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A Study of Differential Outcomes between Sexes in the Clinical Course of Multiple Organ Dysfunction

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ABSTRACT

Organ dysfunction is a common event among intensive care patients, with almost all critically ill patients having some degree of organ dysfunction during their hospital stay. Multiple organ dysfunction, at the extreme end of the continuum of organ dysfunction, is the leading cause of morbidity and mortality in the ICU. The primary objective of this study was to determine whether there are differential outcomes between sexes during multiple organ failure. This was a retrospective cohort study including adult residents admitted to an intensive care unit in the Calgary Health Region. Results of this study demonstrate that the clinical course of organ dysfunction is the same between males and females. Females do, however, experience less organ dysfunction compared to males, as determined by organ dysfunction scores, beginning on the day of admission and throughout their stay in the intensive care unit. This study was a large multi-centre study and has made a contribution to the ongoing discussion and research in this area of intensive care medicine.

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LIST OF ABBREVIATIONS

APACHE II	Acute Physiology and Chronic Health Evaluation
CHR	Calgary Health Region
CNS	Central Nervous System
CV	Cardiovascular
DCCM	Department of Critical Care Medicine
FMC	Foothills Medical Centre
GEE	Generalized Estimating Equation
ICU	Intensive Care Unit
IQR	Inter-quartile range
LOS	Length of Stay
MODS	Multiple Organ Dysfunction Syndrome
PLC	Peter Lougheed Centre
RGH	Rockyview General Hospital
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
TISS	Therapeutic Intervention Scoring System
TRACER	DCCM longitudinal clinical database

A. INTRODUCTION

Differential health outcomes between sexes are increasingly being recognized[1] and have been identified at many levels of biological organization, from biochemical to behavioural. In epidemiological studies, sex is considered to be a classic confounder, and is often controlled for during study design or data analysis. The hypothesis of sex based difference in outcomes of various disease processes, including trauma and sepsis, has prompted numerous clinical investigations. Animal models and clinical studies have suggested that there may be a survival advantage in women during critical illness based on the premise that the immune system in women is different from that of men.[2]

Few studies, however, have investigated differential outcomes between sexes in Multiple Organ Dysfunction Syndrome (MODS). MODS is the detection of altered organ function in an acutely ill patient and commonly follows a systemic inflammatory response, as often seen in trauma or septic patients. One prospective study by Frink et al. has confirmed a sex difference in the development of MODS, with a benefit observed in severely injured females under the age of 50.[3] Dichotomizing MODS as an event that is either present or absent as the limited previous studies have done, however is not entirely accurate. Multiple organ dysfunction is a pattern of multiple, and progressive symptoms, and changes in organ function over time can be useful in prognosis.[4] The Sequential Organ Failure Assessment (SOFA) score was designed for precisely this purpose. Developed by consensus in 1994, the SOFA score can be used to objectively and quantitatively describe the degree of organ dysfunction over time in a group of patients or in an individual patient. One important application considered by the developers of the SOFA score is “to improve our understanding of the natural history of organ dysfunction/failure and the interrelation between the failure of the various organs”.[5]

The primary objective of this study was to determine whether the clinical course of MODS, as measured by the SOFA score, is similar between male and female patients admitted to the Intensive Care Unit (ICU). Secondary objectives include an investigation of whether there are differentials outcomes in MODS, between the sexes, specifically in trauma and sepsis patients and an investigation into the effect of hormone therapy on MODS in women. Overall, this study provides a better understanding of how sex translates into differences in MODS.

B. LITERATURE REVIEW

1. Multiple Organ Dysfunction Syndrome

The detection of altered organ function in an acutely ill patient constitutes a syndrome termed multiple organ dysfunction syndrome (MODS), also known as multiple organ failure syndrome or multiple organ failure. Organ dysfunction is a common event among intensive care patients, with almost all critically ill patients having some degree of organ dysfunction during their hospital stay. Multiple organ dysfunction, at the extreme end of the continuum of organ dysfunction, is the leading cause of morbidity and mortality in the ICU[6] and is increasingly prevalent as a result not only of improvements in life support technology (both medications and devices), but also in the application of these technologies to an increasingly high-risk patient population.[7]

Systemic Inflammatory Response Syndrome (SIRS), a frequent precursor to MODS, is a whole body inflammatory response to a wide variety of severe clinical insults, including trauma and sepsis. The physiological response to critical injury involves both local and systemic reactions, and the extent of the response is generally proportional to the severity of the injury.[8] During an appropriate response, homeostasis is maintained in the body. During an excessive response, however, SIRS may occur and is manifested by two or more of the following conditions: temperature >38^{o}C or <36^{o}C, heart rate >90 beats per minute, respiratory rate >20 breaths/minute or $PaCO_2$ <32mmHg, WBC count > 12, 000/mm^3 or < 4,000/mm^3 or >10% immature neutrophils.[7] This systemic inflammatory response is seen in association with a large number of clinical conditions including infectious insults, and non-infectious pathologic causes, including multiple trauma.[7] When SIRS is the result of a confirmed infectious process, it is termed sepsis, and manifestations are the same as those defined for SIRS. A frequent complication of SIRS is the development of organ system dysfunction, including MODS.

MODS is defined as a progressive dysfunction of one or more organ systems that results from exaggerated and prolonged inflammatory response to severe illness and/or injury.[9] In 1991 the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee developed the following definition of MODS:

> "Presence of altered organ function in an acutely ill person, such that homeostasis, cannot be maintained without intervention. Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself. Secondary MODS develops as a consequence of a host response and is identified within the context of systemic inflammatory response syndrome (SIRS)."[8]

MODS is defined as a syndrome and incorporates a pattern of symptoms, and progressive changes over time which are considered important in prognostication.[7] Although MODS is readily recognized by experienced clinicians, there is no clear consensus with respect to systems whose function is deranged, descriptors that best measure the derangement, or the degree of derangement that constitutes organ dysfunction or failure. Six organ systems are commonly included in the description of multiple organ dysfunction including; the renal system, the hepatic system, the cardiovascular system, the haematological system, respiratory system and the central nervous system (CNS).

Despite major advances in therapies, MODS continues to have a mortality rate of 30% to 50%.[10] Although our understanding of the pathophysiology of organ dysfunction and failure in critically ill patients is improving, descriptions of the epidemiology of this syndrome are still in the beginning stages. We know that MODS describes a continuum of organ dysfunction, but specific descriptions of this continuous process are lacking.

2. Quantification of Organ Dysfunction

The degree of physiological derangement present at the time of ICU admission is a potent determinant of ICU survival, and irreversible organ dysfunction is a common mode of ICU death. Formal quantification of the severity of physiological derangement or the evolution of organ dysfunction over time is not generally incorporated in individual patient care in the ICU. Validated scoring systems, however, have proved invaluable in describing patient populations, assessing ICU morbidity in patient groups and stratifying patients for entry into clinical trials.

There are a number of published systems for quantifying the severity of organ dysfunction in the critically ill. [5 11 12] These systems are all structurally similar, evaluating dysfunction in each of six or seven organ systems on a numerical scale in which more points are assigned for greater degrees of physiological severity, varying primarily with respect to variables used to describe dysfunction.

Organ dysfunction scores can usefully describe the characteristics of patient populations for epidemiological analysis. The numerical scores obtained from a validated scoring system can be applied in a variety of ways.[13] Scores can be calculated on the day of ICU admission to provide a baseline measure of illness severity. Scores can also be calculated daily to track net clinical improvement or deterioration over time and to assess the progression or resolution of organ dysfunction, providing a picture of the evolution of single and overall organ dysfunction in individual patients or groups of patients. Alternatively, the aggregate severity of organ dysfunction over time can by quantified by summing the worst values over time in each of the component systems.

The evolution of our knowledge of organ dysfunction has led to the understanding that it is a process of progressive and sequential impairment, rather than a single event.[5] Organ dysfunction scores have been introduced as one method to improve understanding of the natural history of the course of organ dysfunction by allocating specific numerical values to the degree of organ dysfunction in individual ICU patients.

By following trends in these values, one can follow the evolution of the organ dysfunction over time.

3. The Sequential Organ Failure Assessment Score

The Sequential Organ Failure Assessment (SOFA) score was developed by consensus in 1994 in order to objectively and quantitatively describe the degree of organ dysfunction over time in a group of patients or in an individual patient. One important application considered by the developers of the SOFA score is "to improve our understanding of the natural history of organ dysfunction/failure and the interrelation between the failure of the various organs".[5] The SOFA score individually evaluates the status of six organ systems (Appendix I) on a scale from 0 (normal) to 4 (severe) upon admission and serially during the ICU stay. An increasing score is associated with a worse prognosis. Regular, repeated scoring enables the clinical course of organ dysfunction to be monitored and potentially clarified. Additionally, the SOFA score is a useful tool for stratifying and comparing patients in population studies.

Variants of the SOFA score have also been utilized in order to investigate varying aspects of MODS. Some studies have suggested that using either the sum of the maximum scores for each system (Max SOFA), the admission value, or the changes in the first 48 hours is related to mortality.[6,14] Death from MODS has also been suggested to be a consequence of the severity of physiological derangement at the time of ICU admission[15] or failure of early improvement.[16] Studies such as these have indicated that the SOFA score is a valid measure of multiple organ dysfunction.

4. Differential Outcomes between Sexes in Sepsis and Trauma

Studies have clearly indicated that MODS is related to immunologic disorders.[17,18] The common pathway of multiple organ dysfunction is a severe inflammatory reaction resulting from systemic cytokine release.[19] In response to the initiating proinflammatory reaction, with tumor necrosis factor (TNF-a), interleukin (IL) 1 and IL-6 playing the

predominant role, the body also mounts an immediate anti-inflammatory response. Sex hormones seem to alter immune response by influencing the synthesis and release of cytokines. [20 21] Lower levels of proinflammatory cytokines prevent infiltration of immunocompetent cells, an important step in the development of organ dysfunction.[3] The excessive release of proinflammatory reacting mediators has been found to play a pivotal role in the pathophysiology of MODS.

There is increasing evidence for differential outcomes between sexes in the host defense after trauma, hemorrhage, and sepsis in experimental animals. Androgenic hormones seem to have an immunosuppressive effect[22-25] leading to increased susceptibility and higher mortality after sepsis. Conversely, estrogen has been shown to have beneficial effects in different trauma models.[20] Proestrus female mice showed enhanced immune reactivity after trauma-hemorrhage compared with depressed immune functions in male animals[23 24]. Testosterone depletion by castration of male mice 2 weeks before haemorrhage prevented the depression of splenocyte as well as of macrophage functions in those animals.[23] Other studies revealed that female mice tolerate sepsis better than male mice as demonstrated by increased survival rates of females after a septic challenge[26] and estrogen administration in males prevents immunosupression in various experimental and animal models.[27]

These animal studies suggest that the presence of either decreased estradiol, or increased testosterone results in significant multi-system depression in male animals and a clear association between sexual dimorphism and various immune functions has been suggested.

Recent clinical and epidemiological studies regarding sex differences in host defence following trauma and sepsis, however, have yielded varying results. Some studies suggest that women have a markedly better survival rate following trauma and sepsis and several investigators are attempting to elucidate the influence of sex on an individual's response to trauma, shock and sepsis. Epidemiological studies report that the majority of injured victims are young males.[28] Sex differences, however, exist not

only in the prevalence of trauma, but also in the increased susceptibility to complications following trauma.[29] A report by Wohltmann et al. also showed a survival advantage in severely injured young female patients, less than 50 years of age.[30] In a prospective trial of 52 patients, Schroder et al. showed better prognosis for women suffering from sepsis, perhaps related to the altered inflammatory cytokine profile.[31] A survival advantage in female trauma patients over male patients, but only in those under the age of 45 years, has also been reported.[32] Offner et al. identified male gender as an independent risk factor for the development of severe infection in surgical patients[33], and Bone similarly reported a predominance of morbidity and mortality from sepsis in males compared to females.[4]

5. Differential Outcomes between Sexes in Multiple Organ Dysfunction

Most of the studies, to date, investigating differential outcomes in men and women during sepsis and trauma have focused primarily on mortality as the outcome.[2 3] Few studies have considered the role of sex on the course of organ dysfunction, and whether the immunoprotective properties of female sex hormones, and immunodepressive effects of male sex hormones are important to consider at this level. A prospective study by Frink et al. confirmed a sex difference in MODS, with a benefit observed in females, particularly in females under the age of 50 with an injury severity score greater than 25.[3] A study by Oberholzer et al., similarly showed that the incidence of posttraumatic sepsis and MODS is significantly higher in male patients with an injury severity score >25 compared with a matched female cohort.[2] These studies, however, used the Marshall score, rather than the SOFA score to quantify organ dysfunction and looked at the incidence of MODS following trauma or sepsis as opposed to the course of organ dysfunction.

Additionally, no known studies, to date, have considered the effect of sex following sepsis and trauma on individual organ systems. Animal studies suggest that hormonal differences between genders are important to consider in regards to individual organ

systems. Specifically, one group of investigators found that male rodents had cardiac and hepatocellular depression after hemorrhage, but female rodents had normal cardiac and hepatocellular function.[34] In a complementary study, they found that the immune and cardiac depression in male rodents after hemorrhage was prevented by castration prior to trauma, and when female rodents were administered testosterone prior to hemorrhage, the same degree of immune depression was found in the females as in the males.[25]

6. Important Considerations in Studying Differential Outcomes Between Sexes

Few studies evaluating the differential outcomes betweens sexes during acute injury have taken into consideration declining male sex hormones or HRT in women, despite the fact that there may be clinical consequences. In considering that estrogen may be immunoprotective and androgens may be produce immunodepression it is also important to consider both change in hormone levels throughout an individual's lifespan, and hormone replacement therapies. Aging in men is accompanied by a progressive, but individually variable decline of androgen production, with more than 20% of healthy men over 60 years of age presenting with serum levels below the range for young men.[35] Testosterone, in particular, has been found to reach a peak in the 20's, followed by a gradual decline with age, with the extent of decline differing in each individual.[36] This is in contrast to the abrupt decline of estrogen in women, most of whom show a constant and abrupt decline of estrogen when they reach menopause. By age 50, most women will have undergone changes consistent with menopause. Menopause results in an increase in the testosterone to estradiol ratio, which may explain a hypothesized loss of survival advantage in women 50 years of age or older.

Hormone replacement Therapies (HRT) have been used widely by peri and postmenopausal women for more than 40 years to manage menopausal symptoms.[37] Since July 2002, however, many patients have discontinued HRT or have tapered to very low doses due to evidence from the Women's Health Initiative Hormone Therapy (WHI HT) trial that increased awareness around the risks of HT. The estrogen plus

progesterone trial of the WHI demonstrated that hormone therapy with estrogen/progesterone combination caused increased risk of breast cancer and cardiovascular disease in postmenopausal women.[38] Studies have shown an immediate reduction in HRT after the WHI HT[38, 39] and results are supported by declining national pharmacy sales.[40] Clinical practice has responded rapidly to evidence of the harms associated with HRT with recent estimates of overall hormone cessation after July, 2002 ranging from 38%[40] to 58%[39].

C. STUDY OBJECTIVES

1. Primary Objective

Is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit between May 1, 2003 and April 30, 2006?

2. Secondary Objectives

i) Amongst trauma and sepsis patients only, is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit between May 1, 2003 and April 30, 2006? Are the results found in the entire ICU population similar within the trauma and sepsis groups?

ii) Given that estrogen is considered to be immunoprotective, is there a difference in the clinical course of multiple organ dysfunction, measured by the SOFA score, amongst women from May 1, 2000 to April 30, 2002, a period of time when HRT was commonly prescribed to women over 50, compared to May 1, 2004 to April 30, 2006, a period of time when HRT was not commonly used?

D. RESEARCH DESIGN AND METHODS

1. Study Design

This study is a retrospective cohort comprised of data collected from the Department of Critical Care Medicine TRACER database. This database collects information on all ICU patients prospectively.

2. Population

The Calgary Health Region serves a referral population of 1.5 million people. The study included all consecutive critically ill patients admitted to one of the region's adult multisystem ICUs, Foothills Hospital, Rocky View General Hospital and Peter Lougheed Centre, between May, 2000 and June, 2006. Only a patient's first admission to the ICU during the study time will be considered. Patients were excluded if they were admitted to a coronary care unit, were a postoperative cardiovascular surgery patient, under 18 years of age, or survived the ICU with a length of stay of less than 48 hours after undergoing an uncomplicated elective surgery.

3. Data

Physiologic data in the TRACER database was collected at the bedside by an electronic patient information system (Quantitative Sentinel [QS], GE-Marquette Medical Systems) interfaced to bedside electronic devices. Laboratory data was collected into the QS system through an HL-7 interface with the regional laboratory information system (Cerner PathNet Classic version 306; Kansas City, MO).

The SOFA score is presented in Appendix I. The calculation of the SOFA score followed the method of calculation described by Vincent et al[5]. Organ dysfunction was identified

by retrospectively calculating the daily SOFA score of each patient. The most abnormal daily physiologic, laboratory, or clinical data within each of the six systems was used in calculation of the SOFA score.

4. Data Cleaning

Data was cleaned and organized according to the exclusion criteria and research objectives as depicted in Figure 1 and Table 1 below.

Figure 1. Data Cleaning Process

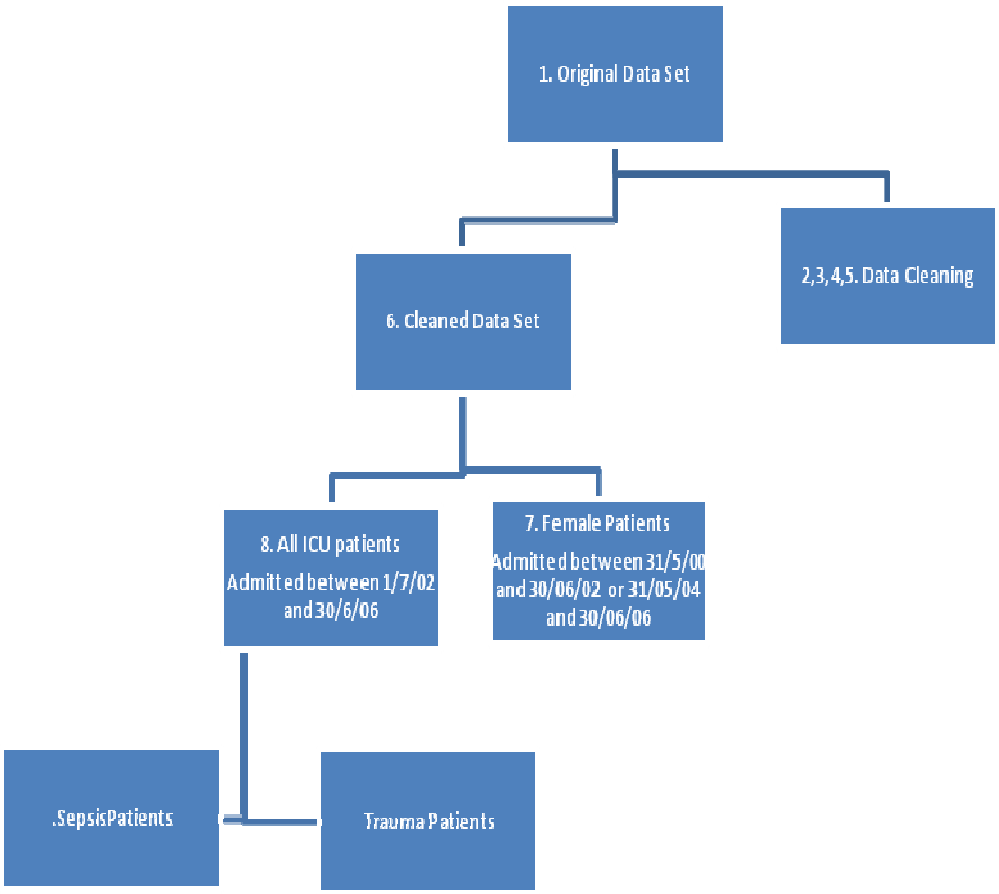


Table 1. Data Cleaning Record

Step	Stage Description	# of Records	# of Admits
1	Original Data Set	107,859	20,586
2	Remove all Age <18 yrs	766	197
3	Remove LOS < 2 and Surgery = Elect	9,378	4,304
4	Remove Age and Sex = Null	98	42
5	Remove Sex = Null	120	29
6	Cleaned Data set	97,497	16,014
7	Between 31/5/00 and 30/6/02 or between 31/5/04 and 30/6/06 and Sex = F and Not Admitted to CVICU	21,472	3,681
8	Between 1/7/02 and 30/6/06 and Not Admitted to CVICU	56,452	8,785

Number of admits in Table 1 may include multiple admits for the same patient over the course of time included in this study. For this reason data was further cleaned to include only the first admission for each patient resulting in 7, 760 unique admits for patients admitted between 1/7/02 and 30/6/06 (primary research question) and 3, 255 females admitted between 31/5/00 and 30/6/02 or between 31/5/04 and 30/6/06 (secondary research question).

Trauma patients were identified based on diagnoses of `trauma` under the system field in the ICU tracer database, resulting in 771 unique admissions between 1/7/02 and 30/6/06. Sepsis patients were classified based on admission diagnoses determined by consensus by two intensive care physicians (appendix 2), resulting in 1, 689 unique admits.

5. Data Analysis

All data was analyzed using STATA-9 (Stata, College Station TX). Organ dysfunction was quantified using the SOFA score, and variants including:

First SOFA: The SOFA score obtained within the first 24 hours of the patients admission to the ICU.
Last SOFA: The SOFA score obtained on the day before discharge or death.
Max SOFA: The sum of the most abnormal SOFA component scores during the patients stay.
Highest SOFA: The largest daily SOFA score obtained during the patients stay.
Delta SOFA: The difference between the max SOFA and the first SOFA.
Average SOFA: The mean SOFA score obtained during the patients stay.

The following analysis was used for each of the three objectives of this study.

Descriptive statistics and box plots were used to in order to make initial comparisons between groups. Normally, or near normally distributed variables were reported as means with standard deviations (SD) and non-normally distributed variables as medians with inter-quartile ranges (IQR). Means were compared using the Student's t-test and medians using the Mann-Whitney U test. Categorical variables were analyzed using Fisher`s exact test. A P-value of less than 0.05 was considered significant and all tests were two sided.

A stratified analysis was done based on sex and age. By age 50, most women will have undergone changes consistent with menopause. For this reason, age was divided accordingly at the age of 50 for both men and women (<50 or ≥50). Since the age of declining male sex hormones is not as clear cut, the age of 50 was used as well.

To address the objective of describing the course of organ dysfunction in males and females, the analysis considered individual error estimation to be of unequal variance

since each individual provides a variable number of data points based on their outcome and ICU length of stay. A population-averaged panel-data model was used as previously used by Doig et al.[15] using a generalized estimating equation (GEE) variant of the generalized linear method,[41] The GEE approach was developed by Liang and Zeger to produce more efficient and unbiased regression estimates for use in analyzing longitudinal data or repeated measures research designs with non normal response variables.[41] The GEE uses all of the data and accommodate the correlated structure of the data[42]

With GEE the relationships between the variables of the model at different time points are analysed simultaneously.[43] The estimated β_1 coefficient reflects the relationship between the longitudinal development of the outcome variable (daily SOFA score) and the longitudinal development of the corresponding predictor variable (day), using all available longitudinal data. GEE is an iterative procedure, using quasi-likelihood to estimate the regression coefficient[41] and assumes that values are missing completely at random.

Since the repeated observations within one subject are not independent of each other, a correction must be made for these within-subject correlations. With GEE, this correction is carried out by assuming a `working` correlation structure for the repeated measurements of the outcome variable Y.[43] In the literature it is assumed that GEE analysis is robust against a wrong choice of correlation matrix, and that the results will be more or less the same regardless of choice of matrix[41], particularly when using robust standard errors to adjust estimates properly for correlation in the data[42]. The use of robust standard errors bypasses the estimation of the correlation matrix to obtain the standard errors directly

An unstructured within-group correlation structure was used with a robust estimator of variance for this analysis. This model allowed for the temporal comparison of the daily SOFA score between groups and clearly depicted similarities and differences in the course of organ dysfunction. The primary outcome measure will be the comparison of

the change in SOFA over change in time (slope) in men vs. women using a Generalized Estimating Equation model.

6. Ethics Approval

Ethics for this study were obtained from the ethics review board for the Calgary Health Region on July 10th, 2007. A copy of the ethics approval can be found in Appendix 3.

E. RESULTS

1. Study Sample Characteristics

A total of 7, 760 patients met the inclusion criteria for ICU admissions to one of Calgary's multi-system ICUs between July 1, 2002 and June 30, 2006 .The characteristics of these patients are shown in Table 2.

Table 2. Patient Demographics

Variable	All Patients	Females	Males
No. of patients (%)	7, 760	3, 304 (42.6)	4, 456 (57.4)
Age, yrs, mean (±SD)	57.3 (18.8)	58.3 (18.6)	56.6 (18.9)
Admission APACHE II score, mean (±SD)	23.3 (9.3)	23.5 (9.1)	23.3 (9.5)
TISS Admission, mean (±SD)	35.7 (13.7)	35.2 (13.5)	36.1 (13.9)
Length of ICU stay, days (median, IQR)	3.0 (1.5, 6.9)	2.9 (1.3, 6.8)	3.1 (1.6, 6.9)

SD=standard deviation
IQR=inter-quartile range

The study sample consists of 42.6% females and 57.4% males. Two sided, two sample t-tests were used on all normally distributed variables in order to assess equality between males and females. The mean difference in the admission APACHE II score of males and females was 0.2 (95% CI: -0.2, 0.62). A difference of 0.2 was not found to be statistically significant at the 5% level (p=0.35). The mean difference in age of the males and females in this study was found to be 1.7 (95%CI: 0.9-2.5), this difference was found to be statistically significant and there is less than 0.01% chance ($p<0.001$) that this difference occurred by chance alone. A difference of less than 2 years in age, however is not considered to be a meaningful clinical difference. A difference of 0.9 (95% CI: -0.28, 1.5) was found between males and females in the admission TISS score. The probability of observing this difference due to chance alone is 0.33%, thus we reject the null hypothesis and conclude this is a statistically significant difference. A difference of 0.9, however, is not necessarily clinically meaningful. Since LOS was positively skewed the Mann Whitney two sample rank sum test was used. Males and Females stayed had a median length of stay that differed by 0.2 days. This difference

was found to be statistically significant (p=0.0033) but again this difference is not deemed clinically significant.

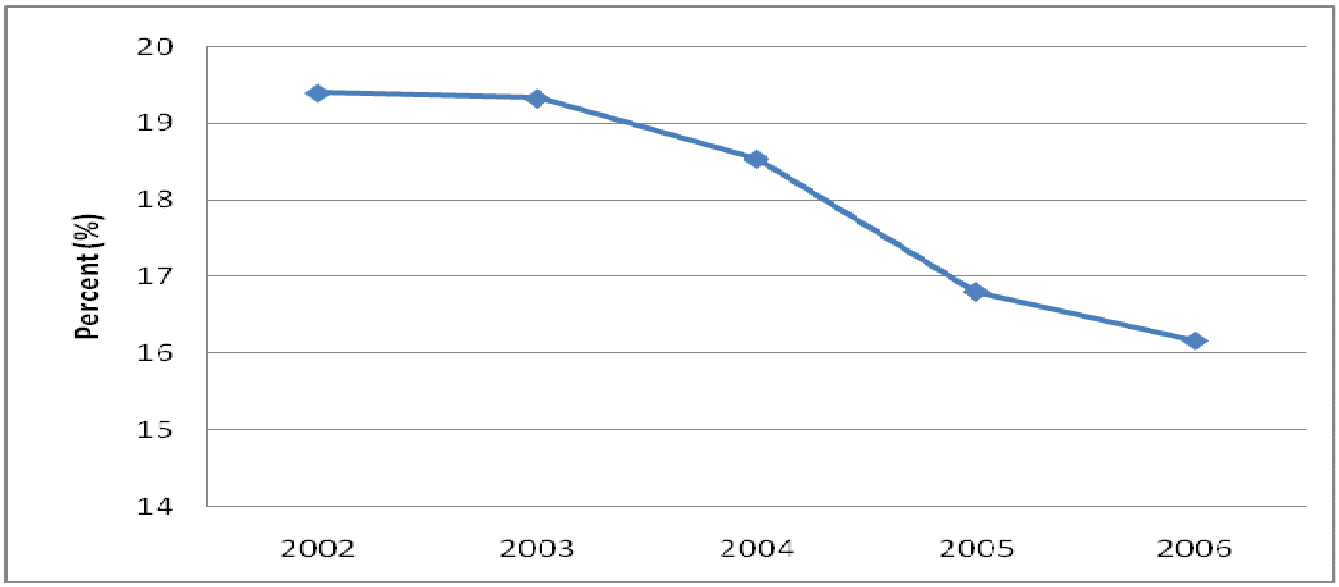
ICU and hospital mortality for this sample is shown in Table 3. A significant difference was not found in the proportion of males vs. females who died in either the ICU (p=0.81) or the hospital (p=0.486) when using a chi squared test. Additionally no significant difference in ICU mortality was found amongst males and females under 50 years of age (p=0.717) or over 50 years of age (p=0.657). Similarly no difference in hospital mortality was found for the under 50 (p=0.371) and over 50 (p=0.719) groups.

Table 3. ICU and hospital mortality stratified by age and sex

ICU Mortality (%)	**All Patients** (n=7, 760)	**Females** (n=3, 304)		**Males** (n= 4, 456)	
	18.1	**Age <50** (n=1, 048)	**Age >= 50** (n=2, 256)	**Age <50** (n=1, 544)	**Age >=50** (n= 2, 912)
		18.0		18.2	
		11.3	21.1	11.7	21.6
Hospital Mortality (%)	**All Patients** (n=7, 275)	**Females** (n=3, 098)		**Males** (n=4, 177)	
	29.3	**Age <50** (n=985)	**Age >= 50** (n=2, 113)	**Age <50** (n=1, 460)	**Age >=50** (n= 2, 717)
		29.7		28.9	
		16.6	35.8	15.2	36.3

Overall, ICU mortality has decreased from 19.4% in 2002 to 16.17% in 2006 as shown in Figure 2.

Figure 2. ICU mortality by year, 2002-2006



During this same time period mortality in males vs. females has remained relatively similar as seen in Figure 3.

Figure 3. ICU mortality by year and sex

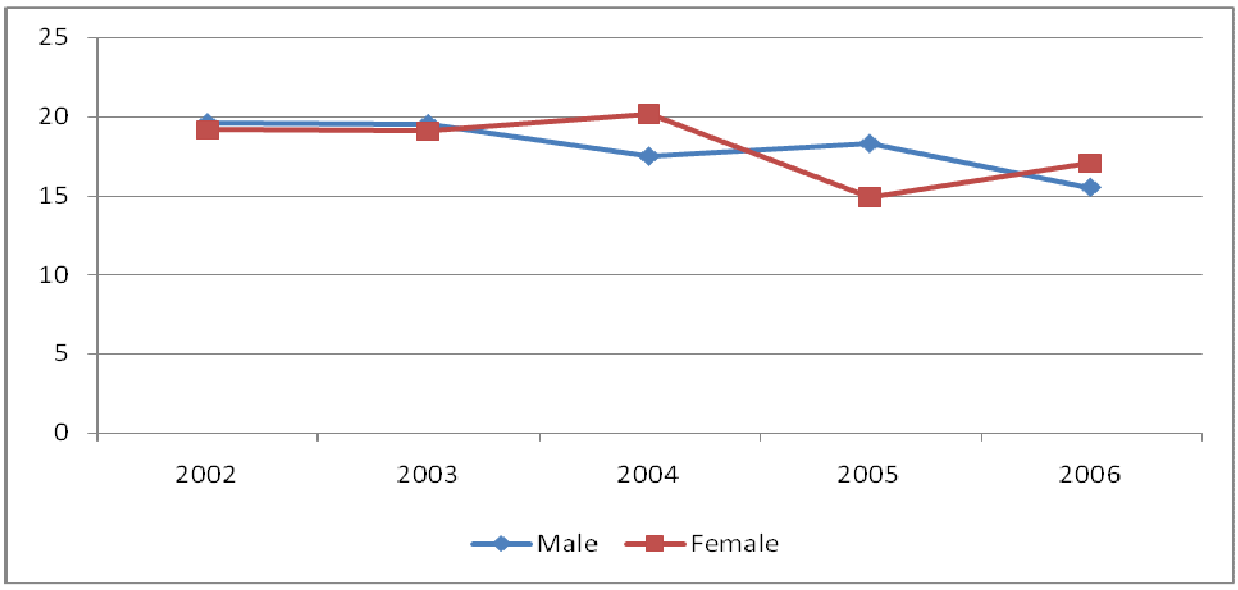


Table 4 shows diagnostic categories stratified by age and sex. The majority of patients are diagnosed with conditions affecting the respiratory (28.5%) or cardiovascular (22.3%) systems.

Table 4. Diagnostic category stratified by age and sex

System,(%)	**All Patients** (n=7, 760)	**Females** (n=3, 304)		**Males** (n=4, 456)	
		Age <50 (n=1, 048)	**Age >= 50** (n=2, 256)	**Age <50** (n=1, 542)	**Age >=50** (n= 2, 914)
Respiratory	28.5	28.9		28.2	
		22.5	31.9	22.6	31.1
Cardiovascular	22.3	23.7		21.9	
		14.6	27.9	11.4	27.5
Neurological	14.5	15		14.1	
		16.8	14.1	16	13.2
Gastrointestinal	9.9	10.6		9.3	
		6.7	12.5	4.8	11.7
Trauma	9.7	5.1		13.2	
		10.2	2.7	27.4	5.6
Other/Missing	15.1	16.7		13.3	
		29.2	10.9	17.8	10.9

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The distribution of each of SOFA scores for this study sample is shown in Figure 4 through Figure 9. The percentage of males and females at each score was plotted for patients who survived while in hospital, and patients who died while in hospital.

Figure 4. First SOFA score for male and female patients who survived (a) or died (b)

a) **b)**

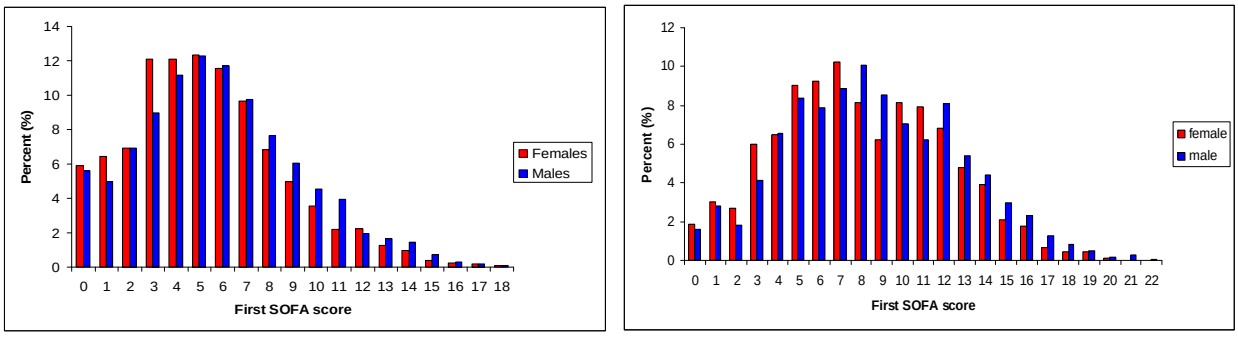


Figure 5. Last SOFA score for male and female patients who survived (a) or died (b)

a) **b)**

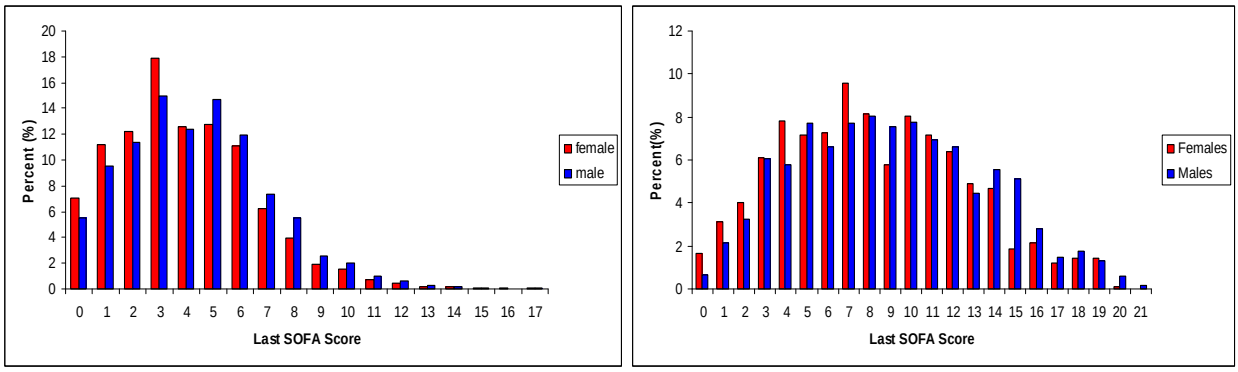


Figure 6. Average SOFA score for male and female patients who survived (a) or died (b)

a) **b)**

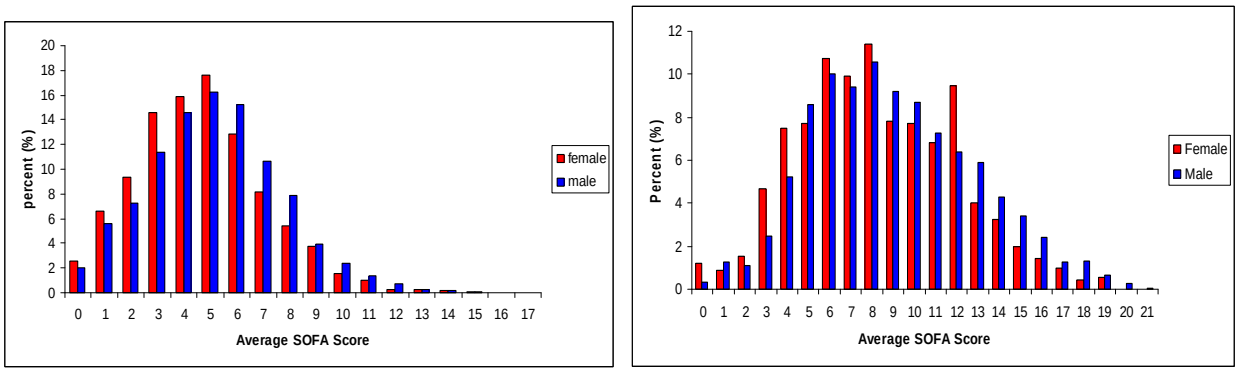


Figure 7. Highest SOFA score for male and female patients who survived (a) or died (b)

a) **b)**

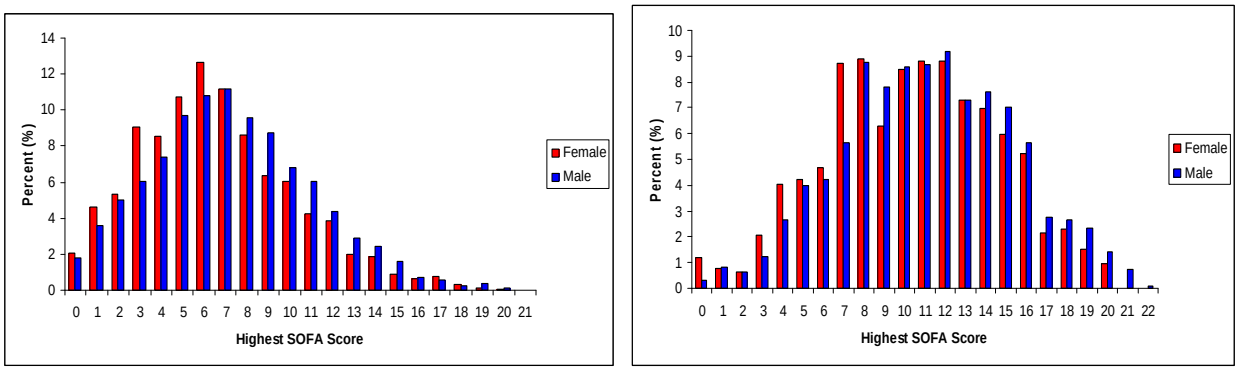


Figure 8. Max SOFA score for male and female patients who survived (a) or died (b)

a) **b)**

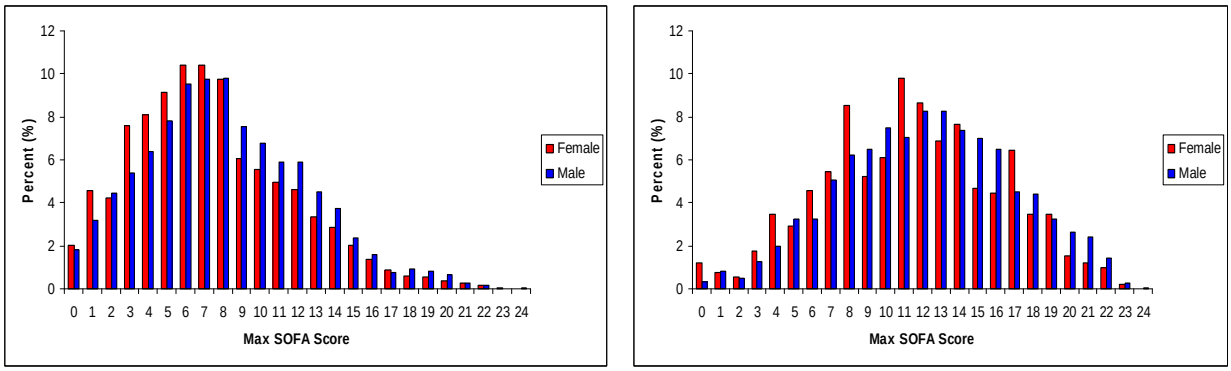
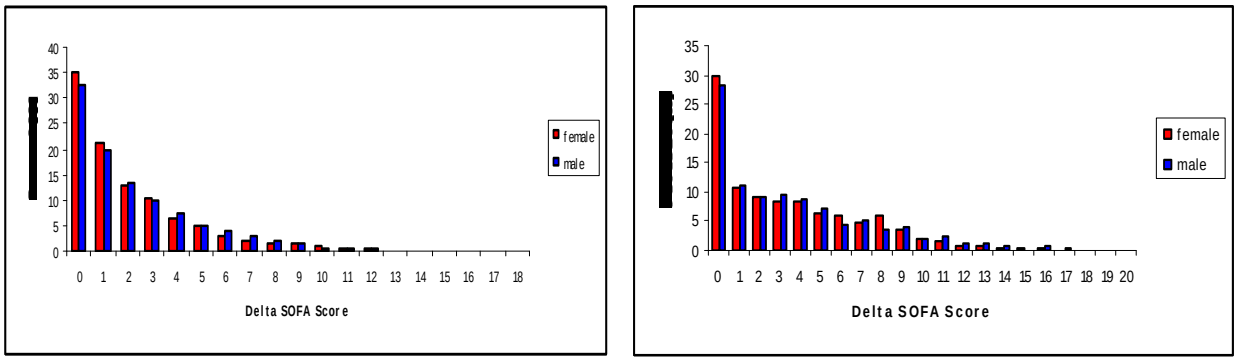


Figure 9. Delta SOFA score for male and female patients who survived (a) or died (b)

a) **b)**



Male and Female patients who survived have lower first, last, average, max and highest SOFA scores than patients who died as seen in the above graphs. In Figures 2 through Figure 8 it is apparent that the percentage of males vs. females at each score is different in all cases, except for the delta SOFA score (Figure 9).

2. Primary Research Question

Is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit?

2.1 Stratified Analysis

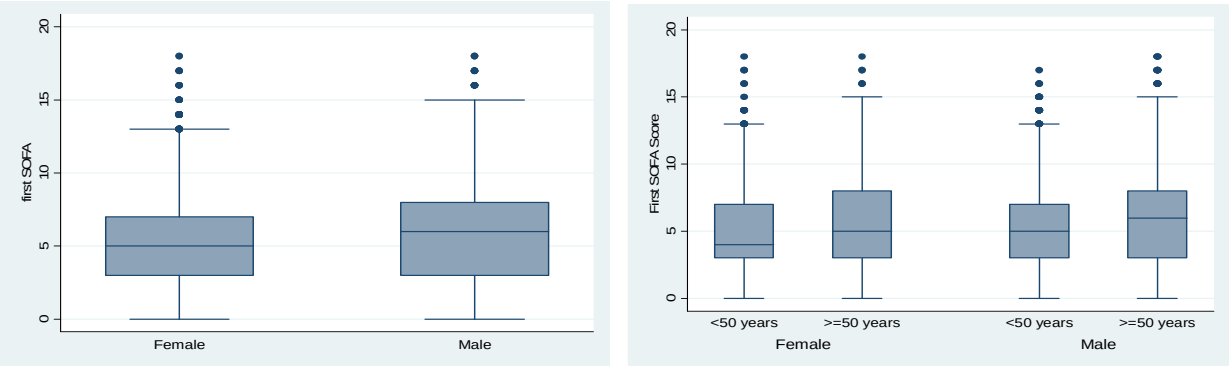
In order to determine whether age and/or sex affect the SOFA score, a stratified analysis was done. Each of the six SOFA variants was calculated for all patients, then stratified by sex, and finally stratified by sex and age. A previous paper by Doig et al.[15] revealed that the course of organ dysfunction differs between survivors and non survivors, for this reason this analysis considered patients who survived separately from those who died. A stratified analysis of SOFA scores for patients who survived is shown in Table 5.

Table 5. SOFA scores in patients who survived stratified by age and sex

SOFA Score, median (IQR)	**All Patients** (n=5, 146)	**Females** (n=2,178)		**Males** (n=2, 968)		*P*
		Age <50 (n=822)	**Age >= 50** (n=1, 356)	**Age <50** (n=1,238)	**Age >=50** (n= 1, 730)	
First SOFA	5 (3, 8)	5 (3, 7)		6 (3, 8)		0.0000
		4 (3, 7)	5 (3, 8)	5 (3, 7)	6 (3, 8)	
Last SOFA	4 (2, 6)	4 (2, 6)		4 (2, 6)		0.0000
		4 (2, 5)	4 (2, 6)	4 (2, 6)	4 (2, 6)	
Average SOFA	5 (3, 6)	5 (3, 6)		5 (3, 7)		0.0000
		4 (3, 6)	5 (3, 6)	5 (3, 6)	5 (3, 7)	
Max SOFA	7 (5, 11)	7 (4, 10)		8 (5, 11)		0.0000
		6 (4, 9)	7 (5, 10)	7 (5,10)	8 (5, 11)	
Highest SOFA	7 (4, 9)	6 (4, 9)		7 (5, 10)		0.0000
		6 (3, 8)	7 (4, 9)	6.5 (4, 9)	7 (5, 10)	
Delta SOFA	1 (0, 3)	1 (0, 3)		1 (0, 3)		0.0021
		1 (0, 4)	1 (0, 3)	1 (0, 3)	1 (0, 3)	

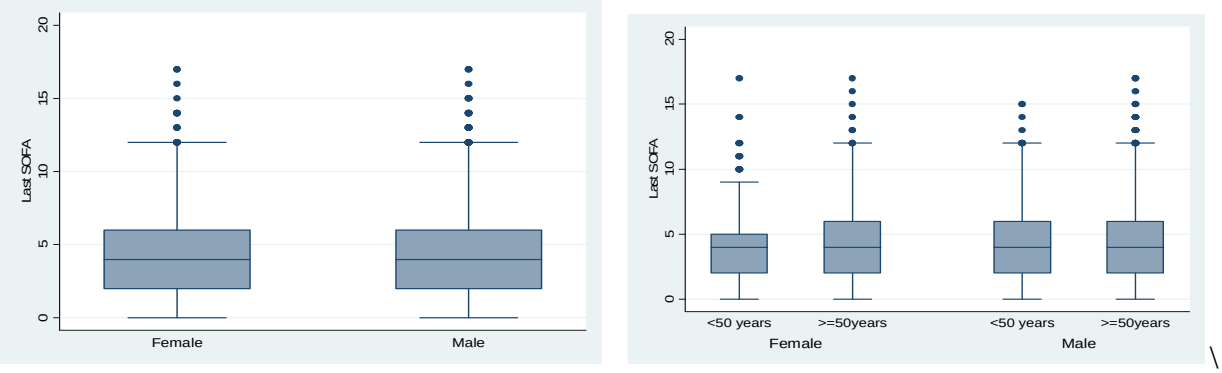
The Mann Whitney two sample ranksum test was used to compare SOFA scores between males and females and was significant in all cases suggesting that males and females have different median SOFA scores. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. This is considered a more conservative test and in all cases the results replicated the p-values represented in Table5. Box plots of these results are shown in Figures 10 to 15.

Figure 10. The First SOFA score in patients who survived stratified by sex only, and by age and sex



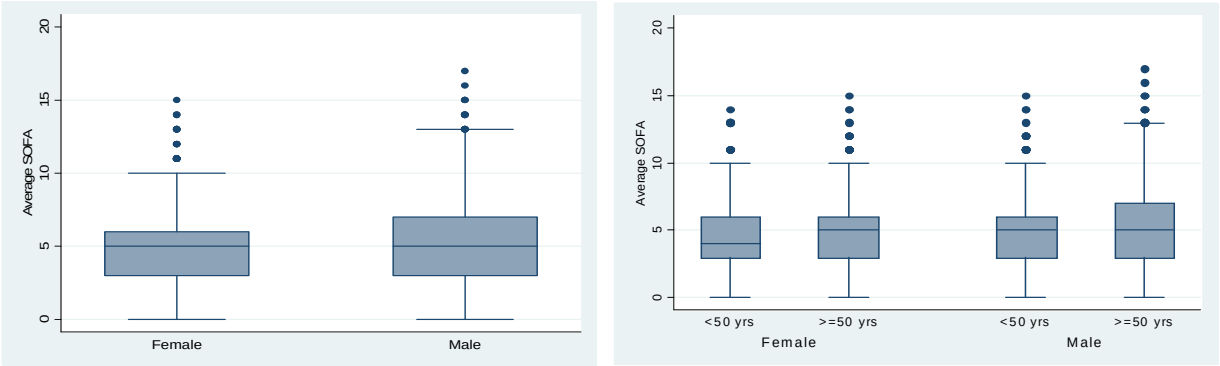
Amongst patients who survived females had a median first SOFA score that was a full point lower than that of males. When stratifying by age and sex it becomes apparent that females under 50 have the lowest median first SOFA score of 4 (3, 7).

Figure 11. The Last SOFA score in patients who survived stratified by sex only, and by age and sex



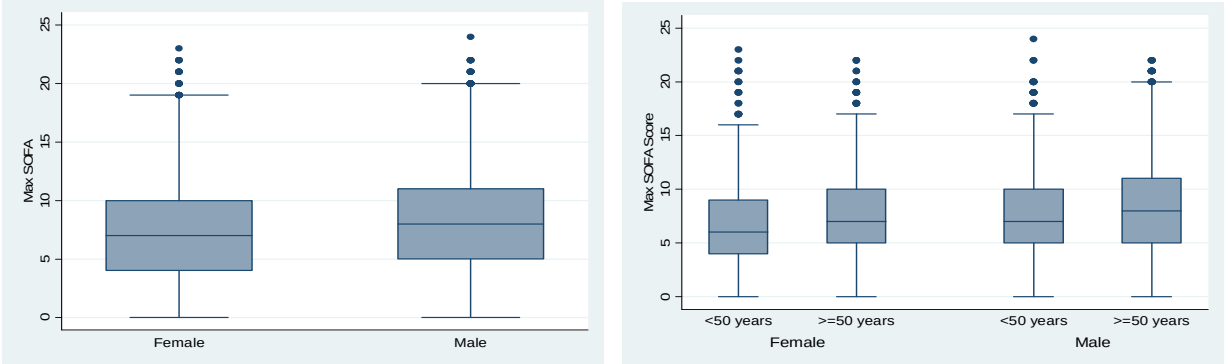
The p-value of the Mann Whitney rank sum test suggests there is a significant difference in the median last SOFA score in men compared to women, this difference is not obvious when looking at the box plots.

Figure 12. The Average SOFA score in patients who survived stratified by sex only, and by age and sex



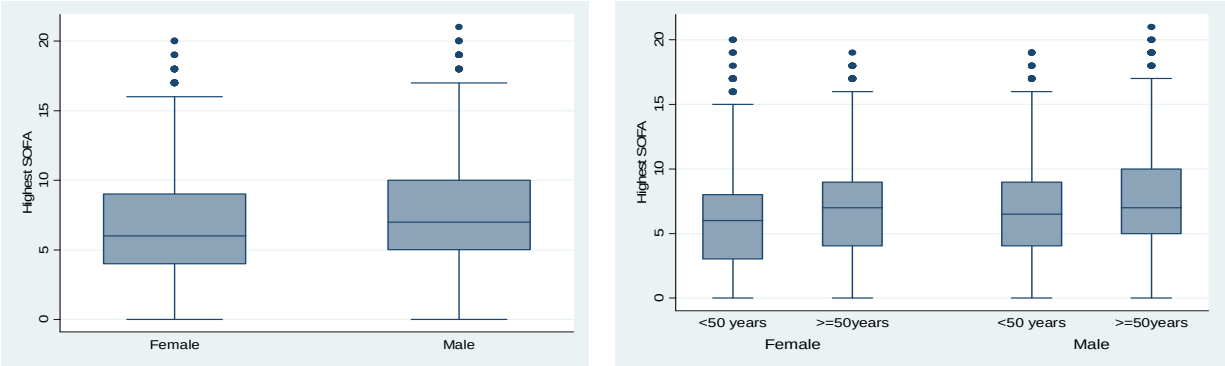
Amongst patients who survived, females under 50 years of age have the lowest median average SOFA score at a median of 4 (3, 6).

Figure 13. The Max SOFA score in patients who survived stratified by sex only, and by age and sex



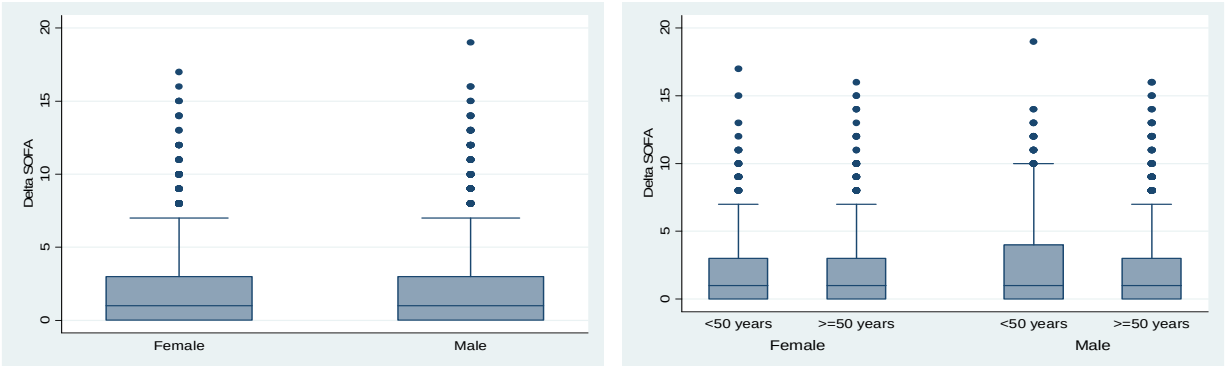
The median Max SOFA score amongst patients who survived is lower in females than in males, this difference is apparent in the box plot above. When stratifying by age and sex females under 50 years of age have the lowest median Max SOFA score of 6 (4, 9) and males over 50 years of age have the highest median Max SOFA score at 8 (5, 11).

Figure 14. The Highest SOFA score in patients who survived stratified by sex only, and by age and sex



Females have a lower median Highest SOFA score compared to males as shown in Table 5 and Figure 14. When stratifying by age and sex females under 50 years of age have a median highest score of 6.5 (4, 9) which is the lowest score of the four groups.

Figure 15. The Delta SOFA score in patients who survived stratified by sex only, and by age and sex



It is difficult to discern a difference in median delta SOFA score between males and females from either Table 5 or Figure 15. The Mann Whitney rank sum test has given a significant p-value of 0.0021. Compared to the other SOFA scores, however, it is difficult to discern any differences from the table or box plots.

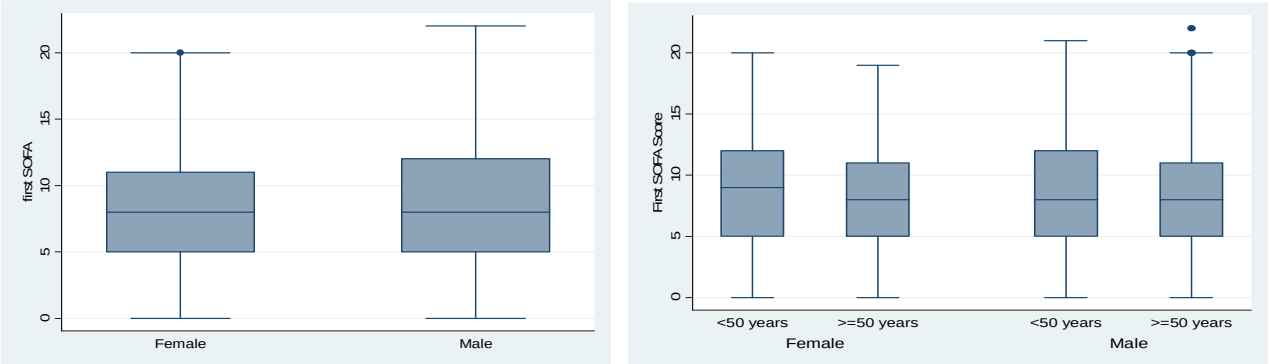
A stratified analysis for patients who died is shown in Table 6.

Table 6. SOFA scores in patients who died stratified by age and sex

SOFA Score, median (IQR)	**All Patients** (n=2, 129)	**Females** (n=920)		**Males** (n=1 ,209)		*P*
		Age <50 (n=163)	**Age >= 50** (n=757)	**Age <50** (n=222)	**Age >=50** (n= 987)	
First SOFA	8 (5, 11)	8 (5, 11)		8 (5, 12)		0.0031
		9 (5, 12)	8 (5, 11)	8 (5, 12)	8 (5, 11)	
Last SOFA	8 (5, 12)	8 (5, 11)		9 (5, 12)		0.0002
		10 (6, 12)	8 (5, 11)	10 (7, 13)	8 (5, 12)	
Average SOFA	8 (6, 11)	8 (6, 11)		9 (6, 12)		0.0002
		9 (6, 12)	8 (6, 11)	10 (7, 12)	8 (6, 11)	
Max SOFA	12 (8, 15)	11 (8, 15)		12 (9, 16)		0.0006
		12 (10, 16)	11 (8, 15)	12 (9, 16)	12 (9, 15))	
Highest SOFA	11 (8, 14)	10.5 (7, 14)		11 (8, 14)		0.0000
		12 (8, 15)	10 (7, 13)	12 (9, 15)	11 (8, 14)	
Delta SOFA	3 (0, 6)	3 (0, 6)		3 (0, 6)		0.4889
		3 (0, 6)	2 (0, 6)	3 (0, 6)	3 (0, 6)	

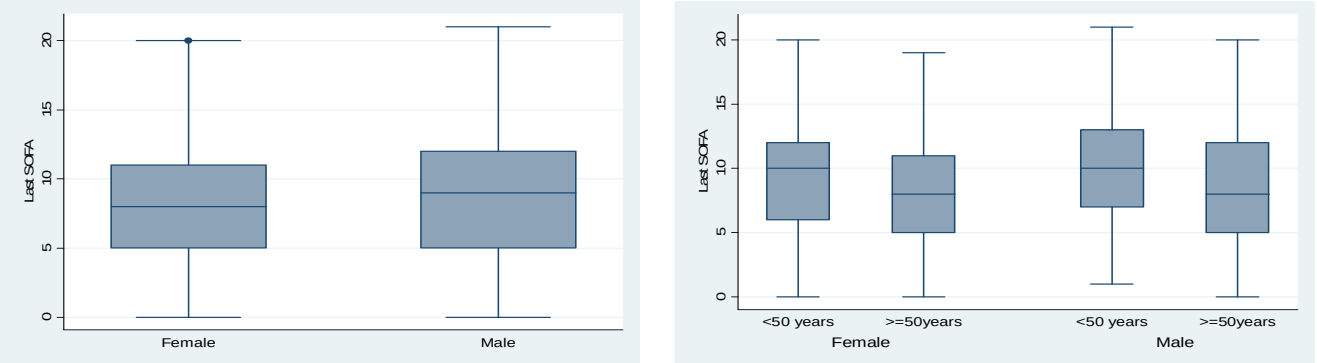
The Mann Whitney two sample ranksum test was used to compare SOFA scores between males and females and was significant, suggesting a difference between males and females, in all cases except for the Delta SOFA score. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. In all cases the results replicated the p-values represented in Table 6. Box plots of these results are shown in Figures 16 to 21.

Figure 16. The First SOFA score in patients who died stratified by sex only, and by age and sex



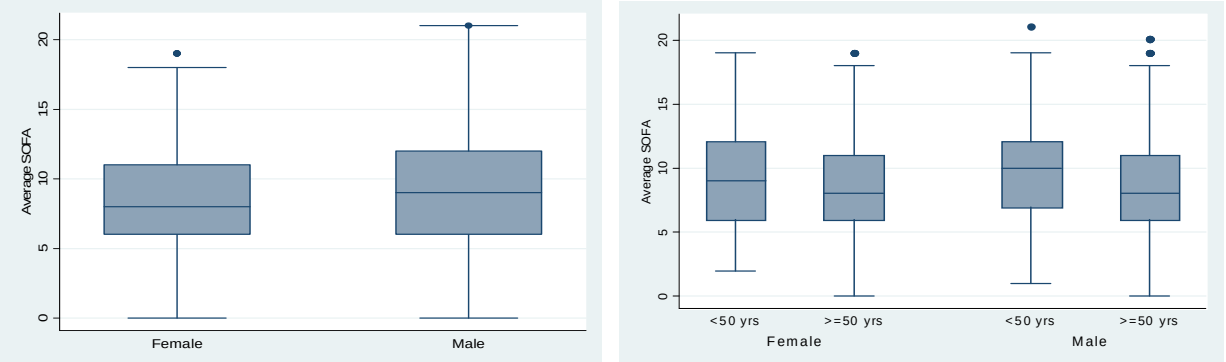
Amongst patients who died there is a significant difference in the median First SOFA score between men and women (p=0.0031). Women under the age of 50 years had the greatest first SOFA score of 9 (5, 12).

Figure 17. The Last SOFA score in patients who died stratified by sex only, and by age and sex



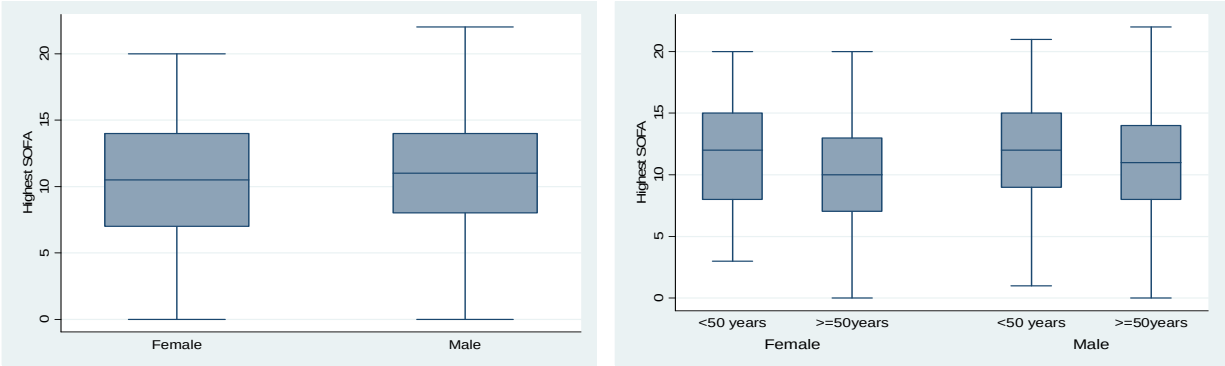
Female patients who died had a lower last SOFA score than males who died (Table 6). When stratifying by age and sex it is apparent that both men and women under 50 years of age have greater Last SOFA scores than men and women over 50 years of age.

Figure 18. The Average SOFA score in patients who died stratified by sex only, and by age and sex



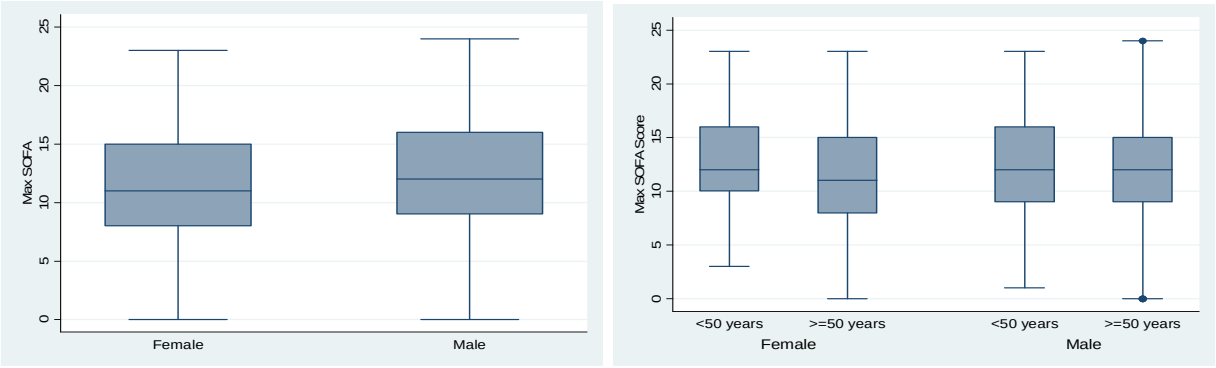
The average SOFA score amongst patients who died is lower in females compared to males (Table 6). When stratifying by age and sex both men and women under 50 years of age have greater last SOFA scores than men and women over 50 years of age.

Figure 19. The Highest SOFA score in patients who died stratified by sex only, and by age and sex



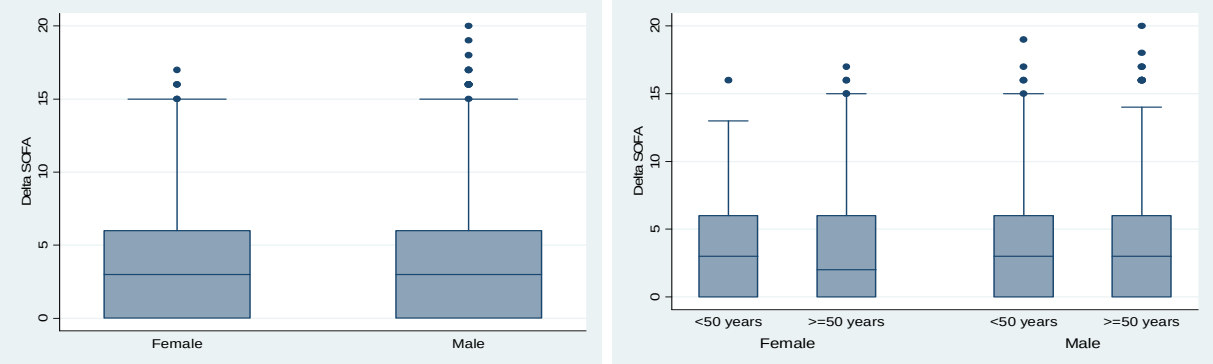
Females who died had a median Highest SOFA score of 10.5 (7, 14) which is slightly lower than that of males at 11 (8, 14). Again, males and females under 50 years who died had greater SOFA scores than their counterparts over 50 years of age.

Figure 20. The Max SOFA score in patients who died stratified by sex only, and by age and sex



Amongst patients who died, females have a lower Max SOFA score than males (Table 6). Patients under 50 years of age have higher median Max SOFA scores than those over 50 years of age (Table 6 and Figure 20).

Figure 21. The Delta SOFA score in patients who died stratified by sex only, and by age and sex



The Mann Whitney Ranksum test gives a non significant p=value of 0.4889 when comparing males and females who died. Additionally there are no discernable differences in the delta SOFA scores between men and women in Table 5 or Figure 19 when stratifying by age and sex suggesting that the delta SOFA score is the same in males and females who died.

Amongst patients who survived and died it is apparent that females have lower SOFA scores compared to males in all cases except when considering the delta SOFA score. The insignificance of the delta SOFA score suggests that the change in SOFA between men and women is not different.

When stratifying the study sample by age and sex it is apparent that younger patients (under 50 years of age) have lower SOFA scores than older patients (greater than 50 years of age) amongst those who survived. When looking at patients who died, however, there is a reversal in this trend with younger patients having higher SOFA scores than older patients.

2.2 Modelling the Clinical Course of Organ Dysfunction in Males and Females

From the stratified analysis it is apparent that females have lower first, last, average, max and highest SOFA scores. The delta SOFA score, however, appears to be similar for males and females. In order to further investigate whether the clinical course of organ dysfunction or rate of change in the daily SOFA score differs between males and females modelling was used. The rate of change in daily SOFA per day for each patient represents a slope. A t-test for the difference in mean slope (and confidence interval for this difference) was performed (response features analysis) and the results are shown in Table 7.

Table 7. Response Features analysis on rate of change in daily SOFA per day for males vs. females

T-test by:	sex	Slope (SE)	95% CI	p-value
Sex	male	-0.40 (0.005)	-0.41, - 0.39	0.0699
	female	-0.38 (0.007)	-0.40, - 0.37	
	difference	0.02 (0.009)	-0.00, 0.03	
Sex, if survived	male	-0.51 (0.006)	-0.52, -0.50	0.0931
	female	-0.50 (0.007)	-0.51, - 0.48	
	difference	0.02 (0.009)	0.00, 0.03	
Sex, if died	male	-0.13 (0.01)	-0.15, -0.11	0.6214
	female	-0.12 (0.01)	-0.14, - 0.09	
	difference	0.01 (0.02)	0.03, 0.05	

The change in daily SOFA per day is the same between males and females (p=0.07) regardless of whether they survived (p=0.09) or died (p=0.6). A response features analysis, however, can not account for missing values or varying lengths of stay and a more accurate model for this situation is the Generalized Estimating Equation (GEE). A GEE model was used to model the population averaged change in mean daily SOFA scores between men and women, and confirms the results of the response features analysis, as shown in Table 8.

Table 8. Generalized Estimating Equation model for change in daily SOFA per day

Model	Variable*	coef (SE)	95% CI	*p*-value
1. All ICU patients	Intercept	6.9 (0.08)	6.7, 7.1	0.000
	Sex	0.59 (0.09)	0.39, 0.78	0.000
	Day	-0.31 (0.01)	-0.33, -0.29	0.000
	Sex x Day	-0.03 (0.01)	-0.05, 0.00	0.080
2. ICU patients who survived	Intercept	6.9 (0.09)	6.8, 7.1	0.000
	Sex	0.57 (0.12)	0.33, 0.81	0.000
	Day	-0.48 (0.02)	-0.51, -0.44	0.000
	Sex x Day	-0.01 (0.02)	-0.06, 0.029	0.520
3. ICU patients who died	Intercept	7.5 (0.12)	7.3, 7.8	0.000
	Sex	0.67 (0.15)	0.36, 0.97	0.000
	Day	-0.12 (0.01)	-0.14, -0.11	0.000
	Sex x Day	-0.00 (0.01)	-0.02, 0.018	0.802
4. ICU patients <50 years old	Intercept	6.8 (0.16)	6.5, 7.1	0.000
	Sex	0.49	0.09, 0.89	0.015
	Day	-0.41	-0.46, -0.36	0.000
	Sex x Day	0.03	-0.04, 0.09	0.387
5. ICU patients >=50 years old	Intercept	6.92 (0.09)	6.8, 7.1	0.000
	Sex	0.62 (0.11)	0.39, 0.84	0.000
	Day	-0.26 (0.01)	-0.29, -0.24	0.000
	Sex x Day	-0.03 (0.02)	-0.06, - 0.01	0.127

* Sex coded as (0) for females (1) for males

These models are represented by the Generalized Estimating Equation shown in Equation 1 below.

Equation 1. GEE for ICU patients who survived or died Hospital Stay

$$\text{Daily SOFA} = \beta_{intercept} + \beta_{sex}(\text{Sex}) + \beta_{day}(\text{Day}) + \beta_{sex*day}(\text{Sex})(\text{Day})$$

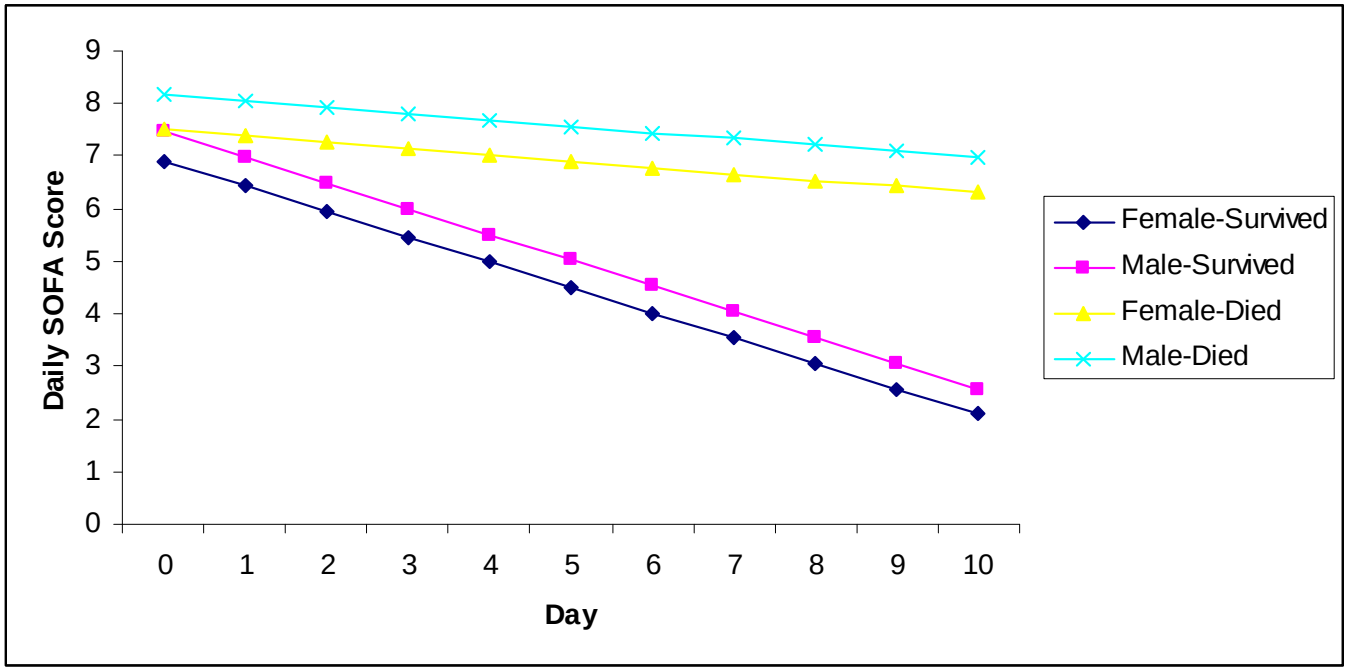
Survived: Daily SOFA= 6.9 + 0.59(Sex) – 0.48(Day) -0.01(Sex)(Day)
Died: Daily SOFA= 7.5 + 0.67(Sex) – 0.12 (Day)-0.00(Sex)(Day)

The outputs for Models 1 through 5 reveal that the course of organ dysfunction, represented by `Sex X Day` interaction term is the same between males and females

because all p-values are non significant. The `Intercept` variable represents Day 0 for females, and `Sex` is the increase in SOFA score for males. In all cases males have a higher daily sofa score, represented by the `Sex` variable.

The mean SOFA at admission in surviving males was 7.5 and in surviving females was 6.9. The mean SOFA at admission for males who died was 8.2 and females who died was 7.5. The mean rate of change of SOFA was -0.49 in surviving males, -0.48 in surviving females, -0.12 in males who died, and –0.12 in females who died. Males and females experience the same change in daily SOFA per day during their ICU stay. Female patients do, however, have daily SOFA scores that are lower than that of males on each day (Figure 22).

Figure 22. Population averaged change in daily SOFA score per day in males and females who survived or died.



Since the Sex X day interaction is not significant, the most parsimonious models do not include this interaction term, as shown in Table 9. Table 9 confirms that males have a

higher SOFA score/day compared to females. The difference is approximately 0.55 in all cases, except amongst patients who died where males have a SOFA score that is 0.76 points greater than females.

Table 9. Generalized Estimating Equation for change in daily SOFA per day not including sexXday interaction.

Model	Variable*	coef (SE)	95% CI	*p*-value
1. All ICU patients	Intercept	6.9 (0.07)	6.8 , 7.1	0.000
	Sex	0.53 (0.09)	0.35, 0.72	0.000
	Day	-0.31 (0.01)	-0.33, -0,30	0.000
2. ICU patients who survived	Intercept	6.9 (0.09)	6.8, 7.1	0.000
	Sex	0.55 (0.12)	0.32, 0.78	0.000
	Day	-0.48 (0.01)	-0.51, -0.46	0.000
3. ICU patients who died	Intercept	8.2 (0.11)	8.0, 8.4	0.000
	Sex	0.76 (0.15)	0.47, 1.05	0.000
	Day	-0.18 (0.00)	-0.19, -0.18	0.001
4. ICU patients <50 years old	Intercept	6.9 (0.15)	6.6, 7.2	0.000
	Sex	0.55 (0.19)	0.16, 0.92	0.005
	Day	-0.40 (0.02)	-0.43, -0.37	0.000
5. ICU patients >=50 years old	Intercept	6.9 (0.08	6.79, 7.11	0.000
	Sex	0.55 (0.11)	0.34, 0.76	0.000
	Day	-0.28 (0.0)	-0.29, -0.26	0.000

2.3 SOFA Component scores

The SOFA score is comprised of 6 component scores obtained from organ systems including; respiration, coagulation, liver, cardiovascular system (CV), central nervous system (CNS) and the renal system. A stratified analysis and modelling was done on the component systems in order to determine whether the clinical course of organ dysfunction in individual systems differed between men and women.

The maximum score obtained in each component system in patients who survived, stratified by age and sex is shown in Table 10.

Table 10. Max SOFA scores in patients who survived, stratified by age and sex

Max Component Scores, median (IQR)	All Patients	Females		Males		*P*
		Age <50	Age >= 50	Age <50	Age >=50	
Respiration	2 (1, 3)	2 (0, 3)		2 (1, 3)		0.0021
		2 (0, 3)	2 (1, 3)	2 (1, 3)	3 (2, 3)	
Coagulation	0 (0, 1)	0 (0, 1)		0 (0, 1)		0.0021
		0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
Liver	0 (0, 0)	0 (0, 0)		0 (0, 0)		0.0001
		0 (0, 0)	0 (0, 0)	0 (0. 0)	0 (0, 0)	
CV	1 (1, 3)	1 (1, 3)		1 (1, 3)		0.6002
		1 (1, 1)	1 (1, 3)	1 (1, 1)	1 (1, 3)	
CNS	3 (2, 4)	3 (2, 4)		3 (2, 4)		0.0000
		3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	
Renal	0 (0, 1)	0 (0, 0)		0 (0, 1)		0.0000
		0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	

The Mann Whitney two sample ranksum test was used to compare SOFA component scores between males and females and was significant in all cases, except for the cardiovascular system, suggesting that males and females have different median SOFA scores in all other systems. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. In all cases the results replicated the p-values represented in Table10.

The distribution of first day and delta component scores for males and females is shown for patients who survived is shown in Figures 23 through 28.

Figure 23. Percentage of first SOFA respiration scores and Delta SOFA respiration scores in males and females who survived

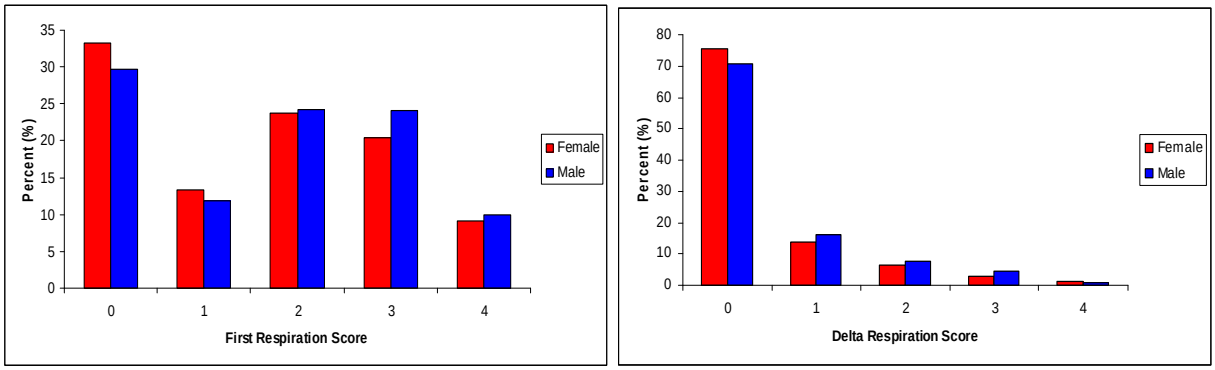


Figure 24. Percentage of first SOFA coagulation scores and Delta SOFA coagulation scores in males and females who survived.

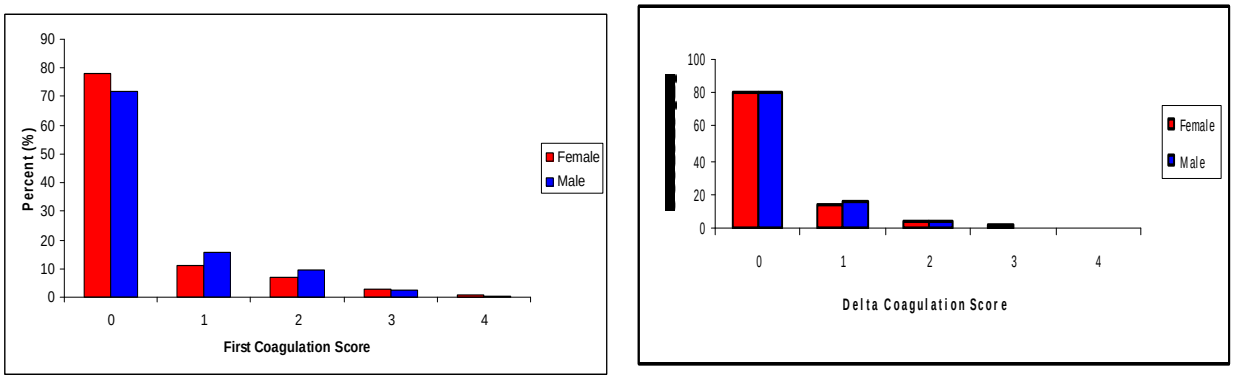


Figure 25. Percentage of first SOFA liver scores and Delta SOFA liver scores in males and females who survived

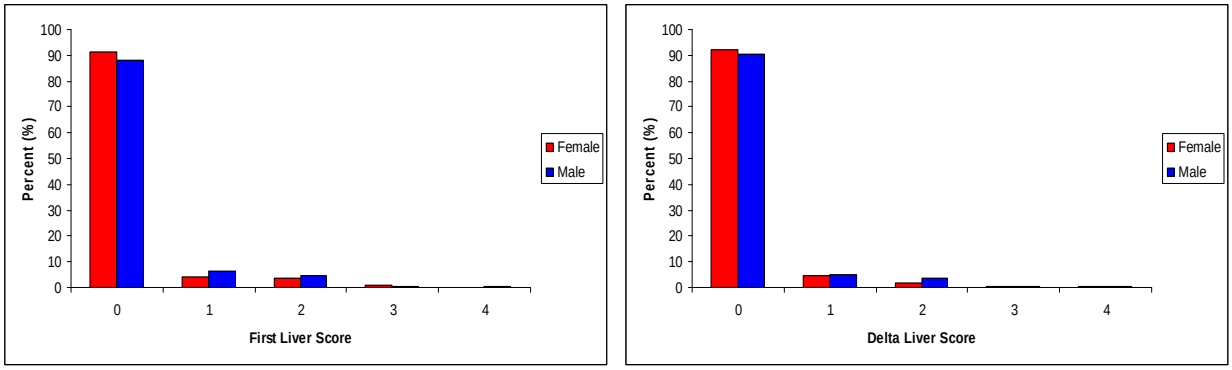


Figure 26. Percentage of first SOFA cardiovascular scores and Delta SOFA cardiovascular scores in males and females who survived

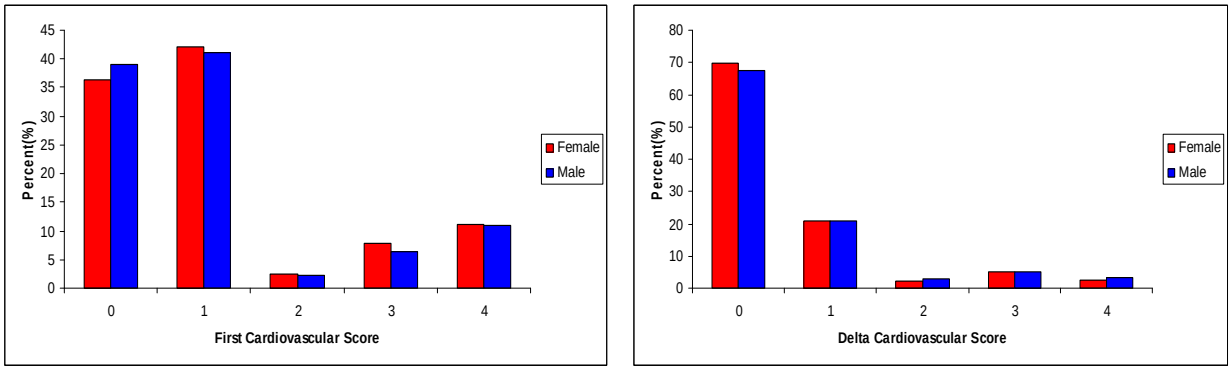


Figure 27. Percentage of first SOFA CNS scores and Delta SOFA CNS scores in males and females who survived

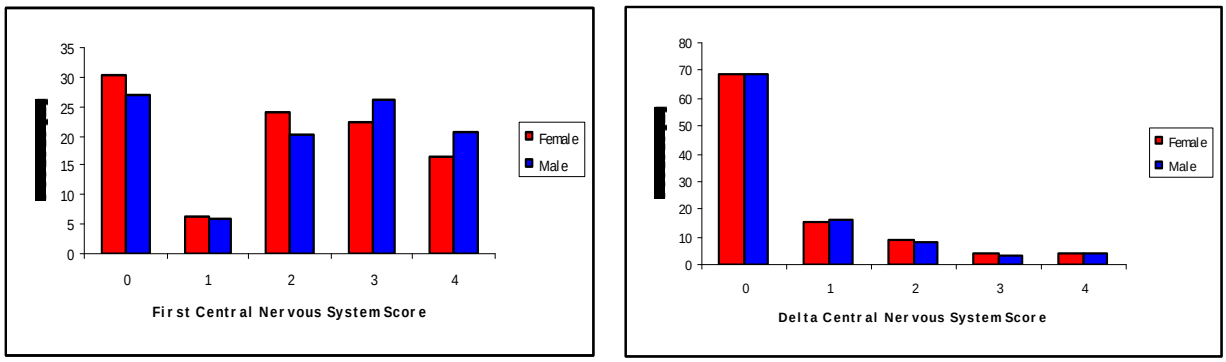
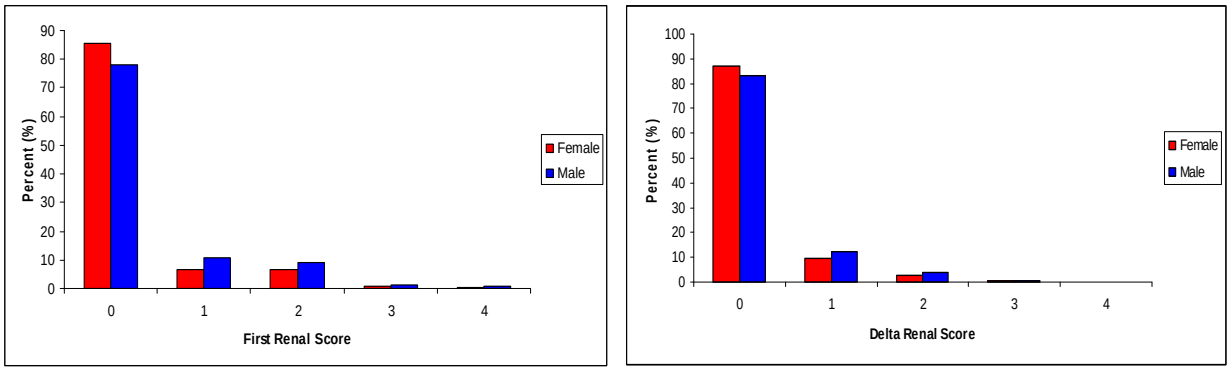


Figure 28. Percentage of first SOFA Renal scores and Delta SOFA Renal scores in males and females who survived



Although the First SOFA component scores vary in the above graphs between males and females, the delta SOFA scores are generally equal.

The maximum score obtained in each component system in patients who died, stratified by age and sex is shown in Table 11.

Table 11. Max SOFA component scores in patients who died, stratified by age and sex

Max Component Scores, median (IQR)	All Patients	Females		Males		*P*
		Age <50	Age >= 50	Age <50	Age >=50	
Respiration	3 (2, 4)	3 (2, 4)		3 (2, 4)		0.0002
		3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	
Coagulation	1 (0, 2)	1 (0, 2)		1 (0, 2)		0.5543
		1 (0, 3)	1 (0, 2)	1 (0, 2)	0 (0, 2)	
Liver	0 (0, 1)	0 (0, 1)		0 (0, 1)		0.2414
		0 (0, 2)	0 (0, 1)	0 (0, 1)	0 (0, 0)	
CV	4 (1, 4)	4 (1, 4)		4 (1, 4)		0.0729
		4 (1, 4)	4 (1, 4)	4 (3, 4)	3 (1, 4)	
CNS	4 (3, 4)	4 (3, 4)		4 (3, 4)		0.0527
		4 (4, 4)	4 (3, 4)	4 (4, 4)	4 (3, 4)	
Renal	1 (0, 2)	0 (0, 2)		1 (0, 2)		0.0000
		0 (0, 1)	1 (0, 2)	0 (0, 2)	1 (0, 2)	

The Mann Whitney two sample ranksum test was used to compare SOFA component scores between males and females and was not significant in all cases, except for the renal and respiratory systems, suggesting that males and females who died do not have differing median SOFA scores in all other cases. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. This is considered a more conservative test and in all cases the results replicated the p-values represented in Table5.

The distribution of first day and delta component scores for males and females is shown for patients who died is shown in Figures 29 through 35.

Figure 29. Percentage of first SOFA respiration scores and Delta SOFA respiration scores in males and females who died

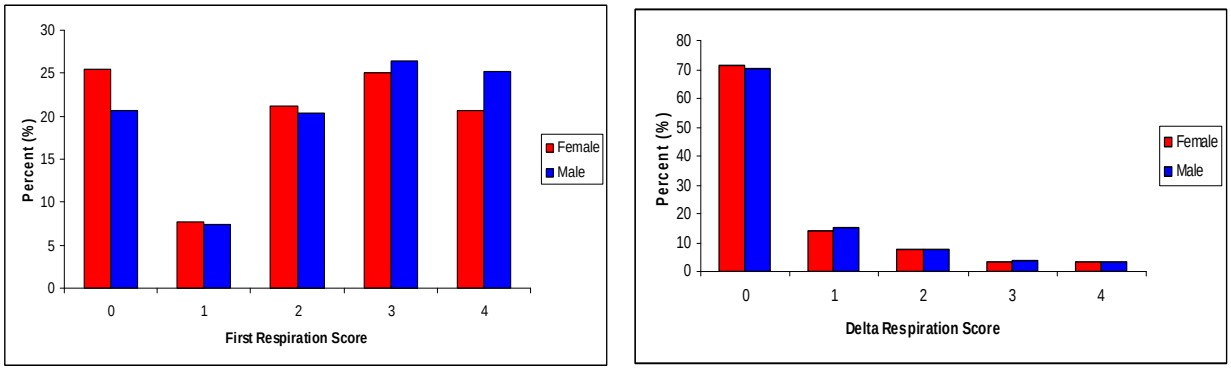


Figure 30. Percentage of first SOFA coagulation scores and Delta SOFA coagulation scores in males and females who died

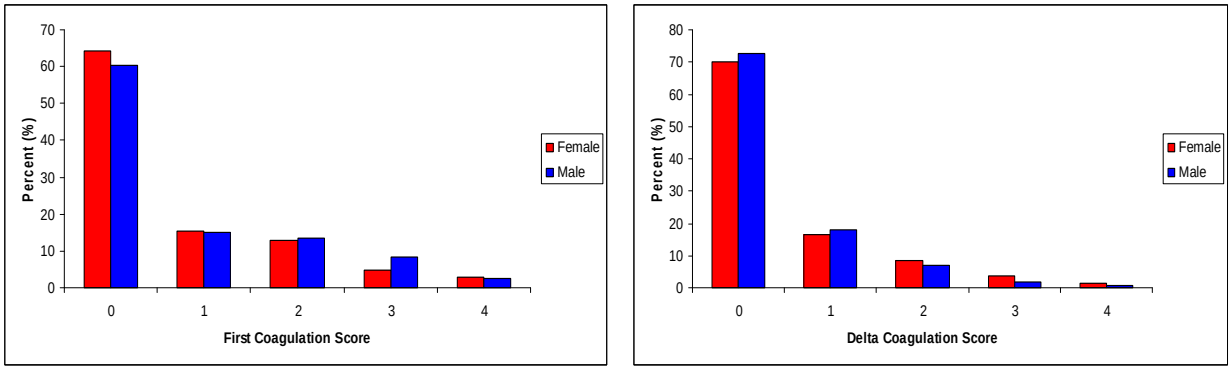


Figure 31. Percentage of first SOFA liver scores and Delta SOFA liver scores in males and females who died

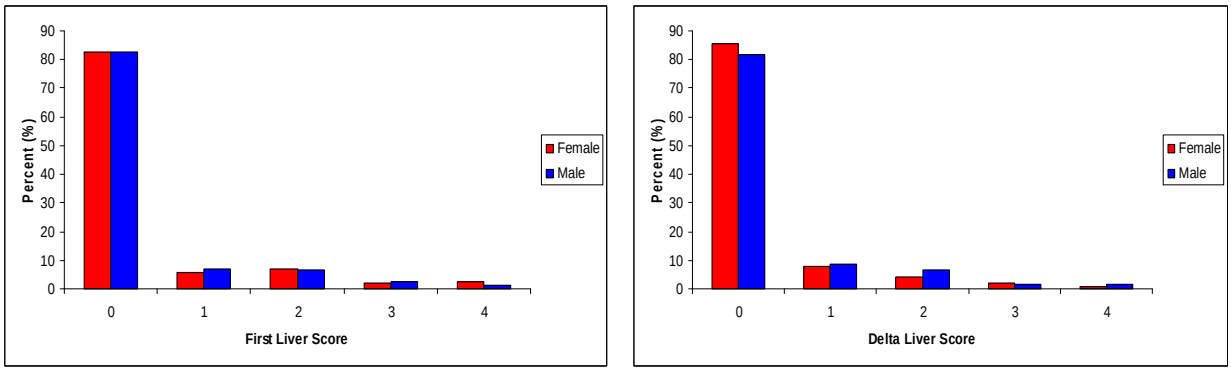


Figure 32. Percentage of first SOFA cardiovascular scores and Delta SOFA cardiovascular scores in males and females who died

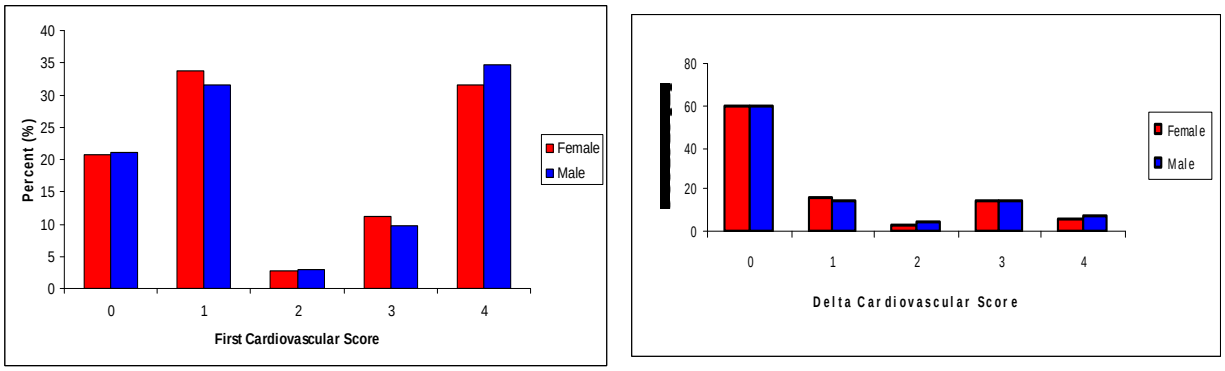


Figure 33. Percentage of first SOFA CNS scores and Delta SOFA CNS scores in males and females who died

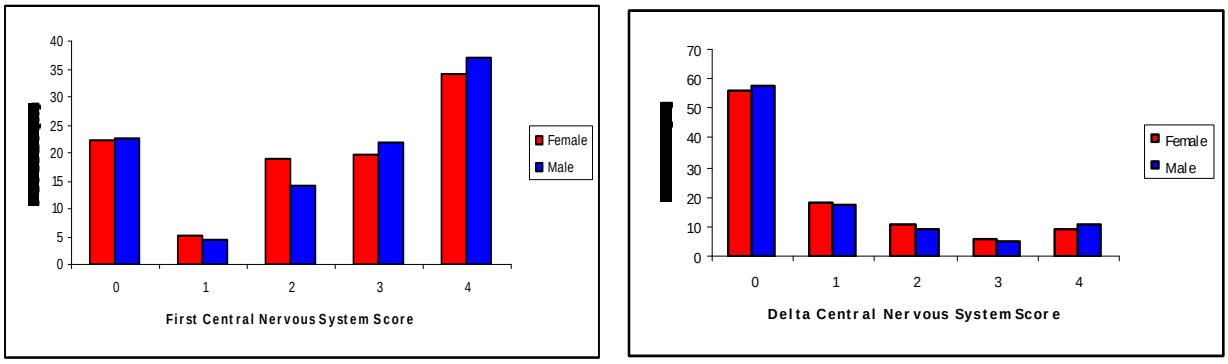
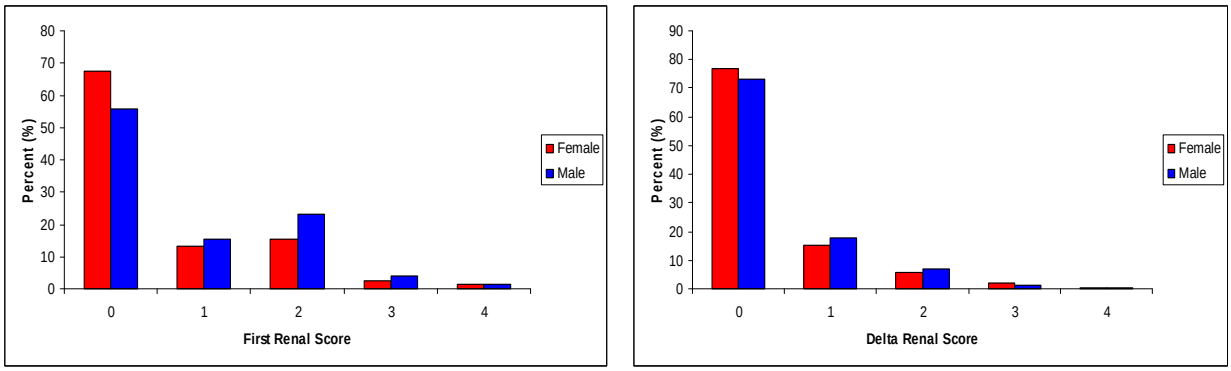


Figure 34. Percentage of first SOFA Renal scores and Delta SOFA Renal scores in males and females who died



Delta SOFA scores appear similar between males and females in all cases. There are apparent differences in the percentage of males vs. females at in the renal and respiratory scores.

A GEE model was run for each SOFA component system for patients who survived or died and the results are shown in Table 12.

Table 12. Generalized Estimating Equation model for change in SOFA component scores per day

		Survived			Died		
Model	Variable	coef (SE)	95% CI	*p*-value	coef (SE)	95% CI	*p*-value
Respiration	Intercept	1.9 (0.03)	1.9, 2.0	0.000	2.0 (0.04)	1.88, 2.04	0.000
	Sex	0.26 (0.04)	0.18, 0.35	0.000	0.2 (0.05)	0.10, 0.30	0.000
	Day	-0.14 (0.01)	-0.15, -0.13	0.000	-0.06 (0.01)	-0.08, -0.05	0.000
	Sex x Day	-0.02 (0.01)	-0.0, -0.0	0.032	-0.01 (0.01)	-0.03, 0.01	0.299
Coagulation	Intercept	0.44 (0.02)	0.41, 0.47	0.000	0.66 (0.03)	0.60, 0.72	0.000
	Sex	0.05 (0.02)	0.01, 0.09	0.023	0.04 (0.04)	-0.04, 0.11	0.335
	Day	-0.03 (0.00)	-0.03, -0.03	0.000	-0.02 (0.00)	-0.02, -0.01	0.000
	Sex x Day	-0.01 (0.00)	-0.01, -0.00	0.029	0.00 (0.00)	-0.00, 0.00	0.596
Liver	Intercept	0.15 (0.01)	0.12, 0.17	0.000	0.32 (0.03)	0.26, 0.37	0.000
	Sex	0.04 (0.01)	0.02, 0.07	0.000	0.06 (0.04)	-0.01, 0.13	0.104
	Day	-0.005 (0.001)	-0.01, -0.00	0.000	-0.00 (0.00)	-0.01, -0.00	0.006
	Sex x Day	-0.005 (0.001)	-0.01, -0.00	0.000	-0.02 (0.00)	-0.02, -0.02	0.000
CV	Intercept	1.5 (0.03)	1.5 , 1.6	0.000	1.9 (0.04)	1.90, 2.01	0.000
	Sex	-0.02 (0.04)	-0.09, 0.05	0.636	0.05 (0.05)	-0.06, 0.15	0.377
	Day	-0.11 (0.00)	-0.11, -0.09	0.000	-0.04 (0.00)	-0.05, 0.04	0.000
	Sex x Day	-0.003 (0.006)	-0.013, 0.08	0.654	0.00 (0.00)	-0.00, 0.01	0.159
CNS	Intercept	2.3 (0.02)	2.2, 2.3	0.000	2.3 (0.03)	2.2 , 2.3	0.000
	Sex	0.29 (0.03)	0.22, 0.35	0.000	0.14 (0.04)	0.06, 0.22	0.001
	Day	-0.1 (0.00)	-0.10, -0.09	0.000	0.01 (0.00)	0.00, 0.01	0.001
	Sex x Day	-0.01 (0.00)	-0.02, -0.08	0.000	-0.00 (0.00)	-0.01, 0.01	0.926
Renal	Intercept	0.31 (0.02)	0.28, 0.35	0.000	0.67 (0.03)	0.62, 0.72	0.000
	Sex	0.10 (0.02)	0.06, 0.14	0.000	-0.02 (0.03)	-0.08, 0.05	0.631
	Day	-0.01 (0.00)	-0.01, -0.00	0.000	-0.02 (0.00)	-0.02, -0.02	0.000
	Sex x Day	-0.004 (0.00)	-0.01, -0.00	0.000	0.01 (0.00)	0.00, 0.01	0.000

Patients who died had greater SOFA component scores and less improvement compared to patients who survived as seen in Figure 33 and Figure 34. The temporal change in SOFA component scores is not considered clinically significant for any of these component scores. Females do, however have lower SOFA scores than males during the course of organ dysfunction when looking at the central nervous system, respiratory system, and the renal system.

Figure 35. Population averaged change in daily SOFA component scores per day in males and females who survived

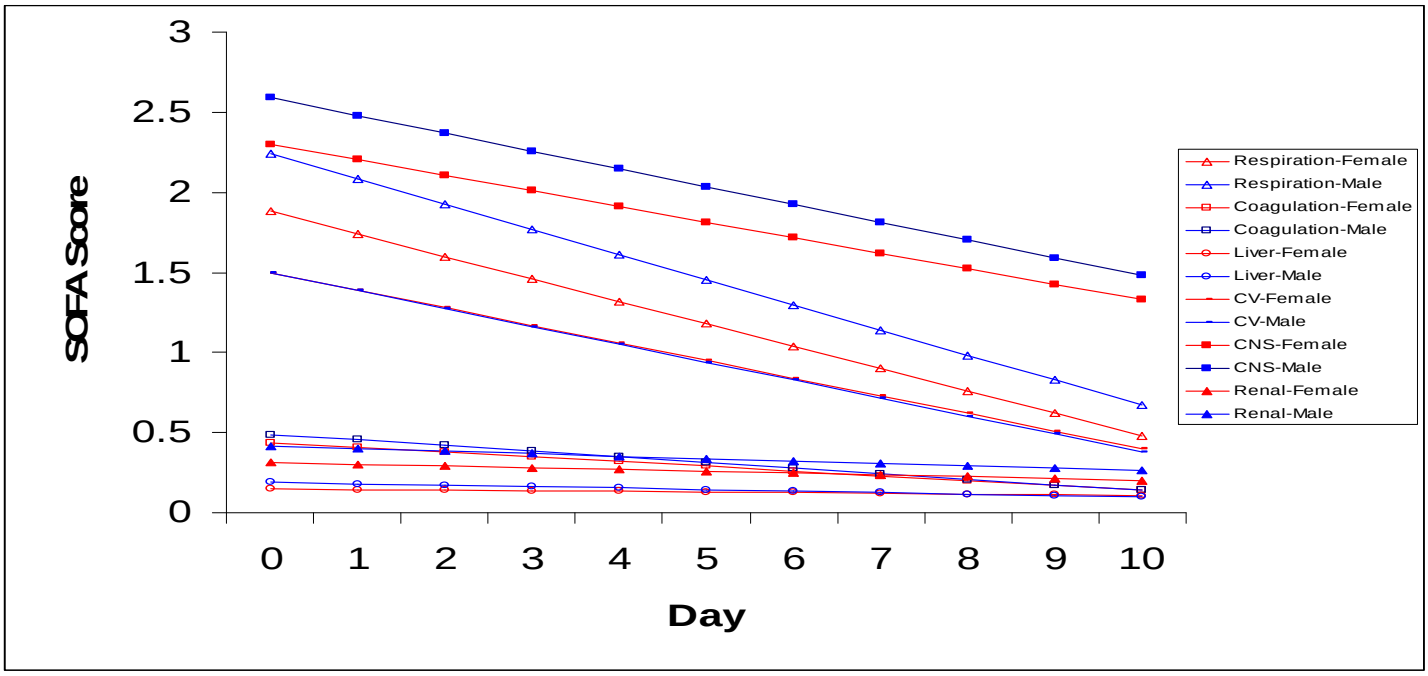
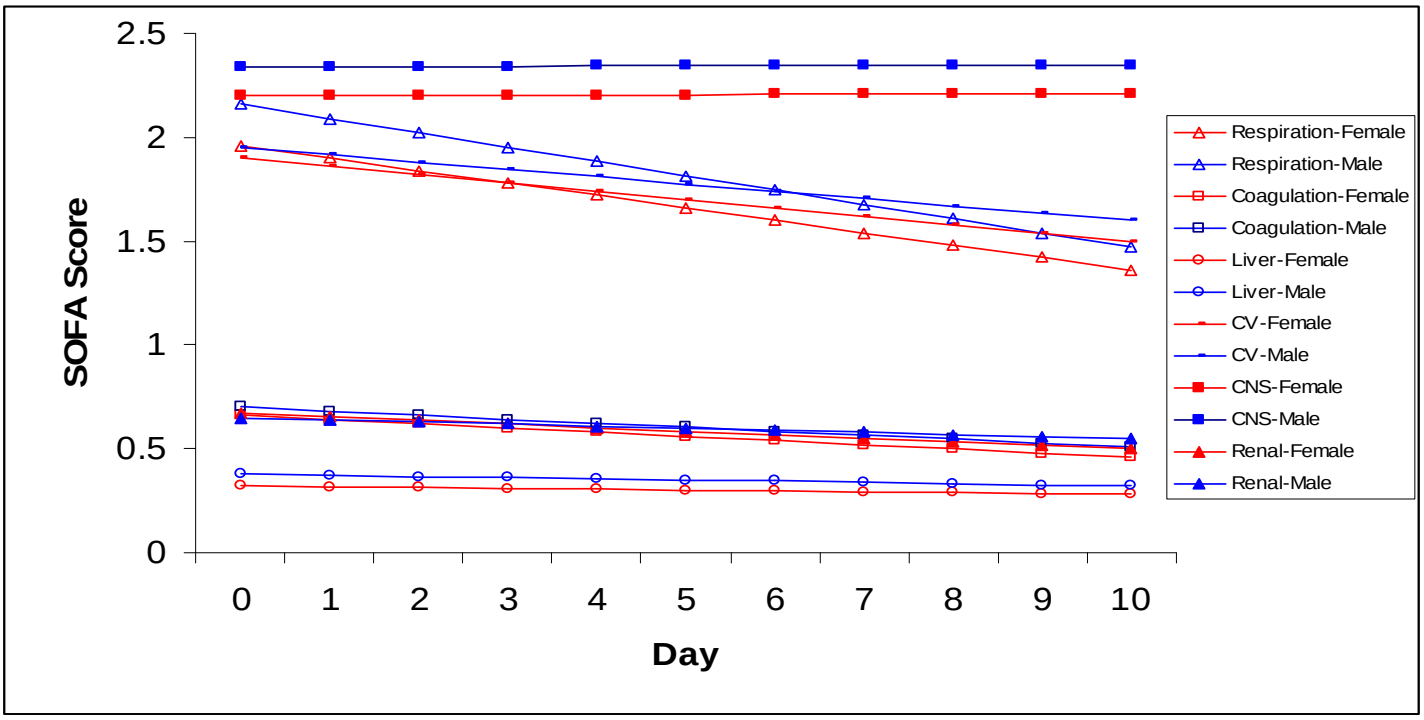


Figure 36. Population averaged change in daily SOFA component scores per day in males and females who died



3. Secondary Research Question # 1

Amongst trauma and sepsis patients only; is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit?

3.1 Trauma Patients

3.1.1 Trauma Patient Demographics

A total of 771 patients were admitted to one of Calgary`s multisystem ICUs with a diagnoses of trauma between July 1, 2002 and June 30, 2006 and met the inclusion criteria for this study. The characteristics of these patients are shown in Table 13. The study sample consists of 22.2% females and 77.6% males.

Table 13. Trauma Patient Demographics

Variable	All Patients	Females	Males
No. of patients (%)	771	173 (22.2)	598 (77.6)
Age, yrs, mean (SD),	41.2 (19.3)	43.6 (21.0)	40.5 (18.8)
APACHE II score	19.6 (7.1)	21.2 (7.4)	19.1 (7.0)
TISS Admission	39.6 (12.4)	40.2 (13.8)	39.5 (12.0)
Length of ICU stay, days (median, quartile)	4.2 (1.8,10.5)	4.7 (1.8, 11.7)	4.1 (1.8, 9.9)

Two sided, two sample, t-tests were used on all normally distributed variables. The difference in APACHE II score between males and females on day of admission was found to be 0.6 (95%CI: 0.89, 3.3) among trauma patients and the p value is rejected at the 5 % significance level. A difference in admission APACHE of 0.6, however, is not clinically significant. A difference of 3.1 (95%CI: -0.2, 6.4) years in age was found between males and females, the probability that this difference exists due to chance alone is 6.2% (p=0.062) so the null hypothesis was not rejected at the 5% level of significance. A difference of 0.7 (95%CI: -1.4, 2.8) was found between males and females in the admission TISS score, this difference is not significant at the 5% significance level (p=0.5053). Since LOS was positively skewed the Mann Whitney two

sample rank sum test was used. There was not a significant difference in LOS (p=0.4200) with females staying longer.

ICU and hospital mortality for this sample is shown in Table 14. No significant difference was found in the proportion of male vs. female mortality in either the ICU (p=0.893) or the hospital (p=0.654) using a chi squared test. Additionally no significant difference in ICU mortality was found amongst males and females under 50 years of age (p=0.393) or over 50 years of age (p=0.296). Similarly no difference in hospital mortality was found for the under 50 (p=0.352) and over 50 (p=0.428) groups.

Table 14**.** ICU and Hospital Mortality for trauma patients stratified by age and sex

ICU Mortality (%)	**All Patients** (n=771)	**Females** (n=173)		**Males** (n= 922)	
	14.1	**Age <50** (n=111)	**Age >= 50** (n=62)	**Age <50** (n=428)	**Age >=50** (n= 170)
		14.5		14.1	
		14.4	14.5	11.5	20.6
Hospital Mortality (%)	**All Patients** (n=745)	**Females** (n=167)		**Males** (n=578)	
	18.0	**Age <50** (n=108)	**Age >= 50** (n=59)	**Age <50** (n=413)	**Age >=50** (n= 165
		19.2		17.7	
		15.7	25.4	12.4	30.9

3.1.2 Stratified Analysis

A stratified analysis for trauma patients who survived is shown in Table 15. A significant difference was not found for any of the SOFA variants except for the average SOFA score, but the median average SOFA score obtained by males and females is the same.

Table 15. SOFA scores in trauma patients who survived stratified by age and sex

SOFA Score, median (IQR)	**All Patients** (n=611)	**Females** (n=135)		**Males** (n=476)		***P***
		< 50 yrs (n=91)	**>= 50 yrs** (n=44)	**< 50 yrs** (n=362)	**>= 50 yrs** (n=114)	
First SOFA	5 (4, 7)	5 (4, 7)		5 (4, 7)		
		5 (4, ,7)	6 (4, 8)	5 (4, 7)	6 (4, 7)	0.4855
Last SOFA	4 (3, 6)	4 (3, 5)		4 (3, 6)		
		4 (3, 5)	4 (2.5, 5)	4 (3, 6)	4 (3, 6)	0.0454
Average SOFA	5 (4, 6)	5 (4, 6)		5 (4, 6)		
		5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	0.0099
Max SOFA	8 (5, 10)	7 (6, 10)		8 (5, 10)		
		7 (6, 10)	8 (6, 10.5)	8 (5, 11)	7 (6, 10)	0.8993
Highest SOFA	7 (5, 9)	7 (5, 9)		7 (5, 9)		
		7 (5, 8)	7 (5, 9)	7 (5, 9)	7 (6, 9)	0.5646
Delta SOFA	2 (0, 4)	2 (0, 4)		2 (0, 4)		
		2 (1, 4)	1 (0, 3)	2 (0, 4)	1 (0, 3)	0.5928

A similar stratified analysis was completed for patients who died in hospital and this is shown in Table 16. A significant difference was only found in the last SOFA score (p=0.038). All other SOFA variants were not different between males and females who died. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. In all cases the results replicated the p-values represented in Tables 15 and 16.

Table 16. SOFA scores in trauma patients who died stratified by age and sex

SOFA Score, median (IQR)	**All Patients** (n=134)	**Females** (n=32)		**Males** (n=102)		***P***
		< 50 yrs (n=17)	**>= 50 yrs** (n=15)	**< 50 yrs** (n=51)	**>= 50 yrs** (n=51)	
		9 (5, 11)		8 (6, 12)		
First SOFA	8 (6, 11)	10 (7, 12)	8 (4, 9)	8 (6, 12)	8 (5, 11)	0.834
		7 (5, 9.5)		9 (7, 12)		
Last SOFA	9 (6, 11)	9.5 (6, 11)	6.5 (4, 8)	10 (8, 13)	7 (5, 10.5)	0.0308
		8.5 (6, 10)		8.5 (7, 11)		
Average SOFA	8.5 (7, 11)	10 (8, 12)	8 (5, 9)	10 (8, 12)	8 (6, 11)	0.442
		10 (8, 12)		11 (9, 14)		
Max SOFA	11 (8, 13)	12 (9, 12)	9 (6, 11)	12 (10, 14)	11 (8, 13)	0.0941
		10 (7.5, 11.5)		11 (8, 13)		
Highest SOFA	11 (8, 12)	11 (9, 12)	9 (6, 10)	12 (10, 13)	10 (7, 12)	0.0644
		2 (0, 4)		2 (0, 4)		
Delta SOFA	2 (0, 4)	2 (1, 4)	1 (0, 3)	2 (0, 4)	1 (0, 3)	0.7529

3.1.3 Modelling the clinical course of organ dysfunction in trauma patients

A GEE model was used to determine whether the clinical course of organ dysfunction amongst trauma patients is different for males vs. females. The results are shown in Table 17.

Table 17. Generalized Estimating Equation model for change in SOFA component scores per day in trauma patients

Model	Variable	coef (SE)	95% CI	*p*-value
1. All trauma patients	Intercept	7.29 (0.28)	6.7, 7.8	0.000
	Sex	0.66 (0.32)	0.03, 1.3	0.040
	Day	-0.32 (0.04)	-0.39, -0.25	0.000
	Sex x Day	-0.05 (0.04)	-0.13 0.03	0.194
2. Trauma patients who survived	Intercept	6.88 (0.32)	6.3, 7.5	0.000
	Sex	0.59 (0.36)	-0.12, 1.3	0.103
	Day	-0.31 (0.04)	-0.39, -0.23	0.000
	Sex x Day	-0.06 (0.05)	-0.14, 0.03	0.241
3. Trauma patients who died	Intercept	8.44 (0.57)	7.3, 9.6	0.000
	Sex	0.63 (0.66)	-0.66, 1.91	0.338
	Day	-0.28 (0.07)	-0.42, -0.15	0.000
	Sex x Day	-0.03 (0.08)	-0.18, 0.12	0.722

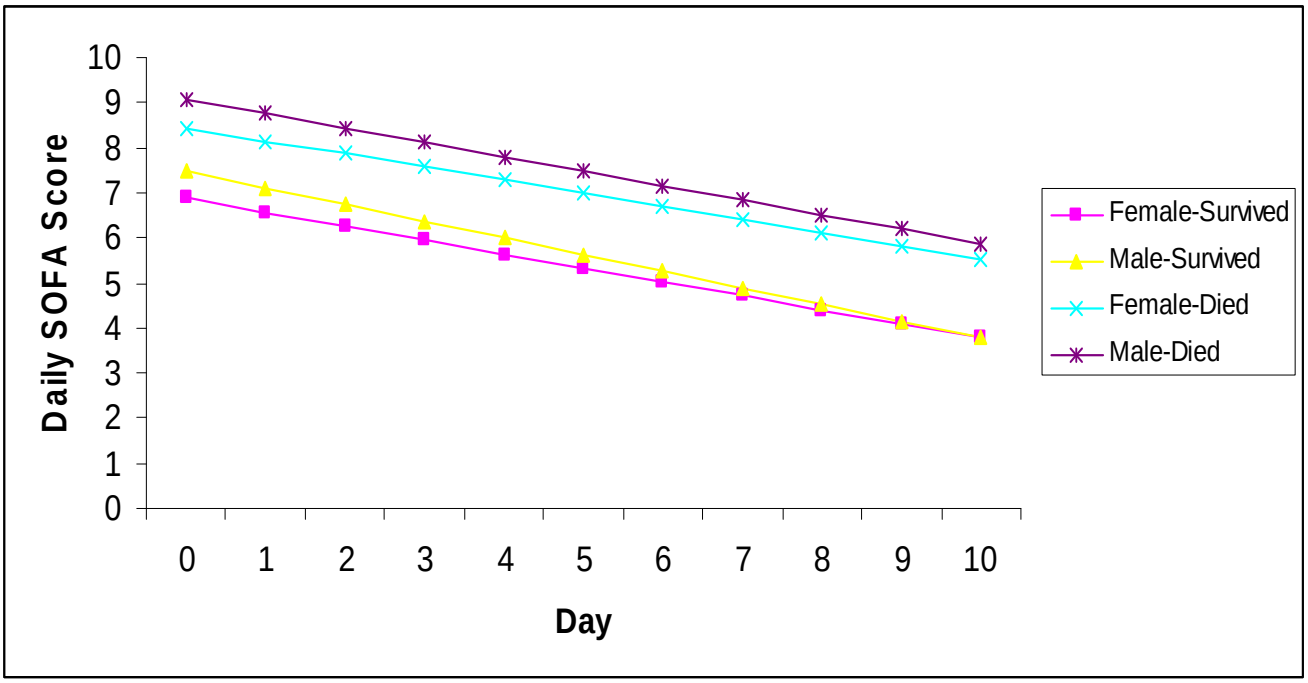
Equation 2. Generalized Estimating Equations for trauma patients

$$\text{Daily SOFA} = \beta_{intercept} + \beta_{sex}(\text{Sex}) + \beta_{day}(\text{Day}) + \beta_{sex*day}(\text{Sex})(\text{Day})$$

Survived: Daily SOFA= 6.9 + 0.59(Sex) – 0.31(Day) -0.06(Sex)(Day)
Died: Daily SOFA= 8.4 + 0.63(Sex) – 0.28 (Day)-0.03(Sex)(Day)

The GEE model shows that the clinical course of organ dysfunction for trauma patients is not significantly different between the sexes. The change in daily SOFA per day is the same for males and females. The difference in daily SOFA scores between males and females who survived (p=0.103) or died (p=0.338) is also not significant. The clinical course of organ dysfunction for male and female trauma patients is depicted in Figure 37.

Figure 37. Population averaged change in daily SOFA score per day in male and female trauma patients who survived or died.



The GEE model was then run without the sexXday interaction term, confirming that sex was still not significantly different amongst patients who survived or died as shown in Table 18.

Table 18. Generalized Estimating Equation for change in daily SOFA amongst Trauma patients, not including sex X day interaction.

Model	Variable	coef (SE)	95% CI	*p*-value
1. All trauma patients	Intercept	7.3 (0.29)	6.8, 7.9	0.000
	Sex	0.70 (0.32)	0.06, 1.34	0.031
	Day	-0.36 (0.02)	-0.39, -0.32	0.000
2. Trauma patients who survived	Intercept	8.5 (0.55)	7.4, 9.6	0.000
	Sex	0.52 (0.61)	-0.69, 1.7	0.404
	Day	-0.29 (0.03)	-0.36, -0.23	0.000
3. Trauma patients who survived	Intercept	7.2 (0.32)	6.6, 7.8	0.000
	Sex	0.71 (0.36)	-0.00, 1.42	0.051
	Day	-0.38 (0.02)	-0.43, -0.34	0.000

3.2 Sepsis Patients

3.2.1 Sepsis Patient Characteristics

Figure 38. Sepsis Patient Demographics

Variable	All Patients	Females	Males
No. of patients (%)	1, 689	767 (45.4)	922 (54.6)
Age, yrs, mean (SD),	62. 8 (16.0)	62.7 (16.18)	62. 9 (15.8)
APACHE II score	27.2 (9.6)	26.9 (9.4)	27.4 (9.8)
TISS Admission	38.9 (13.6)	38.5 (13.1)	39.2 (14.1)
Length of ICU stay, days (median, quartile)	4.3 (1.9, 8.8)	4.4 (1.9, 8.6)	4.2 (2.0, 9.0)

Two sided, two sample, t-tests were used on all normally distributed variables. The difference between males and females in age was 0.2 (95%CI: -1.3, 1.7) the chance of observing this difference due to chance alone is 86.6% so the null hypothesis was not rejected and the difference is not considered statistically different. The difference in the admission APACHE II score between men and women was 0.5 (95%CI: -1.4, 0.42) and this difference is also not considered statistically significant (p=0.2330). The admission TISS score differed by 0.7 (95%CI: -0.6, 2.0). This difference occurs by chance 29.8% of the time and the null hypothesis is not rejected (p=0.2979). Since LOS was positively skewed the Mann Whitney two sample rank sum test was used. There was not a significant difference in LOS (p=0.9903).

ICU and hospital mortality for this sample is shown in Table 20. No significant difference was found in the proportion of male vs. female mortality in either the ICU (p=0.059) or the hospital (p=0.1900) using a chi squared test. Additionally no significant difference in ICU mortality was found amongst males and females under 50 years of age (p=0.204) or over 50 years of age (p=0.157). No difference in hospital mortality was found for the under 50 (p=0.780) and over 50 (p=0.232) groups.

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Table 19. ICU and Hospital Mortality in sepsis patients stratified by age and sex

	All Patients (n=1, 689)	**Females** (n=767)		**Males** (n= 922)	
ICU Mortality (%)	23.9	**Age <50** (n=168)	**Age >= 50** (n=599)	**Age <50** (n=185)	**Age >=50** (n= 737)
		21.8		25.7	
		10.1	25.0	14.6	28.5
	All Patients (n=1, 594)	**Females** (n=724)		**Males** (n=870	
Hospital Mortality (%)	37.5	**Age <50** (n=154)	**Age >= 50** (n=570)	**Age <50** (n=173)	**Age >=50** (n= 697)
		35.8		39.0	
		20.1	40.0	21.4	43.3

3.2.2 Stratified Analysis

A stratified analysis for all sepsis patients who survived is shown in Table 20.

Table 20. SOFA scores in sepsis patients who survived stratified by age and sex

SOFA Score, median (IQR)	**All Patients** (n=996)	**Females** (n=465)		**Males** (n=531)		***P***
		< 50 yrs (n=123)	**>= 50 yrs** (n=342)	**< 50 yrs** (n=136)	**>= 50 yrs** (n=395)	
First SOFA	7 (4, 9)	7 (4, 9)		7 (5, 10)		0.0074
		7 (3, 9)	7 (4, 9)	7 (4, 10)	7 (5, 10)	
Last SOFA	4.5 (2, 6)	4 (2, 6)		5 (3, 7)		0.0041
		4 (2, 6)	4 (2, 6)	4 (2, 6.5)	5 (3, 7)	
Average SOFA	6 (4, 8)	5 (4, 7)		6 (4, 8)		0.0003
		5 (3, 7)	5 (4, 7)	6 (5, 8)	6 (4, 8)	
Max SOFA	9 (6, 13)	9 (6, 12)		10 (7, 13)		0.006
		8 (4, 13)	9 (6, 12)	10 (7, 14)	10 (7, 13)	
Highest SOFA	8 (6, 11)	8 (5, 11)		9 (6, 12)		0.0048
		8 (4, 12)	8 (6, 11)	9 (6, 12)	9 (6, 11)	
Delta SOFA	1 (0, 4)	1 (0, 4)		1 (0, 4)		0.9665
		1 (0, 3)	1 (0, 3)	1 (2, 4)	1 (0, 4)	

The Mann Whitney two sample ranksum test was used to compare SOFA scores between males and females and was significant in all cases, except for delta SOFA, suggesting that males and females have different median SOFA scores but the change in SOFA score is the same.

A stratified analysis for sepsis patients who died is shown in table 21. The Mann Whitney two sample ranksum test was used to compare SOFA scores between males and females and was significant in all cases, except for first and delta SOFA. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. In all cases the results replicated the p-values represented in Tables 20 and 21.

Table 21. SOFA scores in sepsis patients who died stratified by age and sex

SOFA Score, median (IQR)	**All Patients (n=598)**	**Females** (n=259)		**Males** (n=339)		***P***
		< 50 yrs (n=31)	**>= 50 yrs** (n=228)	**< 50 yrs** (n=37)	**>= 50 yrs** (n=302)	
		10 (6, 12)		10 (7, 13)		
First SOFA	10 (6, 12)	9 (7, 12)	10 (6, 12)	12 (7, 15)	10 (7, 13)	0.1780
		8.5 (5, 12)		10 (6, 14)		
Last SOFA	9 (6, 13)	8 (5, 12)	9 (5, 12)	10 (6, 15)	10 (6, 13)	0.0083
		9 (6, 12)		10 (7, 13)		
Average SOFA	10 (7, 13)	10 (6, 13)	9 (6, 12)	12 (10, 15)	10 (7, 13)	0.0086
		13 (10, 17)		14 (11, 17)		
Max SOFA	14 (10, 17)	15 (9, 18)	13 (10, 17)	17 (14, 19)	14 (11, 17)	0.0175
		12 (8, 15)		13 (10, 15)		
Highest SOFA	12 (9, 15)	12 (8, 16)	12 (9, 14)	15 (13, 19)	12 (10, 15)	0.0072
		2 (0, 5)		3 (1, 6)		
Delta SOFA	3 (1, 6)	2 (2, 6)	2 (0, 5)	6 (1, 8)	3 (1, 6)	0.0873

3.2. 3 Modelling the clinical course of organ dysfunction in sepsis patients

A GEE model was created to determine whether the clinical course of organ dysfunction differed between male and female sepsis patients.

Table 22. Generalized Estimating Equation model for change in SOFA component scores per day in sepsis patients

Model	Variable	coef (SE)	95% CI	*p*-value
1. All Sepsis patients	Intercept	7.6 (0.15)	7.3 7.9	0.000
	Sex	1.1 (0.19)	0.73 1.51	0.000
	Day	-0.22 (0.01)	-0.23 -0.20	0.000
	Sex x Day	-0.06 (0.01)	-0.08 -0.05	0.000
2. Sepsis patients who survived	Intercept	7.9 (0.24)	7.5 8.2	0.000
	Sex	0.47 (0.24)	0.01 0.94	0.045
	Day	-0.44 (0.02)	-0.48 -0.40	0.018
	Sex x Day	0.06 (0.03)	0.01 0.12	0.000
3. Sepsis patients who died	Intercept	8.8 (0.2)	8.4 9.2	0.000
	Sex	1.2 (0.28)	0.63 1.8	0.000
	Day	-0.09 (0.00)	-0.10 -0.09	0.000
	Sex x Day	-0.08 (0.00)	-0.09 -0.07	0.000

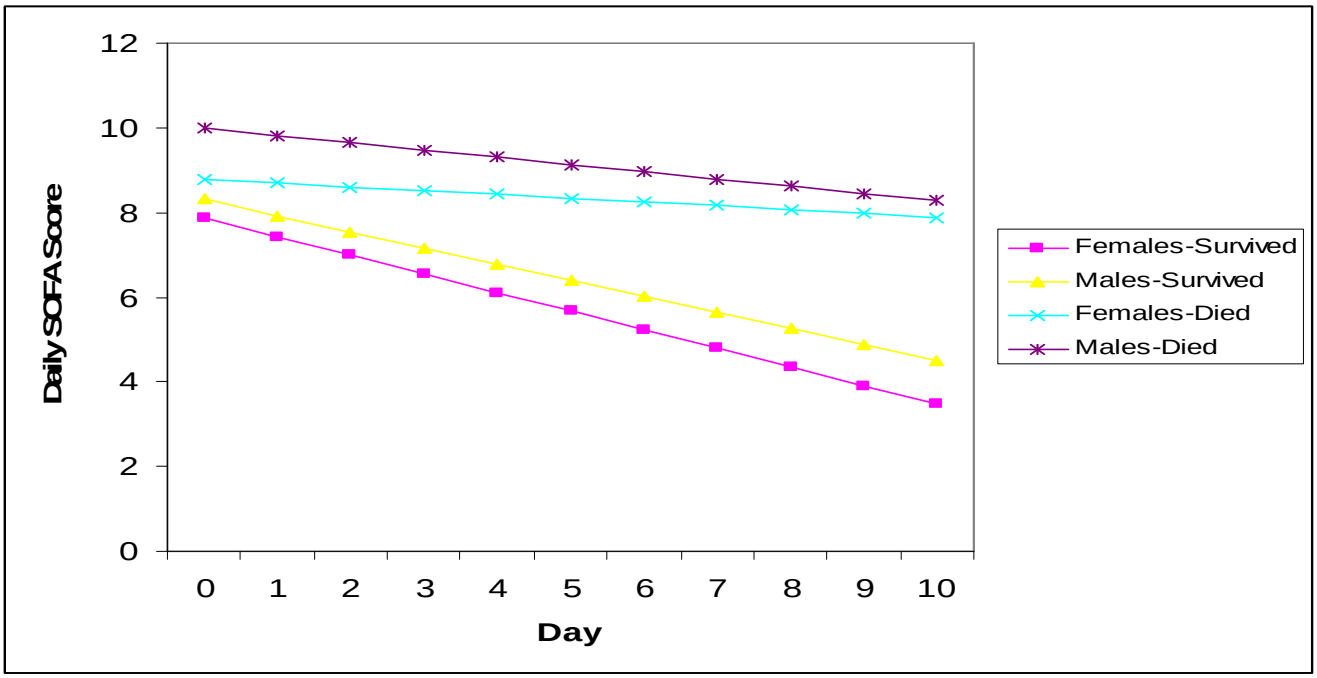
Equation 3. Generalized Estimating Equations for sepsis patients

Daily SOFA= βintercept + βsex(Sex) + βday(Day) + βsex*day(Sex)(Day)

Survived: Daily SOFA= 7.9 + 0.47(Sex) – 0.44(Day) -0.06(Sex)(Day)
Died: Daily SOFA= 8.8 + 1.2(Sex) – 0.09 (Day)-0.08(Sex)(Day)

Females with sepsis who survive have an initial SOFA score of 7.9, compared to 8.37 in males, while Females who died have an initial SOFA of 8.8 compared to 10.0 in males. The change in daily SOFA per day is significantly different between males and females with females who survive changing -0.44/day and males who survive -0.38/day. Amongst patients who died females changed -0.09/day and males -0.17/day. Resultantly the clinical course of organ dysfunction between men and women diagnosed with sepsis is significantly different as shown in Figure 39.

Figure 39. Population averaged change in daily SOFA score per day in male and female sepsis patients who survived or died



3.3 Day to Highest SOFA

In order to determine whether males and females reached their highest SOFA score on the same day the 'day to highest SOFA score' was calculated. The median 'day to highest SOFA' and associated p-value obtained from the Mann-Whitney ranksum test are shown in Table 23.

Table 23. Day to Highest SOFA

	Female	Male	P-value
All ICU Patients			
Survived	1 (1, 2)	1(1,2)	0.1057
Died	2 (1, 3)	2 (1, 4)	0.4076
Trauma Patients			
Survived	2 (1, 3)	2 (1, 3)	0.6097
Died	1 (1, 2)	2 (1, 4)	0.0317
Sepsis Patients			
Survived	1 (1, 2)	1 (1, 2)	0.5748
Died	2 (1, 3)	2 (1, 4)	0.1682

Males and females did not have significantly different ‘day to highest SOFA’ values.

4. Secondary Research Question #2: Female Patients

Given that estrogen is considered immunoprotective, is there a difference in the clinical course of multiple organ dysfunction, measured by the SOFA score, amongst women from May 1, 2000 to April 30, 2002, a period of time when HRT was commonly prescribed to women over 50, compared to May 1, 2004 to April 30, 2006, a period of time when HRT is not commonly used?

4.1 Study Sample Characteristics

When considering female patients only, a total of 1, 480 admissions were made during the 2000 to 2002 period and 1, 775 admissions in the 2004-2006 time period. Patient demographics for this sample are shown in Table 24.

Table 24. Patient Demographics for female patients, 2000-2002 and 2004-2006

Variable	All Patients	2000-2002	2004-2006
No. of patients (%)	3, 255	1, 480(45.5)	1, 775 (54.53
Age, yrs, mean (SD),	58.7 (18.3)	59.3(18.4)	58.1 (18.2)
APACHE II score	23.7 (9.1)	24.2 (9.3)	23.3 (9.0)
TISS Admission	35.3 (13.7)	35.2 (14.2)	35.5 (13.3)
Length of ICU stay, days (median, quartile)	2.9 (1.3, 6.6)	2.7 (1.3, 6.3)	2.8 (1.4, 6.8)

Using a two sampled, two sided t-test, it was found that a difference of 1.2 (95% CI: -0.6, 2.5) years in age between females admitted in the two date ranges is not statistically significant (p=0.0816) along with a difference of 0.1 (95%CI: -0.85, 1.05) admission TISS (p=0.60). A difference of 0.9 (95%CI: 0.27, 1.5) was found between females admitted in the two date ranges for the admission APACHE II score. This difference is observed by chance only 1.1% of the time (p=0.01) and the null is rejected at the 5% significance level, suggesting this difference is statistically significant.

ICU and Hospital mortality for this sample are shown in Table 25. Using the chi squared test a significant difference in ICU mortality was found between date ranges (p=0.027) but not in hospital mortality (p=0.179). For patients under 50 a significant difference was not found in ICU mortality (p=0.972) or in hospital mortality (p=0 .618). For patients over 50 ICU mortality was found to be significantly different (p=0.016) but not hospital mortality (p=0.123).

Table 25. ICU and Hospital Mortality in female patients stratified by age and date of admission

ICU Mortality (%)	**All Patients** (n=3, 255)	**2000-2002** (n=1, 480)		**2004-2006** (n= 1, 775)	
	18.0	**Age <50** (n=441)	**Age >= 50** (n=1, 039)	**Age <50** (n=550)	**Age >=50** (n= 1, 225)
		19.7		16.7	
		10.7	23.5	10.7	19.4
Hospital Mortality (%)	**All Patients** (n=3, 075)	**2000-2002** (n=1, 427)		**2004-2006** (n=1, 648)	
	28.3	**Age <50** (n=421)	**Age >= 50** (n=1, 006)	**Age <50** (n=514)	**Age >=50** (n=1, 134)
		29.4		27.3	
		14.0	35.9	15.2	32.7

4.2 Stratified Analysis

A stratified analysis for female patients who survived is shown in Table 26. All SOFA scores are significantly different between the two date ranges, except for the delta SOFA score.

Table 26. SOFA scores in female patients who survived stratified by age and date of admission

SOFA Score, median (IQR)	All Patients (n=2,206)	2000-2002 (n=1007)		2004-2006 (n=1199)		*P*
		< 50 yrs (n=362)	>= 50 yrs (n=645)	< 50 yrs (n=436)	>= 50 yrs (n=763)	
First SOFA	5 (3, 7)	4 (2, 6)	5 (2, 7)	4.5 (3, 7)	6 (3, 8)	0.000
		4 (2, 6)		5 (3, 8)		
Last SOFA	4 (2, 6)	4 (2, 5)	3 (2, 5)	4 (2, 6)	4 (2, 6)	0.0155
		4 (2, 5)		4 (2, 6)		
Average SOFA	4 (3, 6)	4 (3, 5)	4 (3, 6)	4 (3, 6)	5 (3, 6)	0.000
		4 (3, 6)		5 (3, 6)		
Max SOFA	7 (4, 10)	6 (3, 8)	6 (4, 10)	6 (4, 9)	7 (5, 11)	0.000
		6 (4, 9)		7 (5, 10)		
Highest SOFA	6 (4, 9)	5 (3, 7)	5 (4, 8)	6 (4, 8)	7 (5, 9)	0.000
		6 (3, 8)		6 (4, 9)		
Delta SOFA	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.1475
		1 (0, 3)		1 (0, 3)		

A stratified analysis for female patients who died is shown in Table 27. All SOFA scores are significantly different between date ranges except for the delta SOFA score. In order to ensure the accuracy of these statistical differences all variables were dichotomized by their respective medians and fisher exact tests were applied in order to compare males and females above and below the median. In all cases the results replicated the p-values represented in Tables 26 and 27.

Table 27. SOFA scores in female patients who died stratified by age and admission date

SOFA Score, median (IQR)	**All Patients** (n=869)	**2000-2002** (n=420)		**2004-2006** (n=449)		***P***
		< 50 yrs (n=59)	**>= 50 yrs** (n=361)	**< 50 yrs** (n=78)	**>= 50 yrs** (n=371)	
		7 (4, 9)		9 (6, 12)		
First SOFA	8 (5, 11)	8 (5, 10)	7 (4, 9)	10 (6, 13)	8 (6, 11)	0.000
		7 (4, 10)		8 (5, 12)		
Last SOFA	8 (5, 11)	9.5 (7, 10)	7 (4, 9)	8 (5, 12)	8 (5, 12)	0.000
		7 (5, 10)		9 (6, 12)		
Average SOFA	8 (6, 11)	9 (7, 11)	7 (5, 10)	10 (6, 12)	8 (6, 12)	0.000
		10 (7, 13)		12 (8, 15)		
Max SOFA	11 (8, 14)	11 (9, 13)	10 (7, 13)	12 (10, 17)	12 (8, 15)	0.000
		9 (7, 12)		11 (8, 14)		
Highest SOFA	10 (7, 13)	11 (8, 12)	9 (6, 12)	11 (9, 15)	11 (8, 14)	0.000
		2 (0, 6)		2 (0, 5)		
Delta SOFA	2 (0, 5)	3 (0, 7)	2 (0, 5)	3 (0, 6)	2 (0, 5)	0.9479

4.3 Modelling the clinical course of organ dysfunction in females

A GEE model was created to compare the clinical course of organ dysfunction in females admitted between 2000-2002 with females admitted between 2004-2006. SOFA scores in women admitted in 2004-2006 are significantly higher in all models (Table 28) and the clinical course of organ dysfunction is significantly different between the date ranges with surviving females admitted between 2004-2006 having a more dramatic decrease in SOFA score/day.

Table 28. Generalized Estimating Equation model for change in SOFA component scores per day in female patients

Model	Variable*	coef (SE)	95% CI	*p*-value
1. All ICU patients	Intercept	5.4 (0.09)	5.2, 5.5	0.000
	Date	0.94 (0.12)	0.70, 1.17	0.000
	Day	-0.09 (0.003)	-0.10, 0.09	0.000
	Date x Day	-0.045 (0.01)	-0.05, -0.03	0.000
2. ICU patients who survived	Intercept	5.6 (0.13)	5.3, 5.8	0.000
	Date	1.1 (0.17)	0.75, 1.41	0.000
	Day	-0.32 (0.02)	-0.36, -0.28	0.000
	Date x Day	-0.15 (0.03)	-0.20, -0.09	0.000
3. ICU patients who died	Intercept	6.4 (0.15)	6.1, 6.7	0.000
	Date	1.3 (0.2)	0.95, 1.7	0.000
	Day	-0.05 (0.01)	-0.06, -0.04	0.000
	Date x Day	-0.01 (0.01)	-0.03, 0.01	0.216

* Date=0 for 2000-2002, Date=1 for 2004-2006

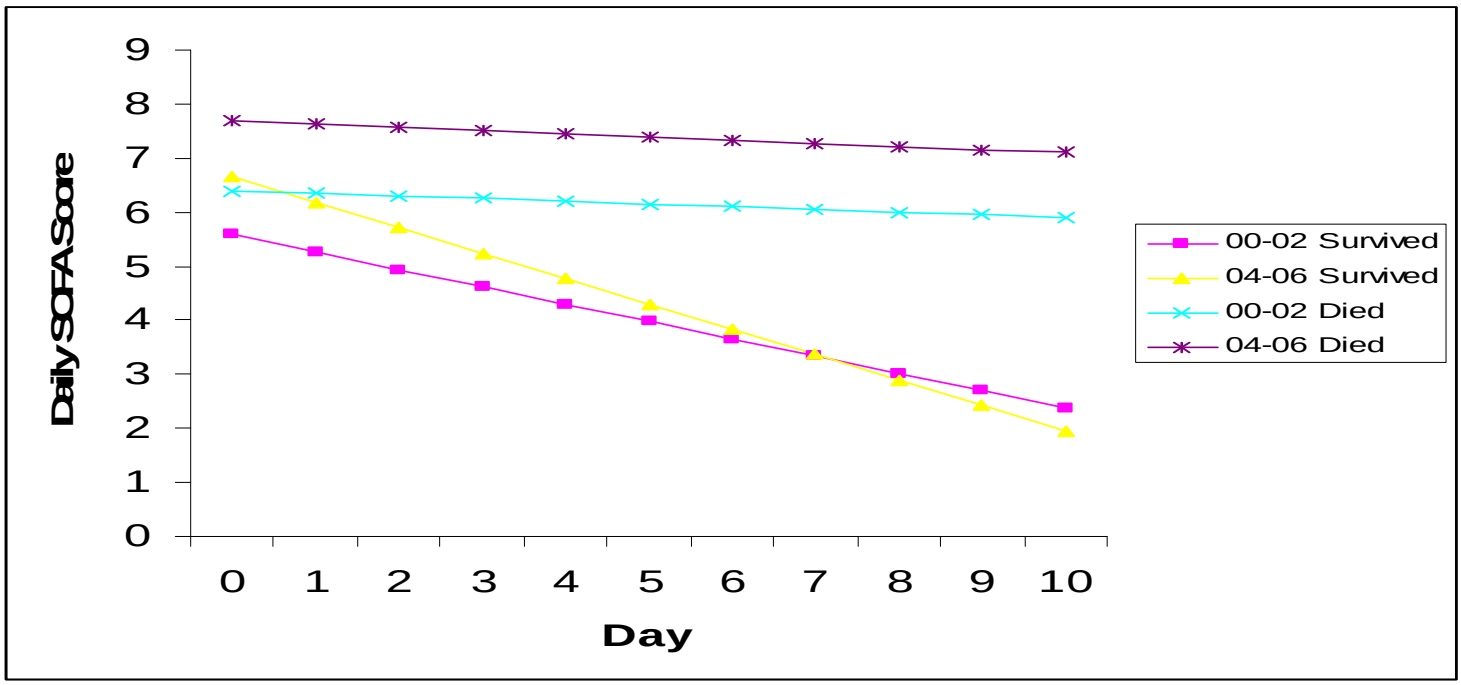
Equation 4. Generalized Estimating Equations for female patients

$$\text{Daily SOFA} = \beta_{intercept} + \beta_{datex}(\text{Date}) + \beta_{day}(\text{Day}) + \beta_{date*day}(\text{Date})(\text{Day})$$

Survived: Daily SOFA= 5.6 + 1.1(Date) – 0.32(Day) -0.15(Date)(Day)
Died: Daily SOFA= 6.4 + 1.3(Sex) – 0.05 (Day)-0.01(Date)(Day)

Figure 40 shows the change in daily SOFA per day for females admitted in both date ranges who either survived or died.

Figure 40. Population averaged change in daily SOFA score per day in female patients admitted between 2000-2002 or 2004-2006 who survived or died in hospital



Females admitted between 2000-2002 had a lower SOFA score upon admission compared to females admitted from 2004-2006, regardless of survivorship status. Females who died had a change in SOFA of -0.5 if admitted between 2000-2002 compared to a change of -0.06 if admitted between 2004-2006. Females who lived had a change in SOFA of -0.32 if admitted between 2000 and 2002 compared to -0.47 if admitted between 2004 and 2006.

F. DISCUSSION

More and more evidence has been accumulated for differential outcomes between males and females in host defence after trauma, haemorrhage, and sepsis in experimental animals. Previous clinical studies examining sex related differences in multiple organ dysfunction, however, have provided inconsistent results. To date it remains unclear whether there are differential outcomes between the sexes in responses to critical injury in humans. Studies investigating differential outcomes between the sexes in MODS have focused on incidence of organ failure as opposed to the clinical course of organ dysfunction. Aspects of morbidity, however, during an ICU stay can provide crucial information regarding a patient's illness and response to treatment. The SOFA score, designed not to predict outcome, but to describe a sequence of complications in the critically ill[5] is a validated measure of morbidity and a quantifiable measure of organ dysfunction. Although any assessment of morbidity must be related to mortality to some degree, the SOFA is not designed specifically to describe organ failure according to mortality.

1. Primary Research Question

Is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit?

1.1 All ICU patients

The results from this study are evidence that the temporal change in organ dysfunction in critically ill ICU patients is not different between males and females. Using a population averaged data model it has been shown that the change in SOFA per day is -0.31 regardless of sex. The results of this study have also confirmed that the temporal change in organ dysfunction is different between survivors and non survivors as previously described.[15] Both males and females who died did not demonstrate

evidence of overall progressive physiologic organ dysfunction before death. The severity of organ dysfunction remained relatively static changing only -0.12 SOFA points per day regardless of sex. Males and females who survived, however, had less physiologic derangement at admission and showed progressive improvement of -0.48 SOFA points per day until discharge regardless of sex. The SOFA score on day of admission (first SOFA) is typically used to establishes baseline severity.[44] Males in this study had SOFA scores that were 0.49 to 0.67 points higher than females from day 1 and throughout the course of stay, regardless of age, sex, day or survivorship. Within each category (survived, died, <50 yrs, ≤50yrs) females had consistently lower scores each day of admission. The difference between males and females is particularly noticeable when taking confidence intervals into account.

Similarly, when considering SOFA component scores: patients who died had greater SOFA component scores and less improvement compared to patients who survived . The temporal change in SOFA component scores was not found to be clinically significant for any of these component scores. Females do, however, have lower SOFA scores than males during the course of organ dysfunction when looking at the central nervous system, respiratory system, and the renal system.

2. Secondary Research Question #1

Amongst trauma and sepsis patients only; is the clinical course of multiple organ dysfunction, as measured by the SOFA score, different for men vs. women admitted to the intensive care unit?

2.1 Trauma Patients

Trauma leads to severe derangements of various immune functions causing immunosuppression and a high susceptibility to infection.[45], [46] MODS is often a complication of trauma.[47] Amongst trauma patients there is not evidence that the temporal change in organ dysfunction in critically ill ICU patients is different between

males and females. Using a population averaged data model it has been shown that the change in SOFA per day in trauma patients is -0.32 regardless of sex. As was seen in all ICU patients there is a baseline difference in SOFA scores with males having a score that is 0.63 points higher than that of females throughout the course of stay (Figure 37). After stratifying according to patients who survived or died in hospital there is still no difference in the clinical course of organ dysfunction between the sexes. There is also not a baseline difference between the sexes as seen in all ICU patients, and when considering all trauma patients despite a difference of 0.59 and 0.63 in survivors and those who died, respectively. This outcome may be due to a lack of power after stratifying by survivorship. The entire sample consists of only 173 females of which 32 died This lack of power is also apparent when looking at the stratified analysis (Table 15 and 16) where, despite obvious differences in scores in some cases, they were not deemed significant. Resultantly, based on the results of this study it is difficult to determine whether the SOFA scores in male and female trauma patients were actually different.

2.2 Sepsis Patients

The temporal change in organ dysfunction in critically ill ICU patients diagnosed with sepsis is statistically different between males and females. Females have lower daily SOFA scores compared to males regardless of survival status. Additionally, amongst survivors, females improved more rapidly than males. From the stratified analysis it is apparent that amongst patients who survived females under 50 had the lowest scores and amongst patients who died males under 50 had the highest scores. Max SOFA measures aggregate severity of organ dysfunction over ICU stay, determines severity of physiologic derangement over a time interval.[44] Females had max sofa scores that were a full point lower than males amongst both survivors and non survivors. Notably, females under 50 who survived had the lowest Max SOFA score.

The results of this study have shown that females, experience less organ dysfunction overall compared to males in the general ICU population and amongst sepsis patients. Reasons for different SOFA scores between males and females may potentially be attributable to a variety of reasons including: differences in immune function between men and women, differences in admission to the ICU, or differences in care and scoring.

3. Immune function in males and females

Several clinical and experimental studies suggest that gender affects humoral and cell mediated immune responses. In the last decade, more and more evidence has been collected to support differential responses in host defence between the sexes after trauma, haemorrhage and sepsis in experimental animals.

Sex hormones seem to alter immune response by influencing the synthesis and release of cytokines. [20 21] The common pathway of multiple organ dysfunction is a severe inflammatory reaction resulting from system cytokine release.[48] In response to the initiation of a proinflammatory reaction with tumor necrosis factor (TNF-α), interleukin (IL) 1 and IL-6 playing the predominant role, the body also mounts an immediate anti-inflammatory response. Among the diverse agents, different interleukins, such as IL-10 have profound antiinflammatory effects that are suggested to control the proinflammatory reaction.[49] Lower levels of proinflammatory cytokines prevent infiltration of immunocompetent cells, an important step in the development of organ dysfunction. Fink et al. have demonstrated that severely injured females under 50 years of age suffered significantly less MODS compared to age-matched males and had lower plasma cytokines.[3] Oberholzer et al. found that the plasma of severly injured males contains significantly higher concentrations of procalcitonin and IL-6 than that of females during the early period after tauma.[2]

High plasma levels of testosterone and low levels of estrogen have also been shown to be associated with the depression of splenic T lymphocyte and splenic macrophage functions. Treatment with testosterone receptor antagonists or estrogen reversed impaired functions in these cells.[50] Experimental studies have also demonstrated improved cell-mediated immune responses in females compared with males.[51] The enhanced immune response in females may be related to the absence of immunosuppressive androgenic hormones, or caused by the immuno-stimulating properties of female sex steroids.[22]

With regards to the underlying mechanisms, receptors for sex hormones have been identified on various immune cells, suggesting direct effects of these hormones on the immune cells. Alternatively, indirect effects of sex hormones, or androgen and estrogen synthesizing enzymes might contribute to gender specific immune responses.

These suggestions are supported by the fact that females under 50 years of age in this study, who survived had lower SOFA scores compared to females over 50 years of age, and when compared to all males. Additionally using a population averaged data model on the entire ICU population and patients diagnosed with sepsis only, it is further apparent that females have overall lower SOFA scores than males. So although the clinical course of organ dysfunction is not different between the sexes, there remain fundamental differences in the SOFA score between males and females which is present from the first day of ICU stay.

There is also a growing body of evidence supporting differences in organ function between the sexes. In this study, specifically, significant differences were found between males and females in the renal, central nervous, and respiratory systems

Significant sex differences have been shown to exist in the response of the kidney to injury. While some of the evidence implicates a protective effect of estrogen, further evidence suggests that testosterone may also have a significant role in renal inury.[52, 53].

The mechanisms by which sex and sex hormones contribute to renal injury remain unclear but preliminary evidence in several different organ systems suggest that sex steroids have an important role in inflammatory injury and programmed cell death. Park et al. demonstrated that female mice are much more resistant to ischemia reperfusion (IR)-induced kidney injury when compared with males.[54] Although estrogen administration partially reduced kidney injury associated with IR, they demonstrated that the presence of testosterone, more than the absence of estrogen, plays a critical role in sex differences in susceptibility of the kidney.[53] Specifically, testosterone has been shown to inhibit the post-ischemic activation of nitric oxide synthetases and the ratio of extracellular signal related kinase to c-jun N-terminal kinase phoshorylation through non androgen receptor mediated mechanisms, leading to increased inflammation and increased functional injury to the kidney.[53] Testosterone has also been shown to accentuate vascular responses to vasopressor agents[55], increase the thromboxane/prostaglandin ratio[56], increase platelet aggregation, and increase monocyte adhesion to endothelial cells[57], properties that can contribute to vasoconstriction and acute renal failure.

The role of female sex hormones in the central nervous system has also been documented. Estrogen is also a potent neuroprotective factor during embryonic and neonatal development[58]. Protective actions of estrogen on the adult brain has more recently been studied in human and animal models. Studies suggest that females are less vulnerable to acute insults associated with cerebral ischemia[59], neurotrauma[60], hypoxia[61] and drug induced toxicity. Understanding that estrogen is a complex pleiotropic hormone that plays important non reproductive functions in the brain is a rapidly emerging field of study. Estrogen protects the central nervous system by directly affection neuronal viability and by acting on other cell types including vascular endothelial cells, astrocytes, and microglia via estrogen receptor dependent and independent mechanisms[62].

It is apparent that there are physiological differences between males and females that may affect the ability to deal with critical illness. The hypothesis of sex based

differences in response to critical injury is based largely on evidence that the immune systems of males and females have fundamental differences which are resultant of either female or male sex hormones. In this study, however, neither hormone levels or cytokine levels were measured. Resultantly it is not possible to determine whether the sex differences noted in this study are due to differences in hormone levels, immune response or other sociological issues such as access to care, exposure to risks, or differences in treatment.

4. Differences in admission to the ICU

Sex differences observed in this study were consistent between males and females. Within females, however there is not a consistently obvious link to menopause, suggesting that the differences may not solely be mediated through sex hormones.

Previous studies have shown that more male patients are admitted to the ICU than female patients. This study confirms this result with 42.6% of admissions attributed to females and 57.4% to males. In experimental and clinical studies[31] mortality rates have been consistently shown to be higher in males than in females. This study however showed no significant differences in mortality rates between sexes when considering all ICU patients, trauma patients or sepsis patients.

Administration to the ICU carries an implicit acceptance of a desire to intervene using measures to subvert a potentially lethal process. ICU care is primarily directed to the support of organs whose dysfunction would otherwise be lethal. It is possible that a female sex advantage may prevent women from developing a more severe state to the same insult, and hence admission to the ICU. Whichmann et al. studied the development of severe sepsis and septic shock in the postoperative state and observed that the mortality from severe sepsis and septic shock was similar for men and women, but more men needed ICU care, and in this subgroup more men developed severe sepsis and septic shock.[63] The detection of any direct sex-related differences between

the sexes may be difficult to detect if patients are studied only in the ICU. Observations from other epidemiologic and clinical sepsis studies have also show reduced incidence of septic complications in women[7]. The incidence of posttraumatic sepsis and MODS in one study was significantly increased in severely injured males with ISS>=25 in comparison to an equivalent group of females.[3] In relation to sepsis specifically, this study found that 45.4% of admissions were female compared to 54.6% males. The fact that sex influences the likelihood of admission to the ICU may support the concept that females are better positioned to deal with critical illness.

5. Differences in care/scoring

In order to determine whether differences in SOFA scores between males and females is due to females presenting to the ICU later than males the `day to highest SOFA` was calculated for all ICU patients, sepsis patients, and trauma patients and was not significantly difference in any case (table 23)..

Multiple studies have shown that despite clinical similarity, health care professionals ICU may not treat the sexes equally. Studies have described different treatments associated with a patient's gender that are not attributable to a patient's clinical characteristics. Differences in treatment associated with a patient's sex have been noted in coronary artery bypass surgery[64], diagnostic workups of pulmonary symptoms[65], prescription of antidepressants and psychiatric assessment[66]. Subtle differences in the ways health professionals treat males and females are also apparent in discretionary areas of care. In one study addressing whether women are treated differently from men, Bernard et al. analyzed resource utilization of hospitalized patients and found that women had longer lengths of stay, yet use fewer ancillary services.[67] If differences in treatment based on a patient's sex and not on clinical characteristics occur consistently, then one may expect that differences in scoring of organ dysfunction may occur consistently.

Two of the hallmarks, and goals of an organ dysfunction scoring system, however is to remove subjectivity in the process of assessing severity. Seven key features of an effective scoring system have been described and include: objectivity, organ specificity, simplicity, availability, patient independence, repeatability and therapeutic independence.[44] Of particular importance to this study are objectivity and patient independence. Objectivity refers to avoiding different interpretation by different physicians and patient independence refers to selecting parameters to be included in a scoring system that are not dependent of patient variables such as gender, age, race etc. Resultantly the variables included in the SOFA score have been chosen carefully. This scoring system consists of laboratory evaluations, and other measures not open to subjectivity (appendix I).

5. Secondary Research Question #2

Given that estrogen is considered immunoprotective, is there a difference in the clinical course of multiple organ dysfunction, measured by the SOFA score, amongst women from May 1, 2000 to April 30, 2002, a period of time when HRT was commonly prescribed to women over 50, compared to May 1, 2004 to April 30, 2006, a period of time when HRT is not commonly used?

The temporal change in organ dysfunction in critically ill ICU patients is significantly different between females who survived admitted between 2000-2002 and 2004-2006, but not significantly different amongst females who died. Females admitted between 2000-2002 had lower SOFA scores than females admitted between 2004-2006. This increase in SOFA score, however, can not be attributed to the reduction in the use of HRT as both women over and under 50 are affected. The higher SOFA scores amongst women in the 2004-2006 date range may be due to an increase in severity of the cases admitted to the ICU from 2000 to 2006, although no studies were found to confirm this and the lower APACHE II scores for women admitted between 2004-2006 compared to 2000-2002 refute this hypothesis

The SOFA score was first used in Calgary Health Region ICU's beginning in 2000 and differences in scoring could potentially be contributed to a period of adjustment during this time. Alternatively, it may have been more useful to determine whether HRT influenced the chances of a female being admitted to the ICU in the first place.

G. LIMITATIONS OF THIS STUDY

The data in the TRACER database was populated prospectively using standardized criteria by individuals unaware of the purpose of this research project. As such, the data should not have suffered systematic measurement bias relevant to the outcome of this project. Standardized data abstraction tools that had been previously validated as well as standardized operational definitions were used throughout this study.

Limitations of this study include that the data has not been collected specifically for this study. The database, however, is robust and contained all of the data elements required for analysis of the research questions. This study also did not directly measure hormone or cytokine levels, making conclusions about differences in hormone levels or immune function difficult. Another limitation is not directly considering hormone replacement therapy, or other exogenous hormone use amongst this patient group, making it difficult to draw concrete conclusions as to why the sex differences do exist.

The study examined the course of organ dysfunction in the ICU, despite the fact that there is the possibility of identifying patients with MODS in the emergency department or admitted to hospital. Admission to the ICU is implicit on severe physical derangement and studying only the ICU population disregards the fact that women may have a lower propensity for admission to the ICU in the first place. There may be important differences in the development of MODS between men and women which are not accounted for when studying the ICU population, this would have underestimated the differences found in this study.

H. CONCLUSION

The clinical course of multiple organ failure depends on the effects of several predictors interacting with each other and with time. Clinical trials should consider that men and women may respond differently to stimuli, although the possible female advantage described in animals has not been definitively described in humans. Additional prospective studies should focus on observing not only sex but also hormonal status (including exogenous hormone use), associated with age and disease status in order to to fully characterize any differences that may exist between males and females during critical care. Further understanding of mechanisms is needed, and future research on sex differences in critical care should focus on understanding the process that lead to the site and type of infection and on understanding whether there are systematic differences in healthcare access and delivery.

Studies to date have focused on MODS as an event, and mortality as the primary outcome when looking at differential outcomes and organ dysfunction. Few studies have considered differential outcomes in males and females in the course of organ dysfunction. This study was a large multi-centre study and has made a contribution to the ongoing discussion and research in this area of intensive care medicine.

APPENDIX I. Calculation of the SOFA Score

SOFA score	1	2	3	4
Respiration				
PaO_2/FiO_2, mmHg	<400	<300	<200	<100
			—— with respiratory support ——	
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin, mg/dl (μmol/l)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (<204)
Cardiovascular				
Hypotension	MAP < 70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system				
Glasgow Coma Score	13–14	10–12	6–9	<6
Renal				
Creatinine, mg/dl (μmol/l) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 ml/day	>5.0 (>440) or <200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

Taken from Vincent et al. (15).

APPENDIX II. Admission Diagnoses used to classify Septic Patients

Skin
To_Sh_Sy
Nec_Faci
Necr_Fas
Nec_Fasc
Fn_Gg_Pt
FoG_PeTi
F_Ga_PeT
FoG_AdW
Cuta_Cel

Shock
Septicae
Sep_Shk

Pneumonia
Pneu_NOI
Bact_Pne

Genito-Urinary
Pyen_Pyo
Perin_Ab
Cy_Py_Ur

Intra abdominal
Vi_I_PVD
Viln_PVD
Tr_SB_Pe
TrP_SmBo
Tr_Ru_Es
TrR_Esop
Tr_LB_PR
TrRP_LaB
TrR_Gast
Tr_Ga_Ru
TrR_Duod
TR_Du_Ru
To_Di_LB
Sp_Ru_Es
SB_Volvu
SB_Intus
SBI_HVA
SB_I_HVA
Repe_abl
Pe_B_T_G
Pe_BT_GB
PaAb_InP
N_T_SB_P
N_T_LBPR
N_I_LBRA
N_I_LBRA
N_Ac_LbR
N_Ac_LbR
G_L_SB_A
Le_SB_An
G_L_Es_A
Le_Es_An
Le_LB_An
LLB_Ana
LB_I_PVD
LB_I_HVA
In_Pe_SB
Inf_Peri
In_Pancr
Inf_Esop
In_Co_Pr
Inf_Chol
Du_Pe_UI
Dive_Dab
App_ApAb
Appe_Abs

APPENDIX IIII. Ethics Approval

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

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2007-07-05

Dr. Christopher J. Doig
Division of Critical Care
Room EG23, Foothills Hospital
Calgary, Alberta

Dear Dr. Doig:

RE: A Study of Differential Outcomes between Sexes in the Clinical Course of Multiple Organ Dysfunction

Ethics ID: E-20996

Student: Ms. U. Dehaeck

The above-named research, including the Thesis Proposal (Thesis Proposal Approval dated May 28, 2007), and Protocol has been granted ethical approval by the Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary, and the Affiliated Teaching Institutions. The Board conforms to the Tri-Council Guidelines, ICH Guidelines and amendments to regulations of the Food and Drugs Act re clinical trials, including membership and requirements for a quorum.

Dr. Christopher Doig-, one of the investigators for this study, is a member of the CHREB but did not participate in the review, was not present during discussion and did not vote on this protocol
Please note that this approval is subject to the following conditions:
(1)consent for access to personal identified health information is not required on grounds considered under Section 50 of the Health Information Act,
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted by **July 05, 2008**, containing the following information:

i) the number of subjects recruited;
ii) a description of any protocol modification;
iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
v) a copy of the current informed consent form;
vi) the expected date of termination of this project.

4) a Final Report must be submitted at the termination of the project.

Please accept the Board's best wishes for success in your research.
Yours sincerely,

Gladys Godlovitch, BA(Hons), LLB, PhD
Chair, Conjoint Health Research Ethics Board

GG/emcg
c.c. Adult Research Committee Dr. P.J.E. Boiteau (information) Research Services Ulrike Dehaeck (Student) Office of Information & Privacy Commissioner

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