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Evaluation of sex-associated differences in validity of the SOFA score in ICU patients

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Summary. *Background.* Most of intensive care scoring systems are helpful to objectively assess the severity of an illness and morbidity. Therefore, scoring systems are used to assess the probability of mortality in ICU-patients and to compare patient populations. Recently, SOFA-score was incorporated into sepsis definition models to improve discrimination of patient populations. During the last decades, sex was recognized as a relevant factor that invoked the need for novel, sex-oriented, approaches to therapy. To date, data evaluating sex-related differences in intensive care scoring systems are not available and current scoring systems may be less precise to women. Therefore, the aim of this study was to explore the validity of different intensive care scoring systems from a sex perspective. *Methods.* In five surgical intensive care units (ICUs) patients were evaluated including daily assessment of 3 different scoring systems (SOFA, SAPS-II, TISS-28). First obtained scores on ICU admission were assessed for sex-specific discrimination of ICU mortality. *Results.* Altogether 1,862 patients fulfilled inclusion criteria. Men showed statistical significant higher admission SOFA-score-values compared to women (5.5 ± 4.1 versus 4.6 ± 3.6, p = <0.001), but mortality was similar (10% men versus 11.6% females, P = 0.257). Logistic regression analysis showed that sex is not significantly interacting with SOFA, SAPS or TISS-28. Additionally, there was no difference between male and females in score discrimination for ICU mortality. *Conclusions.* In a surgical ICU population, sex did not significantly change the validity of common intensive care unit scores. SOFA, SAPS and TISS-28 are comparable in female and male ICU-patients. A sex bias was not detected.

Key words. Sex, SOFA, TISS-28, SAPS-II, mortality, intensive care unit.

Valutazione delle differenze associate al genere nella validità del punteggio SOFA nei pazienti in terapia intensiva

Riassunto. *Background.* La maggior parte dei sistemi che assegnano un punteggio (*score*) alla terapia intensiva sono utili per valutare oggettivamente la gravità di una malattia e la morbilità. Pertanto, i sistemi di punteggio vengono utilizzati per valutare la probabilità di mortalità nei pazienti in terapia intensiva (UTI) e per confrontare le popolazioni di pazienti. Recentemente, il punteggio SOFA è stato incorporato in alcuni modelli di definizione della sepsi, al fine di migliorare la differenziazione delle popolazioni di pazienti. Negli ultimi decenni, il sesso del paziente è stato riconosciuto come un fattore rilevante, che ha invocato la necessità di nuovi approcci alla terapia orientati al genere. A oggi non sono disponibili dati che valutano le differenze correlate al genere nei sistemi di punteggio UTI, e gli attuali sistemi di *scoring* potrebbero essere meno precisi per le donne. Pertanto, lo scopo di questo studio è stato quello di esplorare la validità di diversi sistemi di punteggio di terapia intensiva dal punto di vista del genere. *Metodi.* Sono stati valutati pazienti in cinque unità di terapia intensiva chirurgica, ivi inclusa la valutazione giornaliera di 3 diversi sistemi di punteggio (SOFA, SAPS-II, TISS-28). I primi punteggi ottenuti all'atto del ricovero in terapia intensiva sono stati valutati per la discriminazione genere-specifica della mortalità in terapia intensiva. *Risultati.* In totale, 1862 pazienti hanno soddisfatto i criteri di inclusione. I maschi hanno mostrato valori di punteggio SOFA al ricovero statisticamente più elevati rispetto alle femmine (5,5 ± 4,1 vs 4,6 ± 3,6, p = <0,001), ma la mortalità è stata simile (10% maschi vs 11,6% femmine, p = 0,257). L'analisi di regressione logistica ha dimostrato che il sesso non interagisce in modo significativo con i punteggi SOFA, SAPS o TISS-28. Inoltre, non c'erano differenze tra maschi e femmine nella discriminazione del punteggio per la mortalità in terapia intensiva. *Conclusioni.* In una popolazione in terapia intensiva chirurgica, il sesso non ha modificato in modo significativo la validità dei più comuni punteggi UTI. SOFA, SAPS e TISS-28 sono risultati comparabili nei pazienti di sesso maschile e femminile in terapia intensiva. Non è stato rilevato alcun *bias* relativo al genere.

Parole chiave. Genere, SOFA, TISS-28, SAPS-II, mortalità, unità di terapia intensiva.

Introduction

The consolidation of gender aspects into evidence-based medicine lead to many insights about gender disparity. Phenomena such as having different symptoms for acute diseases,[1] the unequal implementation of general therapeutic treatments[2] or the varying effectiveness of medications[3] are most likely to be attributed to the physiohormonal differences between men and women. These and other findings require us to reconsider non-discriminatory approaches to therapy. One alternative would be a sex-adapted therapy, as proposed by Eachempati et al. (1999).[4]

Many studies address the influence of sex on mortality in severe sepsis. The results, however, are sometimes noticeably conflicting. Women with pneumonia displayed a higher risk of mortality, although the incidence rate was significantly higher among men.[5] Another study showed a higher mortality for female patients with sepsis.[6] These are inconsistent with other studies, such as that by Adrie et al. (2007), where sepsis-related mortality was lower in women,[7] or studies which exhibited no difference with regard to mortality.[8,9]

In the 1980s, scoring systems were introduced as a systematic approach to the prognostic assessment of critically ill patients in ICU.[10,11] The scoring process allowed for standardized objective assertions about patients, and often about their prognosis as well. This is achieved by the sum of various points yielding a score related to the severity of the pathological condition. This systematic approach aims to provide information on a patient's prognosis, disease severity, treatment effort or risk stratification in clinical trials. Scores are being used to detect critically ill patients, especially in intensive care units.[12-14] This study focuses on three different scoring systems, whose scores were recorded for research patients at an intensive care unit upon their day of admission.

SOFA score. The Sequential Organ Failure Assessment (SOFA) score is an internationally well-established score for estimating the degree of organ dysfunction. A guiding principle for its development was to keep data collection as simple as possible, while being able to produce an objective and mostly therapy-independent assessment of the organ dysfunction.[11,15] SOFA evaluates the severity of the organ dysfunction in six organic systems (respiratory, hematology, cardiovascular, hepatic, renal, and central nervous system) of each patient, assigning to each system a value from 0 to 4, with a maximal score of 24.

A higher score is related to a higher mortality rate.[15] The scores can be used in several ways, as individual scores (for each organ) or as the sum of scores on one single ICU day:[11] The coagulation subject-score (hematologic score) can be used as the individual score for the hematologic system.

SAPS II. The Simplified Acute Physiology Score II (SAPS II) is a prognostic scoring system that was developed in 1993 by Le Gall et al.[16] The underlying assumption of SAPS II is the notion that disease severity can be measured by quantifying the degree of deviation of the physiologic variables.[11,16] Twelve physiologic variables were included and rated in addition to age, admission type and the presence of metastatic or blood cancer.

TISS-28. The Simplified Therapeutic Intervention Scoring System (TISS) evaluates 28 diagnostic, therapeutic and nursing measures, thereby indirectly making a statement about the patient's condition. The sicker the patient, the greater the medical effort required.[17]

Jacobson et al. (2012) demonstrated that a higher score in the coagulation sub-group upon admission in ICU represents a stronger risk factor for mortality in women.[18] Nachtigall et al. (2011) also observed higher mortality rates in septic female ICU patients compared to their male counterparts, despite the latter having higher initial scores.[6] According to Vincent et al. (1996), higher SOFA scores correlate with increased mortality.[15]

Given the relation between mortality and the SOFA score, if men have higher initial scores, and yet women die more often, one could argue that perhaps women are inadequately represented in the scoring system, or that the severity of their condition is underestimated. This could indicate an inherent sex bias in the scoring system. In recent years, it has been pointed out that the sex aspects have not been yet addressed in studies about medical scoring systems, and that the score itself does not take gender into account.[13,18] To our knowledge, there is no trial evaluating a sex-related bias in the scoring systems in postsurgical ICU patients. This study aims to examine potential sex-specific differences in ICU score values and whether such a difference transfers into a dissimilar performance of the scoring systems to predict the risk of ICU mortality.

Materials and methods

Data collection

All clinical data from eligible patients were logged during daily medical rounds and could be retrieved from the records of an electronic patient data management system (PDMS; Copra System, Sasbachwalden, Germany). Data regarding pre-existing comorbidities, substance abuse (alcohol, drug, nicotine), diagnosis, medical treatment or vital signs were accessible. In addition, radiological, laboratory and microbiological data were received from the hospital's mainframe computer. Mechanical ventilation (endotracheal intubation or tracheostomy) was assessed for the duration of the utilization period in the ICU. Medical scoring systems like SOFA, TISS-28 and SAPS-II were calculated on a daily basis.

Ethical review

The study was approved by the institutional review board and the data safety authorities of the Charité University Hospital. Due to the observational character of the clinical trial, the ethics review board waived any claim to an informed consent.

Study design & patients

In this prospective, non-interventional clinical study data were acquired during five separated periods, between January 2006 and March 2010, and were subjected to the approval of both the Ethical Committee (EA1/127/07) and the Data Protection Office (ISRCTN54598675). Patients admitted to the ICU of the Charité University Hospital in Berlin, Germany, were screened. For inclusion, a minimum ICU stay of 24 hours was required. Study data were obtained from five mainly post-operative ICUs of two campuses, with 15 to 21 beds under anesthesiologic management. Most of the patients were admitted following surgical procedures like gynecological, abdominal, cardiac or neuro-surgery or after severe trauma, stroke or with an acute respiratory distress syndrome (ARDS).

Measurement & statistical analysis

The primary endpoint of this study was to assess the performance of ICU scoring systems for female and male patients with regard to ICU mortality. Data are presented as numerical values or percentages, with mean and standard deviation or median with first and third quartiles, according to scale level and distribution. For a statistical analysis, the Fisher's exact test, the Mann-Whitney-U test or the Student *t* tests were conducted, as appropriate. A statistical significance level for all tests was defined as an unadjusted two-tailed p-value of <0.05. Logistic regression analyses were performed on the independent variable sex, ICU scores and ICU mortality as dependent variable, to assess a potential interaction of variables. In multiple regression analyses, corresponding odds ratios (ORs) are reported with a 95% confidence interval (CI). To evaluate the discrimination of scores, receiver operating characteristic (ROC) analyses were performed for each scoring system. The resulting area under the curve (AUC) values were compared in pairs for statistical significance. All statistical data were analyzed using the Statistical Software Package for Social Science (SPSS 22.0) and R version 3.3.1.

Results

Patients population's basic characteristics

Altogether, 1,862 ICU patients met the inclusion criteria, with 43% of them being females. Female patients showed a slightly higher mean age compared with men (♀ 63.7 years versus ♂ 61 years, p = <0.001). The most common pre-existing disease in females was diabetes mellitus, whereas men suffered more often from cardiovascular diseases. There was a statistically significant difference in ICU length of stay and in the duration of mechanical ventilation, with male patients requiring longer ICU treatment and longer mechanically ventilation. Other parameters – eg., immunosuppressive status or other comorbidities – did not differ between the sexes (Table 1).

Diagnostic efforts, infection characteristics & antibiotics

Within the study population, men suffered significantly more from various infections during the ICU stay than women (♀ 53.4% versus ♂ 58.0%; p = 0.048). Especially blood and soft tissue infections, as well as pneumonia, were more often diagnosed in men, whereas women suffered from urogenital infections more commonly. Microbiological and radiologic diagnostics differed between sexes just as much as the antibiotic therapy: men received more targeted antibiotic treatment and more diagnostics (Table 1).

Intensive care scoring systems

Comparing intensive care scores on ICU admission, mean SOFA scores were statistically significantly higher in men (Table 1). SAPS-II and TISS-28 were similar between the sexes.

Mortality

No sex-related difference in ICU mortality was observed (♀ 11.6% versus ♂ 10%; p = 0.257). Univariate logistic regression analyses were performed, to evaluate the relationship between each scoring system (SOFA, SAPS-II, TISS-28) and ICU mortality. The resulting odds ratios for the study population showed a statistically significant increase in the risk for SOFA, SAPS-II and TISS-28, respectively (Table 2). When assessing the specific ORs for the two sexes separately, female patients showed a numerically higher increase in the risk of ICU mortality in each of the three scoring systems compared with men. However, this difference was small, and achieved <2% of relative variance in ORs.

Additionally, we did not observe any interaction between the factor sex and SOFA, SAPS-II and TISS-28 scores (data not shown).

To assess the discrimination of the scoring systems with regard to sex, receiver operator characteristics analyses were performed. The resulting areas under the curve (AUC) were compared in pairs, and no statistically significant difference was observed between sex discrimination in SOFA (p = 0.603), SAPS-II (p = 0.118) or TISS-28 (p = 0.972) (Figures 1-3; Table 3). With all resulting values being over 0.7, this model demonstrates an acceptable general discrimination ability.[19] It is worth noting that AUC values higher than 0.5 are not random.

Table 1. Baseline, infective and diagnostic characteristics of N = 1,862 ICU patients. Binary parameters presented in total and percentage (%), metric data in mean ± SD (standard deviation)

	Females N = 800	Males N = 1062	p
Age (years), mean ± SD	63.7 ± 16.4	61 ± 15.6	<0.001
Pre-existing comorbidities, no. (%)			
Cardiovascular diseases	300 (37.5)	500 (47.1)	<0.001
Immunosuppression	71 (8.9)	75 (7.1)	0.164
Chronic pulmonary disease	125 (15.6)	176 (16.6)	0.611
Chronic liver disease	64 (8)	104 (9.8)	0.192
Chronic renal disease	149 (18.6)	219 (20.6)	0.291
Metabolic disease	330 (41.2)	405 (38.1)	0.180
Psychiatric disease	92 (11.5)	144 (13.6)	0.205
Post-surgical patients	651 (81.4)	830 (78.2)	0.093
ICU admission scores, mean ± SD			
SAPS-II	36 ± 16.7	37.1 ± 16.4	0.639
SOFA	4.6 ± 3.6	5.5 ± 4.1	<0.001
TISS-28	32.6 ± 9.5	33.6 ± 10.9	0.081
ICU mortality, no. (%)	93 (11.6)	106 (10)	0.257
ICU stay (days)	8.7 ± 10.1	9.91 ± 11.9	0.036
Invasive ventilation, no. (%)	533 (39.9)	802 (60.1)	<0.001
Duration of ventilation In ventilated patients (hours)	143 ± 259	181 ± 354	<0.001
Infection during ICU stay			
Gastrointestinal	86 (10.8)	98 (9.2)	0.308
Urogenital	80 (10.0)	62 (5.8)	0.001
Bones and joints	23 (2.9)	35 (3.3)	0.687
Endocarditis	17 (2.1)	27 (2.5)	0.645
Soft tissues	81 (10.1)	151 (14.2)	0.009
Meningitis	21 (2.6)	21 (2)	0.350
Blood stream infection	35 (4.4)	89 (8.4)	0.001
Fever of unknown origin	43 (5.4)	56 (5.3)	0.917
Catheter related infection	13 (1.6)	32 (3.0)	0.067
Pulmonary	217 (27.1)	376 (35.4)	<0.001
Diagnostic patterns			
Microbiologic diagnostics	2.5 ± 4.7	3.4 ± 6.0	0.001
Radiologic diagnostics	4.0 ± 4.7	5.0 ± 5.7	<0.001
Antibiotic therapy			
Calculated therapy/ LOS	0.3 ± 0.4	0.3 ± 0.3	0.225
Targeted therapy/ LOS	0.1 ± 0.2	0.1 ± 0.3	<0.001
SOP adherence	0.8 ± 0.3	0.8 ± 0.3	0.588

SOFA: Sequential Organ-Failure Assessment; SAPS: Simplified Acute Physiology Score-II; TISS-28: Therapeutic Intervention Scoring System-28; ICU: Intensive Care Unit; LOS: length of stay.

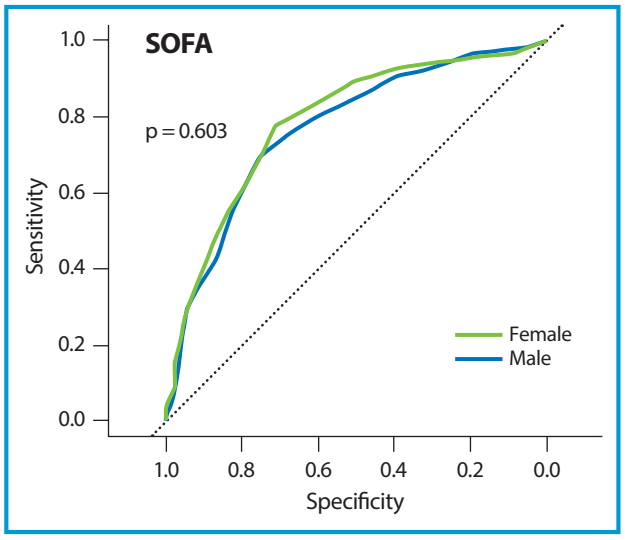

Figure 1. Receiver operator characteristic analyses for SOFA score for female and male ICU patients.

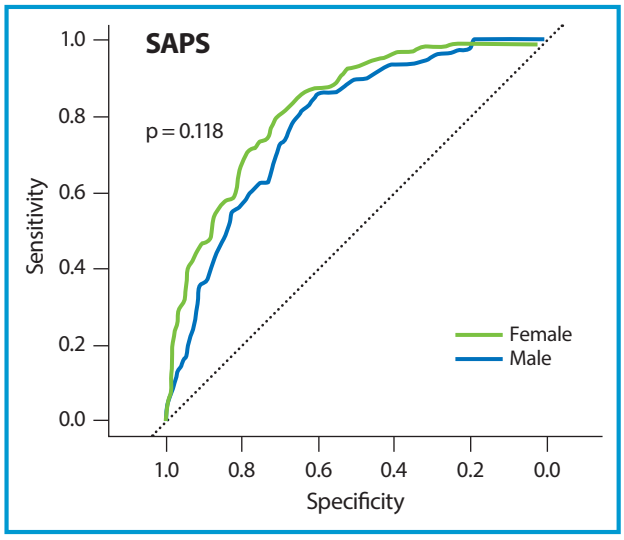

Figure 2. Receiver operator characteristic analyses for SAPS-II for female and male ICU patients.

Table 2. Univariate logistic regression analyses comparing SOFA, SAPS-II and TISS-28 with ICU mortality as dependent variable in 1,862 ICU patients. Data are shown separately for the study populations and for gender-specific odds ratios

	OR (95% CI for OR)	p
SOFA		
All patients	1.245 (1.2-1.292)	< 0.001
SAPS-II		
All patients	1.064 (1.055-1.074)	< 0.001
TISS-28		
All patients	1.090 (1.074-1.107)	< 0.001

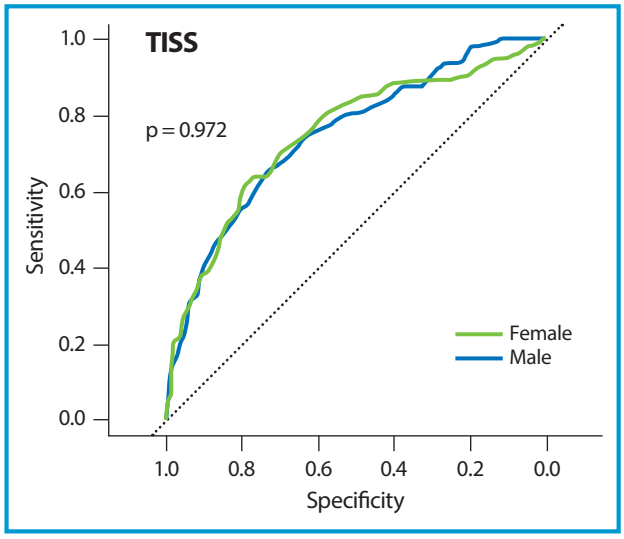

Figure 3. Receiver operator characteristic analyses for TISS for female and male ICU patients.

Table 3. Overview of the comparison of the ROC analysis and the associated values

	SOFA (f)	SOFA (m)	SAPS II (f)	SAPS II (m)	TISS-28 (f)	TISS-28 (m)
Ppv	0.262	0.238	0.266	0.194	0.272	0.212
Npv	0.96	0.956	0.964	0.975	0.942	0.95
Sensitivity	0.774	0.689	0.796	0.858	0.634	0.651
Specificity	0.713	0.755	0.711	0.604	0.777	0.732
Right positive (%)	72	73	74	91	59	69
Right negative (%)	504	722	503	577	549	700
Wrong positive (%)	203	234	204	379	158	256
Wrong negative (%)	21	33	19	15	34	37

(f): female; (m): male; ppv: positive predictive value; npv: negative predictive value.

Discussion

In the present study we investigated whether sex-bias should be taken into consideration in the application of three of the most commonly used ICU scoring systems. Our results did not confirm the existence of such bias. In addition, we demonstrated that, despite male patients in the study population having a higher score than female patients during ICU admission, the mortality was the same.

The outcomes of our analysis of the basic characteristics are in good agreement with the results of other studies. Well-described differences were observed between sexes when comparing age, comorbidities and ICU length of stay: on the ICU admission day, women were older and did not suffer as much as men from cardiovascular diseases.[6,7,20-22]

The duration of the ICU length of stay also varied significantly. Men stayed longer and received mechanical ventilation more often and for longer periods of time; this could be explained by the markedly higher pneumonia, as well as overall infection rate in male patients. Conversely, women were more likely to suffer from urogenital infections. These findings are in line with recent studies.[20,23,24] Men also received targeted antibiotic treatment more often than women. This discrepancy seems to be linked to the fact that male patients underwent microbiological tests more frequently and, as a consequence, more distinct microbiological results were available.

Numerous studies in the field of intensive care have investigated the impact of sex on mortality, yielding variable results. Our findings are consistent with those studies in which mortality rate was the same, such as Esper et al. 2006, Wichmann et al. 2000 or Nachtigall et al. 2011.[6,8,9] It should be noted, however, that while the majority of the aforementioned ICU studies focused on patients suffering from infection, our cohorts had patients from multiple disciplines.

The main aim of this study was to establish whether there are sex differences in the application of various scoring systems, as implied by other human studies. Nachtigall et al. (2011), for example, showed that men received increased intensive medical care compared to women, based on statistically significant differences in the value of TISS-28, a parameter for the intensity of care.[6] In one of the sepsis-subgroups of the aforementioned study, women died more often. One factor could be the potentially missing care.

Then again, another study showed that, despite having received an increased level of care and undergoing more invasive procedures, men presented a similar mortality rate.[25]

There are also inconsistencies in the SOFA score values on admission day. Nachtigall et al. (2011), found that women had lower SOFA score, but an increase in female mortality in a sepsis group, whereas Jacobson et al. (2012), found no SOFA differences on admission day, and yet women in a coagulations subgroup had a higher mortality rate.[6,18]

Nevertheless, according to numerous studies, there is a well-proven relation between mortality and score values, especially for the SOFA score.[15] This leads to the question whether these inconsistencies reflect the limitations of the intensive care scoring systems, or whether the results are influenced by sex issues.

The widespread use of general illness severity scores in the general ICU environment was analyzed in Vincent and Moreno's review (2010), who examined the most commonly used scoring systems.[13] The different scoring systems are useful tools, but they have different purposes and they measure different parameters: outcome prediction, characterization of disease severity and degree of organ dysfunction. Vincent and Moreno believe that the scores should be seen as complementing each other, rather than competing with one another.

Following this logic, we identified one scoring system on admission day from each area.

SAPS-II is used to assess disease severity upon admission, and to subsequently predict the outcome.[13,26]

SOFA is used to assess the degree of organ dysfunction, and – to a certain degree – is predictive of mortality.[15]

TISS-28 is used to assess disease severity and to compare patient care based on the measurement of the nursing workload. It has been shown, albeit indirectly, that higher scores are associated with worse outcomes.[13]

In the base analysis, male patients had a statistically significant higher SOFA and a tendency to higher scores for both SAPS-II and TISS-28, despite having the same ICU mortality rates as female patients.

In order to better assess the sex-score relation, a univariate logistic regression analysis was carried out. It showed a large effect size both in the joint and separate sex analyses in all three scores (all odds ratios are >1, as well as all 95% confidence intervals).

In other words, the hypothesis that scores are equally suitable for both male and female was confirmed. A ROC analysis comparison displayed no sex-specific differences in the test characteristics of the scores, and an equal validity is attested by the lack of interaction in the binary logistic regression analysis of all three scores.

Nevertheless, the theoretical and well-proven correlation between higher SOFA scores and higher mortality rates[15,24,27,28] was not demonstrated in this study population: male patients died as often as female ones. Explaining this lack of a correlation as a result of an increased care treatment for men has already been ruled out by different studies.[20,25] It is more likely that the scores lack a variable that better represents women's mortality risk. For instance, women receive more post-

operative transfusion of erythrocyte concentrate, which is significantly associated with increased post-operative morbidity.

The SAPS-score and the SOFA score, however, only encompass leukocyte concentration and thrombocyte concentration, respectively. Thrombocytopenias can also be associated with mortality,[29] but only if a >30% drop is exhibited over time.[30] A temporal measurement of that nature is not applicable for scoring systems such as SOFA, which are based on data only from the first 24 hours.

In summary, our findings support the hypothesis that there is no sex bias in the application of the three scores examined within our main study population.

Limitations

There are several limitations in this study. On the one hand, given the hypothesis, a classical RCT cannot be carried out. On the other hand, the analysis conditions and definitions used by other studies on this topic are often different. Some studies, for example, mention hospital mortality, while others refer to ICU mortality. In their analysis, some studies examine the mean scores, some the highest scores and others the average scores within a time range, which limit even more any comparison attempt. Furthermore, the majority of gender studies in the area of intensive care are closely related to infective and sepsis conditions.

Conclusions

Despite having higher score values on ICU admission day, men died as often as women during their ICU stay. We were able to demonstrate an absence of sex bias in the three ICU scoring systems examined.

Key messages

What is known

- Scoring systems allow for a standardized, objective assessment of patient morbidity and mortality risk.
- In the last two decades an increasing number of disparities have been detected in evidence-based medicine.

What is new

- No sex bias has been detected in the different scoring systems used within the present study population.

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