The characteristics and outcomes of patients with solid tumours admitted to Intensive Care in the West of Scotland

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Abstract

Cancer is one of the commonest conditions among patients admitted to Intensive Care Units (ICU). However, little is known about how it affects likelihood of ICU admission and subsequent clinical progress. What literature does exist is often not generalisable to current UK practice.

The aims of the studies presented in this thesis are to determine the features that are associated with ICU admission in patients with solid tumours; to describe how the solid tumour population in ICU differs from the ICU population without cancer; how this impacts upon survival; and finally, to describe the long-term outcomes of solid tumour patients that have survived ICU and those features associated with mortality.

I undertook a detailed systematic review of the international literature relating to survival following ICU admission for patients with solid tumours. This revealed a paucity of high quality studies and led to recommendations for improving the conduct and reporting of future research in this field.

Using retrospective cohorts from prospectively collected databases, variables relating to patients in the West of Scotland diagnosed with a cancer between 1st January 2000 and 31st December 2009 were analysed. The rate of ICU admission within two years following cancer incidence was investigated, and the factors associated with admission described. The Scottish Intensive Care Society Audit Group (SICSAG) database was used to detail information pertaining to critical illness and to provide data on patients without an underlying tumour that were admitted to ICU during the same study period. Three cohorts were defined: patients with a solid tumour that were admitted to ICU, patients with a solid tumour that were not admitted to ICU, and ICU patients without a cancer diagnosis.

One in twenty patients diagnosed with a solid tumour (5.2%) were admitted to ICU with the majority receiving organ support during their ICU stay. ICU admission tended to occur soon after cancer diagnosis and was therefore likely related to the cancer diagnosis or its treatment. The rate of ICU admission was greatest for bowel malignancies (16.5% of colorectal cancer patients) and for

those tumours that require peri-operative ICU support for tumour resection surgery such as head and neck cancers (12.8%), stomach cancer (11.3%) and oesophageal cancer (10.2%). When compared with the ICU population without cancer, patients with solid tumours tended to be older (median age 68 years vs. 59 years, respectively), with a higher proportion of elective hospitalisations (52.7% vs. 10.0%) and were predominantly admitted to ICU with a surgical illness (89.3% vs. 55.0%).

Surgical ICU admissions have a favourable ICU and hospital mortality if they have an underlying cancer diagnosis compared with surgical ICU patients without cancer (hospital mortality 22.9% vs. 28.1%, respectively). A potential explanation for this would be a higher proportion of level 2 admissions, lower utilisation of multi-organ support and an opportunity for pre-operative optimisation within the cancer group. ICU cancer patients admitted with a medical diagnosis have poorer short-term survival than those without cancer (hospital mortality 49.1% vs. 41.7%, respectively) and this difference is even more pronounced in those that received organ support (62.5% vs. 46.2%).

In patients that survive an admission to ICU the presence of cancer has the largest impact upon mortality risk in the longer-term with a risk of death over three times greater than in the population of ICU survivors without cancer. Long-term survival varies considerably by underlying tumour type with four-year survival varying from 10.0% in patients with hepatocellular carcinoma to 73.3% in patients with testicular cancer. Cancer-related factors such as tumour stage have an important role in determining mortality risk in the longer term for survivors of ICU with cancer. In patients with colorectal cancer that had survived an ICU admission the risk of death after six-months was significantly higher in patients with Dukes D stage vs. Dukes A (HR 8.66).

The work presented in this thesis systematically reviews and summarises the current published outcomes of patients with solid tumours admitted to ICU, demonstrates that among the solid tumour population ICU admission is common and shows that short-term outcomes vary significantly by features associated with both the critical illness and the underlying tumour type. In patients that survive an ICU admission the presence, type and stage of cancer is important for determining on-going mortality risk. This information may be used when

clinicians are discussing potential outcomes following admission to critical care with cancer patients. Future studies should focus on the administration of treatments for cancer after critical illness and whether they differ from those received by those patients without an ICU admission. Prospective studies are required to describe the pre-ICU deteriorations in physiology in cancer patients with critical illness including those considered, but not admitted, to ICU. Outcomes for this latter group are unknown and given the high burden of illness severity documented in ICUs within the UK, these studies may identify a group of patients for whom critical care would be beneficial but is not currently provided.

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Grants

- Outcome of cancer patients with critical illness admitted to Intensive Care, £185,000. Cancer Research UK Population Research Committee Project Award. Co-applicant with Dr T Quasim, B Sloan, P McLoone, Dr B Laird, Prof J Kinsella and Dr D Morrison. June 2013.

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Presentations

Presented at the Scottish Intensive Care Society Annual Scientific Meeting, St Andrews, January 2013:

- Long-term outcome of ICU survivors with solid tumours.

- Outcome of patients with solid tumours admitted to Intensive Care with a medical diagnosis.

- Organ support and clinical outcomes for patients with solid tumours admitted to Intensive Care.

Presented at the National Cancer Intelligence Network, Brighton, May 2013:

- Outcome of cancer patients with critical illness requiring Intensive Care admission.

Presented at the European Society of Intensive Care Medicine, Paris, October 2013:

- Survival of lung cancer patients requiring ICU versus a matched non-ICU cohort.
- Outcome of patients with solid tumours admitted to Intensive Care with a medical diagnosis.

Presented at the Society of Critical Care Medicine, San Francisco, January 2014:

- Comparison of cancer and non-cancer patients admitted to ICU with a non-surgical diagnosis.
- Factors associated with ICU mortality among critically ill patients with colorectal cancer.
- Do trends in cancer patient ICU admissions reflect population trends in the incidence of cancer?
- Survival in solid cancer patients following Intensive Care: a systematic review and meta-analysis.

Preface

This work was initially undertaken on a part-time basis during a twelve-month attachment to the University department of Anaesthesia, Critical Care and Pain as a trainee. I have continued this work in my own time as a trainee and then subsequently following appointment to a substantive Consultant post.

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Author's declaration

I declare that this thesis is of my own composition, and that the research contained within it is entirely my own unless stated otherwise. No part of the work has been submitted for any other degree or professional qualification.

The systematic review and meta-analysis has been published in the journal *Intensive Care Medicine* 2014, and a summarised version of the chapter describing risk of ICU admission in cancer patients has been published in the journal *JAMA Oncology* 2015.

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List of abbreviations

ACP	Augmented Care Period
AKI	Acute kidney injury
APACHE	Acute physiology and chronic health evaluation
ARDS	Acute respiratory distress syndrome
ASA	American Society Anaesthesiologists
CCI	Charleson Comorbidity Index
CHI	Community Health Index
CI	Confidence Interval
CMM	Cancer Mortality Model
CNS	Central nervous system
CVS	Cardiovascular system
CPR	Cardio-pulmonary resuscitation
ECOG	Eastern Cooperative Oncology Group
ESRF	End stage renal failure
GCS	Glasgow coma scale
GI	Gastrointestinal
GIST	Gastro-intestinal stromal tumour

GU	Genitourinary
Gyn	Gynaecological
HDU	High dependency unit
HR	Hazard ratio
ICD-10	International Classification of Diseases 10th revision
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive care unit
IQR	Inter Quartile Range
ISD	Information Services Division (of NHS Scotland)
IMV	Invasive mechanical ventilation
LIS	Lung Injury Score
LOD	Logistic Organ Dysfunction score
MET	Medical Emergency Team
MI	Myocardial infarction
MICU	Medical Intensive Care Unit
MOS SF-20	Medical Outcome Studies Short Form-20
MPM	Mortality Prediction Model
NRS	National Records for Scotland
NSCLC	Non-small cell lung cancer

OR	Odds ratio
QoL	Quality of life
PICS	Post Intensive Care Syndrome
PH	Proportional hazards
PS	Performance Status
PTSD	Post-traumatic stress disorder
RSCL	Rotterdam Symptoms Check List
RR	Relative risk
RRT	Renal replacement therapy
SAPS	Simplified acute physiology score
SCLC	Small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results- Medicare Registry
SICS	Scottish Intensive Care Society
SICSAG	Scottish Intensive Care Society Audit Group
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
SMR01	Scottish Morbidity Record 01 (General/ Acute and Inpatient Day Case dataset)
SMR06	Scottish Morbidity Record 06 (Scottish Cancer Registry)

SOFA	Sequential Organ Failure Assessment
STROBE	Strengthening the reporting of observational studies in epidemiology guidelines
WoSCSU	West of Scotland Cancer Surveillance Unit

Chapter 1 Introduction

1.1 Intensive Care Medicine

To understand the role that Intensive Care has in the management of patients with cancer, it is relevant to describe what Intensive Care comprises and the clinical factors that are known to influence outcomes. Intensive care units (ICU) have unique systems for monitoring the physiological status of patients and delivering treatments that are not available in standard hospital wards. This specialised area of medicine deals with providing care to the sickest patients in the hospital and, as such, mortality rates in ICU are high. Longer-term outcomes are also affected by an ICU admission with deterioration in chronic disease states, worsening quality of life and elevated mortality risk persisting for several years after discharge from ICU. It is therefore important to identify factors that impact on both short and long-term outcome after patients are admitted to ICU. This will facilitate clinicians to have individualised discussion with patients regarding potential outcome after admission to ICU.

1.1.1 History of Intensive Care Medicine

ICU, also called critical care or intensive therapy units, are departments within a hospital that look after patients with life-threatening conditions who need constant, close monitoring and support from specialist equipment and medication. They have higher levels of staffing, specialist monitoring and treatment equipment only available in these areas and the staff are highly trained in caring for the most severely ill patients.

The need for intensive care arose after a polio epidemic struck Denmark in 1952, when 2722 patients were admitted to Blegdan Hospital in a six-month period. A large proportion of these patients suffered respiratory or airway muscle paralysis

resulting in respiratory failure, pooling of secretions and ultimately death if left untreated. At the time treatment had involved the use of negative pressure respirators, but these devices, while helpful, were limited to six within this hospital site. At times there were up to 70 patients in this institution requiring artificial ventilation and therefore alternative solutions were sought.

Dr Bjorn Ibsen, a Copenhagen anaesthetist, changed management by instituting protracted positive pressure ventilation by means of intubation of the trachea with a cuffed rubber tube and intermittent insufflation of the lungs via manual compression of a rubber bag. Due to the high demand for respiratory support during this time Dr Ibsen enlisted over 200 medical students to deliver this respiratory support by manually pumping oxygen and air into the patients lungs. This was performed on a dedicated ward with each patient allocated his or her own nurse. A total of 232 patients were treated in Copenhagen in this manner and mortality in this cohort decreased from over 87% to approximately 40% [1]. This experience heralded the widespread use of positive pressure ventilation for respiratory failure and is considered to be the origin of intensive care medicine [2].

In the decades that followed there was an expansion of intensive care across Europe and North America. Hospitals started to develop specially equipped areas with a higher proportion of staff and specialist equipment such as heart monitors, arterial blood gas analysers, and mechanical ventilators. Over time the specialty has expanded to include support of other forms of organ failure such as cardiovascular and renal failure. Today the ICU is the area within the hospital where the sickest patients are managed. Medical advances have meant that within the ICU setting it is now possible to temporarily support or replace the function of multiple failing organs. This supportive care is provided both to treat the underlying condition and allow time for the patient to recover.

Not all patients with critical illness require the same level of support and most hospitals with an ICU will also have a high dependency unit (HDU) to provide an intermediate level of care. To determine which patients should be best managed in each location the Department of Health produced recommendations entitled

"Comprehensive Critical Care" [3]. This report defined four different levels of care encompassing all patients in hospital.

The definitions of these levels of care are: [3]

> “Level 0: Patients whose needs can be met through normal ward care in an acute hospital
>
> Level 1: Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care, whose needs can be met on an acute ward with advice and support from the critical care team.
>
> Level 2: Patients requiring more detailed observation or intervention including support for a single failing organ system or post-operative care and those stepping down from higher levels of care.
>
> Level 3: Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure.”[3]

High dependency most commonly provides level 1 or 2 care whereas intensive care usually means level 2 or 3 care. In Scotland, the intensity of treatment is high with 66% of patients treated in ICU or a mixed ICU/ HDU in 2016 requiring level 3 treatment [4].

1.1.2 Critical illness, organ failure and organ support

Critical illness is an illness or injury that acutely impairs the function of one or more vital organ system. Severe infection, cardiac ischaemia, trauma, poisoning, surgical complications and burns can all cause critical illness although this list is not exhaustive. Patients with critical illness are admitted to ICU for monitoring of organ dysfunction, provision of organ support and treatment of the underlying

cause. For patients to recover from their critical illness the underlying disease process must be potentially reversible with treatment.

The management of a patient with critical illness will be individualised depending on the type and degree of organ dysfunction. However, there are principles of organ dysfunction and subsequent support that can be applied to all patients.

1.1.2.1 Respiratory system

The respiratory system involves gas exchange across alveolar membranes in the lungs. Respiratory failure occurs when there is a failure in gas exchange function either oxygenation or carbon dioxide elimination. Hypoxic respiratory failure (type I) is characterised by low arterial oxygen tension (PaO_2) with a normal or low arterial carbon dioxide tension ($PaCO_2$). This is the commonest cause of acute respiratory failure and is caused by intra-pulmonary pathology such as pneumonia, pulmonary oedema, and pulmonary haemorrhage. Hypercapnic respiratory failure (type II) occurs when $PaCO_2$ is elevated and is often associated with low PaO_2 that can usually be overcome with supplemental oxygen. The cause of type II respiratory failure includes reduced consciousness, drug overdose, neuromuscular disease, severe airway disorders and chest wall deformity.

Monitoring of respiratory function includes the use of pulse oximetry to provide continuous measurement of oxygenation and arterial blood gas analysis of PaO_2 and $PaCO_2$. Additional monitors are used in specific situations such as peak expiratory flow for asthma and vital capacity in neurological conditions.

Organ support can be provided with supplemental oxygen via nasal cannula or facemask. In more severe cases specialist equipment can be used to deliver high flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) in either a HDU or ICU environment. Invasive mechanical ventilation (IMV) involves the use of an endotracheal tube and requires ICU care.

There are many different modes of IMV but most provide delivery of a mechanically generated breath to facilitate oxygenation and carbon dioxide removal.

Mechanical ventilation can be a life-saving intervention in acute respiratory failure. However, mechanical ventilation itself can cause damage to the lungs and can worsen or provoke acute respiratory distress syndrome. It is now well established that lung protective ventilation with low tidal volumes reduces ventilator induced lung damage and this strategy is now accepted as a standard of care.[5] Since the widespread adoption of lung protective ventilatory strategies there has been a reduction in mortality due to ventilator-associated lung injury.[6]

In certain extreme circumstances IMV is insufficient to improve gas exchange and life-threatening hypoxia persists. Extra-corporeal membrane oxygenation (ECMO) involves circulating the patient's blood through an external circuit that performs the functions of oxygenation and carbon dioxide removal before returning the blood to the patient. ECMO is only available in a few specialist centres and requires patient transfer to the nearest facility.

1.1.2.2 Circulatory system

The circulatory system is responsible for maintaining the flow of blood through the body and comprises the heart, blood vessels and blood volume. Critical illness can affect each of these components individually or in combination resulting in inadequate tissue perfusion and shock. If shock persists the function of vital organs becomes impaired and can lead to multi-organ failure. Haemodynamic monitoring is therefore of vital importance in the patient with critical illness [7].

Monitoring of the circulatory system requires blood pressure measurement either by the use of a non-invasive blood pressure cuff or with placement of an intra-arterial catheter. Central venous catheters are frequently utilised in ICU to

allow measurement of central venous pressure (CVP) and central venous oxygen saturations in addition to providing a means for safe infusion of drugs. Cardiac output can be measured within the ICU setting by using dilutional techniques such as LiDCO and PiCCO, with oesophageal Doppler ultrasonography, or by insertion of a pulmonary artery catheter.

Circulatory support includes fluid replacement and the provision of vasoactive drugs. These include vasoconstrictor medications to increase vascular tone and inotropic medication to increase cardiac output. Mechanical support in the form of intra-aortic balloon pumps, ventricular assist devices and cardiac-ECMO are generally only provided in cardiac ICUs where specialist expertise is available. Haemodynamic optimisation with adequate pre-load and inotropic support in patients with critical illness has been reported to reduce mortality [8].

1.1.2.3 Renal system

Renal dysfunction is common amongst critically ill patients. This arises as a result of hypotension or shock, sepsis, rhabdomylolysis, or nephrotoxic drugs [9]. Renal replacement therapy (RRT) is the use of haemodialysis or haemofiltration to support the kidneys. This is often employed temporarily in the ICU whilst the patient recovers from the initial insult. RRT is so effective that renal failure, as the only organ failing, is seldom a cause of death in the critically ill patient [10]. However, most patients in ICU requiring RRT have multi-organ failure (MOF) with associated respiratory and circulatory failure [9]. The development of acute renal failure in a patient with MOF indicates that this initial insult was severe and therefore the risk of death is high [11].

1.1.2.4 Other supportive care interventions

In the past most patients in ICU received sedation whilst ventilated to improve synchronisation with mandatory modes of ventilation. However, sedation use is

associated with prolonged ventilator time and can leave patients vulnerable to delirium and critical illness weakness [12, 13]. With improvement in ventilator technology, sedative infusions are utilised less frequently and the majority of ICU patients are awake and thus able to have some form of communication with staff. This allows staff to monitor neurological function using Glasgow Coma Scale (GCS) and confusion assessment method for ICU (CAM-ICU) scoring systems.

During their ICU stay, patients with critical illness may require artificial nutrition either as a consequence of sedation, inability to swallow (due to endotracheal tube) or impaired gastrointestinal (GI) function. Where possible this is provided as enteral nutrition via nasogastric tubes, although parenteral nutrition is occasionally required when enteral nutrition is not tolerated [14]. Artificial nutrition is commenced within the first 72 hours of their ICU stay and continued until the patient is able to recommence adequate oral intake.

Blood glucose concentration is monitored during the critical illness as this is often elevated as a result of increased counter-regulatory hormones. Hyperglycaemia is avoided with the use of insulin infusions although target blood sugar ranges are higher than the normal physiological range [15].

1.1.3 ICU demographics

While many medical specialties deal with specific body systems or organs, intensive care medicine manages patients with a wide range of diseases.

Some hospitals have specialist ICUs that manage specific types of patients. These include paediatric intensive care (PICU), cardiac intensive care (CICU), neurological intensive care (Neuro ICU), and medical intensive care (MICU). Out-with the specialist setting, patients admitted to general ICUs usually reflect the hospital case-mix and require multidisciplinary input.

In 2009 Vincent et al described features of over 1200 ICUs across 75 countries that took part in the EPIC II study to document the point prevalence of

infections in ICU during a single day. The population comprised ICUs from Western Europe (53%), Central and South America (17%), Asia (11%), Eastern Europe (8%), North America (6%), Oceania (4%) and Africa (1%). They found that over 66% of ICUs admitted a general case-mix, the remainder being specialist units with 17% surgical, 11% medical and 7% a mixture of PICU, Neuro ICU and CICU [16]. Of over 13,000 ICU patients included in the study, 39% were admitted after emergency surgery, 23% were planned admissions after elective surgery, 10% were admitted following trauma and 28% were medical admissions. Within this group the mean age was 60.7 years with a male preponderance at 62.3%.

Internationally, there are wide variations in the number of ICU beds available. The UK has fewer ICU beds relative to acute hospital beds in comparison to other European countries. In Germany there are over 20 critical care beds per 100 000 population (5.1% of all inpatient beds) compared with the United Kingdom where there are 6.6 critical care beds per 100 000 population (2.8% of all inpatient beds) [17]. The difference is even more marked in comparison to the United States of America (USA), where critical care accounts for around 9% of all inpatient beds [18]. This leads to critical care beds in the UK admitting more severely ill patients who, on average, require higher levels of organ support than those in other countries. This is demonstrated in the study by Wunsch et al that described mechanical ventilation rates of 68% in UK ICUs compared with 28% in ICUs in the USA [18].

1.1.3.1 Scottish Intensive Care Society Audit Group

The Scottish Intensive Care Society Audit Group (SICSAG) collects data on all patients admitted to ICU within Scotland, which is then summarised in an annual report. From this information the activity and outcomes across ICUs in Scotland can be compared and changes with time noted. The number of patients admitted to ICU has steadily increased over the past 10 years with an expansion in critical care bed numbers both in terms of level 2 and level 3 capacity. In 2016 there were 10,870 patients admitted to general ICU with 56% of patients admitted to units in the West of Scotland [4]. This compares with 7,644 patients

admitted in 2005 [19]. Across Scotland in 2016 66% of patient admitted to ICU or combined ICU/HDU required level 3 care with 60% of patients receiving invasive ventilation, 50% of patients receiving cardiovascular support and 8% of patients receiving renal replacement therapy at some point during their ICU stay.

1.1.4 ICU scoring systems

Various attempts have been made to quantify severity of illness using scoring systems. These scores can allow comparisons or audit of different ICUs as well as an overall measure of health care standards. They can also be used as a method of bench-marking heterogeneous patient groups for research purposes, especially in non-randomised or observational studies [20].

Outcome in ICU depends not only on the level of care or medical input, but also the underlying pathology and pre-existing health of the patient. Advancing age, a greater severity of illness, co-morbidity, emergency surgery immediately before admission and the clinical condition necessitating admission all affect outcome and increase the risk of death. Scoring systems take account of these factors and the resulting score can be used to estimate outcome.

A variety of scoring systems exist, some being disease specific and others generic. The first generic physiological scoring system that quantified severity of illness by patient factors was the acute physiology and chronic health evaluation score (APACHE) [21]. Subsequently the simplified acute physiology score (SAPS) [22] and mortality prediction model (MPM) [23] were developed. Another approach is to assess the degree of organ dysfunction by attributing a score to each organ system based on physiological parameters. This is the basis of the sequential organ failure assessment (SOFA) score [24].

Examples of disease specific scoring systems include Glasgow coma scare (GCS) for assessment of consciousness in patients with head injury [25], Ranson's criteria for mortality prediction in acute pancreatitis [26], and Child-Pugh score in patients with chronic liver disease [27].

Scoring systems can give an estimate of mortality for a group of ICU patients but are not designed to predict individual patient mortality. Instead they are increasingly being used to compare the quality of care provided by different ICUs and hospitals. By providing mortality rates adjusted for severity of illness and case-mix ICUs can be benchmarked against similar institutions and their own performance over time can be monitored.

1.1.4.1 Acute Physiology and Chronic Health Evaluation score

The APACHE II score is the most widely used scoring system within UK ICUs. The original APACHE score was first used in 1981 [21] but was superseded in 1985 [28] by APACHE II which was a simpler version. It combines scores based on age, co-morbidities and physiological parameters during the first 24 hours of ICU admission with a weighting on the acute physiology. It controls for case-mix and emergency/ non-operative admissions. APACHE II is measured during the first 24 hours of ICU admission. Predicted hospital mortality can then be derived from this score and represents the proportion of patients that would be expected to die within a group of patients with the same severity of illness. The maximum APACHE II score is 71 with a score of 25 representing a 50% predicted mortality in non-operative patients and a score of greater than 35 representing a predicated mortality of 80% in all patient groups.

APACHE II has only been validated for use within the ICU setting and is not validated for certain disease states such as patients undergoing coronary artery bypass grafting or patients with burns. It cannot be used as a tool on which to base admission decisions due to the requirement of data collected from the 24 hours after ICU admission.

1.1.4.2 Simplified acute physiology score

The SAPS II [22] calculates a score based on 12 physiological variables, age, type of admission and 3 variables related to underlying disease. Like APACHE the score is obtained from the worst values obtained during the initial 24 hours of admission to ICU. The score can then be converted into a predicted mortality that is represented as a percentage of patients within a similar population expected to die.

1.1.4.3 Mortality prediction model

The MPM II [23] (the second version of MPM) utilises commonly used variables such as physiology, chronic health status, and acute diagnosis to calculate a probability of in-hospital death. It can be calculated at the time of presentation and therefore has the theoretical advantage that it could be used as an ICU admission decision tool. However, it requires a complex mathematical calculation involving 16 variables thus making it cumbersome to calculate at the bedside and while the MPM system performs well at cohort level it cannot accurately predict the outcome for an individual. As such it is not routinely used for informing admission decisions.

1.1.4.4 Sequential organ failure assessment

The SOFA score [24] was initially used to describe the degree of organ dysfunction associated with sepsis but has since been validated to describe the degree of organ dysfunction in patient groups with organ dysfunctions not due to sepsis [29]. Six organ systems—respiratory, cardiovascular, central nervous systems, renal, coagulation, and liver are assigned a point based on physiological parameters and summed to give a total score of between 0 and 24. This score is calculated 24 hours after admission to ICU and repeated every 48 hours to give

sequential scores. Both the mean and highest SOFA scores are predictors of outcome.

1.1.5 Determinants of survival in ICU patients

Survival following critical illness will depend on a number of patient specific and critical illness factors. Organ dysfunction has been noted to impact upon survival with increased risk of death in patients with specific organ failure [30] and in those with increasing number of organ failures [31]. An early paper describing outcomes relating to organ failure was published by Knaus et al [32] in 1985. They described hospital mortality rates by the number of failing organs with 40% for single organ failure, 60% for two-organ failure and 98% for three-organ failure that persisted for three days. While this data is now historical in terms of current ICU practices and expected outcomes, it does demonstrate the impact that disease severity and associated number of organ failures has on mortality.

Central nervous system failure encompasses a wide variety of presentations and has a strong impact upon survival. Subtle changes in cognition can be a sign of delirium and this has been demonstrated to have an impact on mortality following ICU, with hazard ratio for death of 3.2 [33]. The study by Mayr et al found relative risk of ICU mortality 16 times greater and hospital mortality five-times greater in patients suffering CNS failure. The same study reported nearly a 12-fold increase in ICU mortality and four-fold increase in hospital mortality for cardiovascular failure. Renal failure has also been demonstrated to be associated with poorer survival and patients that receive renal replacement therapy have a four-fold increase in hospital mortality [34].

Outcomes following respiratory failure are linked to the underlying cause in addition to complications encountered during mechanical ventilation rather than the presence of respiratory failure itself [35]. The causes of respiratory failure are widespread and can be either due to direct pulmonary injury (such as pneumonia or COPD) or indirect in the case of Acute Respiratory Distress Syndrome (ARDS) secondary to many systemic processes (such as burns,

pancreatitis or sepsis). Higher hospital mortality is seen in patients with ARDS compared with other causes of respiratory failure (OR 1.44) [35].

Admission to ICU following an operative procedure is associated with a more favourable outcome than medical admissions. Hospital mortality is significantly lower for the post-operative group for all APACHE II scores up to a value of 30, such that APACHE mortality prediction takes account of this fact [28]. By dividing patients into operative and non-operative admissions, the study by Rowan et al demonstrated a mortality of nearly twice that in the non-operative ICU population at 37.6% compared with 19.1% in the post-operative ICU population [36]. Furthermore, there were significant differences between those undergoing elective surgery compared with emergency surgery with the latter having a hospital mortality nearly three-times higher (10.2 vs. 29.8%).

Pre-existing factors will also impact upon outcomes in critical illness. Patient's age has been demonstrated to have an association with hospital mortality increasing by 3-4% with each additional year [37, 38]. Co-morbidity influences survival following critical illness with higher mortality seen in patients with any significant comorbidity compared to those without [36]. This was most marked for patients with hepatic disease where hospital mortality was more than double that for patients without hepatic disease. Prior cardiopulmonary resuscitation (CPR) also had a negative impact upon outcome with over twice the hospital mortality seen in the population that did not require CPR.

Severity of illness scores take account of many of these factors and are consistently demonstrated to be related to short-term outcome in patients admitted to ICU [35-39].

1.1.6 Short term survival after critical illness

In 2016 over 80% of patients admitted to ICU in Scotland survived to hospital discharge [4]. This had been steadily improving but appears to have reached a plateau over the last 4 years. Most deaths occur within ICU with an approximate

ICU mortality of 14%. Standardised Mortality Ratio (SMR) is where the actual mortality is compared with the expected mortality calculated by APACHE II. Using a recently recalibrated APACHE II methodology, SMR for ICUs in Scotland was 0.9 in 2016. This would suggest that more patients are surviving ICU than would be expected from their adjusted APACHE II scores.

The mortality rates due to infections and sepsis have decreased with the introduction of better antimicrobial agents and improved supportive care [40]. Large international research collaborations such as the "Surviving sepsis campaign" have played an important role in these improvements [41]. Interventions aimed at improving quality of care, such as standardisation of ICU processes and optimisation of organisational structures have also been reflected in improved outcome of intensive care patients [42]. Furthermore, establishment of multidisciplinary care teams has contributed to lowering of ICU mortality [43]. Collectively, these advances have improved the management of critically ill patients and resulted in increased survival.

1.1.7 Recovery after ICU and longer term survival

ICU survivors have an excessive risk of mortality that may take up to 15 years to return to the population baseline [44]. This increased mortality is most pronounced in older patients and those with severe co-morbidity. The duration of ICU delirium has also been associated with an increased one-year mortality [33].

Post intensive care unit syndrome (PICS) is the experience in an ICU survivor of impairment in cognition, mental health, or physical functions following discharge from ICU [45]. Post ICU cognitive impairment is common and in patients who suffer ICU delirium up to 71% will have continued cognitive impairment at one year [46]. Many ICU survivors will experience post-traumatic stress disorder as a result of traumatic or delusional ICU memories. A systematic review by Davydow et al. assessed the prevalence of PTSD and anxiety in ARDS survivors. They found

that the median prevalence was 28% (range 23 – 35%) and 24% (range 23 - 48%) respectively [47].

Critical illness has a significant impact on physical function both in the short and longer term. A recent UK study by Griffiths et al found that at one-year post discharge 22% of patients required assistance with activities of daily living, 54% had mobility problems and 70% experienced moderated to severe pain [48]. Patients with acute respiratory distress syndrome have been shown to have persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness [49]. In ICU survivors who have experienced critical illness polyneuropathy, 84% to 95% will have continued neuromuscular dysfunction 5 years after discharge [50, 51].

PICS can have a significant impact on day-to-day living for those patients that survive ICU. For example, of those that were in employment prior to their ICU admission, only half have returned to work at one-year post ICU discharge [52]

Quality of life (QoL) is an increasingly important measure of health-related outcomes. A large number of investigations have demonstrated reduced QoL measures following a critical illness that requires ICU admission. A systematic review of the literature pertaining to QoL in ICU survivors described reduction in QoL measures following ICU [53]. However, they also noted that ICU patients have reduced QoL at baseline (i.e. prior to ICU admission) when compared to the general population. While QoL measures fell after ICU they improved to baseline levels by 12 months post ICU discharge. However, only one study in the systematic review followed patients for the full 12-months. A more recent study by Cuthbertson et al followed patients for up to five years post ICU discharge [54]. This study described the same improvement in QoL in the first year, however, noted a subsequent deterioration in the physical components of QoL measures between 2.5 and 5 years.

1.2 Cancer

Having described the role of the ICU in general, it is germane to define cancer and recent trends in outcomes before considering what is known about the two together.

1.2.1 Definition of cancer

Cancer is the term given to a collection of diseases where the body's cells divide without stopping, ultimately spreading into surrounding and occasionally distant tissues. Cancer cells differ from normal cells in ways that allow them to grow out of control. This arises from genetic changes within the cancer cells that may have been inherited or due to damage to DNA caused by environmental exposure to carcinogens such as smoke, radiation or ultraviolet rays.

There are more than 100 different types of cancer. Typically, cancer is named after the organ where the cancer originated (for example, lung cancer when the original cancerous cells started in the lung). However, cancers may also be described by the type of cell that formed them. Carcinomas are the commonest type of cancer and originate from the epithelial cells that cover the surfaces of the body. Subtypes of carcinoma include adenocarcinoma (epithelial cells that produce fluids or mucous such as breast, colon and prostate), squamous cell carcinoma (epithelial cells that lie just beneath the surface of the skin or organ such as stomach, lungs and intestines), basal cell carcinoma (originating in the epidermis of the skin) and transitional cell carcinoma (within the transitional epithelium of the urinary tract). Sarcomas are cancers that form within bone and soft tissues (including muscle, connective tissue and vessels). Osteosarcoma is the most common type of sarcoma and this can be subdivided further based on histological findings. Other solid tumour forming cancers include melanoma (cancer originating from melanocytes), germ cell tumours (cancer originating from cells that differentiate into sperm or eggs), and neuroendocrine tumours (cancer originating from cells that release hormones in response to CNS activation). Leukaemia, lymphoma and multiple myeloma are all cancers of

blood-forming and immune tissue and are regarded as types of haematological malignancies.

1.2.2 Trends in cancer incidence and survival

Over the last 10 years the number of cancers diagnosed in Scotland has increased from 27,095 cases in 2003 to 31,013 in 2013 [55]. Approximately 2 in 5 people in Scotland will receive a diagnosis of cancer during their lifetime. The risk of cancer increases significantly with age and rates are increasing as more people live to an old age [56]. Prostate, lung and colorectal cancers account for 52% of cancers in men, where breast, lung and colorectal cancers account for 56% of cancer in women. While cancer rates are falling for males, there is an increasing trend for females and this is due to a combination of factors across different cancer types. Incidence of breast cancer has increased following improved attendance at the National Screening Programme. Increasing incidence rates for lung cancer in women are likely due to historic trends in smoking prevalence. Changes in factors associated with childbearing such as family size, maternal age at the birth of her first child and increases in levels of obesity may impact upon incidence rates of breast and uterine cancer, both of which are increasing.

The prevalence is increasing as more people are living long enough to develop cancer and the survival following diagnosis improves. It is anticipated that, within the UK, the prevalence of cancer will increase over the next three decades by approximately one million cases per decade [57]. The majority of these patients are expected to be living with a cancer diagnosis made more than five years previously and may be considered to have “survived” their cancer.

Survival following a diagnosis of cancer has been improving over the last 40 years [58]. However, survival rates vary significantly between tumour types, geographical areas, socioeconomic groups, age groups and ethnic backgrounds. Social deprivation is associated with poorer outcomes for all solid tumours and

this change has been consistent in spite of the overall trends in improved survival.

Reasons for the improvement in life expectancy can be attributed to better prevention efforts, improved screening programmes, and treatment that is more aggressive and specific. Cancer care has been leading the way in personalised medicine and has been the forerunner for genomics guided precision medicine [59]. Gene sequencing can be used to better predict prognosis and response to different treatments thus allowing the clinician to match the patient to the most effective drug. In addition to advances in genomics there have been recent successes in anti-cancer immunotherapy such as the use of monoclonal antibodies to bind to cancer antigens [60]. With an increasing number of anti-cancer treatment options and new combinations in modalities, there is the potential for a functional cure for many malignancies. These changes are transforming cancer into a chronic but treatable disease.

1.2.3 Determinants of survival in cancer patients

Multiple factors impact upon survival of patients with cancer. Tumour type is important, with significant variation in one-year survival reported for lung cancer (29.7%) when compared with breast cancer (94.2%) [61]. International variation exists such that outcomes vary for the same tumour type depending on the country of diagnosis. For example, one-year survival following colorectal cancer is 74.7% in England, Northern Ireland and Wales compared with 84.9% in Australia, 83.5% in Canada, 83.8% in Sweden, 82.4% in Norway and 77.7% in Denmark [61].

One of the strongest influences on outcomes is cancer stage at presentation. Cancer staging varies by cancer type but generally takes into account the degree of local invasion, lymph node involvement and distant spread with poorer survival associated with more aggressive disease. Stage one generally means that a cancer is relatively small and contained within its originating organ. Stage two most commonly refers to a larger tumour but may also include local lymph node

spread. Stage three may indicate some local spread or lymph node involvement. Stage four indicates that the cancer has spread to another part of the body i.e. it has metastasised. Table 1-1 describes the one-year net survival for common tumour types at different stages at presentation [62]. Across all cancer types, one-year survival can be seen to decrease with increasing cancer stage.

Site	Sex	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)	Unknown stage (%)
Bladder	Men	95	71	67	35	59
	Women	91	63	56	27	45
Breast	Women	100	99	95	63	85
Colorectal	Men	98	93	89	44	57
	Women	98	91	85	35	50
Kidney	Men	96	89	95	38	73
	Women	94	91	89	34	68
Lung	Men	81	66	42	15	23
	Women	85	69	46	19	28
Melanoma	Men	101	97	92	47	91
	Women	101	98	96	54	95
Ovary	Women	99	94	71	51	46
Prostate	Men	101	101	100	85	88
Uterus	Women	99	94	83	45	53

Table 1-1 Age standardised one-year net survival for common cancers. Adapted from Office for National Statistics, Cancer Survival by stage at diagnosis Statistical bulletin [62]. Note: survival estimates take into account the normal rates of death in the general population and net survival is a measure of the extra deaths caused by the specific cancer.

Studies have shown poorer survival among cancer patients with co-morbidity, with hazard ratios ranging from 1.1 to 5.8 [63]. This may be due to the impact of co-morbidity on the cancer cells themselves or due to limitations to treatment choices. Performance status is an attempt to quantify cancer patients' general well-being and ability to perform activities of daily living. This measure was developed to determine treatment options (particularly chemotherapy) but has been shown to be an independent predictor of survival [64-67]. The most commonly used assessment of performance status is the Eastern Cooperative Oncology Group (ECOG) score (Table 1-2) [68]. A score of three correlates with a prognosis of less than three months and a score of four with a prognosis of less than one month [67].

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

Table 1-2 ECOG Performance status with credit to the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Poor socioeconomic status is associated with poorer survival in patients with cancer, with a review by Kogevinas and Porta reporting relative risks varying between 1 and 1.5 depending on cancer type. The largest differences were noted in patients with breast, uterine, bladder and colorectal cancers [69].

Within the UK, patients with breast cancer belonging to the least deprived scocioeconomic group will survive, on average, one year longer than those from the most deprived group [70]. This might be explained by factors related to the cancer (such as more advanced disease at presentation), the patient (such as increased co-morbidity) or the cancer treatment (patients may have limited access to healthcare, be less able to advocate for themselves and are less likely to interact with screening programs).

The treatment delivered and its intent will have an impact on survival times. Treatment combinations are tailored to the individual patient based on tumour type and stage, patient performance status and co-morbidities, and more recently based on the genomic profile of the patient and the tumour. Successful treatments given with the intention of cure will have the most favourable survival times. However, chemotherapy and radiotherapy may still have a role in extending life where cure is not possible.

A systemic inflammatory response, as measured by elevated C-reactive protein, has been associated with reduced survival [71] and has led to the development of prognostic scores encompassing C-reactive protein and albumin measurement [72]. Activation of the systemic inflammatory response has a detrimental impact on the outcome of patients with cancer although it is unclear whether it is due to the cancer activating the response or a different pathology. This is of particular interest in patients with critical illness where the systemic inflammatory response is often excessive.

1.3 Solid tumour patients in ICU

Having set out the role of ICU, and then trends in cancer occurrence and outcomes, this section considers what is known about their co-existence.

1.3.1 Critical illness in patients with malignancy

Cancer patients may require critical care due to a manifestation of their malignancy or a complication of their treatment, although there are times when the malignancy is not diagnosed until after ICU admission. Examples of oncologic emergencies that may require ICU treatment include malignant pericardial effusion, tumour lysis syndrome, hypercalcaemia of malignancy, or superior vena cava syndrome [73]. Patients with malignancy (particularly gastrointestinal, breast and lung cancers) have an increased risk of thromboembolic events. This risk increases with tumour stage and treatment with chemotherapy [74]. Pulmonary embolism may therefore precipitate ICU admission in patients with cancer. In patients with pelvic malignancy urinary obstruction can lead to renal failure, which may require ICU for temporary renal replacement therapy. While neurological presentations such as confusion, coma or seizures are uncommon, the resulting airway compromise means that ICU may be necessary to provide airway protection. All of these conditions may occur at any time to the patient with cancer and in some cases will be the first presentation of the disease.

The most common drug-related cause of critical illness in cancer patients is sepsis following chemotherapy-induced immunocompromise. This may lead to respiratory failure, circulatory instability, acute renal failure or multi-organ failure with subsequent need for ICU care. Chemotherapy agents can also precipitate anaphylaxis, [75] nephrotoxicity, [76] myocardial infarction [77] or cytokine release syndrome [78] any of which may necessitate ICU admission.

Those cancer patients that undergo surgical intervention are at risk of critical illness in the peri-operative period. This may be due to surgical complications, haemorrhage, or adverse drug reactions. Furthermore, some patients will require routine post-operative monitoring and support in an ICU if the operation has been extensive or the patient has any high-risk co-morbidities.

Rarely, ICU admission is considered for patients with advanced cancer and no curative treatment options. Given the lack of subsequent cure an aggressive ICU approach should not be recommended for this patient group, however, short-

term ICU admission may be appropriate for the management of reversible conditions, such as cardiac tamponade or seizures.

1.3.2 Historical attitudes to cancer patients in ICU

Due to the unpleasant and invasive nature of ICU care it has been reserved for patients for whom there is a likely benefit and where cure can be achieved. In the past, patients with cancer were considered poor candidates for ICU admission due to their underlying disease. Initial studies of cancer patients in ICU described a hospital mortality of 63 - 91% [79-81]. This resulted in reluctance among ICU physicians to admit, with cancer being the second most common cause cited for ICU refusal [82]. Furthermore, recommendations by a task force of the American College of Critical Care Medicine in 1999 suggested that patients with haematological or metastatic solid tumours should be considered poor candidates for ICU admission [83].

As the outcomes for cancer improve it is no longer considered to be the terminal disease it once was. As more treatment options become available there is an increasing demand for these patients to be considered candidates for ICU care. Azoulay et al reported a 30-day mortality in mechanically ventilated cancer patients of 60.9% in those admitted between 1996 and 1998, a significant improvement when compared to a death rate of 81.8% in a historical cohort admitted from 1990 to 1995 [84]. More recently studies that report mortality in critically ill cancer patients have shown promising results with hospital mortality rates less than 50% in a study of cancer patients with respiratory failure [85] and as low as 30% in a large study of all ICU cancer admissions [86].

In 2009, a study by Taccone et al compared survival of solid tumour cancer patients with that of a non-cancer population. They found that ICU and hospital mortality was similar in both groups (20% vs. 18%, and 27% vs. 23%) [87]. In general, the current literature shows a steady trend towards improved outcomes in patients with solid cancers admitted to the ICU. This evidence would suggest

that outcomes for critically ill cancer patients receiving ICU treatment are such that these patients should not be automatically excluded from ICU admission.

1.3.3 Scoring systems and prognostication for cancer patients in ICU

Estimates of prognosis and the appropriateness of ICU admission is a very challenging task but there are several validated measures that have been developed and widely used. Several professional societies provide guidelines for the admission of patients to the ICU. However, those guidelines contain little concrete advice for cancer patients. Reliable, specific evidence-based recommendations for the admission of cancer patients are currently lacking. Many investigators have assessed the predictive value of different criteria for the selection of cancer patients for critical care treatment. While disease severity scores such as APACHE II, SAPS II, or SOFA can be used to give a guide to short term prognosis they are not accurate enough to be used for informing the decision to admit individual cancer patients to the ICU [88, 89].

The ICU Cancer Mortality Model (CMM) was developed by Groeger et al to specifically predict outcome in critically ill cancer patients with initial promising results [90]. Soares et al. conducted a large study to externally validate the CMM along with assessing performance of other general scoring systems including APACHE, SAPS, and MPM [88]. While the CMM performed well, external validation did not find it to be superior to the general ICU scores. Of interest, this study found that the general scores tended to underestimate mortality while in contrast the CMM tended to overestimate mortality.

Currently, there is no single scoring system that can be recommended for evaluating the eligibility of cancer patients for ICU admission. The inconsistent results regarding the prognostic value of many clinical parameters are likely a consequence of the considerable heterogeneity of the cancer patient population. Identifying those cancer patients who are likely to benefit from ICU remains challenging. A study by Thiery et al. found that physicians' judgement in

this situation is an unreliable predictor of outcome for critically ill cancer patients [91]. Of the patients that were considered too sick for ICU admission according to the judgment of the Intensivist, 26% were still alive after 30 days and 16.7% at 180 days. Conversely, of the patients that were judged to be too well for ICU admission 21.3% died within 30 days. This would suggest that clinicians are unreliable at predicting outcomes in this group of patients.

The evolution of organ dysfunction in response to aggressive treatment may be a more reliable predictor of outcome than clinician judgement or static parameters or scores. Rather than basing the decision to provide intensive care therapy on static parameters that can be assessed at the time of admission, the choice to continue full organ support should be based on the trajectory of the patient's condition. In a study by Lecuyer et al. any cancer patient with an unclear benefit from ICU admission was admitted for full treatment with reassessment of the patient's condition at pre-specified intervals [92]. From this study they were able to demonstrate that patients with new organ failure after day three or deteriorating organ dysfunction scores were unlikely to survive. Based on these findings the authors recommend that this 'ICU trial' strategy should be applied to any critically ill cancer patient with any potential to benefit from ICU care with early assessment of response. A recent simulation study comparing time-limited ICU care to time-unlimited aggressive care found that in patients with solid tumours a trial duration of up to four days offered mean survival that was not significantly different from time-unlimited care [93].

1.3.4 Short term survival of solid tumour patients in ICU

Currently, patients with malignancies account for approximately 13 to 21.5% of all ICU patients [86, 87]. The reported mortality rates for cancer patients treated in the ICU vary widely. These variations are partly the result of international differences in ICU admission policies and also due to dissimilarities in types of tumour and reasons for admission. Patients with solid tumours are often admitted to critical care after definitive treatment of the malignancy and at times for routine post-operative care. These patients generally have a good

prognosis and low hospital mortality, recently reported as 4.7% in those patients after elective surgery [94]. Emergency surgical admissions to ICU have a worse severity of illness score and in the same series were found to have a higher hospital mortality of 17.4% [95]. Furthermore, patients admitted with a medical diagnosis had the highest severity of illness scores and a hospital mortality of 44.6%. Similar results have been reported in a study by Soares et al. that described hospital mortality rates of 11% for elective surgical patients, 37% for emergency surgical patients and 58% for medical patients [86]. Variations in case mix between individual studies will therefore have significant impact on reported outcomes and should be interpreted accordingly.

Due to improvements in critical care, several prognostic factors that have previously been important predictors of poor outcome have become less relevant. For instance, neutropenia has been a major negative prognostic factor but with increasing availability of better antimicrobial agents and granulocyte colony stimulating factor (G-CSF), the significance of neutropenia for the prognosis of cancer patients has decreased [96-98]. Sepsis, however, has continued to be associated with an increased mortality in spite of the improvements of supportive care [97, 99, 100].

Negative predictive factors, which have remained relevant over time are age, performance status, need for mechanical ventilation and multi-organ failure. Despite advances in intensive care management, age and poor performance status have maintained their negative prognostic value with poor performance status associated with increased hospital mortality between two- and six-fold [86, 99, 101, 102]. Organ failure has a significant impact upon short-term outcomes. Mechanical ventilation increases mortality by approximately six-fold [103, 104] and acute renal failure is predictive of poor outcome especially if dialysis is required [105, 106]. Vasopressor requirement has also been found to confer a negative prognosis in the short term [100, 103, 107]. Increasing number of organ failures is associated with a corresponding decrease in survival. Taken together, the data demonstrate that severity of disease is the major determinant of outcome in critically ill cancer patients. Individually, these factors can identify patients with a worse prognosis but by themselves are insufficient to determine the appropriateness of ICU admission.

While underlying tumour type has not been demonstrated to be associated with short-term outcomes [86], the stage of the cancer may be important. Studies by Mendoza et al. and Fisher et al. have both demonstrated that in patients with solid tumours, metastatic disease was independently associated with hospital mortality [107, 108]. This has also been demonstrated in patients with head and neck cancer [102]. Furthermore, recurrence or progression of cancer status was associated with hospital mortality in a study by Soares et al. [109] looking at cancer patients on ventilatory support. However, the results are not all consistent across all published studies. Tumour stage was found to be unrelated to short term outcome by studies by Taccone [87], Christodoulou [101] and Maccariello [105].

This initial review of the literature suggested that there were large variations in reported outcomes among ostensibly similar patient groups. It was therefore felt that a systematic review was indicated to comprehensively identify all relevant literature and to identify, if possible, the underlying explanations for variations in outcomes between studies.

1.3.5 Longer term outcomes in solid tumour patients after ICU

Since the majority of studies to date have assessed short-term survival, less is known about the longer-term outcomes of cancer patients with critical illness. In 2000 Staudinger et al. published a study that compared one year mortality of ICU cancer patients with a group of ICU patients without cancer and a group of cancer patients that did not require ICU [110]. The ICU cancer group had a mortality rate of 78%. This compared to 37% in the ICU group without cancer and 44% in the cancer group who were not admitted to ICU. While there are clear differences between the groups, this study is on a historical cohort and both ICU and oncological therapies have developed significantly in the intervening years. Whether this degree of difference still exists between groups is unknown.

More recently, a European study described a cohort of ICU cancer patients with a one-year mortality of only 36% [111]. However, this group consisted of a large

proportion of elective surgery patients and had a very low ICU and hospital mortality at 5% and 13% respectively. This may not represent longer-term outcome for the standard UK ICU patient. A recent UK study found that 6 month mortality in ICU patients with solid tumours was 47.8% [112]. This study was performed in a group of patients admitted to an oncological ICU where admission patterns may vary from that seen in general ICUs. Longer term survival has been demonstrated to be particularly poor in those patients with metastatic disease, with a one year mortality of 88% and two year mortality of 97.6% [113].

Long-term quality of life is an important concern in cancer patients that survive ICU treatment. Oeyen et al. report that quality of life measures in patients with solid tumours decrease significantly after an ICU admission and remain below baseline at one year [111]. Intensive care treatment of cancer patients is therefore associated with a reduced quality of life in survivors.

1.3.6 The future of critical care for cancer patients

While there is an established volume of literature pertaining to outcomes in critical illness, there remains a paucity of information pertaining to the group of patients with an underlying malignancy. Although many problems that are encountered in critically ill cancer patients also apply to patients without cancer, this patient population has specific characteristics and needs. The rising number of patients with malignancies and the resulting increase in cancer patients for whom intensive care is required has led to a growing recognition of the need for evidence-based recommendations for the management of critically ill oncology patients.

In the face of major advances in both critical care and oncology, cancer critical care is likely to continue to develop. Innovations in oncology will result in therapeutic options for a greater number of patients but this is likely to come at the cost of a greater burden of critical illness. While the literature to date suggests that outcomes for cancer patients in ICU are improving, it falls short of providing evidence to guide ICU admission policies. Further detail of which

cancer patients are admitted to ICU and how survival varies by underlying clinical features is needed to allow clinicians to prognosticate with critically ill cancer patients about the likelihood of a good outcome following ICU admission.

1.4 Summary of aims and research questions

Cancers are common among ICU patients but the literature identified in a conventional review suggests that a systematic appraisal is needed to better understand large variations in reported outcomes. With this work I aim to provide a better understanding of the specifics of ICU care for cancer patients and how the survival following critical illness is different in ICU patients with cancer from those without. Furthermore, in addition to short-term outcome I will also describe longer-term survival.

I aim to address the following research questions:

1.4.1 What is already known about short and long-term outcomes for patients with solid tumours admitted to ICU?

To inform data analysis it is first important to understand what is already published on this topic. I will perform a systematic review of the literature pertaining to survival of cancer patients after ICU admission.

1.4.2 What proportions of cancer patients are admitted to ICU and what are the features associated with admission?

To gain a better understanding of the risk of critical illness in cancer patients it is first necessary to establish the baseline rate of ICU admission among cancer patients and to then describe how it varies by patient and cancer specific features. For each cancer type it is important to document the likelihood of ICU admission, as this will be influenced by underlying pathology and treatment regimes. Due to these differences it is possible that mortality rates will vary by cancer type and it is imperative to describe not just overall mortality for ICU cancer patients but also mortality for each tumour type.

1.4.3 What proportions of patients admitted to ICU have a diagnosis of cancer and how do they differ from the non-cancer ICU population?

There is a limited understanding of the clinical indications for ICU admission among patients with cancer and how they are managed during their ICU stay. It is therefore of value to describe the proportion of cancer patients within the ICU population and how they differ from the non-cancer population in terms of reason for admission, severity of illness, organ support and mortality.

1.4.4 What are the longer-term outcomes of cancer patients who have survived an ICU admission?

ICU and hospital survival are inadequate end-points for most patients who are looking for a more meaningful period of survival. It is understood that ICU survivors have a higher mortality rate than the general population for several years following ICU discharge. It has not yet been demonstrated how this increased mortality risk interacts with a co-morbidity such as cancer. It would be

of significant value to understand how long term mortality differs between ICU survivors with and without cancer and which factors are associated with changes to mortality risk.

1.5 Key points

- The ICU is the area within the hospital where the sickest patients are managed. Within this setting it is possible to temporarily support or replace the function of multiple failing organs while the patient recovers from critical illness.

- Mortality is high after admission to ICU, with recent figures for Scotland reporting a hospital mortality of 20%. This is largely determined by the severity of critical illness.

- Morbidity following ICU is common and ICU survivors have an excessive risk of mortality that takes years to return to the population baseline.

- Cancer patients may require ICU care due to a manifestation of their malignancy or a complication of their treatment and approximately 13 – 21.5% of ICU patients have an underlying malignancy.

- Historically, cancer patients were not considered good candidates for ICU admission. However, with recent improvements in ICU and hospital mortality for cancer patients this general rule no longer holds true.

- In spite of the significant proportion of cancer patients within ICU little is known about which factors are associated with admission and subsequent clinical progress.

Chapter 2 Survival in solid cancer patients following intensive care unit admission: a systematic review and meta-analysis

2.1 Introduction

While there have been a number of reports on outcomes of cancer patients after admission to ICU, the large variations in reported outcomes suggest that there may be significant differences in the case-mix or care provided. There has been no attempt to systematically review the literature on outcomes of cancer patients after ICU admission. The aim of this chapter was to assess mortality among cancer patients admitted to ICU by carrying out a systematic review of published studies.

2.2 Methods

A systematic review attempts to identify, appraise and synthesise all the evidence that meets pre-specified eligibility criteria to answer a given research question. This requires an explicit and reproducible protocol to locate and evaluate the available data. By providing a summary of all the available studies addressing a specific clinical question, systematic reviews take into account all relevant findings from research on a particular topic and not just the results of one or two studies known to the author. As a result they can be used to establish whether findings are consistent and generalisable across populations and settings or whether they vary by particular subgroups. As the methods used in systematic reviews are explicit, any potential bias should be clear to those appraising the review.

Prior to performing the systematic review I consulted the Cochrane Handbook for Systematic Reviews of Interventions [114]. This identified the need for a well-framed question specifying the population, intervention and outcomes to be studied, in addition to ensuring definition of eligibility criteria. It emphasised the need for a robust search strategy to ensure identification of all possible data and methods of data collection, in addition to advice of data analysis and assessment of the risk of bias.

A meta-analysis involves the combination of results of individual studies to produce an overall statistic with the aim of providing a more precise estimate of an effect. Advantages of a meta-analysis include an increase in power, an improvement in precision and the ability to analyse data not fully interpreted by the individual studies. However, they can be misleading where studies are included with significant biases or where there is variation across studies. Heterogeneity across the studies should therefore be reported when performing a meta-analysis.

2.2.1 Study question

Among patients with a solid tumour (population) that are admitted to ICU (intervention) what are the subsequent survival rates (outcomes)?

2.2.2 Study identification and eligibility criteria

Studies were included if they reported survival outcomes in patients with known solid tumours who had been admitted to intensive care. Studies that reported outcomes for a mixed group of solid and haematological malignancies were excluded, as survival in haematological cancers has been associated with consistently poorer ICU survival.

2.2.3 Search strategy

OVID MEDLINE and EMBASE to April 2014 were searched using a combination of medical subject headings (MeSH), title and abstract keywords. The MeSH terms "neoplasm" and "critical care"/ "intensive care"/ "intensive care units"/ "critical illness" were exploded and articles containing both terms were combined. We then searched for the terms "death", "mortality", "surviv$", "prognos$", "hospital$" or "outcome". Articles that featured in both searches were then limited to human studies published in English. Paediatric studies and review articles were excluded from the search.

2.2.4 Study selection and data extraction

From the initial search results, a title review was performed by two separate reviewers as per Cochrane recommendations [114]. At this stage editorials, letters or case reports were excluded. Studies were required to report survival outcomes in patients with solid tumours who were admitted to ICU. Where only one reviewer felt that the title might represent an article of interest the abstract was sought. The abstracts were then scrutinised by both reviewers to ascertain whether the article was of significance for this study. The full texts of all relevant articles were then obtained.

Studies were excluded if outcomes were reported for a group of cancer patients consisting of a mix of solid tumours and haematological tumours, if the study reported outcomes from a study population that had already been included in another study or if the study population entirely pre-dated 1st January 2000. This latter criterion was chosen to ensure ICU care was relatively contemporaneous with current management practices [5, 115, 116].

The following information, where available, was collected: study design, country, year of data collection, total number of patients and type of ICU. Data describing the study population including mean/ median age, severity of illness score (APACHE II/III, SAPS II/III, SOFA) and the mix of tumour types were also

collected from each paper. Several studies reported the severity of illness scores and average age for a mixed cohort of patients with solid and haematological tumours and did not differentiate these demographics for patients with solid tumours. We did not place any restrictions on these studies. Reported survival data was collected. This was most commonly ICU mortality, hospital mortality, 6-month mortality and 1-year mortality. The authors were contacted for additional information when clarification was required.

STROBE criteria for reporting on cohort, case-control, and cross-sectional studies were used to examine what was reported in each study [117]. This included features pertaining to study design, variables, data sources, participants, descriptive data and outcome data.

2.2.5 Distribution of mortality estimates

All statistical analyses were performed using Stata version 13.1 (Stata Corporation, College Station,TX).

ICU and hospital mortality with exact 95% confidence intervals (CIs) were calculated for each study. With statistician input, the average of the reported mortality distribution with 95% CIs was calculated using a meta-analysis procedure (Freeman-Tukey). The extent of variation between study outcomes was measured by Mr Philip McLoone, statistician, using the I^2 statistic. This indicates the proportion of the total variation across study outcomes attributable to heterogeneity. Values greater than 50% suggest substantial heterogeneity.

2.2.6 Contributors

Dr David Morrison acted as the second reviewer during paper selection as described earlier. Statistical analysis for this chapter was performed by Mr Philip McLoone, Statistician.

2.3 Results

2.3.1 Study selection

Electronic database searches identified 668 references to April 2014, of which 47 papers were included in the final selection. The studies broadly fell into two groups: those reporting on a mixture of solid cancers together and those reporting on specific tumour types. Details of the selection processes are described in Figure 2-1.

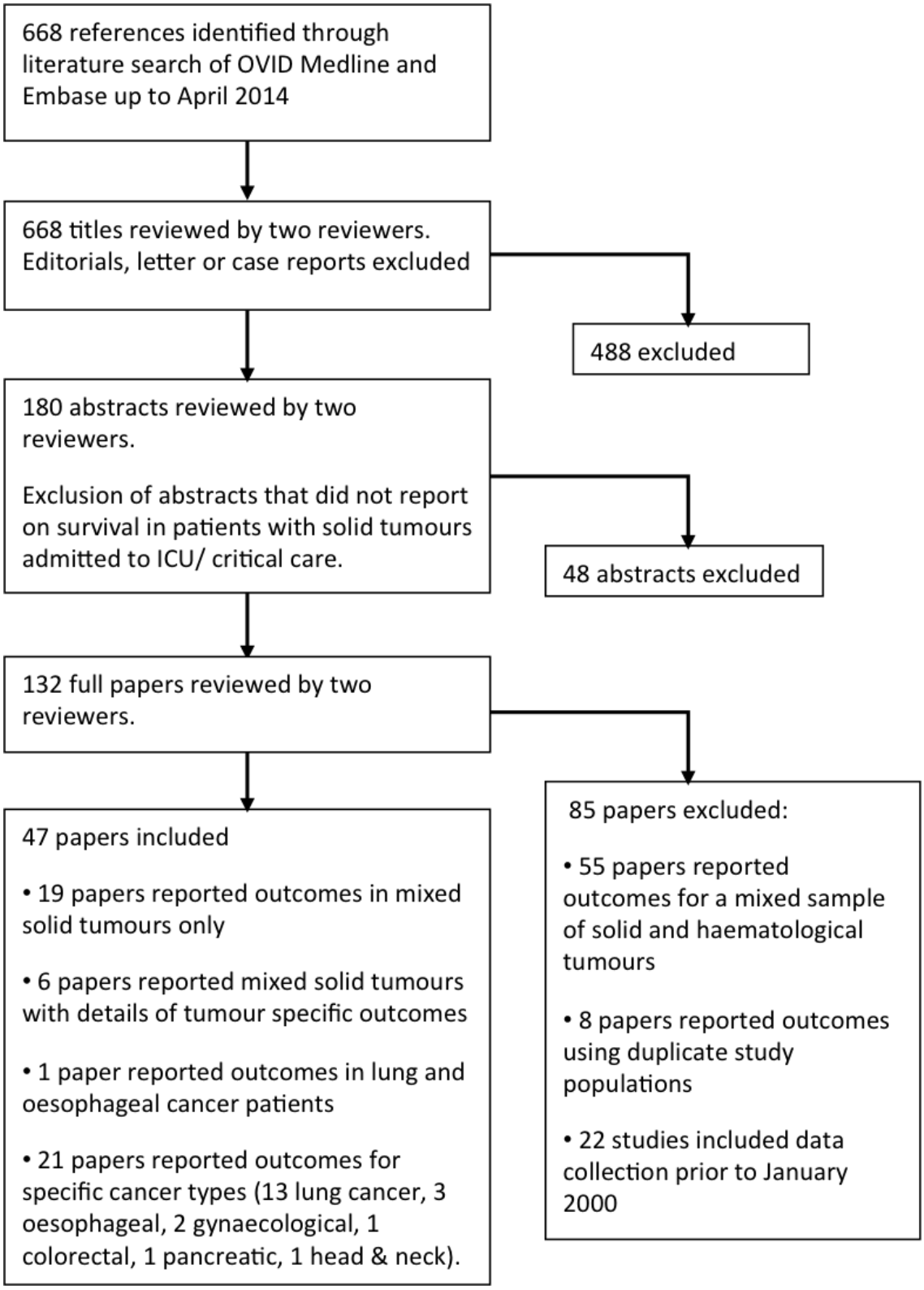


Figure 2-1 Selection of studies for inclusion. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

2.3.2 Description of included studies and assessment of bias

Forty-seven studies that reported mortality (including short-term ICU or in-hospital mortality) for patients with solid tumours after admission to ICU were identified. These studies and their study population are described in Appendix 1 (Tables 8-1 and 8-2) [85-87, 92, 95, 97, 99, 101-107, 111, 113, 118-149]. The populations vary widely in terms of the mix of tumour types, ICU characteristics, survival analysis and overall study aim.

2.3.2.1 Studies that report on an unselected general ICU population with a mix of cancer types

Eight of the identified studies reported outcomes for an unselected group of patients (in terms of ICU and cancer features) admitted to general ICUs. These studies best describe the target population of patients with unspecified solid tumours admitted to ICU.

Bos et al described the largest single cohort of patients [95]. This multi-centre study collected data on all cancer patients with an unplanned admission to ICU in the Netherlands between 2007 and 2011. This cohort included 12,290 patients with solid tumours of which 30% had metastatic disease. The cancer patients were compared to a group of 124,943 non-cancer patients with an unplanned admission to ICU. The authors described the medical and surgical population separately due to the differences in demographics, severity of illness and outcomes. Short-term survival is reported as ICU and hospital mortality. Data was collected retrospectively from a national ICU database. Cancer patients were identified where the reason for ICU admission made reference to malignancy. It is possible that this under-represents the ICU cancer population if cancer patients are coded with a diagnosis that does not directly reference their cancer (for example, a chest infection in a patient with lung cancer).

The study by Christodoulou et al, based in a single centre general ICU in Greece between 2001 and 2005 reported on 69 patients with a mixture of solid tumours

admitted to ICU [101]. This cohort of patients had a number of poor prognostic features; 89.9% of included patients had metastatic disease, a significant proportion of patients had lung cancer (39.1%) and over a third of the group were classified as performance status 3-4. Therefore overall outcomes may be expected to be poor. The study aimed to identify factors that were predictive of short-term outcome and the authors reported ICU and 30-day mortality.

Kopterides et al described the admission characteristics and severity of illness scores of cancer patients admitted to two general ICUs in Greece from 2005 to 2007 [99]. This included 90 patients with solid tumours of which there were a reasonable mix of common cancer types. Data had been collected prospectively allowing for reliable information pertaining to the cancer type and the critical illness. The objective was to compare the effectiveness of APACHE II, SAPS II and SOFA as prognostic models within the cancer population and ICU mortality was reported as part of this. The severity of illness scores for this population were suggestive of a population with a moderate burden of critical illness.

Mendoza et al have reported on 147 patients with solid tumours admitted to a single centre general ICU in the USA from 2003 to 2004 [107]. Patients were identified by retrospective analysis of an ICU database and case note review was subsequently performed. Their population represented most of the common tumour types and metastatic disease was present in 51.7% of these patients, suggesting a group of patients with advanced malignancy. Severity of illness was not reported for this group, however, 63% received invasive mechanical ventilation, 45% received vasopressors and 10% received renal replacement therapy suggesting a moderate degree of critical illness. They described hospital mortality and the proportion of patients that were discharged home.

Oeyen et al have described a cohort of mixed cancer patients admitted to a general ICU in Belgium between 2008 and 2009 [111]. This included 398 patients with solid tumours of which 46% had metastatic disease. Data was collected prospectively allowing reliable detailing of cancer and severity of illness. Median APACHE II score was 13 and SOFA score 3 representing relatively low level of organ support provided (29% IMV, 8% vasoactive drugs, 4% RRT). It is likely that this reflected the high proportion of patients that were admitted following

elective surgery (71%). It is therefore possible that the population described had a large quantity of HDU-type patients that were admitted for post-operative monitoring only. These types of patients were routinely excluded from other studies, as they may not represent typical ICU patients. This study described survival up to one year following ICU admission. This study also assessed quality of life measures in cancer patients following ICU admission.

In 2010, Soares published a multi-centre study that included all patients with cancer admitted across 28 ICUs in Brazil over a two-month period in 2007 [86]. The majority were general ICUs (82%) although a small proportion were dedicated oncological ICUs (18%). There were a total of 717 patients with cancer, of which 667 patients had solid tumours and 29.1% had metastatic disease. The characteristics of those patients are described in addition to outcome analysis and description of variables associated with mortality. The mix of tumour types was representative of the common malignancies. More than half of the patients with solid tumours were admitted to ICU following elective surgery. This group had multiple favourable features including good performance status, low severity of illness scores, fewer comorbidities and low utilisation of organ support. These patients were more likely to represent level 2 admissions rather than the sicker level 3 ICU populations and as such outcomes would be expected to be better.

The study by Taccone et al is a sub-study of the Sepsis Occurrence in Acutely Ill Patients (SOAP) study [87]. The SOAP study collected a large volume of data on all patients admitted to one of 198 general ICUs across Europe during a two-week period in 2002 and aimed to describe the incidence of sepsis among the population. Of the 3,147 patients enrolled, 473 patients had a malignancy of which 404 patients had a solid tumour and 24.8% had metastatic disease. This study was able to compare the demographic characteristics, critical illness features and survival outcomes of patients with solid tumours to those patients with haematological tumours (n= 69) and those patients without cancer (n= 2,674). This was a large multi-centre study with robust prospective data collection. While information pertaining to the ICU features is detailed, there is limited description of the cancer group beyond the term “solid tumour” with and without metastatic disease. Given that this study collected patient data from

nearly 200 sites it seems likely that it represents a large mix of the common tumour types.

Unseld et al describe those patients with malignancy admitted to a general ICU in Switzerland in 2002 [147]. Patients were identified retrospectively using a hospital database. This included 42 patients with solid tumours with a high proportion of urogenital tumours. As a single centre study, the case-mix would have been determined by the specific specialties practicing within that hospital and may not represent the cancer population as a whole. They reported ICU, hospital and one-year survival and described outcome by the number of organ failures present.

2.3.2.2 Studies that report on a specialist oncological ICU population with a mix of cancer types

Seven studies reported on outcomes from single centre oncological ICUs. While oncological ICUs benefit from having a large number of patients with cancer on which to report it is unlikely that the case-mix will be similar to that seen in general ICU in terms of the presenting critical illness.

Caruso et al have described a population of 83 patients with metastatic solid cancer admitted to an oncological ICU in Brazil over a one-year period [113]. They went on to report short and long-term survival up to two years, as well as assessing which factors were associated with hospital mortality. The cohort included a mix of common cancer types with a moderate degree of critical illness as demonstrated by severity of illness score and organ support.

Chawla et al report on a small group of patients within a single centre oncological ICU who were admitted to ICU within 48 hours of planned or actual discharge from hospital [125]. This included 21 patients with solid tumours. The purpose of the study was to determine incidence, reasons for, and outcomes of patients with cancer admitted to the ICU shortly after planned or actual hospital discharge. In addition they analysed whether the need for ICU admission was

related or unrelated to the previous/ current hospitalisation. The inclusion criteria meant that only a subgroup of the ICU cancer admissions were included and therefore they may not be representative of the overall ICU cancer cohort. The group did not report any severity of illness scores although mechanical ventilation and vasopressor medication was utilised for 60% and 32% of all patients respectively.

The study by de Almeida et al described a population of patients with malignancy admitted to a single centre oncological ICU in Brazil during 2009 [127]. This included 106 patients with solid tumours of which 35.2% had metastatic disease. The severity of illness score reported was low, suggesting a low threshold for ICU admission. Although data was collected prospectively, the authors did not report the underlying tumour types that contributed to the solid tumour group. Therefore it was not possible to comment on whether they were representative of the general solid tumour population. The study was designed to assess the impact of positive fluid balance on survival in this group of patients. In addition to ICU mortality they also assessed which factors were associated with mortality.

The study by Libório et al was set in a single centre oncological ICU in Brazil [106]. Patients with cancer admitted from 2006 to 2008 were included of which there were 258 patients with solid tumours made up of a standard mix of tumour types. Severity of illness scores in this group of patients were lower than many of the other studies with a mean APACHE II score of 10.3, SAPS II 35 and SOFA 5.8. The study went on to evaluate the discriminatory value of RIFLE classification of acute kidney injury (AKI) versus other prognostic scores in predicting hospital mortality.

McGrath et al have described cancer patients admitted to a single centre oncological ICU in the UK over 2004 to 2008 [131]. This included 70 patients with solid tumours. Commonest tumour types included lung (21.4%), breast (15.7%), oesophageal (11.4%) and ovarian (5.7%) suggesting tumours that may have been treated with aggressive chemotherapy. Metastatic disease was relatively common within the group at 41.4%. Severity of illness scores suggested a slightly lower burden of critical illness than that described in many of the other studies,

although patients admitted for routine post-operative monitoring were excluded from analysis a priori. The authors reported survival at ICU discharge and at six months.

The first of the studies by Namendys-Silva et al was published in 2010 and described 177 patients with solid tumours admitted to a single centre oncological ICU during 2007 [134]. There was a wide mix of tumour types included although the presence of metastatic disease was not reported. Median APACHE II score was 12 and SOFA score 3 suggestive of an overall low severity of critical illness that may not accurately reflect a standard ICU population. With this study the authors aimed to describe demographic, clinical and survival data (including median survival time) and to identify factors associated with mortality.

Soares et al has published several outcome studies on a cohort of patients from May 2000 variously to December 2004 [150], to December 2005 [151] and to January 2004 [109, 141]. We chose the single most comprehensive of these papers, “Impact of two different comorbidity measures on the 6-month mortality of critically ill cancer patients” published in 2005, [141] for inclusion in the solid tumour analysis. This paper described 772 cancer patients admitted to a single centre oncological ICU in Brazil from 2000 to 2004 and excluded routine post-operative admissions. Within this group there were 642 patients with a solid tumour diagnosis of which 21.4% had metastatic disease. Common tumour types were all represented within the cohort. SOFA and SAPS II scores indicated patients had a moderate severity of critical illness. Data collection was prospective and appeared robust in methodology.

2.3.2.3 Studies that report on cancer patients with a pre-specified critical illness feature on admission to ICU

Features associated with the critical illness are likely to influence the short-term outcomes. By selecting out specific features such as respiratory failure, multi-organ failure, renal failure or septic shock, it would be expected that these

groups were not necessarily representative of all ICU patients with cancer. Nor would they have the same survival outcomes. Eleven of the identified studies assessed outcomes for a group of cancer patients with a specific feature of their critical illness.

The single centre study by Azoulay et al was on a mixed cohort of cancer patients of which there were only 19 patients with solid tumours (ten lung cancer, nine breast cancer) admitted to a general ICU in France between 1997 and 2002 [85]. All patients were admitted with acute respiratory failure. Survival was described in addition to those factors that were associated with mortality. The admission dates to ICU span the 1st January 2000 cut off and the study only identified a subset of the ICU cancer population. However, the number of patients in this study was small and unlikely to overly bias the pooled results.

Darmon et al reported on a population of patients requiring admission to a single centre general ICU in France from 1997 to 2003 [103]. All patients had a new diagnosis of inoperable malignancy (within previous 30 days) and organ failure necessitating ICU admission. In addition, patients had been deemed to be in need of immediate chemotherapy due to life-threatening cancer complications. Within this cohort of 100 patients there were 12 patients with solid tumours. The objective was to determine outcomes in patients with a new cancer diagnosis, organ failure and treatment with chemotherapy in the ICU environment. More than half of the data collection period occurred prior to 2000 and as such may not reflect contemporary ICU practice as previously discussed. The mix of tumour types was unusual with soft tissue sarcomas and adenocarcinoma of unknown primary making up more than half of the cohort. This may be reflective of the case-mix within this single centre hospital or alternatively due to the inclusion criteria of inoperable tumour requiring immediate chemotherapy. Although this group may not represent the standard mix of solid tumours the number is small and unlikely to significantly bias the pooled results of this meta-analysis.

Lecuyer et al studied all consecutive admissions to ICU with active malignancy that required mechanical ventilation and at least one additional organ failure [92]. Patients were excluded if they had a previously untreated malignancy,

acute tumour lysis syndrome, bulky or infiltrating tumours at the earliest phase of treatment or patients who were in complete remission. Patients were then entered into an “ICU Trial” with full aggressive treatment for four days followed, on day five, by a reappraisal of the appropriate level of care based on response to treatment. The study was set in a single general ICU in France over 2001 to 2004 and within this cohort there were 56 patients with solid tumours. By specifying mechanical ventilation with at least one additional organ failure the study was reporting outcomes for a group of cancer patients with multi-organ failure and as such short-term mortality would be expected to be significantly poorer than that for an unselected group of ICU cancer patients.

Maccariello et al report on 773 consecutive patients in ICU that required renal replacement therapy (RRT) for AKI within general ICUs in Brazil from 2004 to 2008 [105]. This group included 86 patients with a variety of common solid tumours of which 31.4% had metastatic disease. They compared short-term outcomes in the cancer group to a group of non-cancer ICU patients with AKI requiring RRT. The use of RRT within the general ICU cancer population tends to be low and therefore this study was not necessarily representative of overall ICU cancer patients. Furthermore, severity of illness scores in this study were higher than that reported by many of the others suggesting a higher burden of critical illness within the population of ICU cancer patients with AKI.

Mourad et al have described a cancer population admitted to an oncological ICU in France during 2009 to 2011 with septic shock requiring vasopressor therapy [133]. The aim of the study was to assess the impact of early diastolic dysfunction, identified using echocardiography, on ICU mortality. They excluded patients with underlying heart disease. Within this group there were 26 patients with solid tumours. There were a number of features suggestive that this group was not representative of the general ICU cancer population. The study was performed in a single centre oncological ICU where the case-mix may be different from that seen in general ICUs. The authors did not report the cancer types included nor the proportion of patients with metastatic disease, which may have influenced outcomes. Median SAPS II was 57 and SOFA 11 for all patients, which is among the highest of all severity of illness scores across the included studies (although this is a median value for all patients within the study

including those with haematological malignancies). As such ICU mortality would be expected to be higher than that seen for the more general group. The authors reported ICU mortality and identified factors that are associated with outcome in this subset of extremely unwell ICU cancer patients.

The second study by Namendys-Silva et al to be included was published in 2011 and reported on a mixed group of cancer patients with septic shock admitted from 2008 to 2010 to a single centre oncological ICU [104]. Within this group there were 56 patients with a mix of solid tumours of which 33.9% had metastatic disease. This group had high severity of illness with mean SOFA scores of 9.1 in survivors and 11.7 in non-survivors (although APACHE II scores were lower, this may be attributable to the relatively young age of patients and the favourable performance status). This paper went on to assess long term outcome following ICU discharge and calculated survival time and hazard ratios for factors associated with death after ICU discharge.

The group led by Song reported outcomes in ICU cancer patients in South Korea. The first study published in 2007 described a group of 94 patients who were readmitted to ICU after initial recovery from major thoracic oncological surgery between 2001 and 2005 [143]. This included surgery for oesophageal and lung cancer but excluded patients undergoing single wedge resection of lung. While this type of intervention represents major surgery it is likely that patients were preselected based on limited comorbidity, good functional status and favourable tumour features. Patients would also have benefitted from pre-operative assessment and the opportunity for optimisation. It is unlikely that this population of lung and oesophageal cancer patients are representative of most patients with these malignancies.

Their second study published in 2011 looked at outcomes in a group of patients who received chemotherapy for the first time in ICU from 2002 to 2008 [144]. This group consisted predominantly of haemato-oncology patients. However, there were 13 patients in the cohort with solid tumours. The study reported survival based on a number of features including solid vs haematological cancer. Features including reason for chemotherapy, reason for admission and severity of illness were only reported for the group as a whole of which 79% were

haematological cancers. It is difficult to ascertain whether these patients were representative of the solid cancer ICU population without this data. While recognising this limitation, with only 13 patients, it is unlikely that this study will bias the overall pooled results significantly.

The third paper published by Song et al in 2012 reported outcomes for cancer patients that were admitted to an oncological ICU via medical emergency team intervention in 2010 [145]. This included 104 patients with an unspecified solid tumour. The study aimed to assess the impact of early intervention by medical emergency team on mortality among critically ill cancer patients admitted to ICU. Medical emergency teams assessed patients on wards with signs of critical illness. The aim was to intervene in an attempt to prevent worsening of disease or to transfer to a critical care setting at a timely point. As such patients may have been admitted to ICU at an earlier stage with a lower burden of critical illness. This did not appear to be the case, with both high severity of illness scores and mortality rates reported. The study did not report the tumour types or proportion of patients with metastatic disease and, as a single centre study, this group may not be representative of the solid tumour population. While severity of illness scores were high for the group overall it this may have been skewed by those patients with haematological malignancy as the scores were not reported for the different tumour groups.

Souza-Dantas et al described a group of neutropenic cancer patients admitted to an oncological ICU and matched them to a group of non-neutropenic ICU cancer patients [97]. There were 188 patients in this study and this included a total of 60 patients with solid tumours. They aimed to assess the impact of neutropenia on the outcomes of critically ill cancer patients. Severity of illness scores were extremely high with median SOFA 11 and SAPS II 61.6, although these values represented all patients including those with haematological malignancy. As this was a specialised oncological ICU it is possible that the case-mix did not reflect that seen within the general ICU setting. It would be unusual, within the general ICU population, for 50% of patients to have neutropenia at presentation. As this was a matched case-control study half of the patients had this clinical feature. However, neutropenia was not found to be associated with outcome and it may be that this is not necessarily a significant prognostic factor.

Zuber et al performed a secondary analysis of a database of 225,481 ICU patients across 41 general ICUs in France from 1997 to 2008 [149]. Their objective was to assess survival and prognostic factors in cancer patients with septic shock. They identified 2,119 patients with solid tumours admitted to ICU with septic shock of which 41.9% had metastatic disease. These patients had a high burden of critical illness as reflected by a mean SAPS II score of 63.4 and frequent use of organ support. Due to the severity of septic shock in terms of severity of illness and associated poor survival it is likely that by reporting only on this subset of ICU cancer patients the outcomes would be worse than that seen in the overall population. They went on to assess trends in survival over time and also the impact of case volume. Within this subgroup of ICU cancer patients with septic shock they demonstrated a significant fall in hospital mortality over time (72.1% in 1997 to 56.1% in 2008). Inclusion of ICU patients pre-2000 may negatively impact upon the overall outcomes reported in this study.

2.3.2.4 Studies that report on a specific cancer type admitted to ICU

Twenty-one studies reported on a specific cancer type admitted to ICU. Lung cancer was the commonest tumour type to be reported upon in this way with 13 studies choosing to report solely on patients with lung cancer. Outcomes for lung cancer patients tend to be worse than for many of the other cancer types, and as a result these patients are often not admitted to ICU. By including a large proportion of papers that report solely on the lung cancer population it may be that this group becomes over-represented and negatively impacted upon the overall outcomes for pooled survival that is later reported for all tumour types.

Adam et al reported outcomes for a cohort of 139 lung cancer patients (69% Non-Small Cell Lung cancer (NSCLC)) admitted to a medical ICU in the USA between 1998-2005 [118]. Of these patients, 40% had metastatic disease. Less than half of the cohort required invasive mechanical ventilation during their ICU stay suggesting a low threshold for ICU admission compared with other studies. ICU mortality and associated risk factors are described along with hospital mortality.

The study by Aldawood was set in a Saudi Arabian general ICU between 1999-2009 and included all patients with a prior diagnosis of lung cancer and excluded postoperative lung resection patients [119]. Over the time period there were 51 patients admitted (51% NSCLC). This study had the highest reported APACHE II score of 25.6 and organ support was provided for the majority of patients reflecting a high severity of illness. In addition to patient characteristics and survival this paper also described the resuscitation status of patients at admission and at discharge from ICU.

Andréjak et al described 76 patients with advanced lung cancer defined as stage IIIB or IV (64.5% NSCLC) admitted to medical ICU in France between 1996 and 2006 [120]. Patients with metastatic disease accounted for 59.2% of this cohort. This group of patients had a significant burden of critical illness with a high proportion of patients receiving organ support. It might be anticipated that negative factors associated with the cancer (lung malignancy associated with metastatic disease in more than half) combined with a significant burden of critical illness would demonstrate poorer outcomes than that expected for a standard population of ICU cancer patients. The authors described short-term survival in addition to risk factors for ICU mortality in this cohort.

Anisoglou et al reported on 105 lung cancer patients (80% NSCLC) with acute respiratory failure admitted to an oncological ICU in Greece between 2008 and 2011 [121]. There were a high proportion of patients with metastatic disease (72.4%) and severity of illness scores were high (mean APACHE II 23.4, SOFA 9.4) with a large utilisation of organ support. These factors are likely to lead to poor survival amongst this group. The authors described ICU, hospital and six-month mortality along with risk factors for poor outcomes.

Bissell et al described 43 patients following elective oesophagectomy for malignancy that subsequently required emergency readmission to ICU during the same hospital stay [122]. None of these patients had metastatic disease. The study was performed in a single centre UK hospital with a general ICU between 1998 and 2009. Short-term and longer-term survival was described in addition to predictors of survival.

The study by Bonomi et al described a large population of lung cancer patients that were admitted to ICU [123]. This multi-centre study from the USA used the Surveillance, Epidemiology, and End Results- Medicare Registry (SEER) and Medicare files between 1992 and 2005. They identified 1,134 patients aged over 65 years with stage IIIB or IV NSCLC admitted to medical ICU with respiratory, cardiac, neurological diseases, renal failure, or sepsis. Of this cohort 54.5% had metastatic disease. The study reported rates and predictors of death during hospitalisation. Longer-term outcome was described as 90 day and one-year survival post hospital discharge. As it was a retrospective review of healthcare files it was unable to provide detail on the characteristics of the critical illness such as severity of illness. Mechanical ventilation was held within the dataset and was received by 26% of patients that died in hospital and 8% of patients that survived hospitalisation. These rates are extremely low and may not reflect typical ICU demographics outwith the USA.

Cense et al have studied a population of 109 patients following elective transthoracic oesophagectomy for adenocarcinoma of the mid-distal oesophagus or gastric cardia between April 1994 and February 2000 [124]. Patients were admitted to ICU following the procedure but length of ICU stay varied. The aim of the study was to analyse the effects of prolonged ICU stay (≥6 days vs. ≤5 days) on quality of life and long-term survival. The vast majority of the study period predated the 1st January 2000 cut off for inclusion and as such the outcomes reported in this study might not be representative of what would be expected with contemporary practice. All patients included in this study were admitted following elective major surgery. They would be subject to selection bias having only been selected due to favourable feature and undergone pre-operative assessment and optimisation.

Chou et al have described 70 patients with stage III or IV lung cancer that were ventilated for sepsis related respiratory failure [126]. The study was set in a single centre general ICU in Taiwan from 2007 to 2008. Severity of illness scores were at the higher end of the range with mean APACHE II 24.3 and SOFA 7.1. Additional negative prognostic factors included advanced lung cancer, sepsis and respiratory failure all of which might have selected out a group of patients at

risk of a poor outcome. The authors reported ICU and hospital survival along with variables associated with survival.

Ertan et al studied patients admitted to a single centre general ICU in Turkey after emergency surgery for colorectal cancer between 1998-2004 [128]. A total of 102 patients were included. The study evaluated the predictive accuracy of different scoring systems in this population including SAPS II, APACHE II, APACHE III, MPM II, and Colorectal physiologic and operative severity score for the enumeration of mortality and morbidity (Cr-POSSUM). While it reported the area under the receiver-operator characteristic curve for each of the scores it did not give detail of the actual severity of illness. There were no features pertaining to the ICU stay or cancer described beyond the type and location of surgical procedure. As a result of this lack of detail little can be determined about the cohort and whether it was representative of the colorectal cancer ICU population.

Jennens et al reported on 20 patients with small cell lung cancer (SCLC) who had been admitted to one of three general ICUs in Australia from 1993 to 2001 [129]. Patients were excluded if they were admitted with complications of chemotherapy. Only 15% of patients were diagnosed with lung cancer prior to ICU admission, with 35% diagnosed during admission and 50% diagnosed after ICU admission. It is unclear if the ICU team knew about the cancer diagnosis in those who were diagnosed after their ICU admission. The study described treatment with chemotherapy in addition to ICU and median survival. Most of the patients were admitted prior to 2000 and outcomes may have been influenced by historical ICU practices, however, this is a small study and unlikely to influence the pooled results in a significant way.

The paper by Leath et al, based in a single centre in the USA over 1999 to 2004 reported on short-term mortality for 185 patients with a gynaecological malignancy that required post operative admission to ICU [130]. Patients were excluded if they were a non-surgical admission. This study reported a relatively low mean APACHE II score (11.6) compared with other studies, suggesting that these patients may have had a lower severity of critical illness. This may be attributable to the elective nature of surgery and the low incidence of co-

morbidity reported in this cohort. By excluding non-surgical admissions and reporting on a group of patients with favourable features it is possible that this paper introduces a bias that flatters outcomes for ICU cancer patients.

Namendys-Silva et al have published a third study that reports on 92 patients with gynaecological malignancy admitted in 2007 to a single centre oncological ICU [135]. The majority of patients had uterine cancer (67.3%). Mean APACHE II score for this group was 12.4 suggesting low severity of illness. Utilisation of mechanical ventilation was high at 76.9%. However, the median duration of ventilation was low at only one day and utilisation of vasopressors was in very few patients. They reported ICU and hospital mortality along with prognostic factors. As an oncological ICU the outcomes may be different from that seen in general ICUs.

Okiror et al have reported on 30 patients admitted to a UK single centre thoracic ICU as an emergency after lung resection for lung cancer between 2003 and 2008 [136]. All of these patients had NSCLC and had been assessed by a number of investigations and a multi-disciplinary team pre-operatively to determine fitness for surgery. The authors did not report features associated with the ICU admission and the severity of illness experienced by these patients is unknown. They assessed which peri-operative factors were associated with ICU admission in addition to reporting ICU mortality. However, there was not enough detail in the results to determine whether this paper introduces potential bias to the results of this meta-analysis.

Park et al have utilised the Intensive Care National Audit and Research Centre (ICNARC) database in England, Northern Ireland and Wales to report on all patients admitted to ICU following elective oesophageal surgery for malignancy from 1995 to 2007 [137]. This spanned 181 ICUs and included 7,227 patients with a mean SAPS II 25.1 and APACHE II 13.9 indicating a low burden of critical illness. The study evaluated prognostic models for this patient population including APACHE II, SAPS II and ICNARC models. While oesophageal cancer generally has a poor prognosis, the subgroup of patients deemed suitable candidates for surgery are different in terms of disease spread and may have benefitted from peri-operative assessment of co-morbidities and optimisation.

They may therefore be expected to perform disparately to the majority of patients. This paper reported outcomes in this favourable subgroup of oesophageal cancer patients who were admitted to ICU with low severity of illness. It would be anticipated that these patients would have significantly better survival outcomes than an unselected population of oesophageal cancer patients admitted to ICU.

Reichner et al described 47 patients with lung cancer that were admitted to a single centre medical ICU in the USA from 2002 to 2004 [138]. This included a mix of NSCLC and SCLC and metastatic disease was present in 64%. Mean SOFA scores and use of mechanical ventilation suggest a moderate degree of critical illness. The aim of the study, in addition to describing short-term outcome and predictors of outcome, was to examine the code status at admission to ICU and prior to death.

Roques et al report the six-month survival for a cohort of 105 lung cancer patients admitted to a general ICU in France from 1997 to 2006 and excluded those patients who were admitted following lung resection [139]. Both NSCLC and SCLC patients were included and 64% had metastatic disease. Nearly half of the group had performance status ≥2, which will have negatively impacted upon short and long-term survival. Mortality was described at discharge from hospital and at six months along with predictive factors for both.

The study by Slatore et al is the largest of the ICU lung cancer studies to be included, with 49,373 lung cancer patients that had been admitted to ICUs across the USA between 1992 and 2007 [140]. These patients were identified using the SEER database. Patients aged over 66 years at diagnosis and who were admitted to an ICU within 5 years of diagnosis, were included. Routine post-operative ICU admissions, carcinoma in situ and post mortem cancer diagnosis were listed as exclusion criteria. The cohort included a mix of NSCLC and SCLC, with 45.7% having metastatic disease. They have reported survival at hospital discharge and at six months along with factors associated with these outcomes. This study is limited by the nature of being a retrospective review of a national cancer database and is unable to provide detail on the characteristics of the critical illness. Mechanical ventilation was provided to 21% of the ICU lung

cancer patients. This might suggest a low burden of critical illness with a low threshold for ICU admission for monitoring. However, it is also possible that patients with severe critical illness were not being treated with mechanical ventilation due to perception of futility. Without additional information pertaining to the critical illness the level of bias introduced by this large study of ICU lung cancer patients was unclear.

Soares has also led groups that have described outcomes in specific tumour types including two studies published in 2007 [102, 142]. The first reported on 121 patients with head and neck cancer (35% of patients with metastatic disease) admitted to an oncological ICU from 2000 to 2005 [102]. There was a moderate burden of critical illness as demonstrated by severity of illness scores and utilisation of organ support. Data was collected prospectively and methodology appeared robust. The second study described 152 lung cancer patients admitted to one of two oncological ICUs, with metastatic disease present in 31% [142]. Patients were identified retrospectively and then underwent case note review allowing detailed reporting of ICU and cancer characteristics. Severity of critical illness was representative of that seen in most other studies with moderate severity of illness scores and utilisation of organ support. Both studies reported survival outcomes in addition to analysis of variables associated with outcome.

Toffart et al included 103 ICU patients with non-resectable lung cancer that were admitted to one of three general ICUs in France from 2000 to 2007 [146]. Within this group of patients, 20% had SCLC and 61% had metastatic disease. While these patients represent a group with unfavourable cancer features their ICU characteristics suggest a low burden of critical illness in terms of severity of illness scores and utilisation of organ support. Hospital and 90-day mortality was reported in addition to factors associated with 90-day mortality.

Welsch et al have reported on 96 patients undergoing resection of pancreatic head adenocarcinomas where the post-operative ICU stay exceeded the standard 24 hours [148]. Other pancreatic tumour types were excluded and only 7% of patients had metastatic disease. The study described the risk factors for extended postoperative ICU stay in addition to survival analysis. Due to the major surgery involved this operation would only have been performed after

thorough pre-operative assessment by a multi-disciplinary team and optimisation of any co-morbidities. These patients represent a subset of the pancreatic cancer population where outcomes are more favourable particularly after successful surgery. However, survival even within this subgroup remains significantly poorer than that for most other tumour types. Any bias that is introduced by this trial is likely to flatter results for the ICU pancreatic cancer group but negatively impact on results for the overall solid tumour ICU group.

2.3.3 Study characteristics

While the inclusion criteria required that admissions from 2000 onward were reported, the studies spanned admissions between 1997 and 2011. Where cancer site-specific outcomes were reported, the commonest were for lung cancers (20 studies) [85, 95, 106, 107, 113, 118-121, 123, 125, 126, 129, 136, 138-140, 142, 143, 146]. Four papers each reported head and neck [102, 106, 113, 125], breast [85, 106, 107, 113] and colorectal cancers [95, 107, 113, 125]. Oesophageal [122, 137, 143] and pancreatic cancers [113, 125, 148] each were reported in three papers. Stomach [113, 125] and gynaecological cancers [130, 135] each had two papers and single papers were identified for upper gastrointestinal [95], all gastrointestinal [106], urological [106], prostate [113] and melanomas [113].

The mean age of patients, where given, ranged from 47 to 75 years and unless tumours were sex-specific, patients comprised a mixture of men and women. When the cancer population comprised a mix of tumours the proportion of different tumour types, when reported, varied considerably with, for example, Song's series comprising 46% lung cancers and Libório's comprising 7% of them. Where the presence of metastatic disease was reported this ranged from 0 – 100%. There was significant variation in population size across the 47 studies. The largest study included was by Slatore et al [140], with 49,373 patients whilst Azoulay, Darmon and Song reported on a mixed cancer cohort of which solid tumours made up 10, 12 and 13 patients, respectively [85, 103, 144]. The majority of the studies (36/47) included a measure of physiological status. The

physiology scoring system used differed between studies and there was wide variation between mean/ median scores; 20 studies provided mean SAPS II scores, ranging from 25.1 to 63.4, and 15 studies gave mean APACHE II scores, ranging from 10.3 to 25.6.

With respect to information or measurement biases, it is possible that studies misclassified whether patients had cancer or not or misclassified the site of the primary tumour. However, because no additional sources of information were available to validate the classification it is not possible to evaluate the extent, if any, of such biases. As all studies reported total and not cause-specific mortality, misclassification of outcomes is unlikely although the timing of death may have been incorrect. Mortality could be misrepresented in those studies that excluded routine postoperative patients, patients with ICU stays of less than 24 hours, readmissions or inclusion only of patients requiring specific interventions, such as renal replacement therapy or mechanical ventilation.

2.3.4 Reported mortality

Short-term mortality was reported for ICU, hospital, 1 and 3 months (Table 2-1)

Author	Number of patients	Mortality (%), 95% CI			
		ICU	Hospital	1 month	3 month
Adam (2008)	139	22.3 (15.7-30.2)	40.3 (32.1-48.9)		
Aldawood (2010)	51	49.0 (34.8-62.4)	60.8 (46.1-74.2)		
Andréjak (2011)	76	47.4 (35.8-59.2)			
Anisoglou (2013)	105	44.8 (35.0-54.8)	56.2 (46.2-65.9)		
Azoulay (2004)	19		57.9 (33.5-79.7)		
Bissell (2013)	43	25.6 (13.5-41.2)	32.6 (19.1-48.5)		
Bonomi (2012)	1134		33.2 (30.4-36.0)		
Bos (2012)	12314	14.4 (13.8-15.0)	24.5 (23.7-25.2)		
Caruso (2009)	83	44.6 (33.7-55.9)	71.1 (61.3-80.8)		
Cense (2006)	109				0.9 (0.0-5.0)
Chawla (2009)	21	14.3 (3.0-36.3)	19.0 (2.3-35.8)		
Chou (2012)	70		58.6 (46.2-70.2)		

Author	Number of patients	Mortality (%), 95% CI			
		ICU	Hospital	1 month	3 month
Christodoulou (2007)	69	46.4 (34.6-58.1)	66.7 (55.5-77.8)		
Darmon (2005)	12		41.7 (15.2-72.3)	40[a] (30.3-50.3)	
de Almedia (2012)	106	17.9 (11.2-26.6)			
Ertan (2007)	102			16.7 (10.0-25.3)	
Jennens (2002)	20	85.0 (62.1-96.7)			
Kopterides (2011)	90	33.3 (23.6-43.1)			
Leath (2006)	185	8.1 (4.6-13.0)	11.4 (7.2-16.8)	12.4 (8.0-18.1)	
Lecuyer (2007)	56		76.8 (65.7-87.8)		
Libório (2011)	258	34.9 (29.1-40.7)			
Maccariello (2010)	86		73.3 (63.9-82.6)		
McGrath (2010)	70	27.1 (16.7-37.6)			
Mendoza (2008)	147	28.6 (21.3-35.9)	39.5 (31.6-47.4)		
Mourad (2014)	72	48.6 (36.7-60.7)			61.1 (48.9-72.4)
Namendys-Silva (2010)	177	21.5 (15.4-27.5)			

Author	Number of patients	Mortality (%), 95% CI			
		ICU	Hospital	1 month	3 month
Namendys-Silva (2011)	56	39.3 (26.5-52.1)			
Namendys-Silva (2013)	52	17.3 (8.2-30.3)	23.1 (12.5-36.8)		
Oeyen (2013)	398	5.0 (2.9-7.2)	12.6 (9.3-15.8)		17.3 (13.7-21.4)
Okiror (2012)	30	16.7 (5.6-34.7)			
Park (2009)	7227	4.5 (34.0-4.9)	10.8 (10.1-11.5)		
Reichner (2006)	47	42.6 (28.3-57.8)	59.6 (44.3-73.6)		
Roques (2009)	105	42.9 (33.2-52.9)	54.3 (44.3-64.0)		
Slatore (2012)	49373		23.5 (23.2-23.9)		
Soares (2005)	642	31.0 (27.4-34.6)	44.2 (40.4-48.1)	42.1[a] (38.6-45.7)	
Soares (2007)	143	42.0 (33.8-50.5)	58.7 (50.2-66.9)		
Soares (2007)	121	38.8 (30.1-48.1)	56.2 (46.9-65.2)		
Soares (2010)	667		28.0 (24.7-31.6)		
Song (2007)	94	33.0 (23.7-43.4)			
Song (2011)	13	53.8 (26.7-80.9)			

Author	Number of patients	Mortality (%), 95% CI			
		ICU	Hospital	1 month	3 month
Song (2012)	104	45.2 (35.4-55.3)			
Souza-Dantas (2011)	60		73.3 (62.1-84.5)		
Taccone (2009)	404	20.0 (16.1-24.0)	27.0 (22.7-31.3)		
Toffart (2011)	103	31.1 (22.3-40.9)	47.6 (37.6-57.6)		63.1 (53.0-72.4)
Unseld (2013)	42	16.7 (7.0-31.4)	28.6 (15.7-44.6)		
Welch (2010)	540		4.6 (3.0-6.8)	2.6 (1.4-4.3)	
Zuber (2012)	2119	57.2 (55.1-59.4)			

Table 2-1 Short-term mortality in solid tumour patients after ICU. ([a] includes a mixed group of solid and haematological malignancy patients) Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

ICU mortality was reported in 35 studies and ranged widely from 4.5% to 85%. Hospital mortality was reported in 31 studies ranging from 4.6% to 76.8%. ICU and hospital mortality were plotted showing the pooled estimate of mortality rates in Figure 2-2.

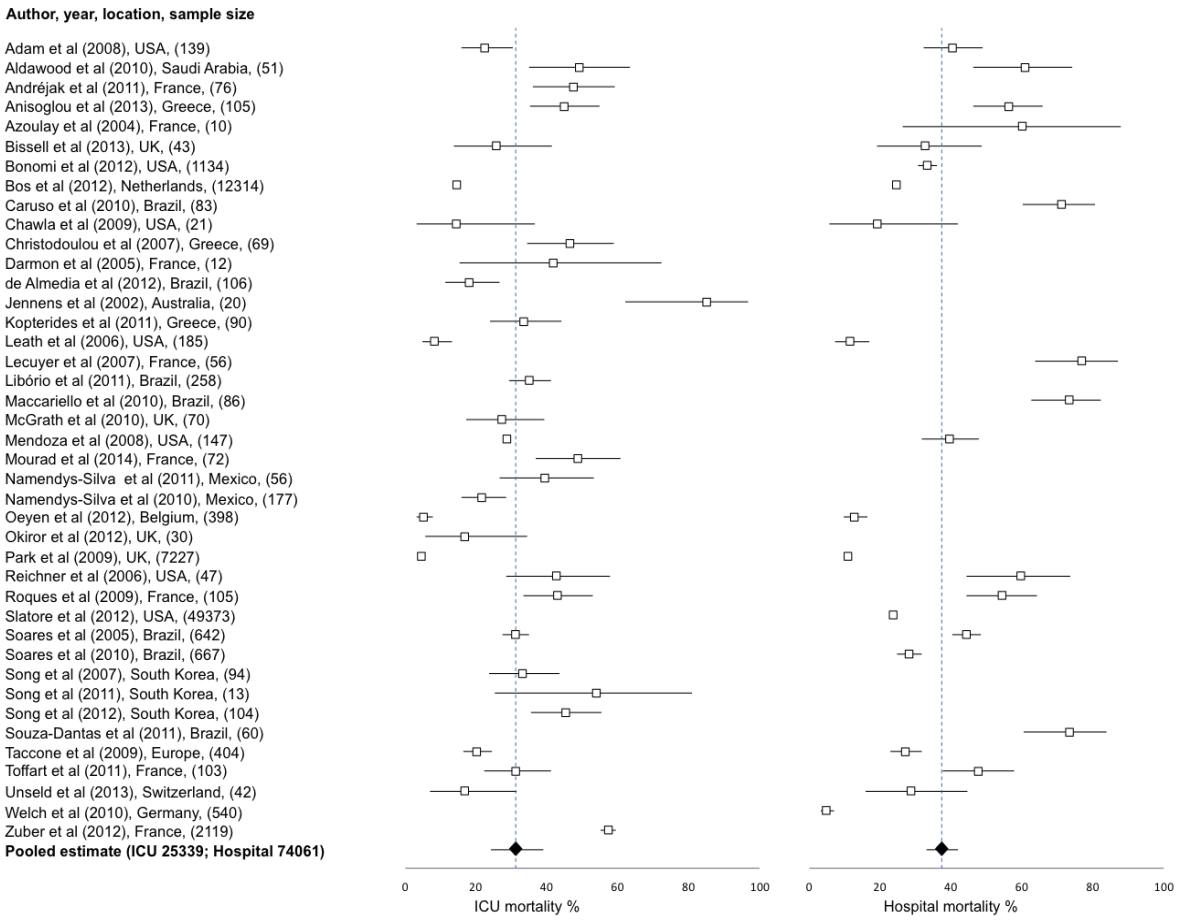


Figure 2-2 Short-term mortality of ICU patients with solid tumours. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

The pooled estimate of mortality summarises only those studies using independent samples, so where several papers reported on the same group of patients, only one representative paper was used. The overall pooled mortality within ICU was 31.2% (95% CI 24.0% to 39.0%) based on a total sample of 25,339 patients with a solid tumour, of which Bos's study comprised nearly half of the

patients. There was substantial variation between studies in the proportion of patients who died in ICU (I^2=99.1%, x2=3483, df=31, p < 0.001). The pooled hospital mortality was 38.2% (95% CI 33.8% to 42.7%) among a total sample of 74,061 patients with solid tumours, of which Slatore's study comprised two thirds of the patients. Again, there was substantial variation in hospital mortality between studies (I^2=98.8%, x2=1829, p<0.001).

Longer-term mortality in ICU patients with solid tumours was reported for 6 months and up to 5 years after ICU admission (Table 2-2).

Author	Number of patients	Mortality (%), 95% CI				
		6 month	1 year	2 year	3 year	5 year
Adam (2008)	139	48.2 (39.7-56.8)				
Anisoglou (2013)	105	77.1 (67.9-84.8)				
Bissell (2013)	43			58.1 (42.1-73.0)		62.8 (46.7-77.0)
Caruso (2009)	83		88.0 (79.0-94.1)	97.6 (91.6-99.7)		
Cense (2006)	109	17.4 (10.8-25.9)	39.4 (30.2-49.3)	56.0 (46.2-65.5)	68.8 (59.2-77.3)	
Oeyen (2013)	398		35.9 (31.2-40.9)			
Roques (2009)	105	72.4 (62.8-80.7)				
Slatore (2012)	49373	65.4 (64.9-65.8)				
Soares (2005)	642	54 (50.1-58.0)				
Soares (2007)	121	71.9 (63.0-79.7)				
Song (2007)	94		54.3 (43.7-64.6)		66.0 (55.5-75.4)	
Toffart (2011)	103		87.4 (79.4-93.1)			

Table 2-2 Longer-term mortality in solid tumour patients after ICU. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

Mortality at one year was reported in five studies and ranged from 35.9% to 88.0% and a single study by Bissell reported 62.8% survival at five years [122]. Figure 2-3 provides summary mortality estimates at all follow-up periods. Generally, mortality increases from the ICU admission period to the first six months after admission. Thereafter, there is little further increase in mortality reported by these studies. However, each time point describes different patient populations and in some cases a single study, so caution is required in making conclusions about mortality over time.

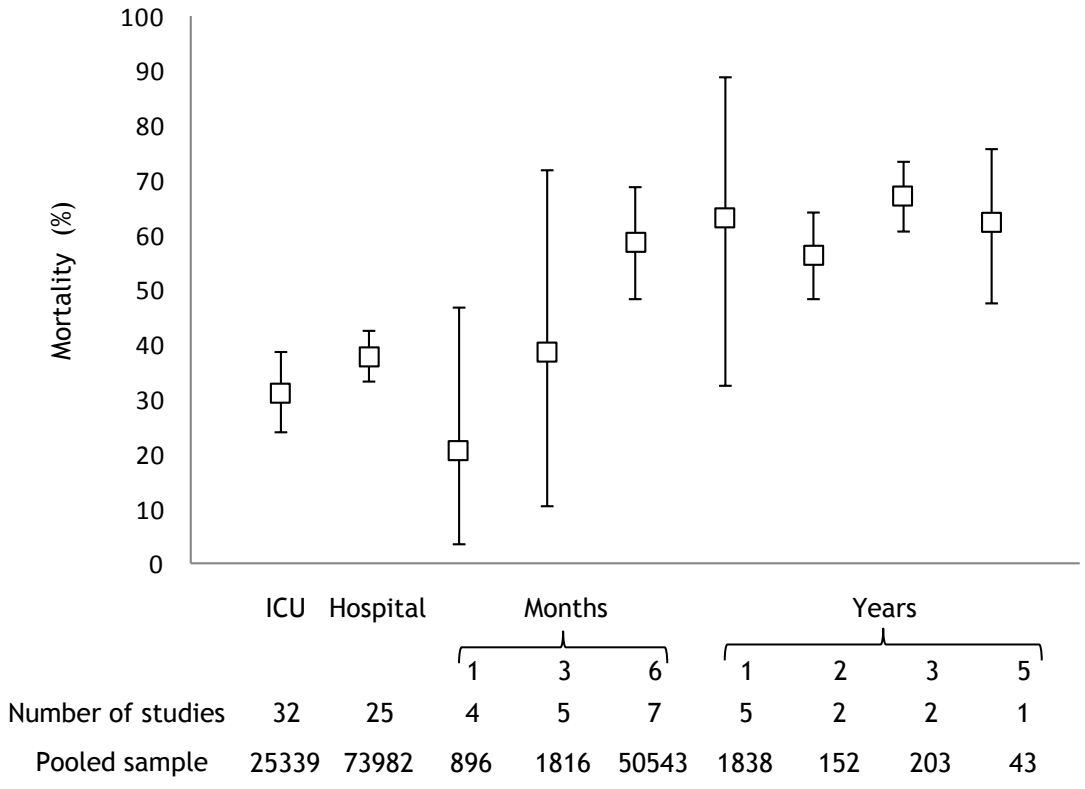


Figure 2-3 Pooled mortality by length of follow-up among ICU patients with solid tumours. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

2.3.5 Predictors of survival

When the effects of risk factors associated with survival have been found to be statistically significant in multivariable analyses these have been described along

with the magnitude of effect (odds ratios unless otherwise stated) in Tables 2-3, 2-4 and 2-5.

Author	Prognostic factors for ICU mortality
Adam (2008)	Vasopressors 8.7 (2.8 – 27) >2 Organ failures 40.8 (5.1 – 328.3)
Andréjak (2011)	IMV 6.61 (1.44 – 30.5) Vasopressors 6.81 (1.77 – 26.26) Platelet count <100000/mm^3 5.13 (1.17-22.5); Admission for complication of cancer management 0.206 (0.058-0.738)
de Almedia (2012)	APACHE II score 1.15 (1.05-1.26) LIS score 2.23 (1.29-3.87) Positive fluid balance >1100ml/24h 5.14 (1.45-18.24)
Kopterides (2011) Model I	APACHE II score 1.16 (1.07-1.26) PS 3-4 6.70 (2.18-20.60) Septic shock 5.51 (1.16-26.10)
Kopterides (2011) Model II	SOFA score 1.2 (1.05-1.38) Medical admission 3.84 (1.14-12.92) PS 3-4 3.88 (1.22-12.39) Infection on admission 3.9 (1.17-13.05)
Kopterides (2011) Model III	SAPS II score 1.04 (1.01-1.08) PS 3-4 6.67 (2.12-21.00) Septic shock 4.75 (1.00-22.73) Anaemia on admission 4.06 (1.30-12.65)
Mourad* (2013)	SOFA score 1.35 (1.05-1.75) IMV 16.6 (3.60-77.15) Diastolic dysfunction (e'≤8cm/s) 16.6 (3.28-84.6)
Namendys-Silva (2010)	APACHE II score 1.92 (1.43-2.58) Vasopressors 22.66 (6.09-84.22)
Song (2011)	SOFA score >10 9.66 (1.43-65.47) IMV 6.26 (1.12-34.95)

Zuber (2012)	SAPS II score 1.04 (1.03-1.04) Medical admission 1.73 (1.29-2.32) IMV 5.52 (4.04-7.54) RRT 1.74 (1.30-2.33 Fungal infection 1.95 (1.18-3.21) Unknown microorganism 1.64 (1.27-2.11) Admission to high vs. low volume unit 0.63 (0.46-0.87)

Table 2-3 Prognostic factors associated with ICU mortality with corresponding odds ratios. *includes haematological malignancies. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

Author	Prognostic factors for hospital mortality
Azoulay* (2004)	Vasopressors 3.19 (1.28-7.95) NIMV followed by conventional IMV 17.46 (5.04-60.52) First-line conventional IMV 8.75 (2.35-32.54) Late NIMV failure 10.64 (1.05-107.83) Congestive heart failure 0.16 (0.03-0.72) Invasive aspergillosis 3.78 (1.05-14.24) No definite diagnosis 3.85 (1.26-11.70)
Bonomi (2012)	Sepsis 5.06 (3.04-8.43) IMV 4.69 (3.02-7.30) Renal failure 2.28 (1.02-5.10) Admission related to respiratory conditions 2.34 (1.43-3.82)
Caruso (2009)	SAPS II 1.09 (1.01-1.18) Thrombocytopenia 26.2 (2.6-267.9)
Christodoulou (2007)	PS 3-4 5.44 (1.48-19.99)
Chou (2012)	SOFA score 1.360 (1.038-1.782)
Lecuyer (2007)	No significant independent predictors of hospital mortality
Libório (2011)	SAPS II score 1.05 (1.02-1.08)

	SOFA score 1.69 (1.37-2.09) APACHE II 1.65 (1.34-2.03) RIFLE score 4.86 (1.68-14.06)
Maccariello (2010)	Medical admission 6.55 (2.29–18.73) Associated organ dysfunction 2.14 (1.25-3.65) ICU days until start of RRT 1.42 (0.97-2.09)
Mendoza (2008)	Vasopressors (value not given) Metastatic disease (value not given)
Namendys-Silva (2013)	APACHE II score 1.43 (1.01-2.09) Vasopressors 8.6 (2.05-36)
Park (2009)	IMV 1.24 (1.03-1.50) Age: 60-69 1.68 (1.07-2.63); 70-79 2.64 (1.69-4.15); ≥80 3.84 (2.14-6.87) [Reference group <50 years) P/F ratio: <10 3.7 (1.7-8.07); 10-19 2.65 (1.49-4.69); 20-29 2.04 (1.17-3.55); 30-39 1.9 (1.08-3.33) [Reference group 50-59kPa] Serum urea ≥14.4 2.49 (1.37-4.53) [Reference group <6.3mmoll^{-1}] Serum creatinine ≥150 2.01 (1.32-3.06) [Reference group 50-99micromoll^{-1}] Serum albumin: <15 2.58 (1.87-3.55); 15-19.9 1.73 (1.31-2.29) [Reference group 25-29.9gl^{-1}] Lowest arterial pH: <7.15 1.85 (1.13-3.01); 7.15-7.24 2.0 (1.49-2.68); 7.25-7.29 1.42 (1.11-1.84) [Reference group 7.3-7.34]
Roques (2009)	PS 3-4 3.6 (1.5-8.7) Acute respiratory failure 3.5 (1.5-8.4)
Slatore (2012)	IMV 6.95 (6.89-7.01)
Soares 2007)	PS 3-4 5.17 (1.84–14.53) Number of acute organ failures 2.87 (1.83–4.50) Stage IV disease 3.80 (1.28–11.28)
Soares (2007)	Number of organ failures 1.95 (1.16-3.28) Age 1.08 (1.02-1.15) Uncontrolled recurrence/ progression of cancer 8.81 (1.56-49.67) Airway obstruction by cancer 3.55 (1.02-12.32)

Soares (2010)	SOFA score 1.25 (1.17-1.34) Medical admission 5.66 (3.43-9.33) PS ≥2 3.40 (2.19-5.26) IMV 2.42 (1.51-3.87) Emergency surgical 2.46 (1.28-4.73) Hospital stay 1.18 (1.01-1.37) Newly diagnosed cancer 2.75 (1.19-6.32) Recurrence/ progression of cancer 2.42 (1.51-3.87)
Song (2007)	APACHE III ≥50 12.100 (2.859–51.206) RRT 3.611 (1.096–11.895) Duration of ventilation ≥5 days 7.859 (2.375–26.006)
Song* (2012)	SOFA score 1.18 (1.03-1.35) MET criteria (3+) 3.09 (1.32-7.23) Time to intervention by MET (hours) 1.45 (1.22-1.72)
Souza-Dantas (2011) Model I	SAPS 1.06 (1.03-1.09) Medical admission 7.82 (1.75-34.88) PS ≥2 2.43 (1.03-5.70) Severe sepsis/ septic shock 4 (1.37-11.73) Chemo before admission 0.19 (0.05-0.78) Hospital days before ICU admission 1.50 (1.08-2.07)
Souza-Dantas (2011) Model II	SOFA score 1.19 (1.06-1.33) Medical admission 7.06 (1.68-29.63) PS ≥2 2.84 (1.26-6.40) Severe sepsis/ septic shock 3.53 (1.20-10.33) Hospital days before ICU admission 1.49 (1.09-2.04)
Taccone (2009)	SAPS II score 1.07 (1.05-1.08) Sepsis 2.1 (1.2-3.7) IMV 2.4 (1.2-4.7) ARDS 2.5 (1.2-5.3)

Table 2-4 Prognostic factors associated with hospital mortality with corresponding odds ratios. *includes haematological malignancies. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

Author	Prognostic factor
30 day Mortality	
Darmon (2005)	IMV 6.36 (1.76-22.94) Vasopressors 6.01 (1.86-19.4) Liver failure 7.76 (1.25-48.27)
90 day Mortality	
Namendys-Silva† (2011)	SOFA 1.11† (1.02-1.19) PS 3-4 1.84† (1.03-3.29)
Toffart (2011) Model I	SAPS 1.03† (1.02-1.05) PS 3-4 1.96† (1.11-3.46)
Toffart (2011) Model II	LOD, per point 1.19† (1.08-1.32) PS 3-4 2.65† (1.43-4.88) Metastasis at ICU admission 1.90† (1.08-3.33)
Roques (2009)	IMV 3.6 (1.35-9.4) Cancer progression 6.1 (2.2-17)
Slatore (2012)	IMV 1.21 (1.16-1.26)
6 month Mortality	
Soares (2005)	IMV 1.34 (1.00-1.78); No. of organ failures: 1–2 1.77 (1.29–2.43); >2 3.89 (2.73-5.53) Age: 40-70 1.66 (1.24–2.23); >70 years 2.07 (1.49–2.88) Surgical patient 0.69 (0.55–0.86) Cancer status: Newly-diagnosed 1.46 (1.11–1.91); Recurrence/ progression 2.20 (1.72–2.82)
Mortality after discharge	
Namendys-Silva (2010)	Vasopressors 2.79† (1.06-7.33) Length of stay in ICU 1.10† (1.007-1.02) CCI>2 5.81† (1.35-25.03)
Bissell (2013)	RRT 5.63† (4.0-7.2) Age 1.05† (1.01-1.09)

Table 2-5 Prognostic factors associated with longer-term mortality with corresponding odds ratios. †Hazard ratios. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

Several studies reported an association between measures of severity of illness and short-term survival. Increasing severity of illness scores such as APACHE, SAPS and SOFA were associated with greater risks of mortality. Renal failure, as assessed by RIFLE score, was associated with mortality when assessed in Liborio's study. The number of organ failures has also been associated with survival and this is likely a surrogate marker for severity of illness. The relationship between higher severity of illness score and increased mortality was reported up to 90 days after admission and was of a similar magnitude to its effect on shorter-term mortality. However, beyond 90 days, severity of illness scores were not assessed for impact upon mortality.

Features associated with organ failure such as specific organ support were also associated with short-term mortality. Invasive mechanical ventilation increased ICU mortality by around six-fold in most studies. The study by Mourad et al reported a much higher figure of a nearly 17-fold increase in ICU mortality for IMV, however, this analysis included haematological patients and the confidence interval around the estimate was wide [133]. Use of vasopressors increased the risks of both ICU and in-hospital mortality. The increased ICU mortality was nearly nine-fold in the paper by Adam [118] and 22-fold in the cohort by Namendys-Silva [134]. Hospital mortality was increased three to eight-fold by the requirement for vasopressors. The increased mortality at 30 days reported by Darmon was of a similar magnitude to that reported in hospital by several authors [103]. This similarity may reflect the duration of hospitalisation in patients with critical illness. Renal replacement therapy had a smaller impact on ICU mortality in the study by Zuber et al with OR 1.74 [149]. Hospital mortality was increased three-fold by RRT in Song's 2007 study [143] and hazard ratio was 5.63 in ICU cancer patients with RRT in the Bissell study [122]. Sepsis increased ICU mortality by five-fold and in-hospital mortality between two- and five-fold.

ICU admission type has an impact upon short-term outcomes in cancer patients with medical admissions (as opposed to surgical) associated with a two- to four-fold increased risk of ICU mortality; and increased risk of in-hospital mortality of between six and eight-fold. In the study by Bos et al [95] this effect was particularly pronounced in the cancer population in comparison to the non-cancer population with in-hospital mortality of medical cancer patients 44.6% vs.

23.7% medical non-cancer patients and 17.4% surgical cancer patients vs. 14.6% surgical non-cancer patients.

WHO Performance Status, which is used to quantify cancer patients' general health and functioning, was associated with survival. Generally, papers compared patients with scores of 3 and 4 (from capable of only limited self-care to completely disabled and confined to bed or chair) with those of 0, 1 and 2. Poorer Performance Status was associated with increased ICU mortality of between four and seven-fold and increased mortality by two to three-fold at 90 days after ICU admission.

The impact of cancer stage has been inconsistently associated with mortality. The study of 147 patients with mixed solid tumours by Mendoza et al found metastatic disease to be independently predictive of hospital mortality on multivariate analysis [107]. Soares' study of patients with head and neck cancer identified that those with stage IV disease had a higher risk of in-hospital death with OR 3.8 (95% CI 1.28 – 11.28) [102]. A further study by Soares of cancer patients receiving >24 hours of invasive mechanical ventilation found that hospital mortality increased in patients with recurrence/ progression of cancer status (OR 3.43, 95% CI 1.81 – 6.53 compared with controlled cancer) and when airway/ pulmonary involvement by the tumour was the reason for ventilation (OR 5.73 CI 1.92 – 17.08) [109]. However, an additional three papers did not find an association between metastatic disease and short-term outcomes such as ICU or hospital mortality [87, 101, 105]. The impact of leukopenia and neutropenia has been assessed in many of the studies and has not been found to be associated with short-term mortality [87, 97, 99, 103, 106].

Studies varied widely in their mean acute illness scores (Appendix 1) and reported mortality (Tables 2-1 and 2-2). Figure 2-4 plots ICU mortality for each study by its acute illness score (APACHE II, SOFA and SAPS II, respectively). Circle sizes are proportionate to sample sizes. In general, studies with higher acute illness scores reported higher ICU mortality. However, there was some variation in mortality between studies with similar acute illness scores. This is likely to be a reflection of differences in other patient characteristics within the cohorts, particularly cancer site.

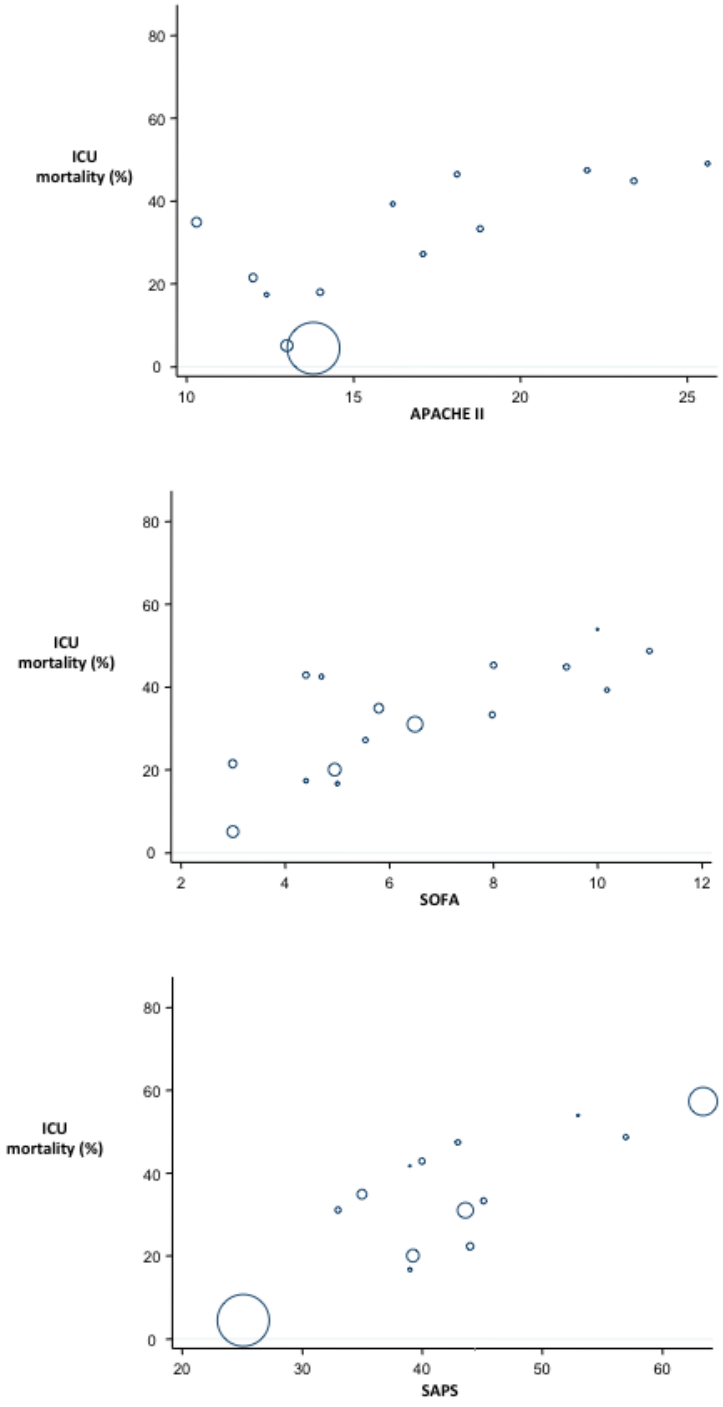


Figure 2-4 Mortality by mean/ median severity of illness score (APACHE II, SOFA and SAPS II, respectively). Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

2.3.6 Tumour specific survival

Table 2-6 and Figure 2-5 summarises short-term mortality where this has been described for specific tumour sites, indicating the site-specific average and overall pooled mortality.

Tumour type	Pooled ICU mortality % (95% CI)	Pooled hospital mortality % (95% CI)
Lung	40.1% (28.6 – 52.2)	46.9% (39.9 – 54.0)
Oesophageal	14.7% (2.5 – 34.6)	19.9% (3.6 – 44.8)
Upper GI	12.3% (10.6 – 14.1)	20.9% (18.8 – 23.2)
Colorectal	19.2% (0 – 62.3)	35.0% (13.7 – 60.2)
Breast	33.3% (10.3 – 59.0)	57.7% (42.1 – 72.7)
Head and neck	34.2% (24.6 -44.6)	54.7% (24.9 – 82.8)
Pancreatic	0% (0 – 70.8)	30.8% (0.4 – 80.5)
Gynaecological	12.0% (4.6 – 22.4)	16.4% (6.7 – 29.3)
Gastrointestinal	15.4% (8.2 – 25.3)	-
Urological	36.4% (24.9 – 49.2)	-
Stomach	0% (0 – 97.5)	50.1% (2.3 – 97.7)
Melanoma	-	100% (48.4 – 100)
Prostate	-	80% (28.4 – 99.5)

Table 2-6 ICU and hospital mortality by tumour type. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

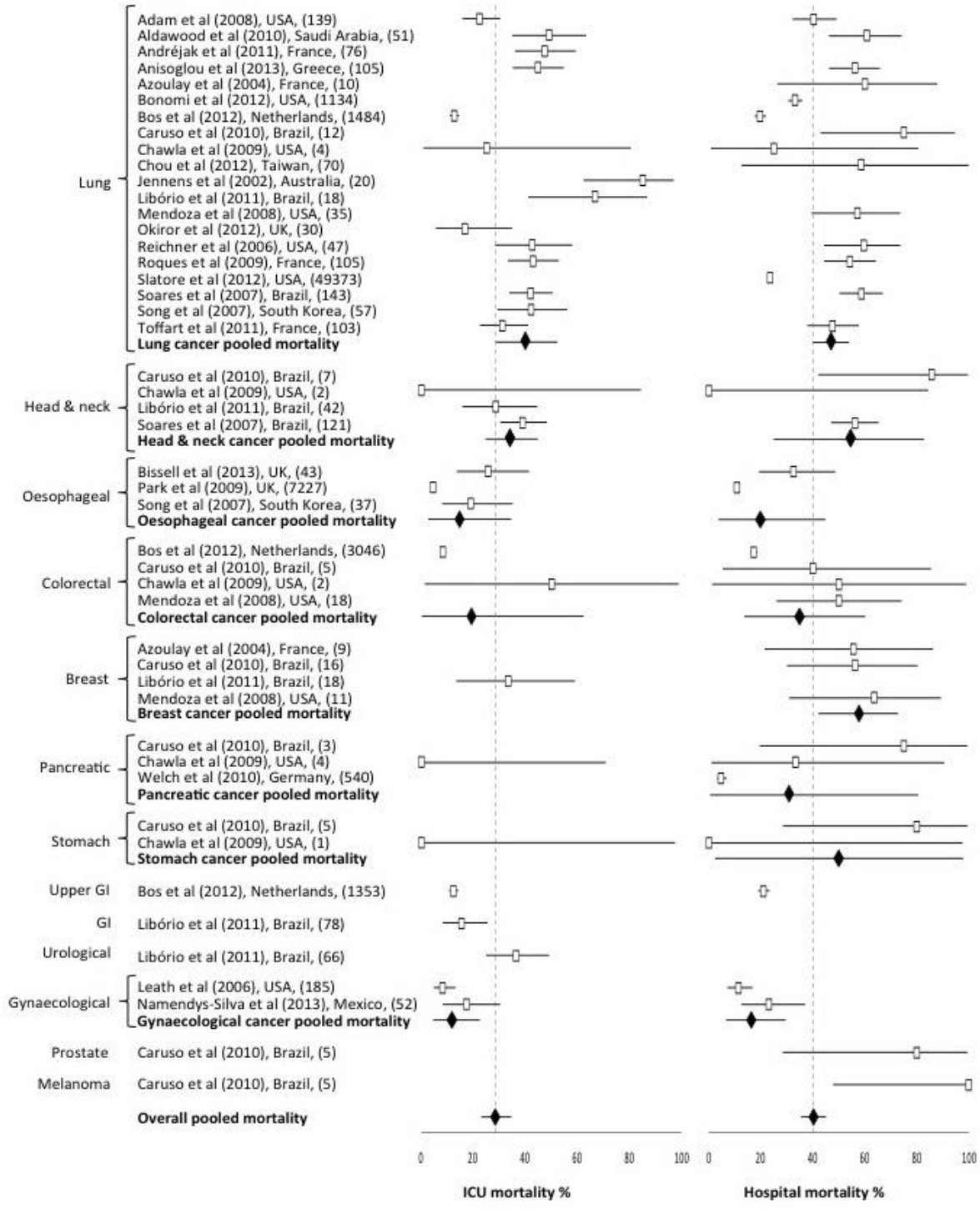


Figure 2-5 Short-term mortality by specific tumour type. Modified from "Survival in solid cancer patients following intensive care unit admission" Puxty et al. Intensive Care Med (2014) with permission.

It is apparent from Figure 2-5 that survival varies between studies on the same cancer site and between different cancer sites. Precision of estimates varied considerably between studies. Generally, mortality was high for patients with

lung cancers with pooled ICU and hospital mortality of 40.1% (95% CI 28.6 – 52.2) and 46.9% (95% CI 39.9 – 54). Hospital mortality was higher in patients with breast cancer at 57.7% (95% CI 42.1 – 72.7) and head and neck cancer at 54.7% (95% CI) 24.9 – 82.8) but numbers were low in these groups and as a result confidence intervals were high. There were large number of patients included with oesophageal cancer and this group of patients tended towards lower mortality with 14.7% (95% CI 2.5 – 34.6) ICU and 19.9% (3.6 – 44.8) hospital. It is likely this is due to the large proportion of post-operative patients within this group. Colorectal cancer was the third largest group reported on with pooled ICU and hospital mortality of 19.2% (95% CI 0 – 62.3) and 35% (95% CI 13.7 – 60.2).

2.3.7 Quality of life in cancer patients after ICU

Quality of life (QoL) was not routinely measured in the majority of the 47 included studies. The paper by Cense et al reported QoL as measured by the generic Medical Outcome Studies Short Form-20 (MOS SF-20) and Rotterdam Symptoms Check List (RSCL) in patients admitted to ICU following elective oesophagectomy for cancer. They compared scores for those patients who had a short ICU stay versus those who had a long ICU stay. They compared ≤5 days with ≥6 days and ≤2 days with ≥14 days. From a preoperative baseline there was a significant decline in QoL measures immediately postoperatively that slowly recovered to baseline. When comparing ICU stay ≤5 days with ≥6 days there was no significant difference in MOS SF-20 scores. However, RSCL outcomes were worse for the group with ICU stay ≥6 days as scores were lower after five weeks and three months in the overall QoL domain and after three months in the physical symptoms and activities of daily living domains. When comparing ICU stay ≤2 days with ≥14 days the MOS SF-20 scores revealed that the prolonged admission group had significantly worse physical and social functioning than the short stay group. RSCL revealed lower scores for activities of daily living in the long stay group at three months and less of an improvement in overall QoL at two years. However, pain scores after one year as assessed by MOS SF-20 were more favourable in the long stay group.

Oeyen et al measured QoL using Medical Outcomes Study 36-item Short Form Health Survey and the EuroQoL-5D in a mixed population of ICU cancer patients. QoL measures were found to decrease after ICU admission as compared to baseline and improved in most areas after one year. Exceptions were mobility and anxiety, which remained lower than baseline.

While Toffart et al did not formally assess QoL they did describe the effect on life after ICU discharge for a population of patients with non-resectable lung cancer in terms of time spent at home. They found that 52% patients were discharged alive from hospital. Of these 11% never returned home, 74% spent more than half of the follow-up time at home with 61% spending more than three quarters of the follow-up time at home.

2.4 Discussion

2.4.1 Summary of findings

This systematic literature review identified a set of studies that describe contemporary outcomes in patients with solid tumours after admission to ICU. The 47 papers that reported on solid cancers were characterised by a wide range of case-mix variables both in terms of critical illness and in tumour types. The broad range of observed outcomes, with ICU mortality ranging from 4.5% to 85%, reflects the heterogeneity of patients described in the available literature. By pooling all available data the average mortality was calculated for 25,339 patients where ICU outcome was known and for 74,061 patients where hospital outcome was known. Average mortality across all included studies demonstrated an ICU mortality of 31.2% and hospital mortality of 38.2%. This is considerably lower than that which has been historically reported for the ICU cancer population [79-81]. Cancer patients should therefore not be excluded from ICU exclusively based on having an underlying malignancy as has previously been suggested and instead those factors that are known to be associated with survival should be taken into account.

2.4.2 Factors associated with survival

A number of studies reported factors that were associated with survival. Poorer physiological status was associated with poorer short-term survival including ICU and hospital survival. However, the range of different severity of illness scoring systems employed, and the absence of any measure from some studies makes summary estimates difficult in this patient group. The total number of organ failures present has also been linked to mortality and it is likely that this is also a reflection of severity of illness. All types of organ failure were associated with a poorer outcome. However, of these, requirement for invasive mechanical ventilation had the strongest effect on mortality. In addition, poor chronic health or limited functional status has been demonstrated to be associated with poorer survival. These findings are consistent with those seen in the general ICU population and are not specific to cancer patients. When compared to surgical admissions to ICU, patients that have a medical admission have an increased risk of short-term mortality. This effect has been demonstrated in the non-cancer population in the past but the paper by Bos et al [95] suggests that it may be exaggerated in patients with cancer. When describing outcomes for cancer vs. non-cancer patients in the surgical population they report ICU mortality of 9% vs. 8.9% ($p = 0.8$) and hospital mortality of 17.4% vs. 14.6% ($p < 0.001$). This compares to the medical patients with an ICU mortality of 30.4% vs. 16.2% ($p < 0.001$) and hospital mortality of 44.6% vs. 23.7% ($p < 0.001$).

Whilst tumour type was not demonstrated to be associated with mortality in any of the individual studies, the average mortality by tumour types described in this systematic review varies widely. This may suggest that there is variation in outcome depending on tumour or may be reflective of the different population that make up each tumour group. For example, the ICU population of upper GI cancers are often elective post-operative patients compared with a larger proportion of medical admissions within the lung cancer group. The impact of disease stage and presence of metastasis has been inconsistently associated with mortality and the exact role these factors play is uncertain. Thus, despite around 15% of ICU admissions being for patients with known malignancies [87],

current literature is unable to predict likely survival of the individual cancer patient after ICU admission.

Bos et al noted that many studies which report on prognostic factors mainly involve specialised oncological ICUs, making it difficult to extrapolate to general ICUs where the mixture of tumour types and expertise is different [95]. They suggested that their own study was most appropriately compared to papers by Taconne et al and Soares et al [86, 87]. Even in this limited comparison there were important differences in terms of study size, duration, and discrimination of emergency admissions, medical and surgical patients. Given the paucity and variability of the published literature, to restrict the inclusion criteria for this review further would have been even less informative as more than half of the published data would have been lost with no increase in precision. This is important because although this review summarises the distribution of reported mortality using the average mortality with 95% confidence intervals, the mortality reference range of published studies is justifiably very wide.

2.4.3 Longer-term outcomes

Longer-term outcomes for ICU cancer patients are only reported in 12 of the 47 included studies. Six month mortality is low for the group in Cense's study of patients following elective oesophagectomy at 17.4% [124], however, in the six other studies that report it this varies at 48.2 – 77.1%. Mortality in the study by Cense increased with time to 39.4%, 56% and 68.8% at one, two and three years.

Oeyen et al described a group that comprised of a large proportion of elective post-operative patients [111]. One-year mortality for this group was 35.9% and is at the lower end of the range due to the nature of admission and likely pre-operative selection of patients with little co-morbidity and potentially curative disease.

The longer-term outcomes reported by Song et al in their 2007 paper pertain to a group patients undergoing major thoracic surgery for either lung or

oesophageal cancer who had been readmitted to ICU during the same hospitalisation [143]. While readmission is a major adverse event for this patient group, they will have almost certainly been subject to selection bias in terms of fitness for major surgery and will have had potentially curative disease. In spite of this, one-year mortality was 54.3% and three year mortality 66% for this group.

The study by Caruso et al reported on patients with metastatic disease at presentation to ICU [113]. Longer-term outcomes in this group were particularly poor with one and two year mortality rates of 88% and 97.6% respectively. Toffart et al studied a group of non-resectable lung cancer patients [146] and described one year mortality of 87.4%, similar to Caruso's group of patients with metastatic disease.

Bissell et al reported longer-term outcomes for their group of patients undergoing elective oesophagectomy that were readmitted to ICU [122]. None of their patients had metastatic disease and again were likely to have the same selection biases as described before for patients undergoing major thoracic surgery. One-year mortality for this group was 58.1% and five-year mortality 62.8%.

The number of patients included in these longer-term follow up studies were low and it remains difficult to make any generalisable summations as the groups were so disparate. Those with advanced disease such as that described by Caruso and Toffart had very poor outcomes in the longer term. It is difficult to know if this was due to the underlying cancer or was in any way attributable to the critical illness. However, even those patients undergoing elective surgical interventions (presumably with curative intent) and pre-operative selection bias had a significant risk of mortality at one, three and even five years.

2.4.4 Conclusions

This systematic review identified 47 papers that reported survival outcomes for cancer patients with solid tumours. The pooled mortality across the published literature was 31.2% ICU mortality and 38.2% hospital mortality. Outcomes appear to vary significantly depending upon underlying tumour types. While several studies identified performance status and cancer stage as impacting upon ICU and hospital mortality the factors associated with short-term outcomes are more commonly related to the critical illness such as severity of illness scores, organ support, medical admissions and sepsis. Current evidence on outcomes in cancer patients after admission to ICU would be improved with additional clinical details, reporting outcomes in clearly defined groups and producing further prognostic information on those factors that are associated with poorer survival.

Whilst oncological ICUs provide a large patient population in which to study these patients, they may not be representative of the general ICU cancer population and therefore additional studies require to be performed on both groups. Where patients are admitted to general ICUs, there is value in reporting comparative outcomes for non-cancer patients to allow calculation of the additional risk posed by having cancer both in the short and longer-term. In addition to describing survival over the short, medium and longer terms, research is needed to describe which cancer patients are likely to require ICU care.

2.4.5 Strengths and weaknesses

This systematic review and meta-analysis has summarised the literature on outcomes for patients with a solid tumour that are admitted to ICU. The findings show heterogeneity in reported mortality reflecting differences in case-mix, patient selection criteria and international ICU bed availability and practices.

This study has a number of strengths including being the first systematic review on outcomes among cancer patients admitted to ICU. It consolidates and summarises a large volume of information form multiple primary published sources. Generalising the findings of individual studies to a local population is problematic for a number of reasons. There are international variations in the definition of ICUs and in the case-mix of patients they treat with corresponding variability in outcomes. Within the same country outcomes may vary between hospitals, particularly where specialised tertiary units are concerned such as oncological, neurosurgical or cardiothoracics. Furthermore, individual studies often focused on a specific population whether that be tumour type, grade or management. By generating pooled mortality for ICU cancer patients this study gives an estimate of the average mortality across the globe but may not reflect what is seen within an individual unit.

The principal weakness of this study is that including all studies within this field has resulted in a heterogeneous population. Studies were included whether the focus was on the general ICU cancer population or a subgroup such as those with sepsis, a specific organ failure or an individual tumour type. The differences in terms of patient population, types of cancer, or type of patients (surgical vs. non-surgical) are selection biases that contribute towards the heterogeneity we report. As a result there are large differences between the study populations of the included papers, which is reflected in the distribution of mortality rates that they report. Outcomes are worse for medical admission versus surgical admissions to ICU and this effect seems to be exaggerated within the oncological population. For example, the three studies with the lowest mortality [111, 130, 137] include mainly elective surgical patients. In contrast, the studies with higher mortality [92, 97, 105, 113] included only a few surgical patients and instead selected patients based on their severity (mechanical ventilation and at least one additional organ failure) [92]; only patients requiring renal replacement therapy [105], the extent of the underlying disease [113] or both. The difference in reported mortality is therefore to be expected.

While the systematic review excluded publications that reported on ICU populations that entirely pre-dated 1st January 2000, there were 15 of the 47 included studies that consisted of a population that partially pre-date the year

2000. The decision was taken to include these studies although it is possible that in doing so this has introduced a small proportion of patients who were managed in ICU with historical practices.

2.4.6 New literature published since performing the systematic review

Since performing the systematic review in 2014, there have been a number of publications pertaining to outcome of cancer patients in ICU. Twelve of the most relevant studies have been summarised in table 7-1. Mortality for a group of mixed solid tumours was reported in papers by Wohlfarth, Champigneulle, Lee, Xia, Fischer, Auclin, Ostermann and Ha [112, 152-158]. ICU mortality varied from 14.9% to 75.3% and hospital mortality from 26.4% to 57.1% suggestive of significant differences in the studied populations. Mortality by specific tumour types were reported by Bos (lung, head and neck, colorectal, pancreatic, oesophageal, urinary tract, breast and prostate) [159], Hawari (lung, gynaecological, breast, gastrointestinal and genitourinary) [160], Soares (lung) [161] and Destrebecq (breast) [162].

Wohlfarth et al describe a population of cancer patients receiving chemotherapy in the ICU [152]. Their cohort was predominantly made up of patients with haematological malignancies. However, they do describe a hospital mortality of 57.1% in the seven solid tumour patients in their cohort.

Champigneulle et al describe a mixed cohort of cancer patients admitted to ICU after cardiac arrest [153]. Among the 81 patients with a solid tumour only 24.7% survived ICU. While the authors advocate for the admission of cancer patients to ICU following cardiac arrest, this should only be undertaken in the context of alternative positive prognostic factors as the outcomes for this group have been demonstrated to be particularly poor.

Author	ICU features	Cancer features	ICU	Hospital	Six month	One year	Two year
Wohlfarth (2014)	Single centre oncological ICU	Mixed tumours receiving chemotherapy in ICU	-	57.1%	-	-	-
Champigneulle (2015)	Multi-centre general ICUs. Patients post cardiac arrest	Mixed solid tumours	75.3%	-	-	-	-
Lee (2015)	Oncological ICU	Mixed solid tumours	-	-	-	26.5%	-
Xia (2016)	Single centre oncological ICU	Metastatic solid tumours	14.9%	29.8%	-	-	-
Fisher (2016)	Single centre oncological ICU, low severity of illness	Mixed solid tumours (42.7% lung cancer) with metastatic disease in 33.3%	-	31%	52.2%	-	-
Auclin (2017)	Age over 64 years. High severity of illness scores	Mixed solid tumours	33.6%	43.9%	-	-	-
Ostermann (2017)	General ICUs included in ICNARC	Mixed solid tumours	17.1%	26.4%	-	-	-
Ha (2017)	Single centre oncological ICU	Metastatic solid tumours	-	35%	-	77%	-

Author	ICU features	Cancer features	ICU	Hospital	Six month	One year	Two year
Bos (2015)	Multi-centre general ICUs	Lung	-	-	36%	47%	
		Head and neck			42%	49%	
		Colorectal			38%	51%	
		Pancreatic			44%	53%	
		Oesophageal			28%	40%	
		Urinary tract			43%	58%	
		Breast			36%	43%	
		Prostate			20%	25%	
Hawari (2016)	Single centre oncological ICU	Lung	41.6%	-	-	-	-
		Gyn	41.4%				
		Breast	36.6%				
		GI	36.0%				
		GU	31.3%				
Soares (2014)	Multi-centre general ICUs. Low use of IMV	Lung cancer (41% with metastatic disease)	28%	39%	55%	-	-
Destrebecq (2016)	Single centre oncological ICU. Low severity of illness scores	Breast cancer	15%	28%	-	-	-

Table 2-7 Mortality reported for solid tumour patients after an ICU admission in publications since April 2014

The study by Lee et al described a population of cancer patients admitted to an oncological ICU after medical emergency team activation [154]. The majority of their results are for a mixed population of haematological and solid tumours but they do report one-year survival for the group with solid tumours at 26.5%. This is poorer than the 65.6% one year survival described in this thesis, however, the population is likely to differ in terms of oncological versus general ICU in addition to the bias introduced by only including those patients that had deteriorated on a ward such that the emergency team were activated.

Xia et al in 2016 reported on 141 patients with metastatic solid tumours admitted to an oncological ICU between 2012 and 2015 in China [155]. Severity of illness scores were reported with median APACHE II 21 and SOFA 9 on admission, suggesting a moderate severity of illness. In this cohort ICU mortality was 14.9%, hospital mortality was 29.8% and median overall survival was 17 months. While these measures of short-term mortality are similar to that described in this thesis the authors do not report any longer-term survival which might be expected to be poor given the underlying metastatic disease.

The study by Fisher et al reported results for patients with a solid tumour from a single centre London oncological ICU [112]. This population had a large proportion of lung cancer patients (42.7%) and one third of all patients had metastatic disease. Of note, the burden of critical illness was low and 37.3% of patients did not have any organ failures at ICU admission. Consistent with this is the relatively low use of organ support reported (20% vasopressors, 8% RRT, 18% IMV). In spite of these favourable features associated with critical illness hospital mortality was 31% with six-month mortality 52.2%. This may represent differences in the selection criteria of patients admitted to oncological ICUs compared with that in general ICUs.

An older ICU cancer population is described by Auclin et al who have reported outcomes for ICU patients with solid tumours that are aged 65 years or older at ICU admission [156]. Severity of illness was high with a mean SAPS II score of 61.9. Mortality was described at 33.6% for ICU, 43.9% for hospital and 51.9% for 90-days. In addition, post-ICU anticancer therapy was described, with only 52.7% of patients with indications for post-ICU treatment receiving it.

In the UK, Ostermann et al have performed a review of the ICNARC database and identified almost 40,000 patients with a solid tumour and admission to general ICUs between 2009 and 2013 [158]. Metastatic disease was present in over one fifth of patients. Median APACHE II score was 17 and less than half of the population received level three support during the first 24 hours. Of all the studies published in this field, the population in this paper most closely resembles the ICU cancer population described in this thesis, being both based in the UK and within general ICUs. It is therefore unsurprising that ICU and hospital mortality is similar (17.1% and 26.4% respectively) to that described in the West of Scotland population (14.7% and 25.7%). However, the study was limited to that information held within the ICNARC database. This dataset was not linked to any cancer registry and the quality of the cancer data may be questionable. Furthermore, the lack of data linkage limits the survival analysis to hospital mortality and longer-term survival is unknown.

In a published abstract by Ha et al survival up to one year was described in a population of 101 ICU patients with metastatic malignancy [157]. This study demonstrated hospital mortality at 35%, comparable with that found in the meta-analysis in addition to one-year mortality of 77%. There is little additional data provided in the abstract in terms of describing the nature of the critical illness and therefore it is unclear whether this cohort is similar to ICU cancer populations previously described.

Bos et al made a further publication in 2015 on their previously described population of the rate of ICU cancer patients in the Netherlands between 2006 and 2011 [159]. This study described the ICU admission rate among cancer patients in addition to tumour specific one and two year survival. This included lung (64% one-year survival and 53% two-year survival), head and neck (58% and 51%), colorectal cancer (62% and 49%), pancreatic (56% and 47%), oesophageal (72% and 60%), urinary tract (57% and 42%), breast (64% and 57%) and prostate cancer (80% and 75%).

Tumour specific ICU mortality was also described in the study by Hawari et al [160]. Their study was based in a single centre oncological ICU in Jordan and also noted that one in five patients with solid tumours admitted to their hospital

required ICU admission. ICU mortality varied by cancer type and was reported for lung (41.6%), gynaecological (41.4%), breast (36.6%), GI (36.0%) and genitourinary tumours (31.3%).

In 2014 Soares et al published a multi-centre international study of lung cancer patients in ICUs admitted during 2011 [161]. They identified 449 patients (88% NSCLC) or which 41% had metastatic disease. Just over half of the group received ventilatory support at admission to ICU and mean SAPS II score was 46.1. Outcomes were described as: ICU mortality 28%, hospital mortality 39%, 30-day mortality 41% and six-month mortality 55%. This survival was more favourable than that described in the majority of previous lung cancer studies or in the average mortality in this meta-analysis. However, the low requirement for ventilatory support may have impacted on the outcomes for this group of patients.

Breast cancer patients admitted to an oncological ICU in Belgium between 2009 and 2014 were described in a study by Destrebecq et al [162]. Median SAPS II score of 34 and median SOFA score of 2 suggest that this cohort had a relatively low burden of critical illness. They reported an ICU mortality of 15% and hospital mortality 28% for their group of 175 patients. While this is lower than that previously reported for breast cancer ICU patients, it is the likely that this reflects the mild severity of illness seen in this group. However, it is worth noting that this is the largest group of breast cancer patients described in the literature and may be reflective of the severity of illness and outcomes seen for this population.

This group of newer publications continue to demonstrate significant variation in outcomes dependent on the population being studied. There is still a tendency to describe outcomes for a mixed group of cancer patients and in spite of clear evidence that survival varies by underlying tumour type. Furthermore, there are differences in the populations studied in terms of ICU and critical illness features including admission criteria, general/ oncological ICUs, severity of illness and organ support utilisation. In addition, some studies are restricted to a subgroup of the ICU cancer population such as those patients aged over 64 years, patients admitted following cardiac arrest, patients with metastatic disease or patients

that receive chemotherapy during their ICU stay. These variations in case mix and inclusion criteria make comparisons between studies unhelpful.

2.5 Key points

- Outcomes vary significantly across studies demonstrating differences in international and hospital specific case-mix and illness severity, in addition to targeted population analyses.

- Pooled estimate of mortality across all reporting studies found mortality within ICU was 31.2% and hospital mortality was 38.2%.

- Factors associated with ICU and hospital mortality were most commonly related to the critical illness such as severity of illness scores, organ support, medical admissions and sepsis.

- Longer-term mortality was rarely reported making pooled estimates unhelpful due to the small numbers.

- ICU and hospital mortality appears to vary by underlying tumour type and generally patients with lung cancer seem to have higher mortality rates than that reported for other tumour types.

Chapter 3 Methods

In a systematic review of the literature on outcomes in cancer patients admitted to ICU, the need for more up-to-date UK-based literature was identified. Given the variation in outcomes based upon case-mix future studies should detail outcomes for subgroups within the study population. In this large retrospective observational study I identified patients resident in the West of Scotland region who had a diagnosis of a solid cancer on the Scottish Cancer Registry between 1st January 2000 and 31st December 2009. I then determined whether they had been admitted to one of the 16 general ICUs located in the region within two years following the date of cancer incidence. I then compared the clinical and demographic features of this group to those ICU patients who did not have a diagnosis of cancer. Finally, long-term survival was assessed in ICU survivors and the degree to which this was affected by a diagnosis of cancer.

3.1 Setting

The West of Scotland region, UK, has a population of 2.4 million and comprises approximately half of the Scottish population. This region was chosen because it is the area that I work within and therefore have links with the ICUs included. It is predominantly urban with the majority of the population living in large towns or within the city of Glasgow, however, it does have a mix of urban and rural population and a good range of socio-economic backgrounds. Scotland has a high incidence rate for cancer. Cancer survival within the UK does not compare favourably with the rest of Europe [163] and cancer is the commonest cause of death within the Scottish population [164].

There were 16 general ICUs in the area during the study period. Some functioned as combined ICU/HDUs for some or all of the period. The total number of funded beds within the West of Scotland ICUs varied during the study period from 77 to

104.25 [165]. Throughout this time the number of funded HDU beds within combined units also varied although was consistently lower than the number of ICU beds funded (Figure 3-1).

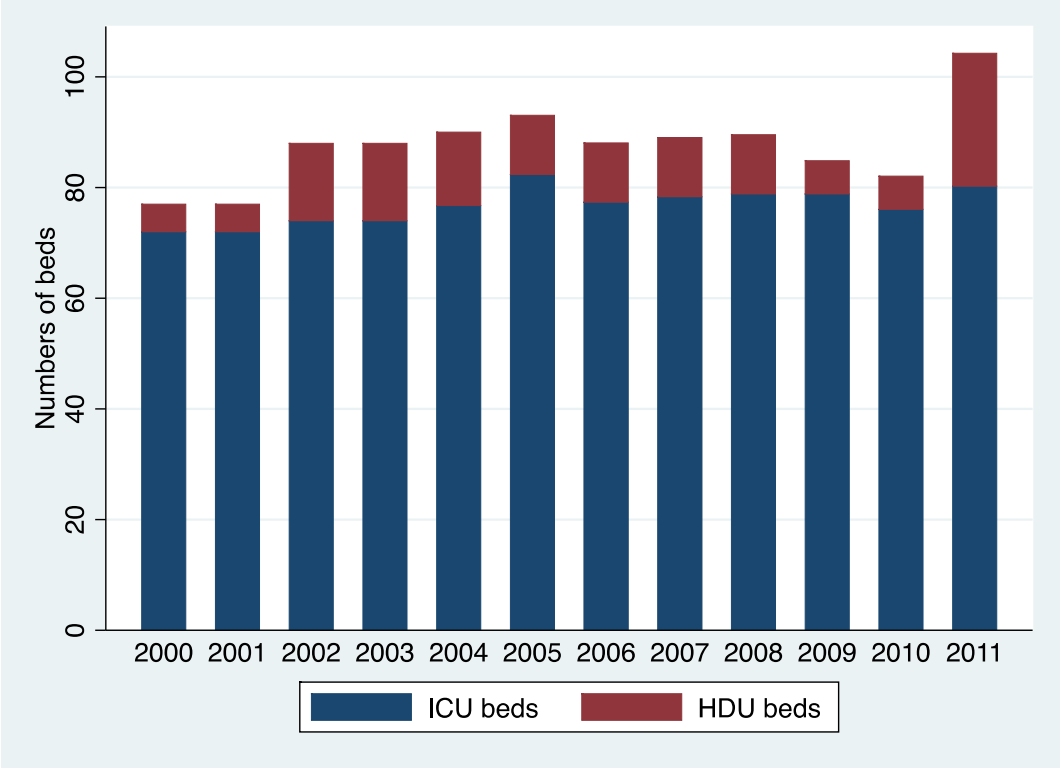


Figure 3-1 Total number of funded beds across the West of Scotland ICU's during the study period by ICU and HDU support.

The participating hospitals comprised of Ayr Hospital, Crosshouse Hospital, Dumfries and Galloway Royal Infirmary, Falkirk and District Royal Infirmary, Forth Valley Royal Hospital, Glasgow Royal Infirmary, Hairmyres Hospital, Inverclyde Royal Hospital, Monklands Hospital, Royal Alexandra Hospital, Stirling Royal Infirmary, Southern General Hospital, Stobhill Hospital, Victoria Infirmary, Western Infirmary and Wishaw General Hospital.

Glasgow Royal Infirmary, Southern General Hospital, Stobhill Hospital, Victoria Infirmary and the Western Infirmary were all city centre teaching hospitals. The remaining hospitals were district general hospitals within the area. Hairmyres Hospital functioned as a combined ICU/ HDU throughout the study period. The unit in Wishaw General Hospital was a combined unit from 2002 – 2008 and the

unit in the Western Infirmary was combined from 2002 - 2010. Falkirk and District Royal Infirmary was a combined unit that transferred to Stirling Royal Infirmary. The HDU beds transferred in 2004 followed by ICU beds in 2005. Stirling Royal Infirmary subsequently transferred to a new site at Forth Valley Royal Hospital in 2011 which functioned as a combined ICU/ HDU. Stobhill hospital closed in 2011 and transferred its ICU beds to Glasgow Royal Infirmary. The new critical care unit at Glasgow Royal Infirmary, which opened in 2011 with the transfer of Stobhill Hospital, also included funding for HDU beds and therefore functioned as a combined unit from that point.

In 2010 the Golden Jubilee National Hospital (GJNH) opened in the West of Scotland and all cardiothoracic procedures including lung resection for cancer were centralised at this time. During the study period the GJNH did not utilise Wardwatcher for collection of ICU data and therefore has not been included in this analysis.

3.2 Approval for data analysis

Permission to use Wardwatcher ICU data was obtained from each of the audit lead Consultants from the ICUs involved in addition to the West of Scotland Critical Care Research Network and the Scottish Intensive Care Society Audit Group (SICSAG) who own the Wardwatcher data.

Use of the West of Scotland Cancer Registry data was authorised by Dr David S Morrison, Director, West of Scotland Cancer Surveillance Unit as data controller of the West of Scotland extract of the cancer registry. Dr Morrison has previously obtained authorisation from all Caldicott Guardians of the West of Scotland Health Boards for use of their cancer registry data for the purposes of improving the quality of cancer services in the NHS.

Ethics approval was sought and granted to create a research database from the local research ethics committee using the Integrated Research Application System, REC reference 12/WS/0075 (Chapter 8-2 Appendices).

The SMR linkage, consistent with other routine NHS hospital care and cancer registration systems, does not require expressed consent from patients, as it is a clinical administration (rather than principally research) system. Any benefits from obtaining patient consent were felt to be outweighed by the potential harms (including contacting deceased patients' relatives). Due to the retrospective nature of the data analysis it was very unlikely that any patient harm was possible.

Following ethics approval an application was made to the Privacy Advisory Committee (PAC) for release of ISD data. This involved completion of PAC application to use personal health information for health research or audit form. The application for this data release was granted from the privacy advisory committee. The requested data was provided and formed the initial dataset that was used for analysis.

3.3 Data sources

The data used for analysis were linked data from four large Scottish datasets: the Scottish Cancer Registry, Scottish Morbidity Record 01 (SMR01), National Records of Scotland death records, and the Scottish Intensive Care Society Audit Group (SICSAG) Wardwatcher ICU database. Information Services Division (ISD) of NHS National Services Scotland collects the data from each of these sources and links them using Community Health Index (CHI) numbers and probabilistic linkage procedures. Every patient in Scotland has a unique ten-digit CHI number that is allocated on first registration and can be used to identify individuals. This linkage of datasets by CHI numbers occurs routinely within ISD.

3.3.1 Scottish Cancer Registry dataset

The Scottish Cancer Registry (SMR06) collects information on all new cases of cancer including primary malignant neoplasms, carcinoma in situ, neoplasms of uncertain behaviour and benign brain and spinal cord tumours. Cancer diagnoses are coded to the International Classification of Diseases 10th revision (ICD-10). The registry began in 1958 collecting personal, demographic and diagnostic information (such as site, histology, behaviour, histological confirmation and hospital of diagnosis) from cancer patients. In 1997, a new electronic cancer recording system was launched as part of a centralisation process at ISD. At this point the registry was extended to include extra information on tumour stage (for breast, cervical and colorectal cancer), tumour grade and treatment information such as surgical interventions, radiotherapy, chemotherapy and hormone therapy. Cancer incidence is dated as the earliest point that the cancer is likely to have existed. This may predate pathological diagnosis if there were symptoms, signs or radiological suggestion of tumour prior to pathological diagnosis. It is possible for patients with a cancer diagnosis only confirmed after death to be entered into the registry if, for example, the patient undergoes laparotomy with resection of tumour but dies prior to pathological result or where the patient has been symptomatic but the diagnosis is only confirmed at post mortem examination.

A wide variety of geographical data is also included in the dataset including Scottish Index of Multiple Deprivation (SIMD), census output area, NHS Board, Electoral Ward and Parliamentary constituency. Each cancer diagnosis constitutes an entry and a patient can have more than one Cancer Registry entries if they have more than one cancer diagnosis. Over 50,000 records of primary invasive and non-invasive cancers are added each year.

Completeness of the patient Community Health Index (CHI) number influences the ability to link data to other indexed datasets deterministically. In the most recent few years completeness is over 99%, and has been over 90% since 2005. Prior to this CHI could not be relied upon for linkage (only present for 56% of

cases in 2000) and patients were linked on probabilistic methods. This involved linkage of two records based on the likelihood of the records being for the same patient. The probability was determined by comparison of other patient identifiers including name, date of birth and postcode.

The West of Scotland cancer registry is a subset of SMR06 held by the West of Scotland Cancer Surveillance Unit pertaining to all of those patients resident in the West of Scotland. This was used for identifying the cancer patients that were not admitted to ICU cohort.

3.3.2 Scottish Morbidity Record 01 dataset

The General/ Acute and Inpatient Day Case dataset (SMR01) has collected episode level data on hospital inpatient and day case admissions from acute specialities in Scottish hospitals since 1961. The dataset contains patient identifiers, demographic data (including age, sex and SIMD) and data pertaining to the clinical episode such as hospital, ward type, admission type, diagnosis (as classified under the international statistical classification of diseases and related health problems version 10 (ICD-10)), operative interventions, and discharge location. Each patient hospitalisation generates a new record and therefore patients may have multiple SMR01 records. Approximately 1.4 million records are added to the SMR01 dataset annually. Multiple episodes can constitute a single admission to hospital as an episode is created when any of the following occur: inpatient/ day case admission to NHS hospital, change in specialty, transfer to another hospital, transfer to another consultant, change in significant facility (including ICU or HDU) or return to hospital after being on pass for greater than five days. The main data fields in the SMR01 database used in this project were patient demographics, dates of admission and discharge and types of admission.

The SMR01 dataset utilises a patient's CHI number to link data deterministically to the other indexed datasets and the CHI number is then attached by ISD to historical records retrospectively to improve linkage. In recent years SMR01 data

has been demonstrated to be 98 – 99% complete and external validation checks are in place within ISD.

3.3.3 National Records of Scotland Death Records dataset

National Records of Scotland (NRS) records all deaths registered in Scotland in a database that has been established since 1974. The dataset includes information pertaining to cause of death, date of death, age at death and place of death. The NRS undergoes regular quality assurance checks to ensure data accuracy and the quality of data is of a high standard. This NRS is linked to the ISD datasets and for patients on the Cancer Registry additional confirmatory checks are made on death data by the Cancer Registry team.

3.3.4 SICSAG Wardwatcher dataset

The SICSAG has maintained a national database of patients admitted to adult general ICUs in Scotland since 1995. The SICSAG Wardwatcher audit system is in place in all general adult ICUs throughout Scotland. It collects data on patient demographic details, admitting specialty, admission diagnosis, patient's prior location, co-morbidities and type of organ support for all ICU admissions. Audit data is collected prospectively and is completed by individuals within the participating unit such as clinicians, nursing staff and clerical staff. It has been routinely linked to ISD data, including SMR01, since 2006 and historically back to 1998. All patients recorded in the SICSAG database should have SMR01 records relating to the same hospital stay. From 1998 to 2014, 96% of all SICSAG episodes were matched to an SMR01 stay.

The data is collected within each unit and directly inputted into the Wardwatcher data collection form and stored on the hospital computer system. With each ICU admission, a form is created with a specific key number for that admission. If a patient has multiple admissions to ICU then they will also have

multiple key numbers thus the key number identifies an ICU admission rather than a patient. For each ICU admission, data is collected pertaining to patient identity and demographics, hospital admission type and source, circumstances of ICU admission, past medical history, diagnosis, severity of illness, organ support and discharge details. The demographic details are collected on an admission page (Figure 3-2).

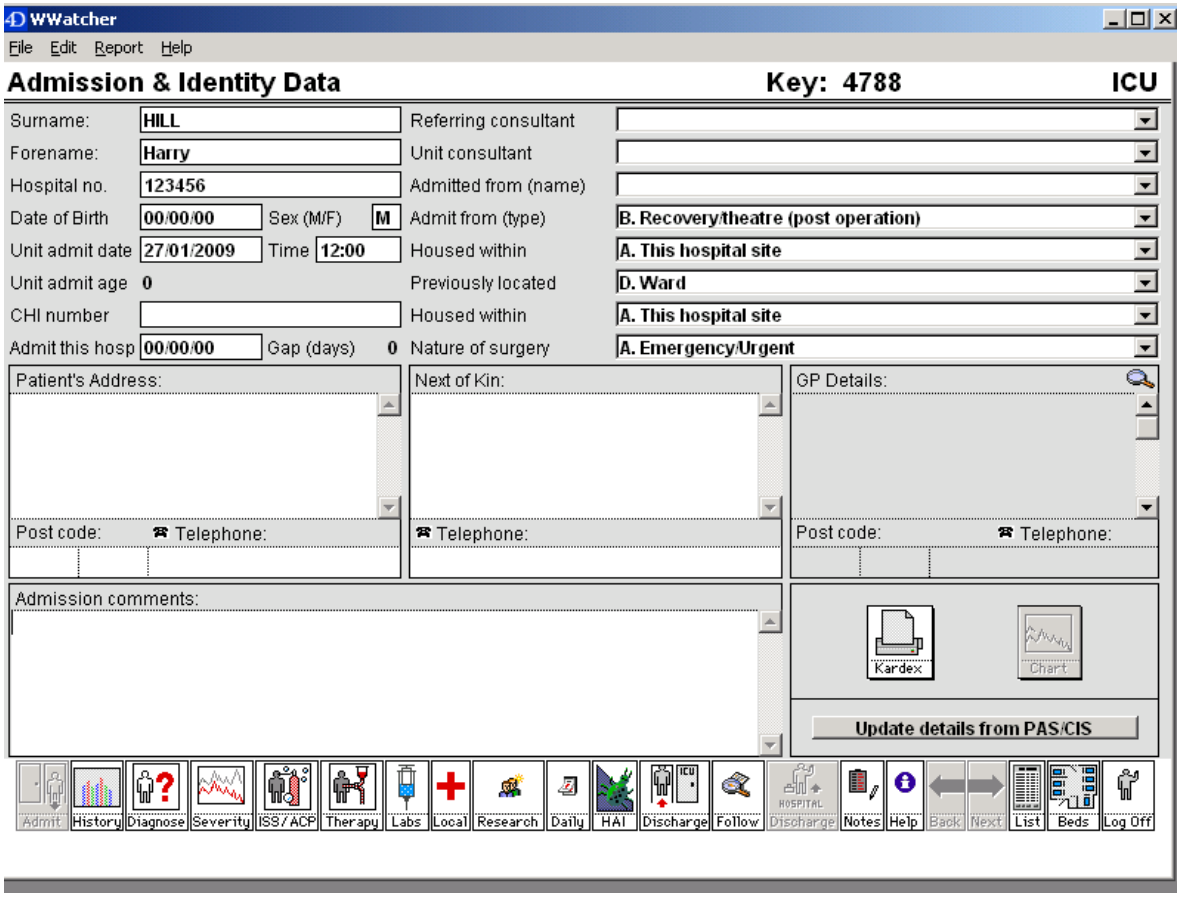


Figure 3-2 SICSAG Wardwatcher admission data entry screen

Separate data entry pages are used for admission circumstances, co-morbidities and diagnosis. Comorbidities recorded on the history section of the Wardwatcher system are strictly defined as per the APACHE definitions. Diagnostic information is collected as a selection from a potential list of 212 APACHE pre determined diagnoses. In addition there is also a section for the SICS diagnostic coding which allows for a larger range of diagnoses in addition to free text options.

The severity of illness section collects data required for the calculation of an APACHE II score. This data may be entered manually or automatically transferred from a clinical computer system if in use.

The Augmented Care Period (ACP) data is collected on a daily basis and records the highest level of care for that period based on the support of five organ systems. This data includes information pertaining to organ support including mechanical ventilation, cardiovascular support (with vasoactive drugs) and renal replacement therapy. Additional information from ACP includes neurological monitoring, nutritional support and requirement for complex dressings.

On ICU discharge the final data entry screen is completed with information on whether the patient is alive or dead at ICU discharge, discharge destination and expected hospital outcome.

SICSAG and Wardwatcher have a number of processes to ensure data quality. At the point of data entry, Wardwatcher has been programmed to query data entries that are incongruous or unexpected. For example, if the ICU discharge date is input for a date prior to ICU admission then the system will query this. In addition, case note validations are undertaken periodically throughout the year by Quality Assurance managers and Co-ordinators during site visits. Finally central validation takes place where missing data fields are queried with the local co-ordinator and age and length of stay are validated against that documented in the SMR01 dataset.

SICSAG episodes were matched to SMR01 stays using the dates of hospital and ICU admission and discharge. This allowed identification of type of hospital admission, admitting specialty and discharge date. All SICSAG records should be represented in the SMR01 dataset as an in-patient stay. However, a small proportion of SICSAG records were unable to be linked to the SMR01 dataset because they fell below the linkage threshold for probabilistic matching. This may be due to inaccuracies with data entry within the patient identifier section.

3.4 Inclusion criteria

3.4.1 Cancer patients

Patients were included in the cancer population if they were aged 16 or older, resident in the West of Scotland, and had a diagnosis of a solid tumour as defined by ICD-10 codes (C00-C76, excluding non-melanoma skin cancer C44 and CNS neoplasms C69-C72) in the Scottish Cancer Registry between 1st January 2000 and 31st December 2009. Patients were excluded if they had a diagnosis of haematological malignancy (ICD-10 codes C81-C96, D45-D47) because there has been a separate series of significant changes in guidance for treatment and support of patients with haematological malignancies over the study period. Patients with CNS neoplasms (ICD-10 codes C71-72, D32-33, D35.2-35.4, D42-D43, D44,3-D44.5)) were excluded because they are more likely to be admitted to a specialised ICU. For simplicity, patients who had more than one cancer were grouped separately under the label “Multiple cancers”. The incidence date of the earliest diagnosed tumour was used in cases of multiple cancers.

3.4.2 ICU patients

The ICU population was defined as having an admission to one of the 16 general adult ICUs in the West of Scotland between 1st January 2000 and 31st December 2011 as identified by the Wardwatcher database. If a patient had more than one ICU admission we used the date and outcome of the first ICU admission. Patients that were admitted to a combined unit during this time were considered to be an ICU patient.

3.4.3 ICU Cancer population

Patients that were identified as having a solid tumour between 1st January 2000 and 31st December 2011 and had an ICU admission up to two years after the date of cancer incidence were defined as the ICU cancer group. This time period was chosen so that the cancer population were likely to have either active disease or be undergoing treatment for their cancer at the time of ICU admission.

3.4.4 ICU Non-Cancer population

The ICU non-cancer population were those patients within the ICU population who do not appear on the Cancer registry at any point. Patients with a diagnosis of cancer after their ICU admission were excluded from this group and included in the "Cancer Non-ICU population". This was to ensure that ICU admissions due to an undiagnosed cancer were not included and to guarantee that cancer did not impact upon survival of patients in the non-cancer group.

3.4.5 Cancer Non-ICU population

Patients with cancer confirmed on the West of Scotland cancer registry (SMR06) that are not admitted to ICU at any point after 1st January 2000 were considered to be the cancer non-ICU population. No restrictions were made on cancer patients that had been admitted to ICU prior to cancer diagnosis.

3.5 Definition of variables

3.5.1 ICU Diagnosis

Within the diagnosis screen of Wardwatcher there are several options for defining the diagnosis that are used for different purposes. These include the APACHE diagnosis, the SICS hospital admission diagnosis and the SICS ICU admission diagnosis.

The APACHE diagnosis pertains to ICU diagnosis and is required to calculate the predicted mortality from the APACHE score. The APACHE diagnosis is a broad classification designed to divide patients into groups whose reason for admission has a similar impact or mortality probability. There are a limited number of options that are determined by whether the patient was admitted from theatre/ recovery (limited to 94 surgical diagnoses) or not (limited to 118 medical diagnoses). In some circumstances patients may be admitted to ICU for medical reasons following surgery (e.g. dysrhythmias during routine surgery). In this case the APACHE diagnosis would be the surgery that the patient underwent. In other circumstances, patients may be admitted to the unit from a ward within hours of undergoing surgery. In this situation the diagnosis would be the medical condition that precipitated admission not the surgical diagnosis. This strict criterion stems from the APACHE methodology and can be misleading when used for descriptive studies.

In addition to APACHE diagnosis, Wardwatcher also collects data from SICS diagnostic coding. This is a list of diagnoses created by the Scottish Intensive Care Society that groups patients into categories that are more useful descriptors of the types of patients being admitted to Scottish units. Within the SICS diagnostic coding there are entries for “Diagnosis requiring hospital admission” and “Diagnosis requiring unit admission” and these options are not limited by whether the patient was admitted from theatre or another source. In addition to the available diagnoses there are options for free text to allow additional details to be provided.

As fewer restrictions are placed on the SICS diagnostic coding this was used as the principle source of ICU diagnosis. Different diagnoses were categorised into diagnostic groups to allow broad descriptions to be made. Details of these categories are listed in Appendix table 8-3.

3.5.2 Admission type

3.5.2.1 Hospital admission specialty

Patients were considered to be surgical or medical hospitalisation depending on the admission sub-specialty documented at hospital admission in the SMR01 dataset. The SMR01 further documents whether the hospitalisation during which the ICU admission occurred was emergency or elective in nature. This allowed categorisation of hospital admission type into elective surgical, emergency surgical, elective medical or emergency medical.

3.5.2.2 ICU admission specialty

ICU admission specialty was taken from the Wardwatcher database using the data collected on the history screen under admission specialty. It is not documented whether the admission to ICU was planned (elective) or emergency in nature.

3.5.3 Organ support

The ACP section of Wardwatcher was used to determine delivery of organ support. Organ support was defined as the patient receiving any of mechanical ventilation via endotracheal tube or tracheostomy, vasoactive support (single or multiple) or renal replacement therapy of any modality, during their ICU stay. Additional information on organ support was available but not utilised.

Neurological support such as intra-cranial pressure monitoring would not routinely be provided in a general ICU and within the West of Scotland and is only available at the specialist Neuro-ICU. Gastrointestinal support was defined on Wardwatcher as receipt of artificial nutrition. However, this would be considered routine practice on a general ward outwith an ICU, as is dermatological support in the form of significant skin dressings. For this reason gastrointestinal support and dermatological support were not considered to be organ support for the purpose of this work.

3.5.4 Socioeconomic circumstances

Socioeconomic circumstances were measured using the Scottish Index of Multiple Deprivation 2006 (SIMD). This was available through linkage to the SMR01 database. It provides an area-based measure of socioeconomic circumstance, based on the postcode of residence. There are 6505 geographical small areas or data zones across Scotland each containing approximately 750 people. The SIMD score provides a relative ranking of these 6505 areas from the most to the least deprived, based on detailed information on seven key subject areas including: (1) income and benefits (2) employment in working age population (3) health and healthcare utilisation (4) educational attainment, skills and training (5) access to services and transport (6) recorded crime rates and (7) housing quality and overcrowding. The score generated for each key subject area (weighted towards income, employment and education) is ultimately combined to create an overall SIMD score for each data zone. Overall, SIMD 2006 scores are presented as quintiles, with 1 representing the least deprived and 5 representing the most deprived; each representing 20% of the Scottish population. Individual SIMD scores can then be assigned to the population, based on the postcode of residence.

Area-based measures of deprivation such as this one can incorporate data about individual living standards, along with broader issues such as crime, the physical environment, access to services or social capital. However, the system only allows a measure of relative deprivation within Scotland and not absolute

deprivation. Nor is it possible to compare different levels of deprivation in one area across different points in time. However, the primary disadvantage of an area-based measure is that it is not able to provide information about individuals. This is known as the ecological fallacy where conclusions are made about individuals based only on analyses of group data from which that individual belongs. Within each area it does not specify the number of individuals within each deprivation group or the form of deprivation experienced by any individual or groups. The practical reality is that the data is not currently available to produce an individual measure with the same detail and comprehensiveness as SIMD and that this is the best available system for making these measurements.

3.5.5 Survival data

Date of death was taken from NRS dataset as this is the most valid basis of identifying a death record. Place of death was defined as occurring in ICU if this had been recorded in WardWatcher as such. Death in hospital was determined when death had not occurred in ICU as per Wardwatcher but had occurred prior to or at the discharge date recorded on the corresponding SMR01 data entry. For patients without a corresponding SMR01 record, Wardwatcher hospital outcome was used to determine hospital survival.

3.6 Missing data

3.6.1 Organ support/ ACP

Data pertaining to organ support was collected daily on the Augmented Care Period (ACP) form within Wardwatcher. The ACP uses the organ support data to

determine the level of care received by the patient on a daily basis and differentiates ICU and HDU patients.

The Wardwatcher data collection form for ACP was changed in 2004. ISD did not collect the ACP data prior to 2004 and this was unavailable on the initial linked dataset. However, the original data pertaining to organ support was still available on the Wardwatcher computers within each hospital site. To ensure the maximum amount of data was available each of the 16 included hospital sites were visited and the Wardwatcher computer interrogated for the pre 2005 ACP data. This data was collected from these original sources and added to the full dataset by means of deterministic matching based on CHI, name, date of birth and postcode. This allowed the dataset to be as complete as possible, however, a proportion of missing data remained. Receipt of organ support could not be fully ascertained for 15% of patients prior to 2005 mainly because of incomplete renal support data. The number who received organ support prior to 2005 is therefore underestimated. However the proportion of patients who received renal support only is small (0.8% of patients admitted after 2004) and thus it is unlikely that the missing organ support data would substantially bias the findings.

When describing or analysing the effects of a specific mode of organ support patients with missing data for that organ support were dealt with separately.

When calculating the numbers of organ supported, patients were categorised as not having received the particular organ support if the data was missing for that particular modality. For example, if a patient was known to receive mechanical ventilation and vasoactive drugs but data regarding renal replacement therapy was missing then they were categorised as have received two organ support. Patients with missing data for all three types of organ support were analysed separately as an unknown group.

Level of care data prior to 2005 was unreliable and poorly completed. It was therefore not possible to identify which patients admitted to combined units were ICU patients and which were HDU patients using the ACP level of care data.

3.6.2 APACHE II

Certain groups of patients are excluded from APACHE scoring including patients aged less than 16 year of age; ICU stay less than 8 hours; readmissions to ICU during the same hospital stay; and primary diagnosis for which the system was not developed of validated (e.g. burns, coronary artery bypass graft, and liver transplant). In addition, clinicians within the individual units could opt out of APACHE scoring of selected patients at their own discretion. As a result there are a significant number of ICU admissions without a corresponding APACHE score. For the purposes of analysis, the group with a missing APACHE score was analysed separately.

3.6.3 Survival data

Not all patients that featured on the Wardwatcher ICU database had a corresponding SMR01 entry. Of the 41,689 ICU admissions 40,585 (97.4%) had a SMR01 record corresponding to the ICU admission. If the patient did not have a SMR01 entry then this could not be used to determine whether the patient died prior to or after discharge. The Wardwatcher dataset documents death in ICU or hospital and this has been used to determine in-hospital mortality for those patients without a corresponding SMR01 entry.

For the ICU admission cohort, follow up time started on the day of ICU admission. All patients were followed up until the date of death, or when four years of follow up was completed. Complete follow up was available for all patients.

3.7 Statistical analysis

Statistical analyses were performed using Stata software (version 14, StataCorp 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

3.7.1 Descriptive analysis

Descriptive analysis involved documenting a cumulative count of numbers followed by a percentage of the studied cohort. Unless otherwise stated, median and inter-quartile ranges were used to summarise continuous variables, and Wilcoxon rank sum test (Mann Whitney) to test for differences in median values. Median values were chosen, as the data was not normally distributed. Pearson's chi-square test and exact 95% confidence intervals were used to compare proportions. A significance level of 5% was accepted.

Wilcoxon rank sum test is a non-parametric test that can be used to determine whether two dependent samples were selected from populations having the same distribution [166]. The variable of interest is ordered and the sum of the ranks for each population is then calculated. Where the population is of differing sizes this is accounted for. The smallest value of the sum of the ranks is then compared with a critical value that represents the smallest value that could be expected if the null hypothesis was true. If it is less than the critical value then the null hypothesis is rejected.

Pearson's chi-squared test is applied to sets of categorical data to evaluate how likely it is that any observed difference between the sets arose by chance [167]. This calculates the difference between an observed frequency and expected frequency, squares this value (to ensure a positive value) and divides it by the expected frequency. This is performed for each of the outcome variables and then summed to give a chi-square value. This value, in addition to the degrees of freedom of the dataset (a measure of the number of variables and potential outcomes that determines the potential for variation within the dataset) is then used to calculate a p-value. The chi-squared test has a number of assumptions.

It requires that the sample data is a random sampling from a fixed population where every member of the population has an equal probability of selection. Furthermore the observations are assumed to be independent of each other and each subject can only contribute to one outcome for one variable. A sample with a sufficiently large size is required to avoid committing a type II error (i.e. Incorrectly accepting a false null hypothesis). A minimum number of 20 subjects has been suggested to avoid this or the use of a correction where the expected frequency of events for any given cell is less than five.

3.7.2 Survival analysis

Survival was described in terms of ICU, hospital and time-defined survival. In addition, Kaplan-Meier survival graphs were plotted for specific subgroups using the log-rank test for equality of survivor functions to calculate a p-value. The log-rank test is a non-parametric test of the null hypothesis that no difference between the population survival curves exists [168]. For each event, the observed number of deaths in each group and the number of deaths expected if there were no differences between the groups is calculated. These calculations are performed each time an event occurs. From the calculations, the number of expected and observed deaths are totalled in each group. This is then used for a x^2 test of the null hypothesis where the observed minus expected value is squared then divided by the expected value for each group. The sum of these values gives the test statistic. The test statistic and the degrees of freedom are compared with a table of x^2 distribution to give a p value. The log-rank test is most likely to detect a difference when the risk of an event is consistently greater for one group than another and is unlikely to detect a difference when survival curves cross. Therefore, when analysing survival data, the survival curves were always plotted.

When assessing factors associated with mortality risk after ICU, hazard ratios were calculated using Cox proportional hazard models. The hazard ratio is the ratio of hazards between two groups. The hazard represents the probability that an individual would experience an event at a particular given point in time. For

the purposes of survival analysis the event is death. The hazard ratio is the odds that an individual in a group with the higher HR reaches the endpoint first. Hazard ratios differ from relative risks (RR) or odds ratios (OR) in that the RRs and ORs are cumulative over an entire study, using a defined end point, while HRs represent instantaneous risk over the study time period.

Univariate analysis describes the difference between groups when only the single variable concerned is accounted for while ignoring the impact of any others. Multivariable analysis allows the impact of a variable to be evaluated following adjustment for all other variables that may also potentially affect the outcome. Cox proportional hazards regression is a method of multivariable analysis that is used for investigating differences in survival due to independent variables and distinguishes the individual contributions of covariates on survival [169].

The Cox model is expressed by the hazard function denoted by *h(t)*. The hazard function is the risk of dying at time *t* and can be represented by [170]:

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

Where t represents the survival time and *h(t)* is the hazard function determined by a set of p covariates ($x_1, x_2,\ldots,x_p$). The coefficients ($b_1,b_2,\ldots,b_p$) measure the impact of the covariates. The baseline hazard ($h_0(t)$) is the baseline hazard when all the covariates are equal to zero (i.e. $exp(0) = 1$).

When comparing two groups and calculating a hazard ratio it is assumed that the ratio of the hazard between the groups remains constant over time. This applies even if the magnitude of the hazards varies over time and the constant ratio is known as the hazard ratio. Thus the mortality rate might be different between the two groups but the pattern of mortality remains the same. It is important to verify that the covariates satisfy the assumption of the proportionality as if this assumption is violated, the Cox model is invalid and more sophisticated analyses are required.

The proportional hazards (PH) assumption can be checked using statistical tests and geographical diagnostics. Using Schoenfeld residuals involves calculating the

observed rate minus the predicted rate for each covariate over time [171]. This difference between observed and expected for each covariate should remain constant over time and is considered to be a zero slope. If the residuals vary with time then there is a non-zero slope which is an indication of a violation of the proportional hazard assumption. Statistical software plots the Schoenfeld residuals and reports p-values for likelihood of any PH violations.

The assumption that the proportional hazards remains constant with time can be visually assessed using a graph that demonstrates the logarithm of the estimated cumulative hazard function over time (log –log plots) [172]. The assumption is equivalent to assuming that the difference between the logarithms of the hazards for the two groups does not change with time and therefore the difference between the logarithms of the cumulative hazard functions is constant. The PH assumption is supported by parallel lines between groups and refuted by lines that cross or nearly cross.

3.8 Data handling and storage

Data received from ISD was stored on a password-protected encrypted file server at the West of Scotland Cancer Surveillance Unit, 1 Lilybank Gardens, Glasgow G12 8RZ. This file server was located in a locked office within a department that requires an entry code to gain access. Outwith office hours the building was locked and alarmed. The file server was backed up in a locked fire safe in a locked basement room.

A user account and password was created for each individual involved with data analysis to allow access to a single PC to work on the data. Passwords were alphanumeric and a minimum of 8 characters long. Password-protected screen savers were activated on all PCs after 5 minutes of inactivity. All patient-identifiable information was removed from the combined dataset prior to data analysis. No identifiable data was released for off-site working and when non-

identifiable data was taken off-site it was transported using an NHS-approved encrypted USB drive.

In accordance with good research practice [173], data will be kept securely in password-protected, encrypted electronic format for at least 10 years after publications have been completed.

3.9 Key points

- ICU data was collected from the 16 West of Scotland ICUs which included a small proportion of HDU patients from those combined units.
- ISD provided data linked between the Wardwatcher ICU database, the hospitalisation database (SMR01), the cancer database (SMR06) and death records (NRS).
- Data was optimised by adding information retrieved from the individual ICU sites.
- Patients groups by whether they had cancer and whether they were admitted to ICU to create three cohorts:
    - Cancer patients that have been admitted to ICU
    - Cancer patients that have not been admitted to ICU
    - ICU patients without cancer
- Approval was sought and granted from individual ICUs, the West of Scotland Critical Care Research Network, the Scottish Intensive Care Society Audit Group, the West of Scotland Cancer Surveillance Unit, the local Ethics committee and the Privacy Advisory Committee (ISD).

Chapter 4 What proportions of cancer patients are admitted to ICU and what are the features associated with admission?

4.1 Introduction

Development of a critical illness requiring ICU support is an important clinical event for a cancer patient and is likely to impact upon survival. There may be certain features that increase a cancer patient's risk of developing critical illness, however, this has not been previously explored. If the factors associated with ICU admission were better understood, then clinicians may be better placed to monitor patients at higher risk in an attempt to minimise morbidity and mortality. The aim of this study was to describe the factors associated with critical illness resulting in ICU admission among patients with solid tumours.

4.2 Study questions

4.2.1 What proportions of patients diagnosed with a solid tumour are admitted to ICU?

I will describe the overall proportion of cancer patients that are admitted to ICU in the first two years following diagnosis and how this varies by patient age, sex, hospital admitting specialty, and socioeconomic status. Overall, the total number of patients admitted to ICU will be examined in addition to the number admitted to ICU that subsequently received organ support.

4.2.2 At what point does the ICU admission occur after cancer diagnosis?

Cancer patients may present to ICU at different points during their illness. The ICU admission may be associated with the initial cancer diagnosis, as a direct consequence of surgery or chemotherapy, due to long-term complications associated with the cancer or its treatment, or due to an unrelated illness. I will describe the time from cancer incidence date to the date of ICU admission up to two years following cancer incidence.

4.2.3 Do rates of ICU admission vary according to underlying tumour types?

It might be expected that different tumour types and their specific treatments may result in different requirements for ICU. I will therefore describe the proportion of patients admitted to ICU for each underlying tumour type and describe them in terms of timing of ICU admission, hospital admission type and receipt of organ support.

4.2.4 Which features are associated with ICU and hospital mortality?

I will report ICU and hospital mortality for all patients admitted to ICU in addition to the following subgroups; hospital admission features, receipt of organ support during ICU, underlying tumour type and socioeconomic status.

4.3 Methods

Cancer patients' and rate of ICU admission was initially calculated using a cumulative count of numbers of ICU admission expressed as a percentage of the incident cancer population. This was described for different age groups, sex, and cancer types. The population was then described in terms of time from cancer diagnosis to ICU admission. Those cancer patients that were admitted to ICU were then described in more detail in terms of hospital admission type (during same inpatient stay as ICU admission) described as emergency or elective, hospital admitting specialty (dichotomised as medical or surgical) and by receipt of organ support. Organ support was used to identify those patients admitted to combined units for routine post-operative care or monitoring. Patients that did not receive organ support during their ICU stay may be regarded as level 2 or HDU patients. Organ support was defined as one of mechanical ventilation, vasoactive drugs or renal replacement therapy.

4.4 Results

In the West of Scotland between 2000 and 2009, 118,541 patients were diagnosed with a solid tumour. Within 2 years of cancer diagnosis 6,116 (5.2%, 95% CI 5.0-5.3%) of these patients experienced a critical illness resulting in admission to ICU.

4.4.1 Cancer patients demographics at admission to ICU

The median age of all cancer patients was 69 (IQR 59-77) and 61,607 (52%) were women. Those aged 60 years and older accounted for three quarters (74.8%) of the cancer population (Table 4-1). Of those cancer patients admitted to ICU the median age was 68 (IQR 60-75) and 2,542 (42%) were women. Admission to ICU

increased with increasing age, rising from 2.2% at ages 16-29 to a maximum of 6.3% between the ages of 60 and 69 and declined thereafter to a low of 1.6% in the 90 years and over age group. A similar pattern was observed in the group of patients who received organ support in ICU. Of the cancer patients aged 16 to 29 years, only 1.4% were admitted to ICU for organ support. This proportion increased with increasing age up to a maximum of 3.7% for those cancer patients aged 60 to 69 years. Following this the proportion falls with increasing age to a low of 0.9% in the 90 years and over age group.

Age Group (years)	All cancer patients, N	Admitted to ICU, N (%)		Received organ support, N (%)		Proportion of cancer population admitted to ICU for organ support
16-29	*1163*	*26*	(2.2)	*17*	(65.4)	1.4%
30-39	*3128*	*90*	(2.9)	*48*	(53.3)	1.5%
40-49	*7844*	*371*	(4.7)	*206*	(55.5)	2.6%
50-59	*17690*	*985*	(5.6)	*618*	(62.7)	3.5%
60-69	*30749*	*1945*	(6.3)	*1151*	(59.2)	3.7%
70-79	*35423*	*1938*	(5.5)	*1159*	(59.8)	3.3%
80-89	*19557*	*712*	(3.6)	*397*	(55.8)	2%
90+	*2987*	*49*	(1.6)	*28*	(57.1)	0.9%
All cancer patients	***118,541***	***6116***	**(5.2)**	***3624***	**(59.3)**	**3.1%**

Table 4-1 Incident cancers by age group with proportion admitted to ICU (and receive organ support) within 2 years of diagnosis. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

Hospital admission data from the same hospitalisation as ICU admission was available for 6040 patients (98.8%). Most ICU admissions followed a surgical hospitalisation with 83.2% (95% CI 82.3-84.1%) versus 15.5% (95% CI 14.6-16.4%) for medical hospitalisations. Admission to ICU occurred followed an emergency

hospitalisation for 43% of patients. Organ support was received by 59.3% of cancer patients admitted to ICU, or 3.1% (95% CI 3.0-3.2%) of all cancer patients. Among patients who received organ support, 18.9% (95% CI 17.6-20.2%) had been admitted to a medical specialty at hospital admission (Table 4-2). The proportion admitted to a medical specialty was higher at younger ages than at older ages with the exception of those aged 90 years and older.

Age group	Medical n (%)		Surgical n (%)	
16-29	*4*	(23.5)	*13*	(76.5)
30-39	*12*	(25)	*36*	(75)
40-49	*48*	(23.3)	*156*	(75.7)
50-59	*117*	(18.9)	*494*	(79.9)
60-69	*216*	(18.8)	*921*	(80)
70-79	*210*	(18.1)	*936*	(80.8)
80-89	*71*	(17.9)	*322*	(81.1)
90+	*7*	(25)	*21*	(75)
All cancer patients	***685***	**(18.9)**	***2899***	**(80)**

Table 4-2 Admitting specialty of patients who receive organ support in ICU by age group (percentages do not sum to 100% because some ICU patients could not be matched to a hospital admission record). Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

The incidence of critical illness was higher in men than in women for all age groups (Figure 4-1). For men, the highest risk of ICU admission occurred in the age 40-49 years group. The peak incidence for women occurred at 60-69 years. These trends are similar to that for ICU admission with organ support and are represented in Figure 4-1 by dashed lines.

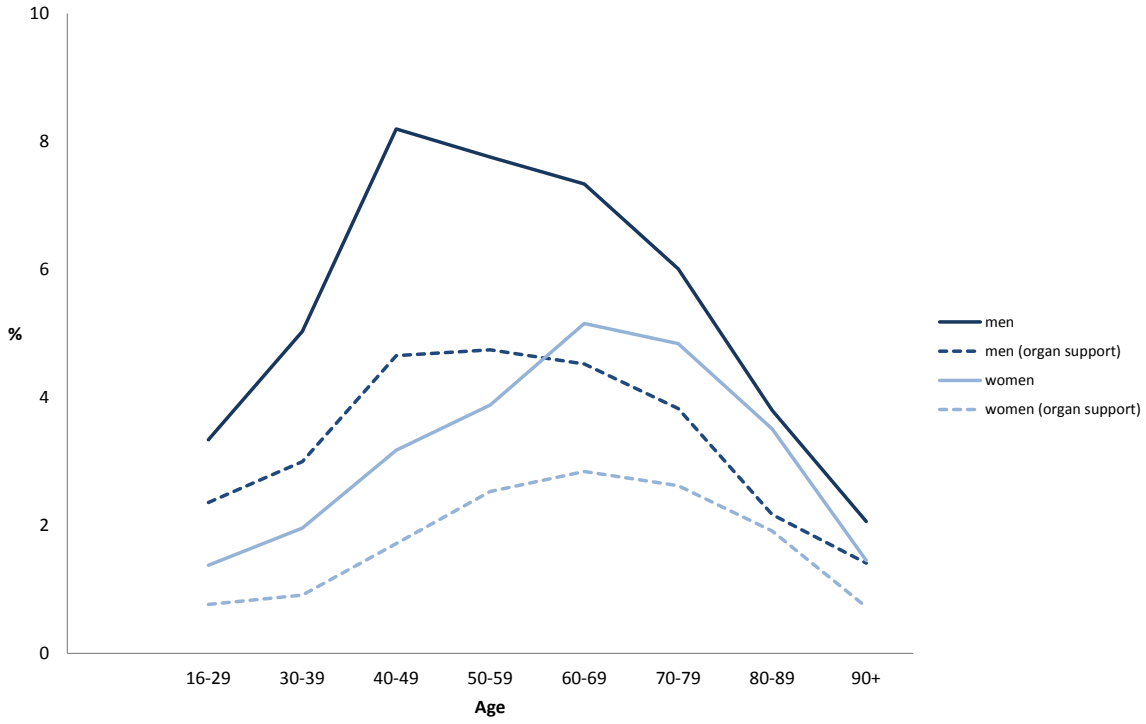


Figure 4-1 Percentage of cancer patients admitted to ICU within 2 years of cancer incidence by sex and age. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

4.4.2 Timing of ICU admission following cancer diagnosis

The time from cancer diagnosis to ICU admission is demonstrated in Figure 4-2. There was an initial sharp increase in the cumulative incidence of ICU admission following cancer diagnosis. By 100 days post diagnosis 3.7% (95% CI 3.6-3.9%) of cancer patients had been admitted to ICU. There was then a slower increase reaching 4.5% (95% CI 4.4-4.6%) by 200 days after diagnosis. Following this there was then a slow but steady climb in the cumulative incidence and at 2 years 5.2% (95% CI 5.0-5.3%) of patients diagnosed with a solid tumour had been admitted to an ICU.

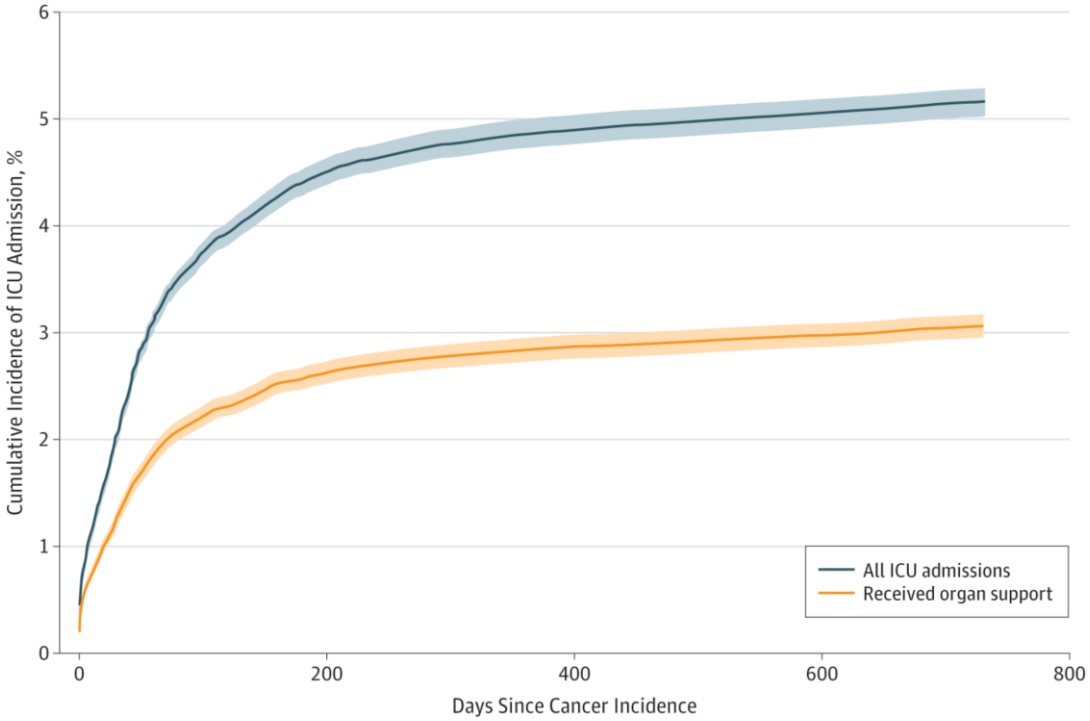


Figure 4-2 Cumulative incidence of admission to ICU by time since cancer incidence date. Shaded areas represent 95% CI. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

Year of cancer incidence had an impact on the rate of admission to ICU. From 2000 to 2009 there was a decline in the proportions of solid tumour patients diagnosed who developed a critical illness and were admitted to ICU (Figure 4-3). This decline was predominantly among patients who did not receive organ support; there were smaller reductions in ICU admissions for patients who required organ support. This change was similar for both of the sexes and is likely to reflect changes within the ICUs during this time period or in patient management.

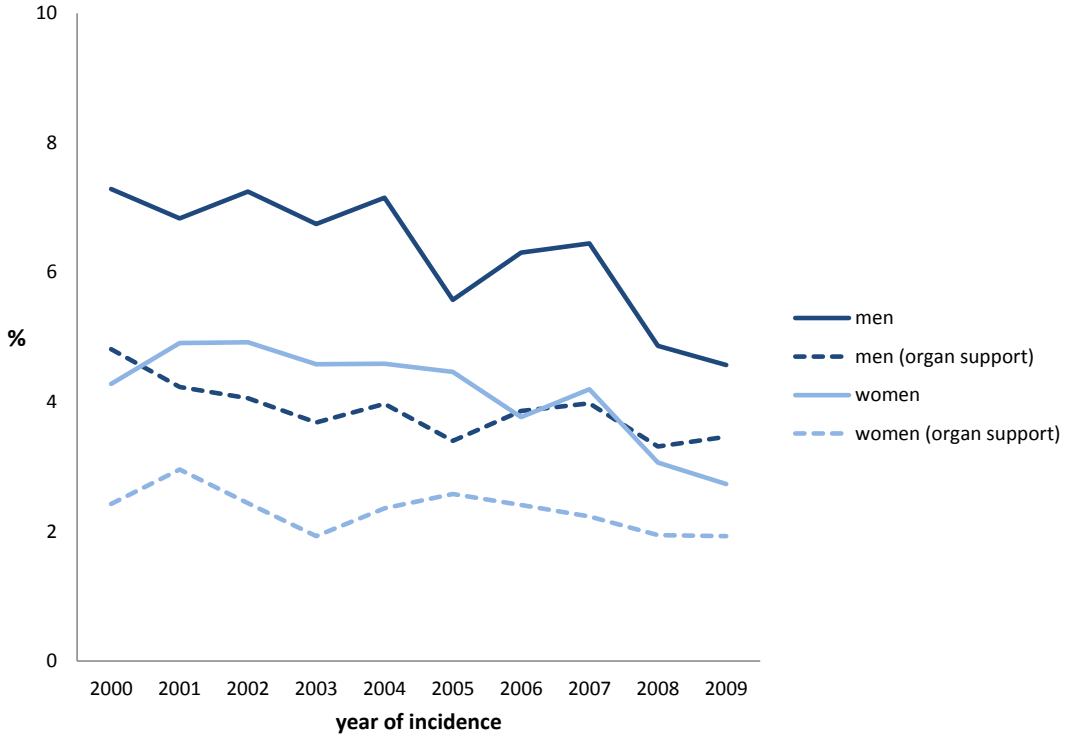


Figure 4-3 Trends in the percentage of cancer patients admitted to ICU by year of incidence. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

4.4.3 Tumour type and risk of ICU admission

For specific solid tumour types the cumulative incidence of critical illness and ICU admission varied (Table 4-3). During 2000-2009 the most frequently diagnosed solid cancers were lung, breast and colorectal malignancies making up 19.8%, 14.8% and 13.1% of all solid tumour diagnoses respectively. However, the pattern of those admitted to ICU did not reflect cancer incidence rates.

Cancer type, N = Incident number of cancers 2000-2009	Admitted to ICU, N (%)	Emergency hospital admission, N (%)	Received organ support, N (%)	Proportion admitted to ICU for organ support
Colorectal N=15,535	*2561* (16.5)	*1167* (45.6)	*1225* (47.8)	7.9%
Head & neck N=4958	*636* (12.8)	*164* (25.8)	*582* (91.5)	11.7%
Stomach N=4045	*456* (11.3)	*129* (28.3)	*234* (51.3)	5.8%
Oesophagus N=3815	*389* (10.2)	*74* (19.0)	*255* (65.6)	6.7%
Lung N=23,443	*381* (1.6)	*230* (60.4)	*285* (74.8)	1.2%
Kidney N=3054	*249* (8.2)	*63* (25.3)	*137* (55)	4.5%
Bladder N=3523	*182* (5.2)	*68* (37.4)	*115* (63.2)	3.3%
Breast N=17,591	*149* (0.8)	*94* (63.1)	*93* (62.4)	0.5%
Ovary N=2910	*138* (4.7)	*84* (60.9)	*68* (49.3)	2.3%
Prostate N=11,337	*136* (1.2)	*71* (52.2)	*85* (62.5)	7.5%
Cervix & corpus uteri N=3721	*113* (3)	*58* (51.3)	*65* (57.5)	1.7%
Unknown N=5722	*121* (2.1)	*103* (85.1)	*88* (72.7)	1.5%
Pancreas N=2920	*81* (2.8)	*61* (75.3)	*56* (69.1)	1.9%
Liver N=2291	*67* (2.9)	*43* (64.2)	*50* (74.6)	2.2%
Small intestine N=319	*55* (17.2)	*43* (78.2)	*33* (60)	10.3%
Thyroid N=700	*28* (4)	*11* (39.3)	*18* (64.3)	2.6%
Testis N=1018	*26* (2.6)	*14* (53.8)	*21* (80.8)	2.1%
Melanoma of skin N=4070	*18* (0.4)	*13* (72.2)	*14* (77.8)	0.3%
Mesothelioma N=1029	*18* (1.7)	*12* (66.7)	*13* (72.2)	1.3%
Other N=3163	*106* (3.4)	*53* (50.0)	*59* (55.7)	1.9%
Multiple N=3377	*206* (6.1)	*74* (35.9)	*128* (62.1)	3.8%
Total N=118,541	***6116* (5.2)**	***2629* (43.0)**	***3624* (59.3)**	**3.1%**

Table 4-3 ICU admissions within 2 years of cancer incidence by cancer type. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

The rate of admission to ICU was greatest for small intestinal and colorectal malignancies (17.2%, 95% CI 13.3-21.8%, and 16.5%, 15.9-17.1%, respectively). Other tumour types that had a high rate of admission were those that are likely to require peri-operative critical care support for tumour resection surgery such as head and neck cancers (12.8%, 95% CI 11.9-13.8%), stomach cancer (11.3%, 95% CI 10.3-12.3%) and oesophageal cancer (10.2%, 95% CI 9.2-11.2%). Although breast cancer had a high incidence, the risk of critical illness and ICU admission was among the lowest of all malignancies at 0.8% (95% CI 0.7 - 1.0%).

Patients with colorectal cancer made up the largest proportion of ICU cancer patients (41.9%). Cancer stage was not recorded for most cancer sites but was available for 77.7% (12071/15535) of colorectal cancers. The ICU admission rate was higher among Dukes stage B and C colorectal patients (22.9%, 95% CI 21.6-24.3% of patients with Dukes B and 23.8%, 95% CI 22.4-25.3% of patients with Dukes C) compared to Dukes A or D (15.8%, 95% CI 14.1-17.6% of Dukes A patients and 9.6%, 95% CI 8.6-10.7% of Dukes D patients).

While lung cancer was the fifth most frequent cancer type admitted to ICU (6.2% of ICU cancer admissions) this under represents the lung cancer population, as this was the most frequently diagnosed tumour type during this time period.

The majority of cancer patients (57%) were admitted to ICU after an elective admission to hospital. The proportion of admissions to ICU which occurred during an emergency hospital admission varied from a low of 25% for kidney and head & neck cancers, to 78% and 85% of patients with cancers of the small intestine and unknown primary, respectively.

Organ support was provided to 59.3% of all solid tumour patients admitted to ICU, corresponding to 3.1% (95% CI 3.0-3.2%) of all patients with solid tumours. Receipt of organ support varied by cancer type and was lowest for colorectal cancer patients (47.8%, 95% CI 45.9-49.8%). Patients with head and neck cancer had the highest frequency of organ support at 91.5% (95% CI 89.1-93.6%) and this is likely to represent ventilation via tracheostomy in this patient subgroup.

The majority (80.0%) of cancer patients who received organ support were surgical patients but there was substantial variation by cancer type (Table 4-4). Over 85% of colorectal, head and neck, stomach, bladder, kidney and oesophageal cancer patients were admitted with a surgical diagnosis. In contrast, over 40% of lung, melanoma, ovarian, cervical and cancers of unknown origin were medical admissions.

Cancer type	Received organ support, N	Medical admission, N (%)		Surgical admission, N (%)	
Colorectal	*1225*	*134*	(10.9)	*1074*	(87.7)
Head & neck	*582*	*47*	(8.1)	*533*	(91.6)
Stomach	*234*	*34*	(14.5)	*199*	(85)
Oesophagus	*255*	*21*	(8.2)	*231*	(90.6)
Lung	*285*	*138*	(48.4)	*145*	(50.9)
Kidney	*137*	*14*	(10.2)	*120*	(87.6)
Bladder	*115*	*13*	(11.3)	*101*	(87.8)
Breast	*93*	*37*	(39.8)	*53*	(57)
Ovary	*68*	*42*	(61.8)	*26*	(38.2)
Prostate	*85*	*25*	(29.4)	*58*	(68.2)
Cervix & corpus uteri	*65*	*44*	(67.7)	*20*	(30.8)
Unknown	*88*	*43*	(48.9)	*45*	(51.1)
Pancreas	*56*	*10*	(17.9)	*45*	(80.4)
Liver	*50*	*19*	(38)	*31*	(62)
Small intestine	*33*	*12*	(36.4)	*21*	(63.6)
Thyroid	*18*	*5*	(27.8)	*13*	(72.2)
Testis	*21*	*7*	(33.3)	*14*	(66.7)
Melanoma of skin	*14*	*6*	(42.9)	*8*	(57.1)
Mesothelioma	*13*	*5*	(38.5)	*7*	(53.8)
Other	*59*	*18*	(30.5)	*40*	(67.8)
Multiple	*128*	*11*	(8.6)	*115*	(89.8)
Total	***3624***	***685***	**(18.9)**	***2899***	**(80)**

Table 4-4 Admitting specialty of cancer patients admitted to ICU for organ support by cancer type. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

4.4.4 Timing of ICU admission by cancer type

Of those cancer patients admitted to ICU 70% were admitted within three months of the date of cancer incidence (Table 4-5). Notable exceptions include breast, bladder, prostate cancer and testicular cancer when over two thirds of patients in each group were admitted later than three months from diagnosis. The highest proportions of early ICU admissions (within three months of cancer diagnosis) were seen with lung cancer (75.6%), colorectal cancer (77.1%), small intestinal cancer (77.2%), liver cancer (77.6%), ovarian cancer (87.6%) and pancreatic cancer (87.7%). With the exception of colorectal and intestinal malignancy these cancer types are those that are associated with poorer survival and thus are less likely to be admitted at a later point.

	Time from cancer incidence to admission to ICU % (N)							
Cancer type	**≤14 days**		**15 days – ≤3 months**		**3 months - ≤6 months**		**>6 months**	
Colorectal N=2561	32.0%	*(820)*	45.1%	*(1155)*	13.3%	*(340)*	9.6%	*(246)*
Head & neck N=636	11.0%	*(70)*	67.3%	*(428)*	8.8%	*(56)*	12.9%	*(82)*
Stomach N=456	17.1%	*(78)*	54.6%	*(249)*	20.8%	*(95)*	7.5%	*(34)*
Oesophagus N=389	7.7%	*(30)*	44.7%	*(174)*	39.3%	*(153)*	8.2%	*(32)*
Lung N=381	37.8%	*(144)*	37.8%	*(144)*	11.0%	*(42)*	13.4%	*(51)*
Kidney N=249	25.3%	*(63)*	47.0%	*(117)*	14.5%	*(36)*	13.3%	*(33)*
Bladder N=182	13.2%	*(24)*	23.6%	*(43)*	26.4%	*(48)*	36.8%	*(67)*
Breast N=149	10.7%	*(16)*	24.8%	*(37)*	8.7%	*(13)*	55.7%	*(83)*
Ovary N=138	54.3%	*(75)*	33.3%	*(46)*	2.9%	*(4)*	9.4%	*(13)*
Prostate N=136	9.6%	*(13)*	18.4%	*(25)*	22.8%	*(31)*	49.3%	*(67)*

Cancer type	Time from cancer incidence to admission to ICU % (N)							
	≤14 days		15 days - ≤3 months		3 months - ≤6 months		>6 months	
Cervix & corpus uteri N=113	11.5%	*(13)*	49.6%	*(56)*	10.6%	*(12)*	28.3%	*(32)*
Unknown N=121	61.2%	*(74)*	25.6%	*(31)*	7.4%	*(9)*	5.8%	*(7)*
Pancreas N=81	45.7%	*(37)*	42.0%	*(34)*	6.2%	*(5)*	6.2%	*(5)*
Liver N=67	34.3%	*(23)*	43.3%	*(29)*	9.0%	*(6)*	13.4%	*(9)*
Small intestine N=55	50.9%	*(28)*	27.3%	*(15)*	9.1%	*(5)*	12.7%	*(7)*
Thyroid N=28	25.0%	*(7)*	39.3%	*(11)*	14.3%	*(4)*	21.4%	*(6)*
Testis N=26	19.2%	*(5)*	11.5%	*(3)*	26.9%	*(7)*	42.3%	*(11)*
Melanoma of skin N=18	0.0%	*(0)*	33.3%	*(6)*	22.2%	*(4)*	44.4%	*(8)*
Mesothelioma N=18	27.8%	*(5)*	44.4%	*(8)*	16.7%	*(3)*	11.1%	*(2)*
Other N=106	25.5%	*(27)*	32.1%	*(34)*	17.9%	*(19)*	24.5%	*(26)*
Multiple N=206	9.2%	*(19)*	35.9%	*(74)*	14.6%	*(30)*	40.3%	*(83)*
Total N=6116	**25.7%**	***(1571)***	**44.5%**	***(2719)***	**15.1%**	***(922)***	**14.8%**	***(904)***
Medical patients N=949	38.6%	*(366)*	31.3%	*(297)*	10.1%	*(96)*	20.0%	*(190)*
Surgical patients N=5091	23.2%	*(1182)*	47.0%	*(2393)*	15.9%	*(811)*	13.8%	*(705)*

Table 4-5 Time from cancer incidence to ICU admission by cancer type. Data are described as percentages (with total numbers). Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

While patients were most commonly admitted between two weeks and three months (44.5%), there were some patients that were admitted within two weeks of diagnosis (25.7%). This is likely to be where patients were admitted at the time of diagnosis or during the same continuous inpatient stay. Patients admitted to ICU with a medical diagnosis were more likely to be admitted to ICU within two weeks of cancer incidence compared to patients admitted to surgical specialties (38.6% compared to 23.2%, p<0.001).

4.4.5 Mortality

ICU mortality for all solid tumour patients admitted to ICU was 14.7% (95% CI 13.8-15.6%). Mortality varied by type of hospital admission, admitting specialty and provision of organ support (Table 4-6).

		ICU Mortality % (95% CI)		Hospital Mortality % (95% CI)	
		Surgical	Medical	Surgical	Medical
Elective admission	**No organ support ***	1.7% (1.1–2.5)	6.3% (2.1–14.2)	4.9% (3.8-6.1)	13.9% (7.2–23.5)
	Organ support	14.5% (12.9–16.3)	21.1% (13.9–30.0)	22.1% (20.2–24.1)	40.4% (31.1–50.2)
Emergency admission	**No organ support ***	5.0% (3.5-6.8)	8.6% (5.0-13.7)	15.3% (12.8–18.1)	33.0% (26.3–40.3)
	Organ support	24.6% (22.1-27.2)	41.7% (37.6–45.8)	41.2% (38.3–44.1)	59.2% (55.1–63.2)

Table 4-6 ICU and hospital mortality by hospital admission type, specialty and organ support. *Includes patients with organ support not known. Data are percentages with 95% confidence intervals

Patients that received organ support had an ICU mortality rate that was six-times higher than that observed in patients who did not receive organ support

(22.3%, 95% CI 21.0-23.7% compared to 3.7%, 95% CI 3.0-4.5%). Deaths among medical patients who received organ support (38.4%, 95% CI 34.7-42.2%) were twice that experienced by the patients admitted from a surgical specialty (18.4%, 95% CI 17.0-19.9%). The lowest ICU mortality of 1.7% (95% CI 1.1-2.5%) occurred among patients who were elective surgical admissions that did not receive organ support. This is likely to represent routine post-operative care in a high-dependency setting. In contrast, 41.7% (95% CI 37.6-45.8%) of patients who were emergency medical admissions with organ support during their stay died in ICU.

A further 10.5% of cancer patients admitted to ICU died prior to hospital discharge giving a crude hospital mortality of 25.7% (95% CI 24.6-26.8%). The proportion of ICU cancer patients who died in hospital was higher among those who received organ support (35.3%, 95% CI 33.8-36.9%) compared to those who had not (11.8%, 95% CI 10.5-13.1%). Following discharge from ICU, hospital deaths among surgical patients who received organ support increased by 11.1% to 29.5% (95% CI 27.8-31.2%) and among medical patients by 17.8% to 56.2% (95% CI 52.4-60.0%). Hospital mortality was lowest in the group of patients who were admitted as an elective surgical patient and did not require organ support (4.9% 95% CI 3.8–6.1%). In contrast, 59.2% (95% CI 55.1-63.2%) of patients who were emergency medical admissions to ICU that received organ support died prior to hospital discharge.

Cancer type	All patients N=6116	Emergency hospital admission N=2629	Received organ support N=3624	Emergency admission + received organ support N=1700
Colorectal N=2561	21.8% (20.2-23.4)	28.0% (25.4-30.7)	35.6% (32.9-38.3)	40.3% (36.5-44.1)
Head & neck N=636	12.3% (9.8-15.1)	23.2% (16.9-30.4)	12.5% (10.0-15.5)	25.0% (18.1-33.0)
Stomach N=456	23.9% (20.1-28.1)	39.5% (31.0-48.5)	38.5% (32.2-45.0)	53.8% (42.2-65.0)
Lung N=381	60.6% (55.5-65.6)	67.4% (60.9-73.4)	68.8% (63.0-74.1)	71.1% (63.9-77.6)
Oesophagus N=389	20.8% (16.9-25.2)	35.1% (24.4-47.1)	26.7% (21.3-32.5)	42.6% (29.2-56.8)
Kidney N=249	16.5% (12.1-21.7)	28.6% (17.9-41.3)	25.5% (18.5-33.7)	39.5% (25.0-55.6)
Bladder N=182	27.5% (21.1-34.6)	51.5% (39.0-63.8)	32.2% (23.8-41.5)	54.8% (38.7-70.2)
Breast N=149	32.2% (24.8-40.4)	42.6% (32.4-53.2)	45.1% (34.8-55.5)	53.7% (41.1-66.0)
Ovary N=138	29.7% (22.2-38.1)	34.5% (24.5-45.7)	39.7% (28.0-52.3)	46.5% (31.2-62.3)
Prostate N=136	28.7% (21.3-37.1)	42.3% (30.6-54.6)	37.6% (27.4-48.8)	48.1%(34.3-62.2)
Cervix & corpus uteri N=113	18.6% (11.9-27.0)	25.9% (15.3-39.0)	29.2% (18.6-41.8)	33.3% (19.1-50.2)
Unknown N=121	72.7% (63.9-80.4)	78.6% (69.5-86.1)	76.1% (65.9-84.6)	82.9% (72.5-90.6)

Cancer type	All patients N=6116	Emergency hospital admission N=2629	Received organ support N=3624	Emergency admission + received organ support N=1700
Pancreas N=81	46.9% (35.7-58.3)	47.5% (34.6-60.7)	55.4% (41.5-68.7)	56.8% (41.0-71.7)
Liver N=67	53.7% (41.1-66.0)	62.8% (46.7-77.0)	58.0% (43.2-71.8)	66.7% (47.2-82.7)
Small intestine N=55	32.7% (20.7-46.7)	30.2% (17.2-46.1)	42.5% (28.1-63.6)	42.3%(23.4-63.1)
Thyroid N=28	10.7% (2.3-28.2)	27.3% (6.0-61.0)	5.6% (1.4-27.3)	12.5% (3.2-52.7)
Testis N=26	42.3% (23.4-63.1)	71.4% (41.9-91.6)	47.6% (25.7-70.2)	75.0% (42.8-94.5)
Melanoma of skin N=18	27.8% (9.7-53.5)	30.8% (9.1-61.4)	35.7% (12.8-64.9)	36.4% (10.9-69.2)
Mesothelioma N=18	50.0% (26.0-74.0)	58.3% (27.7-84.8)	61.5% (31.6-86.1)	70.0% (34.8-93.3)
Other N=106	27.4% (19.1-36.9)	35.8% (23.1-50.2)	40.7% (28.1-54.3)	46.9% (29.1-65.3)
Multiple N=206	18.9% (13.8-25.0)	29.7% (19.7-41.5)	27.3 (19.8-35.9)	39.2 (25.8-53.9)
All N=6116	**25.7%(24.6-26.8)**	**37.2% (35.4-39.1)**	**35.3% (33.8-36.9)**	**47.3% (44.9-49.7)**

Table 4-7 Hospital mortality by cancer site. Numbers are percentages (with 95% CI) of patients who died during the hospital stay in which they were admitted to ICU.

Hospital mortality varied by cancer type (Table 4-7) and was highest for patients with cancers of unknown primary (72.7%, 95% CI 64.7-80.8%), lung (60.6%, 95% CI 55.7-65.6%) and liver (53.7%, 95% CI 41.5-66.0%). The lowest hospital mortalities were observed in patients with thyroid cancer (10.7%, 95% CI -1.5-22.9%), head & neck cancers (12.2%, 95% CI 9.7-14.8%) and kidney cancer (16.5%, 95% CI 11.8-21.1%). For most cancers, hospital mortality was substantially higher among patients who were admitted as an emergency patient or had received organ support. Mortality was higher still among those patients admitted to medical compared to surgical specialties (Table 4-8).

Cancer type	Total N=1700	Surgical N=1124	Medical N=576
Colorectal	40.3% (36.5-44.0)	37.8% (33.7-42.1)	51.7% (42.3-61.1)
Head & neck	25.0% (18.1-33.0)	20.2% (13.0-29.2)	38.9% (23.1-56.5)
Stomach	53.8% (42.2-65.0)	48.9% (34.1-63.9)	60.6% (42.1-77.1)
Lung	71.1% (63.9-77.6)	62.0% (47.2-75.3)	74.6% (66.2-81.8)
Oesophagus	42.6% (29.2-56.8)	27.8% (14.2-45.2)	72.2% (46.5-90.3)
Kidney	39.5% (25.0-55.6)	44.8% (26.4-64.3)	28.6% (8.4-58.1)
Bladder	54.8% (38.7-70.2)	55.2% (35.7-73.6)	53.8% (25.1-80.8)
Breast	53.7% (41.1-66.0)	45.2% (27.3-64.0)	61.1% (43.5-76.9)
Ovary	46.5% (31.2-62.3)	36.4% (17.2-59.3)	57.1% (34.0-78.2)
Prostate	48.1% (34.3-62.2)	40.6% (23.7-59.4)	59.1% (36.4-79.3)

Cancer type	Total N=1700	Surgical N=1124	Medical N=576
Cervix & corpus uteri	33.3% (19.1-50.2)	36.8% (16.3-61.6)	30.0% (11.9-54.3)
Unknown	82.9% (72.5-91.0)	83.3% (67.2-93.6)	82.5% (67.2-92.3)
Pancreas	56.8% (41.0-71.7)	58.8% (40.7-75.4)	50.0% (18.7-81.3)
Liver	66.7% (47.2 -82.7)	78.6% (49.2-95.3)	56.3% (29.9-80.2)
Small intestine	42.3% (23.4-63.1)	41.2% (18.4-67.1)	44.4% (13.7-78.8)
Thyroid	12.5% (3.2-52.7)	25.0% (0.6-80.6)	0% (0-60.2)
Testis	75.0% (42.8-94.5)	40.0% (5.3-85.3)	100% (59.0-100)
Melanoma of skin	36.4% (10.9-69.2)	40.0% (5.3-85.3)	33.3% (-20.9-87.5)
Mesothelioma	70.0% (34.8-93.3)	60.0% (14.7-94.7)	80.0% (28.4-99.5)
Other	46.9% (29.1-65.3)	52.4% (29.8-74.3)	36.4% (10.9-69.2)
Multiple	39.2% (25.8-53.9)	35.7% (21.6-52.0)	55.6% (21.2-86.3)
All	**47.3% (44.9-49.7)**	**41.2% (38.3-44.1)**	**59.2% (55.1-63.2)**

Table 4-8 Hospital mortality by cancer site for emergency admissions that received organ support. Numbers are percentages (with 95% CI) of patients who died during the hospital stay in which they were admitted to ICU.

4.4.6 Socioeconomic trends

More than half (55.6%) of the West of Scotland cancer population are from a deprived area (SIMD quintiles 1 or 2) and this is likely to represent the general population of the West of Scotland. There was no clear trend in the proportions of cancer patients admitted to ICU when examined by socio-economic deprivation (Table 4-9).

SIMD quintile	Total cancer patients* N (%)		ICU admission N (%)		Emergency hospital admission N (%)		Number with organ support N (%)	
Most deprived	*37,333*	(31.5)	*1,842*	(4.9)	*859*	(46.6)	*1,261*	(68.5)
2	*28,550*	(24.1)	*1,650*	(5.8)	*708*	(42.9)	*916*	(55.5)
3	*21,000*	(17.7)	*1,134*	(5.4)	*471*	(41.5)	*609*	(53.7)
4	*16,384*	(13.8)	*806*	(4.9)	*310*	(38.5)	*440*	(54.6)
Most affluent	*15,272*	(12.9)	*684*	(4.5)	*281*	(41.1)	*398*	(58.2)
All	*118,539*		*6,116*	(5.2)	*2,629*	(43.0)	*3,624*	(59.3)

Table 4-9 Cancer incidence and critical illness requiring ICU admission and organ support by socio-economic circumstances. *Missing SIMD data for 2 patients. Modified from "Risk of critical illness among patients with solid tumours." Puxty et al. JAMA Oncology (2015) with permission.

The most deprived SIMD quintile had a higher proportion of patients who were emergency hospital admissions (46.6%, (95% CI 44.3-48.9%)) and that had received organ support (68.5% (95% CI 66.3-70.6%)), compared to the least deprived quintile (41.1%, (95% CI 37.4-44.9%), p=0.0127, and 58.2%, (95% CI 54.4-61.9%), p<0.001 respectively). This corresponded to higher hospital mortality among patients admitted from the most deprived areas (30.1%, 95% CI 28.0-32.3%) when compared to those who lived in the most affluent areas (23.1%, 95% CI 20.0-26.4%), p<0.001 (Table 4-10).

SIMD quintile	Hospital mortality % (95% CI)	
Most deprived	30.1	(28.0–32.3)
2	25.3	(23.2–27.5)
3	22.5	(20.1-25.0)
4	23.2	(20.3–26.3)
Most affluent	23.1	(20.0-26.4)
All	25.7	(24.6-26.8)

Table 4-10 Crude hospital mortality of ICU cancer patients by socio-economic circumstances.

4.5 Discussion

This study has demonstrated that one in twenty patients with a solid tumour developed a critical illness that required admission to an ICU within two years of cancer diagnosis. Requirement for organ support suggests an increased severity of illness and receipt of level 3 care and this was received by 3.1% of all cancer patients in this study. Within the solid tumour population, admission to ICU tends to happen early after cancer incidence with 3.7% of cancer patients admitted to ICU within 100 days of diagnosis. It is likely that the critical illness is therefore linked to the cancer either in terms of directly leading to the illness or following surgical intervention or treatment. This would be consistent with previous studies that have demonstrated that cancer-related hospital activity is highest in the first year following diagnosis [174].

Bos et al performed a similar study in the Netherlands where patients with a cancer diagnosis between 2006 and 2011 were analysed for any ICU admissions during the study period [159]. Similar to the observations made by this study they found that 6.4% of their population were admitted to ICU, although their study included both solid and haematological cancer.

4.5.1 Features associated with ICU admission

The rate of ICU admission increased with age up to 70 years after which there was a decrease in the rate of ICU admission. This pattern may be explained by the increasing prevalence of co-morbidities with increasing age countered by less invasive or aggressive treatment regimens as patients get beyond 70 years old. Cancer patients aged over 90 years were the least likely to be admitted to ICU and this may also reflect a reluctance to admit by the ICU clinical teams due to concern regarding the burden of care.

Within the cohort of cancer patients admitted to ICU, the majority were surgical admissions (83%) and following elective hospitalisation (57%). Peri-operative critical care is often offered to elective patients undergoing major surgical intervention or to those with co-morbidities who are at higher risk of post-operative complications. Enhanced monitoring and management of analgesia such as epidural care means that many patients benefit from a brief post-operative period in ICU/ HDU. Elective cancer surgery therefore contributes a large proportion of the cancer ICU cohort. In addition, there are a group of patients who are admitted to ICU after a complication of elective cancer surgery either at the time of operation or in the post-operative period. While these patients have been admitted to hospital electively, their ICU admission has been unplanned. Emergency surgical admissions contribute the second largest group of ICU cancer patients. These patients often undergo unplanned surgical intervention and therefore have no opportunity for pre-operative optimisation. Many of these patients will have critical illness on admission to hospital due to the underlying condition. Admission may be required as a result of presenting illness, surgical intervention or underlying co-morbidity.

Patients from the most deprived areas had similar rates of ICU admission to other socio-economic groups; however, there was a higher rate of emergency admissions and receipt of organ support within this group. It has been previously established that deprivation is associated with poor uptake in cancer surveillance programmes [175, 176]. This may partly explain patients from poorer socio-economic groups presenting later as an emergency and consequently having a greater requirement for organ support.

There was a modest decline in the rate of ICU admission during the study period although this was predominantly seen among patients that did not receive organ support. During the study period there were changes within the ICU's in terms of total number of beds and proportion of level 2 and level 3 provision, in addition to centralisation of cardiothoracic services to a hospital outwith this dataset. It is likely that the changes in rate of ICU admission relate to these service changes rather than any real change in the treatment of cancer patients.

4.5.2 Impact of underlying cancer type and rate of ICU admission

During the study period the commonest incident cancers were lung, breast and colorectal cancer. However, the pattern of those admitted to ICU was not reflective of these incidence rates. Colorectal cancer was the most frequently admitted cancer type to ICU with 16.5% of all colorectal patients admitted to ICU. Due to the high incidence of colorectal cancer and the high rate of ICU admission, this patient group made up over two fifths of all ICU cancer patients. Colorectal cancer patients had the lowest requirement for organ support (47.8%) and were predominantly made up of surgical admissions (87.7% of those that received organ support). This reflects the large proportion of surgical level 2 patients that require a brief period of post-operative monitoring only following colorectal cancer resection surgery. Other tumour types that require perioperative critical care support for tumour resection surgery such as head and neck cancers, stomach cancer and oesophageal cancer all had ICU admission rates greater than ten percent.

In contrast to colorectal cancer, only a small proportion of lung and breast cancer patients are admitted to ICU (1.6% and 0.8% respectively). Poor long-term survival in patients with lung cancer is likely to influence the ICU physician against admitting these patients and it is possible that this contributes to the low rates of ICU admission. For breast cancer the surgical interventions tend to be minimally invasive and therefore patients are less likely to develop a critical illness at the time of surgery compared with other tumour resections.

4.5.3 Mortality of cancer patients admitted to ICU

Mortality was high, with one in four of all cancer patients that developed a critical illness dying during the same hospital stay. Mortality was observed to be lowest for elective surgical patients. Their outcomes might be expected to be favourable as they have been selected for potentially curative treatment and have benefitted from a period of pre-operative optimisation. Emergency admissions associated with a cancer diagnosis have poorer outcomes than elective, and medical admissions have poorer outcomes than surgical. Again, these observations partly reflect a group of surgical patients for whom the critical illness is likely to have been related to a discrete peri-operative insult rather than an on-going inflammatory process that often occurs with medical patients. Cancer patients admitted to ICU with a medical diagnosis comprise a mixture of those who are suffering from the side effects of treatment, such as sepsis or tumour lysis syndrome, and those suffering from progression of their cancer. While a direct comparison cannot be made with other studies because of differences in case mix, the observation that medical admissions have higher mortality than emergency and elective surgery, respectively, has been made by Soares and others [86]. This is a consistent finding seen in ICU patients regardless of comorbidity and is often accounted for when using ICU mortality prediction scores [22, 28].

Patients that received organ support during their ICU stay had higher mortality rates compared with those who did not receive organ support regardless of whether they were medical/ surgical or elective/ emergency admissions. Receipt of organ support is a coarse reflection of the presence of organ failure and will be associated with an increased severity of illness. It is expected that those patients with organ failure and higher severity of illness would also have a higher mortality.

Mortality by tumour type varied considerably, with hospital mortality ranging from 10.7% of thyroid cancers to 72.7% of cancers of unknown primary. In general, those tumour types that are associated with poor outcomes such as lung, liver, mesothelioma and pancreatic had high hospital mortality after admission to ICU. This may be due to late clinical presentation, limited

treatment options, advanced cancer stage, physician nihilism or a combination of the above. While general survival associated with oesophageal cancer tends to be poor, it is worth noting that in this dataset hospital mortality for those that are admitted to ICU was lower than the average at 20.8%. Those patients with oesophageal cancer that were admitted to ICU were predominantly surgical and are likely to be those who have undergone curative oesophageal resection. This procedure is a major operative intervention and prior to its undertaking the patients undergo extensive investigation and optimisation. There will therefore be a significant selection bias applied to those oesophageal cancer patients who undergo surgical resection compared to those who do not. It is likely that this is reflected in the low hospital mortality within this cohort. This selection bias is amplified by the fact that mortality for oesophageal cancer is very high and pre-operative optimisation prior to surgery is comprehensive. It should be expected that within the elective surgical population this selection bias will be present to a varying extent within each of the tumour type sub-categories.

Survival from most cancers has improved over time but international variations exist, with poorer survival in the UK than other developed countries. Variations in outcomes manifest soon after diagnosis. For example, socio-economic variations in survival from colorectal cancers are largely confined to excess mortality in the postoperative period [177] and international variations in breast cancer survival are most pronounced in the first month and year after diagnosis [178]. However, it remains unclear what mediates better survival. It has been suggested that quality of healthcare may explain international variations in cancer outcomes [163]. While this is often considered in terms of availability and effectiveness of therapeutic interventions, the role of supportive care to prevent or ameliorate critical illness among cancer patients should not be overlooked.

The United Kingdom has considerably lower provision of ICU beds, at 3.5 per 100,000 population, than other European countries, North America and Australasia [179]. Among the EUROCARE countries, those with consistently better survival, such as France and Belgium, have between three and six times greater numbers of ICU beds per head of population than the UK [163, 179]. The UK has both poorer cancer outcomes and considerably lower provision of ICU beds than most other developed countries. From these results I cannot say whether greater

provision of ICU beds would contribute to improvements in cancer survival in the UK. However, it might be hypothesised that if ICUs are effective in reducing mortality following a critical illness, increased surveillance for early signs of critical illness and greater capacity to offer ICU to cancer patients might be beneficial. Studies are needed in which ICU is provided to cancer patients who would not normally be admitted to ICU under current UK provision and outcomes in this group compared to a similar group of cancer patients who did not receive ICU care.

Critical illness may therefore play an important role in determining overall cancer outcomes and may help to explain variations in cancer survival.

4.5.4 Strengths and weaknesses

This study describes the proportion of patients with solid cancers that develop a critical illness necessitating ICU admission, with a comprehensive coverage of tumour types. Patient groups are described in detail by cancer type, admission type and receipt of organ support. The large sample size and reliability of cancer registration and ICU admission data would suggest that this population is representative of the overall population of solid tumour patients that are admitted to ICU in the UK.

The principal limitation is that patients with critical illness who were not admitted to ICU could not be identified. A further limitation is the inability to clearly differentiate high dependency patients from intensive care patients in combined units. To overcome this issue we described the population of patients that received organ support in an attempt to exclude those HDU patients who were receiving monitoring only. Although there was significant variation in mortality between centres it is likely that this reflects differences in case mix. A prospective study is needed in which a range of physiological and functional measures is included to determine outcomes among cancer patients whose critical illnesses do, and do not, result in ICU admission. This study was carried out in one region of the UK and while it is unlikely that admission policies are

significantly different to other parts of the UK, further work to repeat this methodology on other geographic areas is needed.

4.6 Conclusions

The development of a critical illness requiring support in an ICU has received relatively little attention for cancer patients, yet this study demonstrates that one in twenty cancer patients will be admitted to ICU. Those admitted to ICU had high mortality rates with increased risk in those admitted as an emergency, with a medical diagnosis or in those that received organ support. It remains unknown whether the persisting effects of critical illness and ICU care interferes with planned cancer treatment and impacts upon longer term outcomes. Development of a critical illness requiring ICU support may be an important clinical event that contributes to poorer overall survival in patients with malignancy.

4.7 Key points

• 5.2% of patients diagnosed with a solid tumour diagnosed between 2000 and 2009 developed a critical illness necessitating ICU admission within 2 years of diagnosis with 3.1% of patients requiring organ support.

• The rate of ICU admission increased with increasing age up to 70 years after which there was a decline in the rate of admission.

• The majority of ICU admissions in patients with a solid tumour are the result of a surgical hospitalisation (83.2%).

• ICU admission tends to occur soon after cancer diagnosis with 3.7% of solid tumour patients admitted to ICU within 100 days of diagnosis and 4.5% within 200 days.

• The rate of ICU admission was greatest for bowel malignancies and for those tumours that require peri-operative support for tumour resection surgery such as head and neck cancers, stomach cancer and oesophageal cancer.

• Patients with colorectal cancer made up the largest proportion of ICU cancer patients.

• Although lung and breast cancer were the two most commonly diagnosed cancers during the study period, the rate of admission to ICU was low at 1.6% and 0.8% respectively.

• Patients with solid tumours admitted to ICU had an ICU mortality of 14.7% and hospital mortality of 25.7%.

• Mortality varied by cancer type and was higher in emergency admissions, medical admissions and in patients that received organ support.

• Deprivation was not associated with an increased rate of ICU admission, however, the most deprived population were more likely to be admitted as an emergency and receive organ support and this group had a corresponding higher mortality.

Chapter 5 What proportions of patients admitted to ICU have a diagnosis of cancer and how do they differ from the non-cancer population?

5.1 Introduction

The previous chapter established that over 5% of patients with a solid tumour were admitted to ICU within 2 years of diagnosis. To appreciate the impact this might have on ICU work, it is necessary to understand these patients in the context of other ICU patients. A comparison of baseline characteristics and outcomes of solid tumour patients and patients without cancer admitted to general ICUs was therefore made.

5.2 Study questions

5.2.1 What proportions of patients admitted to ICU have a diagnosis of cancer?

In the first instance I will describe the general ICU population in terms of those with and without a diagnosis of cancer as a proportion of the total number of admissions. Because the nature of illness and outcomes vary by whether patients are admitted as a surgical or medical admission I will look at these groups separately and describe the proportion of cancer patients within each subgroup.

5.2.2 Are the features associated with critical illness different in patients with an underlying cancer when compared to the non-cancer population?

I will describe the differences in demographic and clinical features of the ICU cancer group compared with the ICU group without cancer. Patients with cancer may present to ICU with different types of critical illness and may vary in terms of their severity of illness and requirement for organ support. This may be different again depending on whether the ICU admission was medical or surgical in nature and I will therefore analyse these groups separately. Finally, I will describe the differences in features in the subgroup of patients who received organ support during their ICU stay.

5.2.3 Do the ICU features vary according to underlying tumour types?

It might be expected that different tumour types and their specific treatments may result in different presentations to ICU. It is therefore important to analyse the features associated with ICU admission grouped by the type of underlying cancer for surgical and medical admissions separately.

5.2.4 Do ICU outcomes differ between those patients with and without an underlying cancer?

I will report ICU and hospital mortality for patients with and without cancer admitted to ICU in addition to those admitted as medical or surgical ICU admissions and by whether organ support was received in ICU. Longer-term survival of all patients will be described up to four years following ICU admission.

5.3 Methods

Statistical analyses were performed using Stata software (version 14, StataCorp 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Hospital admission type was described for the cancer group and the non-cancer group. This was then compared with ICU admission type.

Descriptive analysis was initially completed for all ICU patients and documented as a percentage of the cohort. ICU patients were separated into those admitted to ICU under a surgical admitting team or a medical admitting team. Further subgroup analysis was performed within these groupings on those patients that had received organ support during their ICU stay. This was to exclude those patients admitted to combined units for routine post-operative care or monitoring. Organ support was defined as one of mechanical ventilation, vasoactive drugs or renal replacement therapy.

Additional descriptive analysis was performed on surgical and medical admissions depending on the underlying tumour type. The most frequently admitted tumour types were explored in more detail.

Unless otherwise stated, median and inter-quartile ranges were used to summarise continuous variables, and Wilcoxon rank test (Mann Whitney) to test for differences in median values. Pearson chi-square test and exact 95% confidence intervals were used to compare proportions. A significance level of 5% was accepted. Survival was described in terms of ICU, hospital and time-defined survival up to four years following ICU admission. In addition, Kaplan-Meier survival graphs were plotted for specific subgroups using the log-rank test for equality of survivor functions to calculate a p-value.

5.4 Results

During the study period 1st January 2000 – 31st December 2011 there were 41,689 patients admitted to general ICUs in the West of Scotland. Of these 6116 (14.7%) had a diagnosis of solid tumour within 2 years prior to admission and 35,573 did not have a cancer diagnosis.

5.4.1 Admission types

Of the 41,689 patients admitted to ICU on Wardwatcher there was corresponding SMR01 hospital admission data available for 40,585 patients (97.4%) including data on emergency/ elective hospitalisation and medical/ surgical hospital admission type data (Table 5-1).

	All ICU admissions	
Hospital admission type	**Patients without cancer N=35,573**	**Patients with cancer N=6116**
Elective medical	498 (1.4%)	188 (3.1%)
Emergency medical	12,636 (35.5%)	761 (12.4%)
Elective surgical	3550 (10.0%)	3223 (52.7%)
Emergency surgical	17,861 (50.2%)	1868 (30.5%)
Unknown	1028 (2.9%)	76 (1.2%)

Table 5-1 Hospital admission type by patients with and without cancer

Patients without cancer were predominantly admitted to hospital as an emergency (88.3% (95% CI 87.9 – 88.6). Half of the ICU non-cancer population had been admitted to hospital as an emergency surgical patient with an additional 10% admitted as an elective surgical patient. Emergency medical hospitalisations contribute over a third to ICU patients without cancer with very few patients admitted to ICU after an elective medical hospitalisation (1.4%).

Patients with cancer were less commonly emergency hospitalisations (43.5% (95% CI 42.3 – 44.8). More than half of the ICU cancer population had been admitted to hospital as an elective surgical patient and a further 30.5% admitted as an emergency surgical hospitalisation. Emergency medical admissions to hospital were less common at 12.4% of all ICU admissions in the cancer population. The proportions of ICU cancer patients admitted after an elective medical hospitalisation was slightly higher at 3.1% and this likely reflects investigation and inpatient management of the underlying cancer.

ICU admission type data was available for all 6116 patients in the cancer group and 35,573 patients (99.7%) in the non-cancer group. Compared to the non-cancer population, patients with cancer were more likely to be admitted to ICU with a surgical diagnosis (89.3% (95% CI 88.5 – 90.1) vs. 55.0% (95% CI 54.5 – 55.5) p<0.001) as demonstrated in Figure 5-1.

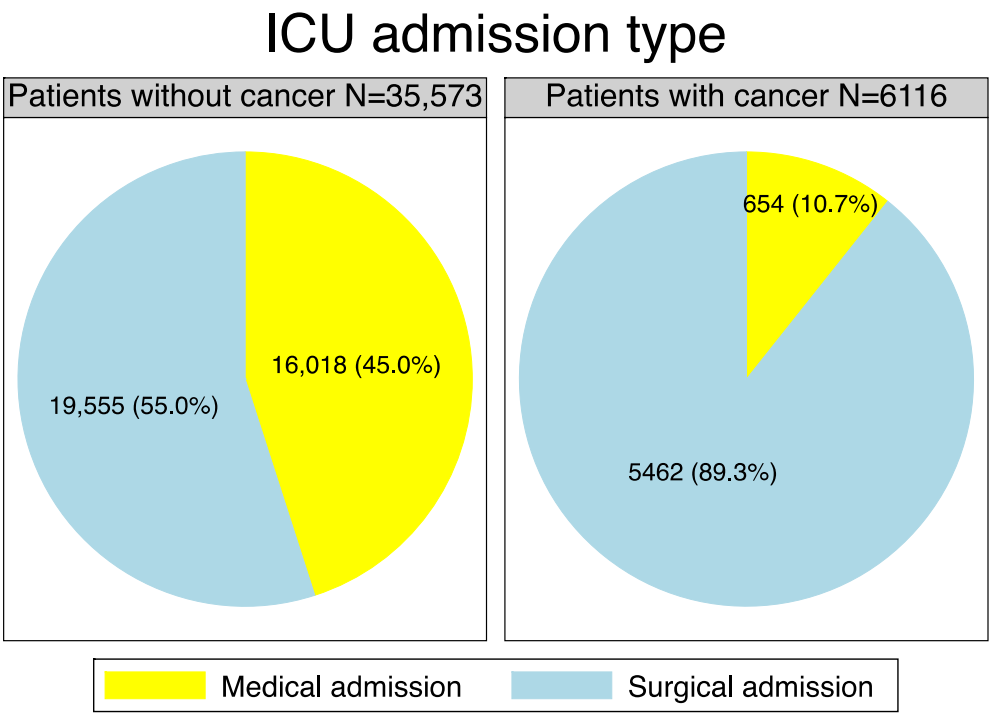


Figure 5-1 ICU admission type by patients with and without cancer

ICU admission type and hospital admission type for patients with and without cancer can be seen compared in Table 5-2. This demonstrates that the original cause of hospitalisation may not be the cause of ICU admission.

	ICU Medical admissions		ICU Surgical admissions	
Hospital admission type	**Non Cancer N=16,018**	**Cancer N=654**	**Non Cancer N=19,555**	**Cancer N=5462**
Elective medical N=686	153 (1.0%)	28 (4.3%)	345 (1.8%)	160 (2.9%)
Emergency medical N=13,397	10007 (62.5%)	344 (52.6%)	2629 (13.4%)	417 (7.6%)
Elective surgical N=6773	141 (8.8%)	122 (18.7%)	3409 (17.4%)	3101 (56.8%)
Emergency surgical N=19,729	5265 (32.9%)	157 (24.0%)	12596 (64.4%)	1711 (31.3%)
Unknown N=1197	452 (2.8%)	3 (0.5%)	576 (2.9%)	73 (1.3%)

Table 5-2 ICU admission type compared with hospitalisation type by patients with and without cancer

Of all ICU patients with an elective surgical hospitalisation, 96.1% are admitted to ICU as surgical patients. Emergency surgical hospitalisations are predominantly admitted to ICU due to a surgical diagnosis although 27.5% have a medical ICU admission. However, within the ICU cancer population 91.6% of emergency surgical hospitalisations are surgical ICU admissions. Within the general ICU population, most patients that were admitted to hospital as an elective medical admission have a surgical ICU admission (73.6%) and this is more pronounced within the cancer population (85.1%). ICU patients with an emergency medical hospitalisation tend to have a medical ICU admission, however, this is less common within the ICU cancer population when compared with the ICU non-cancer population (45.2% vs. 79.2% $p<0.001$).

5.4.2 Demographic and clinical features

Comparative patient demographics for those with and without cancer can be seen in Table 5-3. There were a slightly higher proportion of males within the ICU cancer population compared with the non-cancer population (58.4% vs. 54.5%, p<0.001) in keeping with the higher incidence rates of cancer in males. The median age of cancer patients was 68 years (IQR 60 – 75). ICU patients without a cancer diagnosis were younger (median age 59 years (IQR 43 – 71)). Admission related to underlying malignancy was the commonest reason for admission in the cancer group (39.4%). Of note, 216 patients in the non-cancer group (0.7%) had an ICU admission relating to a malignancy. This may be accounted for by incorrect admission diagnosis (either due to mistaken diagnosis or user error) or by patients with cancer diagnosed outwith Scotland being admitted to a west of Scotland ICU. Within the non-cancer group sepsis was the most frequent admitting diagnosis and this was the third most common diagnosis within the cancer group. Gastrointestinal and Liver disease was a common reason for admission within both groups.

Severity of illness scoring by APACHE II was recorded for 83.8% of non-cancer ICU patients and 70% of cancer ICU patients. Median APACHE II score was lower for cancer patients (17 vs. 19, p <0.0001). This was also reflected in lower use of organ support with 59.3% of cancer patients receiving support compared with 74.6% of non-cancer patients (p<0.001). Each type of organ support was utilised less often within the cancer group compared with the non-cancer group. Multi-organ support was utilised less frequently in the cancer group with two or more organ support provided in 27.2% compared with 38.9% of the non-cancer group (p <0.001). ICU length of stay was similar for both groups. Overall mortality was higher for the non-cancer group with ICU mortality of 22.9% vs. 14.7% (p<0.001) and in-hospital mortality of 34.2% vs. 25.7% (p <0.001).

	ICU Non-cancer patients N=35,573		ICU Cancer patients N=6116		P value
Men	*19,393*		*3573*		<0.001
	54.5% (54.0 – 55.0)		58.4% (57.2 – 59.7)		
Median Age (IQR) years	59 (43 – 71)		68 (60 – 75)		<0.0001
Surgical admission to ICU	*19,555*		*5462*		<0.001
	55.0% (54.5 – 55.5)		89.3% (88.5 – 90.1)		
Emergency hospitalisation	*30,497 / 34,545*		*3411 / 6040*		<0.001
	88.3% (87.9 – 88.6)		43.5% (42.3 – 44.8)		
Reason for admission					<0.001
Malignancy	*261*	0.7%	*2408*	39.4%	
Gastrointestinal/ Liver	*5212*	14.7%	*1106*	18.1%	
Sepsis	*8020*	22.5%	*819*	13.4%	
Surgical complication	*931*	2.6%	*384*	6.3%	
Respiratory disorder	*3102*	8.7%	*310*	5.1%	
Haemorrhage	*1714*	4.8%	*223*	3.7%	
Vascular	*2426*	6.8%	*57*	0.9%	
Drug related	*2262*	6.4%	*15*	0.2%	
Trauma	*1776*	5.0%	*30*	0.5%	
Cardiovascular	*1622*	4.6%	*215*	3.5%	
Post cardiac arrest	*1848*	5.2%	*84*	1.4%	
Renal	*603*	1.7%	*100*	1.6%	
Neurological	*3359*	9.4%	*84*	1.4%	
Median APACHE II (IQR)	19 (13 – 25)		17 (13 – 22)		<0.001
Not recorded	*5759*	16.2%	*1837*	30.0%	<0.001
Organ support type:					
Respiratory support	*25,166 / 35,089*		*3344 / 5939*		
	71.7% (71.2 – 72.2)		56.3% (55.0 – 57.6)		<0.001
Unknown	*484*	1.4%	*177*	2.9%	<0.001
Cardiovascular support	*14,546 / 34,783*		*1879 / 5923*		
	41.8% (41.3 – 42.3)		31.7% (30.5 – 32.9)		<0.001

Unknown	*790*	2.2%	*193*	3.2%	<0.001
Renal support	*3573 / 31,496*		*306 / 5228*		
	11.3% (1.0 – 11.7)		5.9% (5.2 – 6.5)		<0.001
Unknown	*4077*	11.5%	*888*	14.5%	<0.001
Organ support					<0.001
0	*8564*	24.1%	*2321*	37.9%	
1	*12,714*	35.7%	*1958*	32.0%	
2	*10,921*	30.7%	*1427*	23.3%	
3	*2910*	8.2%	*239*	3.9%	
Unknown for all modes	*464*	1.3%	*171*	2.8%	<0.001
ICU length of stay (IQR)	2 (1 – 5) days		2 (1 – 5) days		<0.0001
Unknown	*80*	0.2%	*35*	0.6%	
ICU mortality	22.9% (22.5 – 23.3)		14.7% (13.8 – 15.6)		<0.001
Hospital mortality	34.2% (33.7 – 34.9)		25.7% (24.6 – 26.8)		<0.001

Table 5-3 Patient demographics for ICU patients with and without cancer. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

5.4.2.1 Patients receiving organ support in ICU

Among all ICU patients there were 10,885 patients (26.1%) that did not receive organ support during their ICU stay and a further 635 patients (1.5%) for whom all three types of organ support were unknown. The remaining 30,169 patients received respiratory (94.5%), vasoactive (54.4%) or renal support (12.9%). These patients were analysed separately as a group that received organ support in ICU.

Among patients receiving organ support 3624 (12.0%) had a solid tumour diagnosis. Of these 3,165 patients (87.3%) were admitted to ICU with a surgical diagnosis. This compares with 49.2% of non-cancer patients admitted with a surgical diagnosis. Cancer patients were more likely to be admitted to ICU after

an elective hospitalisation compared with non-cancer patients (52.6% vs. 7.8% p<0.0001).

5.4.3 Surgical admissions to ICU

There were 25,017 ICU surgical admissions of which 5,462 (21.8%) were patients with cancer. Table 5-4 gives patient characteristics for surgical admission to ICU with and without a diagnosis of cancer.

Surgical ICU cancer patients tended to be older than non-cancer patients and there are a slightly higher proportion of male patients within the cancer group. The majority of the cancer population had been admitted to hospital electively compared to the non-cancer group (60.5% vs. 19.8% p<0.001). ICU admission was directly related to underlying malignancy for 42.0% of the cancer group and in 1.2% of the non-cancer group. The most frequent diagnostic groups were similar between the cancer and non-cancer groups with sepsis, gastrointestinal/ liver disease and surgical complications as common causes for admission. Vascular disease and trauma occurred significantly more frequently in the non-cancer group.

APACHE II score was available for 79.2% of non-cancer patients and 69.6% of cancer patients with similar median value for both groups (17 vs. 17, p= 0.1161) although organ support was provided less frequently in the cancer group compared with the non-cancer group (57.9% vs. 66.7%, p<0.001). Single organ support did not differ between the two groups but the provision of multi-organ support was less for the cancer group (25.4% vs. 33.8%, p<0.001). ICU and hospital mortality was lower for the cancer population compared with the non-cancer population at 12.2% vs. 16.8% (p<0.001) and 22.9% vs. 28.1% (p<0.001) respectively.

	ICU Non-cancer patients N=19,555	ICU Cancer patients N=5462	P value
Men	*10,696* 54.7% (54.0 – 55.4)	*3201* 58.6% (57.3 – 59.9)	<0.001
Median Age (IQR)	62 (45 – 74)	68 (60 – 76)	<0.0001
Emergency hospitalisation	*15,255 / 18,979* 80.2% (79.6 – 80.8)	*2128 / 5389* 39.5% (38.2 – 40.8)	<0.001
Reason for admission			<0.001
Malignancy	*244* 1.2%	*2294* 42.0%	
Gastrointestinal/ Liver	*4778* 24.4%	*1020* 18.7%	
Sepsis	*3089* 15.8%	*610* 11.2%	
Surgical complication	*893* 4.6%	*376* 6.9%	
Respiratory disorder	*1174* 6.0%	*244* 4.5%	
Haemorrhage	*1377* 7.0%	*206* 3.8%	
Vascular	*2392* 12.2%	*56* 1.0%	
Trauma	*1702* 8.7%	*30* 0.6%	
Cardiovascular	*769* 3.9%	*180* 3.3%	
Renal	*308* 1.6%	*84* 1.5%	
Median APACHE II (IQR)	17 (12 – 22)	17 (13 – 21)	0.1161
Not recorded	*4073 20.8%*	*1659 30.4%*	<0.001
Organ support type:			
Respiratory support	*12,300 / 19220* 64.0% (63.3 – 64.7)	*2919 / 5306* 55.0% (53.7 – 56.4)	<0.001
Unknown	*335* 1.7%	*156* 2.9%	<0.001
Cardiovascular support	*7103 / 19,080* 37.2% (36.4 -37.9)	*1584 / 5291* 29.9% (28.7 – 31.2)	<0.001
Unknown	*475* 2.4%	*171* 3.1%	0.004
Renal support	*1557 / 16,882* 9.2% (8.8 – 9.7)	*237 / 4674* 5.1% (4.5 – 5.7)	<0.001

Unknown	*2673*	13.7%	*788*	14.4%	0.152
Organ support					<0.001
0	*6186*	31.6%	*2146*	39.2%	
1	*6438*	32.9%	*1779*	32.6%	
2	*5302*	27.1%	*1197*	21.9%	
3	*1306*	6.7%	*189*	3.5%	
Unknown for all modes	*323*	*1.7%*	*151*	*2.8%*	<0.001
ICU length of stay (IQR)	2 (1 – 5) days		2 (1 – 4) days		<0.0001
Unknown	*69*	0.4%	*34*	0.6%	
ICU mortality	16.8% (16.3 – 17.4)		12.2% (11.3 – 13.1)		<0.001
Hospital mortality	28.1% (27.4 – 28.7)		22.9% (21.8 – 24.1)		<0.001

Table 5-4 Surgical admissions to ICU with and without cancer. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

5.4.3.1 Surgical ICU admissions with organ support

There were 16,211 surgical patients that were admitted to ICU and received organ support during the study period. Of these 3165 (19.5%) had a solid tumour diagnosis (Table 5-5). Compared with the surgical population without cancer, the surgical ICU cancer group had a higher proportion of men (61.3% vs. 56.0%, p<0.001) and tended to be older (median age 68 years vs. 63 years, p<0.0001). Elective admission to hospital prior to ICU occurred more frequently in the cancer group with 58.5% vs. 14.1%, p<0.001. Admission to ICU was directly related to the malignancy in 30.4% of patients with cancer. Common causes for ICU admission in both cancer and non-cancer patients included sepsis (17.5% and 20.1%), gastrointestinal/ liver disease (17.1% and 22.6%), surgical complication (9.4% and 5.3%), non-infectious respiratory disorder (6.3% and 6.6%) and haemorrhage (5.3% and 7.6%). Other frequent reasons for admission to ICU in the non-cancer population included vascular disease (10.5%) and trauma (8.5%). However, these were less frequent in the ICU cancer population at 1.0% and 0.6% respectively.

	ICU Non-cancer patients N=13,046		ICU Cancer patients N=3165		P value
Men	*7312* 56.0% (55.2 – 56.9)		*1941* 61.3% (59.6 – 63.0)		<0.001
Median Age (IQR)	63 (46 – 74)		68 (60 – 76)		<0.0001
Emergency hospitalisation	*10,892 / 12,680* 85.9% (85.3- 86.5)		*1299 / 3128* 41.5% (39.8 – 43.3)		<0.001
Reason for admission					<0.001
Malignancy	*80*	0.6%	*961*	30.4%	
Sepsis	*2624*	20.1%	*555*	17.5%	
Gastrointestinal/ Liver	*2949*	22.6%	*540*	17.1%	
Surgical complication	*689*	5.3%	*297*	9.4%	
Respiratory disorder	*863*	6.6%	*198*	6.3%	
Haemorrhage	*992*	7.6%	*168*	5.3%	
Vascular	*1368*	10.5%	*31*	1.0%	
Trauma	*1103*	8.5%	*18*	0.6%	
Cardiovascular	*393*	3.0%	*99*	3.1%	
Neurological	*794*	6.1%	*33*	1.0%	
Median APACHE II (IQR)	18 (14 – 24)		18 (14 – 23)		0.177
Not recorded	*1040*	8.0%	*293*	9.3%	0.018
Organ support type:					
Respiratory support	*12,300* 94.3% (93.9 – 94.7)		*2919* 92.2% (91.2 – 93.1)		<0.001
Unknown	*1*	0.0%	*0*	0%	0.622
Cardiovascular support	*7103* 54.6% (53.7 – 55.4)		*1584* 50.1% (48.4 – 51.9)		<0.001
Unknown	*33*	0.3%	*4*	0.1%	0.181
Renal support	*1557* 13.3% (12.7 – 14.0)		*237* 8.3% (7.3 – 9.3)		<0.001

Unknown		*1365* 10.5%		*301* 9.5%	0.113
Organ support	**1**	*6438*	49.4%	*1779* 56.2%	<0.001
	2	*5302*	40.6%	*1197* 37.8%	
	3	*1306*	10.0%	*189* 6.0%	
ICU length of stay (IQR)		3 (1 – 7) days		2 (1 – 5) days	0.0001
ICU mortality		23.5% (22.8 – 24.2)		18.6% (17.2 – 19.9)	<0.001
Hospital mortality		36.0% (35.1 – 36.8)		31.4% (29.8 – 22.0)	<0.001

Table 5-5 Surgical admissions to ICU that received organ support. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

APACHE II score was available for 92% of ICU non-cancer patients and 90.7% of ICU cancer patients and median value was 18 for both groups. Within this group of patients defined as surgical ICU admissions that had received organ support, respiratory support was the commonest mode of support within both the cancer and non-cancer groups at 92.2% and 94.3% respectively. Cardiovascular support was provided to half of the cancer group (50.1%) and 54.6% of the non-cancer group. Data pertaining to provision of renal replacement therapy (RRT) was missing in 10.5% of non-cancer patients and 9.5% of cancer patients. RRT was not commonly provided in either group but those patients in the cancer group had a lower prevalence of RRT when compared to the non-cancer group (8.3% (95% CI 7.3 – 9.3) vs. 13.3% (95% CI 12.7 – 14.0)). Single organ support was more common in the cancer group with 56.2% of patients compared with 49.4% in the non-cancer group.

ICU length of stay was shorter for the cancer group with a median value of 2 days versus 3 days in the non-cancer group ($p < 0.0001$). Mortality was lower in the cancer group with ICU mortality 18.6% versus 23.5% ($p < 0.001$) and hospital mortality 31.4% versus 36.0% ($p < 0.001$).

5.4.3.2 Features of ICU surgical admissions by underlying tumour type

Table 5-6 lists all tumour types in ICU during the study period along with ICU and hospital mortality. Short-term mortality varied considerably between different cancer types. To explore this further the ICU clinical features were analysed. As expected the clinical features varied by the underlying tumour type and the four commonest tumours admitted to ICU as a surgical admission are described in Table 5-7 (colorectal, head and neck, stomach and oesophageal cancer).

Cancer type	Number of patients	Percent of surgical ICU cohort	ICU mortality	Hospital mortality
Colorectal	*2414*	44.2%	11.6% (10.3 – 12.9)	21.9% (20.2 – 23.6)
Head & Neck	*610*	11.2%	5.6% (3.9 – 7.7)	11.0% (8.6 – 13.7)
Stomach	*419*	7.7%	10.7% (7.9 – 14.1)	22.0% (18.1 – 26.2)
Oesophagus	*355*	6.5%	8.5% (5.8 – 11.8)	17.7% (13.9 – 22.1)
Kidney	*230*	4.2%	9.6% (6.1 – 14.1)	15.2% (10.8 – 20.5)
Lung	*220*	4.0%	35.9% (29.6 – 42.6)	51.4% (44.6 – 58.1)
Bladder	*172*	3.1%	7.0% (3.7 – 11.9)	26.7% (20.3 – 34.0)
Ovary	*130*	2.4%	14.6% (9.0 – 21.9)	29.2% (21.6 – 37.8)
Prostate	*102*	1.9%	8.8% (4.1 – 16.1)	21.6% (14.0 – 30.8)
Uterus	*102*	1.9%	10.8% (5.5 – 18.5)	16.7% (10.0 – 25.3)
Breast	*99*	1.8%	15.2% (8.7 – 23.8)	22.2% (14.5 – 31.7)
Pancreas	*72*	1.3%	25.0% (15.5 – 36.6)	47.2% (35.3 – 59.3)
Liver	*56*	1.0%	32.1 (20.3 – 46.0)	58.9% (45.0 – 71.9)
Small intestine	*50*	0.9%	14.0% (5.8 – 26.7)	32.0% (19.5 – 26.7)
Thyroid	*24*	0.4%	4.2% (1.1 – 21.1)	8.3% (1.0 – 27.0)
Testis	*16*	0.3%	18.8% (4.0 – 45.6)	18.8% (4.0 – 45.6)
Mesothelioma	*13*	0.2%	23.1% (5.0 – 53.8)	46.2% (19.2 – 74.9)
Melanoma	*11*	0.2%	0% (0 – 28.5)*	18.2% (2.3 – 51.8)
Other	*95*	1.7%	12.6% (6.7 – 21.0)	25.3% (16.9 – 35.2)
Unknown	*82*	1.5%	39.0% (28.4 – 50.4)	68.3% (57.1 – 78.1)
Multiple	*190*	3.5%	8.9% (5.3 – 13.9)	17.4% (12.3 – 23.5)
Total	*5462*	100%	12.2% (11.3 – 13.1)	22.9% (21.8 – 24.1)

Table 5-6 Frequency of specific tumour types in the surgical ICU population and short-term mortality. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified. *One sided 97.5% confidence interval

ICU Features	Colorectal N=2414	Head & Neck N=610	Stomach N=419	Oesophagus N=355
Median age (IQR)	71 (63 – 78)	62 (55 – 69)	69 (61 – 76)	64 (57 – 71)
Emergency hospital admission	*1089 / 2372* 45.9% (43.9 – 47.9)	142 / 608 23.4% (20.0 – 26.9)	*109 / 417* 26.1% (22.0 – 30.6)	*54 / 352* 15.3% (11.7 – 19.5)
Sepsis	10.5%	7.9%	10.0%	9.3%
Median APACHE II (IQR)	18 (14 – 22)	15 (12 – 19)	16 (12 – 21)	14 (11 – 19)
Not recorded	*908* 37.6%	*61* 10%	*125* 29.8%	*52* 14.6%
Organ support				
Respiratory support	*1014 / 2350* 44.3% (42.3 – 46.3)	*558 / 598* 93.3% (91.0 – 95.2)	*193 / 401* 48.1% (43.1 – 53.1)	*199 / 151* 56.9% (51.5 – 62.1)
Unknown	*64* 2.7%	*12* 2.0%	*18* 4.3%	*5* 1.4%
CVS support	*733 / 2343* 31.3% (29.4 – 33.2)	*100 / 598* 14.4% (11.7 – 17.5)	*209 / 398* 27.4% (23.1 – 32.1)	*112 / 350* 32.0% (27.1 – 37.2)
Unknown	*71* 2.9%	*12* 2.0%	*21* 5.0%	*5* 1.4%
Renal support	*90 / 2037* 4.4% (3.6 – 5.4)	*16 / 570* 2.8% (1.6 – 4.5)	*16 / 338* 4.7% (2.7 – 7.6)	*15 / 313* 4.8% (2.7 – 7.8)
Unknown	*377* 15.6%	*40* 6.6%	*81* 19.3%	*42* 11.8%
Organ support				
0	*1181* 48.9%	*40* 6.6%	*189* 45.1%	*124* 34.9%
1	*553* 22.9%	*467* 76.6%	*117* 27.9%	*141* 39.7%
2	*540* 22.4%	*83* 13.6%	*84* 20.0%	*70* 19.7%
3	*77* 3.2%	*9* 1.5%	*11* 2.6%	*15* 4.2%
Unknown for all modes	*63* 2.6%	*11* 1.8%	*18* 4.3%	*5* 1.4%

ICU Features	Colorectal N=2414	Head & Neck N=610	Stomach N=419	Oesophagus N=355
ICU mortality	11.6% (10.3 – 12.9)	5.6% (3.9 – 7.7)	10.7% (7.9 – 14.1)	8.5% (5.8 – 11.8)
Hospital mortality	21.9% (20.2 – 23.6)	11.0% (8.6 – 13.7)	22.0% (18.1 – 26.2)	17.8% (13.9 – 22.1)

Table 5-7 ICU features by commonest surgical tumour types. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

Colorectal cancer was the commonest tumour type admitted to ICU as a surgical admission (44.2%). Other common tumours included head and neck tumours (11.2%) and upper gastrointestinal tumours (stomach 7.7%, oesophageal 6.5%). Colorectal cancer had the highest rate of emergency hospitalisation at 45.9% and median APACHE II scores were correspondingly higher. Organ support showed some variation by underlying tumour type. Notably, single organ support was more common in surgical patients with head and neck cancer (76.6%) compared with that seen in other common tumour types (22.9% in colorectal cancer patients to 39.7% oesophageal cancer patients). This was largely accounted for by the high rate of mechanical ventilation for patients with head and neck cancer. There was a high proportion of patients receiving no organ support in the groups with colorectal cancer and stomach cancer (48.9% and 45.1% respectively). These groups also had a larger proportion of patients with missing APACHE II scores. ICU and hospital mortality were lowest for the group of patients with head and neck cancer.

5.4.4 Medical admissions to ICU

During the study period there were 16,672 medical admissions to ICU. Of these 654 patients (3.9%) had a solid tumour diagnosis. Clinical features of those medical patients admitted to ICU with and without a diagnosis of cancer are demonstrated in Table 5-8.

	ICU Non-cancer patients N=16,018	ICU Cancer patients N=654	P value
Men	*8679* 54.3% (53.5 – 55.1)	*372* 56.9% (53.0 – 60.7)	0.194
Median Age (IQR)	55 (41 – 68)	67 (59 – 74)	<0.0001
Emergency hospitalisation	*15,272 / 15,566* 98.1% (97.9 – 98.3)	*501 / 651* 77.0% (73.5 – 80.1)	<0.001
Reason for admission			
Sepsis	*4931* 30.8%	*209* 32.0%	<0.001
Malignancy	*17* 0.1%	*114* 17.4%	
Gastrointestinal/ Liver	*434* 2.7%	*86* 13.1%	
Respiratory disorder	*1928* 12.0%	*66* 10.1%	
Neurological	*2451* 15.3%	*44* 6.7%	
Post cardiac arrest	*1593* 9.9%	*41* 6.3%	
Cardiovascular	*849* 5.3%	*28* 4.3%	
Haemorrhage	*337* 2.1%	*17* 2.6%	
Drug related	*2164* 13.5%	*9* 1.4%	
Endocrine/ Metabolic	*415* 2.6%	*6* 0.9%	
Median APACHE II (IQR)	21 (15 – 27)	22 (17 – 27)	0.0002
Not recorded	*1686* 10.5%	*178* 27.2%	<0.001
Organ support type:			
Respiratory support	*12,866 / 15,869* 81.1% (80.5 – 81.7)	*425 / 633* 67.1% (63.3 – 70.8)	<0.001
Unknown	*149* 0.9%	*21* 3.2%	<0.001
Cardiovascular support	*7444 / 15,703* 47.4% (46.6 – 48.2)	*295 / 632* 46.7% (42.7 – 50.7)	0.719
Unknown	*315* 2.0%	*22* 3.4%	0.013
Renal support	*2016 / 14,614* 13.8% (13.2 – 14.4)	*69 / 554* 12.5% (9.8 – 15.5)	0.369

Unknown		*1404*	8.9%	*100*	15.3%	<0.001
Organ support	**0**	*2016*	12.6%	*129*	19.7%	<0.001
	1	*6276*	39.2%	*179*	27.4%	
	2	*5619*	35.1%	*230*	35.2%	
	3	*1604*	10.0%	*50*	7.6%	
Unknown for all modes		*503*	3.1%	*66*	10.1%	<0.001
ICU length of stay (IQR)		2 (1 – 6) days		3 (1 – 6) days		0.004
ICU mortality		30.3% (29.6 – 31.0)		35.8% (32.1 – 39.6)		0.003
Hospital mortality		41.7% (40.9 – 42.4)		49.1% (45.2 – 53.0)		<0.001

Table 5-8 Medical admissions to ICU with and without cancer. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

Median age at the time of ICU admission was higher in the cancer group at 67 years compared with 55 years in the non-cancer group (p<0.001). 77.0% of hospitalisations were emergency in nature within the ICU cancer group compared with 98.1% in the non-cancer group (p<0.001). Sepsis was the commonest reason for admission affecting 32.0% of cancer patients and 30.8% non-cancer patients. Within the ICU cancer group other reasons for admission included malignancy (17.4%), gastrointestinal/ liver disease (13.1%), non-infectious respiratory disorder (10.1%), neurological conditions (6.7%) and post cardiac arrest (6.3%). Those ICU patients without cancer were admitted with neurological conditions (15.3%), drug related (13.5%), non-infectious respiratory disorder (12.0%) and post cardiac arrest (9.9%).

There was not a clinically significant difference in median APACHE II score although there were a larger proportion of cancer patients with missing APACHE II scores than the non-cancer group (27.2% vs. 10.5%, p<0.001). Respiratory support was provided less frequently in the cancer group compared to the non-cancer group (67.1% vs. 81.1%, p<0.001). Support with vasoactive drugs and renal replacement therapy was similar between both groups. A larger proportion of cancer patients received no organ support during their time in ICU when compared to the non-cancer patients (19.7% vs. 12.6%, p<0.001). However,

multi-organ support was provided to a similar proportion within each groups (42.8% vs. 45.1% p=0.251).

ICU length of stay was slightly longer for cancer patients when compared with non-cancer patients (median duration 3 days vs. 2 days, p=0.004). Mortality was high for both groups but was consistently higher in the ICU cancer population with ICU mortality of 35.8% (95% CI 32.1 – 39.6) vs. 30.3% (95% CI 29.6 – 31.0), p=0.003, and hospital mortality of 49.1% (95% CI 45.2 – 53.0) vs. 41.7% (95% CI 40.9 – 42.4), p<0.001.

5.4.4.1 Medical ICU admissions with organ support

There were 13,958 medical admissions that received organ support during the study period. Only 459 patients (3.3%) had a solid tumour diagnosis (Table 5-9). Compared with the medical population without cancer, the medical ICU cancer group tended to be older (median age 66 years vs. 56 years, p<0.0001). The majority of patients in both groups were admitted to ICU after emergency admission to hospital. The proportion was slightly less for the cancer group at 87.9% (95% CI 84.6 – 90.8) compared with 98.3% (95% CI 981. – 98.5) of the non-cancer group.

The commonest reason for admission in both groups was due to sepsis. This contributed 40.3% of medical ICU cancer admissions and 33.0% of medical ICU non-cancer admissions. Common causes for ICU admission in both cancer and non-cancer patients included non-infectious respiratory disorders (12.2% and 10.6%), neurological disorders (9.3% and 16.3%), post cardiac arrest (8.7% and 11.5%), and gastrointestinal/ liver disease (5.7% and 2.1%). Malignancy was the direct cause for ICU admission in 9.2% of the ICU cancer population. Drug related admissions accounted for 12.9% of the non-cancer ICU medical admissions but only 1.7% in the cancer group.

	ICU Non-cancer patients N=13,499 (%)		ICU Cancer patients N=459 (%)		P value
Men	*7427*		*259*		0.553
	55.0% (54.2 – 55.9)		56.4% (51.8 – 61.0)		
Median Age (IQR)	56 (42 – 68)		66 (59 – 73)		<0.0001
Emergency hospitalisation	*12,890 / 13,108*		*401 / 456*		<0.001
	98.3% (98.1 – 98.5)		87.9% (84.6 – 90.8)		
Reason for admission					<0.001
Sepsis	*4451*	33.0%	*185*	40.3%	
Respiratory disorder	*9*	10.6%	*42*	12.2%	
Neurological	*281*	16.3%	*26*	9.3%	
Malignancy	*1425*	0.1%	*56*	9.2%	
Post cardiac arrest	*2200*	11.5%	*43*	8.7%	
Gastrointestinal/ Liver	*1551*	2.1%	*40*	5.7%	
Cardiovascular	*766*	5.7%	*24*	5.2%	
Haemorrhage	*251*	1.9%	*8*	1.7%	
Drug related	*1743*	12.9%	*8*	1.7%	
Endocrine/ Metabolic	*241*	1.8%	*3*	0.7%	
Median APACHE II (IQR)	22 (16 – 28)		23 (18 – 28)		0.004
Not recorded	*1014* 7.5%		*44* 9.6%		0.099
Organ support type:					
Respiratory support	*12,866 / 12,864*		*425*		0.007
	95.2% (95.0 – 95.7)		92.6% (89.8 – 94.8)		
Unknown	*2* 0.0%		*0* 0%		0.794
Cardiovascular support	*7444 / 7401*		*295*		<0.001
	55.3% (54.5 – 56.2)		64.3% (59.7 – 68.7)		
Unknown	*43* 0.3%		*0* 0%		0.226

Renal support		*2016 / 12,466* 16.2% (15.5 – 16.8)		*69 / 423* 16.3% (12.9 – 20.2)	0.939
Unknown		*1033* 7.7%		*36* 7.8%	0.880
Organ support	**1**	6276	46.5%	179	39.0%	0.001
	2	5619	41.6%	230	50.1%	
	3	1604	11.9%	50	10.9%	
ICU length of stay (IQR)		2 (1 – 7) days		3 (1 – 6) days		0.893
ICU mortality		34.5% (33.7 – 35.4)		48.4% (43.7 – 53.0)		<0.001
Hospital mortality		46.2% (45.4 – 47.0)		62.5% (57.9 – 67.0)		<0.001

Table 5-9 Medical admissions to ICU that received organ support. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

APACHE II score was available for 92.5% of ICU non-cancer patients and 90.4% of ICU cancer patients. The median APACHE II score was slightly higher for the cancer group compared with the non-cancer group (23 (IQR 18 – 28) vs. 22 (IQR 16 – 28), p 0.004). Within this group of patients defined as medical ICU patients that had received organ support, respiratory support was the commonest mode of support within both the cancer and non-cancer groups at 92.6% and 95.2% respectively. Cardiovascular support was provided more frequently in the cancer group at 64.3% (95% CI 59.7 – 68.7) compared with 55.3% (95% CI 54.5 – 56.2) in the non-cancer group (p <0.001). Data pertaining to provision of renal replacement therapy was missing in 7.7% of non-cancer patients and 7.8% of cancer patients. Approximately one in six medical ICU patients that received organ support had renal replacement therapy and this did not differ between the cancer and non-cancer populations (16.3% (95% CI 12.9 – 20.2) and 16.2% (95% CI 15.5 – 16.8)). Single organ support was less common in the cancer group with 39.0% of patients compared with 46.5% in the non-cancer group.

Mortality was higher in the cancer group with ICU mortality 48.4% (95% CI 43.7 – 53.0) versus 34.5% (95% CI 45.4 – 47.0) (p <0.001) and hospital mortality 62.5% (95% CI 57.9 – 67.0) versus 46.2% (95% CI 45.4 – 47.0) (p <0.001).

5.4.4.2 Features of ICU medical admissions by underlying tumour type

Table 5-10 documents the proportion of each tumour type within the group of cancer patients admitted under a medical specialty. ICU and hospital mortality can be seen to vary depending on the underlying cancer type and this may reflect differences in the critical illness experienced by the different subgroups.

Cancer type	Number of patients	Percent of medical ICU cohort	ICU mortality	Hospital mortality
Lung	*161*	24.6%	55.3% (27.3 – 63.1)	73.3% (65.8 – 79.9)
Colorectal	*147*	22.5%	13.6% (8.5 – 20.2)	20.4% (14.2 – 27.8)
Breast	*50*	7.6%	36.0% (22.9 – 50.8)	52.0% (37.4 – 66.3)
Stomach	*37*	5.7%	37.8% (22.5 – 55.2)	45.9% (29.5 – 63.1)
Oesophageal	*34*	5.2%	44.1% (27.2 – 62.1)	52.9% (35.1 – 70.2)
Prostate	*34*	5.2%	32.4% (17.4 – 50.5)	50.0% (32.4 – 67.6)
Head & Neck	*26*	4.0%	19.2% (6.6 – 39.4)	42.3% (23.4 – 63.1)
Kidney	*19*	2.9%	10.5% (1.3 – 33.1)	31.6% (12.6 – 56.6)
Uterus	*11*	1.7%	18.2% (2.3 – 51.8)	36.4% (10.9 – 69.2)
Liver	*11*	1.7%	18.2% (2.3 – 51.8)	27.3% (6.0 – 61.0)
Bladder	*10*	1.5%	20.0% (2.5 – 55.6)	40.0% (12.2 – 73.8)
Testis	*10*	1.5%	70.0% (34.8 – 93.3)	80.0% (44.4 – 97.5)
Pancreas	*9*	1.4%	44.4% (13.7 – 78.8)	44.4% (13.7 – 78.8)
Ovary	*8*	1.2%	37.5% (8.5 – 75.5)	37.5% (8.5 – 75.5)
Melanoma	*7*	1.1%	42.9% (9.9 – 81.6)	42.9% (9.9 – 81.6)
Small intestine	*5*	0.8%	40.0% (5.3 – 85.3)	40.0% (5.3 – 85.3)
Mesothelioma	*5*	0.8%	60.0% (14.7 – 94.7)	60.0% (14.7 – 94.7)
Thyroid	*4*	0.6%	0% (0 – 60.2)*	25.0% (0.6 – 80.6)

Cancer type	Number of patients	Percent of medical ICU cohort	ICU mortality	Hospital mortality
Other	*11*	1.7%	27.3% (6.0 – 61.0)	45.5% (16.7 – 76.6)
Unknown	*39*	6.0%	61.5% (44.6 – 76.6)	82.1% (66.5 – 92.5)
Multiple	*16*	2.4%	31.3% (11.0 – 58.7)	37.5% (15.2 – 64.6)
Total	*654*	100%	35.8% (32.1 – 39.6)	49.1% (45.2 – 53.0)

Table 5-10 Frequency of specific tumour types in the medical ICU population and short-term mortality. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified. *One sided 97.5% confidence interval

ICU clinical features are described for the four commonest tumours admitted to ICU as a medical admission in Table 5-11. The most frequent ICU medical cancer types were lung (24.6%), colorectal (22.5%), breast (7.6%), and stomach (5.7%). The underlying tumour type was unknown in 6.0% of this population.

ICU Features	Lung N=161	Colorectal N=147	Breast N=50	Stomach N=37
Median age (IQR)	65 (60 – 72)	69 (62 – 76)	64 (53 – 69)	69 (63 – 74)
Emergency hospital admission	*150* 93.2% (88.1 – 96.5)	*78* 53.1% (44.7 – 61.3)	*47 / 49* 95.9% (86.0 – 99.5)	*20* 54.1% (36.9 – 70.5)
Sepsis	55.9%	11.6%	32.0%	13.5%
Median APACHE II (IQR)	22 (18 – 27)	19 (13 – 25)	22.5 (17.5 - 29)	22 (15 – 26)
Not recorded	*18* 2.7%	*88* 59.9%	*10* 20%	*12* 32.4%

ICU Features	Lung N=161	Colorectal N=147	Breast N=50	Stomach N=37
Respiratory support	*130 / 159* 81.8% (74.9 – 87.4)	*52 / 137* 38.0% (29.8 – 46.6)	*10 / 49* 79.6% (65.7 – 89.8)	*21 / 33* 63.6% (45.1 – 79.6)
Unknown	*2* 1.2%	*10* 6.8%	*1* 2.0%	*4* 10.8%
CVS support	*86 / 159* 54.1% (46.0 – 62.0)	*35 / 137* 25.5% (18.5 – 33.7)	*25 / 49* 51.0 % (36.3 – 65.6)	*15 / 33* 45.5% (28.1 – 63.6)
Unknown	*2* 1.2%	*10* 6.8%	*1* 2.0%	*4* 10.8%
Renal support	*10 / 142* 7.0% (3.4 – 12.6)	*5 / 107* 4.7% (1.5 – 10.6)	*6 / 45* 13.3% (5.1 – 26.8)	*3 / 26* 11.5% (2.4 – 30.2)
Unknown	*19* *11.8%*	*40* 27.2%	*5* 10.0%	*11* 29.7%
Organ support				
0	*25* 15.5%	*82* 55.8%	*7* 14.0%	*12* 32.4%
1	*50* 31.1%	*23* 15.6%	*19* 38.0%	*8* 21.6%
2	*76* 47.2%	*27* 18.4%	*18* 36.0%	*11* 29.7%
3	*8* 5.0%	*5* 3.4%	*5* 10.0%	*3* 8.1%
Unknown for all modes	*2* 1.2%	*10* 6.8%	*1* 2.0%	*3* 8.1%
ICU mortality	55.3% (47.3 – 63.1)	13.6% (8.5 – 20.2)	36.0% (22.9 – 50.8)	37.8% (22.5 – 55.2)
Hospital mortality	73.3% (65.8 – 79.9)	20.4% (14.2 – 27.8)	52.0% (37.4 – 66.3)	45.9% (29.5 – 63.1)

Table 5-11 ICU features by commonest medical tumour types. Numbers are *cumulative total* followed by percentages (with 95% confidence intervals) unless otherwise specified.

The populations with colorectal and stomach cancer had lower rates of emergency hospitalisation, sepsis and organ support when compared with that seen in patients with lung cancer or breast cancer. Only the colorectal group had

a corresponding lower median APACHE II score with associated lower ICU and hospital mortality. In contrast, lung cancer patients had high rates of sepsis, high use of multi-organ support (over half of the lung cancer cohort) and high ICU and hospital mortality.

5.4.5 Survival following ICU admission

Longer-term survival of ICU patients with and without cancer is demonstrated by the Kaplan Meier graph in Figure 5-2. This demonstrates that the initial survival advantage experienced by ICU cancer patients reverses in the first 12 months following admission. After the initial drop in survival associated with critical illness the group of patients without cancer have a very slow decline in mortality over the following four years. The ICU cancer group, however, has a more pronounced decrease in survival over time.

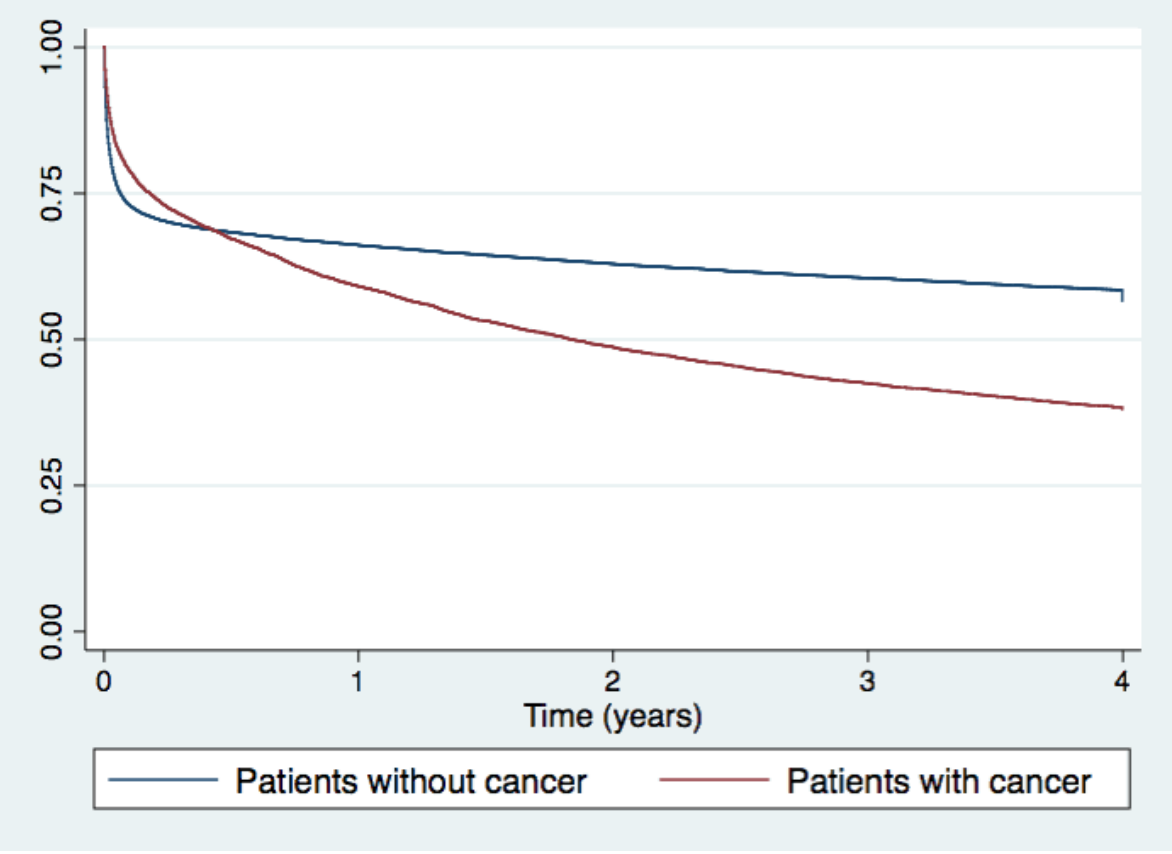


Figure 5-2 Kaplan Meier survival analysis of patients with and without cancer following ICU admission (p <0.0001)

Table 5-12 details the mortality over time up to four years in ICU patients by the cancer and non-cancer subgroup. By one year there is a statistically significant difference in survival between the two groups in favour of those patients without cancer.

Mortality	Patients without cancer	Patients with cancer	P value
Six months	34.7% (34.2 – 35.2)	34.4% (33.2 – 35.6)	0.557
One year	36.8% (36.3 – 37.4)	42.2% (41.0 – 43.5)	<0.001
Four years	45.9% (45.4 – 46.5)	62.8% (61.6 – 64.0)	<0.001

Table 5-12 Mortality up to four years after ICU admission for patients with and without cancer. Numbers are percentages (with 95% confidence intervals) of patients who died during the study period.

The initial survival advantage seen in cancer patients may be explained by the high proportion of surgical cancer admissions as these patients have lower utilisation of organ support and favourable short-term survival compared to surgical patients without cancer and medical patients as previously described. This is in contrast to the smaller proportion of medical cancer admissions where short-term survival is poorer than that in the medical population without cancer. Any survival advantage that the combined cancer group has in the initial period is not sustained in the longer-term. To further understand this surgical and medical ICU patients were analysed separately.

5.4.5.1 Survival of ICU Surgical patients

In the initial period of critical illness surgical cancer patients have a survival advantage over non-cancer patients. Longer-term survival of surgical ICU patients with and without cancer is demonstrated by Kaplan Meier graph in Figure 5-3. While the initial mortality associated with the acute critical illness

appears similar the patients in the cancer group have a higher mortality by six months (Table 5-13). The survival of the cancer group continues to diverge from the non-cancer group throughout the following four years.

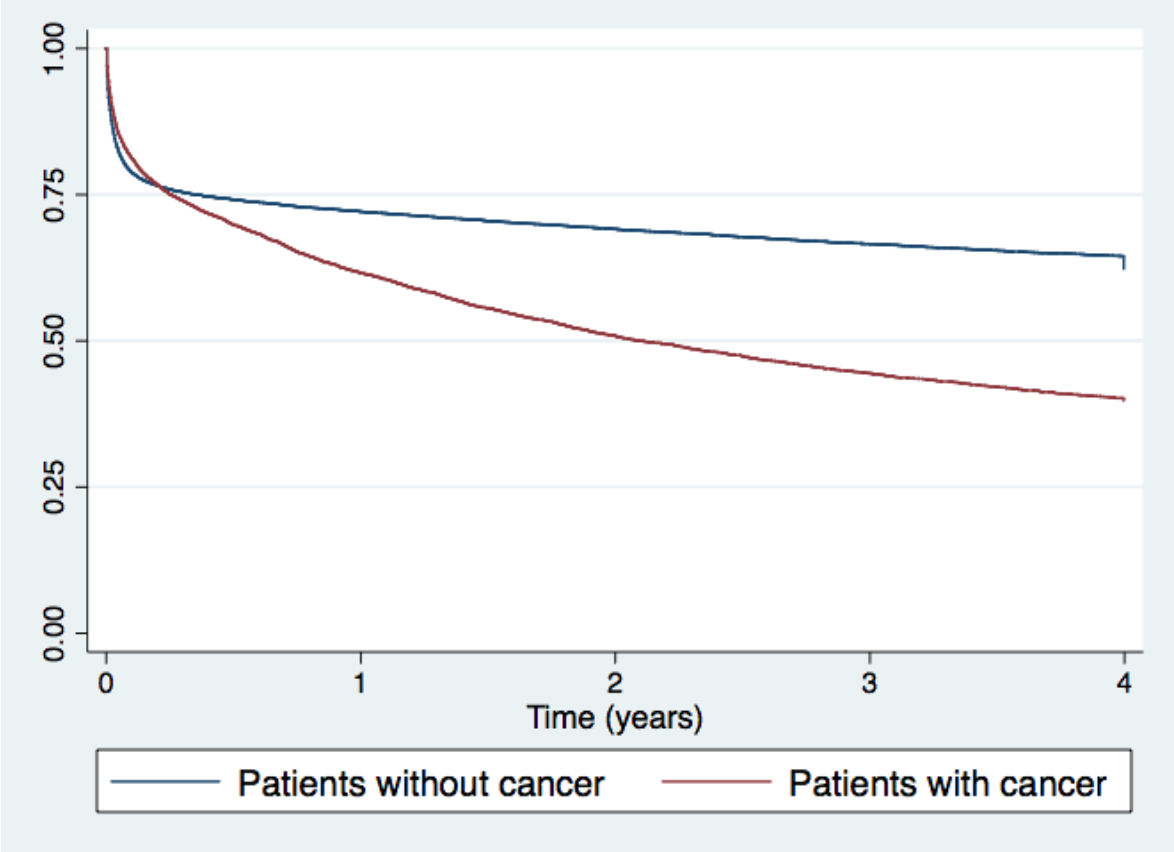


Figure 5-3 Kaplan Meier survival analysis of patients with and without cancer following surgical ICU admission (p <0.0001)

By four years the mortality of surgical ICU cancer patients is 60.9% (95% CI 59.5 – 62.2) compared with 39.7% (39.0 – 40.4) seen in the non-cancer surgical group.

Mortality	Patients without cancer	Patients with cancer	P value
Six months	28.2% (27.6 – 28.9)	31.3% (30.1 – 32.6)	<0.001
One year	30.2% (29.6 – 30.9)	39.4% (38.1 – 40.7)	<0.001
Four years	39.7% (39.0 – 40.4)	60.9% (59.5 – 62.2)	<0.001

Table 5-13 Mortality up to four years after surgical ICU admission for patients with and without cancer. Numbers are percentages (with 95% confidence intervals) of patients who died during the study period.

5.4.5.2 Survival of ICU Medical patients

The initial mortality associated with critical illness in ICU medical patients is greater than that seen in the surgical population. Unlike the surgical population, cancer patients have a higher initial mortality compared to patients without cancer. Figure 5-4 demonstrates long-term survival for ICU medical patients with and without cancer. For those patients without cancer the period following the critical illness has a continued slow decline in mortality. However, for the ICU medical patients with cancer the initial period of marked increase in mortality continues over a longer period.

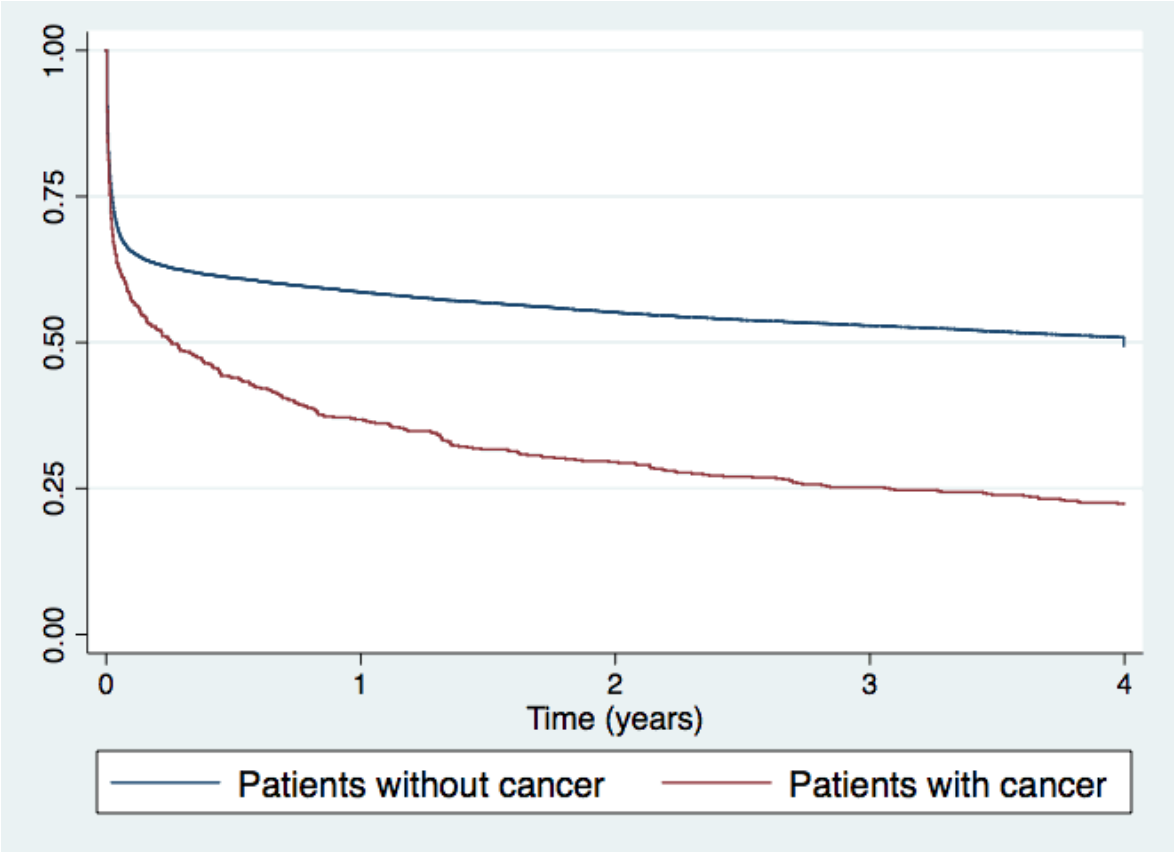


Figure 5-4 Kaplan Meier survival analysis of patients with and without cancer following medical ICU admission (p <0.0001)

Table 5-14 describes the increased mortality observed in medical ICU cancer patients up to four years following ICU admission.

Mortality	Patients without cancer	Patients with cancer	P value
Six months	42.9% (42.1 – 43.6)	59.5% (55.6 – 63.2)	<0.001
One year	45.1% (44.4 – 45.9)	66.1% (62.3 – 69.7)	<0.001
Four years	53.8% (53.0 – 54.6)	79.4% (76.1 – 82.4)	<0.001

Table 5-14 Mortality up to four years after medical ICU admission for patients with and without cancer. Numbers are percentages (with 95% confidence intervals) of patients who died during the study period.

5.4.5.3 Survival by level of organ support

Severity of illness and degree of organ failure would be expected to be associated with short-term outcomes. Kaplan Meier survival analysis was performed on patients with and without cancer for each level of provided organ support (Figure 5-5). This demonstrated an excess long-term mortality in the cancer group for each level of organ support provided.

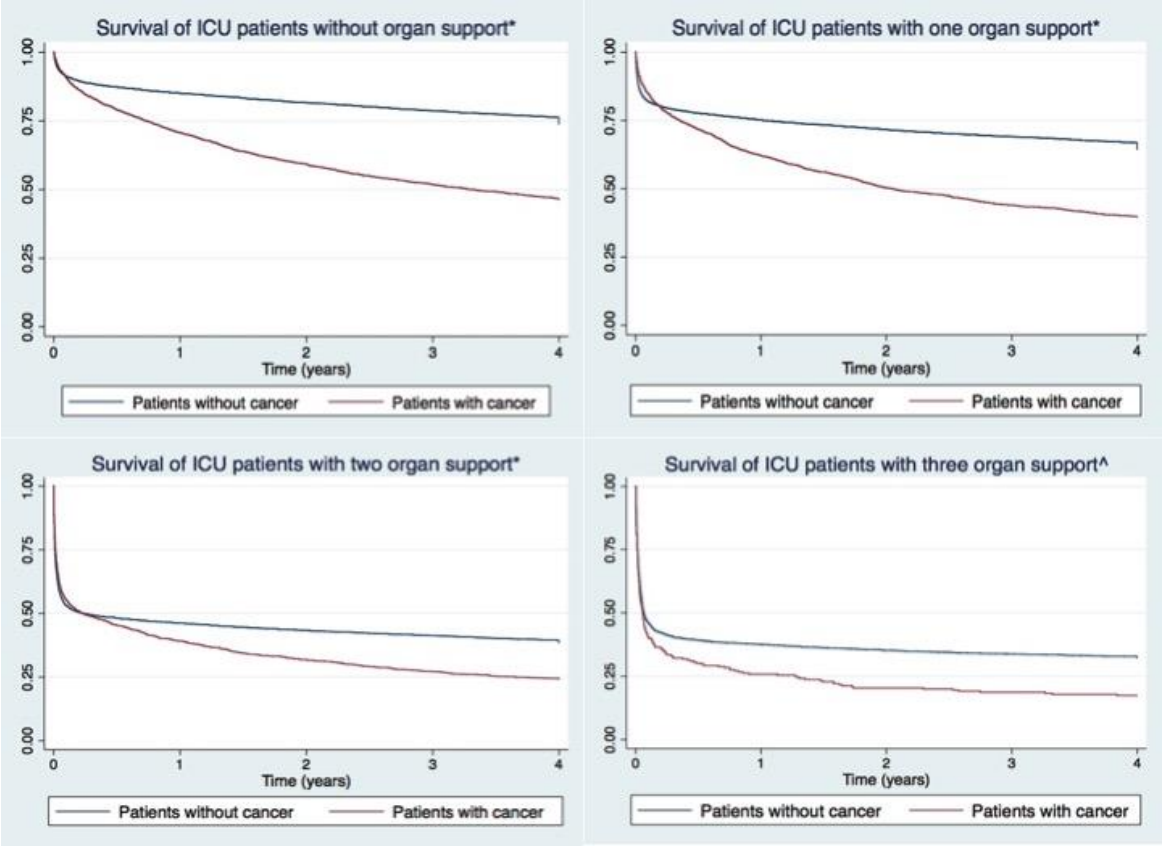


Figure 5-5 Kaplan Meier survival of patients with and without cancer by the number of organ support provided in ICU (*p<0.0001, ^p=0.0001)

5.5 Discussion

5.5.1 Demographic and clinical baseline differences

In an unselected, population-based cohort of general ICU admissions, we found that nearly one in seven ICU patients had been diagnosed with a solid tumour in the two years prior to admission. Cancer patients had a higher proportion of both surgical admissions and elective hospitalisations compared with the non-cancer population. Even those cancer patients with a medical admission to hospital are more likely to be admitted to ICU with a surgical diagnosis. It is likely that the available treatments for patients with solid tumours will lead to a high proportion of patients undergoing elective hospitalisation for a surgical intervention at some point during their cancer treatment plan. Subsequent ICU admission for these patients may be part of planned post-operative care in those units that are combined HDU/ ICUs, due to surgical complications or as a result of unrelated medical or surgical problems.

Compared to patients without cancer, cancer patients were older. In spite of the difference in age, APACHE II scores were slightly lower in the cancer group although this likely reflects the higher proportion of surgical admissions and those patients who did not receive organ support. There were a larger proportion of patients with missing APACHE II scores in the cancer group and this may represent those HDU admissions to combined units as these patients are excluded from APACHE scoring. Organ support was provided to approximately two thirds of cancer patients and over three quarters of non-cancer patients. This difference can be explained either by a lower frequency of organ failure in the cancer group or similar rates of organ failure in both groups but less organ support being offered to the cancer group. The lower APACHE II score in the cancer group suggests lower severity of illness for the cancer group, therefore, it is more likely that the former explanation is more likely and is in keeping with admission of a group of post-operative patients for observation and monitoring.

Malignancy was the commonest reason for admission to ICU for the cancer cohort. This included any illness that was directly related to the tumour including cancer surgery and cancer-related complications. Malignancy was also

related to ICU admission for a small proportion of the non-cancer group (<1%). This may be due to diagnostic error at the time of ICU admission where malignancy has been suspected but not confirmed and the wrong diagnosis has been recorded in Wardwatcher. Alternatively it is possible that a patient with a diagnosis for cancer made outwith Scotland (and therefore not on the SMR06 dataset) has been admitted to a West of Scotland ICU.

Among the group of ICU patients that received organ support one in eight had a preceding diagnosis of solid tumour. Elective hospitalisations and surgical ICU admissions were again more common in the cancer group when compared with the non-cancer group. In addition the cancer group had a lower requirement for multi-organ support with the majority of patients only requiring single organ support, most commonly invasive mechanical ventilation.

For both patients with and without cancer the clinical features varied between ICU surgical admissions and medical admissions and these groups were analysed separately.

5.5.1.1 ICU Surgical admissions

One in five surgical ICU patients had a preceding diagnosis of solid tumour. While cancer patients tended to be older this was less pronounced within the surgical cohort. In contrast to the non-cancer population those ICU surgical cancer patients had a much higher proportion of elective admission to hospital. Malignancy was the commonest reason for ICU admission for the cancer group. Other diagnostic categories were similar between both groups with sepsis, gastrointestinal/ liver disease and surgical complications as common causes for admission. Severity of illness scoring was missing for one in five non-cancer patients and two in five cancer patients. While the APACHE II score was the same for both groups the rate of organ support was less for the cancer group. This might suggest that organ failure was less common in the cancer group. If this were the case we would expect to see lower severity of illness scores in the cancer group. This was not the case, however, there were a higher proportion of

patients without APACHE scores in the cancer group and this might reflect a “well” cohort of patients admitted for post-operative HDU observation and therefore excluded from scoring. This may also explain the apparent beneficial survival of surgical cancer patients compared with the non-cancer group.

Colorectal cancer made the largest contribution to the ICU cancer burden and was predominantly surgical admissions. Within the surgical group less than half of the colorectal cancer patients received any organ support during their ICU stay. It seems likely that the nature of colorectal cancer surgery leads to many patients being admitted for post-operative observation or HDU level care. The high turnover of these patients in ICU/ HDU and high incidence of the disease contributes to the dominance of this tumour type in surgical ICU admissions.

Head and neck cancer was another common cancer within the surgical ICU population. In contrast to colorectal the majority of these patients received organ support during their stay, principally mechanical ventilation. Surgery for head and neck cancer is often carried out near the airway and may require either temporary or permanent formation of tracheostomy and a brief period of respiratory support in the post-operative period. More than two thirds of these patients were elective admissions to hospital and it seems likely that their ICU stay was part of a planned post-operative course.

5.5.1.2 ICU Medical admissions

Less than 4% of ICU medical admissions had a prior solid tumour diagnosis. There was a marked difference in the median age with cancer patients over a decade older. In contrast to surgical admissions the commonest reason for medical admission was sepsis for both cancer and non-cancer patients. Although median APACHE II score was similar for both groups there were a larger proportion of cancer patients with missing APACHE scores and a significantly greater number of patients that received no organ support. Mortality was substantially higher than that seen in the surgical group and there appeared to be an excess mortality in the cancer subgroup. High mortality among lung cancer patients

(who accounted for one in four of all cancer patients admitted from a medical specialty) made a major contribution to the overall higher mortality rate among medical patients.

For those medical ICU patients that received organ support, only 3.3% had a preceding diagnosis of cancer. Although median APACHE II score was similar for the cancer and non-cancer groups, mortality was markedly higher in the cancer group. While respiratory and renal support was similar for both groups cardiovascular support was more common in the cancer group and this is reflected in a higher proportion of patients receiving two or more organ support in the cancer group.

5.5.2 Determinants of short-term survival

ICU and hospital mortality was lower for the cancer group overall. However, given the lower severity of illness score, larger proportion of surgical admissions and less frequent use of organ support it would be anticipated that mortality should be lower for this group.

Surgical admissions had a more favourable outcome when compared with medical admissions and surgical cancer patients had lower ICU and hospital mortality rates than the surgical population without cancer. This may partly be explained by the inclusion of level 2 patients admitted for post-operative care to a combined ICU/ HDU. These patients are often admitted for monitoring purposes only and the cancer group had a higher proportion of patients without any organ support in their group. Additionally, the number of patients with a missing APACHE II score is higher for the surgical cancer cohort than the surgical non-cancer cohort. This may be due to level 2 admissions being excluded from APACHE II scoring. However, further analysis of the subgroup of surgical patients that received organ support found that the APACHE II score was recorded for similar proportions of both groups but that the mortality differences still persisted. Thus, even in the group of patients that received organ support during their ICU stay, outcomes were more favourable in the cancer population

compared with the population without cancer. The surgical cancer group with organ support may still be benefitting from the high proportion of elective hospitalisations where there has been an opportunity for pre-operative optimisation and patient selection. In addition the cancer group had lower utilisation of multi-organ support, with the majority of patients only requiring single organ support, most commonly ventilation. Furthermore, there may be less physiological stress associated with “cancer surgery” compared with surgery in the non-cancer group such as that required for vascular surgery or trauma surgery.

Medical admissions to ICU had higher ICU and hospital mortality rates than the surgical group and these rates were worse for the cancer population when compared with the population without cancer. One in five ICU medical admissions with cancer did not receive any organ support during their time in ICU. This compares with one in eight ICU medical admissions without cancer and yet the outcomes favour those patients without cancer. This difference in mortality between medical patients with and without cancer is even more pronounced when assessing the group of ICU medical admissions that received organ support. This may be partly explained by differences in age as the cancer group had a median age of 12 years older than the non-cancer group. An additional explanation may be the high incidence of sepsis in both groups. Cancer patients are likely to be immunosuppressed due to either their underlying tumour or its treatment. Higher mortality for patients with sepsis might be expected where the immune system is not functioning adequately.

5.5.3 Determinants of longer-term survival

Longer-term survival was worse for cancer patients in both the surgical and medical ICU population when compared to patients without cancer. The mortality rate between the two groups became progressively divergent during the four-year follow up period. Mortality for surgical ICU patients was consistently higher in the cancer group at six months (31.3% vs. 28.2%), one-year (39.4% vs. 30.2%) and four-years (60.9% vs. 39.7%). Longer-term mortality was

even higher in the medical population and greater for those with cancer at six months (59.5% vs. 42.9%), one-year (66.1% vs. 45.1%) and four-years (79.4% vs. 53.8%). The difference in survival between the ICU patients with and without cancer may be attributed to the underlying cancer or the treatment burdens associated with cancer.

Longer-term survival deteriorated with increasing organ support during the ICU stay. Analysis of survival by level of organ support demonstrated worse outcome within the cancer group compared to the non-cancer group for each level. This impact of organ support on longer-term survival has not yet been described in the literature and is a novel finding. The severity of critical illness may impact upon the subsequent therapeutic options available for cancer treatment. For example, major surgery or aggressive chemotherapy may not be considered appropriate in a patient recovering from severe critical illness with multi-organ support. It is possible that the pro-inflammatory state associated with multi-organ failure accelerates the underlying neoplastic process making certain cancers more aggressive. The nature of ICU admission may be important as cancer patients presenting to ICU with advanced disease and complications of the malignancy may be both more prone to critical illness and already likely to have a poor outcome from their underlying tumour. A prospective study is required to assess which of these factors account for the differences observed in this study.

5.5.4 Comparisons with published literature

This study has demonstrated that cancer is a common morbidity in the general ICU population. While one in twenty solid tumour patients are admitted to ICU, one in seven ICU patients has a preceding solid tumour diagnosis. The prevalence is similar to that seen in previous studies by Taccone et al of European general ICUs in 2002 [87] and Bos et al of ICUs in the Netherlands between 2007 and 2011 [95]. In contrast to the study by Taccone et al, who described similar outcomes in cancer and non-cancer patients, this study demonstrated lower hospital mortality for cancer patients in the initial period following admission.

This is partly due to difference in case-mix with nearly 90% of cancer patients having a surgical ICU admission compared to 70% in Taccone et al's study. The lower short-term mortality experienced by ICU cancer patients in this study is only seen in those with a surgical ICU admission. Outcomes were less favourable among the medical cancer patients when compared with medical patients without cancer. This difference was exaggerated further when comparing the medical patients that received organ support where outcomes for the cancer group were particularly poor. While the study by Bos et al demonstrated slightly higher mortality in surgical cancer patients compared with surgical non-cancer patients, this paper was on the subset of ICU patients who had been admitted to ICU as an emergency and elective ICU admissions were excluded. The significantly higher mortality in medical cancer patients compared with medical non-cancer patients demonstrated by Bos et al is in keeping with that which has been described here.

In this study, hospital mortality for lung cancer patients was 51.4% for surgical ICU admissions and 73.3% for medical ICU admissions. Several studies of ICU lung cancer patients report hospital mortalities of between 54-65% [85, 107, 119, 121, 126, 138, 139, 142]. This population differs from these previous investigations in that they had mainly involved specialised ICUs, or subsets of lung cancer patients with specific co-morbidities, thus making extrapolation to general ICUs difficult. Severity of illness for both groups of lung cancer patients within this population was high, with elevated median APACHE II scores and increased use of multi-organ support. Many of the original lung cancer studies were performed in countries where ICU is more readily available and therefore utilised for patients with a lower burden of critical illness. The study by Bos et al, which was based in a general ICU population, described a hospital death rate of 48.6% among unplanned medical lung cancer patients, and 6.5% among surgical patients. The difference in mortality for surgical lung cancer patients is striking and is particularly surprising given that nearly two thirds of the surgical lung cancer population in this study had been an elective hospitalisation. Severity of illness scores and subsequent use of organ support in the Bos population was low and it is likely that they are more representative of an HDU population rather than what would be considered a true ICU population in the UK.

One-year mortality of ICU cancer patients has previously been described ranging from 35.9 – 88.0% [111, 113, 124, 143, 146]. The significant variation in outcomes can largely be attributed to the patient case-mix studied within each publication including exclusively patients with metastatic disease in the study by Caruso et al, non-resectable lung cancer by the study by Toffart et al and elective oesophagectomy patients in the study by Cense et al. Oeyen et al described a mixed group of solid tumour patients with largely surgical ICU admissions (81%) with low severity of illness scores and requirement for organ support. One-year mortality in the Oeyen series was 35.9%, and similar to the 39.4% one-year survival described here in ICU surgical cancer patients. The four-year mortality in surgical ICU cancer patients of 60.9% is similar to that previously described by Bissell et al of 62.8% in a group of post-operative oesophagectomy patients that required a readmission to ICU within the UK [122].

5.5.5 Strengths and weaknesses

This is a large study of a general ICU population across multiple sites within Scotland. Previous studies have often focused within the specialist oncological ICUs or in general ICUs outwith the UK where admission policies are different. As such this data gives a more accurate representation of the ICU features of patients with and without cancer in general ICUs in Scotland. A further strength of this study is the ability to report long-term survival. Limiting the reporting to early survival would have missed the significant changes in survival over time between the groups.

The retrospective nature of this study limits the depth of information available. It is not possible to state which ICU admissions were directly attributable to the underlying cancer or where cancer was an incidental co-morbidity. Organ support has been used as a surrogate marker of organ failure but will underestimate the true prevalence as patients may not have organ failure severe enough to warrant support or they may have treatment limitations in place that preclude the use of organ support in spite of organ failure.

The ICU dataset includes data from several units that were mixed ICU/ HDU during the study period without a clear definition within the dataset as to which patients were level 2 and which were level 3. Due to the high turnover of elective post-operative patients in an HDU setting it may be that the cancer population is over-represented in this cohort by patients that wouldn't be considered as true level 3 ICU patients. For this reason we performed separate analysis of those ICU patients who had received organ support during their ICU stay. The presence of organ support was used as an indication of level 3 admission. It is possible that this will identify level 2 patients as level 3 incorrectly. For example, a post-operative patient with an epidural in situ requiring vasoactive support for associated hypotension would generally be considered level 2 but would be included in the organ support subgroup of this study.

While every attempt was made to minimise missing data it remains a limitation of the study. APACHE II score was missing for a significant proportion of patients. Patients may be excluded from APACHE II scoring for a number of reasons although commonly due to HDU admission rather than ICU admission. Data pertaining to organ support was mostly complete for respiratory and cardiovascular support but missing for renal support in 12% of patients. During the study period not all units had the ability to provide renal support and it is possible that this missing data originates in units where renal replacement therapy was not available. None the less, the true incidence or renal replacement therapy remains unknown as a result.

5.6 Conclusions

Cancer patients contribute a large proportion of ICU admission particularly those admitted under a surgical specialty. Compared to the group of ICU patients without cancer the ICU cancer population tend to be older with a high proportion of elective hospitalisations and are predominantly surgical

admissions. In addition, there is less frequent utilisation of organ support within the cancer population. While short-term outcomes appear to favour ICU cancer patients this effect is confined to the surgical population and is not maintained in the longer term.

5.7 Key points

- When compared with the ICU non-cancer population, ICU cancer patients tend to be older, with a higher proportion of elective hospitalisations and are predominantly admitted to ICU with a surgical problem.

- There are a larger proportion of ICU cancer patients that do not receive organ support and it is possible that these represent a post-operative HDU population.

- ICU and hospital mortality is lower for the ICU cancer population although this is due to the larger proportion of surgical patients.

- Surgical ICU admissions have a favourable short-term mortality if they have an underlying cancer diagnosis. This may be explained by a potentially higher proportion of HDU admissions, lower utilisation of multi-organ support and a larger proportion of elective admissions with the opportunity for pre-operative optimisation and also the nature of the cancer surgery compared with non-cancer surgery.

- ICU cancer patients admitted with a medical diagnosis have poorer short-term survival than non-cancer patients and this difference is even more pronounced in the subgroup of medical patients that received organ support.

- ICU cancer patients have poorer long-term survival than ICU patients without cancer.

Chapter 6 What are the longer-term outcomes of cancer patients who have survived an ICU admission?

6.1 Introduction

Surviving a critical illness is not without consequences. These may include on going organ dysfunction, muscle weakness, functional limitation and psychological distress. All of these elements may contribute to the increased mortality risk seen in ICU survivors that persists for several years after ICU discharge [44]. While this may be problematic for all ICU survivors it may pose a particular difficulty for patients with an underlying cancer diagnosis, who are likely to require further medical interventions and treatment of the cancer. It is possible that treatment options may be limited by the impact of on going effects from the critical illness. Many factors are likely to impact upon long-term survival but it is unclear which factors associated with the critical illness and ICU admission impact on survival following ICU discharge.

This study aims to assess these factors and the degree to which they influence longer-term survival in patients that have survived a critical illness with ICU admission and whether the presence of cancer changes the course of survival. In addition, this analysis seeks to ascertain whether criteria associated with the critical illness or factors relating underlying cancer are more important in determining survival.

6.2 Study questions

6.2.1 How does the longer-term survival of patients that have survived ICU differ between those with and without cancer?

Patients that survive ICU might be expected to have an increased mortality risk that may be impacted by a number of factors associated with the patient, co-morbidities and critical illness. It would be of significant value to understand how long term mortality differs between ICU survivors with and without cancer and which factors are associated with changes to mortality risk. To better understand this I will construct a multivariable model to assess how cancer impacts on mortality risk when taking account of other predictors of mortality.

6.2.2 In ICU cancer survivors how do the features associated with cancer impact upon mortality risk?

Having assessed differences in survival between cancer and non-cancer patients I will then assess how mortality varies by underlying tumour type in patients that have survived ICU. For patients with colorectal cancer I will assess which factors impact on mortality risk (including cancer stage) by constructing a multivariate model.

6.3 Methods

Patients that had an ICU admission during the study period were considered to be an ICU survivor if they were alive 30 days after ICU discharge. This time period was chosen to allow for patients that were discharged to the ward, hospice or home for palliation. This group were then split into those with cancer and those without cancer as described previously. Survival data was available for all patients for the four-years following ICU admission date.

6.3.1 Statistical analysis

Kaplan Meier survival analysis was performed with log-rank test for statistical significance.

Hazard ratios were calculated using Cox proportional hazards model. Those factors known at discharge from ICU were chosen for inclusion in analysis. This included the presence of cancer, patient age, sex, SIMD group, organ support, APACHE II score, ICU admission type (surgical/ medical) and diagnosis of sepsis at ICU admission. Continuous variables (age and APACHE II score) were grouped into those above and below certain cut offs. Various thresholds for these values were tested on univariate analysis and a value that was valuable both in terms of clinical impact and clinical importance were chosen. For age this threshold was a value of ≥60 years and for APACHE II a score of ≥20.

For analysis of the patients with colorectal cancer additional features included year of cancer diagnosis and Dukes stage at diagnosis.

Each variable was checked for proportionality using calculation of Schoenfeld residuals. Any variable with a p-value ≤0.2 had a log –log plot of survival calculated. This was then visually assessed for deviations from parallel lines. Any variable that did not meet the proportionality criteria were excluded from multivariate analysis. The multivariate model was then checked again using Schoenfeld residuals.

6.4 Results

There were 41,689 ICU patients during the study period of which 29,326 (70.3%) were considered to be ICU survivors (alive 30 days following ICU discharge). ICU patients with cancer were more likely to meet this criterion than those ICU patients without cancer (76.9% versus 69.0%, p<0.001, Table 6-1).

	Admitted to ICU	Survived 30 days post ICU discharge	Percent survived
Patients without cancer	35,573	24,624	69.0%
Cancer patients	6116	4702	76.9%
All ICU patients	41,689	29,326	70.2%

Table 6-1 Number of ICU survivors grouped by patients with and without cancer.

6.4.1 Long-term survival of patients that have survived ICU

Long-term survival for ICU survivors with and without cancer is demonstrated by Kaplan Meier survival analysis in Figure 6-1. This demonstrates poorer long-term survival for ICU survivors who have cancer. At the end of four years follow up 80.5% of patients without cancer were still alive compared with only 46.7% in the group of patients with cancer (p<0.001).

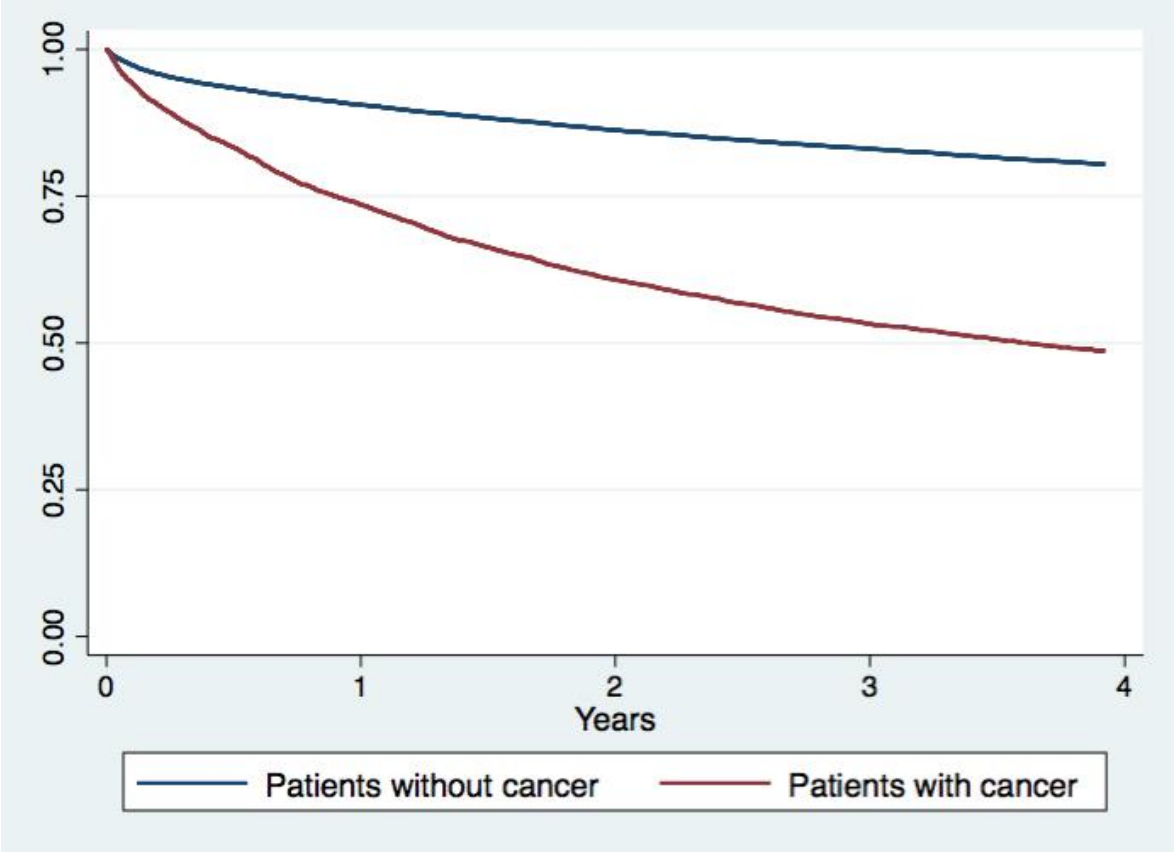


Figure 6-1 Survival of ICU survivors with and without a cancer diagnosis (log rank p<0.0001)

6.4.2 Risk of death following ICU survival

Factors associated with critical illness, patient demographics and presence of cancer were analysed for effect on post-ICU mortality using Cox proportional hazards estimation. These factors are described in Table 6-2 and each variable was checked for meeting the PH assumption.

Several factors potentially did not meet proportionality criteria using Schoenfeld residuals: the presence of cancer (p 0.0652), APACHE II score ≥20 (p=0.0007 overall (APACHE II score ≥20 p=0.0026; APACHE II score missing p=0.275)), and number of organs supported (p<0.0001). These factors underwent additional graphical analysis.

Factor	Number of patients (%) N=29,326 Or median value with IQR	
Cancer	*4702*	(16.0%)
Median Age (IQR)	*58*	(42 – 75)
Age at ICU ≥60 years	*14,069*	(48.0%)
Male sex	*16,177*	(55.2%)
Unknown	*1*	(0.0%)
SIMD		
1	*8792*	(30.0%)
2	*6346*	(21.6%)
3	*4730*	(16.1%)
4	*3116*	(10.6%)
5	*2418*	(8.2%)
Unknown	*3924*	(13.4%)
Multi-organ support	*7246*	(24.7%)
Median APACHE (IQR)	*16*	(12 – 21)
APACHE ≥20	*7055*	(24.1%)
Missing APACHE	*5866*	(20.0%)
ICU Surgical admission	*19,206*	(65.5%)
Sepsis on admission	*4949*	(16.9%)

Table 6-2 Description of critical illness, patient demographics and presence of cancer in ICU survivors.

When assessing the effect the presence of cancer has on mortality risk over time those patients with cancer have an increasing mortality risk as time progresses compared with those without cancer. However, by six months the lines are running parallel suggesting that from six months the effect of cancer on mortality risk is constant.

When comparing the group with APACHE II scores greater or equal to 20 with those less than 20 the lines are very close to parallel with only a slight convergence after one year. The missing APACHE II score and score of less than

20 groups also appear to be close to parallel throughout. Differences detected between these groups are likely due to the large numbers involved rather than being due to a meaningful difference between the groups.

The impact of number of organs supported on mortality over time appears to demonstrate similarity between those with no or one organ support and those with two or three organ support. The patients were therefore grouped as those with or without multi-organ support. The Schoenfeld residual for multi-organ support remained significant at $p<0.0001$. The log -log plot of survival by multi-organ support demonstrated that from six months onwards the lines converge suggesting that prior to six-months the multi-organ support has a fixed effect on risk of mortality but that after six-months this effect is no longer fixed and becomes less with time.

The proportional hazards assumption was therefore rejected for cancer and multi-organ support variables. A decision was made to segment into time periods at six months. This would allow analysis of factors associated with increased early mortality (in the first six months) and later mortality (from six months to four years).

6.4.2.1 Factors associated with risk of death in the first six-months after ICU survival

Patient demographics (age ≥60 years, sex and SIMD category), critical illness features (use of multi-organ support, APACHE II score, surgical admission to ICU and diagnosis of sepsis) and presence of cancer were all analysed for effect on mortality rates during the first six-months following ICU survival. On univariate analysis cancer, age ≥60 years, multi-organ support and APACHE II score ≥20 or missing were associated with an increased hazard ratio (Table 6-3).

Factor	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Cancer	2.66 (2.44 – 2.90)	<0.001	2.37 (2.16 – 2.61)	<0.001
Age at ICU ≥60 years	3.14 (2.86 – 3.44)	<0.001	2.56 (2.33 – 2.82)	<0.001
Male sex	1.05 (0.96 – 1.13)	0.273	-	
SIMD				
1	1	-	-	
2	1.05 (0.94 – 1.18)	0.363	-	
3	0.97 (0.885 – 1.10)	0.595	-	
4	0.97 (0.84 – 1.12)	0.691	-	
5	1.01 (0.87 – 1.19)	0.863	-	
Unknown	1.04 (0.91 – 1.18)	0.606	-	
Multi-organ support	1.46 (1.34 – 1.59)	<0.001	1.22 (1.11 – 1.34)	<0.001
APACHE ≥20	2.12 (1.94 – 2.32)	<0.001	1.70 (1.54 – 1.88)	<0.001
Missing APACHE	1.28 (1.14 – 1.43)	<0.001	1.03 (0.92 – 1.15)	0.658
ICU Surgical admission	1.08 (0.99 – 1.18)	0.067	0.79 (0.72 – 0.87)	<0.001
Sepsis on admission	1.09 (0.98 – 1.21)	0.099	0.98 (0.87 – 1.09)	0.694

Table 6-3 Factors associated with mortality in the first six-months following ICU survival

On checking the proportionality assumption, the test indicated some potential problems with cancer (p<0.0001), age (p=0.0111), multi-organ support (p=0.008) and APACHE II score groups (Global test p=0.036, for APACHE ≥20 vs. APACHE <20 p=0.0113). The log -log plots of survival were generated for each of these variables. Looking at the plots, there was no distinct systematic deviation from parallel curves in those for age, multi-organ support or APACHE score and these factors were all included in the multivariate model. Figure 6-2 evaluates the proportionality assumption for the presence or absence of cancer. Here the curves can be seen to deviate in the first 14 days (ln= 2.6) during which time relatively few events occur. Following this point they remain parallel suggesting

a constant hazard ratio after this point. Given that the ratio is constant for the majority of the follow up period this factor has been included in the multivariate model.

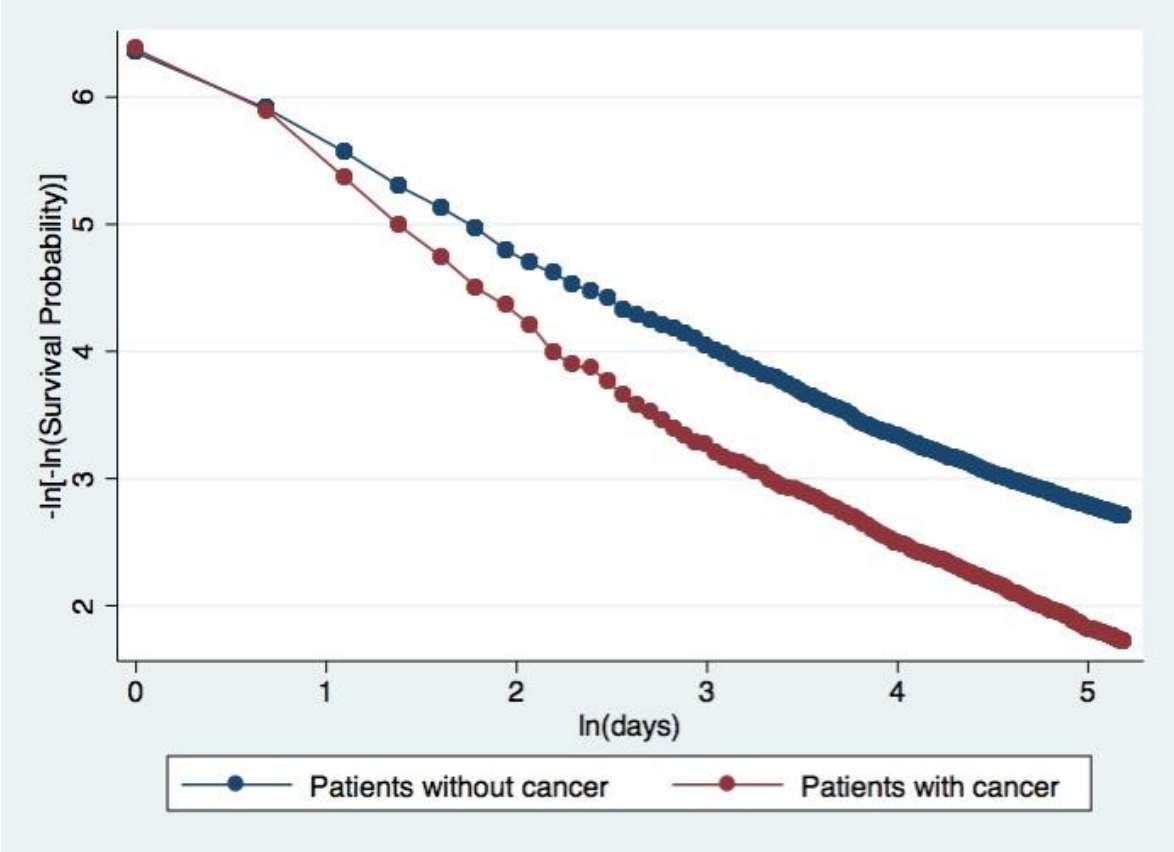


Figure 6-2 Log -log plot of survival by patients with cancer and without cancer

Multivariate analysis identified cancer (HR 2.37), age ≥60 years (HR 2.56), multi-organ support (HR 1.22), and APACHE II ≥20 score (HR 1.7) all to be associated with an increased mortality rate in the first six-months following ICU survival (Table 6-3). Surgical admission to ICU was associated lower mortality rates (HR 0.79).

6.4.2.2 Factors associated with later risk of death after ICU survival

The same factors were also analysed for effect on mortality rates after the first six-months following ICU survival. On univariate analysis cancer, age ≥60 years, male sex, multi-organ support, APACHE II score ≥20 or missing and surgical admission to ICU were associated with an increased hazard ratio (Table 6-4).

Factor	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Cancer	3.64 (3.44 – 3.87)	<0.001	3.40 (3.18 – 3.63)	<0.001
Age at ICU ≥60 years	2.67 (2.51 – 2.83)	<0.001	2.18 (2.04 – 2.32)	<0.001
Male sex	1.08 (1.02 – 1.14)	0.009	1.07 (1.01 – 1.13)	0.03
SIMD				
1	1	-	1	-
2	1.08 (1.0 – 1.17)	0.051	0.95 (0.88 – 1.03)	0.234
3	0.96 (0.88 – 1.04)	0.322	0.84 (0.77 – 0.91)	<0.001
4	1.02 (0.92 – 1.12)	0.752	0.87 (0.79 – 0.96)	0.007
5	0.92 (0.82 – 1.03)	0.168	0.74 (0.66 – 0.83)	<0.001
Unknown	1.06 (0.97 – 1.16)	0.223	0.96 (0.88 – 1.06)	0.416
Multi-organ support	1.15 (1.08 – 1.22)	<0.001	1.01 (0.94 – 1.09)	0.752
APACHE ≥20	1.63 (1.53 – 1.74)	<0.001	1.41 (1.31 – 1.51)	<0.001
Missing APACHE	1.28 (1.19 – 1.37)	<0.001	0.98 (0.90 – 1.05)	0.523
ICU Surgical admission	1.10 (1.04 – 1.17)	0.001	0.74 (0.69 – 0.79)	<0.001
Sepsis on admission	1.07 (0.99 – 1.15)	0.086	1.09 (1.00 – 1.18)	0.042

Table 6-4 Factors associated with mortality in the longer term after ICU survival

On checking the proportionality assumption, the test indicated some potential problems with cancer (p=0.0002) and age (p=0.0181). The log -log plots of survival were generated for each of these variables.

For cancer, there was no meaningful deviation from parallel lines on the plot suggesting the hazard ratio remains fairly constant throughout the study period. Figure 6-3 plots the mortality rates with time between the two age groups. There is variability in the mortality rates between the two groups during the first 18 days (ln= -3) during which time there are relatively few events. Thereafter the difference in the mortality rates appears constant with parallel lines. Given that the lines are parallel for the majority of the follow up period this factor has been included in the multivariate model.

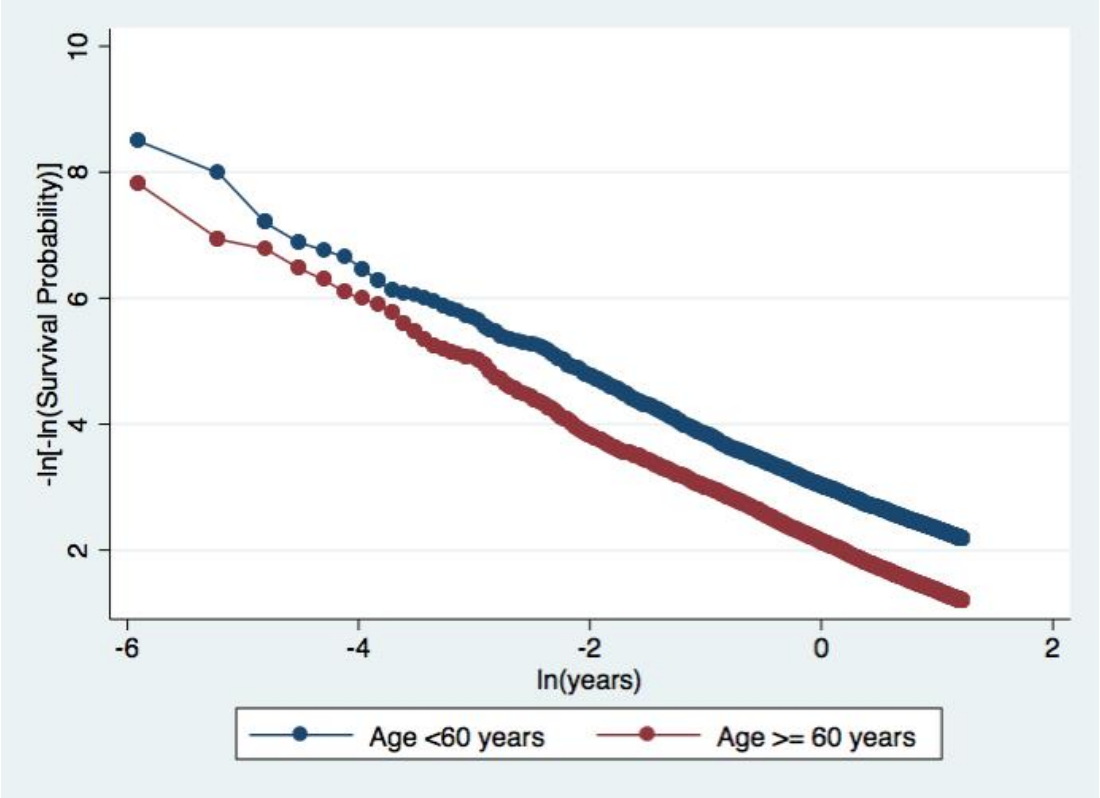


Figure 6-3 Log -log plot of survival by age group

Multivariate analysis identified cancer (HR 3.4), age ≥60 years (HR 2.18), male sex (HR 1.07), APACHE II ≥20 score (HR 1.41) and sepsis on admission to ICU (HR 1.09) all to be associated with an increased mortality rate after six-months following ICU survival (Table 6-4). Lower mortality rates were seen in patients from more affluent SIMD quintiles and in those patients who had been admitted to ICU as a surgical admission (HR 0.74).

6.4.3 Impact of underlying cancer type on long-term outcome of ICU survivors

Having identified cancer as one of the most important determinants of post-ICU survival I progressed to examine how long-term survival varies by underlying cancer type. Figure 6-4 demonstrates the impact of underlying tumour type on long-term survival of ICU survivors. This reports significant variation in survival for colorectal, head and neck, stomach, lung, oesophageal, kidney and breast cancer in addition to the group of patients with cancer of unknown origin.

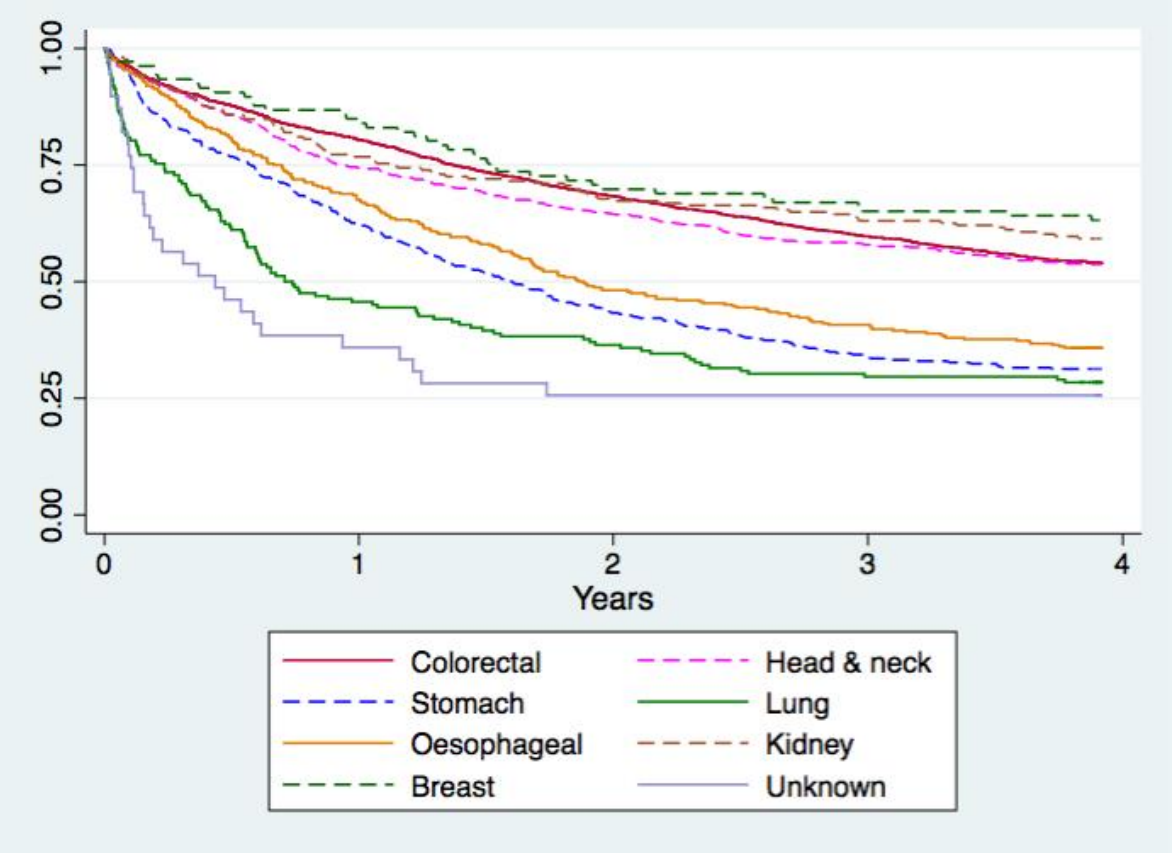


Figure 6-4 Survival following ICU by underlying cancer type (logrank p<0.0001)

While patients with colorectal, head and neck, kidney and breast cancer can be seen to have better survival than other tumour types there is a steady decline in survival with time. Breast cancer patients who appear to have the most

favourable survival have a mortality of 36.8% at the end of the follow up period. Survival by each cancer type at the end of the four-year follow up period is recorded in Table 6-5. Four-year survival varies from 10.0% for those patients with underlying hepatocellular carcinoma to 73.3% in patients with testicular cancer.

Cancer type	Number of ICU survivors	Four-year survival
Colorectal	2069	54.0%
Head and Neck	570	53.7%
Stomach	358	31.3%
Oesophageal	324	35.8%
Kidney	211	59.2%
Lung	162	28.4%
Bladder	144	37.5%
Breast	106	63.2%
Prostate	102	56.9%
Ovarian	101	28.7%
Uterus	88	67.0%
Pancreas	44	15.9%
Small intestine	41	56.1%
Liver	30	10.0%
Thyroid	25	71.0%
Testicular	15	73.3%
Melanoma	8	12.5%
Other	78	50.0%
Multiple	173	45.1%
Unknown	39	25.6%

Table 6-5 Four-year survival of ICU survivors by cancer type

Underlying cancer type has been demonstrated to have a significant impact upon survival in cancer patients following ICU discharge. Cox proportional hazard analysis comparing each tumour type to ICU survivors without cancer did not meet the proportional hazards assumption for any of the time periods. Each tumour type would therefore need to be analysed separately.

6.4.4 Factors associated with mortality in colorectal cancer patients that survive ICU

Of the group of cancer patients that had survived ICU 2,069 had colorectal cancer (44%). This group contributed the largest subgroup of cancer patients and was analysed for factors associated with mortality including patient demographics, critical illness and features associated with the underlying cancer (Table 6-6).

Factor	Number of patients (%) N=2069 Or median value with IQR	
Male sex	*1184*	(57.2%)
Median age (IQR)	*70*	(62 – 77)
Age ≥60 years	*1687*	(81.5%)
SIMD		
1	*504*	(24.4%)
2	*584*	(28.2%)
3	*443*	(21.4%)
4	*272*	(13.1%)
5	*266*	(12.9%)
Year of diagnosis		
2000	*158*	(7.6%)
2001	*200*	(9.7%)
2002	*235*	(11.4%)
2003	*228*	(11.0%)
2004	*239*	(11.6%)
2005	*198*	(9.6%)
2006	*212*	(10.2%)
2007	*258*	(12.5%)
2008	*185*	(8.9%)
2009	*156*	(7.5%)
Dukes stage		
A	*228*	(11.0%)
B	*727*	(35.1%)
C	*672*	(32.5%)
D	*235*	(11.4%)
Unknown	*207*	(10.0%)
Multi-organ support	*348*	(16.8%)
Median APACHE (IQR)	*16*	(13 – 20)
APACHE ≥20	*325*	(15.7%)
Missing APACHE	*901*	(43.6)

Table 6-6 Factors associated with critical illness, patient demographics and presence of cancer.

6.4.4.1 Factors associated with mortality risk in the first six-months following ICU survival

On univariate analysis age ≥60 years, Dukes stage, multi-organ support and APACHE II score ≥20 were associated with an increased hazard ratio for death during the first six-months following ICU survival (Table 6-7). Male sex was associated with a reduced hazard ratio. The strongest influence on mortality risk on univariate analysis was cancer stage. However, the variable Dukes did not meet the proportionality assumption.

When each factor was tested for proportionality, Dukes stage (p=0.0228) was identified as having potential problems. Graphical assessment of mortality risk by Dukes stage demonstrated that the lines can be seen crossing at several points and are not in a fixed relationship with each other. The proportionality assumption must be rejected for this variable and it has been excluded from the multivariate analysis. However, it is worth noting that Dukes stage had the greatest influence on mortality on univariate analysis and is likely to play an important role but cannot be forced to meet the proportionality assumption.

The factors identified on multivariate analysis that impact upon short-term survival were age ≥60 years (HR 1.58) and APACHE II score ≥20 (HR 1.68) and male sex (HR 0.74). The proportionality assumption was met for all included factors on multivariate analysis.

Variable		Univariate HR	P value	Multivariate HR	P value
Male sex		0.76 (0.59 – 0.97)	0.031	0.74 (0.57 – 0.94)	0.016
Age ≥60 years		1.76 (1.20 – 2.60)	0.004	1.58 (1.07 – 2.34)	0.022
SIMD	**1**	1.0	-	1.0	-
	2	1.05 (0.75 – 1.47)	0.778	1.10 (0.79 – 1.54)	0.574
	3	1.04 (0.72 – 1.49)	0.838	1.07 (0.74 – 1.53)	0.723
	4	0.72 (0.46 – 1.15)	0.172	0.75 (0.47 – 1.19)	0.227
	5	0.87 (0.56 – 1.35)	0.530	0.89 (0.57 – 1.38)	0.591
Year of diagnosis					
2000		1	-	-	
2001		1.27 (0.72 – 2.22)	0.409	-	
2002		0.83 (0.46 – 1.50)	0.542	-	
2003		1.07 (0.61 – 1.89)	0.812	-	
2004		1.16 (0.67 – 2.01)	0.606	-	
2005		1.06 (0.59 – 1.90)	0.848	-	
2006		0.82 (0.45 – 1.45)	0.517	-	
2007		0.80 (0.45 – 1.43)	0.456	-	
2008		0.95 (0.52 – 1.73)	0.858	-	
2009		0.71 (0.36 – 1.40)	0.324	-	
Dukes stage					
	A	1		-	
	B	5.04 (1.83 – 13.86)	0.002	-	
	C	6.93 (2.54 – 18.93)	<0.001	-	
	D	19.62 (7.17 – 53.73)	<0.001	-	
	Unknown	10.42 (3.70 – 29.31)	<0.001	-	
Multi-organ support		1.48 (1.10 – 2.00)	0.009	1.19 (0.85 – 1.65)	0.313
APACHE ≥20		1.81 (1.32 – 2.48)	<0.001	1.68 (1.21 – 2.34)	0.002
Missing APACHE		0.87 (0.65 – 1.16)	0.352	-	-
ICU Surgical admission		1.22 (0.68 – 2.18)	0.498	-	
Sepsis on admission		0.94 (0.58 – 1.52)	0.813	-	

Table 6-7 Factors associated with mortality risk in the first six-months in colorectal cancer patients that have survived ICU. Hazard ratios with 95% confidence intervals.

6.4.4.2 Factors associated with mortality risk after six months of survival in CRC ICU survivors

The same factors were assessed for impact on longer-term mortality from six-months to four years. Univariate analysis identified age ≥60 years, year of cancer incidence, Dukes stage and APACHE II score ≥20 as impacting on mortality risk (Table 6-8).

On multivariate analysis, the factors associated with lower mortality rates in the longer term included age <60 years, cancer diagnosis later in the study period and favourable cancer stage. The strongest influence on mortality risk was cancer stage (Dukes). Missing APACHE II score was also favourable.

All factors met the proportionality assumption on both univariate and multivariate analysis.

Variable		Univariate HR	P value	Multivariate HR	P value
Male sex		1.00 (0.86 – 1.17)	0.956	-	-
Age ≥60 years		1.34 (1.10 – 1.64)	0.004	1.49 (1.22 – 1.83)	0.001
SIMD	**1**	1.0	-	1.0	-
	2	0.88 (0.72 – 1.08)	0.229	0.85 (0.69 – 1.04)	0.117
	3	0.90 (0.72 – 1.11)	0.319	0.88 (0.70 – 1.09)	0.247
	4	0.81 (0.63 – 1.04)	0.098	0.79 (0.61 – 1.03)	0.078
	5	0.80 (0.62 – 1.04)	0.096	0.77 (0.59 – 1.00)	0.047
Year of diagnosis					
2000		1	-	1	-
2001		0.70 (0.50 – 0.98)	0.038	0.78 (0.55 – 1.09)	0.146
2002		0.84 (0.61 – 1.14)	0.256	0.89 (0.64 – 1.22)	0.464
2003		0.77 (0.56 – 1.06)	0.104	0.80 (0.57 – 1.11)	0.180
2004		0.64 (0.46 – 0.88)	0.007	0.62 (0.44 – 0.86)	0.005
2005		0.59 (0.42 – 0.84)	0.003	0.66 (0.46 – 0.94)	0.021
2006		0.72 (0.52 – 1.00)	0.048	0.77 (0.55 – 1.08)	0.133
2007		0.61 (0.44 – 0.83)	0.002	0.63 (0.46 – 0.88)	0.006
2008		0.54 (0.38 – 0.77)	0.001	0.48 (0.34 – 0.69)	<0.001
2009		0.51 (0.35 – 0.74)	<0.001	0.49 (0.33 – 0.72)	<0.001
Dukes stage					
A		1		1	-
B		1.78 (1.25 – 2.55)	0.002	1.76 (1.23 – 2.52)	0.002
C		3.72 (2.63 – 5.27)	<0.001	3.89 (2.74 – 5.51)	<0.001
D		8.16 (5.63 – 11.85)	<0.001	8.66 (5.96 – 12.59)	<0.001
Unknown		3.45 (2.32 – 5.12)	<0.001	3.67 (2.46 – 5.48)	<0.001
Multi-organ support		1.17 (0.96 – 1.42)	0.120	1.04 (0.83 – 1.30)	0.936
APACHE ≥20		1.28 (1.03 – 1.57)	0.024	1.21 (0.97 – 1.52)	0.096
Missing APACHE		0.86 (0.73 – 1.01)	0.062	0.80 (0.67 – 0.97)	0.020
ICU Surgical admission		0.91 (0.67 – 1.24)	0.564	-	-
Sepsis on admission		0.93 (0.69 – 1.24)	0.602	-	-

Table 6-8 Factors associated with late mortality risk after the first six-months in colorectal cancer patients that have survived ICU. Hazard ratios with 95% confidence intervals.

6.5 Discussion

6.5.1 Long-term survival of patients that survive ICU

Patients with cancer that survive ICU have an excess mortality when compared to an unmatched cohort of ICU survivors that do not have cancer. By the end of the four-year follow up period 53.3% of cancer patients had died compared with 19.5% in the group of ICU survivors without cancer. While cancer patients tend to be older than the general ICU population, it seems likely that this increased mortality is predominantly attributable to the on going neoplastic process.

6.5.2 Factors associated with increased mortality risk in ICU survivors

This study assessed factors within the general ICU population that were associated with an increased mortality risk in the intermediate and longer-term after ICU survival. In the first six months, factors associated with the critical illness have a modest effect including APACHE II ≥20 score (HR 1.7), multi-organ support (HR 1.22) and surgical admission to ICU (HR 0.79). The presence of cancer, if the proportionality assumption is correct, had a greater impact with a HR 2.37 (95% CI 2.16 – 2.61, $p<0.001$) with a similar effect seen for patient age ≥60 years at admission to ICU (HR 2.56 (95% CI 2.33 – 2.82, $p<0.001$). The persisting impact of critical illness into this stage is not altogether unsurprising as an increased severity of critical illness might be expected to have some lasting effects.

Analysis of those factors associated with differences in mortality in the longer-term (up to four years) demonstrated that the presence of cancer had the greatest impact. There was a three-fold increase in mortality risk in the cancer population when compared with ICU survivors without cancer. Those factors associated with the original critical illness severity had a lesser impact, with the hazard ratio for APACHE II ≥20 score falling to 1.41 and the effect of multi-organ

support no longer statistically significant. Surgical admission to ICU continued to have a protective effect with a HR 0.74 (95% CI 0.69 – 0.79, p<0.001). This may reflect a population of patients with a lower burden of serious co-morbidity than that seen in the medical population. Sepsis on admission to ICU had a very weak impact on increasing mortality risk (HR 1.09). Patient related factors associated with increased mortality in the longer-term included age ≥60 years at ICU admission, which more than doubled mortality risk and male sex, which had a very small impact upon mortality risk (HR 1.07). Analysis of SIMD demonstrated improved survival probability in patients from the more affluent area SIMD quintiles three, four and five.

6.5.3 Factors associated with increased mortality risk in ICU cancer survivors

Within the ICU survivor cancer population the underlying tumour type had a large impact upon post-ICU survival varying from 10.0% at four-years in patients with hepatocellular carcinoma to 73.3% in patients with testicular cancer. Favourable outcomes were demonstrated in patients with breast cancer, testicular cancer, thyroid cancer and uterine cancer where outcomes within the non-ICU population are positive. Other tumour types where selection bias may have meant that those undergoing curative surgery were likely to be admitted to a critical care unit for peri-operative support also performed relatively well. These included patients with colorectal cancer, head and neck cancer or kidney tumours. Prior analysis had described large proportions of surgical admissions for these tumour types and in addition to curative surgical intervention it is likely that these patients had low rates of co-morbidities otherwise major surgical intervention may have been deemed unsuitable.

Colorectal cancer patients that had survived ICU underwent additional analysis. Data pertaining to cancer stage was more available for colorectal cancer patients than many of the other cancer groups. As this group contributed the largest proportion of the cancer subtypes this additional data was used to determine whether cancer specific features were important in determining

mortality risk following ICU survival. While cancer treatment data was available for a large proportion of this population a decision was made to exclude this from analysis. Many treatment options are only available after a certain period of survival or where patients are in good general health and it may be unknown at the time of ICU discharge which treatments will be delivered to any individual patient. Further analysis could include this data but would require complex statistical techniques such as propensity scoring or time dependent survival.

The analysis of the first six months following ICU survival was limited due to cancer stage not meeting the proportionality assumption. Dukes stage was identified on univariate analysis to have the greatest impact on mortality risk and as such it is possible that the most important factor was excluded from the multivariate model. However, Dukes stage clearly violated the proportionality assumption and to include this factor in analysis would lead to inaccurate and unreliable results. It is beyond the scope of this research to perform the sophisticated statistical analysis that would be required to overcome this issue. While the analysis was limited by the lack of stage it did identify other factors that impacted on mortality including a modest effect with age ≥60 years (HR 1.58), APACHE II score ≥20 (HR 1.68) and male sex (HR 0.74).

Examination of those factors associated with longer-term outcome (from six-months to four-years) in colorectal cancer patients that had survived ICU found that cancer stage had the strongest link with mortality risk. Dukes staging classifies patients by degree of tumour invasion (Dukes A no invasion, Dukes B muscle invasion) and by the degree of spread (Dukes C lymph node involvement, Dukes D metastatic disease). In ICU survivors the longer-term mortality risk for patients with Dukes D was eight-fold that of patients with Dukes A disease. Year of cancer incidence also had an important role to play with outcomes for cancer patients (and possibly ICU survivors) improving with time. This demonstrated that those diagnosed at the end of the study period in 2009 had half the mortality risk as those diagnosed at the beginning in 2000. This may represent improvements in both the management of cancer and critical illness but may also be impacted by the increasing number of HDU beds included in the ICUs during the study period. Although high APACHE II score did not impact on longer-term outcome, missing APACHE II data was associated with a mildly favourable

survival. This reduction in mortality risk may represent the cohort of patients who are admitted to ICU as a HDU patient and are therefore excluded from APACHE scoring. These patients are often admitted electively for post-operative monitoring and the favourable outcome may be attributed to pre-operative optimisation, patient selection bias and potential curative intervention.

6.5.4 Comparisons with published literature

This study assessed survival of patients that had survived ICU and identified factors that were associated with mortality. A similar study was published in 2008 by Williams et al of nearly 20,000 patients admitted to a single-centre hospital in Australia between 1987 and 2002 [44]. This identified older age, severe co-morbidity, ICU diagnostic group, new malignancy, high severity of illness score and peak number of organ failures were associated with higher mortality risk in the first year and in the subsequent 15-years, with the addition of male gender and prolonged ICU length of stay. Of these age was the strongest factor associated with mortality risk followed by co-morbidity then new malignancy. New malignancy referred to a cancer that was diagnosed during the same hospitalisation that the ICU admission occurred. In their cohort new malignancy was associated with a HR 4.61 in the first year then HR 2.61 for the following 14 years. The difference in the hazard ratios reported in this analysis (HR 2.37 for the first six-months and HR 3.40 for six-months to four-years) may be explained by a combination of factors. The increased early mortality described by Williams et al may be in part due to the manner in which cancer has been defined, as these patients were presenting to ICU with the cancer diagnosed during the same inpatient stay. This precludes the opportunity to provide any optimisation or advanced planning. Furthermore, cancer and ICU management has changed over the time period studied by Williams et al and that studied in this study. Finally, there were less than 300 cases of new malignancy in Williams et al ICU survivors cohort, so long-term survival analysis will be limited by the relatively small numbers.

Brinkman et al assessed the mortality risk of over 90,000 ICU patients after hospital discharge in a 2013 publication [180]. This Dutch multi-centre study described adjusted hazard ratios for the one-year mortality after discharge for a number of subgroups. Patients admitted to ICU with cancer had a HR 1.94, similar to the six month hazard ratio described in this study (2.37).

Shack et al have previously published on the negative impact of deprivation measured by SIMD quintiles on cancer survival [181]. This is consistent with the results of this study, which noted a small effect on mortality risk in the longer-term for ICU survivors with colorectal cancer. The effect of deprivation was also noted in the non-cancer ICU population. Hutchings et al have previously noted an association between poor socioeconomic status and hospital mortality [182] however, the impact on longer-term outcomes has not been previously assessed. In concordance with the findings of this study, Shack et al also noted that survival in cancer patients was improving over time and this may be explained by screening programmes in addition to more effective and safer treatment combinations.

Cancer stage is known to be an important determinant of long-term survival and was found to be the major factor associated with longer-term outcome in ICU survivors with colorectal cancer. Data from the National Cancer Intelligence Network (NCIN) found that five-year survival varied from 93.2% in Dukes A, 77.0% in Dukes B, 47.7% in Dukes C to 6.6% in patients with Dukes D disease [183]. The effect demonstrated in this study is not quite as striking. However, this may in part be due to selection bias, with patients suffering from Dukes D disease only admitted if all other factors are favourable in addition to those patient with Dukes A disease only requiring an ICU admission due to co-morbidities or additional illness burden.

6.5.5 Strengths and limitations

This multi-centre study is one of the largest of its kind and as a result has facilitated assessment of the impact of a variety of variables on survival

following ICU. The additional data within the colorectal cancer dataset allowed further analysis of the largest subgroup of ICU cancer survivors and the major factors that impact upon mortality.

Due to the retrospective nature of this study there were limitations placed on which variables could be analysed. As a result performance status, which is regarded as an important factor in determining survival from cancer, has not been assessed. Nor has the impact of other specific co-morbidities, which may have an important role to play. Furthermore, the cancer registry only records point specific information such that stage is recorded at cancer incidence but there is no longitudinal data as to how this changes with time. As such it is unknown whether the cancer stage is different at the time of ICU admission.

While every effort has been made to ensure reliability of the results the problems encountered with the proportional hazards assumption led to difficulties. Time segmenting the survival into intermediate and late survival overcame most of these issues. However, when analysing intermediate survival of colorectal cancer ICU survivors I was unable to include cancer stage in the multivariate model due to lack of proportionality. As a result it is likely that the multivariate analysis of factors associated with mortality in the first six months following ICU survival does not include the most important factor- cancer stage.

6.6 Key points

- In ICU survivors the presence of cancer has the largest impact upon mortality risk in the longer-term with a risk of death over three times greater than in the non-cancer population.

- Additional factors associated with higher mortality risk within the first six months following ICU survival included older age, multi-organ support, high APACHE score and medical admission to ICU.

- Between six months and four years the factors associated with higher mortality risk included cancer, older age, male sex, poorer socioeconomic status, high APACHE score, medical admission to ICU and sepsis on ICU admission.

- Survival varies considerably by underlying tumour type.

- Cancer related factors such as tumour type and stage have an important role in determining mortality risk in the longer term for survivors of ICU with cancer.

Chapter 7 Discussion

In the face of major advances in both critical care and oncology, the requirement for cancer critical care is likely to become more widespread. While the literature to date suggests that outcomes for cancer patients in ICU are improving, it falls short of providing evidence to guide ICU admission policies. Realistic medicine involves supporting the patient to reach the treatment decision that is right for them [184]. By identifying factors associated with poor ICU outcome clinicians can highlight the potential for increased risk to an individual in addition to detailing the specific burdens of ICU care. With these discussions patients can have a better understanding of what critical care is likely to entail and the potential for a good outcome after undertaking admission. For some patients this will result in an unrestricted ICU admission but for others the burden of ICU may be too onerous and a preference for palliative care explored. The future of critical care for cancer patients therefore needs to be tailored to the individual patient taking account of their needs and preferences.

This thesis aims to assist in these conversations by describing the outcomes for disparate groups of cancer patients that have received critical care and describing those factors associated with prognosis after ICU admission. It is beyond the scope of this work to comment on patients with critical illness who are not admitted to ICU where outcomes might be expected to be particularly poor.

7.1 Summary of findings and clinical implications

This thesis describes the literature available for outcomes in patients with solid tumours after ICU admission in the manner of a meta-analysis before going on to describe in detail a cohort of ICU cancer patients.

7.1.1 Systematic review and meta-analysis

The meta-analysis performed at the start of this work summarised the results of 47 published papers that described outcomes in patients with solid tumours after admission to ICU. Hospital mortality varied significantly from 4.6% to 76.8%, reflecting variations in case mix with regards to underlying tumour type and ICU admission policies. The average mortality across all studies of 38.2% is difficult to interpret in the face of such wide differences in practice. Survival beyond hospital mortality was only reported in 12 of the identified studies and again varied widely owing to population differences.

Several studies attempted to identify factors associated with survival and a number of common themes were noticeable. Short-term mortality was commonly related to the critical illness with high severity of illness scores, organ support, medical ICU admissions and sepsis associated with mortality. Whilst tumour type was not demonstrated to be associated with mortality in any of the individual studies, the average mortality by tumour types when pooled across all studies varied widely. This likely reflects the different critical illness and admission patterns seen for differing tumour types.

The literature on this subject has been limited, to date, by lack of detail in many of the studies. Outcomes are often reported for an undifferentiated group of “cancer” patients or a subset such as those with metastatic disease or with a specific critical illness. Twelve of the studies did not report any measure of severity of illness in spite of this factor being so closely linked with outcome and varying significantly across publications. Furthermore, many of the studies have been set in specialised oncological ICUs where the mixture of tumour types and expertise may be different to that in a general ICU.

7.1.2 Rate of ICU admission in the solid tumour population

This study has demonstrated that ICU is an important feature for cancer patients, with one in twenty admitted to ICU within two years of diagnosis with a high associated mortality. Admission to ICU tended to occur soon after the cancer diagnosis and was most commonly due to a surgical condition. The rate of ICU admission did not always reflect cancer incidence rates and was greatest for bowel malignancies and for those tumours that require peri-operative support for tumour resection surgery, such as head and neck cancers, stomach cancer and oesophageal cancer.

Mortality for those admitted to ICU was high with one in four dying before hospital discharge. Mortality varied by cancer type and was higher in emergency admissions, medical admissions and in patients that received organ support.

The study was unable to identify patients that suffered a critical illness but were not admitted to ICU or those who were admitted to a stand alone HDU. It is therefore possible that this study underestimates the real need for cancer critical care. It is interesting to note that the UK has both poorer cancer outcomes and considerably lower provision of ICU beds than most other developed countries. While this study cannot conclude that a greater provision of ICU beds would contribute to improvements in cancer survival in the UK it does raise interesting questions. The necessity for ICU after a diagnosis of cancer should not be ignored and further exploration of the benefits of increased surveillance for early signs of critical illness and a greater capacity to offer ICU to cancer patients might be beneficial.

7.1.3 Differences between the ICU cancer population compared with the ICU population without cancer

Compared with the population without cancer, ICU cancer patients tended to be older, with a higher proportion of surgical admissions and less frequent utilisation of organ support. The surgical and medical populations varied

significantly in terms of patient demographics, admission diagnosis, severity of illness and survival and as such it was necessary to describe these groups separately.

When considering short-term outcomes a diagnosis of cancer should not preclude admission to ICU. For those patients admitted from a surgical specialty, hospital mortality favours those with an underlying cancer diagnosis. This may be due to a larger proportion of elective hospitalisations within the cancer group (where pre-operative optimisation has been available) or due to differences in the nature of surgical procedures. In the group of patients admitted to ICU with a medical diagnosis, hospital mortality was higher in the cancer population at 49.1% versus 41.7%, however, this difference became more marked in those that received organ support at 62.5% versus 46.2%. This might be partly explained by the older population, greater use of multi-organ support for the cancer group and the high prevalence of sepsis in a potentially immunocompromised cohort. While mortality is higher for the cancer group it would not necessarily prevent ICU admission, however, the patient and family should be counselled about the potential for poor outcome after admission to ICU.

While the mortality risk is greatest around the time of ICU admission, survival continues to decline in the four years after admission. The mortality difference between those patients with and without cancer becomes more pronounced with time and there is a clear survival disadvantage for the cancer group. By four years approximately one third of ICU cancer patients were alive compared with over half of the ICU patients without cancer. Again, the survival disadvantage was more marked for the medical admission group. The difference in survival between the ICU patients with and without cancer may be attributed to the underlying cancer or the treatment burdens associated with the cancer.

7.1.4 The effect of cancer on survival following ICU

Having survived an ICU admission the factor that had the greatest impact on on going mortality risk after six months was the presence of cancer. Patients with

cancer had a risk of death greater than three times that seen in the population without cancer. Other factors that impacted upon mortality risk included older age, male sex, social deprivation, high APACHE II score, medical admission and sepsis on ICU admission.

Within the group of patients with cancer the survival rates varied significantly by underlying tumour type. For ICU survivors with an underlying diagnosis of colorectal cancer, mortality risk after six months was influenced by tumour stage, year of cancer diagnosis, older age and social deprivation. Of these, tumour stage (Dukes) had the largest impact. These results suggest that details pertaining to the cancer prognosis have the strongest impact upon long-term survival.

While a diagnosis of cancer should not necessarily preclude an admission to ICU it is worth noting that these patients do not have the same life expectancy as the group without cancer. When discussing ICU admission with cancer patients both short and long term survival should be considered particularly with reference to any individual risk factors such as cancer type, cancer stage and patient age. With this information patients can be helped to reach a decision that is acceptable to them in terms of treatment burden and chances of survival following ICU admission thus facilitating individualised care in the era of realistic medicine [184].

7.2 Reflections on the strengths/ weaknesses

This work is based on a large population of patients both in terms of over 100,000 cancer patients and over 40,000 ICU patients. As a result the 6116 ICU patients with cancer studied is one of the largest population of cancer patients in a general ICU population that has been described. These findings therefore are representative of practice in general hospitals and suitable to generalisation.

However, because this study was carried out in a region of a single country, results must be extrapolated with caution.

This thesis used a two-year window between cancer diagnosis and admission to ICU to identify ICU cancer patients. With increasing time since diagnosis, patients become cancer survivors rather than remain cancer patients and thus their malignancy would be of decreasing relevance to subsequent hospitalisations. If the follow up period had been extended to 5 years after diagnosis the sample of ICU cancer patients would have only increased by approximately 10%.

Details pertaining to the underlying malignancy have been taken from verified cancer registration data. As this data is linked to the national death records I have been able to describe survival for this group of patients beyond the standard hospital discharge and up to four years after ICU admission. As demonstrated by the results, survival for ICU cancer patients does not remain static and long-term follow up studies such as this are important for informing future practice.

As with all studies which employ administrative data there were several limitations. These include that the standard of data collection was not as high as that expected in prospective research, and that because of the limitations of the data which was recorded, there were restrictions on what could be evaluated. Many of the studies identified in the systematic review described an association between performance status and survival. Unfortunately, performance status was not documented in the cancer registry or ICU Wardwatcher systems and I was therefore unable to assess the impact of this potentially important factor. A prospective study of this topic would allow collection of detailed baseline information including performance status, in addition to identifying patients with critical illness who were not admitted to ICU. However, such a study would either be limited in survival time data or take a long period of time to complete.

It is possible that the geography involved has introduced bias as a patient from the West of Scotland that was admitted to an ICU outwith the 16 pre-specified West of Scotland ICUs would not be identified. This could potentially occur if a

patient developed critical illness requiring immediate treatment while in a different region of the country. It seems probable that the numbers of patients that this could apply to is small and unlikely to impact significantly on the results of this study. As residency in the West of Scotland was pre-specified, patients with a cancer diagnosis outwith this region that were admitted to a West of Scotland ICU would not have been included in the ICU cohort.

Six of the 16 ICUs functioned as a combined ICU/ HDU at some point during the study period with the proportion of HDU funded beds contributing between 7% to 23% of the total bed numbers. HDU differs from ICU both in terms of staffing and in patient population. Patients admitted to HDU may have a less severe form of critical illness with only one organ failure or may have been admitted for observation and monitoring following an operative procedure. These latter patients are not necessarily suffering from a critical illness although may be at risk of developing one. Due to the high turnover of elective post-operative patients in an HDU setting it may be that the cancer population is over-represented in this cohort by patients that wouldn't be considered as true level 3 ICU patients. While we had information on those HDU patients admitted to a combined ICU/ HDU we did not have data for those patients admitted to a stand alone HDU as those units were not using the Wardwatcher audit database during the time period. The ICU cancer group had a higher proportion of patients with non-recorded APACHE scores and this is unlikely to be random. HDU admissions are excluded from APACHE scoring as the score is not validated for use for these patients and these patients therefore appear to have a missing score. If the ICU cancer group has a greater proportion of HDU patients then they would also be expected to have a greater proportion of non-recorded APACHE scores.

It is possible that this could have introduced a misclassification bias, as patients admitted solely for post-operative monitoring and without critical illness were included in the dataset. For this reason a separate analysis of those ICU patients who had received organ support during their ICU stay was performed. The presence of organ support was used as an indication of level 3 care. It is possible that this will identify level 2 patients as level 3 incorrectly. For example, a post-operative patient with an epidural in situ requiring vasoactive support for

associated hypotension would generally be considered level 2 but would be included in the organ support subgroup of this study.

While every attempt was made to minimise missing data it remains a limitation of the study. In addition to missing APACHE, data pertaining to renal support was absent in 12% of patients. During the study period not all units had the ability to provide renal support and it is possible that this missing data originates in units where renal replacement therapy was not available. None the less, the true incidence or renal replacement therapy remains unknown as a result.

7.3 Implications for further research and practice

This thesis has described, in detail, the ICU cancer population, however, a number of questions remain unanswered.

Long-term mortality of ICU cancer survivors is poor when compared with the group of patients without cancer. However, it is unknown how this compares to the population of cancer patients that are not admitted to ICU. It might be expected that having survived critical illness and the associated inflammatory insult and physiological disturbance, ICU cancer patients have a poorer prognosis than those without an ICU admission. However, it is likely that there is a selection bias associated with ICU admission as ICU physicians are only likely to admit patients with reasonable chronic health and perceived outcomes. Future work should compare long-term survival between these two groups and take account of variables that are likely to impact upon outcome such as tumour type, tumour stage, patient age and social deprivation. If possible, co-morbidities and performance status would also be accounted for. This would be best achieved with a prospective trial that could also account for patients with critical illness that were not admitted to ICU. However, the follow up time required for a long-term survival study would take several years to complete. In

the interim, further retrospective analysis of this dataset would address many of these questions and provide a starting point for future studies.

While this study has demonstrated that one in twenty cancer patients are admitted to ICU, it makes no evaluation of those cancer patients with critical illness who are not admitted. The UK has one of the lowest provisions of ICU beds per head of population in Europe. Furthermore, compared with the rest of Western Europe, survival of cancer patients in the UK is poor. Most of the international differences in cancer survival are explained by early mortality when operative interventions and aggressive anticancer therapy are likely to be administered. This work demonstrates that ICU admission is most common early after cancer diagnosis but it is unknown whether current ICU provision is adequate to meet the demand. A prospective study aimed at assessing the prevalence of critical illness in cancer patients with outcome data for both those that are, and those that are not, admitted to ICU might identify a need for an increase in provision.

Prospective work would also have the advantage of identifying post-ICU treatment delivery. While the intention prior to ICU might be for aggressive treatment with an expected good outcome, it is not clear whether an ICU admission alters this course. It seems likely that critical illness will necessitate some changes to treatment plans such as delays in surgery or chemotherapy or alterations to chemotherapy regimes or dosing. Changes to these may have subsequent impact upon survival such that the outcomes for post-ICU cancer patients follow a different course. Patients treated with chemotherapy at the Beatson Oncology Centre in the West of Scotland have their prescriptions documented on the Chemocare database. There is an opportunity for merging the Chemocare database with this dataset. Analysis of the Chemocare data would allow differentiation of treatment regimes for cancer patients with and without an ICU admission and how this impacts upon survival. This would go some way to informing clinical practice in terms of advising patients of changes to their expected journey following an ICU admission.

Finally, the focus of this thesis has been regarding the ICU care of cancer patients, however, this dataset also allows for analysis of the rates of cancer in

the population of ICU survivors. Critical illness involves a marked inflammatory process. This may be exacerbated by interventions such as invasive mechanical ventilation. Most patients during their ICU stay will undergo exposure to ionising radiation with x-rays and CT scanning common in ascertaining a diagnosis and monitoring treatment. As such, it is possible that ICU survivors have a higher risk of cancer than the general population. Further analysis of this data would allow documentation of tumour-specific rates among those patients that have survived an ICU admission.

Chapter 8 Appendices

8.1 Systematic review additional tables

Table 8-1 and 8-2 describe the setting and patient characteristics of the included studies.

Author	Setting	Design	Study population	Exclusions
Adam (2008)	USA 1998-2005; single centre general ICU	Retrospective	139 lung cancer patients admitted to MlCU	ICU stay <24 hours, routine postoperative care, cancer remission >2 years, ICU readmission
Aldawood (2010)	Saudi Arabia 1999-2009; single centre general ICU	Prospective	51 ICU patients with lung cancer	Postoperative lung resection patients, age <16 years, brain death victims
Andréjak (2011)	France 1996-2006; 2 general MICUs	Retrospective	76 patients with advanced lung cancer (no curative surgical option, stage 3B, 4 NSCLC or SCLC) requiring MICU admission	Lung cancer diagnosed/ staged after ICU admission, disease remission >5 years, ICU stay <24 hours (except if died), routine postoperative care, readmissions
Anisoglou (2013)	Greece 2008-2011; single centre oncological ICU	Retrospective	105 lung cancer patients with acute respiratory failure requiring ICU	ICU stay <24 hours, routine postoperative care
Azoulay (2004)	France 1997-2002; single centre general ICU	Prospective	203 patients with haematological/solid tumours admitted to ICU with acute respiratory failure	Nil
Bissell (2013)	UK 1998-2009; single centre general ICU	Retrospective	43 patients requiring readmission to ICU following elective oesophagectomy for malignancy	Nil

Author	Setting	Design	Study population	Exclusions
Bonomi (2012)	USA 1992-2005; multicentre ICUs	Retrospective	1134 patients with NSCLC stage IIIB/ IV admitted to MICU with respiratory, cardiac, or neurological diseases, renal failure, or sepsis	Age <65 years
Bos (2012)	Netherlands 2007-2011; 80 general ICUs	Retrospective	15211 patients with an APACHE IV diagnosis of haematological or solid tumour and an unplanned admission to ICU.	Elective ICU admission
Caruso (2010)	Brazil; single centre oncological ICU	Retrospective	83 patients with metastatic solid cancer admitted to ICU during 1 calendar year	Readmissions
Cense (2006)	Netherlands 1994-2000; 2 general ICUs	Prospective	109 patients undergoing a transthoracic resection for adenocarcinoma of the middistal oesophagus or gastric cardia	Age <18 years, ASA >3
Chawla (2009)	USA 2004-06, single centre oncological ICU	Retrospective	25 patients with solid/ haematological cancer admitted to ICU within 48 hours of planned or actual hospital discharge	Nil
Chou (2012)	Taiwan 2007-2008, single general ICU	Retrospective	70 patients with stage III-IV lung cancer requiring mechanical ventilator support for sepsis-related respiratory failure	Nil
Christodoulou (2007)	Greece 2001-05; single centre general ICU	Retrospective	69 patients with solid tumours admitted to ICU	Routine postoperative monitoring

Author	Setting	Design	Study population	Exclusions
Darmon (2005)	France 1997-2003; single centre general ICU	Prospective	100 patients with organ failure, inoperable solid tumour or hematologic malignancy diagnosed <30 days before ICU admission, in immediate need of chemotherapy and eligible to receive chemotherapy	Previous chemotherapy
de Almeida (2012)	Brazil 2009; single centre oncology ICU	Prospective	122 patients with solid or haematological tumour admitted to ICU	Age <18 years old, palliative care, haemorrhagic shock, end-stage renal disease, patients in other studies, expected death within 24 h, discharged within 24 hours
Ertan (2008)	Turkey 1998-2004; single centre general ICU	Not stated	102 patients who underwent emergency surgery for colorectal cancer and admitted to ICU	Diagnostic uncertainty or insufficient clinical data
Jennens (2002)	Australia 1993-2001; 3 general ICUs	Retrospective	20 patients with lung cancer (SCLC) admitted to ICU	Nil
Kopterides (2011)	Greece 2005-07; 2 general ICUs	Prospective	126 patients with solid/ haematological cancer admitted to ICU	Age <18 years, ICU readmissions, routine post-op monitoring
Leath (2006)	USA 1999-2004; single centre general ICU	Retrospective	185 gynaecological oncology patients admitted to ICU following surgery	Patients undergoing outpatient procedures or surgery at a different centre or non-surgical admissions
Lecuyer (2007)	France 2001-04, single general ICU	Prospective	188 consecutive patients with solid/ haematological cancer requiring mechanical ventilation and presence of at least one other organ failure	HIV, allogenic stem cell transplant recipients

Author	Setting	Design	Study population	Exclusions
Libório (2011)	Brazil 2006-08; single centre oncological ICU	Prospective	288 patients with solid/ haematological cancer admitted to ICU	ESRF, previous renal transplant, obstructive nephropathy, ICU stay <24 hours, ICU readmissions
Maccariello (2011)	Brazil 2004-08; 14 general ICUs in 3 centres	Prospective	773 consecutive (118 with cancer) patients requiring renal replacement therapy for AKI in ICU	ESRF, ICU stay <24 hours, ICU readmissions, non-AKI indication for RRT
McGrath (2010)	UK 2004-08; single centre oncological ICU	Retrospective 2004-06; Prospective 2006-08	185 patients with solid/ haematological cancer admitted to ICU	Routine post-op monitoring
Mendoza (2008)	USA 2003-04, single centre general ICU	Retrospective	147 patients with solid cancer admitted to ICU	Nil
Mourad (2014)	France 2009-2011; single oncology ICU	Prospective	76 cancer patients with septic shock and persistent hypotension requiring vasopressor therapy	Age <18years, valvular heart disease, regional myocardial ischaemia or previous MI, therapeutic limitation decision prior to admission
Namendys-Silva (2010)	Mexico 2007; single centre oncological ICU	Prospective	177 patients with solid cancer admitted to ICU	Age <16 years, routine post-operative care, ICU readmissions
Namendys-Silva (2011)	Mexico 2008-10; single centre oncological ICU	Prospective	82 patients with solid/ haematological cancer with septic shock in ICU	Age <18 years, ICU readmissions
Namendys-Silva (2013)	Mexico 2007; single centre oncological ICU	Prospective	92 patients with gynaecological cancer admitted to ICU	Age <16 years, routine post-operative care, ICU readmissions

Author	Setting	Design	Study population	Exclusions
Oeyen (2013)	Belgium 2008-2009; single centre general MICU & SICU	Prospective	483 patients with solid or haematological malignancy admitted to ICU	Readmissions, remission >5 years, post op cardiac surgery
Okiror (2012)	UK 2003-2008, single centre thoracic ICU	Retrospective	30 patients with lung cancer admitted to ICU as an emergency following lung resection.	Nil
Park (2009)	UK 1995-2007; 181 general ICUs	Retrospective	7227 patients admitted to ICU following elective oesophageal surgery for malignancy	Nil
Reichner (2006)	USA 2002-04; single centre general ICU	Retrospective	47 patients with lung cancer admitted to ICU	Nil
Roques (2009)	France 1997-2006; single centre general ICU	Prospective	105 lung cancer patients admitted to ICU	Postoperative lung resection patients, ICU readmission
Slatore (2012)	USA 1992-2007; multicentre ICUs	Retrospective	49373 patients with lung cancer admitted to ICU within 5 years of diagnosis	Age <66 years at diagnosis, patient with incomplete or without Medicare billing information, routine postoperative ICU admission, in situ cancer, diagnosis of cancer post mortem
Soares (2005)	Brazil 2000-04; single centre oncological ICU	Prospective	772 consecutive patients with solid/ haematological cancer admitted to ICU	Cancer remission >5 years, ICU stay <24 hours, acute coronary syndrome, routine postoperative care, ICU readmissions

Author	Setting	Design	Study population	Exclusions
Soares (2007)	Brazil 2000 – 2005; single centre oncological ICU	Prospective	121 patients with head and neck cancer admitted to ICU because of severe acute complications	ICU stay <24hours, routine postoperative care, readmission, complete cancer remission >5 years
Soares (2007)	Brazil & France 2000-05; 1 oncology & 1 general ICU	Retrospective	152 lung cancer patients admitted to ICU	Age <18 years, cancer remission >5 years, ICU stay <24 hours, routine postoperative care, ICU readmission
Soares (2010)	Brazil 2007; 28 ICUs	Prospective	753 patients with solid/ haematological cancer admitted to ICU	Age <18 years, cancer remission >5 years, ICU stay <24 hours, routine postoperative care, ICU readmission
Song (2007)	South Korea 2001-05; single centre oncological ICU	Retrospective	94 patients who underwent resection for lung or oesophageal cancer and subsequently required readmission to ICU	Single wedge resection
Song (2011)	South Korea 2002-08; single centre general ICU	Retrospective	62 consecutive patients with solid/ haematological cancer who received chemotherapy in ICU	Patients receiving prior on-going chemotherapy or treatment with corticosteroids only
Song (2012)	South Korea 2010; single centre oncological ICU	Retrospective	199 solid/ haematological cancer patients admitted to ICU via medical emergency team intervention	Limitation of care decision or refusal of ICU admission

Author	Setting	Design	Study population	Exclusions
Souza-Dantas (2011)	Brazil 2000-07; single centre oncological ICU	Prospective	94 patients with solid/ haematological cancer and neutropenia admitted to ICU matched to 94 non-neutropenic patients	Age <18 years, cancer remission >5 years, ICU stay <24 hours, routine postoperative care, ICU readmissions
Taccone (2009)	24 European countries 2002; 198 general ICUs	Prospective	473 patients with solid/ haematological cancer admitted to ICU	Age <15 years old, routine postoperative observation if >24 hours, ICU readmissions
Toffart (2011)	France 2000-07; 3 general ICUs	Retrospective	103 ICU patients with a past or present history of non-resectable lung cancer	Postoperative care
Unseld (2013)	Switzerland 2002; single centre MICU	Retrospective	74 patients with solid/ haematological malignancy admitted to MICU	Nil
Welsch (2011)	Germany 2001-2008; single centre general ICU	Prospective	96 patients with pancreatic head adenocarcinoma admitted to ICU post operatively for >24 hours	Patients with ampullary adenocarcinomas, intraductal papillary mucinous neoplasms, distal bile-duct carcinomas, and other malignant and benign pancreatic pathologies
Zuber (2012)	France 1997-2008; 41 general ICUs	Secondary analysis of prospective database of 225481 ICU patients	3437 patients with solid/ haematological cancer admitted to ICU with septic shock	ICU readmission

Table 8-1 Description of studies included in the systematic review of patients with solid tumours in ICU. [a]includes haematological cancer patients

Author	Number of solid tumour patients; tumour types (%)	Meta-static disease (%)	Severity of illness mean (SD) or median (IQR)	Age mean (SD) or median (IQR)
Adam (2008)	139; NSCLC (69%), SCLC (13%)	40%	SAPS III 41.8 (22.9), APACHE III 59.0 (25.1)	64.2 (10.2)
Aldawood (2010)	51; NSCLC (51%) SCLC (14%)	-	APACHE II 25.6 (8.13)	58 (16.2)
Andréjak (2011)	76; NSCLC (64.5%), SCLC (38.2%)	59.2%	SAPS II 43 (16.5), APACHE II 22 (7.7)	63.0 (9.9)
Anisoglou (2013)	105 lung cancer patients; 80% NSCLC, 13% SCLC	72.4%	APACHE II 23.4, SOFA 9.4	68.3 (10.4)
Azoulay (2004)	19; lung (52.6%), breast (47.4%)	-	-	53[a] (41-63)
Bissell (2013)	43 oesophageal cancer patients; adenocarcinoma (90.7%), squamous cell (4.7%), GIST (4.7%)	0%	-	65 (1.6)
Bonomi (2012)	1134 NSCLC; adenocarcinoma (45.4%), squamous cell (32.2%), large cell (8.6%), other (13.8%)	54.5%	-	73 (69-78)
Bos (2012)	12290 patients with solid tumours	30%	APACHE IV 88.1 (36.3)[a]	-
Caruso (2010)	83; breast (19.3%), lung (14.5%), head & neck (8.4%), colon (6%), stomach (6%), melanoma (6%), prostate (6%), pancreas (4.8%)	100%	SAPS II 47.5 (40-60)	61.4 (51-71)
Cense (2006)	109; oesophageal (100%)	14.7%	-	62

Author	Number of solid tumour patients; tumour types (%)	Meta-static disease (%)	Severity of illness mean (SD) or median (IQR)	Age mean (SD) or median (IQR)
Chawla (2009)	21; bladder (14.3%), colorectal (7.1%), lung (14.3%), pancreatic (7.1%)	-	-	63.9 (15.9)
Chou (2012)	70; lung (100%)		APACHE II 24.3 (6.7) SOFA 7.1 (3.1)	74.5 (12.0)
Christodoulou (2007)	69; lung (39.1%), colorectal (13%), ovarian (8.6%), breast (7.2%), pancreas (5.8%), prostate (5.8%), brain (4.3%), nasopharynx (4.3%), bladder (4.3%), kidney (2.9%), stomach (2.9%), oesophagus (1.4%)	89.9%	APACHE II 18.1 (8.3)	61.3 (13.3)
Darmon (2005)	12; sarcoma (33%), breast (17%), testicular (17%), NSCLC (8%)	-	SAPS II 39 (30-48)	47 (32-61)
de Almeida (2012)	106; not specified	35.2%	APACHE II 14 (10-20) [a]	63 (61-65) [a]
Ertan (2008)	102; colorectal (100%)	-	-	61 (18-97)
Jennens (2002)	20; SCLC (100%)	-	-	67
Kopterides (2011)	90; lower GI (33.3%), upper GI (25.6%), urogenital (14.4%), lung (12.2%), breast (8.9%)	-	SOFA 8.0 (5.0), SAPS II 45.1 (22.2), APACHE II 18.8(10.1)	65.3 (14.4)
Leath (2006)	185; Ovarian (39%), Endometrial (21%), cervical (12%), other (8%), benign disease (20%)	-	APACHE II 11.6	60
Lecuyer (2007)	56; lung and breast (46%)	-	-	51.5[a]

Author	Number of solid tumour patients; tumour types (%)	Meta-static disease (%)	Severity of illness mean (SD) or median (IQR)	Age mean (SD) or median (IQR)
Libório (2011)	258; gastrointestinal (30.2%), urological (25.6%), head & neck (16.3%), lung (6.9%), breast (6.9%)	-	SOFA 5.8 (3.4), SAPS II 35 (19.4), APACHE II 10.3 (5.9)	58.8 (17.4)
Maccariello (2011)	86; lower GI (29%), urogenital (20.9%), liver/ biliary (17.4%), upper GI (12.8%), lung (7%)	31.4%	SOFA 9 (7-11), SAPS II 49.3 (12.7)	70.0 (13.9)
McGrath (2010)	70; lung (21.4%), breast (15.7%), oesophagus (11.4%), ovarian (5.7%)	41.4%	SOFA 5.5, APACHE II 17.1	57.1 (12.8)
Mendoza (2008)	147; lung (23%), colorectal (12%), breast (7%), prostate (6%), pancreas (5%)	51.7%	-	63.5 (13.5)
Mourad (2014)	26; not specified	-	SAPS II 57 (45.7-69)[a], SOFA 11 (9-13)[a]	58 (49-66)[a]
Namendys-Silva (2010)	177; GI (22.6%), head and neck (20.3%), lung (2.3%), genitourinary (5.1)%, gynaecological (29.4%), breast (3.4%), gem-cell (5.6%), prostate (1.1%), sarcoma (4%) skin and soft tissue (6.2%)	-	SOFA 3 (1-8), APACHE II 12 (11-14)	52.4 (17.3)
Namendys-Silva (2011)	56; colorectal (17.9%), cervix (17.9%), sarcoma (12.5%), upper GI (12.5%), breast (8.9%)	33.9%	SOFA[a] 9.1 (3) in survivors vs. 11.7 (3) in non survivors, APACHE II[a] 15 (13-19.5) in survivors vs. 18 (16-23) in non survivors	52.5 (14.7) [a]
Namendys-Silva (2013)	92; cervix (67.3%), ovarian (21,2%)	-	SOFA 4.4 (4), APACHE II 12.4 (2)	56.5 (12.8)
Oeyen (2013)	398; lower GI (26%), upper GI (25%), lung (15%), urogenital (8.5 %), brain (8 %), head and neck (7 %), breast (4 %)	46%	SOFA 3 (2-5), APACHE II 13 (11-18)	62 (54-69)

Author	Number of solid tumour patients; tumour types (%)	Meta-static disease (%)	Severity of illness mean (SD) or median (IQR)	Age mean (SD) or median (IQR)
Okiror (2012)	30; 100% NSCLC	-	-	71 (7)
Park (2009)	7227; oesophageal (100%)	-	SAPS II 25.1 (10.5), APACHE II 13.9 (4.8)	64.3 (9.9)
Reichner (2006)	47; NSCLC (83%), SCLS (15%)	64%	SOFA 4.7 (3.3)	65 (10)
Roques (2009)	105; NSCLC (83%), SCLC (17%)	64%	SAPS II 40 (21) SOFA 4.4 (4.7)	64.8 (10.6)
Slatore (2012)	49373; NSCLC (80.3%), SCLC (13.1%), Other (6.6%)	45.7%	-	75 (71-79)
Soares (2005)	642; GI (17.1%), head & neck (16.2%), brain (16.2%), lung (11.8%), upper GI (11.4%), urogenital (10.1%), breast (5.9%)	21.4%	SOFA 6.5 (3.9), SAPS II 43.6 (18.9)	57.6 (16.4)
Soares (2007)	121; oral cavity (30%); larynx (25%), pharynx (14%), thyroid (9%), salivary gland (7%), paranasal sinuses (6%), other (9%)	35%	SAPS II 49.6 (17.8), SOFA 7.2 (3.6)	63.3 (14.7)
Soares (2007)	143; squamous-cell carcinoma (39%), adenocarcinoma (34%), SCLC (17%), large cell (6%), other (3%)	31%	SAPS II 47.4 (21.0)	61.6 (9.9)
Soares (2010)	667; lower GI (18.3%), urogenital (12.3%), upper GI (12.3%), lung (8.7%), brain (8.5%), head & neck (8.4%), breast (7.5)	29.1%	SAPS II 32.1 (7.2)[a], SAPS III 48.7 (19.0) [a] SOFA 7 (5 -10)[a]	61.2 (15.4)[a]
Song (2007)	94; oesophageal (39.4%), lung cancer (60.6%)	-	APACHE III 53.8 (24.5)	65.9 (7.3)
Song (2011)	13; lung (46.2%), sarcoma (23%), bladder (7.7%), breast (7.7%), gastric (7.7%), germ cell (7.7%)	-	SOFA 10 (6-14), SAPS II 53 (41-68)	50 (37-63)

Author	Number of solid tumour patients; tumour types (%)	Meta-static disease (%)	Severity of illness mean (SD) or median (IQR)	Age mean (SD) or median (IQR)
Song (2012)	104; not specified	-	SAPS III 80 (67-93)[a], SOFA 8 (5-11)[a]	60 (51-70) [a]
Souza-Dantas (2011)	60; GI (26.7%), urogenital (16.7%)	-	SOFA 11 (8-14), SAPS II 61.6 (16.5)	50 (32-65)
Taccone (2009)	404; not specified	24.8%	SOFA 4.6 (3.6), SAPS II 36.8 (17.6)	66.4 (12.1)
Toffart (2011)	103; squamous cell (32%), adenocarcinoma (25%), SCLC (20%), large cell (11%)	61%	SAPS II 33 (25-46) LOD 3 (1-4)	61 (54-68)
Unseld (2013)	42; urogenital (42%), lung (24%), gastrointestinal (16%), head (9%), other (7%)	-	SAPS II 39 (28-53), SOFA 5 (3-9)	66 (57-73)
Welsch (2011)	96; pancreas (100%)	7%	-	-
Zuber (2012)	2119; lung (16.8%), GI (16.6%), genitourinary (16.3%)	41.9%	SAPS II 63.4 (25.1)	62.2 (14.3)

Table 8-2 Patient characteristics from studies included in the systematic review. [a]includes haematological cancer patients.

8.2 Ethics Approval Letter

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 4
Ground Floor, Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT
www.nhsggc.org.uk

Dr David Morrison
University of Glasgow
University of Glasgow
1 Lilybank Gardens
Glasgow
G12 8RZ

Date 7 June 2012
Direct line 0141-211-1722
Fax 0141-211-1847
e-mail evelyn.jackson@ggc.scot.nhs.uk

Dear Dr Morrison

Title of the Research Database:	**West of Scotland Critical Care and Cancer Patient Database**
REC reference:	**12/WS/0075**

Thank you for your letter of 15 May 2012, responding to the Committee's request for further information on the above research database and submitting revised documentation.

The further information was considered by the Alternate Vice-Chair on behalf of the Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation, as revised.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Databases set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Other: Protocol for study	6	09 March 2012
Other: Dr David Morrison's CV	-	27 February 2012
Other: Flowchart	-	-

Other: Data Management Plan	1	-
Other: West of Scotland Cancer Surveillance Unit Standard Operating Procedures	2	01 December 2010
REC application	-	09 March 2012
REC application	-	15 May 2012
Response to Request for Further Information	-	15 May 2012

Research governance

A copy of this letter is being sent to the R&D office responsible for NHS Greater Glasgow and Clyde.

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research databases. There is no need to inform Local Research Ethics Committees.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

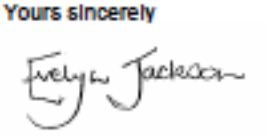
Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Annual Reports. Please refer to the attached conditions of approval.
c) Amendments. Please refer to the attached conditions of approval.

12/WS/0075	Please quote this number on all correspondence

Yours sincerely



for Dr Clair Evans
Alternate Vice-Chair

Enclosures: *Approval conditions*

Copy to: *Professor John Kinsella, University of Glasgow*
R&D Office, Tennent Building, Western Infirmary

West of Scotland REC 4

Attendance at Sub-Committee of the REC meeting on 31 May 2012

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Andrew Clark	Consultant Haematologist	Yes	
Dr Clair Evans	Consultant Paediatric and Perinatal Pathologist	Yes	
Dr Kenneth James	Consultant Anaesthetist	Yes	
Dr Brian Nelly	Consultant Physician	Yes	
Dr Jackie Riley	Statistician	Yes	
Mrs Kathleen Tuck	Retired Teacher (Lay member)	Yes	

8.3 Diagnostic groupings

SICS Diagnosis	Diagnostic group
Anaphylactic shock	Anaphylaxis
Anaphylaxis	Anaphylaxis
Acute lung injury	ARDS
ARDS	ARDS
Burns	Burns related
Carbon monoxide poisoning	Burns related
Smoke inhalation	Burns related
Cardiac Arrest (In hospital)	Cardiac arrest
Cardiac Arrest (Out of hospital)	Cardiac arrest
Cardiac failure	Cardiac failure
Cardiogenic shock	Cardiac failure
Poor left ventricular function	Cardiac failure
Disseminated intravascular coagulation	Coagulation disorder
Other acquired coagulation disorder	Coagulation disorder
Other coagulation disorder	Coagulation disorder
Thrombotic disorders	Coagulation disorder
Venous thrombosis (including DVT)	Coagulation disorder
Adverse reaction to therapeutic drug	Drug related
Alcohol abuse/dependence	Drug related
Drug abuse/dependence	Drug related
Drug overdose/misuse	Drug related
Drug toxicity	Drug related
Fulminant hepatic failure (paracetamol induced)	Drug related
Other drug related problem	Drug related
Self-poisoning	Drug related
Suxamethonium apnoea	Drug related
Toxicity of therapeutic drug	Drug related
Diabetes mellitus (co-existing)	Endocrine/ Metabolic disorder
Diabetic ketoacidosis	Endocrine/ Metabolic disorder
Hypoglycaemia	Endocrine/ Metabolic disorder
Non-ketotic diabetic coma	Endocrine/ Metabolic disorder
Acromegaly	Endocrine/ Metabolic disorder
Cushing's disease	Endocrine/ Metabolic disorder
Hyperthermia	Endocrine/ Metabolic disorder
Hypoadrenalism	Endocrine/ Metabolic disorder
Hypothermia	Endocrine/ Metabolic disorder
Other adrenal disorder	Endocrine/ Metabolic disorder
Other endocrine disorder	Endocrine/ Metabolic disorder
Other pituitary disorder	Endocrine/ Metabolic disorder
Phaeochromocytoma	Endocrine/ Metabolic disorder
Disorders of metabolism (inherited)	Endocrine/ Metabolic disorder

Disorders of metabolism (other)	Endocrine/ Metabolic disorder
Other metabolic disorder	Endocrine/ Metabolic disorder
Obesity	Endocrine/ Metabolic disorder
Goitre	Endocrine/ Metabolic disorder
Hyperthyroidism	Endocrine/ Metabolic disorder
Hypothyroidism	Endocrine/ Metabolic disorder
Other thyroid disorder	Endocrine/ Metabolic disorder
Diverticular disease with perforation	GI perforation
Duodenal ulcer (perforated)	GI perforation
Gastric ulcer (perforated)	GI perforation
Perforated duodenal ulcer	GI perforation
Perforated gall bladder	GI perforation
Perforated gastric ulcer	GI perforation
Lower GI perforation	GI perforation
Oesophageal perforation	GI perforation
Acute appendicitis with perforation	GI perforation
Anastamotic leak	GI perforation
Hysterectomy	Gynaecology
Other gynaecological problem	Gynaecology
Perforated uterus	Gynaecology
Duodenal ulcer (bleeding)	Haemorrhage
Gastric ulcer (bleeding)	Haemorrhage
Gynaecological bleeding	Haemorrhage
Haemorrhage from duodenal ulcer	Haemorrhage
Haemorrhage from gastic erosion/stress ulcer	Haemorrhage
Haemorrhage from gastric ulcer	Haemorrhage
Haemorrhage from stress ulceration	Haemorrhage
Haemothorax	Haemorrhage
Haemothorax (non-traumatic)	Haemorrhage
Hypovolaemic/haemorrhagic shock	Haemorrhage
Lower GI haemorrhage	Haemorrhage
Massive blood loss/transfusion without shock	Haemorrhage
Massive blood transfusion	Haemorrhage
Oesophageal variceal haemorrhage	Haemorrhage
Other/unspecified upper GI haemorrhage	Haemorrhage
Post-partum haemorrhage	Haemorrhage
Retroperitoneal haematoma	Haemorrhage
Retroperitoneal haematoma/coll	Haemorrhage
Pancreatic pseudocyst	Hepatobiliary
Acalculous cholecystitis	Hepatobiliary
Acute cholecystitis	Hepatobiliary
Biliary obstruction	Hepatobiliary
Other gall bladder or bile duct disorder	Hepatobiliary
Other pancreatic disorder	Hepatobiliary
Acute pancreatitis	Hepatobiliary
Chronic pancreatitis	Hepatobiliary

Acute MI	Ischaemic heart disease
Acute myocardial ischaemia	Ischaemic heart disease
Chronic ischaemic heart disease	Ischaemic heart disease
Other ischaemic heart disease	Ischaemic heart disease
Unstable angina	Ischaemic heart disease
Alcoholic liver disease	Liver disease
Cryptogenic cirrhosis	Liver disease
Fulminant hepatic failure (other)	Liver disease
Hepatitis (other)	Liver disease
Hepato-renal failure	Liver disease
Other hepatic disease	Liver disease
Primary biliary cirrhosis	Liver disease
Primary sclerosing cholangitis	Liver disease
Viral hepatitis (any type)	Liver disease
Bladder tumour	Malignancy
Bone tumour	Malignancy
Secondary brain tumour	Malignancy
Breast cancer	Malignancy
Primary brain tumour	Malignancy
Large bowel malignancy	Malignancy
Large/small bowel malignancy	Malignancy
Disseminated malignancy	Malignancy
Gastric carcinoma	Malignancy
Other GI malignancy	Malignancy
Small bowel malignancy	Malignancy
Acute leukaemia	Malignancy
Chronic leukaemia	Malignancy
Hodgkin's lymphoma	Malignancy
Myeloma	Malignancy
Non-Hodgkin's lymphoma	Malignancy
Other haematological malignancy	Malignancy
Hepato-biliary malignancy	Malignancy
Hepatocellular cancer	Malignancy
Hepatic metastases	Malignancy
Carcinoma (bronchus/lung)	Malignancy
Oesophageal carcinoma	Malignancy
Ovarian carcinoma	Malignancy
Pancreatic carcinoma	Malignancy
Prostate tumour	Malignancy
Kidney tumour	Malignancy
Spinal tumour	Malignancy
Teratoma	Malignancy
Thyroid tumour	Malignancy
Upper airway/oral carcinoma	Malignancy
Other genito-urinary tract tumour	Malignancy
Uterine/cervical carcinoma	Malignancy

Other autoimmune disorder	Miscellaneous
Vasculitis	Miscellaneous
Vasulitis	Miscellaneous
HIV/AIDS	Miscellaneous
Immunocompromised (by disease)	Miscellaneous
Immunocompromised (by treatment)	Miscellaneous
Not documented	Miscellaneous
Other haematological disorder	Miscellaneous
Endoscopy	Miscellaneous
Interventional radiology/cardiology	Miscellaneous
Multiple surgical procedures	Miscellaneous
Pre-op assessment/monitoring/optimisation	Miscellaneous
Radiological coiling/embolisation	Miscellaneous
Other surgery	Miscellaneous
Other chronic psychiatric disorder	Miscellaneous
Self-inflicted injury	Miscellaneous
Arthritis	Musculoskeletal
Hip surgery (including replacement)	Musculoskeletal
Knee surgery (including replacement)	Musculoskeletal
Orthopaedic surgery to multiple sites	Musculoskeletal
Osteoporosis	Musculoskeletal
Other bone disease	Musculoskeletal
Other chronic physical disorder	Musculoskeletal
Other lower limb surgery	Musculoskeletal
Other muscular disorder	Musculoskeletal
Other orthopaedic surgery	Musculoskeletal
Other skin disorder	Musculoskeletal
Other soft tissue trauma	Musculoskeletal
Other spinal disorder	Musculoskeletal
Other spinal surgery	Musculoskeletal
Pathological fracture	Musculoskeletal
Pelvic surgery	Musculoskeletal
Peripheral muscular disorders	Musculoskeletal
Rhabdomyolisis	Musculoskeletal
Rheumatoid arthritis	Musculoskeletal
Skull fracture	Musculoskeletal
Spinal fusion	Musculoskeletal
Thoracic/lumbar injury (minus cord damage)	Musculoskeletal
Thoracic/lumbar injury (plus cord damage)	Musculoskeletal
Upper limb surgery	Musculoskeletal
Fat embolism	Musculoskeletal
Central respiratory depression	Neurological disorder
Coma (other)	Neurological disorder
Coma (Unknown cause)	Neurological disorder
Encephalitis	Neurological disorder
Hepatic encephalopathy	Neurological disorder

Metabolic coma	Neurological disorder
Hanging	Neurological disorder
Hypoxic brain damage	Neurological disorder
Near drowning	Neurological disorder
Intracerebral contusions/haematoma	Neurological disorder
Intracerebral haemorrhage	Neurological disorder
Intracranial aneurysm	Neurological disorder
Subarachnoid haemorrhage (aneurysm)	Neurological disorder
Subarachnoid haemorrhage (other)	Neurological disorder
Subdural haematoma	Neurological disorder
Extradural haematoma	Neurological disorder
Cerebral infarction	Neurological disorder
CNS demyelination	Neurological disorder
CNS inflammation	Neurological disorder
Diffuse brain injury	Neurological disorder
Diffuse head injury	Neurological disorder
Guillan Barre syndrome	Neurological disorder
ICU neuropathy/myopathy	Neurological disorder
Multiple sclerosis	Neurological disorder
Myaesthenia gravis	Neurological disorder
Other CNS disorder	Neurological disorder
Other neurological vascular disorder	Neurological disorder
Other peripheral nervous system disorder	Neurological disorder
Paraplegia (existing)	Neurological disorder
Paraplegia (new)	Neurological disorder
Quadraplegia (existing)	Neurological disorder
Quadraplegia (new)	Neurological disorder
Respiratory failure due to neuromuscular disease	Neurological disorder
Spinal myelitis	Neurological disorder
Transient ischaemic attack	Neurological disorder
Amniotic fluid embolism	Obstetric disorder
Ectopic pregnancy	Obstetric disorder
Other obstetric problem	Obstetric disorder
Other obstetric/gynaecological surgery	Obstetric disorder
Toxaemia/PIH/eclampis/pre-eclampsia	Obstetric disorder
Atrial fibrillation	Other Cardiac
Heart block	Other Cardiac
Other arrhythmia	Other Cardiac
Supraventricular tachycardia	Other Cardiac
Ventricular tachycardia	Other Cardiac
Cardiomyopathy	Other Cardiac
Congenital heart disease	Other Cardiac
Essential hypertension	Other Cardiac
Fluid overload	Other Cardiac
Functioning cardiac transplant	Other Cardiac

Mediastinitis	Other Cardiac
Other cardiac disease	Other Cardiac
Other hypertension	Other Cardiac
Other shock	Other Cardiac
Pericardial effusion/disease	Other Cardiac
Secondary hypertension	Other Cardiac
Systemic embolism	Other Cardiac
Aortic regurgitation	Other Cardiac
Aortic stenosis	Other Cardiac
Existing prosthetic valve	Other Cardiac
Mitral regurgitation	Other Cardiac
Mitral stenosis	Other Cardiac
Other or unspecified valvular disease	Other Cardiac
GI obstruction (adhesions)	Other Gastro
GI obstruction (any hernia)	Other Gastro
GI obstruction (ileus)	Other Gastro
GI obstruction (other)	Other Gastro
GI obstruction (tumour)	Other Gastro
GI obstruction (volvulus)	Other Gastro
Large bowel ischaemia/infarction	Other Gastro
Small bowel ischaemia/infarction	Other Gastro
Crohn's disease	Other Gastro
Ulcerative colitis	Other Gastro
Diverticular disease without perforation	Other Gastro
Hernia (incisional)	Other Gastro
Hernia (inguinal)	Other Gastro
Hernia (inguinal, umbilical, or femoral)	Other Gastro
Hernia (umbilical)	Other Gastro
Malnutrition/malabsorbtion	Other Gastro
Other intestinal disease	Other Gastro
Other nutritional disorder	Other Gastro
Other retroperitoneal collection/abscess	Other Gastro
Other retroperitoneal patholog	Other Gastro
Other splenic disorder	Other Gastro
Splenectomy	Other Gastro
Stress ulceration	Other Gastro
Acute appendicitis without perforation	Other Gastro
Functioning renal transplant	Renal disorder
Gomerulonephritis	Renal disorder
Other renal disease	Renal disorder
Acute on chronic renal failure	Renal disorder
ARF (cause unknown)	Renal disorder
ARF (nephro-toxic agent)	Renal disorder
ARF (rhabdomyolysis)	Renal disorder
ATN	Renal disorder
Chronic renal failure (dialysis-dependent)	Renal disorder

Chronic renal failure (NOT dialysis-dependent)	Renal disorder
Non-functional/rejected renal transplant	Renal disorder
Obstructive renal failure	Renal disorder
Other acute renal failure	Renal disorder
Benign prostatic hypertrophy	Renal disorder
Other genito-urinary tract disorder	Renal disorder
Renal/ureteric calculi	Renal disorder
Asthma (acute)	Respiratory disorder
Asthma (co-existing)	Respiratory disorder
Bronchiectasis	Respiratory disorder
Broncho-pleural fistula	Respiratory disorder
Caval obstruction	Respiratory disorder
Chronic respiratory disease (Restrictive/chest wall/spine)	Respiratory disorder
COPD/emphysema (co-existing)	Respiratory disorder
COPD-acute exacerbation	Respiratory disorder
Cystic fibrosis	Respiratory disorder
Existing lung transplant	Respiratory disorder
Existing tracheostomy	Respiratory disorder
Neurogenic pulmonary oedema	Respiratory disorder
Other chest infection	Respiratory disorder
Other chronic respiratory disease	Respiratory disorder
Other pleural disorder	Respiratory disorder
Other pulmonary oedema	Respiratory disorder
Other pulmonary vascular disorder	Respiratory disorder
Other respiratory disease	Respiratory disorder
Pleural effusion	Respiratory disorder
Pneumothorax	Respiratory disorder
Pneumothorax (non-traumatic)	Respiratory disorder
Pulmonary contusion	Respiratory disorder
Pulmonary fibrosis	Respiratory disorder
Pulmonary fibrosis/alveolitis	Respiratory disorder
Pulmonary haemorrhage	Respiratory disorder
Pulmonary hypertension	Respiratory disorder
Pulmonary thromboembolism	Respiratory disorder
Sleep apnoea	Respiratory disorder
Other upper airway problem	Respiratory disorder
Upper airway haemorrhage	Respiratory disorder
Upper airway obstruction	Respiratory disorder
Upper airway trauma	Respiratory disorder
Epileptic (controlled)	Seizure disorder
Seizures (not Status)	Seizure disorder
Status epilepticus	Seizure disorder
Pyelonephritis	Sepsis
Bacteraemia/septicaemia	Sepsis
Cellulitis	Sepsis

Cerebral abscess	Sepsis
Chest infection-Aspiration	Sepsis
Chest infection-Atypical	Sepsis
Chest infection-Bacterial	Sepsis
Chest infection-Clinical (culture negative)	Sepsis
Chest infection-Fungal	Sepsis
Chest infection-PCP	Sepsis
Chest infection-TB	Sepsis
Chest infection-Viral	Sepsis
Chicken pox	Sepsis
Cholangitis	Sepsis
Croup	Sepsis
Empyema	Sepsis
Empyema of gall bladder	Sepsis
Epiglottitis	Sepsis
Hepatic abscess	Sepsis
Infective endocarditis	Sepsis
Meningitis	Sepsis
Meningococcal infection	Sepsis
MRSA	Sepsis
Necrotising fasciitis	Sepsis
Osteomyelitis	Sepsis
Other CNS infection	Sepsis
Other GI infection	Sepsis
Other infection	Sepsis
Other upper GI perforation	Sepsis
Pelvic sepsis	Sepsis
Peritonitis/abscess (no source identified)	Sepsis
Septic shock (GI tract)	Sepsis
Septic shock (renal tract)	Sepsis
Septic shock (respiratory)	Sepsis
Septic shock (source not specified)	Sepsis
Spinal abscess	Sepsis
Urinary tract infection	Sepsis
Extended recovery from anaesthesia	Surgical complication
Other anaesthetic complication	Surgical complication
Post-op respiratory failure	Surgical complication
Surgical complication	Surgical complication
Blunt trauma with brain injury	Trauma
Blunt trauma without brain injury	Trauma
Bowel trauma	Trauma
Cardiac/pericardial trauma	Trauma
Cervical spine injury (minus cord damage)	Trauma
Cervical spine injury (plus cord damage)	Trauma
Facial fracture	Trauma
Fracture of mandible	Trauma

Fractured neck of femur	Trauma
Fractured ribs/sternum	Trauma
Haemothorax (traumatic)	Trauma
Hepatic trauma	Trauma
Kidney/ureteric trauma	Trauma
Large soft tissue injury	Trauma
Liver trauma	Trauma
Lower limb trauma	Trauma
Mediastinal trauma	Trauma
Mesenteric/bowel trauma	Trauma
Multiple procedures for trauma	Trauma
Multiple trauma (excluding brain)	Trauma
Multiple trauma (including diffuse brain injury)	Trauma
Multiple trauma (including extradural haematoma)	Trauma
Multiple trauma (including intracerebral contusions/haemato)	Trauma
Multiple trauma (including subdural haematoma)	Trauma
Myocardial contusions/trauma	Trauma
Other abdominal trauma	Trauma
Other chest/airway trauma	Trauma
Other head trauma	Trauma
Other maxillo-facial trauma	Trauma
Other multiple trauma	Trauma
Other orthopaedic trauma	Trauma
Other spinal trauma	Trauma
Other trauma	Trauma
Other traumatic brain injury	Trauma
Pelvic trauma	Trauma
Pneumothorax (traumatic)	Trauma
Splenic trauma	Trauma
Upper limb trauma	Trauma
Abdominal aortic aneurysm-NOT ruptured/leaking	Vascular
Abdominal aortic aneurysm-ruptured/leaking	Vascular
Aortic aneurysm repair (elective)	Vascular
Aortic aneurysm repair (emergency)	Vascular
Aortic dissection	Vascular
Aortic trauma	Vascular
Arterial aneurysm-other	Vascular
Carotid artery stenosis	Vascular
Carotid surgery	Vascular
Occlusive aortic disease	Vascular
Other aorta surgery	Vascular
Other vascular disease	Vascular
Other vascular surgery	Vascular

Peripheral ishaemia	Vascular
Peripheral vascular disease (other than aorta)	Vascular
Thoracic aortic aneurysm	Vascular
Thoracoabdominal aortic aneurysm	Vascular

Table 8-3 SICS diagnosis and corresponding diagnostic group

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