pathology database to identify those in whom a tissue diagnosis of cancer had been made either before or after their initial blood sample (Appendix 1). Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT) codes, which share certain codes with the International Classification of Diseases, contained in the pathology database were used to identify the site and type of tumour in those with a tissue diagnosis of cancer. Patients were then grouped into those with a pathological diagnosis of cancer and those without. The cancer group were then grouped into those patients with a clear primary cancer diagnosis, those with multiple tumours or those with no clear indication of the primary tumour site. Patients with incomplete identifying details (name, date of birth and hospital number), under 16 years of age, or those with multiple malignancies, metastatic disease or cancer of an unknown origin were excluded. For the purpose of analysis, cancers were grouped according to tumour site; bladder, breast, colorectal, dermatological, endocrinological, gastroesophageal, gynaecological, haematological, head and neck, hepatocellular, musculoskeletal and soft tissue, pancreaticobiliary, pulmonary, prostatic, renal and testicular. The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

The Scottish Index of Multiple Deprivation (SIMD) 2006, as detailed in Chapter 1. and recommended by the ISD on behalf of NHS Scotland and the Scottish Government

Department of Health, was used to measure deprivation with the least deprived being scored as 1 to the most deprived scoring 5 [Bishop J et al., 2004].

SNOMED CT codes were used to identify the site and type of tumour in those with a tissue diagnosis of cancer. Each pathology sample had two SNOMED CT codes, one for type of tumour (morphology) and one for site of tumour (topography). Examples of SNOMED CT cancer morphology codes, of which there are over 400, include metastatic carcinoma (M80106), large cell carcinoma (M80123), small cell carcinoma (M80413-M80416), squamous cell carcinoma (M80703-M80763), adenocarcinoma (M81402-M81406), cholangiocarcinoma (M81603), renal cell carcinoma (M83123-M83126), intraductal carcinoma (M85002-M85003), malignant melanoma (M87202-M87433), mesothelioma (M90501-M90503), lymphoma (M95903-M97003) and leukaemia (M98003-M99403). Examples of SNOMED CT topography codes include bladder (T74000-T74400), breast (T04000-T04400), colorectal (colon T67000- T67995, rectum T68000-T68200, anus T69000-T69200) dermatological (T02100-02870), endocrine (adrenal T93000-T93100, thyroid T96000-T97800), gastroesophageal (oesophagus T62000-T62910, stomach T63000-T63700), gynaecological (uterus with or without cervix T82000- T82900, uterus and ovaries T82920-T82922, cervix T83000-T83300, endometrium T84000-T85000, ovary T86920-T87800), haematological (bone marrow: T06000-T06600, lymph node T08000-T09600), head and neck (pharynx T60000-T61300, upper respiratory tract T21000-T24920, mouth and salivary glands T51000-T55550), liver (T56000-T56020), musculoskeletal and soft tissue (skeletal bone T10000-T12720, skeletal muscle T13000) pancreaticobiliary (gallbladder T57000, bile duct T57600-T58500, pancreas and ampulla T58700-T59300) pulmonary(T26000-T29900), prostatic (T77000-T77350), renal (T71000-T72000) testicular (T78000-T78020). The combination of SNOMED CT morphology and topography codes were used to identify the tumour type and site.

With regards to statistical analysis, the relationships between patient demographics, the presence of cancer, biochemical parameters, the mGPS, tumour site and other biochemical parameters were analysed using the Pearson's chi-square test (linear by linear association). Spearman's rank correlation was used to measure the strength of the relationship between age and biochemical parameters and the interrelationships between biochemical parameters. The relationship between the presence of cancer and patient demographics and biochemical parameters was examined using Cox proportional hazards model multivariate regression analysis; only patients who had a diagnosis of cancer made within two years following their blood test were included in this analysis. This was based on the premise that this group of patients were likely to have had an ongoing malignant process. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

## 4.4. RESULTS

In total 223,303 patients were studied. The majority, 144,900 (65%), were under 65 years of age. There were 120,115 (54%) females and 103,188 (46%) males. Of those patients with an identifiable postcode (86%), the majority were from the Greater Glasgow area (88%). In this cohort, when measured by the SIMD 2006, 14% of cases were from affluent areas (least deprived quintile of the Scottish population) and 45% from deprived areas (most deprived quintile of the Scottish population).

The demographics of non-cancer and cancer patients are shown in Table 4.1. Patients with cancer, when compared to those without a diagnosis of cancer were older and more likely to be female ($p<0.001$). The cancer group had a higher proportion of cases from less deprived areas than those in the non-cancer group ($p<0.001$).

Of 22,715 with a diagnoses of cancer 19,476 (86%) had a single primary tumour while 1299 (6%) had multiple malignancies. In 1940 (8%) cases SNOMED CT codes gave

no definitive indication of the primary site of malignancy. Examples of this include: 1497 cases were SNOMED CT codes stated lung carcinoma, lung adenocarcinoma or lung metastatic carcinoma; 269 cases were SNOMED CT codes stated liver carcinoma, liver adenocarcinoma or liver metastatic carcinoma; 209 cases had SNOMED CT codes stating lymph node carcinoma, lymph node adenocarcinoma or lymph node metastatic carcinoma and 160 cases had SNOMED CT codes stating metastatic carcinoma at other sites.

When the cancer group was categorised (n=22,715) into different tumour sites the following main groups were observed; bladder (n=939, 4%), breast (n=3849, 17%), colorectal (n=1899, 8%), dermatological (n=4907, 22%), endocrinological (n=303, 1%), gastroesophageal (n=1018, 5%), gynaecological (n=1136, 5%), haematological (n=1165, 5%), head and neck (n=610, 3%), hepatocellular (n=55, 0%), musculoskeletal and soft tissue (n=164, 1%), pancreaticobiliary (n=456, 2%), prostate (n=957, 4%), pulmonary (n=1393, 6%), renal (n=527, 2%) and testicular (n=97, 1%).

The relationship between markers of the systemic immune/inflammatory response, biochemical parameters and the presence of cancer is shown in Table 4.2. There were higher circulating concentrations of C-reactive protein and lower albumin levels (and thus a higher proportion of mGPS 1 or 2), in those patients with cancer (all $p<0.001$). Patients in the cancer group were also found to have lower AST and ALT levels but higher adjusted calcium, Alk phos and GGT levels compared with the non-cancer cohort (all $p<0.001$).

The interrelationships between markers of the systemic immune/inflammatory response and biochemical parameters in patients without and with cancer are shown in Tables 4.3 and 4.4. In the non-cancer cohort age was significantly associated with all biochemical parameters (all $p<0.001$) (Table 4.3). Similarly, all biochemical parameters were significantly associated with each other (all $p<0.001$). In the non-cancer cohort the strongest

associations (Spearman's correlation > 0.3) were between C-reactive protein and albumin, C-reactive protein and Alk phos, AST and ALT, AST and GGT and ALT and GGT.

There were similar interrelationships in the cancer cohort (Table 4.4) with the strongest associations (Spearman's correlation > 0.3) existing between C-reactive protein and albumin, C-reactive protein and Alk phos, bilirubin and AST, Alk phos and GGT, AST and ALT, AST and GGT and ALT and GGT.

The temporal relationships between the date of blood samples and cancer diagnoses are shown in Table 4.5. In order to give a clearer indication of the alterations that occur in biochemical parameters around the diagnosis of cancer only patients with a diagnosis within two years of their blood sample were included in the analysis, pre-diagnosis (n=8083) and post-diagnosis (n=5971). Compared with those patients who had pre-diagnosis levels, post-diagnosis patients were more likely to be female and affluent (all $p<0.001$). Patients following a diagnosis of cancer had lower albumin levels and thus higher mGPS ($p<0.001$). Also, post diagnosis patients were more likely to have lower adjusted calcium, bilirubin, Alk Phos, AST, ALT and GGT levels (all $p<0.05$).

The relationship between patient demographics, biochemical parameters and the absence (n= 200,588) or presence (n= 8083) of cancer within two years pre-diagnosis group is shown in Table 4.6. On univariate analysis, those over 65 years of age and living in least deprived areas were more likely to have cancer (all $p <0.001$). Patients with an elevated C-reactive protein, adjusted calcium, Alk phos and GGT levels or low albumin levels were more likely to have cancer (all $p<0.001$). On multivariate analysis, these associations with the presence of cancer persisted in age, deprivation, C-reactive protein, albumin, adjusted calcium, Alk phos and GGT (all $p<0.01$).

The relationships between the mGPS and tumour site in the two year pre-diagnosis group is shown in cancers with more than 50 cases in Table 4.7. The cancers are ranked from those with the highest proportion of mGPS 0 to those with the lowest. The percentage of cases with a mGPS of 1 or 2 ranges from 21% in breast cancer, to 46% in prostate cancer and to 68% in pulmonary cancer. Compared with breast cancer the mGPS was significantly higher in dermatological, bladder, endocrinological, gynaecological, prostate, musculoskeletal, gastroesophageal, haematological, renal, colorectal, head and neck, pancreaticobiliary and pulmonary cancers (all $p<0.001$).

## 4.5. DISCUSSION

The results of the current Chapter show that the presence of a systemic immune/inflammatory response, as evidenced by an elevated C-reactive protein concentration (>10mg/l), was present in 40% and hypoalbuminaemia (<35g/l) was present in 14% of 223 303 patients who were incidentally sampled. Adjusted calcium was elevated in 2.2% (1.8% unadjusted), Alk phos was elevated in 12%, ALT was elevated in 11% and GGT was elevated in 26% of patients studied.

These results are consistent with previous studies including an Austrian cohort of approximately 280,000 patients, in whom 35% had an elevated C-reactive protein concentration [Marsik et al., 2008] and 13% had hypoalbuminaemia [Grimm et al., 2009]. They also reported that 33% had an elevated GGT concentration [Kazemi-Shirazi et al., 2007]. In a Swedish population based cohort of 33,346 patients, 1% were found to have an elevated unadjusted serum calcium [Leifsson and Ahren, 1996]. In a North American cohort of 18,835 patients approximately 9% had an elevated Alk phos [Tonelli et al., 2009]. Another population based cohort from the United States of 14,950 patients reported an

elevated ALT level in 14% of patients [Ruhl and Everhart, 2009]. Therefore, the results of the present Chapter are similar to those previously reported in other large cohort studies.

In the present cohort there were more females in the cohort as a whole, more females in the cancer group and more females had measurements taken post cancer diagnosis. However, gender was not significantly associated with the presence of cancer. The present Chapter shows that when compared with non-cancer, the presence of cancer was associated with a significantly higher proportion of cases with an elevated C-reactive protein (>10mg/L, 47% vs 39%) and lower albumin (<35g/L, 19% vs 14%) concentrations, higher adjusted calcium (>2.60mmol/L, 4% vs 2%), Alk phos (>280U/L, 16% vs 12%) and GGT (>40U/L in females, >70U/L in males, 29% vs 25%), and lower ALT levels (>50U/L, 10% vs 12%). Furthermore, when samples taken following a diagnosis of cancer were compared with those taken prior to a diagnosis of cancer the proportion of cases with albumin (>35g/L, 74% vs 81%) adjusted calcium (>2.60mmol/L, 3% vs 5%), Alk phos (>280U/L, 15% vs 18%), ALT (>50U/L, 10% vs 11%). and GGT (>40U/L, in females, >70U/L in males 29% vs 31%) levels were all lower. When these biochemical parameters together with bilirubin, and ALT were regressed against the presence of cancer, C-reactive protein, albumin, adjusted calcium, Alk phos and GGT were all shown to be independently associated with the presence of cancer. These results would suggest that the presence of cancer influences a number of biochemical parameters that have been previously associated with all-cause mortality [Leifsson and Ahren, 1996; Kazemi-Shirazi et al., 2007; Marsik et al., 2008; Grimm et al., 2009; Tonelli et al., 2009].

The present Chapter also showed that all these biochemical parameters were significantly associated. In particular, C-reactive protein was associated with albumin and Alk phos and GGT associated with AST and ALT in both cancer and non-cancer cohorts. Recently the combination of C-reactive protein and albumin, termed the mGPS, was shown

to be associated in a similar manner in patients with lung cancer [Brown et al., 2007] and predict cancer specific survival in a number of operable [Roxburgh and McMillan, 2010] and inoperable cancers [McMillan, 2009]. These results raise the question of whether the above reported association of these biochemical parameters and all-cause mortality are indeed independent of each of other. Further studies using this cohort will aim to address this question.

In the present Chapter the proportions of mGPS 1 or 2 were greater following a diagnosis of cancer. This appears to be secondary to a reduction in albumin which may be secondary to a number of factors including operative management, adjuvant oncological therapies or tumour progression, a pattern recognised in previous studies within specific tumour types [McMillan et al., 2003; Jamieson et al., 2005]. Interestingly in patients who had blood tests taken following a diagnosis of cancer, adjusted calcium, bilirubin and Alk phos, AST, ALT and GGT levels were all more likely to be within normal limits. The reasons for this are unclear but it is possible that removal or treatment of the underlying malignant process in a proportion of these patients may be responsible.

In the present Chapter it was also of interest to note that, prior to diagnosis, there were significant variations in the proportions of cases with a mGPS of 1 or 2. Indeed, the proportion of patients with an elevated mGPS varied from 21% in breast cancer, to 46% in prostate cancer and to 68% in pulmonary cancer. There is a striking parallel between the proportions of cases with a mGPS of 1 or 2 and reported survival rates in these tumours as detailed in Chapter 1[Cancer Research UK, 2007]. For example, the five year survival rate for breast cancer is approximately 84% and the proportion of patients in the present Chapter with a mGPS of 0 was 79%. In contrast the 5 year survival for lung cancer is 8% and the proportion of patients in the present Chapter with a mGPS of 0 was 32%. These results may suggest that, in addition to the mGPS having prognostic value within tumour types

[McMillan, 2009] it may also have prognostic value across tumour types. Further work is required to confirm this hypothesis.

The present cohort has a number of limitations. The patients were selected on the basis that measurements of C-reactive protein, albumin and calcium had been performed and were therefore not necessarily representative of all non-cancer and cancer patients treated in the North Glasgow area and therefore gives no meaningful information on cancer prevalence. Similarly, as this cohort was not a true representation of the North of Glasgow population, a direct comparison between SIMD measured deprivation and previously reported cancer incidence (figure 1.7) was not possible. Furthermore, sampling was incidental and not performed at a standard time during the course of the disease in the cancer group. It is also recognised that patients in both groups may have concurrent morbidity causing a rise in their C-reactive protein and derangement of their albumin and other biochemical parameters. As inclusion in the cancer cohort was dependent on a pathological diagnosis of cancer it is acknowledged that a small number in the non-cancer group may have had a clinical diagnosis of malignancy. In order to provide more detailed follow up with regards to survival it is important to link the present data with patient outcomes.

In summary, the results of the present Chapter indicate that the systemic immune/inflammatory response is common in a large patient cohort, increased by the presence of cancer and associated with the perturbation of a number of biochemical parameters previously reported to be associated with mortality. Taken together with the myriad effects of the systemic immune/inflammatory response on host metabolism [Gabay and Kushner, 1999] these results have a number of clinical implications particularly for clinical epidemiological studies. Future studies should incorporate a measure of the systemic immune/inflammatory response, such as C-reactive protein or the mGPS, in the study design,

analysis and interpretation. This is required to account for the likely confounding effect of this response on the other measured variables and their relationship with outcomes.

**Table 4.1. The relationship between patient demographics and the presence of cancer**

| n=223,303 | | Non-Cancer n (%) 200,588 | Cancer n (%) 22,715 | p value |
|---|---|---|---|---|
| Age | <65 years | 135,531 (67) | 9369 (41) | |
| | 65-74 years | 31,593 (16) | 6412 (28) | |
| | >75 years | 33,464 (17) | 6934 (31) | <0.001 |
| Sex | Male | 93,313 (46) | 9875 (43) | |
| | Female | 107,275 (54) | 12,840 (57) | <0.001 |
| SIMD 2006 | 1 (least deprived) | 22,902 (14) | 3233 (15) | |
| | 2 | 18,693 (11) | 2578 (12) | |
| | 3 | 21,148 (12) | 2771 (13) | |
| | 4 | 30,850 (18) | 3872 (18) | |
| | 5 (most deprived) | 77,448 (45) | 8844 (42) | <0.001 |

**Table 4.2. The relationship between markers of the systemic immune/inflammatory response, biochemical parameters and cancer**

| n=223 303 | | Non-Cancer n (%) 200,588 | Cancer n (%) 22,715 | p value |
|---|---|---|---|---|
| C-reactive protein | ≤10mg/l | 122,317 (61) | 12,050 (53) | |
| | >10mg/l | 78 ,271 (39) | 10,665 (47) | <0.001 |
| Albumin | <35g/l | 27,515 (14) | 4275 (19) | |
| | ≥35g/l | 173,073 (86) | 18,440 (81) | <0.001 |
| mGPS | 0 | 122,317 (61) | 12,050 (53) | |
| | 1 | 56,357 (28) | 7033 (31) | |
| | 2 | 21,914 (11) | 3632 (16) | <0.001 |
| Adjusted calcium | <2.10mmol/l | 4963 (3) | 577 (2) | |
| | 2.10-2.60mmol/l | 191,429 (95) | 21,323 (94) | |
| | >2.60mmol/l | 4196 (2) | 815 (4) | <0.001 |
| Bilirubin | <20μmol/l | 170,447 (88) | 19,322 (88) | |
| | ≥20μmol/l | 24,258 (12) | 2593 (12) | 0.008 |
| Alkaline phosphatase | <80U/l | 28,168 (14) | 2463 (11) | |
| | 80-280U/l | 148,245 (74) | 16,626 (73) | |
| | >280U/l | 23,954 (12) | 3603 (16) | <0.001 |
| Aspartate | <40U/l | 162,269 (84) | 18,676 (86) | |
| transaminase | ≥40U/l | 30,531 (16) | 3129 (14) | <0.001 |
| Alanine transaminase | <50U/l | 144,468 (88) | 15,872 (90) | |
| | ≥50U/l | 19,043 (12) | 1740 (10) | <0.001 |
| γ-glutamyl transferase | M <70 U/l, F <40U/l | 145,658 (75) | 15,689 (71) | |
| | M ≥70U/l, F ≥40U/l | 49,393 (25) | 6325 (29) | <0.001 |

**Table 4.3. The interrelationships between markers of the immune/inflammatory response and biochemical parameters in patients without cancer**

| n=200,588 | C-reactive protein | Albumin | Adjusted Calcium | Bilirubin | Alkaline phosphatase | Aspartate transaminase | Alanine transaminase | γ-glutamyl transferase |
|---|---|---|---|---|---|---|---|---|
| Age | 0.199*** | -0.286*** | 0.052*** | 0.099*** | 0.177*** | 0.078*** | -0.047*** | 0.148*** |
| C-reactive protein | | -0.362*** | -0.108*** | 0.167*** | 0.320*** | 0.103*** | 0.040*** | 0.193*** |
| Albumin | | | -0.060*** | 0.040*** | 0.022*** | 0.009*** | 0.072*** | -0.116*** |
| Adjusted calcium | | | | -0.077*** | -0.147*** | -0.081*** | -0.028*** | 0.077*** |
| Bilirubin | | | | | 0.143*** | 0.297*** | 0.216*** | 0.169*** |
| Alkaline phosphatase | | | | | | 0.225*** | 0.152*** | 0.243*** |
| Aspartate transaminase | | | | | | | 0.736*** | 0.437*** |
| Alanine transaminase | | | | | | | | 0.550*** |

***p<0.001

**Table 4.4. The interrelationships between markers of the immune/inflammatory response and biochemical parameters in patients with cancer**

| n=22,715 | C-reactive protein | Albumin | Adjusted Calcium | Bilirubin | Alkaline phosphatase | Aspartate transaminase | Alanine transaminase | γ-glutamyl transferase |
|---|---|---|---|---|---|---|---|---|
| Age | 0.103*** | -0.203*** | 0.024*** | 0.127*** | 0.079*** | 0.020** | -0.162*** | -0.062*** |
| C-reactive protein | | -0.439*** | -0.078*** | 0.166*** | 0.308*** | 0.104*** | 0.034*** | 0.239*** |
| Albumin | | | -0.086*** | 0.004 | 0.028*** | 0.007 | 0.073*** | -0.123*** |
| Adjusted calcium | | | | -0.095*** | -0.087*** | -0.053*** | -0.013 | 0.106*** |
| Bilirubin | | | | | 0.166*** | 0.307*** | 0.225*** | 0.177*** |
| Alkaline phosphatase | | | | | | 0.253*** | 0.213*** | 0.346*** |
| Aspartate transaminase | | | | | | | 0.720*** | 0.403*** |
| Alanine transaminase | | | | | | | | 0.505*** |

***p<0.001

**Table 4.5. The relationship between time of diagnosis and biochemical parameters in patients with cancer**

| n=14,054 | | Pre–diagnosis n (%) | Post-diagnosis n (%) | p value |
|---|---|---|---|---|
| | | 8083 | 5971 | |
| Age | <65 years | 3516 (43) | 2690 (45) | |
| | 65-74 years | 2413 (30) | 1626 (27) | |
| | >75 years | 2154 (27) | 1655 (28) | 0.732 |
| Sex | Male | 3806 (47) | 2482 (42) | |
| | Female | 4277 (53) | 3489 (58) | <0.001 |
| SIMD 2006 | 1 (least deprived) | 1140 (15) | 951 (17) | |
| | 2 | 958 (12) | 724 (13) | |
| | 3 | 1080 (14) | 802 (15) | |
| | 4 | 1428 (19) | 1003 (18) | |
| | 5 (most deprived) | 3042 (40) | 2011 (37) | <0.001 |
| C-reactive protein | <10mg/l | 4082 (51) | 2963 (50) | |
| | >10mg/l | 4001 (49) | 3008 (50) | 0.304 |
| Albumin | <35g/l | 1566 (19) | 1545 (26) | |
| | >35g/l | 6517 (81) | 4426 (74) | <0.001 |
| mGPS | 0 | 4082 (50) | 2963 (50) | |
| | 1 | 2666 (33) | 1643 (27) | |
| | 2 | 1335 (17) | 1365 (23) | <0.001 |
| Adjusted Calcium | <2.10mmol/l | 183 (2) | 151 (3) | |
| | 2.10-2.60 | 7501 (93) | 5614 (94) | |
| | >2.60mmol/l | 399 (5) | 206 (3) | <0.001 |
| Bilirubin | <20μmol/l | 6844 (87) | 5163 (90) | |
| | ≥20μmol/l | 994 (13) | 587 (10) | <0.001 |
| Alkaline phosphatase | <80U/l | 788 (10) | 743 (12) | |
| | 80-280U/l | 5805 (72) | 4324 (73) | |
| | >280U/l | 1482 (18) | 898 (15) | 0.003 |
| Aspartate transaminase | <40U/l | 6614 (85) | 4941 (86) | |
| | ≥40U/l | 1175 (15) | 788 (14) | 0.030 |
| Alanine transaminase | <50U/l | 5729 (89) | 4215 (90) | |
| | ≥50U/l | 734 (11) | 450 (10) | 0.004 |
| γ-glutamyl transferase | M<70 U/l, F<40U/l | 5440 (69) | 4100 (71) | |
| | M≥70U/l, F≥40U/l | 2432 (31) | 1667 (29) | 0.012 |

**Table 4.6. The relationship between patient demographics, biochemical parameters and the presence of cancer**

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| n=208,671 | | Odds Ratio | 95% CI | p-value | Odds Ratio | 95% CI | p-value |
| Age | <65/ | 1 | | <0.001 | 1 | | <0.001 |
| | 65-74 | 2.94 | 2.79-3.12 | <0.001 | 2.60 | 2.46-2.75 | <0.001 |
| | >75 | 2.48 | 2.35-2.62 | <0.001 | 2.17 | 2.05-2.30 | <0.001 |
| Sex | Male | 1 | | 0.317 | | | |
| | Female | 0.98 | 0.94-1.02 | 0.317 | | | |
| SIMD | 5 (most deprived) | 1 | | <0.001 | 1 | | <0.001 |
| | 4 | 1.18 | 1.11-1.26 | <0.001 | 1.16 | 1.09-1.24 | <0.001 |
| | 3 | 1.30 | 1.21-1.40 | <0.001 | 1.32 | 1.22-1.42 | <0.001 |
| | 2 | 1.31 | 1.21-1.41 | <0.001 | 1.36 | 1.26-1.46 | <0.001 |
| | 1 (least deprived) | 1.27 | 1.18-1.36 | <0.001 | 1.27 | 1.18-1.36 | <0.001 |
| C-reactive protein | <10mg/l | 1 | | <0.001 | 1 | | <0.001 |
| | ≥10mg/l | 1.53 | 1.47-1.60 | <0.001 | 1.22 | 1.16-1.28 | <0.001 |
| Albumin | <35g/l | 1.51 | 1.43-1.60 | <0.001 | 1.11 | 1.04-1.19 | 0.002 |
| | ≥35g/l | 1 | | <0.001 | 1 | | 0.002 |
| Adjusted calcium | <2.10mmol/l | 0.94 | 0.81-1.09 | 0.425 | | | |
| | 2.10-2.60mmol/l | 1 | | <0.001 | | | <0.001 |
| | >2.60mmol/l | 2.43 | 2.18-2.70 | <0.001 | 1.90 | 1.70-2.21 | <0.001 |
| Bilirubin | <20μmol/l | 1 | | 0.558 | | | |
| | ≥20μmol/l | 1.02 | 0.95-1.09 | 0.558 | | | |
| Alkaline phosphatase | <80U/l | 0.71 | 0.66-0.77 | <0.001 | 0.81 | 0.75-0.87 | <0.001 |
| | 80-280U/l | 1 | | <0.001 | 1 | | <0.001 |
| | >280U/l | 1.58 | 1.49-1.68 | <0.001 | 1.30 | 1.22-1.39 | <0.001 |
| Aspartate transaminase | <40U/l | 1 | | 0.075 | | | |
| | ≥40U/l | 0.94 | 0.89-1.01 | 0.075 | | | |
| Alanine transaminase | <50U/l | 1 | | 0.477 | | | |
| | ≥50U/l | 0.97 | 0.90-1.05 | 0.477 | | | |
| γ-glutamyl transferase | M<70 U/l,F<40U/l | 1 | | <0.001 | 1 | | |
| | M≥70U/l, F≥40U/l | 1.32 | 1.26-1.38 | <0.001 | 1.09 | 1.03-1.15 | 0.003 |

**Table 4.7. The relationship between tumour site and an inflammation-based prognostic score sampled prior to diagnosis**

| Tumour Site | Total n | mGPS n (%) | | | p value* |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | |
| Breast | 1199 | 950 (79) | 207 (17) | 42 (4) | |
| Dermatological | 1126 | 693 (62) | 310 (27) | 123 (11) | <0.001 |
| Bladder | 296 | 174 (59) | 76 (26) | 46 (15) | <0.001 |
| Endocrinological | 145 | 84 (58) | 41 (28) | 20 (14) | <0.001 |
| Gynaecological | 197 | 108 (55) | 60 (30) | 29 (15) | <0.001 |
| Prostate | 267 | 145 (54) | 91 (34) | 31 (12) | <0.001 |
| Musculoskeletal | 78 | 41 (53) | 15 (19) | 22 (28) | <0.001 |
| Gastroesophageal | 503 | 249 (50) | 162 (32) | 92 (18) | <0.001 |
| Haematological | 499 | 245 (49) | 157 (32) | 97 (19) | <0.001 |
| Renal | 294 | 132 (45) | 105 (36) | 57 (19) | <0.001 |
| Colorectal | 784 | 342 (44) | 250 (32) | 192 (24) | <0.001 |
| Head and neck | 156 | 67 (43) | 58 (37) | 31 (20) | <0.001 |
| Pancreaticobiliary | 321 | 122 (38) | 101 (31) | 98 (31) | <0.001 |
| Pulmonary | 820 | 260 (32) | 387 (47) | 173 (21) | <0.001 |

*compared with breast cancer

## 5.0. AN INFLAMMATION-BASED PROGNOSTIC SCORE (mGPS) PREDICTS CANCER SURVIVAL INDEPENDENT OF TUMOUR SITE

### 5.1. ABSTRACT

**Introduction:** The modified Glasgow Prognostic score (a combination of C-reactive protein and albumin) as well as liver function tests including bilirubin, alkaline phosphatase and γ-glutamyl transferase have been reported to predict cancer survival. The aim of the present study was to examine the relationship between the mGPS, biochemical parameters and survival.

**Methods:** Patients (n=21,669) sampled between 2000 and 2006 for C-reactive protein, albumin, liver function tests where available, as well as a diagnosis of cancer were identified. Of this group 9608 patients who had an ongoing malignant process were studied (sampled within two years following diagnosis).

**Results:** On follow up, there were 6005 (63%) deaths of which 5122 (53%) were cancer deaths. The median time from blood sampling to diagnosis was 1.4 months. Increasing age, male gender, and increasing deprivation was associated with reduced 5 year overall and cancer specific survival (all $p<0.001$). An elevated mGPS, adjusted calcium, bilirubin, Alk phos, AST, ALT and GGT were associated with a reduced 5 year overall and cancer specific survival, independent of age, sex and deprivation (all $p<0.001$). An increasing mGPS was predictive of a reduced cancer specific survival in all cancers (all $p<0.001$).

**Conclusion:** The results of the present study indicate that the mGPS is a powerful prognostic factor when compared with other biochemical parameters and independent of tumour site in patients with cancer.

## 5.2. INTRODUCTION

As detailed in Chapter 3, measurement of the systemic immune/inflammatory response has been refined using a selective combination of C-reactive protein and albumin (termed the modified Glasgow Prognostic score, mGPS) and has been shown to have prognostic value, independent of tumour stage, in lung, gastrointestinal and renal cancers [McMillan, 2008; McMillan, 2009]. As has been detailed in Chapter 1, it is also of interest that liver function tests such as bilirubin [Temme et al., 2001], alkaline phosphatase [Tonelli et al., 2009] and γ-glutamyl transferase [Kazemi-Shirazi et al., 2007] as well as serum calcium [Leifsson and Ahren, 1996], have also been reported to predict cancer and non-cancer mortality in large cohort studies.

In Chapter 4 it has been demonstrated, in a large cohort of more than 200,000 patients, that the mGPS is elevated in patients with cancer when compared to those without cancer [Proctor et al., 2010]. Moreover, there were significant interrelationships between the above biochemical parameters, including the constituents of the mGPS [Proctor et al., 2010]. The question is therefore raised whether the mGPS and other routine biochemical parameters have independent prognostic value in patients with cancer and whether this applies across different tumour sites.

The aim of the present Chapter was to examine the relationship between an inflammation based prognostic score (mGPS), biochemical parameters, tumour site and survival in patients with cancer.

## 5.3. MATERIALS AND METHODS

From a cohort previously described in Chapter 4 [Proctor et al., 2010], patients in North Glasgow who were sampled incidentally for the pre-mentioned markers of the systemic immune/inflammatory response as well as liver function tests between the 1st January 2000 and the 31st December 2006 to correspond with Cancer Registry follow-up data, were identified.

Only patients with blood samples taken within two years following their cancer diagnosis were included. This was done with the premise that a prognostic score would be of clinical use during this time period. Biochemical variable thresholds were categorised as detailed in Chapter 4 [Proctor et al., 2010].

Cancer diagnosis was established through linkage with the Scottish Cancer Registry using exact matches of patients' forename, surname and date of birth followed by a Soundex phonetic matching algorithm if initial exact matching was unsuccessful (Appendix 2). At the time of data collection the Scottish Cancer Registry held complete pathological and clinical cancer diagnosis records from the 1st of January 1980 until 31st December 2006 and mortality follow-up until 30th June 2009. In those who had died, cancer specific deaths were classified as patients whose primary cause of death matched their primary cancer diagnosis. All other deaths were classed as non-cancer specific deaths. Only patients who had complete Cancer Registry follow-up were included. Patient numbers in this Chapter differ from those in Chapter 4 as the matching process was through the cancer registry and not the North of Glasgow pathology database.

Cancers were coded in accordance with the International Classification of Disease 10 and broadly grouped according to tumour site. These include breast (C50), bladder (C67), gynaecological (C51-57), prostate (C61), gastroesophageal (C15-16), haematological (C81-96), renal (C64-65), colorectal (C18-20), head and neck (C00-14, C30-32), hepatopancreaticobiliary (C22-25) and pulmonary (C34, C45) cancer. These groups were listed in order of the magnitude of their inflammatory status as shown previously [Proctor et al., 2010]. Deprivation was measured with the Scottish Index of Multiple Deprivation (SIMD) as detailed in Chapter 1 with the least deprived scoring 1 and the most deprived scoring 5.

Statistical analysis was carried out as follows. Survival, overall and cancer specific, was calculated from the time of cancer diagnosis to death. Cancer groups with less than 150 cancer

specific deaths were excluded to ensure statistical power. Analysis was carried on all cancer patients as well as on a sub-group of patients who had a blood sample taken within 2 months of their cancer diagnosis. This was carried out in order to examine the relationships between the mGPS, biochemical parameters and survival in all patients with a history of malignancy (patients sampled within 2 years following a diagnosis of cancer) and those at the time of diagnosis (patients sampled within 2 months following a diagnosis of cancer). When investigating the prognostic value of the systemic immune/inflammatory response and associated biochemical variables only blood samples taken after a diagnosis of cancer were included. This was carried out under the premise that it would be within this time period that the prognostic value of these variable would be of clinical utility. The mGPS and biochemical proportionality assumptions were explored using log-log plots and were found to be satisfactory. Kaplan-Meier estimator was used to analyse the relationship between patient characteristics, mGPS, biological parameters, tumour site and overall and cancer specific survival (Tables 5.3 and 5.4) as well as the relationship between mGPS and survival (Figure 5.2 and Table 5.9). Cox proportional hazards model multivariate regression analysis (stratified by tumour site) was used to determine the relationship between patient characteristics, the mGPS, and each biochemical parameter and survival (Tables 5.5, 5.6, 5.7, 5.8). Chi square (linear by linear) association was used to analyse the relationship between the mGPS, patient characteristics and biochemical parameters (Table 5.9). Due to the number of statistical comparisons a P value of less than 0.01 was considered significant. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

## 5.4. RESULTS

From Glasgow Inflammation Outcome Study of 223,303 patients originally described (Proctor et al, 2010), 21,668 patients were identified as having a diagnosis of cancer in the Scottish Cancer Registry and a blood sample taken between January 2000 and December 2006. There were 9608 patients in this group who had been sampled within two years following a diagnosis of cancer and included in the present Chapter. The majority, 7516 (78%), were under 75 years of age. There were 5116 (53%) females and 4492 (47%) males. All patients had an identifiable post code corresponding to a SIMD 2006 score with 15% of cases being from affluent areas (least deprived quintile of the Scottish population) and 38% being from deprived areas (most deprived quintile of the Scottish population). The minimum follow-up was 29 months and the maximum 112 months (median 61 months for survivors).

The relationship between patient characteristics, tumour site, mGPS, biochemical parameters and mortality in patients with blood samples taken within two years, as well as within two months, following a diagnosis is shown in Table 5.1 and Table 5.2. In those sampled within two years (n=9608), there were 5122 (53%) cancer deaths and the median time from blood sample to diagnosis was 1.4 months. In those sampled within two months (n=5397), there were 2993 (56%) cancer deaths and the median time from blood sample to diagnosis was 0.4 months. Breast and lung cancer were among the most common tumour types studied.

The relationship between the mGPS, biochemical parameters, tumour site and five year survival in patients with blood samples taken within two years, as well as two months, following a diagnosis of cancer is shown in Table 5.3, Table 5.4 and Figure 5.1. Increasing age, male gender and increasing deprivation was associated with reduced 5 year overall and cancer specific survival (all $p<0.001$). An elevated mGPS, adjusted calcium, bilirubin, Alk phos, AST, ALT and GGT were associated with a reduced 5 year overall and cancer specific survival (all $p<0.001$). These tables demonstrate the dramatic survival difference between tumours at

different sites as well as in those with raised markers of the systemic immune/inflammatory response.

In the present cohort sampled within two years, the majority of patients with a low albumin concentration (n=2701) also had an elevated C-reactive protein concentration (n=2419, 90%). Few patients had a low albumin but a C-reactive protein concentration in the normal range (n=282). A low albumin concentration alone was not significantly associated with cancer specific survival in bladder (p=0.913), gynaecological (p=0.737), prostate (p=0.500), gastroesophageal (p=0.893), renal (p=0.945), colorectal (p=0.133), head and neck (p=0.740), and hepatopancreaticobiliary (p=0.209) cancers. In Cox multivariate regression analysis the relationship between a mGPS of 2 and cancer specific survival (HR 3.01, p<0.001) was stronger than that between C-reactive protein alone and cancer specific survival (HR 2.29, p<0.001).

The relationship between the mGPS and cancer specific survival in breast (n=1956), bladder (n=466), gynaecological (n=533), prostate (n=491), gastroesophageal (n=869), haematological (n=974), renal (n=424), colorectal (n=1065), head and neck (n=501), hepatopancreaticobiliary (n=605) and pulmonary (n=1724) cancers are shown in Figures 5.2.

The relationship between the mGPS, biochemical parameters and survival in patients sampled within two years, as well as two months, following cancer diagnosis, adjusted for age, sex, deprivation and stratified by tumour site, is shown in Table 5.5 and Table 5.6. On survival analysis, a raised mGPS, adjusted calcium, bilirubin, Alk phos, AST, ALT and GGT were all associated with increased overall and cancer specific mortality independent of age, sex and deprivation (all p<0.001). These tables illustrate the associations between markers of the systemic immune/inflammatory response, biochemical variables and survival and highlight the relative strength of the mGPS as a predictive factor.

The relationship between the mGPS, patient demographics and survival in patients sampled within two years, as well as within two months, following cancer diagnosis is shown in Table 5.7 and 5.8. On multivariate survival analysis, stratified by tumour site, increasing age and mGPS were associated with increased overall and cancer specific mortality (all $p<0.001$). Patients in the most deprived quintile (5) had a reduced overall and cancer specific survival (both $p<0.01$) but a significant linear relationship across deprivation categories was not observed. These tables illustrate the associations between the mGPS, patient demographics and survival and highlight the relative strength of the mGPS, when compared to patient characteristics, as a predictive factor.

In the present cohort of patients sampled within two months following cancer diagnosis, only a limited number of patients had staging information available from the Scottish Cancer Registry. Tumour staging was available in 533 (39%) patients with breast cancer, 430 (76%) patients with colorectal cancer and 158 (13%) patients with pulmonary cancer. All other cancer groups had no staging available. Therefore, only in colorectal cancer was staging available in over 50% of patients. In these colorectal cancer patients there were 30 Dukes A, 113 Dukes B, 131 Dukes C and 156 Dukes D and 236 died of their cancer. When Dukes stage was included in the multivariate analysis, both Dukes stage (HR 3.59, 95% CI 2.95-4.39, $p<0.001$) and mGPS (HR 1.49, 95% CI 1.26-1.76, $p<0.001$) remained independently associated with survival.

The associations between an activated systemic immune/inflammatory response, as measured by an elevated mGPS. and other biochemical parameters in patients with blood samples taken within two years following a diagnosis of cancer is shown in Table 5.9. An increasing mGPS was also associated with increasing age, male gender, increasing adjusted calcium, bilirubin, Alk phos, AST, ALT and GGT (all $p<0.001$). An increasing mGPS was shown to be associated with a reduction in overall and cancer specific survival (both $p<0.001$).

This table illustrates the correlation between an activated systemic immune/inflammatory response and derangement of a number of other biochemical variables.

Figure 5.2 illustrates the relationship between the mGPS and cancer specific survival ($p<0.001$) in each tumour site. This clearly demonstrates that the mGPS is predictive of survival independent of tumour site.

## 5.5. DISCUSSION

Previously, in large cohort studies, a number of biochemical parameters (other than C-reactive protein and albumin that compose the mGPS) including bilirubin [Temme et al., 2001], Alk phos [Tonelli et al., 2009], GGT [Kazemi-Shirazi et al., 2007] and calcium [Leifsson and Ahren, 1996], have been reported to predict overall and cancer specific survival.

In the present Chapter, the mGPS and the above biochemical parameters were shown to have prognostic value in all patients with a history of malignancy as well as those around the time of diagnosis. Moreover, a mGPS of 2 was associated with an approximate 160% reduction in both overall and cancer specific survival independent of tumour site. In contrast, an increase in adjusted calcium was associated with an approximate 130% reduction in both overall and cancer specific survival; an increase in bilirubin was associated with an approximate 50% reduction in both overall and cancer specific survival; an increase in Alk phos was associated with an approximate 110% reduction in both overall and cancer specific survival: an increase in AST was associated with an approximate 70% reduction in both overall and cancer specific survival; an increase in ALT was associated with an approximate 40% increase in both overall and cancer specific survival and an increase in GGT was associated with an approximate 80% reduction in both overall and cancer specific survival. These results indicate that the mGPS and the biochemical parameters measured have prognostic significance in the tumour sites studied.

Moreover, the results show that a raised mGPS is most closely associated with a reduction in both overall and cancer specific survival, independent of tumour site.

The GPS was originally developed, from the combination of C-reactive protein and albumin, in a cohort of patients with advanced non-small lung cancer [Forrest et al., 2004]. In this Chapter, they were combined to give a score of 0 for both a normal C-reactive protein and albumin, 1 for either an abnormal C-reactive protein alone or albumin alone and 2 for both an abnormal C-reactive protein and albumin. It was clear from this analysis that a low albumin alone was uncommon, accounting for less than 10% of all observations, and raised the possibility that this was not associated with a reduced survival. When examined in a cohort of patients undergoing potentially curable resection for colorectal cancer [McMillan et al., 2007] the results showed that the relationship between an abnormal albumin alone and cancer specific survival was similar to that of a normal albumin. Therefore, the GPS was modified (mGPS) to give a score of 1 only for an elevated C-reactive protein concentration. In the present Chapter, in a much larger cohort, a low albumin alone was associated with poor survival in some tumours (breast, haematological and pulmonary) but not others (bladder, gynaecological, prostate, gastroesophageal, renal, colorectal, head and neck, hepatopancreaticobiliary). Therefore, the present results would suggest the greater consistency of the mGPS and suggest its general use rather than that of the GPS.

In the present Chapter we examined the relationship between the mGPS, biochemical parameters and survival in all patients with cancer as well as a sub group of patients who were sampled within two months following a diagnosis of cancer. This was carried out with the premise that patients sampled within two years following a diagnosis would have a mGPS associated with disease prognosis and those sampled within two months would have a mGPS associated with their cancer diagnosis. With reference to the mGPS, the hazard ratios associated

with survival remained consistent in both analyses and confirms the temporal utility of this inflammation-based prognostic score.

To date the mGPS has been shown to have prognostic value, independent of TNM stage, in lung, gastrointestinal and renal cancers [McMillan, 2008; McMillan, 2009]. In the present Chapter there was insufficient staging information available on all cancer groups, apart from colorectal, to demonstrate that the mGPS is universally prognostic independent of stage. However, the results of the present and previous studies as detailed in Chapter 3 would suggest that the mGPS might also have independent prognostic in other cancer types [McMillan, 2009; Roxburgh and McMillan, 2010]. Further detailed studies, including tumour stage, in breast, bladder, gynaecological, prostate, haematological, head and neck, and hepatopancreaticobiliary cancers are required to confirm this hypothesis. Nevertheless, if this were to prove to be the case, then similar to the TNM staging system, the mGPS may be implemented universally in the assessment of cancer patients. Moreover, that they (TNM stage and mGPS) may be combined in a single staging system which would not only account for tumour stage but also the host systemic immune/inflammatory response.

The present cohort has a number of limitations. The patients were selected on the basis that measurements of C-reactive protein, albumin and calcium had been performed and were therefore not necessarily representative of all cancer patients diagnosed and treated in the North Glasgow area. It is also recognised that patients with cancer may have concurrent morbidity causing a rise in their C-reactive protein and derangement of their albumin and other biochemical parameters. Moreover, a rise in inflammatory markers may have occurred as a result of the initiation of oncological treatments including resectional surgery, radiotherapy and chemotherapy.

In summary, the results of the present Chapter indicate that, in a large patient cohort, the systemic immune/inflammatory response, as evidenced by the mGPS, is common and that the

mGPS is a powerful prognostic factor compared with other biochemical parameters, independent of tumour site in patients with cancer.

**Table 5.1. The relationship between patient characteristics, mGPS, biochemical parameters, tumour site and mortality in patients sampled within two years following cancer diagnosis**

| | | | Patients n= 9608 (%) | All deaths n= 6005 | Cancer deaths n=5122 |
|---|---|---|---|---|---|
| Age | <65 years | | 4577 (48) | 2258 | 2056 |
| | 65–74 years | | 2936 (30) | 2041 | 1729 |
| | ≥ 75 years | | 2095 (22) | 1706 | 1337 |
| Sex | Male | | 4492 (47) | 3269 | 2794 |
| | Female | | 5116 (53) | 2736 | 2328 |
| SIMD 2006 | 1 (least deprived) | | 1419 (15) | 722 | 616 |
| | 2 | | 1198 (13) | 631 | 543 |
| | 3 | | 1445 (15) | 850 | 739 |
| | 4 | | 1858 (19) | 1222 | 1038 |
| | 5 (most deprived) | | 3688 (38) | 2580 | 2186 |
| Tumour site | Breast | | 1956 (20) | 452 | 328 |
| | Bladder | | 466 (5) | 250 | 155 |
| | Gynaecological | | 533 (6) | 298 | 256 |
| | Prostate | | 491 (5) | 244 | 165 |
| | Gastroesophageal | | 869 (9) | 772 | 719 |
| | Haematological | | 974 (10) | 539 | 418 |
| | Renal | | 424 (5) | 265 | 229 |
| | Colorectal | | 1065 (11) | 673 | 571 |
| | Head and Neck | | 501 (5) | 316 | 220 |
| | Hepatopancreaticobiliary | | 605 (6) | 563 | 536 |
| | Pulmonary | | 1724 (18) | 1633 | 1525 |
| Inflammation based score | mGPS | 0 | 3985 (42) | 1647 | 1315 |
| | | 1 | 3204 (33) | 2325 | 2039 |
| | | 2 | 2419 (25) | 2033 | 1768 |
| Biochemical parameters | Adjusted calcium | <2.10mmol/l | 329 (4) | 229 | 177 |
| | | 2.10-2.60mmol/l | 8856 (92) | 5399 | 4601 |
| | | >2.60mmol/l | 423 (4) | 377 | 344 |
| | Bilirubin | <20μmol/l | 7936 (83) | 4693 | 3978 |
| | | ≥20μmol/l | 1342 (14) | 1071 | 942 |
| | Alkaline phosphatase | <80U/l | 177 (2) | 56 | 48 |
| | | 80-280U/l | 6846 (71) | 3704 | 3068 |
| | | >280U/l | 2569 (27) | 2236 | 1999 |
| | Aspartate transaminase | <40U/l | 7609 (18) | 4439 | 3734 |
| | | ≥40U/l | 1678 (79) | 1340 | 1206 |
| | Alanine transaminase | <50U/l | 6350 (66) | 3588 | 3036 |
| | | ≥50U/l | 992 (10) | 741 | 677 |
| | γ-glutamyl transferase | M<70 U/l, F<40U/l | 6082 (63) | 3336 | 2765 |
| | | M≥70U/l, F≥40U/l | 3264 (34) | 2488 | 2212 |

**Table 5.2. The relationship between patient characteristics, mGPS, biochemical parameters, tumour site and mortality in patients sampled within two months following cancer diagnosis**

| | | | Patients n= 5397 (%) | All deaths n= 3405 | Cancer deaths n= 2993 |
|---|---|---|---|---|---|
| Age | <65 years | | 2452 (46) | 1192 | 1093 |
| | 65–74 years | | 1686 (31) | 1172 | 1035 |
| | ≥ 75 years | | 1259 (23) | 1041 | 865 |
| Sex | Male | | 2315 (43) | 1829 | 1620 |
| | Female | | 3082 (57) | 1576 | 1373 |
| SIMD 2006 | 1 (least deprived) | | 802 (15) | 392 | 335 |
| | 2 | | 685 (13) | 344 | 304 |
| | 3 | | 766 (14) | 429 | 388 |
| | 4 | | 974 (18) | 648 | 572 |
| | 5 (most deprived) | | 2170 (40) | 1592 | 1394 |
| Tumour site | Breast | | 1383 (26) | 235 | 166 |
| | Bladder | | 181 (3) | 97 | 60 |
| | Gynaecological | | 188 (3) | 129 | 108 |
| | Prostate | | 159 (3) | 106 | 75 |
| | Gastroesophageal | | 456 (8) | 400 | 371 |
| | Haematological | | 427 (8) | 255 | 211 |
| | Renal | | 179 (3) | 117 | 107 |
| | Colorectal | | 569 (11) | 363 | 309 |
| | Head and Neck | | 191 (4) | 130 | 94 |
| | Hepatopancreaticobiliary | | 486 (9) | 455 | 438 |
| | Pulmonary | | 1178 (22) | 1118 | 1054 |
| Inflammation based score | mGPS | 0 | 2243 (41) | 890 | 743 |
| | | 1 | 1815 (34) | 1385 | 1252 |
| | | 2 | 1339 (25) | 1130 | 998 |
| Biochemical parameters | Adjusted calcium | <2.10mmol/l | 165 (3) | 116 | 91 |
| | | 2.10-2.60mmol/l | 4971 (92) | 3058 | 2685 |
| | | >2.60mmol/l | 261 (5) | 231 | 217 |
| | Bilirubin | <20μmol/l | 4366 (81) | 2558 | 2230 |
| | | ≥20μmol/l | 855 (16) | 720 | 655 |
| | Alkaline phosphatase | <80U/l | 98 (2) | 28 | 25 |
| | | 80-280U/l | 3788 (70) | 2039 | 1746 |
| | | >280U/l | 1502 (30) | 1333 | 1217 |
| | Aspartate transaminase | <40U/l | 4191 (78) | 2409 | 2084 |
| | | ≥40U/l | 1034 (19) | 876 | 812 |
| | Alanine transaminase | <50U/l | 3740 (69) | 2127 | 1847 |
| | | ≥50U/l | 636 (12) | 514 | 483 |
| | γ-glutamyl transferase | M<70 U/l, F<40U/l | 3393 (63) | 1841 | 1581 |
| | | M≥70U/l, F≥40U/l | 1867 (35) | 1472 | 1338 |

**Table 5.3. The relationship between patient characteristics, mGPS, biochemical parameters, tumour site and five year survival in patients sampled within two years following cancer diagnosis**

| n=9608 | | | 5 year overall survival % | p-value | 5 year cancer survival % | p-value |
|---|---|---|---|---|---|---|
| Age | <65 years | | 50 | | 54 | |
| | 65–74 years | | 30 | | 38 | |
| | ≥ 75 years | | 19 | <0.001 | 30 | <0.001 |
| Sex | Male | | 27 | | 34 | |
| | Female | | 47 | <0.001 | 53 | <0.001 |
| SIMD | 1 (least deprived) | | 50 | | 55 | |
| | 2 | | 47 | | 52 | |
| | 3 | | 41 | | 46 | |
| | 4 | | 34 | | 41 | |
| | 5 (most deprived) | | 30 | <0.001 | 37 | <0.001 |
| Tumour site | Breast | | 77 | | 83 | |
| | Bladder | | 57 | | 64 | |
| | Gynaecological | | 44 | | 52 | |
| | Prostate | | 50 | | 64 | |
| | Gastroesophageal | | 11 | | 13 | |
| | Haematological | | 46 | | 54 | |
| | Renal | | 39 | | 38 | |
| | Colorectal | | 37 | | 43 | |
| | Head and Neck | | 34 | | 50 | |
| | Hepatopancreaticobiliary | | 6 | | 7 | |
| | Pulmonary | | 5 | <0.001 | 7 | <0.001 |
| Inflammation based score | mGPS | 0 | 59 | | 65 | |
| | | 1 | 28 | | 34 | |
| | | 2 | 15 | <0.001 | 21 | <0.001 |
| Biochemical parameters | Adjusted calcium | <2.10mmol/l | 30 | | 41 | |
| | | 2.10-2.60mmol/l | 39 | | 45 | |
| | | >2.60mmol/l | 10 | <0.001 | 14 | <0.001 |
| | Bilirubin | <20μmol/l | 41 | | 47 | |
| | | ≥20μmol/l | 20 | <0.001 | 25 | <0.001 |
| | Alkaline phosphatase | <80U/l | 62 | | 66 | |
| | | 80-280U/l | 46 | | 53 | |
| | | >280U/l | 13 | <0.001 | 17 | <0.001 |
| | Aspartate transaminase | <40U/l | 42 | | 48 | |
| | | ≥40U/l | 20 | <0.001 | 24 | <0.001 |
| | Alanine transaminase | <50U/l | 43 | | 50 | |
| | | ≥50U/l | 25 | <0.001 | 28 | <0.001 |
| | γ-glutamyl transferase | M<70 U/l, F<40U/l | 45 | | 52 | |
| | | M≥70U/l, F≥40U/l | 23 | <0.001 | 28 | <0.001 |

**Table 5.4. The relationship between patient characteristics, mGPS, biochemical parameters, tumour site and five year survival in patients sampled within two months following cancer diagnosis**

| n=5397 | | | 5 year overall survival % | p-value | 5 year cancer survival % | p-value |
|---|---|---|---|---|---|---|
| Age | <65 years | | 51 | | 54 | |
| | 65–74 years | | 30 | | 35 | |
| | ≥ 75 years | | 18 | <0.001 | 26 | <0.001 |
| Sex | Male | | 21 | | 26 | |
| | Female | | 49 | <0.001 | 54 | <0.001 |
| SIMD | 1 (least deprived) | | 52 | | 57 | |
| | 2 | | 50 | | 54 | |
| | 3 | | 43 | | 47 | |
| | 4 | | 32 | | 38 | |
| | 5 (most deprived) | | 27 | <0.001 | 32 | <0.001 |
| Tumour site | Breast | | 83 | | 87 | |
| | Bladder | | 48 | | 63 | |
| | Gynaecological | | 33 | | 39 | |
| | Prostate | | 32 | | 46 | |
| | Gastroesophageal | | 12 | | 15 | |
| | Haematological | | 40 | | 47 | |
| | Renal | | 35 | | 39 | |
| | Colorectal | | 37 | | 43 | |
| | Head and Neck | | 29 | | 43 | |
| | Hepatopancreaticobiliary | | 5 | | 6 | |
| | Pulmonary | | 5 | <0.001 | 7 | <0.001 |
| Inflammation based score | mGPS | 0 | 60 | | 65 | |
| | | 1 | 24 | | 29 | |
| | | 2 | 15 | <0.001 | 20 | <0.001 |
| Biochemical parameters | Adjusted calcium | <2.10mmol/l | 29 | | 39 | |
| | | 2.10-2.60mmol/l | 38 | | 43 | |
| | | >2.60mmol/l | 10 | <0.001 | 13 | <0.001 |
| | Bilirubin | <20μmol/l | 41 | | 47 | |
| | | ≥20μmol/l | 15 | <0.001 | 19 | <0.001 |
| | Alkaline phosphatase | <80U/l | 68 | | 69 | |
| | | 80-280U/l | 46 | | 52 | |
| | | >280U/l | 11 | <0.001 | 14 | <0.001 |
| | Aspartate transaminase | <40U/l | 42 | | 48 | |
| | | ≥40U/l | 15 | <0.001 | 18 | <0.001 |
| | Alanine transaminase | <50U/l | 43 | | 48 | |
| | | ≥50U/l | 19 | <0.001 | 21 | <0.001 |
| | γ-glutamyl transferase | M<70 U/l, F<40U/l | 46 | | 51 | |
| | | M≥70U/l, F≥40U/l | 20 | <0.001 | 25 | <0.001 |

**Table 5.5. The relationship between the mGPS, biochemical parameters and survival in patients sampled within two years following cancer diagnosis. Adjusted for age, sex, deprivation and stratified by tumour site**

| n=9608 | | Overall survival | | Cancer specific survival | |
|---|---|---|---|---|---|
| | | HR | p value | HR | p value |
| mGPS | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.79 | <0.001 | 1.92 | <0.001 |
| | 2 | 2.87 | <0.001 | 3.01 | <0.001 |
| Adjusted calcium | <2.10mmol/l | 1.25 | 0.001 | 1.15 | 0.070 |
| | 2.10-2.60mmol/l | 1 | <0.001 | 1 | <0.001 |
| | >2.60mmol/l | 2.30 | <0.001 | 2.38 | <0.001 |
| Bilirubin | <20μmol/l | 1 | <0.001 | 1 | <0.001 |
| | ≥20μmol/l | 1.53 | <0.001 | 1.55 | <0.001 |
| Alkaline phosphatase | <80U/l | 0.71 | 0.012 | 0.74 | 0.037 |
| | 80-280U/l | 1 | <0.001 | 1 | <0.001 |
| | >280U/l | 2.12 | <0.001 | 2.19 | <0.001 |
| Aspartate transaminase | <40U/l | 1 | <0.001 | 1 | <0.001 |
| | ≥40U/l | 1.66 | <0.001 | 1.73 | <0.001 |
| Alanine transaminase | <50U/l | 1 | <0.001 | 1 | <0.001 |
| | ≥50U/l | 1.36 | <0.001 | 1.39 | <0.001 |
| γ-glutamyl transferase | M<70 U/l, F<40U/l | 1 | <0.001 | 1 | <0.001 |
| | M≥70U/l, F≥40U/l | 1.85 | <0.001 | 1.85 | <0.001 |

**Table 5.6. The relationship between the mGPS, biochemical parameters and survival in patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and stratified by tumour site**

| n=5397 | | Overall survival | | Cancer specific survival | |
|---|---|---|---|---|---|
| | | HR | p value | HR | p value |
| mGPS | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.67 | <0.001 | 1.74 | <0.001 |
| | 2 | 2.36 | <0.001 | 2.40 | <0.001 |
| Adjusted calcium | <2.10mmol/l | 1.17 | 0.107 | 1.07 | 0.530 |
| | 2.10-2.60mmol/l | 1 | <0.001 | 1 | <0.001 |
| | >2.60mmol/l | 1.96 | <0.001 | 2.04 | <0.001 |
| Bilirubin | <20μmol/l | 1 | <0.001 | 1 | <0.001 |
| | ≥20μmol/l | 1.49 | <0.001 | 1.49 | <0.001 |
| Alkaline phosphatase | <80U/l | 0.78 | 0.016 | 0.68 | 0.053 |
| | 80-280U/l | 1 | <0.001 | 1 | <0.001 |
| | >280U/l | 1.93 | <0.001 | 1.96 | <0.001 |
| Aspartate transaminase | <40U/l | 1 | <0.001 | 1 | <0.001 |
| | ≥40U/l | 1.66 | <0.001 | 1.71 | <0.001 |
| Alanine transaminase | <50U/l | 1 | <0.001 | 1 | <0.001 |
| | ≥50U/l | 1.34 | <0.001 | 1.37 | <0.001 |
| γ-glutamyl transferase | M<70 U/l, F<40U/l | 1 | <0.001 | 1 | <0.001 |
| | M≥70U/l, F≥40U/l | 1.79 | <0.001 | 1.79 | <0.001 |

**Table 5.7. The relationship between patient characteristics, mGPS and survival in patients sampled within two years following cancer diagnosis. Multivariate analysis stratified by tumour site**

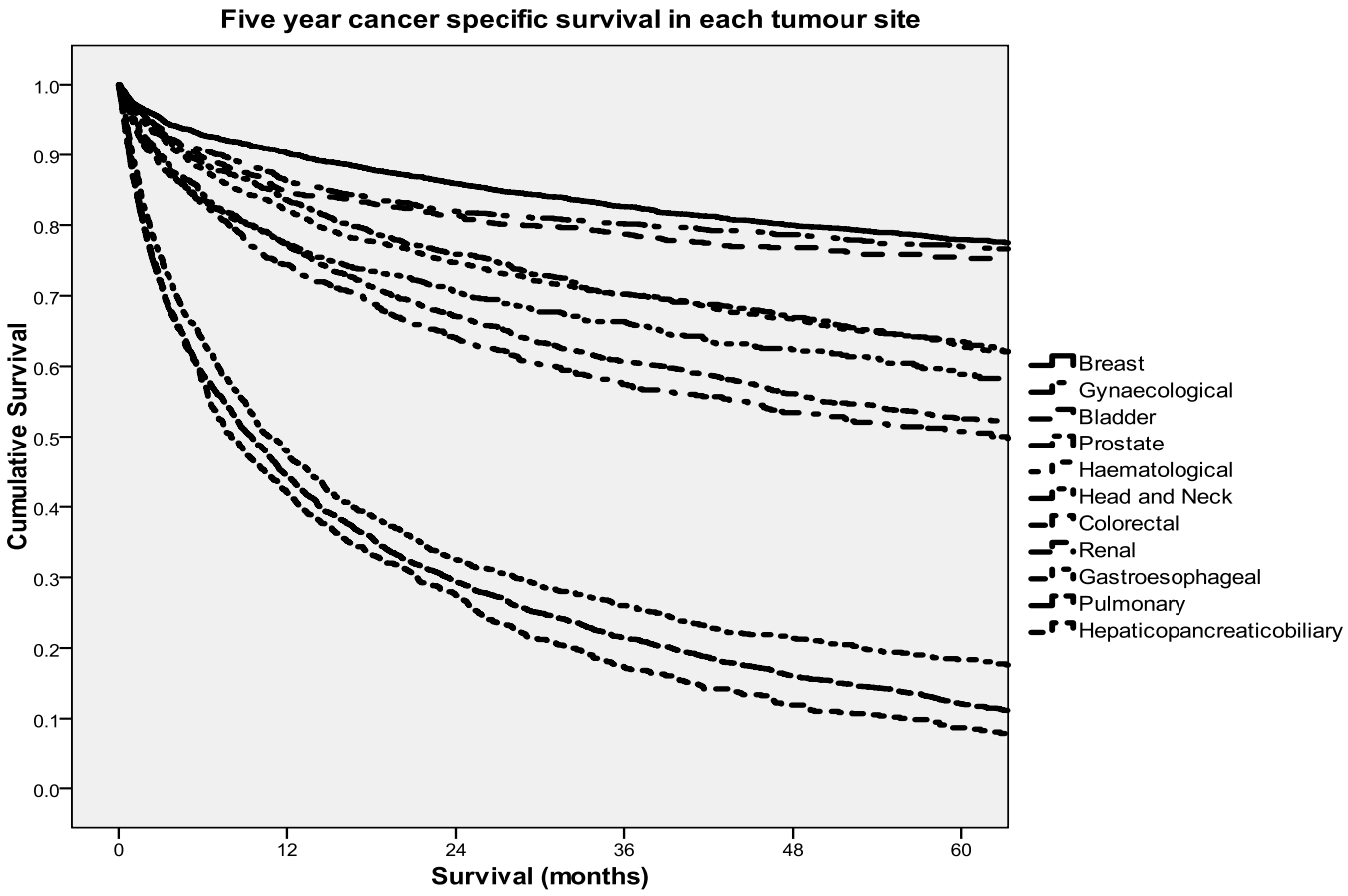
| | | Overall survival | | | Cancer specific survival | | |
|---|---|---|---|---|---|---|---|
| n=9608 | | HR | 95 % CI | p value | HR | 95 % CI | p value |
| Age | <65 years | 1 | | <0.001 | 1 | | <0.001 |
| | 65–74 years | 1.35 | 1.26-1.43 | <0.001 | 1.20 | 1.13-1.29 | <0.001 |
| | ≥ 75 years | 1.93 | 1.80-2.06 | <0.001 | 1.59 | 1.48-1.70 | <0.001 |
| Sex | Male | 1 | | 0.037 | 1 | | 0.132 |
| | Female | 0.94 | | 0.037 | 0.95 | | 0.132 |
| SIMD | 1 (least deprived) | 1 | | <0.001 | 1 | | 0.003 |
| | 2 | 1.02 | | 0.684 | 1.02 | | 0.773 |
| | 3 | 1.09 | | 0.090 | 1.09 | | 0.136 |
| | 4 | 1.16 | 1.06-1.27 | 0.002 | 1.12 | | 0.025 |
| | 5 (most deprived) | 1.22 | 1.12-1.33 | <0.001 | 1.17 | 1.06-1.28 | 0.001 |
| mGPS | 0 | 1 | | <0.001 | 1 | | <0.001 |
| | 1 | 1.79 | 1.68-1.91 | <0.001 | 1.92 | 1.79-2.06 | <0.001 |
| | 2 | 2.87 | 2.68-3.08 | <0.001 | 3.01 | 2.79-3.24 | <0.001 |

**Table 5.8. The relationship between patient characteristics, mGPS and survival in patients sampled within two months following cancer. Multivariate analysis stratified by tumour site**

| | | Overall survival | | | Cancer specific survival | | |
|---|---|---|---|---|---|---|---|
| n=5397 | | | | | | | |
| | | HR | 95 % CI | p value | HR | 95 % CI | p value |
| Age | <65 years | 1 | | <0.001 | 1 | | <0.001 |
| | 65–74 years | 1.31 | 1.20-1.42 | <0.001 | 1.22 | 1.12-1.33 | <0.001 |
| | ≥ 75 years | 1.92 | 1.76-2.10 | <0.001 | 1.70 | 1.55-1.87 | <0.001 |
| Sex | Male | 1 | | 0.340 | 1 | | 0.507 |
| | Female | 0.96 | | 0.340 | 0.97 | | 0.507 |
| SIMD | 1 (least deprived) | 1 | | <0.001 | 1 | | <0.001 |
| | 2 | 1.05 | | 0.503 | 1.08 | | 0.364 |
| | 3 | 1.07 | | 0.342 | 1.11 | | 0.179 |
| | 4 | 1.20 | 1.06-1.36 | 0.005 | 1.20 | 1.05-1.38 | 0.008 |
| | 5 (most deprived) | 1.30 | 1.16-1.45 | <0.001 | 1.28 | 1.14-1.45 | <0.001 |
| mGPS | 0 | 1 | | <0.001 | 1 | | <0.001 |
| | 1 | 1.67 | 1.53-1.83 | <0.001 | 1.74 | 1.59-1.91 | <0.001 |
| | 2 | 2.36 | 2.15-2.59 | <0.001 | 2.40 | 2.17-2.65 | <0.001 |

**Table 5.9. The relationship between the mGPS, patient characteristics, biochemical parameters and survival in patients sampled within two years following cancer diagnosis**

| | | mGPS | | | p value |
|---|---|---|---|---|---|
| n=9608 | | 0 | 1 | 2 | |
| | | n (%) | n (%) | n (%) | |
| Age | <65 years | 2193 (55) | 1464 (46) | 920 (38) | |
| | 65–74 years | 1091 (27) | 1007 (31) | 838 (35) | |
| | ≥ 75 years | 701 (18) | 733 (23) | 661 (27) | <0.001 |
| Sex | Male | 1516 (38) | 1672 (52) | 1304 (54) | |
| | Female | 2469 (62) | 1532 (48) | 1115 (46) | <0.001 |
| SIMD 2006 | 1 (least deprived) | 739 (19) | 383 (12) | 297 (12) | |
| | 2 | 592 (15) | 342 (11) | 264 (11) | |
| | 3 | 633 (16) | 460 (14) | 352 (15) | |
| | 4 | 727 (18) | 613 (19) | 518 (21) | |
| | 5 (most deprived) | 1294 (32) | 1406 (44) | 988 (41) | <0.001 |
| Adjusted calcium | <2.10mmol/l | 76 (2) | 87 (3) | 166 (7) | |
| | 2.10-2.60mmol/l | 3835 (96) | 2972 (93) | 2049 (85) | |
| | >2.60mmol/l | 74 (2) | 145 (4) | 204 (8) | <0.001 |
| Bilirubin | <20μmol/l | 3564 (92) | 2621 (85) | 1751 (76) | |
| | ≥20μmol/l | 324 (8) | 466 (15) | 552 (24) | <0.001 |
| Alkaline phosphatase | <80U/l | 93 (2) | 16 (0) | 68 (3) | |
| | 80-280U/l | 3428 (86) | 2163 (68) | 1255 (52) | |
| | >280U/l | 457 (12) | 1020 (32) | 1092 (45) | <0.001 |
| Aspartate transaminase | <40U/l | 3491 (90) | 2501 (81) | 1617 (70) | |
| | ≥40U/l | 399 (10) | 593 (19) | 686 (30) | <0.001 |
| Alanine transaminase | <50U/l | 3016 (91) | 1982 (85) | 1352 (79) | |
| | ≥50U/l | 301 (9) | 337 (15) | 354 (21) | <0.001 |
| γ-glutamyl transferase | M<70 U/l, F<40U/l | 3071 (79) | 1875 (60) | 1136 (49) | |
| | M≥70U/l, F≥40U/l | 839 (21) | 1242 (40) | 1183 (51) | <0.001 |
| Overall survival in months (mean, CI) | | 70 (68-72) | 37 (36-39) | 22 (21-24) | <0.001 |
| Cancer specific survival in months (mean, CI) | | 77 (75-79) | 43 (41-45) | 27 (26-29) | <0.001 |




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Alive | 9608 | 5492 | 4566 | 3710 | 2732 | 1845 |
| Overall deaths | 0 | 4116 | 5042 | 5898 | 6876 | 7763 |
| Cancer deaths | 0 | 3658 | 4452 | 4795 | 4961 | 5052 |

**Figure 5.1. The relationship between tumour site and cancer specific five year survival. Tumours from top to bottom; breast, gynaecological, bladder, prostate, haematological, head and neck, colorectal, renal, gastroesophageal, pulmonary and hepatopancreaticobiliary**

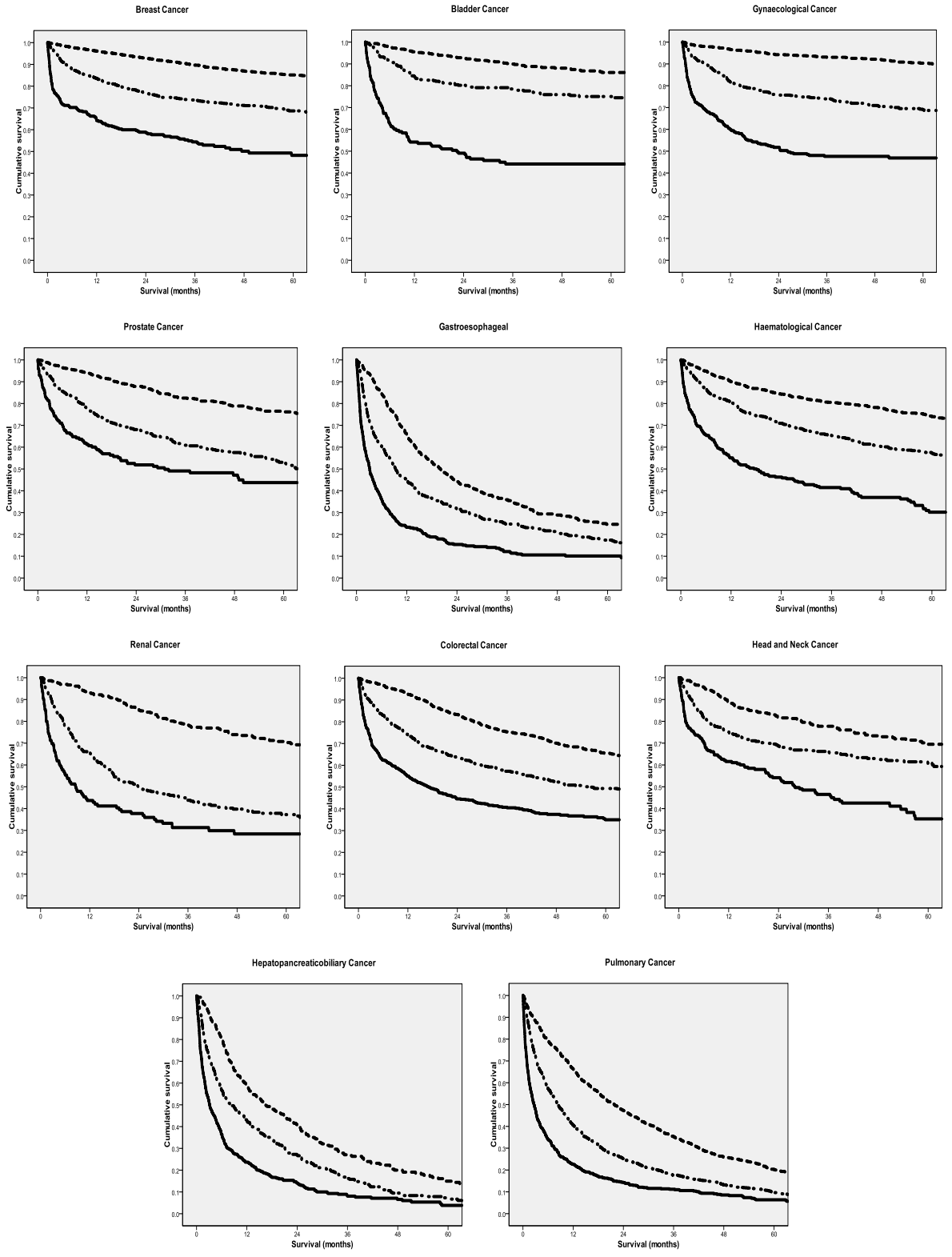



**Figure 5.2. The relationship between the mGPS - 0 (top, small dash line), mGPS 1 (middle, large dash line) and mGPS 2 (bottom, solid line) - and cancer specific survival ($p<0.001$) in each tumour site**

# 6.0. A COMPARISON OF INFLAMMATION-BASED PROGNOSTIC SCORES IN PATIENTS WITH CANCER

## 6.1. ABSTRACT

**Introduction:** Components of the systemic inflammatory response, combined to form inflammation-based prognostic scores including the modified Glasgow Prognostic Score (mGPS), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI) and Prognostic Nutritional Index (PNI), have been associated with cancer specific survival. The aim of the present chapter was to compare the prognostic value of these scores.

**Methods:** Patients (n=27,031) who had an incidental blood sample taken between 2000 and 2007 for C-reactive protein, albumin, white cell, neutrophil, lymphocyte and platelet counts, as well as a diagnosis of cancer (Scottish Cancer Registry) were identified. Of this group 8759 patients who had been sampled within two years following their cancer diagnosis were studied.

**Results:** On follow up there were 5163 deaths, 4417 (86%) of which were cancer related. The median time from blood sampling to diagnosis was 1.7 months. An elevated mGPS, NLR, PLR, PI and PNI were predictive of a reduced cancer specific survival independent of age, sex and deprivation and tumour site (all $p<0.001$). The area under the receiver operator curves was greatest for mGPS and PI. Specifically, in colorectal cancer, an elevated mGPS and PI were predictive of a reduced cancer specific survival independent of age, sex, deprivation and tumour stage (both $p<0.001$).

**Conclusion:** The results of the present study show that systemic inflammation-based scores, in particular the mGPS and PI, have prognostic value in cancer independent of tumour site.

## 6.2. INTRODUCTION

As has been detailed in Chapter 1, while the development of cancer has a genetic basis, there is increasing evidence that the host immune/inflammatory response plays an important role in the development and progression of cancer [Coussens and Werb, 2002; Mantovani et al., 2008; Colotta et al., 2009; McDonald et al., 2009; Tenesa et al., 2010]. The modified Glasgow Prognostic Score (mGPS) has been shown to have prognostic value, independent of tumour stage, in a number of tumour types including lung, gastrointestinal and renal cancers [McMillan, 2008; McMillan, 2009]. As shown in Table 3.1, it is also of interest that other haematological components of the systemic immune/inflammatory response have been combined to form inflammation-based prognostic scores that have been associated with survival in patients with cancer. In addition to those detailed in Chapter 3, the Neutrophil Lymphocyte Ratio (NLR), a combination of circulating neutrophil and lymphocyte counts, has been associated with survival in colorectal [Chua et al., 2011a], lung [Sarraf et al., 2009; Kao et al., 2010a] and ovarian [Cho et al., 2009b] cancers. The Platelet Lymphocyte Ratio (PLR), a combination of circulating platelet and lymphocyte counts, has been associated with survival in patients with pancreatic cancer [Smith et al., 2009]. The combination of C-reactive protein and white cell count in a Prognostic Index (PI) has been associated with survival in patients with lung cancer [Kasymjanova et al., 2010]. Finally, Onodera's Prognostic Nutritional Index (PNI) has also been associated with survival in patients with pancreatic [Kanda et al., 2011] and gastric [Nozoe et al., 2010] cancer.

In Chapter 4 and 5, it has been shown that the mGPS is elevated in patients with cancer [Proctor et al., 2010] and predictive of survival across all tumour sites studied independent of age, sex and deprivation [Proctor et al., 2011b]. Therefore, it is of considerable interest to compare the prognostic value of the mGPS, NLR, PLR, PI and PNI across different tumour sites.

The aim of the current Chapter was to compare the prognostic value of the mGPS, NLR, PLR, PI and PNI adjusted for age, sex, deprivation and tumour site in the Glasgow Inflammation Outcome Study.

## 6.3. MATERIALS AND METHODS

From a cohort previously described in Chapter 4. [Proctor et al., 2010], patients in the North Glasgow who were sampled incidentally for C-reactive protein, albumin, calcium, white cell, neutrophil, lymphocyte and platelet counts between the 1st January 2000 and the 31st December 2007 were included. This time period differed from previous Chapters to correspond with the available follow-up data from the Scottish Cancer Registry at the time of analysis. The limit of detection of C-reactive protein was a concentration of less than 5mg/L. The mGPS, NLR, PLR, PI and PNI were constructed as described in Table 6.1.

Cohort linkage, with the Scottish Cancer Registry, classification of deaths and cancer coding were carried out as described in Chapter 5 and only those patients who had complete Cancer Registry follow-up were included [Proctor et al., 2011b]. Survival was calculated as described in Chapter 5 with cancer registry follow-up available until June the 30th 2009 [Proctor et al., 2011b]. Cancer groups with less than 150 cancer specific deaths were excluded to ensure statistical power. Analysis was carried on all cancer patients who had a blood sample taken within two years of diagnosis as well as on a sub-group of patients who had a sample taken within two months of a diagnosis of cancer. This was carried out in order to examine the relationships between the mGPS, NLR, PLR, PI, PNI and survival in all patients with a recently diagnosed malignancy (patients sampled within two years following a diagnosis of cancer) and those at the time of diagnosis (patients sampled within two months following a diagnosis of cancer). Cancer stage was extracted from the registry where available.

Deprivation was measured with the Scottish Index of Multiple Deprivation (SIMD) as detailed in Chapter 1. Patients with incomplete identifying details (name, date of birth and hospital number), under 16 years of age, or those with multiple malignancies, metastatic disease or cancer of an unknown origin or those without all haematological variables available were excluded. Overall patient numbers were different in this Chapter, when compared to previous, as the inclusion time period was longer as extended cancer registry follow-up was available. The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

Statistical analysis was carried out as follows. The mGPS, NLR, PLR, PI, PNI proportionality assumptions were explored using log-log plots and were found to be satisfactory. Kaplan-Meier estimator was used to analyse the relationship between patient characteristics, mGPS, NLR, PLR, PI, PNI, tumour site and overall and cancer specific survival (Table 6.2, Figures 6.1, 6.2). Cox proportional hazards model multivariate regression analysis (stratified by tumour site) was used to correct for age, sex and deprivation and determine the relationship between patient characteristics, mGPS, NLR, PLR, PI, PNR and survival (Tables 6.3, 6.4). To determine whether one of the independently significant variables was more predictive than the other, the area under the receiver operating characteristic (ROC) curve was calculated. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

## 6.4. RESULTS

From the Glasgow Inflammation Outcome Study of 223,303 patients originally described in Chapter 4. [Proctor et al., 2010], 27,031 patients were identified as having a diagnosis of cancer in the Scottish Cancer Registry and a blood sample for taken for C-reactive protein, albumin, white cell, neutrophil, lymphocyte and platelet counts between

January 2000 and December 2007. Within this group there were 8759 patients who had been sampled for all these variables within two years following a diagnosis of cancer and were included in the present study. The majority, 6857 (78%), were under 75 years of age. There were 4644 (53%) females and 4115 (47%) males. Fifteen per cent of patients lived in affluent areas (least deprived quintile of the Scottish population) and 36% in deprived areas (most deprived quintile of the Scottish population). The minimum follow-up from cancer diagnosis was 18 months and the maximum 115 months (median 51 months for survivors).

The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival is shown in Table 6.2 and Figure 6.1. In total 8759 patients were studied. On follow-up, there were 5163 deaths of which 4417 (86%) were cancer deaths. The median time from diagnosis to blood sampling was 1.7 months, suggesting that most scores reflect status at diagnosis rather that at a later stage. Increasing age, male gender, and increasing deprivation were associated with reduced 5 year overall and cancer specific survival (all $p<0.001$). An elevated mGPS, NLR, PLR, PI and PNI were also associated with a reduced 5 year overall and cancer specific survival (all $p<0.001$). When this analysis was repeated on a subgroup of patients (n=4674) who were sampled within two months following their cancer diagnosis (median time to diagnosis 0.5 months) the above proportions remained similar and the associations significant (all $p<0.001$). The relationship between the mGPS, NLR, PLR, PI and PNI and cancer specific survival in individual tumour groups is shown in Figure 6.2. All were predictive of cancer specific survival in bladder, breast, colorectal, gastroesophageal, gynaecological, prostate, pulmonary and renal cancer (all $p<0.001$). Additionally, the mGPS, NLR, PI and PNI were predictive of cancer specific haematological, head and neck, and hepatopancreaticobiliary cancer survival (all $p<0.001$).

The relationship between inflammation-based prognostic scores and survival, adjusted for age, sex and deprivation and stratified by tumour site is shown in Table 6.3. On survival

analysis of all patients (n=8759), a raised mGPS, NLR, PLR, PI and PNI were associated with reduced overall and cancer specific survival independent of age, sex and deprivation (all p<0.001). When this analysis was repeated on a subgroup of patients (n=4674) who were sampled two months following their cancer diagnosis the above proportions remained similar and the associations significant (all p<0.001).

In all patients, using overall mortality at as an endpoint, the area under the receiver operator curve was for the mGPS 0.718 (95% CI, 0.707-0.729, p<0.001); NLR 0.650 (95% CI, 0.638-0.661, p<0.001); PLR 0.632 (95% CI, 0.620-0.644, p<0.001); PI 0.715 (95% CI, 0.704-0.726, p<0.001) and PNI 0.678 (95% CI, 0.666-0.689, p<0.001). Using cancer-specific mortality at as an endpoint, the area under the receiver operator curve was for the mGPS 0.698 (95% CI, 0.687-0.709, p<0.001); NLR 0.632 (95% CI, 0.620-0.643, p<0.001); PLR 0.632 (95% CI, 0.620-0.644, p<0.001); PI 0.694 (95% CI, 0.682-0.705, p<0.001) and PNI 0.660 (95% CI, 0.649-0.672, p<0.001).

When this analysis was repeated on a subgroup of patients (n=4674) who were sampled within two months following their cancer diagnosis, using overall mortality as an endpoint, the area under the receiver operator curve was for the mGPS 0.730 (95% CI, 0.715-0.745, p<0.001); NLR 0.657 (95% CI, 0.641-0.672, p<0.001); PLR 0.644 (95% CI, 0.628-0.660, p<0.001); PI 0.724 (95% CI, 0.724-0.753, p<0.001) and PNI 0.692 (95% CI, 0.677-0.708, p<0.001). Using cancer-specific mortality as an endpoint, the area under the receiver operator curve was for the mGPS 0.712 (95% CI, 0.697-0.727, p<0.001); NLR 0.640 (95% CI, 0.624-0.656, p<0.001); PLR 0.638 (95% CI, 0.622-0.654, p<0.001); PI 0.719 (95% CI, 0.704-0.733., p<0.001) and PNI 0.673 (95% CI, 0.658-0.689, p<0.001).

In the present cohort only a limited number of patients had staging information available from the Scottish Cancer Registry. Of those patients sampled within two months

following cancer diagnosis, tumour staging was available in 470 (35%) patients with breast cancer, 374 (75%) patients with colorectal cancer and 108 (12%) patients with pulmonary cancer. All other cancer groups had no staging available. Therefore, only in colorectal cancer was staging available in over 50% of patients. In this group there were 31 Dukes A, 113 Dukes B, 113 Dukes C and 117 Dukes D with 227 dying of their cancer on follow-up. The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis adjusted for age, sex, deprivation and Dukes stage is shown in Table 6.4. Given the small numbers of Dukes A, Dukes A and B were grouped together. On survival analysis (n=374), only a raised mGPS and PI were associated with reduced overall and cancer specific survival independent of age, sex, deprivation and Dukes stage (all $p<0.001$).

As mGPS and PI both contain C-reactive protein, the prognostic value of a low albumin (<35g/l) or high white cell count (>11×109/l), independent of each other was of interest. On Cox-regression multivariate survival analysis of the same group of patients (n=374), both a high white cell count (HR 1.57, p=0.011) and low albumin (HR 1.59, p=0.004) were predictive of cancer specific survival independent of age, sex, deprivation and Dukes stage.

## 6.5. DISCUSSION

The results of the present Chapter show clearly that systemic inflammation-based prognostic scores, whether it be the mGPS, NLR, PLR, PI or PNI, predict cancer specific outcome in most cancers. Moreover, scores including C-reactive protein (mGPS and PI) were superior, in terms of differentiating good from poor prognostic groups, to those based on components of the circulating white cell count (NLR, PLR) or in combination with albumin (PNI). Therefore, any further development of prognostic scores, based on the

systemic immune/inflammatory response, should include the prototypical acute phase protein [Gabay and Kushner, 1999], C-reactive protein. Also, based on the present results and the existing validation literature [McMillan, 2009], the mGPS should be included in the routine assessment of all patients with cancer.

In the present Chapter, it was of interest that the combination of C-reactive protein and albumin (mGPS) had similar prognostic value to that of C-reactive protein and white cell count (PI). Although few patients had a low albumin (5%) or a high white cell count (3%) in the presence of a normal C-reactive protein concentration (<10mg\l), both a low albumin concentration and a high white cell count both had prognostic value independent of C-reactive protein. These results would suggest that a white cell count, rather than the NLR or PLR, may be a useful addition to the comprehensively validated mGPS.

It was also of interest that a nutritional index previously shown to have prognostic value (PNI) and used extensively in Japan [Nozoe et al., 2002; Nozoe et al., 2010; Kanda et al., 2011], behaved, in terms of prognostic value, very similar to the systemic inflammation-based prognostic scores (mGPS, NLR, PLR and PI). The present results, while only demonstrating correlation and not causation, add further weight to the proposal that the systemic immune/inflammatory response is a major factor in the relationship between nutritional decline and poor outcome in patients with cancer [McMillan, 2008; McMillan, 2009].

Taken together, the results of the present Chapter highlight the associations between systemic inflammation and outcome in patients with cancer. Therefore, we believe that the present results provide good evidence of systemic inflammation acting as a “common soil” [Fidler and Poste, 2008] promoting the fatal progression in most, if not all, cancers. If this

proves to be the case then moderation of the systemic immune/inflammatory response will become, in the future, as important a therapeutic target as the tumour itself.

In this context it is of interest that Chechlinska, Kowalewska and co-workers [Chechlinska et al., 2010] have proposed that "systemic inflammation is a confounding factor in the interpretation of the biomarker profile of cancer patients" and "to assess the independent predictive value of a biomarker, it should be validated against its expression in inflammatory conditions, and examined in the context of unspecific parameters of systemic inflammation". Also, they have concluded that if this is not done "we will end up using advanced technologies to assess inflammatory reactions in cancer patients", an opinion shared by the authors of the present body of work.

In summary, the results of the present Chapter show that systemic inflammation-based scores mGPS, NLR, PLR, PI and PNI have prognostic value in a variety of cancers. However, in terms of differentiating good from poor prognostic groups in a variety of tumour sites, the extensively validated mGPS is superior. A measurement of systemic inflammation, in particular the mGPS, should be included in the routine assessment of all patients with cancer.

**Table 6.1. Systemic inflammation-based prognostic scores**

| The modified Glasgow Prognostic Score | Score |
|---|---|
| C-reactive protein ≤10 mg/l and albumin ≥35 g/l | 0 |
| C-reactive protein ≤10 mg/l and albumin <35 g/l | 0 |
| C-reactive protein >10 mg/l | 1 |
| C-reactive protein >10 mg/l and albumin <35 g/l | 2 |
| Neutrophil Lymphocyte Ratio | |
| Neutrophil count:lymphocyte count <5:1 | 0 |
| Neutrophil count:lymphocyte count ≥5:1 | 1 |
| Platelet Lymphocyte Ratio | |
| Platelet count:lymphocyte count <150:1 | 0 |
| Platelet count:lymphocyte count 150–300:1 | 1 |
| Platelet count:lymphocyte count >300:1 | 2 |
| Prognostic Index | |
| C-reactive protein ≤10 mg/l and white cell count $\leq 11\times10^9$/l | 0 |
| C-reactive protein ≤10 mg/l and white cell count $>11\times10^9$/l | 1 |
| C-reactive protein >10 mg/l and white cell count $\leq 11\times10^9$/l | 1 |
| C-reactive protein >10 mg/l and white cell count $>11\times10^9$/l | 2 |
| Prognostic Nutritional Index | |
| Albumin (g/L) + 5 × total lymphocyte count $\times10^9$/l ≥45 | 0 |
| Albumin (g/L) + 5 × total lymphocyte count $\times10^9$/l <45 | 1 |

**Table 6.2. The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival**

| | | | Patients n=8759 (%) | Overall survival 5 year % (n of deaths) n=5163 | p-value | Cancer survival 5 year % (n of deaths) n=4417 | p-value |
|---|---|---|---|---|---|---|---|
| Age | <65 years | | 4237 (48) | 52 (1977) | | 55 (1808) | |
| | 65–74 years | | 2620 (30) | 33 (1703) | | 41 (1439) | |
| | ≥ 75 years | | 1902 (22) | 21 (1483) | <0.001 | 31 (1170) | <0.001 |
| Sex | Male | | 4115 (47) | 29 (2844) | | 36 (2432) | |
| | Female | | 4644 (53) | 49 (2319) | <0.001 | 55 (1985) | <0.001 |
| SIMD 2006 | 1 (least deprived) | | 1278 (15) | 51 (609) | | 57 (523) | |
| | 2 | | 1138 (13) | 48 (579) | | 54 (495) | |
| | 3 | | 1391 (16) | 43 (779) | | 48 (683) | |
| | 4 | | 1786 (20) | 37 (1110) | | 44 (940) | |
| | 5 (most deprived) | | 3166 (36) | 33 (2086) | <0.001 | 40 (1776) | <0.001 |
| Tumour site | Breast | | 1853 (21) | 79 (361) | | 85 (263) | |
| | Bladder | | 437 (5) | 48 (226) | | 63 (149) | |
| | Gynaecological | | 460 (5) | 45 (248) | | 51 (217) | |
| | Prostate | | 456 (5) | 53 (206) | | 64 (153) | |
| | Gastroesophageal | | 874 (10) | 12 (754) | | 15 (697) | |
| | Haematological | | 817 (10) | 48 (418) | | 57 (320) | |
| | Renal | | 400 (5) | 38 (242) | | 44 (214) | |
| | Colorectal | | 996 (11) | 39 (583) | | 45 (493) | |
| | Head and Neck | | 555 (7) | 34 (344) | | 51 (239) | |
| | Hepatopancreaticobiliary | | 474 (5) | 7 (430) | | 8 (410) | |
| | Pulmonary | | 1437 (16) | 5 (1351) | <0.001 | 7 (1262) | <0.001 |
| Inflammation based scores | mGPS | 0 | 3673 (42) | 61 (1349) | | 68 (1083) | |
| | | 1 | 2436 (28) | 32 (1640) | | 39 (1425) | |
| | | 2 | 2650 (30) | 16 (2174) | <0.001 | 22 (1909) | <0.001 |
| | NLR | 0 | 5151 (59) | 51 (2401) | | 58 (2021) | |
| | | 1 | 3608 (41) | 23 (2762) | <0.001 | 29 (2396) | <0.001 |
| | PLR | 0 | 2734 (31) | 52 (1253) | | 60 (996) | |
| | | 1 | 3522 (40) | 42 (1993) | | 48 (1716) | |
| | | 2 | 2503 (29) | 23 (1917) | <0.001 | 28 (1705) | <0.001 |
| | PI | 0 | 3084 (35) | 64 (1042) | | 70 (832) | |
| | | 1 | 3460 (40) | 31 (2303) | | 38 (1994) | |
| | | 2 | 2215 (25) | 17 (1818) | <0.001 | 23 (1591) | <0.001 |
| | PNI | 0 | 4342 (50) | 57 (1806) | | 63 (1487) | |
| | | 1 | 4417 (50) | 21 (3357) | <0.001 | 27 (2930) | <0.001 |

**Table 6.3. The relationship between inflammation-based prognostic scores and survival. Adjusted for age, sex, deprivation and stratified by tumour site**

All patients (n=8759)

| | | Overall survival | | Cancer specific survival | |
|---|---|---|---|---|---|
| | | HR | p value | HR | p value |
| mGPS | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.74 | <0.001 | 1.85 | <0.001 |
| | 2 | 2.91 | <0.001 | 3.06 | <0.001 |
| NLR | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.93 | <0.001 | 1.97 | <0.001 |
| PLR | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.22 | <0.001 | 1.31 | <0.001 |
| | 2 | 1.89 | <0.001 | 2.08 | <0.001 |
| PI | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 2.03 | <0.001 | 2.15 | <0.001 |
| | 2 | 2.87 | <0.001 | 3.03 | <0.001 |
| PNI | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 2.24 | <0.001 | 2.34 | <0.001 |

Patients sampled within two months following cancer diagnosis (n=4674)

| | | Overall survival | | Cancer specific survival | |
|---|---|---|---|---|---|
| | | HR | p value | HR | p value |
| mGPS | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.65 | <0.001 | 1.74 | <0.001 |
| | 2 | 2.35 | <0.001 | 2.44 | <0.001 |
| NLR | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.76 | <0.001 | 1.77 | <0.001 |
| PLR | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.19 | <0.001 | 1.24 | <0.001 |
| | 2 | 1.71 | <0.001 | 1.82 | <0.001 |
| PI | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.78 | <0.001 | 1.87 | <0.001 |
| | 2 | 2.44 | <0.001 | 2.51 | <0.001 |
| PNI | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.98 | <0.001 | 2.01 | <0.001 |

**Table 6.4. The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and Dukes stage**

| | | Overall survival | | Cancer specific survival | |
|---|---|---|---|---|---|
| n=374 | | HR | p value | HR | p value |
| mGPS | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.81 | 0.004 | 1.91 | <0.001 |
| | 2 | 2.30 | <0.001 | 2.51 | <0.001 |
| NLR | 0 | 1 | 0.102 | 1 | 0.146 |
| | 1 | 1.27 | 0.102 | 1.25 | 0.146 |
| PLR | 0 | 1 | 0.786 | 1 | 0.560 |
| | 1 | 1.16 | 0.487 | 1.30 | 0.281 |
| | 2 | 1.13 | 0.596 | 1.23 | 0.403 |
| PI | 0 | 1 | <0.001 | 1 | <0.001 |
| | 1 | 1.69 | 0.012 | 1.92 | <0.001 |
| | 2 | 2.83 | <0.001 | 3.07 | <0.001 |
| PNI | 0 | 1 | 0.059 | 1 | 0.095 |
| | 1 | 1.33 | 0.059 | 1.31 | 0.095 |

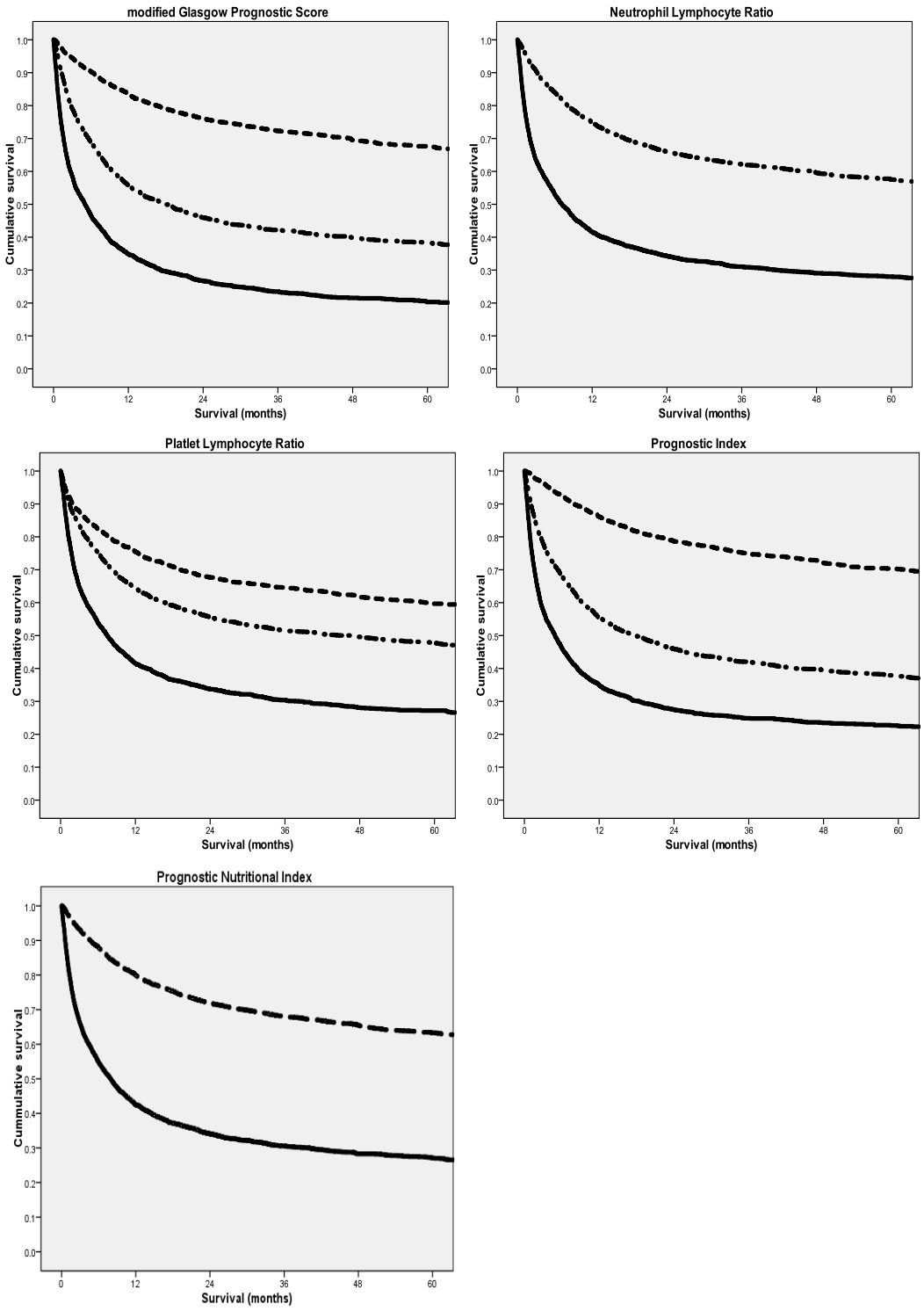
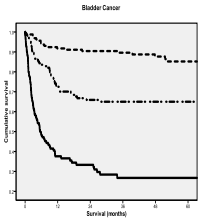
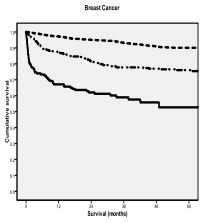
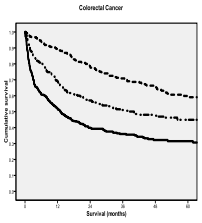


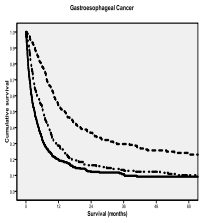

**Figure 6.1. The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in all patients (all <0.001).**

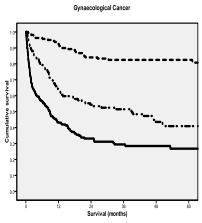
## modified Glasgow Prognostic Score

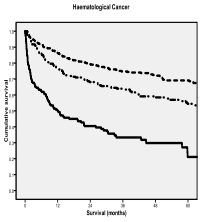


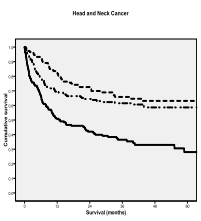



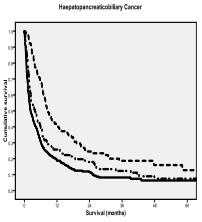



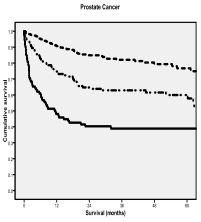



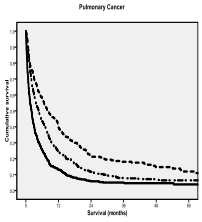



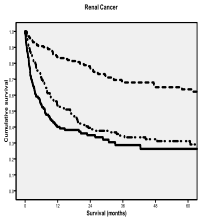



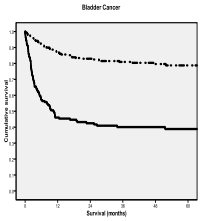



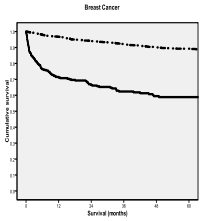



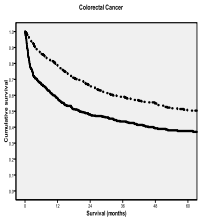



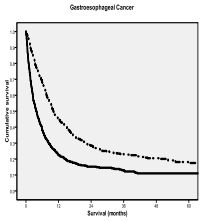



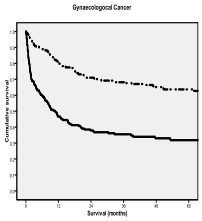

## Neutrophil Lymphocyte Ratio

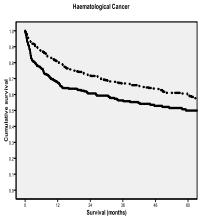


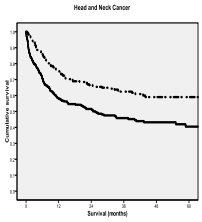



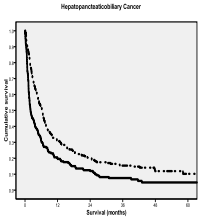



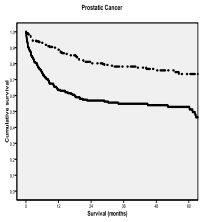



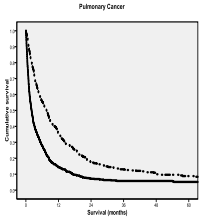



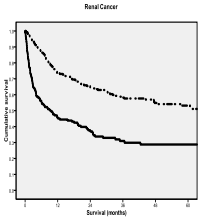



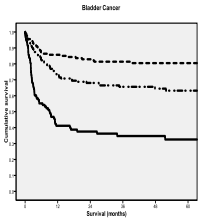



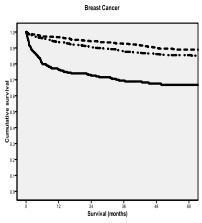



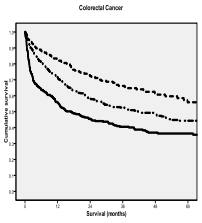



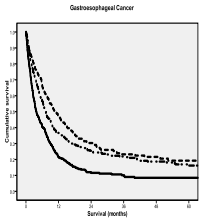



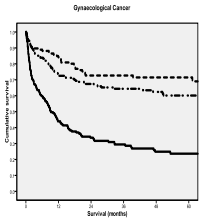
## Platelet Lymphocyte Ratio

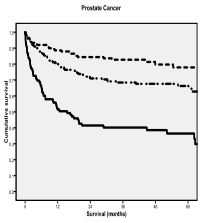


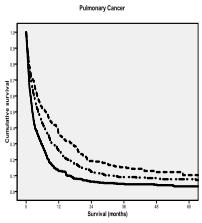



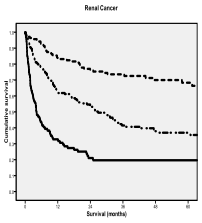



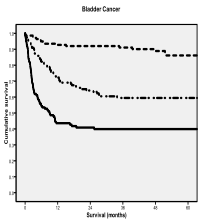



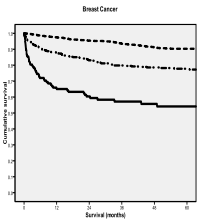



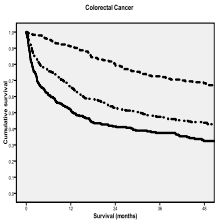



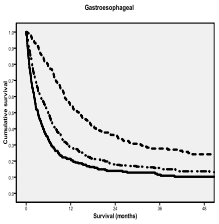



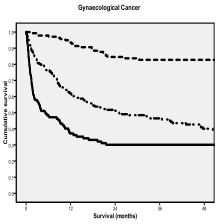

## Prognostic Index

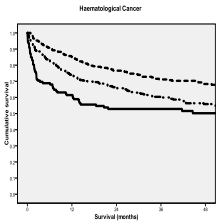


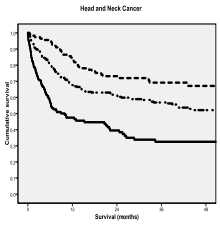



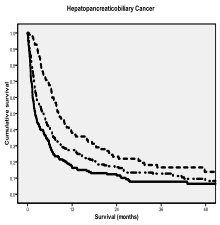



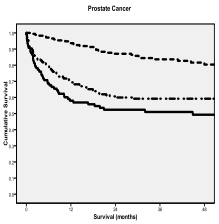



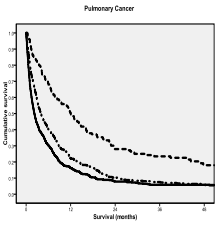



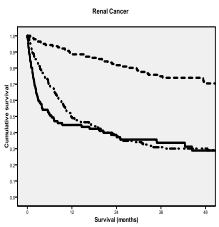



**Prognostic Nutritional Index**

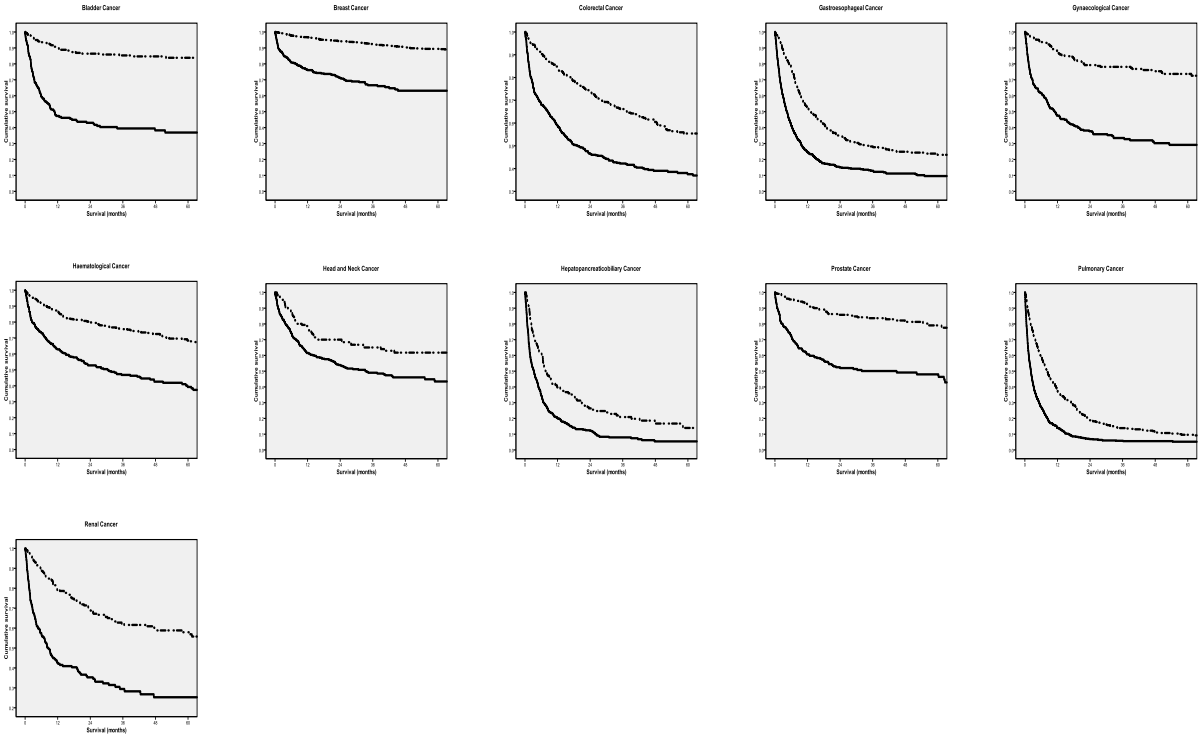



**Figure 6.2.**

**The relationship between the mGPS, NLR, PLR, PI and PNI and survival illustrated by Kaplan–Meier survival plots in each individual tumour type with only those demonstrating statistical significance ($p<0.001$) being shown.**

**For the modified Glasgow Prognostic Score in each plot, the top (small dash) line represents mGPS of 0, the middle (large dash) line represents a mGPS of 1 and the bottom (solid) line represents a mGPS of 2.**

**For the Neutrophil Lymphocyte Ratio in each plot, the top (large dash) line represents an NLR of 0 and the bottom (solid) line represents an NLR of 1.**

**For the Platelet Lymphocyte Ratio in each plot, the top (small dash) line represents PLR of 0, the middle (large dash) line represents a NLR of 1 and the bottom (solid) line represents a NLR of 2.**

**For the Prognostic Index in each plot, the top (small dash) line represents PNI of 0, the middle (large dash) line represents a PNI of 1 and the bottom (solid) line represents a PNI of 2.**

**For the Prognostic Nutritional Index in each plot, the top (large dash) line represents an PNI of 0 and the bottom (solid) line represents an NLR of 1.**

## 7.0. A DERIVED NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTS SURVIVAL IN PATIENTS WITH CANCER

### 7.1. ABSTRACT

**Introduction:** The Neutrophil Lymphocyte Ratio (NLR) has prognostic value in patients with a variety of cancers. Many chemotherapeutic trial databases hold information on white cell and neutrophil counts only. The aim of the present study was to compare the prognostic value of the NLR, with a derived score (dNLR), composed of white cell and neutrophil counts.

**Methods:** Patients (n=27,031) who were sampled incidentally between 2000 and 2007 for neutrophil, lymphocyte and white cell counts, and also had a diagnosis of cancer (Scottish Cancer Registry), were identified. Of this group 12,118 patients who had been sampled within two years of their cancer diagnosis were studied.

**Results:** On follow up, there were 7366 deaths, of which 6198 (84%) were cancer deaths. The area under the Receiver Operating Characteristic (ROC) curve for cancer specific survival was 0.650 for the NLR and 0.640 for the dNLR. The NLR and dNLR were independently associated with survival in all cancers studied (all $p<0.001$).

**Conclusion:** The results of the present study show that the dNLR, based on white cell and neutrophil counts, has similar prognostic value to the NLR. Therefore, the universally available dNLR is to be commended for use in the risk stratification of patients undergoing chemotherapy.

## 7.2. INTRODUCTION

While it has been detailed that the host immune/inflammatory response plays an important role in carcinogenesis and disease progression there is increasing interest in simple, objective methods of measuring this response in patients with cancer. The Neutrophil Lymphocyte Ratio (NLR), as detailed in Chapter 3 and 6, has been well established as a prognostic score in patients with a wide variety of cancers including those undergoing chemotherapy for cancer [Kao et al., 2010b; Chua et al., 2011b]. Although, apparently inferior to other measures of the systemic immune/inflammatory response, such as the mGPS [Proctor et al., 2011a], the NLR does have the advantage of its components being inexpensive and routinely measured in day to day oncological practice and in current chemotherapeutic cancer trials. Clearly, if such extensive data were to confirm the prognostic value and clinical utility of the NLR this would be an important, relevant, clinical translational advance in the identification of cancer patients at high risk [Clarke et al., 2011].

However, on patient entry to chemotherapeutic trials, despite having a differential white cell count carried out, only white cell and neutrophil counts are routinely entered into the clinical trial databases. The differential white cell count is broadly composed of neutrophils (50-60%), lymphocyte (20-40%), monocytes (2-6%), eosinophils (1-4%) and basophils (0.5-1%) In an attempt to allow the widespread utilisation of a similar inflammation-based score in such settings, we aimed to investigate the prognostic value of a derived NLR (dNLR), from a white cell and neutrophil count. Therefore, the aim of the present study was to compare the prognostic value of the NLR and dNLR adjusted for age, sex, deprivation and tumour site in the Glasgow Inflammation Outcome Study.

## 7.3. MATERIALS AND METHODS

From a cohort previously described in Chapter 6 [Proctor et al., 2011a], patients in the North Glasgow who were sampled incidentally for C-reactive protein, albumin, calcium and a differential white cell count between the 1st January 2000 and the 31st December 2007 were included. This time period was as such to correspond with the available follow-up data from the Scottish Cancer Registry at the time of analysis as previously detailed. The NLR was constructed as follows: NLR = Neutrophil count to Lymphocyte count. The dNLR was constructed as follows: dNLR = Neutrophil Count to (White Cell Count – Neutrophil count).

Patients with blood samples taken within two years of their cancer diagnosis were included in the analysis, and split into those sampled prior to and following cancer diagnosis. The dNLR was derived from the assumption that the white cell count is made up primarily of lymphocytes and neutrophils, and therefore, the white cell count minus the neutrophil count would be broadly similar to the lymphocyte count. As different thresholds have been suggested in the past [Ding et al., 2010; Ohno et al., 2010; Kim et al., 2010; Sharaiha et al., 2011], several were examined in order to ascertain the optimal NLR and dNLR.

Cohort linkage, with the Scottish Cancer Registry, classification of deaths and cancer coding were carried out as described in Chapter 5 and only those patients who had complete Cancer Registry follow-up were included [Proctor et al., 2011b]. Survival was calculated as described in Chapter 5 [Proctor et al., 2011b]. Patient inclusion criteria has been previously detailed and only cancer groups previously studied were included [Proctor et al., 2011a]. Cancer groups with less than 150 cancer specific deaths were excluded to ensure statistical power. Cancer stage was extracted from the registry where available.

Deprivation was measured with the Scottish Index of Multiple Deprivation (SIMD) as detailed in Chapter 1. Overall patient numbers were different in this Chapter, when compared to some previous, as the inclusion time period differed to some and longer cancer registry follow-up was available (until June 2009). The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

Statistical analysis was carried out as follows. Kaplan-Meier estimator was used to analyse the relationship between patient characteristics, tumour site and overall and cancer specific survival (Table 7.1). Receiver Operating Characteristic (ROC) curve was used to determine the sensitivity and specificity similarities between the NLR and dNLR (Figure 7.1). Cox proportional multivariate regression analysis, corrected for age, sex, deprivation and tumour site, as well as area under the ROC curve, were used to determine the relationship between different NLR and dNLR thresholds (in whole numbers) and survival in patients sampled before and after diagnosis (Tables 7.2). Box plot was used to demonstrate the relationship between the NLR, dNLR and Dukes stage in patients with colorectal cancer (Figure 7.2). Cox proportional multivariate regression analysis, corrected for age, sex, deprivation and tumour site, as well as area under ROC curve, were used to determine the relationship between optimal NLR and dNLR thresholds and survival in patients with advanced (Dukes C and D) colorectal cancer (Table 7.3). Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

## 7.4. RESULTS

From the Glasgow Inflammation Outcome Study cohort of 223,303 patients previously described in Chapter 4 [Proctor et al., 2010], 27,031 patients were identified as also having a diagnosis of cancer. Within this group, 12,119 patients had been sampled

within two years of their cancer diagnosis. Of this group, 3859 (32%) were sampled prior to a diagnosis and 8260 (68%) were sampled following diagnosis and the possible initiation of surgical or chemotherapeutic interventions.

The majority of patients were under the age of 75 years (n=9097, 75%), were female (n=6217, 51%) and were from the most deprived SIMD quintile (n=4692, 39%). The minimum follow-up from cancer diagnosis was 18 months and the maximum 132 months (median 52 months for survivors).

The relationship between patient characteristics, tumour site, and overall and cancer specific survival in all patients is shown in Table 7.1. In total 12,119 patients were studied. On follow-up, there were 7368 deaths of which 6200 (84%) were cancer related. The median time from blood sampling to diagnosis was 1.6 months in those sampled prior to diagnosis and 2.2 months in those sampled following diagnosis, suggesting that most scores reflect status at diagnosis. Increasing age, male gender, and increasing deprivation were associated with reduced 5 year overall and cancer specific survival (all $p<0.001$).

The ROC curves, using cancer specific death as an end-point (n=12,119), for NLR and dNLR is shown in Figure 7.1. The ROC curves for NLR and dNLR were 0.650 ($p<0.001$) and 0.640 ($p<0.001$) respectively. The Spearman rank correlation between the NLR and dNLR was 0.962 ($p<0.001$).

The relationship between NLR and dNLR thresholds and survival in patients sampled prior to and following diagnosis, adjusted for age, sex, deprivation and stratified by tumour site, is shown in Table 7.2. The optimal thresholds for the NLR (>4:1) and the dNLR (>2:1) in both patients sampled prior to and following diagnosis, as measured by the hazard ratios and area under the ROC curve, are highlighted.

In the present cohort, a limited number of patients had stage related data available with only colorectal cancer having stage data for over 50% of patients. Stage was only available in 29% (n=621) of patients with breast cancer and 10% (n=234) of patients with pulmonary cancer. Other cancer groups had no stage available. Of the colorectal cancer patients with stage available, 90 (9%) were Dukes A, 264 (27%) were Dukes B, 327 (33%) were Dukes C and 312 (31%) were Dukes D.

The relationship between the NLR, dNLR and Dukes stage in all patients is shown in Figure 7.2. The relationship between the NLR, dNLR and survival in patients with advanced colorectal cancer (Dukes C and D) adjusted for age, sex and deprivation is shown in Table 7.3. These patients were studied as they are likely to be similar to those entered into chemotherapeutic trials [Chua et al., 2011c]. On survival analysis (n=639), both the NLR and dNLR were associated with reduced overall and cancer specific survival independent of age, sex and deprivation (all $p<0.001$) with similar Hazard Ratios and area under the ROC curve (both $p<0.001$).

## 7.5. DISCUSSION

The results of the present Chapter show clearly that the NLR and dNLR have similar prognostic value and that they can be used similarly to predict survival in a large cohort of unselected cancer patients. Furthermore, the NLR and dNLR had similar predictive value, in all cancers as well as advanced colorectal cancer. Recently, Chua and co-workers reported that the NLR, as a marker of the systemic immune/inflammatory response, predicted clinically meaningful outcomes in patients with advanced colorectal cancer receiving chemotherapy [Chua et al., 2011a]. Taken together, these results would indicate that the derived NLR is suitable for the risk stratification of patients in chemotherapeutic trials, in particular, colorectal cancer studies.

In the present Chapter, although the ROC analysis of the NLR and dNLR were similar, the prognostic value of different thresholds was examined. It was of interest that, in contrast to the most commonly used NLR threshold of 5:1 [Walsh et al., 2005; Halazun et al., 2008; Gomez et al., 2008b], in the present Chapter 4:1 was found to have superior prognostic value in terms of Hazard Ratio and area under the ROC curve. These results are consistent with the varying NLR threshold reported across and within different tumour types. It is also of interest that the optimal threshold for the dNLR was 2:1, an expected shift from that of the NLR explained by the method of derivation. The results of the present Chapter also suggest that the dNLR has considerable potential to be adopted universally as a stratification factor in all current cancer clinical trials. Moreover, if it were shown to have such clinical utility, the dNLR would identify patients who may respond to anti-inflammatory interventions.

In the present Chapter it was of interest that there was a small but persistent superiority of the prognostic value of the NLR over the dNLR. The basis of this observation is not clear. However, in the dNLR the use of (WBC - neutrophil) as the denominator is broadly mixing two cell types, lymphocytes and monocytes, with possible opposing effects in terms of predictive value. In the normal range the relative proportion of lymphocytes to monocytes is approximately 6:1. In cancer patients there may be a fall in the absolute proportion of lymphocytes and an increase in the absolute proportion of monocytes. Even so their relative proportion is unlikely to fall below 3:1 even in advanced disease [Leitch et al., 2007]. Therefore (WBC – neutrophil) is dominated by lymphocytes and is likely to be a reasonable approximation to the lymphocyte fraction and the potential error introduced by the presence of monocytes in the fraction is therefore likely to be small. Given that different aspects of the differential white cell count have been reported to predict survival [Leitch et al., 2007; Proctor et al., 2011b; Lee et al., 2012] it is possible to derive other ratios such as

the neutrophil: white cell count ratio. However, of the differential white cell count parameters the neutrophil: lymphocyte ratio has been the most extensively validated and it was this that we were attempting to recapitulate when investigating the dNLR in the present Chapter. Clearly, where the NLR is available it should be used. However, there is a wealth of clinical trial data, where only white cell and neutrophil counts have been recorded in computer databases that could be used to examine the clinical value of the systemic immune/inflammatory response. As the present Chapter validates the use of the dNLR, this may help unlock the residual value of such clinical trial databases, and encourage the widespread utilisation of a similarly based systemic inflammation-based scores in such settings.

The results of the present Chapter also confirm the hypothesis that a total white cell count may be a useful addition to currently established prognostic markers of the systemic immune/inflammatory response such as, C-reactive protein, albumin, neutrophil and lymphocytes counts and their combinations [Proctor et al., 2011a]. It was also of interest that the hazard ratios and areas under the curves were greater from patients sampled after diagnosis, compared to patients sampled prior to diagnosis. These results would suggest that the systemic immune/inflammatory response is a more potent stimulator of cancer progression in established disease. This is consistent with the long standing observations on the "seed and soil" nature of cancer progression and metastasis [Fidler and Poste, 2008].

The present cohort has a number of limitations. The patients were selected on the presence of haematological and biochemical variables and were therefore not necessarily representative of all cancer patients in general. Patients may also have concurrent morbidity, including infection, causing alterations in their haematological variables. It is also recognised that demographic variables, such as race, that appear to influence neutrophil counts were not

available. Nevertheless, the optimal prognostic threshold for the NLR in the range of 4-5:1 has been consistently validated in different cancer cohorts (Clarke et al., 2011). It remains to be determined whether a dNLR of 2:1 will be similarly validated in different cancer cohorts.

In summary, the results of the present Chapter show that a derived NLR, based on a white cell and neutrophil counts, has similar prognostic value to the NLR. Therefore, the universally available dNLR is to be commended for use in the risk stratification of patients undergoing chemotherapy.

**Table 7.1. The relationship between patient characteristics, tumour site, and overall and cancer specific survival in all patients**

| | | n= 12,119 (%) | Overall survival 5 year % (n of deaths) n= 7368 | p-value | Cancer survival 5 year % (n of deaths) n= 6200 | p-value |
|---|---|---|---|---|---|---|
| Age | <65 years | 5425 (45) | 50 (2573) | | 54 (2316) | |
| | 65–74 years | 3672 (30) | 32 (2412) | | 39 (2041) | |
| | ≥ 75 years | 3022 (25) | 20 (2383) | <0.001 | 30 (1843) | <0.001 |
| Sex | Male | 5902 (49) | 28 (4096) | | 35 (3437) | |
| | Female | 6217 (51) | 46 (3272) | <0.001 | 52 (2763) | <0.001 |
| SIMD 2006 | 1 (least deprived) | 1698 (14) | 48 (860) | | 54 (732) | |
| | 2 | 1486 (12) | 45 (781) | | 51 (655) | |
| | 3 | 1804 (15) | 42 (1011) | | 48 (866) | |
| | 4 | 2439 (20) | 34 (1541) | | 42 (1284) | |
| | 5 (most deprived) | 4692 (39) | 30 (3175) | <0.001 | 38 (2663) | <0.001 |
| Tumour site | Breast | 2147 (18) | 78 (442) | | 84 (304) | |
| | Bladder | 562 (5) | 48 (286) | | 62 (195) | |
| | Gynaecological | 639 (5) | 47 (325) | | 53 (281) | |
| | Prostate | 709 (6) | 51 (323) | | 64 (222) | |
| | Gastroesophageal | 1085 (9) | 11 (932) | | 14 (851) | |
| | Haematological | 1210 (10) | 47 (627) | | 58 (456) | |
| | Renal | 552 (4) | 39 (324) | | 44 (285) | |
| | Colorectal | 1413 (12) | 39 (820) | | 46 (680) | |
| | Head and Neck | 738 (6) | 35 (452) | | 52 (296) | |
| | Hepatopancreaticobiliary | 721 (6) | 6 (660) | | 7 (626) | |
| | Pulmonary | 2343 (19) | 6 (2177) | <0.001 | 8 (2004) | <0.001 |

**Table 7.2. The relationship between NLR and dNLR thresholds and survival. Adjusted for age, sex, deprivation and stratified by tumour site**

| | | | Overall survival | | | Cancer survival | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | p-value | AUC | HR | p-value | AUC |
| Patient sampled prior to cancer diagnosis n=3859 | | | | | | | | |
| NLR | <1:1 | 78 (2) | 1 | | | 1 | | |
| | >1:1 | 3781 (98) | 1.03 | 0.840 | 0.507 | 0.967 | 0.859 | 0.507 |
| | <2:1 | 589 (15) | 1 | | | 1 | | |
| | >2:1 | 3270 (85) | 1.49 | <0.001 | 0.563 | 1.48 | <0.001 | 0.547 |
| | <3:1 | 1354 (35) | 1 | | | 1 | | |
| | >3:1 | 2505 (65) | 1.55 | <0.001 | 0.593 | 1.52 | <0.001 | 0.560 |
| | <4:1 | 1987 (51) | 1 | | | 1 | | |
| | >4:1 | 1872 (49) | 1.57 | <0.001 | 0.598 | 1.52 | <0.001 | 0.558 |
| | <5:1 | 2435 (63) | 1 | | | 1 | | |
| | >5:1 | 1424 (37) | 1.50 | <0.001 | 0.579 | 1.44 | <0.001 | 0.542 |
| dNLR | <1:1 | 214 (6) | 1 | | | 1 | | |
| | >1:1 | 3645 (94) | 1.17 | 0.098 | 0.518 | 1.16 | 0.163 | 0.516 |
| | <2:1 | 1399 (36) | 1 | | | 1 | | |
| | >2:1 | 2460 (64) | 1.54 | <0.001 | 0.593 | 1.53 | <0.001 | 0.563 |
| | <3:1 | 2461 (64) | 1 | | | 1 | | |
| | >3:1 | 1398 (36) | 1.47 | <0.001 | 0.575 | 1.43 | <0.001 | 0.543 |
| | <4:1 | 2960 (77) | 1 | | | 1 | | |
| | >4:1 | 899 (23) | 1.46 | <0.001 | 0.552 | 1.41 | <0.001 | 0.527 |
| | <5:1 | 3267 (85) | 1 | | | 1 | | |
| | >5:1 | 592 (15) | 1.40 | <0.001 | 0.538 | 1.33 | <0.001 | 0.517 |
| Patient sampled following cancer diagnosis n=8260 | | | | | | | | |
| NLR | <1:1 | 297 (4) | 1 | | | 1 | | |
| | >1:1 | 7963 (96) | 1.16 | 0.094 | 0.505 | 1.89 | 0.069 | 0.506 |
| | <2:1 | 1480 (18) | 1 | | | 1 | | |
| | >2:1 | 6779 (82) | 1.63 | <0.001 | 0.575 | 1.67 | <0.001 | 0.566 |
| | <3:1 | 2984 (36) | 1 | | | 1 | | |
| | >3:1 | 5275 (64) | 1.85 | <0.001 | 0.641 | 1.93 | <0.001 | 0.629 |
| | <4:1 | 4104 (50) | 1 | | | 1 | | |
| | >4:1 | 4155 (50) | 1.86 | <0.001 | 0.661 | 1.92 | <0.001 | 0.646 |
| | <5:1 | 4872 (59) | 1 | | | 1 | | |
| | >5:1 | 3387 (41) | 1.82 | <0.001 | 0.657 | 1.86 | <0.001 | 0.642 |
| dNLR | <1:1 | 656 (8) | 1 | | | 1 | | |
| | >1:1 | 7604 (92) | 1.35 | <0.001 | 0.521 | 1.39 | <0.001 | 0.519 |
| | <2:1 | 3083 (37) | 1 | | | 1 | | |
| | >2:1 | 5176 (63) | 1.76 | <0.001 | 0.630 | 1.83 | <0.001 | 0.620 |
| | <3:1 | 4978 (60) | 1 | | | 1 | | |
| | >3:1 | 3281 (40) | 1.74 | <0.001 | 0.644 | 1.78 | <0.001 | 0.631 |
| | <4:1 | 6034 (73) | 1 | | | 1 | | |
| | >4:1 | 2225 (27) | 1.75 | <0.001 | 0.619 | 1.78 | <0.001 | 0.609 |
| | <5:1 | 6632 (80) | 1 | | | 1 | | |
| | >5:1 | 1627 (20) | 1.76 | <0.001 | 0.595 | 1.80 | <0.001 | 0.589 |

**Table 7.3. The relationship between the NLR, dNLR and survival in patients with advanced colorectal cancer (Dukes C and D). Adjusted for age, sex and deprivation.**

| | | | Overall survival | | | Cancer specific survival | | |
|---|---|---|---|---|---|---|---|---|
| | | n = 639 (%) | HR | p-value | AUC | HR | p-value | AUC |
| NLR | <4:1 | 278 (44) | 1 | | | 1 | | |
| | >4:1 | 361 (56) | 1.60 | <0.001 | 0.584 | 1.60 | <0.001 | 0.565 |
| dNLR | <2:1 | 194 (30) | 1 | | | 1 | | |
| | >2:1 | 445 (70) | 1.61 | <0.001 | 0.575 | 1.67 | <0.001 | 0.566 |

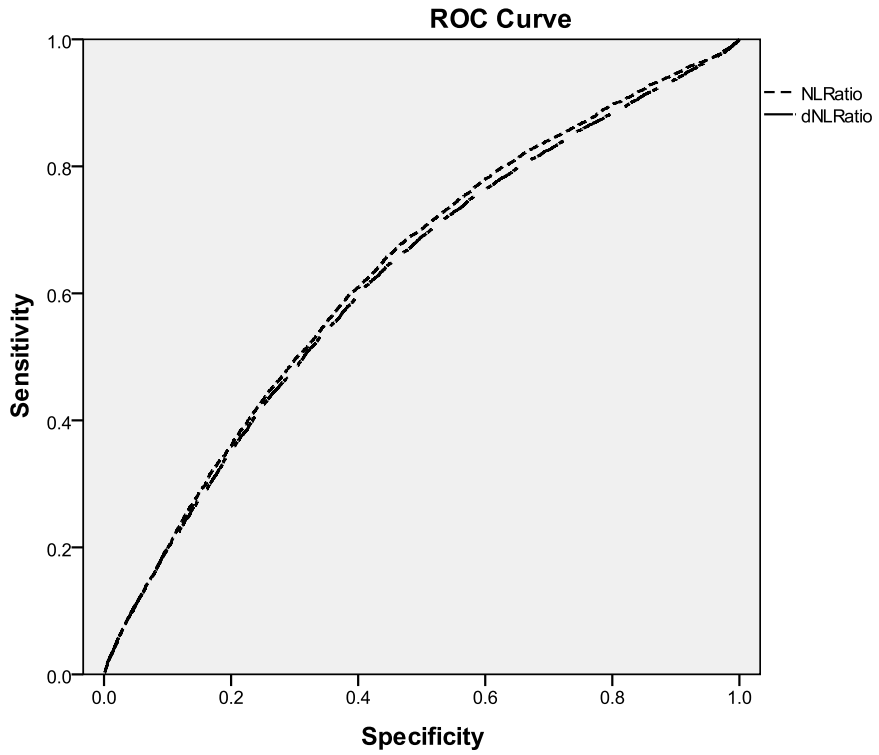



**Figure 7.1. Receiver Operating Characteristic curve for cancer specific survival.**

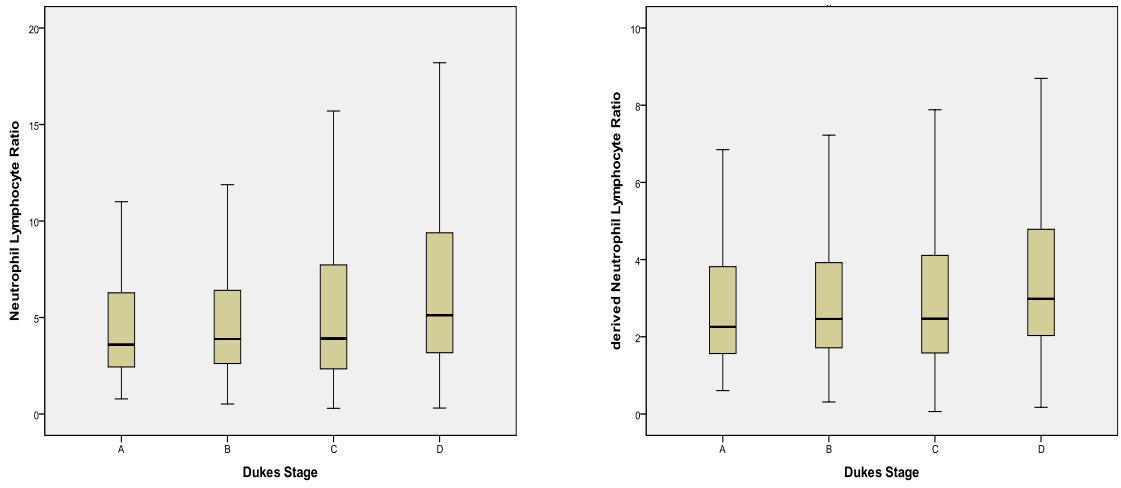



**Figure 7.2. The relationship between NLR, dNLR and Dukes stage in patients with colorectal cancer.**

# CHAPTER 8. OPTIMISATION OF THE SYSTEMIC INFLAMMATION-BASED GLASGOW PROGNOSTIC SCORE IN PATIENTS WITH CANCER (oGPS)

## 8.1. ABSTRACT

**Introduction:** The modified Glasgow Prognostic Score (mGPS), an inflammation-based prognostic score that uses thresholds of C-reactive protein (>10mg/l) and albumin (<35g/l), is independently prognostic of survival in cancer. The aim of the present chapter was to establish whether the addition of a differential white cell count and a high sensitivity C-reactive protein measurement enhances the prognostic value of the mGPS.

**Methods:** Patients (n=12,119) who had an incidental blood sample taken between 2000 and 2007 for C-reactive protein, albumin and a differential white cell count, as well as a diagnosis of cancer made within two years were identified. This group were studied for the prognostic value of neutrophil, lymphocyte, and platelet counts. Also, patients (n=2743) sampled following the introduction of high sensitivity C-reactive protein measurements were studied for the prognostic value of different thresholds.

**Results:** The prognostic value of the mGPS (HR 2.61, p<0.001, AUC 0.715), using cancer specific survival as an end-point, was improved by the addition of neutrophil and platelet counts (HR 4.86, p<0.001, AUC 0.734 ) and a high sensitivity C-reactive protein measurement (>3mg/l, HR 5.77, p<0.001, AUC 0.734).

**Conclusion:** The results of the present chapter showed that the addition of neutrophil and platelet counts, as well as a high sensitivity C-reactive protein measurement, enhanced the prognostic value of the Glasgow Prognostic Score.

## 8.2. INTRODUCTION

As has been detailed in previous Chapters, the host immune/inflammatory response plays an important role in carcinogenesis and disease progression. It has also been demonstrated that a range of inflammation-based scores have prognostic value in patients with cancer [Proctor et al., 2011a]. Moreover, it appeared that the inclusion of a white cell count, may add prognostic value to the validated mGPS [Proctor et al., 2011a]. Also, the recent introduction of high sensitivity C-reactive protein measurements in routine clinical laboratory analysis has resulted in the threshold sensitivity being lowered from approximately 5mg/l to 0.05mg/l. This has raised the possibility that the combination of C-reactive protein and albumin may be further modified to take account of the potential additional prognostic value that could be derived from the components of a differential white cell count (neutrophil, lymphocyte, platelet counts) and high sensitivity C-reactive protein measurement.

The aim of the present Chapter was to establish whether the addition of a differential white cell count or a high sensitivity C-reactive protein measurement could enhance the prognostic value of the Glasgow Prognostic Score.

## 8.3. MATERIALS AND METHODS

From a cohort previously described in Chapter 6 [Proctor et al., 2011a], patients in North Glasgow who were sampled incidentally for C-reactive protein, albumin, calcium and a differential white cell count between the 1st January 2000 and the 31st December 2007 were included. This time period was as such to correspond with the available follow-up data from the Scottish Cancer Registry at the time of analysis. Prior to the introduction of high-sensitivity C-reactive protein measurements, the limit of detection was a concentration of less

than 5mg/L and 0.05mg/l thereafter. Only those patients undergoing blood sampling after the introduction of the routine measurement of high sensitivity C-reactive protein (1st of August 2006), were included in the analysis investigating the prognostic value of high sensitivity thresholds (<5mg/l). Standardised thresholds for white cell count ($>11\times10^9$/l), neutrophil count ($>7.5\times10^9$/l), lymphocyte count ($>3\times10^9$/l) and platelet count ($>400\times10^9$/l) were used. High sensitivity C-reactive protein thresholds, <1mg/l and <3mg/l, previously reported to be associated with survival were investigated [Ridker, 2008]. The validated GPS and mGPS were constructed as described in Table 3.1. Patients with blood samples taken within two years of their cancer diagnosis were included in the analysis, and split into those sampled prior to and following cancer diagnosis. Cohort linkage, with the Scottish Cancer Registry, classification of deaths and cancer coding were carried out as described in Chapter 5 and only those patients who had complete Cancer Registry follow-up were included [Proctor et al., 2011b]. Survival was calculated as described in Chapter 5 [Proctor et al., 2011b]. Cancer groups with less than 150 cancer specific deaths were excluded to ensure statistical power. Cancer stage was extracted from the registry where available.

Deprivation was measured with the Scottish Index of Multiple Deprivation (SIMD) as detailed in Chapter 1 [Proctor et al., 2010]. Patient inclusion criteria has been previously detailed and only cancer groups previously studied were included [Proctor et al., 2011a]. Overall patient numbers were different in this Chapter, when compared to previous, as the inclusion time period differed to some and longer cancer registry follow-up was available (until July 2009). The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

Statistical analysis was carried out as follows. The relationship between patient demographics, tumour site, markers of the systemic immune/inflammatory response and

survival was assessed using the Kaplan-Meier and Cox proportional hazards methods and Area Under the receiver operating characteristic Curve (AUC). Cox proportional hazards model stratified by tumour site, adjusted for age, sex, deprivation, time of sample and stratified by tumour site, and AUC was used to analyse the relationship between the components of a differential white cell count and high sensitivity C-reactive protein and survival. In those patients with a high sensitivity C-reactive protein measurement, the prognostic value of the addition of the components of a differential white cell count and high sensitivity C-reactive protein to the GPS was examined with Cox proportional hazards model stratified for age, sex, deprivation, time of sample and stratified by tumour and the AUC. Given the number of statistical comparisons, a p value of $<0.01$ was considered to have statistical significance in the analysis. Analysis was performed using SPSS software (SPSS, Chicago, IL, USA).

## 8.4. RESULTS

From GIOS cohort of 223,303 patients originally described [Proctor et al., 2010], 27,031 patients were identified as having a diagnosis of cancer in SCR and a blood sample for C-reactive protein, albumin and a differential white cell count taken between January 2000 and December 2007. Within this group, 12,119 patients had been sampled within two years of their cancer diagnosis, 3859 (32%) sampled prior to and 8260 (68%) following. Most patients were under 75 years of age (n=9097, 75%) and female (n=6217, 51%). Thirty nine percent of patients (n=4692) were SIMD 5.

The relationship between patient demographics, tumour site, markers of systemic inflammation and five year survival in all patients (n=12,119) is shown in Table 8.1. There were 7368 deaths in total with 6200 being cancer specific. The median time from blood

sample to diagnosis was 2 months, suggesting that most scores reflect status at diagnosis. The minimum follow-up from cancer diagnosis for all patients was 18 months and the maximum 138 months (median 52 months for survivors). Increasing age, male gender, and increasing deprivation were associated with reduced 5 year overall and cancer specific survival (all $p<0.001$). High C-reactive protein (>10mg/l), white cell, neutrophil and platelet count and low albumin and lymphocyte count were associated with a reduced 5 year overall and cancer specific survival (all $p<0.001$).

The relationship between patient demographics, standard threshold C-reactive protein measurement (>10mg/l), albumin, white cell, lymphocyte, neutrophil and platelet count and survival, stratified by tumour site and time of sample, is shown in Table 8.2. Increasing age, sample prior to diagnosis as well as high C-reactive protein (>10mg/l), neutrophil and platelet count, as well as low albumin were all independently associated with a reduction in overall and cancer specific survival (all $p<0.01$).

When the relationship between high sensitivity C-reactive protein thresholds and survival was investigated in patients sampled following the routine introduction of high sensitivity measurements (n=2742), no statistical difference between a high sensitivity C-reactive protein concentration of <1mg/L and 1-3mg/L was found. A threshold of >3mg/L was therefore used.

The relationship between patient demographics, high sensitivity C-reactive protein measurements (>3mg/l), albumin, white cell, lymphocyte, neutrophil and platelet counts and survival (n=2743): stratified by tumour site in only those patients sampled following the routine introduction of high sensitivity measurements is shown in Table 8.3. Increasing age, sample prior to diagnosis as well as high C-reactive protein (>3mg/l), neutrophil and platelet

count, as well as low albumin were all independently associated with a reduction in overall and cancer specific survival (all $p<0.01$).

The hazard ratios and the areas under the receiver operator characteristic (ROC) curve in patients sampled following the introduction of high sensitivity C-reactive protein measurements (n=2743), adjusted for age, sex, deprivation, tumour site and time of sampling, for a high sensitivity C-reactive protein threshold of >3mg/l for overall and cancer specific mortality were calculated. These were HR 2.47 (95% CI 2.08 - 2.94), AUC 0.636 ($p<0.001$) and HR 2.64 (95% CI 2.19-3.18), AUC 0.625 ($p<0.001$) respectively compared with the HR 2.13 (95% CI 1.89-2.40), AUC 0.676 for overall ($p<0.001$) and cancer specific HR 2.22 (95% CI 1.96-2.52), AUC 0.665 ($p<0.001$) mortality using the standard threshold of 10mg/l. Therefore, since they were similar, when optimising the GPS, both the highly sensitive and standard threshold for C-reactive protein (10mg/l) were taken forward with other measures of the systemic immune/inflammatory response.

When the interrelationships between inflammatory markers in patients sampled following the introduction of high sensitivity C-reactive protein, were explored (n=2743), C-reactive protein was inversely associated with albumin ($rs=0.691$, $p<0.001$), lymphocyte count ($rs=0.334$, $p<0.001$) and directly associated with white cell count ($rs=0.334$, $p<0.001$), neutrophil count ($rs=0.399$, $p<0.001$) and platelet count ($rs=0.172$, $p<0.001$). Albumin was inversely associated with white cell count ($rs=0.268$, $p<0.001$), neutrophil count ($rs=0.352$, $p<0.001$), platelet count ($rs=0.145$, $p<0.001$) and directly associated with lymphocyte count ($rs=0.332$, $p<0.001$). White cell count was directly associated with lymphocyte count ($rs=0.0187$, $p<0.001$), neutrophil count ($rs=0.951$, $p<0.001$) and platelet count ($rs=0.346$, $p<0.001$). Lymphocyte count was inversely associated with neutrophil count ($rs=0.049$,

p<0.05) and directly associated with platelet count (rs=0.179, p<0.001). Neutrophil count was directly associated with platelet count (rs=0.335, p<0.001).

The optimisation of the Glasgow Prognostic Score in patients sampled following the introduction of high sensitivity C-reactive protein is shown in Table 8.4 (n=2743). All combinations of inflammatory markers were predictive of overall and cancer specific survival (all p<0.001) independent of age, sex, time of sample and tumour site. A score combining C-reactive protein, albumin, and neutrophil count had an improved prognostic value, in terms of increased hazard ratio and area under the ROC curve, when compared to the GPS or mGPS. Further addition of a high sensitivity C-reactive improved the hazard ratio range, and thus offers the potential to better differentiate between those who will do well and those that will do badly. However, it did not increase the area under the ROC curve and therefore did not improve its overall prognostic value.

The relationship between the Glasgow Prognostic Scores and survival in patients studied following the introduction of high sensitivity C-reactive protein, is shown in Figure 8.1 (n=2743).

## 8.5. DISCUSSION

The results of the present Chapter show that, in a large cohort (n=12,119) of patients with cancer, routine objective markers of the systemic immune/inflammatory response, elevated neutrophil and platelet counts, enhance the prognostic value of the Glasgow Prognostic Score independent of age, sex, deprivation, tumour site and time of sampling. In a selected cohort of patients (n=2743) with high sensitivity C-reactive protein measurements, a lower threshold for C-reactive protein was associated with a larger range of hazard ratios, thus potential better differentiation of patients who will do particularly well, but no

improvement in the overall AUC of the Glasgow Prognostic Score, when combined with neutrophil and platelet counts.

Taken together, these additions to the GPS, have led to an increase in the hazard ratios associated with overall and cancer specific survival by approximately 100%. Therefore, the refinement of the GPS with other components of the systemic immune/inflammatory response appears to have improved the prognostic value and clinical utility of the Glasgow Prognostic Score.

It is of interest that in the present Chapter of patients with cancer, it was identified that, high sensitivity C-reactive protein measurements >3mg/l were associated with reduced survival. This is consistent with recent publications in cancer cohorts using the same threshold [Koenig et al., 2008; Ito et al., 2011; Nakamura et al., 2012]. The results of the present Chapter are also in agreement with previous workers [Gagnon et al., 2010] who reported, in patients with non-small cell lung cancer, that while an increase risk of mortality occurs with a C-reactive protein measurement above approximately 4mg/l, the risk increase is steeper between 8 and 16 mg/l. Indeed, some workers have adopted other thresholds for C-reactive protein such as >5mg/l into the GPS [Toiyama et al., 2011].

The same high sensitivity C-reactive protein threshold (>3mg/l) has also been used to predict survival in non-cancer cohorts [Tuomisto et al., 2006; Zacho et al., 2010]. Taken together, the results would suggest that a C-reactive protein of 3mg/l is a potentially important threshold in both cancer and non-cancer cohorts. It raises the possibility that inflammation-based prognostic scores such as those examined in the present Chapter will have prognostic value in non-cancer cohorts. Further work in large non-cancer cohorts is required to examine the hypothesis that the Glasgow Prognostic Score, in combination with

neutrophil and platelet counts, as well as high sensitivity C-reactive protein, also independently predicts non-cancer specific survival.

Over the last decade, with the validation and establishment of simple, objective systemic inflammation-based prognostic scores it has become recognised that activation of the systemic immune/inflammatory response has a detrimental impact on the outcome of cancer patients [Roxburgh and McMillan, 2010]. More recently, there has been renewed interest on the beneficial impact of an activated local immune/inflammatory response on the outcome of cancer patients [Pinato et al., 2012]. Therefore, the relationship between the systemic and local immune/inflammatory responses is likely to be of considerable and increasing interest in future years.

The present cohort has a number of limitations. The patients were selected on the basis that measurements of C-reactive protein, albumin and a differential white cell count had been performed and were therefore not necessarily representative of all cancer patients diagnosed and treated in the North Glasgow area. It is also recognised that patients with cancer may have concurrent morbidity causing a rise in their C-reactive protein and derangement of their albumin and other haematological parameters.

In summary, the addition of the constituents of a differential white cell count and high sensitivity C-reactive protein measurements can be used to improved the prognostic value and clinical utility of the Glasgow Prognostic Score. This optimised Glasgow Prognostic Score can be adopted to predict cancer survival where differential white cell counts and high sensitivity C-reactive protein measurements are available.

**Table 8.1. The relationship between patient demographics, tumour site, inflammatory markers and survival in all patients**

| n=12,119 | | | Patients n=12 119 (%) | Overall survival 5 year % (n of deaths) n= 7368 | p-value | Cancer survival 5 year % (n of deaths) n= 6200 | p-value |
|---|---|---|---|---|---|---|---|
| Age | <65 years | | 5425 (45) | 50 (2573) | | 54 (2316) | |
| | 65–74 years | | 3672 (30) | 32 (2412) | | 39 (2041) | |
| | ≥ 75 years | | 3022 (25) | 20 (2383) | <0.001 | 30 (1843) | <0.001 |
| Sex | Male | | 5902 (49) | 28 (4096) | | 35 (3437) | |
| | Female | | 6217 (51) | 46 (3272) | <0.001 | 52 (2763) | <0.001 |
| SIMD 2006 | 1 (least deprived) | | 1698 (14) | 48 (860) | | 54 (732) | |
| | 2 | | 1486 (12) | 45 (781) | | 51 (655) | |
| | 3 | | 1804 (15) | 42 (1011) | | 48 (866) | |
| | 4 | | 2439 (20) | 34 (1541) | | 42 (1284) | |
| | 5 (most deprived) | | 4692 (39) | 30 (3175) | <0.001 | 38 (2663) | <0.001 |
| Tumour site | Breast | | 2147 (18) | 78 (442) | | 84 (304) | |
| | Bladder | | 562 (5) | 48 (286) | | 62 (195) | |
| | Gynaecological | | 639 (5) | 47 (325) | | 53 (281) | |
| | Prostate | | 709 (6) | 51 (323) | | 64 (222) | |
| | Gastroesophageal | | 1085 (9) | 11 (932) | | 14 (851) | |
| | Haematological | | 1210 (10) | 47 (627) | | 58 (456) | |
| | Renal | | 552 (4) | 39 (324) | | 44 (285) | |
| | Colorectal | | 1413 (12) | 39 (820) | | 46 (680) | |
| | Head and Neck | | 738 (6) | 35 (452) | | 52 (296) | |
| | Hepatopancreaticobiliary | | 721 (6) | 6 (660) | | 7 (626) | |
| | Pulmonary | | 2343 (19) | 6 (2177) | <0.001 | 8 (2004) | <0.001 |
| Inflammatory markers | C-reactive protein | <10mg/l | 5146 (42) | 56 (2143) | | 63 (1708) | |
| | | >10mg/l | 6973 (58) | 23 (5225) | <0.001 | 30 (4492) | <0.001 |
| | Albumin | >35g/l | 8354 (69) | 46 (4388) | | 53 (3627) | |
| | | <35g/l | 3765 (31) | 17 (2980) | <0.001 | 23 (2573) | <0.001 |
| | White cell count | $<11\times10^9$/l | 9104 (75) | 42 (5043) | | 49 (4213) | |
| | | $>11\times10^9$/l | 3015 (25) | 21 (2325) | <0.001 | 28 (1987) | <0.001 |
| | Neutrophil count | $<7.5\times10^9$/l | 8334 (69) | 44 (4444) | | 51 (3699) | |
| | | $>7.5\times10^9$/l | 3785 (31) | 21 (2924) | <0.001 | 28 (2501) | <0.001 |
| | Lymphocyte count | $<3\times10^9$/l | 11 554 (95) | 37 (7071) | | 44 (5957) | |
| | | $>3\times10^9$/l | 565 (5) | 44 (297) | <0.001 | 51 (243) | <0.001 |
| | Platelet count | $<400\times10^9$/l | 10 254 (85) | 40 (5889) | | 48 (4884) | |
| | | $>400\times10^9$/l | 1865 (15) | 19 (1479) | <0.001 | 24 (1316) | <0.001 |

**Table 8.2. The relationship between patient demographics, C-reactive protein (>10mg/l), albumin, differential white cell count and survival. Stratified by tumour site**

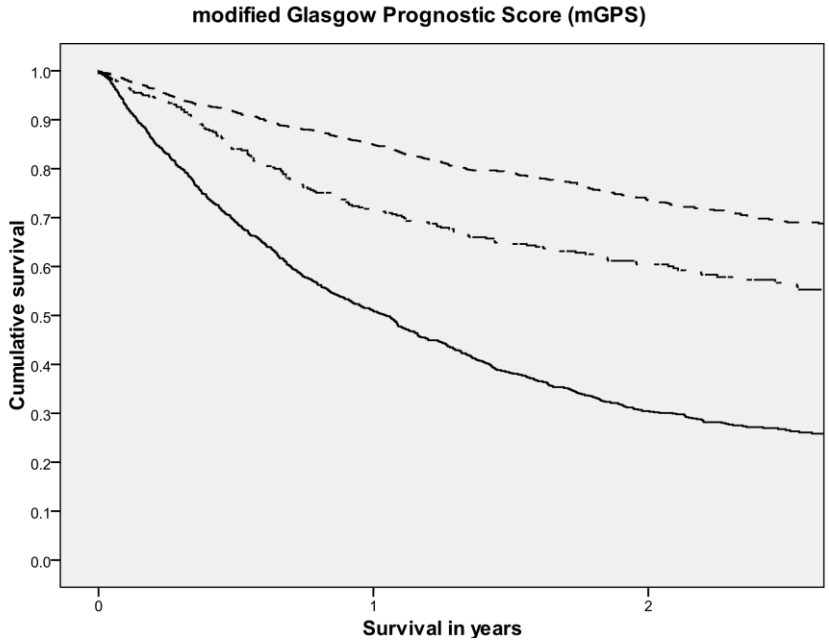
| | | Overall survival | | | | | Cancer specific survival | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | | Univariate | | Multivariate | | |
| n=12,119 | | HR | p-value | HR | p-value | AUC | HR | p-value | HR | p-value | AUC |
| Age | <65/ | 1 | | 1 | | | 1 | | 1 | | |
| | 65-74 | 1.37 | <0.001 | 1.28 | <0.001 | | 1.24 | <0.001 | 1.17 | | |
| | >75 | 2.09 | <0.001 | 1.93 | <0.001 | | 1.73 | <0.001 | 1.60 | <0.001 | |
| Sex | Male | 1 | | | | | 1 | | | | |
| | Female | 0.96 | 0.101 | | | | 0.97 | 0.268 | | | |
| SIMD | 1 | 1 | | | | | 1 | | | | |
| | 2 | 1.04 | 0.343 | | | | 1.02 | 0.735 | | | |
| | 3 | 1.05 | 0.226 | | | | 1.04 | 0.471 | | | |
| | 4 | 1.16 | <0.001 | | | | 1.11 | 0.029 | | | |
| | 5 | 1.23 | <0.001 | | | | 1.17 | <0.001 | | | |
| Time of sample | Pre diag | 1 | | 1 | | | 1 | | 1 | | |
| | Post diag | 0.73 | <0.001 | 0.67 | <0.001 | | 0.78 | <0.001 | 0.70 | <0.001 | |
| C-reactive protein | <10mg/l | 1 | | | | | 1 | | 1 | | |
| | >10mg/l | 1.94 | <0.001 | 1.53 | <0.001 | 0.671 | 2.01 | <0.001 | 1.61 | <0.001 | 0.653 |
| Albumin | >35mg/l | 1 | | | | | 1 | | 1 | | |
| | <35mg/l | 1.82 | <0.001 | 1.55 | <0.001 | 0.620 | 1.82 | <0.001 | 1.53 | <0.001 | 0.607 |
| White cell count | $<11\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>11\times10^9$/l | 1.49 | <0.001 | 1.06 | 0.166 | | 1.48 | <0.001 | 1.05 | 0.237 | |
| Lymphocyte count | $<3\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>3\times10^9$/l | 0.77 | <0.001 | 0.86 | 0.012 | | 0.75 | <0.001 | 0.84 | 0.010 | |
| Neutrophil count | $<7.5\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>7.5\times10^9$/l | 1.59 | <0.001 | 1.28 | <0.001 | 0.608 | 1.58 | <0.001 | 1.26 | <0.001 | 0.593 |
| Platelet count | $<400\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>400\times10^9$/l | 1.37 | <0.001 | 1.15 | <0.001 | 0.560 | 1.41 | <0.001 | 1.17 | <0.001 | 0.560 |

**Table 8.3. The relationship between patient demographics, high sensitivity C-reactive protein (>3mg/l), albumin, differential white cell count and survival. Stratified by tumour site**

| | | Overall survival | | | | | Cancer specific survival | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | | Univariate | | Multivariate | | |
| n=2743 | | HR | p-value | HR | p-value | AUC | HR | p-value | HR | p-value | AUC |
| Age | <65/ | 1 | | 1 | | | 1 | | 1 | | |
| | 65-74 | 1.20 | 0.003 | 1.11 | 0.104 | | 1.12 | 0.085 | 1.03 | 0.657 | |
| | >75 | 1.73 | <0.001 | 1.55 | <0.001 | | 1.50 | <0.001 | 1.34 | <0.001 | |
| Sex | Male | 1 | | | | | 1 | | | | |
| | Female | 1.04 | 0.554 | | | | 1.04 | 0.547 | | | |
| SIMD | 1 | 1 | | | | | 1 | | | | |
| | 2 | 0.94 | 0.558 | | | | 0.94 | 0.576 | | | |
| | 3 | 1.07 | 0.513 | | | | 1.08 | 0.490 | | | |
| | 4 | 1.15 | 0.148 | | | | 1.14 | 0.205 | | | |
| | 5 | 1.21 | 0.034 | | | | 1.17 | 0.093 | | | |
| Time of sample | Pre Diag | 1 | | 1 | | | 1 | | 1 | | |
| | Post Diag | 0.86 | <0.001 | 0.62 | <0.001 | | 0.87 | <0.001 | 0.63 | <0.001 | |
| C-reactive protein | <3mg/l | 1 | | 1 | | | 1 | | 1 | | |
| | >3mg/l | 2.54 | <0.001 | 1.63 | <0.001 | 0.636 | 2.68 | <0.001 | 1.72 | <0.001 | 0.625 |
| Albumin | >35mg/l | 1 | | 1 | | | 1 | | 1 | | |
| | <35mg/l | 2.37 | <0.001 | 1.97 | <0.001 | 0.700 | 2.42 | <0.001 | 2.01 | <0.001 | 0.685 |
| White cell count | $<11\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>11\times10^9$/l | 1.65 | <0.001 | 1.04 | 0.672 | | 1.65 | <0.001 | 1.03 | 0.748 | |
| Neutrophil count | $<7.5\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>7.5\times10^9$/l | 1.78 | <0.001 | 1.39 | <0.001 | 0.621 | 1.76 | <0.001 | 1.35 | <0.001 | 0.609 |
| Lymphocyte count | $<3\times10^9$/l | 1 | | | | | 1 | | | | |
| | $>3\times10^9$/l | 0.76 | 0.043 | | | | 0.69 | 0.012 | | | |
| Platelet count | $<400\times10^9$/l | 1 | | 1 | | | 1 | | 1 | | |
| | $>400\times10^9$/l | 1.58 | <0.001 | 1.26 | 0.001 | 0.575 | 1.68 | <0.001 | 1.31 | <0.001 | 0.578 |

**Table 8.4. Optimisation of the Glasgow Prognostic Score in patients sampled following the introduction of high sensitivity C-reactive protein measurement. Survival adjusted for age, sex, time of sample and stratified by tumour site**

| n=2743 | | | Cancer specific survival | | | Overall survival | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | p-value | AUC | HR | p-value | AUC |
| GPS | 0 | 955 (35) | 1 | | | 1 | | |
| | 1 | 621 (23) | 1.86 | | | 1.88 | | |
| | 2 | 1166 (42) | 3.18 | <0.001 | 0.731 | 3.33 | <0.001 | 0.715 |
| mGPS | 0 | 1204 (44) | 1 | | | 1 | | |
| | 1 | 372 (14) | 1.30 | | | 1.32 | | |
| | 2 | 1166 (42) | 2.49 | <0.001 | 0.707 | 2.61 | <0.001 | 0.695 |
| CRP > 10mg/l | 0 | 847 (30.9) | 1 | | | 1 | | |
| +Albumin >35g/L | 1 | 537 (19.6) | 1.64 | | | 1.70 | | |
| +Neutrophils >7.5×109/l | 2 | 790 (28.8) | 2.65 | | | 2.80 | | |
| | 3 | 568 (20.7) | 3.96 | <0.001 | 0.746 | 4.12 | <0.001 | 0.726 |
| CRP > 10mg/l | 0 | 813 (29.6) | 1 | | | 1 | | |
| + Albumin >35g/L | 1 | 513 (18.7) | 1.59 | | | 1.65 | | |
| + Neutrophils>7.5×109/l | 2 | 706 (25.7) | 2.49 | | | 2.63 | | |
| + Platelets >400×109/l | 3 | 505 (18.4) | 3.59 | | | 3.79 | | |
| | 4 | 205 (7.5) | 4.58 | <0.001 | 0.751 | 4.86 | <0.001 | 0.734 |
| hs-CRP >3mg/l | 0 | 508 (18.5) | 1 | | | 1 | | |
| + Albumin >35g/L | 1 | 635 (23.2) | 1.61 | | | 1.62 | | |
| + Neutrophils>7.5×109/l | 2 | 815 (29.7) | 2.72 | | | 2.88 | | |
| + Platelets >400×109/l | 3 | 571 (20.8) | 4.14 | | | 4.32 | | |
| | 4 | 213 (7.8) | 5.46 | <0.001 | 0.751 | 5.77 | <0.001 | 0.734 |



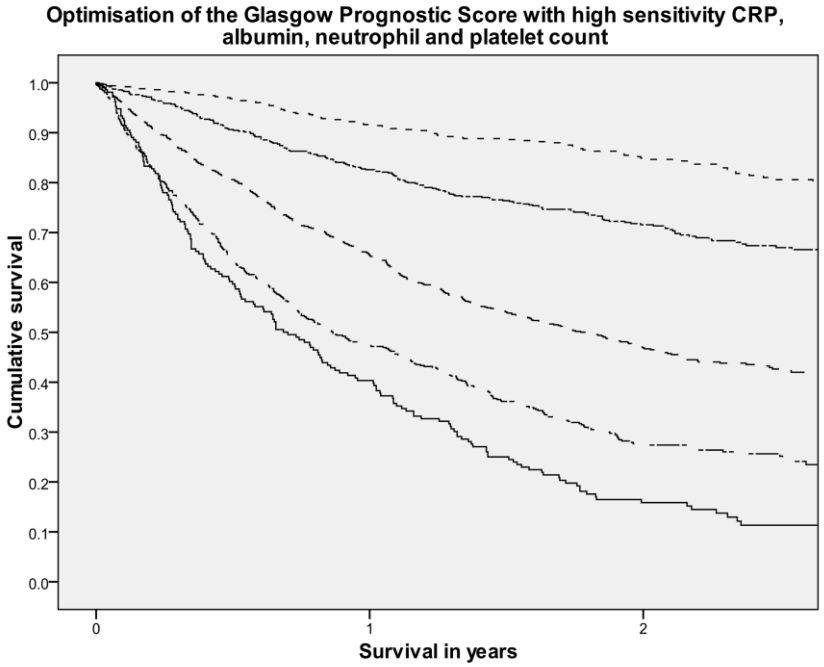




**Figure 8.1. The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line) and the optimisation of the Glasgow Prognostic Score with high sensitivity CRP, albumin, neutrophil and platelet count (0-top, small dash line; 1-upper dot and dash line, 2-middle large dash line, 3-lower separated dot and dash line, 4-bottom, solid line) and survival.**

# CHAPTER 9. SYSTEMIC INFLAMMATION-BASED SCORE PREDICTS ALL-CAUSE, CARDIOVASCULAR AND CEREBROVASCULAR MORTALITY

## 9.1. ABSTRACT

**Introduction:** Markers of the systemic inflammatory response have been shown to be prognostic of survival in patients with cancer. The aim of the present chapter was to examine the prognostic relationship between C-reactive protein, albumin, neutrophil, lymphocyte and platelet counts with all-cause, cancer, cardiovascular and cerebrovascular mortality.

**Methods:** Patients (n=160,481) who had an incidental blood sample taken between 2000 and 2008 were studied for the prognostic value of C-reactive protein (>10mg/l), albumin, neutrophil, lymphocyte and platelet counts. Also, patients (n=52,091) sampled following the introduction of high sensitivity C-reactive protein (>3mg/l) measurements were studied. A combination of these markers were used to make cumulative inflammation-based scores.

**Results:** In all patients (n=160,481) C-reactive protein (>10mg/l) (HR 2.71, p<0.001), albumin (>35mg/l) **(**HR 3.68, p<0.001) and neutrophil counts (HR 2.18, p<0.001) were independently predictive of all-cause mortality. These associations were also observed in cancer, cardiovascular and cerebrovascular mortality before and after the introduction of high sensitivity C-reactive protein measurements (>3mg/l) (n=52,091). A combination of high sensitivity C-reactive protein (>3mg/l), albumin and neutrophil count predicted all-cause (HR 7.37, p<0.001, AUC 0.723), cancer (HR 9.32, p<0.001, AUC 0.731), cardiovascular (HR 4.03, p<0.001, AUC 0.650) and cerebrovascular (HR 3.10, p<0.001, AUC 0.623) mortality.

**Conclusion:** The results of the present study showed that an inflammation-based prognostic score, combining high sensitivity C-reactive protein, albumin and neutrophil counts is prognostic of all-cause mortality.

## 9.2. INTRODUCTION

As has been detailed in previous Chapters, there is now good evidence that inflammation based prognostic scores have independent prognostic value in patients with a variety of cancers. In Chapter 8, constituents of these scores, including high-sensitivity C-reactive protein (>3mg/l), albumin (<35g/l), neutrophils (>7.5 x $10^9$) and platelets (>400 x $10^9$), were combined to form the optimised Glasgow Prognostic Score (oGPS) that improved the prognostic value of the established Glasgow Prognostic Score [Proctor et al., 2013]. Furthermore, Chapter 1 detailed the well established relationship between certain markers of systemic inflammation with atherosclerotic and all-cause mortality, with more recent studies demonstrating similar correlations [Zacho et al., 2010; Phillips et al., 2011; Zamani et al., 2013]. However, it remains to be determined whether such markers, combined in an inflammation-based score, can reliably predict outcome and what the optimal constituents of this score would be.

Therefore, the aim of the present Chapter was to examine the relationship between markers of the systemic immune/inflammatory response and all cause, cancer, cardiovascular and cerebrovascular mortality in a large incidental cohort.

## 9.3. MATERIALS AND METHODS

From the cohort previously described in Chapter 4, patients in North Glasgow, who had a single blood sample taken for C-reactive protein and albumin were considered [Proctor et al., 2010]. Only those patients who also had a differential white cell count available, including lymphocyte, neutrophil and platelet count were included. Patients were sampled incidentally between January 2000 and November 2008. The sample size was originally based on similar work investigating the association between C-reactive protein and all-cause

survival [Marsik et al., 2008]. If multiple samples had been taken during this time period, only the initial set was used. Only those patients undergoing blood sampling after the introduction of the routine measurement of high sensitivity C-reactive protein (1st of August 2006), were included in the analysis investigating the prognostic value of high sensitivity thresholds (<5mg/l). Prior to the introduction of high-sensitivity C-reactive protein measurements, the limit of detection was a concentration of less than 5mg/L and 0.05mg/l thereafter. Standardised thresholds for C-reactive protein (>10mg/l), white cell count ($>11\times10^9$/l), neutrophil count ($>7.5\times10^9$/l), lymphocyte count ($>3\times10^9$/l) and platelet count ($>400\times10^9$/l) were used. High sensitivity C-reactive protein threshold >3mg/l, previously reported to be associated with survival [Ridker, 2003; Ridker, 2008; Lee et al., 2011; Ko et al., 2012] and shown to be the optimal threshold in this cohort [Proctor et al., 2013], was also studied.

As the presence of malignancy is known to be associated with activation of the systemic immune/inflammatory response [Proctor et al., 2010], all patients with a diagnosed malignancy any time prior to or within 14 days of blood sample were corrected for. Whether the patient had been sampled as an inpatient or outpatient was also noted.

Patient outcome and mortality was established through linkage with the Information Services Division (ISD) for Scotland by exact matching surname, forename, sex and date of birth (Appendix 3). If no match on surname then Daitch-Mokotoff followed by NYSIIS soundex algorithms were employed. On remaining unmatched cases, forenames and surnames were switched followed by matching on previous surnames, reversing gender, using first initial opposed to full forename and finally on surname, gender and date of birth only. On all those not with exact matches a manual check on whether to include or exclude was taken. Of the 223,303 patients originally identified, 213,127 were successfully matched

through this linkage and 10 176 were not identified (5%). Of the matched patients, 160 481 patients had C-reactive protein and albumin as well as a complete differential white cell count. The presence of SMR01 records were used to determine whether a patient was sampled during a hospital admission, the length of hospital stay and whether the patient had died. Hospital admission was defined as having been sampled during an continuous inpatient stay. SMRO6 records containing International Classification of Disease (ICD) codes were used to identify those with a diagnosis of cancer prior to, or within 14 days of blood sampling, as previously described [Proctor et al., 2010]. Cancer related mortality was defined as ICD10 codes C00 - C97, cardiovascular (ischaemic heart disease) related mortality was defined as ICD10 codes I20 - I25 and cerebrovascular disease related mortality was defined as ICD10 codes I60 - I69. At the time of data collection, the ISD held complete SMR01 data on registered deaths until May 2011. Survival was calculated from time of blood sample to date of death or censor date (31st of May 2011). Patients were excluded if under the age of 16 years, demographic details were incomplete or if returned ISD fields were inaccurate or incomplete. Overall patient numbers were different in this Chapter, when compared to previous, as the inclusion criteria and matching process differed for ISD compared to the Scottish Cancer Registry linkage.

Deprivation was measured with the Scottish Index of Multiple Deprivation (SIMD) as detailed in Chapter 1 [Proctor et al., 2010]. Ethical approval was granted for the present study by the Research Ethics Committee, North Glasgow NHS Trust.

Statistical analysis was performed as follows. Cox proportional hazard model was used to analyse the relationship between patient demographics, hospital admission, the presence of cancer, C-reactive protein, albumin, neutrophil, lymphocyte and platelet counts with all-cause mortality. Furthermore, cause specific mortality for those dying of cancer,

cardiovascular and cerebrovascular disease were also examined by individually entering these as the primary outcomes into the model.

In those patients with a high sensitivity C-reactive protein measurement, the prognostic value of the combination of C-reactive protein, albumin and neutrophils, adjusted for age, sex, deprivation, hospital admission and the presence of cancer, was analysed using the Cox proportional hazard model and the Area Under the receiver operating characteristic Curve (AUC). During this analysis the proportionality assumptions in the Cox model were explored using a log minus log visual inspection and were found to be satisfactory. The relationship between the optimised Glasgow Prognostic Score and survival was assessed using the Kaplan-Meier log rank. A p value of $<0.05$ was considered to have statistical significance in the analysis. Analysis was performed using SPSS software (SPSS, Chicago, IL, USA).

## 9.4. RESULTS

From GIOS cohort of 223,303 patients originally described [Proctor et al., 2010], 209,148 (94%) were matched with a unique patient record in the ISD dataset. Of this group 160,481 fitted the inclusion criteria and had a differential white cell count available, including neutrophil, lymphocyte and platelet counts. Most patients were under 65 years of age (n=103,779, 65%) and female (n=85,308, 53%). Forty four percent of patients (n=71,156) were SIMD 5 (most deprived). Fifty four percent (n=86,339) of patients were sampled during an inpatient stay. Following the introduction of high sensitivity C-reactive protein, 52,091 patients with high sensitivity C-reactive protein, albumin, neutrophil, lymphocyte and platelet counts, were present.

On follow-up of all patients, there were 42,242 deaths in total of which 13,176 (31%) were cancer related, 6076 (14%) were cardiovascular related and 3638 (9%) were cerebrovascular related. The minimum follow-up from blood sample for all patients was 31 months and the maximum 134 months (median follow-up 69 months for survivors). The relationship between patient demographics, hospital admission, history of cancer, C-reactive protein (>10mg/l), albumin, neutrophil, lymphocyte and platelet counts and survival (n=160,481) is shown in Table 9.1. Increasing age, male gender, increasing deprivation, hospital admission, history of cancer, high C-reactive protein (>10mg/l), neutrophil and platelet counts, as well as low albumin and lymphocyte counts were independently associated with an increase is all-cause mortality (all $p<0.001$). Increasing age, male gender, history of cancer, high C-reactive protein (>10mg/l), neutrophil and platelet counts as well as low albumin and lymphocytes were independently associated with an increase in cancer specific mortality (all $p<0.001$). Increasing age, male gender, increasing deprivation, hospital admission, history of cancer, high C-reactive protein (>10mg/l), neutrophil and platelet counts as well as low albumin was independently associated with an increase in cardiovascular mortality (all $p\leq0.001$). Increasing age, hospital admission, no history of cancer, high C-reactive protein (>10mg/l), neutrophil count as well as low albumin was independently associated with an increase in cerebrovascular mortality (all $p<0.001$). The results of Table 9.1 show that activation of the immune/inflammatory response, as evidenced by an elevated C-reactive protein, predicts all-cause mortality but was most strongly associated with death from cancer (HR 1.85) when compared with cardiovascular (HR 1.54) or cerebrovascular (HR 1.31) disease.

The relationship between patient demographics, hospital admission, history of cancer, C-reactive protein (>3mg/l), albumin, neutrophil, lymphocyte and platelet counts and survival

in patients with a differential white cell count following the introduction of high sensitivity C-reactive protein (n=52,091) is shown in Table 9.2. Increasing age, male gender, hospital admission, history of cancer, high C-reactive protein (>3mg/l), neutrophil and platelet counts as well as low albumin and lymphocyte counts were independently associated with an increase in all-cause mortality (all $p<0.001$). Increasing age, male gender, history of cancer, high C-reactive protein (>3mg/l), neutrophil and platelet counts as well as low albumin and lymphocyte counts were independently associated with an increase in cancer mortality (all $p<0.001$). Increasing age, male gender, hospital admission, history of cancer, high C-reactive protein (>3mg/l) and neutrophil counts as well as low albumin was independently associated with an increase in cardiovascular mortality (all $p<0.001$). Increasing age, hospital admission, history of cancer, high C-reactive protein (>3mg/l) and neutrophil counts as well as low albumin was independently associated with an increase in cerebrovascular mortality (all $p<0.05$). The results of Table 9.2 show that activation of the immune/inflammatory response, as evidenced by an elevated C-reactive protein (>3mg/l), predicts all-cause mortality but was most strongly associated with death from cancer (HR 1.81) when compared with cardiovascular (HR 1.66) or cerebrovascular (HR 1.25) disease.

As C-reactive protein, albumin and neutrophils were consistently predictive of all-cause, cancer, cardiovascular and cerebrovascular specific mortality, these were taken forward to examine the prognostic value of their combination. The relationship between cumulative markers of the systemic immune/inflammatory response (including high sensitivity C-reactive protein, albumin and neutrophil count) and mortality in an incidental cohort (n=52,091) is shown in Table 9.3. The model was built up in a similar manner as previously demonstrated [Proctor et al., 2013] with the area under the curve representing the full model for each outcome. All combinations of these systemic inflammatory markers were

predictive of all-cause, cancer, cardiovascular and cerebrovascular specific survival (all $p<0.01$) independent of age, sex deprivation, hospital admission and the presence of cancer (Figure 9.1). The Kaplan-Meier plot, for a score of 3, shows initial steep curves that subsequently do not diverge. This suggests that systemic inflammation is particularly predictive of early all-cause mortality. The areas under the curve represent the full model for each of the three outcomes.

## 9.5. DISCUSSION

The results of the present Chapter show that, in a large incidentally sampled cohort of patients (n=160,481), a number of routine objective markers of the systemic immune/inflammatory response examined were independently associated with all-cause mortality. Furthermore, of these C-reactive protein, albumin and neutrophils were confirmed to have independent prognostic value not only in patients with cancer but also in patients with cardiovascular and cerebrovascular disease. While these variables do not predict cause of death, there are correlations between lethal pathological processes, such as cancer and atherosclerotic disease, and activation of the systemic immune/inflammatory response. These results implicate the activation of the systemic immune/inflammatory response as a key and common factor in the shortened survival in the most common lethal disease states.

The results of the present Chapter are consistent with previous work using individual markers of the systemic immune/inflammatory response to predict all-cause mortality [Goldwasser and Feldman, 1997; Gillum et al., 2005; Marsik et al., 2008; Grimm et al., 2009; Zacho et al., 2010] and goes further to demonstrate that the combination of C-reactive protein, albumin, neutrophils can further improve the prognostic value of the systemic immune/inflammatory response. Furthermore, these associations remained following

adjustment for hospital admission and a previous diagnosis of cancer, events likely to be associated with raised inflammatory markers and reduced survival.

With reference to cancer, there has been growing interest in the role of markers of the systemic immune/inflammatory response in predicting outcome [McMillan, 2012; Guthrie et al., 2013] and the clinical utility of combining such markers with tumour based factors to provide improved patient counselling and personalised treatment is becoming increasingly recognised [Gakis et al., 2011; Lamb et al., 2012; Inoue et al., 2013; McMillan, 2013]. The present results provide a framework for the further development of a paradigm that uses both patient and tumour based objective factors to assess patient prognosis.

With reference to cardiovascular and cerebrovascular disease the prognostic value of C-reactive protein is well established [Kaptoge et al., 2012]. Indeed, high sensitivity C-reactive protein has been recommended for use in cardiovascular risk stratification in moderate risk, asymptomatic patients [Greenland et al., 2010]. Therefore, the present results also provide further evidence for the clinical utility of systemic inflammation-based scoring systems in predicting outcome in cardiovascular and cerebrovascular disease. Indeed, this approach with C-reactive protein and albumin as core factors has recently been validated in the NHANES III cohort [Van Hemelrijck et al., 2012].

The present Chapter shows that activation of the immune/inflammatory response predicts all-cause mortality, predominantly within the first year following sample, with the strongest association in cancer, followed by cardiovascular and cerebrovascular disease. The basis of the independent prognostic value of C-reactive protein, albumin and neutrophil count over all disease states (and platelets in cancer) is not clear and likely to be complex. However, it is likely that these factors are associated with aspects of the immune/inflammatory response and in particular the innate immune/inflammatory response.

Therefore, it may be hypothesised that the complementary prognostic value of these factors reflects an upregulation of the innate immune/inflammatory response and is likely to identify those with an ongoing pathological process who may die early as a consequence. The consistency of observations across different tumour types and now different disease states suggests that this hypothesis is worthy of further study.

In the present Chapter, the cohort has a number of limitations. The patients were selected on the basis that measurements of C-reactive protein, albumin and a differential white cell count had been performed and were therefore not necessarily representative of all patients treated in the North Glasgow area. It is also recognised that patients may have concurrent morbidity causing a rise in their C-reactive protein and derangement of their albumin and other haematological parameters.

In summary, a number of markers of the systemic immune/inflammatory response, reflecting an optimised Glasgow Prognostic Score, have prognostic utility not only in cancer, but also in cardiovascular and cerebrovascular disease. Further work to validate such findings in other large cohorts is warranted.

**Table 9.1. The relationship between patient demographics, markers of the systemic immune/inflammatory response and mortality**

| | | | All-cause mortality Deaths = 42,242 | | | | Cancer mortality Deaths = 13,176 | | | | Cardiovascular mortality Deaths = 6076 | | | | Cerebrovascular mortality Deaths = 3638 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n (%) | Univariate | | Multivariate | | Univariate | | Multivariate | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | | n=160 481 | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value |
| Age | <65/ | 103,779 (65) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | 65-74 | 26,989(17) | 4.00 | <0.001 | 3.31 | <0.001 | 3.76 | <0.001 | 2.21 | <0.001 | 5.80 | <0.001 | 5.64 | <0.001 | 8.45 | <0.001 | 8.18 | <0.001 |
| | >75 | 29,716 (18) | 8.27 | <0.001 | 6.51 | <0.001 | 4.36 | <0.001 | 2.41 | <0.001 | 12.58 | <0.001 | 12.36 | <0.001 | 28.41 | <0.001 | 26.10 | <0.001 |
| Sex | Male | 75,173 (47) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Female | 85,308 (53) | 0.86 | <0.001 | 0.77 | <0.001 | 0.76 | <0.001 | 0.70 | <0.001 | 0.72 | <0.001 | 0.63 | <0.001 | 1.18 | <0.001 | 0.94 | 0.232 |
| SIMD | 1 | 21,362 (13) | 1 | | 1 | | 1 | | | | 1 | | 1 | | 1 | | | |
| | 2 | 17,778 (11) | 1.03 | 0.216 | 1.11 | <0.001 | 1.03 | 0.459 | | | 1.10 | 0.104 | 1.21 | 0.001 | 0.84 | 0.012 | | |
| | 3 | 20,432 (13) | 1.16 | <0.001 | 1.20 | <0.001 | 1.18 | <0.001 | | | 1.18 | 0.002 | 1.28 | <0.001 | 0.91 | 0.139 | | |
| | 4 | 29,753 (19) | 1.28 | <0.001 | 1.30 | <0.001 | 1.23 | <0.001 | | | 1.42 | <0.001 | 1.47 | <0.001 | 1.00 | 0.986 | | |
| | 5 | 71,156 (44) | 1.25 | <0.001 | 1.36 | <0.001 | 1.00 | 0.882 | | | 1.32 | <0.001 | 1.45 | <0.001 | 1.16 | 0.004 | | |
| Hospital Admission | No | 74,142 (46) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Yes | 86,339 (54) | 1.75 | <0.001 | 1.21 | <0.001 | 1.55 | <0.001 | 1.00 | 0.861 | 1.81 | <0.001 | 1.33 | <0.001 | 2.00 | <0.001 | 1.49 | <0.001 |
| History of Cancer | None | 139,080 (87) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Present | 21,401 (13) | 3.40 | <0.001 | 2.13 | <0.001 | 12.01 | <0.001 | 8.94 | <0.001 | 1.45 | <0.001 | 0.84 | <0.001 | 1.58 | <0.001 | 0.84 | <0.001 |
| C-reactive protein | <10mg/l | 94,544 (59) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | >10mg/l | 65,937 (41) | 2.71 | <0.001 | 1.60 | <0.001 | 3.16 | <0.001 | 1.85 | <0.001 | 2.33 | <0.001 | 1.54 | <0.001 | 2.17 | <0.001 | 1.31 | <0.001 |
| Albumin | >35mg/l | 135,087 (84) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | <35mg/l | 25,394 (16) | 3.68 | <0.001 | 2.02 | <0.001 | 4.25 | <0.001 | 2.08 | <0.001 | 2.36 | <0.001 | 1.33 | <0.001 | 2.54 | <0.001 | 1.41 | <0.001 |
| Neutrophil count | $<7.5\times10^9$/l | 127,736 (80) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | $>7.5\times10^9$/l | 32,745 (20) | 2.18 | <0.001 | 1.49 | <0.001 | 2.51 | <0.001 | 1.41 | <0.001 | 1.89 | <0.001 | 1.51 | <0.001 | 1.89 | <0.001 | 1.52 | <0.001 |
| Lymphocyte count | $>3\times10^9$/l | 12,542 (8) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | $<3\times10^9$/l | 147,939 (92) | 1.87 | <0.001 | 1.21 | <0.001 | 1.84 | <0.001 | 1.19 | <0.001 | 1.58 | <0.001 | 0.97 | 0.564 | 2.00 | <0.001 | 1.11 | 0.272 |
| Platelet count | $<400\times10^9$/l | 143,431 (89) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | $>400\times10^9$/l | 17,050 (11) | 1.64 | <0.001 | 1.07 | <0.001 | 2.03 | <0.001 | 1.39 | <0.001 | 1.17 | <0.001 | 0.81 | <0.001 | 1.51 | <0.001 | 1.03 | 0.584 |

**Table 9.2. The relationship between patient demographics, markers of the systemic immune/inflammatory response (including high sensitivity C-reactive protein) and mortality**

| | | | All-cause mortality Deaths = 8243 | | | | Cancer mortality Deaths = 3480 | | | | Cardiovascular mortality Deaths = 929 | | | | Cerebrovascular mortality Deaths = 553 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate | | Multivariate | | Univariate | | Multivariate | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | | n (%) n=52 091 | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value | HR | p-value |
| Age | <65/ | 36,834 (71) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | 65-74 | 7277 (14) | 4.28 | <0.001 | 2.95 | <0.001 | 4.36 | <0.001 | 2.12 | <0.001 | 6.26 | <0.001 | 5.73 | <0.001 | 7.75 | <0.001 | 7.39 | <0.001 |
| | >75 | 7880 (15) | 8.10 | <0.001 | 5.24 | <0.001 | 4.82 | <0.001 | 2.20 | <0.001 | 14.36 | <0.001 | 13.18 | <0.001 | 24.31 | <0.001 | 22.20 | <0.001 |
| Sex | Male | 25,411 (49) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | | |
| | Female | 26,680 (51) | 0.87 | <0.001 | 0.77 | <0.001 | 0.86 | <0.001 | 0.76 | <0.001 | 0.72 | <0.001 | 0.61 | <0.001 | 1.18 | 0.058 | | |
| SIMD | 1 | 6943 (13) | 1 | | | | 1 | | | | 1 | | | | 1 | | | |
| | 2 | 5972 (12) | 1.07 | 0.141 | | | 1.02 | 0.768 | | | 1.36 | 0.024 | | | 0.92 | 0.639 | | |
| | 3 | 6749 (13) | 1.16 | 0.001 | | | 1.19 | 0.004 | | | 1.23 | 0.133 | | | 0.81 | 0.199 | | |
| | 4 | 9583 (18) | 1.17 | <0.001 | | | 1.07 | 0.275 | | | 1.58 | <0.001 | | | 0.87 | 0.355 | | |
| | 5 | 22 844 (44) | 1.06 | 0.129 | | | 0.83 | <0.001 | | | 1.21 | 0.092 | | | 0.96 | 0.777 | | |
| Hospital Admission | No | 23,616 (45) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Yes | 28,475 (55) | 1.76 | <0.001 | 1.16 | <0.001 | 1.56 | <0.001 | 0.96 | 0.229 | 1.82 | <0.001 | 1.29 | <0.001 | 2.31 | <0.001 | 1.74 | <0.001 |
| History of Cancer | None | 20,917 (40) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Present | 31,174 (60) | 4.74 | <0.001 | 2.49 | <0.001 | 12.75 | <0.001 | 8.00 | <0.001 | 1.57 | <0.001 | 0.74 | 0.002 | 1.78 | <0.001 | 0.77 | 0.032 |
| C-reactive protein | <3mg/l | 20,917 (40) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | >3mg/l | 31,174 (60) | 3.05 | <0.001 | 1.55 | <0.001 | 3.88 | <0.001 | 1.81 | <0.001 | 2.78 | <0.001 | 1.66 | <0.001 | 2.10 | <0.001 | 1.25 | 0.032 |
| Albumin | >35mg/l | 41,010 (79) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | <35mg/l | 11,081 (21) | 5.19 | <0.001 | 2.68 | <0.001 | 6.40 | <0.001 | 2.95 | <0.001 | 3.57 | <0.001 | 1.87 | <0.001 | 2.69 | <0.001 | 1.28 | 0.010 |
| Neutrophil count | $<7.5\times10^9$/l | 41,617 (80) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | $>7.5\times10^9$/l | 10,474 (20) | 2.41 | <0.001 | 1.63 | <0.001 | 2.66 | <0.001 | 1.47 | <0.001 | 1.80 | <0.001 | 1.49 | <0.001 | 2.14 | <0.001 | 1.89 | <0.001 |
| Lymphocyte count | $>3\times10^9$/l | 5391 (10) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | <3×109/l | 46,700 (90) | 2.06 | <0.001 | 1.25 | <0.001 | 2.42 | <0.001 | 1.42 | <0.001 | 1.37 | 0.008 | 0.80 | 0.083 | 1.78 | 0.001 | 1.02 | 0.992 |
| Platelet count | $<400\times10^9$/l | 47,160 (91) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| | $>400\times10^9$/l | 4931 (9) | 2.05 | <0.001 | 1.16 | <0.001 | 2.70 | <0.001 | 1.54 | <0.001 | 1.39 | 0.001 | 0.82 | 0.055 | 1.66 | <0.001 | 1.01 | 0.950 |

**Table 9.3. The relationship between markers of the systemic immune/inflammatory response (including high sensitivity C-reactive protein) and mortality: Adjusted for age, sex, deprivation, hospital admission and the presence of cancer**

| | | | All-cause mortality Deaths = 8243 | | | Cancer mortality Deaths = 3480 | | | Cardiovascular mortality Deaths =929 | | | Cerebrovascular mortality Deaths =553 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n (%) n=52,091 | HR | p-value | AUC | HR | p-value | AUC | HR | p-value | AUC | HR | p-value | AUC |
| | 0 | 26,603 (51) | 1 | | | 1 | | | 1 | | | 1 | | |
| CRP > 10mg/l | 1 | 13,734 (26) | 1.92 | <0.001 | | 1.99 | <0.001 | | 1.66 | <0.001 | | 1.53 | <0.001 | |
| +Albumin >35g/L | 2 | 8635 (17) | 3.45 | <0.001 | | 4.27 | <0.001 | | 2.67 | <0.001 | | 1.76 | <0.001 | |
| +Neutrophils >$7.5\times10^9$/l | 3 | 3119 (6) | 6.45 | <0.001 | 0.720 | 7.95 | <0.001 | 0.728 | 3.49 | <0.001 | 0.645 | 2.50 | <0.001 | 0.612 |
| | 0 | 17,542 (34) | 1 | | | 1 | | | 1 | | | 1 | | |
| hs-CRP >3mg/l | 1 | 19,880 (38) | 1.76 | <0.001 | | 1.94 | <0.001 | | 1.62 | <0.001 | | 1.40 | 0.006 | |
| + Albumin >35g/L | 2 | 11,158 (21) | 3.58 | <0.001 | | 4.44 | <0.001 | | 2.92 | <0.001 | | 1.90 | <0.001 | |
| + Neutrophils>$7.5\times10^9$/l | 3 | 3511 (7) | 7.37 | <0.001 | 0.723 | 9.32 | <0.001 | 0.731 | 4.03 | <0.001 | 0.650 | 3.10 | <0.001 | 0.623 |

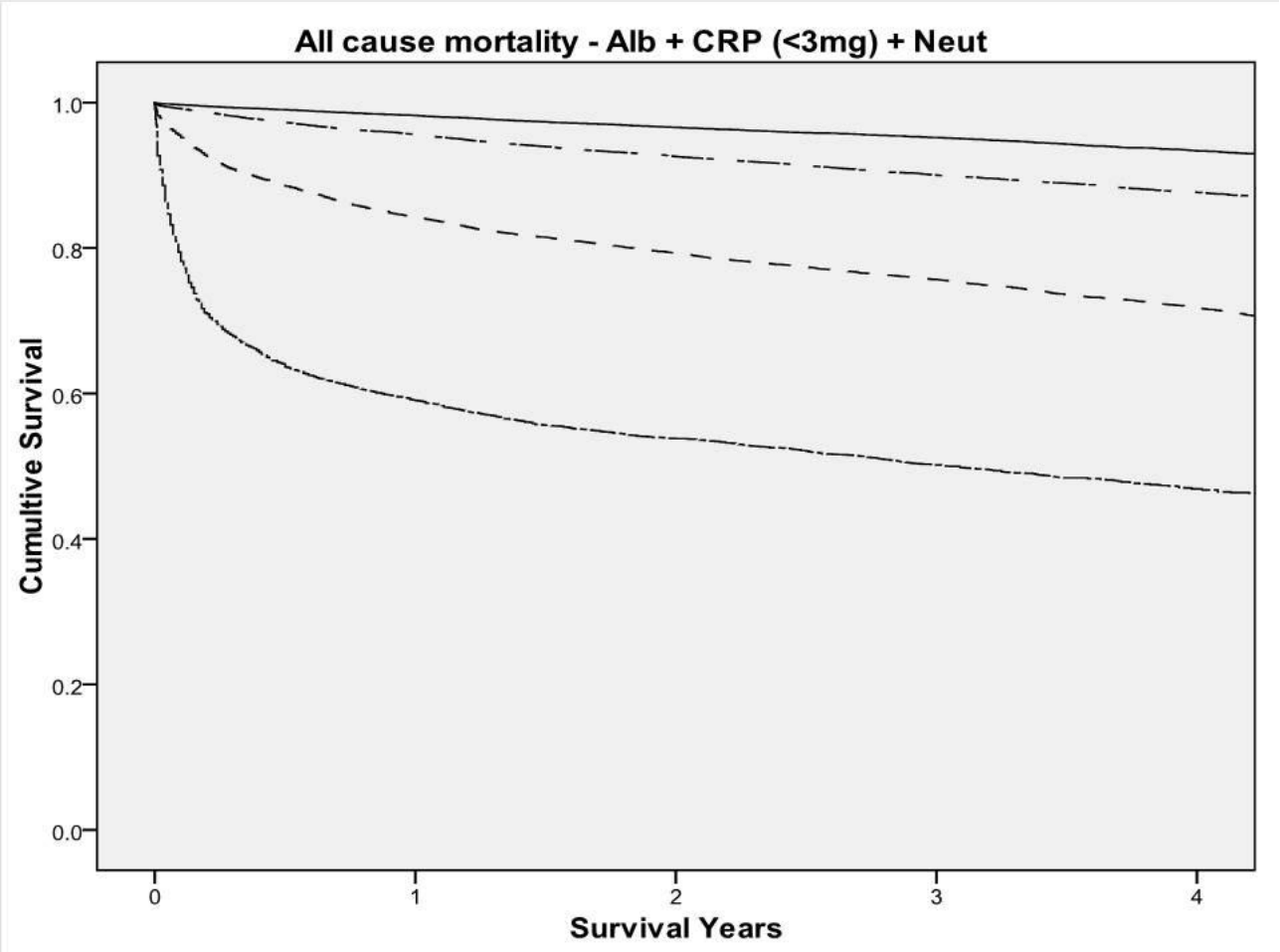



**Figure 9.1. The relationship between cumulative markers of the systemic immune/inflammatory response and all-cause mortality (including high sensitivity C-reactive protein, albumin and neutrophil count) and survival (0-top, solid line; 1-upper separated dot and dash line, 2-middle large dash line, 3-lower close dot and dash line, n=52,091)**

## 10.0. CONCLUSION

At the beginning of this period of research, as detailed in Chapter 1, it was clear that inflammation played an integral role in the pathogenesis and progression of malignancy and atherosclerotic disease. It had also been shown that activation of the systemic immune/inflammatory response, as measured by an objective systemic inflammatory-based score, was associated with reduced survival in particular cohorts with cancer, cardiovascular disease and stroke. However, it was unclear as to whether this was a universal phenomenon affecting all cancer types and what the optimal serum constituents of an inflammation based prognostic score would be for patients with cancer. It had also not been determined whether the link between inflammation and survival in arteriosclerotic disease was measurable by a similar inflammation-based score. The aim of this body of work was to address these issues in a single cohort of patients.

In Chapter 4, the relationships between the presence of cancer, serum levels of markers of systemic inflammation (mGPS) and other routinely sampled biochemical variables were investigated. Indeed, people with cancer were more likely to have an elevated mGPS and derangement of serum biochemical markers, both factors that had previously been associated with mortality. Interestingly, there were also significant interrelationships between markers of the systemic immune/inflammatory response and biochemical variables, suggesting that inflammation may be the underlying pathophysiological mechanism. It was also demonstrated that systemic inflammation (mGPS) across tumour types differed with the proportion of non-inflamed patients correlating with nationally reported five-year survival rates.

In Chapter 5, the relationship between the mGPS, biological parameters, tumour site and survival in patients with malignancy was investigated. It was discovered that that serum C-reactive protein, albumin, liver function tests and calcium were all shown to have independent prognostic value in patients with a recent history of malignancy. Moreover, the relationship between the mGPS and survival was independent of tumour site and thus provided evidence that the systemic immune/inflammatory response is a universal marker of poor outcome in patients with malignancy. It was indicated that further work investigating the potential of combining a measure of the host immune/inflammatory response with conventional TNM staging would be worthwhile.

In Chapter 6, a comparison of the prognostic value of commonly reported systemic inflammation-based prognostic scores was carried out. The mGPS, NLR, PLR, PI and PNI were all shown to be associated with survival in patients with a recent diagnosis of cancer and it was argued that these scores were essentially measuring a common pathological process. Scores incorporating C-reactive protein were identified as having superior predictive nature and it was proposed that the widely validated mGPS should be used in the routine assessment of all patients with cancer. It was also noted that the addition of a white cell count to the mGPS may improve its prognostic value and further work on this issue was recommended.

In Chapter 7, the prognostic value of a derived systemic inflammation-based score (derived Neutrophil to Lymphocyte Ratio) using a white cell and neutrophil count widely available in chemotherapy trial databases was evaluated. The derived Neutrophil to Lymphocyte Ratio (neutrophil count/ white cell count - neutrophil count) had comparable prognostic value to the NLR and was shown to be predictive independent of tumour site. It was suggested that large oncology datasets be analysed, using the derived Neutrophil to

Lymphocyte Ratio, to assess further the clinical utility of this systemic inflammation-based prognostic score.

In Chapter 8, the aim was to examine whether it was possible to improve the prognostic value of the mGPS by including other markers of the systemic inflammatory response. The addition of a high sensitivity C-reactive protein measurement, neutrophil and platelet counts were found to enhance the predictive value (AUC) of the Glasgow Prognostic Score as well as improving the differentiation of patients at different levels of risk. These results were consistent with the concept that the systemic inflammatory response in patients with cancer was primarily due to an upregulation of the innate immune/ inflammatory response.

Given the universal utility of inflammation-based prognostic scores in patients with cancer, it was of interest as to whether a comparable score would be associated with all-cause, cardiovascular and cerebrovascular survival mortality. In Chapter 9, the prognostic value of C-reactive protein and albumin together with neutrophil, lymphocyte and platelet counts were investigated in a large unselected cohort. It was concluded that a similar systemic inflammation-based prognostic score to that used in cancer, containing high sensitivity C-reactive protein, albumin and neutrophils, was also independently associated with all-cause, cardiovascular and cerebrovascular mortality.

There are several areas for future study and potential clinical application of the inflammation-based scores presented in this body of work. Biomarkers are a topic of current interest as they can not only play an important role in disease detection and risk stratification, but can also assist in the personalisation of treatment [La Thangue and Kerr, 2011]. Biomarkers offer advantages over traditional clinical, radiological and pathological prognostic modalities given their objective nature [Strimbu and Tavel, 2010]. Furthermore it

has been suggested that the optimal biomarker, as is the case with the scores presented in the current body of work, would accurately predict outcome and could assist in the tailoring of appropriate treatment while being universally available and financially viable [Paoletti et al., 2004].

With regards to cancer screening, it has been suggested that genetic profiling may assist in the identification of high risk groups that will benefit from intensive surveillance [Dunlop et al., 2013]. However, to date genetic variants associated with an increased risk of colorectal cancer have not been shown to have a detrimental effect on survival [Tenesa et al., 2010]. It is of significance, when considered with the results of the current work, that Tao and co-workers have reported C-reactive protein levels in conjunction with Faecal Occult Blood Tests to improve the sensitivity and specificity of colonoscopy for colorectal cancer screening [Tao et al., 2012]. This clearly raises the possibility that the addition of an inflammation-based prognostic score may help improve this further. When screening for cardiovascular disease it has been recommended that C-reactive protein is also used to identify those at risk as well as help determine who will benefit from Statin therapy [Greenland et al., 2010; Kaptoge et al., 2012]. Interestingly, in those treated, a reduction in C-reactive protein concentrations has also been shown to correlate with improved outcomes independent of cholesterol reduction [Rao and Milbrandt, 2010; Tsai et al., 2012]. This raises the possibility that inflammation-based scores, including a sensitive C-reactive protein measurement, may have clinical utility in the screening and risk stratification of patients with atherosclerotic disease.

As the present body of work has shown, systemic inflammation-based prognostic scores have the potential to predict outcome in patients with cancer. A large number of other predictive biochemical biomarkers have been suggested, including carbonic anhydrase IX in

clear cell renal cancer [Stillebroer et al., 2010] and IMP3 in colorectal cancer [Lin et al., 2013]. Work has also been carried out investigating tumour indicators of survival in cancers with evidence demonstrating particular genetic signatures to be associated with survival [Ogino et al., 2009]. However, these tests are highly specialised with limited clinical availability and significant financial cost. Indeed, Kerr and Midgley stated:

> The genetic model for colorectal (CRC) tumourigenesis proposal by Fearon and Vogelstein two decades ago, although broadly correct, has yielded to a much more complex and multifaceted paradigm. This has led to the clinical community being tantalized, but somewhat lacking in practical examples of biomarkers that can be applied for obvious patient benefit. There is, of course, the example of seeming resistance to anti–epidermal growth factor receptor (EGFR) antibody therapy in tumours carrying mutant K-ras, which has gained clinical traction, but there are no other biomarkers in CRC that are routinely incorporated into any treatment guidelines or algorithms. Many candidates have come and gone (p53,3 thymidylate synthase, loss of heterozygosity of 18q, to name but a few), lost in the fog of underpowered studies, technical variation in means of measurement, and absence of validating data sets with adequate controls [Kerr and Midgley, 2010].

It therefore follows that the simple, widely available, systemic inflammation-based scores presented in the current work may be a superior alternative.

Another potential use for systemic inflammation-based prognostic scores is to assist in the identification of patients that will benefit from particular treatment modalities. For example, anti-inflammatory chemotherapeutic agents, such as aspirin and cyclooxygenase-2 (COX-2) inhibitors, have been suggested to reduce risk of cancer as well as the subsequent

development of metastasis [Rothwell et al., 2012; Chan and Detering, 2013]. It is however worth noting that while Cox-2 inhibitors have a selective anti-inflammatory action, they also inhibit the production of prostacyclin, a prostaglandin that reduces platelet aggregation and arterial vasodilatation. This therefore allows the unchallenged promotion of platelet aggregation and vasoconstriction exerted by COX-1 induces thromboxane $A_2$, and a subsequent increased incidence of heart attack and stroke [Niederberger et al., 2004].

Non-steroidal anti-inflammatory drugs have also been shown to play a potential role in patients with advanced malignancy and cancer cachexia [Solheim et al., 2013]. It is possible that inflammation-based prognostic scores may be useful in identifying those who are systemically inflamed and would benefit from treatment, as well as measure the potential response [McMillan, 2013]. It has also been suggested that, in colorectal cancer patients with stage II disease, an inflammation-based prognostic score (GPS) could help identify patients who will gain a survival benefit from adjuvant chemotherapy [Toiyama et al., 2011]. Similarly, in patients with incurable cancer cachexia, the GPS has been able to identify those that would benefit from supportive parenteral nutrition [Bozzetti et al., 2014]. Also, the NLR has been shown to select those with metastatic prostate cancer that will benefit from Abiraterone hormonal therapy [Leibowitz-Amit et al., 2014].

There is also a growing pool of evidence regarding the use of markers of the systemic immune/inflammatory response when determining who will tolerate potentially toxic systemic therapies, such as palliative chemotherapy. In patients with advanced NSCLC, hypoalbuminaemia has been associated with anaemia, neuropathy, apatite loss, nausea and fatigue [Arrieta et al., 2010]. Furthermore, Gioulbasanis and co-workers demonstrated an association with mucositis, neurotoxicity, neutropenia, requirement for treatment termination and chemotherapy-related toxic deaths in patients with a raised inflammatory status (GPS)

receiving palliative chemotherapy for lung cancer [Gioulbasanis et al., 2012]. Similarly, in patients with advanced nasopharyngeal cancer, the presence of a non-normalising elevated C-reactive protein level after chemotherapy, has been associated with a poor outcome [Xia et al., 2013]. Also, patients receiving trans-arterial chemoembolisation for unresectable hepatocellular carcinoma were found to have worse outcomes in the presence of an activated immune/inflammatory response [Pinato and Sharma, 2012]. The current results show that inflammation-based prognostic scores have universal predictive value across all tumour types studied. They also offer an objective measurement of a patient's physical state, where performance status and physician opinion may vary. Moreover, activation of the systemic immune/inflammatory response has been shown to correlate with the majority of cancer symptoms [Laird et al., 2013] and accordingly, a standardised inflammation-based score, may assist traditional modalities in selecting patients who will benefit from further oncological therapies.

Another potential use for inflammation-based prognostic scores would be to monitor response to treatment. It has been suggested that targeted, immunomodulating therapies may confer a survival advantage and there is ongoing work to investigate such therapies, including anti-angiogenic TNF-α [Balkwill and Mantovani, 2010; Sasi et al., 2012]. It also been put forward been suggested that biomarkers are required to identify those appropriate for such targeted therapies and it is possible that inflammation-based scores may have a role to play in this process [Clarke et al., 2011]. Indeed, Ruxolitinib, a selective Janus kinase inhibitor (JAK1 and JAK2), has recently been shown to offer a survival advantage in patients with metastatic pancreatic cancer, but only in those patients with evidence of an active systemic inflation as measured by a mGPS of 1 or 2 [Hurwitz H et al., 2014]. Moreover, there is also

some evidence that similar immune/inflammatory modification may be employed in cardiovascular disease [Frangogiannis, 2012].

The current piece of work gives an insight into the particular aspect of the immune/inflammatory response that is detrimental in cancer. Of the prognostic indices examined, it was noted that those associated with a reduced survival, including C-reactive protein as well as neutrophil and platelet counts, were predominantly linked to the innate immune response. Indeed, it is becoming clear that up-regulation of the innate response is detrimental as it facilitates angiogenesis and subsequent tumour dissemination [Tazzyman et al., 2013] and prognostic scores focusing on constituents of the innate immune response could be of future benefit.

In summary, this piece of research has demonstrated that a variety of inflammation-based prognostic scores, which essentially measure the same process, to be of universal predictive value in patients with cancer, cardiovascular disease and stroke. It also indicates that the basis of the relationship between the systemic immune/inflammatory response and outcome, particularly in cancer, is primarily due to activation of the innate immune/inflammatory response rather that the down regulation of the adaptive immune/inflammatory response.

## **11.0** Reference List


Abbas AK, Lichtman AH, Pilllai A (2005) *Cellular and Molecular Immunology*. Philadelphia:

Abbasciano V, Bianchi MP, Trevisani L, Sartori S, Gilli G, Zavagli G (1995) Platelet activation and fibrinolysis in large bowel cancer. *Oncology* 52: 381-384

Acanfora D, Gheorghiade M, Trojano L, Furgi G, Pasini E, Picone C, Papa A, Iannuzzi GL, Bonow RO, Rengo F (2001) Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. *Am Heart J* 142: 167-173

Al Murri AM, Bartlett JM, Canney PA, Doughty JC, Wilson C, McMillan DC (2006) Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. *Br J Cancer* 94: 227-230

Alberg AJ, Singh S (2001) Epidemiology of breast cancer in older women: implications for future healthcare. *Drugs Aging* 18: 761-772

Albuquerque KV, Price MR, Badley RA, Jonrup I, Pearson D, Blamey RW, Robertson JF (1995) Pre-treatment serum levels of tumour markers in metastatic breast cancer: a prospective assessment of their role in predicting response to therapy and survival. *Eur J Surg Oncol* 21: 504-509

Alderman MH (1993) Blood pressure management: individualized treatment based on absolute risk and the potential for benefit. *Ann Intern Med* 119: 329-335

Alici S, Bavbek SE, Kaytan E, Eralp Y, Onat H (2003) Prognostic factors in localized aggressive non-Hodgkin's lymphoma. *Am J Clin Oncol* 26: 1-5

Alici S, Kaya S, Izmirli M, Tuncer I, Dogan E, Ozbek H, Sayarlioglu H (2006) Analysis of survival factors in patients with advanced-stage gastric adenocarcinoma. *Med Sci Monit* 12: CR221-CR229

Allin KH, Bojesen SE, Nordestgaard BG (2009) Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J Clin Oncol* 27: 2217-2224

Anderson KM, Wilson PW, Odell PM, Kannel WB (1991) An updated coronary risk profile. A statement for health professionals. *Circulation* 83: 356-362

Ando M, Ando Y, Hasegawa Y, Shimokata K, Minami H, Wakai K, Ohno Y, Sakai S (2001) Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. *Br J Cancer* 85: 1634-1639

Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, Serna-Thome MG, Flores-Estrada D, Diaz-Romero C, Rodriguez CM, Martinez L, Sanchez-Lara K (2010) Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer* 10: 50

Ashby JP, Wright DJ, Rinsler MG (1986) The adjusted serum calcium concept--a reappraisal. *Ann Clin Biochem* 23 ( Pt 5): 533-537

Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Cogliano V (2007) Carcinogenicity of alcoholic beverages. *Lancet Oncol* 8: 292-293

Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Cogliano V (2008) Carcinogenicity of some aromatic amines, organic dyes, and related exposures. *Lancet Oncol* 9: 322-323

Balkwill F, Charles KA, Mantovani A (2005) Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 7: 211-217

Balkwill F, Coussens LM (2004) Cancer: an inflammatory link. *Nature* 431: 405-406

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? *Lancet* 357: 539-545

Balkwill F, Mantovani A (2010) Cancer and inflammation: implications for pharmacology and therapeutics. *Clin Pharmacol Ther* 87: 401-406

Balkwill FR, Burke F (1989) The cytokine network. *Immunol Today* 10: 299-304

Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM (2004) Antiinflammatory properties of HDL. *Circ Res* 95: 764-772

Baumann H, Gauldie J (1994) The acute phase response. *Immunol Today* 15: 74-80

Baumgartner RN, Koehler KM, Romero L, Garry PJ (1996) Serum albumin is associated with skeletal muscle in elderly men and women. *Am J Clin Nutr* 64: 552-558

Bender BS, Nagel JE, Adler WH, Andres R (1986) Absolute peripheral blood lymphocyte count and subsequent mortality of elderly men. The Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc* 34: 649-654

Benitez-Bribiesca L, Wong A, Utrera D, Castellanos E (2001) The role of mast cell tryptase in neoangiogenesis of premalignant and malignant lesions of the uterine cervix. *J Histochem Cytochem* 49: 1061-1062

Berliner JA, Territo MC, Sevanian A, Ramin S, Kim JA, Bamshad B, Esterson M, Fogelman AM (1990) Minimally modified low density lipoprotein stimulates monocyte endothelial interactions. *J Clin Invest* 85: 1260-1266

Bingle L, Brown NJ, Lewis CE (2002) The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J Pathol* 196: 254-265

Bishop J, Clark D, Harris V, Stockton D, and Sutton M. Deprivation and Urban Rural Measurements in ISD. Summary Report. 2004. Edinburgh, ISD Geography, Population, Census and Deprivation Group.
Ref Type: Report

Bishop, J., Clark, D., Harris V, Stockton D, and Sutton M. Deprivation and Urban Rural Measurements in ISD. Summary Report. 2004. Edinburgh, ISD Geography, Population, Census and Deprivation Group.
Ref Type: Report

Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, Akiba T, Keen ML, Young EW, Port FK (2008) High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int* 74: 655-663

Bloom H, Richardson (1957) Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 11: 359-377

Blumenfeld Z, Lorber M, Yoffe N, Scharf Y (1994) Systemic lupus erythematosus: predisposition for uterine cervical dysplasia. *Lupus* 3: 59-61

Bosanquet N, Sikora K (2004) The economics of cancer care in the UK. *Lancet Oncol* 5: 568-574

Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV (2002) The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 55: 244-265

Boyle P, Levin B (2008) World Cancer Report. IARC Nonserial Publications:

Bozzetti F, Santarpia L, Pironi L, Thul P, Klek S, Gavazzi C, Tinivella M, Joly F, Jonkers C, Baxter J, Gramlich L, Chicharro L, Staun M, Van Gossum A, Lo VS, Mariani L (2014) The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-centre observational study with prospective follow-up of 414 patients. *Ann Oncol* 25: 487-493

Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, Ebrahim S (2003) Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ* 327: 1267

Brown DJ, Milroy R, Preston T, McMillan DC (2007) The relationship between an inflammation-based prognostic score (Glasgow Prognostic Score) and changes in serum biochemical variables in patients with advanced lung and gastrointestinal cancer. *J Clin Pathol* 60: 705-708

Cancer Research UK. Cancer incidence by age. 2006. London, Cancer Research UK.
Ref Type: Report

Cancer Research UK. CancerStats Report - Mortality UK. 2007. London, Cancer Research UK.
Ref Type: Report

Cancer Research UK. CancerStats Report - Incidence UK. 2008. London, Cancer Research UK.
Ref Type: Report

Canna K, McArdle PA, McMillan DC, McNicol AM, Smith GW, McKee RF, McArdle CS (2005) The relationship between tumour T-lymphocyte infiltration, the systemic

inflammatory response and survival in patients undergoing curative resection for colorectal cancer. *Br J Cancer* 92: 651-654

Carstairs, A. and Morris, R. Deprivation and health in Scotland. 1991. Aberdeen., Aberdeen University Press.
Ref Type: Report

Casamassima A, Picciariello M, Quaranta M, Berardino R, Ranieri C, Paradiso A, Lorusso V, Guida M (2005) C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy. *J Urol* 173: 52-55

Cassell GH (1998) Infectious causes of chronic inflammatory diseases and cancer. *Emerg Infect Dis* 4: 475-487

Cengiz O, Kocer B, Surmeli S, Santicky MJ, Soran A (2006) Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? *Med Sci Monit* 12: CR240-CR247

Chan AT, Detering E (2013) An emerging role for anti-inflammatory agents for chemoprevention. *Recent Results Cancer Res* 191: 1-5

Chandrasoma P, Taylor C (2005) *Cardinal Clinical Signs. The host response to injury, Chapter 3.* Concise Pathology: New York

Chechlinska M, Kowalewska M, Nowak R (2010) Systemic inflammation as a confounding factor in cancer biomarker discovery and validation. *Nat Rev Cancer* 10: 2-3

Cheung BM, Ong KL, Cheung RV, Wong LY, Wat NM, Tam S, Leung GM, Cheng CH, Woo J, Janus ED, Lau CP, Lam TH, Lam KS (2008) Association between plasma alkaline phosphatase and C-reactive protein in Hong Kong Chinese. *Clin Chem Lab Med* 46: 523-527

Chia KS, Du WB, Sankaranarayanan R, Sankila R, Wang H, Lee J, Seow A, Lee HP (2004) Do younger female breast cancer patients have a poorer prognosis? Results from a population-based survival analysis. *Int J Cancer* 108: 761-765

Chiba T, Ohtani H, Mizoi T, Naito Y, Sato E, Nagura H, Ohuchi A, Ohuchi K, Shiiba K, Kurokawa Y, Satomi S (2004) Intraepithelial CD8+ T-cell-count becomes a prognostic factor after a longer follow-up period in human colorectal carcinoma: possible association with suppression of micrometastasis. *Br J Cancer* 91: 1711-1717

Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, Lee K (2009b) Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer Immunol Immunother* 58: 15-23

Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, Lee K (2009a) Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer Immunol Immunother* 58: 15-23

Choi GH, Kim DH, Kang CM, Kim KS, Choi JS, Lee WJ, Kim BR (2008) Prognostic factors and optimal treatment strategy for intrahepatic nodular recurrence after curative resection of hepatocellular carcinoma. *Ann Surg Oncol* 15: 618-629

Chua W, Charles KA, Baracos VE, Clarke SJ (2011a) Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 104: 1288-1295

Chua W, Charles KA, Baracos VE, Clarke SJ (2011c) Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 104: 1288-1295

Chua W, Charles KA, Baracos VE, Clarke SJ (2011b) Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 104: 1288-1295

Clark EJ, Connor S, Taylor MA, Madhavan KK, Garden OJ, Parks RW (2007) Preoperative lymphocyte count as a prognostic factor in resected pancreatic ductal adenocarcinoma. *HPB (Oxford)* 9: 456-460

Clarke SJ, Chua W, Moore M, Kao S, Phan V, Tan C, Charles K, McMillan DC (2011) Use of inflammatory markers to guide cancer treatment. *Clin Pharmacol Ther* 90: 475-478

Clinton SK, Libby P (1992) Cytokines and growth factors in atherogenesis. *Arch Pathol Lab Med* 116: 1292-1300

Cochran AJ, Huang RR, Lee J, Itakura E, Leong SP, Essner R (2006) Tumour-induced immune modulation of sentinel lymph nodes. *Nat Rev Immunol* 6: 659-670

Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, GA ES, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL (2008) Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 9: 730-756

Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Esteve J (2004) Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer* 90: 1367-1373

Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 30: 1073-1081

Corti MC, Salive ME, Guralnik JM (1996) Serum albumin and physical function as predictors of coronary heart disease mortality and incidence in older persons. *J Clin Epidemiol* 49: 519-526

Coussens LM, Werb Z (2002) Inflammation and cancer. *Nature* 420: 860-867

Crozier JE, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC (2009) Relationship between emergency presentation, systemic inflammatory response, and cancer-

specific survival in patients undergoing potentially curative surgery for colon cancer. *Am J Surg* 197: 544-549

Crumley AB, McMillan DC, McKernan M, Going JJ, Shearer CJ, Stuart RC (2006a) An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. *Br J Cancer* 94: 1568-1571

Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC (2006b) Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. *Br J Cancer* 94: 637-641

Crumley AB, Stuart RC, McKernan M, McDonald AC, McMillan DC (2008) Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer. *J Gastroenterol Hepatol* 23: e325-e329

Currie CJ, Poole CD, Conway P (2008) Evaluation of the association between the first observation and the longitudinal change in C-reactive protein, and all-cause mortality. *Heart* 94: 457-462

Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, Wensley F, Higgins JP, Lennon L, Eiriksdottir G, Rumley A, Whincup PH, Lowe GD, Gudnason V (2008) Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* 5: e78

Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 350: 1387-1397

Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB (2000) Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 321: 199-204

Daniels CE, Jett JR (2005) Does interstitial lung disease predispose to lung cancer? *Curr Opin Pulm Med* 11: 431-437

de Labry LO, Campion EW, Glynn RJ, Vokonas PS (1990) White blood cell count as a predictor of mortality: results over 18 years from the Normative Aging Study. *J Clin Epidemiol* 43: 153-157

de Rijke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA (1996) Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol* 7: 677-685

de Visser KE, Coussens LM (2005) The interplay between innate and adaptive immunity regulates cancer development. *Cancer Immunol Immunother* 54: 1143-1152

de Visser KE, Eichten A, Coussens LM (2006) Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 6: 24-37

den Hertog HM, van Rossum JA, van der Worp HB, van Gemert HM, de Jonge R, Koudstaal PJ, Dippel DW (2009) C-reactive protein in the very early phase of acute ischemic stroke: association with poor outcome and death. *J Neurol* 256: 2003-2008

DeNardo DG, Johansson M, Coussens LM (2008) Immune cells as mediators of solid tumor metastasis. *Cancer Metastasis Rev* 27: 11-18

Desai AA, Nissenson A, Chertow GM, Farid M, Singh I, Van Oijen MG, Esrailian E, Solomon MD, Spiegel BM (2009) The relationship between laboratory-based outcome measures and mortality in end-stage renal disease: a systematic review. *Hemodial Int* 13: 347-359

Di Fiore F, Lecleire S, Pop D, Rigal O, Hamidou H, Paillot B, Ducrotte P, Lerebours E, Michel P (2007) Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. *Am J Gastroenterol* 102: 2557-2563

Di Napoli M, Papa F, Bocola V (2001) C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke* 32: 917-924

Diehl LF, Karnell LH, Menck HR (1999) The American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphocytic leukemia. *Cancer* 86: 2684-2692

Ding PR, An X, Zhang RX, Fang YJ, Li LR, Chen G, Wu XJ, Lu ZH, Lin JZ, Kong LH, Wan DS, Pan ZZ (2010) Elevated preoperative neutrophil to lymphocyte ratio predicts risk of recurrence following curative resection for stage IIA colon cancer. *Int J Colorectal Dis* 25: 1427-1433

Donskov F (2007) Interleukin-2 based immunotherapy in patients with metastatic renal cell carcinoma. *Dan Med Bull* 54: 249-265

Du Clos TW (1996) The interaction of C-reactive protein and serum amyloid P component with nuclear antigens. *Mol Biol Rep* 23: 253-260

Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL (2006) Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. *Am J Cardiol* 97: 993-996

Dunlop MG, Tenesa A, Farrington SM, Ballereau S, Brewster DH, Koessler T, Pharoah P, Schafmayer C, Hampe J, Volzke H, Chang-Claude J, Hoffmeister M, Brenner H, von Holst S, Picelli S, Lindblom A, Jenkins MA, Hopper JL, Casey G, Duggan D, Newcomb PA, Abuli A, Bessa X, Ruiz-Ponte C, Castellvi-Bel S, Niittymaki I, Tuupanen S, Karhu A, Aaltonen L, Zanke B, Hudson T, Gallinger S, Barclay E, Martin L, Gorman M, Carvajal-Carmona L, Walther A, Kerr D, Lubbe S, Broderick P, Chandler I, Pittman A, Penegar S, Campbell H, Tomlinson I, Houlston RS (2013) Cumulative impact of common genetic variants and other risk factors on colorectal cancer risk in 42,103 individuals. *Gut* 62: 871-881

Easton DF (1994) The inherited component of cancer. *Br Med Bull* 50: 527-535

Engelken FJ, Bettschart V, Rahman MQ, Parks RW, Garden OJ (2003) Prognostic factors in the palliation of pancreatic cancer. *Eur J Surg Oncol* 29: 368-373

Erdemir F, Kilciler M, Bedir S, Ozgok Y, Coban H, Erten K (2007) Clinical significance of platelet count in patients with renal cell carcinoma. *Urol Int* 79: 111-116

Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ (2004) C-reactive protein and the risk of incident colorectal cancer. *JAMA* 291: 585-590

Ezzati M, Lopez AD (2003) Estimates of global mortality attributable to smoking in 2000. *Lancet* 362: 847-852

Falconer JS, Fearon KC, Ross JA, Elton R, Wigmore SJ, Garden OJ, Carter DC (1995) Acute-phase protein response and survival duration of patients with pancreatic cancer. *Cancer* 75: 2077-2082

Fentiman IS (1996) Are the elderly receiving appropriate treatment for cancer? *Ann Oncol* 7: 657-658

Fidler IJ, Poste G (2008) The "seed and soil" hypothesis revisited. *Lancet Oncol* 9: 808

Finch CE, Crimmins EM (2004) Inflammatory exposure and historical changes in human life-spans. *Science* 305: 1736-1739

Fleck A (1989) Clinical and nutritional aspects of changes in acute-phase proteins during inflammation. *Proc Nutr Soc* 48: 347-354

Fleck A, Raines G, Hawker F, Trotter J, Wallace PI, Ledingham IM, Calman KC (1985) Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1: 781-784

Fogar P, Sperti C, Basso D, Sanzari MC, Greco E, Davoli C, Navaglia F, Zambon CF, Pasquali C, Venza E, Pedrazzoli S, Plebani M (2006) Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. *Pancreas* 32: 22-28

Foldes-Filep E, Filep JG, Sirois P (1992) C-reactive protein inhibits intracellular calcium mobilization and superoxide production by guinea pig alveolar macrophages. *J Leukoc Biol* 51: 13-18

Ford ES (1999) Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22: 1971-1977

Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dagg K, Scott HR (2005) A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 92: 1834-1836

Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ (2003) Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 89: 1028-1030

Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ (2004) Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. *Br J Cancer* 90: 1704-1706

Frangogiannis NG (2012) Regulation of the inflammatory response in cardiac repair. *Circ Res* 110: 159-173

Frostegard J, Ulfgren AK, Nyberg P, Hedin U, Swedenborg J, Andersson U, Hansson GK (1999) Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. *Atherosclerosis* 145: 33-43

Fumagalli LA, Vinke J, Hoff W, Ypma E, Brivio F, Nespoli A (2003) Lymphocyte counts independently predict overall survival in advanced cancer patients: a biomarker for IL-2 immunotherapy. *J Immunother* 26: 394-402

Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340: 448-454

Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, Petersen P (2004) Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 110: 2287-2292

Gagnon B, Abrahamowicz M, Xiao Y, Beauchamp ME, MacDonald N, Kasymjanova G, Kreisman H, Small D (2010) Flexible modeling improves assessment of prognostic value of C-reactive protein in advanced non-small cell lung cancer. *Br J Cancer* 102: 1113-1122

Gakis G, Todenhofer T, Renninger M, Schilling D, Sievert KD, Schwentner C, Stenzl A (2011) Development of a new outcome prediction model in carcinoma invading the bladder based on preoperative serum C-reactive protein and standard pathological risk factors: the TNR-C score. *BJU Int* 108: 1800-1805

Galkina E, Ley K (2009) Immune and inflammatory mechanisms of atherosclerosis (*). *Annu Rev Immunol* 27: 165-197

Galli SJ, Gordon JR, Wershil BK (1993) Mast cell cytokines in allergy and inflammation. *Agents Actions Suppl* 43: 209-220

Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY (2007) Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. *J Clin Oncol* 25: 2586-2593

Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, Jeffrey RR, Buchan KG, El Shafei H, Hillis GS (2007) Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J* 154: 995-1002

Gillum RF, Ingram DD, Makuc DM (1994) Relation between serum albumin concentration and stroke incidence and death: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol* 140: 876-888

Gillum RF, Makuc DM (1992) Serum albumin, coronary heart disease, and death. *Am Heart J* 123: 507-513

Gillum RF, Mussolino ME, Madans JH (2005) Counts of neutrophils, lymphocytes, and monocytes, cause-specific mortality and coronary heart disease: the NHANES-I epidemiologic follow-up study. *Ann Epidemiol* 15: 266-271

Gioulbasanis I, Pallis A, Vlachostergios PJ, Xyrafas A, Giannousi Z, Perdikouri IE, Makridou M, Kakalou D, Georgoulias V (2012) The Glasgow Prognostic Score (GPS) predicts toxicity and efficacy in platinum-based treated patients with metastatic lung cancer. *Lung Cancer* 77: 383-388

Glen P, Jamieson NB, McMillan DC, Carter R, Imrie CW, McKay CJ (2006) Evaluation of an inflammation-based prognostic score in patients with inoperable pancreatic cancer. *Pancreatology* 6: 450-453

Goldwasser P, Feldman J (1997) Association of serum albumin and mortality risk. *J Clin Epidemiol* 50: 693-703

Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, Prasad KR (2008a) Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. *World J Surg* 32: 1757-1762

Gomez D, Morris-Stiff G, Toogood GJ, Lodge JP, Prasad KR (2008b) Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. *J Surg Oncol* 97: 513-518

Greabu M, Olinescu R, Kummerow FA, Crocnan DO (2001) The levels of bilirubin may be related to an inflammatory condition in patients with coronary heart disease. *Acta Pol Pharm* 58: 225-231

Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Jr., Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC, Jr., Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW (2010) 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 56: e50-103

Grignani G, Pacchiarini L, Ricetti MM, Dionigi P, Jemos V, Zucchella M, Fratino P (1989) Mechanisms of platelet activation by cultured human cancer cells and cells freshly isolated from tumor tissues. *Invasion Metastasis* 9: 298-309

Grigoryev DN, Liu M, Hassoun HT, Cheadle C, Barnes KC, Rabb H (2008) The local and systemic inflammatory transcriptome after acute kidney injury. *J Am Soc Nephrol* 19: 547-558

Grimm G, Haslacher H, Kampitsch T, Endler G, Marsik C, Schickbauer T, Wagner O, Jilma B (2009) Sex differences in the association between albumin and all-cause and vascular mortality. *Eur J Clin Invest* 39: 860-865

Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V (1999) Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 100: 1481-1492

Guillem P, Triboulet JP (2005) Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. *Dis Esophagus* 18: 146-150

Gupta D, Lammersfeld C, Vashi P, Dahlk S, Grutsch J, Lis C (2009) Is Serum Albumin an Independent Predictor of Survival in Ovarian Cancer? *Clinical Ovarian Cancer* 2: 52-56

Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ (2013) The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. *Crit Rev Oncol Hematol*

Halazun KJ, Aldoori A, Malik HZ, Al Mukhtar A, Prasad KR, Toogood GJ, Lodge JP (2008) Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Surg Oncol* 34: 55-60

Halazun KJ, Hardy MA, Rana AA, Woodland DC, Luyten EJ, Mahadev S, Witkowski P, Siegel AB, Brown RS, Jr., Emond JC (2009) Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg* 250: 141-151

Halliwell B, Gutteridge JM (1990) The antioxidants of human extracellular fluids. *Arch Biochem Biophys* 280: 1-8

Han-Geurts IJ, Hop WC, Tran TC, Tilanus HW (2006) Nutritional status as a risk factor in esophageal surgery. *Dig Surg* 23: 159-163

Hanahan D, Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 86: 353-364

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* 100: 57-70

Hansson GK (2005) Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 352: 1685-1695

Hansson GK, Holm J, Jonasson L (1989) Detection of activated T lymphocytes in the human atherosclerotic plaque. *Am J Pathol* 135: 169-175

Hashimoto K, Ikeda Y, Korenaga D, Tanoue K, Hamatake M, Kawasaki K, Yamaoka T, Iwatani Y, Akazawa K, Takenaka K (2005) The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. *Cancer* 103: 1856-1864

Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB (1997) Production of C-reactive protein and risk of coronary events in stable and unstable angina. European

Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 349: 462-466

Hefler LA, Concin N, Hofstetter G, Marth C, Mustea A, Sehouli J, Zeillinger R, Leipold H, Lass H, Grimm C, Tempfer CB, Reinthaller A (2008) Serum C-reactive protein as independent prognostic variable in patients with ovarian cancer. *Clin Cancer Res* 14: 710-714

Hemminki K, Jiang Y (2002) Familial and second gastric carcinomas: a nationwide epidemiologic study from Sweden. *Cancer* 94: 1157-1165

Herberman RB, Holden HT (1978) Natural cell-mediated immunity. *Adv Cancer Res* 27: 305-377

Hespanhol V, Queiroga H, Magalhaes A, Santos AR, Coelho M, Marques A (1995) Survival predictors in advanced non-small cell lung cancer. *Lung Cancer* 13: 253-267

Heys SD, Walker LG, Deehan DJ, Eremin OE (1998) Serum albumin: a prognostic indicator in patients with colorectal cancer. *J R Coll Surg Edinb* 43: 163-168

Hurwitz H, Uppal N Wagner SA Bendell J, Thaddeus BJ, Wade S, Nemunaitis J, Stella P, and Pipas JM. Results from a phase 2 study of ruxolitinib or placebo with capecitabine as second-line therapy in patients with metastatic pancreatic cancer: the RECAP trial. Ann.Oncol. 25 (S), 115-116. 2014.
Ref Type: Abstract

Imada A, Shijubo N, Kojima H, Abe S (2000) Mast cells correlate with angiogenesis and poor outcome in stage I lung adenocarcinoma. *Eur Respir J* 15: 1087-1093

Inoue Y, Iwata T, Okugawa Y, Kawamoto A, Hiro J, Toiyama Y, Tanaka K, Uchida K, Mohri Y, Miki C, Kusunoki M (2013) Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. *Oncology* 84: 100-107

Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K (2007) Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. *Ann Surg* 246: 1047-1051

Ishizuka M, Nagata H, Takagi K, Kubota K (2009) Influence of inflammation-based prognostic score on mortality of patients undergoing chemotherapy for far advanced or recurrent unresectable colorectal cancer. *Ann Surg* 250: 268-272

Ito K, Asano T, Yoshii H, Satoh A, Sumitomo M, Hayakawa M (2006) Impact of thrombocytosis and C-reactive protein elevation on the prognosis for patients with renal cell carcinoma. *Int J Urol* 13: 1365-1370

Ito K, Yoshii H, Sato A, Kuroda K, Asakuma J, Horiguchi A, Sumitomo M, Asano T (2011) Impact of postoperative C-reactive protein level on recurrence and prognosis in patients with N0M0 clear cell renal cell carcinoma. *J Urol* 186: 430-435

Itzkowitz SH, Yio X (2004) Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 287: G7-17

Izaks GJ, Remarque EJ, Becker SV, Westendorp RG (2003) Lymphocyte count and mortality risk in older persons. The Leiden 85-Plus Study. *J Am Geriatr Soc* 51: 1461-1465

Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD (1997) The codependence of angiogenesis and chronic inflammation. *FASEB J* 11: 457-465

Jamieson NB, Glen P, McMillan DC, McKay CJ, Foulis AK, Carter R, Imrie CW (2005) Systemic inflammatory response predicts outcome in patients undergoing resection for ductal adenocarcinoma head of pancreas. *Br J Cancer* 92: 21-23

Janeway CA, Medzhitov R (2002) Innate immune recognition. *Annu Rev Immunol* 20: 197-216

Janeway CA, Travers P, Walport M, Schlomchik J (2001) *Immunobiology: The Immune System in Health and Disease. 5th Edition*. Garland Science: New York

Jass JR, Love SB, Northover JM (1987) A new prognostic classification of rectal cancer. *Lancet* 1: 1303-1306

Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK (1986) Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arteriosclerosis* 6: 131-138

Jonjic N, Peri G, Bernasconi S, Sciacca FL, Colotta F, Pelicci P, Lanfrancone L, Mantovani A (1992) Expression of adhesion molecules and chemotactic cytokines in cultured human mesothelial cells. *J Exp Med* 176: 1165-1174

Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, MacDonald JS, Catalano PJ, Haller DG (2003) Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. *Ann Surg Oncol* 10: 213-218

Joyce JA, Pollard JW (2009) Microenvironmental regulation of metastasis. *Nat Rev Cancer* 9: 239-252

Kalluri R, Zeisberg M (2006) Fibroblasts in cancer. *Nat Rev Cancer* 6: 392-401

Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 24: 2137-2150

Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A (2011) Nutritional predictors of postoperative outcome in pancreatic cancer. *Br J Surg* 98: 268-274

Kannel WB, McGee D, Gordon T (1976) A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 38: 46-51

Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, Clarke SJ (2010b) High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. *Clin Cancer Res* 16: 5805-5813

Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, Clarke SJ (2010a) High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. *Clin Cancer Res* 16: 5805-5813

Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, Walker M, Thompson A, Sarwar N, Caslake M, Butterworth AS, Amouyel P, Assmann G, Bakker SJ, Barr EL, Barrett-Connor E, Benjamin EJ, Bjorkelund C, Brenner H, Brunner E, Clarke R, Cooper JA, Cremer P, Cushman M, Dagenais GR, D'Agostino RB, Sr., Dankner R, Davey-Smith G, Deeg D, Dekker JM, Engstrom G, Folsom AR, Fowkes FG, Gallacher J, Gaziano JM, Giampaoli S, Gillum RF, Hofman A, Howard BV, Ingelsson E, Iso H, Jorgensen T, Kiechl S, Kitamura A, Kiyohara Y, Koenig W, Kromhout D, Kuller LH, Lawlor DA, Meade TW, Nissinen A, Nordestgaard BG, Onat A, Panagiotakos DB, Psaty BM, Rodriguez B, Rosengren A, Salomaa V, Kauhanen J, Salonen JT, Shaffer JA, Shea S, Ford I, Stehouwer CD, Strandberg TE, Tipping RW, Tosetto A, Wassertheil-Smoller S, Wennberg P, Westendorp RG, Whincup PH, Wilhelmsen L, Woodward M, Lowe GD, Wareham NJ, Khaw KT, Sattar N, Packard CJ, Gudnason V, Ridker PM, Pepys MB, Thompson SG, Danesh J (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 367: 1310-1320

Kasymjanova G, MacDonald N, Agulnik JS, Cohen V, Pepe C, Kreisman H, Sharma R, Small D (2010) The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer. *Curr Oncol* 17: 52-58

Kazemi-Shirazi L, Endler G, Winkler S, Schickbauer T, Wagner O, Marsik C (2007) Gamma glutamyltransferase and long-term survival: is it just the liver? *Clin Chem* 53: 940-946

Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, Levy Y, Brook GJ, Aronson D (2005) Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 25: 193-197

Kerr DJ, Midgley R (2010) Defective mismatch repair in colon cancer: a prognostic or predictive biomarker? *J Clin Oncol* 28: 3210-3212

Kew MC (1998) Hepatitis viruses and hepatocellular carcinoma. *Res Virol* 149: 257-262

Khan OA, Alexiou C, Soomro I, Duffy JP, Morgan WE, Beggs FD (2004) Pathological determinants of survival in node-negative oesophageal cancer. *Br J Surg* 91: 1586-1591

Kim HS, Han KH, Chung HH, Kim JW, Park NH, Song YS, Kang SB (2010) Neutrophil to lymphocyte ratio for preoperative diagnosis of uterine sarcomas: a case-matched comparison. *Eur J Surg Oncol* 36: 691-698

Kinzler KW, Vogelstein B (1996) Lessons from hereditary colorectal cancer. *Cell* 87: 159-170

Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN (2009) Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol* 16: 614-622

Ko YJ, Kwon YM, Kim KH, Choi HC, Chun SH, Yoon HJ, Goh E, Cho B, Park M (2012) High-sensitivity C-reactive protein levels and cancer mortality. *Cancer Epidemiol Biomarkers Prev* 21: 2076-2086

Kobayashi T, Teruya M, Kishiki T, Endo D, Takenaka Y, Tanaka H, Miki K, Kobayashi K, Morita K (2008) Inflammation-based prognostic score, prior to neoadjuvant chemoradiotherapy, predicts postoperative outcome in patients with esophageal squamous cell carcinoma. *Surgery* 144: 729-735

Koenig W, Khuseyinova N, Baumert J, Meisinger C (2008) Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. *Clin Chem* 54: 335-342

Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB (1999) C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 99: 237-242

Kohne CH, Cunningham D, Di Costanzo F, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Baron B, Pignatti F, Schoffski P, Micheel S, Hecker H (2002) Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 13: 308-317

Koj A (1996) Initiation of acute phase response and synthesis of cytokines. *Biochim Biophys Acta* 1317: 84-94

Komai Y, Saito K, Sakai K, Morimoto S (2007) Increased preoperative serum C-reactive protein level predicts a poor prognosis in patients with localized renal cell carcinoma. *BJU Int* 99: 77-80

Kraaijeveld AO, de Jager SC, van Berkel TJ, Biessen EA, Jukema JW (2007) Chemokines and atherosclerotic plaque progression: towards therapeutic targeting? *Curr Pharm Des* 13: 1039-1052

Kulkarni AB, Karlsson S (1993) Transforming growth factor-beta 1 knockout mice. A mutation in one cytokine gene causes a dramatic inflammatory disease. *Am J Pathol* 143: 3-9

Kuller LH, Eichner JE, Orchard TJ, Grandits GA, McCallum L, Tracy RP (1991) The relation between serum albumin levels and risk of coronary heart disease in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 134: 1266-1277

Kuller LH, Tracy RP, Shaten J, Meilahn EN (1996) Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 144: 537-547

Kuper H, Adami HO, Trichopoulos D (2000) Infections as a major preventable cause of human cancer. *J Intern Med* 248: 171-183

Kushner I (1982) The phenomenon of the acute phase response. *Ann N Y Acad Sci* 389: 39-48

La Thangue NB, Kerr DJ (2011) Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat Rev Clin Oncol* 8: 587-596

Laird BJ, McMillan DC, Fayers P, Fearon K, Kaasa S, Fallon MT, Klepstad P (2013) The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. *Oncologist* 18: 1050-1055

Lam PT, Leung MW, Tse CY (2007) Identifying prognostic factors for survival in advanced cancer patients: a prospective study. *Hong Kong Med J* 13: 453-459

Lamb GW, Aitchison M, Ramsey S, Housley SL, McMillan DC (2012) Clinical utility of the Glasgow Prognostic Score in patients undergoing curative nephrectomy for renal clear cell cancer: basis of new prognostic scoring systems. *Br J Cancer* 106: 279-283

Laskin DL, Pendino KJ (1995) Macrophages and inflammatory mediators in tissue injury. *Annu Rev Pharmacol Toxicol* 35: 655-677

Lee DH, Jacobs DR (2005) Association between serum gamma-glutamyltransferase and C-reactive protein. *Atherosclerosis* 178: 327-330

Lee S, Choe JW, Kim HK, Sung J (2011) High-sensitivity C-reactive protein and cancer. *J Epidemiol* 21: 161-168

Lee YY, Choi CH, Sung CO, Do IG, Huh S, Song T, Kim MK, Kim HJ, Kim TJ, Lee JW, Kim BG, Bae DS (2012) Prognostic value of pre-treatment circulating monocyte count in patients with cervical cancer: comparison with SCC-Ag level. *Gynecol Oncol* 124: 92-97

Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J, Harris AL (1996) Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma. *Cancer Res* 56: 4625-4629

Leibowitz-Amit R, Templeton AJ, Omlin A, Pezaro C, Atenafu EG, Keizman D, Vera-Badillo F, Seah JA, Attard G, Knox JJ, Sridhar SS, Tannock IF, de Bono JS, Joshua AM (2014) Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. *Ann Oncol*

Leifsson BG, Ahren B (1996) Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab* 81: 2149-2153

Leitch EF, Chakrabarti M, Crozier JE, McKee RF, Anderson JH, Horgan PG, McMillan DC (2007) Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. *Br J Cancer* 97: 1266-1270

Lengauer C, Kinzler KW, Vogelstein B (1998) Genetic instabilities in human cancers. *Nature* 396: 643-649

Leung EY, Crozier JE, Talwar D, O'Reilly DS, McKee RF, Horgan PG, McMillan DC (2008) Vitamin antioxidants, lipid peroxidation, tumour stage, the systemic inflammatory response and survival in patients with colorectal cancer. *Int J Cancer* 123: 2460-2464

Lewis CE, Pollard JW (2006) Distinct role of macrophages in different tumor microenvironments. *Cancer Res* 66: 605-612

Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K (2000) Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343: 78-85

Lien YC, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, Huang MH, Huang BS (2004) Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. *J Gastrointest Surg* 8: 1041-1048

Lim JE, Chien MW, Earle CC (2003) Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg* 237: 74-85

Lin L, Zhang J, Wang Y, Ju W, Ma Y, Li L, Chen L (2013) Insulin-like growth factor-II mRNA-binding protein 3 predicts a poor prognosis for colorectal adenocarcinoma. *Oncol Lett* 6: 740-744

Lin WW, Karin M (2007) A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest* 117: 1175-1183

Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L (2000) Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 343: 1139-1147

Lis CG, Grutsch JF, Vashi PG, Lammersfeld CA (2003) Is serum albumin an independent predictor of survival in patients with breast cancer? *JPEN J Parenter Enteral Nutr* 27: 10-15

Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A (1994) The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 331: 417-424

Lord BI, Bronchud MH, Owens S, Chang J, Howell A, Souza L, Dexter TM (1989) The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor in vivo. *Proc Natl Acad Sci U S A* 86: 9499-9503

Lu H, Ouyang W, Huang C (2006) Inflammation, a key event in cancer development. *Mol Cancer Res* 4: 221-233

Lukito W, Wattanapenpaiboon N, Savige GS, Hutchinson P, Wahlqvist ML (2004) Nutritional indicators, peripheral blood lymphocyte subsets and survival in an institutionalised elderly population. *Asia Pac J Clin Nutr* 13: 107-112

Ma XC, Hattori T, Kushima R, Terata N, Kodama M (1994) Expression of HLA-class II antigen in gastric carcinomas. Its relationship to histopathological grade, lymphocyte infiltration and five-year survival rate. *Acta Oncol* 33: 187-190

Macy EM, Hayes TE, Tracy RP (1997) Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem* 43: 52-58

Maeda T, Ueoka H, Tabata M, Kiura K, Shibayama T, Gemba K, Takigawa N, Hiraki A, Katayama H, Harada M (2000) Prognostic factors in advanced non-small cell lung cancer: elevated serum levels of neuron specific enolase indicate poor prognosis. *Jpn J Clin Oncol* 30: 534-541

Maestu I, Pastor M, Gomez-Codina J, Aparicio J, Oltra A, Herranz C, Montalar J, Munarriz B, Reynes G (1997) Pretreatment prognostic factors for survival in small-cell lung cancer: a new prognostic index and validation of three known prognostic indices on 341 patients. *Ann Oncol* 8: 547-553

Makita S, Nakamura M, Satoh K, Tanaka F, Onoda T, Kawamura K, Ohsawa M, Tanno K, Itai K, Sakata K, Okayama A, Terayama Y, Yoshida Y, Ogawa A (2009) Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. *Atherosclerosis* 204: 234-238

Mantovani A, Romero P, Palucka AK, Marincola FM (2008) Tumour immunity: effector response to tumour and role of the microenvironment. *Lancet* 371: 771-783

Mantovani A, Sozzani S, Locati M, Allavena P, Sica A (2002) Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 23: 549-555

Marsik C, Kazemi-Shirazi L, Schickbauer T, Winkler S, Joukhadar C, Wagner OF, Endler G (2008) C-reactive protein and all-cause mortality in a large hospital-based cohort. *Clin Chem* 54: 343-349

Massberg S, Brand K, Gruner S, Page S, Muller E, Muller I, Bergmeier W, Richter T, Lorenz M, Konrad I, Nieswandt B, Gawaz M (2002) A critical role of platelet adhesion in the initiation of atherosclerotic lesion formation. *J Exp Med* 196: 887-896

Mathers, C, Boerma, T, and Ma Fat, D. The Global Burden of Disease. 2004. Switzerland, World Health Organisation.
Ref Type: Report

Mathew A, Pandey M, Rajan B (2004) Do younger women with non-metastatic and non-inflammatory breast carcinoma have poor prognosis? *World J Surg Oncol* 2: 2

McArdle CS, McMillan DC, Hole DJ (2003) Male gender adversely affects survival following surgery for colorectal cancer. *Br J Surg* 90: 711-715

McDonald B, Spicer J, Giannais B, Fallavollita L, Brodt P, Ferri LE (2009) Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. *Int J Cancer* 125: 1298-1305

McMillan DC (2008) An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc* 67: 257-262

McMillan DC (2009) Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care* 12: 223-226

McMillan DC (2012) The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. *Cancer Treat Rev*

McMillan DC (2013) Cancer and systemic inflammation: stage the tumour and stage the host. *Br J Cancer* 109: 529

McMillan DC, Canna K, McArdle CS (2003) The effect of deprivation and the systemic inflammatory response on outcome following curative resection for colorectal cancer. *Br J Cancer* 89: 612-614

McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS (2007) Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. *Int J Colorectal Dis* 22: 881-886

McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J, McArdle CS (2001) Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. *Nutr Cancer* 41: 64-69

McNiven D. Scotland' Population 2009: The Registrar General's Annual Review of Demographic Trends 155th Edition. 2010. Edinburgh, National Statistics.
Ref Type: Report

Merrill RM, Bird JS (2002) Effect of young age on prostate cancer survival: a population-based assessment (United States). *Cancer Causes Control* 13: 435-443

Mesker WE, Junggeburt JM, Szuhai K, de Heer P, Morreau H, Tanke HJ, Tollenaar RA (2007) The carcinoma-stromal ratio of colon carcinoma is an independent factor for survival compared to lymph node status and tumor stage. *Cell Oncol* 29: 387-398

Mold C, Gewurz H, Du Clos TW (1999) Regulation of complement activation by C-reactive protein. *Immunopharmacology* 42: 23-30

Moller H, Fairley L, Coupland V, Okello C, Green M, Forman D, Moller B, Bray F (2007) The future burden of cancer in England: incidence and numbers of new patients in 2020. *Br J Cancer* 96: 1484-1488

Mori T, Hirota T, Ohashi Y, Kodaira S (2006) Significance of histologic type of primary lesion and metastatic lymph nodes as a prognostic factor in stage III colon cancer. *Dis Colon Rectum* 49: 982-992

Moutsopoulos NM, Madianos PN (2006) Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. *Ann N Y Acad Sci* 1088: 251-264

Nagaoka S, Yoshida T, Akiyoshi J, Akiba J, Torimura T, Adachi H, Kurogi J, Tajiri N, Inoue K, Niizeki T, Koga H, Imaizumi T, Kojiro M, Sata M (2007) Serum C-reactive protein levels predict survival in hepatocellular carcinoma. *Liver Int* 27: 1091-1097

Nair RJ, Lawler L, Miller MR (2007) Chronic pancreatitis. *Am Fam Physician* 76: 1679-1688

Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A (2012) Clinical significance of pretreatment serum C-reactive protein level in soft tissue sarcoma. *Cancer* 118: 1055-1061

Nardin A, Abastado JP (2008) Macrophages and cancer. *Front Biosci* 13: 3494-3505

Nathan C (2006) Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 6: 173-182

National Cancer Institute. Cancer Staging. http://www.cancer.gov/cancertopics/factsheet/detection/staging . 5-3-2009.
Ref Type: Electronic Citation

National Institute for Health and Care Excellence. Staging Colorectal Cancer. Colorectal Cancer Pathway. 2009. Manchester.
Ref Type: Report

Neal CP, Mann CD, Sutton CD, Garcea G, Ong SL, Steward WP, Dennison AR, Berry DP (2009) Evaluation of the prognostic value of systemic inflammation and socioeconomic deprivation in patients with resectable colorectal liver metastases. *Eur J Cancer* 45: 56-64

Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D, Sugimachi K (2002) Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol* 28: 396-400

Nozoe T, Matsumata T, Kitamura M, Sugimachi K (1998) Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *Am J Surg* 176: 335-338

Nozoe T, Ninomiya M, Maeda T, Matsukuma A, Nakashima H, Ezaki T (2010) Prognostic nutritional index: a tool to predict the biological aggressiveness of gastric carcinoma. *Surg Today* 40: 440-443

Nunez J, Nunez E, Bodi V, Sanchis J, Minana G, Mainar L, Santas E, Merlos P, Rumiz E, Darmofal H, Heatta AM, Llacer A (2008) Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 101: 747-752

O'Gorman P, McMillan DC, McArdle CS (2000) Prognostic factors in advanced gastrointestinal cancer patients with weight loss. *Nutr Cancer* 37: 36-40

O'Keefe SC, Marshall FF, Issa MM, Harmon MP, Petros JA (2002) Thrombocytosis is associated with a significant increase in the cancer specific death rate after radical nephrectomy. *J Urol* 168: 1378-1380

Office for National Statistics. Births and Deaths in England and Wales. 2008. Newport, Office for National Statistics.
Ref Type: Report

Ogino S, Nosho K, Kirkner GJ, Shima K, Irahara N, Kure S, Chan AT, Engelman JA, Kraft P, Cantley LC, Giovannucci EL, Fuchs CS (2009) PIK3CA mutation is associated with poor prognosis among patients with curatively resected colon cancer. *J Clin Oncol* 27: 1477-1484

Ohashi Y, Ishibashi S, Suzuki T, Shineha R, Moriya T, Satomi S, Sasano H (2000) Significance of tumor associated tissue eosinophilia and other inflammatory cell infiltrate in early esophageal squamous cell carcinoma. *Anticancer Res* 20: 3025-3030

Ohno Y, Nakashima J, Ohori M, Hatano T, Tachibana M (2010) Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol* 184: 873-878

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5: 649-655

Olsen AH, Parkin DM, Sasieni P (2008) Cancer mortality in the United Kingdom: projections to the year 2025. *Br J Cancer* 99: 1549-1554

Onate-Ocana LF, Aiello-Crocifoglio V, Gallardo-Rincon D, Herrera-Goepfert R, Brom-Valladares R, Carrillo JF, Cervera E, Mohar-Betancourt A (2007) Serum albumin as a significant prognostic factor for patients with gastric carcinoma. *Ann Surg Oncol* 14: 381-389

Pagano JS, Blaser M, Buendia MA, Damania B, Khalili K, Raab-Traub N, Roizman B (2004) Infectious agents and cancer: criteria for a causal relation. *Semin Cancer Biol* 14: 453-471

Paoletti R, Gotto AM, Jr., Hajjar DP (2004) Inflammation in atherosclerosis and implications for therapy. *Circulation* 109: III20-III26

Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F (2008) Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin Chim Acta* 395: 27-31

Parikh NI, Vasan RS (2007) Assessing the clinical utility of biomarkers in medicine. *Biomark Med* 1: 419-436

Parkin DM (2006) The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044

Penel N, Vanseymortier M, Bonneterre ME, Clisant S, Dansin E, Vendel Y, Beuscart R, Bonneterre J (2008) Prognostic factors among cancer patients with good performance status screened for phase I trials. *Invest New Drugs* 26: 53-58

Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. *J Clin Invest* 111: 1805-1812

Phillips A, Shaper AG, Whincup PH (1989) Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet* 2: 1434-1436

Phillips AC, Carroll D, Gale CR, Drayson M, Batty GD (2011) Lymphocyte cell counts in middle age are positively associated with subsequent all-cause and cardiovascular mortality. *QJM* 104: 319-324

Pinato DJ, Mauri FA, Ramakrishnan R, Wahab L, Lloyd T, Sharma R (2012) Inflammation-based prognostic indices in malignant pleural mesothelioma. *J Thorac Oncol* 7: 587-594

Pinato DJ, Sharma R (2012) An inflammation-based prognostic index predicts survival advantage after transarterial chemoembolization in hepatocellular carcinoma. *Transl Res* 160: 146-152

Poggi A, Vicenzi E, Cioce V, Wasteson A (1988) Platelet contribution to cancer cell growth and migration: the role of platelet growth factors. *Haemostasis* 18: 18-28

Pollard JW (2004) Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer* 4: 71-78

Polterauer S, Grimm C, Tempfer C, Sliutz G, Speiser P, Reinthaller A, Hefler LA (2007) C-reactive protein is a prognostic parameter in patients with cervical cancer. *Gynecol Oncol* 107: 114-117

Poludasu S, Cavusoglu E, Khan W, Marmur JD (2009) Neutrophil to lymphocyte ratio as a predictor of long-term mortality in African Americans undergoing percutaneous coronary intervention. *Clin Cardiol* 32: E6-E10

Porcellati S, Gresele P, Stasi M, Buratta S, Horrocks LA, De Franceschi S, Nenci GG, Goracci G (1995) Original Article: Albumin Prevents TxB, Formation from Thrombin-stimulated Human Platelets by Sequestering the Liberated Arachidonic Acid in the Extracellular Space. *Platelets* 6: 381-387

Proctor MJ, Horgan PG, Talwar D, Fletcher CD, Morrison DS, McMillan DC (2013) Optimization of the systemic inflammation-based Glasgow Prognostic Score: A Glasgow Inflammation Outcome Study. *Cancer* NA

Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC (2011a) A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *Eur J Cancer* 47: 2633-2641

Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC (2011b) An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. *Br J Cancer* 104: 726-734

Proctor MJ, Talwar D, Balmar SM, O'Reilly DS, Foulis AK, Horgan PG, Morrison DS, McMillan DC (2010) The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. *Br J Cancer* 103: 870-876

Rakoff-Nahoum S (2006) Why cancer and inflammation? *Yale J Biol Med* 79: 123-130

Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC (2007) Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. *Cancer* 109: 205-212

Rao AD, Milbrandt EB (2010) To JUPITER and beyond: statins, inflammation, and primary prevention. *Crit Care* 14: 310

Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, Tredan O, Verweij J, Biron P, Labidi I, Guastalla JP, Bachelot T, Perol D, Chabaud S, Hogendoorn PC, Cassier P, Dufresne A, Blay JY (2009) Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res* 69: 5383-5391

Read JA, Choy ST, Beale PJ, Clarke SJ (2006) Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. *Nutr Cancer* 55: 78-85

Reid KB, Porter RR (1981) The proteolytic activation systems of complement. *Annu Rev Biochem* 50: 433-464

Ridker PM (2003) Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation* 108: e81-e85

Ridker PM (2008) High-sensitivity C-reactive protein as a predictor of all-cause mortality: implications for research and patient care. *Clin Chem* 54: 234-237

Ridker PM, Hennekens CH, Buring JE, Rifai N (2000) C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342: 836-843

Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM, Jr. (2001) Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 344: 1959-1965

Ritchie RF, Palomaki GE, Neveux LM, Navolotskaia O, Ledue TB, Craig WY (1999) Reference distributions for the negative acute-phase serum proteins, albumin, transferrin and transthyretin: a practical, simple and clinically relevant approach in a large cohort. *J Clin Lab Anal* 13: 273-279

Romano PS, Mark DH (1992) Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 101: 1332-1337

Ross R (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 362: 801-809

Ross R (1999) Atherosclerosis--an inflammatory disease. *N Engl J Med* 340: 115-126

Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z (2012) Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 379: 1591-1601

Roxburgh CS, Crozier JE, Maxwell F, Foulis AK, Brown J, McKee RF, Anderson JH, Horgan PG, McMillan DC (2009a) Comparison of tumour-based (Petersen Index) and inflammation-based (Glasgow Prognostic Score) scoring systems in patients undergoing curative resection for colon cancer. *Br J Cancer* 100: 701-706

Roxburgh CS, McMillan DC (2010) Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol* 6: 149-163

Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC (2009b) Comparison of the prognostic value of inflammation-based pathologic and biochemical criteria in patients undergoing potentially curative resection for colorectal cancer. *Ann Surg* 249: 788-793

Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC (2009c) The relationship between the local and systemic inflammatory responses and survival in patients undergoing curative surgery for colon and rectal cancers. *J Gastrointest Surg* 13: 2011-2018

Ruhl CE, Everhart JE (2009) Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 136: 477-485

Salive ME, Cornoni-Huntley J, Phillips CL, Guralnik JM, Cohen HJ, Ostfeld AM, Wallace RB (1992) Serum albumin in older persons: relationship with age and health status. *J Clin Epidemiol* 45: 213-221

Sant M, Aareleid T, Berrino F, Bielska LM, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D (2003) EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. *Ann Oncol* 14 Suppl 5: v61-118

Santoni A, Herberman RB, Holden HT (1979) Correlation between natural and antibody-dependent cell-mediated cytotoxicity against tumor targets in the mouse. I. Distribution of the reactivity. *J Natl Cancer Inst* 62: 109-116

Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E (2009) Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 137: 425-428

Sasi SP, Yan X, Enderling H, Park D, Gilbert HY, Curry C, Coleman C, Hlatky L, Qin G, Kishore R, Goukassian DA (2012) Breaking the 'harmony' of TNF-alpha signaling for cancer treatment. *Oncogene* 31: 4117-4127

Schindl M, Wigmore SJ, Currie EJ, Laengle F, Garden OJ (2005) Prognostic scoring in colorectal cancer liver metastases: development and validation. *Arch Surg* 140: 183-189

Schlomer B, Figenshau RS, Yan Y, Bhayani SB (2006) How does the radiographic size of a renal mass compare with the pathologic size? *Urology* 68: 292-295

Schmid M, Schneitter A, Hinterberger S, Seeber J, Reinthaller A, Hefler L (2007) Association of elevated C-reactive protein levels with an impaired prognosis in patients with surgically treated endometrial cancer. *Obstet Gynecol* 110: 1231-1236

Schrijvers CT, Mackenbach JP, Lutz JM, Quinn MJ, Coleman MP (1995) Deprivation, stage at diagnosis and cancer survival. *Int J Cancer* 63: 324-329

Schwertner HA, Jackson WG, Tolan G (1994) Association of low serum concentration of bilirubin with increased risk of coronary artery disease. *Clin Chem* 40: 18-23

Shacter E, Weitzman SA (2002) Chronic inflammation and cancer. *Oncology (Williston Park)* 16: 217-26, 229

Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, Altorki NK, Abrams JA (2011) Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol* 18: 3362-3369

Sharma R, Hook J, Kumar M, Gabra H (2008) Evaluation of an inflammation-based prognostic score in patients with advanced ovarian cancer. *Eur J Cancer* 44: 251-256

Shine B, de Beer FC, Pepys MB (1981) Solid phase radioimmunoassays for human C-reactive protein. *Clin Chim Acta* 117: 13-23

Siddiqui A, Heinzerling J, Livingston EH, Huerta S (2007) Predictors of early mortality in veteran patients with pancreatic cancer. *Am J Surg* 194: 362-366

Sierko E, Wojtukiewicz MZ (2004) Platelets and angiogenesis in malignancy. *Semin Thromb Hemost* 30: 95-108

Sloggett A, Joshi H (1998) Deprivation indicators as predictors of life events 1981-1992 based on the UK ONS Longitudinal Study. *J Epidemiol Community Health* 52: 228-233

Smith JA (1994) Neutrophils, host defense, and inflammation: a double-edged sword. *J Leukoc Biol* 56: 672-686

Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P (2009) Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 197: 466-472

Sobin, L. and Wittekind, C. TNM classification of malignant tumours, 6th Edition (UICC). 2002. New York., Wiley-Liss.
Ref Type: Report

Sokunbi DO, Wadhwa NK, Suh H (1994) Vascular disease outcome and thrombocytosis in diabetic and nondiabetic end-stage renal disease patients on peritoneal dialysis. *Adv Perit Dial* 10: 77-80

Solheim TS, Fearon KC, Blum D, Kaasa S (2013) Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. *Acta Oncol* 52: 6-17

Sporn MB (1996) The war on cancer. *Lancet* 347: 1377-1381

Stillebroer AB, Mulders PF, Boerman OC, Oyen WJ, Oosterwijk E (2010) Carbonic anhydrase IX in renal cell carcinoma: implications for prognosis, diagnosis, and therapy. *Eur Urol* 58: 75-83

Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN (1987) Bilirubin is an antioxidant of possible physiological importance. *Science* 235: 1043-1046

Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Cogliano V (2006) Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol* 7: 977-978

Strimbu K, Tavel JA (2010) What are biomarkers? *Curr Opin HIV AIDS* 5: 463-466

Sun LC, Chu KS, Cheng SC, Lu CY, Kuo CH, Hsieh JS, Shih YL, Chang SJ, Wang JY (2009) Preoperative serum carcinoembryonic antigen, albumin and age are supplementary to UICC staging systems in predicting survival for colorectal cancer patients undergoing surgical treatment. *BMC Cancer* 9: 288

Swanson RS, Compton CC, Stewart AK, Bland KI (2003) The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol* 10: 65-71

Takahashi S, Kudo M, Chung H, Inoue T, Ishikawa E, Kitai S, Tatsumi C, Ueda T, Nagai T, Minami Y, Ueshima K (2008) PIVKA-II is the best prognostic predictor in patients with hepatocellular carcinoma after radiofrequency ablation therapy. *Oncology* 75 Suppl 1: 91-98

Tamakoshi K, Toyoshima H, Yatsuya H, Matsushita K, Okamura T, Hayakawa T, Okayama A, Ueshima H (2007) White blood cell count and risk of all-cause and cardiovascular mortality in nationwide sample of Japanese--results from the NIPPON DATA90. *Circ J* 71: 479-485

Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS (2008) Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol* 102: 653-657

Tao S, Haug U, Kuhn K, Brenner H (2012) Comparison and combination of blood-based inflammatory markers with faecal occult blood tests for non-invasive colorectal cancer screening. *Br J Cancer* 106: 1424-1430

Tas F, Aydiner A, Topuz E, Camlica H, Saip P, Eralp Y (1999) Factors influencing the distribution of metastases and survival in extensive disease small cell lung cancer. *Acta Oncol* 38: 1011-1015

Tazzyman S, Lewis CE, Murdoch C (2009) Neutrophils: key mediators of tumour angiogenesis. *Int J Exp Pathol* 90: 222-231

Tazzyman S, Niaz H, Murdoch C (2013) Neutrophil-mediated tumour angiogenesis: subversion of immune responses to promote tumour growth. *Semin Cancer Biol* 23: 149-158

Temme EH, Zhang J, Schouten EG, Kesteloot H (2001) Serum bilirubin and 10-year mortality risk in a Belgian population. *Cancer Causes Control* 12: 887-894

Tenesa A, Theodoratou E, Din FV, Farrington SM, Cetnarskyj R, Barnetson RA, Porteous ME, Campbell H, Dunlop MG (2010) Ten common genetic variants associated with colorectal cancer risk are not associated with survival after diagnosis. *Clin Cancer Res* 16: 3754-3759

Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB, III, Cummings B, Gunderson L, MacDonald JS, Mayer RJ (2001) Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 19: 157-163

Teramukai S, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, Minato K, Mio T, Fujita Y, Yonei T, Nakano K, Tsuboi M, Shibata K, Furuse K, Fukushima M (2009) Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. *Eur J Cancer* 45: 1950-1958

The Scottish Government. Better Cancer Care, An Action Plan. 2008. Edinburgh, The Scottish Government.
Ref Type: Report

Thompson D, Pepys MB, Wood SP (1999) The physiological structure of human C-reactive protein and its complex with phosphocholine. *Structure* 7: 169-177

Tibaldi C, Vasile E, Bernardini I, Orlandini C, Andreuccetti M, Falcone A (2008) Baseline elevated leukocyte count in peripheral blood is associated with poor survival in patients with advanced non-small cell lung cancer: a prognostic model. *J Cancer Res Clin Oncol* 134: 1143-1149

Tillett WS, Francis T (1930) Serological reactions in pneumonia with a non-protein fraction on pneumococcus. *J Exp Med* 52: 561-571

Toiyama Y, Miki C, Inoue Y, Tanaka K, Mohri Y, Kusunoki M (2011) Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. *Exp Ther Med* 2: 95-101

Tonelli M, Curhan G, Pfeffer M, Sacks F, Thadhani R, Melamed ML, Wiebe N, Muntner P (2009) Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. *Circulation* 120: 1784-1792

Tracy RP (1998) Inflammation in cardiovascular disease: cart, horse, or both? *Circulation* 97: 2000-2002

Trock B, Lanza E, Greenwald P (1990) Dietary fiber, vegetables, and colon cancer: critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* 82: 650-661

Tsai NW, Lee LH, Huang CR, Chang WN, Chen SD, Wang HC, Lin YJ, Lin WC, Chiang YF, Lin TK, Cheng BC, Su YJ, Kung CT, Hung SH, Chang HW, Lu CH (2012) The association of statin therapy and high-sensitivity C-reactive protein level for predicting clinical outcome in acute non-cardioembolic ischemic stroke. *Clin Chim Acta* 413: 1861-1865

Tuomisto K, Jousilahti P, Sundvall J, Pajunen P, Salomaa V (2006) C-reactive protein, interleukin-6 and tumor necrosis factor alpha as predictors of incident coronary and cardiovascular events and total mortality. A population-based, prospective study. *Thromb Haemost* 95: 511-518

Ulich TR, del Castillo J, Keys M, Granger GA, Ni RX (1987) Kinetics and mechanisms of recombinant human interleukin 1 and tumor necrosis factor-alpha-induced changes in circulating numbers of neutrophils and lymphocytes. *J Immunol* 139: 3406-3415

Unanue ER (2002) Perspective on antigen processing and presentation. *Immunol Rev* 185: 86-102

Vakkila J, Lotze MT (2004) Inflammation and necrosis promote tumour growth. *Nat Rev Immunol* 4: 641-648

Van Hemelrijck M, Eichholzer M, Faeh D, Rohrmann S (2012) Ability of a biomarker-based score to predict death from circulatory disease and cancer in NHANES III. *BMC Public Health* 12: 895

Vernooy JH, Kucukaycan M, Jacobs JA, Chavannes NH, Buurman WA, Dentener MA, Wouters EF (2002) Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. *Am J Respir Crit Care Med* 166: 1218-1224

Vigushin DM, Pepys MB, Hawkins PN (1993) Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest* 91: 1351-1357

Visbal AL, Williams BA, Nichols FC, III, Marks RS, Jett JR, Aubry MC, Edell ES, Wampfler JA, Molina JR, Yang P (2004) Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg* 78: 209-215

von Hundelshausen P, Weber C (2007) Platelets as immune cells: bridging inflammation and cardiovascular disease. *Circ Res* 100: 27-40

Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M (1998) Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. *Hepatology* 27: 407-414

Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ (2005) Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 91: 181-184

Wang CY, Hsieh MJ, Chiu YC, Li SH, Huang HW, Fang FM, Huang YJ (2009) Higher serum C-reactive protein concentration and hypoalbuminemia are poor prognostic indicators in patients with esophageal cancer undergoing radiotherapy. *Radiother Oncol* 92: 270-275

Weijenberg MP, Feskens EJ, Souverijn JH, Kromhout D (1997) Serum albumin, coronary heart disease risk, and mortality in an elderly cohort. *Epidemiology* 8: 87-92

Whitcomb DC (2004) Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol* 287: G315-G319

Wichmann MW, Muller C, Hornung HM, Lau-Werner U, Schildberg FW (2001) Gender differences in long-term survival of patients with colorectal cancer. *Br J Surg* 88: 1092-1098

Wigmore SJ, Fearon KC, Maingay JP, Lai PB, Ross JA (1997) Interleukin-8 can mediate acute-phase protein production by isolated human hepatocytes. *Am J Physiol* 273: E720-E726

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1990) Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323: 1664-1672

Williams MJ, Williams SM, Milne BJ, Hancox RJ, Poulton R (2004) Association between C-reactive protein, metabolic cardiovascular risk factors, obesity and oral contraceptive use in young adults. *Int J Obes Relat Metab Disord* 28: 998-1003

Williams N, Scott AD (1998) 'What's the serum albumin?'. *Ann R Coll Surg Engl* 80: 157-158

Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA (2004) Environmental and chemical carcinogenesis. *Semin Cancer Biol* 14: 473-486

Wong ND, Pio J, Valencia R, Thakal G (2001) Distribution of C-reactive protein and its relation to risk factors and coronary heart disease risk estimation in the National Health and Nutrition Examination Survey (NHANES) III. *Prev Cardiol* 4: 109-114

Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K (1998) Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis* 140: 199-270

Wyld L, Gutteridge E, Pinder SE, James JJ, Chan SY, Cheung KL, Robertson JF, Evans AJ (2003) Prognostic factors for patients with hepatic metastases from breast cancer. *Br J Cancer* 89: 284-290

Xia WX, Ye YF, Lu X, Wang L, Ke LR, Zhang HB, Roycik MD, Yang J, Shi JL, Cao KJ, Guo X, Xiang YQ (2013) The impact of baseline serum C-reactive protein and C-reactive protein kinetics on the prognosis of metastatic nasopharyngeal carcinoma patients treated with palliative chemotherapy. *PLoS One* 8: e76958

Zacho J, Tybjaerg-Hansen A, Nordestgaard BG (2010) C-reactive protein and all-cause mortality--the Copenhagen City Heart Study. *Eur Heart J* 31: 1624-1632

Zamani P, Schwartz GG, Olsson AG, Rifai N, Bao W, Libby P, Ganz P, Kinlay S (2013) Inflammatory Biomarkers, Death, and Recurrent Nonfatal Coronary Events After an Acute Coronary Syndrome in the MIRACL Study. *J Am Heart Assoc* 2: e003103

Zernecke A, Bot I, Djalali-Talab Y, Shagdarsuren E, Bidzhekov K, Meiler S, Krohn R, Schober A, Sperandio M, Soehnlein O, Bornemann J, Tacke F, Biessen EA, Weber C (2008) Protective role of CXC receptor 4/CXC ligand 12 unveils the importance of neutrophils in atherosclerosis. *Circ Res* 102: 209-217

Zucchella M, Dezza L, Pacchiarini L, Meloni F, Tacconi F, Bonomi E, Grignani G, Notario A (1989) Human tumor cells cultured "in vitro" activate platelet function by producing ADP or thrombin. *Haematologica* 74: 541-545

## APPENDIX 1: GIOS Pathology Dataset

Inflammation Outcome Study - North of Glasgow Biochemical, Haematological and Pathological linkage with creation of GIOS database

Document date: 10th October 2009

(1.) Dataset (ProcExtract 1-6.exe) containing all primary single samples of C-reactive protein, albumin and Calcium between 1st January 2000 and 1st November 2008 in North Glasgow Hospital laboratories - Including Glasgow Royal Infirmary, Stobhill hospital, Gartnavel hospital and the Western Infirmary -extracted from TELEPATH systems with coded algorithm. Other variables extracted where available. 269 959 records extracted with 26 328 having temporary emergency hospital numbers not compatible with cross linkage.

(2.) Dataset (comp_histo_proc_extract 1-6.exe) containing all pathological diagnosis with malignant SNOMED codes in North Glasgow Hospital laboratories - Including Glasgow Royal Infirmary, Stobhill hospital, Gartnavel hospital and the Western Infirmary - extracted from telepath systems with coded algorithm.

(3.) Data cross linked to provide dataset with 223 303 patient (conforming to aforementioned criteria in Chapter 3) identifiers including hospital number gender, DOB, and postcode subsequent check referencing of >500 random samples to ensure accuracy.

(4.) SNOMED Clinical Terms (www.nlm.nih.gov/research/umls/Snomed/snomed_main) converted to ICD codes, subsequent clinical terms and then manual combination of morphology and topography terms to meaningful cancer diagnosis.

(5.) Converted to anonymised password-protected .zip file with the following fields:

Acquired fields:
* ID at time of anonymisation
* DOB date of birth
* SEX gender
* POSTCODE of address at time of blood sample
* DATEOFREQUEST of blood test
* Universal required variables: CRP (C-reactive Protein), ALB (Albumin), CCAL(Calcium)
* Biochemical variables where available: BIL (Bilirubin), ALP (Alkaline Phosphatase), AST (aspartate transaminase), ALT (alanine transaminase) and γ-glutamyl transferase (GGT)
* Haematological variables were available: WCC (White Cell), NEUT (Neutrophil), LYMPH (Lymphocyte), PLT (Platelet count)
* DATEOFSAMPLE of neoplastic pathology diagnosis (1-4 where present)
* Sample SNOMED topography (CATSITE) and morphology (CATTYPE) codes for each individual sample 1-4

Calculated fields:
* AGE
* SIMD 2006 Quintiles
* CARSTAIRS Index

* Blood sample "normal" classification depending on aformentioned range classification (Chapter3)
* Inflammatory score mGPS
* CATYPE1 type of primary malignancy and CASITE1 site of primary malignancy
* NO presence of multiple malignancy or METYPEmetastatic malignancy
* DIFFDATEDAYS difference in days between diagnosis of malignancy and blood test
* CAGROUP broad group of malignancy

See attached file: *GIOS Dataset.SAV*

## APPENDIX 2: GIOS Cancer Registry Dataset

Inflammation Outcome Study - North of Glasgow Biochemical, Haematological and Scottish Cancer Registry linkage to create GIOS database of patients with cancer and follow-up

Document date: 13th September 2010 with update linkage 12th July 2011

(1.) GIOS Dataset.SAV containing identifying variables as well as all primary single samples of C-reactive protein, albumin and Calcium between 1st January 2000 and 1st November 2008 in North Glasgow Hospital laboratories - Including Glasgow Royal Infirmary, Stobhill hospital, Gartnavel hospital and the Western Infirmary - as described in Appendix 1.

(2.) 223 303 records cross linked with Scottish Cancer Registry Data base held at West of Scotland Cancer Surveillance Unit, Faculty of Medicine, University of Glasgow, Glasgow G12 8RZ. Using exact matches of patients' forename, surname and date of birth followed by Daitch-Mokotoff and NYSIIS soundex algorithms were employed. On remaining unmatched cases, forenames and surnames were switched followed by matching on previous surnames, reversing gender, using first initial opposed to full forename and finally on surname gender and date of birth only. On all those not with exact matches a manual check on whether to include or exclude was taken. All unmatched cases were reviewed for manual match.

(3.) Anonymised data set returned to provide 21 668 patient conforming to aforementioned criteria in Chapter 4 with a various mix of ICD 9/10/Oncology codes (www.who.int/classifications/icd/en/) for diagnosis and death where appropriate. A selection of matched cases were reviewed for manual quality check (>500). ICD code manual combination of morphology and topography terms to meaningful cancer diagnosis and cause of death.

(5.) Converted to anonymised password-protected .zip file with the following fields:

Acquired fields:

* ID anonymisation
* AGEATREQ age at blood sample request
* SEX gender
* SIMD as GIOS dataset
* CARSTAIRS Index as GIOS dataset
* Universal required variables: CRP (C-reactive Protein), ALB (Albumin), CCAL(Calcium) as GIOS dataset
* Biochemical variables where available: BIL (Bilirubin), ALP (Alkaline Phosphatase), AST (aspartate transaminase), ALT (alanine transaminase) and γ-glutamyl transferase (GGT) as GIOS dataset
* Haematological variables were available: WCC (White Cell), NEUT (Neutrophil), LYMPH (Lymphocyte), PLT (Platelet count) as GIOS dataset
* SITEICD10, SITEICDO, TYPEICDO regarding cancer diagnosis
* DAYSINCIDENCE from blood sample to cancer incidence
* SURVIVALREQ from cancer incidence to death or censor date
* DESCCAUSE the primary cause of death
* DUKES classification for colorectal cancer patients

Calculated fields:

* Blood sample "normal" classification depending on aformentioned range classification (Chapter3)
* Inflammatory score mGPS, GPS, NLR, PLR, PI
* DESCICD10, DESCICDO3, DESCTYPEICDO2, DESCSITEICDO2 descriptions of cancer type for each code supplied.
* TUMOURGROUPCR the categorical group of tumour type as detailed in Chapter 4.
* DESCDEATHCAUSE the description of the ICD code of death
* DEATHCAT the categorical cause of death

See attached file: *GIOS Cancer Registry Dataset.SAV*

**APPENDIX 3: GIOS ISD dataset**

Inflammation Outcome Study - ISD Linkage

Document date: 19th August 2011

(1.) GIOS Dataset.SAV containing identifying variables as well as all primary single samples of C-reactive protein, albumin and Calcium between 1st January 2000 and 1st November 2008 in North Glasgow Hospital laboratories - Including Glasgow Royal Infirmary, Stobhill hospital, Gartnavel hospital and the Western Infirmary - as described in Appendix 1.

(2.) 223 303 records cross linked with ISD, NHS National Services Scotland, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB, by exact matching surname, forename, sex and date of birth. If no match on surname then Daitch-Mokotoff followed by NYSIIS soundex algorithms were employed. On remaining unmatched cases, forenames and surnames were switched followed by matching on previous surnames, reversing gender, using first initial opposed to full forename and finally on surname gender and date of birth only. On all those not with exact matches a manual check on whether to include or exclude was taken. Successful match of 209 148 cases.

(3.) Anonymised data set returned to provide patient conforming to aforementioned criteria in Chapter 4 with a various mix of ICD 10 (www.who.int/classifications/icd/en/) for death where appropriate. ICD code manual combination of morphology and topography terms to meaningful cause of death.

(5.) Converted to anonymised password-protected .zip file with the following fields:

Acquired fields:
* ID anonymisation
* AGEATREQ age at blood sample request
* SEX gender
* SIMD as GIOS dataset
* Universal required variables: CRP (C-reactive Protein), ALB (Albumin), CCAL(Calcium) as GIOS dataset
* Biochemical variables where available: BIL (Bilirubin), ALP (Alkaline Phosphatase), AST (aspartate transaminase), ALT (alanine transaminase) and γ-glutamyl transferase (GGT) as GIOS dataset
* Haematological variables were available: WCC (White Cell), NEUT (Neutrophil), LYMPH (Lymphocyte), PLT (Platelet count) as GIOS dataset
* ISD_10_CODE of cause of death
* ISD_CIS NUMBER of days continuous in patient hospital stay
* ISD_ADMTYPE at time of blood sample emergency vs elective
* ISD_DAYSFROMADMTOREQUEST days from admission to blood sample
* ISD_INFECTIVECAUSE as primary reason of admission
* ISD_SURVIVALFROMREQ from cancer incidence to death or censor date

Calculated fields:

* Blood sample "normal" classification depending on aformentioned range classification (Chapter3)
* Inflammatory score mGPS, GPS, NLR, PLR, PI
* DESC_ISD_10 descriptions of cancer type for each code supplied.

See attached file: *GIOS ISD Dataset.SAV*

## 13.0 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACS | Acute coronary syndrome |
| Alb | Albumin |
| Alk phos | Alkaline phosphatase |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| AUC | Area under the curve (ROC) |
| Bili | Bilirubin |
| $Ca^{2+}$ | Adjusted calcium |
| CABG | Coronary Artery Bypass Graft |
| CI | Confidence interval |
| DNA | Deoxyribonucleic acid |
| dNLR | derived Neutrophil Lymphocyte Ratio |
| ECOG | Eastern Cooperative Oncology Group |
| GGT | γ-glutamyl transferase |
| g/l | Grams per litre |
| GPS | Glasgow Prognostic Score |
| HR | Hazard Ratio |
| hs-CRP | High sensitivity C-reactive protein |
| ICD | International Classification of Diseases |
| IL | Interleukin |
| ISD | Information Services Division for Scotland |
| LDH | Low density lipoprotein |
| LFT | Liver function test |
| mg/l | Milligrams per litre |
| mGPS | modified Glasgow Prognostic Score |
| mmol/l | millimoles per litre |
| NLR | Neutrophil Lymphocyte Ratio |
| NS | Not significant |
| oGPS | optimised Glasgow Prognostic Score |
| PCA | Percutaneous Coronary Angioplasty |
| PI | Prognostic Index |
| PLR | Platelet Lymphocyte Ratio |
| PNI | Prognostic Nutritional Index |
| p-value | Probability value |
| ROC | Receiver operating characteristic |
| SCR | Scottish Cancer Registry |
| SIMD | Scottish Index of Multiple Deprivation |
| SNOMED CT | Systematized Nomenclature of Medicine – Clinical Terms |
| STEMI | ST elevation myocardial infarction |
| TNM | Tumour Node Metastasis |
| U/l | Units per litre |
| μmol/l | micromoles/litre |
| WBC/WCC | White blood cell count |