Evaluating Outcome in Patients with Faecal Peritonitis Admitted to European Intensive Care Units

A thesis for the degree of Doctor of Philosophy

Ascanio Tridente

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Department of Infection and Immunity

Faculty of Medicine, Dentistry and Health

University of Sheffield

Author: Dr Ascanio Tridente
Consultant in Intensive Care, Consultant Physician
St Helen's and Knowsley Teaching Hospitals NHS Trust
Prescot, Liverpool L35 5DR
Merseyside
UK

Registration number: 110283517

Supervisors
Primary
Professor David Dockrell
Professor of Infectious Diseases
Sheffield University
Consultant, Communicable Diseases
Royal Hallamshire Hospital
Sheffield, United Kingdom

Secondary
Professor Gary H. Mills
Honorary Professor of Critical Care Medicine and Perioperative Medicine
Sheffield University
Consultant Anaesthetist and Intensivist,
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield, United Kingdom

Professor Charles Hinds
Professor of Intensive Care
Barts and the London Queen Mary School of Medicine
London, United Kingdom
Consultant Intensivist
St. Bartholomew's Hospital, London

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The nature of my project involved using two multi-centre databases: one, the GenOSept, resulting from a multi-national effort, which would have not been possible without the dedication and hard work of the numerous investigators across the countries involved, and the second, a multi-centre UK national database, deriving from the GAinS (Genomic Advances in Sepsis) study. A full list of Contributing Centres and Investigators is provided in the appendix, for both sudies. In particular, I would like to thank Professor Julian Bion, Dr Christopher Garrard, Dr Geraldine Clarke, Dr Anthony Gordon, Dr Andrew Walden, Ms Paula Hutton, Professor J-D Chiche, Professor Frank Stueber, Dr Paul Holloway, for having always dedicated time to answer queries, make suggestions, share views, support me in many ways. A special mention goes to Geraldine Clarke, for always sharing her statistical knowledge, supporting and guiding me in my analyses.

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Declaration

This thesis submitted to the University Of Sheffield for the higher degree of Doctor of Philosophy is based on original research on patients with faecal peritonitis admitted to Intensive Care Units (ICUs) across Europe, included in the ESICM (European Society of Intensive Care Medicine) and ECCRN (European Critical Care Research Network) GenOSept study (https://www.genosept.eu/) and in the UKCCG (United Kingdom Critical Care Genomics) group GAinS study (http://www.ukccg-gains.org). In particular, the analyses in the thesis have been conducted on the clinical data from the above mentioned databases, to examine short and long term outcomes of faecal peritonitis and the prognostic factors influencing outcomes in such patients. The planning and data collection for the GenOSept and GAinS studies predated my involvement in these studies. I used these databases to identify a homogeneous patient group, with which to plan and perform a set of studies on faecal peritonitis. I conceived the studies, obtained the necessary agreement of the chief investigators, organised and analysed the data, performed statistical analyses and developed the prognostic model described. I declare that all the research is my own except where additional contributions have been made as outlined in my Acknowledgements section.

Abstract

Faecal Peritonitis is a common cause of sepsis and admission to the Intensive Care Unit (ICU). The Genetics of Sepsis & Septic Shock in Europe (GenOSept) project and the GAinS (Genomic Advances in Sepsis) are genetic epidemiology studies set up to investigate the influence of genetic variation on the host response and outcomes. The studies included two large cohorts of post-operative critically ill patients with sepsis from faecal peritonitis admitted to European and UK ICUs, respectively.

In my thesis, I define the clinical characteristics, outcomes and risk factors for mortality in these patients, relying on the clinical data available from these large databases.

The GenOSept study provided data for 977 faecal peritonitis patients, recruited to 102 centres across 16 countries between 29/09/2005 and 5/01/2011. The median age was 69.2 years (IQR, Interquartile range 58.3-77.1). The most common causes of faecal peritonitis were perforated diverticular disease (32.1%) and surgical anastomotic breakdown (31.1%). The mortality rate at 28 days was 19.1% and 31.6% at six months.

The cause of faecal peritonitis, pre-existing co-morbidities and time from estimated onset of symptoms to surgery did not impact on survival. The strongest independent risk factors associated with an increased rate of death at 6 months included age, higher APACHE (Acute Physiology and Chronic Health Evaluation) II score, acute renal and cardiovascular dysfunction within one week of admission to ICU, hypothermia, lower haematocrit and bradycardia on day 1 of ICU stay.

When analysing trends in all variables available for the first week of ICU stay, the trends over the first 7 days ICU stay (primary analysis) retained in multivariate

analysis as independently associated with 6 months outcome were worsening thrombocytopaenia (mortality Hazard Ratio, HR=1.02, 95% CI 1.01-1.03, p<0.001) and renal function (total daily urine output HR=1.02, 95%CI 1.01-1.03, p<0.001; worsening renal SOFA - Sequential Organ Failure Assessment - sub-score HR=0.87, 95%CI 0.75-0.99, p=0.047), and worsening trends in the highest recorded level of bilirubin (HR=0.99, 95%CI 0.99-0.99, p=0.02) and GCS SOFA sub-score (HR=0.81, 95%CI 0.68-0.98, p=0.028). Changes in renal function (total daily urine output and renal component of the SOFA score), GCS component of the SOFA score, total SOFA and worsening thrombocytopaenia were also independently associated with secondary outcomes (ICU, hospital and 28 day mortality). Dynamic trends over the first 7 days ICU stay in all other measured laboratory and physiological variables and in radiological findings failed to be retained as independently associated with outcome on multivariate analyses. Furthermore, changes in respiratory support, renal replacement therapy and inotrope and/or vasopressor requirements were not independently associated with any of the primary or secondary outcomes.

A further set of analyses aimed to develop two prognostic models for the prediction of 28 day and long term (6 months) mortality, using non-parametric boot-strapping techniques of sampling from the UK portion of the GenOSept cohort, to derive a prognostic model. The non-UK portion of the GenOSept cohort, and the GAinS cohort were used for geographic and temporal external validation purposes of the prognostic model.

Five variables (age, SOFA score, lowest temperature, highest heart rate, haematocrit) were entered into the prognostic models. The discriminatory performance of the 6 month prognostic model yielded an AuROC (Area under the Receiver Operating Characteristic curve) 0.81 (95% Confidence Interval, CI, 0.76 -

0.86), 0.73 (95% CI 0.69 - 0.78), and 0.76 (95% CI 0.69-0.83) for the derivation, geographic and temporal external validation cohorts, respectively. The 28 day prognostic tool yielded an AuROC 0.82 (95% CI 0.77 - 0.88), 0.75 (95% CI 0.69 - 0.80) and 0.79 (95% CI 0.71-0.87) for the same cohorts. These AuROCs were consistently superior to those obtained with the SOFA and APACHE II scores. Hence, the two prognostic models developed for 6 month and 28 day mortality prediction in critically ill septic patients with FP, in the post-operative phase, enhanced the SOFA score's predictive utility by adding few key variables. External validation in larger cohorts of their predictive capability is needed, before introduction of the scores into clinical practice to inform decision making and the design of clinical studies.

Abbreviations

AKI: Acute Kidney Injury

ALI: Acute Lung Injury

APACHE II: Acute Physiology and Chronic Health Evaluation II

APS: Acute Physiology Score (of the APACHE II)

ARDS: Acute Respiratory Distress Syndrome

ARF: Acute Renal Failure

AuROC: Area under the Receiver Operating Characteristic curve

CI: Confidence Interval

CHF: Congestive Heart Failure

CNS: Central Nervous System

CVC: Central Venous Catheter

CVP: Central Venous Pressure

CVS: Cardio-Vascular System

DQ: Data Query

DVT: Deep Vein Thrombosis

ECCRN: European Critical Care Research Network

eCRF: electronic Case Record Form

ESICM: European Society of Intensive Care Medicine

FFP: Fresh Frozen Plasma

FiO_2: fractional inspired oxygen

FP: Faecal Peritonitis

GAinS: Genomic Advances in Sepsis

GCS: Glasgow Coma Score

GenOSept: Genetic Of Sepsis and Septic shock

Ht: Haematocrit

HR: Hazard Ratio

ICNARC: Intensive Care National Audit and Research Centre

ICU: Intensive Care Unit

IDDM: Insulin-Dependent Diabetes Mellitus

IQR: Inter-Quartile Range

LMWH: Low Molecular Weight Heparin

MAP: Mean Arterial Pressure

MODS: Multiple Organ Dysfunction Score

MPI: Mannheim Peritonitis Index

NMBA: Neuro-Muscular Blocking Agent

NYHA: New York Heart Association

PaO_2: arterial oxygen partial pressure

PEEP: Positive End-Expiratory Pressure

P/F ratio: PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen

PH: Proportional Hazards

PIA II: Peritonitis Index Altona II

POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

PPI: Proton Pump Inhibitor

QA: Quality Assurance

ROC: Receiver Operating Characteristic

RR: Respiratory Rate

RRT: Renal Replacement Therapy

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sepsis-related Organ Failure Assessment

WCC: White blood Cell Count

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Chapter 1 - Introduction

Sepsis is a clinical condition with high mortality. Faecal peritonitis is a common cause of admission to the Intensive Care Unit (ICU) with sepsis. Epidemiological data on the outcome and prognostic factors specifically related to patients admitted with faecal peritonitis to critical care are scarce in literature. The present chapter describes sepsis and septic shock, outlines the literature previously reported on secondary peritonitis in general, the limited literature specific to faecal peritonitis and outcomes of patients in the critical care setting, and provides the background on the currently used prognostic indices and tools available to help the clinician assess potential outcomes.

1.1 Sepsis and septic shock

1.1.1 Definitions of sepsis and septic shock

For the purpose of the studies presented in this thesis, I have relied on the definition of sepsis, severe sepsis and septic shock presented here.

1.1.1.1 Sepsis

Sepsis is defined as the presence of a confirmed (or suspected) infection plus a Systemic Inflammatory Response Syndrome (SIRS). SIRS is a physiological response to a triggering factor, not necessarily infective, which is characterized by at least two of the following features (Bone et al. 1992):

- Temperature >38^{o}C or <36^{o}C
- Heart Rate >90 beats/min
- Respiratory rate >20 breaths/min
- White blood Cells count (WCC):

- >12,000/mm^3 or
- <4,000/mm^3 or
- >10% immature neutrophils

1.1.1.2 Severe Sepsis

Severe Sepsis is defined as sepsis accompanied by organ dysfunction or tissue hypoperfusion (Bone et al. 1992; Bernard et al. 2001), as evidenced by cardiovascular instability (refractory hypotension), serum lactate level above the upper limit of normality, renal involvement (urine output of <0.5 ml/kg/hour for 2 hours despite adequate fluid resuscitation), respiratory failure, hepatic function derangement, coagulopathy, central nervous system hypoperfusion, or a combination of these factors (Levy et al. 2003; R Phillip Dellinger et al. 2013).

1.1.1.3 Septic Shock

Septic Shock is defined as sepsis induced hypotension despite adequate fluid resuscitation, with the presence of hypoperfusion abnormalities or organ dysfunction (Bone et al. 1992; R Phillip Dellinger et al. 2013). Sepsis induced tissue hypoperfusion is defined as the presence of hypotension caused by infection with elevated serum lactate and/or oliguria (R Phillip Dellinger et al. 2013).

1.1.1.4 Sepsis 3

Subsequent to the studies presented in this thesis, a task force with expertise in sepsis, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine to develop The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). The task force developed a new set of definitions of the sepsis and septic shock syndromes. These definitions were published in 2016, suggesting that "*sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%*". Furthermore, the new definitions suggest that "*septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone*" (Singer et al. 2016). The document highlights how septic shock patients can be identified by detecting a serum lactate level above 2 mmol/L, and the need to use vasopressors to maintain a mean arterial pressure equal or above 65 mmHg, in the absence of hypovolemia. Patients at risk of increased mortality are those who have two or more of the criteria included in the new quickSOFA (qSOFA) score:

- respiratory rate equal or above 22/min
- altered mentation
- systolic blood pressure equal or below 100 mmHg

The new set of definitions regards the term "severe sepsis" as redundant and does not rely on the use of the SIRS criteria (Singer et al. 2016).

1.1.1.5 The new sepsis criteria: controversies

The introduction of the new set of definitions (Sepsis 3) of the sepsis and septic shock syndromes has generated a vigorous debate in the scientific community about the appropriateness of the criteria used. The major criticisms surround the decreased sensitivity of the Sepsis 3 criteria, which abandon the use of SIRS, leading to the potential under detection of the condition. Such effect is an obviously undesirable feature for a screening tool and crucially, critics argue, likely detrimental to patient care (Simpson 2016). Others have argued that neither of definitions is perfect. The lethality of sepsis requires a highly sensitive screening tool, without necessarily loosing specificity. Furthermore, both definitions fail to adequately cater for those patients with an infection and high risk of mortality who do not meet SIRS criteria nor display features of organ failure at presentation (Bermejo-Martin et al. 2017).

1.1.2 Incidence

The incidence of severe sepsis has been estimated as being around 0.5 - 3 cases / 1000 population / year admitted to Intensive Care Units (ICUs) in both the US and the UK (Angus et al. 2001; Padkin et al. 2003; R Phillip Dellinger et al. 2013). The incidence of severe sepsis has been increasing, as a result of increased awareness and diagnosis, and an ageing population with increasingly complex comorbidities (Iwashyna et al. 2012; R Phillip Dellinger et al. 2013). A study conducted with the aim of establishing the incidence and mortality from severe sepsis in the United States over a period of 6 years (2004-2009) produced estimates relying on four different methodologies. The study highlighted significant differences in the estimates obtained, depending of the method adopted for the calculations, with the average annual incidence varying between 0.3 and 1.03 cases / 1000 population / year. Nevertheless, over the same period, an average annual increase in the incidence of severe sepsis was detected, whichever the method used. Furthermore hospital mortality varied between 14.7% and 29.9%, but decreased across the same period (Gaieski et al. 2013).

1.1.3 Causes

1.1.3.1 Site of infection

A large pan-European study documented the high frequency of sepsis in critically ill patients. The majority of cases are related to infections of the respiratory tract (40-70%), the genitourinary system (10%), the intra-abdominal viscera (10%) or bacteraemia of unspecified origin (10-20%) (Angus et al. 2001; Padkin et al. 2003; R Phillip Dellinger et al. 2013; Vincent et al. 2006). In a study by Mayr and colleagues, a gender related difference regarding the site of infections was highlighted, with the genitourinary site being almost twice as frequent in women compared to men. In both genders the respiratory site is the most common, followed by bacteraemias of unspecified origin, genitourinary, abdominal, indwelling device, wound and other soft tissues, central nervous system, endocarditis and other sites (Mayr et al. 2014).

1.1.3.2 Microbiological isolates

The frequency of isolates being Gram-positive organisms as a cause of sepsis has increased over time, becoming almost as common as Gram-negative infections, possibly as a result of increased proportion of healthcare associated infections and larger use of invasive procedures (Bone 1994). The use of broad-spectrum antimicrobials in the intensive care settings has been related to the development of antimicrobial resistance. The type of organism responsible for severe sepsis is a key prognostic variable. The European Prevalence of Infection in Intensive Care (EPIC II) study showed that isolates from septic patients were more likely to be Gram-negative organisms compared to Gram positive ones (62.2% vs. 46.8%), predominantly *Staphylococcus aureus* (20.5%), *Pseudomonas aeruginosa* (19.9%), Enterobacteriacae (primarily *Escherichia coli*, 16.0%), and fungal species (19%). The organisms associated with hospital mortality were *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp. (Vincent et al. 2009).

1.1.4 Management

The management of patients suffering from severe sepsis and septic shock is based on the principles described in the various versions of the Surviving Sepsis Campaign guidelines (Dellinger et al. 2008; R P Dellinger et al. 2013; Rhodes et al. 2017), summarised below.

Resuscitation and Early Goal Directed Therapy

A protocolised and target driven approach to resuscitation, integral to initial sepsis management, was described by Rivers and colleagues, who introduced the concept of Early Goal Directed Therapy (EGDT) and demonstrated improved outcomes with its utilisation. EGDT aims to adjust the cardiac preload, afterload, and contractility, by employing a combination of resuscitative measures, including intravenous fluids, vasopressors, inotropic support and red blood cells transfusions, to achieve central hemodynamic targets with the aim of improving the balance between delivery and demand of oxygen. According to the principles of EGDT, resuscitation should be initiated early and based on protocols targeting sepsis-related organ hypoperfusion (defined as documented persistent hypotension despite fluid challenge or a lactate concentration ≥ 4 mmol/L) with a set of specific goals within the first 6 hours, such as ensuring a central venous pressure of 8–12 mmHg, a mean arterial pressure ≥ 65 mmHg, a urine output ≥ 0.5 mL/kg/hr, a central venous haemoglobin oxygen saturation of 70% or a mixed venous oxygen saturation 65%. In their single centre randomised controlled trial Rivers and colleagues randomised 263 patients presenting to the emergency department with severe sepsis and septic shock, to receive EGDT or usual care. The intervention arm of the trial received

Early Goal Directed Therapy for six hours, prior to admission to the intensive care unit, versus standard therapy in the control arm. The study demonstrated a significant improvement in the achieved central venous oxygen saturation, lower lactate concentration, lower base deficit and higher pH in the intervention arm. Furthermore, the intervention arm showed an improvement in serial APACHE (Acute Physiology and Chronic Health Evaluation) II scores and significant improvement in hospital mortality, which was 30.5% in the Early Goal Directed Therapy arm, versus 46.5% in the control arm (Rivers et al. 2001). These findings have since been challenged by subsequent large scale randomised controlled trials (Yealy et al. 2014; Peake et al. 2014; Mouncey et al. 2015).

The ProCESS (Protocolised Care for Early Septic Shock) investigators performed a trial, which aimed at re-appraising EGDT and determining whether the components of the protocol described by Rivers and co-workers were all necessary. They randomised 1341 patients with septic shock from 31 emergency departments in the United States to one of three arms: protocol based EGDT, protocol based standard care and standard care. The protocol-based standard therapy differed from the EGDT in the fact that it did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions. The authors found no significant differences in 60 day, 90 day and 1 year mortality rates and need for organ support across all three study arms (Yealy et al. 2014).

The ARISE (Australasian Resuscitation in Sepsis Evaluation) trial was conducted at 51 emergency department (mainly in Australia and New Zealand). It randomly allocated 1600 patients with early septic shock to receive either Early Goal Directed Therapy or standard care. The ARISE trial failed to demonstrate any significant difference in all-cause mortality at 90 days, survival time, hospital

mortality, duration of organ support, or length of hospital stay. The patients enrolled in the intervention arm (EGDT) were, compared to the usual care arm, more likely to received higher volumes of resuscitative intravenous fluids in the first 6 hours, vaso-active and inotropic medications, and red blood cell transfusions, with differences which were highly statistically significant (Peake et al. 2014).

The PROMISE (Protocolised Management in Sepsis) trial investigators conducted a pragmatic randomized controlled trial in 56 hospitals in England, enrolling 1260 patients, who were allocated to receive either EGDT or standard care. Despite the higher intensity of treatments in the EGDT arm (increased use of intravenous fluids, vasoactive medications, and red blood cells utilisation), the patients in such arm had significantly worse organ failure scores, received cardiovascular support for longer periods of time and had longer stays in the intensive care unit, but did not obtain any survival advantages. Implementing the Early Goal Directed Therapy also meant increased costs (Mouncey et al. 2015).

A systematic review and meta-analysis of EGDT for septic shock performed by the ARISE, ProCESS and ProMISe investigators concluded that EGDT is as effective as usual care in the treatment of patients with septic shock, but means higher utilisation of critical care resources (Angus et al. 2015).

As a result of the above studies, EGDT is not currently recommended in its original form. The most recent iteration of the Surviving Sepsis Campaign (2016) guidelines recommends initial intravenous crystalloids resuscitation (at a dose of 30 ml/kg body weight over the first 3 hours), with additional fluids administration guided by regular reassessment of haemodynamic status, targeting a mean arterial pressure of 65 mmHg and aimed at normalising the serum lactate levels (Rhodes et al. 2017). The use of a target Central Venous Pressure (CVP) range is, therefore, no

longer recommended. More emphasis is now placed on the use of dynamic variables (passive leg raises, fluid challenges against stroke volume measurements, systolic or pulse pressure variations to changes in intra-thoracic pressure), over the static ones, and the increasing use of echocardiography (Rhodes et al. 2017).

Micorbiological diagnosis

In order to establish a microbiological diagnosis, cultures (as clinically indicated) are recommended prior to commencement of antimicrobial therapy, unless this causes excessive delays, in which case treatment should be started even before culturing. Imaging studies can be used to aid source identification. Routine microbiological cultures should always include at least two sets of blood cultures (aerobic and anaerobic) (Rhodes et al. 2017).

Antimicrobial therapy

The appropriate antimicrobial therapy should be administered intravenously within one hour of recognition of severe sepsis or septic shock, relying on a combination of one or more such medications in order to obtain a broad spectrum of activity towards all potential etiological agents (bacterial, fungal, viral), with adequate penetration and concentration in the affected tissues (Kumar et al. 2006; Puskarich et al. 2011). The empirical broad spectrum anti-infective treatment should not continue beyond 3-5 days and should be reassessed daily and de-escalated as soon as possible, based on microbiological results, biomarkers of infection, laboratory findings and, most importantly, the overall clinical picture. The duration of antimicrobial treatments is usually 7 to 10 days (R P Dellinger et al. 2013; Rhodes et al. 2017). Where the patient fails to adequately improve or in cases where source

control is not achievable, consideration should be given to prolongation of therapy; this is also appropriate for specific infections, such as those caused by fungal organisms, in cases of *Staphylococcus aureus* bacteraemia, or for immunocompromised / neutropaenic patients (R Phillip Dellinger et al. 2013; Rhodes et al. 2017).

Source control

Source Control should be achieved as soon as feasible, with early consideration of which possible areas are amenable to intervention. This should be performed in the least invasive way and without delay (R Phillip Dellinger et al. 2013; Rhodes et al. 2017), with the exception of the specific case of peri-pancreatic necrotic tissue infection, where it is preferable for treatment to be deferred until non-viable tissue can be clearly distinguished from the viable (Mier et al. 1997; van Santvoort et al. 2010).

Supportive therapy

Crystalloids are the first choice of fluids to initiate resuscitation (at a dose of 30 mL/kg), while hydroxyethyl starches should be avoided. Albumin can be used in cases requiring excessive crystalloids replacement. Fluid challenge is normally continued for as long as it produces hemodynamic improvement (Perner et al. 2012; Myburgh et al. 2012; Schortgen et al. 2001; Rhodes et al. 2017).

When using vasopressor therapy a target mean arterial pressure (MAP) of 65 mmHg should be aimed for, using noradrenaline (0.01 - 1 µg/kg/min) as first choice agent, with the possible addition of vasopressin (0.03 units/min; higher vasopressin doses are for salvage therapy only), or substitution with/addition of adrenaline (0.01 -

1 μg/kg/min). A higher target MAP (80-85 mmHg) may be of benefit for patients with chronic hypertension (Asfar et al. 2014). Dobutamine can be added as inotropic agent where indicated (myocardial dysfunction, low cardiac output states), in presence of optimised cardiac pre-load conditions and adequate vasopressor therapy administration. Hydrocortisone (200 mg/24 hrs) should be reserved for those cases where fluid resuscitation and vasopressor / inotropic agents fail to achieve haemodynamic stabilization, as recommended by the Surviving Sepsis guidelines (R Phillip Dellinger et al. 2013; Rhodes et al. 2017), although the evidence about its benefit is still limited (Patel & Balk 2012). A large randomised controlled trial (The ADRENAL study) is currently recruiting, with the aim of establishing whether low dose corticosteroids are of benefit as adjunctive treatment in critically ill patients with septic shock (Venkatesh et al. 2013).

A target haemoblobin of at least 7 g/dL should be aimed for unless there are conditions such as concurrent myocardial ischemia, severe hypoxemia, acute hemorrhage, ischemic heart disease, requiring higher haemoglobin levels (R Phillip Dellinger et al. 2013; Rhodes et al. 2017). Although anaemia may be associated with a poor outcome, data on the effects of blood transfusion is conflicting, with most reports not demonstrating benefit from transfusion aimed at achieving a higher haemoglobin threshold (Hébert et al. 1999; Holst et al. 2015).

Fresh frozen plasma (FFP) is not recommended to correct laboratory clotting abnormalities in case of non-bleeding patients. In patients with severe sepsis, platelets should be infused when counts are <10,000/mm^3 (10 x 10^9/L), even in absence of obvious bleeding. The threshold for platelets administration should be increased to 20,000/mm^3 (20 x 10^9/L) where significant risk of haemorrhage is present. Even higher platelet counts (≥50,000/mm^3 or 50 x 10^9/L) are recommended

in case of active bleeding, or when surgical or invasive interventions are planned (R Phillip Dellinger et al. 2013; Rhodes et al. 2017).

Invasive mechanical ventilation of sepsis-related acute respiratory distress syndrome (ARDS) should be based on a lung-protective strategy (Brower et al. 2000), using tidal volumes of 6 mL/kg of ideal body weight, plateau pressures ≤30 cm H_2O and application of positive end-expiratory pressure (PEEP). Higher levels of PEEP are applied to patients with sepsis-induced moderate or severe acute respiratory distress syndrome (ARDS), with prone positioning reserved for severe cases (Pao_2/Fio_2 ratio ≤100 mm Hg) (Ranieri et al. 2012; Brower et al. 2000; Brower et al. 2004; Rhodes et al. 2017).

Mechanical ventilation should be performed with head elevation (30-45 degrees), adequate sedation and analgesia, and titrated to pre-specified and personalised targets, avoiding excessive sedation. Protocol based daily interruptions of sedation can be performed in order to facilitate extubation, accompanied by the use of a weaning protocol (Kress et al. 2000; Girard et al. 2008; Mehta et al. 2012). Neuro-muscular blocking agents (NMBAs) can be used in ventilating patients with severe ARDS, as they have been demonstrated to improve survival and increase ventilator-free time without increasing muscle weakness (Papazian et al. 2010; Rhodes et al. 2017).

A fluid strategy aimed at maintaining an even fluid balance should be, ideally, relied upon in patients with sepsis-induced ARDS, in the absence of tissue hypoperfusion (Acheampong & Vincent 2015; Sirvent et al. 2015; Alsous et al. 2000; Rhodes et al. 2017).

When two consecutive blood glucose readings are above the threshold of 180 mg/dL (10 mmol/L), glycaemic control should be initiated based on protocols, aiming

to keep blood glucose levels below such limit. Blood glucose monitoring should be carried out one to two hourly until euglycaemia is reached and every four hours once this is achieved. Tight glycaemic control is no longer recommended (Van den Berghe et al. 2001; Van den Berghe et al. 2006; The NICE-SUGAR Study Investigators 2009; Rhodes et al. 2017).

Renal replacement therapies in the form of continuous and intermittent treatment are deemed equivalent in efficacy for managing septic patients with acute renal failure, with continuous strategies preferred in the hemodynamically unstable septic patients and for the purpose of fluid management (Ronco et al. 2015; Rhodes et al. 2017).

Stress ulcer prophylaxis should be provided in the form of proton pump inhibitors (PPIs) or anti-hystamines (H2 receptor blockers) according to the Survivng Sepsis guidance (Plummer et al. 2014; Rhodes et al. 2017).

Nutrition should be maintained preferably by oral means, or via the enteral route, at least in the first instance. If the oral/enteral routes fail to achieve adequate nutritional intake, parenteral nutrition should be instituted with specialist guidance, but usually not within the first 7 days of critical illness (Casaer et al. 2011; Mueller et al. 2011; Cove & Pinsky 2011; Rhodes et al. 2017).

1.1.5 Prognosis

Mortality from sepsis increases with worsening severity and an increasing number of organs affected: it rises from 25-30% for severe sepsis up to 40-70% for septic shock, reaching 90% with five organ system failure (Padkin et al. 2003; Lever & Mackenzie 2007).

1.1.6 Generic severity of disease classification and scoring systems for prognostic evaluation

Numerous severity of disease classification and scoring systems have been employed for the purposes of either predicting outcomes in patients suffering with sepsis or simply describing a sequence of organ/system deteriorations or improvements. Both disease-independent (generic) and disease-specific systems exist. The most commonly used generic scoring systems are:

- APACHE II (Acute Physiology and Chronic Health Evaluation II) score (Knaus et al. 1985)
- SOFA (Sepsis-related Organ Failure Assessment) score (Vincent et al. 1996)

Table 1 summarises the characteristics of these two generic scoring systems. Disease specific scoring systems have also been developed. Those relevant to peritonitis are described in a subsequent section.

1.1.6.1 APACHE II score

The APACHE II score was developed and validated by Knaus and co-workers in the 1980s (Knaus et al. 1985). The APACHE II score includes three components: the acute physiology score (APS), the age and the chronic health components. The acute physiological part of the score assigns points based on the values of 12 routine physiological measurements on admission to intensive care (temperature, mean arterial pressure [MAP], heart rate, respiratory rate [RR], oxygenation, arterial pH, serum sodium [Na], serum potassium [K], serum creatinine, haematocrit [Ht], white blood cell count [WCC] and Glasgow coma score [GCS]). The age component assigns points based on the patient's age, according to 5 pre-specified ranges, while the chronic health part of the score evaluates the previous health status and, in particular, the presence of severe pre-existing organ system failure, immuno-compromise and operative status (non-operative, elective or emergency). The sum of these three components (ranging from 0 to 71) can be interpreted as providing an overall measure of disease severity. The score was found to correlate closely with hospital mortality in 5815 intensive care patients from 13 hospitals. The APACHE II score, used together with an accurate description of disease, can stratify acutely ill patients based on prognosis (Knaus et al. 1985).

1.1.6.2 SOFA score

The SOFA score was devised by Vincent and co-workers, on behalf of the European Society of Intensive Care Medicine (ESICM) in 1994, with the aim of setting criteria for the definition of a scale indicating the level of organ dysfunction, over time, for the various organs/systems identified (Vincent et al. 1996). The score was developed with the major aims of, first, aiding the comprehension of the natural evolution of organ dysfunction, by quantifying the various organs' improving or deteriorating function with a numerical descriptor, second, describing the relationship between the various failing organs, and, third, evaluating the effects of therapeutic interventions, by assessing the impact on the relevant organs' function. The score assigns a value ranging from 0 to 4 for each of the six organ systems assessed (respiratory, coagulation, liver, cardiovascular, central nervous system [CNS] and renal) (Vincent et al. 1996). Although the score was originally devised for the purpose of tracking and describing changes in various organs' function/dysfunction over time, it is often also employed as a prognostic tool. Multiple studies have reported using the SOFA score, both in isolation (Hynninen et al. 2008; van Ruler et al. 2011; van Ruler, Lamme, et al. 2007; Sumi et al. 2014; Jones et al. 2009) and in combination with other parameters (Zügel et al. 2011; Matsumura et al. 2014), for outcome prediction.

Table 1 Characteristics of the APACHE II and SOFA generic scoring systems

Name	range	Factors evaluated
APACHE II (Knaus et al., 1985)	0-71	- Acute physiological derangement (12 variables) - Age - Chronic Health
SOFA (Vincent et al., 1996)	0-24	- respiratory system - coagulation - liver - cardiovascular system - CNS - renal system

1.2 Peritonitis

1.2.1 Definition of peritonitis

Peritonitis is a potentially lethal condition, characterised by inflammation of the serosal membrane lining the abdominal cavity and the intra-abdominal organs. It frequently occurs in association with infection within the intra-peritoneal cavity, usually accompanied by bacteraemia and sepsis or septic shock (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005).

1.2.2 Classification of peritonitis

Depending on the underlying physio-pathological mechanism, peritonitis may be infective (where the inflammatory reaction is induced by microbiological organisms) or sterile (where a microbiological cause has been excluded).

Peritonitis has been classified as primary, secondary and tertiary (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005).

Primary peritonitis is a peritoneal infection arising without any anatomical damage to the intra-abdominal organs, with invasion of the peritoneal cavity via a haematic, lymphatic or luminal route (as in the context of ascites with liver cirrhosis or peritoneal dialysis) (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005).

Secondary peritonitis develops as a consequence of bacterial or non bacterial contamination of the peritoneum as a result of leakage from an intra-abdominal viscus. Secondary bacterial peritonitis can result from anastomotic breakdown, abscess formation, perforation, ischaemia or necrosis, penetrating injury to the intra-

abdominal contents, or any other event causing loss of barrier function of the gastro-intestinal tract or any other intra-abdominal organ, with consequent bacterial spread from organs normally or pathologically colonised with bacteria or containing some other inflammatory substance, such as gastric acid.

Tertiary (or persisting) peritonitis has been defined as “peritonitis persisting or recurring after 48 hours following apparently successful management of primary or secondary bacterial peritonitis” (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005).

Depending on the site of leakage, the local inflammation can be mainly due to chemical irritation (for example in case of acidic gastric content with relatively low burden of organisms) or bacterial load (in case of faecal soiling) (Longo et al. 2011).

Faecal peritonitis is a specific type of secondary bacterial peritonitis related to spillage of faecal material into peritoneum. Almost inevitably the microbiology of secondary peritonitis is characterized by a multi-microbial flora, with predominant facultative Gram-negative bacilli and anaerobes, especially when the origin is colonic. The most common isolates are Gram negative Bacilli, such as *Escherichia coli*, other *Enterobacteriaceae*, and anaerobes, in particular *Bacterioides fragilis*. (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005). It also involves Gram-positive cocci such as enterococci and in the upper gastrointestinal tract can also involve viridans *Streptococci* (*Streptococcus mutans*, *milleri* group, *mitis*, *oralis*, *sanguinis*, *sobrinus*); it is important to mention the role of Candida spp., particularly in those patients recently treated with broad spectrum antimicrobials (Longo et al. 2011; Berger & Buttenschoen 1998; Calandra & Cohen 2005).

The normal colonic flora below the ligament of Treitz contains approximately 10^{11} anaerobic organisms per gram of faeces and 10^{8} aerobes per gram. Anaerobic species constitute the overwhelming majority of bacteria (Longo et al. 2011).

1.2.3 Pathophysiology of peritonitis

As inflammation develops, organisms contaminate the sterile peritoneal cavity. Intraperitoneal infections cause a severe systemic inflammatory response. Peritoneal defence mechanisms will aim at localising and isolating the infection and, where the untreated patient survives, the natural history usually involves evolution to a peritonitic phase of infection and abscess formation (Berger & Buttenschoen 1998; Calandra & Cohen 2005; Wittmann et al. 1996).

The initial phase of the inflammatory response is characterised by peritoneal macrophage activation, which respond and release pro-inflammatory cytokines. The inflammatory response is responsible for direct and indirect damage to tissues. Bacteria, viruses, and fungi have specific molecules on their external surfaces which are recognised by toll like receptors (TLRs) of immune cells. The lipopeptides of gram-positive bacteria and the lipopolysaccharide of gram-negative bacteria are capable of binding to TLR2 and TLR4, respectively. Activation of the TLR2 and TLR4 receptors is transduced at intracellular level with the activation of the cytosolic nuclear factor kB (NF-kB). The NF-kB factor binds to transcription initiation sites to increase intra-nuclear transcription of cytokines, such as Tumour Necrosis Factor α (TNF-α), Interleukin-1β (IL-1β), and interleukin-10 (IL-10). TNF-α and IL-1β (pro-inflammatory cytokines) trigger the adaptive immune response and add to the inflammatory injury. IL-10 has various anti-inflammatory effects, including the inactivation of macrophages. Endothelial cells, activated by the cytokines, are responsible for enhanced adhesion and recruitment of neutrophils, monocytes, macrophages, and platelets, with subsequent additional release of pro-inflammatory mediators (proteases, oxidants, prostaglandins, and leukotrienes), responsible for

direct damage to endothelial cells, increased permeability, vasodilation, and alteration of the coagulation balance (Russell 2006).

Macrophages and other leukocytes capable of phagocytosis are also responsible for removing dead host cells, via the process of efferocytosis. This is an important process of inflammation resolution (Martin et al. 2014).

1.2.4 The management of peritonitis

Management of secondary peritonitis requires a combination of surgical treatment (Wittmann et al. 1996), source control, medical and supportive therapy, with timely administration of empirical antimicrobial regimens (Wong et al. 2005; Solomkin et al. 2010).

A Cochrane review conducted by the Colorectal Cancer Group aimed at ascertaining the efficacy of different antimicrobial regimens in treating intra-abdominal infections in adults. The review included randomised and quasi-randomised controlled trials comparing different treatment regimens. Forty studies were included, with a total of 5094 adult patients, comparing 16 different regimens. All antimicrobials showed approximate equivalence in terms of clinical success and the mortality did not differ between different regimens. The review therefore made no specific recommendations for first line antimicrobial treatment in secondary peritonitis (Wong et al. 2005). The advantage of routinely adding antifungals remains unclear. Khoury and co-workers evaluated the effects of empirical anti-candida treatment in a retrospectively gathered cohort of patients with peritonitis caused by lower gastrointestinal tract perforation. The cohort included generalized faecal / purulent peritonitis patients. All patients had undergone exploratory laparotomy and had been subsequently admitted to intensive care (Khoury et al. 2010). Two patients'

groups were distinguished: those receiving an empirical course of fluconazole (n=24) and those who did not (n=77). All empirically treated patients and 40 of the 77 non fluconazole treated group required admission to intensive care unit and were included in the authors' study. Postoperative candida infection and mortality rates were similar between the two groups (*Candida* spp. infection 4% for the treated group versus 7% for the untreated group, and mortality 21% for the treated versus 22.5% for the untreated group, respectively, p value not significant). The authors concluded that empirical yeast treatment with fluconazole in patients with perforation peritonitis did not improve patients' outcome, although this was not a randomized controlled trial, and therefore the possibility of confounding and bias must be considered. The choice of antimicrobial therapy also needs to reflect local trends in development of antimicrobial resistance (Sartelli et al. 2011). Timely and judicious antimicrobial therapy is important, but ancillary and complementary to the surgical treatment of peritonitis, which is paramount to achieve infection source control and reduce bacterial and toxins load from the abdominal cavity (Marshall et al. 2004; Schein & Marshall 2004; Sartelli 2010).

The optimal surgical management strategy of severe secondary peritonitis has recently been the object of a randomised controlled trial. The RELAP trial randomised a total of 232 patients to "on-demand" (n=116) or "planned" (n=116) repeat laparotomy, showing no significant difference in the primary end point (death and/or peritonitis related morbidity within 12 months). In the case of planned repeat laparotomies, these were performed at regular intervals (1-2 days) after the initial laparotomy, until the abdomen was deemed macroscopically clean. In the on-demand repeat laparotomy group, the repeat laparotomy was performed in cases where patients were clinically deteriorating, after ruling out other possible (non-

abdominal) causes. Direct medical costs were reduced by 23% using the on-demand strategy (van Ruler, Mahler, et al. 2007).

1.2.5 Natural history and assessment of prognosis in peritonitis

The mortality rates of patients with secondary peritonitis reported in the literature vary widely between 5.8% and 63% (Berger & Buttenschoen 1998; Wittmann et al. 1996; Sartelli et al. 2011; Sartelli 2010; van Ruler, Mahler, et al. 2007). This large variability possibly reflects differences in the studied populations, the type and severity of disease and the treatment practices.

While there is a wealth of literature related to secondary peritonitis from multiple causes, studies specifically investigating faecal peritonitis tend to be less common. Nevertheless, despite the relative paucity of data, this specific sub-set of peritonitis patients is rather frequent. According to the Intensive Care National Audit and Research Centre (ICNARC) database (https://www.icnarc.org/) faecal peritonitis represents 2.8% of all ICU admissions in the UK.

1.3 Prognostic factors and scoring systems in peritonitis

In order to understand the evidence published so far on the topic of prognostic evaluation in faecal peritonitis, a literature search was conducted.

1.3.1 Strategy for reviewing the literature

Before commencing my project I performed a review of the literature to determine the extent of knowledge related to faecal peritonitis. Prior to commencing the search, I drafted a review protocol, to determine the databases to be searched, the search modality and keywords, inclusion criteria for the review, data extraction and aggregation methodology.

Eligibility criteria for inclusion in the review were:

- Studies involving adult patients specifically suffering with faecal peritonitis and admitted to ICUs
- Studies evaluating prognostic factors or indices in faecal peritonitis

The NHS Health Information Resources web interface was adopted (http://www.library.nhs.uk/booksandjournals/default.aspx), which allows simultaneous searching of all major scientific literature databases, including MEDLINE (1950 – present), EMBASE (1980 – present), CINAHL (1981 – present), and other resources.

The search was performed in January 2013 and aimed at identifying studies meeting all of the above eligibility criteria. The search strategy used the following

string: “((((faecal) OR fecal) AND peritonitis) AND (mortality OR death) AND (prognosis OR outcome)).ti,ab”.

There were neither temporal nor language restrictions. I did not include grey literature (academic literature that is not formally published, or not divulgated within the traditional commercial or academic distribution or publishing channels).

1.3.2 Review findings

A total of 102 records were identified through database searching. These included 44 duplicate results, which were removed. The remaining records were screened and assessed for eligibility. Of the non-duplicated 58 records, 18 pertained to studies performed on laboratory animals or experimental models. Of the remaining 40 conducted on humans, 22 were conducted on non-ICU patient outcomes or examined different patient populations altogether (such as those with any cause of secondary peritonitis, or selected patients with chronic ambulatory peritoneal dialysis, iatrogenic post-colonoscopy, cancer-associated, diverticulosis-related or post-radiation-damage perforations), 15 were related to the illustration and description of new surgical techniques or other aspects of surgical treatment (such as post-operative management and/or complication rates) rather than post-operative outcome of the critically ill with the condition, 4 were case reports or small case series, 4 specifically investigated the role of microbiological aetiology, patterns of antimicrobial resistance and antimicrobial regimens. Some of the studies had more than one characteristic that made them not useful for the purposes of evaluating prognostic factors in critically ill patients with faecal peritonitis in the post-operative phase.

Only two records were identified which reported outcomes of faecal peritonitis specifically in the ICU setting, and both were only reported in the form of conference abstracts (Pawa et al. 2009; Sayer et al. 2012). The characteristics of the two abstracts retrieved are summarized in Table 2. The difference in mortality rates reported in the two studies is marked. Sayer et al. reported in-hospital mortality rates of 21.6% and 38.1%, for the malignancy and non-malignancy sub-groups respectively, while Pawa et al. reported 30 days mortality rates of 46% for patients aged <75 years and 78% for patients aged > 75 years, suggesting that, despite the fact that both studies have been conducted in the ICU setting, other factors must have influenced outcomes, such as local practices of admission to ICU, periods considered, evolution in concurrent treatments and underlying characteristics of the populations (other than admission diagnosis). Neither of the two abstracts reported microbiological isolates. Pawa and co-workers report age as the strongest factor influencing outcome. The effect of potential confounding factors appears not to have been fully explored by the authors. The study from Sayer and colleagues suggests that hypo-albuminaemia and the presence of malignancy influence outcome. The authors of both studies were contacted for further information, but no additional data could be obtained.

Figure 1 details the review flow of information diagram, as per the PRISMA statement guidance (Moher et al. 2009). Altogether this emphasises the limited data available on this topic in the existing literature and highlights the need for investigating this condition further.

Figure 1 Flow of information diagram

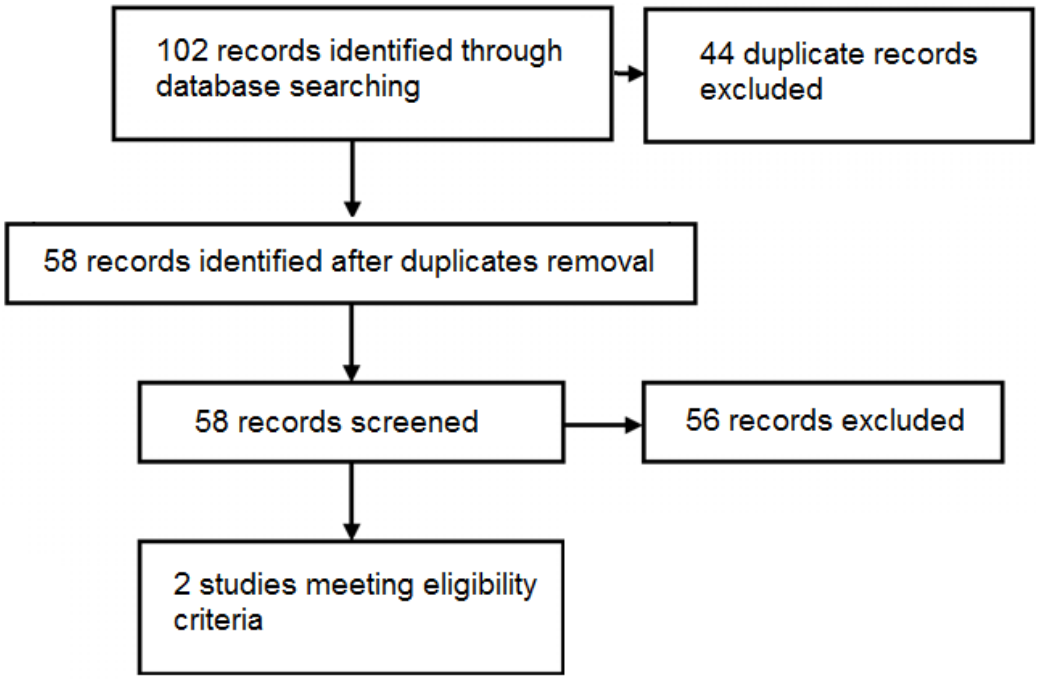


Table 2 Characteristics of previously reported prognostic studies specifically conducted on patients suffering with faecal peritonitis admitted to ICU

Author, Country, year of publication	Number of FP patients included	Study design and period	Reported overall mortality rates	Factors identified as influencing outcome	Microbiological data reported?
Pawa et al. UK, 2009 (Pawa et al., 2009)	360	single UK centre retrospective cohort (1990-2007)	46% (30 day mortality, age <75 years) 78% (30 day mortality, age >75 years)	age	No
Sayer et al. UK, 2012 (Sayer et al., 2012)	133	single UK centre retrospective cohort (2005-2012)	21.6% hospital mortality (malignancy group) 38.1% (non-malignancy)	malignancy (protective) hypo-albuminaemia	No

1.3.3 Prognostic evaluation in secondary peritonitis

Given the scarcity of data with which to inform prognostic evaluation specifically in faecal peritonitis patients, some inferences may be appropriate, based on evidence surrounding secondary peritonitis in general.

Prognostic evaluation of complex intra-abdominal infections, in general, is important to assess severity and predict outcome. A multiplicity of disease-specific and generic (disease-independent) scoring systems have been devised and tested, with the purpose of helping in the process of prognostication. I have described the APACHE II and the SOFA scores in one of the previous sections. These are disease independent scores, but surgical and peritonitis specific scores have been developed, such as the Mannheim Peritonitis Index (MPI) and the Peritonitis Index Altona II (PIA II) (Linder et al. 1987; Wittmann et al. 1987). I will now describe these disease-specific scoring systems.

The Mannheim Peritonitis Index (MPI)

The MPI was developed by Linder and colleagues in 1982-1984. It includes several factors to allow prognostic evaluation of abdominal sepsis: age (using a single cut-off of 50 years), female gender, organ failure (cardiovascular, respiratory, intestinal, renal), presence of malignancy, pre-operative duration of peritonitis (greater or less than 24 hours), non-colonic origin of sepsis, presence of diffuse generalized peritonitis and type of exudate (clear, cloudy/purulent or faecal) (Linder et al. 1987).

The performance of the MPI was evaluated by Billing and others for a set of different populations in a study including 2003 patients from seven European

centres. When using a threshold score of 26, the sensitivity was measured as 86% (range 54-98%), the specificity as 74% (range 58-97%) and the accuracy in predicting mortality as 83% (range 70-94%). For patients with MPI<21 the mortality rate was 2.3% (range 0-11%), for MPI in the range 21-29 mortality rose to 22.5% (range 10.6-50%), while the mortality was 59.1% (range 41-87%) for MPI>29 (Billing et al. 1994).

The Peritonitis Index Altona II

The Peritonitis Index Altona II (PIA II) was developed by Wittmann and colleagues and published in 1987. A cohort of 567 patients who had undergone surgical intervention for infections of intra-abdominal origin was used to identify variables which could discriminate between survivors and non-survivors. The authors relied on discriminant analysis to rank the variables in order of usefulness in classifying patients as likely survivors versus non survivors. The variables selected for this purpose were: male sex, age (with a 60 years cut-off), duration of infection longer than 48 hours, congestive heart failure (CHF), insulin-dependent diabetes mellitus (IDDM), white cell count (WCC) <5 or WCC >26 $\times 10^9$/litre, creatinine, extent and cause of peritonitis (mesenteric infarction, intestinal strangulation, perforated peptic ulcer, perforated appendix, perforated colon). The PIA II was found to correctly classify 89% of all patients in the derivation cohort, and 81.4% of the validation group (Wittmann et al. 1987).

Multiple factors, including age, markers of nutritional state, comorbidities, coexistence of sepsis, extent of organ failures, time from onset of faecal peritonitis to surgical intervention and source control, have been reported in other studies to influence outcome (Christou et al. 1993; Ohmann et al. 1993; Demmel et al. 1994; Billing et al. 1994; McLauchlan et al. 1995; Pacelli et al. 1996; Koperna & Schulz 2000; Koperna et al. 2001; Mulier et al. 2003; Scapellato et al. 2004; Notash et al. 2005; Horiuchi et al. 2007; Torer et al. 2010; Singh et al. 2011).

The characteristics of some of the studies examining factors influencing outcome in peritonitis are summarised in Table 3. It must be emphasised that studies included in this Table report mortality rates regarding heterogeneous populations and measured at different time points; the Table specifies the proportion of patients with peritonitis of colo-rectal origin. It is noteworthy that many studies did not report microbiological isolates and that, for the ones where microbiological isolates were described, no relation was reported between type of microbial isolate and outcome.

Table 3 Characteristics of previous prognostic studies of patients with peritonitis

Author, Country, year of publication	Number and characteristics of patients included	Number (%) in colo-rectal origin subset	Study design and aims	Reported mortality rates	Factors identified as influencing outcome	Microbiological data reported
Christou et al. Canada, 1993 (Christou et al., 1993)	239 Surgical abdominal infection with APACHE II>10	35 (14.6%)	multi-centre, non-randomized, un-blinded trial, aimed at comparing two surgical techniques	31% (peri-operative – closed arm) 44% (peri -operative- open arm) 42% (re-operation group) 27% (non-reoperation group)	APACHE II low albumin NYHA	Yes (no influence on outcome reported)
Ohmann et al. Germany, 1993 (Ohmann et al., 1993)	271 Laparotomy confirmed peritonitis	49 (18.1%)	prospective, multicentre cohort, to evaluate three scoring systems (APACHE II, MPI, PIA II)	37.6% (at 30 days, of which 21% post-operative 79% due to infection) 22% (at 30 days – large bowels perforation subset)	APACHE II MPI PIA II	No
Demmel et al. Germany, 1994 (Demmel et al., 1994)	438 Intra-abdominal infection (multiple causes)	55 (12.6%)	prospective, single centre cohort to validate MPI	14.4% (peri-operative)	pre-operative shock MPI concomitant disease sepsis	No
Billing et al. Germany 1994 (Billing et al., 1994)	2003 Peritonitis (multiple causes)	not reported	prospective, multicentre cohort to evaluate MPI	19.5% (peri-operative)	MPI	No
McLauchlan et al. UK, 1995 (McLauchlan et al., 1995)	125 Abdominal sepsis admitted to ICU	37 (29.6%)	retrospective, single centre cohort to assess factors associated with outcome	63% (Hospital)	age APACHE II Acute Physiology of APACHE II female sex source control	No
Pacelli et al. Italy, 1996 (Pacelli et al., 1996)	604 Intra-abdominal infections (multiple causes)	42 (7%)	retrospective, single centre, case series to identify outcome predictors and compare three scoring systems	13.9% (peri-operative, overall) 26.2% (peri-operative, large bowel origin subgroup)	APACHE II MPI low albumin low cholesterol pre-operative organ impairment	Yes (no influence on outcome reported)
Koperna et al. Austria, 2000 (Koperna and Schulz, 2000)	523 secondary peritonitis	not reported	retrospective single centre, case-control study to compare planned (PR) versus on demand (OR) repeat laparotomy	54.5% (peri-operative – PR group) 50.6% (peri-operative - OR group)	age low albumin APACHE II Goris MOF delayed repeat laparotomy	No
Koperna et al. Austria, 2001 (Koperna et al., 2001)	85 emergency surgical ICU admissions with APACHE II>10	not reported	prospective, single centre cohort to evaluate reliability of APACHE II score	31.7% (ICU)	APACHE II	No
Mulier et al. Belgium, 2003 (Mulier et al., 2003)	96 Generalized postoperative peritonitis admitted to ICU	43 (44.8%)	retrospective, single centre audit to identify outcome predictors	25% (ICU) 30.2% (Hospital)	source control age unconsciousness	No
Scapellato et al. Italy, 2004	255 Secondary acute	32 (12.5%)	retrospective, single centre case series to identify outcome	5.8% (peri-operative)	MPI time to operation	No

(Scapellato et al., 2004)	peritonitis		predictors			
Notash et al. Iran, 2005 (Notash et al., 2005)	80 secondary peritonitis	20 (25%)	prospective, single centre cohort to evaluiate MPI and Goris MOF	17.5% (hospital)	MPI Goris MOF	No
Horiuchi et al. China, 2007 (Horiuchi et al., 2007)	26 colonic perforation	26 (100%)	retrospective, single centre case series, to evaluate three scoring systems (APACHE II, MPI, PIA II)	23.1% (peri-operative)	APACHE II hypotension raised creatinine	No
Torer et al. Turkey, 2010 (Torer et al., 2010)	56 re-operation (post-operative peritonitis)	27 (48.2%)	retrospective, single centre case series to identify outcome predictors	32.1% (peri-operative)	Goris MOF time to reoperation severity of peritonitis source control MPI	No
Singh et al. India, 2011 (Singh et al., 2011)	84 emergency perforation peritonitis	0 (0%)	prospective, single centre cohort to identify outcome predictors	17.8% (peri-operative)	age MPI duration of symptoms pre-operative glycaemia urea creatinine	No
van Ruler et al. The Netherlands 2011 (van Ruler et al., 2007, van Ruler et al., 2011)	221 (of 232 from RCT) secondary peritonitis with APACHE II > 10	147 (71.3%)	Subset from a randomized, non-blinded multicentre trial to evaluate the predictive value of multiple scoring systems	28.6% (12 months- OR arm) 36.3% (12 months- PR arm)	APACHE II SAPS II MPI MODS SOFA APS	No

FP = faecal peritonitis, NYHA = New York Heart Association class, APACHE II = Acute Physiology and Chronic Health Evaluation II score, APS = acute part of APACHE II score, MPI = Mannheim Peritonitis Index, PIA II = Peritonitis Index Altona II, Goris MOF = Goris Multiple Organ Failure score, MODS = Multiple Organ Dysfunction Score, RCT = Randomized Controlled Trial, ICU = Intensive Care Unit, PR = planned repeat laparotomy, OR = on demand repeat laparotomy

Christou et al. performed a non-blinded, non-randomised trial of 239 patients treated with two different surgical techniques, in which the abdomen could not be closed at the first operation in a small proportion of the patients (the “open abdomen” group). The authors stated that there was no statistically significant difference between the two techniques, reporting mortality rates of 31% and 44% for patients treated with a "closed-abdomen" and those treated with variations of the "open-abdomen" technique, respectively. Variables assessed by the authors as potential predictors of mortality were the type of surgical technique used (open versus closed) and other operative factors, origin of peritoneal contamination, previous medical treatments (radiotherapy, steroids, chemotherapy), presence of malignancy, comorbidities (renal failure, diabetes, smoking history) and pre-operative haematological and biochemical variables including haematocrit and bilirubin. After inclusion in multivariate analysis models, to account for confounding factors, this study found no influence of age or site of origin of peritoneal contamination on mortality; only the APACHE II score, serum albumin level, and New York Heart Association (NYHA) cardiac function status were significantly and independently associated with mortality. These findings appear to contradict the authors’ beliefs that the site of peritoneal contamination is a factor influencing mortality, as they use this argument to justify extreme variability of mortality rates amongst previously reported studies. Only 35 (14.6%) of the patients in the trial had suffered peritonitis as a consequence of disease of colorectal origin, hence its findings may not be applicable to the faecal peritonitis population (Christou et al. 1993).

Ohmann et al. performed a prospective multicentre study involving 271 patients from 12 surgical departments in Europe. The patients had peritonitis confirmed at laparotomy and the study aimed to identify factors predictive of mortality

within 30 days of operation, relying on each of three scores: APACHE II, MPI and PIA II. The assessment involved performing ROC curve analysis, as well as evaluating sharpness (degree of confidence associated with each prediction) and reliability (agreement between observed and predicted mortality). Thirty day mortality was 37.6% for the whole cohort, and 22% for the large bowel perforation subset. APACHE II was found to be superior to both MPI and PIA II in terms of discriminatory ability (ROC curve analysis) and reliability, but the other two scores were better at making "sharp" predictions. The authors concluded that none of the three scores can be relied upon to make outcome predictions for individual patients. The report specifies that 49 (18.1%) of the patients in the study had peritonitis of large bowel or rectal origin, which makes it difficult to generalize their findings and conclusions to the faecal peritonitis population (Ohmann et al. 1993).

Demmel et al. conducted a prospective, single centre cohort study of 438 patients with abdominal infection. The study aimed to evaluate the prognostic value of single clinical variables and the MPI. The large majority (300) of the patients enrolled were managed with a “closed” approach, by percutaneous drainage, while 138 underwent planned repeat laparotomies. The mortality was 14.4% (63 patients). On stepwise logistic regression analysis pre-operative shock, MPI, concomitant disease and sepsis were all independent predictors of outcome. Only 55 (12.6%) of the patients in the study could be classified as having peritonitis of colo-rectal origin (Demmel et al. 1994).

The largest study on prognostic evaluation of secondary peritonitis was conducted by Billing et al., who evaluated the sensitivity, specificity and accuracy of the MPI in 2003 patients from seven separate surgical centres in three European countries. The study included a wide variety of patients and reported a relatively low

mortality rate (19.5%), suggesting that the population considered was, overall, of lower prognostic risk compared to other studies. This study was specifically designed to evaluate the MPI prognostication capacity, and it is unclear what percentage of the patients included suffered from peritonitis of colo-rectal origin (Billing et al., 1994).

McLauchlan et al. studied 125 patients with abdominal sepsis admitted to critical care, evaluating the influence of age, diagnosis, APACHE II score and its subcomponents (the Acute Physiology component and the Chronic Health Evaluation components), coexisting diseases, time to operation, to ICU admission, length of stay in ICU, ward and hospital, site and type of sepsis source, presence of septic shock and success in clearance of the focus of infection. At multiple linear regression analysis age, APACHE II score and its Acute Physiology component, clearance of infection and gender were all significantly and independently associated with outcome, while delay to surgery, anastomotic leakage and presence of malignancy did not influence survival significantly. The hospital mortality rate was 63%, suggesting a rather unwell patient sample. In the subset of patients with colonic origin of sepsis (37, 29.6%), those with faecal peritonitis tended to have a worse outcome than those with non-faecal peritonitis (McLauchlan et al., 1995).

Pacelli et al. studied 604 consecutive patients who underwent emergency operations for intra-abdominal infections, including postoperative cases. They assessed the influence of age, sex, type (spontaneous versus postoperative) and extent of infection (localized versus diffuse), preoperative haematological and biochemical markers (albumin, cholesterol, haemoglobin, lymphocyte count) intra-operative factors, pre-operative organ impairment, APACHE II score, the sepsis score of Elebute and Stoner, and the MPI. The authors found that by multivariate

logistic regression analysis APACHE II, MPI, hypoalbuminaemia, hypocholesterolaemia and preoperative organ impairment were independent predictors of mortality. Only 42 (7%) of the patients in the study had peritonitis of colo-rectal origin; their peri-operative mortality was 26.2%, much worse than for the overall cohort (13.9%). The authors also reported microbiological isolates, but a link was not established with outcome (Pacelli et al., 1996).

Koperna et al retrospectively reviewed 523 consecutive patients with secondary peritonitis, specifically focussing on 105 patients, in whom standard surgical treatment of secondary peritonitis failed and who had to undergo repeat laparotomy for persisting abdominal sepsis. Patients with age above 70 years, with diffuse secondary peritonitis, with a greater degree of physiologic compromise (hypo-albuminaemia, preoperative APACHE II scores above 20, and organ failure) were shown to be at higher risk of persistent intra-abdominal infection. The peri-operative mortality was 54.5% for the planned repeat laparotomy subset and 50.6% for the on demand repeat laparotomy group. Timely decisions about repeat laparotomy provided the only surgical option able to significantly improve outcome in this subset of patients. The number of patients with peritonitis of colo-rectal origin was not reported (Koperna & Schulz 2000).

The same authors studied 85 emergency surgical critically ill patients, to evaluate the reliability of APACHE II. There was a significant increase in the APACHE II score after surgical intervention, as compared to prior to surgery. The ICU mortality was 31.7%. After the initial post-operative increase in the score, a continuous decrease in APACHE II in long-term patients from day 7 onwards appeared associated with a favourable outcome, while an increase in the APACHE II score strongly predicted mortality, although in the individual patient these trends

appeared of doubtful clinical significance. It is not clear what proportion of patients had peritonitis of colo-rectal origin (Koperna et al., 2001).

Mulier et al. reported on a retrospective audit on 96 patients with generalised postoperative peritonitis (involving the four abdominal quadrants and occurring in the first month after an abdominal operation). The authors specifically aimed to assess prognostic factors. They evaluated over thirty variables potentially able to predict outcome (including age, sex, components of the APACHE II score, a large number of surgical and operative factors, source of contamination and therapeutic delay). The authors found that age, source control and unconsciousness predicted mortality, which was 25% and 30.2%, for ICU and hospital respectively. Forty-three (44.8%) of the patients had colorectal origin faecal peritonitis (Mulier et al., 2003).

Scapellato et al. reviewed the cases of 255 patients with secondary peritonitis (only 32 patients, 12.5% of the total, had peritonitis of colo-rectal origin). The reported mortality rate was of 5.8%. The authors assessed as potential prognostic factors variables such as the aetiology of secondary peritonitis, age, gender, organ failures and presence of malignancy, concluding that time to intervention appeared the main determinant of outcome in their case series (Scapellato et al., 2004).

Notash et al. studied 80 patients with secondary peritonitis, of which 20 (25%) were of colo-rectal origin. They reported the MPI and the Goris Multiple Organ Failure score as helpful predictors of mortality. The hospital mortality was 17.5% (Notash et al. 2005).

Horiuchi et al. reported a small study of 26 patients, with a peri-operative mortality of 23.1%. The study focussed solely on peritonitis from colonic perforation, and suggested that the APACHE II score was a better predictor of outcome than MPI and PIA II (Horiuchi et al. 2007).

Torer et al. reported a relatively small series of 56 patients who underwent re-operation for postoperative secondary peritonitis (27 patients, 48.2%, had colo-rectal origin of peritonitis). Amongst the factors assessed, the demographic features, comorbidities, presence of malignancy, organ failures, the type and timing of the primary operation, intra-operative findings, aetiology of postoperative peritonitis, number of repeat laparotomies, source control, MPI, time between first operation and repeat laparotomy, and between symptom onset and the second operation were evaluated as potential explanatory variables. The overall peri-operative mortality was 32.1%. In this study, time to surgery and presence of organ failure were found to be the main determinants of outcome (Torer et al., 2010).

A recent study by Singh et al. conducted on a heterogeneous population of 84 patients with emergency perforation peritonitis, identified age, MPI, duration of symptoms, pre-operative glycaemia and markers of renal function (urea and creatinine) as useful predictors of outcome, although it did not include any cases of peritonitis secondary to contamination from a colorectal source. In this study the peri-operative mortality was 17.8% (Singh et al., 2011).

Van Ruler et al. utilized data from 221 patients, originally included in a randomized trial comparing two surgical strategies (van Ruler, Mahler, et al. 2007), for a second study to evaluate the APACHE II, SAPS II, MPI, MODS, SOFA and APS scores (van Ruler et al. 2011). One hundred and forty-seven (71.3%) of the patients had peritonitis of colo-rectal origin. Mortality at 12 month follow-up was 28.6% in the on-demand repeat laparotomy arm, and 36.3% in the planned repeat laparotomy one. While all scores performed satisfactorily in predicting mortality, they all failed to identify patients with ongoing infection needing repeat laparotomy (van Ruler, Mahler, et al. 2007; van Ruler et al. 2011).

1.3.4 Limitations of current evidence

1.3.4.1 Risk of bias in retrospective epidemiological studies

The retrospective nature of many of the studies described above (McLauchlan et al., 1995, Pacelli et al., 1996, Koperna and Schulz, 2000, Mulier et al., 2003, Scapellato et al., 2004, Horiuchi et al., 2007, Torer et al., 2010) lends itself to the risk of selection and information bias. Selection bias can occur when the patients included in one study group present different baseline characteristics compared to those in the other group: if these characteristics are related to the exposure and/or to the outcome being considered the groups may not be comparable. An example of this is the study by Khoury and colleagues, retrospectively comparing two non-randomised samples of patients receiving different treatments (Khoury et al., 2010). In this study it is possible (in fact, likely) that patients treated more aggressively with empirical anti-candida treatment may have been, at baseline, at higher mortality risk than the ones who did not undergo such treatment. Information bias can occur in retrospective epidemiological studies where either the exposure or outcome has been measured inaccurately "*a posteriori*", with the potential of altering any association observed between them.

1.3.4.2 Risk of false positive findings

Many of the studies reported in literature did not perform any corrections for multiplicity of testing, which increases the likelihood of chance findings. The more tests are performed, the higher the experiment-wise error rate (the chance of a false positive finding increases with the number of tests).

1.3.4.3 Limited statistical power

Some of the study populations appear to be too small to afford adequate power to detect statistically significant effects on mortality, even where differences in mortality were reported (Koperna et al., 2001, Mulier et al., 2003, Notash et al., 2005, Horiuchi et al., 2007, Singh et al., 2011, Torer et al., 2010).

1.3.4.4 Heterogeneity of populations examined

Virtually all of the studies described evaluated very heterogeneous populations, instead of focussing on specific aetio-pathological entities, such as faecal peritonitis (Christou et al., 1993, Ohmann et al., 1993, Demmel et al., 1994, Billing et al., 1994, McLauchlan et al., 1995, Pacelli et al., 1996, Koperna and Schulz, 2000, Koperna et al., 2001, Mulier et al., 2003, Scapellato et al., 2004, Notash et al., 2005, Torer et al., 2010, Singh et al., 2011, van Ruler et al., 2011).

1.3.4.5 Limitations of the most commonly used scoring system

The value of the APACHE II score, which has been the most widely utilised prognostic tool and has been found to strongly correlate with outcome in peritonitis, has been criticised as being unable to take into account factors related to surgical intervention, which in turn can potentially alter many physiological parameters. It has also been found to over-estimate or under-estimate mortality in low and high risk populations (Jones & de Cossart 1999; Moreno & Morais 1997; Fraccalvieri & Biondo 2009). APACHE II, like any scoring system, cannot be relied upon for the purposes of making prognostic assumptions on an individual patient (Berger & Buttenschoen 1998; Koperna et al. 2001; Jones & de Cossart 1999), while longitudinal use of APACHE II to detect trends in the ICU has been found to be of no

value, since laboratory and physiological parameters can be kept stable or corrected in the intensive care setting by providing support to the failing organs and therefore addressing physiological and metabolic derangement (Koperna & Schulz 1996).

1.4 Conclusions

The review of the literature presented in this chapter outlines the evidence surrounding secondary peritonitis in general and the scarce epidemiological evidence specifically pertaining to the natural history and outcome of patients with faecal peritonitis admitted to the critical care setting.

1.5 Rationale and opportunity for a new study

The GenOSept (Genetics Of Sepsis and Septic Shock in Europe, https://www.genosept.eu/) study is a pan-European study conceived by the European Critical Care Research Network (ECCRN) of the European Society of Intensive Care Medicine (ESICM). This study aims to investigate the influence of genetics on the host response and outcome in patients with sepsis. The study has recorded comprehensive clinical phenotypic data and collected DNA from patients admitted to ICU with sepsis due to faecal peritonitis. The quality assured phenotypic database includes a wide range of clinical, physiological and laboratory information, as well as outcome data up to six months following ICU admission. Although specifically designed for the purposes of genetic epidemiology studies, to date, as far as the author is aware, the Genosept study cohort represents the largest and diagnostically most homogeneous collection of clinical data regarding intensive care patients specifically suffering with faecal peritonitis.

GAinS (Genomic Advances in Sepsis) is a multi-centre UK-wide study supported by the UKCCG (UK Critical Care Genomics Group), a network of centres undertaking clinical functional genomics research in the critical care setting (http://www.ukccg-gains.org).

Patients included in the GenOSept FP cohort were recruited from 102 centres across 16 European countries and those in the GAinS FP cohort were recruited from 51 UK centres between September 2005 and March 2015.

Analysis of these two large, quality controlled, databases constitutes a unique opportunity to gain insights into important epidemiological characteristics of patients with faecal peritonitis admitted to ICUs across Europe, including factors such as comorbidities, short and long term outcomes and factors influencing prognosis in this

particular subset of patients, where evidence is currently lacking. As these diagnostically homogeneous cohorts include data from FP patients with various degrees of illness severity, including potential risk modifiers and confounding factors (such as comorbidities, indices of acute physiological derangement, organ support, radiological and laboratory findings, origin of faecal peritonitis), they also provide high quality data well suited to the development and testing of a prognostic model specific to this post-operative patient population.

1.6 Hypothesis and Aims

My hypothesis is that there are specific clinical features of sepsis induced by faecal peritonitis (independent of operative / surgical variables and findings), which are predictive of mortality. These aspects can be elicited, in the post-operative phase, on admission to the critical care setting, and described as absolute values, or identified as trends in specific clinical parameters over time.

The thesis aims are to:

- use the information derived from reviewing the existing literature on secondary peritonitis to identify the evidence relevant to patients with faecal peritonitis
- define the methods used to analyse the largest international, and most diagnostically homogeneous, prospectively collected cohort of faecal peritonitis patients (GenOSept)
- describe the epidemiological characteristics of the GenOSept faecal peritonitis cohort
- define the predictors of outcome for the GenOSept faecal peritonitis cohort, based on four time-points: ICU, hospital, 28 day and 6 month mortality
- describe trends in physiological variables in the GenOSept faecal peritonitis cohort and their relationships with outcome
- develop and validate a prognostic modelling tool able to stratify post-surgical critically ill patients with FP, independently from intra-operative surgical findings, using prospectively collected data from both both the GenOSept and GAinS cohort studies

- explore the possibility that the prognostic parameters and trends identified may aid decision making regarding therapeutic support, care escalation and support prognostication

This thesis is focused solely on the clinical aspects characterising the faecal peritonitis cohorts of the GenOSept and GAinS studies, making no attempt to explore the genetic variations underlying the individuals in these cohorts and their relationship to outcome from sepsis (these aspects are dealt with separately within other studies). The enrolment procedures for the two studies were separate and mutually exclusive, as they happened in different time periods. It was not possible to be recruited to both cohorts.

Chapter 2 - Methods

2.1 Ethics, recruitment and data collection

2.1.1 Ethics and consent

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Ethics approval was granted either nationally or locally (for individual centres), or both. Written, informed consent for inclusion in the GenOSept study was obtained from all patients or a legal representative. A list of all ethical bodies that approved the study is included in the appendix.

2.1.2 Recruitment

Patients included in the GenOSept FP cohort were recruited from 102 centres across 16 European countries and those in the GAinS FP cohort were recruited from 51 UK centres between September 2005 and March 2015 (see table 4). A full list of recruiting centres for both studies is provided in the appendix.

The diagnosis of sepsis was based on the International Consensus Criteria of the European Society of Intensive Care Medicine and the American College of Physicians, which define sepsis as “the clinical syndrome defined by the presence of both infection and a systemic inflammatory response” (Levy et al. 2003).

Follow up was for up to 6 months from enrolment, or until death.

The same inclusion and exclusion criteria were used for both cohorts.

Table 4 Datasets used

Study	GenOSept	GenOSept	GAinS
Cohort utilisation (Epidemiological analyses)	Used	Used	Not used
Cohort utilisation (Trends analyses)	Used	Used	Not used
Cohort utilisation (Scoring systems)	Derivation	Geographic validation	Temporal validation
Country	UK	non-UK	UK
Recruitment period	2005-2011	2005-2011	2011-2015
Total number of patients	462	515	323
Results described in Chapter	3, 4, 5	3, 4, 5	5

2.1.3 Inclusion criteria

Inclusion criteria were: adult patients (being aged 18 years or older), admission to a High Dependency Unit (HDU) or Intensive Care Unit (ICU) with faecal peritonitis. Faecal peritonitis was defined as visible inflammation of the serosal membrane that lines the abdominal cavity, secondary to contamination by faeces, as diagnosed by the operating surgeon at laparotomy.

2.1.4 Exclusion criteria

Exclusion criteria were: peritonitis due to gastric or upper GI-tract perforation (e.g. gastric or duodenal ulcer perforation, terminal ileum perforation), patient or legal representative unwilling or unable to give consent; patient pregnant; advanced directive to withhold or withdraw life sustaining treatment or admitted for palliative care only; patient already enrolled in an interventional research study of a novel/unlicensed therapy (patients enrolled in interventional studies examining the clinical application or therapeutic effects of widely accepted, “standard” treatments, were not excluded); patient immuno-compromised (known regular systemic corticosteroid therapy, exceeding 7mg/kg/day of hydrocortisone or equivalent, within three months of admission and prior to acute episode, known regular therapy with other immunosuppressive agents, e.g. azathioprine, known to be HIV positive or have acquired immunodeficiency syndrome as defined by the Centre for Disease Control, neutrophil count less than 1000 mm^{-3} due to any cause, including metastatic disease and haematological malignancies or chemotherapy, but excluding severe sepsis; organ or bone marrow transplant recipients receiving immuno-suppressive therapy).

2.1.5 Database, case report form and quality assurance

The case report form (CRF) for the GenOSept study was developed and tested by Professor Charles Hinds (Barts and The London Queen Mary School of Medicine, London, UK), Dr Christopher Garrard (John Radcliffe Hospital, Oxford, UK), Dr Anthony Gordon (Imperial College, London, UK), Prof Jean-Daniel Chiche (Hospital Cochin, Paris, France) and Dr J. Millo (John Radcliffe Hospital, Oxford, UK) together with other members of the GenOSept Consortium. A specific eCRF (electronic Case Report Form) was developed by Lincoln, Paris, France, using software developed in collaboration with Prof Jean-Daniel Chiche. The database was password protected, allowing investigators to enter data on the eCRF online, and included audit trail capability for data entry and subsequent modifications. The eCRF is accessible online at www.genosept.eu.

To minimize errors, logical range checks were in place so that the investigators would be alerted if an attempt was made to enter data values outside the expected ranges.

Quality Assurance (QA) was performed by Paul Holloway (Imperial College, London, UK), Dr Christopher Garrard, Dr Andrew Walden (Royal Berkshire Hospital, Reading, UK), Dr Anthony Gordon and Professor Charles Hinds, who systematically reviewed all data. Data queries (DQs) were generated within the eCRF for missing or erroneous data, and sent electronically to the relevant investigators for action, where necessary. Up to the end of January 2011 an estimated 3986 valid DQs had been generated, with a response rate by the investigators of approximately 92%. The most common reasons for QA queries were missing information (particularly the Charleson Index, antimicrobial use, estimated day of onset of faecal peritonitis

before ICU admission, information about circumstances of GCS assessment, and outcome data) or data entered in incorrect units.

All patients' eCRFs were reviewed by experienced critical care physicians. Where the patient's eligibility for inclusion in the relevant cohort was unclear, clarification was sought from the investigators. Regular QA reports were provided to the GenOSept Management Committee for review; the National Investigators were contacted regarding quality issues if necessary.

Of the original 1123 records within the GenOSept database, pertaining to patients with any type of peritonitis, 146 were eliminated following QA, as not meeting the criteria for definition of peritonitis of faecal origin, leaving 977 patients records with faecal peritonitis.

The GAinS study database included valid data on 323 critically ill patients, admitted to HDU or ICU following laparotomy, recruited in the UK between January 2011 and March 2015.

The case report form for the GAinS study mirrored the GenOSept CRF. All patients' CRFs were reviewed by experienced critical care physicians, to confirm the patient's eligibility for inclusion. Where necessary, clarification was sought from the investigators. Regular QA reports were created for the GAinS Management Committee to review; the investigators were contacted regarding quality issues, where necessary.

2.2 Patients and data

Patients recruited to GenOSept and GAinS requiring admission to the ICU or HDU for faecal peritonitis were followed for up to a maximum of six months following first admission. As well as genetic epidemiological data, a variety of clinical phenotypes were collected at admission and at regular intervals throughout the admission (on days 1,2,3,5 and 7 of stay), including all variables required to calculate admission APACHE II and daily SOFA scores. Data extracted from the eCRF for the purposes of these analyses pertained either to the first 24 hours of ICU admission, or to the whole first week of admission; data for SOFA scoring, and other selected variables, were collected over the whole of the first week of ICU stay (Vincent et al. 1996).

Investigator coded presence (or absence) of acute renal failure (ARF), corroborated by the renal SOFA score, was used as an objective measure of acute renal dysfunction. The study was started before the international definitions of acute kidney injury (AKI) had been developed.

The cardiovascular SOFA was used to indicate the presence and severity of shock. Calculation of APACHE II scores was based on ICU Day 1 data (Knaus et al. 1985).

Comorbidity data

Comorbidities were classified within the eCRF according to the modified Charlson scoring system (Charlson et al. 1987).

Records comprising 16 summary measures of comorbidity were found for 976 patients. Variables indicating a history of major surgery (majsur) and radiotherapy (chradio) were excluded due to missing values in more than 10% of patients.

2.3 Statistical Methods for day 1 analyses

Continuous data were summarized using mean ± standard deviation (SD) if normally distributed, as median and interquartile ranges (IQR) if not normally distributed.

Patients were right censored at six month follow up. If an individual died during the follow up period, date and cause or causes of death were recorded. The primary study outcome was 6-month mortality. Secondary end-points were ICU, hospital and 28 days mortality. Person time was calculated, in days, from the date of admission to ICU to the date of death, or censor date. Time from estimated faecal peritonitis onset to diagnosis was calculated using the date of symptoms' onset and date of confirmatory laparotomy. Kaplan-Meier survival analysis was performed to determine mortality rates.

To determine risk factors for mortality, all of the 50 clinical variables available were analysed – the full list of variables tested is provided in the appendix. For each variable, Cox proportional hazards (PH) regression analysis, adjusted for age and gender, was performed for association with each endpoint (adjusted single variable analyses).

Variables found to be significant in single variable analyses after Bonferroni correction for multiple testing (p value $<0.001 = 0.05/50$ to take account of the 50 variables tested) were selected for inclusion in the multivariate Cox proportional hazards (PH) model to determine independent risk factors for mortality. Stepwise regression in the multivariate Cox PH regression models was performed to determine independent predictors of mortality with adjustment for potential confounding factors.

2.3.1 Testing the Proportional Hazards assumption

A test for PH using the Schoenfeld residuals was performed and, for covariates indicating evidence of non-proportionality, spline smooth estimates of time dependent hazard ratios with pointwise confidence bands were calculated (Schoenfeld 1982; Therneau & Grambsch 2000).

Schoenfeld residuals for the Cox PH regression model were regressed against time to test for independence between residuals and time and test the PH assumption. The PH assumption was supported by a non-significant relationship between residuals and time, and refuted by a significant relationship.

Where the PH assumption was not supported, smooth estimates of hazard ratios were calculated using the method of Therneau and Grambsch (Schoenfeld 1982; Therneau & Grambsch 2000).

2.3.2 Analyses of antimicrobials usage and effects

A set of analyses were performed concerning the antibacterial and antifungal agents' usage. Combinations of antimicrobials given up to 10 days before and including the day of admission to the ICU were recorded. Antimicrobial combinations occurring less than 10 times were recorded as "other". Adequacy of antimicrobials administered (as judged by the relevant microbiological expert at the recruiting centre) and presence of antifungal agents were also recorded. Cox PH regression models with adjustment for age and gender were fitted to assess the effect of each antimicrobial combination, their adequacy and the presence of antifungal agents on outcome.

2.4 Statistical Analyses (variables trends)

Clinical data of faecal peritonitis patients recruited to GenOSept were collected on days 1,2,3,5 and 7 of ICU stay, including all variables required to calculate admission APACHE II and daily SOFA scores (Knaus et al. 1985; Vincent et al. 1996). Data extracted from the electronic case report form (eCRF) for the purposes of this analysis pertained to the whole first week of ICU admission.

The trends were calculated as linear change over the first week (obtained by subtracting the value on day 1 from the value on day 7), as a prospectively chosen summary measure for the primary analysis. The use of summary measures, to combine data obtained at multiple time points for the same individual, is a recommended statistical procedure; using such a measure allowed the identification of a general trend over the first week of ICU stay, while also avoiding common pitfalls in the analysis of serial measurements (Matthews et al. 1990).

The primary study outcome was 6-month mortality. Secondary end-points were ICU, hospital and 28 day mortality. Shorter term trends were evaluated by subtracting the values on day 1 from the values on days 2, 3 and 5.

Trends in all 35 variables where data were available for the first week of ICU stay were analysed. For each trend, Cox proportional hazards (PH) regression analyses, adjusted for age and gender, were performed, for each mortality endpoint. Trends found to be significant in these analyses, after Bonferroni correction for multiple testing (p value < 0.00143 = 0.05/35 to take account of the 35 variables tested) were entered into a multivariate Cox PH model, to identify those independently associated with mortality, adjusting for potential confounding factors. The full list of variables whose trends were tested is provided in the appendix.

The primary study outcome was 6-month mortality. Secondary end-points were ICU, hospital and 28 day mortality.

2.5 Statistical analyses (prognostic models)

2.5.1 Prognostic model derivation

In order to build the prognostic model, patients recruited up to January 2011 were divided into two subsets of patients; one for derivation and the other for external geographic validation. To limit the effect of potentially unmeasured and unaccounted confounding factors, related to possible differences in national systems of healthcare provision among participating countries across Europe, these patients were divided into UK (derivation) and non-UK (geographic validation) sub-cohorts, with the aim of optimising homogeneity in the datasets and decreasing potential *background noise*, due to potential confounding factors related to different healthcare systems across countries. Subsequent patients, recruited in the UK between January 2011 and March 2015, were included in the temporal validation cohort.

All 50 clinical and laboratory variables available on admission to critical care (day 1) were evaluated (for a full list, see appendix). The primary outcome was 6 month mortality risk with the secondary outcome being 28 day mortality risk. To select the variables to include in the model, Cox proportional hazards regression analysis for 6 month mortality was fitted, using stepwise backwards selection, to determine the predictors to be included in the models from 50 bootstrapped samples derived from the derivation subset (nonparametric bootstrap procedure). Increasing the number of bootstrap replications did not alter the model significantly. The conventional p value cut-off used was 0.05. The same predictor variables were employed to construct a prognostic tool for the secondary outcome, 28 day mortality. The effect of multiple hypothesis testing was mitigated using bootstrapping. Resampling based techniques such as bootstrapping are used for dealing with

multiple hypotheses testing in various settings, including neuropsychological research and genome-wide expression studies (Zhang et al. 2012; Blakesley et al. 2009).

The procedure of bootstrapping is a re-sampling method which relies on random sampling with replacement of the available observations. This procedure allows evaluation of the characteristics of an estimator (such as its variance) by measuring those properties when obtaining multiple samples from the original dataset (and of size equal to the observed dataset) (Chen & George 1985)(Harrell et al. 1996).

A final Cox proportional hazards regression analysis for both 6 month and 28 day mortality was fitted using the set of variables found to be significant in the majority of bootstrap replications, for each outcome respectively.

The proportional hazards assumption was confirmed as met by drawing Kaplan-Meier Curves and Nelson Aalen plots for the covariates after categorisation. Predictors which satisfied the proportional hazard assumption showed very similar curves, with the separation between them remaining proportional across analysis time (Hess 1995). The correctness of this assumption was also assessed testing on the basis of Schoenfeld residuals (Therneau & Grambsch 2000).

In order to assess for the presence of collinearity (which happens when two variables are almost a perfect linear combination of one another), I calculated the variance inflation factors (VIFs). It is generally accepted that variables with VIFs greater than 10 merit further investigation (Slinker & Glantz 1985).

The two models obtained were evaluated using Area under the Receiver-Operator Characteristic curve (AuROC) analysis, which plots sensitivity against 1-

specificity to describe the accuracy of a diagnostic test (Metz 1978; Hanley & McNeil 1982), and to compare the performance of different tests (Zweig & Campbell 1993).

2.5.2 Non-parametric bootstrapping and prognostic model derivation for 6 month and 28 day mortality

The bootstrapping procedure was performed using 50 repetitions based on the UK derivation cohort. A final Cox proportional hazards regression analysis for 6 month mortality was fitted using the set of variables found to be significant in the majority of bootstrap replications. Saturation was reached after 50 bootstrap replications, with additional replications not yielding significantly different results.

A set of 5 variables met this criterion (age, SOFA score, lowest temperature, highest heart rate, haematocrit). The Cox proportional hazards model estimates for those risk variables are presented in Table 5.

The same five variables were employed to formulate the 6 month mortality prognostic tool by entering the estimates obtained from the Cox proportional hazards model in the following equation:

FP score (6 month) = (10^3) * exp((0.0447387*A)+(-0.0313029*H)+(-0.2767377*T) +(0.0114629*HR)+(0.1812872*S))

Where: A = age at admission to critical care, H = haematocrit (as percentage points) on day 1 ICU, T = lowest recorded temperature (as degrees Celsius) on day 1 ICU, HR = highest recorded heart rate on day 1 ICU, S = SOFA score day 1

A separate Cox proportional hazards regression analysis was fitted for the 28 day mortality outcome, utilising the same set of five variables. The resulting model estimates are presented in Table 4. The estimates were utilised to construct the 28 day mortality prognostic tool as described in the following equation:

FP score (28 day) = (10^4) * exp((0.048728*A)+(-0.0125259*H)+(0.2005776*S)+(-0.3591817*T)+(0.0098462*HR))

While haematocrit and high heart rate did not offer independent predictive power in the 28 day mortality model, they were useful in explaining variability when retained in the model.

2.5.3 Comparison of the prognostic models with pre-existing scores

Comparison of the prognostic models with SOFA and APACHE II was performed graphically by drawing the superimposed ROC curves and testing the underlying AuROC obtained, taking into account that the data are correlated, using a nonparametric approach as suggested by DeLong et al. (DeLong et al. 1988).

Table 5 Variables found to be significant in the majority of bootstrap replications run on the UK derivation cohort for the two outcomes

Variable	HR	HR 95% CI	coeff	coeff 95% CI	p
6 month mortality					
Age	1.05	1.03 - 1.07	0.045	0.02 - 0.06	<0.001
SOFA score	1.20	1.12 - 1.28	0.18	0.11 - 0.25	<0.001
low temperature	0.76	0.63 - 0.91	[-0.28]	[-0.46] - [-0.09]	0.004
high heart rate	1.01	1.01 - 1.02	0.01	0.01 - 0.02	0.007
Haematocrit	0.97	0.94 - 0.99	[-0.031]	[-0.059] - [-0.003]	0.028
28 day mortality					
Age	1.05	1.03 - 1.08	0.049	0.03 - 0.07	<0.001
SOFA score	1.22	1.12 - 1.33	0.2	0.11 - 0.29	<0.001
low temperature	0.70	0.55 - 0.88	[-0.36]	[-0.59] - [-0.13]	0.002
high heart rate	1.01	1 – 1.02	0.01	[-0.001] - 0.2	0.07
Haematocrit	0.99	0.95 - 1.02	[-0.013]	[-0.047] - 0.022	0.47

HR, hazard ratio; 95% CI, 95% confidence interval; coeff, coefficient; SOFA, Sequential Organ Failure Assessment; the use of the square brackets [ ] indicates negative values

2.6 Software employed

Statistical analyses were performed using R version 2.11.1 (The R Project for Statistical Computing. <http://www.r-project.org/>) and STATA statistical software (STATA 10; STATA Statistics/Data Analysis, StataCorp, Lakeway Drive, College Station, Texas 77845 USA. <http://www.stata.com>).

Chapter 3 – Faecal peritonitis in the GenOSept cohort - an epidemiological survey

3.1 Introduction

Critically ill patients with faecal peritonitis represent a specific subgroup among septic patients. It is, therefore, important to define and characterise their epidemiological features and risk factors, in order to support clinical decision making and prognostication. As demonstrated in the literature review presented in chapter 1, the existing literature is limited, particularly regarding the features and outcomes of this patient group when admitted to critical care. The studies summarised in chapter 1 section 1.3.3 have suggested that the outcome of patients with faecal peritonitis admitted to intensive care units may depend on key variables, specifically age, presence of malignancy (this feature has been deemed as protective), and hypo-albuminaemia (Sayer et al. 2012; Pawa et al. 2009). I provide here the results of my analyses from the multi-national GenOSept cohort, the largest and most homogeneous cohort gathered of this patient group.

3.2 Baseline characteristics

3.2.1 Patients' baseline characteristics - period

Data presented in this chapter pertains to day 1 admission to ICU (unless otherwise specifically stated) extracted from electronic case record forms (eCRFs). It pertains to 977 patients, admitted to critical care with a diagnosis of faecal peritonitis, following laparotomy, between 29/09/2005 and 05/01/2011. The patients were recruited from 102 centres across 16 countries for the GenOSept study.

3.2.2 Participants' recruitment by Country

A large proportion of patients (462, 47.29%) were enrolled in the United Kingdom, although the majority were from mainland Europe. Table 6 lists participants by Country.

Apart from being the single largest and most homogeneous prospective cohort collected so far on patients admitted with faecal peritonitis to critical care services, the GenOSept faecal peritonitis cohort is the only multinational one. The previously reported studies analysed smaller datasets gathered in single centre UK only cohorts (Pawa et al., 2009, Sayer et al., 2012).

Table 6 Participants' recruitment by Country

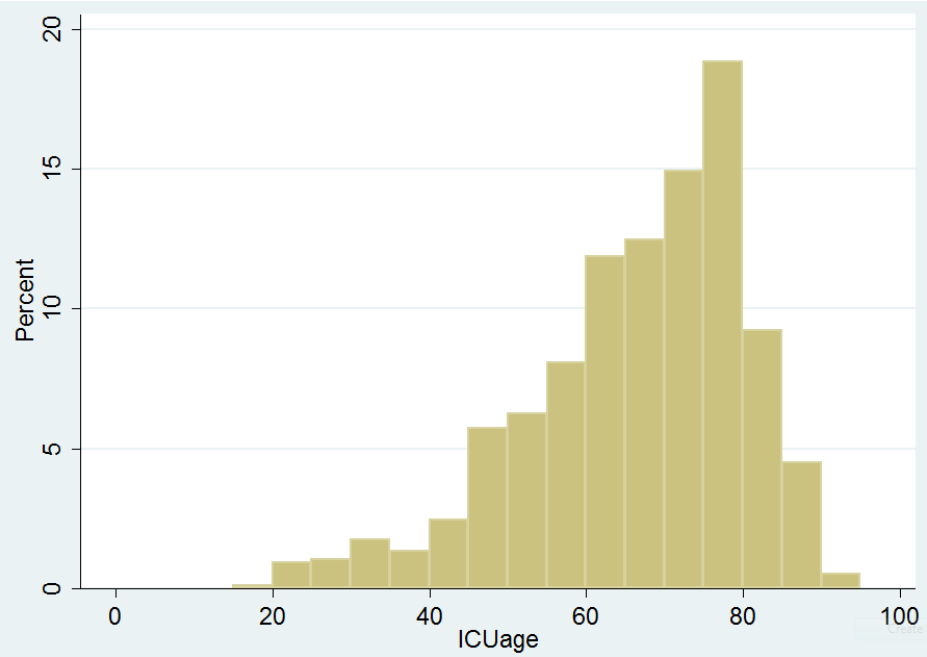
Country	N	n	%
	977		
United Kingdom		462	47.3
Germany		124	12.7
Spain		95	9.7
Czech Republic		68	7.0
Italy		58	5.9
Ireland		49	5.0
Belgium		44	4.5
Poland		36	3.7
Serbia		17	1.7
France		6	0.6
Netherlands		4	0.4
Estonia		4	0.4
Croatia		4	0.4
Israel		3	0.3
Hungary		2	0.2
Greece		1	0.1

N, number of observations; n = count, % = percentage

3.2.3 Age and gender distribution

Average (SD) age was 66.5 (14) years, median age (IQR) was 69.2 (58.3 - 77.1) years. The distribution was largely skewed towards the older ages, with 62.54% of patients being 65 years old or older, as described in Figure 2.

Figure 2 Histogram of the age distribution at ICU admission in the GenOSept faecal peritonitis cohort



Age range (years)	n	%
18-34	36	3.7%
35-44	33	3.4%
45-54	106	10.9%
55-64	191	19.6%
65-74	264	27%
75-84	277	28.4%
85-95	70	7.2%
Total	977	100%

n = count, % = percentage

This age distribution is similar to that described by Pawa and co-workers in their cohort, which had a mean age of 70.8 years (Pawa et al., 2009).

There was a slight male preponderance: of the 977 patients, 530 (54.3%) were male.

3.2.4 Ethnic distribution

Ethnic origin data was available for 970 (99.3%) patients in the cohort: the overwhelming majority (956, 98.6%) were of Caucasian origin (Table 7).

Table 7 Ethnic distribution in the faecal peritonitis cohort

Race	n	%
Caucasian	956	98.6%
Asian	11	1.1%
African	2	0.2%
Mixed	1	0.1%
Total	970	100

n = count, % = percentage

3.2.5 Acute physiological dysfunction

APACHE II and SOFA scores were available for 974 (99.7%) patients in the GenOSept faecal peritonitis cohort. The median (IQR) APACHE II score was 16 (12-21), the median (IQR) SOFA score was 7 (5-10). The distributions of APACHE II and SOFA scores are shown in Figure 3 and 4 respectively. Table 8 reports further indicators of acute physiological derangement.

Figure 3 Histogram of the APACHE II scores distribution in the GenOSept faecal peritonitis cohort

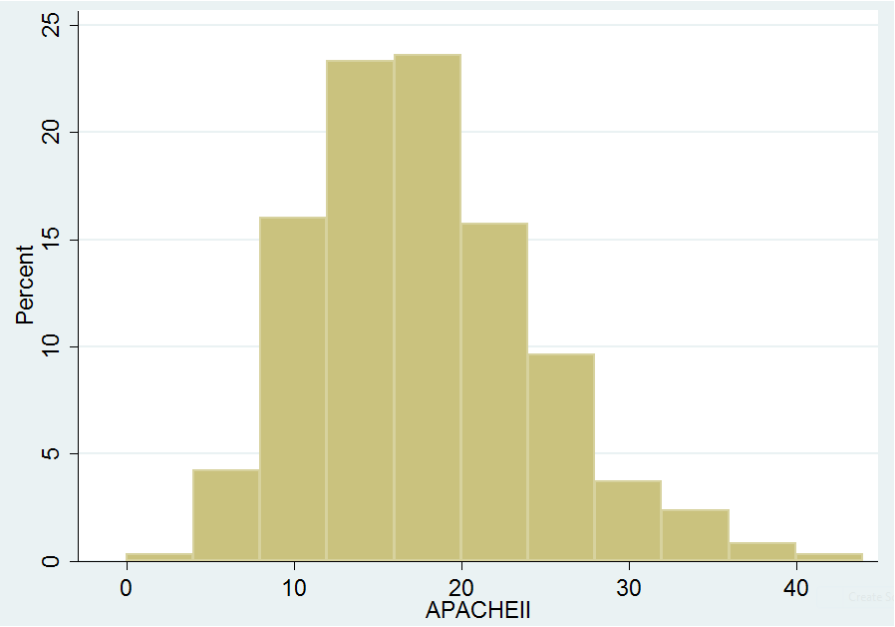


Figure 4 Histogram of the SOFA scores distribution in the GenOSept faecal peritonitis cohort

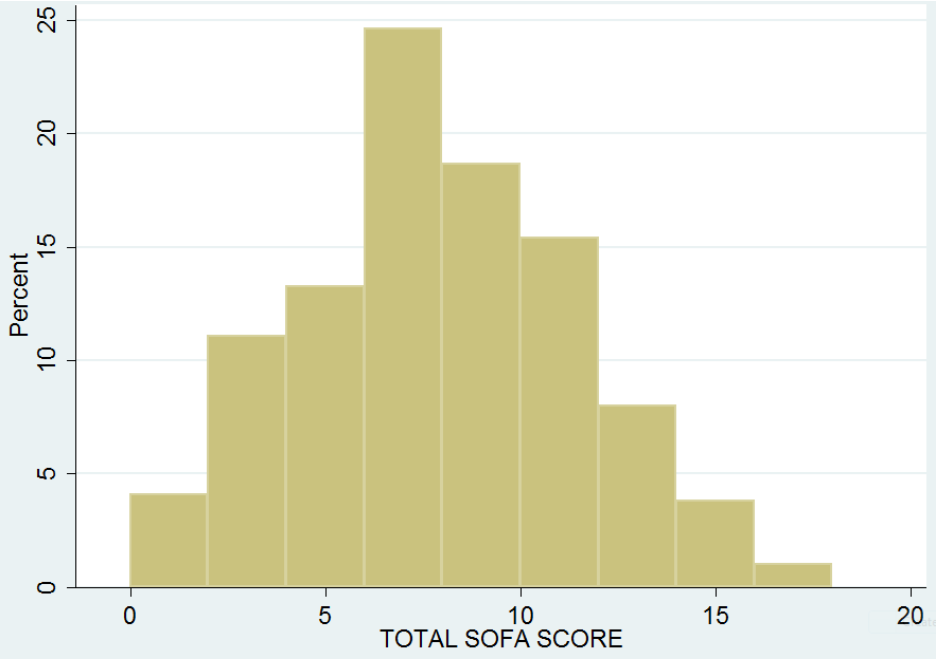


Table 8 Patients' baseline characteristics recorded on day 1

Acute physiology indicator	N	n or Median[a]	% or IQR[b]
	977		
Severe sepsis		959	98.2
Renal SOFA		1[a]	0-2[b]
Renal SOFA≥2		271	27.7
Cardiovascular SOFA		4[a]	1-4[b]
Cardiovascular SOFA≥1		835	85.7
Cardiovascular SOFA≥2		707	72.6
Cardiovascular SOFA≥3		674	69.2
Cardiovascular SOFA≥4		505	51.9
Acute renal failure (as per investigators)		282	29
Renal replacement therapy		115	11.8
Mechanical ventilation		742	76.2
Heart rate (bpm)		85[a]	73-99[b]
Temperature (^{0}C)		36.2[a]	35.7-36.9[b]
pH		7.33[a]	7.25-7.40[b]
Haematocrit (%)		30.2[a]	27-35[b]
Platelets (10^{-9}/l)		212.5[a]	145-300[b]

Bpm, beats per minute; ^{0}C, degrees centigrade; IQR, interquartile range; N, number of available observations; n = count, % = percentage; SOFA, Sequential Organ Failure Assessment.

[a]Median and [b]IQR are shown instead of count and %.

Seven hundred and forty-two patients (76.2%) were mechanically ventilated, 959 (98.2%) had severe sepsis, 835 (85.7%) had a cardiovascular SOFA score ≥1 and 282 (29%) had acute renal dysfunction (based on investigators' opinion), 271 (27.7%) patients had a renal SOFA score ≥2 on day 1 (indicative of moderate to severe renal dysfunction), 11.8% required renal replacement therapy on day 1 and 208 (21.3%) of patients received renal replacement therapy during the first week.

3.2.6 Comorbidities

The most common co-morbidities were cardiovascular, malignant and respiratory diseases: a list is presented in Table 9.

Table 9 Comorbidities in the faecal peritonitis cohort

Medical comorbidities	N	n	%
Cardiovascular disease	976	390	40.0
Respiratory disease	976	244	25.0
Neurological disease	976	106	10.9
Severe renal disease	941	96	10.2
Gastrointestinal disease	976	230	23.6
Malignancy	976	295	30.2
Diabetes	976	163	16.7
Previous serious infection*	976	33	3.4
Other illness	976	339	34.7
Severe exercise restriction	976	9	0.9
Chronic dialysis	971	13	1.3
Chronic steroids use**	976	10	1.0

IQR, interquartile range; N, number of available observations; n = count, % = percentage;

* Serious infection was defined as a serious, prolonged or recurrent infection.

** Chronic steroid use was defined as taking corticosteroids below the immunosuppression dose (>7 mg/kg/days hydrocortisone), which would exclude patient from the study.

3.2.7 Length of stay and time to surgery

The median ICU length of stay (LOS) was 10 days (IQR 5–21, range 1-160 days); the median hospital LOS was 28 days (IQR 15–51). The distribution of the ICU length of stay is presented in Table 10. The median time from the estimated onset of symptoms to surgical intervention was 1 day (IQR 1-3).

Table 10 ICU length of stay

ICU length of stay (days)	n	%
0-3	151	15.5%
4-7	238	24.4%
8-14	222	22.7%
15-28	191	19.5%
29-56	129	13.2%
57-160	46	4.7%

Data available for 977 patients; n = count, % = percentage;

3.2.8 Cause of faecal peritonitis

The most common causes of faecal peritonitis were perforated diverticular disease (32.1%) and surgical anastomotic breakdown (31.1%), followed by malignancy, trauma and other causes as indicated in Table 11. Surgical source control had been attempted in all patients, prior to admission to intensive care.

Table 11 Cause of faecal peritonitis

Cause of faecal peritonitis	n	%
Perforated diverticular disease	312	32.1%
Anastomotic breakdown	302	31.1%
Malignancy	129	13.3%
Trauma	67	6.9%
Other	162	16.7%

Data available for 972 of 977 patients; n = count, % = percentage

3.3 Mortality

3.3.1 Mortality rates

Of the 977 patients admitted to ICU with a confirmed diagnosis of faecal peritonitis, 187 (19.1%) had died at 28 days, 204 (20.9%) died during their ICU stay, 283 (28.7%) in hospital and 309 (31.6%) had died at six month follow-up (Table 12).

Table 12 Mortality at the four time-points for the 977 patients in the GenOSept faecal peritonitis cohort

Outcome time-point	Status	N	Deaths %	Exposure time (person-days)	Crude morality rate (95%CI) (events/1000 person-days)
6 months	Alive	668	31.6%	121498	2.54 (2.27-2.84)
	Dead	309			
ICU	Alive	773	20.9%	16549	12.3 (10.8-14.1)
	Dead	204			
Hospital	Alive	698	28.7%	37644	7.44 (6.62-8.36)
	Dead	283			
28 days	Alive	790	19.1%	23707	7.89 (6.83-9.10)
	Dead	187			

CI, confidence interval; IQR, interquartile range; N, number of available observations, % = percentage

Of those 105 patients who had survived ICU stay but had passed away by 6 months, 31 (29.5%) had limitations in place at the time of death, 29 (27.6%) died with multi-organ and system failure which had failed to resolve, 24 (22.9%) had persistent or recurrent sepsis, 10 (9.5%) intractable cardiovascular failure and only 13 (12.4%) died of causes considered to be unrelated. More than one mode of death was recorded for some patients.

3.3.2 Modes of death

Investigators were asked to choose one or more “modes of death” from a list in the eCRF: more than one mode was recorded for some patients. Modes of death are presented in Table 13.

Table 13 Mode of death for the 977 patients in the GenOSept faecal peritonitis cohort

Mode of death	N	%
Failure to resolve organ system dysfunction	154	49.5%
Limitation of therapy	104	33.7%
Persistent or recurrent sepsis	102	33%
Intractable cardiovascular failure	60	19.4%
Unrelated cardiac / pulmonary event	18	5.5%

Of those patients on whom limitations of therapy had been placed, the majority (73, 70.2%) died in the ICU.

3.3.3 Individual variable analyses - results

All variables measured on day 1 of ICU admission, and two derived from the data pertaining to week one ICU stay (cardiovascular and renal SOFA scores), were analysed to evaluate their influence on the 4 outcomes.

The statistically significant results after Bonferroni correction for multiple analyses ($p<0.001$) are presented in the form of estimated hazard ratios (HRs) in Tables 14 to 17, for the primary (6 month mortality) and the secondary outcomes (ICU, hospital and 28 day mortality) respectively.

The most significant associations with 6-month mortality (primary outcome) were the APACHE II score, total SOFA score on day 1, and the highest renal SOFA score during the first 7 days of ICU admission (used as a cumulative proxy marker of severity of renal dysfunction during this period). Other variables indicative of acute renal dysfunction were also significantly associated with 6-month mortality. These included investigator recorded presence of acute renal failure (ARF), need for renal replacement therapy (RRT), pH, highest and lowest recorded creatinine and highest recorded urea on day 1. The next most significant association with 6-month mortality was for the highest cardiovascular SOFA score during the first week of ICU stay. Many of the variables associated with 6-month mortality were also significantly associated with the other outcomes in single variable analyses.

The variables found to be consistently associated with mortality at all the time points were age, the SOFA and APACHE II scores measured on day 1, indicators of renal dysfunction (highest renal SOFA score over week 1, investigators' opinion of acute renal failure on day 1, pH, highest and lowest measured creatinine, need for renal replacement therapy [RRT] and highest measured urea on day 1 of ICU admission) and hypothermia. Indicators of cardiovascular dysfunction (highest

cardiovascular system [CVS] SOFA score measured over week 1, presence/absence of hypertension, highest and lowest measured heart rate on day 1), haematocrit, temperature and platelets levels, bilirubin levels and P:F ratio (PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen) were also significant predictors of multiple outcomes.

The cause of faecal peritonitis, the presence of co-morbidities, the time from estimated faecal peritonitis onset to surgical intervention and the finding of bilateral infiltrates on chest radiography (seen in 220 patients and suggestive of acute lung injury [ALI]/acute respiratory distress syndrome [ARDS]) had no influence on survival at any time-point.

Hazard ratios for pH value on ICU admission showed evidence of non-proportionality of hazards in a Cox proportional hazards regression for 6-month mortality (*p* value < 0.01). Figure 5 shows the estimated non-proportional time dependent hazard ratios for this variable and suggests that its effect on mortality over 6 months is greatest at admission to ICU and typically decreases to little or no effect over a six month period. The horizontal dotted line shows the estimated fixed hazard ratio.

Figure 5 Estimated hazard ratio (solid line) with 95% confidence intervals (dashed lines) for the variable pH value

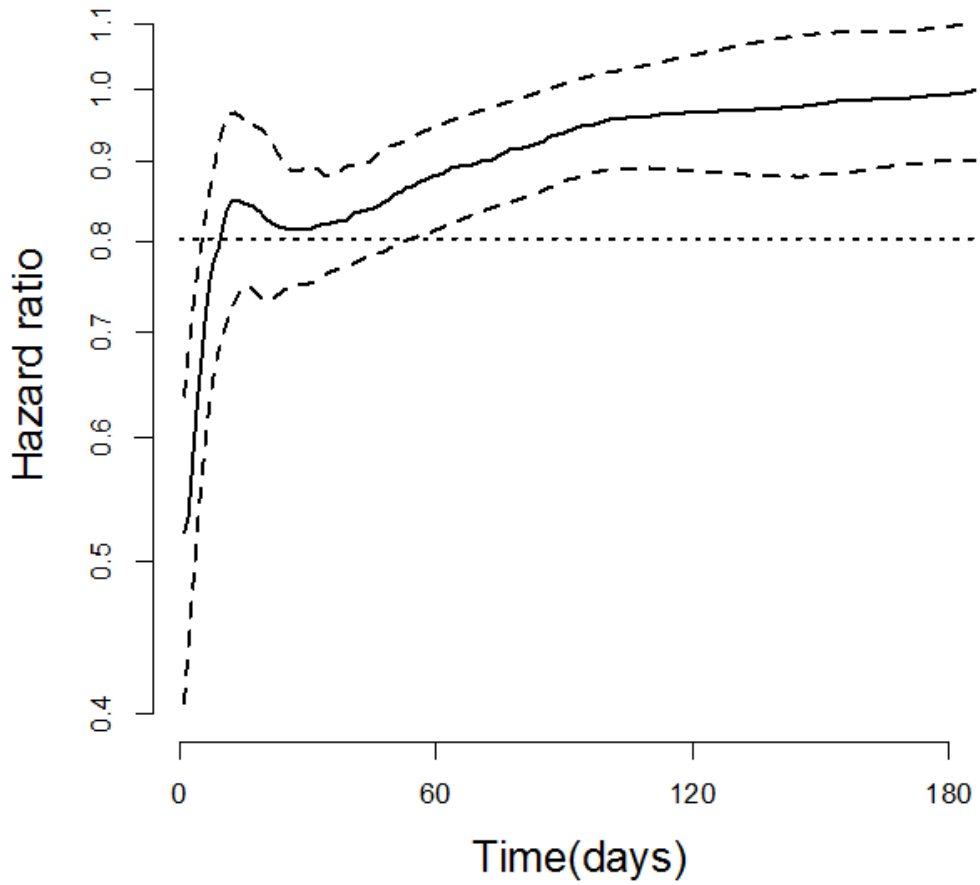


Table 14 Results of Cox PH regression analysis for 6 months mortality

Variable	Unit	HR	95% CI	*p*-value
SOFA day 1	1 point	1.18	1.14-1.21	$<1 \times 10^{-16}$
APACHE II	1 point	1.08	1.07-1.1	$<1 \times 10^{-16}$
Age	1 year	1.04	1.03-1.05	3.3×10^{-16}
Highest renal SOFA [a]	1 point	1.42	1.32-1.52	$<1 \times 10^{-16}$
Acute renal failure		2.32	1.85-2.92	3.2×10^{-13}
pH	1 point	0.80	0.75-0.86	3.9×10^{-9}
Highest creatinine	micromol/l	1.002	1.002-1.003	8.0×10^{-9}
Lowest creatinine	micromol/l	1.002	1.002-1.003	9.5×10^{-8}
RRT		2.22	1.67-2.93	2.9×10^{-8}
Highest urea	mmol/l	1.02	1.01-1.03	4.2×10^{-6}
Haematocrit	%	0.96	0.94-0.98	1.4×10^{-5}
Highest CVS SOFA [a]	1 point	1.40	1.25-1.56	6.4×10^{-9}
Hypertension		1.24	1.14-1.34	1.6×10^{-7}
Highest heart rate	10 bpm	1.12	1.07-1.17	1.0×10^{-6}
Lowest heart rate	10 bpm	1.13	1.06-1.2	2.1×10^{-4}
P:F Ratio	kPa	0.98	0.97-0.99	3.9×10^{-4}
Ventilatory support		1.93	1.40-2.67	6.1×10^{-5}
Lowest platelets	10^{-9}/l	0.98	0.97-0.99	4.7×10^{-5}
Lowest temperature	1^{0}C	0.79	0.70-0.88	6.7×10^{-5}
Highest bilirubin	mmol/l	1.01	1.00-1.01	4.6×10^{-4}

Results are shown for variables with *p*-value < 0.05/50. Results are adjusted for age and gender (apart from age).

CI, confidence interval; bpm, beats per minute; CVS, cardiovascular; HR = Hazard Ratio, PH, proportional hazard; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; RRT, renal replacement therapy; P:F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen. All variables refer to day 1 ICU admission, unless otherwise stated.

[a] Variable recorded over week 1.

Table 15 Results of Cox PH regression analysis for ICU mortality

Variable	Unit	HR	95% CI	*p*-value
SOFA day 1	1 point	1.09	1.04-1.14	7.5×10^{-5}
APACHE II	1 point	1.05	1.03-1.07	1.2×10^{-6}
Age	1 year	1.04	1.02-1.05	4.0×10^{-8}
Highest renal SOFA[a]	1 point	1.33	1.21-1.45	7.7×10^{-10}
Acute Renal Failure		1.99	1.51-2.63	1.3×10^{-6}
pH	1 point	0.84	0.78-0.91	1.8×10^{-5}
Lowest Temperature	1^0C	0.8	0.7-0.91	5.2×10^{-4}

Results are shown for variables with *p*-value < 0.05/50. Results are adjusted for age and gender (apart from age).

CI, confidence interval; bpm, beats per minute; CVS, cardiovascular; HR = Hazard Ratio, PH, proportional hazard; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation. All variables refer to day 1 ICU admission, unless otherwise stated.

[a] Variable recorded over week 1.

Table 16 Results of Cox PH regression analysis for hospital mortality

Variable	Unit	HR	95% CI	*p*-value
SOFA day 1	1 point	1.13	1.09-1.17	4.0×10^{-12}
APACHEII	1 point	1.07	1.05-1.08	6.3×10^{-13}
Age	1 year	1.05	1.03-1.06	1.6×10^{-14}
Highest renal SOFA[a]	1 point	1.33	1.24-1.44	1.8×10^{-13}
Acute Renal Failure		2.1	1.66-2.67	8.4×10^{-10}
pH	1 point	0.84	0.78-0.9	2.5×10^{-6}
Highest Creatinine	micromol/l	1.002	1.001-1.003	6.6×10^{-6}
Lowest Creatinine	micromol/l	1.002	1.001-1.003	4.3×10^{-5}
RRT		1.83	1.37-2.45	5.1×10^{-5}
Haematocrit	%	0.96	0.94-0.98	4.9×10^{-4}
Highest CVS SOFA[a]	1 point	1.3	1.15-1.47	2.5×10^{-5}
hypertension		1.18	1.08-1.28	1.8×10^{-4}
Highest HR	1 bpm	1.009	1.004-1.014	5.4×10^{-4}
Lowest platelets	10^{-9}/l	0.98	0.97-0.99	2.1×10^{-4}
Lowest Temperature	1^{0}C	0.84	0.78-0.9	2.5×10^{-6}

Results are shown for variables with *p*-value < 0.05/50. Results are adjusted for age and gender (apart from age).

CI, confidence interval; bpm, beats per minute; CVS, cardiovascular; HR = Hazard Ratio, PH, proportional hazard; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; RRT, renal replacement therapy. All variables refer to day 1 ICU admission, unless otherwise stated.

[a] Variable recorded over week 1.

Table 17 Results of Cox PH regression analysis for 28 day mortality

Variable	Unit	HR	95% CI	*p*-value
SOFA day 1	1 point	1.16	1.11-1.21	3.1×10^{-12}
APACHE II	1 point	1.08	1.05-1.1	3.5×10^{-12}
Age	1 year	1.05	1.03-1.06	1.4×10^{-11}
Highest renal SOFA[a]	1 point	1.43	1.3-1.57	1.2×10^{-13}
pH	1 point	0.77	0.7-0.84	1.5×10^{-9}
Acute Renal Failure		2.47	1.85-3.3	1.1×10^{-9}
RRT		2.22	1.56-3.17	9.6×10^{-6}
Haematocrit	%	0.95	0.93-0.98	1.7×10^{-4}
Highest CVS SOFA[a]	1 point	1.35	1.17-1.56	4.5×10^{-5}
Hypertension		1.24	1.12-1.38	6.6×10^{-5}
Highest HR	1 bpm	1.01	1.01-1.02	2.1×10^{-5}
P:F Ratio	kPa	0.98	0.97-0.99	9.4×10^{-4}
Lowest platelets	10^{-9}/l	0.97	0.96-0.98	9.33×10^{-6}
Lowest Temperature	1^{0}C	0.73	0.63-0.85	4.35×10^{-5}

Results are shown for variables with *p*-value < 0.05/50. Results are adjusted for age and gender(apart from age).

CI, confidence interval; bpm, beats per minute; CVS, cardiovascular; HR = Hazard Ratio, PH, proportional hazard; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; RRT, renal replacement therapy; P:F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen. All variables refer to day 1 ICU admission, unless otherwise stated.

[a] Variable recorded over week 1.

3.3.4 Antimicrobials analyses - results

The antimicrobial combinations administered on admission to ICU varied widely, but were deemed by the local investigators to be appropriate in 91.8% of cases. The most common combinations were piperacillin-tazobactam (12.1%) cefuroxime/metronidazole (5.4%) and amoxicillin-clavulanate (5.3%). Antifungal agents were included in 5.8% of initial antimicrobial combinations. In a post-hoc exploratory analysis, no specific antimicrobial combination was associated with improved survival for the primary outcome (6 month-mortality), although in a small sub-group the combination of amoxicillin-clavulanate/metronidazole appeared to be associated with significantly increased mortality at hospital discharge and 28-days, and in another the administration of metronidazole alone appeared to be associated with a significant increase in ICU mortality. Neither the co-administration of antifungals, nor the appropriateness of the antimicrobial combinations (as judged by the local investigators) had any significant influence on mortality. The analyses pertaining to the use of antimicrobials were possibly affected by the large number of antimicrobial combinations used (causing data *fragmentation*) and the significant lack of data (not available for 216, 22.1% of patients), both of which reduced the power of the analyses. Table 18 presents information related to the initial anti-microbial and antifungal regimes administered.

The results from the antimicrobials usage analyses are presented in Tables 19 - 22.

Table 18 Initial anti-microbial regimes and appropriateness

Antimicrobials	N		%
Initial anti-biotic regimes[a]	761		
Ceftriaxone/Metronidazole		15	2
Cefuroxime/Gentamicin/Metronidazole		15	2
Cefuroxime/Metronidazole		41	5.4
Fluconazole/Piperacillin-Tazobactam		11	1. 5
Gentamicin		28	3.7
Imipenem/Cilastatine		25	3.3
Amoxicillin-Clavulanate		40	5.3
Amoxicillin-Clavulanate/Metronidazole		17	2.2
Meropenem		27	3.6
Metronidazole		17	2.2
Metronidazole/Piperacillin-Tazobactam		35	4.6
Piperacillin-Tazobactam		92	12.1
Other combinations		291	38.2
No antimicrobials given on day 1		107	14.1
Co-administration of antifungal agent	654		
Fluconazole		35	5.4
Caspofungin		1	0.2
Clotrimazole		1	0.2
Amphotericin B		1	0.2
No antifungal agent used		616	94.2
Appropriateness of antimicrobial treatment [b]	734		
Appropriate		674	91.8
Not appropriate		60	8.2

[a] Data was available for 761 patients. Antimicrobial combinations administered on day one of ICU admission to 10 or more patients are shown, less common combinations are included in the “other combinations” category; for 107 patients no antimicrobial treatment was recorded as having been given in the first 24hrs.

[b] Appropriateness of antimicrobial treatment during first 24 hours ICU admission was based on local investigator opinion

Table 19 Cox PH regression analyses for antimicrobials administered at ICU admission and 6 month mortality

Antimicrobial combination	HR	95% CI	*p*-value
Ceftriaxone/Metronidazole	1.31	0.51-3.38	0.57
Cefuroxime/Gentamicin/Metronidazole	0.49	0.12-2.06	0.33
Cefuroxime/Metronidazole	1.18	0.62-2.26	0.61
Fluconazole/Piperacillin-Tazobactam	1.62	0.68-3.9	0.28
Gentamicin	0.91	0.43-1.92	0.81
Imipenem/Cilastatine	0.82	0.34-1.96	0.65
Amoxicillin-Clavulanate	0.87	0.43-1.78	0.71
Amoxicillin-Clavulanate/Metronidazole	1.73	0.67-4.45	0.26
Meropenem	1.58	0.81-3.07	0.18
Metronidazole	1.18	0.46-3.02	0.73
Metronidazole/Piperacillin-Tazobactam	0.67	0.3-1.52	0.34
Piperacillin-Tazobactam	1.42	0.88-2.3	0.15
Other combinations	1.21	0.81-1.81	0.35
Co-administration of antifungal agent	1.19	0.71-1.98	0.51
Appropriate antimicrobial treatment	0.85	0.54-1.35	0.5

The group with no antimicrobials recorded for the first 24 hours is the reference category. HR, hazard ratio; CI, confidence interval.

Table 20 Cox PH regression analyses for antimicrobials administered at ICU admission and ICU mortality

Antimicrobial combination	HR	95% CI	p
Ceftriaxone/Metronidazole	1.48	0.51-4.31	0.47
Cefuroxime/Gentamicin/Metronidazole	0.7	0.09-5.22	0.73
Cefuroxime/Metronidazole	1.85	0.84-4.04	0.13
Fluconazole/Piperacillin-Tazobactam	1.03	0.24-4.41	0.96
Gentamicin	1.05	0.35-3.12	0.93
Imipenem/Cilastatine	0.50	0.15-1.69	0.27
Amoxicillin-Clavulanate	1.02	0.43-2.39	0.97
Amoxicillin-Clavulanate/Metronidazole	2.77	0.82-9.35	0.10
Meropenem	1.35	0.62-2.94	0.46
Metronidazole	2.77	1.04-7.37	0.04
Metronidazole/Piperacillin-Tazobactam	0.86	0.32-2.27	0.76
Piperacillin-Tazobactam	1.39	0.78-2.49	0.26
Other combinations	1.25	0.76-2.03	0.38
Co-administration of antifungal agent	0.92	0.47-1.81	0.8
Adequate antimicrobial treatment	0.9	0.55-1.46	0.66

The group with no antimicrobials recorded for the first 24 hours is the reference category. HR, hazard ratio; CI, confidence interval.

Table 21 Cox PH regression analyses for antimicrobials administered at ICU admission and hospital mortality

Antimicrobial combination	HR	95% CI	p
Ceftriaxone/Metronidazole	1.26	0.44-3.59	0.67
Cefuroxime/Gentamicin/Metronidazole	0.76	0.18-3.22	0.71
Cefuroxime/Metronidazole	1.61	0.82-3.18	0.17
Fluconazole/Piperacillin-Tazobactam	1.38	0.49-3.95	0.54
Gentamicin	0.83	0.36-1.9	0.65
Imipenem/Cilastatine	0.93	0.38-2.24	0.87
Amoxicillin-Clavulanate	0.8	0.38-1.69	0.55
Amoxicillin-Clavulanate/Metronidazole	3.42	1.31-8.9	0.01
Meropenem	1.5	0.73-3.1	0.27
Metronidazole	1.87	0.72-4.86	0.2
Metronidazole/Piperacillin-Tazobactam	0.62	0.26-1.49	0.28
Piperacillin-Tazobactam	1.60	0.98-2.63	0.06
Other combinations	1.36	0.89-2.07	0.16
Co-administration of antifungal agent	0.89	0.51-1.58	0.7
Appropriate antimicrobial treatment	0.9	0.55-1.46	0.66

The group with no antimicrobials recorded for the first 24 hours is the reference category. HR, hazard ratio; CI, confidence interval.

Table 22 Cox PH regression analyses for antimicrobials administered at ICU admission and 28 day mortality

Antimicrobial combination	HR	95% CI	p
Ceftriaxone/Metronidazole	1.71	0.49-5.92	0.4
Cefuroxime/Gentamicin/Metronidazole	1.16	0.27-5.1	0.84
Cefuroxime/Metronidazole	1.72	0.75-3.93	0.2
Fluconazole/Piperacillin-Tazobactam	1.66	0.48-5.76	0.42
Gentamicin	0.86	0.29-2.62	0.8
Imipenem/Cilastatine	0.84	0.24-2.9	0.78
Amoxicillin-Clavulanate	1.08	0.42-2.78	0.88
Amoxicillin-Clavulanate/Metronidazole	3.36	1.22-9.26	0.02
Meropenem	1.36	0.49-3.73	0.56
Metronidazole	1.96	0.65-5.9	0.23
Metronidazole/Piperacillin-Tazobactam	0.65	0.19-2.24	0.5
Piperacillin-Tazobactam	1.87	0.97-3.61	0.06
Other combinations	1.56	0.89-2.76	0.12
Co-administration of antifungal agent	0.95	0.46-1.94	0.88
Appropriate antimicrobial treatment	0.82	0.45-1.49	0.52

The group with no antimicrobials recorded for the first 24 hours is the reference category. HR, hazard ratio; CI, confidence interval.

3.4 Results of Multivariate analyses

Table 23 reports the results of a multivariate Cox PH regression model retaining the variables independently predictive of mortality at each endpoint. At all time points, age, highest recorded renal SOFA score over the first week of ICU stay and lowest recorded temperature on day 1 remained independently associated with mortality.

For each unit increase in the highest renal SOFA score recorded during the first week of ICU stay, the hazard of death at 6 months increased by 26.4% (HR=1.26, 95% CI 1.16-1.38), and similar increases were seen for ICU and hospital mortality (25.4% and 24.8% respectively). This effect was more marked for 28 day mortality, where for each unit increase in renal SOFA score there was an increase in hazard of 34% (HR=1.34, 95% CI 1.21-1.49).

The other consistent and independent predictor of outcome across all time points was hypothermia during day 1 of admission to ICU. Every degree centigrade increase in the lowest recorded temperature on day 1 reduced the mortality hazard at 6 months by 14.6% (HR=0.85, 95% CI 0.76-0.96). This effect was also present for ICU, hospital and 28 day mortality (17.1%, 12.5% and 18.4% respectively).

The highest cardiovascular SOFA score (HR 1.26, 95% CI 1.16-1.38, per unit change in score), bradycardia (HR 1.08, 95% CI 1.02-1.16, per 10 beats/minute decrease in heart rate), haematocrit (HR 0.97, 95% CI 0.95-0.99, per percentage point) and APACHE II score (HR 1.04, 95% CI 1.02-1.06, per unit change in score) remained predictive of mortality at 6 months after adjustment for other variables in the multivariate model.

While the SOFA score was not retained as an independent predictor for outcome at any time point, the APACHE II score was an independent predictor of 6 months and hospital mortality. For each unit increase in APACHE II score the 6 months and hospital mortality risks increased by 3.5% (HR 1.035, 95% CI 1.015-1.056) and 3.1% (HR 1.031, 95% CI 1.011-1.052) respectively.

The presence of acidosis affected shorter term outcomes: lower values for pH on day 1 being predictive of mortality at 28 days (HR 0.89, 95% CI 0.79-1.0) and in ICU (HR 0.90, 95% CI 0.82-0.99).

Thrombocytopaenia was an independent predictor of 28 day (HR 0.99, 95% CI 0.98-1.0) and hospital (HR 0.99, 95% CI 0.98-1.0) mortality.

A higher haematocrit decreased the risk of death at 6 months (HR 0.97, 95% CI 0.95 – 0.99), 28 days (HR 0.97, 95% CI 0.94 – 0.99) and in hospital (HR 0.98 95%CI 0.96 – 0.99).

Table 23 Independent predictors of outcome, after inclusion in multivariate (stepwise regression) analysis, after adjustment for age and gender

Variable	Unit	HR	95% CI	p value
6-month mortality				
Age	1 year	1.04	1.03-1.05	3.0×10^{-10}
Female gender		1.27	1.0-1.6	0.05
Highest renal SOFA week 1	1 point	1.26	1.16-1.38	9.5×10^{-8}
Highest CVS SOFA week 1	1 point	1.17	1.04-1.32	0.01
Hematocrit	1%	0.97	0.95-0.99	2.9×10^{-3}
Lowest temperature day 1	1^0C	0.85	0.78-0.96	9.3×10^{-3}
Lowest heart rate day 1	10 bpm	1.08	1.02-1.16	0.01
APACHE II	1 point	1.04	1.02-1.06	7.8×10^{-4}
ICU mortality				
Age	1 year	1.04	1.02-1.05	2.8×10^{-7}
Female gender		1.29	0.97-1.72	0.08
Highest renal SOFA week 1	1 point	1.25	1.14-1.38	3.0×10^{-6}
Lowest temperature day 1	1^0C	0.83	0.73-0.94	3.9×10^{-3}
pH day 1	1 point	0.90	0.82-0.99	0.03
Hospital mortality				
Age	1 year	1.04	1.03-1.05	6.1×10^{-10}
Female gender		1.23	0.96-1.58	0.1
Highest renal SOFA week 1	1 point	1.25	1.14-1.36	6.7×10^{-7}
Haematocrit day 1	1%	0.98	0.96-1.0	0.02
APACHE II	1 point	1.03	1.01-1.05	2.0×10^{-3}
Lowest temperature day 1	1^0C	0.88	0.78-0.99	0.03
Lowest platelets day 1	10^{-9}/l	0.99	0.98-1.0	0.03
28 days-mortality				
Age	1 year	1.04	1.03-1.06	3.0×10^{-8}
Female gender		1.09	0.81-1.48	0.57
Highest renal SOFA week 1	1 point	1.34	1.21-1.49	4.1×10^{-8}
Haematocrit day 1	1%	0.97	0.94-0.99	0.01
Lowest platelets day 1	10^{-9}/l	0.98	0.97-1.0	0.01
Lowest temperature day 1	1^0C	0.82	0.70-0.95	0.01
pH day 1	1 point	0.89	0.79-1.0	0.04
Highest heart rate day 1	10 bpm	1.08	1.01-1.15	0.02

bpm, beats per minute; CVS, cardiovascular, HR, hazard ratio, CI, confidence interval

Figures 6 – 13 are selected Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of selected variables measured at day one of ICU admission (APACHE II, SOFA score, haematocrit, age, thrombocytopaenia, hypothermia, acute renal failure, need for renal replacement therapy) that were significant in individual variable analyses. The intervals shown in each graph refer to ranges for the indicated variable.

Of the 104 patients with treatment limitations, 57 (50%) were 75 years of age or older. Of these 57 patients aged above 75 and with treatment limitations, the majority (39, 68.4%) died in ICU.

Figure 6 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of APACHE II (day 1 of ICU admission)

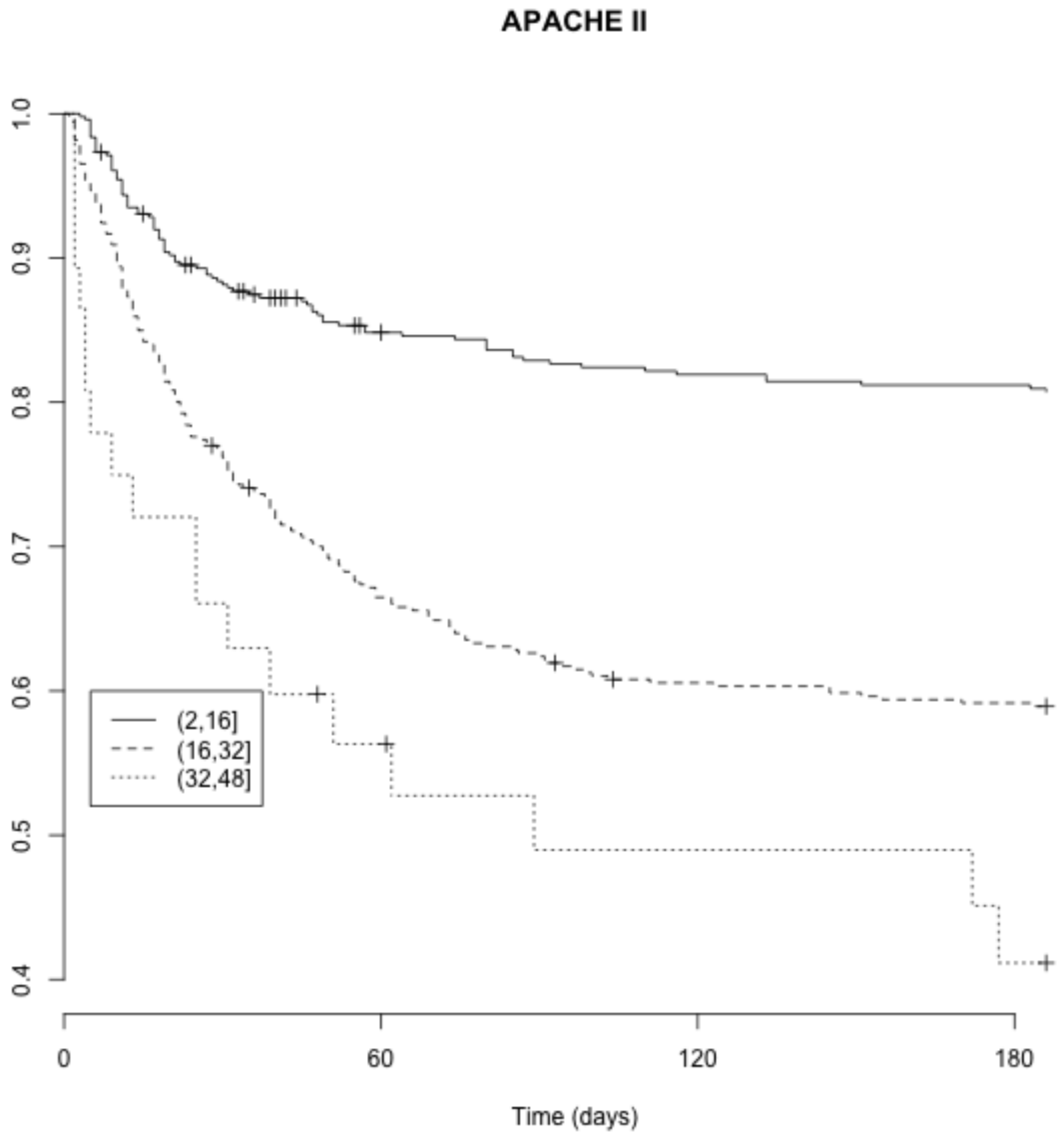


Figure 7 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of SOFA score (day 1 of ICU admission)

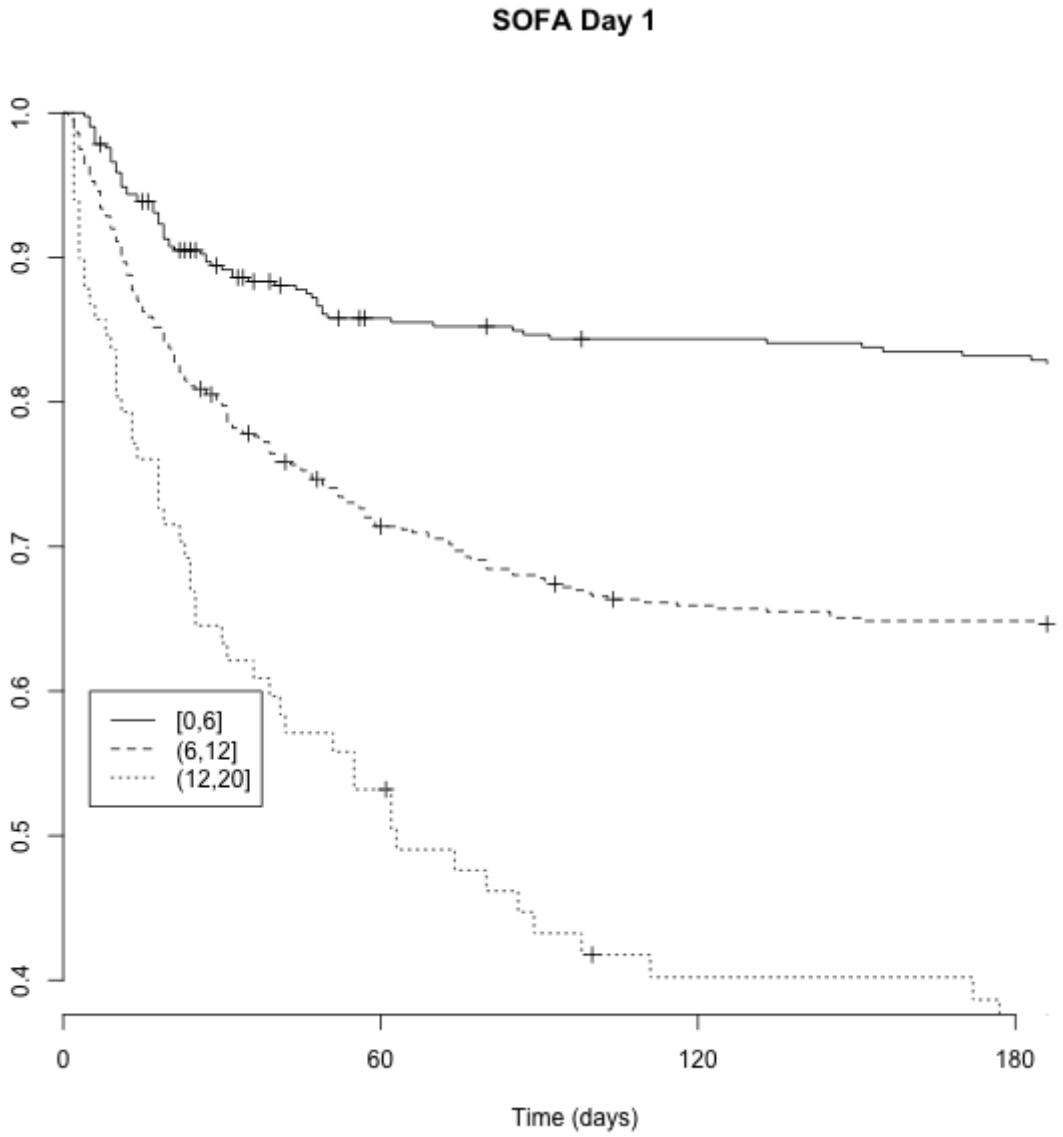


Figure 8 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of haematocrit (day 1 of ICU admission)

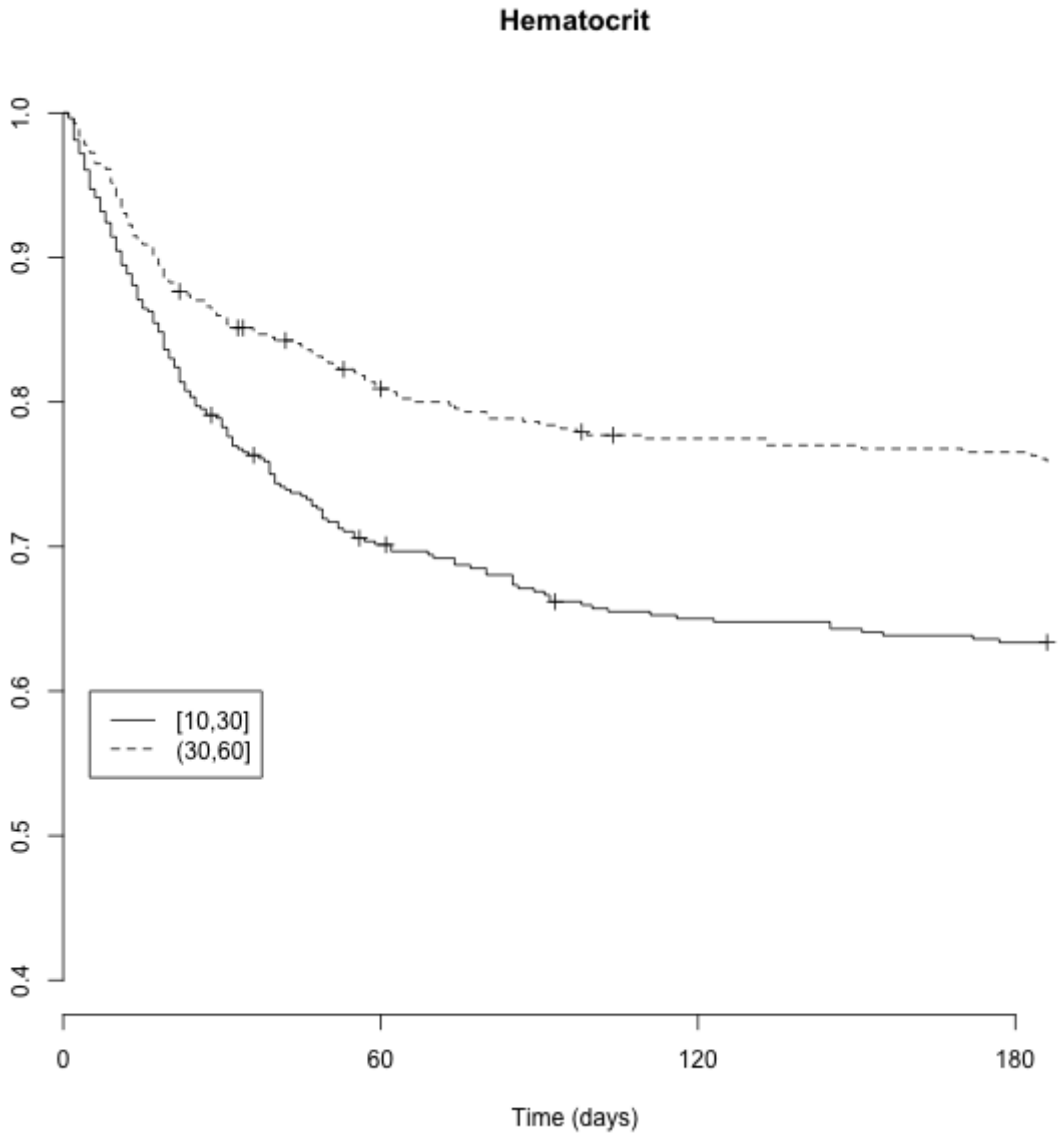


Figure 9 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of age at admission to ICU

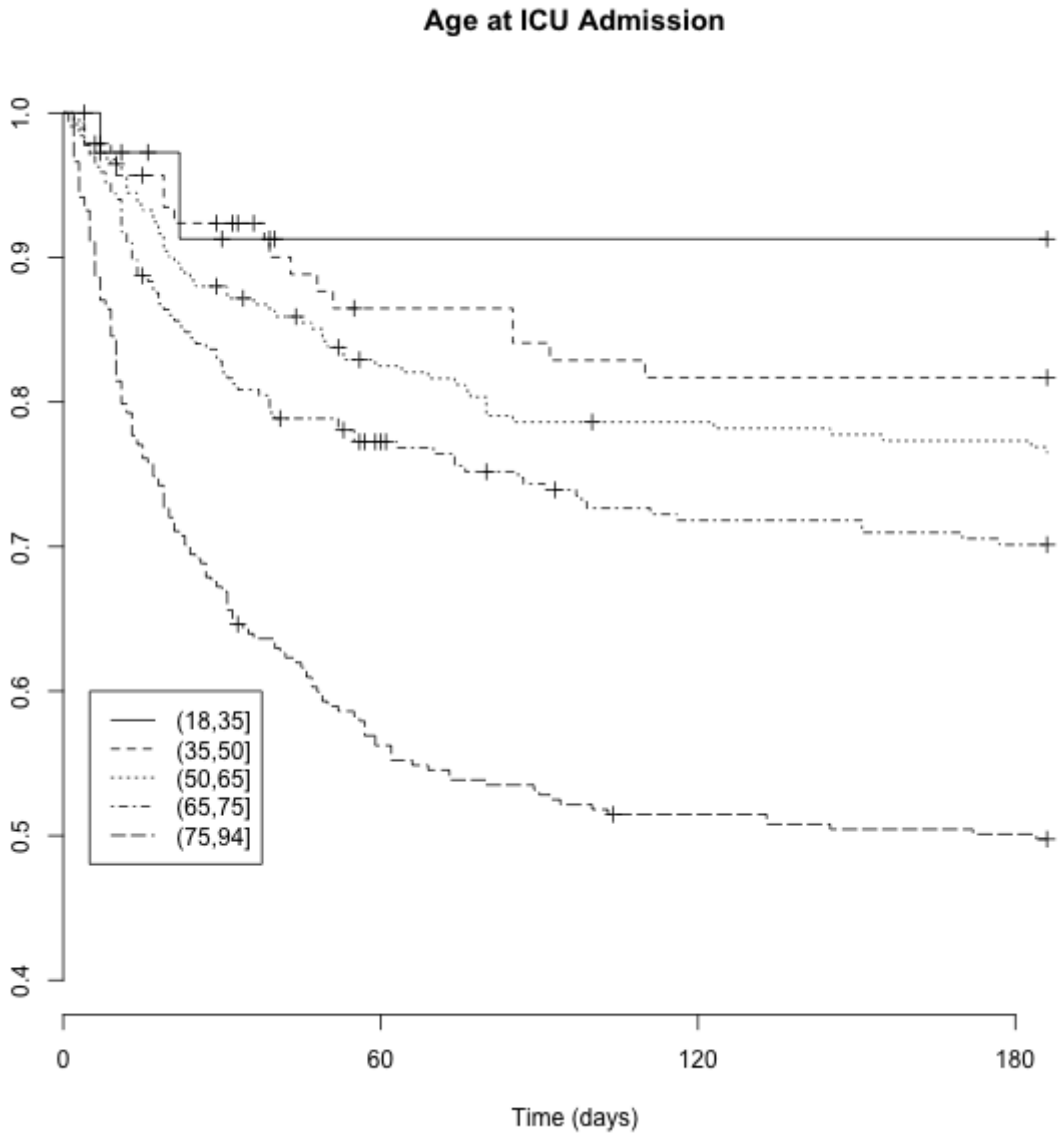


Figure 10 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of thrombocytopaenia (day 1 of ICU admission)

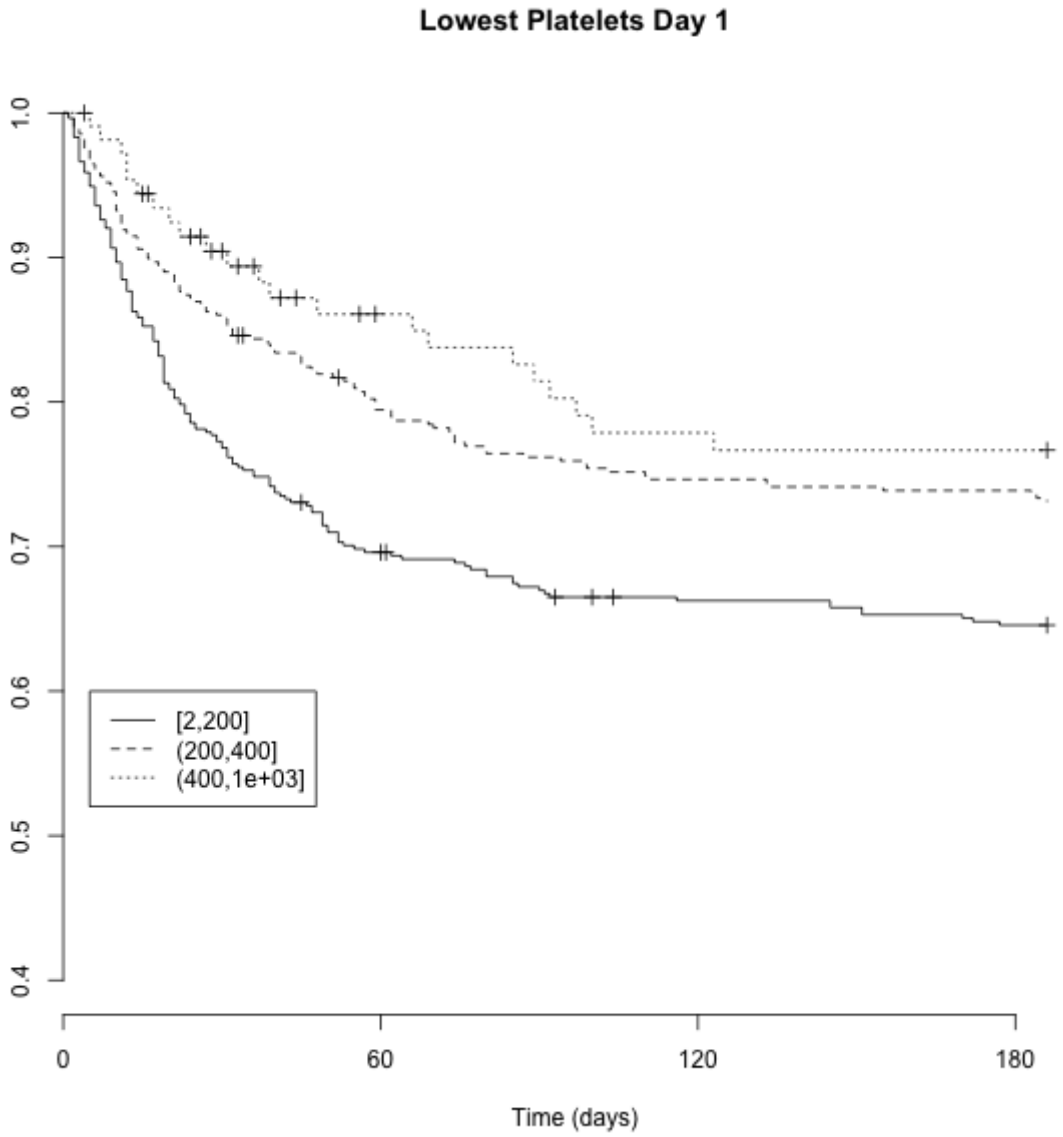


Figure 11 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of hypothermia (day 1 of ICU admission)

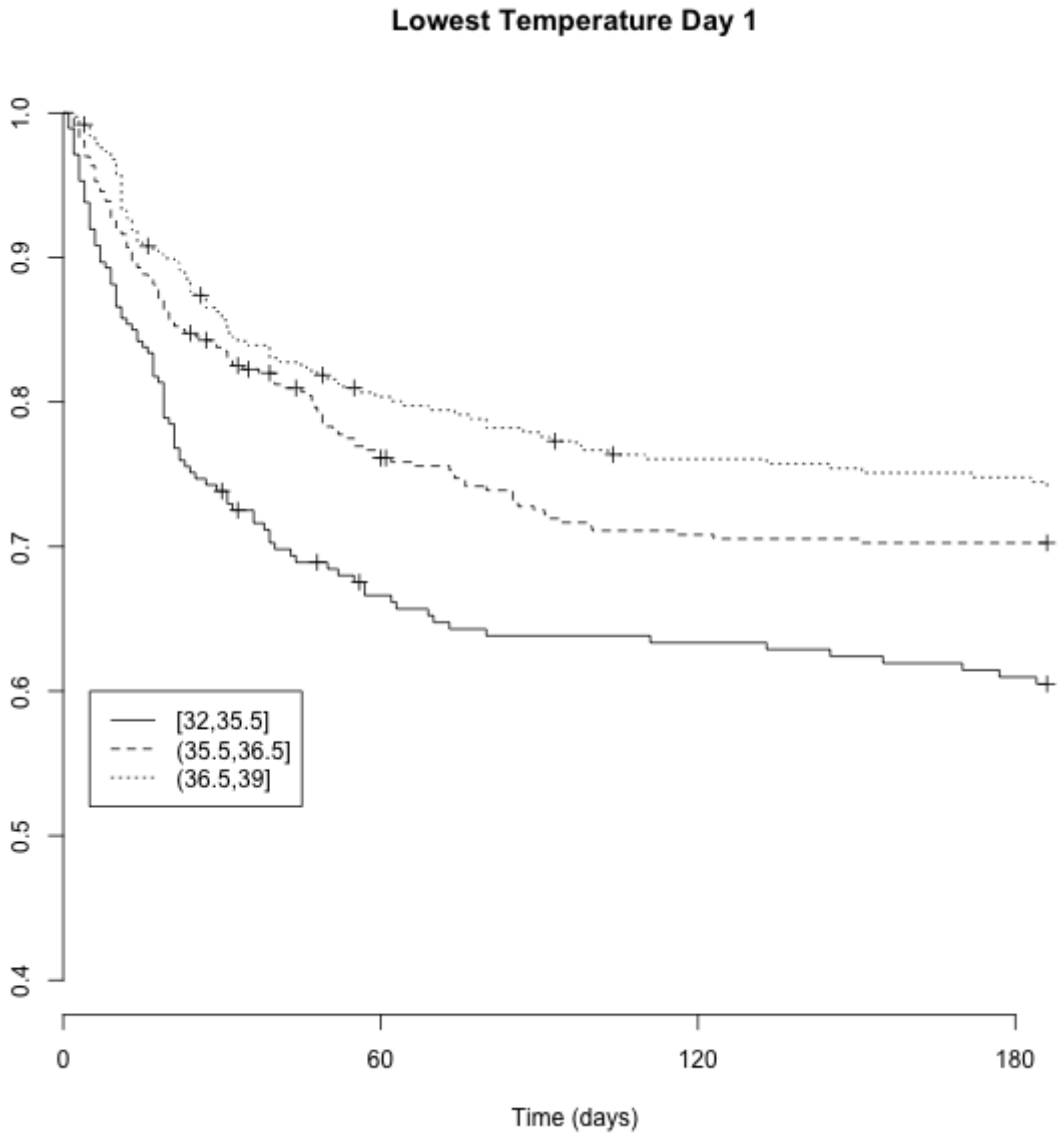


Figure 12 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of investigators' opinion of acute renal failure (ARF) (day 1 of ICU admission)

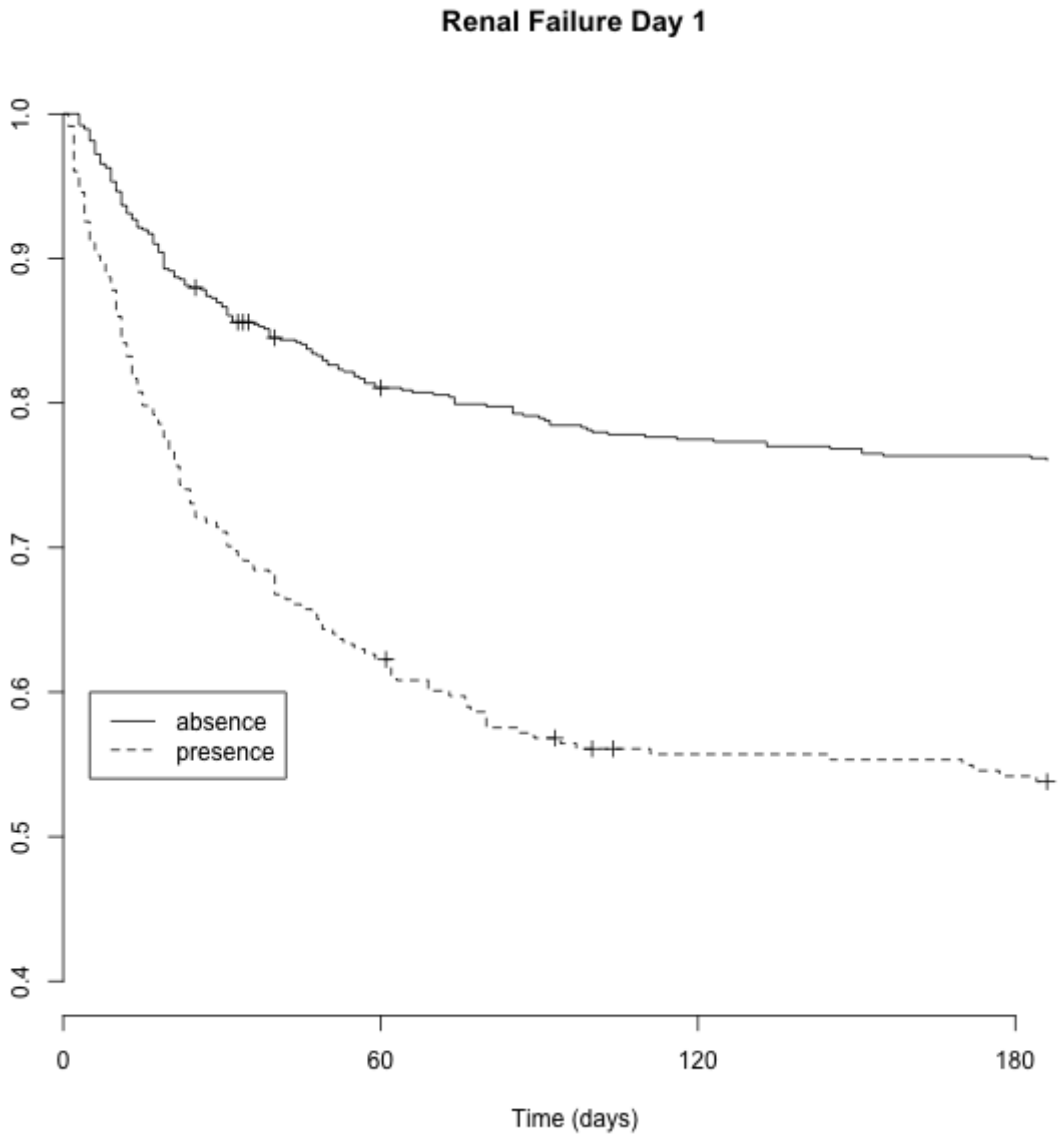
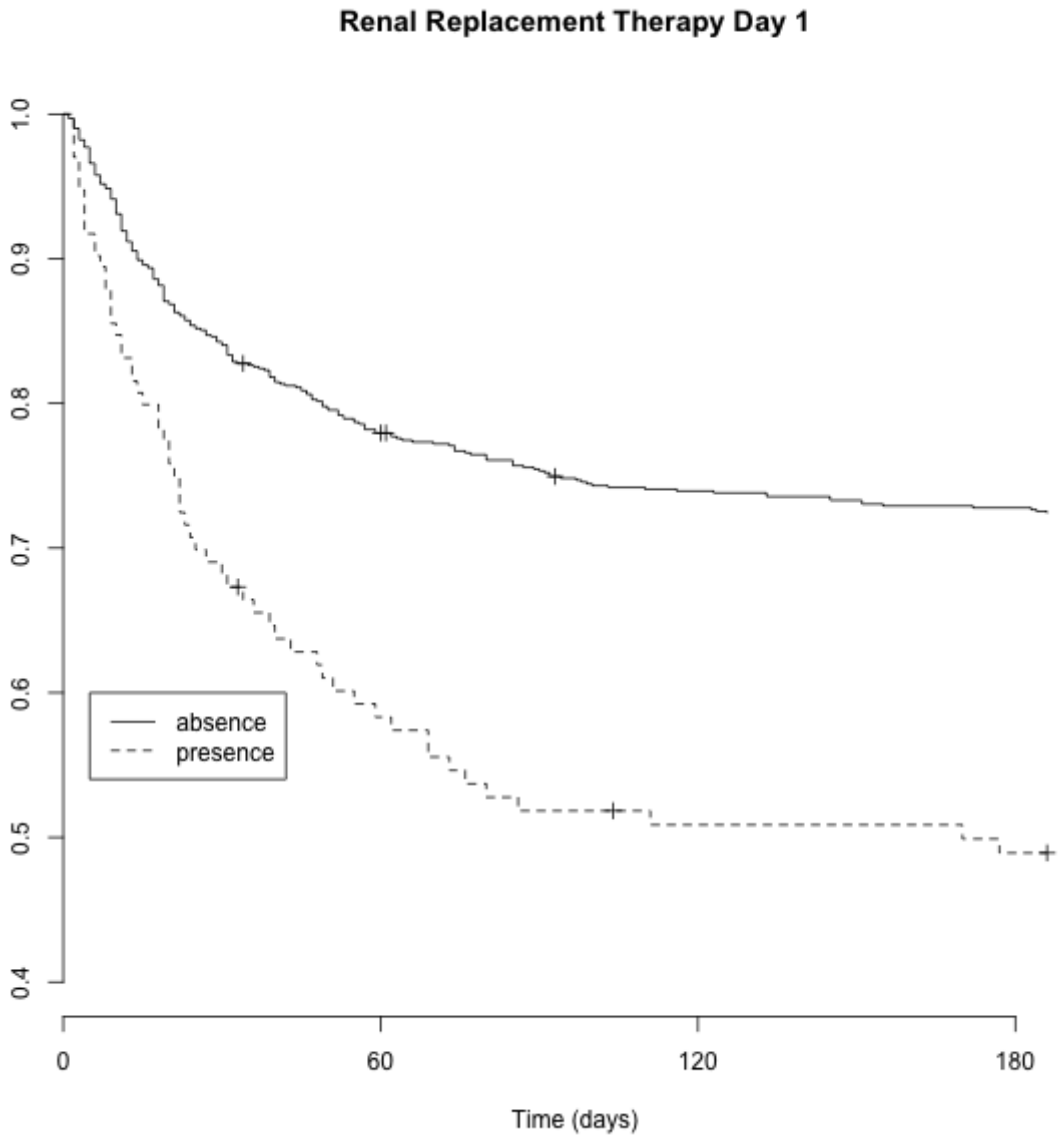


Figure 13 Kaplan-Meier curves for the 6-months survival estimate, showing the influence on survival of investigators' opinion of need for renal replacement therapy (RRT) (day 1 of ICU admission)



3.5 Summary of results

Faecal Peritonitis is a common cause of sepsis and admission to the Intensive Care Unit (ICU). The Genetics of Sepsis & Septic Shock in Europe (GenOSept) project is investigating the influence of genetic variation on the host response and outcomes in a large cohort of patients with sepsis admitted to ICUs across Europe. Here I describe an epidemiological survey of the subset of patients with faecal peritonitis.

I aimed to define the clinical characteristics, outcomes and risk factors for mortality in patients with faecal peritonitis admitted to ICUs across Europe.

Data was extracted from electronic case report forms. Phenotypic data was recorded using a detailed, quality assured clinical database. Patients were followed for six months. Kaplan-Meier analysis was used to determine mortality rates. Cox Proportional Hazards (PH) regression analysis was employed to identify independent risk factors for mortality.

Data for 977 faecal peritonitis patients admitted to 102 centres across 16 countries between 29/09/2005 and 5/01/2011 was extracted. The median age was 69.2 years (IQR 58.3-77.1), with a male preponderance (54.3%). The most common causes of faecal peritonitis were perforated diverticular disease (32.1%) and surgical anastomotic breakdown (31.1%). The ICU mortality rate at 28 days was 19.1%, increasing to 31.6% at six months (the primary outcome measure). The cause of faecal peritonitis, pre-existing co-morbidities and time from estimated onset of symptoms to surgery did not impact on survival. The strongest independent risk factors associated with an increased rate of death at 6 months included age, higher APACHE II score, acute renal and cardiovascular dysfunction within one week of

admission to ICU, hypothermia, lower haematocrit and bradycardia on day 1 of ICU stay.

In this large cohort of patients admitted to European ICUs with faecal peritonitis the 6 month mortality was 31.6%. The most consistent predictors of mortality across all time-points were increased age, development of acute renal dysfunction during the first week of admission and hypothermia on day 1 of ICU admission.

Chapter 4 – Faecal peritonitis in the GenOSept cohort - Association between trends in clinical variables and outcome

4.1 Introduction

Patients admitted to intensive care following surgical management for faecal peritonitis present particular challenges in terms of clinical management and risk assessment. Collaborating surgical and intensive care teams need shared perspectives on trends in illness severity and likely outcomes. Dynamic assessment of trends and the response to treatment, including evaluation of changes in laboratory tests and dependence on organ support, may be more informative than isolated initial measurements when assessing the prognosis of individual patients. Several methods have been evaluated for dynamic assessment of critically ill patients (Bion et al. 1988; Yu et al. 2014; Ferreira et al. 2001; Timsit et al. 2002); including those undergoing surgery, and some have examined dynamic changes in patients with peritonitis (Hernández-Palazón et al. 2013; Paugam-Burtz et al. 2002; Zügel et al. 2011; Hynninen et al. 2008; van Ruler et al. 2011). The burden of data collection is considered by many to be a deterrent to routine use (Barnett & Moonesinghe 2011), however, and one study found that existing scoring systems were inadequate for this purpose (van Ruler et al. 2011). These studies were relatively small, though; the largest reported data on 163 patients only.

Given the paucity of data on the association between trends in clinical variables during the early stages of ICU admission following surgical intervention for faecal peritonitis and outcomes, I have used a large international database of faecal peritonitis patients, with the aim of analysing trends in all available clinical variables during the first week of ICU stay and relating these to outcome.

Intra-abdominal infections and in particular faecal peritonitis, although affecting all age groups, are conditions which typically affect the elderly. The severity of sepsis, and the likelihood of an adverse outcome, are both reflected in persisting organ system failures, and may be aggravated by limited physiologic reserve, the presence of comorbidities, and impaired wound healing (Podnos et al. 2002). With an ageing population, the incidence of faecal peritonitis is likely to increase, adding pressure on already scarce healthcare resources (Angus et al. 2000; Nguyen et al. 2011). In this setting detecting trends in key laboratory and physiological variables, and in the severity of organ dysfunction could prove useful in supporting decision making with regards to escalating, limiting or withdrawing treatment and might help reduce variability in critical care decision-making (Boumendil et al. 2012).

To date the GenOSept cohort includes the largest and diagnostically most homogeneous collection of clinical data on critically ill patients with faecal peritonitis. I have already described the outcome analyses from this cohort, based on data from day 1 of admission to critical care (chapter 3). The aim of the analyses presented in this chapter is to establish potential relationships between trends in key clinical and laboratory parameters and outcomes for this population of FP patients.

4.2 Results

4.2.1 Trends in variables over first week of ICU stay

I analysed trends in physiological and laboratory variables during the first week of ICU stay in the 977 patients from 102 centres across 16 European countries enrolled in the GenOSept cohort. The primary outcome was 6-month mortality. Secondary end-points were ICU, hospital and 28 day mortality. For each trend, Cox proportional hazards (PH) regression analyses, adjusted for age and gender, were performed for each endpoint. Trends remaining significant after Bonferroni correction for multiple testing were entered into a multivariate Cox PH model to determine independent associations with mortality.

Of 977 patients, 937 patients stayed in ICU for at least 2 days, hence they could be included in the analysis of dynamic trends; of the remaining 40 (4.1%), 11 died on day 1 and 29 were discharged alive from ICU on day 1 (of whom 21 were alive at 6 months and 8 were censored alive at hospital discharge). Also 321 individuals did not have data for day 7; 237 did not have data at day 5 and 107 did not have data at day 3, (either because they had died or they had been discharged alive from ICU).

Table 24 describes trends in clinical variables between day 1 and day 7 of ICU stay (for values related to days 2, 3 and 5 see later in this section). During the observed period, the proportion of patients suffering with acute renal failure (ARF) decreased from 29.1% (283 of 974) to 24.1% (159 of 659), the proportion of those receiving ventilatory support, Continuous Positive Airways Pressure (CPAP) or

invasive mechanical ventilation, decreased from 76.3% (743 of 974) to 62.9% (413 of 657), while the proportion of those receiving any inotropic and/or vasopressor therapy decreased from 72.6% (707 of 974) to 34.2% (226 of 660). The median (IQR, interquartile range) SOFA score decreased from 7 (5-10) to 5 (2-8), mainly due to a decrease in the cardiovascular and renal components.

Table 24 Trends in variables during first 7 days ICU stay

Day	Day 1			Day 7		
Characteristics	N	n or Median[a]	% or IQR[b]	N	n or Median[a]	% or IQR[b]
Organ failure and support						
ARF	974	283	29.1	659	159	24.1
RRT	974	115	11.8	659	104	15.8
Ventilatory support	974	743	76.3	657	413	62.9
Inotropes/vasopressors use*	974			660		
None		267	27.4		434	65.8
A		33	3.4		36	5.5
B		169	17.4		105	15.9
C		505	51.9		85	12.9
SOFA	974	7[a]	5-10[b]	659	5[a]	2-8[b]
GCS SOFA	974	0[a]	0-1[b]	674	0[a]	0-1[b]
CVS SOFA	974	4[a]	1-4[b]	671	1[a]	0-3[b]
Coagulation SOFA	974	0[a]	0-1[b]	674	0[a]	0-1[b]
Respiratory SOFA	974	2[a]	2-3[b]	659	2[a]	1-3[b]
Renal SOFA	974	1[a]	0-2[b]	674	0[a]	0-1[b]
Bilirubin SOFA	974	0[a]	0-1[b]	674	0[a]	0-0[b]
Laboratory variables						
Serum bicarbonate	893	21[a]	18-24[b]	580	26[a]	23-29.1[b]
paO_2 (kPa)	945	11.3[a]	9.6-13.9[b]	590	10.8[a]	9.2-13.6[b]
$paCO_2$ (kPa)	938	5.2[a]	4.6-6[b]	535	5.2[a]	4.7-6[b]
Highest creatinine (µmol/l)	974	106.6[a]	76-160[b]	654	81.5[a]	53.9-132[b]
Lowest creatinine (µmol/l)	974	100[a]	70-144[b]	642	81.5[a]	54-130[b]
Highest WCC (10^{-9}/l)	974	12[a]	7.1-18[b]	643	15.3[a]	11-20.4[b]
Lowest WCC (10^{-9}/l)	974	9.4[a]	4.6-15[b]	643	15[a]	10.5-20[b]
Lowest platelets (10^{-9}/l)	974	212.5[a]	145-300[b]	640	234.5[a]	132-352.5[b]
Highest bilirubin (mmol/l)	974	13[a]	8-22[b]	650	10[a]	5-19[b]
Highest urea (mmol/l)	908	11[a]	6.4-17.1[b]	607	11.6[a]	7.2-20.8[b]
Chest radiography findings						
Localised infiltrates	973	115	11.8	672	68	10.1
Lobar infiltrates	973	61	6.3	672	32	4.8
Diffuse bilateral infiltrates	973	148	15.2	672	109	16.2
Physiological parameters						
Highest temperature (°C)	974	37.7[a]	37-38.3[b]	656	37.4[a]	37-38[b]
Lowest temperature (°C)	974	36.2[a]	35.7-36.9[b]	656	36.5[a]	36-37[b]
Highest SBP (mmHg)	974	140[a]	125-155[b]	655	150[a]	135-170[b]
Lowest SBP (mmHg)	972	90[a]	80-100[b]	655	108[a]	95-120[b]
Highest MAP (mmHg)	972	91[a]	82-103[b]	649	98[a]	89-110[b]
Lowest MAP (mmHg)	970	62[a]	56-70[b]	649	71[a]	63-80[b]
Highest Heart Rate (bpm)	974	117[a]	103-130[b]	655	104[a]	90-118[b]
Lowest Heart Rate (bpm)	971	85[a]	73-99[b]	655	80[a]	70-90[b]
Respiratory rate (breath/minute)	966	18[a]	14-24[b]	638	20[a]	16-27[b]
Urine volume (ml/24 hours)	973	1375[a]	790-2100[b]	644	2276.5[a]	1333.5-3411.5[b]
P:F ratio (kPa)	942	27.8[a]	19.6-37.7[b]	573	30.7[a]	23.1-39.2[b]

* Inotropic and vasopressors use was coded as follows: A = Dopamine ≤ 5 µg/kg/min or Dobutamine, B = Dopamine > 5 µg/kg/min or adrenaline/noradrenaline ≤0.1 µg/kg/min, C = Dopamine > 15 µg/kg/min or adrenaline/noradrenaline > 0.1 µg/kg/min

n, absolute count; IQR, interquartile range; N, number of available observations; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; ARF, Acute Renal Failure; RRT, Renal Replacement Therapy; CVS, cardiovascular; paO_2, arterial partial pressure of oxygen; $paCO_2$, arterial partial pressure of carbon dioxide; WCC, White Cell Count; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; bpm, beats per minute; P:F, ratio of partial pressure arterial oxygen and fraction of inspired oxygen;

[a]Median and [b]IQR are shown instead of absolute count (n) and percentage (%).

Table 25 shows the estimated hazard ratios (HRs) for trends in variables that were associated with 6 month, ICU, hospital and 28 day mortality, after adjusting for multiple testing in individual variable analyses and after inclusion in multivariate analyses.

The trends in variables over the first 7 days ICU stay that remained significant and were independently associated with 6 months outcome were: worsening thrombocytopaenia and renal function (total daily urine output and renal component of the SOFA score), highest recorded level of bilirubin and GCS component of the SOFA score.

Changes in renal function (total daily urine output and renal component of the SOFA score), GCS component of the SOFA score, total SOFA and worsening thrombocytopaenia were also independently associated with secondary outcomes.

Dynamic trends in all other measured laboratory and physiological variables and in radiological findings failed to be independently associated with outcome on multivariate analyses. Furthermore, changes in respiratory support, renal replacement therapy and inotrope and/or vasopressor requirements were not independently associated with any of the primary or secondary outcomes.

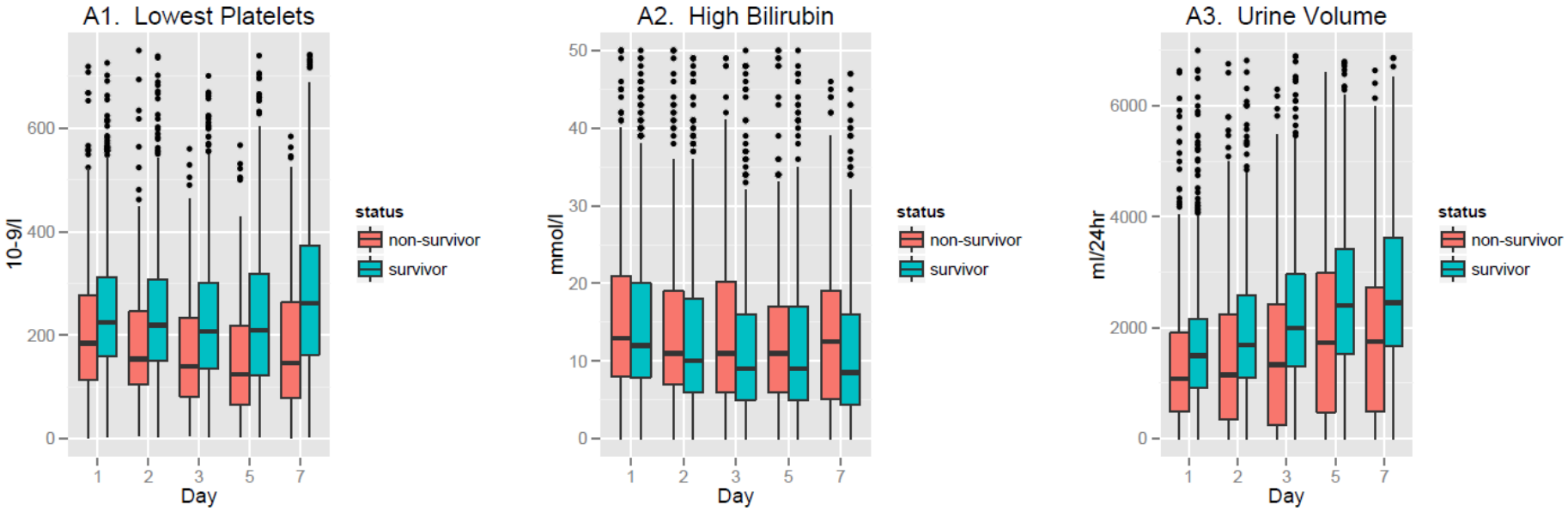
Table 25 Factors independently associated with 6 month, ICU, hospital and 28 day mortality, after adjustment for age and gender

Significant variables grouped by outcome	Unit	HR	95% CI	p value
6 month mortality				
Deterioration of thrombocytopaenia	10 x 10^{-9}/l	1.02	1.01-1.03	<0.001
Decrease in daily urinary volume	100 ml	1.02	1.01-1.03	<0.001
Decrease in highest recorded bilirubin	mmol/l	0.99	0.99-0.99	0.020
Improvement in GCS SOFA	1 point	0.81	0.68-0.98	0.028
Improvement in renal SOFA	1 point	0.87	0.75-0.99	0.047
ICU mortality				
Decrease in daily urinary volume	100 ml	1.02	1.01-1.03	0.005
Improvement in total SOFA	1 point	0.91	0.85-0.98	0.009
Hospital mortality				
Deterioration of thrombocytopaenia	10 x 10^{-9}/l	1.02	1.01-1.03	0.001
Decrease in daily urinary volume	100 ml	1.02	1.01-1.03	<0.001
Improvement in GCS SOFA	1 point	0.8	0.68-0.95	0.011
Improvement in renal SOFA	1 point	0.87	0.77-0.99	0.043
28 day mortality				
Decrease in daily urinary volume	100 ml	1.02	1.01-1.03	0.001
Improvement in GCS SOFA	1 point	0.75	0.61-0.93	0.010
Improvement in renal SOFA	1 point	0.79	0.66-0.95	0.013

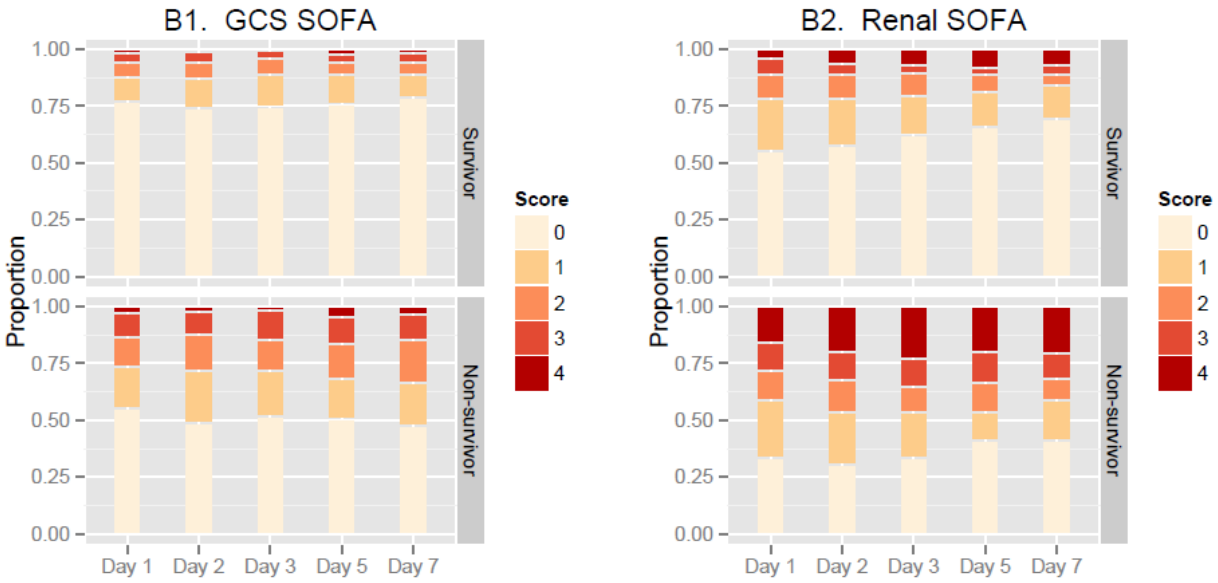
SOFA, Sequential Organ Failure Assessment, SBP, Systolic Blood Pressure; CPAP, Continuous Positive Airways Pressure; CXR, chest radiography; RRT, Renal Replacement Therapy; GCS, Glasgow Coma Score; SBP, Systolic Blood Pressure; HR, Hazard Ratio; CI, confidence interval

Figure 14 displays trends over the first week of ICU admission in the five variables independently associated with 6 month outcome (thrombocytopaenia, daily urinary volume, renal and GCS components of the SOFA score, serum bilirubin concentration).

Figure 14 Trends in variables independently associated with 6 month survival (primary outcome)



Sections A1-A3. Daily lowest platelet count, 24 hour urinary volume, highest recorded bilirubin concentration. The boxes indicate median and inter-quartile range, the whiskers extend to include 1.5 x IQR, dots include outliers outside this range.



Sections B1-B2. Daily GCS and renal components of the SOFA score. Proportions of different values of the renal and GCS components of the SOFA are indicated for survivors and non-survivors.

Survivors and non-survivors displayed differences in both absolute values and trends in these variables during their ICU stay. The platelet count remained consistently lower throughout the observation period and decreased more markedly in non-survivors compared to survivors. The daily total urine output was consistently greater and increased more markedly in survivors compared to non-survivors, throughout the 7 days (Table 26). The highest measured bilirubin showed an improvement during the 7 days observation period in survivors, but not in non-survivors. The GCS component of the SOFA score for non-survivors was worse and, in general, deteriorated further during the observation period, while the renal component of the SOFA scores was consistently worse in non-survivors.

Table 26 Trends during first 7 days ICU stay (in survivors and non-survivors at six months) for variables which were independently associated with outcomes at multivariate analyses

Day	Day 1			Day 7		
Characteristics	N	n or Median[a]	% or IQR[b]	N	n or Median[a]	% or IQR[b]
Lowest platelets (10-9/l)						
Survivors	667	226[a]	159-316[b]	426	267[a]	164-388[b]
Non-survivors	307	185[a]	113-280[b]	214	146[a]	78-274[b]
Urine volume (ml/24 hours)						
Survivors	666	1499[a]	916-2170[b]	429	2460[a]	1680-3633[b]
Non-survivors	307	1080[a]	475-1915[b]	215	1750[a]	471-2774[b]
Highest bilirubin (mmol/l)						
Survivors	667	13[a]	8-21[b]	433	9[a]	5-17[b]
Non-survivors	307	14[a]	8-25[b]	217	14[a]	6-25[b]
GCS SOFA						
Survivors	667	0[a]	0-0[b]	453	0[a]	0-0[b]
Non-survivors	307	0[a]	0-2[b]	221	1[a]	0-2[b]
Renal SOFA						
Survivors	667	0[a]	0-1[b]	453	0[a]	0-1[b]
Non-survivors	307	1[a]	0-3[b]	221	1[a]	0-3[b]

n, absolute count; IQR, interquartile range; N, number of available observations; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale;

[a]Median and [b]IQR are shown instead of absolute count (n) and percentage (%).

4.2.2 Shorter term trends (2, 3 and 5 days)

The analyses of trends over the first 2, 3 and 5 days yielded similar results (Table 27).

The trends over the first 48 hours ICU stay independently associated with outcomes were deteriorating thrombocytopaenia and renal function (urinary output and renal SOFA score) and total SOFA score (Table 28). The trends over the first 3 days ICU independently associated with outcomes were thrombocytopaenia, renal function (urinary output and renal SOFA score), total SOFA score and, for 28 day mortality only, GCS SOFA score, MAP and P:F ratio (Table 29). The trends over the first 5 days ICU independently associated with outcomes were thrombocytopaenia, renal function (urinary output, renal SOFA score and highest recorded serum urea) and total SOFA score (Table 30).

4.2.3 The importance of Trends

Although the hazard ratios presented in tables 25 and 30, for example, appear to be small, the larger the change in the underlying variable, the larger the effect (proportionally) on mortality. For example a reduction in platelet count of 50 (*10-9/l) is associated with a hazard ratio for 6 month mortality of 1.10 (95% confidence interval of 1.05-1.16, $p<0.001$), indicating a 10% increase in risk of death at 6 months. Similarly, a reduction in 24 hour urine output of just 500 ml is associated with a hazard ratio for 6 month mortality of 1.09 (95% confidence interval 1.04-1.14, $p<0.001$), which translates into a 9% increase in risk of death. Such trends are therefore potentially relevant to the practicing clinician and will contribute to bedside assessment of severity of illness in patients with faecal peritonitis.

Table 27 Trends in variables (days 2, 3 and 5 ICU stay)

Day	Day 2			Day 3			Day 5		
Characteristics	N	n or Median[a]	% or IQR[b]	N	n or Median[a]	% or IQR[b]	N	n or Median[a]	% or IQR[b]
Organ failure and support									
ARF	939	274	29.2	873	251	28.8	742	203	27.4
RRT	939	151	16.1	873	158	18.1	743	132	17.8
Ventilatory support	938	627	66.8	872	569	65.3	742	490	66
Inotropes/vasopressors use*	938			873			742		
None		276	29.4		345	39.5		421	56.7
A		31	3.3		50	5.7		47	6.3
B		209	22.3		192	22		119	16
C		422	45		286	32.8		155	20.9
SOFA	939	7[a]	4-10[b]	873	7[a]	3-9[b]	743	6[a]	3-9[b]
GCS SOFA	940	0[a]	0-1[b]	877	0[a]	0-1[b]	755	0[a]	0-1[b]
CVS SOFA	939	3[a]	1-4[b]	877	3[a]	0-4[b]	752	1[a]	0-3[b]
Coagulation SOFA	940	0[a]	0-1[b]	877	0[a]	0-1[b]	755	0[a]	0-1[b]
Respiratory SOFA	939	2[a]	1-3[b]	873	2[a]	1-3[b]	743	2[a]	1-3[b]
Renal SOFA	940	1[a]	0-2[b]	877	0[a]	0-2[b]	755	0[a]	0-2[b]
Bilirubin SOFA	940	0[a]	0-1[b]	877	0[a]	0-0[b]	755	0[a]	0-0[b]
Laboratory parameters									
Serum bicarbonate	845	22.4[a]	20-25,6[b]	782	24[a]	21-27[b]	657	25.2[a]	22.9-29[b]
paO_2 (kPa)	883	10.9[a]	9.6-13.2[b]	807	11[a]	9.2-13.3[b]	679	10.8[a]	9.1-13.2[b]
$paCO_2$ (kPa)	819	5.3[a]	4.7-6.1[b]	749	5.3[a]	4.7-6.1[b]	623	5.3[a]	4.7-6[b]
Highest creatinine (µmol/l)	938	105.3[a]	75-158[b]	870	96.4[a]	68-150[b]	740	87[a]	59.3-141[b]
Lowest creatinine (µmol/l)	935	100[a]	70-150[b]	869	94[a]	66-146[b]	732	85.4[a]	58.3-136[b]
Highest WCC (10^{-9}/l)	937	13.2[a]	9.3-19[b]	870	14.3[a]	9.8-18.9[b]	725	13.5[a]	10.2-18.9[b]
Lowest WCC (10^{-9}/l)	937	12.4[a]	8.4-18[b]	869	13.2[a]	9.4-18.4[b]	725	13[a]	9.8-18.1[b]
Lowest platelets (10^{-9}/l)	937	204[a]	130-294[b]	868	189[a]	115-286[b]	726	180.5[a]	102-285[b]
Highest bilirubin (mmol/l)	938	11[a]	6.8-20[b]	871	10[a]	6-18[b]	739	10[a]	5-19[b]
Highest urea (mmol/l)	874	10.7[a]	7-18[b]	815	10.6[a]	6.7-18[b]	687	11.4[a]	6.6-20.1[b]
Chest radiography findings									
Localised infiltrates	939	76	8.1	876	78	8.9	752	77	10.2
Lobar infiltrates	939	37	3.9	876	28	3.2	752	43	5.7
Diffuse bilateral infiltrates	939	109	11.6	876	122	13.9	752	126	16.8
Physiological parameters									
Highest temperature (°C)	936	37.5[a]	37-38[b]	870	37.3[a]	36.9-38[b]	740	37.4[a]	36.9-38[b]
Lowest temperature (°C)	936	36.4[a]	36-37[b]	870	36.4[a]	36-36.9[b]	740	36.4[a]	36-37[b]
Highest SBP (mmHg)	938	142[a]	130-160[b]	872	150[a]	130.5-168[b]	740	151[a]	135-170[b]
Lowest SBP (mmHg)	936	100[a]	90-110[b]	872	105[a]	93-118[b]	738	110[a]	96-120[b]
Highest MAP (mmHg)	929	95[a]	84-105[b]	860	98[a]	88-110[b]	733	100[a]	88-112[b]
Lowest MAP (mmHg)	927	66[a]	60-74[b]	859	70[a]	61-78[b]	730	70[a]	64-80[b]
Highest Heart Rate (bpm)	938	110[a]	98-125[b]	872	106[a]	94-120[b]	740	103[a]	90-119[b]
Lowest Heart Rate (bpm)	935	83[a]	72-95[b]	871	80[a]	70-90[b]	737	80[a]	70-90[b]
Respiratory rate (breath/minute)	929	18[a]	15-24[b]	861	20[a]	15-24[b]	729	20[a]	16-26[b]
Urine volume (ml/24 hours)	931	1580[a]	926-2460[b]	868	1869[a]	1012.5-2882.5[b]	733	2200[a]	1280-3375[b]
P:F ratio (kPa)	880	29.3[a]	21-39.1[b]	803	30.3[a]	21.4-38.6[b]	666	30.7[a]	22.3-39.1[b]

* Inotropic and vasopressors use was coded as follows: A = Dopamine ≤ 5 µg/kg/min or Dobutamine, B = Dopamine > 5 µg/kg/min or adrenaline/noradrenaline ≤0.1 µg/kg/min, C = Dopamine > 15 µg/kg/min or adrenaline/noradrenaline > 0.1 µg/kg/min

n, absolute count; IQR, interquartile range; N, number of available observations; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; ARF, Acute Renal Failure; RRT, Renal Replacement Therapy; CVS, cardiovascular; paO_2, arterial partial pressure of oxygen; $paCO_2$, arterial partial pressure of carbon dioxide; WCC, White Cell Count; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; bpm, beats per minute;

[a]Median and [b]IQR are shown instead of absolute count (n) and percentage (%).

Table 28 Analyses conducted on trends over the first 2 days ICU stay showing factors independently associated with 6 month, ICU, hospital and 28 day mortality, after adjustment for age and gender

Variable	Unit	HR	95% CI	p value
6 month mortality				
Deterioration of thrombocytopaenia	10 x 10^{-9}/l platelets	1.025	1.01-1.04	0.004
Improvement in total SOFA	1 point	0.93	0.87-0.99	0.02
Decrease in daily urinary volume	100 ml	1.01	1-1.02	0.025
ICU mortality				
Improvement in renal SOFA	1 point	0.84	0.71-0.99	0.05
Hospital mortality				
Improvement in total SOFA	1 point	0.93	0.87-0.99	0.03
Improvement in renal SOFA	1 point	0.86	0.75-0.99	0.04
28 day mortality				
Improvement in total SOFA	1 point	0.87	0.8-0.94	<0.001

SOFA, Sequential Organ Failure Assessment; HR, Hazard Ratio; CI, confidence interval

Table 29 Analyses conducted on trends over the first 3 days ICU stay showing factors independently associated with 6 month, ICU, hospital and 28 day mortality, after adjustment for age and gender.

Variable	Unit	HR	95% CI	p value
6 month mortality				
Deterioration of thrombocytopaenia	10 x 10^{-9}/l platelets	1.03	1.02-1.05	<0.001
Improvement in renal SOFA	1 point	0.78	0.69-0.89	<0.001
Decrease in daily urinary volume	100 ml	1.01	1-1.02	0.040
ICU mortality				
Improvement in renal SOFA	1 point	0.84	0.73-0.97	0.016
Improvement in total SOFA	1 point	0.92	0.87-0.97	0.004
Hospital mortality				
Deterioration of thrombocytopaenia	10 x 10^{-9}/l platelets	1.02	1.01-1.04	0.014
Improvement in total SOFA	1 point	0.94	0.89-0.99	0.025
Improvement in renal SOFA	1 point	0.81	0.71-0.92	0.001
28 day mortality				
Worsening in P:F ratio	1 kPa	1.03	1.02-1.04	<0.001
Improvement in GCS SOFA	1 point	0.78	0.62-0.98	0.033
Improvement in renal SOFA	1 point	0.74	0.61-0.89	0.002
Deterioration in lowest MAP	1 mmHg	1.02	1-1.03	0.024

SOFA, Sequential Organ Failure Assessment, GCS, Glasgow Coma Score; MAP, Mean Arterial Pressure; P:F, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; HR, Hazard Ratio; CI, confidence interval

Table 30 Analyses conducted on trends over the first 5 days ICU stay showing factors independently associated with 6 month, ICU, hospital and 28 day mortality, after adjustment for age and gender

Variable	Unit	HR	95% CI	p value
6 month mortality				
Deterioration of thrombocytopaenia	10×10^{-9}/l platelets	1.02	1.01-1.03	0.003
Improvement in renal SOFA	1 point	0.74	0.56-0.99	0.040
ICU mortality				
Improvement in total SOFA	1 point	0.92	0.88-0.97	0.001
Hospital mortality				
Deterioration of thrombocytopaenia	10×10^{-9}/l platelets	1.02	1-1.03	0.025
Decrease in daily urinary volume	100 ml	1.01	1-1.02	0.010
Improvement in total SOFA	1 point	0.89	0.81-0.99	0.030
28 day mortality				
Improvement in renal SOFA	1 point	0.81	0.69-0.96	0.015
Improvement in highest recorded urea	mmol/l	0.99	0.98-0.99	<0.001

SOFA, Sequential Organ Failure Assessment; HR, Hazard Ratio; CI, confidence interval

4.3 Summary of results

Patients admitted to intensive care following surgery for faecal peritonitis present particular challenges in terms of clinical management and risk assessment. Collaborating surgical and intensive care teams need shared perspectives on prognosis. I aimed to determine the relationship between dynamic assessment of trends in selected variables and outcomes.

I have analysed trends in all variables available for the first week of ICU stay in 977 patients from the GenOSept FP cohort. The primary outcome was 6 month mortality. Secondary end-points were ICU, hospital and 28 day mortality. For each trend, Cox proportional hazards (PH) regression analyses, adjusted for age and gender, were performed for each endpoint. Trends found to be significant in these analyses, after Bonferroni correction for multiple testing, were entered into a multivariate Cox PH model, to determine independent associations with mortality.

The trends over the first 7 days ICU stay (primary analysis) retained as independently associated with 6 months outcome were worsening thrombocytopaenia (mortality HR=1.02, 95% CI 1.01-1.03, $p<0.001$) and renal function (total daily urine output HR=1.02, 95%CI 1.01-1.03, $p<0.001$; renal SOFA sub-score HR=0.87, 95%CI 0.75-0.99, $p=0.047$), highest recorded level of bilirubin (HR=0.99, 95%CI 0.99-0.99, $p=0.02$) and GCS SOFA sub-score (HR=0.81, 95%CI 0.68-0.98, $p=0.028$). Changes in renal function (total daily urine output and renal component of the SOFA score), GCS component of the SOFA score, total SOFA and worsening thrombocytopaenia were also independently associated with secondary outcomes (ICU, hospital and 28 day mortality). Dynamic trends over the first 7 days ICU stay in all other measured laboratory and physiological variables and in radiological findings failed to be retained as independently associated with

outcome on multivariate analyses. Furthermore, changes in respiratory support, renal replacement therapy and inotrope and/or vasopressor requirements were not independently associated with any of the primary or secondary outcomes.

Secondary *post-hoc* analyses of trends over the first 2, 3 and 5 days corroborated these findings.

Chapter 5 - Derivation and Validation of a prognostic model

5.1 Introduction

Prognostic scores and models of illness severity are useful both clinically and for research. They support critical care physicians in decision making through more accurate prognostication, they describe and summarize case mix, and inform health economic evaluations of cost-effectiveness. Many types of models exist and their roles are not mutually exclusive, as their combined use may afford better prognostic reliability (Vincent & Moreno 2010). These tools are usually insufficiently accurate to be useful for predicting individual survival and are generally reserved for benchmarking quality of care and for research studies (Eachempati 2014; Breslow & Badawi 2012; Bouch & Thompson 2008), for example when examining heterogeneity of treatment effect in clinical trials (Iwashyna et al. 2015).

The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit describes intra-abdominal infections as a *"very heterogeneous group of infectious processes that share an anatomical site between the diaphragm and the pelvis"* (Calandra & Cohen 2005). The anatomical, clinical and pathophysiological heterogeneity of these infections, together with their varied etiology and prognosis, have given rise to a range of prognostic instruments tailored to specific populations.

Generic "peritonitis" prognostic tools (aimed at peritonitis of any origin), such as the Mannheim Peritonitis Index (MPI) or the Peritonitis Index of Altona II (PIA II), rely on factors such as age, degree of organ failure, origin of sepsis and intra-operative findings to risk stratify different types of peritonitis, but, given the considerable heterogeneity of intra-abdominal infections, these scoring systems may

not be sufficiently specific in terms of etiology (Wacha et al. 1987; Wittmann et al. 1987). Other scoring systems have been devised to explicitly address the issue of prognostication in selected forms of peritonitis, such as the left colonic Peritonitis Severity Score (PSS), developed for patients with distal large bowel peritonitis of various origins (Biondo et al. 2000). The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) is another risk adjustment model, developed in 1991 for use in surgical patients (Copeland et al. 1991). A modification of this prognostic model, obtained by excluding some of the physiological factors of the original POSSUM, was developed for use specifically in patients undergoing surgery for colorectal cancer (CR-POSSUM) (Tekkis et al. 2004). Importantly, all of these scores incorporate intra-operative findings, and are either designed to cater for the heterogeneous spectrum of peritoneal infections (such as the MPI and PIA II), or to focus on a very narrow subset of peritonitis, identified by location (left colonic, in the case of PSS) or aetiology (colorectal malignancy, as in CR-POSSUM). To date no prognostic score has been developed for the critically ill patient with FP in the post-operative phase.

International multicentre prospectively collected patient datasets, such as The GenOSept and GAinS cohorts, provide an opportunity to develop and evaluate such prognostic systems.

5.2 Results

5.2.1 Baseline and outcome data

The derivation cohort included 462 patients with FP recruited in the United Kingdom between September 2005 and January 2011. Their median (Inter-Quartile Range, IQR) age was 69.4 (58.6-77.2) years. The geographic validation (non-UK) cohort included 515 FP patients recruited to the GenOSept study from the other European countries during the same period. Their median (IQR) age was 69.1 (58-77) years. The temporal validation cohort included 323 FP patients recruited in the UK between January 2011 and March 2015 to the GAinS study. Their median (IQR) age was 68.3 (57.6-77.2) years. For details of the recruiting centres, please see appendix.

The baseline characteristics and the outcomes of the three cohorts are presented in Tables 31 and 32, respectively.

The age distribution was not significantly different across the cohorts, although the derivation cohort had a higher proportion of patients aged over 75. Males predominated in all cohorts. The racial distribution was more heterogeneous in the geographic validation cohort, while the derivation and the temporal validation cohorts were almost entirely Caucasian. Among the comorbidities diabetes, previous serious infections and other illnesses were more prevalent in the geographic validation cohort, compared to the other cohorts. The underlying causes for faecal peritonitis varied across cohorts, with anastomotic breakdown being particularly common in the geographic validation cohort. Baseline SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores and prevalence of mechanical ventilation on day one were comparable across the cohorts. The occurrence of acute renal failure on day one

was more frequent in the geographic validation cohort, with differences with the other cohorts (32.7%, 42.8% and 23.3% for the derivation, geographic and temporal validation cohorts, respectively), accompanied by a difference in the utilisation of renal replacement therapy (21%, 21.3% and 7.5% for the derivation, geographic and temporal validation cohorts, respectively) on day one. The geographic validation cohort was characterised by higher mortality rates (at all time points) and longer ICU stay, compared to the other two cohorts; this latter feature was also reflected, although to a lesser extent, in the length of hospital stay.

Table 31 Patients' baseline characteristics for the derivation, geographic and temporal external validation sub-cohorts

Cohort	Derivation (UK until Jan 2011) GenOSept UK		Geographic validation (non-UK) GenOSept Europe		Temporal validation (UK post Jan 2011) GAinS	
Total number of patients	462		515		323	
Characteristics	Median or n	IQR or %	Median or n	IQR or %	Median or n	IQR or %
Age						
Available data	462	100%	515	100%	323	100%
18-34	11	2.4%	25	4.9%	11	3.4%
35-44	15	3.3%	18	3.5%	16	5%
45-54	54	11.7%	52	10.1%	38	11.8%
55-64	93	20.1%	98	19%	73	22.6%
65-74	113	24.5%	151	29.3%	88	27.2%
75-84	149	32.3%	149	28.9%	75	23.2%
85-95	27	5.8%	22	4.3%	22	6.8%
Gender						
Available data	462	100%	515	100%	323	100%
Male	236	51.1%	304	59%	171	52.9%
Female	226	48.9%	211	41%	152	47.1%
Race						
Available data	460	99.6%	510	99%	323	100%
Caucasian	454	98.7%	502	98.4%	315	97.5%
Asian	4	0.9%	7	1.4%	3	0.9%
African	1	0.2%	1	0.2%	3	0.9%
Mixed	1	0.2%	0	0%	2	0.6%
Medical comorbidities						
Available data	462	100%	515	100%	323	100%
Heart and vascular disease	187	40.6%	202	39.2%	117	36.2%
Respiratory disease	111	24.1%	133	25.8%	97	30%
Neurological disease	48	10.4%	57	11.1%	24	7.4%
Severe renal disease	39	8.6%	21	4.3%	16	5%
Gastrointestinal disease	98	21.3%	132	25.7%	76	23.5%
Malignancy	135	29.3%	160	31.1%	84	26%
Diabetes	61	13.2%	102	19.8%	44	13.6%
Previous serious infection*	8	1.7%	25	4.9%	5	1.6%
Other illness	130	28.2%	210	40.8%	83	25.7%
Severe exercise restriction	3	0.7%	6	1.2%	1	0.3%
Chronic dialysis	5	1.1%	8	1.6%	5	1.6%
Chronic steroids use**	2	0.4%	9	1.8%	5	1.6%
Cause of FP						
Available data	461	99.8%	511	99.2%	323	100%
Perforated diverticulum	137	29.7%	175	34.3%	89	27.6%
Anastomotic breakdown	115	25%	187	36.6%	61	18.9%
Malignancy	65	14.1%	64	12.5%	35	10.8%
Trauma	22	4.8%	45	8.8%	16	5%
Other	122	26.5%	40	7.8%	124	38.4%
Time to surgery (days)	1	1-3	1	1-3	1	1-3
Acute physiology						
Available data	461	99.8%	513	99.6%	321	99.4%
APACHE II score	15	12-20	17	13-22	16	12-21
SOFA score	7	5-9	7	5-11	6	5-8
Acute renal failure	129	32.7%	214	42.8%	70	21.8%
Renal replacement therapy	81	21%	105	21.3%	26	8.1%
Mechanical ventilation	346	75.1%	397	77.4%	228	71%

APACHE, Acute Physiology and chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment;

* Serious infection was defined as a serious, prolonged or recurrent infection.

** Chronic steroid use was defined as taking corticosteroids below the immunosuppression dose (>7 mg/kg/days hydrocortisone), which would exclude patient from inclusion in the study.

Table 32 Outcomes for the derivation, geographic and temporal external sub-cohorts

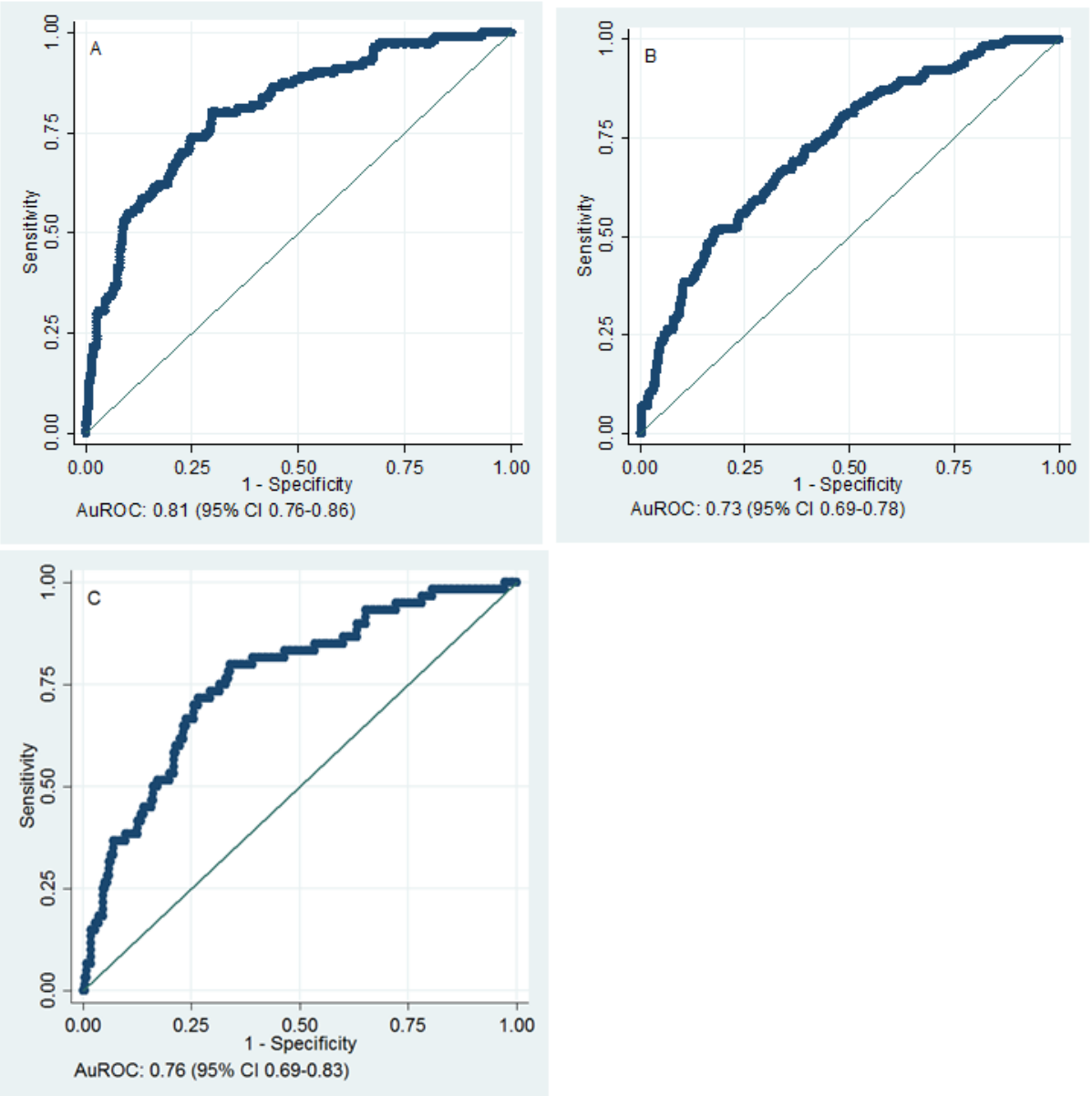
Cohort	Derivation (UK until Jan 2011)		Geographic validation (non-UK)		Temporal validation (UK post Jan 2011)	
Total number of patients	462 GenOSept UK		515 GenOSept Europe		323 GAinS	
Characteristics						
Length of stay (days)	Median	IQR	Median	IQR	Median	IQR
Available data	462	100%	515	100%	322	99.7%
ICU	7	4-14	14	7-29	6	3-11
Hospital	26	14-47	30	17-54	29	18-47
Mortality	n	%	n	%	n	%
Available data	462	100%	515	100%	321	99.4%
6 month	124	26.8%	185	35.9%	64	19.9%
ICU	73	15.8%	131	25.4%	24	7.5%
Hospital	109	23.6%	171	33.2%	29	9.8%
28 day	79	17.1%	171	33.2%	40	12.4%

5.2.2 Performance of the prognostic tools

When evaluated using a Receiver Operator Characteristics (ROC) curve the discriminatory performance of the 6 month prognostic model in the UK derivation sub-cohort yielded an AuROC of 0.81 (95% Confidence Interval, CI, 0.76 - 0.86) as indicated in Figure 15 (panel A). At geographic validation in the non-UK sub-cohort, the 6 month prognostic model produced an AuROC of 0.73 (95% CI 0.69 - 0.78; Figure 15, panel B). At temporal validation the 6 month model yielded an AuROC of 0.76 (95% CI 0.69-0.83; Figure 15, panel C).

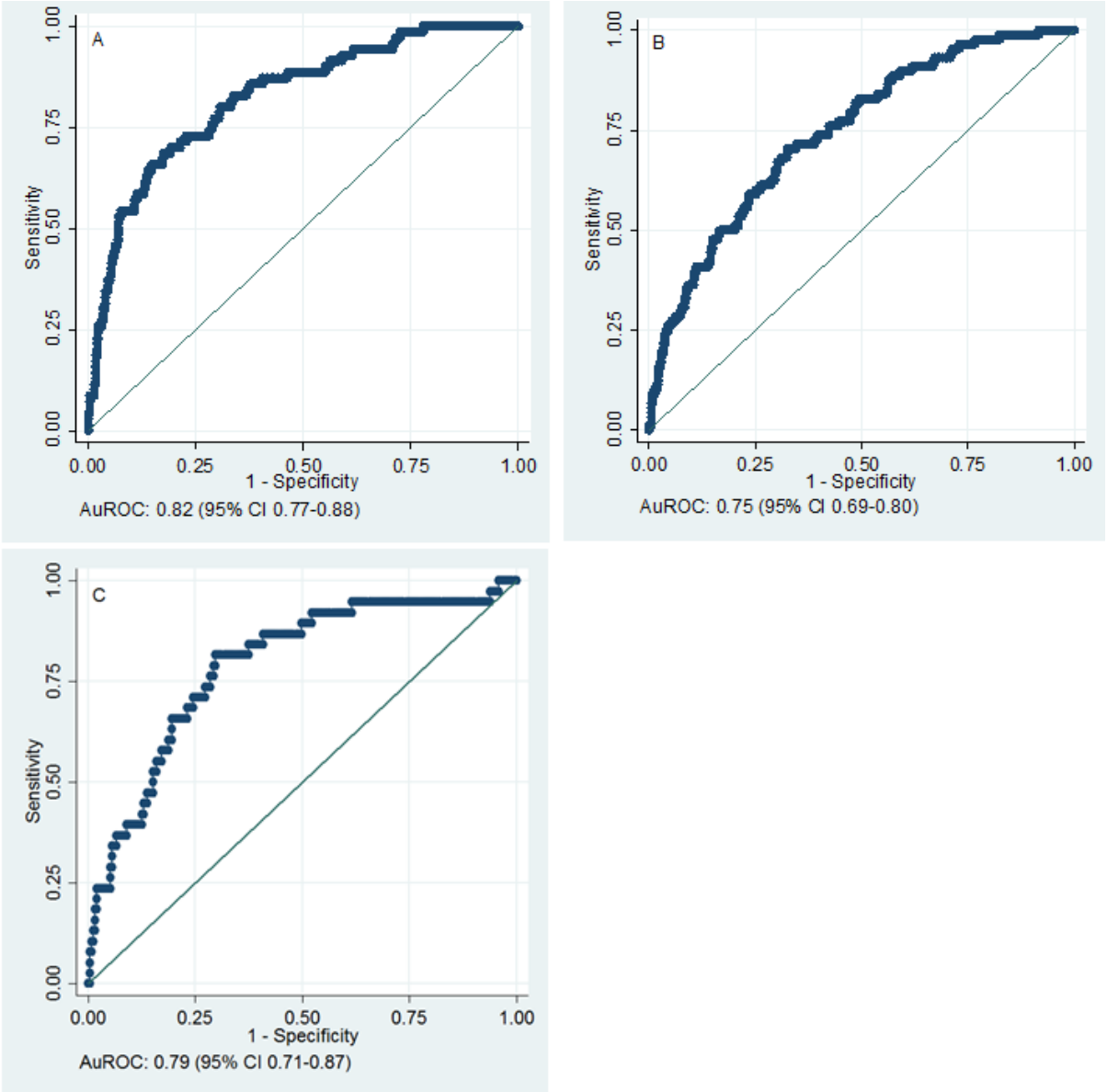
The 28 day prognostic tool also performed similarly, yielding an AuROC 0.82 (95% CI 0.77 - 0.88; Figure 16, panel A) for the derivation UK sub-cohort. At geographic validation in the non-UK sub-cohort, the 28 day prognostic model produced an AuROC of 0.75 (95% CI 0.69 - 0.80; Figure 16, panel B). In the temporal validation cohort the 28 day model yielded an AuROC of 0.79 (95% CI 0.71-0.87; Figure 16, panel C).

Figure 15 Receiver Operator Characteristics (ROC) curve obtained when applying the 6 month prognostic model to the derivation (panel A), geographic validation (panel B) and temporal validation sub-cohorts (panel C) respectively



AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval;

Figure 16 Receiver Operator Characteristics (ROC) curve obtained when applying the 28 day prognostic model to the derivation (panel A), geographic validation (panel B) and temporal validation sub-cohorts (panel C) respectively



AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval;

The 6 month FP score produced numerical values which can be stratified within 5 intervals (0 to 2; above 2 to 4; above 4 to 6; above 6 to 12; above 12) corresponding to five levels of 6 months mortality risk. The 28 day mortality FP score produces values classified within 5 intervals, corresponding to different risk categories for the outcome (0 to 2; above 2 to 4; above 4 to 8; above 8 to 16; above 16). The observed mortality rates corresponding to each class of risk for the two scoring systems are presented in Table 33 for all three cohorts (Figures 17 and 18 display the corresponding histograms of mortality). A 6 month FP score above 12 is consistently associated with a greater than 50% mortality risk at 6 months across all cohorts. A 28 day FP score above 16 is associated with a greater than 40% mortality risk for the 28 day outcome for the derivation and geographic validation cohorts, but not for the temporal validation cohort, in which the highest observed mortality risk was around 22%.

Table 33 Observed 6 month and 28 day mortality rates for the derivation, geographic and temporal external validation sub-cohorts, stratified by FP score interval

Cohort	Derivation (UK until Jan 2011)	Geographic validation (non-UK)	Temporal validation (UK post Jan 2011)
FP score	Deceased	Deceased	Deceased
6 month mortality			
0 to 2	3 (3.7%)	14 (13.7%)	5 (6.3%)
>2 to 4	11 (10.8%)	25 (22.5%)	7 (10.5%)
>4 to 6	14 (20%)	29 (36.3%)	12 (26.1%)
>6 to 12	29 (31.9%)	44 (40.7%)	15 (28.9%)
>12	67 (57.3%)	73 (64%)	22 (59.5%)
28 day mortality			
0 to 2	0 (0%)	10 (9.9%)	2 (2.7%)
>2 to 4	8 (8.3%)	12 (12%)	3 (5.4%)
>4 to 8	10 (9.5%)	17 (15.3%)	8 (11.1%)
>8 to 16	14 (16.5%)	27 (26.2%)	12 (22.2%)
>16	47 (45.6%)	42 (42%)	15 (22.4%)

Figure 17 Observed 6 month mortality in the derivation, geographic and temporal validation sub-cohorts, by FP score interval

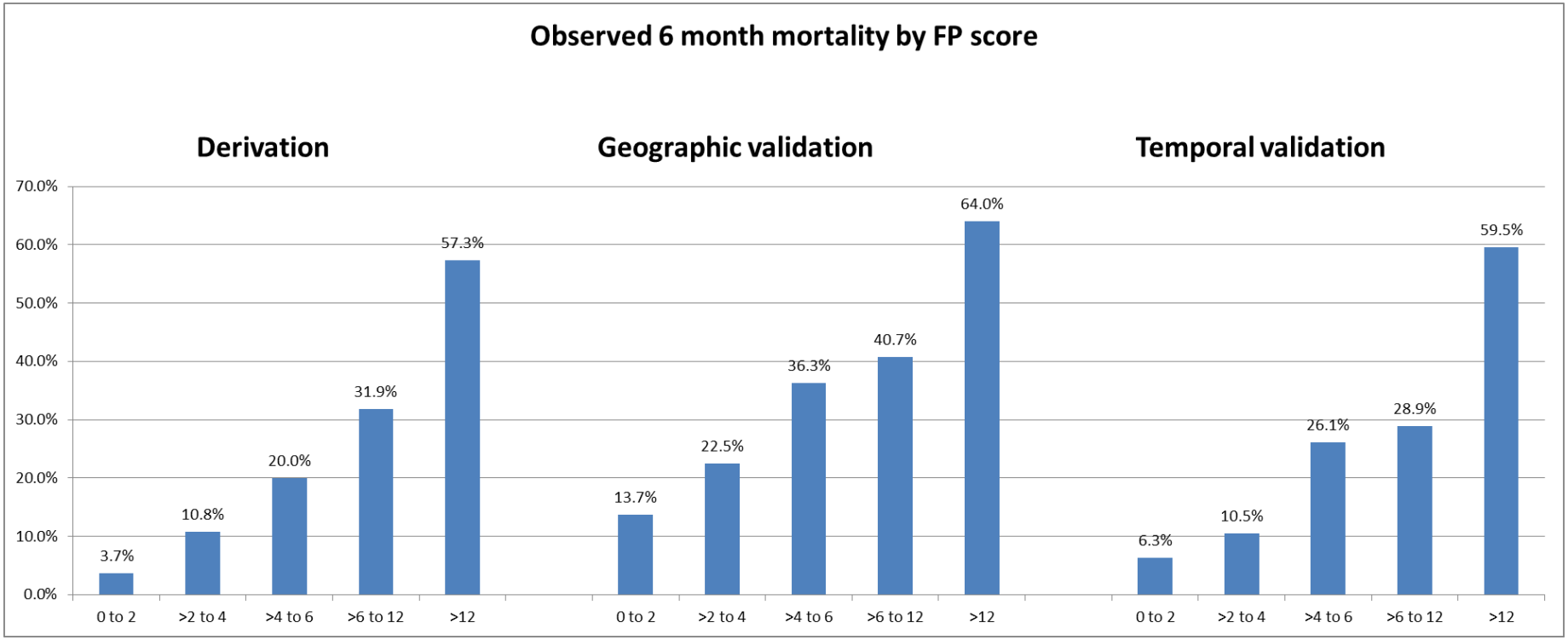
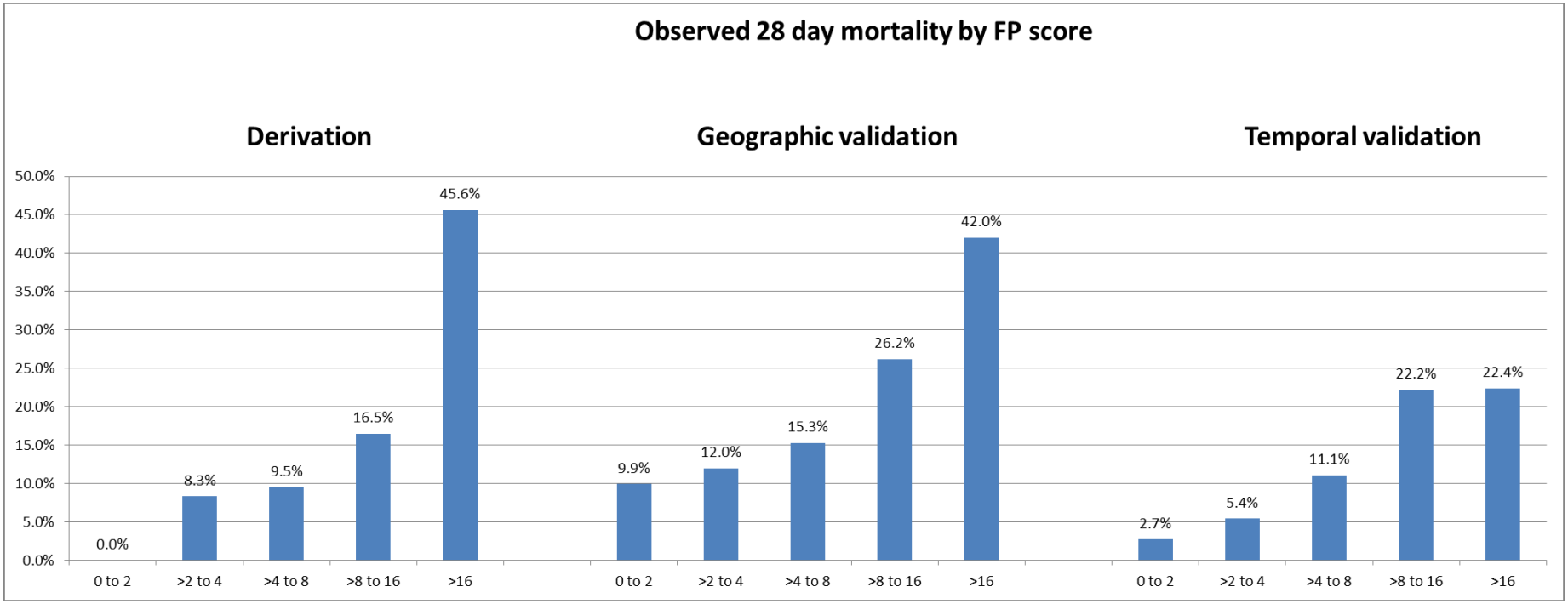


Figure 18 Observed 28 day mortality in the derivation, geographic and temporal validation sub-cohorts, by FP score interval



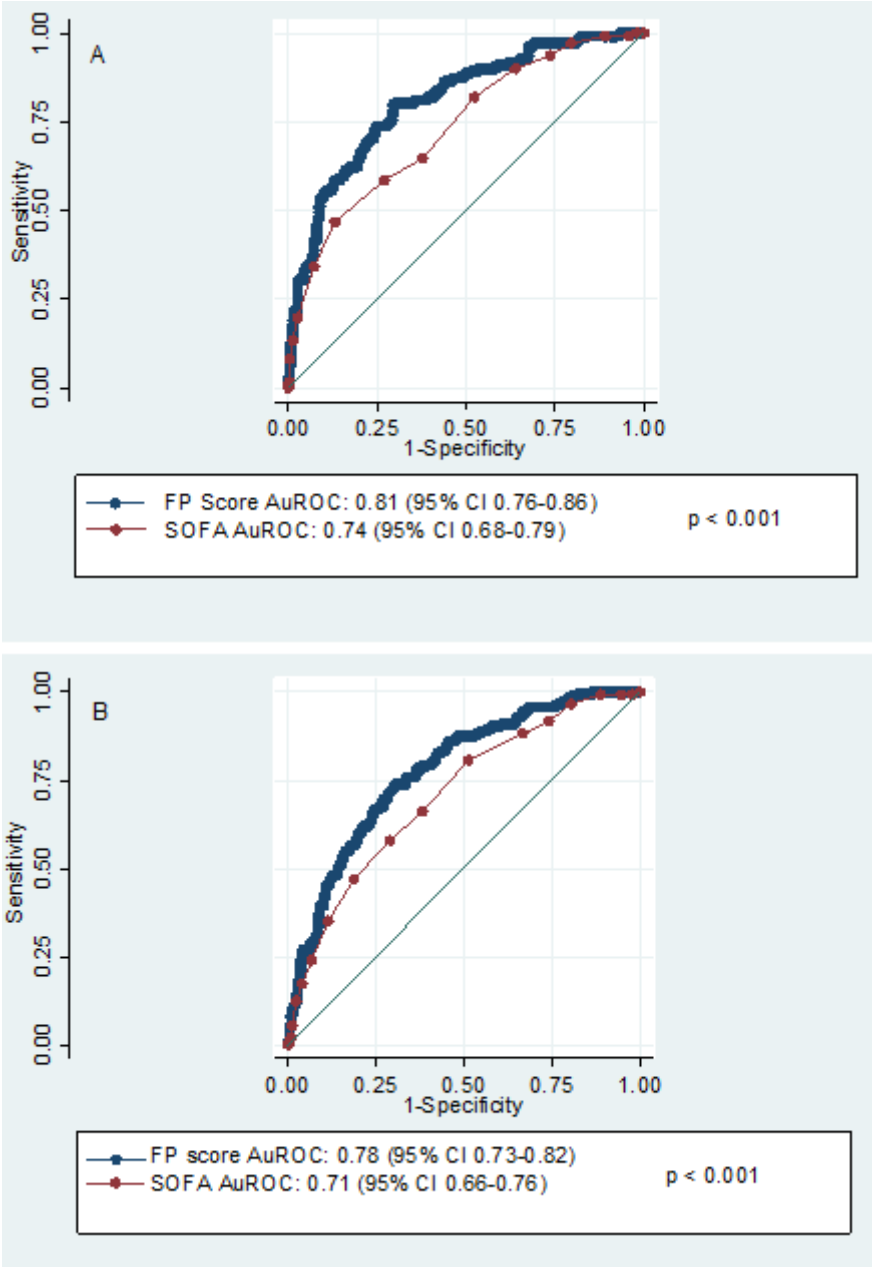
5.2.3 The discriminatory capabilities of the FP prognostic tools versus the SOFA and APACHE II scores in the FP cohorts

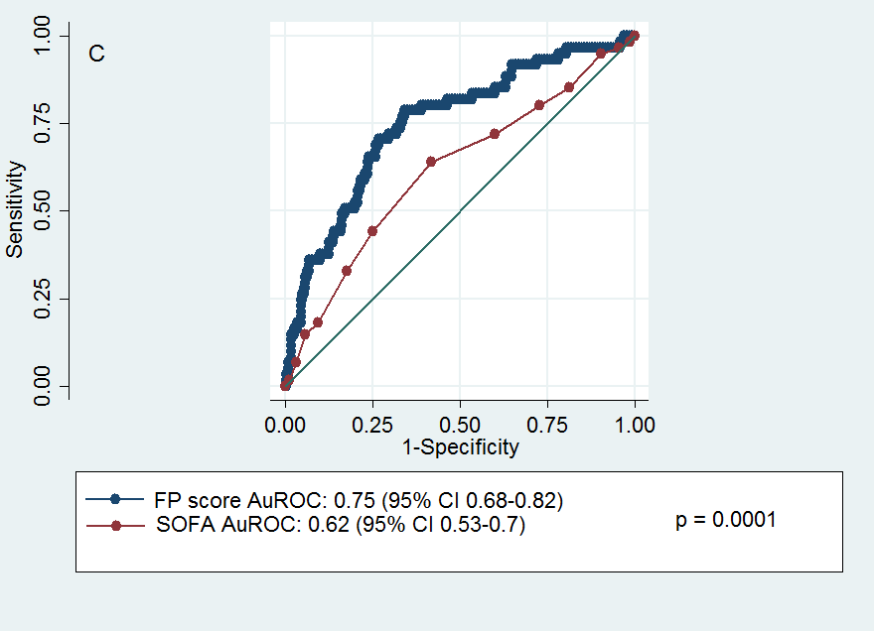
To assess how the FP models compare, as prognostic tools, to the routinely used SOFA and APACHE II scores, I calculated AuROCs for these scoring systems, to predict 6 month and 28 day mortality, in order to compare each tool across all cohorts and for both outcomes. For 6 month mortality, the SOFA score produced AuROCs of 0.73 (95% CI 0.68-0.78), 0.68 (95% CI 0.63-0.72) and 0.62 (95% CI 0.54 - 0.7) in the derivation, geographic and temporal external validation cohorts, respectively, while the APACHE II score yielded AuROCs of 0.74 (95% CI 0.7-0.79), 0.71 (95% CI 0.66-0.75) and 0.69 (95% CI 0.62-0.77) for those cohorts, respectively. For the 28 day mortality outcome, the SOFA score produced AuROCs of 0.76 (95% CI 0.7-0.82), 0.66 (95% CI 0.6-0.73) and 0.67 (95% CI 0.58-0.77) in the derivation, geographic and temporal external validation cohorts, respectively, while the same AuROCs for the APACHE II score were 0.71 (95% CI 0.64-0.77), 0.69 (95% CI 0.63-0.75) and 0.75 (95% CI 0.67-0.83), respectively.

The AuROCs obtained using the FP scores were consistently superior to those obtained with the SOFA score, with statistical significance across all cohorts (derivation, geographic and temporal external validation) and for both 6 month and 28 day mortality outcomes (Figures 19 and 20, respectively).

The AuROCs obtained using the FP scores were also superior to those derived using the APACHE II score for both outcomes, although statistical significance was not consistently achieved across all cohorts (Figures 21 and 22, for 6 month and 28 day mortality, respectively).

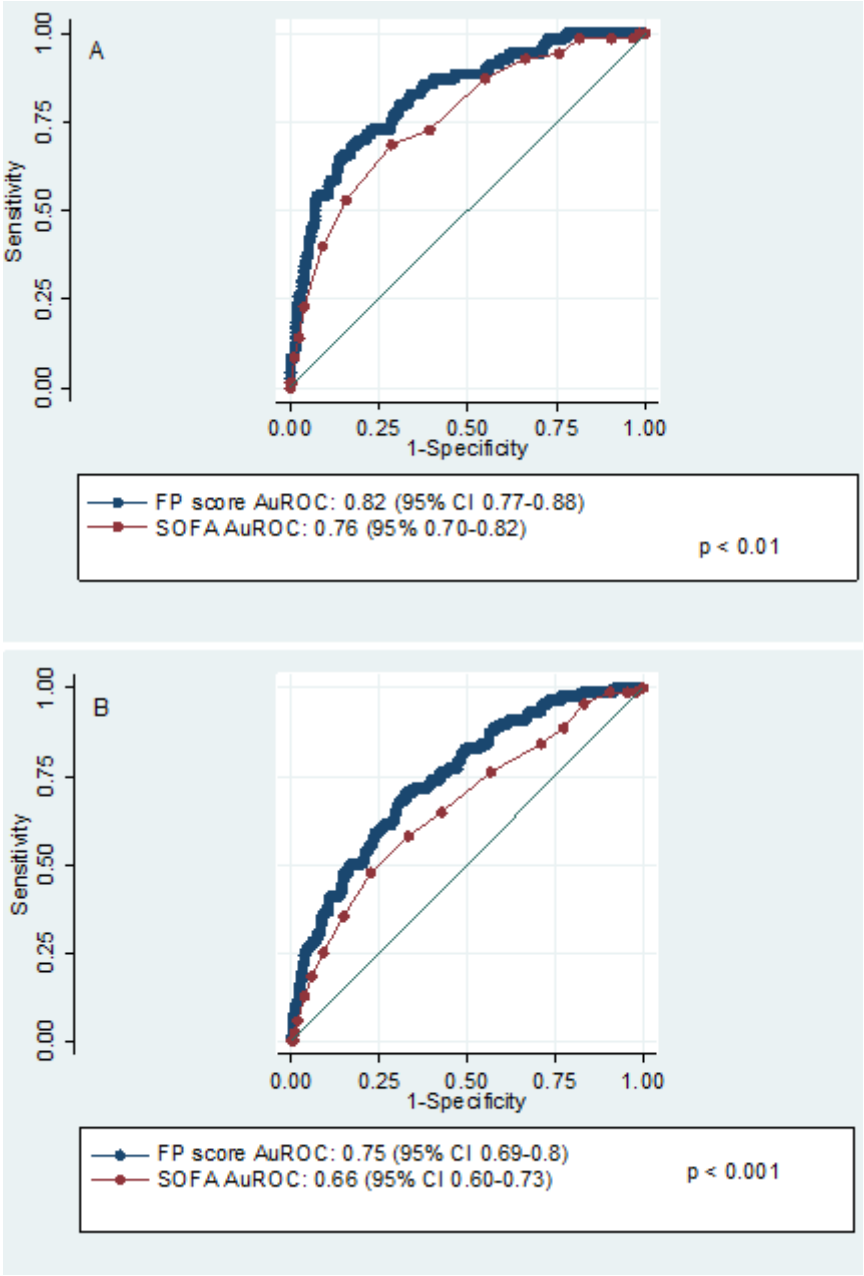
Figure 19 Comparison of the AuROCs obtained when applying the SOFA and the FP scores, for 6 month mortality outcome, to the derivation (panel A), geographic (panel B) and temporal validation sub-cohorts (panel C)

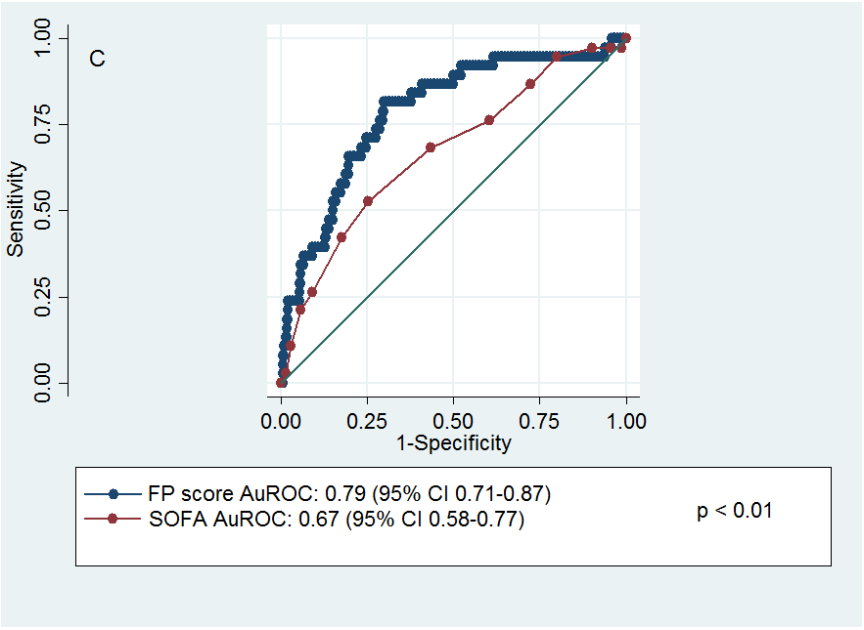




AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval

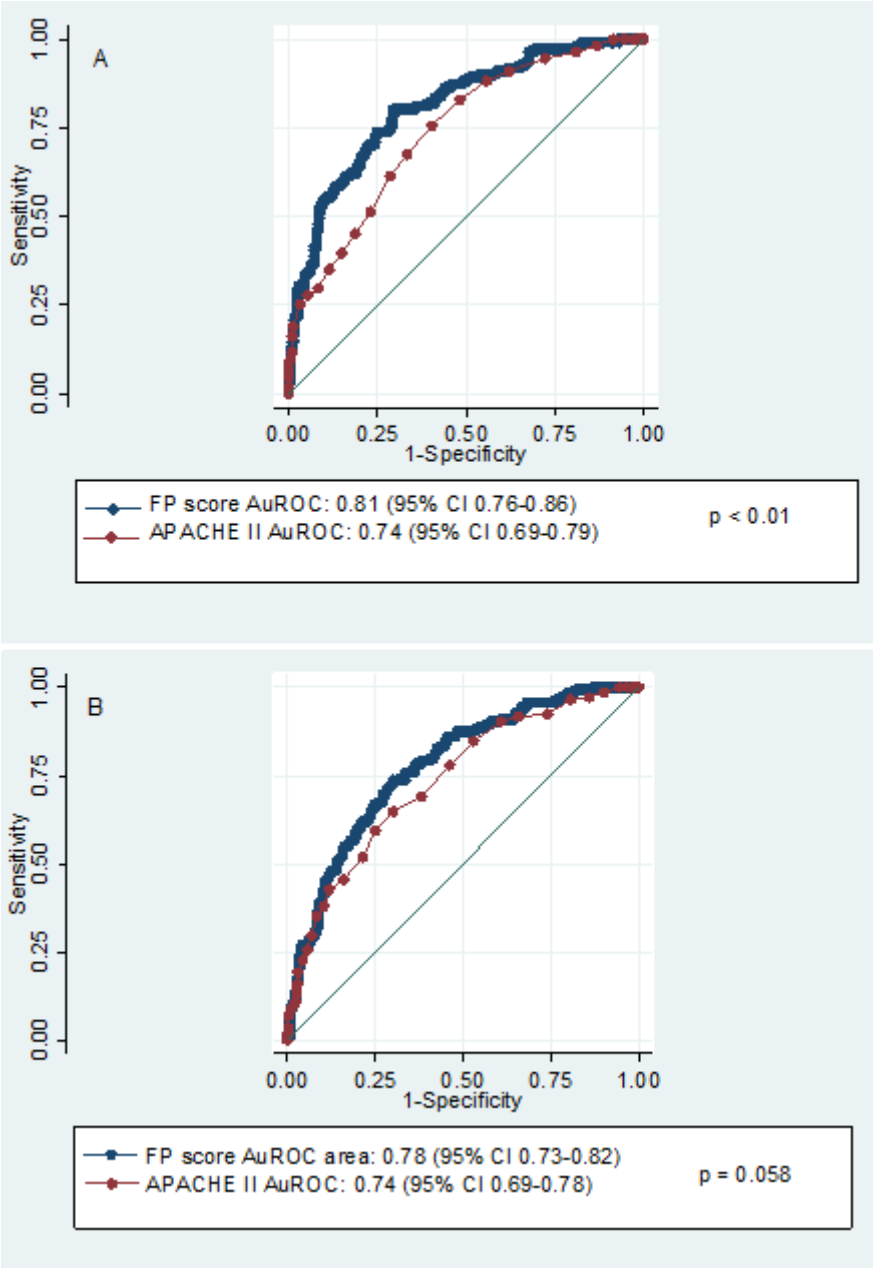
Figure 20 Comparison of the AuROCs obtained when applying the SOFA and the FP scores, for 28 day mortality outcome, to the derivation (panel A), geographic (panel B) and temporal validation sub-cohorts (panel C)

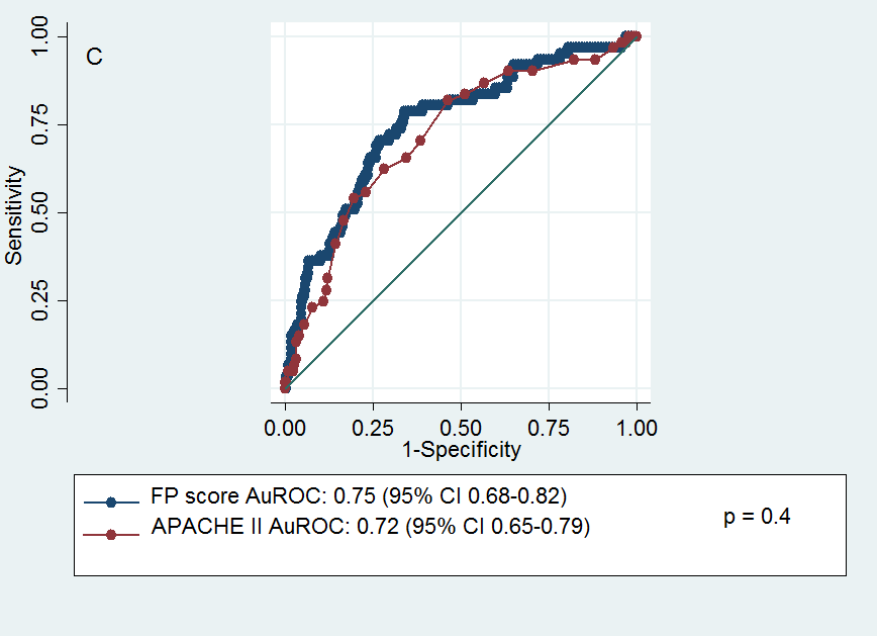




AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval

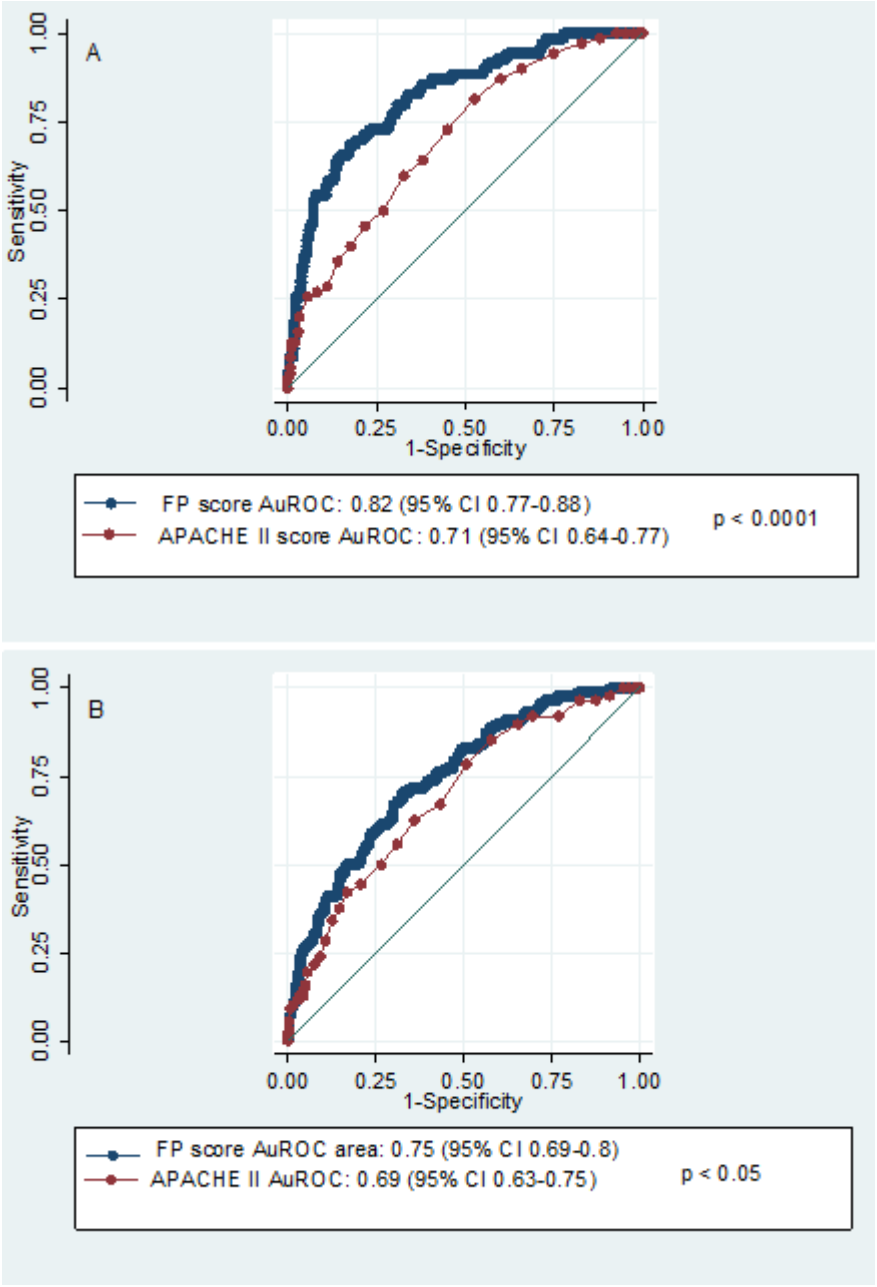
Figure 21 Comparison of the AuROCs obtained when applying the APACHE II and the FP scores, for 6 month mortality outcome, to the derivation (panel A), geographic (panel B) and temporal validation sub-cohorts (panel C)

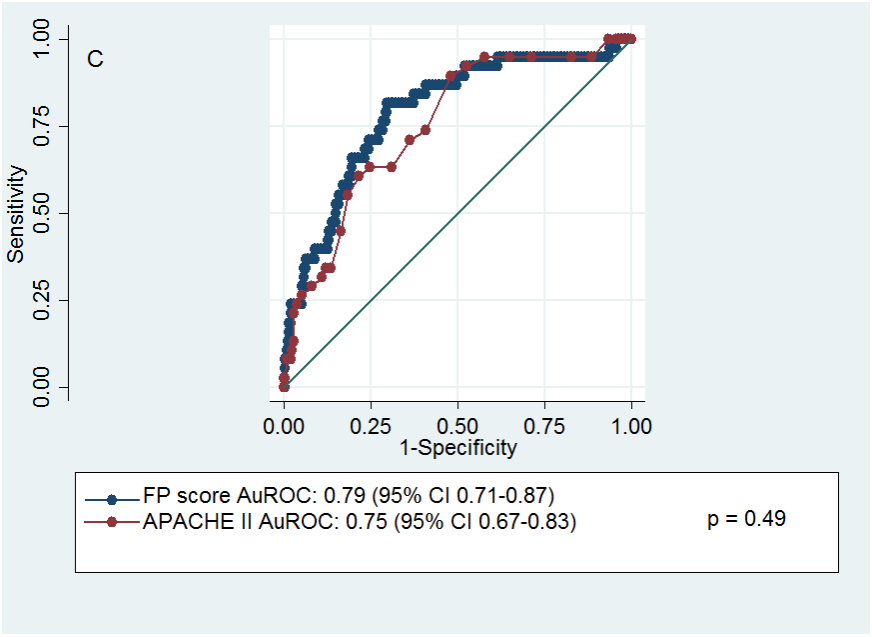




AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval

Figure 22 Comparison of the AuROCs obtained when applying the APACHE II and the FP scores, for 28 day mortality outcome, to the derivation (panel A), geographic (panel B) and temporal validation sub-cohorts (panel C)





AuROC, Area under the Receiver Operating Characteristic curve; CI, Confidence Interval

5.3 Summary of results

Prognostic scores and models of illness severity are useful both clinically and for research. The aim of the analyses in this chapter was to develop two prognostic models for the prediction of long term (6 months) and 28 day mortality of post-operative critically ill patients with faecal peritonitis.

Five variables (age, SOFA score, lowest temperature, highest heart rate, haematocrit) were entered into the prognostic models. The discriminatory performance of the 6 month prognostic model yielded an AuROC 0.81 (95% Confidence Interval, CI, 0.76 - 0.86), 0.73 (95% CI 0.69 - 0.78), and 0.76 (95% CI 0.69-0.83) for the derivation, geographic and temporal external validation cohorts, respectively. The 28 day prognostic tool yielded an AuROC 0.82 (95% CI 0.77 - 0.88), 0.75 (95% CI 0.69 - 0.80) and 0.79 (95% CI 0.71-0.87) for the same cohorts. These AuROCs were consistently superior to those obtained with the SOFA and APACHE II scores.

Hence, the two prognostic models developed for 6 month and 28 day mortality prediction in critically ill septic patients with FP, in the post-operative phase, enhanced the SOFA score's predictive utility by adding few key variables: age, lowest recorded temperature, highest recorded heart rate and haematocrit. External validation in larger cohorts of their predictive capability is needed, before introduction of the scores into clinical practice to inform decision making and the design of clinical trials.

Chapter 6

6.1 Discussion

In my thesis I have presented a contemporary pan-European view of the clinical characteristics, outcomes and independent risk factors for mortality for patients admitted to ICU with faecal peritonitis. The data used has been derived from two of the largest, prospectively collected and most diagnostically homogeneous cohort of critically ill patients with faecal peritonitis, the GenOSept and the GAinS cohorts. These rigorously quality assured cohorts have provided unique insights into the epidemiology and associations between trends in clinical variables and short and long term outcomes of post-operative critically ill patients with this condition (relying on the GenOSept cohort only). The derivation of a prognostic model has been possible in the UK subset of the GenOSept cohort. The non-UK subset of the GenOSept cohort, and the patients subsequently recruited to the GAinS cohort have been used as geographic and temporal external validation, respectively.

Faecal peritonitis continues to be associated with a high mortality. Approximately one out of five critically unwell patients with FP in Europe will die in the intensive care unit. Mortality in this cohort was 19.1% at 28 days, 20.9% in the ICU, 28.7% at hospital discharge and 31.6% at 6 months. The ICU mortality is similar to that observed in the APACHE II 2011 model (23.4%) and that found in a recently reported, smaller single-centre study specifically investigating faecal peritonitis outcome in ICU (Sayer et al., 2012), although much higher mortality rates were reported in another earlier study (Pawa et al., 2009). Both these studies were smaller and only reported in the form of conference abstracts. Sayer et al. have

reported in-hospital mortality rates of 21.6% and 38.1%, for the malignancy and non-malignancy sub-groups respectively (Sayer et al. 2012), while Pawa et al. reported 30 day mortality rates of 46% for patients aged <75 years and 78% for patients aged > 75 years, suggesting that different local practices of critical care admission, periods considered, evolution in concurrent treatments and underlying characteristics of the populations (other than admission diagnosis) may have influenced results (Pawa et al. 2009). Pawa and co-workers report age as the strongest outcome predictor, while Sayer and colleagues suggests that hypo-albuminaemia and the presence of malignancy influence mortality (Pawa et al. 2009). None of the studies reported microbiological isolates or the relationship between trends in clinical variables and outcomes. Other studies have evaluated heterogeneous populations of patients with peritonitis of multiple aetiologies, with several different predictors of outcome identified. The variability in determinants of outcome and in mortality rates is high, depending on the patient case mix (van Ruler et al. 2011; Torer et al. 2010; Horiuchi et al. 2007).

The prognostic factors identified

In my research, the strongest independent risk factors, on admission, associated with an increased rate of death at 6 months included age, higher APACHE II score, acute renal and cardiovascular dysfunction within one week of admission to ICU, hypothermia, lower haematocrit and bradycardia on day 1 of ICU stay. The most consistent predictors of mortality across all time-points were increased age, development of acute renal dysfunction during the first week of admission and hypothermia on day 1 of ICU admission. When evaluating the trends over the first 7 days ICU stay, the variables retained as independently associated

with outcomes, most consistently across the various time points, were worsening thrombocytopaenia, deteriorating renal function (urine output and renal SOFA sub-score) and deterioration in GCS SOFA sub-score. The risk prediction models described in this chapter improved the SOFA score's predictive power for mortality at 6 months and 28 days, by adding a few key variables: age, lowest recorded temperature, highest recorded heart rate and haematocrit on admission to intensive care. I am not aware of any prognostic tool designed to assess the risk of long term mortality specifically in the critically ill post-surgical FP patient. The 6 month mortality model demonstrates AuROCs of 0.81 (0.76-0.86), 0.73 (0.69-0.78) in the derivation and geographic validation cohorts, respectively, while the 28 day prognostic tool yielded AuROCs of 0.82 (0.77-0.88) and 0.75 (0.69-0.80) for the same cohorts. An area under the ROC curve over 0.8 is generally regarded as indicating a good discriminatory capacity (Tape 2016). When validated externally, the 6 month and 28 day mortality models yielded AuROC of 0.76 (95% CI 0.69-0.83) and 0.79 (0.71-0.87), respectively. The models, therefore, retained reasonable discriminatory capability, and systematically outperformed the other scoring systems tested (SOFA and APACHE II), in these cohorts.

This FP prognostic tool may, therefore, be useful to complement the currently used risk scores and bedside clinical assessment, enhancing the critical care clinician’s capacity to predict long term outcome and thereby supporting the clinical decision making process in the post-operative phase.

Effect of Age

Although not exclusively, faecal peritonitis is a condition presenting primarily in older age, a fact highlighting the relevance of contemporary studies on this subject, conducted on ageing populations, such as the European and other across the Western countries. This aspect of the condition has wide implications, especially in the context of finite resources, with important ethical ramifications. Unexpectedly, given its importance, the topic of faecal peritonitis appears to be a relatively "evidence free" area, with scarcity of studies detected on the specific topic in literature.

The GenOSept faecal peritonitis cohort was characterized by an elderly population, with a high prevalence of cardiovascular, malignant and respiratory co-morbidities. Populations across Western countries are aging, with an inevitable impact on the use and availability of critical care resources (Angus et al., 2000). This cohort reflects this trend; more than 60% of patients included were aged above 65 years and almost one third were more than 75 years old. In keeping with previous studies I found older age to be significantly and consistently associated with an increased risk of death (Rosenthal et al., 2002, Van Den Noortgate et al., 1999). It is possible that a potential confounding effect, in this study, of the relationship between mortality and age, may be related to treatment limitations in the more elderly patients, particularly those above the age of 75.

Effect of Acute renal dysfunction

Acute renal dysfunction has been shown in previous large series of critically ill patients to be independently associated with higher ICU and hospital mortality rates (Uchino et al. 2005; Metnitz et al. 2002; Ostermann & Chang 2008; Barrantes et al.

2008). In the GenOSept faecal peritonitis cohort, the presence of acute renal dysfunction during the first week of ICU stay was strongly associated with mortality, the effect being more marked for the shorter term outcomes (ICU and 28 day mortalities), but remaining significant at 6 months. Raised creatinine and urea, acute renal dysfunction and the need for renal replacement therapy (RRT) on day 1 of admission to ICU were also all associated with worse outcomes in the single variable analyses. Debate continues as to whether the excess mortality associated with renal dysfunction is simply a reflection of the severity of the underlying illness, or whether the worse outcomes are directly attributable to the effects of renal dysfunction. While renal impairment tends to accompany other organ dysfunctions in the critically ill, there is evidence to suggest that acute kidney injury contributes independently to poor outcomes (Barrantes et al., 2008).

Impaired renal function has also been linked to impaired immune function (Barrantes et al. 2008; Ostermann & Chang 2008; Ostermann & Chang 2005; Mehta et al. 2011). In the study by Barrantes et al. of 496 critically ill patients, the mortality rate of patients with acute kidney injury (AKI) was significantly higher than those without (Barrantes et al. 2008). Ostermann et al. examined the effect of AKI on over 22000 adult general ICU patients, and found that the AKI classification correlated with outcome (Ostermann & Chang 2008). In a study conducted in an unselected ICU population of almost 42000 patients, the same authors examined the criteria for acute renal injury, acute renal failure syndrome and severe acute renal failure syndrome, and found that worsening degrees of renal impairment correlated with mortality (Ostermann & Chang 2005). Mehta et al. studied 611 unselected ICU patients, highlighting the higher incidence of sepsis amongst those with AKI (Mehta et al. 2011).

Effect of Hypothermia

The adverse effect of hypothermia on the outcome of critically ill patients has been described by other authors, although data on the relevance of hypothermia to outcomes remains conflicting (Laupland, Zahar, Adrie, Minet, et al. 2012; Tiruvoipati et al. 2010). An association between severe hypothermia and the risk of ICU acquired infections has also been reported among medical patients (Laupland, Zahar, Adrie, Schwebel, et al. 2012). A large multicentre cohort study, including over 10,000 patients (not undergoing therapeutic hypothermia) suggested that after controlling for confounding variables, hypothermia was a strong and independent predictor of mortality (Laupland et al., 2012b). Tiruvoipati et al. reported data from 175 elderly ICU patients, identifying lower temperatures and the Simplified Acute Physiology Score II (SAPS II) during the first day of ICU admission as being independently associated with higher hospital mortality (Tiruvoipati et al. 2010; Le Gall et al. 1994). At present it is not known whether active re-warming to correct hypothermia improves outcomes (Tiruvoipati et al., 2010).

Effect of Haematocrit

A low haematocrit on day 1 was associated with worse short and long term outcomes in this study. The reason for this is unclear, but anaemia in patients undergoing both cardiac and non-cardiac surgery, has previously been shown to be associated with worse outcomes (Shander et al., 2004, Qiu et al., 2010, Vignot and Spano, 2005, Halm et al., 2004, Beattie et al., 2009), although the effects of blood transfusion have not been fully clarified (Oliveros and Linares, 2012, Hung et al., 2011). All of the patients with faecal peritonitis in the GenoSept study underwent

laparotomy (a requirement for making the diagnosis). In addition, a significant proportion of patients (40%) were documented to have cardiovascular co-morbidity, a group in which anaemia has been shown to be associated with increased mortality and major adverse cardiovascular events. A previously reported large observational study showed a higher 30-day survival rate in patients who received a blood transfusion compared to those who did not receive a transfusion (Vincent et al., 2008). The contribution of dilutional anaemia as a result of fluid resuscitation is unclear, but this could also be postulated to have had an adverse effect by compromising tissue oxygen delivery during early (<6 hours) fluid resuscitation (Rivers et al. 2001). Beattie and co-workers performed a retrospective observational study of 7759 non-cardiac surgical patients to establish the relationship between preoperative anemia and postoperative mortality, and found that preoperative anemia was common and strongly linked with postoperative mortality, even after adjustment for major confounders (Beattie et al. 2009).

Although anaemia may be associated with a poor outcome, data on the effects of blood transfusion is conflicting, with most reports not demonstrating benefit from transfusion aimed at achieving a higher haemoglobin threshold (Hébert et al. 1999; Holst et al. 2015).

The effect of Acidosis

The observation that acidosis influenced short term outcomes, (ICU and 28 day mortality) suggests a possible association with renal dysfunction. This association is unlikely to reflect acid-base disturbance secondary to respiratory acidosis, as none of the respiratory variables seemed to have an effect on any

mortality end-point. Alternatively metabolic acidosis may reflect impaired tissue perfusion and inadequate resuscitation.

The effect of Thrombocytopaenia

Thrombocytopaenia on admission was amongst the independent predictors of hospital and 28 day mortality. A link between thrombocytopaenia and the outcome of critical illness has been previously reported. Thrombocytopenia is a marker of disease severity, co-administration of blood products and development of consumption coagulopathy, with an increased risk of death (Stephan et al. 1999; Lee et al. 1993; Williamson et al. 2013; Crowther et al. 2005; Sharma et al. 2007; Vanderschueren et al. 2000; Strauss et al. 2002). My findings suggest that thrombocytopaenia is a marker of severity of illness in patients admitted to ICU with faecal peritonitis, perhaps in association with the development of consumption coagulopathy. Furthermore, the importance of the role of platelets in the innate immune response is increasingly being recognised (Morrell et al. 2014).

In the GenOSept cohort, worsening thrombocytopaenia over the first 7 days ICU stay was also found to be independently associated with the primary (6 month mortality) and two of the secondary outcomes (hospital and 28 day mortality). Thrombocytopaenia is a common finding following operative intervention for intra-abdominal sepsis, and a falling platelet count has been reported to be useful for distinguishing *infected* from *non-infected* peritonitis (Iberti et al. 1986). In the study by Vanderschueren and colleagues, in an unselected population of intensive care patients, the development of thrombocytopaenia and a reduction from baseline of 50% or more in platelet count had more explanatory power for ICU mortality than admission variables (Vanderschueren et al. 2000). The study by Williamson et al.

examined the effects of prevalent and incident thrombocytopenia in an unselected population of over 20000 critically ill patients, demonstrating an independent association of low platelet counts with mortality. This association was stronger for specific admission diagnoses, in particular for the cancer, respiratory, digestive, genitourinary, and infectious categories (Williamson et al. 2013). In the study by Strauss et al. a decrease in platelet count ≥30% was significantly linked to higher mortality in 145 unselected critically ill patients (Strauss et al. 2002). A prospective observational study by Sharma et al. evaluated the incidence of various degrees of severity of thrombocytopenia in 69 septic shock patients, concluding that thrombocytopenia is associated with worse clinical outcomes in this unselected population of critically ill patients (Sharma et al. 2007). Crowther et al. also found that the development of thrombocytopaenia was strongly associated with mortality in 261 unselected critical care patients (Crowther et al. 2005).

Effect of Comorbidities, Time to surgery and Cause of FP

Unexpectedly, neither the presence of co-morbidities nor time from presumed onset of symptoms to surgery, nor the underlying cause of faecal peritonitis appeared to influence survival. In the present study there appeared to be no effect of co-morbidities on mortality at any time point. This finding is in agreement with most (Koperna & Schulz 2000; Ohmann et al. 1993; Billing et al. 1994; van Ruler et al. 2011; Singh et al. 2011) but not all (Pacelli et al. 1996; Demmel et al. 1994) of the previously published studies of patients with secondary peritonitis. Differences in the populations studied and their heterogeneity may explain such discrepancies. Interestingly, neither the cause of faecal peritonitis nor the time from onset of symptoms to surgery influenced survival in this cohort. This finding contrasts with

previously published studies of secondary peritonitis in which time to reoperation, source control and indices of physiological derangement have been the strongest outcome predictors (Pacelli et al. 1996; Koperna & Schulz 2000; Ohmann et al. 1993; Demmel et al. 1994; Billing et al. 1994; van Ruler et al. 2011; Singh et al. 2011). It is possible that in the GenOSept cohort the degree of acute physiological derangement overwhelmed the influence of the time to operative intervention, or that significant delay was unusual. In the cohort reported here the median time delay between onset of symptoms and surgery was 1 (IQR = 1-3) day, which is comparable with previously published data (Singh et al., 2011).

Effect of Antimicrobial Therapy

As might be expected in a pan-European study involving a large number of centres from 16 countries, a wide variety of initial antimicrobial combinations were administered to these patients with faecal peritonitis. Consequently it was not possible to draw firm conclusions from this observational study as to whether the initial choice of antimicrobial (which was considered by the local investigator to be appropriate in more than 90% of cases) might influence outcome. These observations are in keeping with a recent Cochrane review that studied 16 different antimicrobial regimes but was unable to make any specific recommendations for the first line treatment of secondary peritonitis as all showed equivalent efficacy (Wong et al., 2005). I am not aware of any other epidemiological studies of patients with faecal peritonitis that have documented antimicrobial regimes or identified any associations with outcome.

The inability to detect a correlation between outcome and the use of different antimicrobial therapies requires additional investigation, to establish whether there is

a potential antimicrobial combination able to yield survival benefit. It is possible that, as the GenOSept and GAinS studies had not been designed to explore the effect of different antimicrobial combinations, the analyses were under-powered and affected by data incompleteness and *fragmentation*.

Effect of SOFA

The SOFA score was developed in a mixed (medical and surgical) ICU population (Vincent et al. 1996) and has been subsequently externally validated in various populations (Vincent & Moreno 2010), such as cardiac surgical patients (Ceriani et al. 2003) and critically ill burn patients (Lorente et al. 2009).

Although the SOFA score was originally conceived as a tool for describing the evolution of dysfunction in various organs, rather than to predict outcome, both admission SOFA and trends in the global SOFA scores (and in the specific components renal and GCS), were closely associated with mortality. Furthermore, the FP prognostic indices included SOFA together with few additional key variables. In the prognostic indices analyses, neither the SOFA nor the APACHE II scores, when used in isolation, performed as well as the tools developed in this thesis. In fact SOFA has been used in combination with other parameters in previous studies (Zügel et al. 2011; Matsumura et al. 2014), for the purpose of outcome prediction.

These findings are compatible with those from a recently reported prospective observational cohort study, investigating the systems that most contribute to the development of multiple organ system failure (MOSF). That study of 102 patients with abdominal sepsis highlighted the importance of trends in the SOFA score, demonstrating how the value on day 4 (as opposed to admission SOFA) had a high precision in predicting 28 day mortality, with MOSF being mainly contributed to by

renal, central nervous and respiratory system dysfunction (Hernández-Palazón et al. 2013). In another study, which included 62 critically ill patients with post-operative peritonitis, investigators demonstrated the importance of trends in SOFA scores calculated serially over a 5 day post-operative period to distinguish between patients with or without persistent post-operative intra-abdominal sepsis (Paugam-Burtz et al. 2002). In a prospective observational study of 56 secondary peritonitis patients, researchers measured several inflammatory parameters and multiple severity scoring systems pre-operatively and over a 5 days post-operative period, in a serial fashion. That study showed that combining the SOFA scores with measurement of serum neopterin concentration (a specific cellular immune system activation marker) and TNF (Tumour Necrosis Factor) receptor II levels yielded the highest predictive sensitivities and specificities for pre- and post-operative outcomes (Zügel et al. 2011). In a study of 163 consecutive ICU patients with secondary peritonitis, hospital mortality was accurately predicted by the post-operative SOFA score (Hynninen et al. 2008). In a large trial comparing on-demand versus planned repeat laparotomy for severe peritonitis, the SOFA score showed good discriminatory power to predict hospital mortality, although it was unable to predict the need for repeat laparotomy (van Ruler, Mahler, et al. 2007; van Ruler et al. 2011). In a retrospective cohort study by Sumi et al. both the SOFA and POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity) scores were able to risk stratify patients undergoing surgical intervention for colorectal perforation (Copeland et al. 1991; Sumi et al. 2014). Similarly, Matsumura et al. studied 218 general medical and surgical ICU patients, and showed that serum procalcitonin levels and SOFA score at ICU discharge could predict post-ICU mortality and survival time (Matsumura et al. 2014). Jones et al. studied 248 emergency department patients with severe sepsis

and evidence of hypoperfusion at presentation, concluding that the SOFA score had prognostic value for in-hospital survival (Jones et al. 2009).

When considering the importance of the GCS component of the SOFA score, a relevant study was reported by Mulier et al., who have previously demonstrated the influence of coma on mortality in a study of generalized post-operative peritonitis patients, independently of age and source control (Mulier et al. 2003).

Effect of Heart rate

An increased heart rate is a physiological response to infection and sepsis, and part of the systemic inflammatory response syndrome (SIRS).

Sprung and colleagues found that the presence of SIRS predicts infection, severity of illness, organ failure and outcome, with the two most common SIRS criteria met during ICU stay being respiratory rate (82%) and heart rate (80%) (Sprung et al. 2006). Morelli and co-workers randomised a total of 154 septic shock patients to receive a continuous infusion of esmolol (targeting a heart rate of 80-94 bpm) or standard treatment in an open label trial. The patients in the esmolol arm achieved lower heart rates, without an increase of adverse events. Interestingly, an improvement in survival and other secondary outcomes was also reported (Morelli et al. 2013). Others have found that a high daily mean heart rate was a significant predictor of ICU mortality (Park et al. 2011).

Effect of Hyperbilirubinaemia

Post-operative hyperbilirubinaemia has been linked to persistent post-surgical infection and a poor prognosis (Nishida et al. 2002). In a study of patients with peritonitis, hyperbilirubinaemia, together with age and organ/system failures, was

found to be amongst a number of mortality predictors on univariate analysis (Barthlen et al. 1992).

6.2 Limitations

Although larger than any previous series of patients admitted to ICU with faecal peritonitis, these analyses have a number of important limitations.

Firstly recruitment was based on a clinical diagnosis of faecal peritonitis, but participating centres were at liberty to decide which patients they would recruit. While the inclusion and exclusion criteria were very precisely defined, making the population under exam extremely homogeneous, the subjects were not enrolled consecutively, thereby introducing a potential for selection bias. A second potential issue is the considerable variation in the numbers of patients recruited in each country. Some centres contributed very small numbers of patients. Nevertheless the wide range in participant ages, severity of physiological derangement and other characteristics, suggests that a significant systematic selection bias is unlikely. Therefore, for the two reasons identified above, this observational prospective cohort study may have suffered from some selection bias. Nevertheless there was a wide range in participant ages, severity of physiological derangement and co-morbidities, suggesting that a significant systematic selection bias is unlikely.

Thirdly, the Bonferroni correction to address multiple tests performance (in the analyses of day one predictor variables and trends) was used. This technique is a very conservative method and avoids the scientific concerns related to the risks of false positive results. Such an approach is justified given the large amount of tests performed and the importance of avoiding excessive false positive results.

Furthermore, in common with all but one of the previous epidemiological studies of peritonitis (which found no relationship between microbial isolates and outcome) (Pacelli et al., 1996) microbiological data were not collected. The GenOSept and GAinS studies were not designed to evaluate the influence on

outcome of the timing and adequacy of source control or antimicrobial treatment. All patients included in these cohorts received source control via surgical laparotomy prior to recruitment and the overwhelming majority of the patients (91.8%) received antimicrobial therapy deemed to be adequate. As the timing and adequacy of source control or antimicrobial treatment were not a focus of the epidemiological data collected, it is difficult to establish how these factors may have influenced outcomes, or how they could have affected the performance of the prognostic models.

The failure to detect a relationship between outcome and antimicrobial use was almost certainly an inevitable product of insufficient power resulting from the many drug combinations utilised.

The potential for unmeasured (known or unknown) factors to confound the associations detected must be acknowledged, in this as in any other observational study. Subsequent prospective studies, specifically aimed at confirming the potential predictive accuracy of the day one admission factors and the trends identified here as of prognostic value, would be required to further assess their value in clinical practice.

The prognostic models presented here have some strengths, particularly as they have been derived and externally validated using large and recently gathered cohorts of FP patients (hence reflecting current practices and therapies). They could not be compared to other scoring systems such as the colorectal POSSUM, the MPI, PIA II or the PSS using the GenOSept and GAinS datasets, as these systems all require some intra-operative or pre-operative findings, not available to me. The lack of comparison with alternative and more recent versions of the severity scores, such as the Simplified Acute Physiology Score (SAPS) 3, the APACHE III or IV or the Mortality Prediction Model (MPM) III, may have an impact on the validity of the

results. Nevertheless, multiple studies have shown that the performance of such tools, even in their more recent versions, is not significantly improved (Lee et al. 2014). Furthermore, despite the existence of updated versions, the APACHE II score has remained the most widely used severity scoring system in the ICU (Vincent & Moreno 2010; Eachempati 2014; Bouch & Thompson 2008) and the comparator of choice in multiple other recently published studies (Donnino et al. 2013; Naeini et al. 2015). The SOFA score may be a less than ideal comparator, as it had not been developed for prognostication. Nevertheless, SOFA has been used for that purpose in multiple studies, both in isolation (Hynninen et al. 2008; van Ruler et al. 2011; van Ruler, Lamme, et al. 2007; Sumi et al. 2014; Jones et al. 2009) and in combination with other parameters (Zügel et al. 2011; Matsumura et al. 2014), for outcome prediction. Biondo and colleagues have recently evaluated the performance of the MPI as a predictor of immediate postoperative mortality, demonstrating an AuROC of 0.72 (95% CI 0.65-0.79), while, for the more specific left colonic Peritonitis Severity Score (PSS), the AuROC was 0.79 (95% confidence interval 0.72-0.85) for this outcome (Biondo et al. 2006).

The overwhelming majority of patients enrolled in this study were Caucasian and, therefore, caution should be exercised when extrapolating these findings to different ethnic populations. My findings are applicable to faecal peritonitis patients who stayed in ICU for at least 2 days. Only 40 (4.1%) of the 977 faecal peritonitis patients in this cohort had a shorter stay, hence I consider it unlikely that this generated significant bias.

6.3 Summary and Implications of the findings

This is the largest cohort of patients admitted to ICU with faecal peritonitis reported to date, providing a contemporary European view of their clinical characteristics, outcomes and prognostic features. The ICU mortality rate was 20.9%, reaching 31.6% at six months. The studies reported in the thesis examine the impact on outcome of admission variables and trends, presenting novel, and sometimes unexpected, findings. Age, renal dysfunction, hypothermia and lower haematocrit on admission were consistently associated with an increased risk of death. Changes in routinely measured, readily available at the bedside, clinical, physiological and laboratory parameters were also associated with outcome. In particular, the deterioration in renal function, thrombocytopaenia and SOFA score over the first 2, 3, 5 and 7 days were consistently associated with mortality. Derangement in other laboratory variables, radiological findings, physiological parameters or even changes in respiratory support, renal replacement therapy and inotrope and/or vasopressor requirements, as analysed here on admission or over multiple time intervals, appeared not to be independently and consistently associated with any of the primary or secondary outcomes.

The data also allowed the development of two prognostic models for the risk of 6 month and 28 day mortality in critically ill septic patients with FP, following laparotomy for source control. The tools incorporate five of the major independent risk factors identified (SOFA score, age, heart rate, temperature and haematocrit), and combine them to produce a numerical value associated with mortality risk over 6 months or 28 days. In the setting of post-operative FP patients admitted to critical care, the tools outperformed other existing scoring systems, such as SOFA and APACHE II.

External validation in larger cohorts, such as the NELA (National Emergency Laparotomy Audit) or other databases (Odor & Grocott 2016), of the reliability of the admission variables and dynamic trends identified, and the predictive capability of the scoring tools are needed. In particular, further confirmation would be needed if the scores are to be relied upon for prognostication and escalation of care purposes.

6.4 Future Research

Subsequent prospective cohort studies should be specifically aimed at confirming (or refuting) whether the few key variables and the specific dynamic trends identified in my thesis can explain variability in outcomes. Ideally, they should aim at recruiting patients by enrolling consecutively all suitable candidates and across multiple centres and countries. Also, as the overwhelming majority of patients enrolled in this study were Caucasian, confirming these findings across other populations remains necessary.

Furthermore, a new prospective cohort study should collect variables useful for stratifying patients based not only on acute physiological derangement, comorbidities and organ support requirements, but also additional relevant factors. The supplementary variables to be considered are surgical techniques (collecting data for the calculation of other scoring systems, such as the colorectal POSSUM, the MPI, PIA II or the PSS, to compare to those developed here), type of healthcare system, other existing or novel surgical scoring systems, microbiological isolates and antimicrobial therapies used (to overcome the power limitations of the current analyses). Further evaluation of the predictive accuracy of the models described here, to decide their value in clinical practice, would be more feasible with a larger and adequately structured database.

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Appendix

Lists of variables available for analyses

List of Variables included in the Cox proportional hazard univariate analysis (day 1 epidemiological survey)

Generic
Cause of faecal peritonitis
APACHE II score
Time to surgery

Variables related to organ failure and support
Presence of acute renal failure (ARF) (day 1)
Need for renal replacement therapy (RRT) (day 1)
Need for ventilatory support (day 1)
Total SOFA score (day 1)
Highest renal component of SOFA score (during first week of admission)
Highest cardiovascular component of SOFA score (during first week of admission)

Comorbidities
Cardiovascular disease
Respiratory disease
Gastroenterological disease
Neurological disease
Renal disease
Underlying malignancy
Diabetes mellitus
History of previous serious infection
History of severe exercise limitation
Chronic dialysis
Other illness
History of chronic steroids use

Laboratory parameters (day 1)
Haematocrit
Highest recorded serum sodium
Lowest recorded serum sodium
Highest recorded serum potassium

Lowest recorded serum potassium
pH value
Serum bicarbonate
Arterial partial pressure of O_2
Arterial partial pressure of CO_2
Highest recorded serum creatinine
Lowest recorded serum creatinine
Highest recorded WCC (White Cell Count)
Lowest recorded WCC
Lowest recorded platelets
Highest recorded serum bilirubin
Highest recorded serum urea

Radiological changes (day 1)
Diffuse bilateral infiltrates on chest radiography (day 1)

Physiological parameters (day 1)
Highest recorded temperature
Lowest recorded temperature
Highest recorded SBP (systolic blood pressure)
Lowest recorded SBP
Highest recorded MAP (mean arterial pressure)
Lowest recorded MAP
Highest recorded HR (heart rate)
Lowest recorded HR
Respiratory rate
Urine volume
P:F ratio
Use of inotropes/vasopressors

List of variables available for trends testing

Variables related to organ failure and support
Presence of acute renal failure (ARF)
Need for renal replacement therapy (RRT)
Need for ventilatory support
Total SOFA (Sequential Organ Failure Assessment) score
GCS (Glasgow Coma Scale) SOFA score
CVS (Cardiovascular) SOFA score
Coagulation SOFA score
Respiratory SOFA score
Renal SOFA score
Bilirubin SOFA score

Laboratory parameters
Serum bicarbonate
Arterial partial pressure of O_2
Arterial partial pressure of CO_2
Highest recorded serum creatinine
Lowest recorded serum creatinine
Highest recorded WCC (White Cell Count)
Lowest recorded WCC
Lowest recorded platelets
Highest recorded serum bilirubin
Highest recorded serum urea

Radiological changes
Localised infiltrates on chest radiography
Lobar infiltrates on chest radiography
Diffuse bilateral infiltrates on chest radiography

Physiological parameters
Highest recorded temperature
Lowest recorded temperature
Highest recorded SBP (systolic blood pressure)
Lowest recorded SBP
Highest recorded MAP (mean arterial pressure)
Lowest recorded MAP
Highest recorded Heart Rate
Lowest recorded Heart Rate
Respiratory rate
Urine volume
P:F ratio
Use of inotropes/vasopressors

List of Variables used for derivation of the prognostic model

Variables related to organ failure and support
Presence of acute renal failure (ARF)
Need for renal replacement therapy (RRT)
Need for ventilatory support
Inotropic support
Total SOFA (Sequential Organ Failure Assessment) score
GCS (Glasgow Coma Scale) SOFA score
CVS (Cardiovascular) SOFA score
Coagulation SOFA score
Respiratory SOFA score
Renal SOFA score
Bilirubin SOFA score

Laboratory parameters
Serum bicarbonate
Arterial partial pressure of O_2
Arterial partial pressure of CO_2
Highest recorded serum creatinine
Lowest recorded serum creatinine
Highest recorded WCC (White Cell Count)
Lowest recorded WCC
Lowest recorded platelets
Highest recorded serum bilirubin
Highest recorded serum urea

Radiological changes
Localised infiltrates on chest radiography
Lobar infiltrates on chest radiography
Diffuse bilateral infiltrates on chest radiography

Physiological parameters
Highest recorded temperature
Lowest recorded temperature
Highest recorded SBP (systolic blood pressure)
Lowest recorded SBP
Highest recorded MAP (mean arterial pressure)
Lowest recorded MAP
Highest recorded Heart Rate
Lowest recorded Heart Rate
Respiratory rate
Urine volume
P:F ratio

List of Study Personnel Responsible for Database Development and Quality Control

C.H. – Charles Hinds, Professor of Intensive Care Medicine, William Harvey Research Institute, Barts and the London Queen Mary School of Medicine
C.G. – Dr Chris Garrard, Consultant in Intensive Care Medicine, John Radcliffe Hospital, Oxford.
A.G. – Prof Anthony Gordon, Professor of Anaesthesia and Critical Care, Imperial College London.
P.H. – Ms Paula Hutton, Senior research nurse, John Radcliffe Hospital, Oxford
A.W. – Dr Andrew Walden, Consultant in Acute and Intensive Care Medicine Royal Berkshire Hospital, Intensive Care Unit, Berkshire, UK
J-D.C. – Prof Jean-Daniel Chiche, Réanimation Médicale, Hôpital Cochin, Paris, France

Additional Information

The GenOSept (Genetics of Sepsis and Septic Shock in Europe) and GAinS (Genomic Advances in Sepsis) are prospectively gathered cohorts of adult critically ill septic patients with faecal peritonitis (FP), admitted to intensive care units, from multiple centres in Europe. Patients included in the GenOSept FP cohort were recruited from 102 centres across 16 European countries and those in the GAinS FP cohort were recruited from 51 UK centres between September 2005 and March 2015.

GenOSept study - additional information

GenOSept (Genetics Of Sepsis and Septic Shock in Europe) is a multi-centre pan-European part-FP6-funded study conceived by the ECCRN (European Critical Care Research Network) of the ESICM (European Society for Intensive Care Medicine) to investigate the potential impact of genetic variation on the host response and outcomes in sepsis (https://www.genosept.eu/).

GenOSept study consortium: ESICM, Belgium; University of Bonn, Germany; Wellcome Trust Centre for Human Genetics, Oxford University, UK; Cochin Institute, France; University of Torino, Ospedale San Giovanni Battista, Italy; University Roviri and Virgili of Terragona, Hospital Joan XXIII, Spain; Helmholtz Zentrum Munchen, Germany; Hadassah Medical Centre, Israel; SIRS-Lab GMBH, Germany; University of Ulm, Germany; University of Jena, Germany; Mazaryk University, Czech Republic; National Medical Centre, Hungary; Tartu University Clinics, Estonia.

GenOSept study - List of Contributing Centres

Belgium:

Intensive Care Unit, AZ-VUB university hospital, 101 Laarbeeklaan, Brussels; Intensive Care Unit, Chu Charleroi, 92 Boulevard Janson, Charleroi; Soins Intensifs, Clinique Saint Pierre, 9 Avenue Reine Fabiola, Ottignies; Intensive Care, Cliniques Universitaires Saint Luc (UCL), 10 Avenue Hippocrate, Brussels; Intensive Care, University hospital, 185 De Pintelaan, Gent; Soins Intensifs, Cliniques de l'europe - St Michel,150 Rue de Linthout, Brussels.

Croatia:

Medic, Emergency and Intensive Care Medicine/Internal Medicine, Clinical hospital Rebro, 12 Kispaticeva, ZagrebAnestesiology and ICU, Clinical Hospital Rebro, 12 Kispaticeva, Zagreb.

Czech Republic:

Anesteziologicko-reuscitacni klinika, Fakultní Nemocnice u Svaté Anny, 53 Pekařská, Brno; Anesteziologicko-resuscitacni oddeleni, Fakultni Nemocnice Brno, 20 Jihlavská, Brno-Bohunice; Klinika anestezie, resuscitace a intenzivni mediciny, Fakultni Nemocnice Hradec Kralove, 581 Sokolská, Hradec Kralove; Chirurgicka klinika, Fakultní Nemocnice s Poliklinikou Ostrava, 1790 listopadu, Ostrava-Poruba; Anesteziologicko-resuscitacni klinika, Fakultni Nemocnice Plzen, 80 Alej Svobody Plzen; Anestezie, resuscitace a intenzivni medicina, Masarykova Nemocnice, 3316/12A Sociální péče, Ústi Nad Labem; Anesteziologicko-resuscitacni oddeleni, Nemocnice Znojmo, 11 Janského, Znojmo; Anesteziologicko-resuscitacni oddeleni, Krajska Nemocnice Liberec, 10 Husova, Liberec.

Estonia:

General ICU, Tartu University Hospital, 1a L. Puusepa, Tartu; Pulmonary ICU, Tartu University Hospital,1a L. Puusepa, Tartu.

France:

Service de Réanimation Médicale, Hopital Cochin, 27 rue du Fbg St Jacques, Paris; Service de Réanimation Médicale, HEGP, 20 rue Leblanc, Paris; Service de Réanimation Médicale, Hotel Dieu, 1 place du Parvis Notre Dame, Paris; Service de Réanimation Médicale, Saint Joseph, 185 rue Raymond Losserand, Paris; Service de Réanimation Médicale, Chru Angers, 4 rue Larrey, Angers; Service de Réanimation Médicale, Chu de Nice, Rte St Antoine Ginestière, Nice; Service de Réanimation Médicale, Chu Purpan, Chu Toulouse- Hôpital Purpan, Toulouse; Service de Réanimation Médicale, Ch Versailles, 177 rue de Versailles, Le Chesnay.

Germany:

Klinik für Herzchirurgie, Klinikum der Stadt Ludwigshafen am Rhein GGMBH, 79 Bremserstraße, Ludwigshafen; Klinik und Poliklinik für Anästhesiologie und Intensivmedizin, Klinikum Greifswald, 23b Friedrich-Loeffler-Straße, Greifswald; Klinik fur Anästhesiologie und operative Intensivmedizin, Klinikum Augsburg, 2 Stenglinstr., Augsburg; Klinik und Poliklinik für Anaesthesiologie und Intensivtherapie, Universitätsklinikum Dresden, 74 Fetscherstrasse, Dresden; Klinik für Anästhesiologie und Intensivtherapie, Klinikum der Friedrich Schiller Universität, 101 Erlanger Allee, Jena; Klinik für Anästhesie und Intensivmedizin, Westküstenklinikum Heide, 50 Esmarchstraße, Heide; Abt. fur Anästhesiologie und Intensivtherapie, Fachkrankenhaus Coswig - centre for pneumology and thoracic surgery, 21 Neucoswiger Str., Coswig; Klinikum der Medizinischen Fakultät der Martin Luther Universität Halle-Wittenberg, 40 Ernst-Grube-Str., Halle; Klinik für Intensivmedizin, University medical center Eppendorf, 52 Martinistr., Hamburg; Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin (Turmgebäude 2OG Zimmer 221), Universitätsklinikum Bonn, 25 Sigmund-Freud-Str., Bonn; Internal Medicine, Universitätsklinikum Mainz, 1 Langenbeckstrasse, Mainz.

Greece:

Intensive Care, Sismanoglion general hospital, Marousi, Athens; Critical care, Attikon university hospital, 1 Rimini, Xaidari.

Hungary:

Surgery 1St, Semmelweis University, 78 Ulloi Ut, Budapest

Eire:

Intensive care unit, St James hospital, James Street, Dublin; Intensive care unit, Adelaide Meath and national children’s hospital, Tallaght, Dublin; Anaesthesia and Intensive care, National university hospital Galway, Newcastle Road, Galway; Anaesthesia & Intensive Care Medicine, James Connolly memorial hospital, Blanchardstown, Dublin; Department of Anaesthesia and Intensive Care Medicine, Cork university hospital, Wilton, Cork.

Israel:

Carmel medical center, Haifa; General Intensive care unit, Haemek medical center, Afula; Anaesthesiology and critical care medicine, Hadassah medical center, Kiryat Hadassah, P.O. Box 12000, Jerusalem

Italy:

Anestesiologia e Rianimazione 3, Ospedale S. Giovanni Battista – Molinette, 88 Corso Bramante, Torino; Anestesia e Rianimazione, Ospedale S.Giovanni Bosco, 3 Piazza Donatori del Sangue, Torino; Dr Rianimazione SOD 2, AOU Careggi, 85 Viale Morgagni, Firenze; Anestesia e Rianimazione, Ospedale Maggiore, 35 Via Francesco Sforza, Milano; Terapia Intensiva, Universita Degli Studi Milano Bicocca A.O. San Gerardo, 106 Via Donizetti, Monza; Anestesia e Rianimazione, Ospedale

S.Orsola Malpighi, 9 Via Massarenti, Bologna; Anestesia e Rianimazione, Ospedale S.Giovanni Addolorata, 8 Via dell'Amba Aradam, Roma; Scienze Anestesiologische, Medicina Critica e Terapia del Dolore, Policlinico Umberto I, 155 Viale del Policlinico, Roma.

Netherlands:
Intensive care unit, Erasmus medical centre, 230 Gravendijkwal, Rotterdam.

Poland:
Anaesthesiology and Intensive Therapy, Medical university, 7 Debinki St, Gdansk; Klinika Anestezjologii i Intensywnej Terapii sp Centralny Szpital Kliniczny Sam; Military teaching hospital; Szpital Wojewodzki/regional hospital; University hospital n°2; Szpital Wojewodzki; University hospital of Bydgoszcz; Wroclaw medical University.

Serbia:
Military medical academy; Clinical center Kragujevac.

Spain:
Coordinating centre: Universitat Roira & Virgili / Hospital Universitari Joan XXIII de Tarragona, CIBERES. University hospital de Bellvitge; hospital Universitario Puerta del Mar; hospital Universitario de Gran Canaria; hospital de la Princesa; hospital Nostra Senyora de Meritxell; hospital de Mataro; hospital clinico San Carlos; hospital Universitari de Terragona Joan XXIII; hospital Sagunt; centro medico Delfos; hospital de Huesca; hospital general de Segovia; Basurto hospital; hospital Universitario Arnau de Vilanova; hospital general Yague; hospital Universitario Puerto Real; hospital Universitario de Girona; hospital General de Vic; Hospital Verge De La Cinta.

United Kingdom:
Aberdeen Royal Infirmary; Addenbrooke's Hospital; Barts and the London NHS trust; Broomfield hospital; Charing Cross Hospital; Chelsea and Westminster Hospital; Cheltenham general hospital; Colchester General Hospital; Freeman Hospital; Frimley Park hospital; Hammersmith hospital; Homerton University hospital; Hope hospital; Huddersfield royal infirmary; Hull royal infirmary; Ipswich hospital NHS trust; John Radcliffe hospital; Leeds general infirmary; Leicester royal infirmary; Manor hospital, Walsall; Norfolk & Norwich NHS trust; Queen Elizabeth hospital, King's Lynn ; Queen Elizabeth University hospital; Royal Berkshire Hospital; Royal Hallamshire hospital, Sheffield; Royal Preston hospital; Royal Sussex county hospital; Royal Victoria infirmary; Southend hospital NHS trust; st James University hospital; the Great Western hospital; the James Cook University hospital; The Whittington hospital; UCLH Middlesex hospital; University hospital Lewisham; University hospital of Wales; University hospital, Coventry; Worthing hospital; Wythenshawe Hospital

GenOSept study - National Co-ordinators

Austria	H Novak
Belgium	P Damas
Croatia	V Gasparovic
Czech Republic	V Sramek
Estonia	S Sarapuu
France	J-D Chiche
Germany	F Bloos
Greece	A Armagandis
Hungary	I Bobek
Ireland	T Ryan
Israel	Y Weiss
Italy	P Cotogni
Netherlands	J Hazelzet
Poland	A Mikstacki
Serbia	M Surbatovic
Spain	J Rello
United Kingdom	C Hinds

GenOSept study - Principal Investigators

Austria AT
H Novak

Belgium BE
H Spapen
P Biston
T Dugernier
P.F. Laterre
P Damas
V Collin

Croatia HR
M Grgic Medic
T Mahecic

Czech Republic CZ
V Sramek

J Mannova
D Bares
O Marek
I Satinsky
I Novak
M Panko
S Vojtech
I Zykova

Estonia EE
S Sarapuu

France FR
J D Chiche
J L Diehl
A Rabbat
B Misset
P Asfar
H Hyvernat
P Sanchez
J-P Bedos

Germany DE
F Isgro
M Grundling
U Jaschinski
M Ragaller
F Bloos
S Schroder
J Krassler
A Nierhaus
C Putensen
M Weiss
Prof Larsen
M Lauterbach

Greece GR
D Evrenoglou
A Armaganidis

Hungary HU
K Darvas
I Okros

Ireland IE
T Ryan
M Donnelly
J Laffey
C Cody
C Motherway
D Breen

Israel IL
R Pizov
A Lev
Y Weiss

Italy IT
V. M Ranieri
S Livigni
P Pelaia
R Tufano
A.R De Gaudio
L Gattinoni
A Pesenti
M Capuzzo
G Sangiorgi
F Turani
F Conforto
F Bilotta

Netherlands NL
B Van Der Hoven

Poland PL
A Siemiatkowski
D Maciejewski
M Wujtewicz
E Karpel
A Ziajka
R Gajdosz
W Gaszynski
A Nestorowic
W Kowalski
A Mikstacki
L Drobnik

L Krawczyk
J Jastrzebski
A Kanski
W Koscielniak
M Mikaszweska-
Sokolewicz
K Kusza
A Kubler
B Jozef

Serbia RS
M Surbatovic
J Jevdjic

Spain ES
X L Perez-Fernandez
R l Sierra
J Sole-Violan
N Carrasco
A Margarit-Ribas
J C Yebenes
A Valverde-Conde
G Sirgo
E Gomez-Martinez
F F Dorado
L Labarta
L Cambra
M A Vidarte-Ortiz
M B Castello
J L Fernandez
J Gil Cebrian
J M Sirvent
M C Martin

United Kingdom UK
C Hinds
C Garrard
A Johnston
D Watson
S Baudouin
M Watters
R Venn

J Bion
D Higgins
M J. Garfield
S Pambakian
J Thompson
J Durcan
A Kapila
G Bellingan
S Fletcher
A Bentley
A Mallick
R Bailie
I Krupe
M Oram
M Hayes
E Wheatley
S Murdoch
S Bonner
N Webster
G Findlay
M Blunt
G Mills
G Thomas
S Drage
A Timmins
S Pesian
A Gordon
M Kuper
P Hall
P Venkatesh
J Moreno Cuesta
S Laha
A Guleri
I Smith
A Krige
P Watt

GenOSept study - Research Nurses and Fellows

E Svoren
A Purdy
E McLees
P Hutton
P Parsons
A Smith
R Farras-Arraya
C Higham
C Ryan
C Pirie
K Mayell
K Challis
S Morris
N Waterhouse
V Flitchett
J Margalef
Dr Mowatt
P Hudson
R Gupta
J Wilde
S Lees
A Nillson
S Andrews
E Simpson
S Mappleback
S Burfield
L Sherrard Smith
V Jamieson
K Williamson
E Thomson
S Rogers
N Wilson
S Bowrey
N Rich
N Griffin-Teal
C Mitchell-Inwang
S Williams
K Swan
S Smolen
C Jones

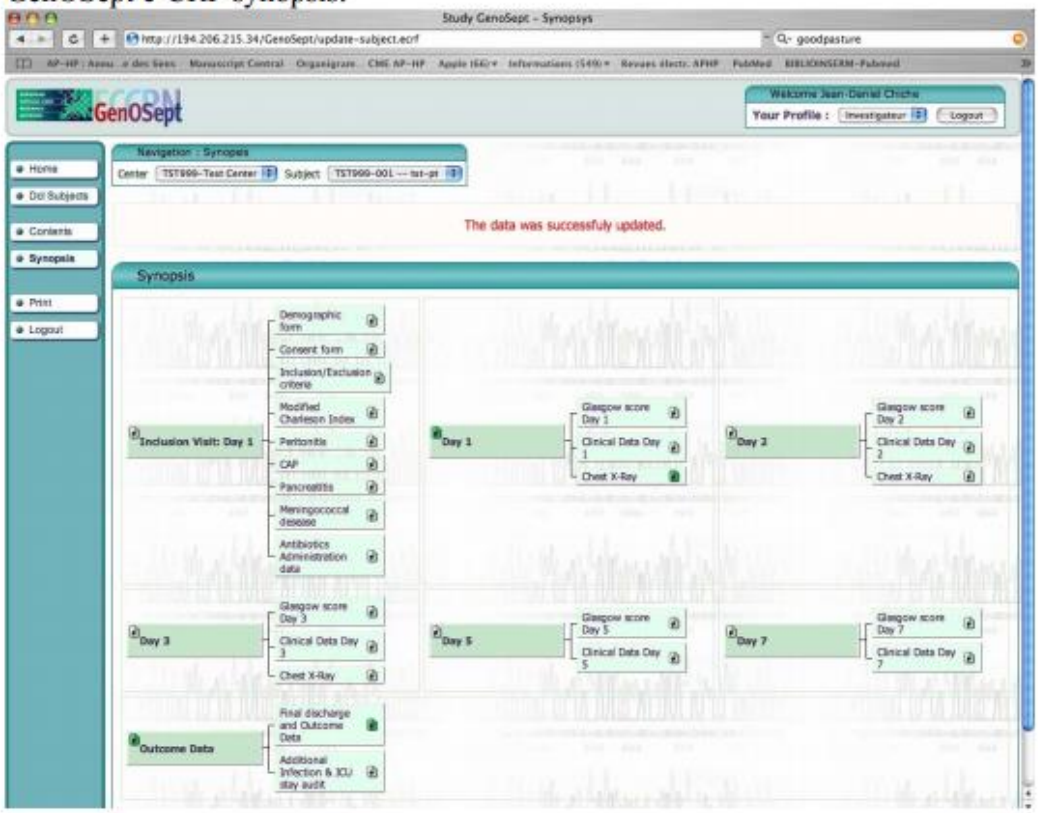
H Prowse
N Jacques
J Atkinson
S Boluda
A Bakarr Karim
J Hyun Ryu
J Nagle
G Bercades
M Rosbergen
G Glister
F Jefferies
D Downs
K Millward
S Elliot
J Thornton
D Mawer
J Calderwood
I Whitehead
V Goodridge
K Hugill
K Colling
S Roughton
H Tennant
J Taylor
S Hall
J Addison
L Macchiovello
E Hutcheon
C Underwood
K Wong
J Collins
N Mills
E Calton
J Sorrell
S Lowes
L Ortiz-Ruiz De Gordoa
A Ghosh
O Thunder
N Wheatley
M Templeton
R Wilson
C Gibbs
L Mountford

J Gonzalez-Moreno
M Ainsworth
S Pahary
S Musaad
J Hewlett
J England
G Ward
S Nyabadza
S Clay
C Gibson
E Archer
K Hotchkiss
D Gocher
J Daglish
M Dlamini
J Baldwin
N Doherty
J Cocker
N Waddington
N Smith
D Harrison
M Bland
L Bullock
P Raymode
G Sirgo
T Lisboa
E Diaz

GenOSept study – Electronic case report form

GenOSept e-CRF synopsis (from GenOSept publishable executive summary - https://www.genosept.eu/doc/Executive%20summary%20year%202.pdf)

GenOSept e-CRF synopsis:



Gains study - additional information

GAinS (Genomic Advances in Sepsis) is a multi-centre UK-wide study supported by the UKCCG (UK Critical Care Genomics Group), a network of centres undertaking clinical functional genomics research in the critical care setting (http://www.ukccg-gains.org).

GAinS study Sponsor: University of Oxford

GAinS study collaborators: Sainsbury Family Charitable Trust; Wellcome Trust Centre for Human Genetics, Oxford; Queen Mary University of London; Barts and The London School of Medicine and Dentistry

GAinS Study ClinicalTrials.gov identifier: NCT00131196 (https://clinicaltrials.gov/ct/show/NCT00131196)

GAinS study - List of Contributing Centres

Broomfield Hospital, Chelmsford, UK
Addenbrookes Hospital, Cambridge, UK
Charing Cross Hospital, London, UK
Chelsea & Westminster Hospital, London, UK
Colchester General Hospital, Colchester, UK
Hammersmith Hospital, London, UK
Homerton University Hospital, London, UK
Ipswich Hospital, Ipswich, UK
Queen Elizabeth Hospital, Kings Lynne, UK
University Hospital of Lewisham, London, UK
North Middlesex Hospital, London, UK
Norfolk & Norwich University Hospital, Norwich, UK
Southend University Hospital NHS Foundation Trust, Westcliff-on-Sea, UK
St Bartholomew's Hospital (Barts), London, UK
University College Hospital, London, UK
Whittington Hospital, London, UK
St Marys Hospital, London, UK
University Hospital Coventry, Coventry, UK
Leicester General Hospital, Leicester, UK
Leicester Royal Infirmary, Leicester, UK
Queen Elizabeth Hospital Birmingham, Birmingham, UK
Wythenshawe Hospital, Manchester, UK
Royal Hallamshire Hospital, Sheffield, UK
Northern General Hospital, Sheffield, UK
Hope Hospital, Manchester, UK
Manor Hospital, Walsall, UK
Glenfield General Hospital, Glenfield, UK
Aberdeen Royal Infirmary, Aberdeen, UK
Antrim Area Hospital, Antrim, UK
Royal Blackburn Hospital, Blackburn, UK
Blackpool Victoria Hospital, Blackpool, UK
Calderdale Royal Hospital, Calderdale, UK
Huddersfield Royal Infirmary, Huddersfield, UK
Castle Hill Hospital, Hull, UK
Hull Royal Infirmary, Hull, UK
Leeds General Hospital, Leeds, UK
St James Hospital, Leeds, UK
James Cook University Hospital, Middlesbrough, UK
Royal Victoria Infirmary, Newcastle, UK
Freeman Hospital, Newcastle, UK
Royal Preston Hospital, Preston, UK
Royal Sussex County Hospital, Brighton, UK

Southmead Hospital, Bristol, UK
Frenchay Hospital, Bristol, UK
Cardiff University Hospital, Cardiff, UK
Cheltenham General Hospital, Cheltenham, UK
Frimley Park Hospital, Frimley, UK
Kettering General Hospital, Kettering, UK
John Radcliffe Hospital, Oxford, UK
Royal Berkshire Hospital, Reading, UK
Great Western Hospital, Swindon, UK
Worthing General Hospital, Worthing, UK
Southlands Hospital, Shoreham-by-Sea, UK

GAinS study - Chief Investigators

Charles Hinds
Christopher Garrard

GAinS study - Principal Investigators

Charles Hinds
Christopher Garrard
Andrew Johnston
Dave Watson
Simon Baudouin
Malcolm Watters
Richard Venn
Julian Bion
David Higgins
Mark J. Garfield
Samuel Pambakian
Jonathan Thompson
John Durcan
Atul Kapila
Geoff Bellingan
Simon Fletcher
Andrew Bentley
Abhiram Mallick
Ingrid Krupe
Matt Oram
Michelle Hayes
Elizabeth Wheatley
Stuart Murdoch
Stephen Bonner
Nigel Webster
George Findlay
Mark Blunt
Gary Mills
Gareth Thomas
Stephen Drage
Andrew Timmins
Siamek Pesian
Anthony Gordon

GAinS study - Research Nurses and Fellows

Dr Eduardo Svoren
Alice Purdy
Eleanor McLees
Carmen Correia
Ying Hu
Phoebe Bodger
Paula Hutton
Penelope Parsons
Alexandra Smith
Roser Farras-Arraya
Charley Higham
Charlotte Ryan
Catherine Pirie
Verity Calder
Helen Walsh
Sarah Nutbrown
Heather Payne
Karen Mayell
Karen Challis
Sarah Morris
Paul Liddiard
Nicky Waterhouse
Valerie Flitchett
Jordi Margalef
Dr Chris Mowatt
Paul Hudson
Ritu Gupta
Jude Wilde
Sarah Lees
Annette Nillson
Colin Bergin
Lauren Day-Cooper
Aisling Clarkson
Joanne Millar
Annette Nilsson
Elsa Jane Perry
Sarah Andrews
Dr Emily Simpson
Sarah Mappleback
Sharon Burfield
Loida Sherrard Smith
Verona Jamieson
Kim Williamson

Emily Thomson
Sarah Rogers
Nicola Wilson
Sarah Bowrey
Natalie Rich
Nicola Griffin
Prem Andreou
Dawn Hales
Sandra Kazembe
Christine Mitchell-Inwang
Sarah Williams
Karen Swan
Susan Smolen
Fiona McNeela
Carys Jones
Heather Prowse
Nicola Jacques
Abby Brown
Susana Boluda
Abu-bakarr Karim
Jung Hyun Ryu
Georgia Bercades
Melissa Rosbergen
Georgina Glister
Fiona Jefferies
David Downs
Karen Millward
Katie Mccalman
Fiona Jefferies
Stuart Elliot
Zoe Beardow
Judith Thornton
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James Calderwood
Dr Iain Whitehead
Victoria Goodridge
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Jenni Addison

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Elizabeth Hutcheon
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Kathrine Wong
Jane Collins
Nathaniel Mills
Emily Calton
John Humphreys
Julie Sorrell
Rachel Walker
Verena Hauer
David Kitson
Emily Errington
Adaeze Ochelli-Okpue
Mark Ainsworth
Sarah Lowes
Laura Ortiz-Ruiz De Gordoa
Alison Ghosh
Orla Thunder
Natalie Wheatley
Maie Templeton
Robert Wilson
Claire Gibbs
Laura Mountford
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Sheik Pahary
Michele Bianchi
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Steven Clay Catherine Gibson
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Mabandla Dlmini
Jacqueline Baldwin
Angela Walsh
Nicola Doherty
Natalia Waddington
Neil Smith

Vicky Mendham
Martin Bland
Lynne Bullock
Donna Harrison
Parizade Raymode
Sally Grier
Elaine Hall

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List of ethical bodies that approved the studies

MREC, Multicentre Research Ethics Committee

The MRECs gave overall approval for the studies to be conducted in the UK

- Scotland A Research Ethics Committee
- Berkshire Research Ethics Committee

REC, Research Ethics Committee

Ethic Commissions / Bodies	Address
Ethikkommission Land Salzburg Ethik Kommission fur das Bundesland Salzburg	Ethikkommission für das Bundesland Salzburg Sebastian-Stief-Gasse 2 5020 Salzburg Postanschrift: Amt der Salzburger Landesregierung Ethikkommission für das Bundesland Salzburg Postfach 527 5010 Salzburg
Comite d'Ethique ISPPC	Chu - Charleroi Boulevard Zoé Drion, 1 6000 Charleroi
Comite d'Ethique Hospitalo-Faculatiare de Liege	Centre Hospitalier Universitaire de Liège Domaine Universitaire du Sart Tilman Bâtiment B 35 B-4000 Liège Belgique Clinique Saint Pierre, Avenue Reine Faibiola, 9 1340 Ottignies
Multicenter Ethics Committee Stanovisko multicentricke Eticke Komis Fakultni Nemoncnice U SV. Anny V Brno	Faculty hospital Brno Jihlavská 20 625 00 Brno Czech Republic

Ethics Committee of Faculty Hospital Hradec Kralove	Sokolaska 581, 500 05 Hradec Czech Republic
Ethics Committee of the University Hospital and Faculty of Medicine Palacky University in Olomouc	I.P. Pavlova 6, 775 20 Olomouc Czech Republic
Ethics Committee at University Hospital Ostrava	Ethics Committee Fakultní nemocnice s poliklinikou Ostrava 17. listopadu 1790, 708 52 Ostrava Poruba, Czech Republic
Ethics Committee Rozhodnuti Eticke Komise Fakultni Nemocnice Pizen	FN a LF UK Plzeň tř. Dr. E. Beneše 13 305 99 Plzeň Czech Republic
Ethics Committee of Masaryk's Hospital Usti n.Labem	Socialni pece 3316/12 A 401 13 Usti n. Labem Czech Republic
Eticka Komise Nemocnice Znojmo	Nemocnice Znojmo, příspěvková organizace MUDr. Jana Janského 11 669 02 Znojmo Czech Republic
Ethics Committee for multicenter clinical trials County Hospital Liberec	Husova 10, Liberec, Czech Republic
Eticka Komise pro multicentricka hodnoceni Krajska nemocnice Liberec	Liberec, Husova 10 460 63 Liberec 1 Czech Republic
Ethics Committee on Human Research of the University of Tartu	TU Biomeedikum Room 3050 Ravila Str 19 51014, Tartu, Estonia
Ethik Kommission Landesarztekammer Rheinland-Pfalz	Postfach 29 26 55019 Mainz Germany
Ethik Kommission Arztekammer Mecklenburg-Vorpommern	Ernst Moritz Amdt Universitat Greifswald, Friedrich-Loeffler Str. 23d 17487 Greifswald Germany
Ethik Kommission Bayerishe	Mühlbaurstr.16

Landesarztekammer	D-81677 München Germany
Ethik commission Technische Universtat Dresden	Ethikkommission Technische Universität Dresden Fetscherstraße 74 01307 Dresden Germany
Ethik Kommission Univesitatsklinikum Rheinisch Westfalische Technische Hochschule Aachen	Universitätsklinikum Aachen Pauwelsstraße 30 52074 Aachen Germany
Ethik Kommission Universitatslinikum Jena der Friedrich –Schiller	Bachstrasse 18, D-07740 Jena Germany
Ethik Kommission Schleswig-Holstein	Arnold-Heller-Straße 3 - Haus 18 24105 Kiel Germany
Ethik Kommission for Arztekammer Hamburg	Humboldstrasse 67a – 22083 Hamburg Germany
Ethik Kommission Universitat Heidelberg	Maybackstrasse 14-15, D68169 Mannheim Germany
Ethik Kommission Friedrich-alexander Universitat Erlangen-Nuremberg	Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg Krankenhausstraße 12 91054 Erlangen Germany
Ethik Kommission Rheinische Friedrich-Wilhelms Universitat	Reuterstr. 2b 53113 Bonn Germany
Ethik Kommission Universitat Ulm	Helmholtzstrasse 20 D-89081 Ulm Germany
Ethik Kommission Arztekammer des Saarlandes	Faktorestrasse 4 66111 Saarbrucken Germany
Helsinki Ethics Committee	Kiryat Hadassah, POB 12000 Jerusalem, 91120, Israel
Sismanoglio Geniko Nosokomeio	Sismanogliou 1

	Marousi 151 26 Greece
Ethics Commission University College Cork, Ireland	Lancaster Hall, 6 Little Hanover Street, Cork, Ireland
Ethics Commission The Adelaide & Meath Hospital, Dublin	Tallaght, Dublin 24, Ireland
Ethics Commission Merlin Park Hospital, Galway	Unit 4, Merlin Park Hospital Galway Ireland
Comitato Etico dell'Azienda Sanitaria Ospedaliera "San Giovanni Battista" di Torino	Corso Bramante 88-90 10126 Torino Italy
Comitato Etico Universita' degli studi di Napoli Federico II comitato etico per le attivita' biomediche	Via Sergio Pansini 5 80131 Napoli Italy
Comitato Etico Azienda Ospedaliiero Universitaria Ospedali Rhuniti, Ancona	VIA CONCA 71 60126 ANCONA (Ancona) Italy
Comitato Etico Azienda Ospedaliera Universitaria Careggi, Firenze	Viale Peiraccini 28 50139 Firenze Italy
Comitato Etico Azienda Ospedaliera San Gerardo, Monza	Via Pergolesi 33 20053 Monza (MI) Italy
Comitato Etico Azienda Ospedaliero Universitaria Di Ferrara	Via A.moro 8 Cona (FE) Italy
Ethische Commissie Erasmus MC Universitai Medisch Centrum Rotterdam	Postbus 2040 3000 Ca Rotterdam Netherlands
Komisja Karol Marcinkowski University of Medical Sciences in Poznan	Collegium Maius Fredry 10 61-701 Poznań Poland
Ethics Committee of Military Medical Academy	17 Crnotravska Serbia

Ethics Committee of Clinical Center Kragujevac	CLINICAL CENTER KRAGUJEVAC Zmaj Jovina street 30 Kragujevac Serbia
Comite Etico de Investigacion Clinica del Hospital General Universitario de Alicante	Hospital General Universitario de Alicante Pintor Baeza, 12, 03010 Alicante, Spain
Comite Etico Hospital Universitario Dr. Peset	Av. de Gaspar Aguilar, 90, 46017 València, Valencia, Spain
Comite Etico de Investigacion Clinica del Hospital de Bellvitge Barcelona	Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain
Comite Etico Hospital Universitario Puerta Del Mar	Av. Ana de Viya, 21, 11009 Cádiz, Spain
Comite Etico Hospital Universitario de Gran Canaria	Calle Dr. Alfonso Chiscano Díaz, 338 35010 Las Palmas de Gran Canaria, Las Palmas, Spain
Comite Etico Hospital Universitario de La Princesa Madrid	Calle de Diego Leon, 62, 28006 Madrid, Spain
Comite Etico Hospital General Universitario Reina Sofia de Murcia	Av. Intendente Jorge Palacios, 1, Murcia, Spain
Comite Etico Hospital Virgen de la Victoria Malaga	Campus de Teatinos, s/n, 29010 Málaga, Spain
Comite Etico Hospital De Mataro, Consorci Sanitari del Maresme	Carrer Prolongació Cirera, s/n, 08304 Mataró, Barcelona, Spain
Comite Etico Hospital Clinico San Carlos	Profesor Martín Lagos, S/N Madrid - 28040 Spain
Comite Etico Hospital Universitari De Tarragona Joan XXIII	C/ Dr. Mallafrè Guasch, 4, 43005 Tarragona, Spain

Comite Etico Hospital de Sagunto	Avenida Ramón y Cajal, S/N, 46520 Sagunt, Valencia, Spain
Comite Etico Centro Medico Delfos	Av. de Vallcarca, 151, 08023 Barcelona, Spain
Comite Etico Hospital Universitari Joan XXIII de Tarragona	C/ Dr. Mallafrè Guasch, 4, 43005 Tarragona, Spain
Comite Etico de investigacion Clinica De Aragon (CEICA)	Avenida Gomez Laguna 25 planta 3 50009 Zaragoza Spain
Comite Etico Hospital de Basurto	Montevideo Etorb., 18, 48013 Bilbao, Vizcaya, Bizkaia, Spain
Comite Etico Hospital Santa Maria del Rosell	Paseo de Alfonso XIII, 61 , 30203 Cartagena , Spain
Comite Etico Hospital Universitario Arnau de Vilanova de Lleida	Avenida Alcalde Rovira Roure, 80 25198 Lleida Spain
Comite Etico Hospital Universitario de Burgos	Avda. Islas Baleares, 3, 09006 Burgos, Spain
Comite Etico Hospital Universitario Puerto Real	Carretera Nacional IV, km 665, 11510 Puerto Real, Cádiz, Spain
Comite Etico Hospital Universitari de Girona Doctor Josep Trueta	Avenida França, s/n, 17007 Girona, Spain
Comite D'Etica d'Investigacio Clinica Consorci Hospitalari de Vic	Av. de França, s/n 9a planta A - Despatx 913 17007 - Girona Spain

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Peer reviewed publications

A. Tridente, G.M. Clarke, A. Walden, S. McKechnie, P. Hutton, G.H. Mills, A.C. Gordon, P.A.H. Holloway, J-D. Chiche, J. Bion, F. Stuber, C. Garrard, C. Hinds and the GenOSept Investigators
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PMID: 25939380
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Phenotypic factors associated with outcome in 977 intensive care patients with faecal peritonitis: analysis of trends in the genosept cohort
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