The systemic inflammatory response syndrome criteria and their differential association with mortality

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Title: The Systemic Inflammatory Response Syndrome Criteria and Their Differential Association with Mortality

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Study Highlights

Individual or combined SIRS criteria may not be equivalent or interchangeable. In a study of**:** more than 130,00 patients with infection and organ failure, different individual and combinations of SIRS criteria were associated with marked differences in mortality. These differences remained unchanged after adjustment and over time and imply that individual SIRS criteria are not equivalent or interchangeable

Abstract

Purpose: Despite the recent Sepsis-3 consensus, the Systemic Inflammatory Response Syndrome (SIRS) criteria continue to be assessed and recommended. Such use implies equivalence and interchangeability of criteria. Thus, we aimed to test whether such criteria are indeed equivalent and interchangeable.

Materials and Methods: From 2000 to 2015, we identified patients with infection, organ failure, and at least one SIRS criterion in 179 Intensive Care Units in Australia and New Zealand. We studied the association of different SIRS criteria with hospital mortality.

Results: Among 131,016 patients with infection and organ failure, mortality increased from 10.6% for the respiratory rate criterion to 15.8% for the heart rate criterion (P<0.01); from 10.1% for the high leukocyte count criterion to 20.0% for a low count and from 10.1% for a high temperature to 14.4% for a low temperature criterion. With any two SIRS criteria, hospital mortality varied from 11.5% to 30.8% depending on the combination of criteria. This difference remained unchanged after adjustments and was consistent over time.

Conclusions: Different individual and combinations of SIRS criteria were associated with marked differences in hospital mortality. These differences remained unchanged after adjustment and over time and imply that individual SIRS criteria are not equivalent or interchangeable.

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Key words: Sepsis, systemic inflammatory response syndrome, intensive care, critical illness, hospital mortality.

Introduction

Severe sepsis is a major cause of intensive care unit admission and mortality [1, 2]. Until recently, sepsis, severe sepsis and septic shock were defined by the consensus statement of the American College of Chest Physicians and the American Society of Critical Care Medicine in 1992 [3]. Since then, randomized controlled trials in sepsis have used such criteria for patient enrolment [4-11], including the need for at least two Systemic Inflammatory Response Syndrome (SIRS) criteria. The sensitivity of this approach in identifying intensive care unit patients with severe sepsis, however, was recently challenged by a large observational study, which found that one in eight septic patients did not have two or more SIRS criteria [12]. This observation and well documented concerns about specificity [13, 14] have recently led the joint American Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) Task Force on Sepsis to remove the SIRS criteria from the definition of sepsis [15]. Despite such decision, however, strong support remains for the continued use of SIRS criteria [16, 17], and their assessment continues to be reported as part of the diagnosis of sepsis [18], thus fuelling a continuing controversy about the validity and clinical usefulness of such criteria.

Such strong support for the continued application of the SIRS criteria as originally described logically implies that each SIRS criterion must be considered equivalent and interchangeable with another. Thus, for example, patients with an elevated respiratory rate and fever are, by definition, taken to be broadly equivalent in terms of pathophysiological state and mortality risk to patients with a low white cell count and tachycardia (both groups would have 2 SIRS criteria). Whether this assumption is correct has significant bearing on the scientific,

pathophysiological and clinical validity of the SIRS criteria and their continued use, for example, to assist with patient enrolment into sepsis trials. However, the robustness of this assumption for both different individual criteria and different combinations of criteria has never been tested.

We hypothesized that individual SIRS criteria have markedly different associations with hospital mortality in intensive care unit patients with infection and organ failure and that various combinations of two or three SIRS criteria identify septic intensive care unit patients with markedly different mortality risks. Moreover, we hypothesized that the two SIRS criteria (white cell count and temperature) that carry a high or a low value SIRS inclusion trigger have markedly different associations with mortality depending on their fulfilment on the basis of a high vs. low value. Finally, we hypothesized that such differential associations have held steady over more than a decade despite major changes in hospital mortality overall and in each subgroup.

Methods

Study Design

We conducted a retrospective study of intensive care unit (ICU) patients from January 1, 2000, to December 31, 2015, using data from the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD), run by the ANZICS Centre for Outcome and Resource Evaluation [19]. Data were gathered by means of clinical registry surveillance by data collectors for quality-assurance and benchmarking as previously described [12, 20] and capture data on more than 80% of all intensive care unit admissions in ANZ. The study was

approved by the Alfred Hospital Human Research Ethics Committee, Melbourne, Australia, with a waiver of informed consent.

Definitions

We used the consensus definition of the American College of Chest Physicians-Society of Critical Care Medicine to identify patients with sepsis, severe sepsis, and septic shock [3].

First, infection-related diagnoses at intensive care unit admission and confirmed at ICU discharge were defined according to the Acute Physiology and Chronic Health Evaluation (APACHE) III to infer the presence of suspected or proven infection (Supplementary Appendix) [12]. We then defined organ failure in the first 24 hours after ICU admission using the Sequential Organ Failure Assessment (SOFA) score system [12, 20].

We applied the consensus SIRS criteria to data analyses, except for analyses where the criteria with dual nature (high/low) were considered as separate criteria. All patients with infection and organ failure fulfilling at least one SIRS criterion were included into the study.

Statistical analysis

Data are presented as percentages (number), means (standard deviation, SD), medians (interquartile range, IQR) or proportion (95% confidence interval, CI). Chi-square tests for equal proportion, student's t-tests or Wilcoxon Rank Sum test were used to test differences. No assumptions were made for missing or unavailable data, with multivariable analysis performed on patients with complete data only. Where data were missing, the available the number of data points has been reported.

To determine the nature of the relationship between SIRS criteria and hospital mortality, logistic regression models were fitted adjusting for year of admission and patient severity with patients nested within site and site treated as a random effect. To estimate patient severity independent of SIRS components, each patient's predicted risk of death was calculated with SIRS components removed in accordance with the Australian and New Zealand calibrated Risk of Death model (ANZROD)[21], which controls the case-mix for admission diagnosis and which has been shown to consistently perform better than APACHE III in ANZ [22, 23]. To ascertain if the change in outcome over time differed between SIRS categories, an interaction term between severe sepsis and year of admission was fitted with year of admission treated first as a categorical variable and then as a continuous variable following verification of linearity. For increased interpretability, when analysis were performed to differentiate between extremes, patients who met both high and low criteria for Temperature (n=5496) and White Cell Count (n=954) were removed from the analysis. All logistic regression results have been reported using Odds Ratios (95%CI). All data were analyzed by SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided P –value of 0.01 was considered to be statistically significant.

RESULTS

Study population

A total of 1,557,844 patients above 16 years old were treated during the assessment period in the 179 study ICUs. The exclusion process of patients is presented in Table E1. The final study population constituted of 131,016 patients with infection, organ failure and with at

least one SIRS criterion. The baseline characteristics of study patients stratified by survivorship are presented in Table 1. Overall, septic shock was present in two thirds of patients, mechanical ventilation was applied to approximately half and renal failure was present in approximately one in every five patients. The median number of SIRS criteria on day one was three and survivors more often had only one or two SIRS criteria ($p<0.001$). The annual incidence of SIRS criteria per intensive care unit admission is presented in Figure E1.

Mortality according to SIRS criteria

In patients fulfilling any (but only one) of the four SIRS criteria, hospital mortality rate increased from 10.6% with respiratory rate to 11.3% with any (low and high combined) white cell count to 13.5% with any (low and high combined) temperature to 15.8% with heart rate criteria fulfilment (Figure 1, Table E2). The absolute and adjusted mortalities with any combinations of two and three SIRS criteria are also presented in Figure 1 and Table E2.

Mortality in patients with high or low white cell count and temperature criteria

Patients with a low white cell count had a hospital mortality rate of 20.0% vs. 10.4% in patients with high white cell count patients (Figure 2, Table E3). The respective numbers for high and low temperature were 10.1% and 14.4%. After adjustments, the highest odds for hospital mortality were 1.97 (1.26-3.06) for low white cell count with high temperature as a referent (Figure 2, Table E3).

In patients fulfilling only one SIRS criterion, unadjusted hospital mortality increased from 10.1% for high temperature to 14.4% for low temperature, to 15.8% for tachycardia and to 20.0% for a low white cell count (Figure 3, Table E4). After adjustment for confounders,

there were only small changes in the order of increasing hospital mortality, with a low white cell count carrying highest odds for hospital mortality of 1.94 (1.25-3.03) (Figure 3, Table E4).

Mortality according to various combinations of SIRS criteria

Patients fulfilling only two SIRS criteria had the lowest hospital mortality if the combination of criteria were respiratory rate and high temperature (11.5%). The highest hospital mortality was seen for the combination of low white cell count and fast heart rate (30.8%) (Figure 3, Table E4). When adjusted for APACHE score, there were only minor changes in hospital mortality risk, the highest OR being 2.03 (1.56-2.64) for heart rate and low white cell count (Figure 3, Table E4). Patients fulfilling only the low white cell count criterion (1 SIRS criterion only) had hospital mortality rate of 20.0%. This mortality rate was higher than the mortality rate in 88% of patients meeting any two SIRS criteria (Figure 3, Table E4).

Secular Changes in mortality for SIRS criteria

During a decade and a half, hospital mortality in patients fulfilling different individual SIRS criteria decreased over time for each criterion in a similar way (Figure 4). The adjusted annual odds (95% confidence interval) for decline in mortality for separate SIRS criteria were 0.95 (0.93-0.98) for heart rate, 0.96 (0.93-0.99) for temperature, 0.93 (0.91-0.96) for white cell count, and 0.91 (0.88-0.94) for respiratory rate.

The absolute decrease in hospital mortality from 2000 to 2015 was from 53.6% to 28.0% in patients with low white cell count criterion and from 34.1% to 16.6% in patients with high white cell count criterion (Figure 5). The adjusted annual odds ratios (95% CI) were 0.94 (0.93-0.95) for low white cell count and 0.95 (0.95-0.96) for high white cell count criterion.

There was a significant difference in the adjusted decline in mortality between low and high white cell count criteria ($p<0.001$ for interaction) due to a greater decrease in low white cell count patients. Similar changes occurred in patients with the low vs. high temperature criteria (Figure 5) due to a greater decrease in the low temperature criteria patients.

DISCUSSION

Key findings

We performed a multicenter observational study of ICU patients with sepsis to assess the prognostic equivalence and interchangeability of SIRS criteria in terms of their individual, combination-related, and high vs. low value association with hospital mortality. We found that, in a cohort of more than 130,000 sepsis patients, separate individual SIRS criteria had different associations with hospital mortality. Moreover, we found that separate combinations of SIRS criteria and separate low vs. high values for the white cell count and temperature SIRS criteria all had markedly different associations with hospital mortality. Finally, we found that these difference held steady over 15 years of observation despite a progressive decline in associated hospital mortality.

Relationship with previous studies

To our knowledge, this is the first study to assess whether individual SIRS criteria have different associations with mortality in ICU patients with infection and organ failure; whether various combinations of two or three SIRS criteria also identify septic patients with different mortality risks, and, finally, whether individual SIRS criteria (white cell count and temperature) carry markedly different associations with mortality depending on whether

they are fulfilled because of a high (leukocytosis and fever) or low value (leukopenia and hypothermia).

Previous studies of SIRS criteria have focused on the specificity or sensitivity of SIRS criteria in identifying patients with sepsis [12-14, 24]. Such studies while addressing an important aspect of their validity, did not address the key issue of equivalence or interchangeability which is implied when, for example, any two criteria are required to define the presence of SIRS. Such equivalence or interchangeability has been implied and assumed since the 1992 definition of sepsis but has never been tested. This is despite its importance in terms of defining the biological credibility, clinical robustness, pathophysiological plausibility and face validity of the SIRS criteria.

Implications of study findings

Our findings imply that individual SIRS criteria do not describe pathophysiological phenotypes with equivalent risk of death and, logically, cannot be used interchangeably to describe similar risk states. Moreover, they imply that such concerns also apply to combinations of SIRS criteria or even to each criterion with dual fulfilment where low-value based presence carries a markedly different risk compared to high-value based presence. Finally, by showing that such differences in risk have held steady over a decade and a half despite marked changes in overall mortality, our findings suggest that such differential risk may represent the epidemiological expression of abiding clinical phenotypes and underlying pathophysiological outcome predictors.

The original purpose of SIRS criteria was to define the presence of sepsis [3]. According to the current sepsis definition, Sepsis 3, the significance of disturbance in homeostasis in infection was defined by a mortality of >10% [15]. Accordingly, we studied the significance of SIRS criteria not in defining sepsis but defining the prognostic significance of various SIRS criteria (or their subcomponents) in patients with infection and organ failure

Strengths and Limitations

This study has several strengths. It used data from a large cohort of >130,000 septic patients, in two countries over a decade and a half. It is the first study to assess the concept of equivalence of risk for SIRS criteria. It assessed such equivalence for individual criteria, for combination of criteria and for criteria with dual fulfilment, thus providing a full assessment of the concept. Moreover, it assessed such differential risk over 15 years to establish its robustness despite secular mortality trends. Finally, its findings have important implications in relation to the continued use of two SIRS criteria in clinical practice and trial medicine.

Our study also carries some limitations. Our observations pertain to the first 24 hours after ICU admission only. Thus, we cannot comment on the equivalence of SIRS criteria prior to ICU admission or after the first 24 hours. Similarly, the diagnosis of severe sepsis/septic shock only applied to patient characteristic during the first 24 hours in ICU. Thus, patients who developed sepsis later while in the ICU were not part of this analysis. The accuracy of sepsis diagnosis could not be confirmed by independent adjudication. However, data were collected by trained collectors and we used physiological coding for SIRS and organ failure, which are less subject to coding artefact. Moreover, coders could not be a source of conscious selection bias as they would not have known the data would later be used for this

purpose. We also accounted for the APACHE admission diagnoses of sepsis as well as APACHE admission diagnoses for infection to ensure that diagnostic coding changes would not fail to identify all patients of interest. In addition, the diagnostic criteria for sepsis were kept constant throughout the study period enabling us to detect changes in the equivalence of criteria over time, if any existed. Despite such consideration, we acknowledge that Finally, we can only use mortality risk at hospital discharge to assess equivalence. Although, such outcome can be used as a surrogate for 30-day mortality [25], we cannot comment on 90-day mortality or long-term mortality.

Conclusions

In patients with sepsis, we aimed to assess the equivalence and interchangeability of individual, combinations, and dual-fulfilment (high vs. low) SIRS criteria in terms of hospital hospital mortality. We found that, in a cohort of more than 130,000 patients, separate individual SIRS criteria, separate combinations of SIRS criteria and separate low vs. high values for the white cell count and temperature criteria all had markedly different associations with hospital mortality. We also found that such differences held steady over 15 years of observation. Our findings contradict the interchangeable use of different SIRS criteria, suggest that they may represent different pathophysiological states and challenge the long standing clinical basis for the use of any two SIRS criteria as equivalent.

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Contributionship:

KMK, MB, DP, DJC, RB: Substantial contributions to the conception or design of the work

MB, DP: Acquisition of the data

MB: analysis of the data

KMK, MB, DP, DJC, RB: interpretation of data for the work;

KMK, MB, DP, DJC, RB: Drafting the work or revising it critically for important intellectual content;

KMK, MB, DP, DJC, RB: Final approval of the version submitted for publication;

KMK, MB, DP, DJC, RB: Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interest:

KMK: none

MB: none

DP: none

DC: none

RB: none

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Figure legends:

Figure 1: *Upper panel:* Unadjusted mortality according to fulfillment of one, two or three Systemic Inflammatory Response Syndrome (SIRS) criteria.

Lower panel: Adjusted mortality according to SIRS criteria. Analyses were performed using logistic regression adjusting for patient severity (ANZROD) and year of admission with patients nested within site and site treated as a random effect.

RR Respiratory rate, WCC White cell count, Temp Temperature, HR Heart rate.

Figure 2. Unadjusted mortality (upper panel) and logistic regression adjusted (severity, year with patients nested within sites and sites treated as a random effect) odds (lower panel) for mortality (95% Confidence intervals) in sepsis patients fulfilling either high or low systemic inflammatory response syndrome criteria for white blood cells (WCC) and temperature (Temp).

Figure 3: Absolute and adjusted mortality in sepsis patients fulfilling various SIRS criteria (with WCC and temperature considered as high and low values) and various combinations of SIRS criteria. Analyses were performed using logistic regression adjusting for patient severity (ANZROD) and year of admission with patients nested within site and site treated as a random effect.

TH Temperature high, TL temperature low, RR respiratory rate, WH White Cell Count high, WL White Cell Count low, HR heart rate.

Figure 4. Unadjusted mortality during the study period according to Systemic Inflammatory Response Syndrome (SIRS) criteria. The P-value for interaction was 0.05.

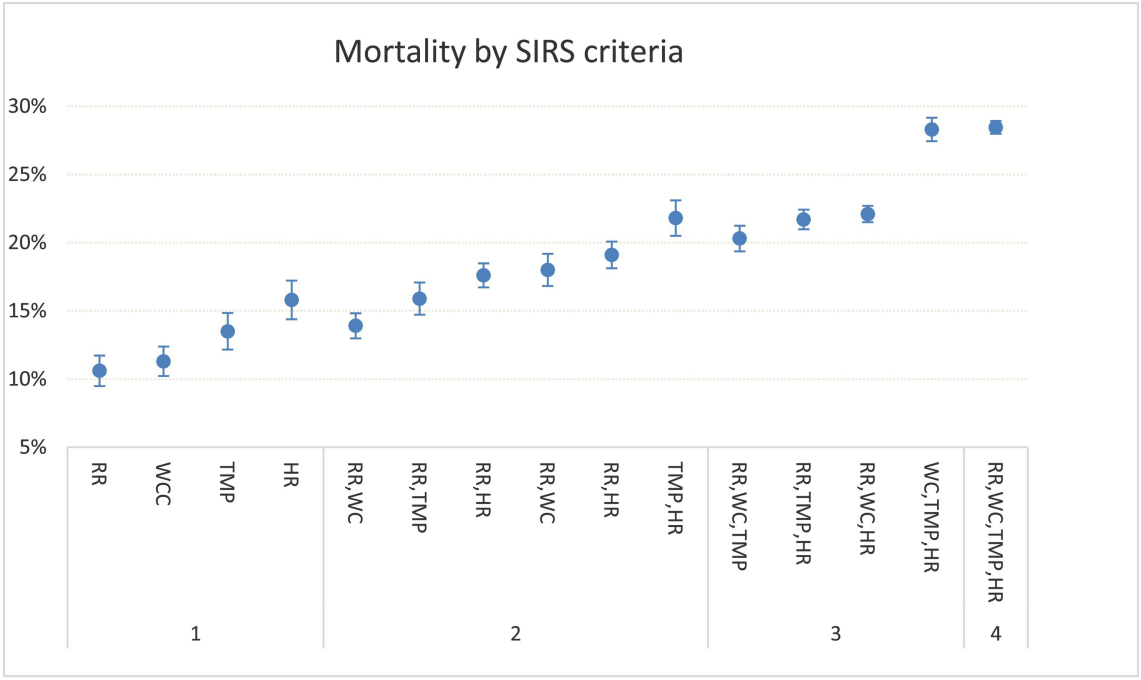
Figure 5. Upper panel: Mortality over time in sepsis patients with either high or low white cell count criteria. The annual odds for decline in mortality (95% confidence intervals) was 0.94 (0.93-0.95) for low white cell count and 0.95 (0.95-0.96) for high white cell count ($p<0.001$ for interaction between high and low).

Lower panel: Mortality over time in sepsis patients with high or low temperature criteria. The annual odds for decline were 0.94 (0.94-0.95) for low temperature and 0.96 (0.95-0.97) for high ($p<0.001$ for interaction).

Table 1: Characteristics and outcomes of study patients according to survival

	All patients (n=131016)	Alive (n=101793)	Deceased (30540)	p-value
Age, mean (SD)	63.4 (17.1)	61.8 (17.4)	69 (14.5)	<0.0001
Male gender, % (n)	55% (71765)	54% (55065)	57% (16700)	<0.0001
Hospital Admission Source: Home, % (n)	66% (86731)	67% (67992)	64% (18739)	<0.0001
Other Hospital, % (n)	24% (31342)	24% (24178)	25% (7164)	0.007
Chronic Care, % (n)	2% (2556)	2% (1819)	3% (737)	<0.0001
Other ICU, % (n)	2% (2410)	2% (1762)	2% (648)	<0.0001
Unknown, % (n)	6% (7977)	6% (6042)	7% (1935)	<0.0001
Apache III score, Mean (SD)	70.7 (29.3)	63.45 (24.39)	95.88 (31.11)	<0.0001
Apache III Risk of Death, Median (IQR)	0.21 [0.09-0.45]	0.16 [0.07-0.33]	0.53 [0.3-0.76]	<0.0001
Australian and New Zealand Risk of Death, Median (IQR)	0.10 [0.03-0.26]	0.07 [0.03-0.17]	0.35 [0.15-0.62]	<0.0001
Length of stay: ICU (days), median (IQR)	3.3 [1.7-6.9]	3.3 [1.7-6.7]	3.3 [1.3-8.0]	<0.0001
Hospital (days), Median (IQR)	12.8 [6.6-24.8]	13.6 [7.5-26.2]	9.1 [3.2-20.0]	<0.0001
Documentation of treatment limitation	5% (6914)	4% (3656)	11% (3258)	<0.0001

Septic shock, % (n)	68% (88946)	66% (67591)	73% (21355)	<0.0001
Mechanical ventilation, % (n)	50% (65478)	46% (47298)	62% (18180)	<0.0001
Acute renal failure, % (n)	18% (23819)	14% (13907)	34% (9912)	<0.0001
Total number of SIRS criteria met, median (IQR)	3 [2-4]	3 [2-4]	3 [3-4]	<0.0001
>1 SIRS criteria, % (n)	91% (119285)	90% (91541)	95% (27744)	<0.0001
Met 0 SIRS criteria, % (n)	0% (0)	0% (0)	0% (0)	1.00
Met 1 SIRS criteria, % (n)	9% (11731)	10% (10252)	5% (1479)	<0.0001
Met 2 SIRS criteria, % (n)	24% (31692)	26% (26112)	19% (5580)	<0.0001
Met 3 SIRS criteria, % (n)	39% (51059)	39% (39291)	40% (11768)	<0.0001
Met 4 SIRS criteria, % (n)	28% (36534)	26% (26138)	36% (10396)	<0.0001


Mortality by SIRS criteria
30%
25%
20%
15%
10%
5%
RR
WCC
TMP
HR
RR,WC
RR,TMP
RR,HR
RR,WC
RR,HR
TMP,HR
RR,WC,TMP
RR,TMP,HR
RR,WC,HR
WC,TMP,HR
RR,WC,TMP,HR
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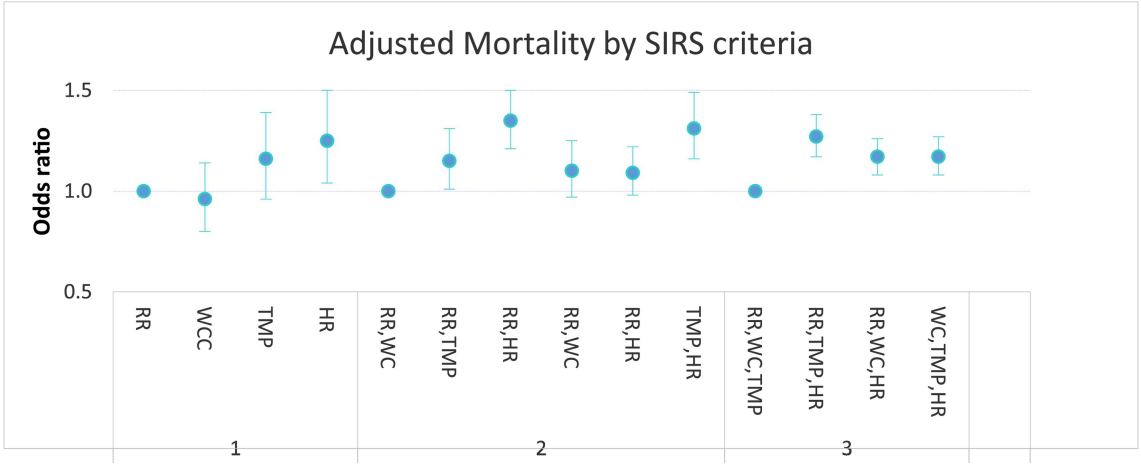
Adjusted Mortality by SIRS criteria
Odds ratio
1.5
1.0
0.5
RR
WCC
TMP
HR
RR,WC
RR,TMP
RR,HR
RR,WC
RR,HR
TMP,HR
RR,WC,TMP
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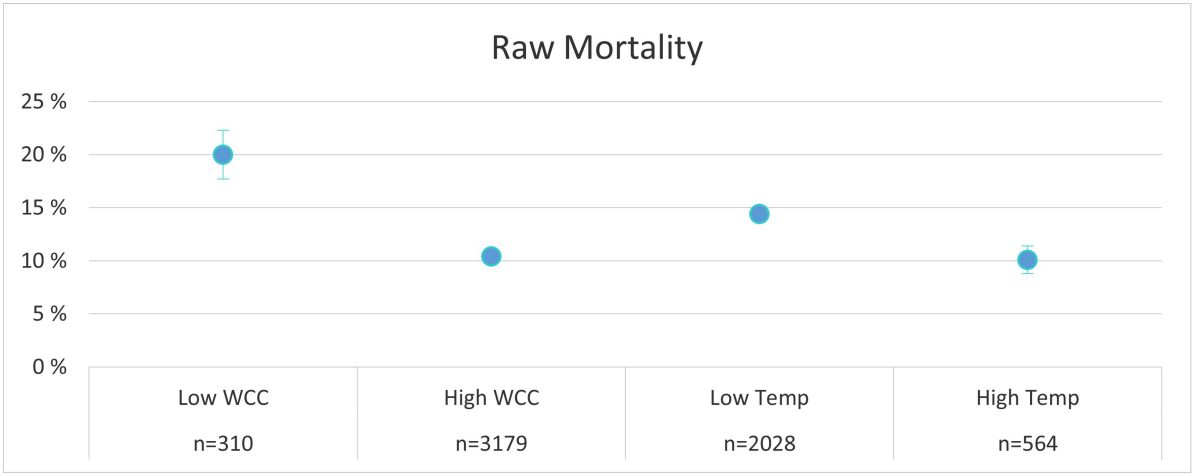
RR,WC,HR
WC,TMP,HR
1
2
3

Figure 1


Raw Mortality
25 %
20 %
15 %
10 %
5 %
0 %
Low WCC
n=310
High WCC
n=3179
Low Temp
n=2028
High Temp
n=564

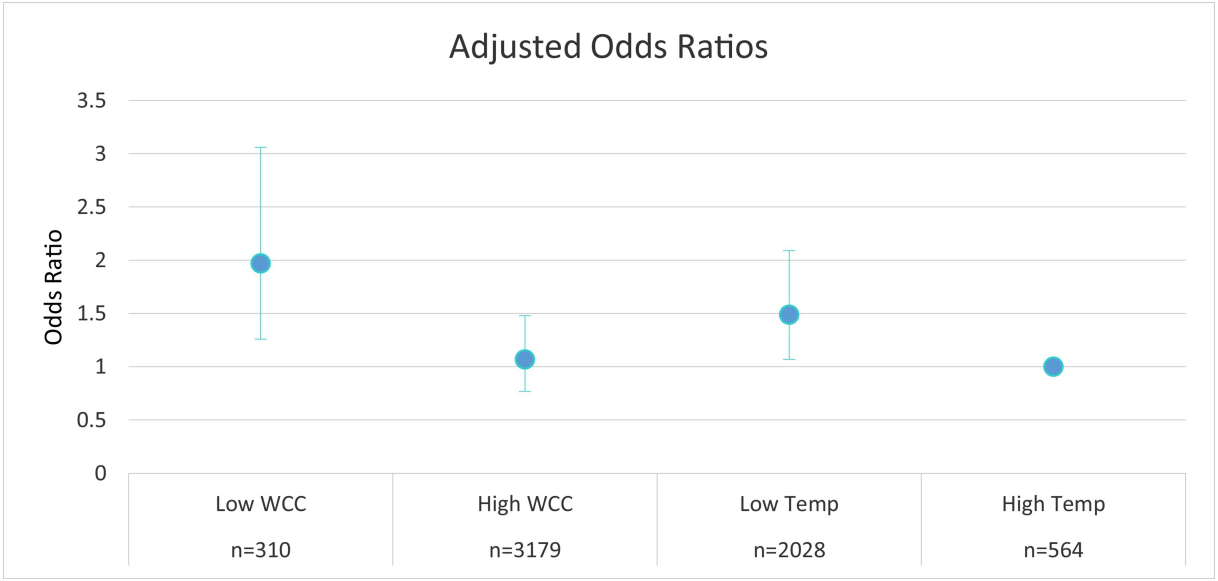

Adjusted Odds Ratios
Odds Ratio
3.5
3
2.5
2
1.5
1
0.5
0
Low WCC
n=310
High WCC
n=3179
Low Temp
n=2028
High Temp
n=564

Figure 2

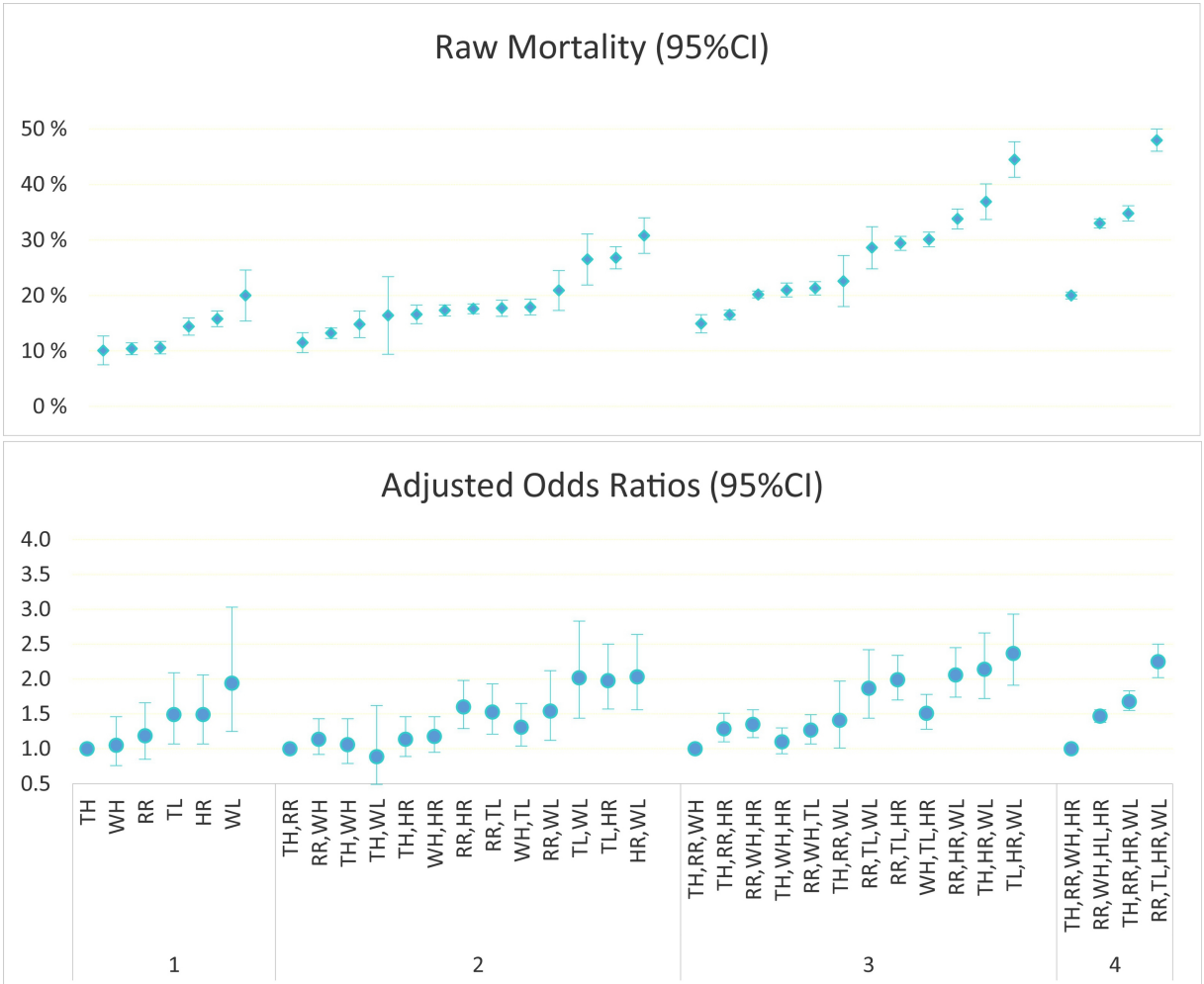

Raw Mortality (95%CI)
50 %
40 %
30 %
20 %
10 %
0 %
Adjusted Odds Ratios (95%CI)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
TH
WH
RR
TL
HR
WL
TH,RR
RR,WH
TH,WH
TH,WL
TH,HR
WH,HR
RR,HR
RR,TL
WH,TL
RR,WL
TL,WL
TL,HR
HR,WL
TH,RR,WH
TH,RR,HR
RR,WH,HR
TH,WH,HR
RR,WH,TL
TH,RR,WL
RR,TL,WL
RR,TL,HR
WH,TL,HR
RR,HR,WL
TH,HR,WL
TL,HR,WL
TH,RR,WH,HR
RR,WH,HL,HR
TH,RR,HR,WL
RR,TL,HR,WL
1
2
3
4

Figure 3

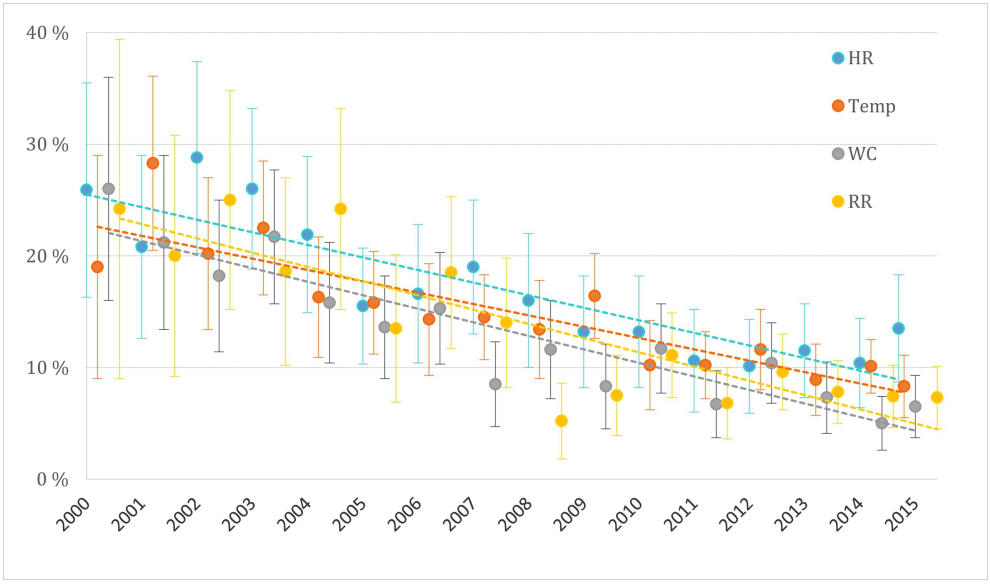
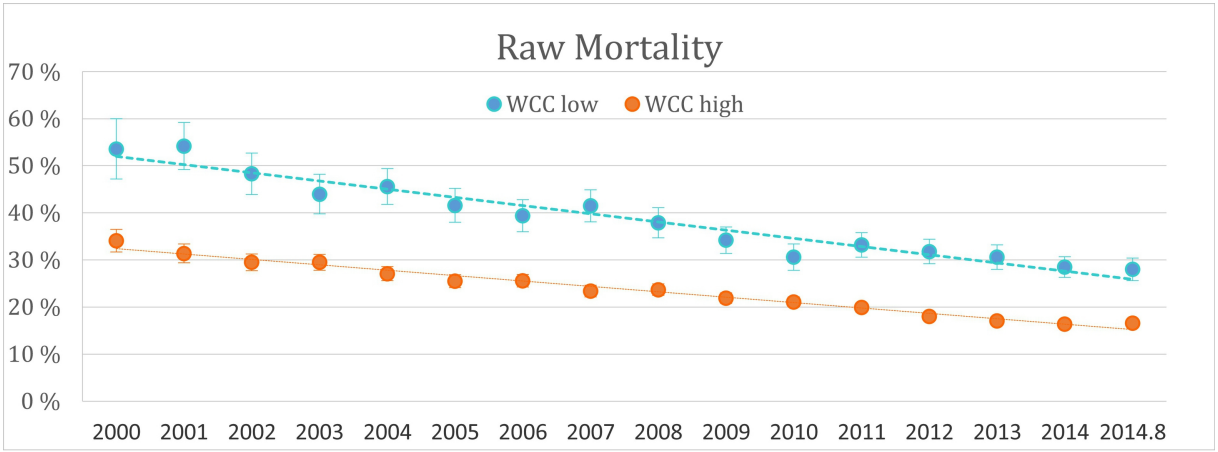

40 %
30 %
20 %
10 %
0 %
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
HR
Temp
WC
RR

Figure 4


Raw Mortality
WCC low
WCC high
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2014.8

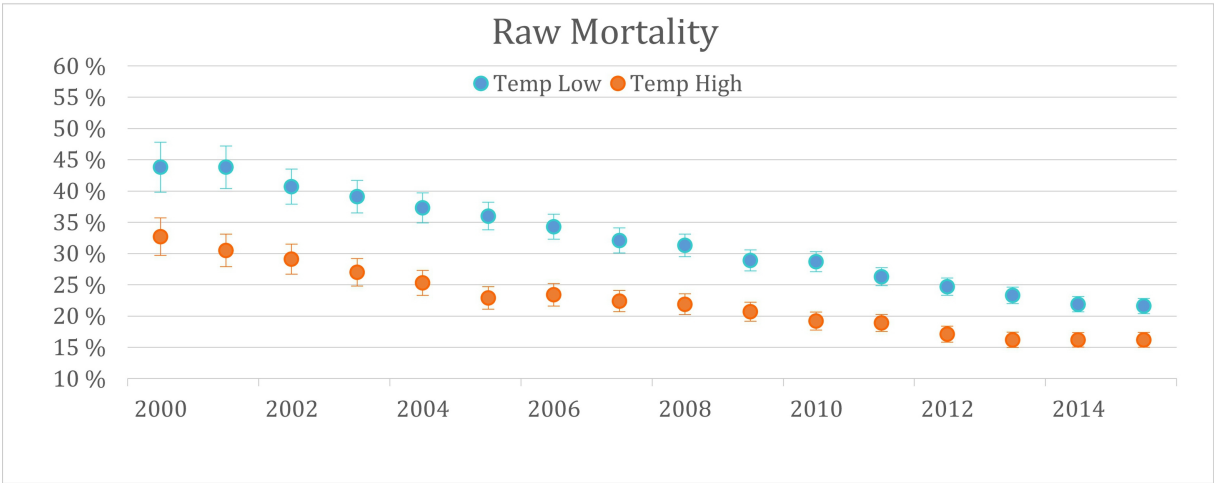

Raw Mortality
Temp Low
Temp High
60 %
55 %
50 %
45 %
40 %
35 %
30 %
25 %
20 %
15 %
10 %
2000
2002
2004
2006
2008
2010
2012
2014

Figure 5