Epidemiology and outcomes of patients admitted to hospital with a burn injury in Scotland

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Abstract

Burn injuries are a significant cause of both morbidity and mortality throughout the world. The prevalence of burn injuries and the demographics of those affected vary across the globe, especially between developed and developing countries. However, the risk of burn injury remains consistently higher in individuals from a background of socioeconomic deprivation.

With advances in medical care in recent decades, the chances of survival following major burn injury have increased significantly. With individuals now surviving much more substantial injuries, there is an increasing appreciation of the long-lasting pathophysiological and psychological consequences that can occur following such an injury. Common sequelae include chronic pain, pruritus, depression or anxiety, post-traumatic stress disorder and an increase in the risk of cardiovascular disease, cancer and various infections.

However, the exact aetiology and risk factors associated with being more likely to suffer such detrimental consequences are incompletely understood. Additionally, the deterioration in health conditions after injury may be explained by both the risk factors common to sustaining a burn injury and the physiological impact of the burn injury itself.

The studies detailed in this thesis aim to explore the epidemiology of, and mortality from, burn injuries in Scotland; investigate the effectiveness of using neuropathic agents to manage the symptoms of burn-related pruritus; describe the prevalence and predictors of pruritus after burn injury; explore the use of a protocolised treatment regimen for pruritic symptoms; and use national administrative databases to explore the long-term consequences following survival of a burn injury including the use of drugs to manage pain and mental health conditions and the likelihood of death in the following years.

This thesis includes a systematic review and meta-analysis to explore the effectiveness of drugs commonly used to treat neuropathic pain in the management of burn-related pruritus. Although there is a paucity of evidence that exists, gabapentinoids appear to be effective at reducing pruritus severity

scores by 2.96 (95% CI 1.20, 4.73) on a zero to ten scale when compared to antihistamine or placebo.

Using prospective data collected as part of a quality improvement project in a tertiary referral burn ward, this study explored the factors associated with pruritus severity in patients with a burn injury. Multivariable linear regression analysis demonstrated that increasing size of burn, as measured by surface area, flame burns, a history of smoking and history of alcohol use disorder were all associated with an increase in pruritus severity. Although low serum vitamin D levels were prevalent among this cohort of patients, with 83% of patients having serum vitamin D levels <50nmol/L, the presence or severity of this apparent deficiency did not correlate with the severity of pruritic symptoms. The use of a protocolised approach to pruritus management with various antihistamine drugs and gabapentin in the presence of neuropathic features was consistently effective at reducing pruritus severity scores.

The remaining chapters of this thesis used large linked national datasets to describe the epidemiology and outcomes for patients that suffered a burn injury requiring hospital admission in Scotland. The results show that males are more likely to sustain a burn injury than females, accounting for 63% of admissions. Children were more likely to sustain a scald injury (63% of injuries) with flame burns being relatively rare in children (6%) but much more prevalent in adults (29%). Patients from areas of socioeconomic deprivation made up a greater proportion of both the adult and paediatric cohort. Children from an ethnic minority background were found to be at a higher proportion than would be expected for the general population in Scotland, a pattern not seen in the adult cohort.

Of the adult population, 2.73% died within 30 days of their burn injury. Multivariable cox proportional hazards regression analysis demonstrated that, in keeping with multiple previous studies, increasing age (HR 1.08), increasing size of burn (HR 1.12) and the presence of smoke inhalation injury (HR 14.54) were all associated with an increased mortality. Additionally, a pre-existing history of depression or neurological disorder were also independently associated with mortality (HR 13.65 and 6.48 respectively).

Pre-injury use of drugs such as opioids was significantly higher in this burn-injured cohort compared to the general population in Scotland (25.8% vs 18% respectively). Following burn injury, the use of opioids increased from 25.8% to 38.5% of patients. This increase was evident in prescriptions for both strong and weak opioids. An increase was also seen in the number of patients receiving recurrent (three or more) prescriptions. Factors associated with an increase in opioid use after injury included female gender, previous opioid use, increasing age, socioeconomic deprivation and increasing comorbidity burden.

Compared with the general population of Scotland, the pre-injury use of various drugs for mental health conditions were all higher in this burn-injured cohort including antidepressants (15.2% vs 26.6% respectively), antipsychotics (1.5% vs 6%) and anxiolytics (6.8% vs 16.3%). This study did not demonstrate a higher proportion of patients using these drugs post-injury, however, following a burn, there was a higher burden of drug utilisation, with more patients receiving multiple drugs for mental health conditions, and a higher frequency of prescriptions. Factors associated with this increase in the use of these drugs were found to be similar to that seen with opioids, namely female gender, history of alcohol excess, depression and previous opioid use. Gabapentinoid use was also higher in the burn cohort pre-injury (6%) compared to the general population (4.1%), with their use increasing further after burn injury to 9.5%.

Lastly, for patients that survived to 30 days following burn injury, one in twenty died in the follow-up period to a maximum of four years. Multivariable Cox proportional hazards analysis demonstrated that increasing age and increasing comorbidity burden were associated with increased hazards ratios (1.06 and 3.51 respectively). As were the presence of airway burn or smoke inhalation (HR 2.8) and the pre-injury use of anxiolytic drugs (2.13).

The work presented in this thesis systematically reviews the existing evidence for neuropathic agents in managing burn-related pruritus; assesses a protocolised approach to managing such pruritus; outlines the epidemiology of burns in Scotland; describes the mortality from burns and the associated risk factors; describes the burden of pain and mental health conditions using drug prescription data as a surrogate measure of these conditions; and describes the factors associated with death in the years after surviving a burn injury.

This information may be used by clinicians to inform decisions regarding management of burn-related pruritus. This work also provides a deeper understanding of the complex interplay between mental health conditions, drug use, comorbidity burden and socioeconomic deprivation that often affect those that suffer a burn injury. It also highlights some of the important outcomes following survival of a burn injury with an increased risk of chronic opioid use, especially among those with certain characteristics.

Future research should focus on exploring the influence of the pathological effects of the burn injury compared to the high prevalence of pre-existing conditions that can similarly contribute to morbidity and mortality.

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Grants

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Publications

- **McGovern C**, Puxty K, Paton L. Major burns: part 2. Anaesthesia, intensive care and pain management. *BJA Educ*. 2022 Apr;22(4):138-145. doi: 10.1016/j.bjae.2022.01.001

- **McGovern C**, Quasim T, Puxty K, Shaw M, Ng W, Gilhooly C, Arkoulis N, Basler M, Macfarlane A, Paton L. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. *Trauma Surg Acute Care Open*. 2021 Oct 25;6(1):e000810. doi: 10.1136/tsaco-2021-000810

- **McGovern C**, Puxty K, Shaw M, Quasim T. Epidemiology of burn injuries in Scotland. *Intensive Care Medicine Experimental* 2021, 9(1): 001100

Presentations

Presented at the International Society for Burn Injuries Annual Congress, June 2021:

- Long-term morbidity and mortality after a burn injury: Using linked national data.

- Vitamin D and pruritus in burn injuries.

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- Epidemiology of burn injuries in Scotland.

Preface

This work was undertaken partly as a two-year post as a clinical research fellow with the University of Glasgow department of Anaesthesia, Critical Care and Pain. I continued this work during my time as a specialty trainee and later as a consultant in anaesthesia and intensive care medicine.

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Author's Declaration

I declare that this thesis is of my own composition. The research stated within is entirely my own unless stated otherwise. Preliminary analysis of chapter 4 was carried out by a medical student as part of a BSc course at the University of Glasgow under my supervision. No part of this work has been submitted for any other degree or professional qualification.

Summarised extracts from the introductory chapter have been published in the journal *BJA Education* 2022. The systematic review and meta-analysis detailed in chapter 3 has been published in the journal *Trauma Surgery Acute Care Open* 2021. Any tables and figures from these publications reproduced in this thesis have been done so with expressed permission from the publishers and are labelled as such.

Christopher McGovern

May 2023

Definitions/Abbreviations

5-HT	Serotonin
AIC	Akaike's Information Criteria
ATC	Anatomical Therapeutic Chemical
BBA	British Burn Association
BMI	Body Mass Index
BNF	British National Formulary
BPI-SF	Brief Pain Inventory - Short Form
BSPAS	Burn Specific Anxiety Scale
CAS	Clinical Audit System
CBT	Cognitive Behavioural Therapy
CENTRAL	Cochrane Central Register of Controlled Trials
CGRP	Calcitonin Gene Related Peptide
CHI	Community Health Index
COBIS	Care of Burns in Scotland
CRP	C-Reactive Protein
EASR	European Age Standardised Rate
eDRIS	electronic Data Research and Innovation Service
GABA	Gamma Aminobutyric Acid
G-CSF	Granulocyte Colony Stimulating Factor
GDPR	General Data Protection Regulations
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IASR	International Association for the Study of Pain
ICD-10	International Classification of Diseases 10th Edition

ICU	Intensive Care Unit
IES-R	Impact of Event Scale Revised
IQR	Interquartile Range
ISBI	International Society for Burn Injuries
ISS	Injury Severity Score
IT	Information Technology
IVDU	Intravenous Drug User
LOCF	Last Observation Carried Forward
MCCD	Medical Certificate of the Cause of Death
MRC	Medical Research Council
MRR	Mortality Rate Ratio
NHS	National Health Service
NHS GGC	National Health Service Greater Glasgow and Clyde
NICE	National Institute for Clinical Excellence
NMDA	N-Methyl D-Aspartate
NPS	Nauropathic Pain Scale
NRS	National Records Scotland
NSS	National Services Scotland
PFT	Pulmonary Function Test
PHS	Public Health Scotland
PIS	Prescription Information System
PTSD	Post Traumatic Stress Disorder
RCPSG	Royal College of Physicians and Surgeons Glasgow
RoB2	Cochrane Risk of Bias Tool
SIMD	Scottish Index of Multiple Deprivation
SIR	Standardised incidence Ratio

SMR01	Scottish Morbidity Record 01
SMR04	Scottish Morbidity Record 04
SOFA	Sequential Organ Failure Assessment
STN	Scottish Trauma Network
TBSA	Total Body Surface Area
TENS	Transcutaneous Electrical Nerve Stimulation
UR8	Scottish Government 8-fold Urban Rural Classification
VAS	Visual Analogue Scale
WHO	World Health Organisation

Chapter 1 Introduction

1.1 What is a Burn Injury?

1.1.1 Epidemiology

Burn injuries are a major cause of morbidity and mortality across the globe. The World Health Organisation (WHO) estimates that over 180,000 people die from burn injuries every year, the majority occurring in African and South-East Asian countries[1]. Non-fatal burns carry a significant morbidity burden, with globally around 11 million people requiring medical attention for a burn in 2004[2].

More recent epidemiological data from the Global Burden of Disease Study across 195 countries has provided estimates of burn injury incidence, prevalence, mortality and measures of subsequent disability from 1990 to 2017, describing trends over this time and across measures of socioeconomic development, age and sex. Globally, the age-standardised prevalence of burn injury has declined by 9.7% during this time, with an incidence of 119 injuries per 100,000 population in 2017 and the age-standardised mortality rate has reduced by 46.6%, equating to an estimated 120,623 deaths in 2017[3].

Unfortunately, both the incidence of burn injuries and the consequences of sustaining such an injury, including death, disproportionately affect middle- and low-income countries. Mortality rates from burn injury can vary from over 11 deaths per 100,000 population per year in South East Asia, to around 1 death per 100,000 population per year in higher income regions such as North America[4].

The wide variations in the epidemiology of burn injuries globally are multifactorial. Several studies have highlighted the impact and cost-effectiveness of various public health interventions in reducing burn injuries, including health and safety regulations, burn prevention programmes and use of devices such as smoke detectors[5]. Such measures are often poorly implemented in low- and middle-income countries, resulting in the WHO producing a document outlining a plan for burn prevention and care[4].

1.1.2 Risk Factors

The risk factors associated with sustaining a burn injury can be categorised based on geographical or infrastructure factors including health and safety regulations such as those involving the use of gas, electricity and fuel. Additionally, at an individual level, risk factors include overcrowding, occupation and various medical conditions such as epilepsy, peripheral neuropathy or physical and cognitive impairments. Substance misuse, including alcohol excess and smoking are also recognised risk factors that are perhaps more apparent in higher income nations.

Socioeconomic factors also play a role in the risk of sustaining a burn injury. As already demonstrated, populations living in lower income countries are at higher risk, but this pattern is also reflected within countries, with individuals of lower socioeconomic status consistently being more likely to sustain a burn injury.

Of note, worldwide, females have an increased risk of death from burn injury compared to males. This is not consistent with the fact that the incidence of injury from almost any other mechanism is generally higher in males. This contrast may be due to the higher exposure of females to open fire cooking or other unsafe cooking or domestic heating methods, as well as interpersonal violence potentially contributing to this anomalous statistic[6].

Age also contributes to the risk profile of burn injuries, with children particularly at risk. Burns are the fifth most common cause of childhood injury worldwide with some studies demonstrating a particularly high incidence of injury in young children including 782 non-fatal burns per 100,000 children years in the 1-4 years age group in Bangladesh[7].

1.1.3 Causes

A burn injury results in the destruction of cells, usually skin, from four main mechanisms. Thermal trauma accounts for the majority of burn injuries which includes heat from liquids (scalds), solid objects (contact burns) and flames. Other causes include chemicals, electricity and radiation.

From 2008 to 2017 thermal injury accounted for 86% of admissions to burns centres in the USA, with 41% caused by fire or flame, 35% due to scalds and 10% caused by thermal contact[8]. Electrical and chemical burns accounted for only 3% each of all burns.

1.1.4 Classification

1.1.4.1 Depth of Burn

In 1597 Peter Lowe, founder of what is now known as the Royal College of Physicians and Surgeons of Glasgow (RCPSG), was the first to describe a method of categorising burn injuries based on severity[9]. In his textbook, The Whole Course of Chirurgerie[10] (the Scots Language word for surgery), the first comprehensive text on surgery to be written in English primarily for the benefit of medical students, he described burns as being superficial, average or great:

"The superficial are subject to inflammation, the great ones to excoriation and exulceration, those which are meane have little blisters on the skinne"[10].

In 1610, Fabricius Hildanus, known as the "Father of German surgery", further expanded on the concept of categorising burn injury by severity[11]. His categorisation divided burns into three degrees. First degree burns are characterised by pain and erythema; second degree burns exhibit swelling and blister formation and the most severe third degree burns result in eschar formation, potentially involving other structures underlying the skin. He also developed the concept that the severity of the burn was related to the mechanism of burn, both in its temperature and duration of contact with the patient's skin.

This categorisation of degrees of burn injury persisted, with numerous, often subtle, variations proposed over the centuries. The modern nomenclature used to classify burn injuries is remarkably similar to these historic methods, echoing the recognition of the depth of burn injury by its clinical appearance.

Burn severity by depth is now more commonly described based on the anatomical involvement of the layers of skin affected:

- Superficial epidermal burn injuries only involve the top layer of skin, the epidermis. They are characterised by uniform erythema that blanches to the touch. Although usually very painful, tissue destruction is minimal, they heal quickly and rarely form blisters.

- Dermal burns involve the layer underlying the epidermis. Such injuries here are often sub-categorised in to superficial dermal and deep dermal. Clinical features include pink, often mottled appearance to the burn, blisters are often present and the capillary refill is reduced. Deeper dermal burns may involve the loss of hair follicles and a reduction in sensation as nerve fibres are damaged.

- Full thickness burns involve total destruction of the epidermis and dermis, with the potential for involvement of other underlying structures such as muscle or bone. Such burns are classically white, waxy or even charred. The areas of deepest burn are often insensate and painless, owing to the destruction of nerve fibres found in the dermis. Indeed, only the edges of such extensive burns are painful. Full thickness burns do not heal spontaneously, usually requiring viable skin to contract over the burned tissue whereby healing occurs by secondary intention. Such extensive burns will usually require surgical intervention.

1.1.4.2 Surface Area

The extent of a burn injury is classified not only by the depth of tissue affected, but the surface area of the body affected. This is commonly expressed as a percentage of total body surface area (TBSA).

A variety of methods exist for use in clinical practice to aid such an assessment. Dr Charles Lund and Dr Newton Browder used their experience caring for patients involved in the Cocoanut Grove fire in Boston in 1942 to devise a method to estimate the surface area of a burn, taking in to account the varying mass to surface area ratios of young children versus adults. This tool, known as the Lund and Browder chart, uses simple diagrams to allocate a percentage to each anatomical region[12].

A simple method of quickly estimating the surface area of a burn wound uses the "rules of nine" method. First described by Samuel Berkow in 1924[13] and later published by Alexander Wallace in 1951[14], this method divides the body into anatomical regions whereby each represents either 9% of TBSA or a multiple of such (Figure 1-1). For example, an entire upper limb accounts for 9%, the anterior torso is 18% and one side of the head accounts for 4.5%.

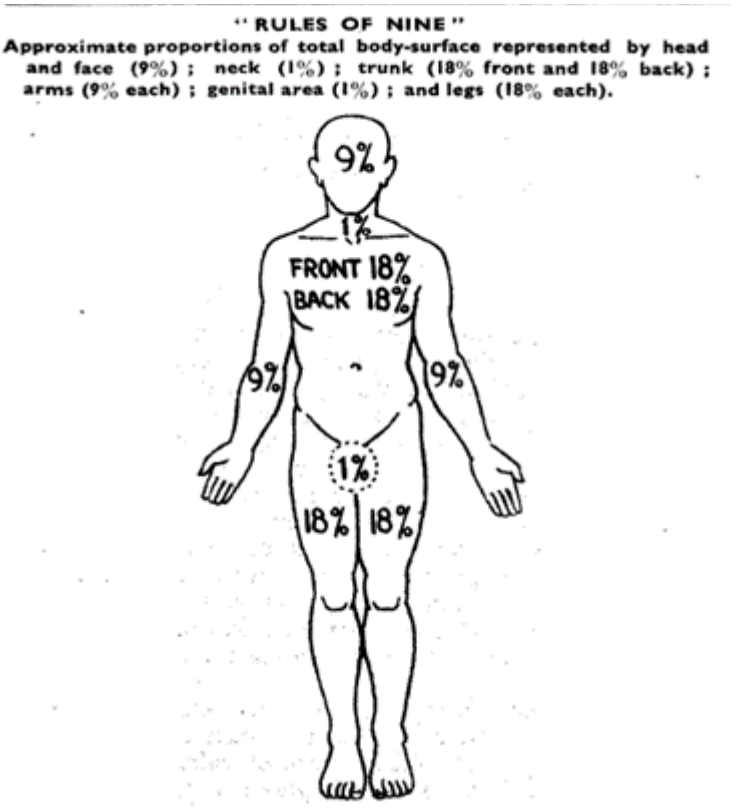

Figure 1-1 "Rules of Nine". Reprinted from Wallace A, The exposure treatment of burns. The Lancet. 1951; 257(6653): 501-504 with permission from Elsevier

Such methods of estimation often rely on user experience and can suffer from inaccuracy due to proportional differences in children versus adults or variations in body habitus. For example, using the rule of nines in patients with a high body mass index (BMI) will often overestimate the size of the burn injury.

1.1.5 Pathophysiology

Sustaining a burn injury will result in both local and systemic effects, with the magnitude of such pathophysiological changes being dependent on the severity

of the injury. In the case of a thermal injury this is dictated by the temperature the skin is exposed to and the duration of exposure.

1.1.5.1 Local Changes

The immediate local pathological changes that occur to skin injured by a burn was first described by Jackson in 1953[15]. He described three zones of a burn based on the cellular changes that occur:

- The zone of coagulation. This is the central portion of a burn wound, where maximal cellular damage occurs with tissue loss due to coagulation of proteins found within cells and destruction of the blood vessels.

- The intermediate zone of stasis. Around the area of maximal damage there is an impairment in tissue perfusion due to microcirculatory changes impairing blood and nutrient delivery. Tissue here is vulnerable to further damage by hypotension, oedema or infection, potentially resulting in extension of the injury and further loss of tissue.

- The outer zone of hyperaemia. This is the peripheral area where perfusion is increased owing to vasodilation in response to inflammation. Tissue here will usually recover.

1.1.5.2 Systemic Changes

Depending on the extent and location of a burn injury, patients can experience a multitude of systemic complications. These can include fluid and electrolyte disturbances or even a profound systemic inflammatory response resulting in end organ impairment and dysfunction of the immune system.

Major burns injuries, especially those affecting greater than 20% TBSA (total body surface area) can result in overwhelming multi-organ dysfunction. This is due to the release of pro-inflammatory mediators such as histamine, bradykinin, nitric oxide, tumour-necrosis factor (TNF) and interleukins (IL). The extent to which this occurs will depend on the size and depth of burn, presence of other injuries, especially inhalation injury, or other underlying comorbidities.

Cardiovascular changes include cardiac myocyte dysfunction as a result of pro-inflammatory cytokines including TNF-α, IL-1ß and IL-6[16]. This results in an immediate reduction in cardiac output which, when combined with hypovolaemia from fluid and electrolyte losses from burn wounds, can result in tissue hypoperfusion and the phenomenon known as "burn shock"[17,18]. This initial "ebb" phase of a burn injury generally lasts for around 48 to 72 hours.

The proceeding "flow" phase is characterised by a hyperdynamic and hypermetabolic physiological state. A tachycardia will persist and cardiac output will increase, often two to three times above baseline, although a degree of myocardial dysfunction may remain.

Many of the widespread systemic changes can be attributed to the metabolic and endocrinological changes that occur following such trauma. A sustained increase in stress hormones such as catecholamines and glucocorticoids results in a profound and persisting catabolism, loss of muscle mass, a negative nitrogen balance, higher basal metabolic rate, increased insulin resistance and impaired haematopoiesis[19].

Complex inflammatory and immune changes that occur in response to a burn injury can be detrimental. The initial pro-inflammatory response intended to mobilise immune cells, lyse microbes, promote phagocytosis and clear damaged cells can be overwhelming and potentially result in multi-organ failure and death. Additionally, an anti-inflammatory phase can then follow, often leaving patients with a relative immunoparesis. Several studies have demonstrated such immune dysfunction following burn injury with reduced immunoglobulin levels[20] and neutrophils being affected by impaired chemotaxis, weakened phagocytic function and reduced bactericidal capability[21].

Further research has aimed to describe this complex immune and inflammatory response caused by burn injury in more detail. Xiao et al explored the circulating leukocyte transcriptome in the days following burn injury, comparing this with individuals that suffered blunt trauma or healthy subjects exposed to low dose bacterial endotoxin[22]. The authors describe a "genomic storm" that results in alteration of over 80% of the leukocyte transcriptome, occurring rapidly within 4 to 12 hours of injury. This genomic response was similar

between each cohort but noted to be more prolonged following burn injury, whereby more than half of messenger RNA levels had not returned to baseline by 90 days. The authors postulate that previously described pathophysiological models of acute inflammatory response to injury and illness do not correlate with these new findings but rather the acute inflammatory response is the same between patients and conditions, perhaps only differing in the duration and severity in those with poorer outcomes. This research offers a novel model to explain the pathophysiological effects of severe illness and injury.

1.1.6 Associated Injuries and Complications

1.1.6.1 Airway burn and inhalational injury

Although burn injuries most commonly involve the skin, an additional injury to the respiratory tract can further complicate the clinical course of patients and significantly increases the risk of death.

The term "inhalation injury" covers a spectrum of clinical disease, whereby the respiratory tract is exposed to heat or toxic materials. The clinical manifestation and severity of such an injury will depend on the substances inhaled, the thermal energy dissipated to the tissues and the duration of exposure[23].

The extent of exposure to such agents will also depend on the environment in which the injury occurs. Enclosed spaces with poor ventilation provide ideal conditions for incomplete combustion of materials and accumulation of noxious fumes that an individual will inhale. Clinical manifestations can include either thermal or chemical injury to the respiratory tract or harmful systemic effects by absorption into the bloodstream.

Thermal injuries to the proximal respiratory tract, such as the oropharynx and nasopharynx, can cause rapid tissue oedema that can quickly progress to airway obstruction, asphyxia and death. Due to the dissipation of heat in the upper airways, thermal injury below the level of the vocal cords is rare but can occur with the inhalation of substances such as superheated steam[24].

Damage by particulate matter and chemical irritants is more likely to be a feature of tissues damaged below the level of the vocal cords. Particulate matter such as soot can cause luminal obstruction, impairing gas flow through the lungs. Chemical irritants can cause both a localised and systemic inflammatory cascade leading to increased pulmonary vascular permeability, alveolar oedema, ventilation/perfusion mismatch and further luminal obstruction with the formation of thrombus and airway casts.

Systemic absorption of chemicals can have other multisystem effects. The inhalation of carbon monoxide, commonly produced by the combustion of carbonaceous material in an oxygen poor environment, causes tissue hypoxia by avidly binding haemoglobin, thereby preventing oxygen binding, and inhibits oxygen binding with cytochrome oxidase in mitochondria, impairing aerobic respiration.

1.1.6.2 Acute Respiratory Distress Syndrome

Burn injuries can result in damage to lung parenchyma even in the absence of any associated inhalational injury. Acute Respiratory Distress Syndrome (ARDS) is characterised by non-cardiogenic pulmonary oedema and lung inflammation driven by the profound inflammatory response initiated by the burn injury. There are few specific treatment options other than supportive therapy for this heterogeneous condition that can occur in almost any critical illness including pneumonia, sepsis, trauma and pancreatitis. ARDS is categorised based on its severity, reflecting the degree of respiratory dysfunction by measuring the ratio of the partial pressure of oxygen in arterial blood to the inspired oxygen concentration[25].

1.1.6.3 Compartment syndrome

A compartment syndrome occurs when the pressure within a compartment increases to the point where the blood flow is restricted causing distal tissue ischaemia and eventually necrosis. In burn injuries this most commonly occurs in limbs and extremities due to constriction of deeply burned skin circumferentially around a limb or digits. This can also occur as a result of

oedema of deeper tissues such as muscle, more commonly seen in electrical burns.

Circumferential burns involving the thorax can also result in restriction of chest wall movement, thereby impairing respiratory mechanics resulting in respiratory failure and difficulty in mechanical ventilation.

Compartment syndrome is a medical emergency and requires the rapid release of the restricting tissues, either by escharotomy of burned skin or fasciotomy of muscle compartments, to restore adequate perfusion to the affected tissues.

1.1.6.4 Acute Kidney Injury

Acute kidney injury (AKI), as defined and categorised by a rise in serum creatinine level and reduction in urine output, can occur for a variety of reasons in burn injured patients. The loss of fluids and electrolytes due to the loss of the protective skin barrier can result in hypovolaemia and therefore inadequate perfusion of the kidneys. Additionally, AKI can result from a combination of acute tubular necrosis, low cardiac output and vasoplegia. An increase in anti-diuretic hormone release as a normal physiological response to injury can also result in oliguria.

Other more specific causes of AKI include rhabdomyolysis when muscle tissue is either directly damaged by a burn, such as an electrical burn, or as a consequence of a compartment syndrome. This results in the release of the intracellular contents of skeletal muscle, namely myoglobin, into the bloodstream. Myoglobin accumulates in the renal tubules, forming casts and obstructing flow through the renal tubules and collecting system.

Abdominal compartment syndrome can also occur, most commonly due to the significant tissue oedema following fluid resuscitation. Raised intra-abdominal pressures can impair both arterial blood supply and venous drainage to the kidneys, causing substantial damage.

1.1.6.5 Infection

Skin is the body's primary barrier to infection. It's loss due to burn injury, coupled with the degree of immunosuppression evident in major burn injury, results in an increased risk of infectious complications. Infections contribute significantly to the morbidity associated with burn injury and account for 42-65% of deaths from burn injury[26].

Burn wounds can become colonised with a variety of organisms, whereby low concentrations of bacteria are present on the surface of wounds. However, invasive wound infection, characterised by surrounding cellulitis, can result in extension of the existing burn depth, eschar separation or further necrosis of affected tissues.

Patients may also develop systemic complications as a result of sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[27]. In the context of a major burn injury and resulting multi-system effects associated with it, the clinical diagnosis of sepsis can be difficult to make, relying on sound clinical judgement, biomarkers such as C-reactive protein (CRP), procalcitonin (PCT) and microbiological evidence of infection. Recognising these challenges, the International Society for Burn Injuries (ISBI) published guidance that both echoes the pre-existing surviving sepsis campaign[28] and Sepsis-3 guidance[27], but also highlights the difficulties and differences in diagnosing and managing infectious complications in burns[29]. This document was produced following review of the available literature and a meeting of experts and stakeholders to develop consensus statements covering a variety of aspects of sepsis in burns. Clinical features such as thrombocytopaenia or gastrointestinal dysfunction were highlighted as additional clinical clues that may indicate sepsis in burn-injured patients. This work both highlights the Sepsis-3 guidance and supplements this with information more specific to burn injuries where diagnosis and management can be particularly challenging.

1.1.7 Mortality from Burn Injuries

Mortality from burn injuries has improved dramatically with multiple advances in burn care in recent decades. In 1961, Baux developed a tool to predict

mortality in burn injuries[30]. The simple calculation, known as the Baux score, was the sum of the patient's age and the percentage surface area burned. This total is frequently misquoted as equating to the percentage risk of death, whereas the original paper stated that a score >75 indicated "almost certain death".

As burn management improved, this tool for mortality prediction became obsolete as the predictions were increasingly pessimistic. However, several others have built upon this concept as a foundation to develop more accurate prediction models. Osler and colleagues found that both increasing age and percent surface area burned contributed almost equally to mortality, but that the additional presence of an inhalation injury increased risk by an equivalent 17 years of age (or 17% TBSA burn)[31].

Such observations resulted in a Revised Baux Score: Age in years + TBSA % (+17 if inhalation injury present). This result of this calculation exhibits a non-linear relationship with mortality risk on a scale from zero to a maximum of 220 (theoretically a 103 year old patient with a 100% TBSA burn plus an inhalation injury). The authors found that patients with a score of less than 65 rarely died, whereas those with a score over 165 usually died[31].

Further studies have stated that the "point of futility", where predicted mortality is 100%, is a revised Baux score of 160; and the LD50, the point at which predicted mortality is 50%, is a score of 109.6 (95% CI 105.9 – 133.4)[32].

Although the size of burn injury, as measured by TBSA, the increasing age of an individual and the presence of an inhalation injury all consistently contribute to mortality prediction, other studies have tried to build on these predictors with other variables to improve accuracy. Steinvall and colleagues incorporated the use of the Sequential Organ Failure Assessment (SOFA) score and admission serum lactate levels to further improve mortality prediction in major burns[33].

1.2 Modern Burn Care

The survival from burn injuries has improved dramatically in recent decades. In the USA, Brigham et al described estimates of both the incidence and mortality

from burn injury across several decades, demonstrating a reduction in the estimates of deaths from burn injuries from around 9000 in 1971 to 5500 in 1991[34]. Although much of this reduction in mortality can be explained by a similar reduction in burn incidence, other studies such as that conducted by Capek et al have demonstrated an equally striking reduction in mortality of around 2% per year from 1989 to 2017 by using a multiple regression analysis of patient level data, accounting for factors such as severity of injury[35].

Much of the improved survival after burn injury can be attributed to a greater understanding of the underlying pathophysiology and advances in medical and surgical therapies for these patients. Some of the most significant advances involve fluid resuscitation, surgical techniques, delivery of nutrition and improvements in a variety of drug therapies.

1.2.1 Fluid Management

Major burn injuries result in a loss of fluid requiring replacement in far higher volumes than any other form of trauma or illness. The first evidence of recognition that fluid and electrolyte replacement would benefit burn victims was in 1921 when Frank Underhill cared for victims of the Rialto Theatre fire at the New Haven Hospital. He recognised "a state of concentration of the blood" and linked this to the loss of fluid from the intravascular space to the injured tissue whereby, "fluid rushes to the burned skin with great rapidity and is lost to the body, or if the skin is intact blisters are formed"[36]. Underhill analysed the exudative losses from patients' burn wounds and demonstrated "that it has essentially the same composition as the blood plasma from which it came. In other words, the fluid poured out in the burned area must be regarded as blood plasma, containing similar proportions of proteins and inorganic salts"[36].

From this point, adequate fluid and electrolyte replacement in proportion to the extent of the burn injury and consequent fluid losses became of great importance. Several methods were developed to guide fluid resuscitation and in 1968, Baxter and Shires developed the Parkland formula[37]. This study summarised evidence from various animal studies and clinical cases. The authors recommended that during the first 24 hours following a burn injury, 4ml of balanced crystalloid solution should be given per kilogram of body weight for

every percentage of burned body surface area. This formula remains the most widely used in clinical practice today and provides a starting point to guide fluid resuscitation.

The fluid requirements of patients can vary significantly, and methods to ensure the optimal fluid delivery remain a point of debate. Under-resuscitation with inadequate fluid replacement can result in extension of burn depth and inadequate end organ perfusion resulting in multi-organ failure. Conversely, over-resuscitation can result in extensive oedema of both burned and uninjured tissues. Complications can ensue such as increased lung water impairing gas exchange and excessive intra-abdominal fluid leading to intra-abdominal hypertension and potentially abdominal compartment syndrome.

The most commonly used and accessible indicator of adequate fluid replacement is urine output, targeting an hourly volume of 0.5-1ml/kg ideal body weight. Failure to meet this target, or excess urine production, should prompt clinical reassessment and adjustment of fluid delivery rates.

Other methods to guide fluid replacement include biochemical markers such as lactate, haematocrit and acid-base balance as well as clinical examination. Cardiac output monitors have also been used with some benefits in improving cardiac output, oxygen delivery and markers of organ dysfunction[38].

1.2.2 Surgery

One of the most significant advances in burn care came with the recognition that early excision of the necrotic tissue of deep burns improved mortality. Dr Oliver Cope and colleagues, from experience caring for victims of the Cocoanut Grove nightclub fire of 1942, recognised that partial thickness wounds, with a dead but intact epithelium, were somewhat protected from infectious complications. Whereas full thickness burns with no intact epidermis “offers an enticing culture medium to organisms”[39]. Their approach of aggressive early excision of burn eschar and closure of the wound was thought effective at reducing not only mortality, but resulted in “a short period of hospitalisation, an economy of manpower and a hopeful outlook by the patient”[39].

The techniques used to excise burn eschar were limited by the surface area of the wound, ability to graft enough autologous skin and the complications of extensive blood loss. As surgical techniques developed, tangential excision, whereby repeated slices of skin are removed parallel to its surface down to viable tissue, was developed by Dr Zora Janzekovic working in Yugoslavia in the 1960s[40]. This technique became common practice in the 1970s and remains the standard today.

Further advances in surgical techniques have included the use of cadaveric skin for grafting and the development of bioengineered dermal substitutes, including culture-derived human skin allograft containing active keratocytes or an acellular dermal matrix from donor cadaver skin. Some dermal substitutes can even be prepared by culturing the patient's own healthy skin cells to create an epidermal autograft.

1.2.3 Nutrition

Major burn injuries are associated with an increase in the individual's basal metabolic rate, occasionally by more than double. This increased energy expenditure and need for increased substrate can result in loss of lean body mass, immune compromise and impaired wound healing. The extent of loss of body mass correlates with an increased risk of adverse outcomes including infectious complications and death[41].

The aim of nutritional support following major burn injury is to deliver the correct amount of carbohydrate, protein and lipids to provide substrates for respiration, immune function, wound healing and minimise loss of lean body mass while avoiding the risks of overfeeding that can lead to hyperglycaemia, hypertriglyceridemia and hepatic steatosis. There is also recognition that vitamins and trace elements such as copper, selenium and zinc can be lost in large quantities in burn exudate. Prompt replacement of these micronutrients may improve antioxidant defences, prevent infectious complications and improve wound healing.

There has been widespread recognition that establishing early enteral nutrition can modulate the stress hormone response, improve gut integrity, improve wound healing and help avoid infectious complications[41].

1.2.4 Analgesia

The pain experienced from a burn injury is significant and frequently difficult to manage. The severity of pain experienced during an acute admission with a burn injury has been associated with poorer outcomes including, depression, anxiety, suicidal ideation, symptoms of post-traumatic stress disorder (PTSD), poor physical function and increased likelihood of chronic pain[42,43].

Although the burn injury itself is likely to be the focus of pain, other medical interventions can contribute to this pain burden including invasive lines and catheters, skin autograft donor sites and musculoskeletal pain from immobility. Given the severity of pain associated with major burn injury, opioids remain the mainstay of treatment. However, given their adverse effects including ileus, respiratory depression, delirium and risks of tolerance, dependence and addiction, a multimodal analgesic regimen is favoured to minimise the risks of these sequalae and maximise analgesic effect. Simple analgesics and adjuncts including paracetamol and non-steroidal anti-inflammatory drugs are used to reduce opioid requirements. Additional agents such as ketamine and α-2 receptor agonists such as dexmedetomidine can also be used as part of this multimodal strategy or to facilitate painful interventions such as dressing changes. Other agents such as gabapentinoids may be employed when clinical features of neuropathic pain are evident or in an effort to reduce opioid requirements. Non-pharmacological strategies have also been used to address pain including acupuncture and cognitive behavioural therapy.

1.2.5 Pharmacotherapy

Given the hypermetabolic response associated with major burn injuries, there has been substantial interest in the use pharmacological agents to supress this potentially harmful aspect of these injuries.

Beta-adrenergic blocking drugs such as propranolol act to supress the catabolic effects of excessive endogenous catecholamines. Although the evidence so far has failed to show any convincing effect on outcomes such as mortality[44], some studies have demonstrated reduced muscle catabolism[45] and improved wound healing[46].

Anabolic steroids such as oxandrolone, a synthetic testosterone analogue used in certain catabolic conditions including HIV associated myopathy, have been used to stimulate protein synthesis and muscle growth after burn injury. Some studies have demonstrated benefits such as reduced hospital length of stay and maintained lean body mass[47].

1.2.6 The Multidisciplinary Team

Beyond the targeted resuscitation and early surgical interventions that have yielded such improvements in patient outcomes, there has been a growing recognition of the role of the multi-disciplinary team in caring for patients in a holistic manner, beyond the initial pathology of the burn wound.

International guidelines and standards have highlighted the importance of a multi-faceted approach to caring for these patients[48]. The role of physiotherapy is crucial in promoting mobilisation, maintaining muscle mass and strength, managing contractures of healed wounds and guiding the rehabilitation of patients that can often become significantly deconditioned after prolonged critical care and hospital admissions.

Dieticians play a vital role in ensuring the complex nutritional needs of these patients are met by ensuring adequate macro- and micro-nutrient delivery while avoiding harmful overfeeding.

As more people survive major burn injuries, the lasting psychological harm that can ensue is actively considered and managed by teams of psychologists. This integral part of a modern burn care team provide support and interventions to both patients and their relatives at an early stage in their recovery.

As a result of the significant improvements in burn care over recent decades, the multi-disciplinary team now care for patients that have survived burns of increasing severity, often requiring numerous and often complicated surgical interventions and can be left with ongoing morbidity of considerable complexity.

1.3 Long-Term Consequences of Surviving a Burn Injury

As advances have been made in the acute management of burn injuries and patients are now surviving more significant injuries, the lasting consequences of these injuries have become more apparent.

1.3.1 Chronic Pain

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[49]. This definition describes the link between a physical injury resulting in an unpleasant sensation, but also highlights the more subjective elements of pain. This includes the emotional aspect of pain that can impact on mood, behaviour and sleep.

The physiology of pain can be described by the "pain pathway". This is a series of nerves and their connections from the source of pain via the spinothalamic tract to the somatosensory cortex as well as the thalamus, hypothalamus and limbic system affecting mood, behaviour and memory.

Direct damage or persisting stimulation of these neurones can result in pathological changes resulting in chronic pain syndromes. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system[49]. This often exhibits classic clinical features whereby patients will describe dysaesthesia (abnormal sensations), allodynia (pain from a non-painful stimulus), paraesthesia (numbness) or sensations such as "pins and needles", "electric shocks" or pruritis.

Chronic pain and neuropathic pain are recognised features of burn injuries. It has also become an area of increasing research in the setting of elective and

emergency surgery as the disease burden of chronic pain following an operation or injury becomes increasingly apparent[50,51].

Choiniere et al[52] conducted structured telephone interviews with 104 patients more than one year following hospitalisation with a burn injury. They discovered that 82% of patients reported some form of altered sensation such as numbness or tingling and that 35% complained of ongoing pain. This early study in 1991 was the first to build on anecdotal reports of chronic pain following a burn injury.

Other studies have built upon this. Dauber et al[53] conducted a mail survey of members of the Phoenix Society for Burn Survivors. They asked questions regarding the prevalence and characteristics of pain, both remembered from the initial injury and treatment, and pain at the time of the survey. Of the 358 respondents, with an average TBSA of 59%, 52% had ongoing pain at the time of the survey, with 45% of respondents stating that pain interfered with their daily lives. Most striking from this study is that the average time from injury to completing the survey was 12 years, highlighting the vast time that these symptoms can persist.

Gauffin et al[54] investigated the link between pain, quality of life and post-traumatic stress disorder (PTSD) following survival of a burn injury. They prospectively investigated adult patients admitted to a single burn centre over a seven-year period. Of the 112 eligible patients, 67 completed follow-up. They measured pain using the Brief Pain Inventory-Short Form (BPI-SF), Health-Related Quality of Life (HRQoL) using the EQ-5D and symptoms of PTSD using a Swedish version of the Impact of Event Scale-Revised (IES-R). The authors reported that one-third of patients still reported mainly mild to moderate pain and interference with daily life at 2 to 7 years following the injury. Interference commonly included general activities, work, enjoyment of life and mood. Symptoms of post-traumatic stress disorder (PTSD) were also more evident in patients still experiencing pain at 12 months following the burn.

Browne et al[55] investigated not only the incidence of chronic pain following a burn, but the link between persisting pain and measures of mental health, depression and PTSD. In a mail survey of 492 patients, 18% reported chronic

pain, 27% had depressive symptoms and 14% demonstrated symptoms of PTSD. This study also demonstrated that patients who reported ongoing pain were far more likely to report symptoms of depression or PTSD and were also more likely to recall significantly higher acute pain levels during their initial treatment.

Such studies have highlighted the significant burden of chronic pain that can persist for many years following a burn injury, impacting on the quality of life of those individuals affected.

Other studies have focused on the impact of acute pain during the initial burn injury and the interventions carried out during a patient's treatment on long term patient-centred outcomes. Indeed, similar studies have been carried out in other surgical populations to demonstrate that poorly controlled acute post-operative pain results in increased incidence of chronic pain[56,57].

Patterson et al[43] carried out a prospective study to investigate the mental health of patients in the month before the burn injury and pain during admission including interventions such as wound debridement. They also investigated pain, physical and psychological functioning, psychiatric symptoms and symptoms of PTSD following discharge. From the 122 patients investigated, those that reported greater pain during hospital admission also reported poorer adjustment up to two years following discharge. The investigators note that causality cannot be conclusively determined from this study, but it does highlight the importance of adequate analgesia in the acute phase of a burn injury.

Aaron et al[58] investigated the link between anxiety and pain by using a burn specific anxiety scale (BSPAS) to demonstrate a link between increased levels of anxiety regarding burn treatment and burn pain to increased perception of pain during procedures and increased analgesia use. The authors also investigated the degree to which anxiety associated with pain impacted on daily activities and physical function, demonstrating that increased pain and anxiety levels result in interference with physical performance. They highlight the potential detrimental impact that this can have on the physical therapy and rehabilitation process.

1.3.2 Pruritus

The unpleasant sensation of itch is a common but potentially under-recognised complaint among burn survivors. Some studies have reported an incidence as high as 93% at hospital discharge[59], 67-73% at 2 years[59,60] and persisting as high as 44.4% at 4-10 years[59].

Pain and pruritus have similar but distinct neurophysiological pathways, with an increasing understanding that there is likely to be a pathological process similar to that seen in neuropathic pain syndromes to account for the development of chronic pruritus after burn injury[61,62].

Although potentially seen as a minor symptom, the consequences of persisting pruritus can have a detrimental impact on sleep quality, mood, quality of life and psycho-social well being[63,64].

1.3.3 Psychological Impact

Given the distressing circumstances in which burn injuries can occur, for example a house fire, the associated prolonged hospital admission, significant pain and multiple interventions often involved in the treatment of burn injuries, the risk of psychological distress and harm is significant.

Post-traumatic stress disorder (PTSD) is characterised by symptom clusters including re-experiencing the traumatic event, avoidance of potential triggers, alterations in mood or cognition and a state of hyperarousal or perceived increased threat. Longitudinal studies have suggested that the incidence of PTSD after burn injury can be as high as 45%[65], with predictors of those being at increased risk hard to identify. For example, the extent of burn injury, as measured by TBSA, does not seem to correlate with the risk of developing PTSD. However, an individual's perceptions, social support network and poor coping strategies are all thought to increase risk[66].

The diagnosis of PTSD can be difficult to make as many patients exhibit no symptoms until after hospital discharge. Equally, reliable assessment of patients can be hampered by the distress caused by other factors such as pain and sleep disturbance.

Anxiety and depression are also common following burn injury, with some studies suggesting an incidence between 7 and 46%[65]. Factors that can impact this include altered body image due to often disfiguring scars patients may be left with, the traumatic nature of such an injury, the financial implications of a prolonged hospital admission or impaired physical functioning after injury.

A population based retrospective study conducted by Duke and colleagues found that individuals that had sustained a burn injury had a significantly increased risk of being admitted to hospital with a mental health disorder when compared to an uninjured cohort matched by age and gender[67]. The authors reported an incident risk ratio of 4.89 (95% CI 3.52-6.79), with 4% of the burn injured cohort requiring a hospital admission for a mental health condition, mainly self-harm or behavioural conditions due to alcohol or drug misuse.

Additionally, the presence of pain will often impact an individual's mental health. Several studies have investigated whether there is a link between pain and psychiatric disease.

Edwards et al[68] explored the link between acute pain and the risk of suicidal ideation following a burn injury. This longitudinal study investigated patients at discharge, 6 months and 12 months following a burn injury. Of the 128 participants that completed the follow-up period, 9.4% had active thoughts of suicide at discharge, 11.7% at 6 months and 14.8% at 12 months. Pain severity at hospital discharge was found to be the only predictor of suicidal ideation at follow-up.

Corry et al[42] investigated 171 patients admitted to a regional burn centre. They conducted questionnaires on pain, PTSD and quality of life until 24 months following hospital discharge. They discovered that the incidence of pain or symptoms of PTSD resulted in poorer function such as social interaction and physical mobility.

McGhee et al[69] investigated the link between acute pain scores at presentation and the development of PTSD in soldiers sustaining a burn injury in battle. They demonstrated that an increased pain severity at presentation was associated with an increased incidence of PTSD symptoms, regardless of the size and extent

of the burn injury or the injury severity score (ISS). Although this does not necessarily denote causality, it highlights the importance of adequate analgesia during the acute phase of injury and its potential to impact other long-term outcomes.

With the increasing awareness of the psychosocial impact that can occur after burn injury, there is a recognition that increased resource should be focused on understanding these wide-ranging consequences, quantifying them and implementing therapies to help burn survivors. Projects such as the Life Impact Burn Recovery Evaluation (LIBRE) group at Boston University, in collaboration with a variety of academic institutes, charities and professional bodies, focus on the challenges of returning to everyday life after burn injury and have published a variety of literature on developing methods to measure the social impact of burns[70,71], social problems after work-related injuries[72] and the impact of peer support on social reintegration[73].

1.3.4 Persisting Inflammation and Hypermetabolism

Although the acute hypermetabolic and catabolic effects of a burn injury are well recognised, it is only relatively recently that we have begun to appreciate the extent to which such systemic inflammatory and metabolic changes can persist for years.

Jeschke et al conducted a study in 977 children with burns involving greater than 30% TBSA and found significant physiological changes persisting for at least three years after the initial injury. These including increased cortisol and catecholamine levels, increased resting energy expenditure, elevated heart rate and cardiac output and elevated serum cytokines such as Interleukins IL-6, IL-8 and Granulocyte Colony Stimulating Factor (G-CSF)[74]. Such persisting pathological processes may result in a sustained loss of lean body mass[75], reduced bone density[76,77] and impaired muscle strength[78,79].

1.3.5 Infections and Immunity

Following the initial hyperinflammatory response seen shortly after burn injury, a more complex interplay of both pro- and anti-inflammatory cytokines can

persist for years. Cytokines such as IL-10, shown to remain elevated after burn injury, have been shown to impair the response to infection by supressing T helper cells and inhibiting cytotoxic T cell and macrophage activity[74,80–82].

This persisting immune dysfunction may be a contributing factor accounting for the higher rates of hospital admissions for infectious diseases in burn survivors seen in population-based studies[83]. Respiratory illnesses such as pneumonia and influenza were found to be common reasons for hospital admission in survivors of burn injuries[84].

1.3.6 Cardiovascular Disease

Following burn injury an increased risk of cardiovascular disease has been demonstrated in both adult and paediatric cohorts.

A prospective observational study by Hundeshagen and colleagues compared echocardiographic images and exercise tests of children that had sustained a burn injury of greater than 30% TBSA at least five years earlier with those of age-matched healthy controls. They demonstrated a reduced ejection fraction, impaired diastolic function and lower exercise tolerance in the burn injured cohort[85]. The authors also reported that 18% of the burn cohort had evidence of myocardial fibrosis on echocardiogram.

A longitudinal observational study of 23,450 patients conducted by the Western Australia Population-based Burn Injury Project found that adult survivors of burn injury were more likely to be admitted to hospital with cardiovascular disease, heart failure or cerebrovascular disease when compared to an uninjured cohort.[86]

1.3.7 Cancer

Considering the recognised interaction between immunosuppression and increased cancer risk, there has been growing interest concerning whether the immune system changes that occur after burn injury impact on the risk of developing a malignancy later in life.

Duke et al considered this question as part of the Western Australia Population-based Burn Injury Project, investigating the incidence of cancer in a cohort of patients admitted from 1983 to 2008. The results demonstrated no increase in risk for males, but a non-significant increase in risk for females with a standardised incidence ratio (SIR) of 1.12 (95% CI 1.00-1.28). When investigating a sub-cohort of patients admitted from 1983 to 1987, with maximal follow-up time, the authors reported an SIR of 1.39 (95%CI 1.15-1.69) in cancer risk for females[87].

Other studies have demonstrated conflicting results. Lindelof et al conducted a similar population-based study of 37,095 burn injury admissions and reported a slightly increased risk to both genders (SIR 1.11, 95% CI 1.06-1.16). However, a study of 16,903 burn survivors in Denmark by Mellemkjaer and colleagues found no change in cancer risk for either gender (SIR 0.99, 95% CI 0.93-1.06).

Duke and colleagues expanded their initial investigation to include a cohort of 37,890 burn injured patients from Scotland. This demonstrated a small but statistically significant increase in cancer risk for both genders from the Scottish data (SIR 1.09, 95% CI 1.05-1.10) but a more significant risk for females (SIR 1.3, 95% CI 1.2-1.4)[88].

Although there seems to be conflicting results from some of these studies, there remains biological plausibility for an increase in cancer risk following burn injury. The recurring results indicating a gender disparity in cancer risk after burn injury has sparked debate over the differences in immunopathology between genders. Some authors point to the impact of oestrogen on immune function, increased incidence of autoimmune disease in females and the altered response to illness and injury to account for this[89].

Several studies have demonstrated a gender dimorphism when focusing on other outcomes after burn injury. George et al demonstrated an adjusted risk of death after burn injury was approximately 30% lower in males, with this effect mostly accounted for by individuals aged 20 to 34[90].

1.3.8 Long-term Mortality in Burn Injury Survivors

Given the multitude of problems patients face following a burn injury, the psychological harm that can occur and the multi-system pathophysiological changes that persist, there is a strong indication that survivors of a burn injury are at an increased risk of early death.

Several longitudinal studies have highlighted this increased mortality risk. Duke and colleagues have published several papers from the Western Australia Population-based Burn Injury Project highlighting the increased risk of death across all age groups after burn injury[91-93]. In a cohort of 6014 patients over 45 years old that sustained a burn injury, the risk of death was 1.4 times greater (95% CI 1.3-1.5) when compared to a matched uninjured cohort. Of note, this increased mortality was risk was evident in both severe and minor burns, indeed even higher in those with minor burns (mortality rate ratio (MRR) 2.1, 95% CI 1.9-2.3)[93].

Mason et al conducted a retrospective study of 1965 adults that had survived a major burn injury in Ontario Canada between 2003 and 2013.When compared to a cohort matched by age, gender, socioeconomic deprivation and comorbidity, the authors reported an increased five-year mortality risk (Hazard Ratio (HR) 4.15 95% CI 3.17-5.42)[94]. The authors noted that the cause of death was frequently associated with mental health problems or trauma.

1.4 Burn Care in Scotland

Scotland is part of the United Kingdom, with a population of 5.46 million. The majority reside in the larger towns and cities of the central belt, although the geography of Scotland is such that many of the population live in more remote highland and island areas.

Similar to other developed nations, Scotland has an ageing population, with those over 65 years old now accounting for 19% of the population. Although deaths in Scotland have outnumbered births for five consecutive years, with the lowest number of births recorded in 2019 since records began, the population is growing due to increasing levels of migration[95].

Around 500 patients are admitted to hospital each year with a burn injury. The single most common cause of injury is by hot liquids (44%), but this number is even higher for children, accounting for 68% of injuries.

Reflecting a trend seen internationally, burn injuries are more likely to affect individuals residing in areas of socioeconomic deprivation, with those in the lowest quintile three times more likely to suffer a burn injury than those in the highest quintile[96].

1.4.1 COBIS (Care of Burns in Scotland)

COBIS is a national managed clinical network established in 2007 to enhance the delivery of care to patients who have suffered a severe burn injury. The network is comprised of a multidisciplinary team including medical, nursing, psychology, allied health professional staff, representatives from the Scottish Ambulance Service and Scottish Fire and Rescue Service, as well as input from third sector partners including charities.

The network and its members have multiple aims[96]:

- Improve the resources available for patients, their families and carers.
- Support the maintenance of a skin bank to supply skin allografts.
- Provide education and training to those involved in the management of patients with burns.
- Plan for major incidents to manage mass casualties where burn injuries feature.
- Maintain a database of complex burn injuries in Scotland.
- Audit the treatment of burns against nationally agreed standards.
- Maintain a website that provides guidance for both the public and protocols and educational material for medical professionals.

1.4.2 Tertiary Referral Centres

Individuals that suffer minor burn injuries are usually managed by local health services in Scotland. However, more complex burns were initially managed in one of the four adult or two paediatric tertiary referral centres. More recently, the burn care network in Scotland has evolved whereby all major adult and paediatric burn injuries are managed in centralised burn centres at Glasgow Royal Infirmary and the Royal Hospital for Children. Both centres are located in Glasgow, Scotland's largest and most populous city. Such injuries requiring tertiary referral input include:

- More extensive burns (greater than 25% TBSA in adults or 15% TBSA in children).
- All patients requiring level 3 intensive care unit (ICU) input and substantial early surgical intervention.
- Deep burn injuries requiring more than 10% TBSA excision.
- Burns involving areas such as the face, hands, feet or perineum.
- Circumferential, chemical or electrical burns.

1.4.3 Standards of Burn Care

In Scotland, the management of patients that have sustained a burn injury is held to various standards of care set by the British Burn Association (BBA) document, "National Standards for Provision and Outcomes in Adult and Paediatric Burn Care"[48]. This document was compiled by representatives from all aspects of the multi-disciplinary team involved in burn care, patients, survivor groups and charities. It details the elements considered essential to ensure high quality care of burn victims including[48]:

- How to ensure delivery of "patient-centred care" with advice regarding effective communication and support to patients and their families.

- The multi-disciplinary team that should be involved in burn care, the training and education for the team members and competences they should attain.

- The level of other clinical services that should be available including a wide range of medical specialties.

- The facilities, resources and environment necessary to provide specialist burn care including bed capacity, operating theatres, equipment and links to rehabilitation services.

- The policies and procedures, both clinical and operational, that are essential to a burn care service.

- Outline of clinical governance strategies including audit, research and data collection.

- The maintenance of a clinical network, linking centres that deliver burn care over geographical regions.

- Measuring clinical outcomes of interest that must be monitored and reported.

1.5 Research Aims and Questions

The vast majority of burn injuries are survivable with modern care, especially in a developed nation with a robust healthcare system such as Scotland. However, with this increasing survival is a realisation that these individuals can suffer long lasting and often profound consequences. As such, we should strive to better understand the impact of surviving a burn injury, quantify the burden placed upon healthcare resources and implement interventions to support the victims of burn injuries that experience this myriad of challenges.

I will utilise various national administrative and clinical databases to explore the long-term impacts of surviving a burn injury, focusing on morbidity, drug use and mortality.

This work will provide a detailed overview of the epidemiology of burn injuries in Scotland and the long-term consequences of sustaining such an injury. This work will help inform and focus future healthcare utilisation for this patient group.

I will aim to address the following research questions:

1.5.1 Are drugs used in the management of neuropathic pain effective in treating pruritus associated with burn injury?

Although now recognised as a common symptom after burn injury, the management of pruritus is often difficult. In recent years, drugs used for the management of neuropathic pain have been of increasing interest, including those initially licensed for use as anti-epileptics such as gabapentinoids. I will perform a systematic review and meta-analysis to explore the evidence behind the use of such medications in burn related pruritus.

1.5.2 Does a protocolised approach to managing pruritus improve symptom control?

Given the variability in pruritic symptoms and myriad of various treatment options available, does a protocolised method of drug administration and escalation of therapies result in effective management of pruritus after burn injury? I will analyse data collected in an adult burn tertiary referral centre to assess the utility of such a protocol and aim to quantify the effectiveness of each of the drugs used.

1.5.3 What are the epidemiological features of those affected by burn injuries in Scotland?

Using large national administrative health data, I will describe the patterns of burn injury that present to hospitals in Scotland and the demographics of the population they affect. I will explore the differences in burn injuries seen in children compared to those in adults. I will also describe the burden of comorbidity in the adult population, with a particular focus on mental health conditions, alcohol excess and drug misuse.

1.5.4 What factors are associated with mortality from a burn injury in Scotland?

I will describe the mortality of burn injuries in Scotland. In doing so, I will explore the impact that common predictors of mortality have in this population, including the size of the burn injury, age of the individual and presence of an inhalation injury. Beyond this, I will explore the impact that other factors such as sex, socio-economic deprivation and pre-existing comorbidity has on mortality.

1.5.5 What is the incidence of prescription drugs use to manage pain and mental health conditions in patients that suffer a burn injury?

Burn injuries and mental health conditions are intricately linked. Pre-existing mental health conditions, including alcohol and drug misuse, are recognised risk factors for sustaining a burn injury and may be associated with poorer outcomes[97–99]. Equally, the psychological harm that can occur as a consequence of burn injury is well recognised but potentially under-reported[100].

I will explore the prevalence of mental health and chronic pain conditions among patients that sustain burn injuries using drug prescription data to identify those taking antidepressants, anti-psychotics, benzodiazepines and opioids. This will improve our understanding of the link between mental health conditions and the risk of sustaining a burn injury.

1.5.6 Following burn injury, what factors are associated with increased use of opioids, benzodiazepines and other drugs used in mental health conditions?

Using drug prescription data regarding opioids, gabapentinoids and other agents used in pain management, we will explore the use of these drugs both before and after burn injury. This will help inform us of the incidence of chronic pain and analgesic use after injury, as well as the incidence of chronic use of such drugs. I hypothesise that the persisting consequences of a burn injury, including the multi-system pathophysiological changes and the psychological sequelae of such an injury, will result in an increase in the use of prescription drugs for

conditions such as depression, anxiety and pain. I will explore what factors are associated with any such increase in the use of these drugs.

1.5.7 What factors are associated with death in the years following burn injury?

Some studies demonstrate an increased risk of death in the years after burn injury[91-93]. The explanation for this may be due to the persisting pathological inflammatory and immune changes that persist after burn injury. Equally, excess mortality may also be due to pre-existing health problems that may even have contributed to the original risk of sustaining such a burn injury. I will investigate the mortality in the years after injury in more detail, describing the causes of death, time to death and identify any factors that may help predict early death after burn such as age, injury severity, socioeconomic deprivation, comorbidity and pre-injury drug use.

Chapter 2 Methods

This thesis describes studies using varying methods and data sources. Firstly, a service improvement project is described using local paper and electronic health record data.

Secondly, a retrospective observational study was carried out using national clinical and administrative datasets to identify patients that had been admitted to hospital for treatment of a burn injury between January 2012 and December 2015.

2.1 Setting

These studies were carried out in Scotland, a country within the United Kingdom, with a population of 5.46 million. Around 500 individuals are admitted to Scottish hospitals every year as a result of a burn injury, with many more managed in emergency departments or in the community as outpatients.

During the period of this study, specialist burn care was delivered by a nationally managed clinical network which included burn centres at Glasgow Royal Infirmary and St John's Hospital, Livingston where the most severely injured adult patients were cared for. Other burn facilities were available at Aberdeen Royal Infirmary and Ninewells Hospital, Dundee. Specialist paediatric burn units cared for patients under 16 years old at specialist children's hospitals in the largest cities of Glasgow and Edinburgh.

Burn care in Scotland has since evolved with the formation of a "hub and spoke" model to centralise major and complex burn care for adults and children within NHS Greater Glasgow and Clyde, the largest health board in Scotland. Such a realignment of services allows expertise in major and complex burn care to be concentrated in one area of the country. This model also includes strengthening links between the existing Care of Burns in Scotland (COBIS) network and the Scottish Trauma Network (STN).

Scotland's healthcare service is delivered primarily by the National Health Service, a publicly funded body operating across 21 health boards. This system

allows central registration of patient information to maintain health records at an individual, institutional and national level.

2.2 Data Sources

Data used in this study was linked across various sources using the Community Health Index (CHI) number, a unique 10-digit identifier allocated to an individual on first registration with an NHS Scotland health service. This unique identifier allows rapid identification of an individual across any area of the health service, remains constant throughout a patient's life and allows linkage of data across multiple sources.

2.2.1 COBIS (Care of Burns in Scotland)

COBIS is a national managed clinical network established in 2007 to enhance the delivery of care to patients who have suffered a burn injury. Members of the network caring for patients, usually nurses or clinicians, input patient level data, linked to a patient's CHI number, using the electronic Clinical Audit System (CAS). This data includes details regarding patient demographics and comorbidities as well as burn injury details including size and depth, mechanism of injury and any interventions carried out.

The data collected by COBIS is managed by a data sub-group and is commissioned by the National Service Division of NHS national Services Scotland to submit bi-annual progress reports to be measured against various objectives and quality indicators.

2.2.2 SMR01 (Scottish Morbidity Record 01)

The SMR01 dataset has recorded all inpatient and day case admissions to acute specialties within NHS hospitals in Scotland since 1961. Each patient admission generates a new SMR01 record which is linked to the patient's unique CHI number. A single hospital admission may generate more than one SMR01 record, with a new episode being created following events such as change of specialty, change of consultant or transfer to another facility.

The primary condition resulting in hospital admission is recorded using the World Health Organisation (WHO) International Classification of Diseases 10th revision (ICD-10) codes, as are up to five other conditions related to the patient's reason for admission or existing comorbidities. Other demographic information is recorded including age at admission, ethnicity, Scottish Index of Multiple Deprivation (SIMD) and Urban Rural (UR8) classification. The conclusion of an episode is recorded, noting whether this was due to hospital discharge, transfer to another facility or death.

The SMR01 dataset is regularly subject to external validation and audit and consistently demonstrated to be greater than 98% complete.

2.2.3 SMR04 (Scottish Morbidity Record 04)

The SMR04 dataset is similar in structure to the SMR01 dataset but is used to record care episodes that occur within psychiatric facilities including inpatient admissions and day case episodes whereby the primary pathology of concern is a mental health condition.

2.2.4 PIS (Prescription Information System)

The PIS database records all NHS Scotland prescriptions dispensed in the community. The data are sourced from monetary claims made by pharmacy contractors when a medicinal product is dispensed to a patient. This will not record medicines that are prescribed but not dispensed, therefore never taken by the patient.

This database will not record any private prescriptions whereby the patient pays for a medicine. This situation is generally rare in Scotland as all prescription charges were abolished in April 2011. Generally, the only medicines dispensed on a private prescription would be certain travel vaccines, malaria prophylaxis and certain drug treatments felt to be inappropriate to spend public money on such as branded drugs when a cheaper generic equivalent is available.

This database is frequently monitored for accuracy, with audits of random samples of 5% of all prescriptions carried out regularly, routinely meeting the 98% accuracy target.

2.2.5 NRS (National Records of Scotland)

The National Records of Scotland (NRS) is a non-ministerial department of the Scottish Government that collects and stores data regarding a variety of information including all births, deaths and marriages in Scotland.

This study used the death registration data from NRS which includes individual level data from the Medical Certificate of the Cause of Death (MCCD). This is completed by a medical practitioner and states the date of death, age at death and place of death. This data also includes details regarding the condition or disease that directly led to death, any antecedent of intermediate causes of that disease or condition and the underlying cause of death ie. "the disease or injury which initiated the chain of morbid events leading directly to death"[101,102].

2.2.6 Local patient level data

The study described in chapter 4 was carried out in the burns ward at Glasgow Royal Infirmary, a tertiary referral centre for adult burn injuries covering the west of Scotland. Data was collected prospectively from patients regarding pruritus severity using a paper proforma that was retained in the patient's clinical notes. Data regarding demographics, clinical details, laboratory results and drug prescription data were collected retrospectively using the Clinical Portal (Orion Health, Glasgow, UK) electronic patient record system and the Care of Burns in Scotland (COBIS) national managed clinical network audit database.

2.3 Approvals

2.3.1 Nationally linked data

All data obtained from nationally linked records included COBIS, SMR01, SMR04, PIS and NRS databases. An application for release of the required data was granted by the Public Benefit and Privacy Panel, a patient advocacy panel that scrutinises applications for access to NHS Scotland health data when it is to be used for purposes other than direct patient care. The panel consists of representatives from a variety of backgrounds including senior NHSS Board representatives, Caldicott guardians, information governance practitioners,

research community representatives, Information Technology (IT) security specialists and the public.

Datasets were accessed and linked by the electronic Data Research and Innovation Service (eDRIS), part of Public Health Scotland (PHS), that support researchers and provide access to administrative datasets.

Ethical approval was not sought for this study as any secondary analysis of such National Services Scotland (NSS) data, accessed through eDRIS, has been approved by the East of Scotland NHS Research Ethics Service. To meet these conditions a study must fulfil the following criteria:

- be in the field of Health or Social care research.
- not involve any contact with research participants/subjects.
- have undergone scientific peer review.
- include data held in and accessed via the national safe haven.
- be carried out by UK based researchers only.

Consent from individuals included within the data was not required. The National Data Guardian for Health and Care document "Review of Data Security, Consent and Opt-Outs" states that the use of national linked data is required for running the health and social care system, improving the safety and quality of care and research[103].

2.3.2 Local patient level data

Caldicott guardian approval was granted for the collection and analysis of patient level data, as well as the dissemination and publication of any results.

Caldicott guardians are responsible for agreeing and reviewing internal protocols governing the protection and use of patient-identifiable information by the staff within their organisation and across organisational boundaries. Caldicott guardians apply these protocols using a set of eight Caldicott principles[104]:

- The purpose of using confidential information must be justified.
- Confidential information must be used only when necessary.
- The minimum confidential information necessary must be used.
- Access to confidential information must be on a strictly need-to-know basis.
- Each individual with access to the information is aware of their responsibilities.
- Use of confidential information complies with the law.
- The duty to share information for individual patient care is as important as the duty to protect patient confidentiality.
- Patients and service users should be informed about how their confidential information is used.

2.4 Data Access

2.4.1 Nationally linked data

Data linkage was carried out by the electronic Data Research and Innovation Service (eDRIS). Data was anonymised of patient identifiable information prior to use by the project investigators and stored in accordance with the General Data Protection Regulations (GDPR) and the Data Protection Act 1998 in the National Safe Haven via National Services Scotland (NSS).

Any individuals accessing and analysing data had completed the Medical Research Council (MRC) e-learning course in Research Data and Confidentiality and signed the eDRIS User Agreement which details acceptable use and penalties for misuse. As per the eDRIS User Agreement, researchers would inform the Safe Haven research co-ordinator of any breaches. Access to the National Safe Haven is routinely monitored and audited.

The National Safe Haven uses the NSS Document Storage, Retention and Disposal Policy. Study data will be archived for 5 years in the NSS Safe Haven. The National Safe Haven uses NHS Scotland Information Security Policy for guidance regarding the destruction of data.

2.4.2 Local patient level data

Data were collected and stored on password protected National Health Service Greater Glasgow & Clyde (NHS GGC) computers or an encrypted USB memory stick. All data were anonymised with the removal of names, dates of birth and post-codes before storage.

2.5 Population

Exploring the nationally linked data, the population of interest were patients admitted to hospital with a primary diagnosis of burn injury. All hospitalisations as recorded in the COBIS dataset between 2012 and 2015 were identified. Using the unique CHI numbers, data from SMR01, SMR04, PIS and NRS (deaths) were linked to the COBIS data for the duration of the study and the 5 years previous to the index admission for each patient. No restrictions were made regarding the age of patients.

2.6 Definition of Variables

2.6.1 Index Burn Injury

The data provided by the COBIS database provided information on the details of the burn injuries sustained by individuals in the study. This included the date of injury, age at injury, anatomical site or sites injured, percentage of TBSA affected, depth of burn and mechanism of injury.

Any missing data from these fields was substituted by data extracted from the SMR01 dataset, whereby TBSA of injury is categorised as per the ICD-10 diagnosis according to T20-T25, “burns and corrosions of external body surface”, specified by site and the supplementary code in T31, “burns classified by extent of body surface area involved”.

These methods of identification of burn injured patients are effective at identifying those admitted to a burn unit or facility and cared for by specialists in burn care. This data does not identify patients with minor burns managed as an outpatient, those admitted under a specialty other than a burn care unit or those who die in the emergency department or before arrival at hospital.

2.6.2 Comorbidities

Comorbidities were extracted from the COBIS, SMR01 and SMR04 databases. Comorbidity information is input using the CAS system to the COBIS database by clinical staff directly caring for the patient concerned. This data is input using a drop-down menu with a limited number of 16 broad comorbidities such as epilepsy, diabetes mellitus, alcohol dependence syndrome, intravenous drug user (IVDU) and psychiatric history.

Given the lack of detail available within the COBIS data to fully determine the comorbidities of patients within the study, this was supplemented with data from the SMR01 and SMR04 databases. These datasets record the primary condition resulting in hospital admission, in addition to up to five associated conditions relating to the patient's admission or underlying health conditions. This method of extracting comorbidity data using these administrative healthcare databases has been previously validated by comparing these data with clinical records[105].

These conditions are recorded using alphanumeric ICD-10 codes. These codes allow for categorisation of disease or injury using the first three characters, with the first character denoting the body system affected or group of illnesses and subsequent characters providing the type of injury or disease. Increasing levels of detail can be provided by subsequent characters to a maximum of seven. This system allows for simple categorisation and comparison with increasing levels of detail and complexity as needed.

Comorbidity data was also used to calculate the Elixhauser comorbidity index to summarise the burden of comorbidity for each patient[106]. This method uses ICD codes to identify comorbidities from 30 broad categories. The sum of these comorbidities results in a single comorbidity score, with a higher score

predicting increased mortality and healthcare resource use. The Elixhauser method was also chosen in preference to other methods such as the Charlson[107] comorbidity score due it its inclusion of domains including alcohol excess, illicit drug use and psychiatric disease. These are common risk factors among adults that suffer burn injuries.

This method of comorbidity assessment has been updated since its initial conception to reflect changes in ICD coding and advances in healthcare and chronic disease management[108,109]. Additionally, other researchers have expanded upon the original work done by Elixhauser et al in an attempt to condense the extensive list of comorbidities into a single numeric. Van Walraven et al developed a modified Elixhauser index using 21 of the comorbidity categories that independently predicted hospital mortality[110]. Moore at al validated a weighted index using the Elixhauser categories to predict hospital mortality using data from over 10 million hospital admissions [108].

These methods of comorbidity assessment assign a weight, positive or negative, to each Elixhauser comorbidity. A positive value associated with a particular comorbidity signifies increased likelihood of mortality. A negative value would indicate a reduced risk of death, the explanation for such comorbidities, including valvular disease, obesity and depression, has been hypothesised to be a reflection of potential bias in coding of minor ailments in relatively healthy patients due to a lack of other more significant diseases to document[110]. Both studies by Van Walraven et al and Moore et al reported improved discrimination of such indices when compared to non-weighted counts of comorbidities, therefore both of these indices were incorporated into the comorbidity analysis of this study.

Data from the PIS database of community drug prescriptions was further used as a surrogate marker of comorbidity and burden of ill-health. The PIS database records each drug dispensed with its corresponding British National Formulary (BNF) item code. The BNF is a widely used pharmaceutical reference book. The item codes relate to the chapter and sub-sections which are ordered by body systems such as cardiovascular or respiratory system, therefore allowing identification by broad disease category. Additionally, drugs of specific interest, especially those used in chronic pain or mental health conditions, such as

opioids, anxiolytics and antidepressants were investigated in more detail, being used as surrogate markers of underlying chronic pain or mental health problems.

2.6.3 Socioeconomic Measures

Socioeconomic deprivation is estimated using the Scottish Index of Multiple Deprivation (SIMD) based on an individual's postcode of residence. To calculate the SIMD, Scotland is divided in to 6976 geographical areas and ranked from the least to the most deprived. This method takes into account variables such as income and benefits, employment, health and healthcare utilisation, educational attainment, access to services and transport, crime rates and housing quality. Scores generated for each domain contribute varying weight to the overall SIMD score for each geographical area. These are then presented as quintiles with 1 representing the least deprived and 5 the most.

The SIMD is a coarse, area-based estimate of relative deprivation but does not provide enough granularity to make individual level assessment of deprivation. Rather it is the best available assessment of deprivation by describing the geographical area in which the individual resides.

2.6.4 Survival data

The date and cause of death were taken from the NRS dataset. Cause of death is described using ICD-10 codes and summarised into categories based on these codes.

2.6.5 Drug Prescriptions

Drug prescription data from the PIS dataset was used to supplement information regarding comorbidities of patients in the study, with a particular focus on the use of analgesics and drugs used in mental health conditions. This dataset was also used to describe prescribing patterns of these medications following injury.

Medications were explored broadly in terms of the chapters and sub-sections in which they appear in the BNF, but also by specifically named drugs or classes of drugs of particular interest including opioids, benzodiazepines and gabapentinoids.

Drug prescriptions were described in terms of their time to first prescription following discharge after burn injury and the duration for which a drug is prescribed. Any individual prescribed a drug for three or more months within a 12-month period was considered a "recurrent user"[111].

2.7 Statistical Analysis

Statistical analyses were performed using R version 3.6.1 (Foundation for Statistical Computing, Vienna, Austria), a free software environment for statistical computing and graphics.

2.7.1 Descriptive Analysis

The descriptive analysis of categorical variables including patient demographics and injury patterns were expressed as frequencies and percentages. Continuous variables were summarised using median values and inter-quartile ranges unless otherwise stated.

Pearson's Chi-squared test, Fishers exact test and Wilcoxon rank sum test were used to assess for differences in any subgroups, for example when describing the differences in demographics and burn injury patterns between adults and children.

Pearson's Chi-squared test is a statistical test of the null hypothesis applied to categorical data to evaluate the likelihood of any observed differences occurring by chance. To conduct this test the squared difference between the observed frequency and expected frequency were divided by the expected frequency for each outcome and summed to give a Chi-square value. This value in addition to the degrees of freedom were used to calculate a p-value. This test relies on various assumptions of the data including that the sample is random, the sample size is sufficiently large, the expected cell count is at least 5 in all cells and each observation is independent of the others. In the event of such small sample sizes, a Fisher's exact test was used instead.

The Wilcoxon rank sum test, also known as the Mann-Whitney U test, is a non-parametric test that can be used to determine whether two samples were likely

to derive from the same population with the same distribution. Variables were ranked in order and the sum of those ranks for each population calculated. A U-statistic was then calculated to either reject or accept the null hypothesis.

2.7.2 Survival Analysis

Survival analysis was conducted to explore two outcomes; death due to burn injury (chapter 5) and death following survival of the index burn injury (chapter 7). The former was defined as any patient that died within 30 days of sustaining a burn injury. The latter outcome excluded patients that died within 30 days of injury.

Kaplan Meier survival curves were plotted, including for specific subgroups determined by factors including age, gender, SIMD quintile, TBSA burned and pre-existing comorbidities. The Kaplan Meier estimator is a non-parametric statistic used to estimate the survival function of a group over a period of time. A Kaplan Meier curve is a graphical representation used to describe the survival times of each group. The advantage of Kaplan-Meier analysis in conducting such observational survival analysis is that it takes account of various forms of censoring, especially “right-censoring” whereby the length of follow-up time available for each individual in a study may differ significantly.

A survival function is a mathematical representation to describe the probability that, in this case, a patient will survive beyond a certain time point. Survival functions can manifest as a variety of distributions including normal, exponential, Weibull and others. Non-parametric distributions can be accounted for by using the Kaplan-Meier technique. The log-rank test was used to compare groups, with a p-value <0.05 signifying statistical significance. The log-rank test is a non-parametric test whereby the null hypothesis states that no difference between two differing groups survival curves exists. Calculations are performed each time an event occurs, computing the observed and expected number of events for each group to obtain a summary across all time points. For this reason, the log-rank test is most effective when the risk of the event is consistently different for one group over another, being less likely to detect a difference if the survival curves cross at any point. Hence, Kaplan-Meier curves were always visualised when analysing this data.

Further survival analysis to explore variables, commonly termed covariates in survival analysis literature, associated with mortality risk was carried out using Cox proportional hazard models. This statistical technique is used to calculate a hazard ratio, the odds that an individual within a group reaches the event, in this case death, first.

The hazard function can be represented mathematically as:

$$h(t) = h_0(t) \times \exp(b_1x_1 + b_2x_2 + \ldots + b_px_p)$$

This can be interpreted as the hazard function h(t) represents the risk of an event at time t, determined by a set of covariates (x1, x2, xp). The coefficients (b1, b2, bp) represent the effect size of each covariate and h0 is the baseline hazard if all covariates are equal to zero.

Hazard ratios represent the risk for the duration of the entire study period and rely on the assumption that the ratio of hazards between groups remains constant through time. This assumption of proportionality must be adhered to as any violation may invalidate the analysis. The proportionality of hazards assumption can be assessed by visualising the data or using statistical tests such as Schoenfield residuals. Schoenfield residuals are calculated for all covariates for each individual at the time of event, with the differences between each individual's value and the corresponding risk-weighted average covariate value for all individuals. The difference between the measured and expected value for each covariate should remain constant over time. Statistical software within the R package can plot the Schoenfield residuals and report the p-values to describe the likelihood of any violations of the assumption of proportionality. Any variables that violate the assumption of proportionality can be accounted for by providing an interaction with time or using another method beyond Cox regression for analysis.

Construction of a Cox proportional hazards model begins with univariable analysis, whereby each variable of interest is explored separately while ignoring the impact of other variables. Any variables found to be statistically significant as determined by a p-value of <0.1 were then included in a multivariable Cox-proportional hazards model. This method of multivariable regression analysis

was used to describe the impact of each variable while adjusting for other variables with independent effects on the outcome of interest. Selection of variables that remained significant within the multivariable model were identified using a backwards stepwise approach whereby non-significant variables were eliminated using a p-value of <0.05 as a cut-off.

2.7.3 Drug Prescription Analysis

Drug prescription patterns following burn injury were analysed using a multi-level Poisson non-linear regression model to explore variables associated with an increase in prescription drug use after the injury (chapter 6).

A Poisson regression can be conducted when the distribution of the response variable, in this case drug prescriptions, follows a Poisson distribution. This describes the discrete probability distribution that a number of events occurs in a fixed interval of time and occur independently of each other.

Multilevel models, also known as mixed-effect models, nested models or random effects models, are statistical models that allow for variation of parameters at more than one level. This method of analysis is advantageous in that it accounts for variation between individuals or groups. In this case, the level being accounted for was the variation in drug prescribing patterns between individual patients, such that the variation in available follow-up time and influence of pre-injury prescription drug use can be built into the model. The nature of this data, with repeated measures over time, also lends itself to multi-level modelling whereby the varying number of prescriptions and varying time intervals between them present a form of hierarchical data with within-patient variability. This method of analysis helps account for heteroscedasticity and assumptions of independence between drug prescriptions within an individual.

Univariable analysis was first conducted to assess any variables associated with an increase in prescription drug use following burn injury. Any variables with a p value <0.1 were included in the multivariable analysis and a backwards stepwise regression approach used to build a model. Statistical significance was set at a p value <0.05. Akaike's Information Criteria (AIC) and chi-squared difference test

were used to assess model fit. Residual plots and quantile-quantile plots were used to assess the assumptions of each model.

2.7.4 Pruritus treatment analysis

In order to assess the effectiveness of various drugs used in the management of pruritus (chapter 4), a multilevel interrupted time series analysis was carried out. This method of statistical analysis describes the time series as the data over the specified time period and the interruption as the intervention of interest. The effects of the intervention are measured by the change in level of the time series data and the slope of change following the intervention whereby statistical significance can then be assessed.

Similar to previous analysis used to explore drug prescription data, a multilevel approach was used to account for the 'between-patient' variability in the outcome of interest, namely the severity of pruritus. A multilevel approach allowed for variation in length of time each individual was investigated and variation in the severity of pruritus experienced between individuals.

An interrupted time series analysis uses a regression model with three time-based covariates to produce regression coefficients to describe the pre-intervention slope, the change at the intervention point and the change in slope after intervention. A time series analysis can be represented mathematically as:

$$Y = \beta_0 + \beta_1(\text{Time}) + \beta_2(\text{Intervention}) + \beta_3(\text{Time*Intervention})$$

- Y = Outcome variable.
- β_0 = Intercept.
- β_1 = Slope of trend before intervention.
- β_2 = Change in slope at intervention.
- β_3 = Change in slope of trend after intervention.

Chapter 3 Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis

3.1 Introduction

Although burn injuries occur as acute traumatic insults, there is increasing recognition that such injuries can have far reaching and long-lasting consequences. There is a high prevalence of sensory disorders such as chronic pain, paraesthesia and pruritis in survivors of burn injuries[52,63]. The incidence of pruritus has been reported to be 93% at hospital discharge[59], 67-73% at 2 years[59,60] and 44% at 4-10 years[59]. Factors such as deep dermal injury, greater total body surface area (TBSA) burned, an increased number of surgical interventions, female gender and symptoms of post-traumatic stress disorder (PTSD) increase the risk[60].

Although pruritus may be thought of as a fairly minor symptom, the impact it can have on an individual's quality of life can be immense. Several studies have demonstrated that persisting pruritus can affect sleep, mood, the ability to carry out daily activities and psychological well-being, including increasing the risk of suicidal thoughts[60,112].

3.1.1 Pathophysiology of pruritus

The pathophysiology underlying the sensation of pruritus is complex and multifactorial. A subset of afferent slow conducting C-fibres are activated by pruritogens such as histamine, produced from mast cell degranulation and as a by-product of collagen formation. However, other pruritogens such as acetylcholine, calcitonin gene-related peptide (CGRP), bradykinin, leukotrienes, prostaglandins and various cytokines also play important roles in the activation of such nerve fibres[61].

Following activation, these C-fibres conduct impulses in a similar manner to the pain pathway via the dorsal root ganglion, spinothalamic tract, thalamus and then to various higher centres including the somatosensory cortex[61,62]. Although the neuronal pathways involved in the perception of pain have been extensively

explored, the equivalent neuroanatomical basis for pruritus remains less clearly understood. Pain and pruritus share a similar neurophysiological basis, thought to be a consequence of evolutionary changes. The pain pathway evolved to elicit a withdrawal reflex, whereas the pruritus pathway provokes a desire to scratch the affected area. This action may have conveyed an evolutionary advantage, whereby toxic or harmful material would be removed from the skin before any damage could be done[61].

Additional similarities have been drawn between chronic pruritus and neuropathic pain. Clinical features such as hyperknesis (increased sensitivity to pruritic stimuli) and alloknesis (pruritic sensation evoked by a stimulus that is not normally pruriceptive) mirror the hyperalgesia and allodynia seen in neuropathic pain[62,113,114]. Such pathological processes are reflected in the classification of pruritis, demonstrating the differing pathological process occurring at different points along the pruritus pathway:[114]

- Pruritogenic. The source of pruritus originates in the skin.
- Neuropathic. A pathological process has affected some part of the afferent pruritus pathway.
- Neurogenic. Central nervous system dysfunction occurs, with or without anatomical pathology.
- Psychogenic. Pruritus associated with an underlying psychiatric condition.

3.1.2 Management of pruritus

Achieving meaningful control of burn related pruritus symptoms can be difficult and there is a paucity of clinical trials evaluating interventions[115–119]. A survey carried out in the UK showed that over 90% of burns units use antihistamine drugs as the first line treatment[120]. However, the involvement of various other peripherally acting pruritogens and the pathophysiological changes that occur more centrally mean that antihistamine monotherapy is often inadequate, especially in chronic pruritus[62].

Drugs classically used in the management of neuropathic pain have been postulated as being potentially beneficial in the treatment of burn-related pruritus. Drugs such as gabapentin may inhibit the release of excitatory neurotransmitters such as glutamate along the pruritic pathway, offering an alternative therapeutic target beyond peripheral pruritogens. Many clinicians have advocated for the use of these drugs as first line agents in the management of pruritus from burn wounds[112,121].

The use of such neuropathic pain drugs may confer additional benefits as analgesic agents and potentially reduce opioid requirements. The anti-neuropathic effects of drugs such as tricyclic antidepressants and gabapentinoids are increasingly being used in a spectrum of painful and pruritic conditions, often in the absence of licensing[122–131]. Such expanded use of these drugs has seen an increase in gabapentinoid prescriptions across the UK, Europe and North America[111,132–134]. However, the potential harm from such agents, particularly gabapentinoids, is becoming clear. A systematic review of 59 studies highlighted the increasing use of gabapentinoids for recreational use and abuse, particularly in those with existing drug abuse disorders or psychiatric conditions[135]. In Scotland, gabapentinoids are increasingly implicated in drug related deaths, with toxicology reports from 2017 implicating gabapentin in 14% of such deaths and pregabalin in 12%[111]. Robust evidence is therefore required to ensure that the benefits of using such medications to manage burn-related pruritus outweigh the risks.

The objective of this systematic review and meta-analysis is to evaluate the effectiveness of agents used in neuropathic pain, as detailed by the National Institute of Clinical Excellence (NICE)[136], in the management of pruritus following a burn injury.

3.2 Methods

This review was registered on the PROSPERO Register of Systematic Reviews, ID number CRD42020164777. The PRISMA guidelines for the conduct of systematic reviews were followed throughout[137].

3.2.1 Eligibility Criteria

Articles were included that investigated the management of pruritus in patients of any age that had sustained a burn injury with the use of neuropathic agents that are listed in the NICE Guideline (CG173) "neuropathic pain in adults: pharmacological management in non-specialist settings"[136]. Given the likelihood of several studies being observational in nature, no restrictions were made regarding the use of a control group. Animal studies, human volunteer studies, literature reviews and conference abstracts were excluded, otherwise no restrictions on the type of study were made.

3.2.2 Search Strategy

Three databases, MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched with no time period or language restrictions (last accessed 07/01/2021).

3.2.3 Study Selection

Following amalgamation of search results from the three sources and removal of duplicates, two reviewers independently conducted a title review, abstract review then full article review to select articles for inclusion. Any disagreement between the two reviewers was resolved by a third reviewer. The references of all titles included in the data analysis were screened for further articles to be included.

3.2.4 Data Extraction

Data was extracted using a pre-defined spreadsheet which included study design, patient demographics, interventions and outcomes. In the event of missing data, study investigators were contacted.

3.2.5 Outcomes Measured

The outcome of interest was the severity of pruritus at any time point. No specific restrictions were used, with all quantitative severity scales, qualitative measures and questionnaire methods of assessment included. For inclusion in

meta-analysis, any quantitative scales were converted to an 11-point continuous scale and the mean difference between groups reported.

3.2.6 Risk of Bias Assessment

Each included study was assessed independently by two reviewers using a specific risk of bias tool. The RoB2 (the updated Cochrane risk of bias tool) was used for randomised control trials, and ROBINS-I tool for non-randomised studies. The quality of evidence for the outcomes of interest were assessed using the GRADE system[138].

3.2.7 Data Synthesis

Studies were categorised based on the intervention studied, specifically the neuropathic agent of interest, and are presented in tables for each class of agent. In controlled studies using the same drug or class of drug (e.g. gabapentinoids) and comparable outcome measures (e.g. a continuous variable such as visual analogue scale), results were collated using a random-effects meta-analysis, and two-sided p-values and 95% confidence intervals were calculated. Heterogeneity was expressed as an I^2 statistic for studies included in meta-analyses, with a measure of 25%, 50% and 75% representing small, moderate and significant heterogeneity respectively.

No specific sensitivity analyses were carried out; however, studies were stratified by their risk of bias and meta-analyses were conducted separately for those at high and low/moderate risk and then combined.

For agents where only case series or observational studies were available, a narrative review of the study findings was undertaken.

Numeric data were extracted from graphs if the required data was not included elsewhere in an article using Graphgrabber (v2.0.2, Quintessa Ltd). Meta-analysis was conducted using the software package Revman 5.4.1 (The Cochrane Collaboration).

3.3 Results

3.3.1 Study Inclusion

The literature search returned 5469 articles after removal of duplicates. The PRISMA flowchart (Figure 3-1) details the selection process. One paper required translation from Chinese.

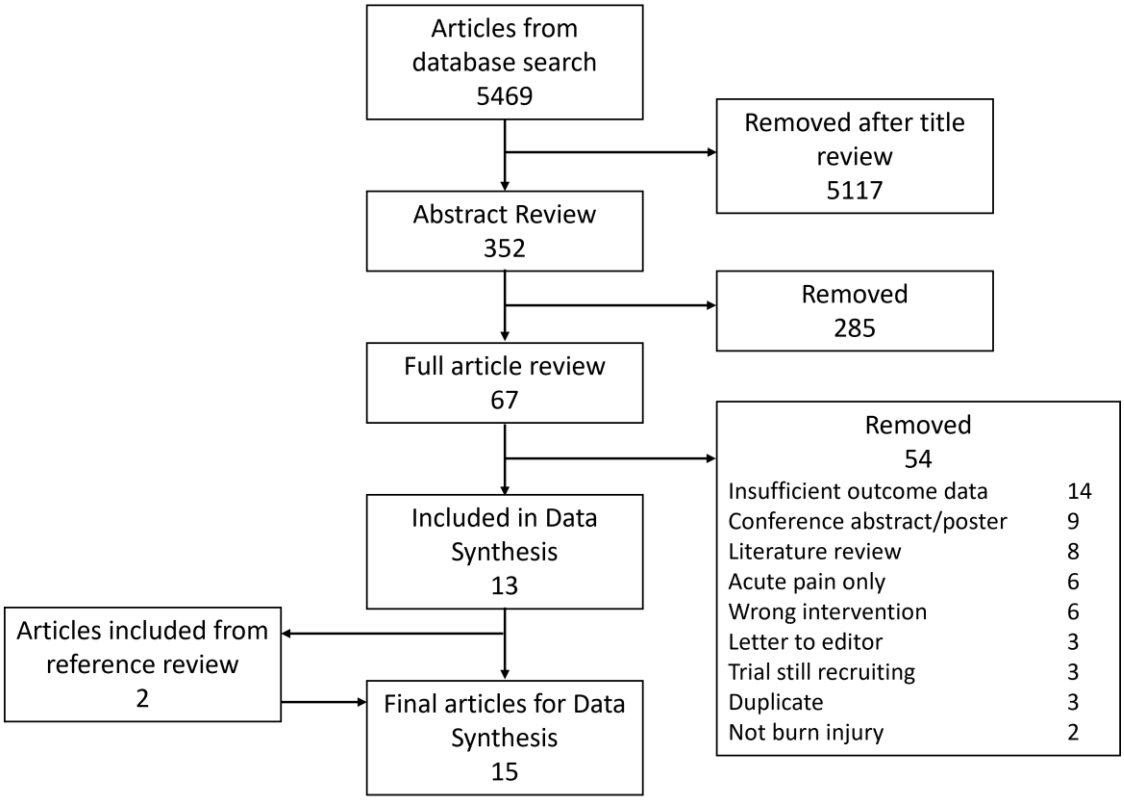

Figure 3-1 PRISMA flowchart of study selection. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Three main classes of neuropathic agents were investigated in the articles included in the final analysis:

- Gabapentinoids (gabapentin and pregabalin).
- Topical doxepin.
- Topical local anaesthetic agents.

3.3.2 Gabapentinoids

Ten articles[139-148] investigated gabapentinoids in the management of pruritus after burn injury. Four studies were randomised control trials (Table 3-1) and 6 were observational studies with varying methodology (Table 3-3).

3.3.2.1 Randomised Controlled Trials

Three RCTs provided sufficient data to perform meta-analyses. A risk of bias assessment is presented for each study (Table 3-2). Two studies[139,148] included groups comparing gabapentin to a control arm given cetirizine, an antihistamine. Both studies demonstrated a mean reduction in pruritus severity, measured on 0-10 VAS (Visual Analogue Scale) of around 6 points in the gabapentin group over the 28-day trial period. Those treated with cetirizine had a reduction of 3.9 and 3.5. The meta-analysis demonstrated a greater reduction in VAS score of 2.19 (95% CI 1.74-2.63) with gabapentin compared to cetirizine (Figure 3-2).

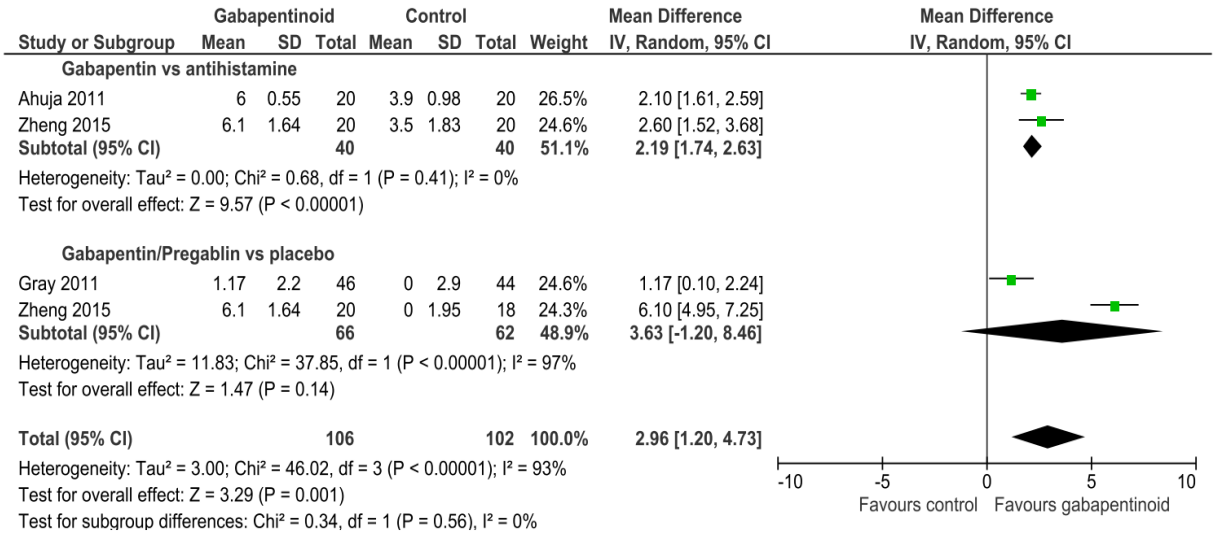

Figure 3-2 Forest plot showing the reduction in mean VAS (Visual Analogue Scale) in each treatment arm, comparing gabapentinoids to controls. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Table 3-1 Randomised control trials of gabapentinoids NPS: Neuropathic Pain Scale; QOL: Quality of Life. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Study	Year	Setting/Design	Inclusion Criteria	Patient Number	Age	Intervention Groups	Gabapentinoid Dosing Regimen	Outcomes	Follow-up
Zheng et al[148]	2015	Single centre RCT	>5%TBSA, 2nd degree burn, >80% healed or healed within 3 months	58	18-60yrs	1. Gabapentin 2. Cetirizine 3. Placebo	Gabapentin 300mg BD	Pruritus VAS	28 days
Ahuja RB et al[140]	2013	Single centre RCT	>5% TBSA, 80% epithelialised or healed within 1 month	80	18-60yrs	Four groups: 1. Antihistamine 2. Pregabalin & Antihistamine 3. Placebo 4. Pregabalin	Pregabalin varied with severity of pruritus: Mild - 75mg BD Moderate - 75mg TDS Severe - 150mg BD	Pruritus VAS	28 days
Ahuja RB et al[139]	2011	Single centre RCT	>5% TBSA, 80% epithelialised or healed within 1 month	60	12-70yrs	Three groups: 1. Cetirizine 2. Gabapentin 3. Combination Cetirizine & Gabapentin	Gabapentin varied with severity of pruritus: Mild – 300mg OD Moderate – 300mg BD Severe – 300mg TDS	Pruritus VAS	28 days
Gray et al[142]	2011	Single centre RCT	Admitted to burn unit, >5% TBSA	90	18-65yrs	1. Pregabalin 2. Placebo	Pregabalin 75mg BD, titrated up to 150mg BD or 300mg BD based on clinical response	NPS (includes itch score 0-10) Procedural pain score 0-10 4-point side effect scale	28 days

Table 3-2 Risk of bias assessment using the RoB2 (Cochrane risk of bias tool) for randomised control trials investigating gabapentinoids. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Paper	Randomisation Process	Deviations from intended intervention	Missing outcome data	Measurement of the Outcome	Selection of Reported Results	Overall
Ahuja 2011[139]	Low	Some concern	Low	Some concern	Some concern	Some concern
Ahuja 2013[140]	Low	Some concern	Some concern	Some concern	Low	Some concern
Gray 2011[142]	Low	Low	Low	Low	Low	Low
Zheng 2015[148]	Some concern	Some concern	Low	Low	Low	Some concern

Studies by Gray et al[142] and Zheng at al[148] included cohorts treated with a placebo. Gabapentinoids differed between studies, with Gray et al using pregabalin 150-600mg daily and Zheng et al using gabapentin 600mg daily. Meta-analysis demonstrated an improvement in 0-10 itch severity score of 3.63 (95% CI -1.20-8.46) when a gabapentinoid was used in comparison to placebo (Figure 3-2).

Combination of the above subgroup meta-analyses demonstrated an improvement in VAS of 2.96 (95% CI 1.20-4.73) when gabapentinoids are compared to control.

Although pruritus was not reported as a primary outcome in the study by Gray et al, it did report elements of the NPS (Neuropathic Pain Scale) including a 0 to 10 scale of pruritus severity. The effect of pregabalin on pruritus appeared much smaller than that demonstrated by the other studies included in the meta-analysis, with an improvement in mean scores of 1.17 (95% CI 0.10 – 2.24).

A further RCT was not included in the meta-analysis[140]. Although the percentage changes in mean VAS scores were reported, the analysis did not include sufficient information regarding the distribution of the sample data, such as standard deviations, to allow inclusion[140]. This trial did however demonstrate a 78.9% fall in mean pruritis VAS scores in the group given pregabalin in comparison to 33.3% in the placebo group when focusing on patients with the most severe initial VAS scores (9-10). The placebo and antihistamine groups in

this study suffered high dropout rates however, potentially reflecting inadequate symptom relief.

Both RCTs conducted by Ahuja et al[139,140] also included groups given a gabapentinoid and antihistamine in combination but found no additional benefit when compared to gabapentinoid alone.

3.3.2.2 Observational Studies

Of the 6 observational studies (Table 3-3), three were considered to be at serious risk of bias, two at moderate risk and one to be of low risk (Table 3-4). Sources of possible bias were primarily outcome measurements, which were often generated by research staff rather than patient reported.

Mendham et al[145] reported improvements in itch intensity when gabapentin was used in children with persisting itch despite treatment with antihistamines. Unfortunately, this outcome was measured solely on subjective reporting by nursing staff and parents.

Goutos et al[141] investigated the use of two antipruritic protocols, with early or late introduction of gabapentin as part of incremental pharmacotherapy. In 41.5% of patients given gabapentin as the first line agent satisfactory itch control was achieved, in comparison to just 10% when cetirizine was used first line.

Table 3-3 Observational studies of gabapentinoids. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Study	Year	Setting/Design	Population	Size	Age	Intervention Groups	Dosing Regimen	Outcomes	Follow-up
Kneib et al[144]	2019	Single centre retrospective cohort study	Admitted to burn unit, complained of itch	411	>14yrs	Use of neuropathic pain protocol. Analysed by group: 1. Gabapentin at <72 hours 2. Gabapentin >72 hours 3. No gabapentin	Gabapentin 300mg OD increased every 2 days if NRS ≥5 to max 900mg TDS	Morphine equivalent dose Total gabapentin use Pain and itch NRS Short Form-12 survey	24 months.
Nieuwendijk et al[146]	2018	Single centre prospective observational study	Itching wound in burn ward/ outpatient clinic	413	<13yrs	Not protocolised. Mixture of no treatment, gabapentin and antihistamine	Gabapentin 5mg/kg	Itch Man Scale 0-4 Itch NRS (Numeric Rating Scale 0-10)	1 week to 3 months
Kaul et al[143]	2018	Single centre retrospective observational study	Pruritus or neuropathic pain on gabapentinoid	136	<20yrs	Gabapentin only or in combination with pregabalin	Gabapentin doses from 50mg TDS to 1200mg TDS. Pregabalin 50-100mg TDS added if inadequate response to gabapentin	Retrospective review to describe effective dose of drugs	Unclear
Zachariah et al[147]	2012	Single centre prospective observational study	Burn 6wk to 2yrs old, pruritis with failure of cetirizine and emollients	23	4-60yrs	Gabapentin added if cetirizine inadequate	Adults – Gabapentin 100mg BD, increased to max 300mg TDS Children - 5mg/kg BD to max 5mg/kg TDS	Itch severity scale (7-21 points)	6 months
Goutos et al[141]	2010	Single centre prospective observational study	Within 72hrs of injury, admitted to burn unit, sense of itch and urge to scratch	91	Adults and Children	Two consecutive protocols. Gabapentin introduced early or late, compared with pre-protocol data.	Adult 300mg OD titrated to 300mg TDS over 3 days Children 5mg/kg OD titrated to 5mg/kg TDS over 3 days	Itch Man Scale 0-4	Unclear. Only inpatient data.
Mendham et al[145]	2004	Single centre prospective observational study	Itching burn wound, admitted to burns unit	35	Children	Gabapentin (no comparator or control)	5mg/kg TDS to max 5mg/kg BD plus 10mg/kg nocte	Staff or parent reporting of itch reduction	Unclear. Some followed

									up for 18 months.

Table 3-4 Risk of bias assessment using ROBINS-I tool for non-randomised studies investigating gabapentinoids. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Paper	Confounding	Patient Selection	Classification of Intervention	Deviations from Intervention	Missing Data	Measurement of Outcome	Selection of Reported Results	Overall
Goutos 2010[141]	Low	Moderate	Low	Low	Low	Serious	Moderate	Serious
Kaul 2018[143]	Low	Moderate	Low	Low	Low	Serious	Low	Serious
Kneib 2019[144]	Low	Low	Low	Low	Low	Low	Low	Low
Mendham 2004[145]	Low	Low	Low	Low	Low	Serious	Serious	Serious
Nieuwendijk 2018[146]	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate
Zachariah 2012[147]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate

Zachariah et al[147] reported improved mean itch severity scores when gabapentin was given to paediatric and adult patients complaining of pruritus with inadequate relief on antihistamines and emollients. On a scale ranging from 7 to 21, mean itch severity scores fell from 13.35 to 8.36 within one month of treatment and this effect was sustained for the six month follow up period.

Kaul et al[143] conducted a retrospective review of drug prescribing data of 136 mainly paediatric patients given gabapentin, pregabalin or a combination of both for pruritus or neuropathic pain. Although 91.4% of patients had an adequate response to treatment with gabapentin alone for pruritus, the measure of this outcome relied on adequate documentation in the patient medical notes and there was no comparator or control group.

Nieuwendijk et al[146] investigated the incidence, severity and risk factors associated with pruritus in paediatric burn injury, then went on to describe pharmacotherapies used with 17.9% having received gabapentin. Unfortunately, as the study was principally designed to explore factors associated with pruritus, no conclusions could be drawn on the effectiveness of the pharmacological therapy.

Kneib et al[144] conducted a retrospective cohort study investigating the use of a neuropathic pain and pruritus protocol. Patients were commenced on incremental doses of gabapentin if itch scores remained greater than 4 (on 0-10 Numeric Rating Scale) despite initial treatment with cetirizine. Comparison was made between various groups including pre- and post-protocol introduction as well as patients that received gabapentin early (<72 hours), late (>72 hours) or not at all. There was no difference in itch severity odds ratios between any group at discharge through to 24 months.

3.3.3 Topical Doxepin

Doxepin is a tricyclic antidepressant agent, but due to its potent anti-histaminergic activity, is used topically to treat pruritus in eczema. Four studies[149-152] investigated the use of topical doxepin on pruritic burn scars in

adult patients (Table 3-6). Given significant differences in both the results of these studies and the risk of bias assessments, meta-analyses are presented on studies at high risk and low/moderate risk of bias separately and then combined (Figure 3-3).

Demling et al carried out two single centre RCTs comparing topical doxepin to standard care[149,150]. The results of both trials showed a marked improvement in itch VAS scores at all time points compared to standard care (Figure 3-3). The results of a meta-analysis including these studies demonstrated an improvement in mean VAS score of 3.10 (95% CI 2.73-3.47). Both of these studies were found to be at high risk of bias from a lack of blinding and unclear randomisation methods (Table 3-5). Additionally, the control arm of "standard care" involved titration of oral antihistamines that all participants were already taking prior to enrolment rather than introduction of another therapy or placebo.

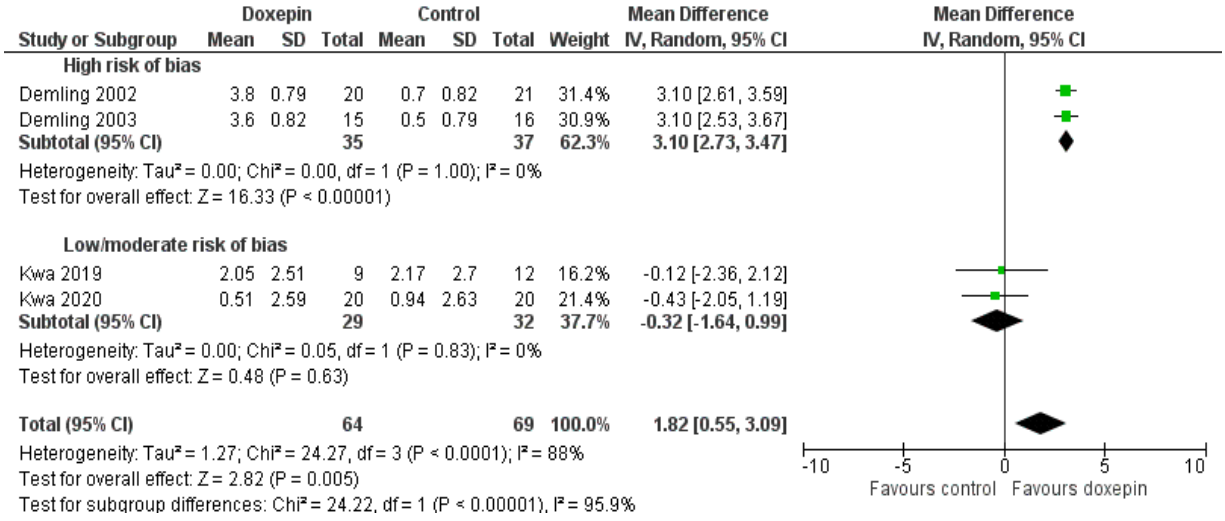

Figure 3-3 Forest plot showing the reduction in mean VAS (Visual Analogue Scale) in each treatment arm comparing topical doxepin to controls. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Kwa et al conducted two multicentre, blinded randomised control trials investigating the use of doxepin cream. The first study[151] showed no difference in itch intensity at any time point between doxepin cream and the control group. Due to difficulty recruiting to the trial and a high drop-out rate, this study was underpowered. A second study[152] addressed these recruitment issues using a cross-over study design comparing doxepin against placebo without the

inclusion of an antihistamine. Again, this demonstrated no difference in itch intensity between groups. A meta-analysis of both papers by Kwa et al (Figure 3-3) using outcome data at 14 days showed no difference in changes in VAS scores in comparison to placebo or antihistamines, with a mean VAS change of -0.32 (95% CI -1.64-0.99).

All four studies investigating doxepin have been included in the final meta-analysis (Figure 3-3) with no adjustment made for the risk of bias assessment. This demonstrated a reduction in mean VAS of 1.82 (95% CI 0.55-3.09). This result should be interpreted with caution, principally due to the high risk of bias in the included studies (Table 3-5).

Table 3-5 Risk of Bias assessment using the RoB2 (Cochrane risk of bias tool) for randomised control trials investigating topical doxepin. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Paper	Randomisation Process	Deviations from intended intervention	Missing outcome data	Measurement of the Outcome	Selection of Reported Results	Overall
Demling 2002[149]	Some concern	High risk	Low	High risk	Low	High risk
Demling 2003[150]	Some concern	High risk	Low	High risk	low	High risk
Kwa 2019[151]	Low	Low	Some concern	Low	Low	Some concern
Kwa 2020[152]	Low	Low	Low	Low	Low	Low

Table 3-6 Studies of topical doxepin BIQ: Burn Itch Questionnaire; QOL SF-36: Quality of Life Short Form 36 questionnaire. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Study	Year	Setting/Design	Inclusion Criteria	Patient Number	Intervention	Control	Outcomes	Follow-up
Kwa et al[152]	2020	Multicentre cross-over RCT	Healed burn, itch VAS ≥3, pruritic area <10%.	27	Doxepin cream	Placebo cream	Pruritus VAS BIQ at wk 2 and wk 5	5 weeks
Kwa et al[151]	2019	Multicentre RCT	Healed burn, itch VAS ≥3	31	Doxepin cream and placebo tablet	Placebo cream and antihistamine tablet	Pruritus VAS BIQ QOL SF-36 Somnolence Erythema.	12 weeks
Demling et al[150]	2003	Single centre RCT	Healed, <35% TBSA partial thickness burn, pruritic area <20%	31	Doxepin	Standard care	Pruritus VAS Erythema (Vancouver Scar Scale)	12 weeks
Demling et al[149]	2002	Single centre RCT	Healed burn, pruritic area <15%	41	Doxepin	Standard care	Pruritus VAS Erythema (Vancouver Scar Scale)	12 weeks

3.3.4 Topical Local Anaesthetics

One study[153] investigated the use of a topical local anaesthetic agent in the management of pruritis after burn injury in children 1-5 years old. EMLA cream, a mixture of prilocaine and lidocaine, was applied to healed partial thickness burns with persisting pruritus in five patients. The main purpose of this study was to assess the safety and pharmacokinetics of this therapy.

This study was carried out over 3 days, with the first two days acting as a control for the treatment being implemented on day 3. There was an improvement in itch intensity as measured by a visual analogue scale and number of pruritic episodes. Owing to the young age of the children, outcome measures were made by parents, nursing staff and the study investigators, potentially introducing an element of bias. This study suggested that the use of such topical local anaesthetic agents was safe and may have potential benefit.

Table 3-7 Risk of bias assessment using ROBINS-I tool for non-randomised studies investigating topical lidocaine. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Paper	Confound-ing	Patient Selection	Classification of Intervention	Deviations from Intervent-	Missing Data	Measurement of Outcome	Selection of Reported	Overall
Kopecky 2001[153]	Low	Moderate	Low	Low	Low	Serious	Low	Serious

3.3.5 Assessment using GRADE system

Each meta-analysis carried out is summarised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence (Table 3-8)[138]. The GRADE Working Group grades of evidence are summarised as follows[138]:

- High certainty: Very confident that the true effect lies close to that of the estimate of the effect.

- Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different .

- Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

- Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 3-8 Summary of GRADE assessment of evidence in each meta-analysis within this study. Reproduced with permission from McGovern C et al. Neuropathic agents in the management of pruritus in burn injuries: a systematic review and meta-analysis. Trauma Surg Acute Care Open. 2021 Oct 25;6(1):e000810

Meta-analysis	Participants (studies)	Improvement in mean VAS (95% CI)	Certainty of evidence (GRADE)
Gabapentin vs antihistamine	80 (2 studies)	2.19 (1.74-2.63)	Moderate[1]
Gabapentinoid vs placebo	128 (2 studies)	3.63 (-1.20-8.46)	Low[1,2,3]
Gabapentinoid vs control (All studies)	208 (4 studies)	2.96 (1.20-4.73)	Moderate[1,2]
Doxepin vs control (High risk bias studies)	72 (2 studies)	3.10 (2.73-3.47)	Very low[4]
Doxepin vs control (Low/moderate risk bias studies)	61 (2 studies)	-0.32 (-1.64-0.99)	Moderate[1,3]
Doxepin vs control (All studies)	133 (4 studies)	1.82 (0.55-3.09)	Very low[4]

[1] Risk of bias - Some concerns
[2] Indirectness - Inclusion of participants with neuropathic pain being the primary symptom rather than pruritus
[3] Imprecision - Confidence intervals cross the threshold for meaningful effect
[4] Risk of Bias - Serious concerns, high risk of bias

3.4 Discussion

3.4.1 Gabapentinoids

This systematic review identified 15 studies investigating the use of various drugs often used to manage neuropathic pain to treat pruritus after burn injury. The analysis has demonstrated that gabapentin is effective in treating pruritus following a burn injury, resulting in an improvement of around 2 points on a visual analogue scale when compared to antihistamines.

When compared to placebo, gabapentinoids were also beneficial, although the confidence intervals in the meta-analysis were wide. The drugs used in each of the two included studies also differed, as did the indication for their initiation. While Zheng et al[148] investigated gabapentin in the management of pruritus, Gray et al[142] investigated the use of pregabalin in patients with neuropathic pain, demonstrating a much smaller improvement in pruritic symptoms. This perhaps reflects the patient selection in this study whereby pain was the cardinal symptom, rather than pruritus. Given these limitations, it is therefore not possible to conclude whether this improvement is reproducible among the class of gabapentinoids or only evident with gabapentin.

Gabapentinoids are now used for a wide variety of indications beyond their initial development as anticonvulsants. Although structurally similar to the inhibitory neurotransmitter GABA (gamma aminobutyric acid) found throughout the central nervous system, they do not act upon GABA receptors. Their benefit in the management of pain and pruritus is likely to be due to action at voltage-gated calcium channels and NMDA (N-methyl D-aspartate) receptors within the spinal cord and brain, inhibiting the release of excitatory neurotransmitters[154].

Previous studies have demonstrated the benefit of gabapentinoids in reducing central sensitisation and wind-up phenomenon to an acute painful stimulus in an effort to treat neuropathic pain[155,156]. Such pathophysiological changes are characterised by alterations in the function of nociceptive neuronal pathways in response to persistent activation, inflammation or injury. These changes lower the thresholds by which nociceptive neurons are activated, resulting in chronic pain syndromes and additional features such as hyperalgesia and allodynia[157]. Given similar theories have been outlined to explain the pathological changes that result in chronic pruritus following burn injury it is therefore logical that gabapentinoids may improve itch[62].

The anti-neuropathic effects of gabapentinoids are increasingly utilised in a spectrum of pruritic and painful conditions, many of which these drugs are not licensed for[122–131]. Such expanding uses of these drugs have seen an increase in gabapentinoid prescriptions across the UK, Europe and North America[111,132–134]. However, the potential harm from such agents, particularly gabapentinoids, is becoming clear. A systematic review of 59 studies highlighted the increasing use

of gabapentinoids for recreational use and abuse[135]. In Scotland, gabapentinoids are increasingly implicated in drug related deaths, with toxicology reports from 2017 implicating gabapentin in 14% of such deaths and pregabalin in 12%[111]. Given the risks of dependence and harm with the use of these drugs,[111,158-160] gabapentin and pregabalin were categorised as Class C controlled substances in the United Kingdom in April 2019[161]. In the US pregabalin has been a Schedule 5 controlled substance since its release in 2005 and some states have recently reclassified gabapentin in the same category. Patients with a previous history of psychiatric comorbidity, alcohol or drug misuse are at even higher risk of harm when prescribed gabapentinoids[135,158]. In the context of individuals suffering a burn injury, such comorbidities are not uncommon, prompting vigilance when prescribing these drugs[162-164].

Furthermore, more work is required to establish the clinical significance of a reduction in VAS of around 2 points when compared to antihistamines alone, particularly given the potential for harm. The threshold whereby a treatment effect measured on such a scale is considered beneficial remains a topic of debate[165].

3.4.2 Topical doxepin

Although topical doxepin showed promise in healed burn wounds in early studies, such results have not been replicated in more recent trials described in this review. Although our meta-analysis of all studies investigating doxepin suggests an improvement in pruritic symptoms, this should be interpreted with caution due to the high risk of bias of two of the included studies and variations in the study participants between studies.

The earlier studies carried out by Demling et al[149,150] were conducted on patients with healed burn scars at a maximum of 12 months old, while both studies by Kwa et al[151,152] investigated patients up to 24 months after injury. Additionally, the individuals in the studies by Demling et al did not undergo skin grafting, whereas those in Kwa et al often did. These variations in both chronicity of scar formation and treatment modality could also play a role in the effectiveness of the treatment.

3.4.3 Topical lidocaine

This review has described one study presenting observational data that suggests topical EMLA may be a safe and potentially effective therapeutic option when used on healed burn wounds in children. Such therapy will be limited by the size of pruritic area as systemic absorption and the risk of local anaesthetic toxicity must always be considered, particularly with larger areas of application. Topical lidocaine is increasingly being used in multiple conditions[166–170] but the evidence for benefit in neuropathic pain is lacking, with the National Institute for Health and Care Excellence (NICE) concluding that the evidence is insufficient to issue any recommendation on its use[136]. Topical lidocaine however has been effective in managing pruritus in animal models[171], pruritus ani[172] and notalgia paraesthetica[173].

3.4.4 Strengths and limitations

This systematic review has posed a question examining the effectiveness of a broad class of drugs that are being increasingly used beyond their initial purposes or license. It has demonstrated that drugs such as gabapentinoids may be beneficial in the management of burn-related pruritus, but has also served to highlight the paucity of studies investigating the effectiveness and safety profile of these drugs in this population. With increasing evidence of harm from gabapentinoids, there is a growing need for robust evidence to demonstrate a favourable risk-benefit analysis of these agents.

This systematic review has several limitations. The scarcity of randomised control trials included in our final analysis reflects the quality of evidence investigating these drugs in burns patients. This resulted in only small numbers being included in the meta-analyses and a narrative review being conducted for the remaining studies.

The drugs investigated in this study are classically used to manage neuropathic pain. However, this review did not explore this specific pain condition, but rather pruritus given the increasing use of such drugs in other pruritic disorders and the recognised clinical and pathophysiological similarities between neuropathic pain and pruritus. Although some studies have demonstrated a

reduction in morphine consumption and improved acute pain scores with the use of gabapentin[174–176], there is a lack of evidence studying their specific use in neuropathic pain in burns patients[177]. A systematic review exploring the use of this broad class of drugs in the management of burn-related pain would add to this area of practice that is currently lacking in any robust evidence.

The VAS or other numerical scoring systems was commonly used to report pruritis outcomes. However, other methods included itch episodes, breakthrough doses of antihistamines and the itch severity scale. The heterogenous methods of pruritus severity reporting therefore limited the ability to conduct an accurate meta-analysis of the results. Similar issues have been highlighted in other systematic reviews, often from pain management literature, highlighting the difficulties in standardising and validating such outcome measures[178].

This systematic review also limited the interventions being investigated to those drugs listed by NICE for the management of neuropathic pain. Despite this wide inclusion criteria including multiple drugs and drugs classes, the literature search did not return any information on therapies such as other tricyclic antidepressants, including amitriptyline, or selective serotonin reuptake inhibitors that have been used to manage pruritus in other conditions[179,180]. Other therapies beyond pharmacological management may be of benefit in pruritis, namely psychotherapy such as cognitive behavioural therapy (CBT), transcutaneous electrical nerve stimulation (TENS) and acupuncture[181]. These were not addressed in this review.

3.4.5 Conclusions

Gabapentinoids appear effective in the management of pruritus associated with burn injury. Topical lidocaine may be a safe and effective option for managing pruritus in small surface area healed burns. Topical doxepin, although used to manage pruritus in eczema, does not appear to be effective in burn injuries.

Chapter 4 Pruritus after burn injury: Predictors of severity and pharmacological management

4.1 Introduction

Sensory disorders such as chronic pain, paraesthesia and pruritis are common following burn injury[52,63]. The incidence of pruritus has been reported to be as high as 93% at hospital discharge and 44% at 4-10 years[59]. Factors such as increasing depth of dermal injury, larger total body surface area (TBSA) burned, numerous surgical interventions, female gender and symptoms of post-traumatic stress disorder (PTSD) all increase the risk of developing long-lasting pruritic symptoms[60].

4.1.1 Physiology of pruritus

As discussed in chapter 3, the neuroanatomical and physiological basis for the perception of pain, commonly known as the "pain pathway", is well understood, but the equivalent pathway responsible for the perception of pruritus has been less extensively explored. Various pruritogens including histamine, acetylcholine, bradykinin and various cytokines activate afferent C-fibres which conduct impulses to the spinal cord. Synapses here then travel via the spinothalamic tract to the somatosensory cortex within the brain[61,62].

Given the similarities in physiology between pain and pruritus, parallels have been drawn between chronic pruritus and chronic or neuropathic pain. Such pathophysiological changes may be caused by peripheral and central sensitisation whereby persistent stimulatory input results in a chronic pruritic sensory disorder.

This evolving understanding of the mechanisms underlying the sensation of pruritus have sparked an interest in therapeutic targets at various sites throughout this pruritic pathway. Equally, given the variability in severity by which patients experience pruritus, there is growing interest in being able to predict which individuals are most likely to develop significant symptoms with the hope that early, aggressive treatment may improve outcomes. Other multi-system inflammatory and immune changes that occur following burn injury have

also been implicated in the development of pruritic symptoms and this chapter will explore some of those in more detail.

4.1.2 Vitamin D

Vitamin D, produced by keratinocytes in the skin, has an important role in calcium homeostasis, electrolyte absorption and bone health. Given the significant damage that can be inflicted on skin due to burn injury there is a potential for persisting vitamin D deficiency, with research suggesting deficiency and reduced bone density up to seven years after injury[182].

The pathophysiological effects related to vitamin D metabolism may not simply be a result of reduced synthesis in skin cells, but also a reflection of the acute hyperinflammatory effects and capillary leak associated with a burn injury, dilutional effects of fluid resuscitation and utilisation by tissues[183,184]. Low serum Vitamin D levels have also been demonstrated in other populations including trauma and up to 77% of patients with critical illness[185]. Other research has demonstrated a negative correlation between the magnitude of the inflammatory response and the plasma concentration of micronutrients including vitamin D[186].

Low serum vitamin D levels may also be associated with poor outcomes in critically ill patients including higher rates of infection and sepsis[187,188], increased incidence of acute kidney injury[189], increased length of stay[190] and mortality[188,191]. Whether low serum vitamin D levels in this acute phase represent true deficiency is not entirely clear. Such "deficiency" may instead reflect the extent of inflammatory response, haemodilution or sequestration of vitamin D to tissues.

Attempts to supplement vitamin D in critical illness have failed to yield convincing evidence of benefit. The VITdAL-ICU randomised clinical trial, investigating the use of high dose vitamin D in critically ill patients, found no difference in mortality or length of hospital stay[192]. However, a lower mortality was observed in a sub-group of patients with more severe vitamin D deficiency.

Low vitamin D levels have also been associated with increased complications as well as hospital and ICU length of stay in burn patients[193]. Studies in children following burn injury have demonstrated a persisting vitamin D deficiency, associated reduced bone mineral density increased incidence of long bone fractures[182,194], with supplementation potentially beneficial in reducing fracture risk[195].

Beyond burn injuries and critical illness, vitamin D deficiency has been associated with idiopathic pruritus and successfully managed with simple supplementation[196]. However, the role of vitamin D supplementation on patient-centred outcomes, including pruritus, after burn injury is poorly understood[197].

4.1.3 Management of pruritus

Achieving meaningful control of symptoms has been recognised to be difficult with a paucity of clinical trials evaluating interventions[115-119]. A survey carried out in the UK showed that over 90% of burns units use antihistamines as the first line treatment in the management of pruritus[120].

Antihistamine agents, or H1-receptor antagonists fall into two main categories: first- and second-generation agents. First-generation agents such as chlorphenamine not only block H1-receptors, but also have anticholinergic effects as well as acting at α-adrenergic and 5-HT (serotonin) receptors. Second-generation antihistamines such as cetirizine are much more selective for peripheral H1-receptors, minimising any side effects from central antihistamine antagonism such as sedation or other side-effects from poor receptor selectivity.

H2-receptor antagonists such as ranitidine or cimetidine, more commonly used to reduce gastric acid production in conditions such as gastro-oesophageal reflux or peptic ulcer disease, have also been shown to reduce wheal, flare and pruritus in individuals with a history of atopy[198]. Other studies have demonstrated improvements in pruritic symptoms when combined with H1-antagonists in patients with chronic urticaria[199] and pruritic burn wounds[200,201].

Although histamine from mast cell degranulation and as a by-product of collagen formation is thought to be a major contributor to the development of pruritus,

the involvement of various other peripherally acting pruritogens and the pathophysiological changes that occur more centrally mean that antihistamine monotherapy is often inadequate, especially in chronic pruritus[62].

The anti-neuropathic effects of drugs such as tricyclic antidepressants and gabapentinoids are being increasingly used to manage a spectrum of painful and pruritic conditions including pruritus due to uraemia in haemodialysis patients[122], brachioradial pruritus[123], idiopathic pruritus[124], chronic post-surgical pain[125] and post-herpetic neuralgia[126]. Their use has expanded to further unlicensed indications including fibromyalgia[127], post-operative pain[125,128,129] and joint arthroplasty[130,131] with varying degrees of success and conflicting results from multiple trials and reviews.

Gabapentinoids have been used to treat pruritic symptoms associated with both acute burn injuries and healed wounds. The appeal of these agents has been due to several factors including their additional benefit as analgesic agents, potential to reduce opioid consumption, as well as their mechanism of action beyond the peripheral actions of histamine. Several literature reviews have advocated for the inclusion of these drugs as first line agents in the management of pruritus from burn wounds[112,121].

Vitamin D supplementation is not routinely used for the management of burn-related pruritus. However, with a recognition that supplementation in patients with vitamin D deficiency can alleviate symptoms of pruritus and the documented phenomenon of reduced plasma vitamin D levels occurring following acute burn injury, this may be an area of therapeutic intervention worth exploring.

4.1.4 Study aims

This study will describe the factors associated with an increase in pruritic symptoms after burn injuries in adult patients admitted to a tertiary referral burn unit in Scotland. This study will also explore whether there is an association between plasma vitamin D levels and pruritus severity.

Lastly, this study will review the efficacy of a pruritus management protocol that has been implemented in the unit, including the effectiveness of various antihistamine agents, gabapentin and vitamin D supplementation for those patients found to be deficient.

4.2 Methods

4.2.1 Study setting and design

This study was carried out in the burns ward at the Glasgow Royal Infirmary, a tertiary referral centre for adult burn injuries covering the West of Scotland. This study was conducted as a quality improvement project to quantify the presence and severity of pruritus among adult patients admitted with an acute burn injury and assess the effectiveness of a pruritus management protocol.

4.2.2 Approvals and data management

As this project was carried out as a service improvement project, ethical approval was not sought. Caldicott guardian approval was granted for the collection and analysis of patient level data, as well as the dissemination and publication of any results. Data was collected and stored on password protected National Health Service Greater Glasgow & Clyde (NHS GGC) computers or an encrypted USB memory stick. All data was anonymised with the removal of names, dates of birth and post-codes before storage. Any demographic variables involving less than 6 patients were censored from reporting to prevent possible identification of individuals.

4.2.3 Inclusion and exclusion criteria

All adult patients over 16 years of age admitted to the Glasgow Royal Infirmary burn ward with an acute burn injury from November 2019 to February 2021 were included.

Patients were excluded if they were admitted to the ward with a condition relating to an old burn injury such as a healed burn scar, they were admitted prior to the introduction of the pruritus management protocol or no record of pruritus severity was found.

4.2.4 Intervention

As part of a quality improvement project, all patients admitted with an acute burn injury were asked daily to rate the intensity of pruritus using an 11 point (0 to 10) Visual Analogue Scale (VAS). Management of pruritus was addressed using a stepwise approach to pharmacological treatment (Figure 4-1). This protocol also included clinical investigations and a prompt to consider referral to the Clinical Psychology team as appropriate.

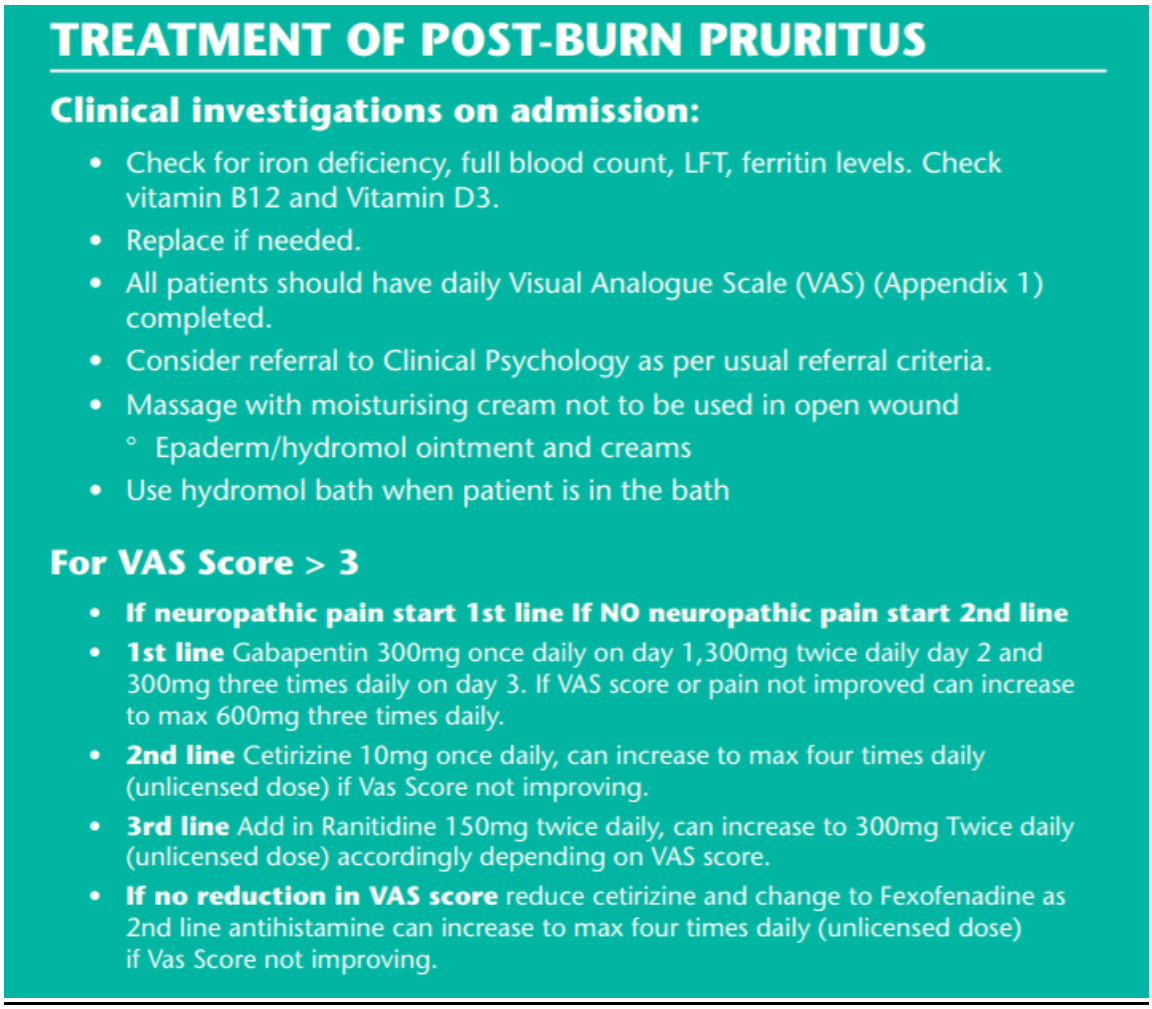

Figure 4-1 Protocol for assessment and management of burn related pruritus. Reproduced with permission, Ward 45, Burns Unit, Glasgow Royal Infirmary.

4.2.5 Data Collection

Pruritus severity scores as measured using the VAS method were collected on a daily basis by ward staff and recorded in the patients notes using a pre-printed proforma. Demographics, clinical details, laboratory results and drug prescription data were collected retrospectively using the Clinical Portal (Orion

Health, Glasgow, UK) electronic patient record system and the Care of Burns in Scotland (COBIS) national managed clinical network audit database.

Laboratory data was collected regarding serum vitamin D and corresponding C-Reactive Protein (CRP) level within 48 hours of each other. The limit of detection of serum vitamin D was 14nmol/L, with any values reported as <14nmol/L considered to be 13nmol/L for the purpose of analysis. Serum vitamin D levels were categorised as normal (≥50nmol/L), inadequate (30-49nmol/L), low (15-29nmol/L) and severely low (≤14nmol/L).

Data regarding pruritus VAS scoring and drug prescriptions were collected until hospital discharge or transfer out of the burn ward.

4.2.6 Statistical analysis

Statistical analysis was performed using R version 4.0.0 (The R Foundation for Statistical Computing). Descriptive analysis of categorical variables were expressed as frequencies and percentages. Continuous variables were summarised using median values and inter-quartile ranges (IQR) unless otherwise stated.

Pruritus severity was categorised based on the VAS results as no pruritus (0-1), mild (2-5), moderate (6-8) and severe (9-10) based on similar studies[139]. Missing VAS data were accounted for using the "last observation carried forward" (LOCF) method[202]. Variables and their association with pruritus severity were explored using a univariable linear regression model. Any variables reaching significance with a p-value <0.1 were then used to build a multivariable linear regression model using a backwards elimination technique. Regression coefficients are reported with 95% confidence intervals and a p-value <0.05 was considered statistically significant.

Analysis of the effectiveness of each drug used in the pruritus management protocol was done using a multilevel interrupted time series analysis. This method was chosen due to the wealth of data available from daily VAS scores recorded for each patient, allowing increased power of analysis rather than simplifying this data to averages before and after each intervention. An

interrupted time series analysis uses a regression model with three time-based covariates to produce regression coefficients to describe the pre-intervention slope, in this case change in VAS, the change at the intervention point and the change in slope after intervention. A time series analysis can be represented mathematically as:

$$Y = \beta_0 + \beta_1(\text{Time}) + \beta_2(\text{Intervention}) + \beta_3(\text{Time*Intervention})$$

- Y = Outcome variable.
- β_0 = Intercept.
- β_1 = Slope of trend before intervention.
- β_2 = Change in slope at intervention.
- β_3 = Change in slope of trend after intervention.

Each coefficient can be interpreted as either positive or negative, representing an increase or decrease in VAS respectively, over the time being reported; either before, immediately after or in the days following the introduction of a drug therapy. For example, a β_3 coefficient of -1.4 would represent a reduction in VAS of 1.4 each day after the intervention.

This multilevel approach to the analysis allowed for variation in pruritus severity between individuals to be accounted for by treating such variation as a random effect within the model.

4.3 Results

A total of 351 patients were admitted to the burn ward during the study period, of which 96 were excluded as they were admitted for a reason other than an acute burn injury (Figure 4-2). A further 103 patients were excluded due to no record of pruritus severity being documented and a further 2 were excluded as they were admitted before the implementation of the pruritus management protocol. A total of 150 patients were included in the final analysis.

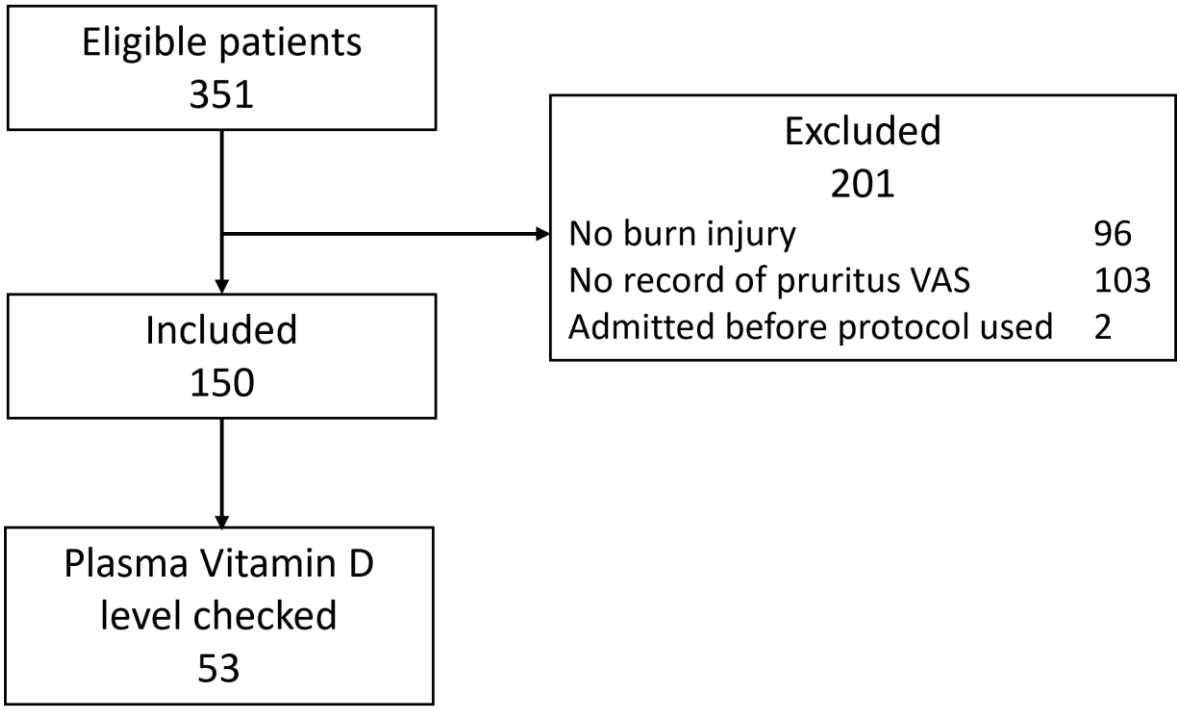

Figure 4-2 Consort diagram of patient eligibility

4.3.1 Patient characteristics

The median age of patients admitted to the burn ward was 44.5 years (IQR 32.2,56.8) with 104 (69.3%) being male (Table 4-1). The most common mechanisms by which burn injuries were sustained were flame burns (37.3%) and hot liquids (34%). The vast majority of burns were relatively minor with a median TBSA of 3% (IQR 1,6) and only 10 patients (7%) sustained a burn involving greater than 15% of total body surface area (TBSA).

Smoking was prevalent among this cohort of patients, with 32% of patients tobacco smokers. The most commonly documented comorbidities included alcohol use disorder (20%), pre-existing psychiatric history (14%) and recreational drug use (12%). Other comorbidities are not reported due to the low number of patients in these categories.

Table 4-1 Patient demographics

	All Patients N=150 (%)
Gender	
Female	46 (30.7)
Male	104 (69.3)
Age at Injury (Years)	
Median [IQR]	44.5 [32.2,56.8]
Mechanism of Burn	
Flame	56 (37.3)
Hot liquid	51 (34.0)
Hot object	10 (6.7)
Chemicals	10 (6.7)
Heat exposure	8 (5.3)
Electricity	7 (4.7)
Other	8 (5.3)
TBSA (%)	
Median [IQR]	3.00 [1,6]
Comorbidity	
Smoking	48 (32.0)
Alcohol use disorder	30 (20.0)
Psychiatric illness	21 (14.0)
Recreational drug use	18 (12.0)
Hypertension	16 (10.7)
Epilepsy	14 (9.3)
Diabetes	11 (7.3)

4.3.2 Pruritus severity

Half of the cohort, 75 patients (50%), had no complaints of pruritus during the study period, corresponding to a VAS of 0-1. 37 patients (24.7%) reported mild pruritus with a maximum VAS of 2-5, 29 (19.3%) had moderate pruritus and 9 (6.0%) had severe symptoms with a maximum VAS of 9-10 (Table 4-2).

Table 4-2 Variables associated with maximum pruritus severity (VAS) scores

	No Pruritus (VAS 0-1) N=75 (50%)	Mild Pruritus (VAS 2-5) N=37 (24.7%)	Moderate Pruritus (VAS 6-8) N=29 (19.3%)	Severe Pruritus (VAS 9-10) N=9 (6.0%)
Gender				
Female	27 (36.0)	11 (29.7)	6 (20.7)	2 (22.2)
Male	48 (64.0)	26 (70.3)	23 (79.3)	7 (77.8)
Age at Injury (Years)				
Median [IQR]	45.1 [30.9,59.3]	47.6 [37.1,58.1]	37.1 [27.3,46.9]	49.8 [43.7,55.9]
Mechanism of Burn				
Flame	19 (25.3)	19 (51.4)	11 (37.9)	7 (77.8)
Hot liquid	27 (36.0)	10 (27.0)	12 (41.4)	2 (22.2)
Other	24 (32)	8 (21.6)	6 (20.7)	0 (0)
TBSA (%)				
Median [IQR]	2.00 [1,3]	3.00 [1.5,5.5]	4.00 [1,7]	11.0[7,15]

To explore factors that may be associated with an increase in pruritic symptoms, univariable linear regression analysis was carried out (Table 4-3). Gender did not seem to have any influence on the development of pruritus, although increasing size of burn and flame burns were associated with higher pruritus VAS scores. The presence of various comorbidities including alcohol use disorder, illicit drug use, a history of epilepsy and tobacco smoking were all associated with higher VAS scores.

Table 4-3 Univariable analysis of characteristics associated with increasing maximum pruritus VAS

	β-coefficient*	95% confidence interval	p-value
Gender			
Male	0.99	-0.13-2.13	0.082
Age at Injury (Years)	-0.02	-0.05-0.01	0.222
Mechanism of Burn			
Flame	1.87	0.83-2.91	<0.001
Hot liquid	-0.31	-1.42-0.80	0.576
Hot object	0.96	-3.06-1.15	0.364
Chemicals	-1.06	-3.17-1.04	0.313
Heat exposure	-1.76	-4.08-0.56	0.131
Electricity	-0.98	-3.47-1.51	0.431
Other	-2.16	-4.47-0.15	0.064
TBSA (%)	0.17	0.09-0.25	<0.001
Comorbidity			
Smoking	1.28	0.18-2.39	0.022
Recreational drug use	2.07	0.48-3.65	0.01
Alcohol use disorder	2.3	1.04-3.56	<0.001
Psychiatric illness	0.46	-1.05-1.97	0.543
Epilepsy	2.04	0.26-3.82	0.023
Diabetes	0.52	-1.55, 2.58	0.62
Hypertension	-1.59	-3.25, 0.08	0.06

*B-coefficient correlates to corresponding increase in maximum VAS in presence of each variable

Any variables that reached a significance level with a p-value <0.1 were included in a multivariable linear regression analysis and a backwards stepwise approach taken to build a model. The increasing size of a burn injury, burn caused by flame injury, smoking tobacco and alcohol use disorder all remained significant predictors of increasing pruritus in this multivariable analysis. The results are reported in (Table 4-4).

Table 4-4 Multivariable analysis of characteristics associated with increasing pruritus VAS

	β-coefficient*	95% confidence interval	p-value
TBSA (%)	0.13	0.04-0.21	0.003
Flame burn	1.18	0.14-2.22	0.025
Smoking	1.13	0.11-2.16	0.029
Alcohol use disorder	1.76	0.56-2.96	0.004

*B-coefficient correlates to corresponding increase in maximum VAS in presence of each variable

4.3.3 Vitamin D

A total of 53 patients (35.3%) had a vitamin D level tested during admission. The median serum vitamin D level was 30.0nmol/L (IQR 17,43). Only 9 of the 53 patients (17.0%) with a result available were found to have vitamin D levels within normal limits (≥50nmol/L). 18 patients (34.0%) had inadequate levels (30-49nmol/L), 21 (39.6%) were low (15-29nmol/L) while 5 (9.4%) were found to be severely low (≤14nmol/L) (Figure 4-3).

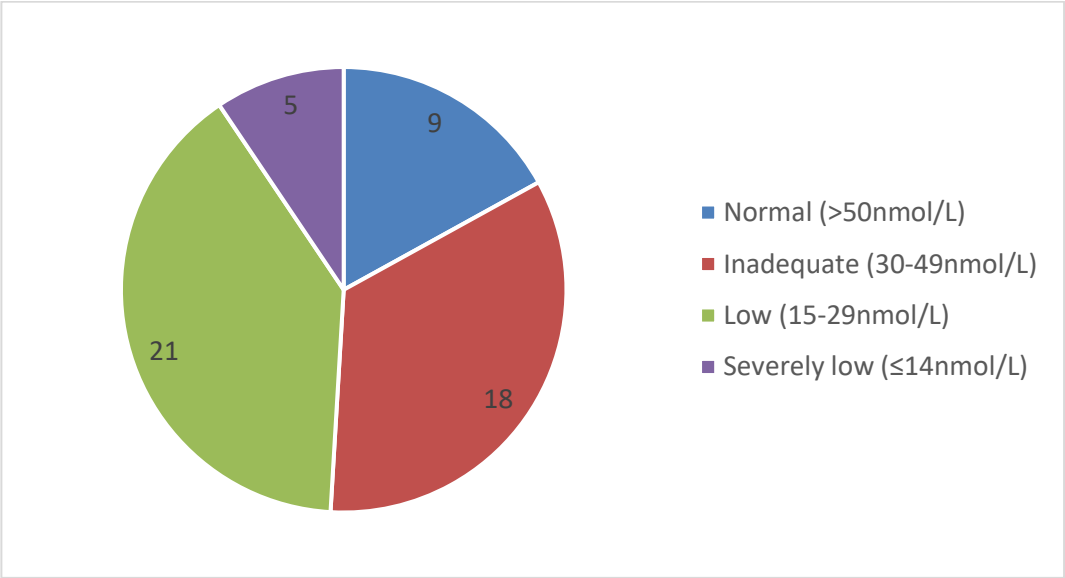

Figure 4-3 Number of patients with vitamin D levels within pre-specified ranges

Vitamin D levels did not seem to have any correlation with severity of pruritus symptoms (Figure 4-4). This was confirmed by linear regression analysis (p=0.56).

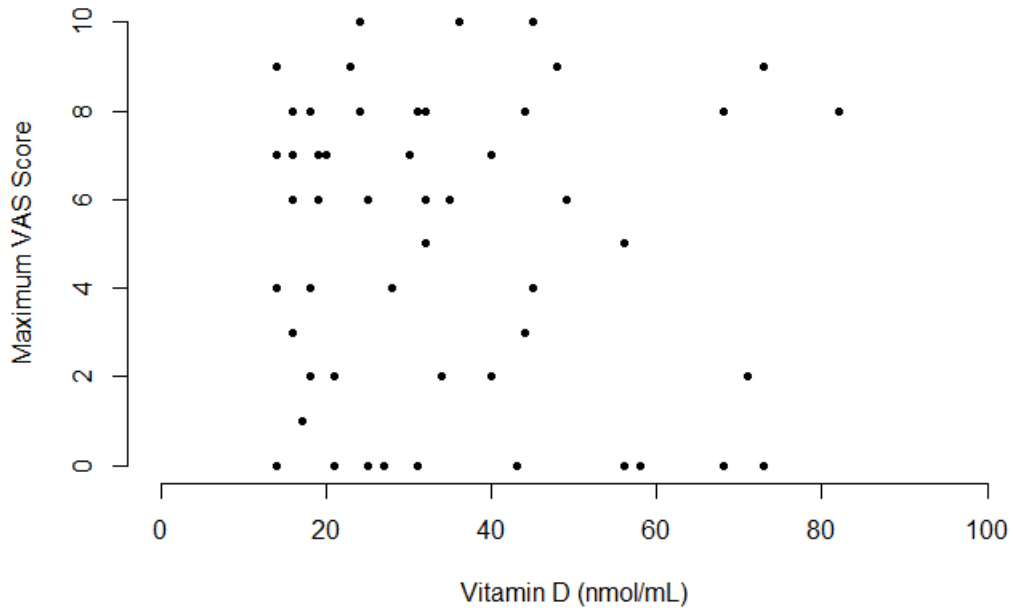

Figure 4-4 Scatterplot of vitamin D levels and corresponding maximum VAS score

There was no demonstrable relation using linear regression analysis between the magnitude of inflammatory response, as measured by CRP levels, and plasma vitamin D levels (p=0.57) (Figure 4-5).

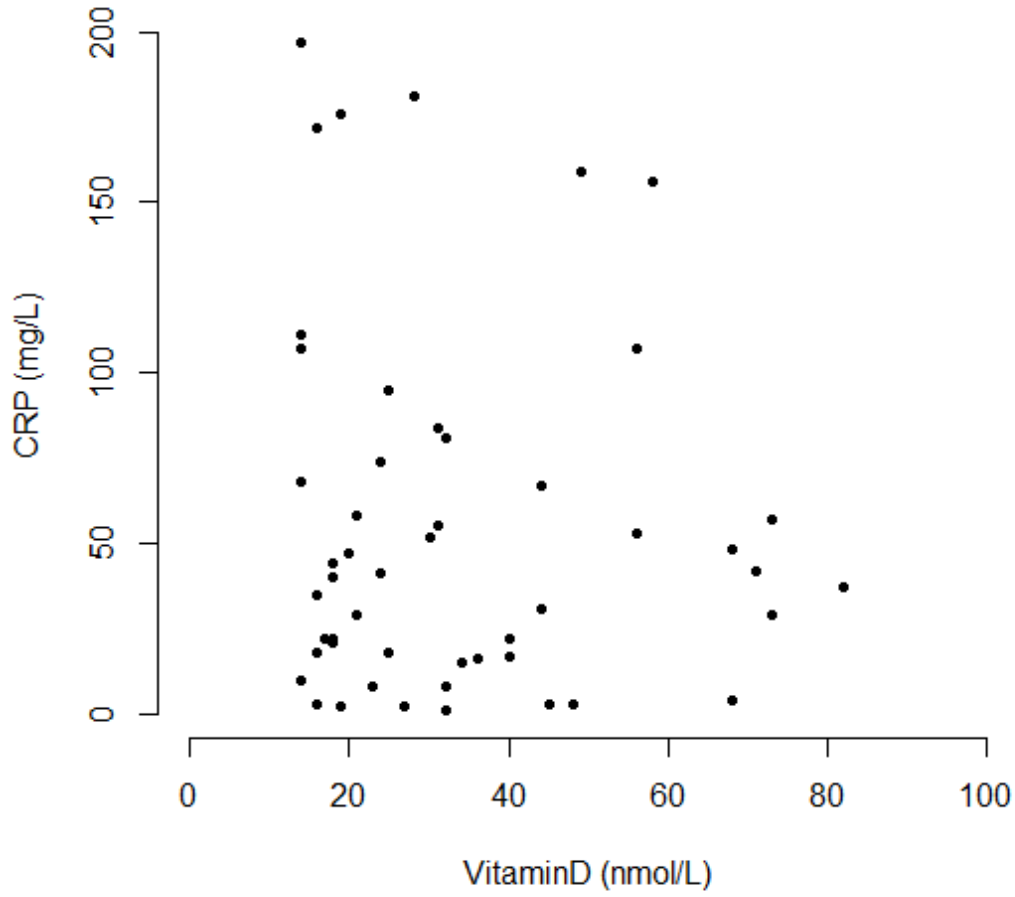

Figure 4-5 Scatterplot of vitamin D levels and corresponding CRP level

4.3.4 Drug interventions

The number of patients prescribed each of the drugs used in the pruritus management protocol are detailed in Table 4-5. Cetirizine was the most commonly used agent, being prescribed to 53 (35.3%) of patients. All of the 26 patients found to be low or severely low in vitamin D were commenced on Fultium D3 replacement therapy. Gabapentin was prescribed to 12 patients during the study period, with an additional 3 patients having already been prescribed the agent before admission to hospital.

Although chlorphenamine was not included in the pruritus management protocol, multiple patients were prescribed it. Given the widespread use, it was therefore included in the data collection. The number of patients who were prescribed one antihistamine or re-prescribed a second- or third-line antihistamine are detailed in Table 4-5.

Table 4-5 Number of patients prescribed each of the pruritic protocol drugs

	All Patients N=150 (%)
Gabapentin	
Before Admission	3 (2.0)
During Admission	12 (8.0)
Cetirizine	
Before Admission	1 (0.7)
During Admission	53 (35.3)
Ranitidine	
Before Admission	1 (0.7)
During Admission	5 (3.3)
Fexofenadine	
Before Admission	0 (0)
During Admission	3 (2.0)
Chlorphenamine	
Before Admission	0 (0)
During Admission	25 (16.7)
Fultium D3	
Before Admission	1 (0.7)
During Admission	26 (17.3)
Number of H1-Antihistamines	
0	86 (57.3)
1st line	45 (30.0)
2nd line	16 (10.7)
3rd line	3 (2.0)

The efficacy of each drug was assessed using a multilevel interrupted time series analysis (Table 4-6). For each drug, with the exception of fexofenadine, a consistent upward trend in VAS scores is seen before each drug intervention, as described by the positive β_1 coefficients. There was no demonstrable immediate change in VAS with any drug intervention, as described by the β_2 coefficients. However, each drug intervention was shown to produce a consistent and statistically significant downward trend in VAS after its introduction, as described by the β_3 coefficients.

Table 4-6 Multilevel interrupted time series analysis of drug interventions for pruritus

	Slope of trend before drug (β_1)*	p-value	Immediate change in pruritus severity (β_2) †	p-value	Change in slope of trend after intervention (β_3)*	p-value
Gabapentin	0.48	<0.001	0.46	0.35	-0.52	<0.001
95% CI	(0.32, 0.66)		(-0.53, 1.45)		(-0.68, -0.36)	
Cetirizine	0.31	<0.001	-0.11	0.712	-0.31	<0.001
95% CI	(0.22, 0.41)		(-0.71, 0.49)		(-0.41, -0.21)	
Ranitidine	0.19	0.007	-2.02	0.011	-0.11	0.19
95% CI	(0.05, 0.33)		(-3.58, -0.46)		(-0.29, 0.06)	
Fexofenadine	0.2	0.112	-1.54	0.154	-0.29	0.027
95% CI	(-0.05, 0.44)		(-3.70, 0.62)		(-0.55, -0.03)	
Chlorphenamine	0.37	<0.001	0.59	0.223	-0.38	<0.001
95% CI	(0.19, 0.55)		(-0.38, 1.55)		(-0.59, -0.17)	
Fultium D3	0.24	<0.001	-0.49	0.178	-0.28	<0.001
95% CI	(0.15, 0.34)		(-1.21, 0.24)		(-0.38, -0.18)	

*β_1 and β3-coefficients describes the change in pruritus VAS each day, with a negative coefficient denoting a reduction in VAS and a positive coefficient denoting an increase.
†β2-coefficent describes the immediate change in VAS in the day following introduction of each drug

Cetirizine, as the most commonly prescribed drug in this study, demonstrated a 0.31 VAS increase each day before introduction of the drug, followed by a 0.31 decrease each day following introduction of the drug. The most pronounced effect was seen in the use of gabapentin, with a more significant increase in pruritic symptoms before starting the drug, with a 0.48 VAS increase each day and a 0.52 VAS decrease each day after starting gabapentin. The use of vitamin D replacement therapy, Fultium D3, was also associated with a reduction in VAS by 0.28 each day after starting therapy.

Ranitidine was the only drug not found to be effective in reducing VAS scores. The results regarding the use of ranitidine and fexofenadine should be interpreted with caution given the very low number of patients prescribed these drugs; 5 and 3 respectively.

Further analysis was carried out to assess the benefit of changing from one antihistamine to another, categorised as first-, second- and third-line agents. Sixteen patients were prescribed a second-line antihistamine while only 3 were prescribed a third-line agent. Results of interrupted time series analysis on the effect of changing antihistamine agents are presented in Table 4-7. Before each intervention, there remained a consistent increase in VAS followed by a

consistent improvement following the introduction of the first- or second-line antihistamines. Patients prescribed a second-line antihistamine, most commonly changing from chlorphenamine to cetirizine in 16 of the 19 cases, demonstrated an immediate reduction in VAS of 1.3 (95% CI -2.21, -0.37, p=0.005). The change to a third-line antihistamine did not seem to confer any benefit with a VAS change of -0.23 (95% CI -0.50, 0.04, p=0.092), although this analysis only included 3 patients.

Table 4-7 Interrupted time series analysis of the use of first, second or third line H1-antagonist antihistamine agents

	Slope of trend before drug (β_1)*	p-value	Immediate change in pruritus severity (β_2) †	p-value	Slope of trend after intervention (β_3)*	p-value
1 Antihistamine	0.3	<0.001	0.41	0.173	-0.27	<0.001
95% CI	(0.18, 0.42)		(-0.19, 1.02)		(-0.39, -0.14)	
2nd line Antihistamine	0.35	<0.001	-1.3	0.005	-0.38	<0.001
95% CI	(0.19, 0.51)		(-2.21, -0.37)		(-0.53, -0.22)	
3rd line Antihistamine	0.26	0.011	-0.6	0.553	-0.23	0.092
95% CI	(0.06, 0.47)		(-2.64, 1.43)		(-0.50, 0.04)	

*β_1 and β3-coefficients describes the change in pruritus VAS each day, with a negative coefficient denoting a reduction in VAS and a positive coefficient denoting an increase.
†β2-coefficent describes the immediate change in VAS in the day following introduction of each drug

4.4 Discussion

This study has described the incidence and severity of pruritus in a cohort of adult patients that were admitted to hospital with a burn injury, explored the link between pruritus and low serum vitamin D levels and assessed the effectiveness of a pruritus management protocol introduced in a tertiary referral burn ward.

4.4.1 Incidence and predictors of pruritus

This study has demonstrated that burn associated pruritus remains a significant problem, affecting 50% of the individuals in this cohort. This study has also added to the knowledge regarding risk factors for burn-related pruritus. Increasing surface area of a burn injury is positively correlated with worsening pruritic symptoms. This finding is in keeping with previous research, with such studies also indicating that increasing depth of burn and numerous surgical procedures also contributing factors[59,60]. Flame burns, tobacco smoking and

alcohol excess were all associated with worse pruritus in this study. However, female gender and younger age were not found to be significant predictors in this study, but have been in previous research[59,60].

4.4.2 Vitamin D and pruritus

The optimal plasma concentration of vitamin D remains much debated, with some physicians advocating an optimal concentration as high as 75nmol/L, or even over 90nmol/L[203]. Low serum vitamin D was common among patients who had a level checked, with 44 patients (83%) found to be below 50nmol/L and 22 patients (41.5%) had levels below 25nmol/L. Vitamin D deficiency is prevalent in Scotland, with one study reporting 33% of the Scottish population having a level below 25nmol/L[204]. This figure may reach as high as 47% in areas of greatest socioeconomic deprivation.[204] Other research has found that 92.2% of the Scottish population have vitamin D levels below 75nmol/L during the winter months[205]. Such research has prompted the Scottish government to issue guidance that everyone, including children, should consider taking daily supplements, especially during winter months[206].

This study has been unable to find any clear correlation between plasma vitamin D levels and severity of pruritus or the magnitude of inflammatory response measured by CRP. However, the protocol being used simply prompted the staff caring for these patients to check plasma vitamin D levels once they complained of itch. Any patients without pruritus would not routinely have their vitamin D levels measured. Additionally, 75 (50%) complained of pruritus at some point but only 53 patients (35.3%) had vitamin D levels checked. This highlights the difficulty in implementing such protocols in a busy ward environment, especially outside the strict controls of randomised trials. These factors limit the ability of this study to draw any firm conclusions on the correlation between vitamin D levels and pruritus in burn injured patients.

Existing research has more robustly demonstrated that burn injury has the potential to cause a reduction in vitamin D levels. This may result in associated health problems developing without both recognition or appropriate intervention. This can be due to both the pathophysiological inflammatory effects on micronutrient levels and reduced ability to synthesise vitamin D in

burned skin due to either scar formation or individuals reducing skin exposure to sunlight due to the aesthetic concerns of a burn scar. These pathophysiological changes compounded by the high prevalence of vitamin D deficiency among the Scottish population and the fact that it is often more pronounced in individuals from areas of socioeconomic deprivation may result in amplification of such detrimental health effects in this group of patients. Although this study has not been able to show a correlation between pruritus and vitamin D levels, using an admission with a burn injury in patients that are frequently from deprived areas as an opportunity to detect deficiency and act upon it should be considered in a holistic approach to patient centred care.

4.4.3 Pruritus management protocol

This study has demonstrated that the pruritus management protocol implemented in the Glasgow Royal Infirmary is effective in reducing pruritus VAS scores. With the exception of ranitidine, each drug used in the protocol showed a consistent reduction in VAS scores following their introduction.

Cetirizine was the most commonly prescribed antihistamine in this study, being given to 53 patients and demonstrating a reduction in VAS of 0.31 each day following treatment. Chlorphenamine was the second most commonly used antihistamine, being prescribed to 25 patients. Although this agent did not form part of the pruritus protocol, it may have been prescribed by staff either unfamiliar with the protocol or for another indication such as opioid related pruritus.

The use of Fultium D3 to address vitamin D deficiency in patients with pruritus was associated with a reduction in VAS of 0.28 each day after being prescribed. Given the lack of any clear association between vitamin D deficiency and pruritus severity, the multitude of other drugs being prescribed at a similar time and the confounding effects these will have, this result should be interpreted with caution.

Analysis of using differing antihistamines, described as first-, second- and third-line agents, suggested that switching to a second antihistamine may be beneficial should the first agent prove ineffective. The majority, 16 of the 19

cases, where this occurred was when changing from the first-generation drug, chlorphenamine, to the second-generation drug, cetirizine. This analysis does not necessarily conclude that cetirizine is more effective than chlorphenamine, as 10 of the 26 patients prescribed chlorphenamine did not change to a different antihistamine at any stage, suggesting adequate symptom control with this drug. However, it does suggest that should symptom control with one antihistamine prove ineffective, switching to another antihistamine, and potentially from a first-generation to a second-generation agent, may be of benefit. As the purpose of this study was not to compare the effectiveness of different antihistamine agents, it is limited in its ability to suggest one agent over another. However, given the signal of benefit in changing from chlorphenamine to cetirizine, we will continue to use cetirizine as our first line antihistamine for burn-related pruritus. This study cannot comment on the possible benefits of trying a third-line agent as only 3 patients were included in this analysis, with the results not reaching statistical significance.

Gabapentin was associated with the greatest improvement in pruritus VAS scores with a daily reduction in VAS of 0.52 following its introduction. However, it should be noted that such drugs are not without their problems. Gabapentinoids are increasingly being used recreationally and as drugs of abuse, with mounting evidence of harm, especially among individuals with existing drug or psychiatric problems[135,158]. In Scotland, gabapentinoids are increasingly being implicated in drug related deaths[111]. With a high prevalence of drug, alcohol and psychiatric conditions among burn injured patients, such drugs should be prescribed with caution in the context of such potential for harm[162–164].

4.4.4 Strengths and limitations

This study has demonstrated that some previously unrecognised factors may be associated with an increased risk of suffering more severe pruritus following burn injury, including pre-existing alcohol use disorder and tobacco smoking. The study has also demonstrated that the pruritus management protocol in use at Glasgow Royal Infirmary is broadly effective in reducing pruritus severity scores.

However, the incidence of pruritus was not as high as would have otherwise been expected, with 50% of patients complaining of symptoms during their admission. Other, larger studies have reported as many as 93% of patients complaining of itch[59,60]. However, these studies either investigated patients with larger burns or were followed up beyond discharge. This study was unfortunately limited to the time during hospital admission. Since pruritus may become more apparent during the later phases of burn wound healing due to histamine released during collagen formation, many of those individuals with short hospital admissions who underwent conservative management of their injury may have developed pruritus following discharge.

This study has not been able to confidently draw any conclusions regarding the association between low serum vitamin D levels and the presence or severity of pruritus following burn injury. Whether such measured low levels of vitamin D represent true deficiency, or are perhaps a marker of inflammation, a response to acute injury or utilisation of the vitamin by damaged tissues remains unclear.

Unfortunately, not all patients within this study had vitamin D levels checked, indeed vitamin D levels were often only checked once an individual complained of pruritus, prompting staff to check this. This highlights the difficulties in investigating such clinical features in real-world practice and outside the strict protocols of a clinical trial.

Although this study has demonstrated that the pruritus protocol used in this cohort is generally effective in reducing pruritus scores, the observational nature of this study makes interpretation in any more detail difficult. In order to draw firm conclusions on the effectiveness of each individual drug in comparison to any other would likely require a randomised controlled trial. Equally, this study did not explore drug dosing in any detail, with the potential for higher than standard dosing of antihistamines potentially being beneficial in other conditions[207].

This study did not explore any additive or synergistic effect of, for example, the addition of gabapentin to antihistamine therapy. Such analysis was limited by the fact that this was an observational study of an ongoing service improvement project rather than a randomised control trial. The analysis was also limited by

the variation in antihistamines used, varying timings of drugs interventions and the additional complexity of gabapentin being used first-line when associated features of neuropathic pain were present.

As with any observational methodology, drawing firm conclusions regarding the efficacy of drugs treatments is limited. It is possible that the therapeutic effect of each drug used in this study has been exaggerated and the observations made regarding improvement in pruritus severity scores may simply be the natural evolution of burn-related pruritus in the acute setting whereby itch symptoms increase in the days after injury and then abate regardless of any interventions.

The method by which effectiveness of drug therapy was assessed in this study, using an interrupted time-series analysis, has described the daily change in VAS following the introduction of each drug. Translating this analysis into a meaningful patient-centred outcome, such that pruritus is controlled to a satisfactory level for an individual patient, is limited. Whether a modest reduction in a severity score, such as VAS used in this study, is of any great consequence to the individual concerned is a matter for debate. The interpretation of such outcomes has consistently been an issue in medical literature, for example when investigating pain severity, whereby standardising and validating such measures and interpreting the level of clinical effectiveness can be fraught with difficulty[178].

4.4.5 Conclusion

This study has demonstrated that pruritus remains a common problem following burn injury in the adult population. The link between vitamin D deficiency, the systemic inflammatory response and the severity of pruritus requires more research to further explore any possible correlation. In this analysis of a quality improvement project in a single-centre setting, pruritus severity diminished with the use of antihistamine and gabapentin therapy. However, the temporal association between drug therapy and improvement in symptoms may simply be a reflection of the natural course of pruritus severity rather than the therapeutic effect of these drugs. A blinded randomised controlled trial would be required to better define the therapeutic effects of these drugs.

Chapter 5 Epidemiology and mortality of burns in Scotland

5.1 Introduction

The incidence of burn injuries in Scotland has been falling for several years, mostly due to health and safety, educational and legislative measures[208]. The epidemiology of burn injuries in Scotland is vastly different to that seen in the developing world where major burn injuries are more common[209,210]. The Scottish Fire and Rescue Service attend almost 5000 dwelling fires every year, with around 60% occurring due to cooking appliances[211]. The number of fire fatalities is relatively small, varying from between 27 and 62 in the years 2009 to 2021[211]. Of note, there is a five-times higher rate of fatality from fire in the most deprived areas of Scotland compared to the least deprived[211].

Statistics from the Scottish Fire and Rescue Service provide a small piece of the picture of burn injuries in Scotland, with far more injuries occurring from other mechanisms and not requiring the services of Fire and Rescue teams. The purpose of this chapter is to explore the demographics and patient characteristics associated with a burn injury in Scotland and describe the features associated with mortality attributable to a burn injury in this cohort.

With a diverse population, geography with very remote areas and an increasing ethnic minority population, there is a need to accurately describe the pattern of burn injuries seen in Scottish hospitals.

The mortality resulting from burn injuries has been falling for several decades across the world. This study seeks to describe the mortality associated with a burn injury in Scotland, compare this with nations with similar healthcare systems and resources and describe the factors associated with an increased risk of death.

5.2 Methods

5.2.1 Study design and setting

This study was carried out as a retrospective cohort study using linked national data in Scotland, which has a population of 5.46 million. Rural areas account for 98% of the country's land mass, but only 17% of the population reside here[212]. The healthcare service is primarily delivered by the government funded National Health Service (NHS).

5.2.2 Data sources

Patients admitted to hospital under the care of a specialist burn team were identified by searching the national managed clinical network COBIS (Care of Burns in Scotland) from January 2012 to December 2015.

Around 450 to 500 patients are entered in to the COBIS (Care of Burns in Scotland) clinical database each year[210]. This records those patients managed by a burn specialist team in both the inpatient and outpatient setting. Patients with minor burns that were managed locally in non-specialist centres or in the community were not included in this database, nor were patients that died at the scene or where palliative care was delivered in the emergency department.

This data was then linked to other national administrative healthcare databases including SMR01 (acute hospital admissions), SMR04 (psychiatric hospital admissions) and NRS (National Records Scotland) death registration data.

5.2.3 Covariates and Missing Data

Patient characteristics such as age, gender, TBSA (total body surface area) burned, mechanism of injury and date of injury were initially extracted from the COBIS data source. This relies on the input of data by clinical staff directly involved in the patient's care. Any missing data were extracted from the SMR01 dataset.

Variables such as TBSA are recorded differently in COBIS (rounded to nearest percentage) and SMRO1 (recorded as percentage deciles as per ICD-10 codes).

All TBSA figures are reported as percentage deciles in the descriptive analysis. However, in the event of missing TBSA details from the COBIS data, the SMR01 data describing the TBSA in deciles were converted to a numeric value for statistical analysis. For example, an SMR01 ICD-10 classification of 10-19% TBSA was changed to 15%; 20-29% changed to 25% and so on.

Other COBIS related variables such as smoke inhalation and airway burn could be recorded as yes, no or uncertain. Given the lack of any clinical information beyond this, any patient categorised as "uncertain" were considered to have not sustained such an injury.

The mechanism of injury was recorded in the COBIS dataset and included 12 categories including flame burns, scalds and electricity. With certain mechanisms of injury being rare such as chemical burns, especially in major burn injuries, potentially allowing identification of individuals, some of these categories were amalgamated before analysis.

The SIMD (Scottish Index of Multiple Deprivation) is a measure of socioeconomic deprivation that takes into account variables such as income, government welfare and benefit use, employment, healthcare utilisation and crime rates. This measure is derived from geographical area and reported in quintiles whereby 1 represents the most deprived and 5 the least deprived. The SIMD quintile reported is that for the patient at the time of the burn injury admission.

The geographical location of the settlement in which an individual resides in Scotland is classified using the UR8 (Scottish Government 8-fold Urban Rural Classification)[213]. This varies from 1 which indicates a large urban area with a population of 125,000 or greater, through to category 8, a very remote rural settlement with a population less than 3000 and drive time greater than 60 minutes to a settlement with 10,000 people or more.

Comorbidity data was extracted for all patients over 16 years old from COBIS, SMR01 and SMR04. COBIS relies on clinical staff inputting data manually into an online audit system from a drop-down menu of common comorbidities. SMR01 and SMR04 are administrative databases whereby admission diagnosis and underlying comorbidities are recorded by administrative coding staff who record

this data corresponding to the relevant ICD-10 codes. Comorbidity data from COBIS was converted to ICD-10 codes and all three data sources then used to extract all known comorbidity data using the Elixhauser comorbidity method. A look-back of 5 years prior to the index burn admission was used to derive comorbidity data using SMR01 and SMR04.

The Elixhauser categories of comorbidity were analysed using the method described in the original paper by Elixhauser et al, whereby each separate comorbidity category is treated independently of the others[106]. A count of the number of comorbidities each individual had was also used to categorise patients based on multimorbidity. Further analysis regarding comorbidity data was done using variations of the Elixhauser comorbidity measure whereby an index is derived from the initial data. These techniques have been validated by various studies[108,110].

5.2.4 Inclusion/Exclusion

All patients admitted to a burns specialist centre in Scotland from January 2012 to December 2015 as recorded on the COBIS database were included in the analysis.

Due to the infrequency by which children die of a burn injury in Scotland, there was a risk of identification of individuals in reporting such data. Therefore, mortality analysis excluded those under 16 years old. Patients under 16 years old were also excluded from the comorbidity analysis.

5.2.5 Outcomes

The primary outcome was mortality within 30 days of burn injury, as identified by NRS death certificate data.

5.2.6 Statistical analysis

The descriptive analyses of categorical variables are expressed as frequencies and percentages while continuous variables are summarised using median values and inter-quartile ranges unless otherwise stated.

Time-to-event analysis for mortality was analysed using Kaplan-Meier curves. Hazard ratios and 95% confidence intervals were calculated using a univariate then multivariable Cox proportional hazards regression model as described in chapter 2.

5.3 Results

5.3.1 Patient characteristics

During the study period, 2005 patients were identified from the COBIS database. Twenty-eight patients were removed from analysis, having either sustained the burn injury before 2012 or no evidence of burn injury recorded on either the COBIS or SMR01 databases. A total of 1977 patients were included in the final analysis. The majority of patients, 1252 (63%), were male, with a median age of 30 years (IQR 4-51) with the vast majority, 1441 (90%), of burns involving less than 10% TBSA (Table 5-1).

Although the median age at injury was 29.5 years, there was a clear pattern of age groups far more likely to be affected by an injury (Figure 5-1). Paediatric patients (<16 years old) accounted for 653 (33%) of the cohort, with a median age of 2 years (IQR 1-4) and 78.1% of all children being under 5 years old. Among adult patients, the median age was 45 (IQR 29-58). However, within this cohort, two age groups seem to account for more injuries, with patients in their late teens and early twenties showing a slight rise in case numbers, as well as another increase in those age around 45 to 50 years old.

Table 5-1 Characteristics of patients included in study with comparison between adult and paediatric patients.

Characteristic	Overall N=1977	Adults ≥16 years old N=1324[1]	Children <16 years old N=653[1]	p-value[2]
Gender				0.004
Male	1252 (63)	868 (66)	384 (59)	
Female	723 (37)	455 (34)	268 (41)	
Not Recorded	2	1	1	
Age at injury	30 (4, 51)	45 (29, 58)	2 (1, 4)	<0.001
Airway burn	25 (1.3)	19 (1.4)	6 (0.9)	0.3
Smoke inhalation injury	28 (1.4)	*>22 (>1.6)	*<6 (<0.9)	<0.001
Mechanism of injury				<0.001
Hot liquid	729 (42)	400 (33)	329 (62)	
Flame	376 (22)	344 (29)	32 (6.0)	
Hot Object	219 (13)	137 (11)	82 (16)	
Steam	25 (1.4)	23 (1.9)	<6	
Electrical	54 (3.1)	48 (4.0)	<6	
Other[3]	325 (19)	247 (21)	78 (15)	
Unknown	249 (12.6)	125 (9.4)	124 (19)	
SIMD				0.018
1 (most deprived)	687 (35)	430 (33)	257 (40)	
2	429 (22)	295 (23)	134 (21)	
3	332 (17)	231 (18)	101 (16)	
4	288 (15)	209 (16)	79 (12)	
5 (least deprived)	218 (11)	143 (11)	75 (12)	
Unknown	23 (1.2)	16 (1.2)	7 (1.1)	
TBSA Burned				0.017
<10%	1441 (90)	1024 (89)	417 (91)	
10-19%	100 (6.2)	69 (6.0)	31 (6.8)	
>20%	63 (3.9)	55 (4.8)	8 (1.8)	
Unknown	373 (18.9)	176 (13.3)	197 (30.2)	
Ethnicity				<0.001
White	1228 (62)	800 (60)	428 (66)	
Ethnic Minority	86 (4.4)	26 (2.0)	60 (9.2)	
Unknown	663 (34)	498 (38)	165 (25)	
Urban-Rural Classification				0.022
Urban area	1497 (75.7)	981 (74.1)	516 (79)	
Small town	224 (11.3)	151 (11.4)	73 (11.2)	
Rural area	233 (11.8)	176 (13.3)	57 (8.7)	
Unknown	23 (1.2)	16 (1.2)	7 (1.1)	

[1]n (%); Median (IQR)
[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test
[3]Includes chemical burns, heat exposure, cold exposure
*Exact numbers censored due to <6 individuals being involved

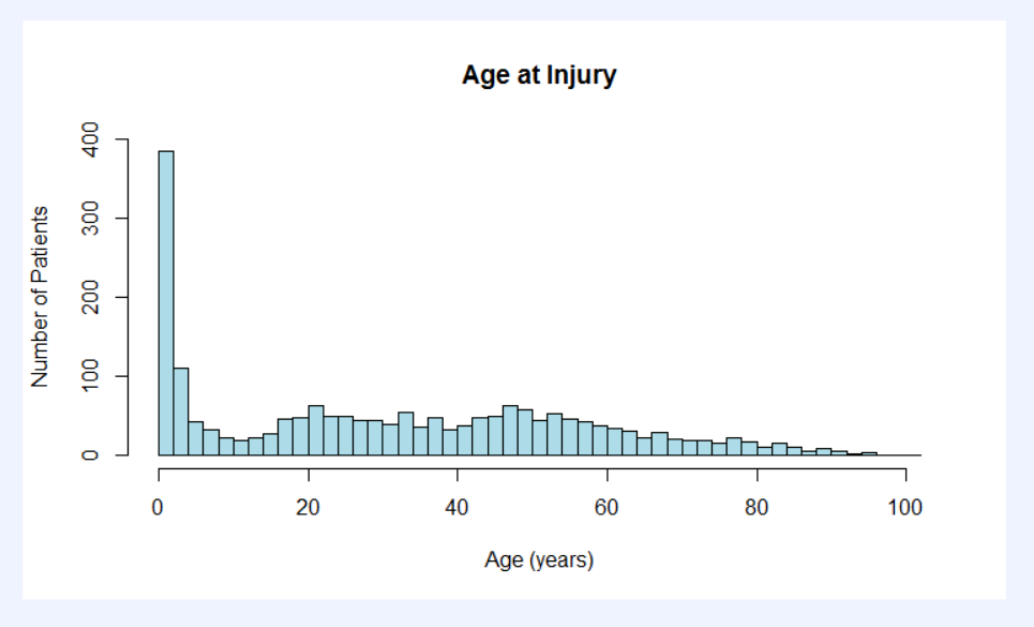

Figure 5-1 Histogram of number of patients in each age group at time of injury.

5.3.2 Differences Between Adults and Children

There were significant differences in both the demographics and pattern of injury seen between adults and children (Table 5-1). Children were more likely to be injured by hot liquids, accounting for 62% of paediatric injuries, with flame injuries being relatively rare (6%). Conversely, flame burns were more common in adults (29%). Bearing this in mind, smoke inhalation injuries were far more likely to be present in adults (2% vs 0.2%, $p<0.001$) and airway injuries, although more common in adults (1.4% vs 0.9%), did not reach statistical significance ($p=0.3$).

Male patients accounted for the majority of all burn injuries (63.3%) and although this pattern was constant in those under 16 years old (59%) it was more pronounced among adult patients (66%) ($p=0.004$).

The vast majority of burn injuries involved <10% TBSA (1441, 72.9%) with major burns, >20% TBSA, occurring in 63 patients (3.9%). Major burns were more likely to occur in adults (4.8%) and remained relatively rare in children (1.8%) ($p=0.017$).

Patients of a white ethnic background accounted for the majority of all admissions (62%). However, children from an ethnic minority background, broadly categorised as Afro-Caribbean or Asian, accounted for a greater proportion of admissions within the paediatric cohort (9.2%) than in the adult population (2%) ($p < 0.001$).

Within both adult and paediatric cohorts, patients were more likely to reside in an area of relative socioeconomic deprivation with 1116 (57%) residing in lowest two SIMD quintiles. This pattern seemed to be more pronounced within the paediatric cohort, with children in the lowest SIMD quintile accounting for 40% of burn injuries while 33% of the adult population were in this SIMD category ($p=0.018$).

The majority of burn injuries occurred in populations that reside in urban areas or accessible towns (UR8 1-3), accounting for 1679 (84.9%) of all patients, while only 275 (13.9%) patients resided in remote or rural areas (UR8 4-8) of Scotland. A similar distribution was seen in both the adult and paediatric cohorts, although proportionally less children from remote or rural areas suffered burn injuries (10.2%) compared with a higher proportion of adults residing in remote or rural areas (16%, $p=0.022$).

5.3.3 Comorbidities

Comorbidity details were extracted from the adult cohort only. Data was extracted and amalgamated from three sources; SMR01, SMR04 and COBIS; for all patients over 16 years old (Table 5-2). Alcohol abuse was the most common comorbidity, affecting 104 (7.9%) of patients. 82 (6.2%) patients had a diagnosis classified under “other neurological disorders”, as determined by the Elixhauser comorbidity method. This classification included epilepsy, Parkinson’s disease, degenerative or demyelinating disorders, systemic atrophies and various other conditions.

Table 5-2 Number of patients with each comorbidity according to Elixhauser domains

Elixhauser Comorbidity	N = 1324
Congestive heart failure	9 (0.7)
Cardiac arrhythmia	21 (1.6)
Valvular disease	0
Pulmonary circulation disorder	11 (0.8)
Peripheral vascular disorder	11 (0.8)
Hypertension (uncomplicated)	3 (0.2)
Hypertension (complicated)	<6 (<0.5)
Paralysis	6 (0.5)
Other neurological disorder	82 (6.2)
Chronic pulmonary disease	29 (2.2)
Diabetes (uncomplicated)	10 (0.8)
Diabetes (complicated)	10 (0.8)
Hypothyroidism	0
Renal failure	<6 (<0.5)
Liver disease	13 (1.0)
Peptic ulcer disease	8 (0.6)
HIV/AIDS	<6 (<0.5)
Lymphoma	<6 (<0.5)
Metastatic cancer	<6 (<0.5)
Solid tumour	30 (2.3)
Rheumatoid arthritis/Collaged vascular disease	<6 (<0.5)
Coagulopathy	<6 (<0.5)
Obesity	0
Weight loss	<6 (<0.5)
Fluid/electrolyte disorder	13 (1.0)
Blood loss anaemia	<6 (<0.5)
Deficiency anaemia	11 (0.8)
Alcohol abuse	104 (7.9)
Drug abuse	17 (1.3)
Psychoses	18 (1.4)
Depression	27 (2.0)

Psychoses and depression were present in 18 (1.4%) and 27 (2.0%) patients respectively. Using the SMR04 database of psychiatric hospital admissions allowed for this information to be available, as only one of each of these conditions would have been discovered using the SMR01 and COBIS databases alone.

The Elixhauser method of comorbidity assessment represents the non-weighted measure of comorbidities for each patient. The majority of patients (76%) had no pre-existing comorbidities, with only 8 patients (0.6%) having 4 or greater (Table 5-3). Two further methods of converting the Elixhauser method into a

weighted index as described by Moore et al[108] and Van Walraven et al[110] as described in chapter 2 were also reported, demonstrating similar spreads of categorised indices (Table 5-3). In the original studies by Moore et al and Van Walraven et al, an increased numerical index was associated with an increased risk of death.

Table 5-3 Various methods of assessment of Elixhauser comorbidity

Elixhauser Comorbidity Assessment	N = 1324[1]
Number of comorbidity domains	
0	1005 (76)
1	226 (17)
2	66 (5.0)
3	19 (1.4)
≥4	8 (0.6)
AHRQ index[2]	
<0	60 (4.9)
0	1107 (84)
1-4	52 (3.9)
≥5	105 (7.9)
Van Walraven index[3]	
<0	8 (0.6)
0	1145 (86)
1-4	51 (3.9)
≥5	120 (9.1)

[1]n (%)
[2]Agency for Healthcare Research & Quality, Moore et al[108]
[3]Van Walraven et al[110]

5.3.4 Mortality

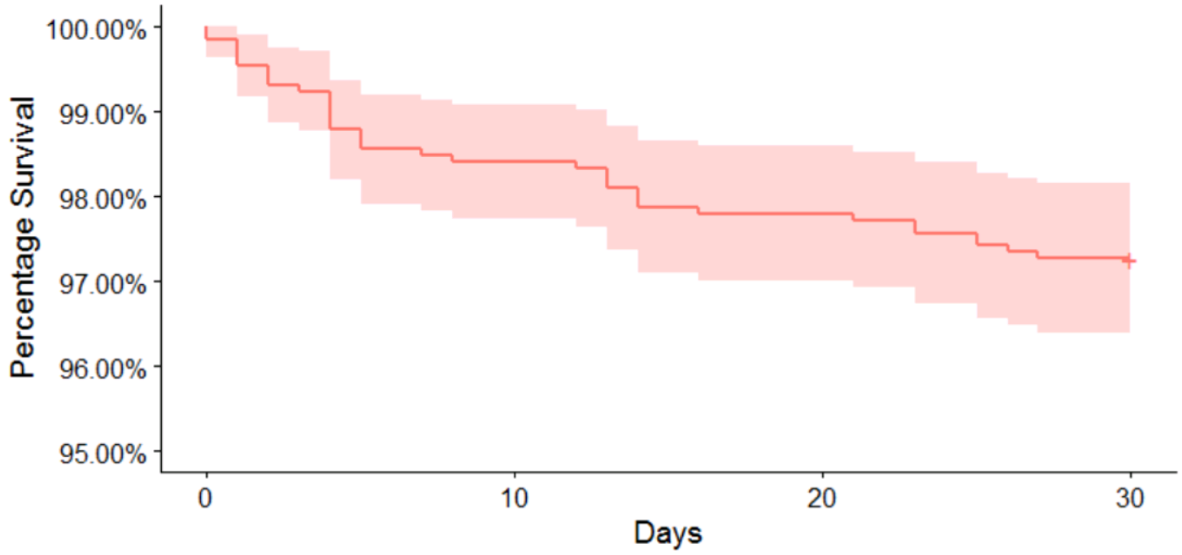

Figure 5-2 Kaplan Meier curve of all patients, survival to 30 days.

Following exclusion of all individuals less than 16 years of age at the time of injury, 1324 patients were included in the survival analysis. 36 patients (2.73%) died within 30 days of sustaining a burn injury (Figure 5-2).

Univariable analysis using a Cox proportional hazards model demonstrated that increasing age, presence of an airway burn, smoke inhalation injury, increasing size of burn and flame burn all increased the risk of death within 30 days (Table 5-4).

Table 5-4 Univariable cox proportional hazards regression exploring patient demographic and burn injury details data

Characteristic	Hazard Ratio	95% CI	p-value
Gender (Male)	0.62	0.23-1.21	0.16
Age*	1.05	1.03-1.06	<0.0001
Airway burn	6.9	2.12-22.5	0.001
Smoke inhalation	8.87	3.45-22.81	<0.0001
% TBSA†	1.09	1.08-1.11	<0.0001
SIMD			
1 (most deprived)	Reference		
2	0.58	0.23-1.5	0.26
3	0.62	0.23-1.69	0.35
4	0.68	0.25-1.88	0.46
5 (least deprived)	0.8	0.26-2.41	0.7
Urban-rural classification			
Urban area	Reference		
Small town	0.72	0.22-2.38	0.59
Rural area	1.04	0.40-2.70	0.94
Ethnicity			
White	Reference		
Ethnic minority	Insufficient Data		
Unknown	1.04	0.53-2.03	0.91
Mechanism of injury			
Hot Liquid	Reference		
Flame	4.83	1.98-11.82	0.0006
Other	0.58	0.16-2.07	0.41

*Calculated for each 1-year increase in age.

†Calculated for each 1% increase in TBSA burned.

Further univariable analysis using the Elixhauser comorbidity data showed that a history of alcohol excess or depression were associated with an increased risk of death (Table 5-5). Unfortunately, due to the small number of patients with many of the comorbidities listed using the Elixhauser method, there was often insufficient data to conduct a regression analysis.

Table 5-5 Univariable cox proportional hazards regression exploring Elixhauser comorbidity data

Comorbidity	Hazard Ratio	95% CI	p-value
Congestive heart failure	4.26	0.58-31.21	0.15
Cardiac arrhythmia		Insufficient Data	
Valvular disease		Insufficient Data	
Pulmonary circulation disorder		Insufficient Data	
Peripheral vascular disorder		Insufficient Data	
Hypertension (uncomplicated)		Insufficient Data	
Hypertension (complicated)		Insufficient Data	
Paralysis		Insufficient Data	
Other neurological disorder	2.47	0.96-6.35	0.06
Chronic pulmonary disease		Insufficient Data	
Diabetes (uncomplicated)		Insufficient Data	
Diabetes (complicated)		Insufficient Data	
Hypothyroidism		Insufficient Data	
Renal failure		Insufficient Data	
Liver disease	2.91	0.40-21.22	0.29
Peptic ulcer disease		Insufficient Data	
HIV/AIDS		Insufficient Data	
Lymphoma		Insufficient Data	
Metastatic cancer		Insufficient Data	
Solid tumour	2.62	0.63-10.89	0.19
Rheumatoid arthritis/Collaged vascular disease		Insufficient Data	
Coagulopathy		Insufficient Data	
Obesity		Insufficient Data	
Weight loss		Insufficient Data	
Fluid/electrolyte disorder	2.98	0.41-21.73	0.28
Blood loss anaemia		Insufficient Data	
Deficiency anaemia		Insufficient Data	
Alcohol abuse	3.44	1.57-7.56	0.002
Drug abuse		Insufficient Data	
Psychoses	2.15	0.29-15.75	0.45
Depression	4.64	1.42-15.14	0.01

Further analysis of variations of the Elixhauser comorbidity measures and their influence on mortality are presented in Table 5-6. Comorbidity was first assessed simply by comparing those patients with no comorbidity against those with one or more comorbidities, demonstrating a significantly increased risk of death in comorbid patients with a hazard ratio of 2.89 (95% CI 1.50-5.56, p=0.001). Further analysis to assess whether multimorbidity contributed to mortality risk was carried out by categorising patients into no comorbidities; one comorbidity; and two or more comorbidities. Although this demonstrated that those with one comorbidity had an increased risk of death with a hazard ratio of

3.37 (95% CI 1.69-6.72, p<0.001), the presence of multiple comorbidities did not seem to have the same influence of mortality (hazard ratio 1.71, 95% CI 0.51-5.78, p=0.39).

Table 5-6 Univariable cox proportional hazards regression analysis of different Elixhauser comorbidity assessment methods

Elixhauser Comorbidity Assessment	Hazard Ratio	95% CI	p-value
Elixhauser (number of comorbidities)			
0	Reference		
≥1	**2.89**	1.50-5.56	0.001
Elixhauser (number of comorbidities)			
0	Reference		
1	3.37	1.69-6.72	<0.001
≥2	1.71	0.51-5.78	0.39
AHRQ index[1]			
<0	Reference		
0	0.24	0.11-0.53	<0.001
1-4	0.26	0.03-2.06	0.2
≥5	0.77	0.29-2.08	0.61
Simplified AHRQ index[1]			
≤0	Reference		
1-4	0.83	0.11-6.06	0.85
≥5	2.45	1.07-5.61	0.034
Van Walraven index[2]			
<0	Reference		
0	0.27	0.08-0.89	0.032
1-4	0.38	0.06-2.30	0.3
≥5	0.54	0.14-2.17	0.39
Simplified Van Walraven index[2]			
≤0	Reference		
1-4	1.32	0.31-5.23	0.71
≥5	1.85	0.77-4.47	0.17

[1]Agency for Healthcare Research & Quality, Moore et al[108]
[2]Van Walraven et al[110]

Further analysis of comorbidity status was carried out using the weighted Elixhauser index scores described by Moore et al[108] and Van Walraven et al[110]. These indices were categorised firstly into four as described in Table 5-6. This demonstrated no evidence that increasing comorbidity burden increased the risk of mortality. Indeed, those patients with an AHRQ or Van Walraven index of zero appeared to be a reduced risk of death in comparison to the reference group with an index of less than zero.

Owing to the small number of patients with an index of less than zero in both methods of assessment, the categories were simplified by amalgamating two categories to include all patients with an index of zero or less. This method of categorisation did not demonstrate any association between increasing index and mortality risk using the Van Walraven method. However, using the AHRQ method, those patients with an index of five or more were at an increased risk of death with a hazard ratio of 2.45 (95% CI 1.07-5.61, p0.034).

Multivariable analysis is presented as adjusted hazards ratios (Table 5-7). Increasing age, increasing TBSA burned and the presence of a smoke inhalation injury were all strongly associated with increased 30-day mortality.

Table 5-7 Multivariable cox proportional hazards regression

Characteristic	Hazard Ratio	95% CI	p-value
Age*	1.08	1.05-1.11	<0.0001
Smoke inhalation	14.54	4.63-45.68	<0.0001
% TBSA†	1.12	1.10-1.14	<0.0001
Depression	13.65	3.56-52.31	<0.0001
Other neurological disorder	6.48	2.02-20.82	0.002

*Calculated for each 1 year increase in age.
†Calculated for each 1% increase in TBSA burned.

Although flame burns were associated with increased risk of death using a univariable analysis, this association was no longer significant once the TBSA burned was accounted for. Additionally, although univariable analysis using various methods of Elixhauser comorbidity assessment were suggestive that increasing comorbidity burden may be associated with increasing mortality risk, such an association was no longer statistically significant once TBSA and age were included in the multivariable model.

Regarding specific comorbidities, the presence of alcohol abuse was associated with mortality using a univariable analysis. However, this association was no longer apparent once adjusted for TBSA, age and the presence of a smoke inhalation injury. The presence of depression remained significant on multivariable analysis and a diagnosis of “other neurological disorder” was also found to be independently associated with mortality on multivariable analysis having not reached this threshold on univariable analysis.

5.4 Discussion

5.4.1 Epidemiology of burn injuries in Scotland

This study has described the epidemiology of burn injuries requiring hospital admission in Scotland. As is demonstrated in other developed nations, such injuries are more likely to affect male patients, with this difference becoming more pronounced among adults[214]. Burn injuries are also more likely to affect those from areas of socioeconomic deprivation[215]. Although other studies have highlighted the increased prevalence of burn injuries in rural communities, this does not seem to be reflected in the Scottish population, with 17% of the Scottish population residing in a rural area, only 13.9% of burn injuries occur in those residing in remote or rural areas.

This study has highlighted some of the important differences between the burn injuries seen in children and those in adults. Pre-school age children make up a significant proportion of burn injury admissions, being more likely to sustain an injury from hot liquid than any other mechanism, reflecting the common hazards around the household. Flame injuries are relatively rare in children, accounting for only 6% of injuries, while flame injuries are much more common in adults at 29% of all injuries. Although major burns, defined as affecting greater than 20% TBSA, are generally rare in Scotland, they are even rarer in children accounting for 1.8% of childhood burns, while making up 4.8% of adult injuries. Such differences reflect the varying mechanisms and circumstances in which burn injuries are sustained between children and adults.

Children from an ethnic minority background accounted for a greater proportion of burn injuries in comparison with the adult population, with 9.2% of the paediatric cohort being from an ethnic minority background with only 2% from the adult group. Unfortunately, a significant proportion of patients did not have ethnicity recorded (25% of the paediatric cohort and 38% of the adult cohort), no doubt impacting upon the accuracy of this data.

In the general Scottish population, as per the 2011 census, 96% of the population reported their ethnicity as white (Scottish, British or other). Non-white ethnic minorities accounted for 4% of the population, with those from an Asian background accounting for 3% and African, Caribbean or black groups accounting for 1% of Scotland's population[216]. This suggests a far higher proportion of children from an ethnic minority background are suffering burn injuries than would otherwise be expected when looking simply at the census figures. The increased risk of burn injury in ethnic minority children in developed nations has been highlighted in multiple studies throughout the United Kingdom, Europe and North America[217–219]. Such differences may be accounted for by unsafe cooking practices, poor knowledge of household safety and language barriers[217].

Unfortunately, this description of the link between children from ethnic minority backgrounds and a potentially increased risk of burn injury may be an underestimate as 663 patients (34%) had no ethnicity data recorded. The disparity in healthcare experiences and outcomes for individuals of black and ethnic minority descent has been highlighted in recent years during the COVID-19 pandemic[220] and in other areas of healthcare including maternity[221,222] and cancer care[223,224]. As demonstrated in this study, the collection of data regarding ethnicity in healthcare is often lacking. This has prompted multiple organisations and healthcare providers to both quantify this problem and take steps to address it[225,226].

5.4.2 Comorbidity assessment

Comorbidity data was collected and assessed using the method described by Elixhauser et al[106]. This method was chosen as it uses hospital administrative data based on ICD codes to define categories of comorbidity and has been validated in data prediction of in-hospital mortality. The majority of patients (76%) did not have any comorbidity documented using this method of assessment. This most likely reflects both the relatively low median age of the adult cohort (45 years) and the limitations of using such healthcare administrative data to extract detailed clinical information.

This study has demonstrated that neurological conditions and alcohol excess are among the most commonly identified health problems affecting adult burn

patients in Scotland. Neurological conditions such as epilepsy have been previously recognised as risk factors for sustaining a burn injury[227,228]. Other studies have similarly highlighted the association between alcohol excess, both acute intoxication and alcohol dependency, and an increased risk of burn injury[229,230].

The Elixhauser scoring method was selected for this study due to its inclusion of psychiatric illness and substance abuse domains. Although recognised as areas of concern among burn injured patients, little data exists on the extent of the association between such conditions and burn injuries among the Scottish population. Additionally, this study is the first we are aware of that has used ICD-10 codes derived from psychiatric hospital admissions to further inform pre-existing comorbidity data. This method resulted in individuals being identified as having depression or psychoses that would otherwise not have been recognised by using acute hospital admission data alone. All but two of the diagnoses of depression or psychosis were only apparent due to previous psychiatric hospital admission. This serves to further highlight the limitations of administrative health data in robustly identifying potentially significant comorbidities.

5.4.3 Mortality from burn injury

In this cohort of adult patients admitted with a burn injury of widely varying severity, there was an overall mortality rate of 2.73%. This is broadly comparable with rates in other developed nations, with some studies reporting mortality rates between 1.5 and 6.9%[231,232].

Prediction of mortality due to burn injury is classically done using the Baux or revised Baux score which use age, TBSA burned and the presence of inhalation injury as the mainstays of prognostication[30,233]. Although the original Baux score was developed in 1961, more recent studies have reinforced the persisting and consistently strong relationship between these three factors and mortality risk[31,32].

This study has reflected these findings, demonstrating similar hazard ratios for increasing age and TBSA burned as other studies[234,235]. Multivariable analysis

showed at each one-year increase in age and one-percentage increase in body surface area burned were associated with hazard ratios of 1.08 and 1.12 respectively. The presence of an inhalation injury significantly contributes to the risk of death following burn injury. This study reported an adjusted hazards ratio of 14.54 for those that suffered an inhalation injury, with a wide confidence interval of 4.63-45.68. This likely reflects the relatively small number of patients suffering such an injury, affecting only 2% of the adult cohort. However, the significant effect of such an injury on mortality risk has been replicated in other studies, with some reporting an odds ratio as high as 45.35 in those with features of severe inhalation injury on bronchoscopy[236].

5.4.4 Effect of comorbidity on mortality

Compared to the influence of the variables used in the Baux score, the effect of pre-existing comorbidity on mortality risk has been less well researched. Some studies have demonstrated a correlation between increasing comorbidity and increased risk of death in burn injured patients[237,238]. A retrospective observational study of over 31,000 patients over a ten-year period demonstrated that various medical conditions as defined by the Charlson or Elixhauser comorbidity measures predicted burn mortality, with specific medical conditions such as renal or liver disease and metastatic cancer all being strongly predictive of poor outcomes [239].

This study has demonstrated a relatively high prevalence of conditions such as mental illness, alcohol and drug misuse among adults admitted to hospital with a burn injury. Such conditions may also be associated with an increased risk of death from burn injury, as patients with a diagnosis of depression or other neurological disorder were at an increased risk of death in the multivariable analysis. However, these conditions were also among the most commonly identified comorbidities. The fact that other conditions did not seem to have an impact on mortality may simply be due to such comorbidities being under-recorded due to the aforementioned limitations of using administrative data.

Additionally, the physiological rationale for an increased risk of death from burn in the context of depression or neurological disease is not immediately apparent. Rather, the presence of these conditions may be a reflection of other significant

health problems. The diagnosis of depression was most often made in patients that had been admitted to a psychiatric inpatient facility for this condition, implying a degree of severity far more than the majority of individuals with a depressive illness managed in the community. Equally, the diagnosis of "other neurological disorder" included many differing conditions with a widely varying severity and physiological consequences. For example, the mortality associated with advanced Parkinson's disease is likely to be much higher than that of well controlled epilepsy, although they both contribute to the category of "other neurological condition". This serves to again highlight the limitations of such administrative healthcare databases and the methods used to analyse them.

Although specific comorbidities such as depression or neurological disorder seemed to increase the risk of death, no such correlation could be found with the number of comorbidities as measured by the Elixhauser score. Although patients with an Elixhauser score of 1 had a hazard ratio of 3.37 (95% CI 1.69-6.72, $p<0.001$) when compared to those with no comorbidities, multi-comorbid patients with a score greater than 1 were not found to be at increased risk of death with a hazard ratio of 1.71 (95% CI 0.51-5.78, $p=0.39$). Of note, only 27 patients (2%) had three or more comorbidities, significantly reducing the power to reach any meaningful conclusions. Another reason for this lack of correlation between increasing comorbidity and mortality has been alluded to by the authors of the original Elixhauser study, noting that with increasing severity of a patient's acute condition the likelihood of common, less serious pre-existing comorbidities (such as hypertension) being included in administrative coding data reduces[106]. Conversely, relatively healthy patients would be more likely to have relatively minor comorbidities recorded due to the lack of other serious diagnoses to record.

In the original study by Elixhauser et al which detailed the eponymously named method of comorbidity measurement, the authors highlighted that each comorbidity category had independent effects on the outcomes measured and should not be simplified as an index due to the heterogeneous patient groups it was both derived from and could be applied to[106]. However, this has not deterred further researchers from expanding on this work in an attempt to build

predictive models using weighted scores from the original Elixhauser comorbidity categories[108,110].

Van Walraven et al condensed the variables in the Elixhauser classification into a single numeric to increase ease of reporting and analysis when using the system[110]. The authors reported that 21 of the comorbidities were independently associated with hospital mortality in an undifferentiated population of over 345,000 hospital admissions. In this study of burn injured adults, the modified Elixhauser index described by Van Walraven et al did not correlate with any increased risk of death in univariable survival analysis.

A further method using the Elixhauser classification system described by Moore et al[108] developed two further weighted indices to predict hospital mortality and 30-day readmission separately. The study was conducted on data of over 10 million hospital admissions and demonstrated a c-statistic of 0.777 when using the mortality prediction index. When applied in this study of exclusively burn-injured patients, this method of Elixhauser analysis only predicted mortality in patients with a comorbidity index ≥5 (p=0.034) in an unadjusted univariable analysis. This association was no longer significant when using a multivariable approach.

The association between substance abuse and increased risk of burn injury has been previously well documented[240]. Although this study did not find any association between illicit drug use and an increased risk of death from burns, other studies have demonstrated its association with sustaining larger surface area burns and flame burns[241]. In the study by Haum et al, positive blood alcohol levels on admission with a burn injury and a history of chronic alcohol abuse were both associated with increased mortality when compared to controls[230]. McGill et al demonstrated that although drug abuse was not a predictor of mortality when adjusted for age, TBSA and inhalation injury, alcohol abuse did remain an independent predictor of death[242].

The results from this study demonstrated that although alcohol abuse remained a contributor to mortality when adjusted for TBSA and age (HR 2.75, 95% CI 1.11-6.83, p=0.029), the statistical significance fell when smoke inhalation was also included (HR 1.64, 95% CI 0.57-4.73, p=0.36). Although we have not

demonstrated an independent mortality risk associated with alcohol abuse, its presence as the most common comorbidity among the adult cohort (7.9%) reflects the likely role it plays in the increased risk of sustaining a burn injury.

5.4.5 Strengths and limitations

This study has used large national datasets from various sources to gather as much information as possible on the variables of interest. By using specialty specific databases such as COBIS and SMR04 (psychiatric hospital admissions) we have been able to provide a level of detail not previously possible by using only acute hospital admission data. This study has therefore been able to describe burn injury patterns and pre-existing comorbidities in far greater detail.

However, given this study's reliance on administrative data to determine comorbidities, drawing any firm conclusions on the influence of various comorbidities on burn-related mortality is difficult. Studies have highlighted the deficiencies of using such comorbidity measures within burn injured cohorts, with one study demonstrating that the Charlson comorbidity index did not identify 67% of comorbidities[243]. Hence, the description of the comorbidity burden in this study is likely to be an underestimate, not only due to the inadequacies of relying on administrative data to gather detailed clinical information, but that specific conditions such as alcohol abuse are less common than would be expected compared to other studies[230]. Additionally, the diagnosis of alcohol abuse in this study relies on a patient having a prior admission to hospital with an alcohol related condition. Given that the prevalence of hazardous or harmful drink is estimated to be as high as 24% in the Scottish population, the majority of patients drinking to excess are not likely to require hospital admission[244]. Furthermore, the influence of acute alcohol intoxication has not been assessed with this study's methodology. Similarly, the incidence of drug abuse in this cohort (1.3%) reflects a similar prevalence of 1.62% seen throughout the Scottish adult population[245]. However, given the concerns of such methods to robustly identify comorbidities, this too is likely to be an underestimate of the true prevalence in this cohort.

Owing to the relatively small sample size and only 36 deaths, the statistical analysis is limited when building a multivariable model investigating mortality.

The inclusion of five variables in the final model is at the limits of such an analysis with a risk of committing a type 2 error. Therefore, these results should be interpreted with caution and further research is likely required to truly assess the impact of such comorbidities on mortality risk from burn injury.

Conditions such as alcohol excess may result in an impaired ability to extricate oneself from a fire making it more likely that an individual sustains a burn injury, especially a major burn. This is reflected in the association between alcohol abuse and mortality in univariable analysis, but lack of association in a multivariable analysis once accounting for the size of burn. However, increasing age, history of depression or presence of "other neurological disorder" were independently associated with mortality on multivariable analysis, indicating that it was not simply any associated increased risk of sustaining a burn injury that contributed to mortality, but rather other related detrimental physiology that may have increased this mortality risk.

Patients were identified for this study using the COBIS database, with data input only possible if the patient was admitted under the care of a specialist burn team. Patients may not be included in the COBIS database if specialist burn team input was not required, the injury was managed conservatively in a local hospital, overwhelming injuries resulted in the decision to provide palliative care or patients died before arrival at hospital or in the emergency department. Indeed, a total of 117 fire related fatalities were recorded in Scotland from 2012-2015, a far greater number than in our study over the same period[246]. Hence, this method of cohort selection may have also introduced an element of selection bias.

5.5 Conclusions

This study has demonstrated the significant differences in burn injury pattern seen between children and adults. Children from ethnic minority backgrounds seem to be disproportionately represented in this cohort of patients, highlighting an area of focus for public health interventions with the aim of reducing this area of health inequality.

Psychiatric illness and alcohol abuse were more prevalent among this cohort of adult patients than various other comorbidities, although this is still likely to be an underestimate. Such conditions are likely to play a significant role in the risk of sustaining a burn injury.

Although this study has not replicated the results seen elsewhere whereby increasing comorbidity burden has a clear impact on mortality risk, it has raised concerns over the impact of neurological and psychiatric conditions on the risk of death after burn injury. Such results should be interpreted with caution given the limitations of using administrative healthcare data to infer comorbidity burden, potential elements of selection bias and risk of type 2 error.

Chapter 6 Drug prescription data to explore health burden after burn injury

6.1 Introduction

6.1.1 Health problems following burn injury

In recent years it has become increasingly recognised that individuals who suffer a burn injury are often faced with significant ongoing health problems in the years after the initial injury[247]. These can include chronic pain[52] and pruritus[59,60]; psychological distress[65,66] that can manifest as depression, anxiety or symptoms of post-traumatic stress disorder (PTSD) and even persisting pathophysiological inflammatory changes that may increase the risk of infections[83], cardiovascular disease[86], cancer[87,88] and early death[91,93].

The understanding of these long-term sequalae after burn injury has relied on observational studies that have explored hospital admissions and death registration data as well as patient questionnaires to explore outcomes such as pain, psychological distress and quality of life[52,53]. Although such research techniques have helped improve our understanding of the long-term consequences of such injuries, they may only represent the tip of the iceberg. By focusing on outcomes such as mortality or relying on those that respond to questionnaires, there may be a significant burden of long-lasting morbidity that is simply hidden. Well-maintained and comprehensive healthcare administrative databases are invaluable tools that may allow a more detailed understanding of long-term consequences of burn injuries.

6.1.2 Drug use after burn injury

The link between illicit drug use and burn injury has been explored previously, with several studies highlighting the high prevalence of drug abuse among burn injured patients.[230,241] Other studies have highlighted the risk of sustaining a larger burn or associated inhalation injury in those individuals with a history of drug or alcohol abuse, as well as an increased mortality in this cohort.[242,248]

However, the link between prescription drug use and burn injury has not been fully explored. It is well recognised that chronic pain is a common consequence

of burn injury. Previous research has highlighted the potential risk of developing opioid dependency following injury, with 4.2% of previously opioid-naive patients either developing chronic opioid use or an opioid use disorder following burn injury[249]. Given the often-overwhelming pain experienced by patients following burn injury and the lack of suitable alternatives, opioids remain the mainstay of analgesic management. This inevitably introduces the potential for harm and dependency, as highlighted in recent studies.[250,251]

With increasing concern over the potential harm from a variety of prescription drugs, the Scottish and UK Governments commissioned reviews to explore the magnitude and causes of prescription drug dependency and how to address them[252,253]. These took the form of mixed methods reviews of both Scottish and English prescribing data for five classes of drugs: antidepressants, opioids, gabapentinoids, benzodiazepines and non-benzodiazepine anxiolytics and hypnotics such as zopiclone commonly referred to as "z-drugs". Additionally, the monitoring of many of these drugs form part of the Scottish Government's Mental Health Strategy 2017-2027,[254] including publication of the use of medicines used in mental health[255]. As of 2019/2020, 21.6% of adults in Scotland were prescribed an antidepressant, 17.8% prescribed an opioid, 5% a benzodiazepine, 4.1% a gabapentinoid and 3.2% a "z-drug"[252].

Although there is recognition that burn injuries are associated with increased opioid use, this phenomenon may not be isolated to this class of drug. With a high use of drugs for mental health conditions in Scotland and the potential for an increased need for such treatments following burn injury, there is a need to identify and quantify the use of these drugs after such an injury.

6.1.3 The use of drug prescription data in research

In 1976, the World Health Organisation (WHO) developed the Anatomical Therapeutic Chemical (ATC) classification system whereby the active ingredients of drugs are classified according to the organ or system on which they act and their pharmacological properties.[256] This system was developed to help monitor drug use and aid research by standardising the nomenclature used to describe drugs. Various studies have used this system or other similar methods to identify comorbidities based on medication use[257–261].

In Scotland, following an individual's discharge from the care of a burns team, the ongoing care falls upon the patient's general practitioner. Robust data on the problems that individuals may face in this phase of their recovery is difficult to ascertain. The true prevalence of chronic pain and mental health problems is difficult to quantify. The surrogate use of community drug prescription data may allow for some degree of understanding of the prevalence of ongoing health problems in the years after burn injury.

6.2 Study Questions

The first aim of this study was to use community drug prescription data to describe the health burden and comorbidities of a cohort of adult patients that have sustained a burn injury requiring hospital admission, with particular focus on drugs used in the management of pain and mental health problems. This analysis focused on drugs with recognised potential of harm from dependency and withdrawal; namely opioids, antipsychotics, antidepressants, anxiolytic and hypnotics agents and gabapentinoids.

The second aim of this study was to describe whether there is an increase in the use of these drugs after burn injury and explore factors that may be associated with any increased use. This analysis was conducted by first exploring the use of opioids as a surrogate marker of pain after burn injury. Further analysis then amalgamated the remaining classes of drugs (antipsychotics, antidepressants, anxiolytic and hypnotics agents and gabapentinoids) for use as a surrogate marker for mental health conditions.

6.3 Methods

6.3.1 Approvals

Release of the required data was granted by the Public Benefit and Privacy Panel, a patient advocacy panel that scrutinises applications for access to NHS Scotland health data. Ethical approval was not required, nor sought, for this study. Datasets were linked by the electronic Data Research and Innovation Service (eDRIS), part of Public Health Scotland (PHS).

6.3.2 Data sources

Data sources including Care of Burns in Scotland (COBIS), SMR01, SMR04 and the National Records Scotland (NRS) have been detailed in previous chapters. Comorbidity data was extracted [98]as previously detailed and the overall Elixhauser score was simplified to categorise patients as either multimorbid (having two or more comorbidities) and those with one or less. Additionally, owing to the relevance of pre-existing drug misuse and mental health conditions in the outcomes of interest, four specific comorbidity domains were also selected for inclusion in the final analysis: alcohol abuse, drug abuse, psychoses and depression. These approaches to categorising comorbidity data were used due to both the small number of patients with three or more comorbidities and to address the issue of collinearity with the specific comorbidities of interest as noted. Drug prescription data was extracted from the Prescription Information System (PIS) as detailed in chapter 2.

6.3.3 Inclusion & exclusion criteria

This study was carried out as a retrospective cohort study, using linked national data in Scotland. Patients were identified using the Care of Burns in Scotland (COBIS) national audit system database.

All adult patients, aged 16 years or older, who were admitted to hospital under the care of a specialist burn team from January 2012 to December 2015 were included in the analysis. Patient demographics, injury details and comorbidities have been previously detailed in chapter 5. Any results involving less than 6 patients were censored in the interests of preventing possible identification of individuals.

When exploring drug prescriptions following discharge from hospital, all patients that died within 60 days of burn injury were excluded from analysis to account for either death from burn injury or those that may have died shortly after discharge and may have received the drugs of interest as part of a palliative care plan. However, these patients remained in the pre-injury descriptive analysis in order to give a fuller picture of the drug prescription patterns pre-injury.

6.3.4 Prescription data

Drug prescriptions taken from the PIS database were categorised in terms of the chapters and sub-sections in which they appear in the BNF. Each chapter details drugs used in each organ system or disease category, for example respiratory system or cardiovascular system. Specific drugs and classes of drugs of particular interest including opioids, anxiolytics, antipsychotics, gabapentinoids and antidepressants were explored separately in more detail. Patients prescribed a drug for three or more months in a twelve-month period were considered a "recurrent user"[111].

Pre-injury drug prescriptions were analysed for the year preceding the date the burn injury was sustained. Post-injury drug prescriptions were analysed for one year from the date of hospital discharge after the index injury.

6.3.5 Statistical Analysis

Statistical analyses were performed using R version 3.6.1 (Foundation for Statistical Computing, Vienna, Austria). Analysis of factors associated with pre-injury opioid, antidepressant, gabapentinoid, antipsychotic and anxiolytic drug use were carried out using Pearson's Chi-squared test, Wilcoxon rank sum test and Fisher's exact test where appropriate.

Post-injury prescriptions of opioids were analysed separately as the indications for opioid prescriptions, namely pain, differed significantly from the common indications for the use of the other classes of drugs. Post-injury use of antidepressant, gabapentinoid, antipsychotic and anxiolytic drugs were amalgamated and broadly categorised as mental health drugs. This method was chosen due to the overlapping clinical indications for these drugs and to better represent the surrogate outcome of mental health problems in greater fullness than exploring each drug class separately would allow.

Post-burn opioid prescriptions were analysed by counting the number of opioid prescriptions dispensed to each patient before and after burn injury. A multi-level Poisson non-linear regression model was then used to explore factors associated with an increase in the number of opioid prescriptions following

injury. This method accounted for patients that were either opioid naïve pre-injury and those already prescribed opioids by measuring the change in number of opioid prescription dispensed following burn injury. Post-injury mental health prescriptions were analysed by counting the number of classes of mental health drugs dispensed to each patient before and after burn injury. A multi-level Poisson non-linear regression model was used to explore the factors associated with changes in the number of drug class prescriptions pre- and post-burn injury. For example, an individual may be prescribed one class of drug, an antidepressant pre-burn injury, then be prescribed two classes, both an antidepressant and anxiolytic, after the injury.

A multi-level regression model approach was chosen to account for the random variation of drug prescriptions within individual patients, the variation in follow-up time available for each patient and the influence of pre-injury drug use. This method was also chosen due to the repeated measure nature of the data. With multiple drug prescriptions being dispensed to patients and varying numbers of prescriptions and time intervals between them, this data could be viewed as hierarchical in terms of the 'within-patient' variability of said prescriptions. This allows analysis of each data point, rather than simplifying this data to averages, allowing for a far more detailed and complete picture of the data as well as increasing the power of the analysis. Such analysis also accounts for any heteroscedasticity and assumptions of independence between drug prescriptions within an individual.

Fixed coefficients are assumed to be the same across different contexts, in this case individual patients. However, this method of mixed effect modelling allows for the analysis to take account of the random effects that may occur whereby the intercepts and slopes of a regression model are allowed to vary between individuals in the study.

Univariable analysis was conducted first to assess any variables associated with an increase in opioid or mental health drug use. Any variables with a p value <0.1 were included in the multivariable analysis and a backwards stepwise regression approach used to build a model. Statistical significance was set at a p value <0.05. Akaike's Information Criteria (AIC) and chi-squared difference test

were used to assess model fit. Residual plots and quantile-quantile plots were used to assess the assumptions of each model.

6.4 Results

During the study period from 2012 to 2015, 2005 patients were identified from the COBIS database. Twenty-eight patients were removed from analysis, having either sustained the burn injury before 2012 or no evidence of burn injury was recorded on any databases and 653 were excluded as they were under 16 years of age at the time of injury. The demographics of these adult patients have previously been described in chapter 5. A total of 1324 patients were included in the pre-injury drug use analysis.

6.4.1 Pre-injury drug prescriptions

In the year preceding the index burn injury 33,317 prescriptions were dispensed to 1053 (79.6%) patients. The classes of drugs are categorised by the BNF chapter or subsection in which they appear and are summarised in Table 6-1. Drugs for infections were the most commonly dispensed drug, with 36% of individuals being prescribed at least one agent. Other common prescriptions included analgesics (35%), drugs for gastrointestinal system disorders (33%) and cardiovascular conditions (29%).

Table 6-1 Number of patients pre-burn injury prescribed drug by BNF category and subcategory

Drug	N = 1324 (%)	Drug	N = 1324 (%)
Infections		**Anxiolytics & Hypnotics**	
Total	476 (36)	Total	216 (16)
Recurrent Users	154 (12)	Recurrent Users	134 (10)
Analgesia		**Ear, Nose & Oropharynx**	
Total	460 (35)	Total	168 (13)
Recurrent Users	265 (20)	Recurrent Users	38 (2.9)
Gastrointestinal System		**Antiepileptics**	
Total	437 (33)	Total	165 (12)
Recurrent Users	300 (23)	Recurrent Users	137 (10)
Cardiovascular System		**Obstetrics, Gynaecology & Urinary Tract Disorders**	
Total	385 (29)		
Recurrent Users	334 (25)	Total	146 (11)
Skin Conditions		Recurrent Users	86 (6.5)
Total	367 (28)	**Eye Conditions**	
Recurrent Users	156 (12)	Total	102 (8)
Antidepressants		Recurrent Users	33 (2.5)
Total	352 (27)	**Antipsychotics**	
Recurrent Users	282 (21)	Total	79 (6)
Musculoskeletal & Joint Disease		Recurrent Users	71 (5.4)
		Parkinson's & Related Conditions	
Total	325 (25)	Total	16 (1.2)
Recurrent Users	135 (10)	Recurrent Users	13 (1.0)
Respiratory System		**Other Central Nervous System Drugs**	
Total	299 (23)	Total	97 (7.3)
Recurrent Users	183 (14)	Recurrent Users	37 (2.8)
Nutrition & Blood		**Malignant Disease & Immunosuppression**	
Total	247 (19)	Total	13 (1.0)
Recurrent Users	151 (11)	Recurrent Users	10 (0.8)
Endocrine System		**Drugs for Substance Dependence**	
Total	220 (17)	Total	71 (5.3)
Recurrent Users	173 (13)	Recurrent Users	68 (5.1)

6.4.2 Pre-injury opioid use

460 (34.7%) patients were prescribed an analgesic medication in the year preceding their burn injury. Of these, 342 (25.8%) were prescribed an opioid of some form, of which 192 (14.5%) were recurrent users. The median number of opioid prescriptions per individual was 3.0 (IQR 1.0, 6.8), with a maximum of 66 dispensed in one year.

Despite females only accounting for 34% of patients in this study, they were overly represented among those receiving opioids, accounting for 47% of all pre-

injury opioid prescriptions (Table 6-2). Opioid users were also more likely to be prescribed to older patients (median age 49 vs 42, p<0.001) and to those from an area of socioeconomic deprivation (p=0.002).

Table 6-2 Patient characteristics associated with pre-burn opioid use.

Characteristic	All Patients N=1324	No Opioids N = 982	Opioid Prescribed N = 342	p-value
Gender n (%)				<0.001
Female	455 (34.4)	294 (29.9)	161 (47.1)	
Male	868 (66.6)	687 (70.0)	181 (52.9)	
Unknown	1 (<0.1)	1 (<0.01)	0	
Age Median (IQR)	45 (29,58)	42 (27,57)	49 (38,60)	<0.001
Ethnicity n (%)				0.4
White	800 (60.4)	574 (58.5)	226 (66.0)	
Ethnic Minority	32 (2.4)	25 (2.5)	7 (2.0)	
Unknown	492 (37.2)	383 (39.0)	109 (32.0)	
SIMD n (%)				0.002
(most deprived) 1	430 (33.5)	293 (29.8)	137 (40.1)	
2	295 (22.3)	213 (21.7)	82 (24.0)	
3	231 (17.4)	179 (18.2)	52 (15.2)	
4	209 (15.8)	162 (16.5)	47 (13.7)	
(least deprived) 5	143 (10.8)	119 (12.1)	24 (7.0)	
Unknown	16 (1.2)	16 (1.6)	0	
Urban/Rural Classification n (%)				0.051
Urban Area	981 (74.1)	709 (72.2)	272 (79.5)	
Small Town	151 (11.4)	115 (11.7)	36 (10.5)	
Rural Area	176 (13.3)	142 (14.5)	34 (9.9)	
Unknown	16 (1.2)	16 (1.6)	0	

Weak opioids such as co-codamol and dihydrocodeine were the most commonly prescribed drugs (Table 6-3) with 314 patients (23.7%) receiving at least one weak opioid in the twelve months preceding burn injury. A total of 1411 prescriptions for weak opioid medications were dispensed in this period.

Strong opioids were prescribed to 127 patients (9.6%) pre-burn injury. Tramadol and morphine were the most commonly prescribed strong opioids, with other agents including oxycodone, fentanyl and tapentadol (Table 6-3). Further breakdown of these figures were censored due to the small number of individuals concerned. A total of 904 prescriptions for strong opioids were dispensed to patients pre-burn injury.

Table 6-3 Number of patients prescribed opioids pre-burn injury, by specific drug (note multiple patients were prescribed more than one drug over the duration of this study)

Drug	N = 1324 (%)
Weak Opioids	
Co-codamol	
Total	222 (16.8)
Recurrent Users	89 (6.7)
Co-dydramol	
Total	32 (2.4)
Recurrent Users	11 (0.8)
Dihydrocodeine/Codeine	
Total	60 (4.5)
Recurrent Users	37 (2.8)
Strong Opioids	
Tramadol	
Total	90 (6.8)
Recurrent Users	47 (3.5)
Morphine	
Total	20 (1.5)
Recurrent Users	14 (1.1)
Other	
Total	17 (1.3)
Recurrent Users	13 (1.0)

6.4.3 Post-injury opioid Use

Patients that died within 60 days of burn injury (75 patients) were excluded from analysis of post-burn drug use. A total of 1249 patients were included in the analysis.

In the year following discharge after burn injury, 481 (38.5%) patients were prescribed an opioid, with 248 (19.9%) receiving 3 or more prescriptions. 259 (20.7%) patients prescribed an opioid following burn injury had never received an opioid prescription in the year preceding burn injury, with 88 (7.0%) of these patients becoming recurrent users, receiving 3 or more prescriptions. The median number of opioid prescriptions dispensed in the twelve months following a burn was 9.9.

A mean of 14.6 opioid prescriptions per 100 patients were dispensed in the twelve months preceding burn injury. This increased to a maximum of 30.3

prescriptions at one month following burn injury and a sustained increase compared to pre-injury prescription rates, with a mean of 20.2 prescriptions for the twelve months following injury (Figure 6-1).

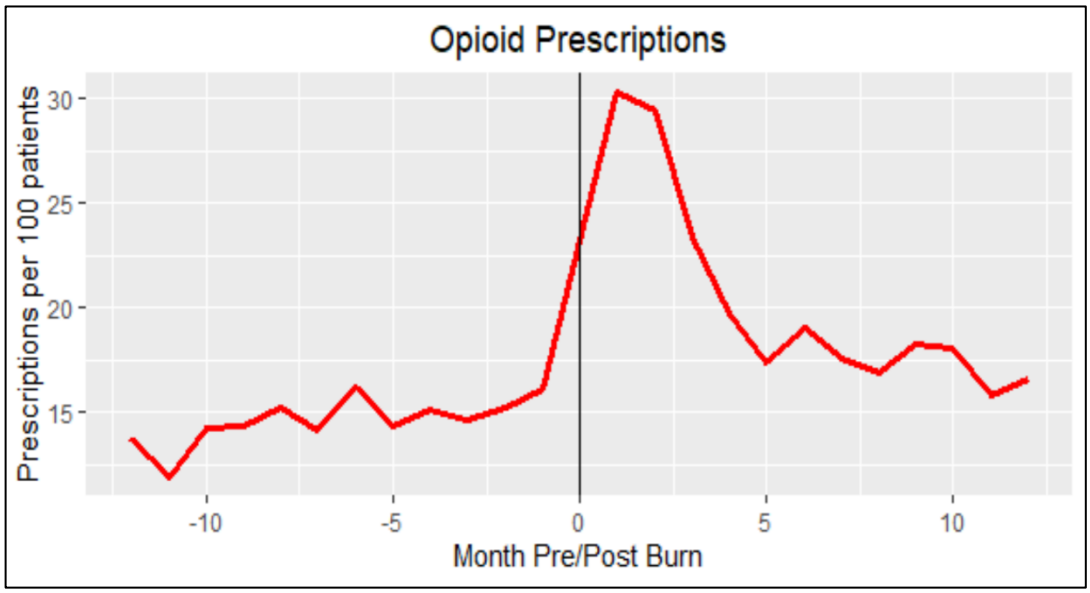

Figure 6-1 Opioid prescriptions dispensed pre- and post- burn injury, adjusted for deaths each month following burn.

Weak opioids such as co-codamol and dihydrocodeine were the most commonly prescribed agents, with 440 patients (35.2%) prescribed such a drug in the twelve months following burn injury (Table 6-4). Strong opioids such as tramadol, morphine and oxycodone were lesser used, but the number of patients prescribed such a drug had increased from 127 (9.6%) pre-injury to 217 (17.4%) after injury.

Table 6-4 Number of patients prescribed opioids pre- and post-burn injury, by specific drug (note multiple patients were prescribed more than one drug)

Drug	Pre-Burn N = 1324 (%)	Post-Burn N = 1249 (%)
Weak Opioids		
Co-codamol		
Total	222 (16.8)	249 (19.9)
≥3	89 (6.7)	100 (8.0)
Co-dydramol		
Total	32 (2.4)	37 (3.0)
≥3	11 (0.8)	10 (0.8)
Dihydrocodeine/Codeine		
Total	60 (4.5)	164 (13.1)
≥3	37 (2.8)	59 (4.7)
Strong Opioids		
Tramadol		
Total	90 (6.8)	144 (11.5)
≥3	47 (3.5)	64 (5.1)
Morphine		
Total	20 (1.5)	47 (3.8)
≥3	14 (1.1)	32 (2.6)
Other		
Total	17 (1.3)	25 (2.0)
≥3	13 (1.0)	16 (1.3)

The total number of opioid prescriptions dispensed increased by 27.9% from 2315 in the twelve months pre-burn injury to 2962 post-burn injury. Strong opioid prescriptions also increased by 51.9% from 904 pre-burn, accounting for 39% of all opioid prescriptions, to 1373 post-burn, now accounting for 46.4% of opioid prescriptions.

A generalised multilevel Poisson non-linear regression model was used to explore the factors associated with increased opioid use following burn injury. Univariable analysis is documented in Table 6-5.

Table 6-5 Univariable analysis of factors associated with an increase in post-burn opioid use

	Risk Ratio	95% CI	p-value
Pre-Burn Opioid Use	4.57	3.16-6.60	<0.001
Gender			
Male	(Reference)		
Female	3.01	2.18-4.17	<0.001
Age *	1.03	1.02-1.04	<0.001
TBSA †	1.02	0.99-1.06	0.13
Length of Hospital Stay ‡	1	0.99-1.01	0.49
Airway burn	1.42	0.29-6.84	0.66
Smoke Inhalation	1	0.28-3.57	0.99
SIMD			
(most deprived) 1	(Reference)		
2	0.81	0.53-1.24	0.33
3	0.6	0.38-0.95	0.03
4	0.49	0.30-0.79	0.003
(least deprived) 5	0.29	0.17-0.52	<0.001
Urban/Rural Classification			
Urban area	(Reference)		
Small town	0.75	0.46-1.24	0.26
Rural area	0.5	0.31-0.80	0.004
Ethnicity			
White	(Reference)		
Ethnic Minority	0.49	0.18-1.35	0.17
Mechanism of burn			
Other	Ref		
Flame	0.69	0.13-1.0	0.05
Comorbidity			
Alcohol excess	3.46	1.95-6.12	<0.001
Illicit Drug use	2.34	0.63-8.71	0.2
Psychosis	3.12	0.85-11.5	0.087
Depression	5.29	1.84-15.2	0.002
Elixhauser Comorbidity Score			
0-1	(Reference)		
2 or more	5.28	2.93-9.53	<0.001

*Calculated for each 1 year increase in age.
†Calculated for each 1% increase in TBSA burned.
‡Calculated for each day increase in length of hospital stay.

Any variables with a p value <0.1 were included in the multivariable analysis and a backwards stepwise regression approach used to build the model (Table 6-6). The use of opioids in the year preceding burn injury was the strongest predictor of an increase in opioid use following injury. However, female gender and increasing comorbidity burden were also strongly associated with an increase in

opioid use. Patients from areas of socioeconomic affluence were less likely to be prescribed opioids.

Table 6-6 Multivariable analysis of factors associated with post-burn opioid use

	Risk Ratio	95% CI	p-value
Pre-Burn Opioid Use	3.11	2.20-4.38	<0.001
Gender			
Male	(Reference)		
Female	2.24	1.65-3.05	<0.001
Age *	1.02	1.01-1.03	<0.001
SIMD			
(most deprived) 1	(Reference)		
2	0.85	0.58-1.27	0.45
3	0.73	0.47-1.12	0.15
4	0.54	0.34-0.84	0.007
(least deprived) 5	0.30	0.18-0.52	<0.001
Elixhauser Comorbidity Score			
0-1	(Reference)		
2 or more	2.80	1.61-4.86	<0.001

*Calculated for each 1 year increase in age.

6.4.4 Pre-injury mental health drug use

Pre-injury use of hypnotics and anxiolytics, gabapentinoids, antidepressants and antipsychotics are described separately for the 1324 patients included in the pre-injury drug use analysis.

6.4.4.1 Hypnotic and anxiolytic drug use

216 (16.3%) patients were prescribed an anxiolytic or hypnotic agent in the year preceding their burn injury, of which 134 (10.1%) were recurrent users. The median number of prescriptions in the 12 months period was 5.0 (IQR 1,12), with a maximum of 40 prescriptions dispensed in one year. Females were again over-represented despite the male predominance of the cohort, accounting for 50% of those prescribed an anxiolytic agent (Table 6-7). Patients were also more likely to be older (48 vs 44, p<0.001), reside in an urban area (p<0.001) and come from a more deprived region (p=0.001).

Table 6-7 Patient characteristics associated with pre-burn hypnotic and anxiolytic use

Characteristic	All Patients N=1324	No Anxiolytics N = 1108	Anxiolytic Prescribed N=216	p-value
Gender n (%)				<0.001
Female	455 (34.4)	347 (31.3)	108 (50.0)	
Male	868 (66.6)	760 (68.6)	108 (50.0)	
Unknown	1 (<0.1)	1 (<0.1)	0	
Age Median (IQR)	45 (29,58)	44 (27,58)	48 (40,58)	<0.001
Ethnicity n (%)				0.2
White	800 (60.4)	*<659 (<59.5)	*>141(>65.3)	
Ethnic Minority	32 (2.4)	*>26 (>2.3)	*<6(<2.8)	
Unknown	492 (37.2)	423 (38.2)	69 (31.9)	
SIMD n (%)				0.001
(most deprived) 1	430 (32.5)	340 (30.7)	90 (41.7)	
2	295 (22.3)	237 (21.4)	58 (26.9)	
3	231 (17.4)	203 (18.3)	28 (13.0)	
4	209 (15.8)	184 (16.6)	25 (11.6)	
(least deprived) 5	143 (10.8)	128 (11.6)	15 (6.9)	
Unknown	16 (1.2)	16 (1.4)	0	
Urban/Rural Classification n (%)				<0.001
Urban Area	981 (74.1)	797 (71.9)	184 (85.2)	
Small Town	151 (11.4)	135 (12.2)	16 (7.4)	
Rural Area	176 (13.3)	160 (14.4)	16 (7.4)	
Unknown	16 (1.2)	16 (1.4)	0	

*Exact numbers censored due to <6 individuals being involved

The most common drugs prescribed were the benzodiazepines diazepam and temazepam (Table 6-8). Zopiclone was another commonly used agent, with others including chlordiazepoxide and nitrazepam. Of those prescribed an anxiolytic, 67 (31%) were prescribed multiple agents during the year pre-injury. Co-prescription of anxiolytic medication with opioids was common, with 116 of the 216 (53.7%) patients also prescribed an opioid in the year preceding burn injury.

Table 6-8. Number of patients prescribed hypnotic and anxiolytic agents pre-burn injury by specific drug.

Drug	N = 1324 (%)
Diazepam	
Total	125 (9.4)
Recurrent Users	70 (5.3)
Temazepam	
Total	40 (3.0)
Recurrent Users	29 (2.2)
Zopiclone	
Total	73 (5.5)
Recurrent Users	33 (2.5)
Other	
Total	62 (4.7)
Recurrent Users	34 (2.6)

6.4.4.2 Gabapentinoid use

In the year preceding burn injury, 79 (6.0%) patients were prescribed gabapentin or pregabalin on at least one occasion, with 63 (4.8%) being recurrent users (Table 6-9). Gabapentin was the more commonly used drug, being prescribed to 55 (4.2%) patients, whereas pregabalin was prescribed to 30 (2.3%) patients, with 6 (0.5%) patients having received prescriptions for both drugs during the twelve month period.

Gabapentinoids accounted for 47.8% of all antiepileptic prescriptions in this cohort. Despite gabapentinoids original licensed indication as anticonvulsants, less than 6 individuals who were prescribed a gabapentinoid had a history of epilepsy documented.

Females were again disproportionately over-represented, accounting for 47% of those prescribed a gabapentinoid. Similar to opioid prescriptions, patients tended to be older (53 vs 44, $p<0.001$). However, measures of socioeconomic deprivation did not seem to be a factor in gabapentinoid use ($p = 0.6$).

Table 6-9 Patient characteristics associated with pre-burn gabapentinoid use

Characteristic	All Patients N=1324	No Gabapentinoids N = 1245	Gabapentinoid Prescribed N = 79	p-value
Gender n (%)				0.016
Female	455 (34.4)	418 (33.6)	37 (46.8)	
Male	868 (65.6)	826 (66.3)	42 (53.2)	
Unknown	1 (<0.1)	1 (<0.1)	0	
Age Median (IQR)	45 (29,58)	44 (29,58)	53 (41,62)	
Ethnicity n (%)				>0.9
White	800 (60.4)	*<753 (<60.5)	*>47(>59.5)	
Ethnic Minority	32 (2.4)	*>26 (>2.1)	*<6(<7.6)	
Unknown	492 (37.2)	461 (37.0)	26 (32.9)	
SIMD n (%)				0.6
(most deprived) 1	430 (32.5)	405 (32.5)	25 (31.6)	
2	295 (22.3)	272 (21.8)	23 (29.1)	
3	231 (17.4)	218 (17.5)	13 (16.5)	
4	209 (15.8)	197 (15.8)	12 (15.2)	
(least deprived) 5	143 (10.8)	137 (11.0)	6 (7.6)	
Unknown	16 (1.2)	16 (1.3)	0	
Urban/Rural Classification n (%)				0.9
Urban Area	981 (74.1)	920 (73.9)	61 (77.2)	
Small Town	151 (11.4)	142 (11.4)	9 (11.4)	
Rural Area	176 (13.3)	167 (13.4)	9 (11.4)	
Unknown	16 (1.2)	16 (1.3)	0	

*Exact numbers censored due to <6 individuals being involved

Co-prescriptions of gabapentinoids with other agents were common, with 55 of the 79 patients (69.6%) prescribed a gabapentinoid also prescribed an opioid, 33 (41.8%) prescribed an anxiolytic or hypnotic agent and 25 (31.6%) prescribed all three classes of drug.

6.4.4.3 Antidepressant use

A total of 352 (26.6%) individuals were prescribed some form of antidepressant in the year preceding their burn injury, with 282 (21%) being recurrent users. Females were again more likely to be prescribed an antidepressant in this cohort, accounting for 58% of antidepressant use (Table 6-10). Increasing age ($p<0.001$) and socioeconomic deprivation ($p=0.003$) were also associated with antidepressant use.

Table 6-10 Patient characteristics associated with pre-burn antidepressant use

Characteristic	All Patients N=1324	No Antidepressant N = 972	Antidepressant Prescribed N = 352	p-value
Gender n (%)				<0.001
Female	455 (34.4)	252 (25.9)	203 (57.7)	
Male	868 (66.6)	719 (74.0)	149 (42.3)	
Unknown	1 (<0.1)	1 (<0.1)	0	
Age Median (IQR)	45 (29,58)	43 (27,58)	48 (37,57)	<0.001
Ethnicity n (%)				0.13
White	800 (60.4)	*<577 (<59.4)	*>223(>63.4)	
Ethnic Minority	32 (2.4)	*>26 (>2.7)	*<6(<1.7)	
Unknown	492 (37.2)	368 (37.9)	123 (34.9)	
SIMD n (%)				0.003
(most deprived) 1	430 (32.5)	290 (29.8)	140 (39.8)	
2	295 (22.3)	213 (21.9)	82 (23.3)	
3	231 (17.4)	171 (17.6)	60 (17.0)	
4	209 (15.8)	169 (17.4)	40 (11.4)	
(least deprived) 5	143 (10.8)	113 (11.6)	30 (8.5)	
Unknown	16 (1.2)	16 (1.6)	0	
Urban/Rural Classification n (%)				0.2
Urban Area	981 (74.1)	707 (72.7)	274 (77.8)	
Small Town	151 (11.4)	110 (11.3)	41 (11.6)	
Rural Area	176 (13.3)	139 (14.3)	37 (10.6)	
Unknown	16 (1.2)	16 (1.6)	0	

*Exact numbers censored due to <6 individuals being involved

The most common class of antidepressant prescribed was selective serotonin reuptake inhibitors, such as citalopram and fluoxetine, accounting for 234 (50.9%) of the 460 antidepressant prescriptions issued in the 12 months pre-burn injury. Tricyclic antidepressants such as amitriptyline and related drugs such as trazodone accounted for 118 (25.7%) of antidepressants issued. Other agents such as the α-2 antagonist mirtazapine accounted for 74 (16.1%) of prescriptions with other agents such as serotonin and noradrenaline reuptake inhibitors and monoamine-oxidase inhibitors accounting for the remaining 34 (7.4%) prescriptions.

6.4.4.4 Antipsychotic use

Antipsychotic agents were prescribed to 79 (6.0%) patients in the year preceding burn injury. Females accounted for 57% of these prescriptions, with older patients and those from more deprived socioeconomic backgrounds also being more likely to receive such a drug (p=0.025) (Table 6-11).

Table 6-11 Patient characteristics associated with pre-burn antipsychotic use

Characteristic	All Patients N=1324	No Antipsychotic N = 1245	Antipsychotic Prescribed N = 79	p-value
Gender n (%)				<0.001
Female	455 (34.4)	410 (32.9)	45 (57.0)	
Male	868 (66.6)	834 (67.0)	34 (43.0)	
Unknown	1 (<0.1)	1 (<0.1)	0	
Age Median (IQR)	45 (29,58)	44 (29,58)	51 (41,60)	0.001
Ethnicity n (%)				>0.9
White	800 (60.4)	*<762 (<61.2)	*>38(>48.1)	
Ethnic Minority	32 (2.4)	*>26 (>2.1)	*<6(<7.6)	
Unknown	492 (37.2)	457 (36.7)	35 (44.3)	
SIMD n (%)				0.025
(most deprived) 1	430 (32.5)	397 (31.9)	33 (41.8)	
2	295 (22.3)	271 (21.8)	24 (30.4)	
3	231 (17.4)	219 (17.6)	12 (15.2)	
4	209 (15.8)	204 (16.4)	†10 (12.7)	
(least deprived) 5	143 (10.8)	138 (11.1)		
Unknown	16 (1.2)	16 (1.3)	0	
Urban/Rural Classification n (%)				0.073
Urban Area	981 (74.1)	915 (73.5)	66 (83.5)	
Small Town	151 (11.4)	142 (11.4)	†13 (16.5)	
Rural Area	176 (13.3)	172 (13.8)		
Unknown	16 (1.2)	16 (1.3)	0	

*Exact numbers censored due to <6 individuals being involved
†Categories combined to censor small numbers of individuals

Second generation, or atypical, antipsychotic agents were the most commonly prescribed agents with quetiapine being prescribed to 27 (34.2%) of the 79 patients on an antipsychotic agent. Other atypical drugs such as olanzapine and risperidone were dispensed to 17 (21.5%) and 13 (16.5%) patients respectively. First generation antipsychotic agents were less commonly used with haloperidol

and levomepromazine being prescribed to less than 6 (<7.6%) patients, although chlorpromazine was still commonly used, being given to 19 (24.1%) patients. Drugs used in the management of mania or hypomania such as lithium or valproate were prescribed to 9 (11.4%) individuals. 17 (21.5%) patients were prescribed more than one antipsychotic agent in the twelve months pre-injury.

6.4.5 Post-injury mental health drug use

Patients that died within 60 days of burn injury (75 patients) were excluded from analysis of post-burn drug use. A total of 1249 patients were included in the analysis.

Mental health drugs were explored using four broad classes: antidepressants, antipsychotics, anxiolytics/hypnotics and gabapentinoids. Excluding patients that died within 30 days of a burn injury, the number of patients prescribed at least one mental health drug increased from 416 (33.3%) to 466 (37.3%). In addition, the number of patients being prescribed two or three drugs from these classes also increased (Table 6-12).

Table 6-12 Number of patients prescribed mental health drugs (excluding patients that died within 30 days of burn injury)

Number of Mental Health Drug Classes	Pre-Burn n. (%)	Post-Burn n. (%)
0	833 (66.7)	783 (62.7)
1	234 (18.7)	248 (19.9)
2	134 (10.7)	153 (12.2)
3	39 (3.1)	57 (4.6)
4	9 (0.7)	8 (0.6)

Pre and post-burn injury mental health drug prescribing patterns are illustrated in Figure 6-2. Antidepressants were the most commonly prescribed drug with 361 (28.9%) patients prescribed one at some point in the year after burn injury, 99 (7.9%) of which had not received an antidepressant prescription in the year preceding injury.

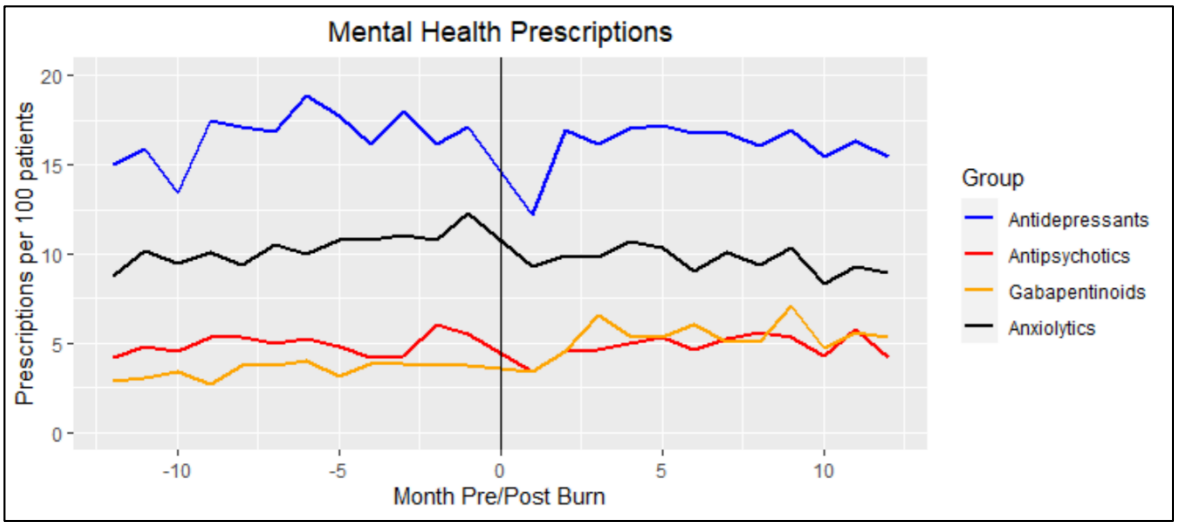

Figure 6-2 Mental health drug prescriptions dispensed pre- and post- burn injury, adjusted for deaths each month following burn

Anxiolytic and hypnotic drugs were second most commonly prescribed agents with 201 (16.1%) patients prescribed such a drug in the year after burn injury. 121 (9.7%) patients were recurrent users, receiving 3 or more prescriptions. 75 (6.0%) of these patients had never received an anxiolytic prescription in the year preceding burn injury.

Gabapentinoid prescriptions increased following burn injury with 119 (9.5%) patients receiving at least one prescription, 92 (7.4%) of which receiving 3 or more prescriptions. 65 (5.2%) of these patients had not been prescribed a gabapentinoid in the year preceding their burn injury.

76 (6.1%) patients were prescribed an antipsychotic medication in the year following burn injury, 19 (1.5%) of which had not been prescribed such a drug in the preceding year.

Univariable analysis of factors associated with an increase in mental health drug prescriptions are explored in using a multilevel Poisson non-linear regression model as seen in Table 6-13.

Table 6-13 Univariable analysis of factors associated with an increase in post-burn mental health drug use

	Risk Ratio	95% CI	p-value
Gender			
Male	(Reference)		
Female	2.58	2.12-3.13	<0.001
Age *	1.02	1.01-1.02	<0.001
TBSA †	1.02	1.01-1.04	0.008
Length of Hospital Stay ‡	1.00	0.99-1.00	0.59
Airway burn	0.65	0.23-1.83	0.41
Smoke Inhalation	1.86	0.92-3.74	0.081
SIMD			
(most deprived) 1	(Reference)		
2	0.98	0.76-1.26	0.89
3	0.75	0.56-0.99	0.043
4	0.54	0.39-0.73	<0.001
(least deprived) 5	0.57	0.40-0.80	0.001
Urban/Rural Classification			
Urban area	(Reference)		
Small town	0.81	0.59-1.10	0.17
Rural area	0.58	0.43-0.79	<0.001
Ethnicity			
White	(Reference)		
Ethnic Minority	0.61	0.32-1.16	0.13
Mechanism of burn			
Other	Ref		
Flame	0.97	0.78-1.22	0.82
Comorbidity			
Alcohol excess	3.24	2.36-4.43	<0.001
Illicit Drug use	3.58	1.79-7.17	<0.001
Psychosis	3.88	1.96-7.71	<0.001
Depression	6.22	3.61-10.7	<0.001
Elixhauser Comorbidity Score			
0 or 1	(Reference)		
2 or more	3.67	2.65-5.08	<0.001
Pre-Burn Drug Use			
Opioids	3.62	2.98-4.39	<0.001
Gabapentinoids	6.92	5.11-6.93	<0.001
Antipsychotics	8.05	5.95-10.9	<0.001
Antidepressants	8.62	7.41-10.0	<0.001
Anxiolytics & Hypnotics	7.29	6.10-8.71	<0.001

*Calculated for each 1-year increase in age.
†Calculated for each 1% increase in TBSA burned.
‡Calculated for each day increase in length of hospital stay.

Any variables with a p value <0.1 were then included in a backwards stepwise regression approach to perform multivariable analysis (Table 6-14). Female

gender, previous alcohol excess, a pre-existing history of depression and previous opioid use were all associated with an increase in mental health drug prescriptions following burn injury.

Table 6-14 Multivariable analysis of factors associated with an increase in post-burn mental health drug use

	Risk Ratio	95% CI	p-value
Gender			
Male	(Reference)		
Female	2.00	1.67-2.39	<0.001
Age *	1.01	1.00-1.01	<0.001
TBSA †	1.03	1.01-1.04	<0.001
SIMD			
(most deprived) 1	(Reference)		
2	0.99	0.79-1.24	0.92
3	0.97	0.75-1.25	0.82
4	0.62	0.46-0.82	<0.001
(least deprived) 5	0.65	0.47-0.90	0.009
Comorbidity			
Alcohol excess	2.00	1.52-2.64	<0.001
Depression	2.33	1.48-3.66	<0.001
Pre-Burn Drug Use			
Opioids	2.58	2.14-3.11	<0.001

*Calculated for each 1-year increase in age.
†Calculated for each 1% increase in TBSA burned.

6.5 Discussion

6.5.1 Opioid prescriptions

The prescribing of opioids has been consistently increasing in recent years in Scotland, with over 948,000 individuals (18% of the population) prescribed an opioid in 2012[262]. There are significant variations in the rates of prescribing between different health boards and across socioeconomic groups, with those in the most deprived areas being more than three times more likely to be prescribed an opioid[262]. Within this study, 342 (25.8%) patients were prescribed an opioid in the year preceding the burn injury. This appears significantly higher than figures reported for the general Scottish population.

This study demonstrated that after burn injury, the prevalence of opioid use increased to 38.5% of patients. Additionally, the proportion of recurrent opioid users also increased from 14.5% to 19.9%. The use of strong opioids also

increased from 39% of all opioids dispensed pre-injury to 46.4% after injury. Factors associated with increased opioid prescriptions included pre-existing opioid use, female gender, increasing age, socioeconomic deprivation and increasing comorbidity.

Although the majority of opioid prescriptions were for weaker opioids such as co-codamol and dihydrocodeine, the potential harm from these drugs should not be underestimated. Several researchers have highlighted the concerns of addiction, dependence and withdrawal; the true extent of which is not fully known[263,264].

With such a significant number of patients already regularly taking opioids prior to sustaining a burn injury and the likely requirement for an increase in analgesia to manage the pain of a burn, there exists a potential to further exacerbate the problem of opioid dependency. This study has demonstrated that previous opioid use, female gender and increasing comorbidity seem to be the factors most associated with increased opioid use after burn injury. The size of burn does not seem to have any significant bearing.

6.5.2 Mental health drug prescriptions

Given the close link between mental health conditions and burn injuries, it is important to explore the link between drugs used in the management of mental health diagnoses and burn injuries. Equally, with almost 34% of the Scottish adult population now prescribed at least one of the five classes of medicines that are subject to review due to their potential for dependence and harm, it is important to quantify their use in the burn-injured population[252].

A recent report into medicines used in mental health across Scotland reported that antidepressant use has been steadily increasing, with over 718,000 individuals prescribed such a drug in 2011/2012, increasing to over 814,000 by 2014/2015, accounting for around 13.7-15.2% of the Scottish population[265]. This figure continues to increase, with 21.6% of the adult Scottish population prescribed an antidepressant in 2019/2020[252]. Within this study, 26.6% were prescribed an antidepressant in the year preceding their burn injury, significantly higher than the 15.2% reported for the population at that time[252].

National statistics report around 365,000 individuals were prescribed some form of hypnotic or anxiolytic each year from 2011 to 2015, equating to around 6.8% of the population[265]. Such prescriptions were much higher in this study, with 16.3% prescribed such a drug in the year preceding burn injury. This pattern is also evident in the use of antipsychotic medications whereby 6.0% received a prescription pre-injury in this study. This compares to a prevalence of around 1.5% for the general Scottish population[265].

Following burn injury, the prevalence of antidepressant use increased slightly (26.6% to 28.9%) but there was no significant change in the use of anxiolytic drugs (16.3% to 16.1%) or antipsychotics (6.0% to 6.1%). Multiple patients were commenced on such medications in the year following burn injury, having not been prescribed them in the year preceding injury. Antidepressants were dispensed to 99 such patients, equating to around one in ten patients without prior antidepressant use being commenced on an antidepressant following burn injury. Similarly, anxiolytics were prescribed to 75 patients without prior use and antipsychotics to 19 such patients.

Although this study cannot determine whether suffering a burn injury increases the risk of being prescribed such medications, it has demonstrated common factors that are associated with being started on one of these agents. Female gender, a history of alcohol excess or depression and previous opioid use were all strongly associated with an increase in mental health drug use.

6.5.3 Gabapentinoid prescriptions

The use of gabapentinoids has been increasing in general, not only in Scotland[111], but in many parts of the UK[133], Europe[266] and North America[132]. Although these drugs are licensed for the management of peripheral neuropathic pain in the UK, they have not been extensively investigated in the burn-injured population.

In recent years there has been an emerging picture of the potential harm from gabapentinoids including dependence, suicidal behaviour, overdose, road traffic accidents, drug related deaths and crime[111,158–160]. This concern has been

reflected in the recategorisation of gabapentinoids as a Class C controlled substance in the UK in 2019[161].

The prevalence of gabapentinoid use in the general adult population in Scotland is 3.7-4.1%.[111,252] In this study, 6.0% of patients were prescribed a gabapentinoid in the year preceding the burn injury, already higher than the general population. Following burn injury, the prevalence of gabapentinoid use increased to 9.5%. Unfortunately, the granularity of the data available does not include the indication for any drug prescribed. However, the temporal nature of the rise in gabapentinoid use suggests that issues related to the burn such as pain, pruritus or anxiety may be indications for their use.

Caution should be exercised when prescribing such drugs following a burn injury. Individuals with a history of psychiatric comorbidity or substance misuse are at higher risk of harm from gabapentinoids.[135,158] Such comorbidities occur frequently in those that have suffered a burn injury.[162–164]

6.5.4 Implications

This study has highlighted the increased use of opioids following burn injury and the factors associated with such an increase. This study has also demonstrated higher than expected pre-injury use of opioids, gabapentinoids, antidepressants, anxiolytics and antipsychotics in a cohort of adult patients that suffered a burn injury requiring hospital admission. This serves to highlight not only the overlap in mental health conditions and an increased risk of sustaining a burn injury, but also, given the possible detrimental impact on mental health after burn injury, the potential for even greater deterioration in an already vulnerable cohort.

One area of concern is the discrepancy in gender seen throughout this study. Although male patients account for the majority of adult burn injuries, females were consistently over-represented in the use of each pre-injury drug class. Equally, female gender was also associated with an increased risk of being prescribed an opioid or mental health drug after burn injury.

With the recognised potential for dependence and harm from the various classes of drugs that have been explored, this study has highlighted the need for

cautious and vigilant prescribing practices in patients after burn injury. As it is widely recognised that burn survivors are potentially more vulnerable to mental health problems[162], including drug and alcohol misuse,[163,164] prescriptions of these agents should be dispensed with an appreciation for the potential for harm. Robust measures should be in place involving the multidisciplinary team including clinicians, pharmacists and psychologists to ensure such patients have access to appropriate support and are fully counselled on the risks of harm from such medications.

Echoing the concern over the potential for harm from antidepressants, anxiolytics, gabapentinoids and opioids, recommendations set forth by the Public Health England and Short Life Working Group following their respective consultations on prescriptions medicines include[252,253]:

- Increased availability and use of data on such prescription medications.
- Specific clinical guidelines to inform clinicians on best practice.
- Improving information for patients and carers regarding the risks and benefits of such drugs.
- Better support for patients experiencing consequences such as dependence or withdrawal from prescribed medicines.
- Further research on the prevention and management of dependence and withdrawal from prescribed medicines.

Such recommendations are particularly pertinent when considering the use of such drugs in patients with burn injuries. The careful and considered use of these agents is especially relevant in Scotland, where drug related deaths have continued to rise year-on-year, with 1264 recorded in 2019.[267]

6.5.5 Strengths and Weaknesses

This is the first study we are aware of that has used community drug prescription data to explore important patient-centred outcomes in burn-injured patients.

The robust national databases integrated within Scotland's healthcare system allow for wide-ranging analysis of various aspects of healthcare.

However, as with the use of any administrative database, the information that can be taken from it is often limited by its lack of granularity. For example, the PIS database does not give the clinical indication for each drug prescribed, simply when it was dispensed. The use of administrative databases to elicit comorbidity data to explore the clinical indications for any medications is also likely to be inadequate. For example, as discussed in previous chapters, the diagnoses of depression or psychoses were only elicited using psychiatric hospital admission data (SMR04) and therefore unable to identify what are likely to be the majority of patients with such conditions who were managed in the community. This therefore limits any interpretation, especially when considering drugs such as tricyclic antidepressants or gabapentinoids, where the clinical indications can vary widely.

Although the PIS database is comprehensive with regular audits consistently demonstrating over 98% accuracy, it does not record any information on compliance with medications or any illicit drugs use. The latter is of increasing interest, especially in Scotland, with the use of non-prescribable "street" benzodiazepines such as etizolam rising sharply in recent years, prompting both public health warnings[268] and the National Records of Scotland (NRS) to record deaths from these drugs separately to "prescribable" benzodiazepines in all reports from August 2020 onwards.[267]

A significant focus of this study was on the use of opioids as classified in the analgesia section of the BNF. However, opioids such as methadone and buprenorphine are also classified under the section on drugs for use in substance dependence. These were not specifically explored as they are less likely to reflect opioid prescriptions for analgesic purposes. However, by excluding drugs in this category this study has potentially underestimated the number of opioid prescriptions.

Using community prescription data has served to highlight those patients that have been prescribed a drug by their family doctor. Such information implies that the individual has considered their symptomatology severe enough to merit

consultation with a clinician and embark on a pharmacological therapy in the hope of improving those symptoms. However, this therefore fails to document those individuals who may have significant symptoms, be that pain, anxiety, depression or any other distressing symptom, but they have chosen either to manage the problem without pharmacotherapy or not to seek help from a health care professional at all. Hence, this method of using prescription data as a surrogate measure to quantify either disease or symptomatology is likely to be an underestimate of the true prevalence and severity of each condition. For example, the simple presence of a prescribed analgesic does not give any information on either the severity of pain nor its impact on mobility, functionality, social interaction, mood or quality of life.

This study was limited to one year before and after burn injury, limiting any interpretation beyond that time frame. Previous research has highlighted that mental health problems can persist for several years after burn injury and may not become apparent until later than one year after injury[67]. Further research exploring the use of opioids and mental health drugs beyond one year after injury would provide a clearer picture of the long-term problems these patients face.

As with any longitudinal observational analysis, the results of this study may have been influenced by the loss of patients due to inadequate follow-up time, in many cases due to death. Although this study found no change in the prevalence of the use of antidepressants, anxiolytics and antipsychotics, this may be due to many of the patients previously prescribed these drugs having died in the year after burn injury.

6.5.6 Conclusion

Burn-injured adult patients requiring admission to hospital in Scotland are often at higher risk of mental health problems and chronic pain as demonstrated by an increased pre-injury use of drugs used for such conditions. This serves to highlight the significant overlap in mental health conditions and increased risk of sustaining a burn injury in the adult population.

Opioid prescriptions increase sharply following burn injury and their use is sustained during the following twelve months. Factors such as social deprivation, increasing age, comorbidity burden and previous opioid use are all associated with an increase in opioid use after burn injury, with the size of the burn having much less impact.

Although burn injuries in adults more often affect males in Scotland, the pre-injury use of drugs detailed in this study are more common among females. Female gender is also associated with an increased likelihood of being prescribed a mental health drug or opioid following a burn injury.

Chapter 7 Long-term mortality following burn injury

7.1 Introduction

The mortality directly associated with burn injuries has been extensively investigated. Some of the earliest research in this area was conducted in the 1960s with the development of the Baux score, demonstrating an increased risk of death with increasing age and size of burn[30]. Although advances in modern burn care have resulted in improved mortality rates, further studies have consistently demonstrated that increasing surface area of a burn, increasing age and the presence of a smoke inhalation injury are all associated with an increase in short-term mortality[31,32].

7.1.1 Long-term mortality

In recent years there has been growing interest in the pathophysiological changes that persist for years after burn injury and the potential impact this may have on life expectancy. Longitudinal observational studies have postulated that survivors of burn injury are at increased risk of all-cause mortality when compared to the general population. Duke et al reported a 1.4-1.8 times greater rate of mortality in burn-injured adults when compared with a cohort matched by age and sex[91,93]. This phenomenon has been demonstrated not only in adults, but also in children. Duke et al also conducted a 33-year observational study comparing 10,426 children under 15 years old with a non-injured cohort matched to age and gender[92]. The authors demonstrated a 1.6 times greater rate of mortality in the burn cohort. However, the burn-injured cohorts in these studies differed from the non-injured cohort in multiple ways that may have impacted these results including greater socioeconomic deprivation, increased comorbidity, higher proportion from an aboriginal background and increased remoteness of residence.

Further studies have aimed to address these discrepancies. Mason et al compared a cohort of 1965 burn survivors with a general population cohort matched to age, sex, physical and psychological comorbidity, socioeconomic deprivation, ethnicity and rurality[94]. The authors reported an increased

mortality in the burn cohort, being greatest during the first year with a hazard ratio of 4.15, falling to 1.65 at five years.

7.1.2 Study questions

The aims of this study are to describe the long-term mortality of survivors of burn injury requiring hospital admission, explore the factors that may be associated with an increased risk of death and describe the causes of death.

7.2 Methods

7.2.1 Study design and setting

This study was carried out as a retrospective cohort study using linked national data in Scotland. The healthcare service is primarily delivered by the government funded National Health Service (NHS). All patients coming in to contact with these health services are allocated a unique identifier known as a CHI (Community Health Index) number. This method of patient identification allows consistent and robust data management across all health records at an individual patient level, but also allows linkage of other national datasets for the purposes of research, audit and quality improvement.

7.2.2 Data sources

Patients admitted to hospital under the care of a specialist burn team were identified by searching the national managed clinical network COBIS (Care of Burns in Scotland) from January 2012 to December 2015. Using patient CHI numbers, this data was linked to national administrative healthcare databases: SMR01 (acute hospital admissions), SMR04 (psychiatric hospital admissions) and NRS (National Records Scotland) death registration data as detailed in chapter 2. Data was then de-identified of unique identifiers such as CHI number, date of birth and post code before being accessible to the researchers.

7.2.3 Inclusion/Exclusion

All patients admitted to hospital with a burn injury under the care of a specialist burn team from January 2012 to December 2015 as recorded on the COBIS

database were included in the analysis. Patients that died within 30 days of initial burn injury were excluded from analysis. Children under 16 years of age were also excluded due to the infrequency of such deaths in this age-group and therefore risk of possible identification of individuals.

7.2.4 Covariates and missing data

Methods for extracting data regarding patient characteristics, burn injury details, associated injuries, comorbidities and handling of missing data have been described in previous chapters.

Certain categorical variables were often re-categorised to a simpler form due to small numbers of individuals present in each subcategory to both improve the power of analysis and prevent possible identification of individuals or groups. An example includes the use of ethnicity data, whereby detailed subcategorisation of ethnic group were simplified to broader categories. Urban-rural (UR8) classification was also simplified from eight standard categories to three broad categories which included urban areas, small towns and rural areas. Given the frequent overlap between airway burn and smoke inhalation injury, and potential for co-linearity between these two variables, they were amalgamated into one variable.

Pre-injury drug prescription data, specifically regarding the use of opioids, anxiolytics, antidepressants, antipsychotics and gabapentinoids, as detailed in a previous chapter, were also used as variables to explore their influence on mortality risk.

7.2.5 Outcomes

The primary outcome was mortality, as identified by NRS death certificate data, from 30 days after the index burn injury to the end of study period at 31/05/2016. Mortality data was extracted from the NRS database which included date of death and cause of death.

An exploratory secondary outcome was the cause of death. This was broadly categorised according to the ICD-10 classifications assigned from death certification data.

7.2.6 Statistical analysis

The descriptive analyses of categorical variables are expressed as frequencies and percentages while continuous variables are summarised using median values and inter-quartile ranges unless otherwise stated.

Time-to-death analysis was analysed using Kaplan-Meier curves and the log-rank test. Hazard ratios and 95% confidence intervals were calculated using a univariate Cox proportional hazards regression model. Any variable reaching significance with a p-value <0.1 was then included in a multivariable Cox proportional hazards model. Proportionality of hazards was assessed by examining Schoenfeld residuals and assessment of non-linearity was made using Martingale residuals.

7.3 Results

During the study period, 2005 patients were identified from the COBIS database. Twenty-eight patients were removed from analysis, having either sustained the burn injury before January 2012 or no evidence of burn injury recorded on either the COBIS or SMR01 databases. A further 653 children less than 16 years of age were removed, as were 36 individuals that died within 30 days of burn injury. A total of 1288 patients were included in the final analysis (Figure 7-1), the characteristic of which are described in Table 7-1. Follow-up time varied from 39 days to 4.7 years, with a median of 2.4 years.

Figure 7-1 Consort diagram of population included in the analysis

Table 7-1 Characteristic of patients included in study

Characteristic	Overall N=1288	Survivors N=1221	Non-Survivors N=67
Gender n (%)			
Male	849 (66)	804 (66)	45 (67)
Female	439 (34)	417 (34)	22 (33)
Age at injury Median (IQR)	44 (29,57)	43 (28,56)	66 (53,77)
Airway Burn / Smoke inhalation injury n (%)	22 (1.7)	*>16 (>1.3)	*<6 (<8.9)
Mechanism of injury n (%)			
Hot liquid	394 (31)	368 (30)	26 (39)
Flame	320 (25)	301 (25)	19 (28)
Hot Object	133 (10)	128 (10)	†9 (13.4)
Steam	23 (1.8)	23 (1.9)	
Electrical	48 (3.7)	48 (3.9)	
Other	247 (19)	243 (20)	
Unknown	123 (9.5)	110 (9.0)	13 (19)
SIMD			
1	415 (32)	395 (32)	20 (30)
2	289 (22)	273 (22)	16 (24)
3	226 (18)	214 (18)	12 (18)
4	204 (16)	195 (16)	9 (13)
5	139 (11)	129 (11)	10 (15)
Unknown	15 (1.2)	15 (1.2)	0 (0)
TBSA Burned			
<10%	1019 (79)	970 (79)	49 (72)
10-19%	62 (4.8)	56 (4.6)	†8 (11.9)
20-29%	19 (1.5)	17 (1.4)	
≥30%	15 (1.1)	14 (1.1)	0 (0)

Unknown	173 (13)	164 (13)	9 (13)
Ethnicity			
White	778 (60)	*<735 (<60)	*>43 (>64)
Ethnic Minority	32 (2.5)	*>26 (>2.1)	*<6 (<8.9)
Unknown	478 (37)	460 (38)	18 (27)
Urban-Rural Classification			
Urban area	954 (74)	900 (74)	54 (81)
Small town	148 (11)	142 (12)	6 (9.0)
Rural area	171 (13)	164 (13)	7 (10)
Unknown	15 (1.2)	15 (1.2)	0 (0)

*Exact numbers censored due to <6 individuals being involved
†Categories amalgamated due to small numbers of individuals

7.3.1 Survival analysis

A total of 67 patients (5.2%) died during the study period. This is illustrated in Figure 7-2.

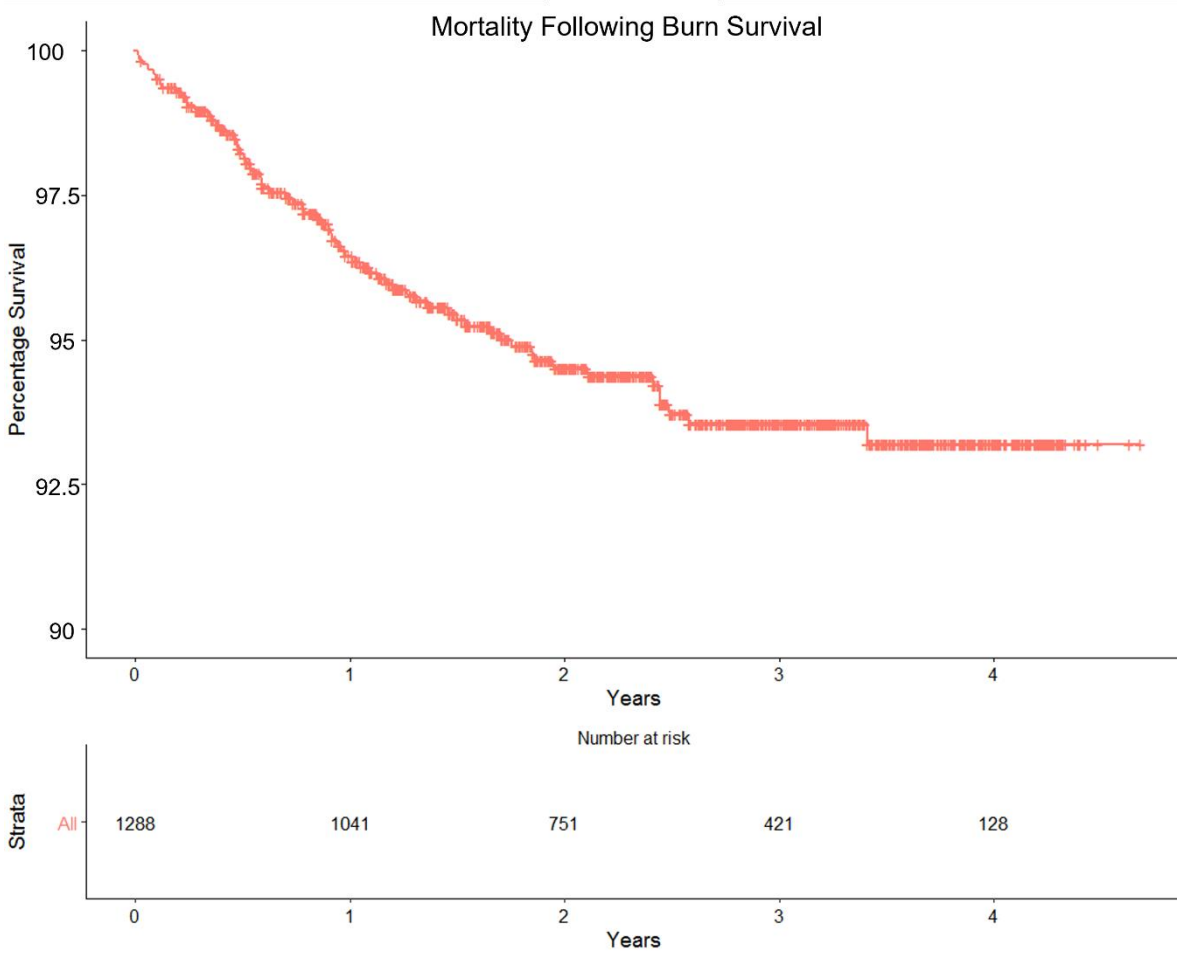

Figure 7-2 Kaplan-Meier curve of survival function for all patients following burn injury

There was no indication of any difference in mortality rates between genders (Figure 7-3) or measures of socioeconomic deprivation (Figure 7-4) when analysed using Kaplan-Meier and log-rank analysis.

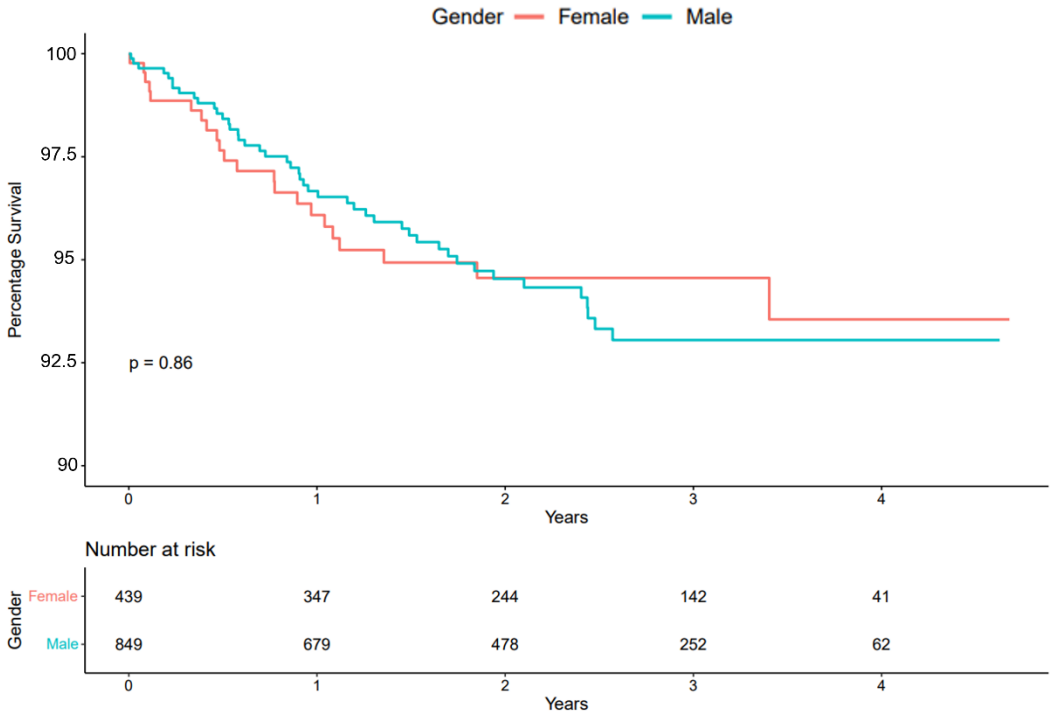

Figure 7-3 Kaplan-Meier curve of survival function by gender. P-value denotes log-rank test.

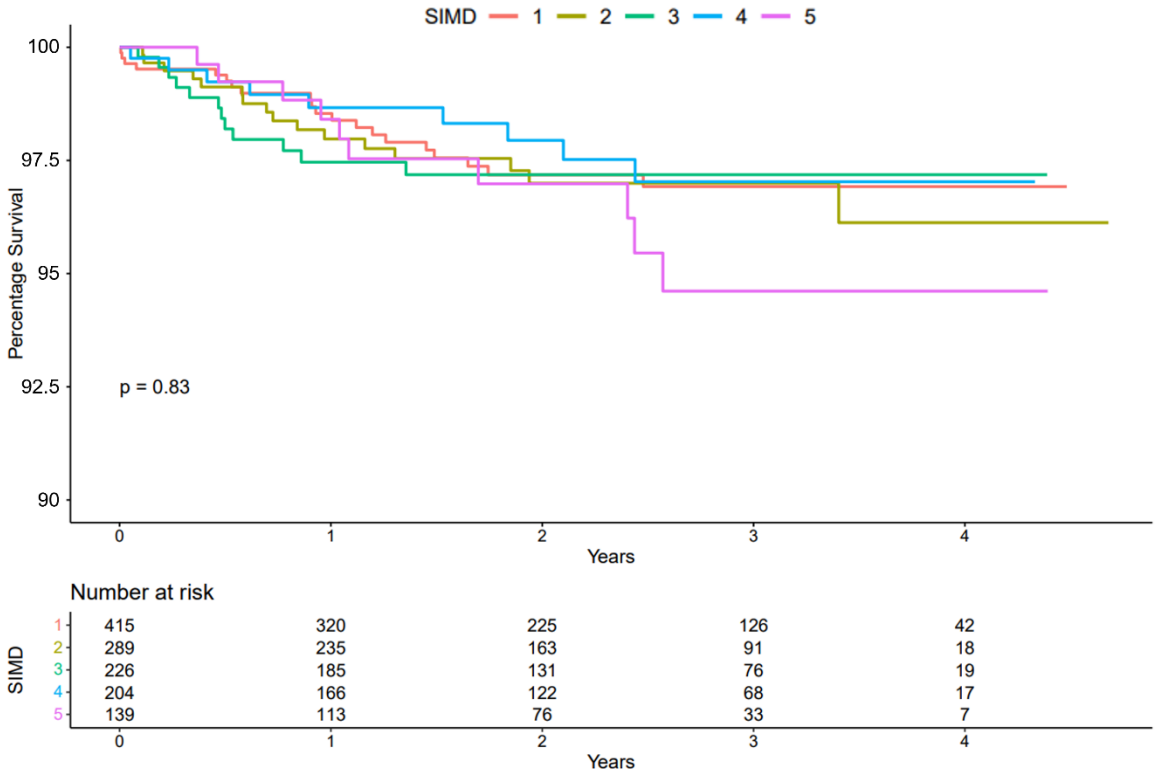

Figure 7-4 Kaplan-Meier curve of survival function by SIMD (Scottish Index of Multiple Deprivation). P-value denotes log-rank test.

Neither the size of a burn, as measured by surface area (log rank p-value = 0.21), nor mechanism of burn injury (log rank p-value = 0.22) had any impact on the mortality risk in this study. However, the presence of an airway burn or smoke inhalation injury were associated with an increase in mortality following survival of the initial burn injury (log rank p-value = 0.022). The Kaplan-Meier curves of these analyses are not displayed owing to the small number of individuals in certain categories.

Other factors that were associated with an increased risk of death included increasing comorbidity burden (Figure 7-5), the pre-injury use of anxiolytic medications (Figure 7-6), opioids (Figure 7-7) and alcohol excess (Figure 7-8).

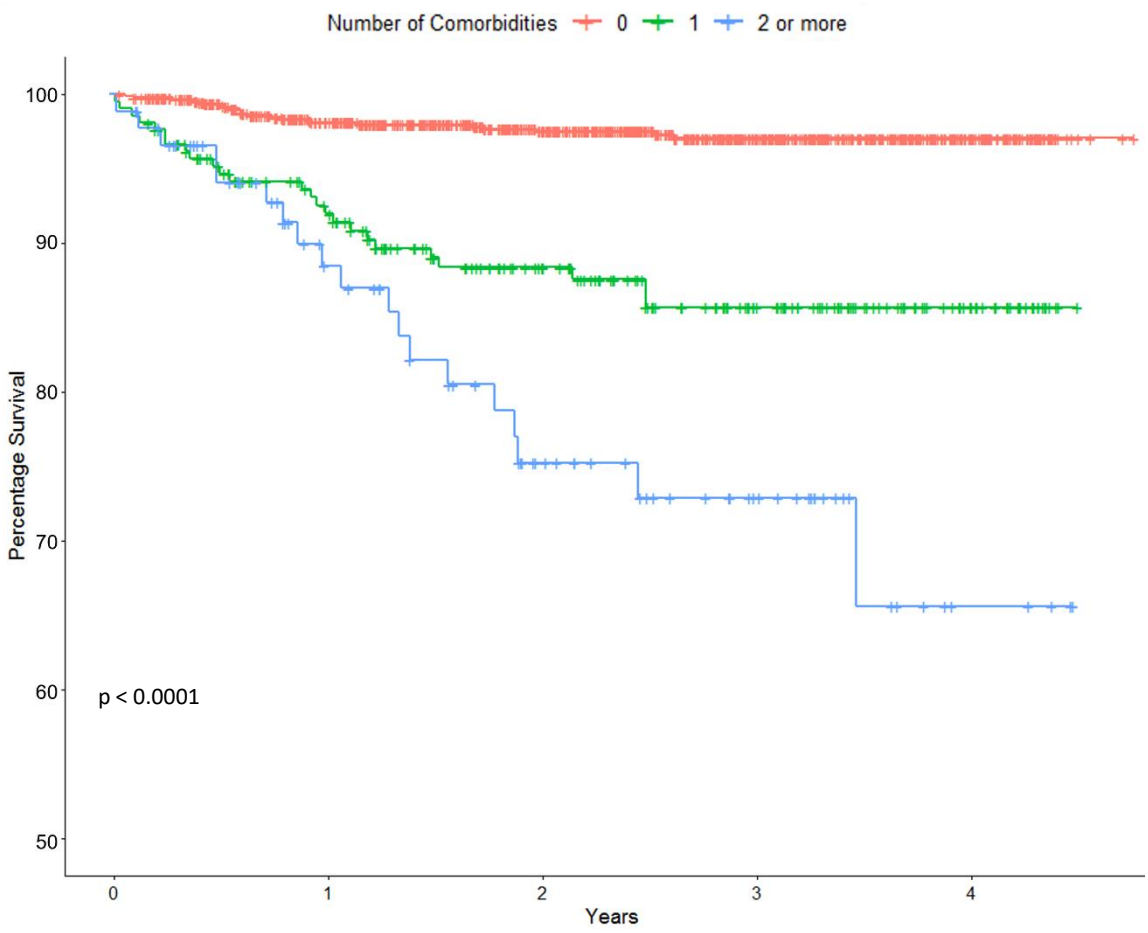

Figure 7-5 Kaplan-Meier curve of survival function by number of comorbidities using Elixhauser score. P-value denotes log-rank test. Risk table not included due to small

number of individuals at certain time points.

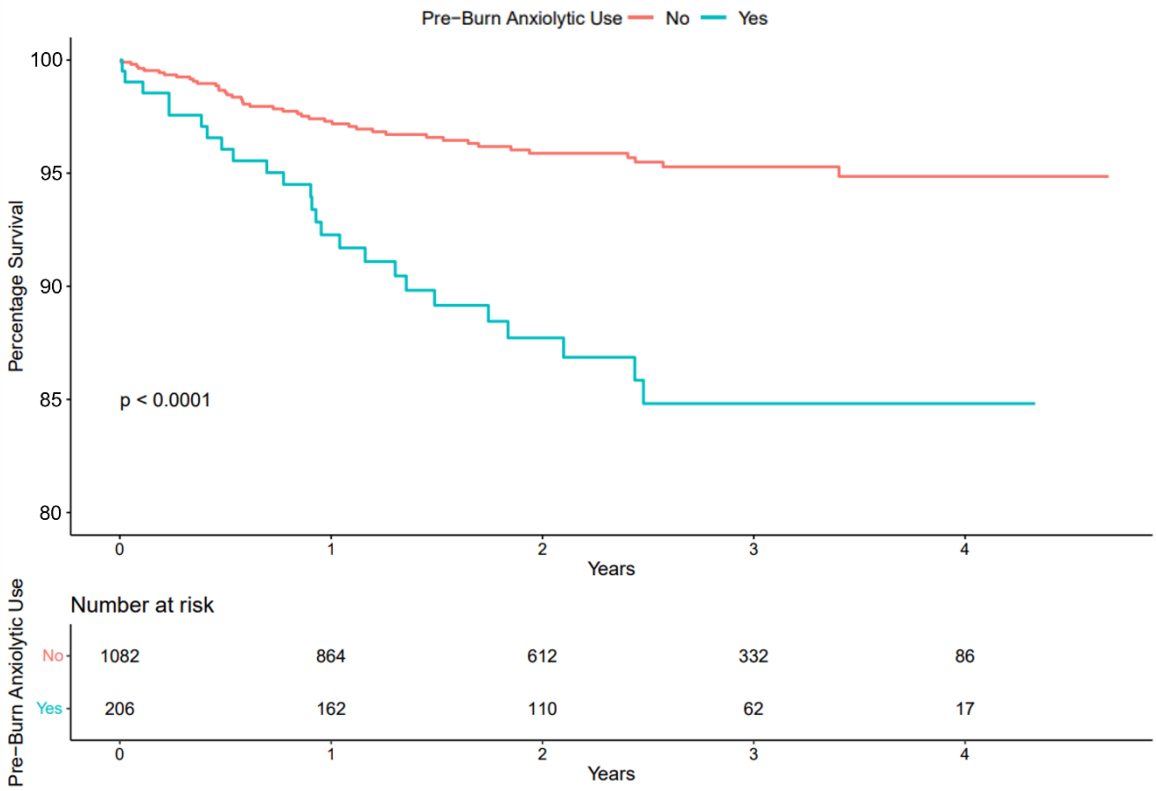

Figure 7-6 Kaplan-Meier curve of survival function by pre-burn use of anxiolytic medications. P-value denotes log-rank test.

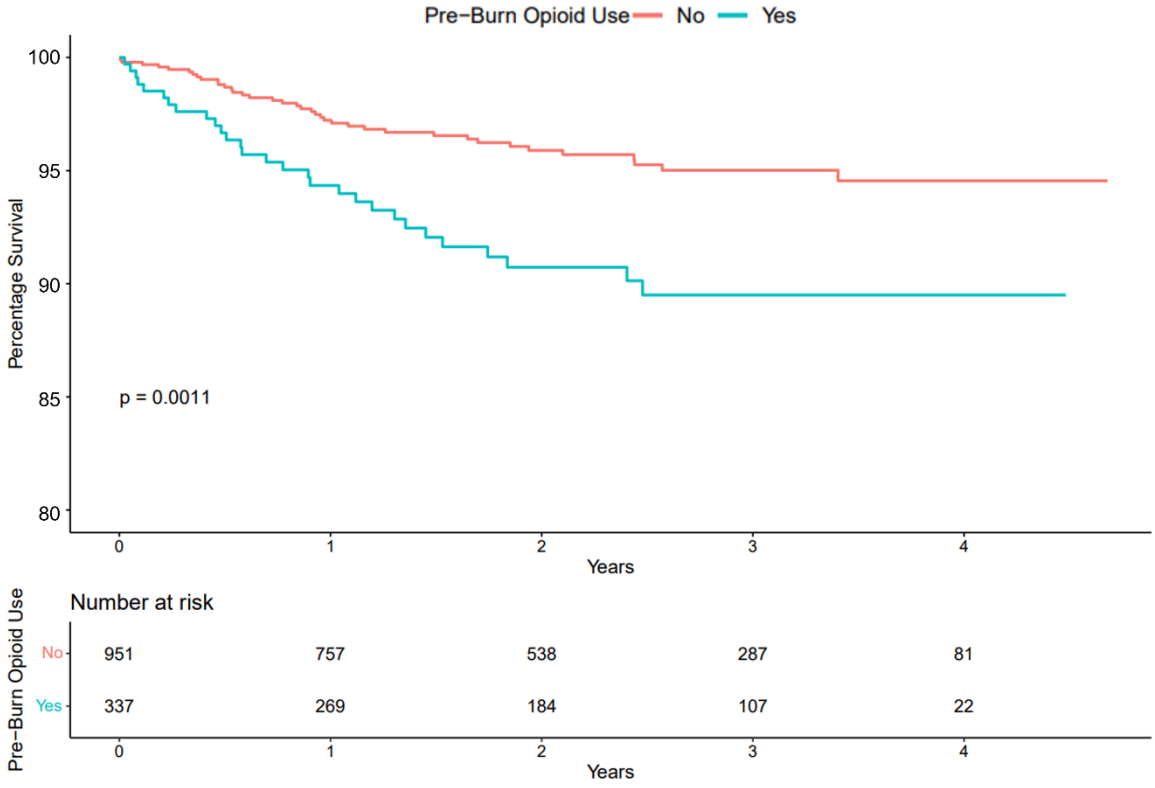

Figure 7-7 Kaplan-Meier curve of survival function by pre-burn use of opioid. P-value denotes log-rank test.

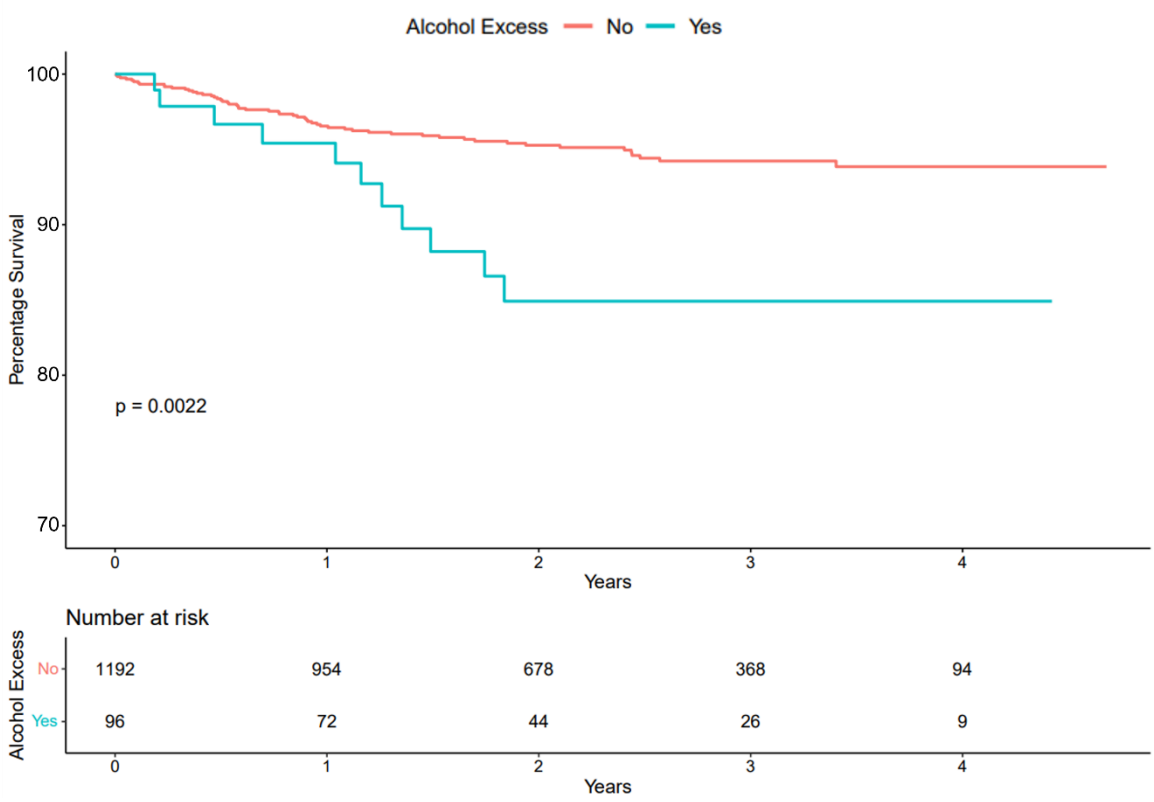

Figure 7-8 Kaplan-Meier curve of survival function by pre-burn history of alcohol excess. P-value denotes log-rank test.

A univariable Cox-proportional hazards regression model is illustrated in Table 7-2. This demonstrated that increasing age was associated with an increased risk of death with a hazard ratio of 1.06. Additionally, the presence of smoke inhalation or airway burn had a hazard ratio of 3.24. Increasing comorbidity burden was strongly associated with increased mortality (HR 6.11) and the presence of pre-existing anxiolytic or opioid use were also associated with an increased mortality risk (HR 3.16 and 2.19 respectively).

Table 7-2 Univariable Cox-proportional hazards regression model of mortality beyond 30 days after burn injury

	Hazard Ratio	95% CI	p-value
Gender (Male)	1.05	0.63-1.75	0.86
Age*	1.06	1.05-1.07	<0.001
Airway burn	6.42	2.34-17.66	<0.001
Smoke Inhalation	3.30	1.04-10.52	0.043
Airway Burn or Smoke Inhalation	3.24	1.18-8.91	0.022
% TBSA†	1.02	0.99-1.05	0.21
Mechanism of Injury			
Other	Reference		
Flame	1.42	0.81-2.48	0.22
SIMD			
1	Reference		
2	1.11	0.57-2.14	0.76
3	1.05	0.52-2.16	0.89
4	0.89	0.41-1.96	0.77
5	1.48	0.69-3.16	0.31
Ethnicity			
White	Reference		
Ethnic Minority	0.49	0.07-3.58	0.48
Urban Rural Classification			
Urban Area	Reference		
Small Town	0.70	0.30-1.62	0.4
Rural	0.69	0.31-1.51	0.35
Elixhauser Comorbidity Score			
0-1	Reference		
2 or more	6.11	3.59-10.41	<0.001
Pre-Burn Drug Use			
Antipsychotics	1.74	0.75-4.03	0.19
Antidepressants	1.46	0.88-2.43	0.15
Anxiolytics	3.16	1.93-5.19	<0.001
Gabapentinoids	1.60	0.69-3.70	0.27
Opioids	2.19	1.35-3.55	0.001

*Calculated for each 1 year increase in age.

†Calculated for each 1% increase in TBSA burned.

Further univariable cox-proportional hazards regression analysis was conducted for each individual comorbidity as measured using the Elixhauser comorbidity score (Table 7-3). Conditions associated with an increased risk of death included the presence of congestive heart failure (HR 23.0), paralysis (HR 6.2), other neurological disorders (HR 2.28), chronic pulmonary disease (HR 7.17), liver disease (HR 8.14), deficiency anaemia (HR 7.51), alcohol abuse (HR 2.64) and depression (HR 3.75). Metastatic cancer and solid tumours were also associated with increased mortality, with hazard ratios of 10.74 and 4.66 respectively.

Figures for several of the domains were unable to be reported due to an absence of events in each of these categories.

Table 7-3 Univariable Cox-proportional hazards regression model of mortality beyond 30 days after burn injury by specific Elixhauser comorbidity domains

Comorbidity	Hazard Ratio	95 % CI	p-value
Congestive heart failure	23.0	9.93-53.28	<0.001
Cardiac arrhythmia	2.71	0.85-8.64	0.091
Valvular disease		Insufficient Data	
Pulmonary circulation disorder	3.32	0.81-13.56	0.095
Peripheral vascular disorder	3.8	0.93-15.54	0.063
Hypertension (uncomplicated)		Insufficient Data	
Hypertension (complicated)		Insufficient Data	
Paralysis	6.2	1.52-25.34	0.011
Other neurological disorder	2.28	1.09-4.78	0.028
Chronic pulmonary disease	7.17	3.42-15.02	<0.001
Diabetes (uncomplicated)	2.22	0.31-15.99	0.429
Diabetes (complicated)	1.74	0.24-12.52	0.58
Hypothyroidism		Insufficient Data	
Renal failure	4.13	0.57-29.78	0.16
Liver disease	8.14	2.96-22.38	<0.001
Peptic ulcer disease		Insufficient Data	
HIV/AIDS		Insufficient Data	
Lymphoma	5.57	0.77-40.21	0.088
Metastatic cancer	10.74	1.49-77.51	0.019
Solid tumour	4.66	2.02-10.79	<0.001
Rheumatoid arthritis/Collaged vascular disease	4.3	0.59-30.97	0.15
Coagulopathy		Insufficient Data	
Obesity		Insufficient Data	
Weight loss		Insufficient Data	
Fluid/electrolyte disorder	3.41	0.83-13.92	0.09
Blood loss anaemia		Insufficient Data	
Deficiency anaemia	7.51	2.73-20.65	<0.001
Alcohol abuse	2.64	1.38-5.04	0.003
Drug abuse	1.71	0.24-12.35	0.59
Psychoses		Insufficient Data	
Depression	3.75	1.36-10.31	0.01

Multivariable analysis was conducted by including any variables that reached a significance level with a p-value <0.1 and a backwards stepwise selection method used to eliminate non-significant variables. Results are presented in Table 7-4. Increasing age, the presence of an airway burn or smoke inhalation injury, increasing comorbidity burden and the pre-burn use of anxiolytic medications were all associated with an increased risk of death.

Table 7-4 Multivariable Cox-proportional hazards regression model of mortality beyond 30 days after burn injury

	Hazard Ratio	95% CI	p-value
Age*	1.06	1.04-1.07	<0.001
Airway Burn or Smoke Inhalation Injury	2.80	1.01-7.73	0.047
Elixhauser (2 or more comorbidities)	3.51	1.99-6.18	<0.001
Pre-Burn Anxiolytic Use	2.13	1.26-3.60	0.005

*Calculated for each 1-year increase in age

7.3.2 Causes of death

The underlying causes of death, as categorised by ICD-10 classifications based on information on death certification, are detailed in Table 7-5. Cardiovascular disease, including cerebrovascular disease, was the leading cause of death among this cohort. Drugs and alcohol related deaths were the second leading cause, followed by cancer. Deaths attributed to suicide occurred in fewer than 6 individuals with further details not reported in the interests of preventing any possible identification of individuals.

Table 7-5 Underlying cause of death as per ICD-10 categorisation

Underlying Cause of Death	N = 67 (%)
Cardiovascular disease	21 (31.3)
Drugs/Alcohol	12 (17.9)
Cancer	9 (13.4)
Respiratory disease	9 (13.4)
Other	8 (11.9)
Dementia	<6 (<9.0)
Suicide	<6 (<9.0)

7.4 Discussion

7.4.1 Mortality Rate

Of the 1288 individuals included in this study, 67 (5.2%) died. At a maximum of four years follow-up only 128 individuals were still included in the Kaplan-Meier analysis due to censoring, with a mortality rate of around 7% evident at this time point. The mortality rates appeared much higher in certain subgroups, with multi-morbid patients (those with two or more Elixhauser comorbidities) having a mortality rate of around 35% at four years using Kaplan-Meier analysis. Additionally, the mortality rates of patients with a pre-existing history of alcohol excess, opioid use or anxiolytic drug use approached 10-15%.

7.4.2 Survival Analysis

This study has explored the factors associated with death following survival of a burn injury in the Scottish population. The association between increasing age, increasing comorbidity and the risk of death are easily explained beyond the specific risks that may be linked to the burn injury. For example, the strong association between congestive heart failure and increased mortality is likely to be independent of any lasting physiological effects of the burn injury itself[269].

The presence of an airway burn and/or smoke inhalation injury were found to increase the risk of death in this cohort with a hazard ratio of 2.8 on multivariable analysis. Research exploring the long-term impact of smoke inhalation injuries on patient-centred outcomes are rare. Several of the studies exploring long term mortality in burn survivors by Duke et al[91–93] and Mason et al[94] have not included data on such associated injuries in their analysis. As such, the long-term consequences and potential impact on life expectancy of suffering a smoke inhalation injury are poorly understood. One study explored the long-term respiratory health of a selection of patients that survived an inhalation injury from domestic fires, performing chest radiographs, pulmonary function tests (PFTs) and respiratory symptom assessments, finding only a small number complaining of dyspnoea and all patients having PFTs within normal limits[270]. A study of victims of the 1987 King's Cross underground station fire found that 11 of the 14 patients had evidence of small airway obstruction at 6 months post-injury, persisting in 7 patients at 2 years[271]. Other case reports have suggested a link between smoke inhalation injury and the development of bronchiectasis later in life[272,273].

The signal of increased long-term mortality risk after smoke inhalation injury in this study should be interpreted with caution. Several other factors should be taken into account including the circumstances around why an individual could not extricate themselves from a smoke-filled room quickly enough; did they have a physical limitation, frailty or drug intoxication that impaired their ability to escape? Such factors could additionally contribute to excess long-term mortality. Additionally, the mortality excess demonstrated in this study is based on a very small number of patients that suffered such an injury and should therefore be viewed with caution.

This study has shown that pre-burn anxiolytic drug use is associated with an increased mortality risk in the years after burn injury. Previous research has highlighted that anxiolytic and hypnotic drug use is associated with an increased mortality rate in the general population as a whole[274,275]. Such findings may be due to the correlation between anxiolytic drug use and increased comorbidity burden, however, in this study, pre-burn anxiolytic use remained a significant contributor to mortality even when adjusting for comorbidity. There may also be a causative effect, as postulated by various studies that demonstrate an increase in mortality, cancer diagnosis and infections perhaps due to immune-modulating or carcinogenic effects of these drugs[276–278].

Gender did not seem to have any influence on mortality in this cohort. Previous studies have highlighted a gender disparity in several outcomes with females being worse affected than males. Such outcomes include death from burn injury[279,280], cancer risk[87,88] and long-term mortality after burn injury[91]. These differences in outcomes have been postulated to be due to variations in the inflammatory and immune responses between genders. Although this study found no such difference between genders, it may simply have been underpowered compared to the aforementioned studies of much larger cohorts with longer follow-up times.

Although increasing surface area of a burn is strongly associated with an increase in short-term mortality directly attributed to the injury, this effect has not been reflected in the longer-term mortality risk to patients in this study. Similar results have been found in other longitudinal studies[91,93]. Such disparity may be explained by survivorship bias, whereby those patients who survived more significant burn injuries had greater physiological reserve and fewer underlying comorbidities. However, one study focusing on paediatric patients did find that an increasing size of burn resulted in more pronounced excess mortality in the years after the injury[92]. As this study focussed on adult patients, no comment can be made regarding paediatric patients.

7.4.3 Causes of death

The most common cause of death in this study was cardiovascular disease, accounting for 31.3% of all deaths. This is in keeping with the general

population, whereby cardiovascular disease accounted for 27.3% of deaths in Scotland in 2015[281]. Previous research has demonstrated a link between burn injury and an increase in cardiovascular comorbidity[85,86,282]. However, with relatively small numbers included in this study and the lack of any control group for comparison, no such link in this cohort can be demonstrated.

17.9% of all deaths in this study were attributed to drug or alcohol abuse. This lies in stark contrast to the general population, whereby alcohol related deaths accounted for 6.5% of all deaths in 2015[283] and drug-related deaths accounted for 1.2% during the same period[284]. This serves to highlight the high prevalence of alcohol and substance abuse among adults who sustain a burn injury and potentially the deterioration in such conditions after burn injury.

We are unable to report the exact figures from suicide due to the small number of individuals concerned, nor confer any relationship between burn injury and risk of suicide. The European Age-Standardised Rate (EASR) of suicide in Scotland was 12.5-14.7 suicides per 100,000 of population[285] during the years of this study, equating to an incidence of between 0.0125 and 0.0147%. With even one death in this study being the result of suicide would result in an incidence of greater than 1%, although with such small numbers any meaningful interpretation is limited. A recent systematic review investigating suicidality after burn injury found that such patients are more likely to have thoughts of suicide and an increased prevalence of suicide attempts[286]. However, research on completion of suicide is scarce and with conflicting results. One prospective observational cohort study of 156 burn survivors reported that 5 patients (3.2%) died by suicide in the 18-month follow-up period[287]. Another study reported 5 (4.5%) of 111 deaths in a cohort of burn survivors being due to suicide[288]. Suicide as a cause of death was 4 times more common in burn survivors compared to matched controls in a study by Mason et al[94]. A study of 830 US military combat burn patients reported a total of 11 death, none of which were attributed to suicide[289]. However, the authors did report that 5 of the 11 deaths were due to accidental poisoning by exposure to drugs, highlighting the overlap in substance abuse problems that burn survivors may face.

7.4.4 Strengths and limitations

This study has utilised large and robust data sources to investigate the mortality of adult patients that have survived hospitalisation due to a burn injury. The structure of publicly funded healthcare delivery in Scotland, methods of identification of individuals across healthcare settings and the large, robust administrative databases associated with them have allowed an accurate and detailed description of this cohort of patients.

This is the first study we are aware of that has used drug prescription data to provide more detail of comorbidity burden and assess the influence of drug prescribing patterns on an important outcome such as mortality in this group of often vulnerable patients.

However, the study has several limitations. As with any observational study, results can be subject to various sources of bias. Patients in this study were selected from the COBIS database of burn injured patients. This could introduce selection bias whereby those with less significant burns or managed by non-burn specialists were not included, potentially excluding many patients.

Burn injuries, especially major burns or those requiring hospital admission, are thankfully rare in Scotland. As such, this study investigated adult patients admitted between 2012 and 2015, resulting in 1288 individuals with a median follow-up time of 2.4 years and maximum of 4.7 years. During this period, 67 patients died. Such relatively small numbers of deaths and limited follow-up time have likely limited the wealth of information that would otherwise have been available with data extracted over a longer period. Such studies carried out by Duke et al covered significantly longer time periods, up to 33 years[91–93].

Although this study has been able to describe some of the factors associated with mortality in the years following burn injury, it is limited in its ability to draw any firm conclusions on whether such factors are unique to burn injured patients or are potentially of influence in other conditions. Nor can this study comment on the impact of any lasting pathophysiological changes after burn injury on mortality without the inclusion of an appropriate control group for comparison.

7.4.5 Conclusions

This study has shown that the presence of a smoke inhalation or airway burn may have an impact on the long-term survival of patients after burn injury. Such results should be interpreted with caution given the wide confidence intervals reported, likely a reflection of the small number of individuals with such injuries in this study. Although there is a clear understanding that inhalation injury has a significant influence on morbidity and mortality immediately following burn injury, further research is warranted into the potential long-term effects of such injuries on general health and outcomes such as mortality.

Although previous studies have explored the hypothesis that suffering a burn injury and the resulting inflammatory and immunological changes that occur thereafter may lead to an increased risk of early death, this phenomenon may not be unique to burn-injured patients. A similar pattern has been seen in survivors of sepsis, demonstrating a higher risk of all-cause mortality [290,291] and major adverse cardiovascular events when compared to a propensity matched control group[291]. Similar results have been seen in other populations including patients admitted with pneumonia[292], adult trauma patients[293,294] and ICU survivors[295]. Further research investigating the persisting inflammatory and immune changes that occur in burn injuries and the long-term patient-centred outcomes should be conducted using other illnesses and injuries as a comparator to better understand the lasting health problems of such conditions.

Given the close association between mental health conditions and burn injuries, the increased mortality risk associated with anxiolytic drug use and increased number of deaths due to alcohol or drug abuse demonstrated in this study, there should be significant effort made to robustly follow-up and provide support to patients with underlying mental health conditions and substance addiction. Such patients are not only at higher risk of sustaining a burn injury but may also be at higher risk of deteriorating health after such an injury.

Chapter 8 Discussion

Burn injuries remain a major cause of morbidity and mortality worldwide, with the prevalence of such injuries being significantly higher in low and middle-income countries. In addition, individuals affected are often from areas of socioeconomic deprivation, a feature evident in both developing and developed countries.

The management of burn injuries has developed over recent decades with an associated improvement in survival. With such improvements have come a group of patients that are left with persisting and significant health problems, both physical and psychological, as a consequence of their burn injury.

The aim of this thesis was to gather more information on the long-term sequalae of burn injury by exploring the existing evidence regarding the management of pruritus, evaluate the use of a pruritus management protocol, describe the epidemiology and mortality associated with burn injuries in Scotland, describe the association between prescription drug use and burn injury and finally explore the mortality burden in the years after burn injury.

8.1 Summary of findings and their implications

8.1.1 Systematic review and meta-analysis

Pruritus following burn injury is a common problem. The pathophysiology underlying this phenomenon is not fully understood and is likely to be multifactorial, involving complex interactions between peripheral pruritogens and pathological changes within the central nervous system. Hence, an optimal treatment of this condition does not yet exist.

Drugs commonly used to treat neuropathic pain are being increasingly used for indications beyond their original purposes. This broad class of drugs include medications originally developed as antidepressants or anticonvulsants. These drugs are now often used to manage chronic pain, neuropathic pain and pruritus of various causes. The systematic review and meta-analysis conducted as part of

this thesis sought to gather the existing research exploring the use of such drugs in the management of burn related pruritus.

This review has highlighted the paucity of research that has been conducted into the management of burn related pruritus with drugs normally used to treat neuropathic pain. Gabapentinoids were the most extensively researched, being compared to either placebo or antihistamines in four randomised control trials. Six further observational studies contributed to the systematic review. The gathered evidence suggests effectiveness of gabapentinoids in managing burn related pruritus, with an improvement in pruritus severity scores of around 2 points on a 0-10 visual-analogue scale when compared to antihistamine therapy.

This systematic review did not specifically explore the potential harms associated with gabapentinoid therapy. However, there is mounting evidence of harm associated with gabapentinoids including in their use as recreational drugs, increasing implication in drug-related deaths and reclassification as controlled substances in various countries. Although this review has demonstrated a modest improvement in pruritic symptoms with the use of gabapentinoids, this must be weighed against the potential for harm, especially in more vulnerable individuals with existing psychiatric comorbidity or history of substance abuse.

The evidence for other drugs classes was found to be incredibly sparse, with only topical doxepin and lidocaine being explored. Topical doxepin, a tricyclic antidepressant with potent antihistamine effects, showed promising results in two early trials but they suffered from a high risk of bias. Two further trials failed to replicate these positive results. Topical lidocaine, a local anaesthetic agent, was only described in one observational study exploring the use of EMLA cream, a mixture of lidocaine and prilocaine. This study demonstrated the treatment was safe but making more meaningful conclusions on the effectiveness as an anti-pruritic is limited.

8.1.2 Use of a pruritus management protocol

This chapter set out to quantify the incidence and severity of pruritus in a cohort of burn-injured patients admitted to a tertiary referral burn centre,

explore the association between vitamin D deficiency and itch severity and assess the effectiveness of a pruritus management protocol.

This study demonstrated that burn-related pruritus is a common problem, affecting 50% of the individuals in this cohort. However, the methodology of this study limited its ability to delineate any association between plasma vitamin D levels and pruritus severity. Vitamin D deficiency is common in Scotland, owing to the latitude and therefore reduced exposure to sunlight, and evident even more-so in individuals from areas of socioeconomic deprivation. These factors, combined with the pathophysiological effect of burn-induced inflammatory response in reducing micronutrient levels and impaired ability of burned skin to synthesise vitamin D, may result in health problems associated with vitamin D deficiency. Although this study has been unable to demonstrate any clear link between vitamin D deficiency and pruritus severity, nor any significant improvement in patient centred outcomes by prescribing vitamin D replacement therapy, the question of whether routine measurement and replacement of vitamin D may be of benefit to patients for acute symptom management and prevention of long-term consequences to health remains an important one. With increasing evidence of the important role that vitamin D plays in immune-modulation and as an anti-inflammatory, some clinicians advocate the routine replacement of vitamin D in patients with deficiency following major burn[296].

Another aim of this study was to evaluate the effectiveness of a pruritus management protocol. Given the variability in pruritus severity both over time for individual patients and between individuals, a method of statistical analysis was chosen that would account for these sources of variability. Other studies that have explored pruritus severity have often focused on mean severity scores before and after a single intervention. However, this study used a novel statistical method to assess severity scores over fairly short period in an observational study, using a wealth of individual data-points in a complex multi-intervention study. This method demonstrated that a protocolised approach to the pharmacological management of burn-related pruritus was largely effective in reducing severity scores with the use of 1st and 2nd line antihistamines and gabapentin when indicated.

However, the population within this study was relatively small, as were the effect sizes of each drug, limiting any conclusions that could be reached regarding the efficacy of individual medications. Additionally, with such a complex multi-intervention observational study, further levels of complexity were not taken into account, including any interactions or synergy between various drugs. To truly delineate the effectiveness of any single drug a blinded, placebo controlled, randomised trial would likely be required.

8.1.3 Epidemiology and mortality of burn injury in Scotland

The epidemiology of burn injuries in Scotland is similar to that seen in other developed nations. Burn injuries are more likely to affect males and those from areas of socioeconomic deprivation. This pattern is evident in burn injuries affecting both children and adults. However, the cause of burn injury seen in children is more likely to be due to scald injury, with flame injuries being relatively rare. Additionally, major burn injuries rarely affect children.

Of note, children from ethnic minority backgrounds seem to be over-represented among this burn injured cohort. This pattern has been seen in other studies throughout other developed nations, but this is the first study to our knowledge to explore this phenomenon in Scotland.

This study also explored the comorbidity burden of adults admitted to hospital with a burn injury. Although the extent of comorbidities is likely to be an underestimate due to the nature of using administrative data to explore patient level clinical questions, the results did highlight common comorbidities among this cohort. These included neurological conditions and alcohol dependence. Such conditions may be potential contributors to an increased risk of sustaining a burn injury due to either high risk behaviour or an inability to extract oneself from a source of thermal injury owing to neurological impairment or intoxication.

Thirty-day mortality from a burn injury in this cohort of adult patients was 2.73%, broadly comparable with rates in other developed nations. The factors strongly associated with an increased risk of death include increasing age, increasing surface area burned and the presence of an inhalation injury. Such

factors have been extensively explored in previous research and their influence on mortality remain strongly linked in this study.

This study explored the influence of pre-existing comorbidity on risk of death due to burn injury. Multivariable Cox proportional hazards regression analysis suggested that the presence of depression or neurological disorder contributed to the risk of death from burn injury. The physiological rationale for depression contributing to increased mortality is not immediately clear. However, the biological plausibility of a neurological condition contributing to an increased mortality risk may be a little easier to understand, with such conditions, perhaps degenerative in nature, being associated with increasing mortality. Indeed, sustaining a burn injury due to deteriorating neurological conditions may simply be a marker of increasing frailty. Such an injury could be considered similar to the aetiology of hip fractures, whereby around one in ten patients will die within a month of sustaining the injury and one-third will die within the following year[297]. Such a phenomenon may account for the increased mortality in this burn injured cohort, with such an injury perhaps being a reflection of an individual approaching the end of their life.

Although not investigated in this study, the impact of frailty on mortality and other outcomes has been of increasing interest in various parts of the medical literature, particularly in critical care, but also in patients with burn injury. A study by Iles et al investigated the influence of frailty on healthcare use, intensive care admission, morbidity and mortality after burn injury. The authors reported that increasing frailty was associated with increased 30 day mortality even when accounting for age, TBSA and the presence of inhalation injury[298].

8.1.4 Community drug prescriptions and burn injuries

The use of various classes of drugs associated with mental health conditions and chronic pain have been increasing in recent years throughout Scotland. Opioid prescribing has been increasing in many parts of the developed world, with an increased focus in recent years on the “opioid crisis” of North America. It is estimated that in the USA and Canada over 600,000 people have died from an opioid overdose in the last twenty years[299].

Opioids are more likely to be prescribed to individuals from areas of socioeconomic deprivation, a feature common among individuals who suffer burn injury. This study has served to highlight the high prevalence of opioid prescribing among burn-injured adults, with 25.8% receiving an opioid prescription in the year preceding their burn injury.

Following burn injury, the use of opioids increased to 38.5% of patients, with one in five patients being prescribed an opioid on three or more occasions. Several factors were associated with increasing opioid use after burn injury including previous opioid use, female sex and increased comorbidity burden.

In a similar pattern to that seen in opioid prescribing, the pre-injury use of antidepressants, anxiolytics, antipsychotics and gabapentinoids were all higher in the cohort in this study compared to the rates of prescriptions for the general population in Scotland. Although this study did not demonstrate any clear increase in any single class of these drugs other than gabapentinoids, the methodology used did not account for loss of patients due to censoring during the follow-up period or death.

With such a high pre-injury use of the drugs explored in this chapter among patients that suffered a burn injury and the recognised potential for harm from many of these drugs, their initiation or dose escalation should be done with caution.

8.1.5 Long-term mortality after burn injury

Following the initial survival of a burn injury, over 5% of patients in this study died in the following four years. The mortality rate was significantly higher in patients with multiple comorbidities, reaching around 35% in patients with two or more comorbidities at four years.

The influence that the burn injury itself has on mortality is difficult to examine in any detail, especially in the absence of any control group. However, certain features of the injury could be explored regarding their influence on long-term mortality. For example, the severity of burn, as measured by the total body surface area, did not seem to have any influence on mortality risk in the four

years after injury. This may simply be due to survivorship bias and a reflection of robust physiological reserve in patients that have been fit enough to survive a major burn injury.

The presence of a smoke inhalation injury did seem to contribute to mortality risk in this study. However, the results should be interpreted with caution given the small number of patients that suffered such an associated injury. Existing research has produced conflicting results regarding the long-term health consequences of smoke inhalation injury. A recent analysis of Scottish firefighters over a twenty-year period found that mortality from various causes, frequently cardiovascular disease or malignancy, were significantly higher when compared to general population mortality rates[300]. Although this study implies a potential harmful and perhaps carcinogenic occupational exposure risk, this is more likely to be in the context of repeated exposure rather than a single episode of inhalation injury and should therefore be treated with caution when comparing these very different populations.

Anxiolytic drug use appeared to be associated with increased mortality in this study. The rationale for this is unclear. This may be a reflection of poor underlying health in general and therefore associated excess mortality. Additionally, there may be directly acting detrimental effects on health of such drugs, as postulated by various studies that detail the immune-modulating and carcinogenic effects of these drugs[276–278].

8.2 Reflections on strengths and weaknesses

This thesis can be divided into three sections: a systematic review and metanalysis; an assessment of a protocolised approach to burn-related pruritus and a retrospective observational study using national administrative healthcare data.

The systematic review and metanalysis is the first to explore the use of a broad class of drugs that are being used with increasing frequency to manage conditions beyond their initial development or licence. This review gives an important and well needed evaluation of the existing evidence behind these medications to inform clinicians who may prescribe these medications.

However, this review is limited by the paucity of research that has been conducted in the management of burn-related pruritus with drugs commonly used to treat neuropathic pain.

Chapter four details the evaluation of protocolised approach to burns-related pruritus in a busy adult tertiary referral centre. The methodology used is fairly novel in its approach to assessing pruritus, a symptom that can vary significantly between patients and at different times. The statistical method of multilevel interrupted time series analysis helped to account for these sources of variation rather than relying on simplified mean scores before and after each intervention. Although this analysis showed a consistent improvement in pruritus scores with the use of a protocolised approach to pharmacological treatments, the ability of such an observational study to determine greater efficacy of one drug over another is limited and is better assessed in a blinded and randomised trial.

Additionally, the exploration of factors associated with pruritus severity, specifically vitamin D deficiency, was limited by the potential bias introduced by only testing vitamin D levels once the pruritus protocol was triggered. Definitive exploration of the association between vitamin D deficiency and pruritus following burn injury should be carried out by measuring plasma vitamin D levels in all patients admitted with a burn injury and accounting for potential confounders such as change over time, surgical interventions, opioid use and comorbidity.

The remaining chapters of this thesis explored the use of administrative healthcare data to investigate epidemiology, prescription drug use and mortality of a cohort of patients admitted to Scottish hospitals with a burn injury. The healthcare system in Scotland is fortunate to have a wide-reaching system to record such data. The audit systems in place to monitor these databases ensure the information collected is robust. However, despite the wealth of data available using such methods, the granularity of patient level information can be lacking, especially regarding complex medical issues such as pre-existing comorbidity, the severity of these conditions, frailty, functional capacity and performance status. Therefore, utilising such data in an observational study has the potential to exclude valuable information regarding patient demographics

and any estimate of, for example comorbidity burden, is likely to be an underestimate.

8.3 Implications for further research and practice

This thesis has added to the existing research on the management of burn-related pruritus. It has demonstrated that gabapentinoids are likely to be beneficial in managing this condition, although noting the relative scarcity of such evidence and highlighting the existing literature that demonstrates the potential harms associated with these drugs. This information can help clinicians who may prescribe these drugs and inform future research in pursuit of more robust evidence to demonstrate meaningful improvements in patient centred outcomes with additional focus on the potential harms associated with these medications.

A protocolised approach using antihistamines and gabapentin to manage burn-related pruritus appears effectiveness at reducing severity scores. Although this study is limited in recommending one specific agent over another, it has shown that a formalised protocol is effective at reducing severity scores and allows for a consistent approach to management of such symptoms.

This thesis has described the epidemiology of burn injuries across Scotland. Of note, children from ethnic minority backgrounds seem to be at higher risk of sustaining a burn injury. Individuals from areas of socioeconomic deprivation are also more likely to be admitted with a burn injury, a pattern seen in both adults and children. Comorbidities including mental health disorders, alcohol excess and neurological conditions are common among burn injured adults. As are the use of opioids, gabapentinoids and medications to treat mental health conditions. These analyses serve to highlight the significant overlap in poverty and common health conditions that put individuals at risk of burn injury. A focus on improving these common social and health inequalities in Scotland's population would hopefully reduce the incidence of burn injury.

In recent years, there has been growing interest in the long-term consequences of sustaining a burn injury. This thesis has explored the mortality of a cohort of burn-injured adults over a four year period to explore common factors

associated with death in the years soon after injury. Although increasing age and comorbidity burden were associated with an increased risk of death, these are likely to be independent of the burn injury. Smoke inhalation injury and anxiolytic drug use were also found to be linked to increased risk of death. The influence of a lasting pathophysiological effect following burn injury on long-term mortality cannot be fully explored with this methodology and likely requires the comparison with a matched control group. Future research of this nature should focus on trying to separate the influence of the pathological effects of the burn injury from the high prevalence of pre-existing comorbidities that can equally contribute to morbidity and mortality.

Appendices

9.1 Initial PBPP Approval Letter

Public Benefit and Privacy Panel for Health and Social Care
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Dr Charlotte Gilhooly
COBIS c/o University of Glasgow
Room 2.71 New Lister Building
Glasgow Royal Infirmary
Glasgow
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Date: 16th February 2016
Your Ref:
Our Ref: 1516-0445

Dear Dr Gilhooly

Re: Application 1516-0445: Mortality and morbidity after burn injury in Scotland

Thank you for your application for consideration by the Public Benefit and Privacy Panel for Health and Social Care. Your application has undergone proportionate governance review and has been approved.
This approval is given to process data as specified in the approved application form, and is limited to this. Approval is valid for the period specified in your application. You are required to notify the Panel Manager of any proposed change to any aspect of your proposal, including purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure, or any other relevant change.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection. In particular you should be aware that once personal data (irrespective of de-identification or other controls applied) has been extracted from NHSS Board(s) and transferred to you, that you will then become the Data Controller as defined by the Data Protection Act (1998).

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (www.informationgovernance.scot.nhs.uk).

I hope that your proposal progresses well,

Yours Sincerely

Ashley Gray
Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: nss.PBPP@nhs.net

9.2 PBPP amendment approval letter

Public Benefit and Privacy Panel for Health and Social Care
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Dr Christopher McGovern
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Date: 28th August 2019
Ref: 1516-0445

Dear Doctor McGovern

Re: Mortality and morbidity after burn injury in Scotland
Version: 5

Further to your approval issued by the Public Benefit and Privacy Panel for Health and Social Care on 16th February 2016, I am writing to confirm that we accept the amendment(s) to the proposal notified on 23rd August 2019.

The approved amendments are:

- Applicant details changed
- Sponsor details changed
- Information custodian details changed

Please note that any conditions attached to your original approval remain in place and you should continue to comply with those conditions outlined in the approval letter. It is the responsibility of the applicant and their organisation to ensure that their study complies with current legislation at all times during the study.

This approval is given to process data as specified in the approved application form, until 16th February 2021 and is limited to this.

Requests for access to NHS Scotland data as part of this approved application should be supported by providing a copy of your approval letter and approved application to the relevant local board contacts/data providers.

I would take this opportunity to remind you of the declaration you have made in your application committing you to undertakings in respect of information governance, confidentiality and data protection.

Yours sincerely

Phil Dalgleish
Panel Manager
NHS Scotland Public Benefit and Privacy Panel for
Health and Social Care Email: nss.PBPP@nhs.net

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