AN INVESTIGATION OF SYSTEMIC INFLAMMATION AND CLINICAL OUTCOMES IN PATIENTS WITH COMMON SOLID TUMOURS

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Abstract

Systemic inflammation is increasingly recognised as a key determinant of clinical outcomes in patients with solid tumours, influencing tumour progression, treatment response, and survival. This thesis evaluated the prevalence, prognostic value, and clinical utility of systemic inflammation–based markers and scores across common cancers, including non-small cell lung cancer (NSCLC), oesophagogastric (OGC), and colorectal cancer (CRC). A series of retrospective cohort studies and a systematic review/meta-analysis were conducted to assess markers, including the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), C-reactive protein/albumin ratio (CAR), and the modified Glasgow Prognostic Score (mGPS).

The findings demonstrate that systemic inflammation is common across these cancers but varies in magnitude by tumour type, stage, and host fitness, with advanced NSCLC showing the highest inflammatory response. CRP-based scores (CAR, mGPS) consistently provided more substantial prognostic value than ratios derived from differential white cell counts, particularly in operable OG and CRC, where baseline inflammation was lower. In NSCLC, systemic inflammation was associated with nutritional decline, survival after immunotherapy, and prognosis independent of conventional clinicopathological factors. The meta-analysis further confirmed the predictive utility of inflammatory biomarkers in NSCLC patients receiving immunotherapy.

Overall, this thesis highlights systemic inflammation as a clinically relevant prognostic factor across multiple solid tumours, with CRP-based measures emerging as the most sensitive and reliable indicators. These findings support the routine use of CRP in prognostication and patient stratification and suggest its potential role as both an inclusion criterion and an outcome measure in future interventional studies of anti-inflammatory therapies in cancer.

Contents

List of tables

List of figures

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Author's declaration

The work presented in this thesis was undertaken between 2019 and 2024 in the academic unit of surgery at Glasgow Royal Infirmary. (With one year of maternity leave and two months of suspension during the COVID-19 lockdown due to the death of my father).

Work presented in this thesis was undertaken by me, except for the following:

- Hugo Bench assisted with data collection for Chapter 2.
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Publication

The work presented in this thesis has resulted in the following publication:

1. Saeed R, McGovern J, Bench H, Dolan RD, McMillan DC, Cascales A. The relationship between clinicopathological variables, systemic inflammation, and CT-derived body composition with survival in patients with advanced non-small cell lung cancer receiving nivolumab as a second-line treatment. Cancer Med. 2023;12(24):22062-22070. doi:10.1002/cam4.6805

2. Saeed R, McSorley S, Cascales A, McMillan DC. The prognostic/ predictive value of the systematic inflammatory response in patients receiving immunotherapy for non-small cell lung cancer: a systematic review and meta-analysis. BMC Cancer. 2025;25(1):994. Published 2025 Jun 4. doi:10.1186/s12885-025-13822-9

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The work presented in this thesis has resulted in the following presentation:

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Definitions / Abbreviations

ADC	Adenocarcinoma
Alb	Albumin
ALI	Advanced lung cancer inflammation index
ALK	Anaplastic lymphoma kinase
anti-PD-1	Anti-programmed cell death ligand-1
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
ctDNA	circulating tumour deoxyribonucleic acid
CT-SS	CT-Sarcopenia score
DNA	Deoxyribonucleic acid
DXA	Dual-energy X-ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group - Performance Status (ECOG-PS)
EGFR	Estimated glomerular filtration rate

GLIM	Global leadership initiative on malnutrition
GORD	Gastro-oesophageal reflux disease
GPS	Glasgow prognostic score
GPS/mGPS	Glasgow prognostic score/modified Glasgow prognostic score
GPS/NLR	Glasgow prognostic score/ Neutrophil to lymphocyte ratio
HCC	Hepatocellular carcinoma
HR	Hazard ratios
HU	Hounsfield unit
ICI	Immune checkpoint inhibitors
IL-1	Interleukin-1
IL-6	Interleukin-6
irAEs	Immune-related adverse events
L3	Lumber vertebrae 3
LADCs	Lung adenocarcinomas
LC	Lung cancer
LMR	Lymphocyte to monocyte ratio
LSQCC	Lung squamous cell carcinoma
mGPS	Modified Glasgow prognostic score
MTV	Metabolic tumour volume

N	Node
NHS	National Health Service
NLR	Neutrophil to lymphocyte ratio
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall survival
PCI	Prophylactic cranial irradiation
PET	Positron emission tomography
PETCT	Positron emission tomography (PET) scan and a computed tomography (CT) scan.
PFS	Progression-free survival
PLR	Platelet-to-lymphocyte ratio
RATS	Robotic-assisted thoracic surgery
SBRT	Stereotactic body radiation therapy
SCLC	Small-cell lung cancer
SFI	Subcutaneous fat index
SIG	Systemic inflammatory response
SIPS	Scottish inflammatory prognostic score
SIRI	Systemic inflammatory response index
SMA	Skeletal muscle area

SMD	Skeletal muscle radiodensity
SMI	Skeletal muscle index
STAGE I	Stage one
STAGE II	Stage two
STAGE III	Stage three
STAGE IV	Stage four
STROBE	Strengthening the reporting of observational studies in epidemiology
T12	Thoracic vertebra 12
TFA	Total fat area
TNF	Tumour necrosis factor
TNF-a	Tumour necrosis factor alpha
TNM	Tumour-Node-Metastasis
UK	United Kingdom
VATS	Video-assisted thoracoscopic surgery
VFA	Visceral fat area
WBCs	White blood cells
WHO	World health organization
WOS	Web of science

Dedication

This thesis is devoted to the memory of my beloved father, Farouq, whose unwavering support and encouragement inspired me to pursue this research. Sadly, he passed away during my second year.

A special feeling of gratitude to my mother, Nafisa, and my husband, Walid, who always assisted.

Chapter 1, overview of epidemiology, risk factors, etiology, and diagnosis of lung, oesophageal, and colorectal cancer

1. Introduction

A solid tumour is an abnormal mass of tissue that often lacks liquid-filled areas or cysts. These solid tumours differ by origin, including lymphomas (tumours originating from the lymphatic system), sarcomas (tumours originating from connective tissue), and carcinomas (tumours originating from epithelial tissue). The term "solid tumour" is used to differentiate hematologic malignancies, such as leukemia, which affect the blood and bone marrow, from neoplastic conditions that present as localized tissue masses (NCI, 2025). Currently, lung cancer, oesophagogastric, and colorectal are solid tumour malignancies with the fastest-rising incidence among other malignancies (Fernandes et al., 2020; Li et al., 2022).

1.1 Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide, accounting for approximately 2.1 million new cases each year, representing about 12% of all newly diagnosed malignancies, and the leading cause of cancer-related mortality globally, accounting for around 1.8 million fatalities each year (18% of cancer-related deaths) (Bray et al., 2024). Lung cancer is the leading cause of death in the United Kingdom, claiming roughly 35,000 lives each year. It accounts for around one-fifth of all UK cancer fatalities (21%) and one-seventh (13%) of all new UK cancer cases (NHS England, 2022).

Lung cancer causes more deaths among women than breast cancer (NHS England, 2022), and despite being labeled as a "smoker's disease," around 6000 individuals who have never smoked die from it each year, making it the eighth leading cause of cancer-related mortality in the UK (LoPiccolo et al., 2024).

Lung cancer is classified into two basic categories depending on how the cells look under a microscope. Small cell lung cancer (SCLC) is characterized by small cells, which are less prevalent than non-small cell lung cancer and affect almost exclusively heavy smokers (Nicholson et al., 2022). Non-small cell lung cancer (NSCLC) is a catch-all phrase for a variety of lung malignancies. Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are examples of non-small cell lung malignancies (Nicholson et al., 2022).

1.1.1 Epidemiology

- Incidence of Lung Cancer

According to the most recent GLOBOCAN numbers, 2,094,000 new cases of lung cancer were detected worldwide in 2018, making lung cancer the top cause of cancer death (Bray et al., 2024). Lung cancer is the second most prevalent cancer in males, after prostate cancer, and the second most common cancer in women, after breast cancer, with an estimated 725,000 cases. The age-standardized cumulative lifetime risk of lung cancer diagnosis is 3.8% in males and 1.77% in women (Bray et al., 2024).

Lung cancer is most common in poorer countries where cigarette smoking is most popular, with a 20-fold difference in incidence between locations (Bray et al., 2024). While prostate cancer is the most prevalent disease among males in 104 countries, lung cancer is the most common cancer among women in 37 countries, including Russia, China, and much of Eastern Europe, the Middle East, and Southeast Asia (Bray et al., 2024). In one country, North Korea, lung cancer is the most frequent malignancy among women (Bray et al., 2024). Micronesia/Polynesia has the most significant incidence of lung cancer in the world, with 52.2/100,000 cases among males, whereas Hungary has the highest incidence, with 77.4/100,000 cases among men Bray et al., 2024). Women in North America, Northern, and Western Europe are most prevalent worldwide. Men and women had the lowest frequency in Western, Central, and Eastern Africa Bray et al., 2024).

In England, 38,381 cases of lung cancer (20,560 men and 17,821 women) were reported in 2016. For men, lung cancer made up 13.3% of all cancer registrations, whereas for women, it made up 12.0% (NHS England, 2022). The difference in the incidence of lung cancer in men and women has reduced over time. Male lung cancer's age-standardized rate has dropped from 101.5 cases per 100,000 men in 2006 to 89.8 cases per 100,000 in 2016, whereas female lung cancer's incidence has risen during the same period, rising from 57.9 cases per 100,000 females in 2006 to 65.5 cases per 100,000 in 2016. Since smoking is the most prevalent cause of lung cancer, changes in smoking behaviors during the past ten or so years may account for this rise in occurrence (Collatuzzo et al., 2023).

1.1.2 Risk Factors

Non-Modifiable Risk Factors

Age

In the UK, those 75 years of age and older make up more than 4 out of 10 cases of lung cancer diagnosis (Non-Small Cell Lung Cancer Treatment (PDQ®)–Patient Version, 2025). The delayed course is attributed to tumorigenesis and biological aging (Tufail et al., 2024). Younger patients, particularly those under 55, are more likely to be female, nonsmokers, and have advanced adenocarcinoma, suggesting a more heritable mutation-related course. They are more likely to undergo intensive therapy and live longer (Ganti et al., 2021).

Gender

Men are more than twice as likely to be diagnosed with and die from lung cancer as women, primarily due to their higher smoking rates (Florez et al., 2024). Transgender men and women in the United States now smoke at a greater rate than the national average (35.5% vs. 13.7%) (Hughto et al., 2021). Women are more likely to have predisposing mutations and carry a larger familial risk.

Hormonal factors, such as estrogen receptors, may also play a role in lung cancer risk. Hormone replacement therapy has shown no significant risk (Castellanos et al., 2023). In the UK, the estimated lifetime risk of developing lung cancer is 1 in 13 for males and 1 in 15 for females (Cancer Research UK, 2024).

Race/ethnicity

The incidence of lung cancer in the United States varies among races and ethnicities, with African American men having the highest incidence (87.9/100,000), followed by Caucasian Americans (57.6/100,000) (Siegel et al., 2020). Despite having a substantially lower incidence of reported cigarette usage, Chinese women are just as likely as Western European women to be diagnosed with lung cancer (Bray et al., 2024). In England (2013-2017), the Asian and Black ethnic groupings, as well as those of mixed or multiple ethnicities, have lower lung cancer incidence rates than the White ethnic group (UK cancer statistics, 2021).

Family History

Family history plays a significant role in lung cancer risk, with a positive family history increasing the risk by 1.7 times (Citarella et al., 2024). Genetic variants in chromosomal regions, such as the 5p15 locus and 15q25-26 loci, have been linked to increased heritable lung cancer risk (Citarella et al., 2024). Although no specific germline genetic mutations or predisposing syndromes have been identified for lung cancer, considering family history and genetic risk may improve the effectiveness of early screening programs (Long et al., 2022).

- **Modifiable Risk Factors**

In the UK, 79% of lung cancer cases are avoidable. Many variables influence a person's chance of acquiring cancer, including age, genetics, and exposure to risk factors (including some possibly preventable lifestyle factors) (American Cancer Society, 2024).

Smoking is responsible for 72% of lung cancer cases in the United Kingdom. Secondhand smoke (passive smoking) also increases the risk of cancer.

Workplace exposure to substances such as asbestos and radon accounts for around 13% of cases.

Air pollution (8%) and **ionizing radiation** (5%) (American Cancer Society, 2024).

1.1.3 Etiology

The most significant connections between lung cancer and smoking are with SCLC and squamous cell lung cancer. Among the various organic and inorganic carcinogens in cigarette smoke are polycyclic aromatic hydrocarbons (PAHs), aromatic amines, N-nitrosamines, benzene, vinyl chloride, arsenic, and chromium. The degree of smoking exposure and the relative risk of lung cancer have a dose-dependent relationship. The amount of smoke inhaled varies depending (Basumallik and Agarwal, 2023) on the kind of cigarette, the length of inhalation, and the existence of a filter (Nasriawati et al., 2021; Constantin et al., 2023).

1.1.4 Diagnosis

Lung Cancer

The United Kingdom has one of the lowest survival rates in Europe and among comparable nations (World Cancer Research Fund, 2024). Lung cancer patients in the UK are diagnosed with more advanced illnesses than patients in many other countries, with around one-third being diagnosed through an emergency admission to hospital (Royal College of Physicians, 2020), resulting in a worse prognosis. Earlier detection is thus crucial for increasing lung cancer survival.

- **Non-Small Cell Lung Cancer (NSCLC)**

NSCLC is frequently misdiagnosed until it has progressed to an advanced stage (Ziora et al., 2025). Cough is the most prevalent symptom, occurring in 50% to 75% of patients, followed by hemoptysis, chest discomfort, and dyspnea (Ziora et al., 2025). Laboratory

abnormalities and paraneoplastic disorders are two less common signs. Biopsy is required for histologic confirmation of the diagnosis (Leiro-Fernández et al., 2021). The tumour size must also be determined to identify the TNM stage, which will ultimately dictate cancer therapy options (Leiro-Fernández et al., 2021). A Danish randomized trial compared staging using positron emission tomography (PET) paired with Computed Tomography (CT) to standard invasive staging alone (mediastinoscopy and mediastinal lymph node biopsy with echo-endoscopy) and found that PETCT provided superior categorization of N-stage (Leiro-Fernández et al., 2021). Any PET-CT-positive node verified by the analysis of a secondary objective from another randomized study must be sampled. Patients who are being treated with curative intent or who have indications or symptoms indicative of brain metastases should have a computed tomography or magnetic resonance imaging of the head performed. Obtaining adequate tissue samples is required, according to the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society interdisciplinary categorization of lung cancer (Prisadov et al., 2023). The possibility of identifying mutations and tailoring treatment has ramifications for the first examination of all suspected lung malignancies.

- **Small Cell Lung Cancer (SCLC)**

SCLC is a high-grade malignant epithelial tumour. To confirm the diagnosis, the tumour's specific light-microscopic features are assessed using hematoxylin and eosin staining (Sasaki et al., 2024). Immunohistochemistry (IHC) aids in diagnosing SCLC by detecting neuroendocrine markers—synaptophysin, chromogranin A, and CD56, which are usually positive in SCLC cells. The current WHO classification recognizes two subtypes: SCLC and combined SCLC (Sasaki et al., 2024). When lung cancer symptoms appear, they may include a chronic cough that gets worse over time, chest pain, haemoptysis, dyspnoea, fatigue, hoarseness, wheezing, and swelling of the face or neck due to tumour compression of blood vessels. Many tests are used to make a diagnosis: positron emission tomography combined with CT (PET-CT) assesses distant metastases and metabolic activity; a computed tomography (CT) scan provides detailed cross-sectional images to evaluate tumour size, location, and spread; and biopsy techniques, such as bronchoscopy, CT-guided transthoracic needle aspiration, or surgical sampling, are used to confirm malignancy by microscopic examination of tissue (Sasaki et al., 2024). Combined SCLC includes any non-small-cell histological subtype of non-small-cell carcinoma. Cytology is a powerful procedure that can be more definitive than microscopic biopsies in SCLC, because it yields more representative cells and

fewer artifact-affected cells by avoiding crushing or necrosis that can occur in small biopsy samples (Sasaki et al., 2024).

1.1.5 Management

1.1.5.1 Surgical Treatments

Surgery remains a cornerstone in the management of early-stage NSCLC (Stages I and II), often involving lobectomy, which is considered the gold standard (Solta et al., 2024). For patients with compromised pulmonary function, less extensive surgeries such as segmentectomy or wedge resection may be viable alternatives. In cases where the disease is more localized but extensive, pneumonectomy may be necessary. Recent advancements in minimally invasive surgical techniques, including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS), have improved surgical outcomes, reducing recovery time and postoperative complications (Solta et al., 2024). Surgery for early-stage illness (stage I-II) is the therapy of choice for medically fit patients with stage I-II NSCLC. Wedge resection is recommended over anatomical resection. The typical surgical strategy is an anatomical lobectomy with systematic nodal dissection or lobe-specific nodal sampling. However, pneumonectomy may be necessary for hilar or proximal tumours. Sub-lobar resections may be tolerated in individuals with peripheral tumours if a lobectomy is not possible due to comorbidities or poor lung function. When technically feasible, video-assisted thoracic surgery is the preferred strategy.

1.1.5.2 Adjuvant Therapy

In adjuvant treatment, the recurrence rate following surgery is substantial, with nearly half of patients developing metastases. Adjuvant (postoperative) platinum-based chemotherapy (preferably cisplatin vinorelbine) for four cycles is recommended for patients with nodal involvement or node-negative tumours 4 cm in size. The absolute effect of adjuvant treatment improves with tumour stage, with 11.6% improvement in overall survival at 5 years in patients with involved hilar nodes (N1) and 14.7% in patients with involved mediastinal nodes (N2). After an incomplete resection (involving broncho-vascular margins), postoperative irradiation is required and should be considered in situations with implicated N2 nodes.

Radiation Therapy

Radiation therapy is integral to the treatment of lung cancer, particularly for patients who are not candidates for surgery. Techniques such as stereotactic body radiotherapy (SBRT)

have proven highly effective in targeting early-stage NSCLC, delivering high doses of radiation with precision while sparing adjacent healthy tissues. For more advanced stages, conventional radiation therapy is often combined with chemotherapy to enhance effectiveness (Shroff & de Groot). In SCLC, prophylactic cranial irradiation (PCI) is frequently employed to reduce the risk of brain metastases, a common site of disease progression (Solta et al., 2024). Emerging advancements, such as proton beam therapy and adaptive radiotherapy, hold promise for further improving precision and minimizing treatment-related toxicity (Solta et al., 2024).

Chemotherapy in Lung Cancer

Chemotherapy continues to play a pivotal role in the treatment of both NSCLC and SCLC, particularly in advanced stages. Platinum-based regimens, such as cisplatin or carboplatin combined with agents like paclitaxel, pemetrexed, or docetaxel, remain the cornerstone of first-line therapy (Solta et al., 2024). The integration of chemotherapy into multimodal treatment strategies, such as neoadjuvant and adjuvant settings, has demonstrated benefits in reducing tumour size and improving resectability. Ongoing research seeks to optimize these protocols by minimizing toxicity while maintaining efficacy, thereby enhancing patients' quality of life during treatment (Solta et al., 2024).

1.1.6 Challenges Facing Clinical Practice in the Treatment of Lung Cancer

Clinical practice in the treatment of lung cancer faces multifaceted challenges that hinder optimal outcomes for patients. One significant issue is the heterogeneity of lung cancer itself, with diverse genetic and molecular profiles requiring highly tailored therapeutic strategies (Solta et al., 2024). While targeted therapies and immunotherapies have revolutionized treatment for advanced non-small cell lung cancer (NSCLC), resistance mechanisms such as tumour heterogeneity and the emergence of secondary mutations present ongoing obstacles. In addition, small cell lung cancer (SCLC) continues to lack substantial advancements, with treatment protocols essentially unchanged over decades (Solta et al., 2024).

Another significant hurdle is integrating cutting-edge diagnostics, such as circulating tumour DNA (ctDNA) analysis, into routine clinical practice. Despite their potential to provide real-time insights into tumour evolution, these tools are not yet universally accessible or standardized. Moreover, global disparities in healthcare resources exacerbate these challenges, particularly in low- and middle-income regions where molecularly targeted therapies remain largely unavailable (Coque et al., 2023).

Patient enrollment in clinical trials also poses a considerable challenge. Factors such as protocol complexity, stringent eligibility criteria, and limited patient awareness hinder participation rates, thereby slowing the evaluation of promising therapies.

1.2 Oesophagogastric Cancer

About 1.5 million people worldwide have oesophagogastric cancer each year, which encompasses malignancies of the stomach, esophagus, and oesophagogastric junction (Bray et al., 2024). With over 9,400 new cases each year, oesophageal cancer ranks as the 14th most frequent cancer in the UK and accounts for 2% of all new cases. With 2,900 new cases, it ranks as the 16th most prevalent cancer in women and the 9th most common in men (6,500 new cases). People aged 85-89 had the highest incidence rates (Bray et al., 2024). The intricacy of oesophagogastric cancer is highlighted by its multiple causes, which include environmental factors, genetic predispositions, and lifestyle factors, including smoking and drinking (Abdulkarim et al., 2022).

According to the average from 2017 to 2019, there are over 6,600 new cases of stomach cancer in the UK annually (Stomach cancer statistics, 2024). In the UK over that same time period, stomach cancer claimed about 4,200 lives annually (Stomach cancer statistics, 2024).

Survival for ten years: In the UK, 16.1% of patients with stomach cancer go on to live for ten years or more (Stomach cancer statistics, 2024). According to NHS England data, the one-year survival rate for stomach cancer is approximately 40%, while the five-year survival rate is approximately 17% (NHS England, 2022).

1.2.1 Epidemiology

Incidence of Oesophagogastric cancer. Over 450000 people worldwide have oesophageal cancer, and the frequency is rising quickly (Yang et al., 2024). Due to its extraordinarily aggressive character and low survival rate, oesophageal cancer is currently the eighth most prevalent incident of cancer worldwide (Cancer Research UK, 2024).

Between 2023–2025 and 2038–2040, stomach cancer mortality rates (age-standardized) are expected to decrease by almost 13% (Stomach cancer statistics, 2024).

1.2.2 Risk Factors

- **Non-Modifiable Risk Factors**

Age

As people age, their risk of developing oesophageal cancer rises—people under the age of 55 account for less than 15% of instances. People aged 85 to 89 had the highest incidence rates; 41% of new cases are detected in people aged 75 years or older in the UK (Cancer Research UK, 2024).

In the UK, those between the ages of 85 and 89 had the highest incidence rates of stomach cancer (2017-2019) (Stomach cancer statistics, 2024).

Gender

Oesophageal cancer in the UK ranks 16th most prevalent in women, with over 2,900 new cases annually. Men also face the ninth most prevalent cancer, accounting for 6,500 new cases annually (Cancer Research UK, 2024).

With over 2,300 new cases annually, stomach cancer ranks as the 19th most prevalent cancer in women in the UK. That represents 1% of all new cases of cancer among women in the UK between 2017 and 2019. With about 4,200 new cases annually, stomach cancer ranks as the 14th most prevalent disease in men in the UK. In the UK, that represents 2% of all new instances of male cancer from 2017 to 2019 (Stomach cancer statistics, 2024).

Race/ethnicity

In England, Asian and Black ethnic groupings had lower incidence rates of oesophageal cancer than White ethnic groups (2013-2017) (Oesophageal cancer statistics, 2024). Blacks had about twice the age-adjusted incidence of esophageal cancer as whites (8.63/100000 vs. 4.39/100000). The average age of diagnosis for various forms of oesophageal cancer is 67 years, and the risk rises with age. White males were more likely to be diagnosed with adenocarcinoma, whereas Black and white females were more likely to be diagnosed with squamous cell carcinoma (Delhey et al., 2025).

In England, the incidence of stomach cancer is lower among Asians, higher among Blacks, and similar among people of mixed or multiple ethnicities as compared to the White ethnic group (2013-2017) (Stomach cancer statistics, 2024).

Family History

According to a cohort study in the UK, 7 out of 100 patients with Barrett's oesophagus cancer had a family history of oesophageal cancer, which may marginally raise the risk (Eusebi et al., 2021). One in four oesophageal cancers is caused by an unhealthy body weight or a body

mass index (BMI) of 30 kg/m2 or above; this is due to gastroesophageal reflux, which raises the risk of oesophageal adenocarcinoma. The higher the BMI, the higher the risk (Eusebi et al., 2021).

- **Modifiable Risk Factors**

Your chance of developing oesophageal cancer is increased by smoking, being overweight or obese, drinking alcohol, Barrett's esophagus, gastro-oesophageal reflux disease (GORD), achalasia, and radiation therapy (Bray et al., 2024).

1.2.3 Etiology

Chronic oesophageal inflammation that interferes with normal cell signaling and development frequently precedes oesophageal cancer. For instance, it has been demonstrated that excessive alcohol use raises the risk of oesophageal cancer (Zeng et al., 2024). It has been shown that the risk of oesophageal cancer is increased by low income, vitamin A and C deficiency, zinc deficiency, hot beverages, infections (such as human papillomavirus), and intrinsic oesophageal disorders (Zeng et al., 2024).

1.2.4 Diagnosis

The gold standard for identifying oesophageal cancer is gastroscopy. Adjunct techniques, including chromoendoscopy, virtual chromoendoscopy, magnification endoscopy, and other sophisticated endoscopic imaging methods, may increase the sensitivity for identifying early-stage cancer (Rai et al., 2023). Targeted biopsies can confirm the diagnosis of oesophageal cancer. While the depth of the tumour dictates the viability of therapy, accurate staging information is essential for making the right treatment decisions for oesophageal cancer. Therefore, endosonographic, abdominal ultrasonographic, and computed tomographic scans of the abdomen and thorax should be performed before treatment to determine staging (Rai et al., 2023).

1.2.5 Management

Radiation therapy uses high-energy X-rays to destroy cancer cells or inhibit their growth. There are two categories: external and internal radiation therapy. Administration depends on the type and stage of cancer. Intraluminal intubation and dilation prevent blockage during radiation treatment (National Cancer Institute, 2024).

Chemotherapy inhibits cancer cell proliferation by either eliminating cells or preventing their reproduction. Systemic chemotherapy is administered orally or intravenously, while regional chemotherapy targets specific locations. Combining chemotherapy and radiation therapy enhances their effects (National Cancer Institute, 2024).

Laser therapy uses a concentrated beam of light to destroy cancerous cells. Electrocoagulation involves applying an electric current to eliminate cancer cells. Immunotherapy uses the patient's immune system to combat disease. Researchers are exploring immune checkpoint inhibitor therapy for advanced oesophageal cancer and recurrent cancer. These proteins regulate immune responses, making tumour cells resistant to immune T-cell attack and destruction(National Cancer Institute, 2024).

Neoadjuvant therapy, which is administered before surgery for esophagogastric cancer, attempts to reduce tumour size and treat micro metastases, increasing surgical success and possibly long-term results. It has become the norm in many patients.

Although its use after neoadjuvant treatment is still up for dispute, adjuvant therapy is administered following surgery to eradicate any remaining cancer cells. It is beneficial for patients with more advanced disease. The cancer type, stage, and effectiveness of neoadjuvant treatment will determine which strategy—or a mix of them—is used. Perioperative chemotherapy, combining neoadjuvant and adjuvant therapy, has shown encouraging outcomes, including improved survival (Yang et al., 2023).

1.3 Colorectal Cancer

Colorectal cancer (CRC) accounts for around 10% of all cancer cases, making it the third most frequent cancer overall and the second leading cause of cancer-related deaths worldwide. In terms of incidence and mortality, colorectal cancer (CRC) represents over 10% of all malignancies worldwide, with an estimated 1.93 million new cases diagnosed and 0.94 million deaths in 2020 (Bray et al., 2024). CRC is still a significant public health concern since it is the second most common cause of cancer-related deaths and the fourth most common type of cancer in the UK (Sturley et al., 2023).

1.3.1 Epidemiology

It was anticipated that over 1.9 million new instances of colorectal cancer and over 930,000 deaths from the disease occurred globally in 2020. There were significant regional differences in the incidence and fatality rates. Europe, Australia, and New Zealand had the greatest incidence rates, whereas Eastern Europe had the highest fatality rates. The annual

burden of colorectal cancer is expected to rise to 3.2 million new cases (a 63% increase) and 1.6 million deaths (a 73% increase) by 2040 (Siegel et al., 2020).

Colorectal cancer incidence rates have declined in high-income nations as a result of effective screening programs. (Siegel et al., 2020). CRC in the UK is the fourth most frequent malignancy, accounting for 11% of all new cancer cases from 2017 to 2019. It is the third most common cancer among women, accounting for 19,600 new cases annually, and the third most common among men, accounting for 24,500 new cases annually.

1.3.2 Risk Factors

Non-Modifiable Risk Factors

Age

As you age, your chance of developing colorectal cancer rises. Individuals aged 85-89 had the greatest incidence rates, with over 43% of newly diagnosed CRC cases per year occurring in those aged 75 and above in the UK (World Cancer Research Fund, 2024).

Gender

CRC among women, accounting for 19,600 new cases annually, and the third most common among men, accounting for 24,500 new cases annually, in the UK (World Cancer Research Fund, 2024).

Race/ethnicity

Compared to the White ethnic group, the incidence of CRC is lower among Asian and Black individuals, as well as those who are mixed or multiethnic in England (2013-2017) (Survival prevention bowel cancer incidence, 2020).

Family History

Certain gene alterations are linked to a few uncommon hereditary disorders or syndromes. Inheriting these gene alterations increases the risk of colon cancer in family members. Among these is familial adenomatous polyposis (FAP). Less than 1 in 100 instances, or less than 1% of all bowel malignancies, are caused by FAP. Every person with this condition will most likely have colon cancer by their 40s if treatment is not received (UK Cancer statistics, 2021).

Lynch syndrome, also called hereditary nonpolyposis colorectal cancer (HNPCC), is a genetic condition that raises the risk of developing some cancers, especially endometrial and

colorectal cancers, frequently before the age of fifty. It is brought on by a genetic mutation that affects the body's capacity to correct DNA errors and stop the development of cancer. These genes include MLH1, MSH2, MSH6, PMS2, and EPCAM (Abu-Freha et al., 2025).

- **Modifiable Risk Factors**

Colorectal cancer (CRC) modifiable risk factors include smoking, excessive alcohol consumption, sedentary lifestyles, and eating a diet heavy in saturated fats and processed meats or low in fruits, vegetables, and fibre (World Health Organization, 2023).

1.3.3 Etiology

When cells in the colon or rectum have DNA alterations that may impair their ability to regulate growth and division, colorectal cancer develops. Although the precise origin of CRC is unknown, several risk factors are significantly associated with a higher chance of getting the disease: dietary habits, tobacco usage, smoking, and heavy drinking (World Health Organization, 2023).

A commonly recognised multistep model, the Vogelstein model explains how colorectal cancer (CRC) develops through the accumulation of genetic abnormalities that confer a selective growth advantage, gradually transforming healthy colonic tissue into cancerous tumours. Unchecked proliferation and tumour growth result from key events such as the inactivation of the TP53 tumour suppressor gene, the activation of the KRAS oncogene, and the inactivation of the APC tumour suppressor gene. The transition from normal cells to adenomas and ultimately to invasive carcinomas that can metastasize depends on this linear accumulation of mutations, or driving events (Abdi, E., Latifi-Navid, S., & Latifi-Navid, H., 2022).

1.3.4 Diagnosis

CRC mortality and incidence can be decreased with screening. Therefore, to identify and eliminate preneoplastic adenomas and detect malignancies at an early stage, prevention and early diagnosis are essential. Faecal immunochemical test (FIT), flexible sigmoidoscopy, and colonoscopy are recognized screening methods (Roshandel et al., 2024).

Regarding bowel screening methods, the Faecal Immunochemical Test (FIT) is a straightforward, at-home test that is sent to a laboratory for analysis. It detects very small amounts of blood in the stool that cannot be identified without a magnifying glass. This test is

part of the Uks national screening for those aged between 50 to 70 years and symptomatic patients.

A colonoscopy is a procedure where a doctor inserts a long, flexible tube with a camera into the rectum and colon to search for polyps or cancer. During this exam, polyps can be taken out. Colon CT scan: A type of imaging test that produces 3D pictures of the colon to assist in identifying polyps and other colon irregularities. A flexible sigmoidoscopy is similar to a colonoscopy, with the exception that it only examines the lower part of the colon (Roshandel et al., 2024).

1.3.5 Management

For cancers at an extremely early stage, the tumor can typically be taken out via the anus with the aid of an endoscope during a colonoscopy. Surgical removal of part or all of the colon is known as a colectomy. The tumor's location determines the specific type: 1. Right hemicolectomy involves the surgical removal of the right colon. 2. Sigmoid colectomy or left hemicolectomy involves the removal of the sigmoid colon or the left colon. 3. A partial or segmental colectomy is a surgical procedure that involves removing a segment of the colon. 4. Rectal proctectomy is a surgical procedure that involves the complete removal of the rectum. 5. En bloc resection involves removing the tumour along with any attached organs that the cancer has invaded (Irani et al., 2023; Wang et al., 2022).

It is unequivocal that surgery serves as the definitive treatment for localized colorectal cancer, and the patient must undertake proper preoperative preparation. Mechanical bowel cleansing is commonly used, yet studies involving randomized trials have not found it to have a substantial impact (Irani et al., 2023).

To minimise the tumour, enhance results, and lower the risk of local recurrence, neoadjuvant therapy for rectal cancer entails administering chemotherapy, radiation, or both before surgery. Following surgery, adjuvant chemotherapy is administered to eradicate any cancer cells that may still be present and reduce the chance of cancer recurrence.

Neoadjuvant chemoradiotherapy (nCRT), which combines chemotherapy (often 5-FU) and radiation, followed by surgery and adjuvant chemotherapy, is a frequent treatment for rectal cancer. In patients with locally advanced rectal cancer, the more recent approach known as Total Neoadjuvant Therapy (TNT), which administers all or most of the chemotherapy and

radiation before surgery, shows promise for enhancing both overall and disease-free survival (Wang et al., 2022).

With stages ranging from A (confined to the gut wall) to D (far dissemination), the Duke's staging system is an older approach to categorising colorectal cancer according to tumour invasion and spread. Although Duke's staging offered a preliminary framework, the more thorough Tumour, Node, Metastasis (TNM) method has essentially replaced it. TNM (T- primary tuumor, N- regional lymph nodes, M- distant metastases) is currently utilised for more accurate treatment decisions and contemporary clinical practice (Banias et al., 2022).

Individuals with stage C colorectal cancer should be evaluated for 5-fluorouracil-based adjuvant chemotherapy. It appears that preoperative radiation therapy for rectal cancer is more beneficial than postoperative treatment. The use of preoperative radiotherapy decreases the likelihood of local rectal cancer recurrence, although its combination with total mesorectal excision remains under further clarification (Chen et al., 2022).

Personalised therapy in lung and colorectal cancer

Personalised or precision therapy has become a cornerstone of modern oncology, particularly in the management of lung and colorectal cancers. Advances in molecular profiling have enabled the identification of key genetic alterations that drive tumour growth and influence treatment response. One of the most clinically significant targets is the epidermal growth factor receptor (EGFR) pathway. In NSCLC, activating EGFR mutations predict sensitivity to tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, afatinib, and osimertinib, which have demonstrated superior efficacy compared with conventional chemotherapy. Recent large-scale trials, such as the FLAURA2 study, confirmed that osimertinib combined with chemotherapy significantly prolonged overall survival compared with osimertinib alone (median OS 47.5 vs. 37.6 months; HR ≈ 0.77) (Zhang et al., 2025). Furthermore, the MARIPOSA trial (2023–2024) showed that the combination of amivantamab and lazertinib achieved superior progression-free survival compared with osimertinib monotherapy in EGFR exon 19 deletion and L858R-mutated NSCLC (Cho et al., 2024)

In CRC, the use of EGFR monoclonal antibodies, such as cetuximab and panitumumab, has become standard therapy for patients with wild-type RAS tumours. The PARADIGM trial (2023) demonstrated that panitumumab plus mFOLFOX6 significantly improved overall survival compared with bevacizumab plus mFOLFOX6 in RAS wild-type metastatic colorectal

cancer (mCRC), particularly in left-sided tumours (Yoshino et al., 2022). Recent studies have also explored biomarker-guided EGFR rechallenge strategies, showing benefit in patients with RAS/BRAF wild-type ctDNA profiles (Roque et al., 2025).

Nivolumab: Mechanism of Action and Current Clinical Use

Nivolumab is a fully human IgG4 monoclonal antibody that targets the programmed death-1 (PD-1) receptor on activated T cells. It belongs to the class of immune checkpoint inhibitors, which have transformed cancer therapy by enhancing the host's immune response against malignant cells (Paik et al., 2022; Meng et al., 2024). Under normal physiological conditions, the interaction of PD-1 with its ligands, PD-L1 and PD-L2, transmits an inhibitory signal that reduces T-cell activation and prevents autoimmune damage. Tumour cells exploit this mechanism by overexpressing PD-L1 to evade immune surveillance (Meng et al., 2024). Nivolumab binds to PD-1 and blocks its interaction with PD-L1/PD-L2, thereby releasing the inhibitory checkpoint and restoring T-cell proliferation and cytotoxic activity against tumour cells (Paik et al., 2022; Carbone et al., 2025). Unlike cytotoxic chemotherapy, nivolumab does not directly induce tumour cell death but reactivates the immune system to recognise and eliminate cancer cells (Meng et al., 2024).

Clinically, nivolumab has received approval for multiple malignancies, including NSCLC, melanoma, renal cell carcinoma, head and neck squamous cell carcinoma, urothelial carcinoma, esophageal and gastric cancers, Hodgkin lymphoma, and microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer (Paik et al., 2022; Andre et al., 2024). In NSCLC, current guidelines recommend nivolumab either as monotherapy following progression on platinum-based chemotherapy or in combination with *ipilimumab* (with or without chemotherapy) as a first-line treatment for PD-L1-positive tumours without *EGFR* or *ALK* mutations (Carbone et al., 2025). In colorectal cancer, nivolumab—alone or in combination with ipilimumab—is indicated for patients with MSI-H or dMMR metastatic disease who have progressed after standard chemotherapy (Andre et al., 2024). The recommended dosing schedules are 240 mg intravenously every two weeks or 480 mg every four weeks, continued until disease progression or unacceptable toxicity (Paik et al., 2022). Like other immune checkpoint inhibitors, nivolumab can lead to immune-related adverse events (irAEs), including pneumonitis, colitis, hepatitis, endocrinopathies, and dermatologic toxicities, necessitating careful monitoring and management with corticosteroids or discontinuation of treatment when severe (Paik et al., 2022; Meng et al., 2024). Collectively,

nivolumab exemplifies the paradigm shift toward biomarker-guided immunotherapy, offering durable clinical benefits through immune system reactivation rather than direct cytotoxicity (Meng et al., 2024; Carbone et al., 2025).

A study by Kuusisalo et al. (2023) analyzed 329 patients with NSCLC to determine whether baseline plasma C-reactive protein levels and tumor PD-L1 expression have predictive and prognostic value, particularly in patients treated with immune checkpoint inhibitors (Kuusisalo et al. 2023). The researchers found that low CRP levels (≤10 mg/L) were an independent predictor of improved overall survival across the entire study cohort. In patients treated with ICI, both low CRP levels and high PD-L1 expression (≥50%) were linked to significantly improved progression-free survival. Notably, the combination of high CRP levels and high PD-L1 expression identified individuals who received minimal benefit from ICIs, experiencing progression-free survival comparable to those with low PD-L1 expression. Overall, the study shows that CRP is a strong, independent prognostic biomarker in NSCLC and enhances the predictive value of PD-L1, suggesting that assessing systemic inflammation in addition to PD-L1 expression can improve patient selection for immunotherapy (Kuusisalo et al. 2023).

1.4 Systemic inflammation

Over the last 20 years, there has been an increasing interest in the role of systemic inflammation in the nutritional and functional decline of patients with cancer. Key to this has been the numerous publications demonstrating the independent prognostic value of markers of the systemic inflammatory response, such as C-reactive protein, albumin, white cell count (and its components, neutrophils, lymphocytes, macrophages, platelets), and their combination scores. In particular, the prognostic value of the combination of C-reactive protein and albumin (Glasgow Prognostic Score, GPS) and the combination of neutrophils and lymphocytes (neutrophil to lymphocyte ratio, NLR) has been extensively validated in both early (primary disease amenable to surgery) and advanced disease (not amenable to surgery). Although markers of the systemic inflammatory response (including GPS/NLR) have been extensively associated with nutritional decline (weight and skeletal muscle loss, reduced intake, Global Leadership Initiative on Malnutrition (GLIM) criteria, and less work), less work has examined the relationship between such markers and objective measurements of functional decline. In particular, the association between the mGPS/NLR scores and objective measures of functional decline is in its infancy.

1.4.1 Cachexia and Inflammation

Cachexia is defined as a multifactorial metabolic wasting syndrome characterized by the ongoing, involuntary loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support alone and leads to progressive functional impairment (Ni et al., 2020; Lv et al., 2025). This syndrome is a major complication of chronic illnesses, especially advanced cancers (hence, cancer cachexia), and is a leading cause of cancer-related mortality. Recent definitions highlight that cachexia is fundamentally a chronic, systemic disease-related malnutrition driven by inflammation and metabolic abnormalities, rather than by inadequate food intake (Muscaritoli et al., 2021; Azeez et al., 2025). Markers of systemic inflammation, such as elevated C-reactive protein (CRP) and a high Neutrophil-to-Lymphocyte Ratio (NLR), are routinely associated with the presence and severity of the condition, and are even incorporated into prognostic scoring systems like the Glasgow Prognostic Score (GPS) for its clinical assessment (Dudhat et al., 2025; Lv et al., 2025).

The intricate link between cachexia and inflammation is the engine of the syndrome's metabolic derangement. Pro-inflammatory cytokines, particularly Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and Interleukin-1 (IL-1), are released by the tumor itself and the host's immune cells, coordinating a state of hypercatabolism and anabolism resistance (Lv et al., 2025; Azeez et al., 2025). These mediators disrupt protein homeostasis by activating the ubiquitin-proteasome system in muscle cells, thereby accelerating the breakdown of muscle protein (proteolysis) while simultaneously inhibiting anabolic pathways that promote tissue growth. Furthermore, inflammation promotes insulin resistance and increases the body’s resting energy expenditure (hypermetabolism), contributing to a persistent negative energy balance that is refractory to nutritional intervention (Dudhat et al., 2025; Lv et al., 2025). This chronic, low-grade systemic inflammation ensures that the body remains in a constant state of accelerated tissue destruction, thereby defining cachexia as an inflammation-driven syndrome of metabolic dysfunction.

1.4.2 Inflammation and cancer: A dual role

Inflammation plays a paradoxical role in cancer biology, functioning both as a defence against tumour development and as a promoter of tumour progression (Venakteshaiah et al., 2021; Xie et al., 2025). On one hand, the immune system can detect and eliminate nascent malignant cells through a process known as immunosurveillance, involving cytotoxic T

lymphocytes, natural killer (NK) cells, and macrophages that recognise and destroy aberrant cells before they proliferate (Verma et al., 2024). These form the basis of the cancer immunoediting concept, which encompasses three sequential phases—elimination, equilibrium, and escape. During elimination, the immune system effectively eradicates transformed cells; in the equilibrium phase, residual tumour cells may persist in a dormant state under immune control; and in the escape phase, tumour variants evolve mechanisms to evade immune detection, leading to clinically apparent cancer (Verma et al., 2024; Gubin et al., 2022).

Conversely, chronic inflammation can create a tumour-promoting microenvironment that supports cancer initiation, growth, angiogenesis, and metastasis (Xie et al., 2025; Dong et al., 2024). Persistent inflammatory signals lead to continuous activation of immune cells, production of cytokines (e.g., IL-6, TNF-α, IL-1β), chemokines, and growth factors, and generation of reactive oxygen and nitrogen species (ROS/RNS), which can induce DNA damage and genomic instability (Dong et al., 2024; Choi et al., 2023). The NF-κB, STAT3, and COX-2/PGE_2 pathways are central mediators linking inflammation to oncogenesis by promoting cell proliferation, inhibiting apoptosis, and facilitating angiogenesis Choi et al., 2023; Hanahan et al., 2022). Tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) further sustain an immunosuppressive environment that favours tumour survival and spread (Hanahan et al., 2022). This dichotomy illustrates that while acute inflammation can eliminate tumours, chronic inflammation often fuels their progression.

1.4.3 Molecular pathologies underlying inflammation-related cancers

The molecular landscape of inflammation-associated cancers involves a range of genetic and epigenetic alterations that drive malignant transformation. Among the most frequently affected are oncogenes and tumour suppressor genes, which regulate critical cellular processes such as proliferation, apoptosis, and DNA repair (Lahouel et al. 2020).

In CRC, mutations in the APC gene represent early events that activate the Wnt/β-catenin pathway, leading to uncontrolled cellular proliferation (Hallajzadeh et al., 2020). Subsequent mutations in KRAS (a member of the RAS family) promote constitutive activation of the MAPK/ERK signalling cascade, enhancing cell growth and survival (Hallajzadeh et al., 2020; Myall et al., 2024). Loss-of-function mutations in TP53 occur later in the adenoma–carcinoma sequence, impairing cell-cycle control and apoptotic response (Myall et al., 2024). Inflammatory mediators such as prostaglandin E_2 and interleukin-6 can further enhance

RAS/RAF/MEK/ERK and PI3K/AKT pathway activity, linking chronic inflammation to molecular carcinogenesis (Dong et al., 2024; Hanahan et al., 2022).

In NSCLC, activating mutations in EGFR and KRAS, and rearrangements involving ALK, ROS1, and RET, define distinct molecular subtypes that guide targeted therapy (Attili et al., 2024). EGFR mutations (exon 19 deletions, L858R) lead to continuous activation of downstream pathways, including PI3K/AKT and RAS/RAF/MEK/ERK, promoting proliferation and inhibiting apoptosis (Attili et al., 2024). Conversely, KRAS mutations—often associated with smoking—activate similar downstream pathways but predict resistance to EGFR-targeted therapies (Sposito et al., 2025). Loss of tumour suppressors such as TP53 and STK11/LKB1 further accelerates tumour progression and modulates the immune microenvironment, often conferring resistance to immunotherapy (Sposito et al., 2025).

1.4.4 Acute and chronic inflammation

Inflammation is a protective, localized reaction that produces edema, erythema, warmth, pain, and loss of function in response to harmful insults such as microbial infections, physical factors (trauma, radiation, temperature), chemical substances (irritant and corrosive chemicals), and tissue necrosis and hypersensitivity reactions. It involves interactions among various innate immune cells, inflammatory cells, chemokines, cytokines, and pro-inflammatory mediators to restore homeostasis after injury, promoting either regeneration or fibrosis (Figure 1-1). Inflammation also plays a significant role at different stages of cancer development, including initiation, promotion, malignant conversion, invasion, and metastasis (L Kiss A., 2022).

There are two types of inflammation: acute (which occurs immediately upon injury and lasts only a few days) and chronic (which lasts for months or years). Acute inflammation is the primary response, characterized by the increased movement of plasma and innate immune cells, such as neutrophils and macrophages, from the blood into the injured tissues. Chronic inflammation is a progressive change in the type of cells present at the site of the inflammatory reaction. It is characterized by simultaneous destruction and healing of the injured tissue (Yadav et al., 2024). The inflammatory response consists of vascular and cellular events. The vascular events include changes in vessel diameter (vasodilation), resulting in increased blood flow (causing redness and heat) and increased vascular permeability, leading to loss of plasma into the tissue and the formation of fluid exudate. Cellular events involve the movement of

leukocytes from the blood vessels into the injured tissue. Some act as phagocytes, ingesting bacteria, viruses, and cellular debris. Others release enzymatic granules that damage pathogenic invaders. Leukocytes also release inflammatory mediators that develop and maintain the inflammatory response. In general, acute inflammation is mediated by granulocytes, whereas chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes. Although injury initiates the inflammatory response, chemical factors released in response to this stimulation trigger vascular and cellular changes mentioned above (Johnkennedy et al., 2022).

The vascular and cellular events of inflammation are mediated by a variety of chemical mediators (Meizlish et al., 2021), derived from cells or plasma. Mediators released during inflammation intensify and propagate the inflammatory response. However, most perform their biological activity by binding to specific receptors on target cells; some have direct enzymatic activity, and others mediate oxidative damage. Cell injury is followed by a cascade of events that leads to the inflammatory response, which is divided into three phases. The first phase of inflammation is initiated by the activation of local tissue macrophages, which exert phagocytic activity, and mast cells, which release cytokines and vasoactive substances. Cytokines are divided into pro-inflammatory and immune regulatory chemokines. Pro-inflammatory cytokines trigger the second phase of inflammation, while chemokines generate a chemotactic gradient. Immune regulatory cytokines prepare the adaptive phase of the immune response. A certain number of vasoactive substances mediate an initial local vasoconstriction aiming to restrict the cause of tissue injury (Meizlish et al., 2021). This vasoconstriction is followed by broader local vasodilation and an increased permeability of the vascular wall. These last events permit inflammatory cells and macromolecules to reach the site of tissue injury. Many vasoactive substances, such as histamine, bradykinin, prostaglandins, leukotrienes, and nitric oxide, participate in these actions. During the second phase of inflammation, blood cells, following a chemotactic signal, move to the site of injury and begin phagocytic activity. The third phase of inflammation relates to tissue repair (Soliman et al. 2022).

Cancer is initiated and progresses, in part, through inflammatory cells and signals. The transformation of a normal cell into a cancerous one can occur before chronic inflammatory conditions caused by infection or injury. Chronic inflammatory conditions may promote genomic instability, leading to DNA damage, oncogene activation, or compromised tumour suppressor function. On the other hand, an inflammatory microenvironment that promotes tumour cell growth can be triggered by cancer unrelated to inflammation. In the tumour

microenvironment, inflammation and inflammation-related stimuli, whether chronic or tumor-derived, allow cancer cells to proliferate and survive, encourage the development of blood and lymphatic vessels, and facilitate invasion and metastasis (Nishida & Andoh, 2025). A favourable reaction to many regularly used anti-cancer antibodies and chemotherapeutic drugs can be successfully mitigated by the inflammatory state of the tumour microenvironment, which can also suppress the body's natural immune response. The molecular processes and effects of inflammation, especially those associated with the tumour microenvironment, may be beginning to be understood, according to new findings. This new information implicates novel cellular targets that may improve the detection and treatment of solid cancers (Nishida Andoh, 2025).

1.4.5 Acute phase reactants (APR)

Acute-phase reactions are markers of inflammation associated with systemic and metabolic changes that occur within hours of an inflammatory stimulus and are critical to the body's ability to respond to injury. The concentration of many plasma proteins increases during inflammatory states, largely in response to inflammation-associated cytokines. Interleukins such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumour necrosis factor (TNF) have a strong effect on liver cells, stimulating them to produce a class of acute-phase proteins. Most components of the acute phase response reflect adaptation and defense mechanisms that occur before the body mounts an immunological response. Acute phase reactants can be classified as positive or negative, depending on their serum concentrations during inflammation. Positive acute phase reactants are upregulated and increase during inflammation, including procalcitonin, C-reactive protein, ferritin, fibrinogen, hepcidin, and serum amyloid A. Negative acute phase reactants are downregulated. Their concentrations decrease during inflammation and include albumin, prealbumin, transferrin, retinol-binding protein, and antithrombin (Hannoodee and Nasuruddin, 2024).

Although the concentrations of multiple components of the acute-phase response commonly increase together, not all of them increase uniformly in all patients with the same disease. Thus, febrile patients may have normal plasma CRP concentrations. Conditions that commonly lead to significant changes in the plasma concentrations of acute-phase proteins include trauma, infection, burns, surgery, tissue infarction, and advanced cancer. Moderate changes occur after hard exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses. These variations, which indicate that the components of the acute-phase response are individually regulated, may be explained in part by differences in the

patterns of production of specific cytokines or their modulators in different pathophysiologic states (Rooijakkers, S. 2025).

1.4.6 Prognostic Biomarker

Recent studies have begun to unravel the mechanism linking the host inflammatory response to tumour growth, invasion, and metastasis. Inflammation-based prognostic scores have been extensively studied across a variety of malignant solid tumours and are emerging as promising prognostic indicators. Recently, many markers of inflammatory response, including C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), albumin (Alb), globulin, and the Glasgow Prognostic Score/modified Glasgow Prognostic Score (GPS/mGPS) were demonstrated as independent predictive factors of cancer (Sambataro et al., 2023) (**Table 1-1**).

Table 1-1. Definitions of Prognostic Biomarkers

Variables	Score/Ratio
Neutrophil lymphocyte ratio (NLR)	
Neutrophil count: lymphocyte count	≤ 3
Neutrophil count: lymphocyte count	3–5
Neutrophil count: lymphocyte count	>5
Neutrophil lymphocyte score (NLS)	
Neutrophil count ≤ 7.5×10^9/l and lymphocyte count ≥ 1.5×10^9/l	0
Neutrophil count > 7.5×10^9/l and lymphocyte count ≥ 1.5×10^9/l	1
Neutrophil count ≤ 7.5×10^9/l and lymphocyte count < 1.5×10^9/l	1
Neutrophil count > 7.5×10^9/l and lymphocyte count < 1.5×10^9/l	2
Platelet lymphocyte ratio (PLR)	
Platelet count: lymphocyte count	≤ 150
Platelet count: lymphocyte count	>150
Platelet lymphocyte score (PLS)	
Platelet count ≤ 400×10^9/l and lymphocyte count ≥ 1.5×10^9/l	0
Platelet count > 400×10^9/l and lymphocyte count ≥ 1.5×10^9/l	1
Platelet count ≤ 400×10^9/l and lymphocyte count < 1.5×10^9/l	1

Platelet count > 400 × 10^9/l and lymphocyte count < 1.5 × 10^9/l	2
Lymphocyte monocyte ratio (LMR)	
lymphocyte count: monocyte count	≥ 2.40
lymphocyte count: monocyte count	< 2.40
Lymphocyte monocyte score (LMS)	
Lymphocyte count ≥ 1.5 × 10^9/l and monocyte count ≤ 0.80 × 10^9/l	0
Lymphocyte count < 1.5 × 10^9/l and monocyte count ≤ 0.80 × 10^9/l	1
Lymphocyte count > 1.5 × 10^9/l and monocyte count > 0.80 × 10^9/l	1
Lymphocyte count < 1.5 × 10^9/l and monocyte count > 0.80 × 10^9/l	2
Neutrophil platelet score (NPS)	
Neutrophil count ≤ 7.5 × 10^9/l and platelet count ≤ 400 × 10^9/l	0
Neutrophil count > 7.5 × 10^9/l and platelet count ≤ 400 × 10^9/l	1
Neutrophil count ≤ 7.5 × 10^9/l and platelet count > 400 × 10^9/l	1
Neutrophil count > 7.5 × 10^9/l and platelet count > 400 × 10^9/l	2
C-reactive protein albumin ratio (CAR)	
C-reactive protein: albumin	≤ 0.2
C-reactive protein: albumin	0.2-0.4
C-reactive protein: albumin	>0.2
Modified Glasgow Prognostic Score (mGPS)	
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
Modified Glasgow Prognostic Score/Glasgow Prognostic Score (mGPS/GPS)	
C-reactive protein≤10mg/l and albumin ≥ 35 g/l	0
C-reactive protein>10 and albumin ≥ 35 g/l	1
C-reactive protein>10 and albumin <35 g/l	2
C-reactive protein-to-albumin ratio (CAR)	
C-reactive protein/ albumin	<0.2
C-reactive protein/ albumin	0.2-0.4
C-reactive protein/ albumin	>0.4
Scottish Inflammatory Prognostic Score (SIPS)	
Albumin ≥35g/l and neutrophil ≤7.5×10^9/l	0

Albumin ≥35g/l and neutrophil >7.5×10^9/l	1
Albumin <35g/l and neutrophil ≤7.5×10^9/l	1
Albumin <35g/l and neutrophil >7.5×10^9/l	2
Advanced Lung Cancer Inflammation Index (ALI)	
Body mass index (BMI) ×serum albumin / Neutrophil lymphocyte ratio (NLR) >18	Low inflammation
Body mass index (BMI) ×serum albumin / Neutrophil lymphocyte ratio (NLR)<18	High inflammation
The CRP-albumin-lymphocyte (CALLY) index	
Albumin× lymphocyte count /CRP×10^4	≤1.12
Albumin× lymphocyte count /CRP×10^4	>1.12
The Onodera's Prognostic Nutritional Index (OPNI)	
10× Albumin+0.005×lymphocyte count (per mm^3) ≥ 40	High
10× Albumin+0.005×lymphocyte count (per mm^3) <40	Low

The biomarker CRP is an acute-phase protein produced mainly by the liver in response to tissue injury or infection. Plasma CRP levels are also moderately elevated in response to chronic inflammatory diseases and cancer. Recent epidemiologic studies suggest that elevated CRP levels not only mark the presence of prevalent cancer but also are associated with an increased risk of future cancer in apparently healthy individuals. Several studies reported an association between elevated CRP levels and poor prognoses in patients with several types of solid cancer receiving surgery, chemotherapy, or radiotherapy, with a broad variety of malignancies. Additionally, some tumours that synthesize CRP are associated with poor outcomes. Thus, not only plasma CRP levels but also intertumoural CRP expressions may be a useful tool for predicting prognosis. However, it remains unknown if circulating CRP is produced by the tumour, liver, or both. The combined evidence suggests that elevated CRP levels are associated with poor prognoses independent of tumour stage. Thus, elevated CRP levels seem to be associated with poor prognoses in advanced cancer patients. In addition, the combined use of interleukin-6 (IL-6) and CRP as a marker of inflammation associated with cancer cachexia might provide better prediction in patients with advanced cancer. However, measuring plasma IL-6 and other cytokines, such as IL-1 and tumour necrosis factor alpha (TNF-α), is difficult because of their short plasma half-lives and the high cost of such an approach; this makes CRP the preferred marker in those with advanced cancer (Puhr et al., 2023; Sambataro et al., 2023).

By combining CRP and albumin, the GPS/mGPS reflects both the systemic inflammatory response and nutritional status. The GPS score ranges from 0 to 2: patients with both an elevated CRP (>10 mg/l) and decreased albumin (<35 mg/l) are assigned a score of 2, whereas those with either an elevated CRP or decreased albumin alone are assigned a score of 1. Patients with normal CRP and albumin levels are assigned a score of 0. The main difference between GPS and mGPS is that mGPS classifies patients without elevated CRP who are hypoalbuminemic as having low risk (mGPS = 0). A 2003 study by Forrest et al. demonstrated the utility of GPS as a prognostic indicator in patients with non-small-cell lung cancer. Subsequently, an increasing number of studies have demonstrated the predictive value of GPS/mGPS in other cancers, such as pancreatic, liver, and esophageal cancers(Puhr et al., 2023).

A complete blood count (CBC) is an inexpensive and easy-to-perform diagnostic test widely used in everyday clinical practice. It is of great importance for the diagnosis and monitoring of various medical conditions, not only hematological ones. Although used for years, new applications for CBC are still being discovered. Recently, numerous studies have focused on the proportions of different leukocyte types in various medical conditions. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are among the many surrogate biomarkers of inflammation associated with outcomes in gastrointestinal cancers.

NLR, defined as the ratio of neutrophil to lymphocyte counts in peripheral blood, is a useful marker that predicts not only disease progression but also mortality in various inflammatory diseases, making it a notable new biomarker of inflammation. NLR is a reproducible, easily measured, inexpensive marker of subclinical inflammation and is indicative of an impaired cell-mediated immunity associated with systemic inflammation. The prognostic role of NLR has been documented in multiple cancers, disease settings, and treatments, including malignancies of the colon, ovaries, urothelium, pancreas, and kidneys. Presence of high NLR is correlated with worse outcomes in many malignancies, such as colorectal cancer, head and neck squamous cell carcinoma, soft tissue sarcoma, biliary tract cancers, ovarian cancer, gastrointestinal cancer, and breast cancer (Li et al., 2022; Sambataro et al., 2023)

The platelet-to-lymphocyte ratio (PLR) is a novel inflammatory marker that can be used in many diseases to predict inflammation and mortality. PLR can be easily calculated and is a widely available, attractive, and cost-effective blood-derived prognostic marker, as well as an

inflammation- and immune-related prognostic score, to evaluate the prognosis of several solid tumours. Indeed, studies showed that elevated PLR was associated with poor prognosis for colorectal cancer. Moreover, several studies showed that elevated PLR was a good predictor of poor prognosis in gastric cancer and lung cancer (Huang et al., 2024).

Furthermore, the lymphocyte-to-monocyte ratio (LMR), which also reflects systemic inflammation, has recently been reported to correlate with survival in various malignancies, including diffuse large B-cell lymphoma, colon cancer, esophageal carcinoma, and lung cancer (Yang et al., 2025).

The level of CRP has been reported as a good prognostic marker in patients with advanced cancer. It is elevated in those with chronic inflammatory disease as well as in advanced cancer patients and is related to an increased cancer risk, anorexia, fatigue, weight loss, and pain in cancer patients (Sambataro et al., 2023).

It is now becoming clear that the tumour microenvironment plays a crucial role in cancer metastasis and significantly affects therapeutic response and overall patient outcome. Immune cells are important participants in the tumour microenvironment, where they play multiple roles at all stages of cancer development. Among the immune cells infiltrating tumours, myeloid cells can play a dual role in sculpting cancer behavior. Indeed, they can promote or inhibit cancer initiation and progression (Akkız et al., 2025).

Accumulating evidence suggests that neutrophils may also play a key role in multiple aspects of cancer biology. Moreover, neutrophils, as a critical factor in the tumour microenvironment, play an essential regulatory role in cancer progression and are the primary responsive cell type in the innate immune response (Hedrick and Malanchi, 2022).

1.4.7 ECOG-Performance Status and tools used for assessment

The Eastern Cooperative Oncology Group (ECOG) Performance Status is a standardized clinical tool used to quantify a patient's functional status and ability to perform daily activities. It helps clinicians evaluate how a patient's disease affects their overall well-being and physical capabilities, and it plays a crucial role in determining eligibility for clinical trials, guiding treatment decisions, and predicting prognosis in oncology (Mischel & Rosielle, 2022).

ECOG status is graded on a five-point scale (0–4), where (**Table 1-2**):

- 0 = Fully active, able to carry on all pre-disease performance without restriction.
- 1 = Restricted in physically strenuous activity but ambulatory and able to perform light work.
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; up >50% of waking hours.
- 3 = Capable of only limited self-care; confined to bed or chair >50% of waking hours.
- 4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

  (Some references also include 5 = dead, for record-keeping purposes) (Freites-Martinez et al., 2021).

The tools used to assign ECOG parameters are primarily clinical observation and patient-reported functionality, not laboratory or imaging data. Physicians or oncology nurses assess the patient through:

- Direct clinical evaluation (mobility, physical endurance, level of fatigue, self-care ability)
- Patient interview (ability to perform daily tasks, work, and physical activities)
- Caregiver input, when appropriate
- Sometimes combined with other scales, such as the Karnofsky Performance Status (KPS), which provides a more granular 0–100 score that can be cross-mapped to ECOG categories (Oguz et al., 2021).

Table 1-2: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

1.5 Summary of the Introduction

This thesis introduces solid tumours as aberrant tissue masses lacking liquid components, distinguishing them from leukemias, and identifies colorectal, oesophagogastric, and lung cancers as solid tumour malignancies with the fastest-rising incidence. The subsequent sections delve into lung cancer, the leading cause of cancer-related mortality globally, detailing its classification (SCLC and NSCLC), epidemiology (highest incidence in regions with high smoking rates), and risk factors (dominated by smoking, but also including age, gender, and family history). It then outlines the complexities of its diagnosis (often advanced at presentation in the UK) and its current management strategies, which include surgery (lobectomy being the gold standard for early NSCLC), adjuvant therapy, radiation (especially SBRT), and chemotherapy, while acknowledging the significant challenges of tumour heterogeneity and treatment resistance. Finally, the text sets up the following discussions on oesophagogastric cancer and colorectal cancer, providing initial epidemiological and risk factor data for both, including incidence rates, age- and gender-related disparities, and the importance of screening, thereby establishing the three major solid tumour types that form the focus of the entire document.

1.6 Aims of the Introduction

The overarching aim of this thesis was to examine the prevalence and prognostic significance of markers of the systemic inflammatory response across a range of tumour types, and to evaluate their clinical utility in predicting treatment outcomes and survival. Specifically, the work compared the prognostic value of systemic inflammatory markers in various malignancies, including non-small cell lung cancer (NSCLC), oesophagogastric cancer, and colorectal cancer.

In NSCLC, the thesis aimed to investigate the relationship between pretreatment clinicopathological variables, systemic inflammation, CT-derived body composition, and 12-month survival in patients treated with nivolumab as second-line therapy (n=92). Given the modest sample size a systematic review and meta-analysis were also undertaken to evaluate the role of systemic inflammation in predicting immunotherapy efficacy (17 studies, n=2948); investigating a systemic inflammation–first approach to assessing nutritional decline (n=535); comparing albumin-based prognostic inflammatory scores and survival (n=535); and evaluating systemic inflammatory ratios and scores using a C-reactive protein (CRP)-based comparison (n=535). In addition, the research aimed to assess the prevalence and prognostic significance of systemic inflammatory markers in oesophagogastric cancer patients undergoing

neoadjuvant chemotherapy (n=335), evaluate systemic inflammatory ratios and scores in primary operable colorectal cancer through a CRP-based comparison (n=446), and analyze systemic inflammation–based prognostic ratios and scores in a range of common solid tumours at TNM Stage III (n=440).

The research presented in this thesis evolved through a series of interlinked studies, each building on the findings and limitations of the previous work. The progression was shaped by data availability, clinical relevance, and emerging hypotheses concerning systemic inflammation and cancer outcomes.

Initial clinical study – NSCLC Cohort, the research began with a retrospective observational study conducted in collaboration with a clinical oncologist at the Beatson Cancer Centre. This collaboration provided access to a dataset of 92 patients with non-small cell lung cancer (NSCLC), enabling an initial analysis of systemic inflammatory markers and their relationship to immunotherapy outcomes.

Recognising the limitations posed by the small sample size in the initial study, and no CRP recorded for most of the patients, we conducted a systematic review and meta-analysis to investigate the broader relationship between systemic inflammation and immunotherapy efficacy across published literature. This approach enabled a more comprehensive assessment of existing evidence and helped identify consistent inflammatory markers with prognostic value.

Nutritional status and inflammation (Chapter 4). As nutritional status is closely associated with systemic inflammation and patient outcomes, particularly in NSCLC, Chapter 4 focused on the role of nutritional markers and their interactions with inflammation. This study aimed to determine whether nutritional parameters contributed independently or synergistically to prognostic stratification. Exploration of inflammatory markers based on the Glasgow prognostic score (Chapters 5–6) The Glasgow prognostic score (GPS), derived from serum C-reactive protein (CRP) and albumin levels, emerged as a key prognostic tool in our initial findings. In Chapters 5 and 6, we extended our investigation to assess other CRP- and albumin-based inflammatory indices, aiming to validate and compare their prognostic utility in the NSCLC cohort. To evaluate the generalisability of CRP-based inflammatory markers beyond NSCLC, we applied the same analytical framework to two additional tumour types: oesophagogastric OG cancer and colorectal cancer, chapters 7 and 8. Substantial differences in prognostic trends were observed between NSCLC, OGC, and colorectal cancers. In response,

we conducted a pooled analysis focusing on patients with TNM stage III disease across all three tumour types (**Figure 1-2**).

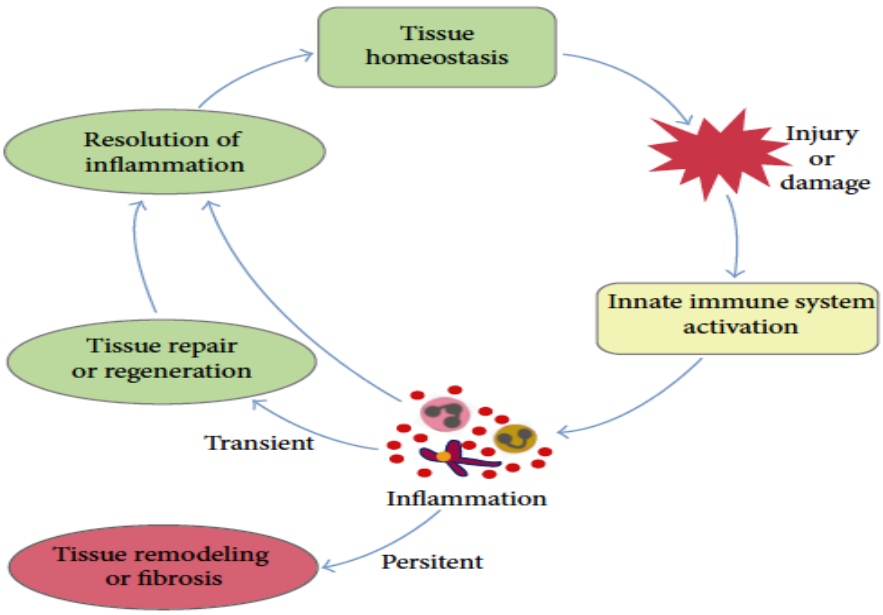

Figure 1 - 1: The role of the innate immune system in regaining tissue homeostasis (Coffelt et al., 2016; Peinado et al., 2017).

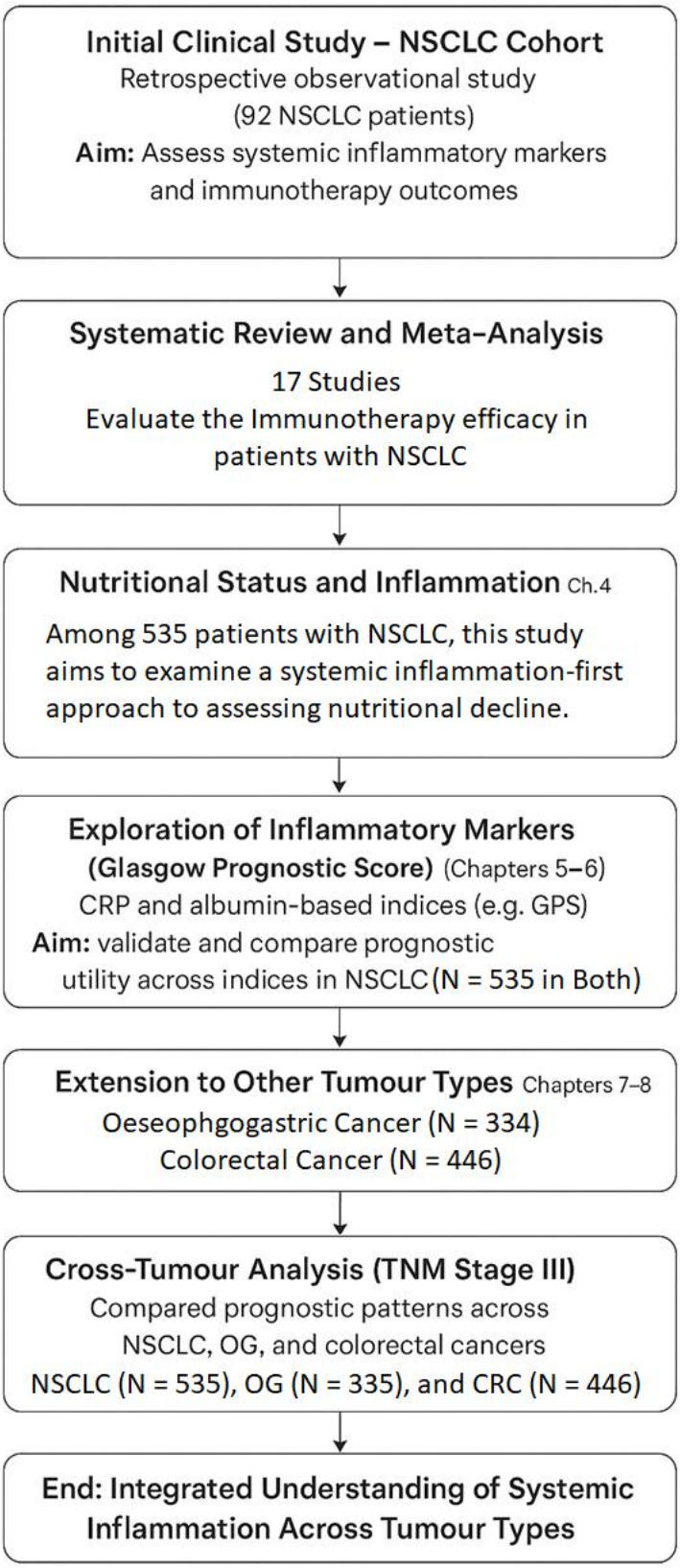

Figure 1 – 2: Flowchart of thesis chapter arrangement and research progression

Chapter 2, The relationship between pretreatment clinicopathological variables, systemic inflammation, CT-derived body composition, and 12-month survival in advanced non-small cell lung cancer patients who received nivolumab as a second treatment

2.1 Introduction

Despite declining incidence rates, lung cancer accounts for 13% of all newly diagnosed cancers in the United Kingdom (UK) and is still the third most common malignancy. It is the leading cause of cancer death in the UK, accounting for 21% of all cancer fatalities(Cancer Research UK, 2024); this is partly because most patients present with TNM stage III or IV illness at diagnosis and are thus treated with a palliative aim (R. Chen et al., 2020). Individuals with distal metastatic illness (stage IV), for instance, had a 1-year survival rate of just 15%–20%, in contrast to 81%–85% for stage I (GOV.UK, 2016).

Long the cornerstone for patients with advanced NSCLC, chemotherapy has improved survival (R. Chen et al., 2018). However, clinical results have improved over the past 10 years with the development of immune checkpoint inhibitors (ICIs), with a plethora of evidence demonstrating that they increase overall survival in NSCLC patients compared with hemotherapy alone (Liu et al., 2021). However, only around 20% of NSCLC patients benefit from ICI treatment (Horvath et al., 2020). To identify individuals with NSCLC who may benefit most from these innovative treatment drugs, there is ongoing interest in the association between host phenotype and clinical outcomes in patients receiving ICI.

Host phenotypic features such as weight loss, low body mass index (BMI), sarcopenia, and systemic inflammation have long been linked to poor outcomes in patients with advanced NSCLC (Matsubara et al., 2020; M. P. Petrova et al., 2020; Tenuta et al., 2021). BMI has limitations because it does not account for body composition factors, such as muscle volume or regional fat distribution, which may have different impacts on survival (Xiao et al., 2022). Recent research has discovered that sarcopenia and fat tissue (rather than BMI) are independent risk factors for ICI efficacy in tumours (Xiao et al., 2022). Obesity and reduced muscle quantity and quality were linked to poor results in one trial of ICI-treated melanoma patients (Young et al., 2020). The loss of lean tissue is a key indicator of cancer cachexia (Baracos et al., 2019). Shiroyama and colleagues discovered that baseline sarcopenia was significantly associated with poor survival outcomes in patients with advanced non-small cell lung cancer treated with ICIs (Shiroyama et al., 2019)

As a result, the current study examines the relationship between host features, including systemic inflammation and CT-derived body composition, and survival in patients with advanced NSCLC receiving second-line Nivolumab with palliative intent.

This chapter hypothesised that pretreatment clinicopathological characteristics, systemic inflammation, and CT-derived body composition measurements would be independently associated with 12-month survival in patients with advanced NSCLC treated with nivolumab.

The relationship between pretreatment clinicopathological variables, systemic inflammation, CT-derived body composition, and 12-month survival in advanced non-small cell lung cancer patients who received nivolumab as a second treatment (n=92 patients)

2.2 Patient and methods

All patients with advanced NSCLC who received at least one cycle of Nivolumab as a second, third, or subsequent line of therapy in three Scottish health boards (NHS Greater Glasgow and Clyde, Lanarkshire, Ayrshire, & Arran) between September 2016 and January 2019 had their data collected retrospectively. Patients were eligible for this retrospective database cohort study if they had an abdominal CT scan (3 months) and a full blood count (1 month) before starting Nivolumab medication.

An FY1doctor (Hugo Bench) collected the primary clinical data such as age, sex and community health index CHI number, while I obtained the body composition data. Initially, I attempted to locate height and weight measurements through the electronic portal and by reviewing all available clinical correspondence; however, these variables were not documented. Then, with the support of a clinical oncology consultant at the Beatson Cancer Centre, I was subsequently granted access to retrieve the required data from Chemo Care, which then enabled the calculation of body mass index BMI and body composition. Using each patient's community health index CHI number, I then accessed and downloaded all relevant CT imaging from PACS via the standard authorized unit login. After downloading each CT scan obtained within one month prior to initiating nivolumab, I anonymized the data by deleting patients' names and CHI identifiers using the H keyboard shortcut. Then I performed the body composition analysis.

Caldicott Guardian Approval (NHS Greater Glasgow and Clyde) was obtained for this audit study. This study was conducted in response to the Helsinki Declaration. ("World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," 2013). The survival date was determined from the moment Nivolumab was administered to death or the censor day.

Clinicopathological characteristics

Before starting Nivolumab, routine demographic information about each patient was gathered. This information comprised age, sex, histology, BMI, neutrophil-to-lymphocyte ratio (NLR), and hypoalbuminemia. Age-based groups were >65, 65–74, and <75 years old. A medical practitioner or clinical researcher working at the facility where the patient was being treated created the Eastern Cooperative Oncology Group-Performance Status (ECOG-PS).

Participants were assigned to “0,” “1,” or “> 2” ECOG-PS categories. Four BMI categories were “<20, 20–24.9, 25–29.9, and ≥30” kg/m^2. NLR was classified as “<3, 3–5, and >5” based on the patient's total blood count, calculated as the neutrophil count divided by the lymphocyte count. Less than 35 g/L of serum albumin was considered hypoalbuminemia.

CT body composition analysis

As previously stated, CT images were obtained at the third lumbar vertebral level. Images lacking regions of interest or exhibiting notable motion artifacts were excluded. A freeware program called Version 1.47 of the NIH ImageJ software (http://rsbweb.nih.gov/ij/) was used to analyze each picture and was found to produce accurate measurements(Doyle et al., 2013). Total fat area (TFA, cm^2), visceral fat area (VFA, cm^2), and skeletal muscle area (SMA, cm^2) were calculated as ROIs using standard Hounsfield Unit (HU) values (adipose tissue −190 to −30, and skeletal muscle −29 to +150). The subcutaneous fat area (SFA, cm^2) was computed by subtracting the VFA from the TFA. After normalizing the SFA and SMA for height 2, the skeletal muscle index (SMI, cm^2/m^2) and subcutaneous fat index (SFI, cm^2/m^2) were calculated. Skeletal muscle radiodensity (SMD, HU) was measured using the same ROI to compute SMI, with SMD defined as the ROI's mean HU. These indices were then compared to preset body composition cutoff thresholds.

For males, a high SFI was defined as >50.0 cm^2/m^2, and for females, ≥42.0 cm^2/m^2(McSorley et al., 2018). For male patients, visceral obesity was defined as VFA >160 cm^2, and for female patients, >80 cm^2 (Abbass et al., 2020) According to Martin et al., a low SMI was defined as follows: <43 cm^2/m^2 if BMI <25 kg/m^2, <53 cm^2/m^2 if BMI ≥25 kg/m^2 in patients who were male, and <41 cm^2/m^2 in patients who were female if the BMI < or ≥ 25 kg/m^2. In individuals with a BMI < 25 kg^2/m^2 and > 25 kg^2/m^2, the skeletal muscle radiodensity (SMD) is <41 HU and < 33 HU, respectively(McGovern et al., 2021).

Statistical analysis

We analyzed the retrieved data with SPSS version 25 (IBM); a p-value of 0.05 was considered statistically significant. For categorical data, results were summarized as counts (n) and percentages (%), and comparisons were performed using the Chi-square test. The 95% confidence interval (CI) and odds ratio (OR) were calculated. The relationship between ECOG-PS and hypoalbuminemia and 12-month survival in patients with advanced NSCLC treated with nivolumab was investigated using a Kaplan–Meier curve and a log-rank test. To find determinants of 12-month survival, the Cox regression model was applied. The researchers

conducted univariate and multivariate Cox regression analyses, reporting hazard ratios (HRs), 95% confidence intervals (CIs), and p-values. Variable by variable, missing data were removed from the study.

2.3 Results

A total of 104 patients were initially assessed for eligibility. Thirteen patients were excluded, including one who tested positive for an EGFR mutation, one with no available CT scan data, and eleven with unsuitable scans. The final study cohort included 92 patients (Figure 2-1). Patients with advanced NSCLC receiving Nivolumab in second-line treatment were included in the present study.

The clinicopathological characteristics of the patients enrolled are shown in Table 2-1. Chemotherapy was given to all patients as a first-line treatment in various combinations. 51% (n = 47) of the patients were above the age of 65, and 53% (n = 49) were female. Squamous cell carcinoma affected 40% (n = 37) of patients, whereas adenocarcinoma affected 53% (n = 49). 44% (n = 40) of patients had hypoalbuminemia, and 70% (n = 64) had an NLR greater than 3. 54% (n = 50) of the patients had a high VFA, and 70% (n = 64) had a high SFI. Low SMI (n = 61) and SMD (n = 54) were found in 66% (n = 61) and 59% (n = 54) of the patients, respectively. The median overall survival (OS) after initiating Nivolumab was 15 months.

The association between systemic inflammation, CT-derived body composition measures, clinicopathological features, and 12-month survival in patients with advanced NSCLC receiving nivolumab as a second-line treatment is shown in Table 2-2. During the 12-month follow-up, the total number of patients alive had dropped to 36, while the number of deceased had risen to 56. In both the living (63%) and deceased (64%) groups, ECOG-PS of “1” was substantially higher than ECOG-PS of “0” or “>2” (p-value = 0.015). Hypoalbuminemia was substantially greater (55%) in the deceased group (p-value = 0.015; Table 2-2).

ECOG-PS, NLR, BMI, and hypoalbuminemia were significant independent predictors of 12-month survival in patients with advanced NSCLC receiving Nivolumab treatment, according to Cox regression (p-value = 0.039, 0.026, 0.001, and 0.055, respectively; Table 2-3). Only NLR and Hypoalbuminemia were significant predictors in the multivariate Cox regression.

The Kaplan–Meier curves in Figure 2A, B show the relationship between ECOG-performance status, hypoalbuminemia, and 12-month survival in patients with advanced NSCLC on second-

line Nivolumab treatment: (A) The relationship between ECOG-PS and 12-month survival in patients with advanced NSCLC receiving Nivolumab (Log Rank P-value = 0.001); (B) The relationship between hypoalbuminemia and 12-month survival in patients with advanced NSCLC receiving Nivolumab (Log Rank P-value = 0.001).

The connection between ECOG-PS and CT-derived body composition in patients with advanced non-small cell lung cancer (NSCLC) receiving nivolumab as second-line treatment is shown in Table 2-4. SFI was substantially linked with the ECOG-PS categories (p-value = 0.042). Low SMD, SMI, and high VFA, on the other hand, were not linked with ECOG-PS categories (p-values = 0.808, 0.053, and 0.47, respectively). Hypoalbuminemia was substantially linked with ECOG-PS categories “0” and “1” (p-value = 0.001; Table 2-4).

2 .4 Discussion

To the best of our knowledge, this is the first study to examine the association between systemic inflammation, CT-BC, pre-treatment clinicopathological features, and survival in NSCLC patients receiving nivolumab for palliative care. Hypoalbuminemia was substantially correlated with survival in the current group, independent of ECOG-PS and body composition, which was particularly interesting and may be instructive for the use of ivolumab in NSCLC patients (Tomasik et al., 2021).

The current study's findings are in line with a recent review by Tomasik and colleagues of 26,442 patients with advanced NSCLC from 67 studies, which found that patients with poor performance status (ECOG-PS) were twice as likely to benefit from ICI as patients with a performance status of 0–1. Furthermore, the present results are consistent with previous studies demonstrating that systemic inflammatory response markers, regardless of c, have prognostic importance in patients with advanced cancer (Simmons et al., 2019). Because ECOG-PS reflects the patient's physiological reserve, and the systemic inflammatory response captures the catabolic effect on that reserve, the combination of ECOG-PS and the systemic inflammatory response may have predictive value. Even though sarcopenia has been linked to poor outcomes in cancer treatment (Singh et al., 2019), Tenuta and colleagues found no correlation between sarcopenia and survival in 47 patients with advanced non-small cell lung cancer (NSCLC) who underwent ICI and used dual-energy X-ray absorptiometry (DXA) for body composition measurement. They found that, whereas overall survival was unaffected, sarcopenia was linked to a shorter progression-free survival PFS (X. Zhang et al., 2021).

As a result, it is unclear whether body composition assessments enhance the predictive value of ECOG-PS and systemic inflammation. A recent study by Hacker and colleagues found that, when compared to sarcopenia, the tumour-associated systemic inflammatory response was the strongest predictor of prognosis in the phase III EXPAND trial involving good-performance status patients with gastro-esophageal cancer. Furthermore, there was no clear link between sarcopenia and survival. As a result, further studies should be conducted on the therapeutic targeting of systemic inflammation as a possible method to improve sarcopenia, as well as on the effectiveness and tolerability of cancer treatment (Hacker et al., 2022).

The current investigation demonstrated no statistically significant relationship between NLR and 12-month survival; this conclusion contradicted a previous study that found a link between elevated NLR and poor progression-free survival (PFS),(Lim et al., 2021) quicker time to

treatment failure, and overall survival (OS)(Singh et al., 2019). Similarly, Pavan and colleagues demonstrated that the platelet/lymphocyte ratio (PLR) and normalized lymphocyte ratio (NLR) predicted the occurrence of immune-related adverse events (irAEs) in 184 patients with advanced NSCLC who received ICI (pembrolizumab, nivolumab, or atezolizumab) as second-line therapy.(Pavan et al., 2019) Furthermore, some studies indicate that irAEs are associated with poor survival outcomes. In contrast, others indicate that irASs produce a long-term, sustained disease response in NSCLC patients taking nivolumab (Haratani et al., 2018). Karayama and colleagues found that increased GNRI, calculated from body weight and serum albumin, was associated with better PFS and OS in patients with NSCLC receiving nivolumab, regardless of tumour PD-L1 expression or ECOG-PS. As a result, albumin may be effective in predicting ICI efficacy (Karayama et al., 2021).

Because of the small sample size and retrospective study design, the current study had limitations. It is tough to extrapolate these findings to current clinical practice because immunotherapies are increasingly used as first-line therapy, and systemic therapy used in second-line treatment of NSCLC is no longer considered standard of care. The current study, on the other hand, provides therapeutically relevant information on the link between systemic inflammation and body composition as prognostic factors in NSCLC patients. Prospective research is required to validate prognostic variables for immunotherapy.

Despite these limitations, the findings highlight the clinical importance of simple inflammatory biomarkers and objective CT-based measurements for risk stratification, suggesting that integrating mGPS, ECOG-PS, and sarcopenia indicators into pretreatment assessment may improve prognostic accuracy and inform personalised immunotherapy decision-making.

2.5 Conclusion

Baseline high ECOG-PS and hypoalbuminemia were linked with poor survival in patients with advanced NSCLC receiving nivolumab as a second-line therapy. In addition to ECOG-PS, hypoalbuminemia may be a useful predictor of clinical outcomes.

Table 2- 1: Clinicopathological characteristics of included patients.

Demographics	**Counts and Percentages (%)**
Age (Years)	
<65	45 (49)
65–74	33 (36)
>74	14 (15)
Sex	
Male	43 (47)
Female	49 (53)
Histology	
Adenocarcinoma	49 (53)
Squamous cell carcinoma	37 (40)
Other/Unknown	6 (7)
Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)	
0	21 (23)
1	58 (63)
>2	13 (14)
Neutrophil to lymphocyte ratio (NLR)	
<3	28 (30)
3–5	25 (27)
>5	39 (42)
Albumin	
>35 g/L	52 (56)
<35 g/L	40 (44)
Body mass index (BMI) (kg/m^2)	

<20	15 (16.3)
20–24.9	35 (38)
25–29	26 (28.3)
>30	16 (17.4)
High subcutaneous fat index (SFI)	
No	28 (30)
Yes	64 (70)
High visceral fat area (VFA)	
No	42 (46)
Yes	50 (54)
Low skeletal muscle index (SMI)	
No	31 (34)
Yes	61 (66)
Low skeletal muscle radiodensity (SMD)	
No	38 (41)
Yes	54 (59)
12-Month survival	
Yes	36 (39)
No	56 (61)

*Data presented as a number (percentage).

Table 2- 2: The relationship between clinicopathological variables, systemic inflammation, CT-body composition measurements, and 12-month survival in patients with advanced NSCLC receiving second-line Nivolumab therapy.

Variables	All (N = 92)	Alive (N = 36)	Dead (N = 56)	p-Value
Age (Years)				0.799
<65	45 (49)	18 (50)	27 (48)	
65–74	33 (36)	13 (36)	20 (63)	
>74	14 (15)	5 (14)	9 (16)	
Sex				0.725
Male	43 (47)	16 (44)	27 (48)	
Female	49 (53)	20 (56)	29 (52)	
Histology				0.33
Adenocarcinoma	49 (53)	17 (47)	32 (57)	
Squamous	37 (40)	16 (45)	1 (38)	
Others	6 (7)	3 (8)	3 (5)	
Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)				0.015
0	21 (23)	12 (33)	9 (16)	
1	58 (63)	22 (61)	36 (64)	
>2	13 (14)	2 (6)	11 (20)	
Neutrophil to Lymphocyte Ratio (NLR)				0.113
<3	28 (30)	14 (50)	14 (50)	
3–5	25 (27)	10 (40)	15 (60)	
>5	39 (42)	12 (31)	27 (69)	
Albumin				0.015
>35 g/L	52 (57)	27 (75)	25 (45)	
<35 g/L	40 (43)	9 (25)	31 (55)	
Body Mass Index (BMI) (kg/m^2)				0.356
<20	15 (16)	5 (14)	10 (18)	
20–24.9	35 (38)	14 (39)	21 (38)	
25–29	26 (28)	8 (22)	18 (32)	

>30	16 (17)	9 (25)	7 (12)	
High Subcutaneous Fat Index (SFI)				0.659
No	28 (30)	10 (28)	18 (32)	
Yes	64 (70)	26 (72)	38 (68)	
High Visceral Fat Area (VFA)				0.143
No	42 (46)	13 (36)	29 (52)	
Yes	50 (54)	23 (64)	27 (48)	
Low Skeletal Muscle Index (SMI)				0.401
No	31 (34)	14 (39)	17 (30)	
Yes	61 (66)	22 (61)	39 (70)	
Low Skeletal Muscle Radiodensity (SMD)				0.42
No	38 (41)	13 (36)	25 (45)	
Yes	54 (59)	23 (64)	31 (55)	

*A p-value of ≤ 0.05 of the Chi-square was considered significant.

Table 2- 3: Cox Regression between clinicopathological variables, systemic inflammation, CT-body composition measurements, and 12-month survival in patients with advanced NSCLC receiving second-line Nivolumab therapy.

Variables	Groups	Univariate		Multivariate	
		HR (95%CI)	P-Value	HR (95%CI)	P-Value
Age (years)	<65 65-74 >75	1.038 (0.765 - 1.409)	0.809	1.01 (0.75 - 1.76)	0.928
Sex	Female Male	0.992 (0.644 – 1.528)	0.971	1.12 (0.71 - 1.76)	0.642
Histology	Adenocarcinoma Squamous Others	0.988 (0.692 - 1.410)	0.946	_	_
ECOG-PS	0 -1 2 3	1.506 (1.022 – 2.221)	0.039	1.37 (0.923 - 2.04)	0.118
Neutrophil lymphocyte ratio (NLR)	<3 3-5 >5	1.332 (1.032 - 1.719)	0.026	1.03 (1.01 - 1.05)	0.010
Albumin	> 35 g/l <35g/l	2.092 (1.343 - 3.258)	0.001	1.78 (1.12 - 2.85)	0.016
Body mass index (BMI)	<20 20 -24.9 25 -29 >30	0.807 (0.648 - 1.005)	0.055	1 (0.95 - 1.05)	0.998
High subcutaneous fat index (SFI)	No Yes	0.828 (0.518 - 1.324)	0.430	_	_
High visceral fat area (VFA)	No Yes	0.736 (0.476 – 1.137)	0.167	_	_

Low skeletal muscle index (SMI)	No Yes	1.143 (0.721 – 1.810)	0.569	_	_
Low skeletal radiodensity (SMD)	No Yes	0.920 (0.594 – 1.426)	0.711	_	_

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): These values indicate that if the entire interval is above 1.00, the risk is higher; if below 1.00, the risk is lower.

Table 2- 4: The relationship between ECOG-PS, CT-body composition, and hypoalbuminemia in patients with advanced NSCLC receiving Nivolumab therapy.

Body Composition	**PS 0**	**PS 1**	**PS 2**	**p-Value**
Body mass index (BMI) (kg/m^2)				0.445
<20	3 (14)	10 (17)	2 (15)	
20–24.9	7 (33)	23 (40)	5 (38.5)	
25–29	6 (29)	15 (26)	5 (38.5)	
>30	5 (24)	10 (17)	1 (8)	
High subcutaneous fat index (SFI)				0.042
No	2 (7)	21 (75)	5 (18)	
Yes	19 (30)	37 (58)	8 (12)	
High visceral fat area (VFA)				0.47
No	10 (24)	28 (67)	4 (9)	
Yes	11 (22)	30 (60)	9 (18)	
Low skeletal muscle index (SMI)				0.053
No	10 (32)	19 (61)	2 (7)	
Yes	11 (18)	39 (64)	11 (18)	
Skeletal muscle radiodensity (SMD)				0.808
No	8 (21)	26 (68)	4 (11)	
Yes	13 (24)	32 (59)	9 (17)	
Albumin				0.001
>35 g/L	17 (81)	32 (55)	3 (23)	
<35 g/L	4 (19)	26 (45)	10 (77)	

*A p-value of ≤ 0.05 of the Chi-square was considered significant.

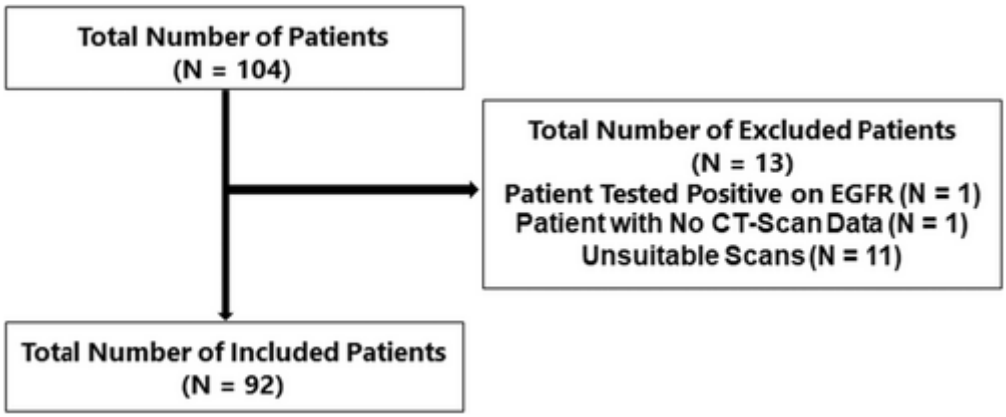

Figure 2- 1: Flow chart diagram of a total of 104 patients who were initially assessed for eligibility.

*Thirteen patients were excluded, including one who tested positive for epidermal growth factor receptor EGFR mutation, one with no available CT-scan data, and eleven with unsuitable scans

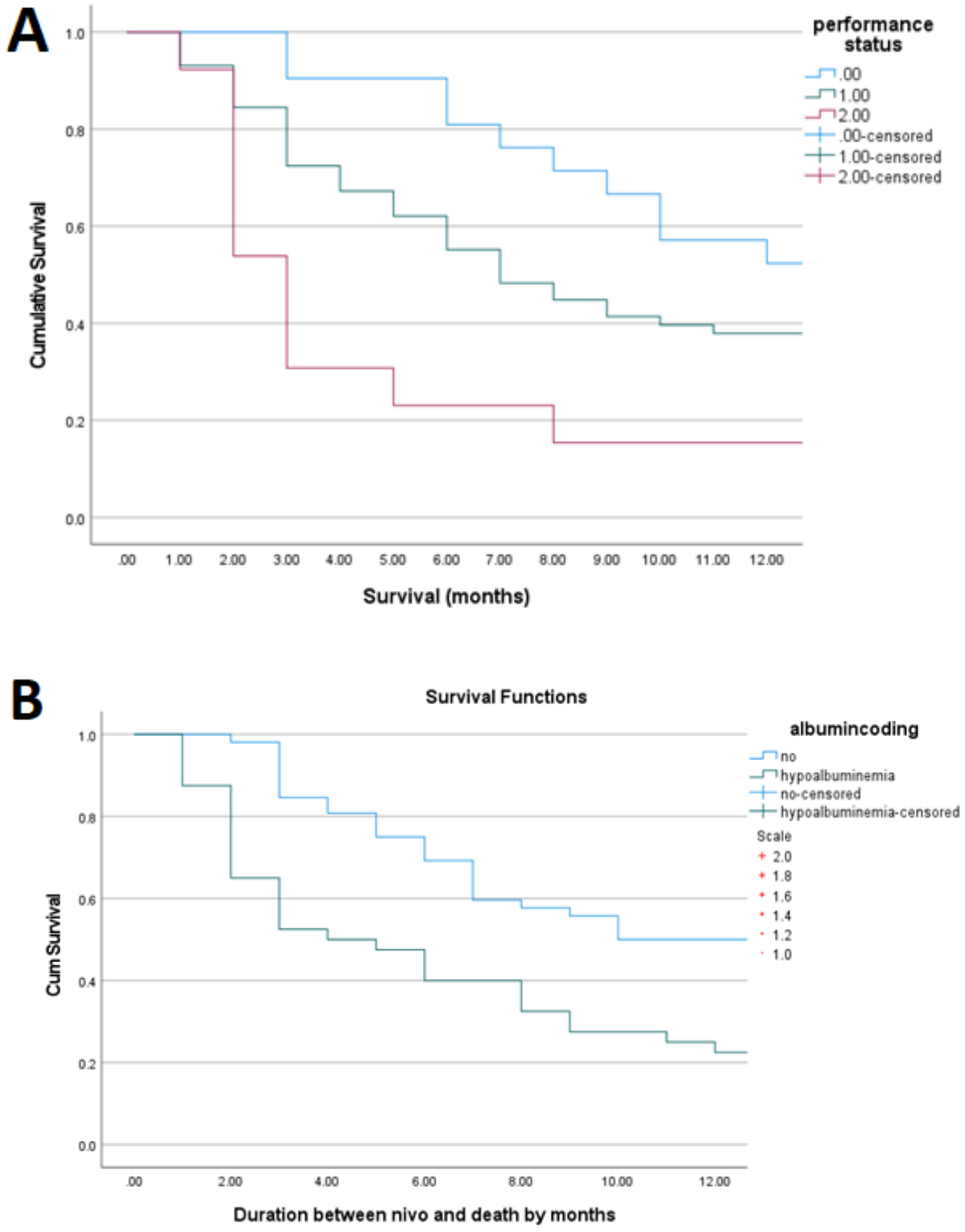

Figure 2-2: (A) The relationship between ECOG-PS and 12-month survival in patients with advanced NSCLC receiving Nivolumab (Log Rank P-value = 0.001); (B) The relationship between hypoalbuminemia and 12-month survival in patients with advanced NSCLC receiving Nivolumab (Log Rank P-value = 0.001).

Chapter 3, Systematic review and meta-analysis about how systemic inflammatory response can predict the efficacy of immunotherapy in patients with non-small cell lung cancer

3.1 Introduction

With 2.21 million diagnoses and 1.80 million deaths from cancer-related causes in 2020 worldwide, lung cancer (LC) is the second-most frequent malignancy after breast cancer (Ferlay et al., 2021). Adenocarcinoma (ADC) and squamous cell carcinoma (SQCC) are the two histologic subtypes of NSCLC(Travis et al., 2013). The type and stage of the disease greatly impact the treatment and prognosis. Early-stage NSCLC can be treated by surgical excision (Duma et al., 2019). Although there have been substantial improvements in the oncological care of late-stage NSCLC in recent years, survival rates for most patients remain low because they present with advanced disease diagnosis (stage III or IV) (Duma et al., 2019).

Nevertheless, the development of anti-programmed cell death-1 (anti-PD-1) and anti-programmed cell death ligand-1 (anti-PD-L1) has significantly changed the treatment landscape for various solid cancers, including NSCLC (Chmielewska et al., 2021). This change has a significant beneficial impact on overall survival (OS) and progression-free survival (PFS) (Chmielewska et al., 2021). Tumour PD-L1 expression is the most studied biomarker for selecting patients for immunotherapy. A worse prognosis and reduced overall survival are typically associated with higher PD-L1 expression in NSCLC (Zhang et al., 2017). PD-L1 expression may determine the efficacy of first-line immunotherapy in patients with advanced NSCLC (Chmielewska et al., 2021). Such immune checkpoint inhibitors (ICIs) may be used as monotherapy or in combination with other traditional therapies, such as chemotherapy, as first- or second-line treatment for advanced NSCLC (Chmielewska et al., 2021; Stock-Martineau et al., 2021).

Therefore, it is of interest that meta-analyses have shown that systemic inflammatory response markers are associated with poor prognosis in patients with NSCLC. For example, in more than 7,000 patients, a high Glasgow Prognostic Score (GPS) was associated with poor clinical outcomes (C. L. Zhang et al., 2022). Similarly, in more than 1500 patients, the neutrophil-lymphocyte ratio (NLR) was associated with poor clinical outcomes (B. Peng et al., 2015). Although these meta-analyses primarily reflect the prognostic value of markers of the systemic inflammatory response in patients with NSCLC across all disease stages and treatment modalities, they suggest a role for such markers in patients receiving immunotherapy for

NSCLC. Indeed, there is some evidence that this may be the case (Ahern et al., 2021; Stares et al., 2022).

The systematic review and meta-analysis hypothesised that systemic inflammatory markers, particularly CRP and NLR, would predict the efficacy of immunotherapy in NSCLC.

This meta-analysis aims to evaluate the prognostic/predictive value of inflammatory biomarkers, including NLR, ALI, PLR, CRP, and mGPS, and their potential association with overall survival in NSCLC patients receiving immunotherapy as first- or second-line treatment. Systematic review and meta-analysis on how systemic inflammatory response can predict the efficacy of immunotherapy in patients with NSCLC (studies=17, n=2948 patients).

3.2 Methods

A meta-analysis was conducted using the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2020). The report was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

Data sources and search strategy

A search was carried out across the following electronic databases: PubMed, Cochrane Library, and Web of Science (WOS) for relevant studies published in the literature, and articles were retrieved up to 1st January 2022. The complete research strategies and search terms included: (Non-Small-Cell Lung OR NSLC OR lung cancer* OR lung carcinoma* OR lung tumour* OR non-small cell*) AND (Immunotherapy and inflammation (CRP +Neutrophils +WCC)). The search included studies reported in English and did not impose any additional search limits. The reference lists of the retrieved articles, including paper citations for potentially relevant papers, were also reviewed.

Eligibility criteria

All studies with the following criteria were included: (1) retrospective observational studies written in English, "if written in another language English translation was present"; (2) patients had advanced non-small lung cancer; (3) patients were treated with immunotherapy; and (4) the study should evaluate the overall survival of at least one of systematic inflammatory biomarkers.

Moreover, the exclusion criteria were animal studies, in-vivo & in-vitro studies, clinical trials, case reports, case series, systematic reviews, meta-analyses, clinical study protocols, letters, comments, correspondence, or editorials.

Study selection

The search results were imported into EndNote to screen and remove duplicate studies. The titles and abstracts of the included studies were reviewed according to the inclusion and exclusion criteria. Another reviewer was consulted when there was doubt about whether to include the study. These reviewers independently screened the full-text articles to resolve any conflicts.

Data extraction

The data were independently extracted through two Excel sheets: 1. Summary (first author name: year of publication, country, study design, total participants, systematic treatment, aim/objectives, and conclusions). 2. Systemic Inflammatory Biomarkers (Neutrophil-to-lymphocyte ratio (NLR), Advanced lung cancer inflammation index (ALI), Platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), Modified Glasgow Prognostic Score (mGPS).

NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, often from peripheral blood samples and cells that infiltrate tissue, such as tumour cells. At the same time, PLR is calculated by dividing the platelet count by the lymphocyte count (10,13). ALI was calculated as follows: body mass index (kg/m2) × serum albumin (g/dL) ÷ NLR. Serum CRP and albumin levels were used to calculate the modified Glasgow prognostic score (mGPS); the modified Glasgow prognostic score (mGPS) emphasizes the significance of CRP; if CRP is increased, even patients with abnormal albumin levels are given a score of 1 (Ahern et al., 2021).

Data synthesis

Meta-analysis was performed using the Review Manager (RevMan 5.4.1). The hazard ratios (HRs) with 95% confidence intervals (CIs) were presented in the meta-analysis results for overall survival outcomes. Results with a P-value < 0.05 were considered significant in the Z-test. The Chi-square test was used to assess heterogeneity; substantial heterogeneity was observed ($P < 0.1$). The degree of heterogeneity in a meta-analysis was assessed using the I^2 statistic, which quantifies the proportion of variation across studies attributable to heterogeneity rather than chance. The I^2 value ranged from 0% to 100%: [0% to 25%: Low heterogeneity, 25% to 50%: Moderate heterogeneity, 50% to 75%: Substantial heterogeneity, and 75% to 100%: High heterogeneity]. The HRs and 95% of CIs were directly retrieved from the article. If Several estimates were reported for the same marker, the multivariate estimation was used in preference to the univariate analysis. In meta-analysis, when assessing the effect of a treatment, one common approach is to compute the mean change from post- to pre-treatment for each study and then pool those results across studies.

3.3 Results

After searching the databases, 633 records were identified. Forty-three duplicates were removed, leaving 590 records for screening. After the title and abstract screening, 555 records were deemed irrelevant, leaving 35 full-text articles for review. Finally, 17 articles were included in the systematic review and the meta-analysis. A PRISMA flow chart illustrates the study selection process (Figure 3-1).

- The neutrophil-to-lymphocyte ratio (NLR)

Meta-analysis of 13 studies showed a significant association between NLR and overall survival (HR = 2.87; 95% CI 1.91 – 4.30; P-Value < 0.00001), with moderate heterogeneity (P-Value = 0.002; I2 = 61%) (Figure 3-2-A). The heterogeneity was reduced by omitting five studies (P-Value = 0.21; I2 = 28%), and the association remained significant (HR = 2.15; 95% CI 1.60 – 2.87; P-Value < 0.00001) (Figure 3-2-B). The possibility of publication bias was related to the method and the high intensity of retrospective studies (Supplementary Figure 1). Meta-analysis of thirteen studies showed that NLR with a threshold of ≥5 in five studies(Bagley et al., 2017; Baldessari et al., 2021; Diem et al., 2017; L. Peng et al., 2020), NLR > 5 in four studies (20–23), NLR ≥4 in two studies (Banna et al., 2022; Petrova, Eneva, et al., 2020), and identified as high vs low in one study (25).

- Advanced lung cancer inflammation index (ALI)

The forest plot of four studies showed a significant association between ALI and overall survival (HR = 1.72; 95% CI 1.22–2.43; P-Value = 0.002), with moderate heterogeneity (P-Value = 0.15; I2 = 44%) (Figure 3-3-A). The heterogeneity was reduced by omitting one study (P-Value = 0.27; I2 = 23%), and the association became more significant (HR 2.03; 95% CI 1.43 – 2.88; P-Value < 0.0001) (Figure 3-3-B).

The forest plot of four studies showed that ALI was >18 in two studies (Baldessari et al., 2021; Mountzios et al., 2021), ≥18 in one study (26), and < 18 in one study (Ogura et al., 2021).

- Platelet-to-lymphocyte ratio (PLR)

The pooled analysis of six studies showed a significant association between PLR and overall survival (HR = 4.06; 95% CI 2.14–7.67; P-value < 0.0001), without heterogeneity (P-value = 0.23; I2 = 28%) (Figure 3-4). The pooled analysis of six studies showed that PLR with a

threshold of > 262 in these studies (Mountzios et al., 2021)and identified as high vs low in three studies (Matsubara et al., 2020), (Baldessari et al., 2021), (Petrova, Eneva, et al., 2020).

- C-reactive protein (CRP)

The forest plot of seven studies showed a significant association between CRP and overall survival (HR = 4.22; 95% CI 2.14–8.31; P-value < 0.0001), with substantial heterogeneity (P-value < 0.00001; I2 = 82%) (Figure 3-5-A). The heterogeneity was resolved by omitting one study (P-Value = 0.80; I2 = 0%), and the association became more significant (HR = 5.37; 95% CI 3.90 – 7.39; P-Value < 0.00001) (Figure 3-5-B). The forest plot of seven studies showed that CRP with a threshold of ≥ 10 mg/l in three studies (Adachi et al., 2020; Hung et al., 2024; Oya et al., 2017), CRP > 8.9 mg/l in one study (Katayama et al., 2020), CRP ≥ 26mg/l in one study (18), CRP >50 mg/l in one study (29), and identified as high vs normal in one study (Baldessari et al., 2021).

- Modified Glasgow Prognostic Score (mGPS)

The pooled analysis of four studies showed a significant association between mGPS and overall survival (HR = 3.27; 95% CI 1.26 – 8.28; P-Value = 0.01), without heterogeneity (P-Value = 0.28; I2 = 23%) (Figure 3-6). The pooled analysis of four studies showed that mGPS with a threshold of ≥1 was identified in three studies (Araki et al., 2021; Beppu et al., 2018; Ogura et al., 2021) and in one study (Matsubara et al., 2020) as high vs low.

3.4 Discussion

The present meta-analyses showed that inflammatory biomarkers, including NLR, ALI, PLR, CRP, and mGPS, were significantly and independently associated with overall survival in NSCLC patients, highlighting their role as prognostic and potential predictive factors of immunotherapy efficacy. Specifically, an elevated systemic inflammatory response, however measured, was associated with poorer treatment efficacy and overall survival, either as second-line or first-line therapy. Furthermore, the predictive efficacy of ALI (Mountzios et al., 2021) and mGPS (Alharbi & Alateeq, 202was specifically examined, confirming the relationship between immunotherapy efficacy and overall survival in patients with NSCLC. Therefore, the systemic inflammatory response has considerable potential to select patients likely to benefit from immunotherapy. However, it remains to be determined which systemic inflammation-based prognostic score should be used, its optimal threshold, and its implications for clinical practice. Nevertheless, markers of the systemic inflammatory response should be routinely measured alongside established prognostic factors in these patients.

The present meta-analysis of 13 studies showed a significant association between NLR and overall survival (HR = 2.87; 95% CI 1.91 – 4.30; P-Value < 0.00001), with moderate heterogeneity (P-Value = 0.002; I2 = 61%). NLR pooled analysis in the Wang et al. (2019) study also showed a significant association between NLR and overall survival (HR = 2.50; 95% CI 1.60–3.89; P-value < 0.0001), with substantial heterogeneity (I2 = 79.9%). NLR pooled analysis of Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor treatment in the Chan et al. study (Chan et al., 2021) showed a significant association between NLR and overall survival (HR = 1.97; 95% CI 1.56–2.49; P-value < 0.00001), without heterogeneity (I2 = 12%). NLR pooled analysis in the Platini et al., 2022 study showed a significant association between NLR and overall survival (HR = 2.68; 95% CI 2.24 – 3.21; P-Value < 0.00001), without heterogeneity (I^2 = 17%). Therefore, there would appear to be consistent evidence that NLR has prognostic value.

The present meta-analysis of six studies showed a significant association between PLR and overall survival (HR = 4.06; 95% CI 2.14–7.67; P-value < 0.0001), without heterogeneity (P-value = 0.23; I2 = 28%). PLR pooled analysis of the Platini et al. (2022) study on immunotherapy showed a significant association between PLR and overall survival (HR = 2.14; 95% CI 1.72–2.67; P-value < 0.00001), with mild heterogeneity (I2 = 37%). PLR pooled analysis of immune checkpoint inhibitors in NSCLC Patients in the Xu et al. (2019) study

showed a significant association between PLR and overall survival (HR = 1.52; 95% CI 1.27 – 1.82; P-Value < 0.00001), without heterogeneity (I2 = 0%). While PLR pooled analysis of Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor treatment in Chan et al. study (Chan et al., 2021)showed a non-significant association between PLR and overall survival (HR= 0.87; 95% CI 0.62 – 1.22; P-Value = 0.41) without heterogeneity (I2 = 0%). Therefore, there appears to be inconsistent evidence that PLR has consistent prognostic value.

Furthermore, across a variety of common solid tumours (Chan et al., 2021)treated with immunotherapy, an increase in NLR at six weeks from baseline was significantly associated with shorter OS (HR, 4.11; 95% CI, 1.86 – 9.11; P < 0.001) in patients with melanoma, gastrointestinal, lung, or head and neck cancers (20.0%) (Bilen et al., 2019; Qiu et al., 2018). Similarly, GPS has been shown to have prognostic value in such solid tumours (Bilen et al., 2019; Qiu et al., 2018). These observations align with those made more generally in patients with advanced cancer (Rocha et al., 2023). Indeed, the combination of ECOG-PS and mGPS is a powerful prognostic framework that has been widely used in patients with advanced cancer, including those with SCLC (Simmons et al., 2019b). ECOG-PS is the most widely validated prognostic indicator in patients with advanced cancer. However, it is a subjective measure, prone to interindividual variation and overestimation compared with the patient assessment (Simcock et al., 2020). Therefore, combining the subjective ECOG-PS with the objective systemic inflammation-based prognostic score (NLR, mGPS) is an important step forward in the treatment allocation and should form the basis of future stratification of patients receiving immunotherapy. However, greater tumour cell molecular characterization leads to greater stratification of NSCLC and different treatment pathways and outcomes (e.g., EGFR- and ALK-driven NSCLC). The present work highlights the importance of the host systemic inflammatory response in this tumour type and in immunotherapy treatment. Therefore, it will be important that future randomized trials of immunotherapy in NSCLC include measures of the systemic inflammatory response, so that the prognostic importance of the tumour and host is better understood.

The present systematic review and meta-analysis have limitations inherent to the methodology. There were few prospective studies in the present study, the majority being retrospective analyses of datasets. In the present meta-analysis, the thresholds of each index were not entirely consistent, which may have introduced error into the pooled analysis. In particular, across the NLR studies, different thresholds were applied, and it would be important to standardize

thresholds in future prospective studies. However, this is a feature of the evolving literature to date, except for the mGPS, and has not been addressed in previous meta-analyses. Indeed, the problem may be compounded by composite scores such as the systemic inflammatory response index (SIRI), which combines neutrophils, lymphocytes, and monocytes, such that an abnormal threshold is generated by values of neutrophils, lymphocytes, or monocytes that fall within the normal range (Miura et al., 2015). Also, with threshold standardization, the degree of heterogeneity may decrease in future systematic reviews and meta-analyses.

The date of the present comprehensive literature search was 1st January 2022, and this is an area of considerable ongoing interest. Nevertheless, the present study identified that, among the systemic inflammation-based prognostic scores, NLR and mGPS were the most consistent prognostic/predictive factors. Therefore, future work should focus on these markers. Recently, a meta-analysis of the relationship between the Glasgow Prognostic Score and outcome in NSCLC patients treated with immunotherapy was carried out, confirming the present results (C. L. Zhang et al., 2022). Specifically, the pooled results indicated that a higher baseline mGPS was associated with poorer OS and PFS in non-small cell lung cancer patients treated with immune checkpoint inhibitors, and these findings were robust after subgroup and sensitivity analyses. However, only seven studies with 833 patients were identified, and further work is required.

Limitations included heterogeneity across included studies, variability in biomarker cut-off values, incomplete adjustment for confounders, publication bias, and the predominance of retrospective data.

Nevertheless, the results imply that inflammatory biomarkers hold substantial predictive and prognostic utility for immunotherapy outcomes, supporting their incorporation into future clinical trial stratification, routine assessment before immunotherapy, and potentially as markers to guide treatment escalation or early supportive interventions.

3.5 Conclusions

The present systematic review and meta-analysis showed that markers of the systemic inflammatory response, particularly the Neutrophil-to-Lymphocyte Ratio (NLR) and the modified Glasgow Prognostic Score (mGPS), have significant clinical prognostic/predictive value in patients with NSCLC undergoing immunotherapy. Given their ease of measurement in routine clinical practice, these markers can serve as effective tools for risk stratification and personalized treatment planning. By incorporating NLR and mGPS into clinical decision-making, healthcare providers may better allocate treatment resources, potentially improving patient outcomes and optimizing therapeutic strategies in this challenging patient population.

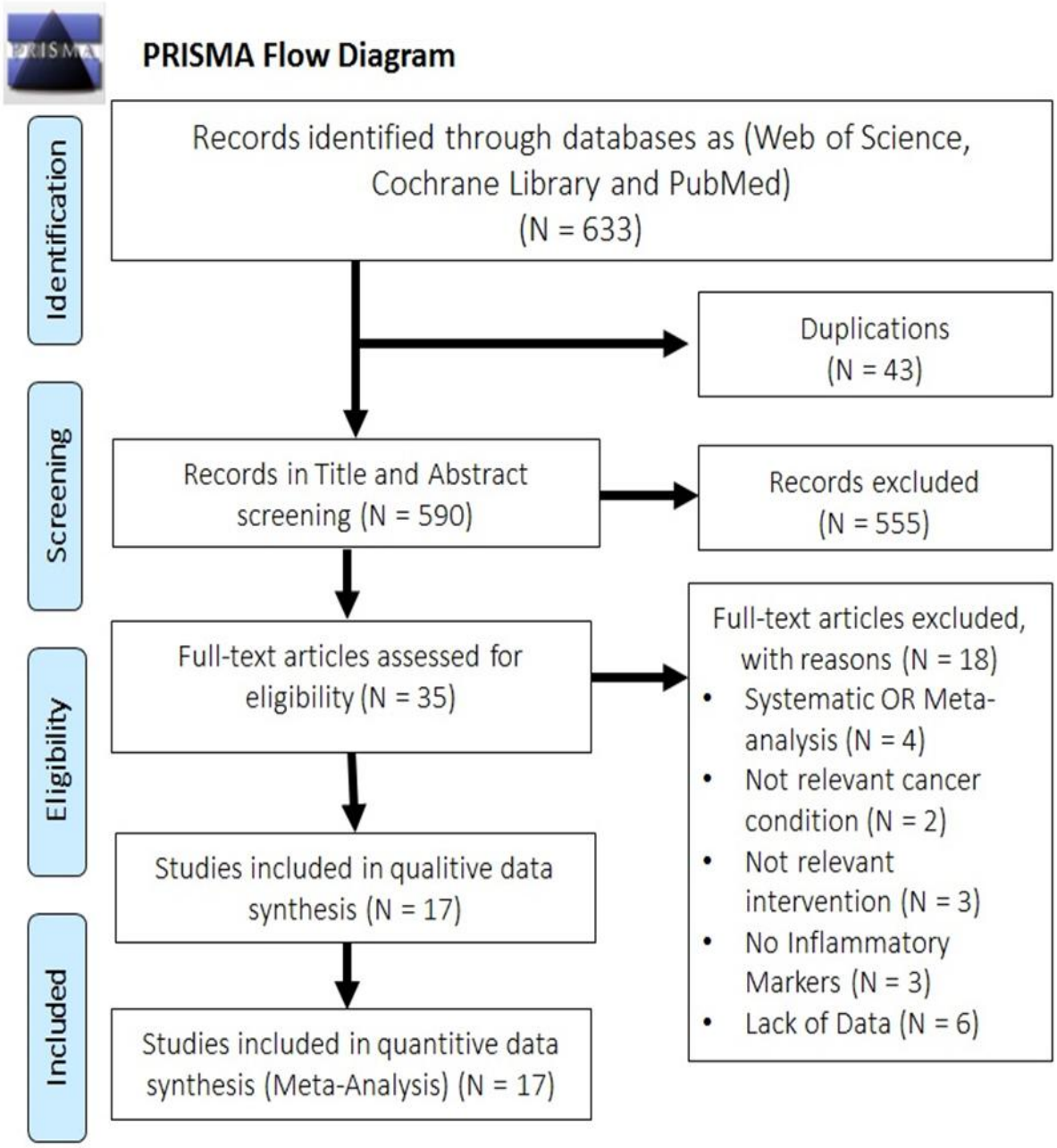

Figure 3- 1: PRISMA flow diagram illustrating the study selection process.

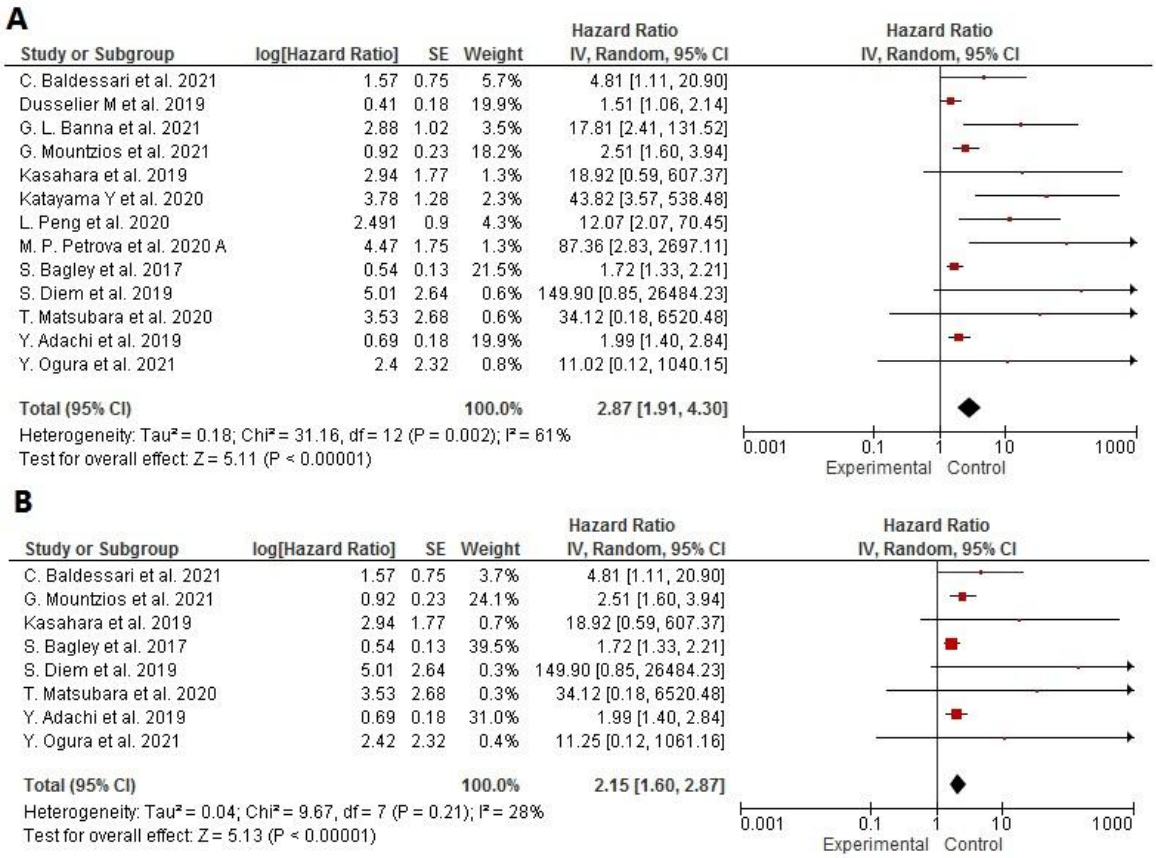

Figure 3- 2: A) The forest plot of the neutrophil-to-lymphocyte ratio (NLR) with 95% confidence intervals (CIs), hazard ratio, and standard error (SE), B) Sensitivity Analysis by omitting studies with high heterogeneity.

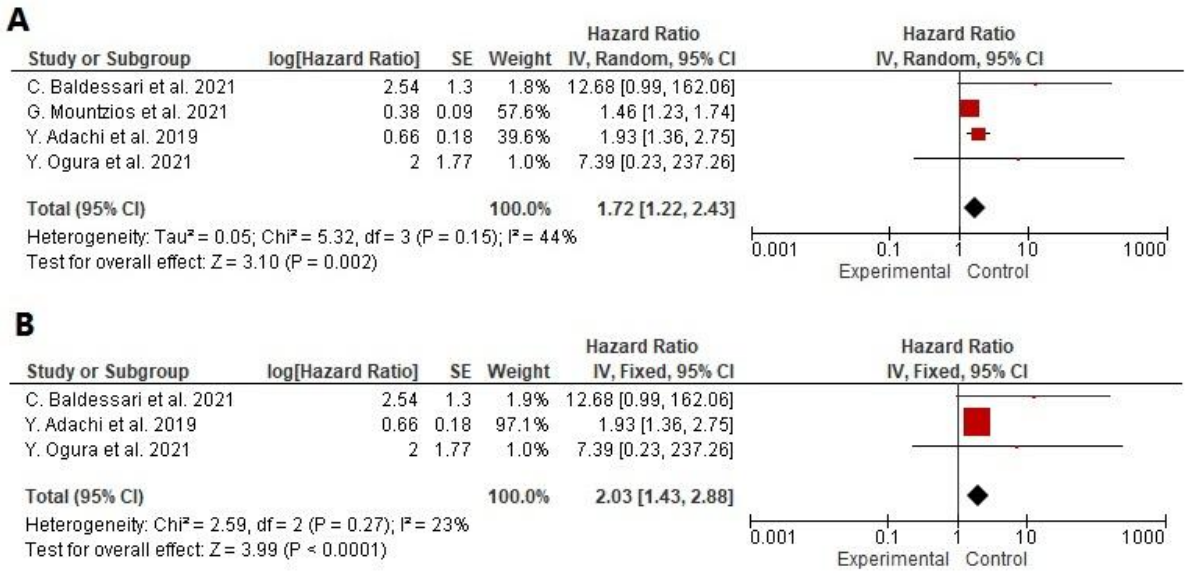

Figure 3- 3: A) The forest plot of the advanced lung cancer inflammation index (ALI) with 95% confidence intervals (CIs), hazard ratio, and standard error (SE), B) Sensitivity Analysis by omitting studies with high heterogeneity.

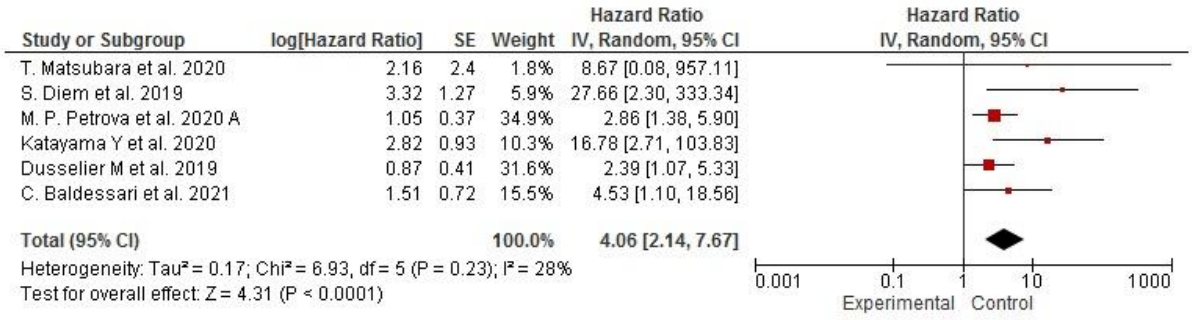

Figure 3- 4: The forest plot of the platelet-to-lymphocyte ratio (PLR) with 95% confidence intervals (CIs), hazard ratio, and standard error (SE).

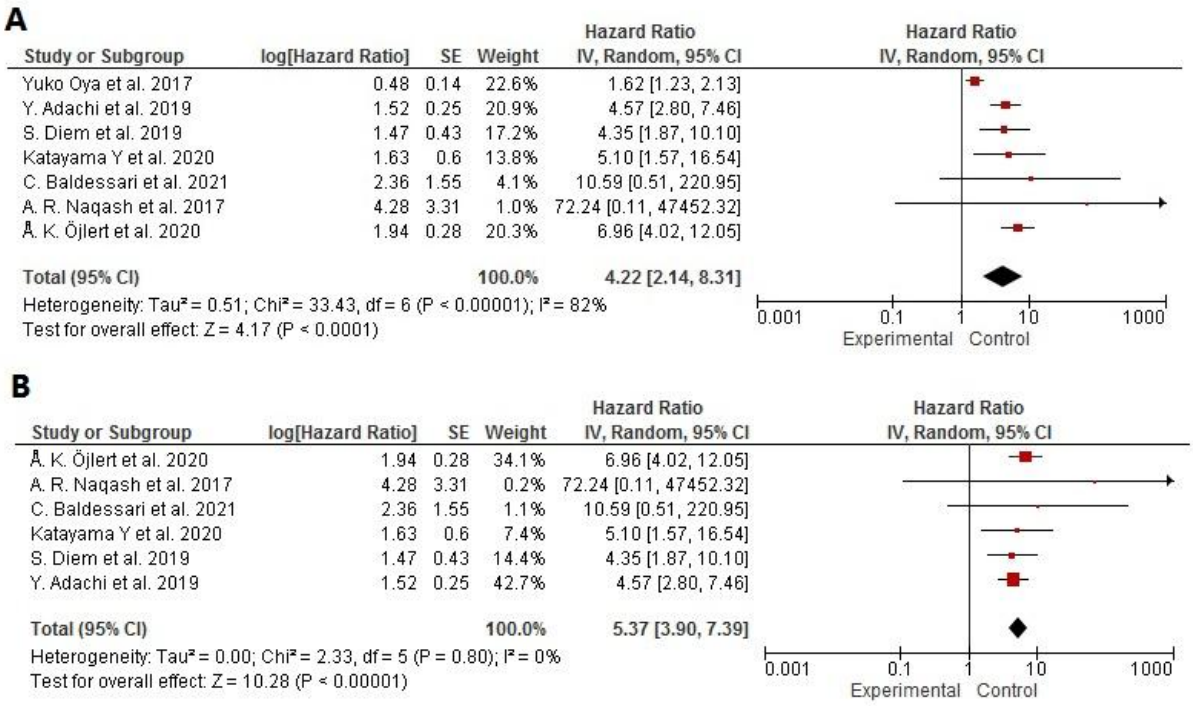

Figure 3- 5: A) The forest plot of the C-reactive protein (CRP) with 95% confidence intervals (CIs), hazard ratio, and standard error (SE), B) Sensitivity Analysis by omitting studies with high heterogeneity.

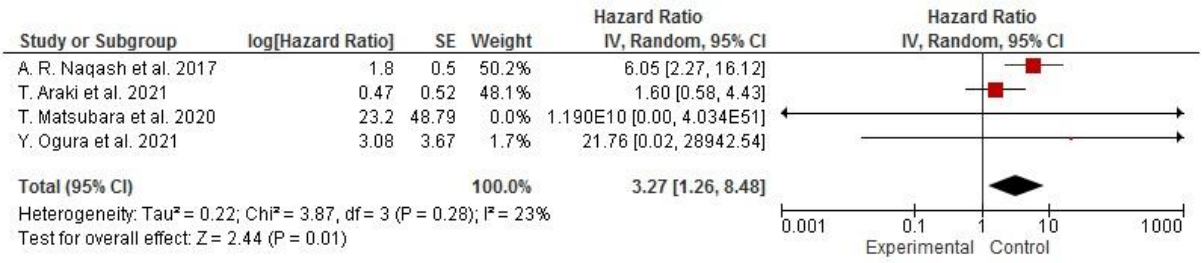

Figure 3- 6: The forest plot of the Modified Glasgow Prognostic Score (mGPS) with 95% confidence intervals (CIs), hazard ratio, and standard error (SE).

Chapter 4, A systemic inflammation first approach to the assessment of nutritional decline in patients with non-small cell lung cancer

4.1 Introduction

Non- small cell lung cancer NSCLC remains the top cause of cancer-related mortality globally (Herbst et al., 2018)despite recent improvements in medical and surgical therapy. According to recent research, the average 5-year survival rate for NSCLC is 16% (Sinkevicius et al., 2014).

As the NSCLC progresses, it is frequently associated with cachexia (Deutz et al., 2019; Jafri et al., 2015). Weight loss and body mass index (BMI) have historically been used as indications of malnutrition and cancer cachexia, and efforts are still being made to describe body composition in cancer patients (Collins et al., 2014) more accurately. The loss of muscle mass and function (sarcopenia) is a key cause of morbidity in lung cancer patients (Ali & Garcia, 2014; Boutin et al., 2015). Sarcopenia has been identified as an independent risk factor for mortality in operable and inoperable patients with NSCLC (Buentzel et al., 2019; Shinohara et al., 2020). Furthermore, in patients with TNM stage I disease, sarcopenia was associated with poorer short- and long-term outcomes following surgical resection (Takahashi et al., 2021).

Recently, image-based techniques, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and dual-energy X-ray absorptiometry (DEXA), have been used to assess body composition. For adipose tissue and skeletal muscle, good agreement has been documented between DEXA, CT, and MRI (Borga et al., 2018; Bredella et al., 2010; Mourtzakis et al., 2008; Shen et al., 2004). As a possible predictive tool for people with cancer, CT-based body composition analysis has attracted interest (McGovern et al., 2021). In prior studies, CT measurements were mainly used to determine whether patients were sarcopenic, a condition known as CT-derived sarcopenia (Suzuki et al., 2016).

The preoperative systemic inflammatory response (SIR) is based on composite ratios or cumulative scores of circulating white blood cells or acute phase proteins (Dolan et al., 2018). Currently, the most common scoring methods are the modified Glasgow Prognostic Score (mGPS) and neutrophil–lymphocyte ratio (NLR) (Tang et al., 2021), which are considered reliable prognostic biomarkers in cancer. Furthermore, an overall systemic inflammatory grade (SIG) has been computed by adding the mGPS and the NLR (Platini et al., 2022). Indeed, over the past 10 years, markers of the SIR have become clinically useful for identifying patients at high risk of death in various common solid tumours, particularly lung cancer (Dolan, Lim, et

al., 2017a; Dolan, McSorley, et al., 2017b). Moreover, the mGPS and ECOG-PS have been integrated into patients with advanced cancer to stratify quality of life and survival accurately (Dolan, Lim, et al., 2017a; B. J. A. Laird et al., 2016a).

In recent years, the Global Leadership Initiative on Malnutrition (GLIM) approach has provided an accepted, overarching framework for diagnosing disease-related malnutrition (Cederholm et al., 2019a; B. J. A. Laird et al., 2016a). The GLIM approach to malnutrition diagnosis is based on assessment of three phenotypic (weight loss, low body mass index, and reduced skeletal muscle mass) and two etiologic (reduced food intake/assimilation and disease burden/inflammation) criteria, with diagnosis confirmed by fulfilment of any combination of at least one phenotypic and at least one etiologic criterion(Cederholm et al., 2019b).

To our knowledge, no study has examined, in the context of objective GLIM criteria, how a systemic inflammation-first approach improves the prediction of overall survival.

This chapter hypothesised that systemic inflammation, measured through mGPS and NLR, would be more closely associated with nutritional decline than chronological age in patients with NSCLC.

This study aims to examine a systemic inflammation-first approach to assessing nutritional decline in patients with NSCLC (n=535).

4.2 Patient and method

A single-centre retrospective cohort study was conducted. Clinicopathological characteristics and clinical outcome data were collected from the prospectively maintained database at The Beatson West of Scotland Cancer Institute from January 2009 to February 2017. Patients were followed up until death or 1st October 2019, which was used as the censor date. The present cohort study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies and checklist for cohort studies (Dolan et al., 2019).

Patients with advanced non-small cell lung cancer and blood results within one month pre-treatment were included. We included patients aged ≥18 years, of both sexes, with the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) grades 0, 1, 2, and 3. Patients with ECOG-PS grade 4 were excluded from the analysis.

The study was a retrospective observational cohort study and was approved by the West of Scotland Research Ethics Committee for data collection and analysis.

Clinicopathological Characteristics

Each patient's routine demographic information, such as age, sex, ECOG performance status, BMI, modified Glasgow prognostic score (mGPS), and NLR.

Age was classified into <65, 65-74, and >75years, and BMI was divided into underweight (< 20), normal (20 – 24.96), overweight (25 – 29.9), and obese (>30) kg/m2. According to their ECOG-PS, patients were divided into groups 0, 1, and >2. NLR values were categorized as <3, 3-5, and >5. mGPS was classified as 0, 1, and 2.

Body Composition Analysis

CT has become the gold standard for body composition analysis, and single-slice cross-sectional analysis at the Lumber Vertebrae 3 (L3) level is a valid tool for this purpose. CT scans performed as part of staging before commencing treatment were used for analysis. L3 was located using fixed anatomical landmarks by counting downwards from thoracic vertebra 12 (T12), where the 12th rib attaches, or from the sacrum upwards to the L3 level. Body composition analysis was performed using National Institutes of Health (NIH) image software ImageJ (https://imagej.nih.gov.ij/) by establishing thresholds of 29 to 150 Hounsfield units (HU) for skeletal muscle, and -190 to -30 HU for adipose tissue as previously described [35].

Using this technique, visceral fat area (VFA), subcutaneous fat index (SFI), skeletal muscle index (SMI), skeletal muscle density (SMD), and CT-Sarcopenia score (CT-SS) were measured.

Subcutaneous adiposity was defined as an increased subcutaneous fat index (SFI) of >50 cm2/m2 in males and >42 cm2/m2 in females (von Elm et al., 2008). Visceral obesity was defined as visceral fat area (VFA) >160cm2 in males and >80cm2 in females (Doyle et al., 2013). Martin and co-worker thresholds were used to calculate skeletal muscle index (SMI) and low skeletal muscle radiodensity (SMD) in lung cancer (LC) [40]. SMI indicates the amount of skeletal muscle area normalized for height; SMD indicates the amount of fat infiltration in muscle, also called myosteatosis. In males, low SMI was <43 cm2/m2 if BMI <25 and <53 if BMI≥25. In females, low SMI was <39 if BMI <25 and <41 if BMI ≥25 kg/m2. In males/ females, low SMD was <41 if BMI <25 and <33 if BMI ≥25. Sex and BMI were used to define these thresholds. VFA, SFI, SMI, and SMD were categorized as high and low, while CT-SS was classified as 0, 1, and 2.

Statistical Analysis

The data were summarized in the following tables and figures. Categorical variables were presented as numbers (n) and percentages (%). For non-normally distributed data, the data were presented as median and range (minimum and maximum). Overall survival was defined as the time in months from the start of treatment to death or last follow-up. The median follow-up duration was 18 months. The mortality rate was 98%. Survival analysis was performed using Cox regression, and p-values ≤ 0.01 were considered significant, accounting for multiple comparisons. All statistical analyses were performed using SPSS version 29.

4.3 Results

Five hundred thirty-five patients with advanced NSCLC with available pre-radiotherapy CT scans were included in the study (Table 4-1). Most patients were >65years old (69%), male (52%), had good performance status (62%), evidence of a systemic inflammatory response, mGPS (74%) and NLR (61%), were of normal weight or overweight (83%), had high VFA (72%) and SFI (75%) and low SMI (57%) and SMD (66%). ECOG-PS, mGPS, and NLR were significantly associated with overall survival (all p-values < 0.01). In contrast, sex, BMI, VFA, SFI, SMI, and SMD were not significantly associated with overall survival. The relationships between mGPS, age, and the 12-month survival rate are shown in Table 4-2. The mGPS significantly stratified survival by age group ($p<0.01$), but not vice versa. The relationships between NLR, age, and the 12-month survival rate are shown in Table 4-3. NLR significantly stratified survival by age group ($p<0.01$), but not vice versa. The relationship between mGPS, ECOG-PS, and 12-month survival rate is shown in Table 4-4. Both mGPS and ECOG-PS significantly stratified survival in their respective groups ($p<0.01$). The relationship between NLR, ECOG-PS, and 12-month survival rate is shown in Table 4-5. Both NLR and ECOG-PS significantly stratified survival in their respective groups ($p<0.01$). The relationship between mGPS, BMI, and 12-month survival rate is shown in Table 4-6. mGPS significantly stratified survival by BMI group ($p<0.01$), but BMI did not stratify survival by mGPS group ($p=0.12$). The relationship between NLR, BMI, and 12-month survival rate is shown in Table 4-7. NLR significantly stratified survival by BMI group ($p<0.01$), but not vice versa.

The relationship between mGPS, SFI, and 12-month survival rate is shown in Table 4-8. The mGPS significantly stratified survival in the SFI groups ($p<0.01$) but not vice versa. The relationship between NLR, SFI, and 12-month survival rate is shown in Table 4-9. The NLR significantly stratified survival in the SFI groups ($p<0.01$) but not vice versa. The relationship between mGPS, VFA, and 12-month survival rate is shown in Table 4-10. The mGPS significantly stratified survival in the VFA groups ($p<0.01$) but not vice versa. The relationship between NLR, VFA, and 12-month survival rate is shown in Table 4-11. The mGPS significantly stratified survival in the VFA groups ($p<0.01$) but not vice versa. The relationship between mGPS, SMI, and 12-month survival rate is shown in Table 4-12. Both mGPS and SMI significantly stratified survival in the SFI groups ($p<0.01$). The relationship between NLR, SMI, and 12-month survival rate is shown in Table 4-13. NLR significantly stratified survival in the SMI groups ($p<0.01$) but not vice versa. The relationship between mGPS, SMD, and 12-month survival rate is shown in Table 4-14. The mGPS significantly stratified survival in the

SMD groups ($p<0.01$) but not vice versa. The relationship between NLR, SMD, and 12-month survival rate is shown in Table 4-15. NLR significantly stratified survival in the SMD groups ($p<0.01$) but not vice versa.

4.4 Discussion

The results of the present study showed significant associations between mGPS, NLR, and 12-month survival rates when stratified by age, ECOG-PS, BMI, VFA, SFI, SMI, and SMD. In contrast, only ECOG-PS provided prognostic value independent of mGPS and NLR, whereas age, BMI, VFA, SFI, SMI, and SMD did not. Therefore, these results show ECOG-PS, mGPS, and NLR have superior prognostic value compared with measures of body composition. These results have implications for the use of GLIM criteria to assess the nutritional status of the patient with non-small cell lung cancer.

The present results are consistent with previous reports in large cohorts showing that ECOG-PS and mGPS are the cornerstones of predicting outcome in patients with advanced cancer (B. J. Laird et al., 2013; McGovern et al., 2024a). Recently, in a large, multicenter, prospective cohort study by Zhang and co-workers, the prognostic value of weight loss and systemic inflammation (as evidenced by NLR) was compared in 11,423 patients with advanced cancer; systemic inflammation was found to dominate the prognostic value of weight loss. Therefore, the present study consolidates the prognostic value of the ECOG-PS/ mGPS or NLR framework in the context of GLIM phenotypic criteria.

In the present study, the basis for the finding that none of the GLIM phenotypic criteria had independent prognostic value is unclear but may reflect that the majority of patients were over the age of 65 years (69%), since many of the features of cachexia are apparent in the elderly. Indeed, Bozzetti has recently questioned whether aging-related and cancer-related sarcopenia are indeed separate entities. (Bradley et al., 2024). Furthermore, Bradley and coworkers have reported that, in a comparison between cancer and non-cancer cohorts, older age and systemic inflammation appear to be important determinants of loss of skeletal muscle mass and quality irrespective of disease (Bradley et al., 2024). Therefore, it may be that in elderly patients with cancer, GLIM phenotypic criteria have less prognostic value.

Recently, McGovern and coworkers reported that, in patients with advanced cancer with good performance status, mGPS may dominate the prognostic value of CT-derived sarcopenia (McGovern et al., 2022). The results of the present study in a different cohort validate these findings; therefore, mGPS, rather than body composition, should be used as a prognostic adjunct for good-performance-status patients with advanced cancer. Moreover, they question the prognostic utility of body composition measures in the presence of a systemic inflammatory response.

The present study has some limitations; it is a retrospective cohort study, which is inherently limited. However, data were collected using a prospective pro forma, which ensured well-documented clinicopathological data and reduced the risk of bias. The observational nature of the data limited the study, potentially missing CT-body composition variables, and the lack of longitudinal follow-up to assess dynamic nutritional changes. Still, the findings underline the central role of inflammation in driving nutritional and functional deterioration, with implications for using mGPS and NLR to identify high-risk patients early and for prioritising anti-inflammatory and supportive nutritional interventions as part of routine cancer care. Therefore, further prospective and longitudinal studies examining the relative prognostic value of GLIM phenotypic and aetiologic criteria are warranted in patients with advanced cancer.

4.5 Conclusion

ECOG-PS, mGPS, and NLR had superior prognostic value compared with measures of body composition. Using the GLIM criteria to assess the patient's nutritional status with NSCLC was recommended.

Table 4- 1: Clinical characteristics of patients with non-small cell lung cancer and overall survival.

Variables		**N (%)**	**HR (95%CI)**	**P-Value**
Age group	<65	154 (29)	0.91 (0.81-1.01)	0.085
	65-74	206 (38)		
	>74	175(33)		
Sex	Female	256 (48)	1.06(0.89-1.26)	0.511
	Male	279 (52)		
Eastern Cooperative Oncology Group (ECOG) performance status	0 – 1	329 (62)	1.33(1.18-1.51)	<0.001
	2	146 (27)		
	3	60(11)		
Modified Glasgow Prognostic Score (mGPS)	0	138(26)	1.28(1.15-1.42)	<0.001
	1	142(26)		
	2	255(48)		
Neutrophil lymphocyte ratio (NLR)	<3	186(36)	1.24(1.11-1.37)	<0.001
	03-5	143(28)		
	>5	182(36)		
Body Mass Index (BMI) categories	Underweight (BMI < 20)	89(17)	0.92(0.84-1.01)	0.073
	Normal (BMI 20 – 24.96)	220(41)		
	Overweight (BMI 25 – 29.9)	139(26)		
	Obese (BMI >30)	87(16)		

High visceral fat area (VFA)	Low	141(27)	0.95(0.79-1.16)	0.639
	High	385(73)		
High subcutaneous fat index (SFI)	Low	126(24)	0.95 (0.77-1.16)	0.586
	High	400(76)		
Low skeletal muscle index (SMI)	Low	304(57)	1.13(0.95-1.35)	0.162
	High	231(43)		
Low skeletal muscle radiodensity (SMD)	Low	182(34)	1.04 (0.87-1.24)	0.683
	High	353(66)		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant.

Table 4- 2: The relationship between mGPS and age and the 12-month survival rate.

Age	Modified Glasgow Prognostic Score (mGPS)			
	0	1	2	P-Value
	(n=138)	(n=142)	(n=255)	
<65 (n=154)	27	17	4	0.001
65-74 (n=206)	37	26	16	<0.001
>74 (n=175)	25	19	23	0.277
P-Value	0.123	0.541	0.082	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 3: The relationship between NLR, age, and the 12-month survival rate.

Age	Neutrophil to lymphocyte ratio (NLR)			
	<3	**3-5**	**>5**	**P-Value**
	(n=186)	(n=143)	(n=182)	
<65 (n= 154)	15	19	6	0.004
65-74 (n= 206)	32	25	17	0.001
>74 (n= 175)	23	30	16	0.101
P-Value	0.074	0.983	0.144	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 4: The relationship between mGPS, ECOG-PS, and the 12-month survival rate.

Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)	Modified Glasgow Prognostic Score (mGPS)			
	0	**1**	**2**	**P-Value**
	(n=138)	(n=142)	(n=255)	
0 – 1 (n=329)	30	24	18	0.014
2 (n=146)	33	16	13	<0.001
3 (n=60)	13	9	7	0.373
P-Value	0.552	0.302	0.001	

*A P-value of ≤ 0.05 was considered significant,12-month survival rate.

Table 4- 5: The relationship between NLR and ECOG-PS in patients at 12-month survival

Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)	Neutrophil to lymphocyte ratio (NLR)			
	<3	**3-5**	**>5**	**P-Value**
	(n=186)	(n=143)	(n=182)	
0 – 1 (n=311)	26	30	15	0.002
2(n=140)	24	18	13	0.001
3(n=60)	0	14	10	0.14
P-Value	0.032	0.004	0.072	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 6: The relationship between mGPS and BMI in patients at 12-month survival.

Body mass index (BMI)	Modified Glasgow Prognostic Score (mGPS)			
	0	**1**	**2**	**P-Value**
	(n=138)	(n=142)	(n=255)	
<20 (n=89)	25	16	10	0.005
20-24.99 (n=220)	29	15	16	0.015
25-29.99 (n=139)	26	32	14	0.008
>30 (n=87)	44	25	20	0.013
P-Value	0.445	0.117	0.046	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 7: The relationship between NLR and BMI in patients at 12-month survival.

Body mass index (BMI)	Neutrophil to lymphocyte ratio (NLR)			
	<3	**03-5**	**>5**	**P-Value**
	(n=186)	(n=143)	(n=182)	

<20 (n=89)	24	19	7	0.003
20-24.99 (n=220)	21	28	11	<0.001
25-29.99 (n=139)	24	22	22	0.221
>30 (n=87)	30	32 910)	17	0.444
P-Value	0.865	0.275	0.135	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 8: The relationship between mGPS and SFI in patients at 12-month survival.

High subcutaneous fat index (SFI)	Modified Glasgow Prognostic Score (mGPS)			
	0	**1**	**2**	**P-Value**
	(n=138)	(n=142)	(n=255)	
Low (n=126)	37	20	14	<0.001
High(n=400)	28	22	17	<0.001
P-Value	0.896	0.695	0.826	

*A P-value of ≤ 0.05 was considered significant,12-month survival rate.

Table 4- 9: 2h The relationship between NLR and SFI in patients at 12-month survival.

High subcutaneous fat index (SFI)	Neutrophil to lymphocyte ratio (NLR)			
	<3	3-5	>5	**P-Value**
	(n=186)	(n=143)	(n=182)	
Low (n=126)	27	24	11	0.005
High (n=400)	23	23	12	<0.001
P-Value	0.231	0.735	0.852	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 10: The relationship between mGPS and VFA in patients at 12-month survival.

High visceral fat area (VFA)	Modified Glasgow Prognostic Score (mGPS)			
	0	**1**	**2**	**P-Value**
	(n=138)	(n=142)	(n=255)	
Low (n=141)	37	11	12	0.007
High (n=385)	27	25	16	<0.001
P-Value	0.671	0.369	0.804	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 11: The relationship between NLR and VFA in patients at 12-month survival.

High visceral fat area (VFA)	Neutrophil to lymphocyte ratio (NLR)			
	<3	3-5	>5	**P-Value**
	(n=186)	(n=143)	(n=182)	
Low (n=141)	23	22	13	0.004
High (n=385)	24	26	14	<0.001
P-Value	0.455	0.697	0.646	

*A P-value of ≤ 0.05 was considered significant,12-month survival rate.

Table 4- 12: The relationship between mGPS and SMI in patients at 12-month survival.

Low skeletal muscle index (SMI)	Modified Glasgow Prognostic Score (mGPS)			
	0	**1**	**2**	**P-Value**
	(n=138)	(n=142)	(n=255)	
Low(n=304)	26	26	14	<0.001
High(n=231)	35	11	16	0.002
P-Value	0.877	0.004	0.516	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 13: The relationship between NLR and SMI in patients at 12-month survival.

Low skeletal muscle index (SMI)	Neutrophil to lymphocyte ratio (NLR)			
	<3 (n=186)	3-5 (n=143)	>5 (n=182)	**P-Value**
Low(n=126)	21	28	15	0.004
High(n=400)	27	21	12	<0.001
P-Value	0.928	0.038	0.217	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 14: The relationship between mGPS and SMD in patients at 12-month survival.

Low skeletal muscle radiodensity (SMD)	Modified Glasgow Prognostic Score (mGPS)			
	0 (n=138)	**1** (n=142)	**2** (n=255)	**P-Value**
Low(n=182)	30	22	13	0.006
High (n=353)	29	21	16	<0.001
P-Value	1.000	0.346	0.262	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Table 4- 15: The relationship between NLR and SMD in patients at 12-month survival.

Low skeletal muscle radiodensity (SMD)	Neutrophil to lymphocyte ratio (NLR)			
	<3 (n=186)	3-5 (n=143)	>5 (n=182)	**P-Value**
Low (n=182)	22	22	13	0.033
High(n=353)	25	27	14	<0.001
P-Value	0.739	0.463	0.589	

*A P-value of ≤ 0.05 was considered significant, 12-month survival rate.

Chapter 5, Comparison of albumin-based prognostic inflammatory scores and survival in patients with non-small cell lung cancer

5.1 Introduction

Every day, over one hundred people in the United Kingdom die from lung cancer(Corby et al., 2024).

Albumin is a protein produced by the liver and is the most abundant protein in plasma (Caraceni et al., 2013). It has long been an indicator of a patient's nutritional status, including dietary intake and body composition. However, it has become clear that albumin concentration is affected by systemic inflammation, as evidenced by C-reactive protein (CRP) and changes in differential white blood cell (WBC) counts. Therefore, in the presence of a systemic inflammatory response, albumin may not reflect nutritional status (Bullock et al., 2020).

Albumin is a vital component in several prognostic measures in patients with cancer. For example, albumin has been combined with CRP in the mGPS and CAR to predict clinical outcomes in NSCLC patients treated with surgery (Matsubara and Okamoto, 2017; Proctor et al., 2010), chemotherapy (Jia-min et al., 2022), and stereotactic body radiation treatment (SBRT)(Z. Chen et al., 2021), with higher values predicting poorer treatment outcomes. Albumin has also been combined with components of the differential WBC, such as in the Scottish inflammatory prognostic score SIPS (Stares et al., 2022), advanced lung cancer inflammation index ALI (Olmez et al., 2023), C-reactive protein-albumin-lymphocyte CALLY (Hashimoto et al., 2024), and Onodera's prognostic nutritional index OPNI.

The chapter hypothesised that albumin-based inflammatory scores (CAR, mGPS) would outperform other scores in predicting survival in NSCLC.

Therefore, the present study aimed to compare albumin-based prognostic inflammatory scores/ratios and survival in patients with advanced NSCLC (n=535).

5.2 Patient and methods

A single-centre retrospective cohort study conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies and the Checklist for Cohort Studies.

Clinicopathological characteristics and clinical outcome data were collected from the prospectively maintained database at The Beatson West of Scotland Cancer Institute from January 2009 to February 2017. Patients were followed up until death or 1st October 2019, which was used as the censor date.

Patients with advanced non-small cell lung cancer and blood results within one month pre-treatment were included. We included patients aged ≥18 of both sexes with ECOG-PS grades 0, 1, 2, and 3. Patients with missing data or transferred to other medical facilities with unknown outcomes were excluded. Each patient's routine demographic information, such as gender, age, ECOG-PS performance status, and blood results, was recorded, and mGPS, CAR, SIPS, ALI, CALLY, and OPNI were calculated according to the criteria in Table 5-1.

The present study was a retrospective observational study and was approved by the West of Scotland Research Ethics Committee for the data collection and analysis.

Statistical analysis

The data were summarized in the following tables. Categorical variables were presented as numbers (n) and percentages (%). For non-normally distributed data, the data were presented as median and range (minimum and maximum). Overall survival was defined as the time in months from the start of treatment to death or last follow-up. The median follow-up duration was 18 months. The mortality rate was 98%. Survival analysis was performed using Cox regression, and p-values ≤ 0.01 were considered significant. All statistical analyses were performed using SPSS version 29.

5.3 Results

Following exclusion criteria, there were a total of 535 patients with advanced non-small cell lung cancer NSCLC (Table 5-2). Most patients were aged > 65 years (71%), male (52%), and had ECOG performance status 0-1 (62%). Most patients had a low albumin concentration (54%) and abnormal mGPS (74%), CAR (79%), SIPS (66%), ALI (56%), CALLY (96%), and OPNI (85%). All albumin-inclusive systemic inflammatory scores and ratios (mGPS, CAR, SIPS, ALI, CALLY, and OPNI) were significantly associated with survival ($p<0.01$). However, only baseline mGPS and CAR had CRP concentrations within the normal reference range (< 10 mg/L; Table 5-2).

In a multivariate survival analysis, including age, sex, BMI, ECOG-PS, mGPS, and CAR, there was a significant independent association between age ($p=0.012$), ECOG-PS ($p <0.001$), mGPS ($p<0.001$), and overall survival (n=535; Table 5-3). In multivariate analysis among patients with good performance status (0-1), including age, sex, BMI, mGPS, and CAR, there was a significant independent association between CAR ($p=0.013$) and overall survival (n=329; Table 5-4).

5.4 Discussion

To our knowledge, this is the first study to compare albumin-based prognostic scores in patients with advanced NSCLC comprehensively. In the present study, all albumin-based systemic inflammatory scores were significantly associated with overall survival in patients with non-small cell lung cancer. However, except for mGPS and all albumin-based measures, at baseline, were associated with CRP concentrations above the normal reference range (> 10 mg/l) and therefore did not exclude systemic inflammation from the baseline group. Both mGPS and CAR measures of systemic inflammation appeared to have prognostic value independent of ECOG-PS. These results have implications for the development of novel albumin-based prognostic scores in patients with cancer.

It has long been recognized that C-reactive protein is the prototypical marker of the systemic inflammatory response (Abay, 1999), that albumin is inversely associated with CRP and directly associated with muscle mass (McMillan et al., 2001). More recently, this has been confirmed using another measure of muscle mass (Almasaudi et al., 2020). Taken together, these findings suggest that hypoalbuminemia and its prognostic value in patients with cancer reflect both increased nutritional risk and a greater systemic inflammatory response. Therefore, the prognostic value of hypalbuminaemia is due in part to it reflecting both nutritional risk and systemic inflammation.

It is of interest that Gray and Axelsson reported that the combination of an elevated CRP (>10mg/l) and hypalbuminaemia (<30g/l) could be termed as laboratory cachexia, as they become increasingly abnormal before death (Gray & Axelsson, 2018). In the present study, although albumin was within the normal range (> 35 g/L), the median CRP value was 32 mg/L, which is well above the normal range (< 10 mg/L). Even when the hypoalbuminemia threshold was set at <40g/l, this was associated with a median CRP value of 59 mg/l, still above the normal range. Therefore, the CRP-evidenced systemic inflammatory response is likely to occur before hypoalbuminemia.

In the present study, both mGPS and CAR were sensitive to systemic inflammation, as evidenced by CRP, and both had prognostic value independent of ECOG-PS; therefore, both are clinically useful and can be used to predict survival in patients with advanced NSCLC. However, CAR is a ratio, and its calculation may be open to misinterpretation, whereas mGPS, as a score, is simple to calculate and puts CRP before albumin in the calculation, reflecting the disease process.

Importantly, as immunotherapy has become the standard of care for advanced NSCLC, it is increasingly clear that mGPS has robust prognostic value in patients receiving immunotherapy and is now incorporated into routine clinical practice (C. L. Zhang et al., 2022; Rashdan & Gerber, 2019).

Therefore, it may be that moderating mGPS before immunotherapy improves outcomes in patients with advanced NSCLC (Pan et al., 2021).

Limitations include the single-centre design, retrospective data collection, varying timing of biomarker measurement, and the inability to evaluate other potential confounders, such as comorbidities or socioeconomic factors.

Despite these constraints, the findings demonstrate the superior prognostic performance of CRP-based and albumin-based scores, supporting their use as robust, clinically practical tools for prognostication and guiding therapeutic decisions and patient counselling.

5.5 Conclusion

In summary, in the present study, all albumin-based systemic inflammatory scores were significantly associated with overall survival in patients with advanced non-small cell lung cancer. However, except for mGPS and all albumin-based scores, at baseline, were associated with CRP concentrations above the normal reference range (> 10 mg/l).

Table 5- 1: Systemic inflammation-based prognostic scores.

Variables		**Score/ratio**
Modified Glasgow Prognostic Score/Glas-gow Prog-nostic Score (mGPS/GPS)	C-reactive protein≤10mg/l and albumin ≥ 35 g/l	0
	C-reactive protein>10 and albumin ≥ 35 g/l	1
	C-reactive protein>10 and albumin <35 g/l	2
C-reactive protein-to-albumin ratio (CAR)	C-reactive protein/ albumin	<0.2
	C-reactive protein/ albumin	0.2-0.4
	C-reactive protein/ albumin	>0.4
Scottish In-flammatory Prognostic Score (SIPS)	Albumin ≥35g/l and neutrophil ≤7.5×10^9/l	0
	Albumin ≥35g/l and neutrophil >7.5×10^9/l	1
	Albumin <35g/l and neutrophil ≤7.5×10^9/l	1
	Albumin <35g/l and neutrophil >7.5×10^9/l	2
Advanced Lung Cancer Inflammatio n Index (ALI)	Body mass index (BMI) ×serum albumin / Neutrophil lymphocyte ratio (NLR) >18	Low inflammation
	Body mass index (BMI) ×serum albumin / Neutrophil lymphocyte ratio (NLR)<18	High inflammation
The CRP-albumin-lymphocyte	Albumin× lymphocyte count /CRP×10^4	≤1.12
	Albumin× lymphocyte count /CRP×10^4	>1.12

(CALLY) index		
The Onodera's Prognostic Nutritional Index (OPNI)	10× Albumin+0.005×lymphocyte count (per mm^3) ≥ 40	High
	10× Albumin+0.005×lymphocyte count (per mm^3) <40	Low

Table 5- 2: Clinical characteristics of patients with non-small cell lung cancer and 12-month survival

Variables		**N (%)**	**HR (95%CI)**	**P-Value**	**CRP (mg/l) Median (range)**
Age Group	<65	154 (29)	0.91(0.81-1.01)	0.085	61 (<1-431)
	65-74	206 (38)			59 (<1-357)
	>74	175(33)			46(<1-309)
Sex	Female	256 (48)	1.06(0.89-1.26)	0.511	51(<1-287)
	Male	279 (52)			59(<1-431)
ECOG Performance Status	0 – 1	329 (62)	1.28(1.13-1.45)	<0.001	47(<1-358)
	2	146 (27)			66(<1-357)
	3	60(11)			75(<1-431)
Albumin	>=35g/l	246(46)	1.51(1.27-1.80)	<0.001	32(<1-286)
	<35g/l	289(54)			75(<1-431)
Albumin	<40g/l	455(85)	1.39(1.09-1.77)	0.009	59(0-431)
Modified Glasgow Prognostic Score (mGPS)	0	138(26)	1.31(1.18-1.46)	<0.001	5 (<1-10)
	1	142(26)			51 (2-286)
	2	255(48)			85 (6-431)

C-reactive protein-to-albumin ratio (CAR)	>0.2	111(21)	1.28(1.15-1.42)	<0.001	4 (<1-8)
	0.2-0.4	66(12)			29 (<1-431)
	>0.4	358(67)			54 (71-85)
Scottish Inflammatory Prognostic Score (SIPS)	0	173(34)	1.33(1.19-1.50)	<0.001	25(<1-185)
	1	207(40)			54(<1-286)
	1				57(<1-358)
	2	131(26)			96(<1-431)
Advanced Lung Cancer Inflammation Index (ALI)	>=18	288(56)	1.48(1.24-1.77)	<0.001	30(<1-431)
	<18	223(44)			223(84-272)
The CRP-albumin-lymphocyte (CALLY) index	=<1.12	19(4)	0.65(0.51-0.82)	<0.001	115(14-431)
	>1.12	492(96)			18(<1-63)
The Onodera's Prognostic Nutritional Index (OPNI)	≥40	75(15)	1.42(1.10 -1.83)	0.007	32(1-286)
	<40	436(85)			60(<1-431)

*Data presented as a number (percentage). *A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower; if it contains 1.00, the result is not statistically significant.

Table 5- 3: Clinical characteristics of patients with non-small cell lung cancer and survival multivariate analysis

Variables		**HR (95%CI)**	**P-Value**
Age group	<65	0.87(0.78 - 0.98)	0.012
	65-74		
	>74		
Sex	Female	-	0.998
	Male		
BMI	<20	-	0.203
	20- 24.99		
	25-29.9		
	>30		
ECOG Performance Status	0 – 1	1.26(1.10-1.43)	<0.001
	2		
	3		
Modified Glasgow Prognostic Score (mGPS)	0	1.29(1.15 -1.43)	<0.001
	1		
	2		

C-reactive protein-to-albumin ratio (CAR)	<0.2	-	0.549
	0.2-0.4		
	>0.4		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower; if it contains 1.00, the result is not statistically significant.

Table 5- 4: Clinical characteristics of patients with non-small cell lung cancer and overall survival multivariate analysis in ECOG-PS 0-1

Variables		**HR (95%CI)**	**P-Value**
Age group	<65	-	0.297
	65-74		
	>74		
Sex	Female	-	0.891
	Male		
Body mass index (BMI)	<20	-	0.392
	20- 24.99		
	25-29.9		
	>30		
Modified Glasgow Prognostic Score (mGPS)	0	-	0.510
	1		
	2		
C-reactive protein-to-albumin ratio (CAR)	<0.2	1.18(1.04- 1.35)	0.013
	0.2-0.4		
	>0.4		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower; if it contains 1.00, the result is not statistically significant.

Chapter 6, Evaluation of systemic inflammatory markers ratios and scores for prognosis in patients with non-small lung cancer: A C-reactive protein-based comparison

6.1 Introduction

Although traditional tumour-based prognostic factors such as tumour site, histological subtypes, grade, nodal stage, and metastasis are the cornerstone of clinical practice, they have been shown to predict clinical outcome inadequately. More recently, host-based factors such as the systemic inflammatory response have been shown to improve the prediction of clinical outcome (Min et al., 2024). As predictive indicators of overall survival (OS) in lung cancer, inflammation scores based on general inflammatory markers have been proposed (Min et al., 2024).

Systemic inflammatory markers correlate strongly with the development and effectiveness of cancer therapy(Balkwill & Mantovani, 2001). In the past decade, it has become apparent that indicators of the systemic inflammatory response can be used in clinical settings to identify individuals at high risk of developing several common solid tumours, particularly lung cancer (Dolan et al., 2017a; Dolan et al., 2017b). These include white blood count parameters such as neutrophils, lymphocytes, monocytes, platelets, as well as their ratios and scores, including the neutrophil-lymphocyte ratio (NLR), neutrophil-lymphocyte score (NLS), platelet-lymphocyte ratio (PLR), platelet-lymphocyte score (PLS), lymphocyte-monocyte ratio (LMR), lymphocyte-monocyte score (LMS), neutrophil-platelet score (NPS) (Coussens & Werb, 2002; Dolan, Lim, et al., 2017b; Dolan, McSorley, et al., 2017a). However, it has become clear that white cell count-derived scores and ratios may not clearly differentiate between those with evidence of systemic inflammation (as evidenced by CRP) and those without. However, cumulative scores based on normal reference ranges are simpler to use clinically.

CRP is the prototypical acute-phase protein (derived from the liver) that increases up to 1,000-fold in response to tissue injury, infection, and inflammation and is therefore one of the most sensitive routinely available measures of systemic inflammation (Sproston & Ashworth, 2018).

This chapter hypothesised that CRP-based inflammatory biomarkers would be more prognostically valuable than ratio-based markers such as NLR, PLR, and LMR in advanced NSCLC.

Therefore, the present study aimed to evaluate systemic inflammatory marker ratios and scores for prognosis in patients with NSCLC: a C-reactive protein-based comparison (n=535).

6.2 Patient and methods

A single-center retrospective cohort study was carried out in patients with advanced lung cancer (stage III-IV) undergoing radiotherapy. Clinicopathological characteristics and clinical outcome data were collected from the prospectively maintained database at the West of Scotland Beatson Cancer Institute between January 2009 and February 2017. Patients were followed up until death or 1st of October 2019, which was used as the censor date. In total, 662 patients with lung cancer, who received radiotherapy, were identified. Of those, 13 patients with stage II disease were excluded since they did not have advanced disease. One hundred seventeen patients received radiotherapy with radical intent, and 526 with palliative intent. This study was approved by the Health Research Authority Ethics Committee (17/NW/0190) of Greater Glasgow and Clyde NHS Health Board.

The Eastern Cooperative Oncology Group (ECOG) score was used to predict patients' performance status. Serum concentrations of inflammatory markers were measured at two time points: baseline and 3 months. The modified Glasgow Prognostic score (mGPS) was calculated from a combination of CRP and albumin, and a neutrophil-to-mphocyte ratio (NLR) >3 was considered raised (Douglas & McMillan, 2014).

Clinicopathological characteristics

Each NSCLC patient's data, including CRP, NLR, NLS, PLR, PLS, LMR, LMS, NPS, CAR, and mGPS, were extracted from the database (Table 6-1).

Statistical analysis

Categorical variables were compared using the square test. The time between the date of initial CT and death from any cause was used to define overall survival (OS). Survival data were analyzed using univariate Cox regression. ECOG, mGPS, and NLR were used as categorical variables and analyzed using Cox proportional hazards regression. Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 29.0, SPSS Inc., Chicago, IL, USA). For non-normally distributed data, the data were presented as median and range (minimum and maximum). The median overall survival was 12 months, the median duration of follow-up was 18 months, and the mortality rate was 98%.

6.3 Results

Out of 662 patients with advanced lung cancer, 535 patients had advanced non-small cell lung cancer NSCLC. The median CRP concentration did not differ significantly with age or sex, but was higher in patients with poorer performance status ($p<0.001$, Table 6-2). The median CRP varied according to NLR ($p<0.001$), NLS ($p<0.001$), PLR ($p<0.001$), PLS ($p<0.001$), LMR ($p<0.001$), LMS ($p<0.01$), NPS ($p<0.001$), mGPS ($p<0.001$), and CAR ($p<0.001$). The baseline median CRP for mGPS was below 10 mg/L, whereas for NLR, NLS, PLR, PLS, LMR, LMS, and NPS, the baseline median values were 15 mg/L, 17 mg/L, 15 mg/L, 19 mg/L, 21 mg/L, 18 mg/L, and 17 mg/L, respectively.

The greatest range in median CRP was observed in CAR, with a >10-fold higher median CRP concentration as the score or ratio increased.

Most patients were aged >65 years (69%), male (52%), and of good performance status (62%). Most patients had a systemic inflammatory response as evidenced by NLR > 3 (64%), NLS>0 (62%), PLR >150 (63%), PLS (65%), LMR <2.4 (52%), LMS>0 (69%), NPS>0 (55%), mGPS>0 (74%), and CAR>0.2 (79%) (Table 6-3). The prognostic value of clinical characteristics and systemic inflammation-based ratios and scores is shown in Table 6-3. There were significant association between ECOG-PS (<0.001), NLR ($p<0.001$), NLS ($p<0.001$), PLR ($p=0.07$), PLS ($p<0.01$), LMR ($p=0.09$), LMS ($p<0.01$), NPS ($p<0.001$), CAR ($p<0.001$), mGPS ($p<0.001$) and overall survival.

The relationships between CRP concentrations and NLR, PLR, and LMR are shown in Figures 6-1a, 6-1b, and 6-1c (R^2= 0.062, 0.027, and 0.033), respectively. From the regression lines in these figures, a CRP of 10 mg/L was equivalent to a threshold of NLR of 7, PLR of 250, LMR of 0.9.

6.4 Discussion:

The results of the present study showed that a variety of systemic inflammation-based scores, whether cumulative or ratio-based, have prognostic value in patients with NSCLC. However, to understand what these inflammatory markers are capturing, they were all referenced to a CRP concentration. It was of interest that NLR, NLS, PLR, PLS, LMR, LMS, and NPS at the lowest threshold had a significant elevation of CRP (above the normal range, >10mg/l). Therefore, although these ratios and scores have prognostic value, they capture different levels of systemic inflammation than CRP-based scores such as mGPS and CAR. These results have implications for the continued use of cumulative scores or ratios based on a differential white cell count.

In the present study, it was shown for the first time in an unselected cohort that even cumulative scores based on the normal range of components of a differential white cell count had CRP concentrations above the normal range. These results suggest that the components of a differential white cell count are relatively insensitive to a systemic inflammatory response. Therefore, given their greater sensitivity and dynamic range, CRP-based ratios and scores are preferred over those based on components of a differential white cell count. Of the composite ratios and cumulative scores based on the components of a differential white cell count used to predict likely outcome in patients with cancer, the most commonly used is the NLR and has been the subject of many systematic reviews and meta-analyses (Douglas & McMillan, 2014). However, the thresholds for a low and high NLR vary widely. Therefore, in the present study, the threshold used for a normal NLR was <3, slightly raised 3-5, and highly raised >5, based on the literature. An NLR<3 was associated with a median CRP of 15 mg/L, and an NLR>5 was associated with a median CRP of 66 mg/L, a 4-fold increase in CRP concentration relative to the ratio. Among CRP-based cumulative scores used to predict the likely outcome in patients with cancer, mGPS is the most commonly used, and its thresholds have been established (Watt et al., 2015). A mGPS=0 was associated with a median CRP of 5mg/l, and a mGPS=2 was associated with a median CRP of 64mg/l, a 12-fold increase in CRP concentrations over the score. These specific examples illustrate the greater sensitivity and range of the based score compared with a differential white cell ratio. Furthermore, it is clear from Figures 6-1a and 6-1c that a simple conversion between differential white cell count-based measures and CRP-based measures is not reliable. In contrast, CRP is highly correlated with albumin (Figure 6-1d).

Limitations include retrospective data, moderate sample size, and the inability to account for fluctuations in inflammatory markers over time or for infection-related confounding. The implications of this chapter are significant, reinforcing CRP-based scores as superior prognostic markers and supporting the clinical use of CRP as a primary indicator for risk stratification, outcome prediction, and the development of streamlined prognostic pathways in NSCLC.

6.5 Conclusion

Compared with white cell markers, mGPS and CAR appear to be more reliable, prevalent, and prognostic markers.

Table 6- 1: Systemic inflammation-based prognostic ratios and scores:

Neutrophil lymphocyte ratio (NLR) Neutrophil count: lymphocyte count Neutrophil count: lymphocyte count Neutrophil count: lymphocyte count	 ≤ 3 3–5 >5
Neutrophil lymphocyte score (NLS) Neutrophil count ≤ 7.5×10^9/l and lymphocyte count ≥ 1.5×10^9/l Neutrophil count > 7.5×10^9/l and lymphocyte count ≥ 1.5×10^9/l Neutrophil count ≤ 7.5×10^9/l and lymphocyte count < 1.5×10^9/l Neutrophil count > 7.5×10^9/l and lymphocyte count < 1.5×10^9/l	 0 1 1 2
Platelet lymphocyte ratio (PLR): Platelet count: lymphocyte count Platelet count: lymphocyte count	 ≤ 150 >150
Platelet lymphocyte score (PLS) Platelet count ≤ 400×10^9/l and lymphocyte count ≥ 1.5×10^9/l Platelet count > 400×10^9/l and lymphocyte count ≥ 1.5×10^9/l Platelet count ≤ 400×10^9/l and lymphocyte count < 1.5×10^9/l Platelet count > 400×10^9/l and lymphocyte count < 1.5×10^9/l	 0 1 1 2
Lymphocyte monocyte ratio (LMR) lymphocyte count: monocyte count lymphocyte count: monocyte count	n ≥ 2.40 < 2.40
Lymphocyte monocyte score (LMS) Lymphocyte count ≥ 1.5×10^9/l and monocyte count ≤ 0.80×10^9/l	 0

Lymphocyte count < 1.5×10^9/l and monocyte count ≤ 0.80×10^9/l	1
Lymphocyte count > 1.5×10^9/l and monocyte count > 0.80×10^9/l	1
Lymphocyte count < 1.5×10^9/l and monocyte count > 0.80×10^9/l	2
Neutrophil platelet score (NPS)	
Neutrophil count ≤ 7.5×10^9/l and platelet count ≤ 400×10^9/l	0
Neutrophil count > 7.5×10^9/l and platelet count ≤ 400×10^9/l	1
Neutrophil count ≤ 7.5×10^9/l and platelet count > 400×10^9/l	1
Neutrophil count > 7.5×10^9/l and platelet count > 400×10^9/l	2
C-reactive protein albumin ratio (CAR)	
C-reactive protein: albumin	
C-reactive protein: albumin	≤ 0.2
C-reactive protein: albumin	0.2-0.4
	>0.2
Modified Glasgow Prognostic Score (mGPS)	
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

Table 6- 2: Comparison of systemic inflammation-based prognostic ratios and scores in patients with advanced NSCLC

Variables		n (%)	CRP median (range)	P-value
Age group	<65	154 (29)	33 (1-431)	0.285
	65-74	206 (38)	31 (1-357)	
	>74	175 (3)	26 (1-309)	
Sex	Female	256 (48)	27 (1-287)	0.233
	Male	279 (52)	33 (1-431)	
ECOG performance status	0 – 1	329 (62)	23 (1-358)	<0.001
	2	146 (27)	37 (1-357)	
	3	60 (11)	45 (1-431)	
TNM	0 / I	-	-	0.061
	II	14(3)	36(4-169)	
	III	216(40)	27(1-358)	
	IIII	305(57)	32(1-431)	
Neutrophil lymphocyte ratio (NLR)	<3	186 (36)	15 (1-358)	<0.001
	3-5	143 (28)	38 (1-308)	
	>5	182 (36)	58 (1-431)	
Neutrophil lymphocyte score (NLS)	0	200 (39)	17 (1-358)	<0.001
	1	221 (43)	40(1-431)	
	2	90 (18)	67 (1-309)	
Platelet lymphocyte ratio (PLR)	<=150	168 (37)	15 (1-358)	<0.001
	>150	289 (63)	44 (1-431)	
	0	207(45)	19 (1-431)	<0.001
	1	215 (47)	45 (1-309)	

Platelet lymphocyte score (PLS)	2	35 (8)	67 (1-264)	
Lymphocyte monocyte ratio (LMR)	>=2.40	234 (46)	21(1-358)	<0.001
	<2.40	275(54)	49 (1-431)	
Lymphocyte monocyte score (LMS)	0	164 (33)	18 (1-431)	<0.001
	1	272 (54)	37 (1-358)	
	2	64 (13)	60 (1-264)	
Neutrophil platelet score (NPS)	0	244 (53)	17 (1-358)	<0.001
	1	153 (34)	49 (1-431)	
	2	60 (13)	68 (4-308)	
C-reactive protein albumin ratio (CAR)	<0.2	374 (70)	15 (1-71)	<0.001
	0.2 -0.4	92 (17)	86(50-139)	
	> 0.4	69 (13)	185(84-431)	
Modified Glasgow Prognostic Score (mGPS)	0	-26	5 (1-10)	<0.001
	1	142 (26)	31 (2-286)	
	2	255 (48)	64 (6-431)	

*Data presented in numbers (percentages). *A P-value of ≤ 0.05 of chi-square was considered significant.

Table 6- 3: Prognostic value of clinical characteristics and systemic inflammation-based

ratios and scores in patients with advanced NSCLC.

Variables		N (%)	HR (95%CI)	P-value
Age group	<65	154 (29)	0.91 (0.86-1.02)	0.104
	65-74	206 (38)		
	>74	175 (33)		
Sex	Female	256 (48)	1.02 (0.86-1.21)	0.803
	Male	279 (52)		
ECOG performance status	0 – 1	329 (62)	1.26 (1.11-1.44)	<0.001
	2	146 (27)		
	3	60 (11)		
Neutrophil lymphocyte ratio (NLR)	<3	186 (36)	1.21 (1.09-1.34)	<0.001
	3-5	143 (28)		
	>5	182 (36)		
Neutrophil lymphocyte score (NLS)	0	200 (39)	1.27 (1.12-1.44)	<0.001
	1	221 (43)		
	2	90 (18)		
Platelet lymphocyte ratio (PLR)	<=150	168 (37)	1.30 (1.07-1.58)	0.007
	>150	289 (63)		
Platelet lymphocyte score (PLS)	0	207 (45)	1.33 (1.14-1.56)	<0.001
	1	215 (47)		
	2	35(8)		
Lymphocyte monocyte ratio (LMR)	>=2.40	234 (46)	1.16 (0.97-1.39)	0.096
	<2.40	275 (54)		
Lymphocyte monocyte score (LMS)	0	164 (33)	1.15(1.09-1.32)	<0.001
	1	272 (54)		
	2	64 (13)		
	0	244 (53)	1.26 (1.11-1.44)	<0.001
	1	153 (34)		

Neutrophil platelet score (NPS)	2	60 (13)		
C-reactive protein albumin ratio (CAR)	<0.2	374(73)	1.09 (0.93-1.10)	<0.001
	0.2 -0.4	68(13)		
	> 0.4	69(14)		
Modified Glasgow Prognostic Score (mGPS)	0	138 (25)	1.30 (1.17-1.44)	<0.001
	1	142 (27)		
	2	255 (48)		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower; if it contains 1.00, the result is not statistically significant.

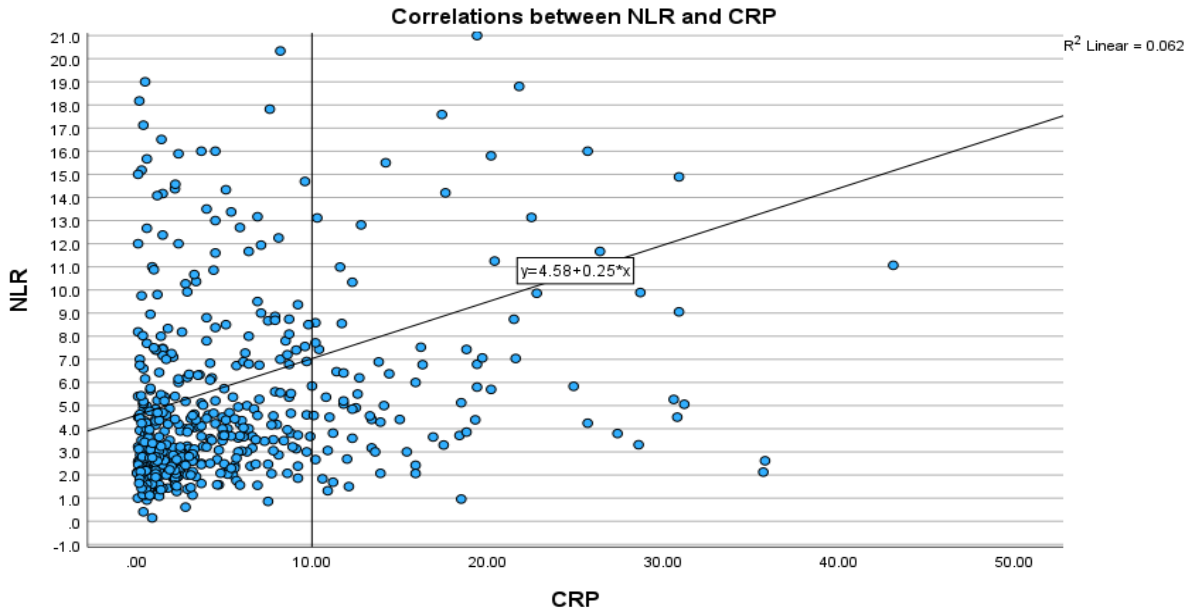

Figure 6- 1a: A scatter plot of the correlations between Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP). (NSCLC).

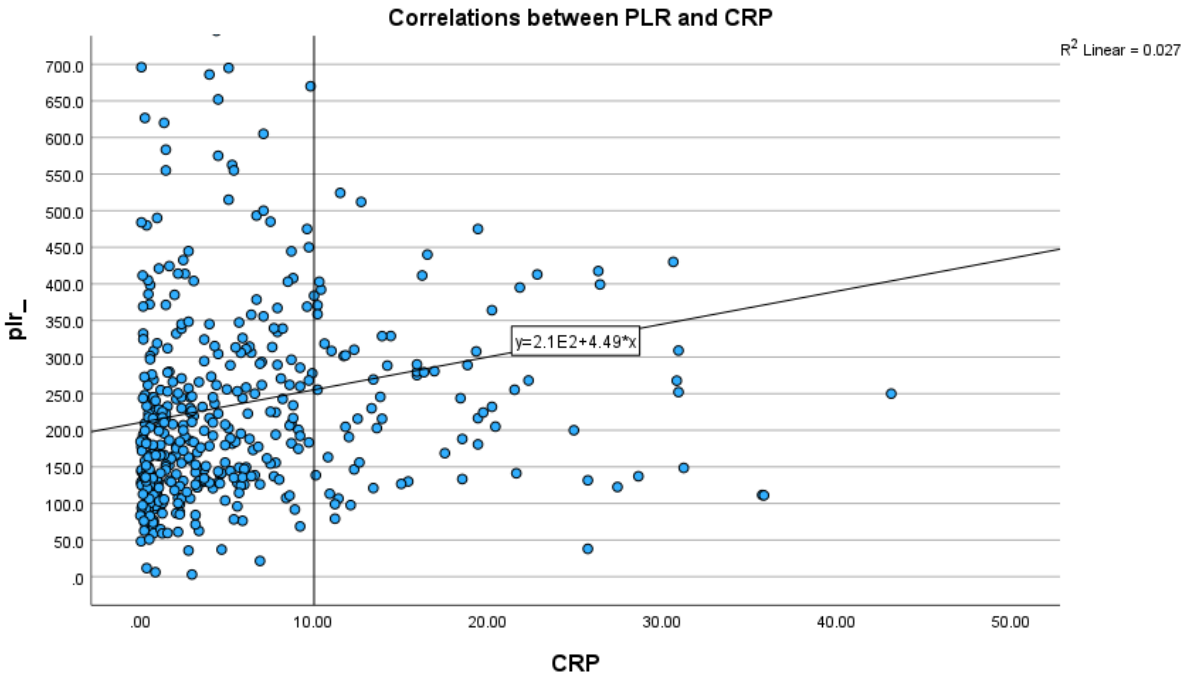

Figure 6-1b: A scatter plot of the correlations between Platelet-to-Lymphocyte Ratio (PLR) and C-Reactive Protein (CRP). (NSCLC).

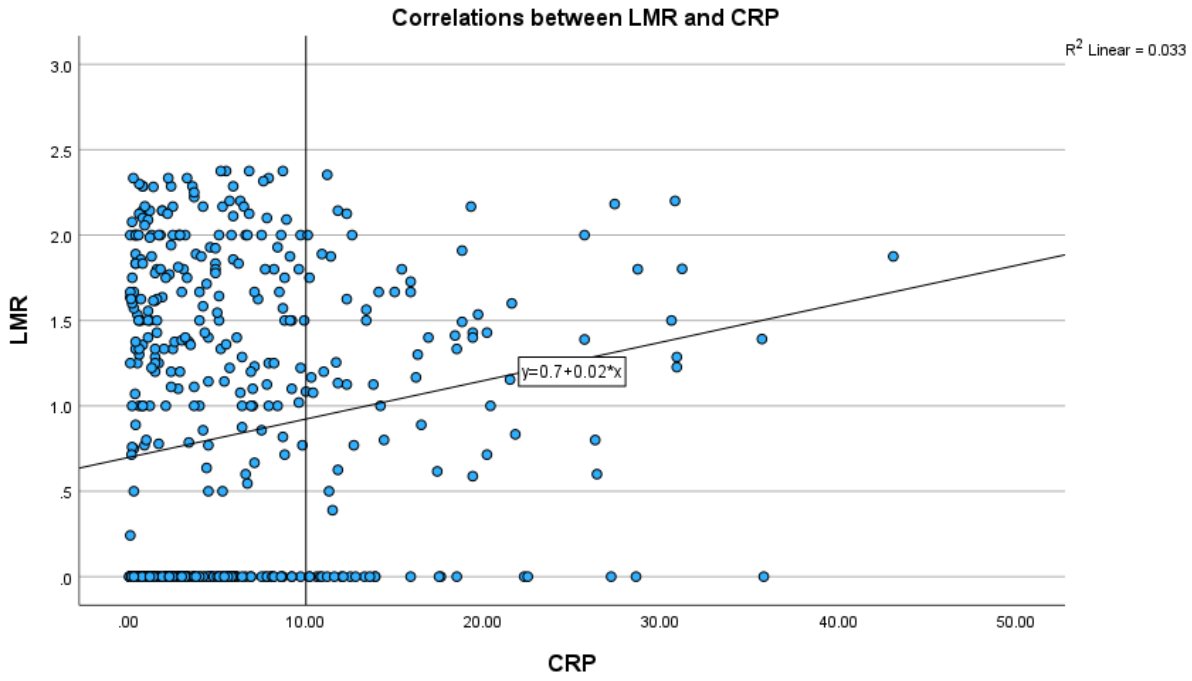

Figure 6-1c: A scatter plot of the correlations between Lymphocyte-to-Monocyte Ratio (LMR) and C-Reactive Protein (CRP). (NSCLC).

Chapter 7, The prevalence and prognostic value of systemic inflammatory markers in patients with oesophagogastric cancer undergoing neoadjuvant chemotherapy. A C-reactive protein-based comparison

7.1 Introduction

About 1.5 million people worldwide have oesophagogastric cancer each year, which encompasses malignancies of the stomach, esophagus, and oesophagogastric junction (Bray et al., 2018). With over 9,400 new cases each year, oesophageal cancer ranks as the 14th most frequent cancer in the UK and accounts for 2% of all new cases. With 2,900 new cases, it ranks as the 16th most prevalent cancer in women and the 9th most common in men (6,500 new cases). People aged 85-89 had the highest incidence rates (Bray et al., 2018). The intricacy of oesophagogastric cancer is highlighted by its multiple causes, which include environmental factors, genetic predispositions, and lifestyle factors, including smoking and drinking (Dong & Thrift, 2017).

For oesophagogastric cancer, surgery is acknowledged as the best therapeutic option; the highest survival rates are frequently achieved with radical surgical resection. Typically, these patients have one of two treatment options: chemotherapy followed by surgery and then more chemotherapy, or chemotherapy and radiation followed by surgery and no further treatment (Ling et al., 2023). However, not every patient will benefit from surgery, particularly if they have advanced oesophagogastric cancer or have significant comorbidities (Ling et al., 2023).

In clinical practice, neoadjuvant therapy has grown more common as a primary treatment for oesophagogastric cancer (Ling et al., 2023). Compared with neoadjuvant chemotherapy (NAC), neoadjuvant chemoradiotherapy offers several safety and effectiveness benefits for patients with resectable gastric cancer (Ling et al., 2023). Consequently, NAC has considerable promise as a therapeutic intervention for respectable gastric tumours (Ling et al., 2023). The strategy entails giving chemotherapy or radiation therapy before surgical excision to shrink the tumour and increase the possibility of total resection, which raises the chances of overall survival (Debela et al., 2021). Specifically, early targeting micrometastases and reduction of tumour load enable efficient disease downstaging and, hence, attempts at curative surgical resection (Debela et al., 2021).

In patients with oesophageal-gastric cancer, systemic inflammatory markers have become important prognostic indicators since systemic inflammation may contribute to tumour growth and metastasis through numerous routes (Greten & Grivennikov, 2019). For example, the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein-to-albumin ratio (CAR) have been validated as useful prognostic markers for oesophageal cancer. NLR was the only inflammation-based prognostic biomarker linked to histopathological stage and to poor

disease-free survival and overall survival following potentially curative oesophagectomy for cancer.

The present study aimed to examine the prevalence and prognostic value of systemic inflammatory markers in patients with oesophagogastric cancer undergoing neoadjuvant chemotherapy. A C-reactive protein-based comparison (n=335) and to compare the results with the results from previous chapter.

7.2 Patient and methods

A retrospective cohort study of patients with oesophagogastric cancer between 1 January 2010 and 31 December 2015, from six regional health boards, was identified from a prospectively maintained database of the West of Scotland and South-East of Scotland cancer networks that included patients undergoing chemotherapy.

Clinicopathological characteristics and clinical outcome data were collected from this database, and follow-up was for at least 5 years from the date of initiation of neoadjuvant treatment.

All patients with locally advanced (T3-4) or at least N1 disease, who received neoadjuvant chemotherapy with different combinations, with a plan of subsequent surgical resection. The most frequently used regimens were cisplatin + 5-fluorouracil (ECF), or combinations of epirubicin with cisplatin + 5-fluorouracil, cisplatin + capecitabine (ECX), or oxaliplatin + capecitabine (EOX).

Statistical Analysis

Categorical variables were compared using the chi-square test. For non-normally distributed data, the data were presented as median and range (minimum and maximum). The time between the date of initial CT and death from any cause was used to define overall survival (OS). Survival data were analysed using univariate Cox regression analysis. ECOG, mGPS, and NLR were used as categorical variables and analysed using categorical Cox regression survival analysis. Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 29.0, SPSS Inc., Chicago, IL, USA).

7.3 Results

In total, 335 patients with OG cancer were included (Table 7-1); most patients were aged < 65 years old (47%), male (71%), and of reliable performance status (79%). Most patients had low inflammatory markers: NLR < 3 (62%), NLS 0 (63%), PLR > 150 (55%), PLS 0 (61%). LMR >2.40 (68%), LMS 0 (55%). NPS (80%), CAR <0.2 (57%), and mGPS 0 (71%).

For TNM staging, 22 patients (8%) were classified as stage 0 and 49 (19%) as stage I, with a CRP median of 5 (range 1–25). Stage II included 107 patients (40%) with a CRP median of 4 (range 1–109), stage III included 55 patients (21%) with a CRP median of 6 (range 1–136), and stage IV included 31 patients (12%) with a CRP median of 3 (range 1–95). Of 183 patients (62.5%), 110 (37.5%) did not receive adjuvant chemotherapy. Regarding the Duke's grading system, eight patients (1.9%) achieved complete regression, while grade A included 105 patients (25.2%), grade B included 152 patients (36.5%), and grade C included 151 patients (36.3%) (Table 7-1).

The median CRP concentration did not significantly differ with age, sex, or ECOG-PS (p-values = 0.226, 0.128, and 0.526, respectively). The median CRP concentration varied according to NLR ($p<0.01$), NLS ($p<0.01$), LMR ($p<0.05$), LMS ($p<0.001$), NPS ($p<0.001$), CAR ($p<0.001$), and mGPS ($p<0.001$). The baseline median CRP for all ratios and scores was below 10 mg/L. The greatest range in median CRP was observed for NPS, mGPS, and CAR, with median CRP concentrations approximately 10-fold higher at higher scores and ratios (Table 7-2).

The relationship between the clinicopathological variables and survival in patients with oesophagogastric cancer is shown in Table 7-2. Age ($p<0.05$), sex ($p<0.05$), and performance status ($p<0.05$) were significantly associated with overall survival. Of the composite ratios and cumulative scores, only LMR ($p<0.01$) and mGPS ($p<0.05$) were significantly associated with overall survival (Table 7-2).

The relationship between CRP concentration and NLR, PLR, and LMR is shown in Figures 7-1a to 7-1c.

From the regression line in Figure 7-1a, a CRP of 10mg/l was equivalent to a threshold for NLR of 3.2, to a threshold for PLR of 170 (Figure 7-1b), and to a threshold for LMR of 3.4 (Figure 7-1c).

7.4 Discussion

The present study examined the relationships between systemic inflammatory composite ratios and cumulative scores, such as NLR, NLS, PLR, PLS, LMR, LMS, and NPS, in patients with operable oesophagogastric cancer. It showed that there was a similar prevalence of systemic inflammation across the various ratios/scores, and that the lowest ratio or score had a CRP concentration below the 10 mg/L threshold; this contrasted with that reported in the previous chapter for patients with advanced NSCLC, where the lowest ratio or score had a CRP concentration above 10 mg/L. Furthermore, not all composite ratios or cumulative scores had prognostic value in the present study, unlike in the previous chapter. Taken together, these results suggest that the relationships between components of a differential white cell count, the acute-phase protein CRP, and survival may differ according to tumour type and stage.

The basis for the difference in the relationship between components of a differential white cell count and the acute-phase protein CRP between the tumour types is unclear. However, the previous NSCLC cohort, compared with the present OG cohort, had more aggressive disease (TNM stage), poorer host fitness (ECOG-PS), and greater systemic inflammation, all of which may have impacted this relationship. With reference to the latter, it may be that the relationship between components of a differential white cell count and the acute-phase protein CRP breaks down at elevated levels of systemic inflammation (Watt et al., 2015).

Irrespective, to better understand the relationship between components of a differential white cell count and the acute phase protein CRP, it will be important to study this relationship across different tumour types and to control for tumour stage, performance status, and the magnitude of the systemic inflammatory response.

The basis for the differences in the relationships between components of a differential white cell count, the acute phase protein CRP, and survival between the tumour types is unclear. In the present study, compared with the NSCLC cohort, the magnitude of the systemic inflammatory response was lower. The majority of patients are not considered systemically inflamed. Therefore, the composite ratios and cumulative scores based on the differential white cell count may have lacked sensitivity to survival compared with the CRP-based ratios and scores (McGovern et al., 2024b).

The present results have implications for the use of systemic inflammation-based scores to predict survival across different tumour types, since CRP-based prognostic scores are more sensitive and reliable measures of the magnitude of cancer-related inflammation. Indeed, the measurement of CRP is now recommended by the Global Initiative for Malnutrition for monitoring inflammation in malnutrition (Roxburgh & McMillan, 2010). The level of inflammation (i.e., CRP) in patients with cancer is several-fold greater than that reported in

other chronic disease states, for example, cardiovascular disease (Bradley et al., 2024), and therefore the threshold is set at > 10 mg/l, well above normal patient and day-to-day variation (<3 mg/l). The measurement of CRP in routine clinical laboratories is well standardised (unlike most cytokines that are not measured routinely) and therefore allows comparison of chronic disease (including cancer) cohorts at a national and international level (McGovern et al., 2024b). Furthermore, CRP has been used extensively as an outcome marker in cardiovascular disease trials and can therefore be considered an important outcome marker in patients with cancer. Therefore, measurement of CRP can be considered both as an inclusion criterion and as an outcome marker in future studies of anti-inflammatory treatments in patients with cancer.

Limitations include heterogeneity in chemotherapy regimens, small subgroup sizes, and a lack of post-treatment longitudinal inflammatory data. Nonetheless, the findings strengthen evidence that systemic inflammation is common and prognostically relevant in OGC, and they support integrating CRP-based scoring into preoperative risk assessment and therapeutic planning for patients undergoing neoadjuvant treatment.

7.5 Conclusion

In the present study of patients with operable oesophagogastric cancer, there was a similar prevalence of systemic inflammation across the various ratios/scores, and the lowest ratio, or score, had a CRP concentration below the 10mg/l threshold; this contrasted with that previously reported in patients with advanced NSCLC, where the lowest ratio or score had a CRP concentration above this threshold and not all composite ratios or cumulative scores had prognostic value. The relationships between components of differential white cell counts, the acute-phase protein CRP, and survival may differ according to tumour type and stage.

Table 7- 1: Comparison of systemic inflammation-based prognostic ratios and scores in patients with oesophagogastric cancer pre-chemotherapy.

Variables		**n (%)**	**CRP median (range)**	**P-value**
Age group	<65	156(47)	4(1-137)	0.226
	65-74	137(41)	6(1-110)	
	>74	41(12)	7(1-109)	
Sex	Female	97(29)	4(1-137)	0.128
	Male	238(71)	7(1-136)	
ECOG performance status	0	263(79)	5(1-137)	0.526
	1	54(16)	8(1-136)	
	2	18(5)	5(1-52)	
TNM	0 / I	22(8) / 49(19)	5(1-25)	0.787
	II	107(40)	4(1-109)	
	III	55(21)	6(1-136)	
	IV	31(12)	3(1-95)	
Surgery	Yes	299 (89)	4(1-109)	<0.001
	No	36(11)	10(1-137)	
Adjuvant Chemotherapy	Yes	110(37)	4(1-95)	0.062
	No	183 (63)	4(1-109)	
Neutrophil lymphocyte ratio (NLR)	<3	183(62)	4(1-110)	0.002
	3-5	79(27)	6(1-137)	
	>5	31(11)	16(1-82)	
Neutrophil lymphocyte score (NLS)	0	186(63)	3(1-95)	0.004
	1	98(33)	8(1-137)	
	2	11(4)	9(1-77)	
Platelet lymphocyte ratio (PLR)	<=150	134(45)	5(1-136)	0.477
	>150	161(55)	5(1-137)	
Platelet lymphocyte score (PLS)	0	179(61)	4(1-136)	0.168
	1	104(35)	7(1-137)	
	2	12(4)	4(1-77)	

Lymphocyte monocyte ratio (LMR)	>=2.40	199(68)	4(1-136)	0.046
	<2.40	96(32)	7(1-137)	
Lymphocyte monocyte score (LMS)	0	159(55)	3(1-110)	<0.001
	1	123(42)	7(1-137)	
	2	9(3)	17(4-77)	
Neutrophil platelet score (NPS)	0	257(88)	4(1-137)	<0.001
	1	26(9)	11(1-136)	
	2	10(3)	53(4-82)	
C-reactive protein albumin ratio (CAR)	<0.2	132(57)	3(1-8)	<0.001
	0.2 -0.4	41(18)	9(7-15)	
	> 0.4	57(25)	26(14-137)	
Modified Glasgow Prognostic Score (mGPS)	0	207(71)	3(1-10)	<0.001
	1	47(16)	19(10-109)	
	2	37(13)	37(10-137)	

*Data presented in numbers (percentages). *A P-value of ≤ 0.05 of chi-square was considered significant.

Table 7- 2: Comparison of systemic inflammation-based prognostic ratios and scores in patients with oesophagogastric cancer pre-chemotherapy.

Variables		n (%)	HR (95%CI)	P-value
Age group	<65	156 (47)	1.12(0.89-1.39)	0.034
	65-74	137 (41)		
	>74	41 (12)		
Sex	Female	97 (29)	1.44(1.03-2.01)	0.033
	Male	238 (71)		
ECOG performance status	0	263 (79)	1.33(1.03-1.71)	0.027
	1	54 (16)		
	2	18(5)		
TNM	0/1	22(8)/49(19)	1.75(1.48 – 2.07)	<0.001
	II	107(40)		
	III	55(21)		
	IV	31(12)		
Surgery	Yes	299(89)	0.15 (0.1 – 0. 22)	<0.001
	No	36(12)		
Adjuvant Chemotherapy	Yes	110(37)	0.763(0.55 – 1.59)	0.106
	No	183(63		
Neutrophil lymphocyte ratio (NLR)	<3	183 (62)	1.22(0.97-1.53)	0.086
	3-5	79 (27)		
	>5	31 (11)		
Neutrophil lymphocyte score (NLS)	0	186 (63)	1.22(0.93-1.60)	0.144
	1	98(33)		
	2	11 (4)		
Platelet lymphocyte ratio (PLR)	<=150	134 (45)	1.31(0.97-1.78)	0.077
	>150	161(55)		
Platelet lymphocyte score (PLS)	0	179(61)	1.01(0.77-1.33)	0.93
	1	104 (35)		
	2	12(4)		
	>=2.40	199 (68)	1.51(1.11-2.06)	0.009

Lymphocyte monocyte ratio (LMR)	<2.40	96(32)		
Lymphocyte monocyte score (LMS)	0	159(55)	1.28(0.98-1.67)	0.069
	1	123 (42)		
	2	9(3)		
Neutrophil platelet score (NPS)	0	257 (88)	1.25(0.92-1.7)	0.148
	1	26 (9)		
	2	60 (3)		
C-reactive protein albumin ratio (CAR)	<0.2	132 (57)	1.08(0.89-1.30)	0.461
	0.2 -0.4	41(18)		
	> 0.4	57 (25)		
Modified Glasgow Prognostic Score (mGPS)	0	207(71)	1.24(1.01-1.52)	0.042
	1	47 (16)		
	2	37 (13)		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower.

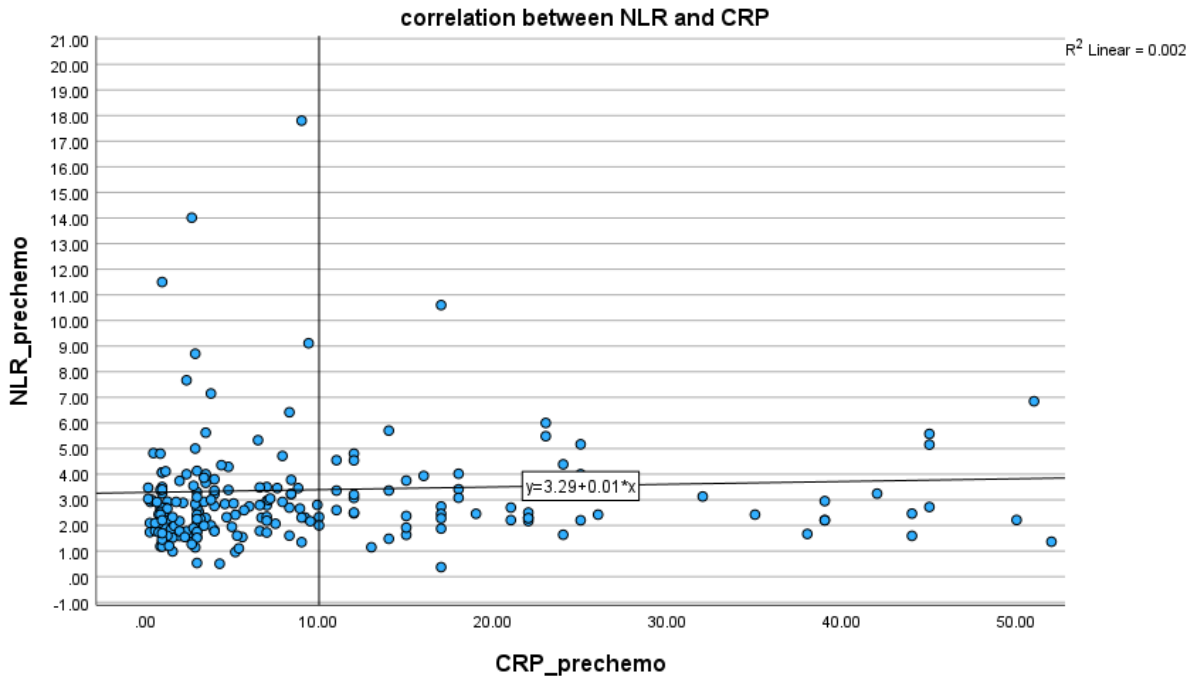

Figure 7- 1a: A scatter plot of the correlations between Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP). (OGC).

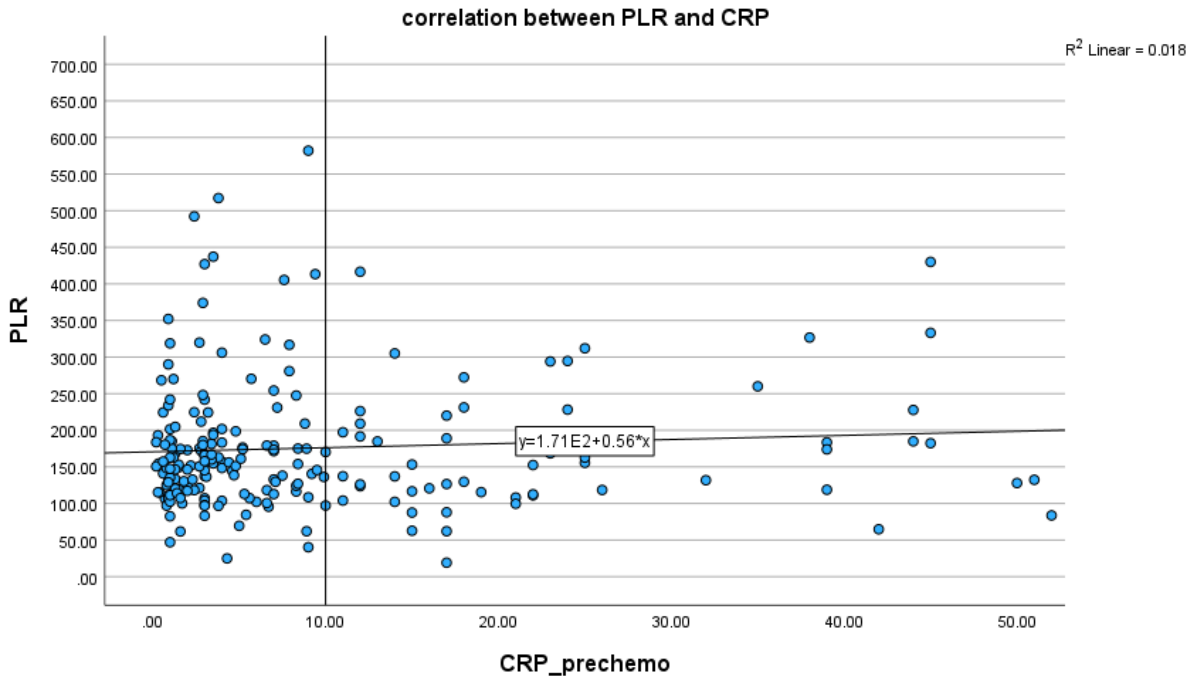

Figure 7-1b. A scatter plot of the correlations between Platelet-to-Lymphocyte Ratio (PLR) and C-Reactive Protein (CRP). (OGC).

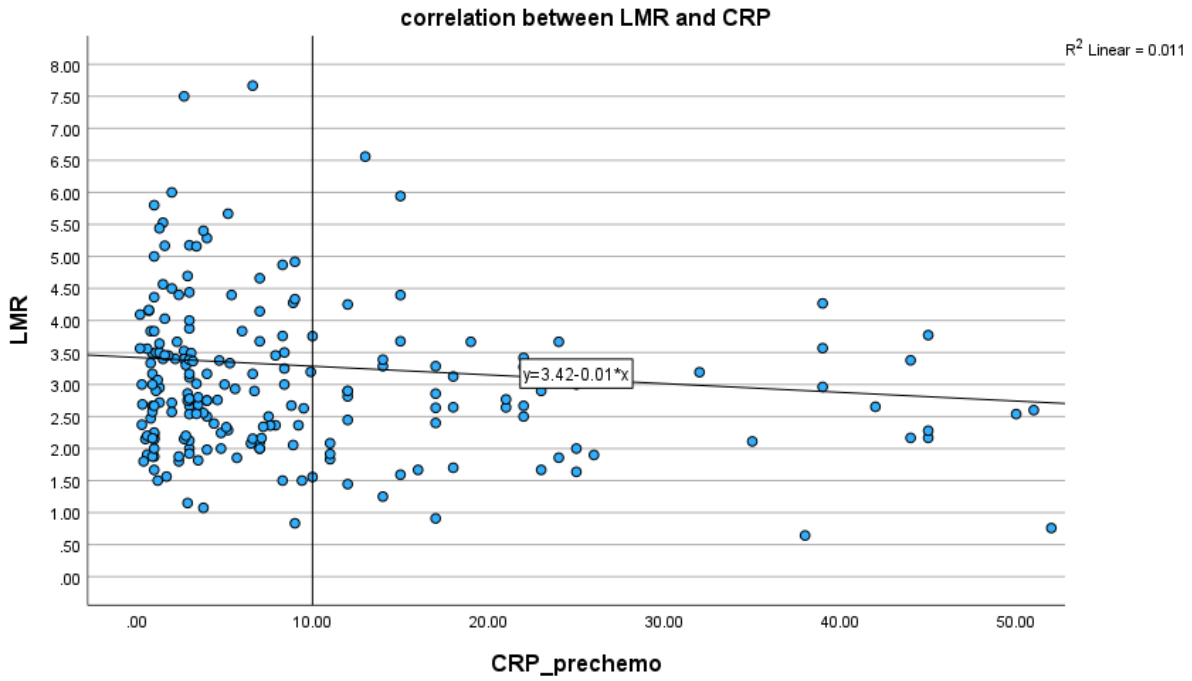

Figure 7- 1c: A scatter plot of the correlations between Lymphocyte-to-Monocyte Ratio (LMR) and C-Reactive Protein (CRP). (OGC).

Chapter 8, Evaluation of systemic inflammatory ratios and scores for prognosis in patients with primary operable colorectal cancer: A C-reactive protein-based comparison

8.1 Introduction

Globally, approximately 10% of all cancer cases are colorectal cancer (CRC), making it the second most prevalent cause of cancer-related deaths (World Health Organization, 2023). There were approximately 1.93 million new cases diagnosed and 0.94 million deaths in 2020 (Bray et al., 2018). In the UK, CRC is the second most prevalent cause of cancer-related fatalities and the fourth most common type of cancer, and therefore is a serious public health concern (Shrotriya et al., 2018).

Due to the advancements in screening and treatment modalities in primary operable and advanced inoperable CRC, the survival outcomes for patients with colorectal cancer have improved in recent years, especially rectal cancer (Conces & Mahipal, 2024; Huang et al., 2020). However, each person's reaction to surgery/oncology may differ independently of TNM stage; therefore, finding prognostic/predictive biomarkers that aid in customising treatment plans is required (Koike et al., 2008).

The liver produces acute-phase proteins, in particular C-reactive protein (CRP), in response to injury/inflammation. In patients with colorectal cancer, elevated CRP levels (>10mg/l) are frequently a sign of an underlying systemic inflammatory state that can affect tumour/ host behaviour and subsequently produce poorer outcomes (Koike et al., 2008). Systemic inflammation, driven by pro-inflammatory cytokines such as IL-6, supports tumour progression in several ways, including fostering angiogenesis, accelerating cell proliferation, and enabling immune evasion, thereby making the host's inflammatory response a crucial factor in predicting prognosis (Nishida & Andoh, 2025). Several ratios/scores based on CRP and whole-blood count measures, particularly neutrophils, have been proposed as prognostic and/or predictive tools (Ross D. Dolan et al., 2017). The most commonly researched indicators of how the body balances pro-inflammatory and anti-inflammatory responses are the neutrophil-to-lymphocyte ratio (NLR) and the modified Glasgow Prognostic Score (mGPS). The higher the ratio or score, the poorer the survival or treatment response.

In the previous chapters, we examined the prognostic value of various ratios and scores in advanced NSCLC and operable oesophagogastric cancer, and related these to CRP levels and

overall survival (OS). In advanced NSCLC, a normal ratio/score was associated with CRP values above the normal range and better OS. In contrast, in operable oesophagogastric cancer, a normal ratio/score was associated with CRP values within the normal range and better OS. It remains unclear which type of inflammatory biomarker—in either cell form (NLR) or protein form (mGPS/CRP)—provides the most reliable prognostic information for primary operable colorectal cancer compared to oesophagogastric and lung cancers.

This chapter hypothesised that systemic inflammatory ratios and scores would have distinct prognostic abilities in primary operable colorectal cancer, with CRP-based measures likely outperforming blood-cell-derived ratios.

The basis for this discrepancy between CRP-based and white cell-based ratios/scores was unclear, and therefore, the present study aimed to examine these relationships in another primary operable cancer, colorectal cancer. A C-reactive protein-based comparison (n=446).

8.2 Patient and methods

A retrospective cohort study of patients with colorectal cancer who underwent potentially curative resections within the National Health Service (NHS) Greater Glasgow and Clyde, between April 2008 and 2018, using a prospectively maintained database. Patients who underwent pre-operative assessment and had TNM stage I-III were included.

Clinicopathological characteristic

Routine demographic details, such as age, sex, and TNM stage, were collected and grouped. For example, age was grouped into <65, 65-74, and >74.

The date of the last follow-up or last review of electronic records was 21st March 2023, which served as the censor date.

Statistical analysis

Categorical variables were compared using the chi-square test. For non-normally distributed data, the data were presented as median and range (minimum and maximum). The time between the date of initial CT and death from any cause was used to define overall survival (OS). Survival data were analysed using univariate Cox regression analysis. ECOG, mGPS, and NLR were used as categorical variables and analysed using categorical Cox regression survival analysis. Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 29.0, SPSS Inc., Chicago, IL, USA).

8.3 Results

In total, 446 patients with colorectal cancer were included in the study (Table 8-1). Most patients were aged <65 years (43%), male (51%), and with superior performance status/low comorbidity (79%). Most patients had low inflammatory markers: NLR < 3 (53%), NLS 0 (52%), CAR < 0.2 (67%), and mGPS 0 (75%). The median follow-up was 78 months, and 31% of patients died during the follow-up.

For tumor site, 244 patients (54.7%) had colon cancer, while 202 patients (20.2%) had rectal cancer. Regarding TNM staging, 117 patients (26%) were classified as stage I with a CRP median of 3 (range 1–141), 160 patients (36%) were stage II with a CRP median of 5 (range 1–130), and 169 patients (38%) were stage III with a CRP median of 5 (range 1–235). A statistically significant difference in CRP levels was noted across TNM stages ($P < 0.001$). In the nonadjuvanted therapy group, 371 patients (83.9%) received no adjuvant treatment, while 71 patients (16.1%) did not (Table 8-1).

The median CRP concentration did not differ significantly with age or sex but did differ with TNM stage and American Society of Anesthesiologists (ASA) score ($p<0.01$; Table 8-1). The median CRP concentration varied significantly with NLR, NLS, CAR, and mGPS (all $p<0.001$). The baseline median CRP for all ratios and scores was below 10 mg/L. The greatest range in median CRP was observed for NLS, mGPS, and CAR, with median CRP concentrations more than doubling as scores and ratios increased.

The relationship between clinicopathological variables and survival in patients with colorectal cancer is shown in Table 8-2. Age ($p<0.01$), TNM ($p<0.001$), and ASA ($p<0.05$) were significantly associated with overall survival. Of the inflammatory markers, NLR ($p<0.05$), NLS ($p<0.01$), CAR ($p<0.01$), and mGPS ($p<0.01$).

The relationship between CRP concentration and NLR is shown in Figure 8-1. From the regression line in Figure 8-1, a CRP of 10mg/l was equivalent to a threshold for NLR of 3.2.

8.4 Discussion

The present study examined the relationship between systemic inflammatory composite ratios and cumulative scores, including NLR, NLS, CAR, and mGPS, in patients with operable colorectal cancer. It showed that there was a similar prevalence of systemic inflammation across the various ratios/scores, and that the lowest ratio or score had a CRP concentration below the 10 mg/L threshold; this contrasted with that reported in patients with advanced NSCLC (Chapter 6), where the lowest ratio or score was associated with a CRP concentration above 10 mg/L, but was consistent with that reported in operable OG cancer (Chapter 7). Taken together, these results provide further evidence that the relationships between components of a differential white cell count, the acute phase protein CRP, and survival may differ according to tumour type, stage of disease, and patient fitness.

To better understand the relationship between components of a differential white cell count and the acute-phase protein CRP, it will be important to examine this relationship across different tumour types and to control for tumour stage and patient fitness. Nevertheless, it was of interest that neither in advanced NSCLC (Chapter 6), operable OG (Chapter 7) cancer, nor operable CRC (Chapter 8) was TNM stage significantly associated with CRP concentrations. Similarly, poorer performance status/comorbidity was not consistently significantly associated with higher CRP concentrations. Therefore, tumour type would appear important in determining the magnitude of the systemic inflammatory response (CRP).

The basis for the difference in the magnitude of the relationship between components of a differential white cell count and the acute-phase protein CRP, and between tumour types, is unclear. In the present study, compared with the NSCLC cohort, the magnitude of the systemic inflammatory response was lower. The majority of patients are not considered systemically inflamed. Therefore, the composite ratios and cumulative scores based on the differential white cell count may have lacked sensitivity to survival compared with the CRP-based ratios and scores (Watt et al., 2015).

The reasons why NSCLC, compared with OG and CRC, elicits such a profound systemic inflammatory response are unclear. However, it may be speculated that more aggressive tumours are more likely to develop necrotic areas and therefore give rise to a greater systemic inflammatory response(Gonzalez-Gutierrez et al., 2024).

Limitations include the retrospective nature of the study, absence of long-term follow-up data, and potential confounders not controlled for (e.g., postoperative complications, comorbidities).

Despite these limitations, the results emphasise that CRP-derived scores remain superior prognostic indicators even in operable CRC where baseline inflammation is typically low, supporting their integration into routine preoperative evaluation and postoperative surveillance strategies.

8.5 Conclusion

In the present study of patients with operable CRC, there was a similar prevalence of systemic inflammation across the various ratios/scores, and the lowest ratio or score had a CRP concentration below the 10 mg/L threshold (such as operable OG cancer); this contrasted with that previously reported in patients with advanced NSCLC, where the lowest ratio or score had a CRP concentration above this threshold. The relationships between components of differential white cell counts, the acute-phase protein CRP, and survival may differ according to tumour type and stage.

Table 8- 1: Comparison of systemic inflammation-based prognostic ratios and scores in patients with colorectal cancer.

Variables		**n (%)**	**CRP median (range)**	**P-value**
Age group	<65	193(43)	4(1-235)	0.277
	65-74	153(34)	4(1-198)	
	>74	100(23)	6(1-100)	
Sex	Female	217(49)	4(1-119)	0.747
	Male	229(51)	7(1-135)	
Primary Site	Colon	244 (54.7)	5(1-235)	0.276
	Rectum	202 (202)	3(1-198)	
TNM	I	117(26)	3(1-141)	<0.001
	II	160(36)	5(1-130)	
	III	169(38)	5(1-235)	
Neoadjuvant Therapy	Yes	371 (83.9)	4(1-235)	0.201
	No	71 (16.1)	3(1-141)	
Type of surgery	Right colectomy	162(36)	5(1-134)	0.261
	Anterior resection	149(33)	3(1-141)	
	Abdominoperineal resection	41(9)	3(1-90)	
	Hartman/left colectomy	37(8)	7(1-219)	
	Other type of surgery	57(14)	11(1-198)	
ASA	1	120(27)	3(1-141)	0.004
	2	218(49)	4(1-134)	
	>3	108(24)	6(1-235)	
Neutrophil lymphocyte ratio (NLR)	<3	238(53)	3(1-90)	<0.001
	3-5	139(31)	5(1-198)	
	>5	69(16)	9(1-235)	
Neutrophil lymphocyte score (NLS)	0	232(52)	4(1-90)	<0.001
	1	195(44)	4(1-219)	
	2	19(4)	57(3-235)	

C-reactive protein albumin ratio (CAR)	<0.2	300(67)	3(1-7)	<0.001
	0.2 -0.4	58(13)	10(7-14)	
	> 0.4	88(20)	37(13-235)	
Modified Glasgow Prognostic Score (mGPS)	0	335(75)	3(1-10)	<0.001
	1	39(9)	15(11-198)	
	2	72(16)	36(11-235)	

*Data presented in numbers (percentages). *A P-value of ≤ 0.05 of chi-square was considered significant.

Table 8- 2: Comparison of systemic inflammation-based prognostic ratios and scores in patients with colorectal cancer.

Variables		n (%)	HR (95%CI)	P-value
Age group	<65	193(43)	1.60 (1.18-2.06)	0.002
	65-74	153(34)		
	>74	100(23)		
Sex	Female	217(49)	1.20 (0.79-1.94)	0.355
	Male	229(51)		
TNM	I	117(26)	1.95 (1.42-2.69)	<0.001
	II	160(36)		
	III	169(38)		
ASA	1	120(27)	1.40 (1.05-1.97)	0.025
	2	218(49)		
	>3	108(24)		
Neutrophil lymphocyte ratio (NLR)	<3	238(53)	1.40 (1.08-1.92)	0.013
	3-5	139(31)		
	>5	69(16)		
Neutrophil lymphocyte score (NLS)	0	232(52)	1.70 (1.17-2.46)	0.005
	1	195(44)		
	2	19(4)		
C-reactive protein albumin ratio (CAR)	<0.2	300(67)	1.50 (1.18-1.94)	0.001
	0.2 -0.4	58(13)		
	> 0.4	88(20)		
Modified Glasgow Prognostic Score (mGPS)	0	335(75)	1.50 (1.17-1.96)	0.002
	1	39(9)		
	2	72(16)		

*A p-value of ≤ 0.05 of the Cox Regression was considered significant. Confidence Interval (CI) and Hazard Ratio (HR): showed that if the entire interval is above 1.00, risk is higher; if below 1.00, risk is lower; if it contains 1.00, the result is not statistically significant.

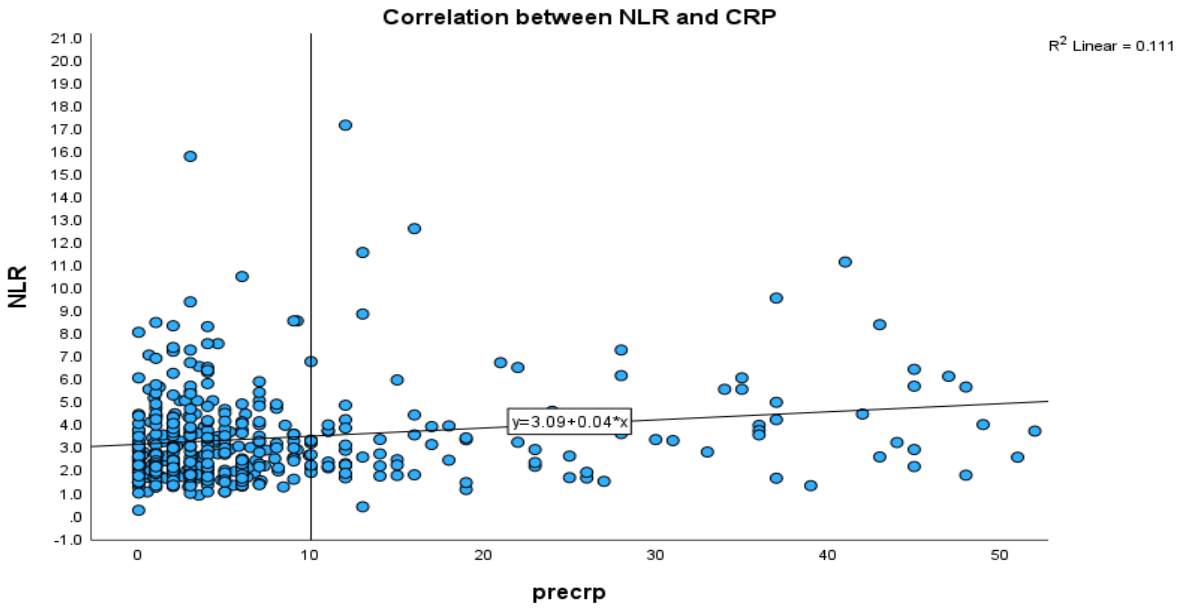

Figure 8-1: A scatter plot of the correlations between Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP). (CRC).

Chapter 9, Systemic Inflammation-Based Prognostic Ratios and Scores in a variety of common solid tumours in TNM Stage III disease

9.1 Introduction

In cancer research, inflammation is a defining characteristic, and inflammation-based prognostic metrics, such as neutrophil-based and C-reactive protein (CRP)-based ratios and scores, are important indicators of patient survival (McGovern et al., 2024). These biomarkers indicate the interaction between tumour cell activity and the host's systemic responses. The origins and degree of chronic inflammation can differ substantially among cancer types and at different stages of cancer progression (National Institutes of Health, 2007). NSCLC is associated with elevated systemic inflammation, often linked to tumour-induced immune suppression and heightened production of inflammatory cytokines, which may be less pronounced than in gastrointestinal malignancies (Ramachandran et al., 2021).

Systemic inflammation is a crucial factor in the development of cancer, influencing tumour growth, cancer cell spread, and the body's immune response to the disease. Furthermore, systemic inflammation-based ratios and scores are recognized to have prognostic value in a variety of common solid tumours (Dolan, McSorley, et al., 2017b). In the previous chapters, we examined the relationship between these ratios and scores and noted that they varied by tumour stage. In particular, the most commonly used ratios and scores, the NLR and mGPS, showed different levels of inflammation in patients with advanced inoperable cancer compared with those with primary operable cancer.

A variety of factors impact the level of inflammation. Advanced TNM staging is associated with increased inflammatory responses resulting from larger tumour size, greater immune cell infiltration, and elevated cytokine production Grivennikov et al., 2010). Tumour biology at its core also plays a significant role. Some types of cancer, notably lung cancer, are thought to directly produce pro-inflammatory cytokines, possibly impacting distant organs like the liver differently from myeloid tissues, compared with other tumours such as colorectal cancer (Dunlop et al., 2000; Greten & Grivennikov, 2019).

The TNM classification system offers a uniform framework for assessing the anatomical spread of cancer, thereby facilitating prognosis and treatment planning. TNM system considers three primary factors: the size and spread of the tumour (T), the involvement of lymph nodes (N), and the presence of distant metastases (M) (Bertero et al., 2018). Therefore, TNM Stage III

cancers offer the opportunity to directly compare different ratios and scores without the confounding of disease stage.

In addition, the presence of age, comorbidities, and various treatment approaches may further complicate the relationship between different markers of the systemic inflammatory response, particularly NLR and mGPS. For example, elderly patients or those with chronic inflammatory diseases may show an overactive inflammatory response that is not linked to the tumour per se. Still, they may upregulate aspects of the host systemic inflammatory response. Investigating these relationships is crucial for improving predictive models and creating tailored treatment approaches (Bertero et al., 2018).

The chapter hypothesised that inflammatory markers would demonstrate consistent prognostic value across different solid tumours at TNM stage III, despite variation in tumour site.

The present study aimed to examine the differences in systemic inflammation-based prognostic ratios and scores at a defined stage of disease, TNM Stage III, in common solid tumours, namely NSCLC, OGC, and CRC.

9.2 Patients and methods

A retrospective cohort design was employed to compare various systemic inflammation-based prognostic ratios and scores across these three cancer types, using a biorepository at the West of Scotland Beatson Cancer Institute.

Data collection

The patient cohort consisted of 216 NSCLC cases, 55 OG cancer cases, and 169 CRC cases. Clinical data were extracted from patient records, including demographic information (age, sex), TNM staging, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), the American Society of Anesthesiologists (ASA), and laboratory values associated with inflammation (NLR, NLS, CAR, and modified Glasgow Prognostic Score (mGPS)). The primary focus was on CRP levels, which were reported as median (range) in each cancer group.

Statistical analysis

Statistical comparisons of systemic inflammation biomarkers were made across various groups using appropriate tests. The differences in CRP values across different age groups, gender, and cancer types (NSCLC, OGC, CRC) were examined using the Chi-squared test. P-values < 0.05 were considered statistically significant. For non-normally distributed data, the data were presented as median and range (minimum and maximum).

9.3 Results

In Table 9-1, the study included 535 patients with non-small cell lung cancer (NSCLC), 335 with oesophagogastric (OG) cancer, and 446 with colorectal cancer (CRC). CRP levels did not differ significantly between age groups in NSCLC (P = 0.285), OGC (P = 0.226), or CRC (P = 0.277). No significant differences in CRP levels were observed between males and females across cancer types. For NSCLC (P = 0.233), OGC (P = 0.128), and CRC (P = 0.747).

The distribution of CRP levels across different TNM stages revealed marked differences. For patients with stage III disease, NSCLC patients had a median CRP of 27 (1-358), OG cancer patients had a median of 6 (1-136), and CRC patients had a median of 5 (1-235). The CRP value was statistically significant in CRC (P < 0.001). In contrast, there was no significant difference in CRP levels between TNM stages in NSCLC (P = 0.061) or OG (P = 0.787) (Table 9-1).

The systemic inflammation-based prognostic ratios and scores were evaluated in patients with TNM stage III: NSCLC (n =216), (OGC) cancer (n =55), and CRC (n =169). CRP levels did not differ significantly between age groups in NSCLC (P = 0.569), OGC (P = 0.211), or CRC (P = 0.980). No significant differences in CRP levels were observed between males and females across cancer types. For NSCLC (P = 0.222), OG cancer (P = 0.962), and in CRC (P = 0.935) (Table 9- 2).

The analysis of inflammation-based prognostic scores showed significant differences in the NLR, NLS, CAR, and mGPS across the three cancer types regarding TNM III, as shown in Table 9-2:

NLR: In NSCLC, NLR <3 was associated with CRP above the normal range, with a median CRP of 12 (P < 0.001). On the other hand, in OGC and CRC patients with an NLR < 3, the median CRP level was 5 (p=0.679) and 4 (p-value >0.001), respectively.

NLS: Patients with NLS scores of 0 had higher CRP levels in NSCLC patients, with a median of 14 (p=0.003), whereas in OGC and CRC the median CRP levels were 5 (p=0.667) and 4 (p=0.010), respectively.

CAR: In NSCLC, a CAR <0.2 was associated with a median CRP of 13 (P < 0.001), while those with CAR >0.4 had much higher CRP levels, with a median of 180. This trend was observed in both OG cancer (P < 0.001) and CRC (P < 0.001).

mGPS: mGPS score 0 was associated with normal CRP levels across all cancer types, whereas higher mGPS scores correlated with elevated CRP levels. For NSCLC, the median CRP for mGPS 2 was 91($P < 0.001$). Similarly, OGC cancer patients with mGPS 2 had a median CRP of 33 ($P < 0.001$), and CRC patients with mGPS 2 had a median of 28 ($P < 0.001$).

Figure 9-1 showed a scatterplot of the correlation between two systemic inflammatory markers, Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP), specifically in patients with Stage III (TNM-III) cancer across three different tumour types: Non-Small Cell Lung Cancer (NSCLC), Oesophagogastric Cancer (OGC), and Colorectal Cancer (CRC). For all three Stage III solid tumour types, the correlation between NLR and CRP is very weak to negligible, as indicated by the low R2 values (all below 0.10 or 10%); this suggests that while both are markers of systemic inflammation, CRP alone does not strongly predict the NLR value in these Stage III patient groups.

9.4 Discussion

The present study examined the inflammatory status in three different tumour types in patients with TNM stage III. From NSCLC to OG cancer to colorectal cancer, there was a greater systemic inflammatory response (irrespective of ratio or score) and poorer 3-year survival (also when controlled for TNM stage III). Therefore, suggesting differences in the inflammatory milieu between cancer types and an impact on survival.

An increasing body of evidence supports the notion that systemic inflammatory biomarkers in blood are effective prognostic indicators across most cancer types. Systemic inflammation has been characterized by elevated levels of circulating neutrophils, platelets, and CRP, and by lower levels of circulating lymphocytes and albumin; this is reflected in the fact that mGPS and NLR are the most commonly used biomarkers of systemic inflammation in patients with cancer. However, elevated serum CRP is considered the foremost clinical indicator of inflammation (acute or chronic). In contrast, white cell counts and their components, such as neutrophils and lymphocytes, are not considered reliable biomarkers (Jensen et al., 2024). In addition to CRP, there is continuing interest in the use of albumin as a proxy for inflammatory activity, since, unlike CRP, albumin declines precipitously in severe inflammatory states. Long considered an indicator of malnutrition, strong consensus now suggests that albumin lacks validity for diagnosing malnutrition in the setting of inflammatory conditions. Indeed, the mGPS combines the interpretation of albumin levels with CRP testing, such that if albumin is low and CRP is elevated, it is highly likely that inflammatory activity is manifest (mGPS 2). Furthermore, CRP and albumin are associated with compromised physical condition, malnutrition, and cachexia (McGovern et al., 2022).

The implications of the present study are profound, as different tumour types produce varying levels of systemic inflammation, and these levels are associated with survival in these tumour types. Therefore, the interaction intensity between various cancers and their hosts differs, leading to diverse inflammatory burdens (as evidenced by NLR compared with mGPS) among cancer patients. The early identification of systemic inflammation may facilitate timely interventions that significantly enhance patient outcomes, particularly anti-inflammatory or other immune-modulating therapies. Indeed, the efficacy of immunotherapy is known to vary with tumour type and with the magnitude of the systemic inflammatory response. Irrespective, the basis of such a relationship is unclear and warrants further study.

It may be that a greater systemic inflammatory response is related to tumour or host characteristics. For example, in patients with NSCLC, a higher preoperative CRP level has been reported to be associated with both pathological tumour size and lymph vascular invasion (Shalata et al., 2021). On the other hand, research has shown that NLR influences several elements of the progression of colorectal cancer, including primary and metastatic forms (Bhattacharjee & Quirke, 2021). In patients with colorectal cancer who undergo surgery, a high CAR has been linked to a poor overall survival rate. Furthermore, in patients with colon cancer, mGPS has been demonstrated to have predictive significance independent of TNM stage. The precise mechanism linking abnormal levels of GPS and CAR to tumour malignancy grade remains unclear.

Limitations include tumour-type heterogeneity, differences in treatment pathways among NSCLC, OGC, and CRC, and the limited ability to standardise biomarker timing across cohorts. However, the findings reveal that systemic inflammation—particularly CRP-based scores—retains strong prognostic value irrespective of tumour type, highlighting inflammation as a universal hallmark of cancer progression and supporting CRP-based prognostication as a cross-cancer clinical tool.

9.5 Conclusion

In summary, the present study identified significant variations in systemic inflammation-based prognostic ratios and scores in TNM stage III NSCLC, OG cancer, and CRC. These ratios and scores were notably higher in NSCLC compared to oesophagogastric and colorectal cancers, suggesting a more pronounced systemic inflammatory response in NSCLC. Based on these findings, we recommend further experimental studies to investigate the underlying causes of the elevated inflammation-based prognostic ratios and scores observed in different common solid tumours, controlling for tumour stage.

Table 9- 1: Comparison of systemic inflammation-based prognostic ratios and scores in patients with NSCLC, OG cancer, and colorectal cancer.

		NSCLC (N=535)			OG cancer (N=335)			CRC (N=446)		
Variables		**N (%)**	**CRP** median (range)	**P-value**	**N (%)**	**CRP** median (range)	**P-value**	**N (%)**	**CRP** median (range)	**P-value**
Age group	<65	154(29)	33(1-431)	0.285	156(47)	4(1-137)	0.226	193(43)	4(1-235)	0.277
	65-74	206(38)	30(1-357)		137(41)	6(1-110)		153(34)	4(1-198)	
	>74	175(3)	26(1-309)		41(12)	7(1-109)		100(23)	6(1-100)	
Sex	Female	256(48)	27(1-287)	0.233	97(29)	4(1-137)	0.128	217(49)	4(1-119)	0.747
	Male	279(52)	33(1-431)		238(71)	7(1-136)		229(51)	7(1-135)	
TNM	0 / I	-	-	0.061	22(8) 49(19)	5(1-25)	0.787	117(26)	3(1-141)	<0.001
	II	14(3)	36(4-169)		107(40)	4(1-109)		160(36)	5(1-130)	
	III	216(40)	27(1-358)		55(21)	6(1-136)		169(38)	5(1-235)	
	IIII	305(57)	32(1-431)		31(12)	3(1-95)		-	-	
ECOG-PS/ASA	0/1	329(62)	23(1-358)	<0.001	263(79)	5(1-137)	0.526	120(27)	3(1-141)	0.004
	½	146(27)	37(1-357)		54(16)	8(1-136)		218(49)	4(1-134)	
	2/>3	60(11)	45(1-431)		18(5)	5(1-52)		108(24)	6(1-235)	
Neutrophil lymphocyte ratio (NLR)	<3	186(36)	15(1-358)	<0.001	183(62)	4(1-110)	0.002	238(53)	3(1-90)	<0.001
	3-5	143(64)	38(1-308)		79(27)	6(1-137)		139(31)	5(1-198)	
	>5	182(36)	58(1-431)		31(11)	15(1-82)		69(16)	9(1-235)	
Neutrophil lymphocyte score (NLS)	0	200(39)	17(1-358)	<0.001	186(63)	4(1-110)	0.004	232(52)	4(1-90)	<0.001
	1	221(43)	40(1-431)		98(33)	8(1-137)		195(44)	4(1-219)	
	2	90(18)	67(1-309)		11(4)	9(1-77)		19(4)	57(3-235)	
C-reactive protein albumin	<0.2	374(70)	15(1-71)	<0.001	132(57)	3(1-8)	<0.001	300(67)	3(1-7)	<0.001
	0.2 - 0.4	92(17)	86(50-139)		41(18)	9(7-15)		58(13)	10(7-14)	
	> 0.4	69(13)	185(84-431)		57(25)	26(14-137)		88(20)	37(13-235)	

ratio (CAR)										
Modified Glasgow Prognostic Score (mGPS)	0	138(26)	5(1-10)	<0.001	207(71)	3(1-10)	<0.001	335(75)	3(1-10)	<0.001
	1	142(26)	31(2-286)		47(16)	19(10-109)		39(9)	15(1-198)	
	2	255(48)	64(6-431)		37(13)	37(10-137)		72(16)	36(11-235)	

*Data presented in numbers (percentages). *A P-value of ≤ 0.05 of chi-square was considered significant.

Table 9- 2: Comparison of systemic inflammation-based prognostic ratios and scores in patients with TNM stage III in NSCLC, OG cancer, and colorectal cancer.

	NSCLC (N=216)	**OG cancer (N=55)**	**CRC (N=169)**

Variables		N (%)	CRP median (range)	P-value	N (%)	CRP median (range)	P-value	N (%)	CRP median (range)	P-value
Age group	<65	52(24)	32(1-358)	0.569	30(55)	5(1-39)	0.596	76(45)	4(1-235)	0.980
	65-74	86(40)	29(1-312)		19(34)	6(1-82)		56(33)	5(1-198)	
	>74	78(36)	21(1-309)		6(11)	5(1-21)		37(22)	7(1-100)	
Sex	Female	95(44)	22(0-286)	0.211	14(26)	5(1-24)	1	72(43)	4(1-219)	0.935
	Male	121(56)	30(1-358)		41(74)	5(1-82)		97(57)	5(1-235)	
ECOG-PS/ASA	0/1	41(19)	16(1-358)	0.295	73(85)	5(1-82)	0.361	37(22)	3(1-85)	0.019
	½	95(44)	21(1-309)		11(13)	8(2-14)		86(51)	5(1-134)	
	2/>3	62(29)	37(1-312)		2(2)	10(10-11)		46(27)	7(1-235)	
	3	18(8)	27(1-188)							
Neutrophil lymphocyte ratio (NLR)	<3	88(42)	12(1-358)	<0.001	41(57)	5(1-39)	0.679	95(56)	4(1-57)	<0.001
	3-5	64(30)	36(1-286)		22(31)	3(1-25)		45(27)	6(1-198)	
	>5	60(28)	44(1-312)		9(12)	6(3-82)		29(17)	10(1-235)	
Neutrophil lymphocyte score (NLS)	0	95(45)	14(1-358)	0.003	47(64)	5(1-39)	0.667	86(51)	4(1-57)	0.010
	1	98(46)	33(1-312)		23(32)	4(1-82)		77(46)	5(1-219)	
	2	19(9)	45(2-309)		3(4)	4(1-82)		6(3)	75(3-235)	
C-reactive protein albumin ratio (CAR)	<0.2	161(75)	13(1-71)	<0.001	26(63)	3(1-7)	<0.001	109(64)	3(1-7)	<0.001
	0.2 -0.4	31(14)	87(50-139)		8(20)	9(7-14)		20(12)	10(7-14)	
	> 0.4	24(11)	180(120-358)		7(17)	27(21-82)		40(24)	31(14-235)	
Modified Glasgow Prognostic Score (mGPS)	0	68(32)	4(1-10)	<0.001	36(75)	4(1-10)	<0.001	112(71)	3(1-93)	<0.001
	1	57(26)	32(2-286)		8(17)	19(11-39)		18(11)	18(0-198)	
	2	91(42)	56(11-358)		4(8)	33(21-82)		28(18)	27(5-235)	
3-year survival	Yes	35(17)	14(1-312)	0.136	23(44)	0-1	0.476	133(79)	5(1-235)	0.341
	No	172(83)	30(1-358)		29(56)	0-1		36(21)	4(1-219)	

*Data presented in numbers (percentages). *A P-value of ≤ 0.05 of chi-square was considered significant.

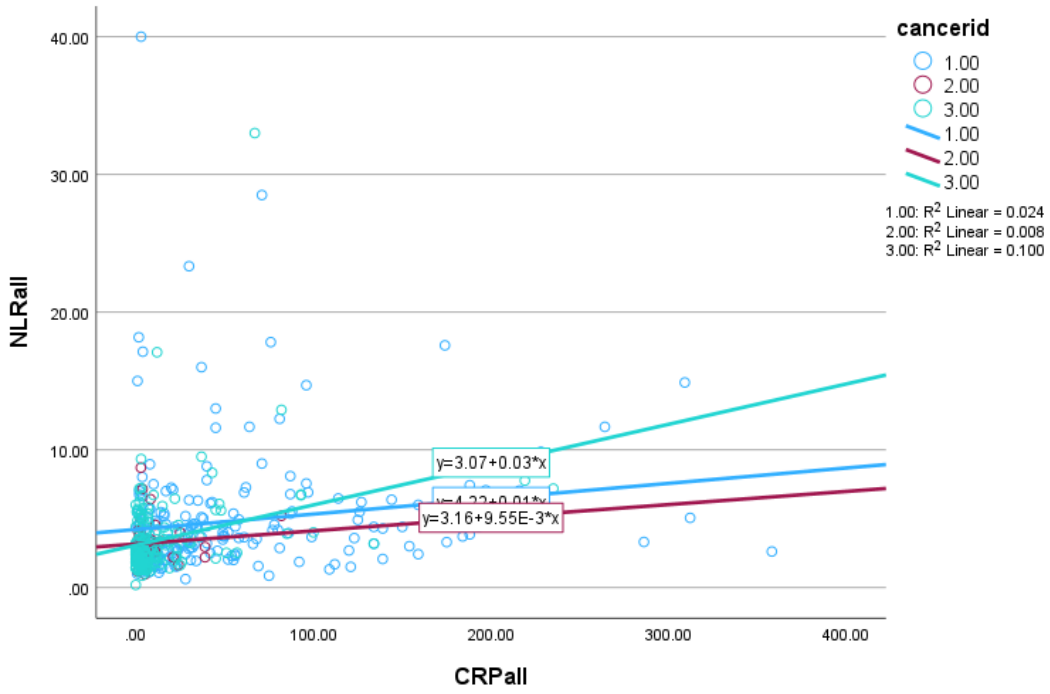

Figure 9- 1: A scatter plot of the correlations between Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP) at TNMIII in NSCLC, OGC, and CRC

Summary of Results

Among 535 patients with advanced NSCLC, three studies were conducted.

Firstly, to compare albumin-based prognostic inflammatory scores and survival in patients with NSCLC, and found, through multivariate survival analysis, that ECOG-PS and mGPS were significant independent factors with CAR (P-values = <0.001 and <0.001, respectively). Also, multivariate analysis in NSCLC patients with good ECOG-PS (0-1) showed that mGPS was significantly associated with overall survival in patients receiving CAR (P-value = 0.013).

Secondly, to assess systemic inflammation as a first approach in evaluating the nutritional decline in advanced NSCLC patients. All NLR and mGPS levels were stratified significantly with ECOG-PS (0-1 and 2) through 12-month survival (P-values < 0.001). All NLR and mGPS levels were significantly stratified by BMI for 12-month survival (P-values < 0.01). All NLR and mGPS levels were significantly stratified by SFI for 12-month survival (P-values < 0.01). All NLR and mGPS levels were stratified significantly with VFA through 12-month survival (P-values < 0.01). All NLR and mGPS levels were significantly stratified by SMI with respect to 12-month survival (P-value < 0.01). All NLR and mGPS levels were significantly stratified by SMD in 12-month survival (P-value < 0.01).

Thirdly, in a study evaluating the prognostic significance of various composite ratios and cumulative scores related to CRP in 535 patients with advanced NSCLC, the median CRP levels demonstrated significant variability across multiple systemic inflammation-based metrics, including the NLR, NLS, PLR, PLS, LMR, NPS, mGPS, and CAR, all showing p-values below 0.001, which approached significance.

Notably, clinical characteristics, including ECOG-PS, and several inflammation ratios, such as NLR, NLS, and mGPS, were significantly correlated with overall survival (p<0.001). These findings underscore the critical role of systemic inflammation in prognosticating advanced NSCLC, highlighting its potential utility in clinical assessments based on CRP levels.

A meta-analysis was conducted to evaluate the role of systemic inflammatory response in predicting the efficacy of immunotherapy in non-small cell lung cancer. A meta-analysis of 13 studies showed a significant association between NLR and overall survival (HR = 2.87; 95% CI 1.91–4.30; P-value < 0.00001). The forest plot of four studies showed a significant association between ALI and overall survival (HR = 1.72; 95% CI = 1.22 –2.43; P-value = 0.002). The pooled analysis of six studies showed a significant association between PLR and

overall survival (HR = 4.06; 95% CI = 2.14 –7.67; P-value < 0.0001). The forest plot of seven studies showed a significant association between CRP and overall survival (HR = 4.22; 95% CI 2.14–8.31; P-value < 0.0001). The pooled analysis of four studies showed a significant association between mGPS and overall survival (HR = 3.27; 95% CI 1.26–8.28; P-value = 0.01).

A published article among ninety-two patients with advanced NSCLC receiving nivolumab as a second-line treatment showed that after the 12-month follow-up, the total number of patients alive had dropped to 36. In contrast, the number of deceased had risen to 56. In Cox regression, ECOG-PS and hypoalbuminemia were significant predictors of 12-month survival in patients with advanced NSCLC receiving nivolumab (P-values = 0.047 and 0.014, respectively). SFI and hypoalbuminemia were substantially linked with the ECOG-PS categories (P-value = 0.042 and 0.001).

In this cohort of 335 patients with oesophagogastric cancer, the majority were male (71%), younger than 65 years (47%), and of good performance status (79%). Most patients had low systemic inflammatory scores, including NLR <3 (62%), NLS 0 (63%), PLS 0 (61%), LMS 0 (55%), NPS 0 (80%), CAR <0.2 (57%), and mGPS 0 (71%). Median CRP concentrations did not differ significantly by age, sex, or performance status. Still, they varied significantly across several inflammatory markers, including NLR, NLS, LMR, LMS, NPS, CAR, and mGPS, with baseline values generally below 10 mg/L. The greatest variation in CRP was observed with NPS, mGPS, and CAR, each showing up to a 10-fold increase with higher scores. In survival analyses, age, sex, and performance status were significantly associated with overall survival, while among the inflammatory indices, only LMR and mGPS demonstrated significant prognostic value. Regression modelling indicated that a CRP concentration of 10 mg/L corresponded to thresholds of NLR 3.2, PLR 170, and LMR 3.4.

In this study of 446 patients with colorectal cancer, most were younger than 65 years (43%), male (51%), and of good performance status/low comorbidity (79%). The majority had low systemic inflammation, with NLR <3 (53%), NLS 0 (52%), CAR <0.2 (67%), and mGPS 0 (75%). Over a median follow-up of 78 months, 31% of patients died. Median CRP concentrations did not vary significantly by age or sex but were significantly associated with TNM stage and ASA score ($p<0.01$). CRP levels also varied significantly with NLR, NLS, CAR, and mGPS (all $p<0.001$), with baseline values below 10 mg/L and the greatest variation observed with NLS, mGPS, and CAR, each showing more than a twofold increase with higher

scores. In survival analysis, age ($p<0.01$), TNM stage ($p<0.001$), and ASA score ($p<0.05$) were significantly associated with overall survival. In contrast, among the inflammatory markers, NLR ($p<0.05$), NLS ($p<0.01$), CAR ($p<0.01$), and mGPS ($p<0.01$) were prognostic. Regression modelling showed that a CRP level of 10 mg/L corresponded to an NLR threshold of 3.2.

Discussion and future work

The relationship between cancer and chronic inflammation was first described over 150 years ago by Rudolf Virchow (Balkwill F, et al., 2001). In recent decades, a large body of work has linked inflammation to both malignancy and tumour biology (Grivennikov et al., 2010). It has been proposed that chronic inflammation accounts for approximately 20-40% of all human cancers, the majority secondary to chronic infections. For example, several cancer types are strongly linked to inflammatory reactions to infectious agents, such as Helicobacter pylori for gastric cancer or Hepatitis C virus for Hepato-Cellular Carcinoma (HCC). Many cancers arise from sites of infection, chronic irritation, and inflammation. Furthermore, it is now becoming clear that the tumour microenvironment plays a crucial role in cancer growth, invasion, and metastasis, and significantly affects therapeutic response and overall patient outcome McAllister & Weinberg, 2010).

However, in addition to the tumour microenvironment, it is increasingly recognized that systemic inflammation plays an important role in cancer metastasis (McAllister & Weinberg, 2014). This thesis primarily concerns itself with the measurement of the host systemic inflammatory response in patients with cancer. In the last two decades many markers of inflammatory response, including C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), albumin (Alb), globulin, and the Glasgow Prognostic Score/modified Glasgow Prognostic Score (GPS/mGPS) were demonstrated as independent predictive factors of cancer outcome and in particular survival (Dolan RD, etal.,2017; Dolan,etal., 2017).

Of these prognostic biomarkers, CRP, an acute-phase protein mainly produced by the liver in response to tissue injury or infection, is the most well-established. Particularly in cardiovascular disease and malnutrition, its use has been incorporated into routine clinical care Amezcua-Castillo et al., 2023). However, CRP is significantly upregulated in patients with cancer compared with those with cardiovascular disease (Ali et al., 2023). Therefore, CRP may act as a reference measurement of inflammation across human disease states.

A central question addressed in this thesis was whether the different systemic inflammation–based prognostic scores and ratios, when applied at their validated thresholds, reflect the same degree of inflammation. The findings suggest that they do not. Specifically, scores and ratios derived from components of the differential white cell count were associated with elevated CRP levels, even when those scores appeared “normal.” In contrast, CRP-based scores and

ratios were more closely aligned with normal CRP values. This discrepancy raises concerns about the clinical utility of white cell–based scores and ratios compared with CRP-based measures. However, where a direct comparison of mGPS and NLR, the most popular score and ratio has been carried out in modern immunotherapy regimens, both appear to have independent prognostic value (Yang et al., 2017). Further comparisons should be evaluated using large prospective datasets, such as the UK Biobank.

Although both the mGPS and NLR have prognostic value (Yang et al., 2017) it is not clear why systemic inflammation is greater in cancer patients compared to patients with other chronic diseases such as cardiovascular disease even when controlling for age (Bradley et al., 2024) and why it is greater in some tumour types compared with others (Proctor et al., 2011). Therefore, further work is required to understand how cancer activates the systemic inflammatory response in the liver (mGPS) and myeloid tissue (NLR), and how this varies across chronic diseases such as cardiovascular disease. Work on linking the tumour microenvironment with the systemic inflammatory response may be informative.

In this thesis, several studies examined the association between various systemic inflammatory biomarkers in patients with advanced NSCLC. In a relatively large cohort of patients, both ECOG-PS and mGPS measures of systemic inflammation appeared to have prognostic value independent of CAR. In contrast, previous research demonstrated that in individuals with NSCLC (Ni et al., 2018) and who had surgical resection (Matsubara et al., 2021), CAR was a more reliable prognostic predictor than mGPS. Also, a previous study in individuals with stage IIIA lung adenocarcinoma and pN2 showed that CAR was a better prognostic marker than mGPS(Matsubara et al., 2021). These results highlight whether the combination of CRP and albumin should be used as a score (mGPS) or as a ratio (CAR). The advantage of mGPS is that its score thresholds are based on the normal ranges of CRP and albumin. The disadvantage is that it may lack sensitivity. The advantage of CAR is its sensitivity, as it is a continuous ratio based on CRP and albumin values. The disadvantage of CAR is that the clinical actionable thresholds are not well defined, such as that of NLR (Dolan et al., 2018). Therefore, future work should determine whether mGPS and CAR have complementary prognostic value and how they might be used to predict survival in patients with cancer.

Regarding oesophagogastric cancer, this thesis examined the relationship between systemic inflammatory composite ratios and cumulative scores (e.g., NLR, NLS, PLR, PLS, LMR, LMS, NPS) and CRP in patients with operable oesophagogastric (OG) cancer. A similar prevalence

of systemic inflammation was observed across these ratios and scores, with the lowest values corresponding to CRP concentrations below 10 mg/L; this contrasted with findings in advanced NSCLC, where the lowest scores were associated with CRP levels above 10 mg/L, and where more ratios and scores showed prognostic value. The results suggest that the relationship between differential white cell count–derived indices, CRP, and survival may vary according to tumour type, stage, and host fitness. Compared with NSCLC, the OG cohort demonstrated lower systemic inflammation, better performance status, and less aggressive disease, which may explain why composite white cell–based scores were less sensitive than CRP-based measures. Importantly, CRP emerged as a more reliable and standardised prognostic marker across tumour types, with greater sensitivity for capturing cancer-related inflammation. Given its reproducibility, international comparability, and established use in other chronic disease and anti-inflammatory trials, CRP should be considered both as a key inclusion criterion and as an outcome marker in future studies investigating the role of systemic inflammation and anti-inflammatory treatments in cancer.

Regarding colorectal cancer, this thesis investigated the relationship between systemic inflammatory composite ratios (e.g., NLR, NLS, CAR) and cumulative scores (e.g., mGPS) in patients with operable colorectal cancer, and compared findings with those in advanced NSCLC and operable oesophagogastric (OG) cancer. In colorectal cancer, systemic inflammation was similarly prevalent across ratios and scores, with the lowest values corresponding to CRP levels below 10 mg/L, in contrast to advanced NSCLC, where the lowest ratios or scores were associated with CRP levels above this threshold, but consistent with findings in OG cancer. Collectively, the results suggest that the association between differential white cell count–derived markers, CRP, and survival varies according to tumour type, disease stage, and patient fitness. Interestingly, CRP concentrations were not consistently associated with TNM stage or performance status across tumour groups, suggesting that tumour type itself is a major determinant of the systemic inflammatory response. Compared with NSCLC patients, colorectal cancer patients exhibited a lower level of systemic inflammation, which may have reduced the sensitivity of white cell–based scores for predicting survival compared with CRP-based measures. The underlying reasons why NSCLC elicits a stronger systemic inflammatory response remain unclear. Still, it has been proposed that more aggressive tumours, such as NSCLC, may develop necrosis more readily, thereby provoking a heightened inflammatory response.

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