Sequential Organ Failure Assessment Score (SOFA) scores differ between genders in a sepsis cohort: Cause or effect?

1Sofie Jacobson MD, 1Eva Liedgren Research nurse, 1Göran Johansson MS, 2Martin Ferm Statistician, 1Ola Winsö MDPhD

1Dept. of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care
Umeå University, S-901 85 Umeå, Sweden
2Jämtland County, Östersund, Sweden

Short title: Gender and sepsis.

Correspondence to Dr Sofie Jacobson
Department of Surgical and Perioperative Sciences
Anesthesiology and Intensive Care, Umeå University
S-901 85 Umeå, Sweden
e-mail: sofie.jacobson@anestesi.umu.se
Phone: +46-90-7850000
Fax: +46-90-131388
Abstract

**Background:** Controversy exists regarding the influence of gender on sepsis events and outcome. Epidemiological data from other countries may not always apply to local circumstances. The aim of this study was to identify gender differences in patient characteristics, treatment and outcome related to the occurrence of sepsis at admission to the ICU.

**Methods:** A prospective observational cohort study on patients admitted to the ICU over a three-year period fulfilling sepsis criteria during the first 24 hours. Demographic data, APACHE II score, SOFA score, TISS 76, aetiology, length of stay (LOS), mortality rate and aspects of treatment were collected and then analysed with respect to gender differences.

**Results:** There were no gender related differences in mortality or length of stay. Early organ dysfunction assessed as SOFA score at admission was a stronger risk factor for hospital mortality for women than for men. This discrepancy was mainly associated with the coagulation sub score. CRP-levels differed between genders in relation to hospital mortality. Infection from the abdominopelvic region was more common among women whereas infection from skin or skin structures were more common in men.

**Conclusion:** In this cohort, gender was not associated with increased mortality during a two year follow up period. SOFA score at ICU-admission was a stronger risk factor for hospital mortality for women than for men. The discrepancy was mainly related to the coagulation SOFA sub score. Together with differences in CRP-levels this may suggest differences in inflammatory response patterns between genders.

**Key words:** APACHE II, gender, ICU length of stay, mortality, septic shock, Severe sepsis, SOFA

Introduction

A common observation in epidemiological studies of sepsis/severe sepsis is that men account for approximately 60% of patients but the impact of gender on outcome is less clear (1-5). Despite animal studies showing an advantage in survival from a sepsis challenge for female mice (6-7) this observation is not consistently supported by human studies. Gender related differences in immune response have been ascribed the influence of sex hormones as well as genetic polymorphism (8-9). A French study showed that the overall hospital mortality from severe sepsis was lower in women and that this discrepancy was due to lower mortality in postmenopausal women (10). Other studies have reported a higher incidence of sepsis in men, but no gender related differences in mortality (11-13). However, there are reports of higher case fatality rates among women suffering from sepsis (14), of female gender being an independent predictor of increased mortality in patients with documented infection (4), and studies of mainly surgical patients report a poorer outcome from severe sepsis for women (15-16).

A German study found no difference in ICU mortality between genders in a large cohort of ICU patients, but in the subgroup of patients with sepsis the probability for ICU mortality was nearly twice as high for women (16). In a recent study on patients with severe sepsis or septic shock, Pietropaoli et al found that women had a higher risk of dying in hospital. They found differences in delivery of care between genders, but these disparities did not explain the higher mortality in women. After multivariable adjustment the likelihood for hospital mortality was approximately 10% higher for women(17). Thus, there are discrepancies in study results regarding gender related differences in the occurrence and outcome of sepsis. The impact of case mix, ethnicity, socio-economic factors and local therapeutic traditions on the results from different studies are not easy to assess. We therefore conducted this study with the aim to investigate the occurrence of sepsis within 24 hours after admission to the ICU, with special attention to gender related differences in patient characteristics, treatment and outcome.
Material and methods

This is a prospective observational cohort study, regarding analysis of data from septic patients admitted to the ICU of Umeå University Hospital, from the 1st of January 2003 to the 31st of December 2005. The study was approved by the ethical committee at Umeå University. Umeå University Hospital is an 800-bed hospital in Northern Sweden, with a tertiary referral population of approximately 900 000. The ICU is a multidisciplinary, 14 bed unit.

Patients eligible for the study were identified by daily reviews of patient charts during weekdays. Data were retrieved from medical records, hospital mainframe computer and patient data management system, (Picis, Dräger Medical, Sweden AB). Inclusion criteria were age ≥18 years and an admission diagnosis of sepsis or development of severe sepsis or septic shock within 24 hours after ICU admission, according to standard definitions (18). Sequential Organ Failure Assessment Score (SOFA) as a marker for organ dysfunction and disease severity was calculated at admission (SOFA_0) and then daily for the first 14 days and on the day of discharge, if after the initial 14 days (19). The daily SOFA score was based on the worst value during each 24 hour period from 06.00 am to 06.00 am. SOFA max was defined as the maximum value of the SOFA score during the ICU stay. A SOFA organ sub-score of 2 was considered a sign of organ dysfunction and a SOFA organ sub-score of 3 or more was considered a sign of organ failure.

APACHE II was used for assessment of severity of illness at admission (20). Therapeutic Intervention Scoring System; TISS -76, -was registered once daily and used as an estimate of personnel workload (21). Patients were characterised according to referral pattern, reason for admission, co-morbidities, source of infection, primary infection site and infection causing microorganism. Microbiological cultures were considered relevant only if acquired within 48 hours before or after admission to the ICU. Aspects of treatment included cardiovascular-, respiratory- and renal support, transfusions, administered nutritional solutions and other fluids, sedation, antibiotics and medication relevant for the treatment of sepsis as well as surgical interventions. Mechanical ventilation was defined as ventilation of patients who were endotracheally intubated or tracheostomised. Antibiotics, antifungal and anti-viral drugs were registered and grouped in accordance with the Anatomic Therapeutic Chemical classification system (ATC). Pre-existing diseases were defined as described by Knaus et al (20). Data on hospital length of stay and hospital mortality was obtained from the hospital record system. Two year follow up mortality was obtained from a national database.

To assure data quality a second evaluation of each patient’s data was conducted by one of the authors not responsible for the primary data collection. For patients admitted more than once to the ICU, only the first sepsis related admission was included.

Statistics

Data were collected on a spreadsheet (Microsoft Excel). For statistical analysis SPSS ver. 19; SPSS Inc., Chicago IL, USA) was used. Data are presented as numerical values or percentages for categorical variables, and mortality rates are presented as proportions with 95% confidence intervals (CI). Continuous data are presented as mean with standard deviation or median and first and third quartiles, according to distribution. For statistical comparisons between gender, depending on sample size, Pearson Chi-Square Tests or Fisher’s exact test were used for categorical values and for continuous variables two-tailed t-test or Mann-Whitney U-test according to proof of normality. Odds ratios (OR) are reported with 95% CI. A p-value < 0.05 was considered significant, and all p-values reported are two-sided. No adjustment was made for multiple testing.

Univariate logistic regression was performed to evaluate independent risk factors for hospital mortality. Covariates were all variables in Table I, scorings (APACHE II, TISS 76, SOFA
scores), septic shock, maximum lactate level during first 24 hours, and maximum creatinine-
and CRP level during ICU-stay.
An interaction analysis was performed between the independent variables and gender, with
hospital death as outcome variable. Organ sub scores for SOFA_0 and SOFA_1 were
included in this analysis.
A multivariate backward stepwise logistic regression adjusted for age and gender was per-
formed with hospital mortality as dependent variables. Independent variables were variables
from the univariate logistic regression analysis with a p-value of <0.05. APACHE II,
SOFA_0, and SOFA_max were entered separately in the regression model and all were sta-
tistically significant. Co-linearity existed between the APACHE II score and SOFA scores.
Only SOFA_0 was used in the final model.

Results

Demographic data
During this 3-year period, 2271 patients (1388 men and 883 women) were admitted to the
ICU, with a mean ICU-length of stay of 4.1 days and an overall ICU mortality of 8.5 %.
Of the 2271 patients, 127 patients fulfilled the inclusion criteria for severe sepsis or septic shock
during the first 24 hours after ICU-admission. Sixty percent of the 127 patients were men.
Patient characteristics, referral patterns and admission categories are presented in table I.
Women were significantly more often admitted after emergency surgery (p= 0.006) and men
significantly more often due to medical reasons (p= 0.019).

Infection characteristics
The majority of patients had a community-acquired infection (73%). There was a significant
gender related difference in source of infection. Infection from the abdominopelvic region
was significantly more common in women (p=0.002) while sepsis originating from skin or
skin structures was significantly more common in men (p=0.012). Positive blood cultures
were obtained from 52 patients (41%). In 37 patients (29%) cultures other than from blood
were positive, while in 38 patients (30%) microbiological cultures, including blood, urine,
liquor, wound, airway, and others, were negative. Ten patients, 5 men and 5 women, had
fungi as single infecting microorganism. No patient had multi resistant bacteria as primary
infecting agent. There were no differences between men and women regarding proportion of
positive microbiological cultures, or infection with gram positive, gram negative bacteria or
fungi (Table I).

Treatment
Of the treatment modalities presented in table II, there were no differences between genders
regarding frequency or duration of treatment, except that women received surgical drainage
more often. Of the patients not endotracheally intubated, all had intermittent respiratory sup-
port via face mask, CPAP or Bi-level support. Renal replacement therapy was needed in 27
(21%) patients, of which five patients had only intermittent haemodialysis (HD) and 22
patients had HD and/or continuous renal replacement therapy. Cardiovascular monitoring
with echocardiography performed by specially trained echo-cardiographers, or pulse contour
intermittent thermo dilution cardiac output monitoring technique (PiCCO, Pulsion Medical
Systems AG, Munich, Germany) were used to a similar extent in men and women.
No patient was treated with Rh-APC. All patients were treated with parenteral antibiotics
during the whole ICU length of stay. Regarding the choice of antibiotics there was no differ-
ence in proportion of administered treatment other than for tetracycline, which was adminis-
tered to five men only and benzyl penicillin, administered to one woman and 12 men. Women
received significantly more cefuroxime (p=0.025) and ampicillin (p=0.036), compared to men (Table II).

Volumes of resuscitation fluids administered within 24 hours after ICU-admission and during the whole ICU-length of stay are summarised in Table II. Administration of fluids within 2 hours from admission to the ICU did not differ between genders. At 24 hours after ICU-admission significantly more women than men had received transfusion with packed red blood cells (p = 0.042). There was no significant difference between men and women in total volumes of resuscitation fluids or blood products administered during the ICU stay (Table II).

**Outcome data**

There were no gender related differences in mortality rates or length of stay (table III).

Concerning scoring, there were no significant differences between genders in total SOFA scores at admission, day one or maximum score (Table III). The proportion of men and women with SOFA organ sub scores of 2, indicating organ dysfunction (data not shown), or sub scores of 3 or more, indicating organ failure, were similar, (Fig 1).

SOFA_0 and SOFA_1 were significantly higher in non-surviving compared to surviving women. Men differed in that respect, SOFA_0 was not significantly higher in non-surviving than in surviving men (Fig. 2A) and SOFA_1 was significantly lower among non-surviving compared to surviving men (Fig. 2B). SOFA_max was significantly higher among hospital non-survivors compared to survivors in women and men (Fig. 2C).

APACHE II score was significantly higher among both non-surviving men and women compared to hospital survivors (women p = 0.029, men, p = 0.010), but no difference was found between genders (data not shown).

TISS 76-scores, neither totally nor per day, differed between genders, regardless of outcome (data not shown).

![Figure 1](image.png)

**Figure 1.** Proportion of patients with SOFA organ sub score ≥3 as a sign of organ failure (females and males) and proportion of patients with SOFA organ sub score <3 (females and males). Circ- circulatory, resp- respiratory, renal- renal, coag- coagulation, CNS- central nervous system, hep- liver function sub score, respectively.
Figure 2. Differences between genders in SOFA scores and CRP max in relation to hospital outcome.
Panel A. SOFA score at admission (SOFA_0) was significantly higher in non-surviving than surviving women (p=0.001), but not among surviving compared to non-surviving men.
Panel B. SOFA score day 1 (SOFA_1) was significantly higher among hospital non-surviving compared to surviving women (p =0.008), but in men SOFA_1 was significantly lower in non surviving men compared to surviving men (p=0.035).
Panel C. SOFA_max were significantly higher among hospital non-survivors compared to survivors in both women (p=0.001) and men (p=0.017).
Panel D. The interaction between gender and CRP as a risk factor for hospital mortality.
CRP_max was significantly lower in surviving women than in non surviving women (p=0.035). Men displayed a different pattern with higher CRP in surviving men than non-surviving men, although the difference was not statistically significant (p=0.081).
CRP; C-Reactive Protein. Data are presented as mean ± 95% confidence intervals.
Predictors of mortality

Results from the univariate logistic regression analysis with hospital mortality as dependent variable are displayed in table IV. Neither gender, nor sources of infection or infective microbiological agents were identified as risk factors for hospital mortality. As opposed to other scores, total TISS scores or TISS score/day were not associated with mortality.

A multivariate logistic regression analysis, adjusted for age and gender, showed admission type medical, chronic corticosteroid medication and SOFA_0 as significant risk factors for hospital death (table IV).

Interaction analysis between gender and independent variables revealed significant interaction with SOFA_0 (p=0.026) and SOFA_1 (p=0.001) as implied from Fig 2A-B. Further analysis of SOFA organ sub scores showed significant interaction between gender and SOFA_0 coagulation sub score (p=0.024), SOFA_1 coagulation sub score (p=0.002), and SOFA_1 renal sub score (p=0.003). Also, CRP at admission (p=0.028) and maximal CRP (p=0.016) during ICU-LOS showed a significant interaction with gender as a risk factor for hospital death. The effect of this interaction between gender and CRP on hospital mortality is illustrated in figure 2D.

A univariate logistic regression was performed with each aspect of treatment as covariate in order to assess their association with hospital mortality (table IV). Of the treatment modalities associated with hospital mortality, only number of days of platelet transfusion was significantly associated with hospital mortality when introduced in the multivariate analysis, (OR 1.66 95% CI 1.34 - 2.43, p=0.009, adjusted for gender, age, SOFA_0, medical status at admission and chronic corticosteroid treatment).

Discussion

In this cohort of patients, we found disparities between men and women in the significance of early SOFA scores, as a risk factor for hospital mortality. SOFA score at admission or day 1 was a stronger risk factor for hospital mortality for women than for men. This discrepancy was significant despite no discernible differences in total SOFA or SOFA organ sub scores between genders. The difference between genders in SOFA scores as a risk factor for mortality was mainly related to the coagulation sub score, i.e. the platelet count. There were also discrepancies between genders in the pattern of C-reactive protein in relation to hospital mortality.

In the present study SOFA score was considered a measure of organ dysfunction as originally intended (15). SOFA score was developed as a mean to evaluate morbidity in septic patients over time, but not to predict mortality. Even so, many studies have reported a good to excellent ability of the SOFA score to discriminate between survivors and non survivors in intensive care patients in general, and some studies have investigated the discriminative power of individual organ scores (22). A majority of studies evaluating differences between scoring systems, different derivatives of the SOFA score, and the significance of temporal development of organ dysfunctions, have included mixed intensive care patients and not specifically patients with sepsis. Above all, the gender aspects have not been addressed in these studies and the score itself does not take gender into account.

There is a growing body of evidence that thrombocytopenia is related to an adverse outcome in critically ill patients (23). Several studies have reported low platelet count as independently related to ICU-mortality, both in patients with bloodstream infection (24), and in general ICU populations (25-26). Low initial platelet counts as well as a reduction during the ICU stay seem to increase the risk of death, but the aspect of gender is not explicitly evaluated.

In studies from the intensive care community, when reported, the proportion of men is often 60% or more (10, 12, 27-28). In terms of evaluation of risk factors or effects of treatments based on study cohorts, whether from a general population or from sepsis subgroups, the fact
that a majority of intensive care patients are men, are a source of concern. The predominance of male gender in study cohorts may abolish the effect of treatment or the effect of risk factors that actually exist in the female gender.

Site of infection may constitute a confounder regarding outcome of sepsis, and there are inconclusive data concerning the influence of site of infection on both mortality and length of stay (12, 29). It has been stated that infections originating from the urinary tract are associated with a favourable outcome, and that abdominal infections are associated with increased risk of ICU death (29). If this holds true between genders is not clear, but the urinary tract is more frequently reported as a source of sepsis in women (10, 12, 17). Crabtree and co-workers showed that women with infection from skin and skin structures had a higher hospital mortality rate than men (30). A common finding is that the lungs and abdomen are the most frequent sites of infection in ICU patients (1, 5, 31-32). A sub analysis of the SOAP study on the impact of infection originating from the lungs or the abdomen found differences in patient profiles and hospital LOS, but the mortality rate was identical (32). In that study, septic shock was more common at admission in patients with abdominal infection and they were more likely to have early coagulation failure and acute renal failure. However, there was no analysis regarding differences related to gender.

Whether the difference between genders in early SOFA score, and especially coagulation sub-score, as a risk factor for mortality in the present cohort, is related to differences in source of infection, with abdomen as the predominant focus for women and a pre-ICU admission insult in terms of emergency surgery, or differences in the primary inflammatory response where platelets play different roles in men and women remains to be elucidated. Differences between genders in CRP-levels in relation to outcome may also represent a part of gender related inflammatory response pattern or be related to differences in source of infection.

There were minor discrepancies in the treatment of men and women but none of these treatment modalities were associated with mortality. The only treatment modality associated with mortality in the multivariate analysis was transfusion of platelets which was evenly distributed among genders. Specifically, mortality was not related to the total amount administered, but the number of days that platelet transfusion was required. However, since a treatment is instituted because of a condition or an underlying disease it can be disputable to consider treatment per se as a risk factor. In line with a recent study, volume of resuscitation fluids and treatment with vasopressors was not significantly associated with hospital mortality (33).

Differences in antibiotic treatment were attributed to differences in sources of infection. All patients were considered to have adequate antibiotic treatment, in accordance with national guidelines, within 24 hours from ICU admittance. Time to first dose of antibiotics was not considered in the prospective data collection, and it proved to be difficult to obtain robust data retrospectively, since in a majority of the patients antibiotic treatment was already instituted before ICU-admission.

We did not detect any statistically significant difference in mortality during a 2 year follow up period among genders. Men had higher mortality rates in hospital, at three and six months, but as stated above, these discrepancies were not statistically significant. The mortality rates are in line with recent Scandinavian studies ((34-35). There was no statistically significant difference in ICU- or hospital LOS between genders, but a tendency for longer hospital LOS among women, even when comparing survivors only.

This study represents the standard of care of an unselected patient population at a university hospital. From a socioeconomic and ethical perspective this cohort represents a homogenous group of patients which reduces the influence of these factors on outcome. No specific intervention was made before the start of this observational study. The study was planned and data collection started before the guidelines from the Surviving Sepsis Campaign were published, thus the aim was not to study adherence to specific bundles or protocols.
To conclude, gender was not associated with increased hospital mortality. SOFA score at ICU-admission and day 1 was a stronger risk factor for mortality for women. The discrepancy was mainly related to the coagulation SOFA sub score. There were also differences between genders in CRP-levels in relation to hospital mortality. Whether this discrepancy represents a gender related difference in inflammatory response or is a consequence of differences in source of infection, or differences in time to institution of care remains to be further elucidated.

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Table I. Patients characteristics.

|                  | Women n=50 | Men n=77 | p=  |
|------------------|------------|----------|-----|
| **Referral pattern** |            |          |     |
| Admission from the community | 6(12) | 10(13) | ns |
| ICU transfer from within hospital | 35(70) | 54(70) | ns |
| Transfer from other institution | 9(18) | 13(17) | ns |
| **Patient category** |            |          |     |
| Medical* | 28(56) | 59(76) | 0.019 |
| Surgical elective | 6(12) | 9(12) | ns |
| Surgical emergency* | 16(32) | 9(12) | 0.006 |
| **Co-morbidities** |            |          |     |
| Congestive heart failure | 3(6) | 3(4) | ns |
| Chronic lung disease | 4(8) | 4(5) | ns |
| Chronic liver disease | 0(0) | 3(4) | ns |
| Chronic renal insuff. | 1(2) | 5(6) | ns |
| Diabetes | 11(22) | 16(21) | ns |
| Cancer |            |          |     |
| Hematological | 5(10) | 8(10) | ns |
| Localized | 9(18) | 9(12) | ns |
| Metastatic | 3(6) | 3(4) | ns |
| **Immunosuppressants** |            |          |     |
| Chronic steroids | 3(6) | 6(8) | ns |
| Chemotherapy | 7(14) | 8(10) | ns |
| Radiotherapy | 4(8) | 2(3) | ns |
| Other immunosuppression | 2(4) | 5(6) | ns |
| Other chronic disabling conditions | 7(14) | 19(25) | ns |
| **Number of co-morbidities** |            |          |     |
| 0 | 19(38) | 22(28) | ns |
| 1 | 11(22) | 29(38) | ns |
| 2 | 9(18) | 18(23) | ns |
| >3 | 11(22) | 8(10) | ns |
| **Infection characteristics** |            |          |     |
| Community acquired | 35(70) | 58(75) | ns |
| Nosocomial | 15(30) | 19(24) | ns |
| **Primary infection site** |            |          |     |
| Pneumonia | 10(20) | 17(22) | ns |
| Abdominopelvic* | 17(34) | 8(10) | 0.002 |
| Urinary tract | 3(6) | 14(18) | ns |
| Other | 14(28) | 23(30) | ns |
| Skin or Skin structures* | 0(0) | 9(12) | 0.012 |
| Indwelling catheter | 4(8) | 3(4) | ns |
| Unknown | 2(4) | 3(4) | ns |
| **Microorganism** |            |          |     |
| Gram positive cocci | 18(36) | 27(35) | ns |
| Gram positive rods | 0(0) | 2(3) | ns |
| Gram negative rods | 11(22) | 19(24) | ns |
| Fungi | 6(12) | 8(10) | ns |
| other | 3(6) | 7(9) | ns |
| mixture | 5(10) | 5(6) | ns |

Other chronic disabling conditions include patients with Myelomeningocele and urinary bladder dysfunction, patients with tetraplegia of various underlying causes, patients with inflammatory bowel disease and patients with multiple diseases other than those defined above. Other immunosuppressant includes azathioprine, ciclosporin and TNF-alfa inhibitors. Community acquired; defined as infection developed within 48 hours after hospital admittance. Type of microorganism retrieved from cultures from blood, urine, cerebrospinal fluid, synovial fluid, pleural fluid and tissues. * Denotes statistical significant difference between genders.
### Table II. Treatment, fluids and antibiotics.

| Modality                        | Women n=50 | Duration (days) | Median (25-75 percentil) | Men n=77 | Duration (days) | Median (25-75 percentil) | p=  |
|---------------------------------|------------|-----------------|--------------------------|----------|-----------------|--------------------------|-----|
| Vasopressor support             | 37(74)     | 5.0(2.0/6.5)    |                          | 55 (71)  | 3.0(2.0/7.0)    |                          | ns  |
| Endotracheally intubated        | 34(68)     | 7.5(4.0/8.0)    |                          | 48(62)   | 8.0(4.0/8.0)    |                          | ns  |
| CRRT/HD                         | 12(24)     | 7.0(5.0/8.0)    |                          | 15(19)   | 8.0(3.0/8.0)    |                          | ns  |
| Low dose steroids               | 28(56)     | 6.5(4.0/8.0)    |                          | 41(53)   | 7.0(2.0/8.0)    |                          | ns  |
| Sedation                        | 36(72)     | 8.0(4.0/8.0)    |                          | 51(66)   | 7.0(3.0/8.0)    |                          | ns  |
| Parenteral nutrition            | 37(74)     | 5.0(2.0/8.0)    |                          | 52(68)   | 5.0(2.0/8.0)    |                          | ns  |
| Enteral nutrition               | 37(74)     | 5.0(2.5/8.0)    |                          | 56(73)   | 6.0(2.0/8.0)    |                          | ns  |
| Platelet transfusion            | 12(24)     | 2.5(1.0/4.0)    |                          | 19(25)   | 1.0(3.0/3.0)    |                          | ns  |
| Low molecular weight heparin    | 39(78)     | 7.0(3.0/8.0)    |                          | 56(73)   | 7.0(3.0/8.0)    |                          | ns  |
| Surgical procedures*            | 25(50)     |                 |                          | 24(31)   |                 |                          | 0.041|
| **Monitoring**                  |            |                 |                          |          |                 |                          |     |
| Ecchocardiography               | 27(54)     |                 |                          | 43(56)   |                 |                          | ns  |
| PICCO                           | 14(28)     |                 |                          | 19(25)   |                 |                          | ns  |
| **Fluids**                      |            |                 |                          |          |                 |                          |     |
| Total volume at 2 hours         | 43(86)     | 2.0(1.0/2.5)    |                          | 63(82)   | 2.0(1.0/3.5)    |                          | ns  |
| Crystalloids                    | 44(88)     | 2.6(1.0/4.0)    |                          | 71(92)   | 3.0(2.0/5.0)    |                          | ns  |
| Human albumin 5%                | 38(76)     | 1.0(0.5/1.6)    |                          | 45(68)   | 1.0(0.8/1.5)    |                          | ns  |
| Human albumin 20%               | 27(64)     | 0.2(0.1/0.4)    |                          | 46(60)   | 0.2(0.1/0.4)    |                          | ns  |
| Synthetic colloids              | 21(42)     | 1.0(0.5/1.0)    |                          | 30(39)   | 1.0(0.5/1.5)    |                          | ns  |
| Total volume at 24 hours        | 48(96)     | 4.0(2.0/5.0)    |                          | 77(100)  | 3.8(2.5/6.0)    |                          | ns  |
| Fresh frozen plasma             | 24(48)     | 1.0(0.5/1.5)    |                          | 35(44)   | 1.0(0.5/1.5)    |                          | ns  |
| Red blood cells*                | 36(72)     | 0.8(0.6/1.2)    |                          | 41(53)   | 0.6(0.6/1.2)    |                          | 0.042|
| ICU-LOS                         |            |                 |                          |          |                 |                          |     |
| Human albumin 5%                | 46(92)     | 2.2(1.0/3.7)    |                          | 64(83)   | 2.2(1.0/3.8)    |                          | ns  |
| Human albumin 20%               | 39(78)     | 0.5(0.3/1.2)    |                          | 55(71)   | 0.5(0.2/1.2)    |                          | ns  |
| Synthetic colloids              | 24(48)     | 0.9(0.5/1.4)    |                          | 42(54)   | 1.0(0.5/2.0)    |                          | ns  |
| Fresh frozen plasma             | 29(58)     | 1.5(1.0/3.8)    |                          | 42(54)   | 1.8(0.5/3.3)    |                          | ns  |
| Red blood cells                 | 40(80)     | 1.4(0.8/2.3)    |                          | 52(67)   | 1.2(0.6/2.6)    |                          | ns  |
| Platelets                       | 12(24)     | 0.8(0.3/1.4)    |                          | 19(25)   | 0.6(0.3/1.2)    |                          | ns  |
| **Antibiotics**                 |            |                 |                          |          |                 |                          |     |
| Total administered doses        | 67(134)    |                 |                          | 107(184) |                 |                          | ns  |
| **Type of antibiotic**          |            |                 |                          |          |                 |                          |     |
| Meropenem                       | 23(46)     | 11(6/28)        |                          | 42(54)   | 17(9/24)        |                          | ns  |
| Ciprofloxacin                   | 21(42)     | 9(2/15)         |                          | 29(38)   | 10(4/14)        |                          | ns  |
| Piperacillin-tazobactam         | 20(40)     | 16(6/33)        |                          | 28(36)   | 10(5/24)        |                          | ns  |
| Cefuroxim*                      | 11(22)     | 9(4/23)         |                          | 16(21)   | 1(1/4)          |                          | 0.025|
| Clindamycin                     | 8(16)      | 11(3/41)        |                          | 19(25)   | 18(3/33)        |                          | ns  |
| Vancomycin/Teicoplanin          | 9(18)      | 6(3/15)         |                          | 18(23)   | 3.5(1/13)       |                          | ns  |
| Aminoglycosides                 | 11(22)     | 8(1/14)         |                          | 15(19)   | 3(2/4)          |                          | ns  |
| Cefotaxim/Ceftazidam            | 6(12)      | 18(9/25)        |                          | 13(17)   | 12(3/23)        |                          | ns  |
| Ampicillin*                     | 5(10)      | 9(9/18)         |                          | 10(13)   | 6(3/9)          |                          | 0.036|
| Antimycotics (J02A)             | 20(40)     |                 |                          | 29(38)   |                 |                          | ns  |

Surgical procedures include removal of gastro intestinal-, biliary- and urinary obstructions, debridement, drainages of abscesses, pleural space, -joints- and surgical drainages*. CRRT - Continuous Renal Replacement Therapy, HD - haemodialysis, PICCO-Puls contour Intermittent thermodilution Continuous Cardiac Output monitoring. Crystalloids defined as Ringers-Acetate and isotonic NaCl; synthetic colloid solutions include Hydroxyethyl starch 130/0.4 6%, Hydroxyethyl starch 200/0.5 6%, and Dextran 70, 6%; blood products includes packed red blood cells, fresh frozen plasma and platelets. Total volumes at 2 and 24 hours defined as fluid administered for purpose of volume substitution (maintenance drip, nutritional solutions, infusions and blood products excluded). Aminoglycosides includes Netilmicin, Amikacin, Gentamicin. Benzyl penicillin and Tetracycline is omitted from the table, for information see text. * denotes statistical significant difference between genders.
Table III. Scoring and outcome.

|                      | Women n=50 | Men n=77 |
|----------------------|------------|----------|
|                      | Mean       | SD       | Mean    | SD       | p=     |
| **Age (years)**      | 61.3       | 15.66    | 63.3    | 13.63    | ns     |
| **Scoring(point)**   |            |          |         |          |        |
| APACHE II-score      | 19.6       | 6.01     | 20.0    | 6.88     | ns     |
| SOFA_0               | 7.5        | 3.88     | 8.1     | 3.87     | ns     |
| SOFA_1               | 8.5        | 4.54     | 7.4     | 4.17     | ns     |
| SOFA_max             | 9.4        | 4.45     | 10.2    | 4.27     | ns     |
| TISS-76/ICU-day      | 26.1       | 8.13     | 26.9    | 9.50     | ns     |
| **LOS(days)**        | Median     | 25/75 percentil | Median | 25/75 percentil |  |
| ICU                  | 8          | (3/13.2) | 6       | (3/13)   | ns     |
| survivors            | 7          | (3.2/13.8)| 8     | (3.2/14.8)| ns     |
| non-survivors        | 8.5        | (2/14.2) | 3       | (2/8.5)  | ns     |
| Hospital             | 24.5       | (12/37)  | 17      | (9/35)   | 0.055  |
| survivors            | 31         | (15/64)  | 18      | (12/35.5)| 0.082  |
| non-survivors        | 18         | (9/22)   | 8       | (3/34)   | ns     |
| **Mortality(%)**     | No(%)      | 95% CI   | No(%)   | 95% CI   |  |
| ICU                  | 10(20)     | 0.11 - 0.33 | 17(22) | 0.14 - 0.33| ns     |
| 28-days              | 12(24)     | 0.14 - 0.38 | 22(29) | 0.20 - 0.40| ns     |
| Hospital             | 11(22)     | 0.13 - 0.35 | 25(32) | 0.23 - 0.44| ns     |
| 3 month              | 12(24)     | 0.14 - 0.38 | 30(39) | 0.29 - 0.50| ns     |
| 6 month              | 15(30)     | 0.19 - 0.44 | 32(42) | 0.31 - 0.53| ns     |
| 1 year               | 21(42)     | 0.29 - 0.56 | 35(46) | 0.35 - 0.57| ns     |
| 2 year               | 21(42)     | 0.29 - 0.56 | 35(46) | 0.35 - 0.57| ns     |

APACHE II- Acute Physiology and Chronic Health Evaluation score. SOFA- sequential organ failure score. SOFA_0 defined as SOFA at admission, SOFA_1 based on the highest values during the first whole 24 hour period from 06.00 am to 06.00, and SOFA_max defined as the highest score during the ICU-LOS. TISS 76 - Therapeutic Intervention Scoring System (76 items). ICU-intensive care unit, LOS-length of stay.
Table IV. Analysis of risk factors for hospital death.

| Background variables | Unadjusted Odds Ratio (95% CI) | p   |
|----------------------|-------------------------------|-----|
| Gender               | 1.70 (0.75-3.88)              | 0.203|
| Age (years)          | 1.05 (1.01-1.08)              | 0.007|
| Admission type Medical | 2.98 (1.13-7.90)            | 0.028|
| APACHE II            | 1.12 (1.05-1.20)              | 0.001|
| SOFA_0               | 1.22 (1.09-1.36)              | <0.001|
| SOFA_1*              | 1.01 (0.92-1.10)              | 0.883|
| SOFA_max             | 1.26 (1.13-1.41)              | <0.001|
| Haematological disease | 7.25 (2.07-25.42)            | 0.002|
| Chronic corticosteroid medication | 10.74 (2.11-54.62) | 0.004|
| Septic shock         | 2.65 (1.11-6.31)              | 0.028|
| C-Reactive Protein*  | 1.00 (0.997-1.004)            | 0.621|

| Treatment modalities | Unadjusted Odds Ratio (95% CI) | p   |
|----------------------|-------------------------------|-----|
| Vasopressor support  | 1.13 (0.99-1.29)              | 0.076|
| Endotracheally intubated | 0.98 (0.89-1.10)           | 0.781|
| CRRT/HD              | 2.86 (1.19-6.88)              | 0.019|
| Low dose steroids    | 3.35 (1.42-7.91)              | 0.006|
| Sedation             | 0.99 (0.88-1.10)              | 0.825|
| Parenteral nutrition | 0.93 (0.82-1.05)              | 0.241|
| Enteral nutrition    | 0.37 (0.16-0.85)              | 0.019|
| Platelet transfusion | 1.46 (1.10-1.92)              | 0.008|
| Low molecular weight heparin | 0.90 (0.80-1.01) | 0.067|
| Surgical procedures  | 0.51 (0.22-1.19)              | 0.119|

| Multivariate logistic regression analysis | Adjusted Odds Ratio (95% CI) | p   |
|------------------------------------------|-----------------------------|-----|
| Medical admission type                   | 3.92 (1.18-12.99)           | 0.025|
| Chronic corticosteroid treatment         | 14.21 (1.90-106.44)         | 0.010|
| SOFA_0                                   | 1.25 (1.10-1.43)            | 0.001|

Unadjusted OR; univariate analysis with hospital death as dependent variable. Adjusted OR; multivariate stepwise backward logistic regression analysis, adjusted for age and gender, hospital death as dependent variable.

* denotes factors with significant interaction with gender, see under results and fig. 2 for further information.