University of Calgary

PRISM Repository **https://prism.ucalgary.ca**

The Vault Open Theses and Dissertations

2013-07-10

An Analysis of a Cohort of Surgical-Related Intra-Abdominal Sepsis with PIRO

Posadas Calleja, Juan Gabriel

Posadas Calleja, J. G. (2013). An Analysis of a Cohort of Surgical-Related Intra-Abdominal Sepsis with PIRO (Master's thesis, University of Calgary, Calgary, Canada). Retrieved from https://prism.ucalgary.ca. doi:10.11575/PRISM/24829

http://hdl.handle.net/11023/780

Downloaded from PRISM Repository, University of Calgary

UNIVERSITY OF CALGARY

An Analysis of a Cohort of Surgical-Related Intra-Abdominal Sepsis with PIRO

by

Juan Gabriel Posadas-Calleja

A THESIS SUBMITED TO THE FACULTY OF GRADUATE

STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF MASTERS OF SCIENCE

DEPARMENT OF MEDICAL SCIENCE

CALGARY, ALBERTA

JUNE, 2013

© Juan Gabriel Posadas-Calleja 2013

Abstract

Introduction: Sepsis constitutes an important cause of morbidity and mortality; mortality in patients with intraabdominal sepsis remains high. The PIRO concept is a classification scheme for sepsis.

Methods: Retrospective analysis of a prospective observational cohort.

Results: 905 patients were analyzed. A PIRO score was developed including the following variables: age > 65 years, comorbidities, leukopenia, hypothermia, cardiovascular, renal, respiratory, and CNS failure, one point was given for each present feature. The mean PIRO score was significantly higher in nonsurvivors than in survivors (3.9 vs. 2.3 respectively, $p < 0.0001$). When the patients were distributed according PIRO scoring, mortality rate increased ($p < 0.0001$). The aROC showed consistent mortality discrimination by PIRO score (0.80, 95%CI 0.79 to 0.83), outperforming APACHE II (0.72, 95%CI 0.68 to 0.75) and SOFA (0.72, 95%CI 0.68 to 0.76) $p <0.0001$.

Conclusion: The PIRO score performed well as an ICU mortality predictor tool for surgical-related intra-abdominal sepsis.

Table of Contents

Abstract……..……..ii
Table of contents……iii
List of tables……...iv
List of figures……v
Chapter one: Introduction……...1
Chapter two: The PIRO framework……...5
2.1 Predisposition……...5
2.2 Infection……...7
2.3 Response……..8
2.4 Organ dysfunction……9
Chapter three: Methods……11
3.1 Patient selection…….....11
3.2 Operational definition of PIRO……..12
3.2.1 Predisposition.…….....12
3.2.2 Infection…….....13
3.2.3 Response……..……13
3.2.4 Organ dysfunction…….……..14
3.3Analysis plan…….…….....……..15
Chapter four: Results……..…….....17
4.1 General……..……17
4.2 Predisposition……..…….....18
4.3 Infection……..……...19
4.4 Response……..…..……19
4.5 Organ dysfunction…….…….....21
4.6 Multivariate analysis……..…..…….....23
Chapter five: Discussion……..…..…….....33
Chapter six: Conclusion…….…….....43
Bibliography……..……44

List of Tables

4.1 Baseline characteristics of the study population…….....17

4.2 Mortality distribution by diagnostic categories……...18

4.3 Model 1, including SOFA……24

4.4 Model 2, including dysfunctions separately……25

4.5 PIRO score # 1…….25

4.6 Variable distribution and association with mortality……...26

4.7 Model 3, excluding APACHE II score as variable…….....28

4.8 PIRO score # 2……29

List of figures

Figure 4.1 Mortality rate by SIRS criteria…….20

Figure 4.2 Mortality rate by number of dysfunctions……22

Figure 4.3 Distribution of patients (survivors and nonsurvivors) according to PIRO score…….26

Figure 4.4 Mortality rate distribution by PIRO score # 1……..27

Figure 4.5 Comparison of PIRO score # 1, APACHE II score and SOFA score using aROC….28

Figure 4.6 Mortality rate distribution by PIRO score # 2……..30

Figure 4.7 Comparison of PIRO score # 1 and PIRO score # 2 using aROC……...…31

Figure 4.8 Comparison of PIRO score #1, PIRO score #2, APACHE II and SOFA by aROC…32

Chapter One: Introduction

Sepsis, severe sepsis, and septic shock constitute an important cause of admission to the intensive care units (ICU) [1-3]. The incidence rate has been estimated between 2.4 to 3 cases per 1,000, and the CDC reported a surprisingly 140% increase in the incidence of sepsis from 1990 to 2000. Despite important advances in the knowledge of pathophysiology of sepsis and relevant improvements in monitoring and care support in the ICU, the overall hospital mortality rate is approximately 29%, it continues to be the leading cause of death in non-cardiologic ICU's, and the average LOS is 20 days [1, 4]. Costs per case have been estimated approximately between $22,000 to $50,000, resulting in an economic impact of nearly $17 billion annually in the US alone [5]. Furthermore, sepsis is associated with a reduced quality of life among those who survive [6].

Surgical patients are vulnerable to infectious complications during hospitalization because of several factors, including old age, preexisting chronic conditions, poor nutritional status, prolonged periods of hospitalization, extensive surgical trauma, emergency surgeries, and severe disturbances in immune defenses [7, 8]. Several attempts have been made to identify patients who are at higher risk for developing complications to better plan pre- and intraoperative management and to decrease mortality [8-10]. A large observational study reported postoperative complications in only 12.5% of surgical procedures, but these patients accounted for more than 80% of the related deaths [11]. Cardiovascular complications are the traditional focus, but few studies exist on the frequency of sepsis in critically ill patients in the postoperative period [12, 13]. A recent epidemiologic study described that sepsis has a high incidence and mortality in surgical patients admitted to the ICU, with mortality rate of 18.2% [14].

Although data from individual studies and reports provide a perspective on the epidemiology of severe sepsis, there is a lack of uniformity in the diagnostic criteria that limit a comprehensive epidemiologic analysis about severe sepsis. In 1991 the American College of Chest Physicians and the Society of Critical Care Medicine developed a consensus document to define the inflammatory response to infection (sepsis). The definition included sepsis-associated organ dysfunction (severe sepsis) and cardiovascular failure with refractory hypotension despite adequate fluid resuscitation (septic shock) [15]. However, problems remain with the clinical application of these consensus definitions and the overall clinical relevance of this classification has been questioned [16, 17]. In 2001, a survey among critical care specialists showed that approximately 70% of the surveyed felt that the existing definitions were confusing and not clinically useful [18]. The most recent international definition consensus effort was published in 2003 [19]; basically there were no major changes in the previous definitions; nonetheless, it was pointed out that current definitions fail to discriminate between patients at various stages of sepsis and the need of a new strategy of classification.

The following are the consensus definitions currently in use:

SIRS. Implies a clinical response arising from a non-specific insult and includes two or more of the following criteria [15]:

1. Temperature greater than 38^{o}C or lower than 36^{o}C.
2. Heart rate higher than 90/min.
3. Hyperventilation evidenced by respiratory rate higher than 20/min or $PaCO_2$ lower than 32 mmHg.
4. White blood cell count higher than 12,000 cells/µl or lower than 4,000 cells/µl, or normal white blood cell count with > 10% immature forms [19].

Infection. Pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. Sepsis may only be strongly suspected, without being microbiologically confirmed [19].

Sepsis. Clinical syndrome characterized by the presence of SIRS criteria in response to an infection [15]

Severe sepsis. Sepsis complicated by 1 or more major organ dysfunctions [19]. Organ dysfunction can be defined by using either the sequential organ failure assessment (SOFA) [20], or the multiorgan dysfunction score (MODS) [21] or the logistic organ dysfunction score (LOD) [22].

Septic shock. It is defined as a state of severe sepsis complicated by persistent hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 60 mmHg or a reduction of systolic blood pressure of more than 40 mmHg from baseline) refractory to early fluid therapy [19].

In 1995 Rangel-Frausto et al, showed progressively higher mortality rates as more severe inflammatory response criteria were met among a cohort of septic patients [23]. The same results have been reproduced in other studies [24-26].

During the 2001 conference, an innovative concept for analyzing the essential components of sepsis was described: PIRO as a hypothesis-generating model for future research. PIRO stands for Predisposition, Infection (or injury), Response and Organ dysfunction. It was modeled after the TNM classification for cancer staging, trying to better understand the complexity of sepsis and give to clinicians and researchers a more reliable and consistent system to classify septic patients [19].

To date, despite numerous expensive clinical trials on immunomodulatory therapy, there was only one treatment that showed modest improvement in survival in sepsis (activated protein C) [27]; however, the initial results were questioned [28], and a recent study demonstrated no significant difference in mortality at 28 and 90 days in patients with septic shock [29]. One reason for the absence of clinical trials to demonstrate a benefit has been the heterogeneity of the patients enrolled in these clinical trials [30]. The PIRO approach may have a benefit beyond epidemiologic research examining risk factors and outcomes in that it may permit a more homogeneous sample of patients enrolled into clinical trials.

Chapter two: The PIRO Framework

2.1 Predisposition

There is some evidence that the genetic constitution is a major contributor to the lifetime risk of severe infection [31]. Sorensen et al studied a cohort of adult adoptees and assessed general and cause specific mortality rates relative to the ages and causes of death of both biologic and adoptive parents. They reported that if a biological parent died of an infection between 50 and 70 years of life, adoptees had an almost five-fold increase in the risk of death due to infection; moreover, the associated risk of death related to severe infection in first-degree relatives was much higher than the associated risk of death from cancer or cardiovascular diseases in their biological parents [32].

Over the past 15 years several candidates genes associated with the risk of infection had been identified. Specific defects in innate immune response such as complement deficiencies [33], neutrophil defects, pattern recognition molecules [34, 35], and polymorphisms [36] have been recognized associated with increased mortality. Nevertheless, confirmatory clinical studies in humans are needed because of the fact that multiple genetic-environmental relationships potentially alter the degree to which these elements increase the risk of infection and the systemic host response.

Host genetic factors are known to be important in susceptibility to infectious diseases and can also influence the progression and severity of infection. Numerous polymorphisms related to immune deficiencies have been demonstrated [37-47]. To date, there are reports on the alleles responsible for TNFα, IL-1/IL-1ra, and IL-10 production. Two polymorphisms in the TNF locus, TNFα-308 and TNFβ-252, correlate with immune dysfunction. In trauma patients homozygous for either the TNFβ-252 TNFB1 or the TNFB2 allele were shown to have greater susceptibility

to severe episodes of sepsis [48]. Moreover, the haplotype TNF1:TNFB2 has a negative correlation with sepsis, which would confer genetic resistance to septic shock [48].

Furthermore, there are clear discrepancies in the incidence and severity of several medical conditions on the basis of race and sex. It has been shown that African Americans have higher prevalence of essential hypertension, ovarian cancer and worse outcome of breast cancer. Padkin et al showed a predominance of men (58.8%) in their cohort of patients with severe sepsis [49]. In the study of Martin et al, after adjustment for gender in the population of the US, men were more likely to have sepsis than women in every year of their 22 year study with a mean annual relative risk 1.28 (95% CI, 1.24 to 1.32) [1]. Both African Americans and other nonwhite subjects had a similarly elevated risk of sepsis compared with whites (mean annual RR of 1.89, 95% CI, 1.8 to 1.98, and 1.90, 95% CI 1.8 to 2.0, respectively) [1]. The risk of developing sepsis was particularly elevated in African Americans men with a mortality of 23%. Race and gender disparities in sepsis related to the source of infection have been examined [50].

Comorbidity can play an important role in different types of research. In prognosis studies comorbidity can act as a confounder, or an effect modifier, which if the effect on observed associations are not recognized, can threaten both internal and external validity of the results [51].

The influence of comorbidities in different settings has been evaluated by using tools like the Charlson comorbidity index (CCI). The CCI is the most extensively studied comorbidity index; it was originally designed to classify prognostic comorbidity in longitudinal studies [52]. The 19 diseases included in the index have been selected and weighted on the basis of the strength of their association with mortality [53]. It has been used in a number of studies to

stratify patients in order to control for the confounding influence of comorbid conditions on overall survival.

2.2 Infection (injury)

Certain sources of infection and types of organisms are more likely to cause severe sepsis/septic shock. [54] Gram-positive bacteria, gram-negative bacteria, fungi and viruses activate different pathways in the innate immune response of the human antimicrobial defense system. These differences alter the basic molecular pathogenesis of sepsis [55-57]. The site of infection responsible for the induction of severe sepsis has been demonstrated to have an impact on outcome. As such, septic patients from pulmonary, abdominal and central nervous system sources carry a significant higher risk of death when compared with sepsis originated from genitourinary tract, skin or soft tissues [58, 59]. Similar pattern occurs in bacteremic patients whom generally do worse than septic patients without a bacteremia; however, this association has not been found with all organism or in all studies [59]. Moreover, individuals with primary bacteremia (i.e. intravascular device-associated) do better than those with secondary bacteremia (i.e. secondary to lung or abdominal abscess), probably related with higher burden of pathogen and the ease to remove the source of infection [60]. In 2004 Cohen et al published an extensive review of the microbiology of severe sepsis/septic shock patients; they reported significant differences in mortality related with type of organism and site of infection. Mortality with *Staphylococcus aureus, Streptococcus pyogenes and Pseudomonas aeruginosa* was higher compared with less virulent organisms (i.e. coagulase-negative staphylococci) [61]. On the other hand, there is a narrow link between the nature of the infecting agent and the host response to infection, this relationship is illustrated by the differences in prognosis among patients whom develop fungal infection; *Candida* sepsis in subjects otherwise healthy, with catheter-related

infection have better outcome than those with *Candida* infection related to intra-abdominal abscess and leukemia. [62, 63].

2.3 Response

As stated above, the severity of sepsis has been graded according to the ACCP/SCCM classification in three groups of increasing severity: sepsis, severe sepsis and septic shock, which are viewed as a continuum of risk [19, 23]. One of the main purposes of identifying SIRS and sepsis among different stages of the systemic response to infection is to help identify patients at risk of progression to a more severe stage, for early therapeutic intervention, and possible enrollment into clinical trials of new therapies.

The complexities of the host response and the variations between patients in response to infection increase our understanding of the pathophysiology of sepsis. It is recognized that multiple clinical and laboratory variables have the capacity to affect the host response to microbial challenge. Many of these variables are straightforward like age, gender, genetic background and underlying diseases could affect the host innate and acquired immune response to infection. Nevertheless, multiple interactions with positive and negative feedback increase the complexity of the response. This relationship varies from patient to patient; it is clearly influenced by predisposing factors like nutritional status, genetic background, diseases that decrease the innate and/or acquired immune responses, etc. Differential responses occur depending on the individual immune status and that should be taken into account when classifying patients with severe sepsis. It is recognized that some patients have a marked systemic response induced by specific microorganisms (i.e. meningococcemia) [64]; while others have a markedly impaired systemic response (i.e. neutropenic patients) [56].

Despite significant advances in detection and identification of biological markers of infection, its systematic generalization and availability to every hospital is not yet feasible. As a result, the SIRS criteria continue to be the most sensitive tool to detect septic patients; as such those criteria should not be disregarded in the initial stratification of individuals with confirmed or suspected infection. On the other hand, since its development in 1981, the acute physiology and chronic health evaluation (APACHE) has become the most commonly used survival prediction model in ICUs worldwide [65]. The APACHE II score, a revised and simplified version of the original project, uses a point score based on initial values of 12 routine physiologic measures, age and previous health status to provide a general measure of severity of disease. The values recorded are the worst taken during the first 24 hours in the ICU. In order to get an estimate of the probability of death, the score was incorporated into an algorithm involving the admission diagnosis and the physiologic score. The maximum possible APACHE II score is 71 and high scores correlated well with mortality [65]. Although the versions III and IV have been developed over the last 20 years, the need to pay a fee for using the predictive equations and only small differences in the ability of prediction, have limited their use.

2.4 Organ dysfunction

Organ failure is the final pathway in response to severe sepsis [20, 66]; Multi-organ dysfunction syndrome is the leading cause of morbidity and mortality for patients admitted to an ICU [67]. Epidemiological data from the US showed that the syndrome develops during 15% of all ICU admissions [68], is responsible for up to 80% of all ICU deaths [69], and results in ICU cost of more than $100,000 per patient [70] or approximate $500,000 per survivor [71]. The hallmark of the multi-organ dysfunction syndrome is the development of progressive physiologic

dysfunction in two or more organ systems after an acute threat. Despite of this evidence, it is not clear why some patients develop certain type of organ dysfunction and others not the same insult. Since 1994 the Sequential Organ Failure Assessment (SOFA) score has been used to evaluate the number and severity of organ dysfunction or failure on a daily basis [20]. The score evaluates six organ systems: respiratory, coagulation, liver, cardiovascular, central nervous and renal. A score of 0-4 is assigned for each organ according to function (0 being normal function through to 4 for most severe dysfunction); individual organ scores are added for a total score which has a maximum score of 24. The worst score for each organ system in each 24-hour period is taken for calculation. A high total SOFA score (SOFA max- the addition of the highest scores within each organ system irrespective of day) and a high delta SOFA (the day with the highest SOFA minus the admission total SOFA) have been related with a worse outcome [20, 72]. Another tool commonly used is the multiple organ dysfunctions (MODS) scoring system. It was developed by a literature review of clinical studies of multiple organ failure from 1969 to 1993. Six organ systems were chosen, a score from 0 to 4 was assigned for each organ according to function (0 for normal function and 4 for the more severe dysfunction). The worst score for each organ system in each 24 hours period is taken for calculation. A high initial MODS correlated with ICU mortality and the delta MODS (calculated as the MODS over the whole ICU stay less the admission MODS) had a stronger correlation with mortality [21]. The main difference between MODS and SOFA is the method for the evaluation of cardiovascular dysfunction. The MODS uses a composed variable (heart rate multiplied by the ratio of central venous pressure and mean arterial pressure); SOFA uses the blood pressure and the level of vasopressor support.

Chapter three: Methods

3.1 Patient Selection

The present study was conducted in four general medical/surgical ICU's of three hospitals within the Calgary Health Region. All patients older than 18 years old, admitted to the ICU's from the operating room with diagnosis of sepsis from intra-abdominal source proven/suspected between the years 2005 and 2010 were included into the initial screening.

Primary outcome was ICU mortality, defined as the clinical status by ICU discharge Alive (0), dead (1).

Definition criteria from the 2001 consensus conference were used as follow: SIRS was defined as the presence of two or more criteria described above; Sepsis was defined as the presence of SIRS induced by infection; Severe sepsis was defined as the presence of at least two SIRS criteria in the setting of a proven/suspected infection and one or more organ dysfunction.

Septic Shock was defined as the presence of severe sepsis, where the organ dysfunction is cardiovascular, defined by persistent hypotension refractory to fluid resuscitation and the need of vasopressor support.

SIRS criteria were obtained during the first 24 hours since admission to the ICU through the TRACER database. The details of data collection using TRACER have been described elsewhere [73].

Patients with intra-abdominal sepsis were identified using the Intensive Care National Audit & Research Centre (ICNARC) diagnostic coding scheme. The ICNARC system codes patients based on their status as immediately post-operative or non-operative, based on organ

system (for example gastrointestinal), and based on underlying process (for example inflammation, perforation, haemorrhage, etcetera). The following strategy was used:

1. Two critical care specialists (JP, DN) independently reviewed all diagnostic codes within the gastrointestinal system to identify those that may be associated with intra-abdominal sepsis. After independent coding, the 2 physicians met and reviewed any discordant codes. If there was not immediate agreement on inclusion or exclusion, a third independent critical care specialist (DZ) reviewed and resolved.

2. Patients were identified based on the use of operative diagnostic code (Code 1).

3. Final diagnosis were grouped as follow:

    a. Abscesses (any site)

    b. Gallbladder abnormalities

    c. Pancreas abnormalities

    d. Small Bowell abnormalities

    e. Vascular problems

    f. Gastric abnormalities

    g. Miscellaneous

3.2 Operational definition of PIRO

PIRO components were defined as follow:

***3.2.1 Predisposition*:**

Age: Recorded in years, and categorized as <65 years (0) or >=65 years (1).

Sex: male (0) and female (1)

Race: due to the reports of correlation between race and different outcomes in sepsis, it is ideal to have the variable within the study; however, there is no way to obtain a reliable source of race, neither in administrative nor clinical databases (TRACER). As such, race was not included.

Comorbidities were recorded as present (1) if the TRACER record indicated that the Chronic Health Points in APACHE II charting was 2 or 5, or absent (0) if it was recorded as zero.

3.2.2 Infection:

The presence (1) or absence (0) of bacteremia was recorded.

The type of microorganism recovered from the first set of blood cultures was recorded and was classified as gram-positive cocci, gram-positive bacilli, gram-negative cocci, gram-negative bacilli and fungi.

Within the positive blood cultures, the presence (1) or absence (0) of multiresistant bacteria were identified.

3.2.3 Response:

SIRS criteria during the first 24 hours were recorded as present (1) or absent (0) for each one of the criteria if they meet the requirements according to the definition of SIRS:

Maximum (more than 12,000)-minimum (less than 4,000) white blood cell count,

Maximum (more than 90 beats per minute) heart rate,

Maximum (more than 20 breaths per minute) respiratory rate and/or

Worst partial pressure of carbon dioxide within arterial blood (PaCO2) (less than 32 mmHg),

Maximum (more than 38º C)-minimum (less than 36º C) temperature,

Maximum APACHE II score during the first 24 hours,

3.2.4 Organ dysfunction It was determined by using the SOFA criteria present during the first 24 hours in accordance with published standards [20]:

Respiratory organ system score:

PaO2/FiO2 >400 (0 points),

PaO2/FiO2 <400 (1 point),

PaO2/FiO2 <300 (2 points),

PaO2/FiO2 <200 (3 points),

PaO2/FiO2 <100 (4 points).

Renal organ system score:

creatinine 92-145 (1 point),

creatinine 146-259 (2 points),

creatinine 260-374 or urine output < 500 ml/day (3 points),

creatinine >382 or urine output <200 ml/day (4 points)

Coagulation organ system score:

platelets <150 (1 point),

platelets <100 (2 points),

platelets <50) (3 points),

platelets <20 (4 points)

Cardiovascular organ system score: arterial hypotension defined as systolic blood pressure <90 mmHg, mean arterial blood pressure <70 mmHg or a systolic blood pressure decrease > 40mmHg in adults or < 2 SD below normal for age.

MAP <70 (1 point),

dopamine ≤5 or dobutamine any dose (2 points),

dopamine > 5 or epinephrine ≤0.1 or norepinephrine ≤0.1 (3 points),

dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 (4 points).

Neurologic organ system score:

GCS 13-14 (1 point),

GCS 10-12 (2 points),

GCS 6-9 (3 points),

GCS <6 (4 points).

Liver organ system score:

Bilirubin 20-32.5 mmol/L (1 point),

bilirubin 32.6-100.9 mmol/L (2 points),

bilirubin 101-203 mmol/L (3 points),

bilirubin >203 mmol/L (4 points)

The final total SOFA score for the first 24 hours was recorded as a continuous variable and then categorized as binomial variable as < 10 (0) and >=10 (1).

For each individual system analysis, acute organ dysfunction was defined as SOFA score of >=2 for the organ in question [74, 75].

3.3 Analysis Plan:

Statistical analysis was performed using STATA/IC 10.1 for Mac (StataCorp LP, Aug 11, 2008).

Continuous variables were reported using summary statistics and graphical plots. Summary statistics for variables with a normal distribution were reported as means +/- standard deviations.

Univariate analysis was performed to identify significant risk factors associated with ICU mortality. Proportions were analyzed using Chi-Square and continuous variables were analyzed with T-Test. These were two-sided tests, and statistical significance was accepted at $p < 0.05$.

Statistically significant variables in the univariate analysis were introduced in a stepwise backward elimination logistic regression with ICU mortality as the dependent variable to get the most parsimonious model. The effect on ICU mortality of intra-abdominal sepsis was considered statistically significant if the regression coefficient associated with mortality had a $p < 0.05$.

Chapter four: Results

4.1 General

From January 1, 2005 to December 31, 2010, a total of 1,052 critically ill patients were admitted from the operating room with the diagnosis of abdominal sepsis into the four general medical/surgical ICU's within three hospitals in Calgary. Among the 1,052 patients, 905 (86.03%) met at least 2 of the SIRS criteria and were included in the study. The baseline characteristics of the study population are summarized in Table 4.1. The overall ICU mortality rate in our cohort was 21.3%, the ICU mortality among those patients with sepsis (n=317) was 8.2%, among those with severe sepsis (n=248) 11.7% and those with septic shock (n=340) 40.6%. The median ICU length of stay was 3 days (interquartile range 2-8). Fifty five percent of patients were male.

Table 4.1 Baseline characteristics of the study population

Variable	All patients	ICU survivors	ICU nonsurvivors
No of patients	905	712	193
Age, years	64 ± 17	63 ± 18	70 ± 14
Sex, % female	45	46	44
Diagnostic category, %			
Abscess	5.4	6.2	2.6
Gallbladder	7.0	7.9	3.6
Pancreas	2.4	2.4	2.6
Small bowel	26.2	26.7	24.4
Large bowel	48.0	46.4	53.9
Vascular	3.0	2.0	6.7
Stomach	3.9	4.2	2.6
Miscellaneous	4.2	4.4	3.6
APACHE II score	20 ± 8	18 ± 6	28 ± 9
SOFA score	8 ± 4	7 ± 4	11 ± 4
ICU length of stay, days			
Median	3	3	3
IQR	2-8	2-8	1-11
Sepsis, %	8		
Severe sepsis, %	12		
Septic shock, %	45		

Diagnoses were classified based on anatomic site in eight categories: Abscesses (any location), gallbladder and biliary tract, pancreas and spleen, stomach, small bowel, large bowel, vascular and miscellaneous (Table 4.2). Vascular associated diagnoses (i.e. SMA thrombosis with bowel ischemia) were associated with the highest mortality (48.2%), whereas abscesses and gallbladder and biliary tract problems were associated with the lowest mortality (10.2% and 11.1% respectively).

Table 4.2 Mortality distribution by diagnostic categories.

Diagnostic category	N (%)	Mortality rate (%)
Abscesses	49 (5.4)	10.2
Gallbladder	63 (7.0)	11.1
Pancreas	22 (2.4)	22.7
Small Bowel	237 (26.2)	19.8
Large Bowel	434 (48.0)	24.0
Vascular	27 (3.0)	48.2
Stomach	35 (3.9)	14.3
Miscellaneous	38 (4.2)	18.4

Using the PIRO framework, the variables were grouped within the Predisposition (age, sex, comorbidities) Infection (bacteremia, type of infection, resistant microorganisms) Response (SIRS criteria, APACHE II) and Organ dysfunction (SOFA score) categories.

4.2 Predisposition

Among the 905 patients, the mean age was significantly higher on those patients who died than those patients who survived (69.9 years vs. 62.9 years respectively, $p < 0.0001$). 494 (54.6%) patients were men. There was no difference in mortality between men and women (21.9% vs. 20.7% respectively, $p = 0.332$).

The presence of severe comorbidities (i.e. end-stage renal disease, lung disease, liver disease, immunosuppression, cancer) was associated with higher mortality, related with those who did not have those comorbidities (29.6% vs. 17.3% respectively; OR 2.02 95%CI 1.35-2.83, $p < 0.001$).

4.3 Infection

Among the 905 patients, there were 75 (8.29%) with positive blood cultures. There was a significant difference in mortality between those patients who developed bacteremia than those who did not (34.7% vs. 20.1% respectively; OR 2.10, 95%CI 1.22-3.57 p=0.0016).

From the 75 bacteremic patients, 14 (18.6%) grew Gram-positive cocci, 5 (6%) Gram-positive bacilli, 42 (56%) Gram-negative bacilli and 14 (18.6%) grew fungi. There was no significant difference in mortality between the different microorganisms (Gram-positive cocci 35.7%, Gram-positive bacilli 40%, Gram-negative bacilli 35.7% and fungi 28.6%, $p = 0.959$).

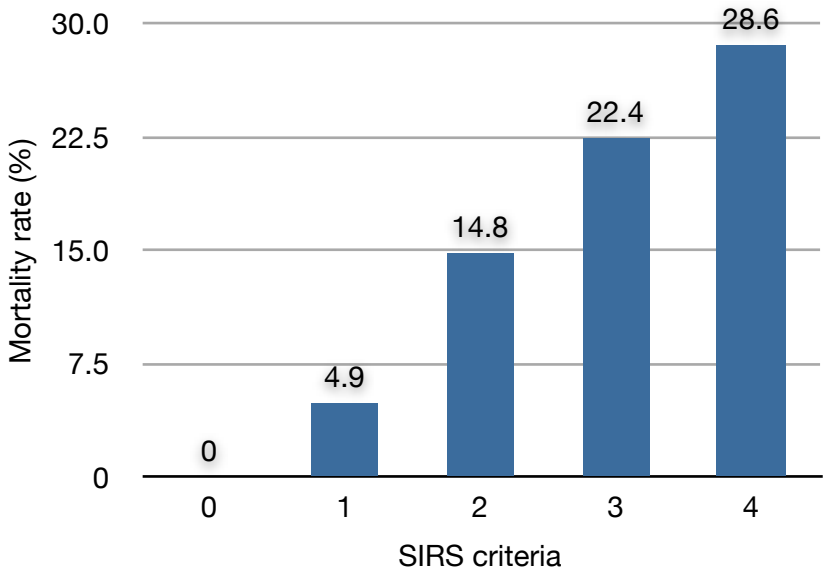
Among the 75 positive blood cultures, there were 8 (10.6%) multiresistant microorganisms. The presence of multiresistant microorganisms showed a tendency towards increasing mortality relative to sensitive microorganisms; however, this difference in mortality did not reach statistical significance (50% vs. 38.2% respectively, p 0.167).

4.4 Response

Figure 1 shows that ICU mortality rate increased from those with zero SIRS criteria to those with four SIRS criteria. There were 23 (2.1%) patients with zero criteria, 123 (11.7%) with one criterion, 317 (30.1%) with two criteria, 357 (33.9%) with three criteria and 231 (21.9%) with four criteria.

There was a significant difference in mortality between those categories ranging from zero with no SIRS criteria to 28.6% with four SIRS criteria (0%, 4.9%, 14.8%, 22.4% and 28.6% respectively, p= 0.0004).

Figure 4.1 Mortality rate by SIRS criteria



Among the 905 patients who met two or more SIRS criteria, 718 (79.3%) patients met the respiratory SIRS criteria (respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg), in which there was a trend towards a difference in mortality (22.6% vs. 16.6%, p = 0.07). 840 out of 905 (92.8%) patients met the heart rate SIRS criteria (heart rate > 90 beats per minute), again in which there was a trend towards a difference in mortality (22.0% vs. 12.3%, p= 0.065). 330 out of 905 (36.5%) patients met the temperature SIRS criteria (Temperature > 38° C or < 36°C) and its presence was associated with higher mortality (25.2% vs. 19.1, OR 1.42 95%CI 1.01-1.99, p = 0.016); moreover, the presence of hypothermia (temperature < 36° C) was strongly associated with higher mortality (36.2% vs. 18.6%, OR 1.86 95%CI 1.30-2.67, p = 0.0004), whereas, the presence of hyperthermia (Temperature > 38° C) did not show a significant difference in

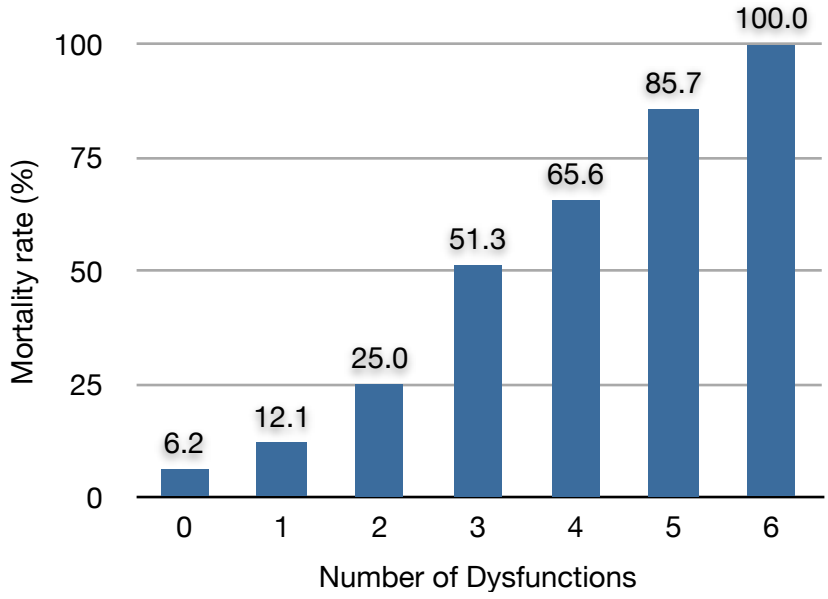
mortality (22.1% vs. 15.7%, p=0.131). 585 out of 905 (64.6%) patients met the WBC criteria (WBC either > 12,000 or < 4,000 or the presence of > 10% bands) and even though there was not a significant difference in mortality (22.4% vs. 19.4%, p = 0.144),141 out of 905 (15.6%) had leukopenia (WBC < 4,000) which was strongly associated with higher mortality (36.2% vs. 18.6%, OR 2.48 95%CI 1.64-3.72, p < 0.0001).

The APACHE II score was significantly higher among those patients who died than those who survived (27.8 vs. 17.8 respectively, p < 0.0001). By categorizing the APACHE II score in ≥ 25 (224/905 patients [24.8%]) and <25 (681/905 patients [75.2%]), there was a strong association with mortality (50.4% vs. 11.7%, OR 7.65 95%CI 5.30-11.03, p < 0.0001).

4.5 Organ dysfunction

The SOFA score was significantly higher in those patients who died than in those who survived (11.0 vs. 6.6, p < 0.0001). By categorizing the SOFA score in ≥ 10 and < 10, it showed a significant difference in mortality (46.4% vs. 10.9%, OR 7.05 95%CI 4.92-10.1, p < 0.0001). The subsets of the SOFA score were categorized as Organ failure (2 or more points) and No Organ Failure (less than 2 points) and were individually analyzed. Distribution and mortality according to the number of organ dysfunctions are shown in Figure 2.

Figure 4.2 Mortality rate by number of dysfunctions



430 out 905 patients (47.5%) had cardiovascular failure, and those patients showed a significant higher mortality (34.9% vs. 9.7%, OR 5.4 95%CI 3.6-7.9, $p < 0.0001$). 467 (51.6%) patients presented respiratory failure and its presence was associated with high mortality (29.8% vs. 12.3%, OR 3.0 95%CI 2.1-4.3, $p < 0.0001$). 22.5% of the patients (204/905) developed renal dysfunction, and there was a significant difference in mortality related to those patients who did not develop renal failure (36.2% vs. 17.0%, OR 2.8 95%CI 1.9-4.0, $p < 0.0001$). Central nervous system failure was present in 72 out of 905 patients (7.9%), its presence was associated with higher mortality (54.2% vs. 18.5%, OR 5.2 95%CI 3.1-8.8, $p < 0.0001$). Coagulation system failure was present in 70 patients (7.7%), and it was associated with a significant difference in mortality (47.1% vs. 19.2%, OR 3.8 95%CI 2.2-6.4, $p < 0.0001$). Finally, liver dysfunction was present in only 18 patients (1.9%) and was associated with higher mortality (50% vs. 20.8%, OR 3.8 95%CI 1.3-11.0, $p = 0.0027$).

4.6 Multivariate analysis

Those variables in each PIRO subset that reached a p-value of ≤ 0.1 were entered into a stepwise backward elimination logistic regression. Variables were sequentially removed from the full model. In the first round of backward stepwise iterations, the regression terms were each removed from the full starting model. The regression calculation was performed to find the improvement in the residual sum of squares for each of these resulting models relative to the starting model. When all of the models missing one term have been created, the backward stepwise procedure selected the term associated with the highest p-value as the first round candidate for removal from the model.

Initially, two models were developed, one including categorical SOFA score (0: < 10, 1: >=10) as the variable for organ dysfunction assessment, and a second model including the individual system dysfunction (cardiac, respiratory, renal, CNS, coagulation, liver) for organ failure assessment.

The variables included in the models were:

Model 1

P: Age (0: <65 years, 1: >=65 years), Comorbidities (0= No, 1= yes)

I: Bacteremia (0= No, 1= Yes)

R: APACHE II score (0: <25, 1: >=25), Leukopenia (0= NO, 1= Yes), Hypothermia (0=No, 1=Yes)

O: SOFA (0: <10, 1: >=10)

Model 2

P: Age (0: <65 years, 1: >=65 years), Comorbidities (0= No, 1= yes)

I: Bacteremia (0= No, 1= Yes)

R: APACHE II score (0: <25, 1: >=25), Leukopenia (0= NO, 1= Yes), Hypothermia (0=No, 1=Yes)

O: Cardio/SOFA (0= No organ dysfunction, 1=Organ dysfunction), Respiratory/SOFA (0= No organ dysfunction, 1=Organ dysfunction), Renal/SOFA (0= No organ dysfunction, 1=Organ dysfunction), CNS/SOFA (0= No organ dysfunction, 1=Organ dysfunction), Coagulation/SOFA (0= No organ dysfunction, 1=Organ dysfunction) and liver/SOFA (0= No organ dysfunction, 1=Organ dysfunction).

In Model 1, the term bacteremia was removed from the final model, and the other terms are shown in Table 4.3.

Table 4.3 Model 1, including SOFA.

Variable	OR	95% CI	p
Age > 65 years	2.2	1.5-3.3	<0.0001
Comorbidities	1.6	1.1-2.3	0.019
Leukopenia	1.7	1.1-2.7	0.028
Hypothermia	1.5	1.1-2.3	0.038
APACHE II > 25	3.2	2.1-4.9	<0.0001
SOFA > 10	3.7	2.5-5.6	<0.0001

In model 2, the terms bacteremia, liver/SOFA and coagulation/SOFA were removed from the final model, the other variables showed statistical significance and the results are shown in Table 4.4.

Table 4.4 Model 2, including dysfunctions separately.

Variable	OR	95% CI	p
Age > 65 years	2.3	1.5-3.3	<0.0001
Comorbidities	1.7	1.1-2.5	<0.0001
Leukopenia	1.7	1.1-2.6	0.031
Hypothermia	1.6	1.1-2.4	0.027
APACHE II > 25	2.7	1.8-4.2	<0.0001
Cardio SOFA	2.7	1.7-4.1	<0.0001
Respiratory SOFA	1.6	1.1-2.5	0.020
Renal SOFA	1.8	1.2-2.7	<0.0001
CNS SOFA	2.4	1.3-4.7	0.004

Despite the fact that both models showed similar performance in mortality prediction (aROC 0.8234 vs 0.8253, for model 1 and model 2 respectively), Model 2 was chosen to develop our first PIRO score because we considered that there are differences in how each organ dysfunction affects mortality. A clinical score based on PIRO for our population was calculated and one point was given for each one of the variables present (range 0-9 points) as shown in table 4.5:

Table 4.5 PIRO score # 1.

Score	Variable	Point
Predisposition	Age > 65 years	1
	Comorbidities	1
Response	Leukopenia	1
	Hypothermia	1
	APACHE II > 25	1
Organ failure	Cardiovascular failure	1
	Respiratory failure	1
	Renal failure	1
	CNS failure	1

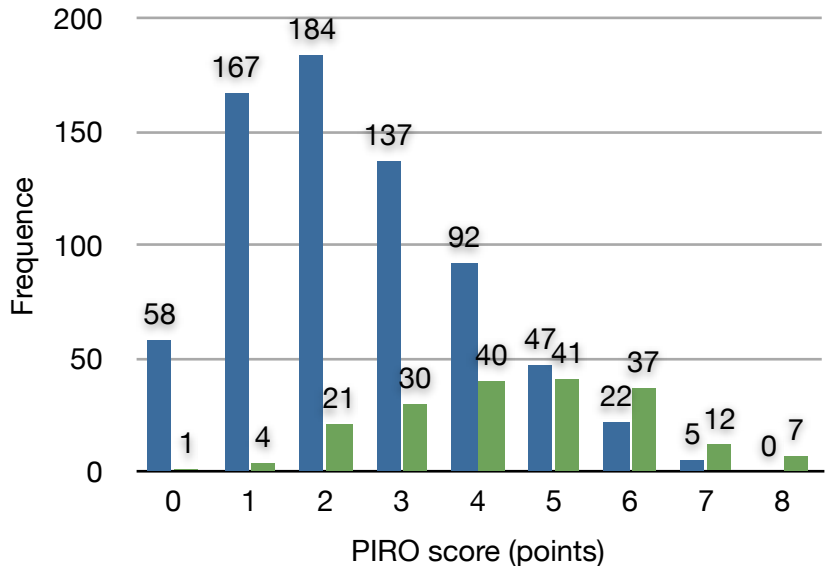
Distribution and association with mortality for each variable considered in the PIRO score are detailed in Table 4.6.

Table 4.6 Variable distribution and association with mortality.

Variable	Incidence n (%)	Mortality OR Univariate
Age > 65 years	519 (57.4)	2.5 (1.7-3.6)
Comorbidities	297 (32.8)	2.0 (1.4-2.8)
Leukopenia	141 (15.6)	2.5 (1.6-3.7)
Hypothermia	225 (24.9)	1.9 (1.3-2.7)
APACHE II > 25	224 (25.0)	7.6 (5.3-11.0)
Cardiovascular failure	430 (47.5)	5.4 (3.7-8.0)
Respiratory failure	467 (51.6)	3.0 (2.1-4.4)
Renal failure	204 (22.5)	2.8 (1.9-4.0)
CNS failure	72 (8.0)	5.2 (3.1-8.8)

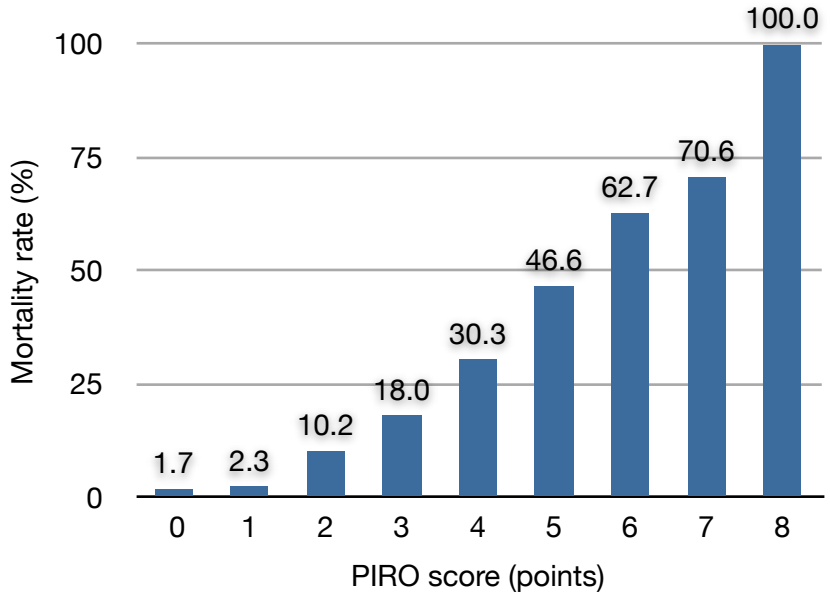
Distribution of 905 patients (survivors and nonsurvivors) according with PIRO score are shown in Figure 4.3.

Figure 4.3 Distribution of patients (survivors and nonsurvivors) according to PIRO score.



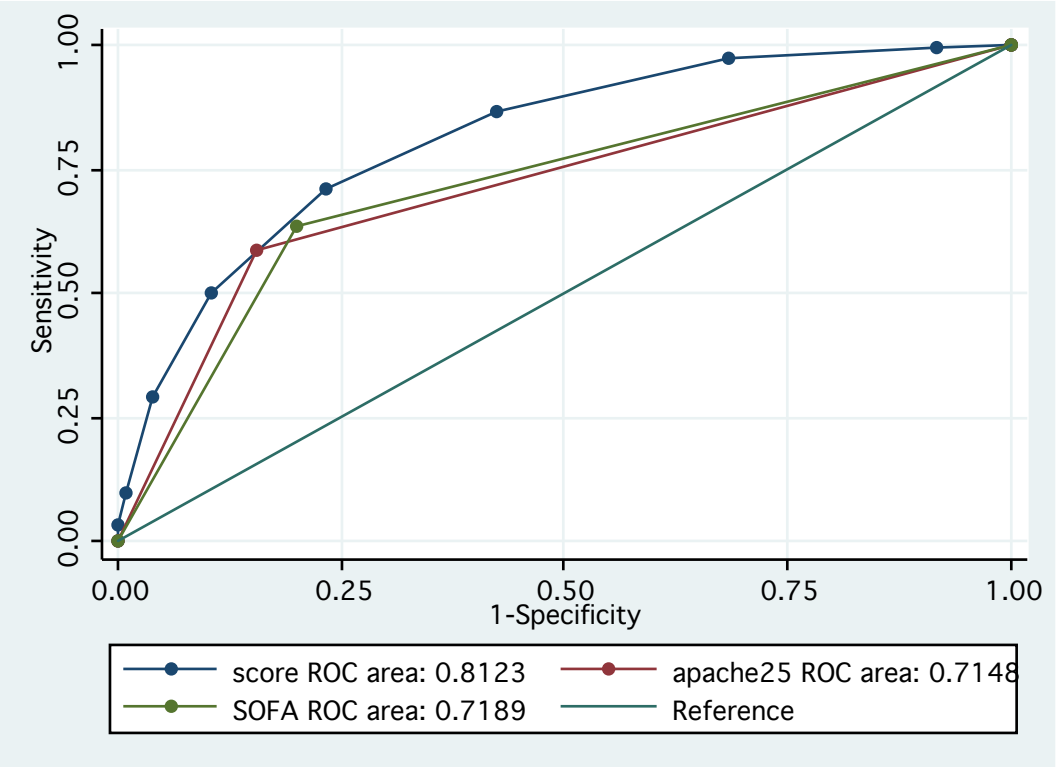
The mean PIRO score for all patients was 2.9 ± 1.8, being significantly higher in nonsurvivors than survivors (4.5 vs. 2.4 respectively, $p < 0.0001$). When the patients were distributed according PIRO scoring, the mortality rate increased significantly ($p < 0.0001$) (Figure 4.4).

Figure 4.4 Mortality rate distribution by PIRO score # 1.



Discrimination of PIRO score was assessed using ROC curves. The area under ROC curve (Figure 4.5) showed consistent mortality discrimination by PIRO score (0.81, 95%CI 0.78 to 0.84) with better performance ($p = 0.21$) than APACHE II score (0.72, 95%CI 0.68 to 0.75) and SOFA score (0.72, 95%CI 0.68 to 0.76).

Figure 4.5 Comparison of PIRO score # 1, APACHE II score and SOFA score to predict ICU mortality using aROC



After this analysis, we decided to develop a third model now excluding APACHE II as a risk factor, because most of the variables content within the APACHE II score are included by separate in the PIRO score and the possibility of interaction is present. In model three, the terms bacteremia and liver SOFA were excluded and the model was integrated as shown in Table 4.7.

Table 4.7 Model 3, excluding APACHE II score as variable.

Variable	OR	95% CI	p
Age > 65 years	2.4	1.6-3.6	<0.0001
Comorbidities	2.0	1.4-3.0	<0.0001
Leukopenia	1.7	1.1-2.7	0.026
Hypothermia	1.6	1.1-2.4	0.020
Cardio SOFA	3.3	2.2-4.9	<0.0001
Respiratory SOFA	2.0	1.3-2.9	0.001
Renal SOFA	2.1	1.4-3.1	<0.0001
CNS SOFA	3.7	2.1-6.6	<0.0001

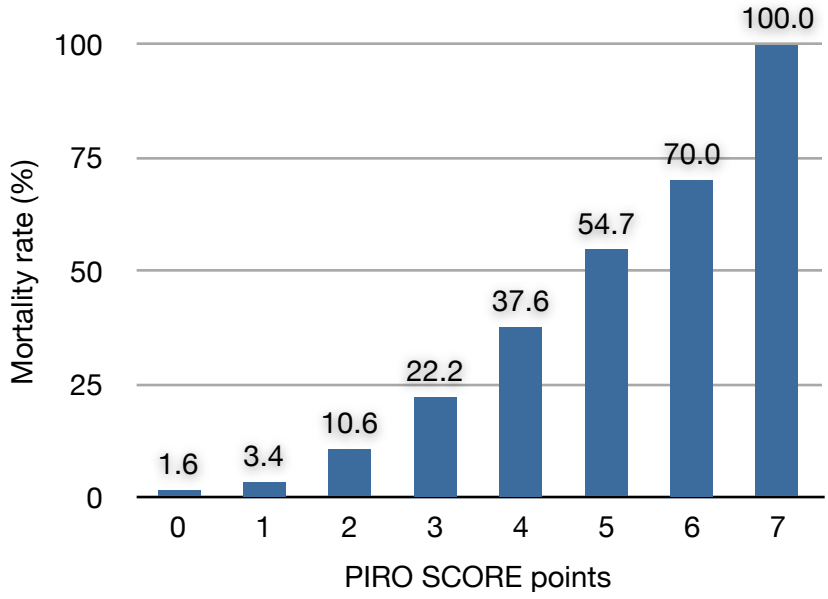
As noted, there was not a significant change in the OR from the different variables, and given that APACHE II score contains several of the variables included in the PIRO score and there is clear interaction, we decided to produce a new PIRO score with model 3 shown in Table 4.8.

Table 4.8. PIRO score # 2.

Score	Variable	Point
Predisposition	Age > 65 years	1
	Comorbidities	1
Response	Leukopenia	1
	Hypothermia	1
Organ failure	Cardiovascular failure	1
	Respiratory failure	1
	Renal failure	1
	CNS failure	1

The mean PIRO score # 2 for all patients was 2.6 ± 1.5, being significantly higher in nonsurvivors than survivors (3.9 vs. 2.3 respectively, $p < 0.0001$). When the patients were distributed according PIRO scoring, the mortality rate increased significantly ($p < 0.0001$) (Figure 4.6).

Figure 4.6 Mortality rate distribution by PIRO score # 2.



The area under ROC curve (Figure 4.7) showed consistent mortality discrimination by PIRO score # 2 (0.80, 95%CI 0.79 to 0.83), but slightly worse than PIRO score with APACHE II included (0.81, 95%CI 0.78 to 0.85); however, still better than APACHE II score (0.72, 95%CI 0.68 to 0.75) and SOFA score (0.72, 95%CI 0.68 to 0.76) p <0.0001, (Figure 4.8).

Figure 4.7 Comparison of PIRO score # 1 and PIRO score # 2 using aROC

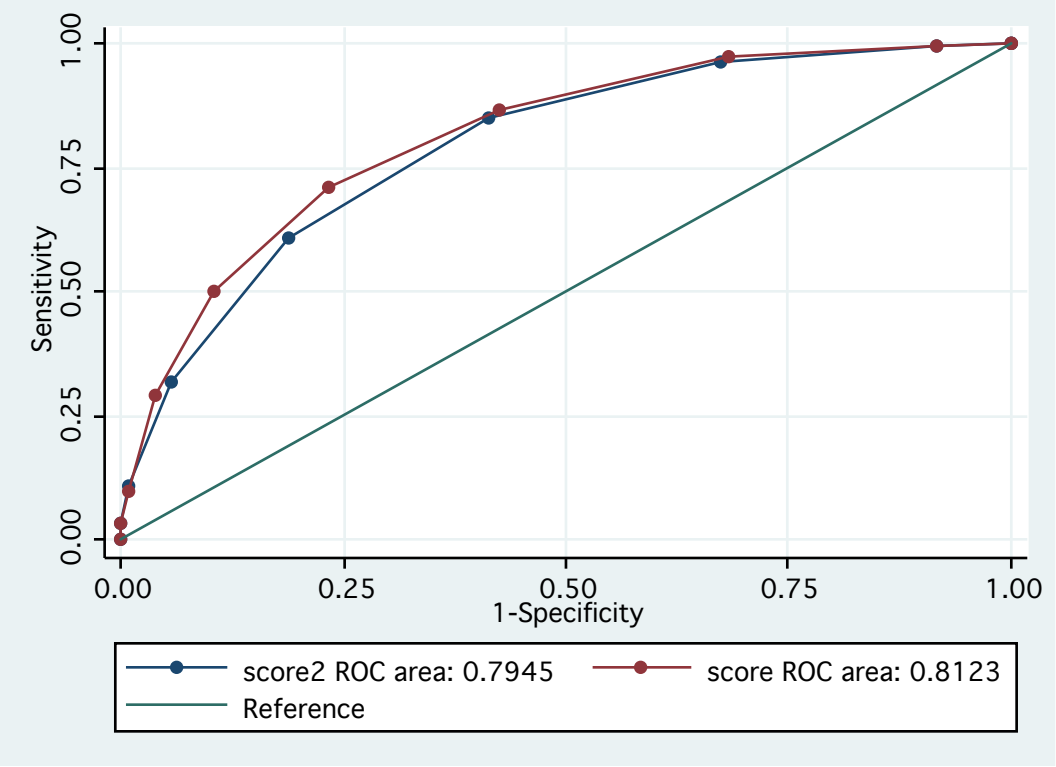
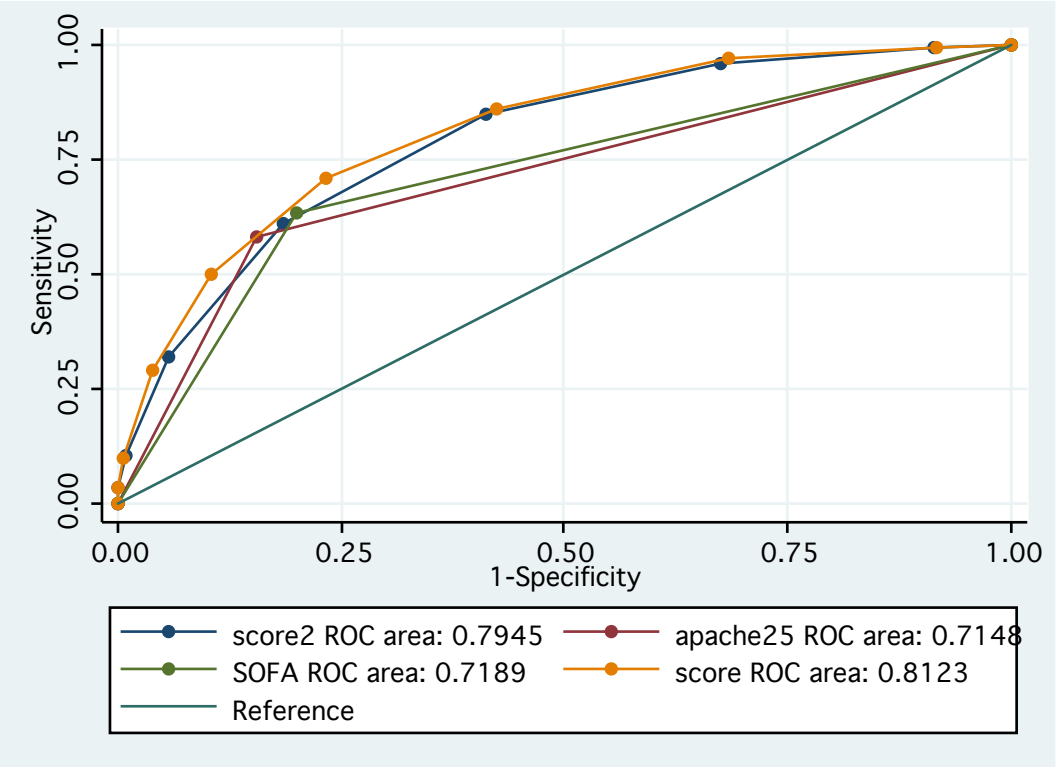


Figure 4.8 Comparison of PIRO Score # 1, PIRO score # 2, APACHE II and SOFA using aROC.



Chapter five: Discussion

The present study evaluated the ability of PIRO to predict ICU mortality in a specific population of surgical-related abdominal sepsis. Our results show that the use of PIRO as a model can accurately predict mortality in surgical-related abdominal sepsis and, furthermore, it outperformed two of the commonest mortality predictor scores: APACHE II and SOFA.

Numerous tools are available to assess prognosis in critically ill patients Acute Physiology and Chronic Health Evaluation (APACHE II, III and IV), Sequential Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Score (MODS), Simplified Acute Physiologic Score (SAPS), etc. However, these scoring systems have limitations in that they primarily focus only in the physiologic abnormalities and they leave out some of the important variables that may contribute to sepsis-related mortality.

Severity scores such as APACHE II and SOFA have been advocated as entry criteria for clinical trials and in clinical decision-making; however, the relationship between severity scores and outcome is not straightforward. Severity scores were not designed for use in individual patients or for therapeutic decision-making for specific interventions, these scores were developed to assess the risk of hospital death and calibrated to maximize predictive capacity across a spectrum of illnesses rather than to detect differential clinical response of a specific intervention for a particular disease [65]. Generic severity scores are not exclusively measures of the severity of physiological dysfunction but are risk predictors that combine measures of potentially modifiable severity (the acute physiologic score) and non-modifiable patients risk factors of age and comorbidities; furthermore the final value can be heavily influenced by the chronic part of the score, but does not necessarily reflect the potential to benefit from the therapeutic intervention. Although chronic health points clearly contribute to the global

assessment of intensive care unit mortality risk, it is less clear whether such patients are optimal candidates for therapeutic interventions with experimental agents. Furthermore, the use of APACHE II score when the patient is already in the ICU has never been properly validated, although some studies have suggested using the changes in (delta) APACHE II [76, 77]. Another problem associated with severity scores is their influence by the lead-time bias. APACHE II score was developed and calibrated for use within the first 24 hours of intensive care unit admission, and the acute physiologic component changes significantly over time; moreover, application of severity scoring systems to individual patients results in frequent misclassification [78], and changing patients mixes can affect the performance of severity scores [79].

The overall ICU mortality rate in our study's cohort was 21.3%, which was lower than those reported in a general septic population by Lisboa et al (37%), as well as in the Rello et al report of CAP septic patients (28%). Kumar et al [80], reported a 33.7 mortality rate in their intra-abdominal sepsis population. In our population of abdominal sepsis, the APACHE II score was outperformed by PIRO in its ability to predict ICU mortality.

We believe this is the first attempt to describe and apply a PIRO score for intra-abdominal sepsis. The PIRO concept is a classification scheme for sepsis that includes predisposing conditions, the nature and extent of insult, the nature and magnitude of the host response and the degree of concomitant organ dysfunction. Our PIRO score was built on this concept, and includes variables significantly associated with mortality in multivariate analysis in our database. Our PIRO score identified eight independent variables associated with mortality, allowing assessment of intra-abdominal sepsis episode severity. The selection of these parameters was based on prior evidence supporting their association with poor prognosis and their good fit with the PIRO definitions.

A potential strength of this score is its validity in different subsets of intra-abdominal sepsis patients. Despite the fact that our cohort included a specific set of surgical-related patients, the source of sepsis was very heterogeneous (from gallbladder diseases to vascular problems) with different risk factors and described mortality attributable.

Another strength of our PIRO score is its simplicity; based on eight variables associated with ICU mortality and easily obtained at the bedside. It allows classifying patients into different risk categories with reasonable mortality discrimination. To maintain simplicity, we decided to give one point to every significant variable regardless of its coefficient. Initially we included APACHE II score as part of the host response in the model; nevertheless, APACHE II score includes several variables already in the PIRO score, as such, we decided to eliminate APACHE II score from the model. In spite of the elimination of APACHE II score from the model, the mortality discrimination from Model 1 (including APACHE II) and Model 2 (without APACHE II), was not statistically different (aROC 0.81 vs 0.80 respectively), and Model 2 still outperformed APACHE II score and SOFA score alone (aROC 0.80, 0.72 and 0.72 respectively).

Within the predisposition category, age >65 years and the presence of comorbidities were significantly associated with ICU mortality in our model. The same finding has been described in the reports from Moreno et al (age, comorbidities, as well as location from which the patient was admitted to the ICU, length of stay before ICU admission and reason from ICU admission) [81]; Lisboa et al (comorbidities) [82], Rello et al (age >70 years and comorbidities) [83], Rubulotta et al (age categories from <46 years to 64-85 years and congestive cardiomyopathy) [84], and Howell et al (age 65 to 80 years, age >80 years, chronic obstructive pulmonary disease, any liver disease, any malignancy, malignancy with metastasis and nursing home resident) [85].

Our results are in agreement with studies that have identified greater risk of mortality in septic patients with higher number of comorbidities using a large US National Hospital Discharge Survey database from 1979 through 2003 [86]. Comorbidities as a predictor of mortality and hospital LOS had been reported in patients with cancer [87], patients with cirrhosis [88], critically ill patients in ICU [89], and general hospital population [90]. This association showed a possible synergy between the effects of sepsis and comorbidities, which suggest that treatment of comorbidities should be considered an integral part of clinical care for patients with sepsis. Successful treatment of comorbidities would reduce the mortality attributable to comorbidity itself and perhaps also the mortality attributable to the synergy between sepsis and comorbidity.

Many studies have confirmed that age is a predictor of outcomes in patients with sepsis [91] and critically ill patients [92]. Also, susceptibility to sepsis has been documented as a result of aging in animal models [93, 94]. Our study results are in line with the conclusion that older patients showed a dramatically increased risk of mortality. The reason for higher mortality may be multifactorial. Impaired immune responses in the older individuals, such as failed antigen processing by leukocytes and altered inflammatory cytokine expression [94], are possible explanations. The type of infection and its propensity for causing sepsis may also be related with age, as studies have found that pneumonia is more common in older patients and more frequently is associated with severe septic episodes [95].

In the Infection/injury category, we found that the presence of bacteremia was associated with increased mortality in the univariate analysis; however, in the multivariate analysis, this association did not reach statistical significance in either Model 1 (with APACHE II score), or Model 2 (without APACHE II score). This finding was different from the reports by Lisboa [82]

and Rello [83] where bacteremia was independently associated with mortality and it was part of the final VAP and CAP PIRO score respectively. Interestingly, in our cohort, the presence of multiresistant microorganism was not associated with ICU mortality in the univariate analysis in contrast with several reports where both, bacteremia and multiresistant bacteria were independent risk factors for hospital mortality. A study of risk factors and mortality in patients with nosocomial *Staphylococcus aureus*, the presence of bacteremia was independently associated with hospital mortality and the mortality associated with the presence of MRSA was revealed to be 1.78 times higher than MSSA [96]. It is possible that due to the small numbers of patients in our cohort with either bacteremia or multiresistant organisms, an association may be present (type II error). However, this would take a much larger study to examine and therefore, may not be as important a variable as others that are included in our model.

The nature and magnitude of the host response to injury in our study showed that leukopenia and hypothermia were independent risk factors of ICU mortality. Leukopenia is a well-known risk factor for severe infections in immunocompromised patients (e.g. leukemia, lymphoma, chemotherapy); however, evidence for its association with worse outcome in immunocompetent patients is scarce. Leukopenia has been associated with high morbidity and mortality in patients with pneumococcal bacteremia, particularly in patients with concomitant alcohol abuse [97].

Fever is known to be an important feature of sepsis and was thought to be an adaptive response to aid in defense of the invading organisms. However, the exact role of temperature in influencing the outcome of sepsis is still unclear. Some experimental studies suggest that induced hypothermia may have a beneficial effect by reducing energy requirement and activating cell-protecting pathways [98]. The clinical studies; however, suggest inability to mount a febrile

response to be associated with increased mortality in patients with sepsis [99, 100]. Clemmer et al [101] evaluated the consequences of clinical hypothermia associated with severe sepsis and septic shock. In their study, patients with hypothermia had a higher frequency of central nervous system dysfunction (88% vs. 60%), increased serum bilirubin concentration (35% vs. 15%), prolonged prothrombin time (50% vs. 23%), shock (94% vs. 61%), failure to recover from shock (66% vs. 26%) and death (62% vs. 26%). Ravindranath et al showed hypothermia to be an independent predictor of mortality in elderly patients with sepsis [102]. Experimental data suggests that preventing or early correction of hypothermia by rewarming in sepsis was associated with improved outcomes. Xiao and Remick [103] demonstrated from their studies on mice that warming could augment innate immunity and improve survival. Whether correcting hypothermia (by active rewarming) in septic patients will improve mortality remains to be evaluated.

PIRO was created as a hypothesis-generating model during the 2001 joint SCCM/ ESICM/ACCP/ATS/SIS conference. Since then, several authors have developed their own model in different disease-specific populations. In 2008 Moreno et al [81], reported a multicenter multinational cohort study using the SAPS 3 database. A total of 2,628 patients with signs of infection and with at least 48 hours of ICU stay were evaluated with the objective to empirically test whether a modified definition of PIRO (PIR) could be useful for predicting mortality in patients with sepsis. The authors reported a very good discrimination of their final model with an aROC of 0.772, which actually was better than that of the SAPS 3 admission model in that specific cohort (aROC: 0.735).

Lisboa et al published their Ventilator-Associated Pneumonia (VAP) PIRO score in 2008 [82]. The authors included 441 patients who met pre-established VAP criteria. They reported an

overall ICU mortality rate of 37.0%, ICU medical mortality 38.1% and ICU surgical mortality 58.0%. Four variables were independently associated with ICU mortality in the multivariate analysis, one in each of the PIRO subsets. VAP PIRO score was then calculated based on the presence of those variables. The mean VAP PIRO score was higher among the non-survivors than in the survivors (2.2 ± 1.0 vs. 1.0 ± 0.9; median 2.0 vs. 1.0, $p < 0.001$). On the basis of the observed ICU mortality according to VAP PIRO score, the patients were stratified into three levels of risk: mild, high, and very high. The aROC showed consistent mortality discrimination by the VAP PIRO score (0.81; 95% CI, 0.77 to 0.85) better than APACHE II score (0.53; 95% CI, 0.47 to 0.58).

Rello et al [83] published their PIRO score for community-acquired pneumonia (CAP) based on a historical cohort including all patients with CAP that required ICU admission recorded in a database. 529 consecutive patients with CAP admitted in the ICU in 33 hospitals in Spain were enrolled. Primary end-point was 28-day survival. They reported an overall mortality rate of 28%. The authors developed a composite PIRO score for CAP including age > 70 years, comorbidities (chronic obstructive pulmonary disease or immunocompromise), bacteremia, multilobar opacities in chest radiograph, shock, severe hypoxemia, acute renal failure and acute respiratory distress syndrome, with a 0 to 8 points range. Considering the observed mortality for each PIRO score, the patients were stratified in four levels of risk: a) Low 0-2 points (hazard ratio 3.1; 95%CI 1.1-2.9; $p<0.05$); b) Mild, 3 points; c) High, 4 points (hazard ratio 3.1; 95%CI 2.0-4.7; $p<0.001$); and d) Very high, 5-8 points (hazard ratio 6.3; 95%CI 4.2-9.4; $p<0.001$). The area under ROC curve showed consistent mortality discrimination for PIRO CAP (0.88, 95% CI 0.83-0.9) and better performance than APACHE II score (0.75, 95%CI 0.70-0.80).

Rubulotta, et al [84] published in 2009 a model based on PIRO; it was developed and validated by using two large sepsis databases: PROWESS (840 patients) and PROGRESS (10,610 patients). Through a complex process using regression trees, the authors developed a composite PIRO score with a 0 to 4 stratification levels within each PIRO domain. Each of the four PIRO components had similar OR in multivariate logistic regression. In PROWESS, the correlation of the PIRO score and in-hospital mortality rate was 0.974 ($p < 0.0001$), and in PROGRESS the correlation of the PIRO score and hospital mortality rate was 0.998 ($p < 0.0001$).

In 2011, Howell et al [85], developed a PIRO score based on a population of 2,132 adult patients admitted to the emergency department with the diagnosis of sepsis. The overall mortality was 3.9%, significantly lower than the other studies, showing the differences between a broader population of patients who presented to the emergency department and those admitted into the ICU. This difference in mortality was preserved among the patients with infection without SIRS (0.4%), sepsis (2%), severe sepsis (4.5%) and septic shock (29%). This model was validated in two independent cohorts including an internal validation of 4,618 patients from the center where the model was derived, and 1,004 patients in the external validation cohort from another hospital within the country (USA). The PIRO score accurately predicted mortality in both validations sets with respective areas under the receiver operating characteristics curve of 0.86 and 0.83, with a clear stepwise increase in mortality with increasing PIRO score.

In 2012, Furtado et al [104], reported a study aimed to validate the VAP PIRO score developed by Lisboa et al [82], against the Acute Physiology and Chronic Health Evaluation (APACHE II) and VAP APACHE II in an independent group of patients. The authors included one hundred and forty-eight patients who match the radiographic and clinic criteria for VAP

established in the derivation study. The aROC for predicting ICU mortality with the VAP PIRO, APACHE II and VAP APACHE II were 0.605 (p=0.03), 0.631 (p=0.01) and 0.724 (p=0.0001) respectively. Variables independently associated with mortality were bacteremia and APACHE II; however, VAP PIRO score was not a good predictor of ICU mortality, opposite to the results from the original derivation study by Lisboa.

There are important limitations in this study. First, we used a very specific septic population, which reduces significantly the external validity of our data and as such its generalization. Second, we did have a small amount of patients with bacteremia (a proven risk factor for predicting mortality) and it did not reach statistical significance in the multivariate analysis. A larger database of bacteremic patients would improve the power and confirm the trend towards being an independent predictor of mortality in intra-abdominal sepsis. Third, although all selected variables were significantly associated with ICU mortality they were selected arbitrarily. Moreover, the same weight (presence/absence) was adjudicated for each variable, although odds ratios were different, to enhance simplicity. Nevertheless, PIRO score performed very well and predicted ICU mortality better than other available tools such as APACHE II score and SOFA. Further studies should validate PIRO score in populations with different degrees of severity (e.g. emergency department) and for hospital mortality. For this same reason, whether our findings may be extrapolated to patients out of the ICU (e.g. surgical ward) is unknown.

We believe our study has implications for future research in sepsis. First, our PIRO model could be use to stratify patients for inclusion into a severe sepsis trial. Second, as this model is reviewed and refined over time, it could be used as the TNM system to determine prognosis and ideally individual treatment recommendations for an individual patient suffering

from severe sepsis. We believe that future research could include validating our model in a cohort of patients that have been enrolled in a clinical trial in intra-abdominal sepsis, and in particular comparing the performance of our PIRO model to a more 'generic' model such as published by Rubulotta et al [84].

Conclusion

Sepsis constitutes an important cause of morbidity and mortality in the ICU. The overall hospital mortality rate is approximately 28%. Despite advances in diagnosis and treatment of severe sepsis/septic shock, the incidence and mortality rate of sepsis in the surgical patient is still high. The use of severity score systems like APACHE II score or SOFA score to predict individual mortality is increasingly inaccurate and there is a need for new prognostic tools. PIRO was developed as a hypothesis-generating concept. To date, there have been several attempts to develop clinical prediction tools in different septic populations. We believe that this is the first attempt to develop and apply the PIRO framework in the surgical-related intra-abdominal sepsis population. We developed a PIRO score, which performed well predicting ICU mortality in our study's cohort; furthermore, PIRO score outperformed APACHE II score and SOFA. We believe that this study sets a framework to conduct new clinical trials in intra-abdominal sepsis model to validate our score and even compare it on more generic septic populations.

Bibliography

1. Martin, G.S., et al., *The epidemiology of sepsis in the United States from 1979 through 2000.* N Engl J Med, 2003. **348**(16): p. 1546-54.
2. Fisher, C.J., Jr., et al., *Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group.* N Engl J Med, 1996. **334**(26): p. 1697-702.
3. Bone, R.C., C.J. Grodzin, and R.A. Balk, *Sepsis: a new hypothesis for pathogenesis of the disease process.* Chest, 1997. **112**(1): p. 235-43.
4. Angus, D.C., et al., *Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care.* Crit Care Med, 2001. **29**(7): p. 1303-10.
5. Wheeler, A.P. and G.R. Bernard, *Treating patients with severe sepsis.* N Engl J Med, 1999. **340**(3): p. 207-14.
6. Perl, T.M., et al., *Long-term survival and function after suspected gram-negative sepsis.* JAMA, 1995. **274**(4): p. 338-45.
7. Álvarez, C.F. and M.C. Farinas, *Analysis of risk factors for nosocomial sepsis in surgical patients.* 2000.
8. Davenport, D.L., et al., *Multivariable predictors of postoperative cardiac adverse events after general and vascular surgery: results from the patient safety in surgery study.* 2007. **204**(6): p. 1199-1210.
9. *ACC/AHA task force report. Special report: guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of*

Cardiology/American Heart Association Task Force on practice guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). 1996. p. 540-552.

10. Pearse, R., et al., *Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445].* 2005. **9**(6): p. R687-93.
11. Jhanji, S., et al., *Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust.* 2008. **63**(7): p. 695-700.
12. Machado, A.N., C.S. Mdo, and W.J. Filho, *... factors for mortality among patients above the 6th decade undergoing non-cardiac surgery: cares-clinical assessment and research in elderly surgical patients.* 2008.
13. Pinho, C., et al., *Multicenter study of perioperative evaluation for noncardiac surgeries in Brazil (EMAPO).* 2007.
14. Elias, A., et al., *Incidence and risk factors for sepsis in surgical patients: a cohort study.* 2011.
15. *American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.* Crit Care Med, 1992. **20**(6): p. 864-74.
16. Marshall, J.C., *SIRS and MODS: what is their relevance to the science and practice of intensive care?* Shock, 2000. **14**(6): p. 586-9.
17. Vincent, J.L., *Dear SIRS, I'm sorry to say that I don't like you.* Crit Care Med, 1997. **25**(2): p. 372-4.
18. Poeze, M., et al., *An international sepsis survey: a study of doctors' knowledge and perception about sepsis.* Crit Care, 2004. **8**(6): p. R409-13.

19. Levy, M.M., et al., *2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.* Crit Care Med, 2003. **31**(4): p. 1250-6.

20. Vincent, J.L., et al., *The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.* Intensive Care Med, 1996. **22**(7): p. 707-10.

21. Marshall, J.C., et al., *Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.* Crit Care Med, 1995. **23**(10): p. 1638-52.

22. Le Gall, J.R., et al., *The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group.* JAMA, 1996. **276**(10): p. 802-10.

23. Rangel Frausto, M.S., et al., *The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study.* JAMA, 1995. **273**(2): p. 117-123.

24. Alberti, C., et al., *Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients.* Am J Respir Crit Care Med, 2003. **168**(1): p. 77-84.

25. Baue, A.E., *Sepsis, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and multiple organ failure: are trauma surgeons lumpers or splitters?* J Trauma, 2003. **55**(5): p. 997-8.

26. Damas, P., et al., *Intensive care unit acquired infection and organ failure.* Intensive Care Med, 2008. **34**(5): p. 856-64.

27. Bernard, G.R., et al., *Efficacy and safety of recombinant human activated protein C for severe sepsis.* N Engl J Med, 2001. **344**(10): p. 699-709.

28. Sandrock, C.E. and T.E. Albertson, *Controversies in the treatment of sepsis.* Semin Respir Crit Care Med, 2010. **31**(1): p. 66-78.

29. Ranieri, V.M., et al., *Drotrecogin alfa (activated) in adults with septic shock.* N Engl J Med, 2012. **366**(22): p. 2055-64.

30. Waxman, A.B., et al., *Roundtable debate: Controversies in the management of the septic patient--desperately seeking consensus.* Crit Care, 2005. **9**(1): p. E1.

31. Angus, D.C., et al., *The PIRO concept: P is for predisposition.* Crit Care, 2003. **7**(3): p. 248-51.

32. Sorensen, T.I., et al., *Genetic and environmental influences on premature death in adult adoptees.* N Engl J Med, 1988. **318**(12): p. 727-32.

33. Merino, J., et al., *[Recurrent meningococcal sepsis associated with congenital C8 deficiency: description of 2 families].* Med Clin (Barc), 1983. **81**(18): p. 789-93.

34. Gibot, S., *Clinical review: role of triggering receptor expressed on myeloid cells-1 during sepsis.* Crit Care, 2005. **9**(5): p. 485-9.

35. Lorenz, U., et al., *Immunodominant proteins in human sepsis caused by methicillin resistant Staphylococcus aureus.* Adv Exp Med Biol, 2000. **485**: p. 273-8.

36. Fang, X.M., et al., *Comparison of two polymorphisms of the interleukin-1 gene family: interleukin-1 receptor antagonist polymorphism contributes to susceptibility to severe sepsis.* Crit Care Med, 1999. **27**(7): p. 1330-4.

37. Barnes, K.C., *Genetic determinants and ethnic disparities in sepsis-associated acute lung injury.* Proc Am Thorac Soc, 2005. **2**(3): p. 195-201.

38. Dahmer, M.K., et al., *Genetic polymorphisms in sepsis.* Pediatr Crit Care Med, 2005. **6**(3 Suppl): p. S61-73.

39. De Maio, A., M.B. Torres, and R.H. Reeves, *Genetic determinants influencing the response to injury, inflammation, and sepsis.* Shock, 2005. **23**(1): p. 11-7.

40. Lin, J., et al., *[Association between a genomic polymorphism within the CD14 locus and severe sepsis susceptibility as well as prognosis in patients after extensive burns].* Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 2004. **16**(5): p. 271-3.

41. McIntyre, L. and K.R. Walley, *Importance of underlying mechanism and genotype on outcome of sepsis trials.* Crit Care Med, 2001. **29**(3): p. 677-9.

42. Nadel, S., *Helping to understand studies examining genetic susceptibility to sepsis.* Clin Exp Immunol, 2002. **127**(2): p. 191-2.

43. Shu, Q., et al., *IL-10 polymorphism is associated with increased incidence of severe sepsis.* Chin Med J (Engl), 2003. **116**(11): p. 1756-9.

44. Stuber, F., et al., *Cytokine promoter polymorphisms in severe sepsis.* Clin Infect Dis, 2005. **41 Suppl 7**: p. S416-20.

45. Tabrizi, A.R., et al., *Genetic markers in sepsis.* J Am Coll Surg, 2001. **192**(1): p. 106-17; quiz 145-6.

46. Wurfel, M.M., *Genetic insights into sepsis: what have we learned and how will it help?* Curr Pharm Des, 2008. **14**(19): p. 1900-11.

47. Wurfel, M.M., et al., *Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis.* Am J Respir Crit Care Med, 2008. **178**(7): p. 710-20.

48. Majetschak, M., et al., *Tumor necrosis factor gene polymorphisms, leukocyte function, and sepsis susceptibility in blunt trauma patients.* Clin Diagn Lab Immunol, 2002. **9**(6): p. 1205-11.

49. Padkin, A., et al., *Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland.* Crit Care Med, 2003. **31**(9): p. 2332-8.

50. Esper, A.M., et al., *The role of infection and comorbidity: Factors that influence disparities in sepsis.* Crit Care Med, 2006. **34**(10): p. 2576-82.

51. de Groot, V., et al., *How to measure comorbidity. a critical review of available methods.* J Clin Epidemiol., 2003. **56**(3): p. 221-9.

52. Charlson, M., et al., *Validation of a combined comorbidity index.* J Clin Epidemiol, 1994. **47**(11): p. 1245-1251.

53. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

54. Alberti, C., et al., *Systemic inflammatory response and progression to severe sepsis in critically ill infected patients.* Am J Respir Crit Care Med, 2005. **171**(5): p. 461-8.

55. Vincent, J.L., et al., *The PIRO concept: I is for infection.* Crit Care, 2003. **7**(3): p. 252-5.

56. Opal, S.M. and J. Cohen, *Clinical gram-positive sepsis: does it fundamentally differ from gram-negative bacterial sepsis?* Crit Care Med, 1999. **27**(8): p. 1608-16.

57. Cohen, J., et al., *Diagnosis of infection in sepsis: an evidence-based review.* Crit Care Med, 2004. **32**(11 Suppl): p. S466-94.

58. Opal, S.M., et al., *Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated).* Clin Infect Dis, 2003. **37**(1): p. 50-8.

59. Gluck, T. and S.M. Opal, *Advances in sepsis therapy.* Drugs, 2004. **64**(8): p. 837-59.

60. Paez, J.I. and S.F. Costa, *Risk factors associated with mortality of infections caused by Stenotrophomonas maltophilia: a systematic review.* J Hosp Infect, 2008. **70**(2): p. 101-8.

61. Cohen, J., et al., *New method of classifying infections in critically ill patients.* Crit Care Med, 2004. **32**(7): p. 1510-26.

62. Agvald-Ohman, C., et al., *Invasive candidiasis in long-term patients at a multidisciplinary intensive care unit: Candida colonization index, risk factors, treatment and outcome.* Scand J Infect Dis, 2008. **40**(2): p. 145-53.

63. Chow, J.K., et al., *Factors associated with candidemia caused by non-albicans Candida species versus Candida albicans in the intensive care unit.* Clin Infect Dis, 2008. **46**(8): p. 1206-13.

64. Cohen, J., *Meningococcal disease as a model to evaluate novel anti-sepsis strategies.* Crit Care Med, 2000. **28**(9 Suppl): p. S64-7.

65. Chang, R.W., S. Jacobs, and B. Lee, *Use of APACHE II severity of disease classification to identify intensive-care-unit patients who would not benefit from total parenteral nutrition.* Lancet, 1986. **1**(8496): p. 1483-7.

66. Vincent, J.L., et al., *The PIRO concept: O is for organ dysfunction.* Crit Care, 2003. **7**(3): p. 260-4.

67. Livingston, D.H., A.C. Mosenthal, and E.A. Deitch, *Sepsis and multiple organ dysfunction syndrome: a clinical-mechanistic overview.* New Horiz, 1995. **3**(2): p. 257-66.

68. Tran, D.D., et al., *Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit.* Crit Care Med, 1990. **18**(5): p. 474-9.

69. Livingston, D.H. and E.A. Deitch, *Multiple organ failure: a common problem in surgical intensive care unit patients.* Ann Med, 1995. **27**(1): p. 13-20.

70. DeCamp, M.M. and R.H. Demling, *Posttraumatic multisystem organ failure.* JAMA, 1988. **260**(4): p. 530-4.

71. Beal, A.L. and F.B. Cerra, *Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction.* JAMA, 1994. **271**(3): p. 226-33.

72. Moreno, R., et al., *The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM.* Intensive Care Med., 1999. **25**(7): p. 686-96.

73. Doig, C.J., et al., *Study of clinical course of organ dysfunction in intensive care.* 2004. **32**(2): p. 384-390.

74. Ferreira, F.L., et al., *Serial evaluation of the SOFA score to predict outcome in critically ill patients.* JAMA, 2001. **286**(14): p. 1754-8.

75. Cheng, B., et al., *Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China.* Crit Care Med, 2007. **35**(11): p. 2538-46.

76. Chang, R., S. Jacobs, and B. Lee, *Predicting outcome among intensive care unit patients using computerised trend analysis of daily Apache II scores corrected for organ system failure.* 1988.

77. Yzerman, E.P., et al., *Delta APACHE II for predicting course and outcome of nosocomial Staphylococcus aureus bacteremia and its relation to host defense.* 1996. **173**(4): p. 914-919.

78. Booth, F.V., et al., *Application of a population-based severity scoring system to individual patients results in frequent misclassification.* 2005. **9**(5): p. R522-9.

79. Murphy-Filkins, R.L., D. Teres, and S. Lemeshow, *Effect of changing patient mix on the performance of an intensive care unit severity-of-illness model: how to distinguish a general from a specialty intensive care unit.* 1996.

80. Kumar, P.S., Rao, C.S., *Prognosis in intra-abdominal sepsis.* . Indian Journal of Gastroenterology, 1995. **14**(1): p. 8-10.

81. Moreno, R.P., et al., *Sepsis mortality prediction based on predisposition, infection and response.* Intensive Care Med, 2008. **34**(3): p. 496-504.

82. Lisboa, T., et al., *The Ventilator-Associated Pneumonia PIRO Score: A Tool for Predicting ICU Mortality and Health-Care Resources Use in Ventilator-Associated Pneumonia.* 2008. **134**(6): p. 1208-1216.

83. Rello, J., et al., *PIRO score for community-acquired pneumonia: A new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia*.* 2009. **37**(2): p. 456-462.

84. Rubulotta, F., et al., *Predisposition, insult/infection, response, and organ dysfunction: A new model for staging severe sepsis.* 2009. **37**(4): p. 1329-1335.

85. Howell, M.D., et al., *Proof of principle: The predisposition, infection, response, organ failure sepsis staging system*.* 2011. **39**(2): p. 322-327.

86. Esper, A.M., et al., *The role of infection and comorbidity: Factors that influence disparities in sepsis.* 2006.

87. Tetsche, M.S., et al., *The impact of comorbidity and stage on ovarian cancer mortality: a nationwide Danish cohort study.* 2008. **8**: p. 31.

88. Jepsen, P., et al., *Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study.* 2008.

89. Pittet, D., et al., *Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients.* 1993. **19**(5): p. 265-272.

90. Sundararajan, V., et al., *New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality.* 2004. **57**(12): p. 1288-1294.

91. Martin, G.S., D.M. Mannino, and M. Moss, *The effect of age on the development and outcome of adult sepsis.* 2006. **34**(1): p. 15-21.

92. Azoulay, E., et al., *Determinants of postintensive care unit mortality: a prospective multicenter study.* 2003. **31**(2): p. 428-432.

93. Turnbull, I.R., et al., *Effects of age on mortality and antibiotic efficacy in cecal ligation and puncture.* 2003. **19**(4): p. 310-313.

94. Gabriel, P., I. Cakman, and L. Rink, *Overproduction of monokines by leukocytes after stimulation with lipopolysaccharide in the elderly.* 2002. **37**(2-3): p. 235-247.

95. Wheeler, A.P. and G.R. Bernard, *Treating patients with severe sepsis.* 1999.

96. Wang, F.D., et al., *Risk factors and mortality in patients with nosocomial< i> Staphylococcus aureus</i> bacteremia.* 2008.

97. Perlino, C.A. and D. Rimland, *Alcoholism, leukopenia, and pneumococcal sepsis.* 1985.

98. L'Her, E., et al., *Effects of mild induced hypothermia during experimental sepsis.* 2006. **34**(10): p. 2621-2623.

99. Arons, M.M., et al., *Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group.* 1999. **27**(4): p. 699-707.

100. Sprung, C.L., et al., *Impact of encephalopathy on mortality in the sepsis syndrome. The Veterans Administration Systemic Sepsis Cooperative Study Group.* 1990. **18**(8): p. 801-806.

101. Clemmer, T.P., et al., *Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group.* 1992. **20**(10): p. 1395-1401.

102. Ravindranath, T., et al., *Hypothermia predicts mortality in critically ill elderly patients with sepsis.*

103. Xiao, H. and D.G. Remick, *Correction of perioperative hypothermia decreases experimental sepsis mortality by modulating the inflammatory response.* 2005. **33**(1): p. 161-167.

104. Furtado, G.H., et al., *Performance of the PIRO score for predicting mortality in patients with ventilator-associated pneumonia.* 2012. **40**(2): p. 285-291.