Intensive Care Med (2020) 46:727–736
https://doi.org/10.1007/s00134-019-05910-9

ORIGINAL

Sex-based differences in ED management of critically ill patients with sepsis: a nationwide cohort study

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Abstract

Purpose: To compare management and outcomes for critically ill women and men with sepsis in the emergency medical services (EMS), the emergency department (ED) and the ICU.

Methods: We used two prospectively compiled Swedish national quality registers, the National Quality Sepsis Registry and the Swedish Intensive Care Registry to identify a nationwide cohort of 2720 adults admitted to an ICU within 24 h of arrival to any of 32 EDs, with a diagnosis of severe sepsis or septic shock between 2008 and 2015.

Results: Patients were 44.5% female. In the EMS, a higher fraction of men had all vital signs recorded—54.4 vs 49.9% ($p=0.02$) and received IV fluids and oxygen—40.0 vs 34.8% ($p=0.02$). In the ED, men had completed 1-h sepsis bundles in 41.5% of cases compared to 30.0% in women ($p<0.001$), and shorter time to antibiotics—65 (IQR 30–136) vs 87 min (IQR 39–172) ($p=0.0001$). There was no significant difference between men and women regarding ICU nursing workload, mechanical ventilation or ICU length of stay. In severity-adjusted multivariable analysis, OR for women achieving a completed sepsis bundle, compared to men was 0.64 (CI 0.51–0.81). Thirty-day mortality was 25.0% for women and 23.1% for men (p = 0.24). Adjusted OR for female death was 1.28 (CI 1.00–1.64), but the increased mortality was not mediated by differential bundle completion.

Conclusions: Women and men with severe sepsis or septic shock received differential care in the ED, but this did not explain higher odds of death in women.

Keywords: Sepsis, Sex, Mortality, Management, ICU, ED, Emergency medical services

Introduction

Women receive differential care compared to men in coronary heart disease [1, 2], stroke [3], cancer [4], joint replacements [5], trauma [6], and other medical conditions. In the ICU, men are more likely to receive invasive procedures such as mechanical ventilation and catheterization [7–9], incur higher nurse workload, and receive longer ICU stays [10].

Sepsis contributes to one in every two to three hospital deaths [11]. Among the few interventions associated with improved survival are short time to antibiotics [12–15], and completion of sepsis bundles [13–16].

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The impact of patient sex on management of sepsis has been sparsely investigated. In a previous small study on severe sepsis and septic shock, we observed that men received antibiotics more rapidly than women [17]. We have identified only one single-center study systematically focused on the influence of sex on the management of critically ill septic patients in the ED [18, 19]. It found that men received antibiotics more promptly than women. Reports on sex and mortality from sepsis have shown conflicting results [9, 18, 20–25].

The aim of this multicenter study was to investigate if men and women with community-acquired severe sepsis or septic shock received differential management in the emergency medical services (EMS), the emergency department (ED) or the ICU; whether mortality differed and; if differential management in the ED explains differences in mortality.

Take-home message

In this nationwide cohort study of adults with severe sepsis or septic shock admitted via the emergency department within 24 h to the ICU, sepsis bundle completion was lower and time to antibiotics slower in women compared to men. Women had higher adjusted odds of dying, but the increase was not mediated by differential bundle completion.

Methods

Study design

We created a historical cohort based on all patients registered in the prospectively compiled National Quality Sepsis Registry (NQSR) [26] with concurrent registration in the Swedish Intensive Care Registry (SIR) www.icuregswe.org [27]. The NQSR comprises patients, aged 18 and over, admitted to an ICU with a diagnosis of community-acquired severe sepsis or septic shock within 24 h of arrival to an ED [26]. In NQSR, infectious disease (ID) specialists at each site screen hospital records. Eligible patients are entered into the NQSR database. The SIR currently covers all general ICUs in Sweden but has not had complete coverage during the study period. This report includes patients registered in NQSR from January 2008 until December 2015 and follow-up on 30-day mortality until data extraction on March 1 2016. Data on NQSR patients were then extracted from SIR. Additional information on comorbidity was obtained from the Swedish National Inpatient Register [28] and the Swedish Prescribed Drug Register [29].

Data collection, exclusion criteria, definitions and variables

Severe sepsis and septic shock were diagnosed using a modified version of the 1992 sepsis definition [30], in practice accepting a diagnosis of severe sepsis on the basis of infection + organ dysfunction (Online supplement). Processes of care in the EMS, ED and ICU are listed in Table 2, including sepsis bundle and time to antibiotics as the main variables of interest. The sepsis bundle required: IV fluids; lactate/base excess measured; blood cultures before antibiotics and; administered antibiotics—all within 1 h. A composite nursing workload score was built from quartiles of three nursing workload scores. For further details on data collection, variables in NQSR and SIR and definitions, including SAPS3 and tSAPS3, see Online supplement.

Cohort

By December 2015, 3240 patients were recorded in NQSR. Of these, 520 were excluded yielding 2720 in the final cohort, Fig. 1. Patients were admitted via 32 EDs to 42 ICUs; 904 in 7 university hospitals and 1816 patients in 25 county hospitals.

Statistical methods

Chi square and Wilcoxon rank sum tests were used to assess the distribution of risk factors for sepsis bundle completion and 30-day mortality between men and women. Logistic regression was used to estimate odds ratios (ORs) for sepsis bundle completion and 30-day mortality. Generalized estimating equations (GEEs) were used to account for the possibility of dependency between individuals admitted through the same ED. In the analysis of associations between sex and ED processes of care, we selected a priori standard clinical variables known or expected to be potential confounders of the sex quality of care association: arrival by ambulance [31]; age; vital signs (generally used for triage scoring); comorbidities; and suspected infectious focus. The selected covariates were assessed in several multivariable models, representing successive decision points in the management of a septic patient, from initial triage using just age and mode of arrival, adding vital signs, past medical history and finally suspected diagnosis for the main model. As an auxiliary analysis, we adjusted for SAPS3, which is not calculated until ICU admittance, up to 24 h after ED triage, but is the best global measure of severity in the database, and a potential confounder. ORs were also estimated in subgroups of participants classified according to age, body temperature, Charlson score, SAPS3 score, year of inclusion and hospital type. Homogeneity of estimates across subgroups was assessed using likelihood ratio tests.

Among risk factors for mortality, we similarly selected a priori potential confounders to the sex–mortality association. SAPS3 was used as measure of disease severity alongside body temperature, which we have shown to be an important determinant of outcome [32] and

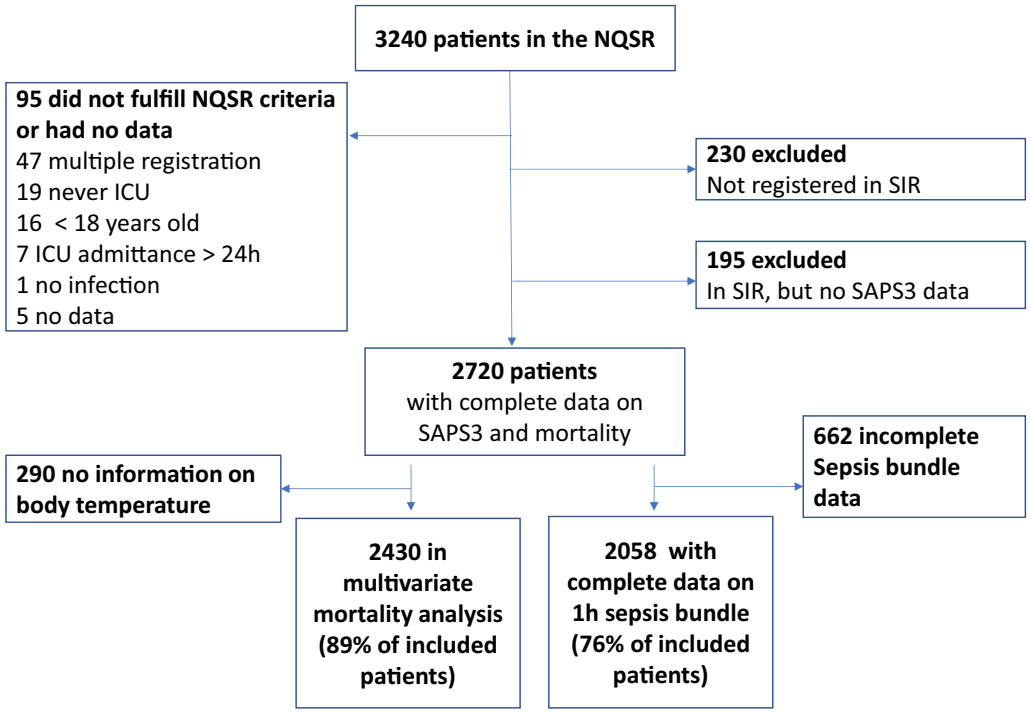

Fig. 1 Study flow chart. *NQSR* National Quality Sepsis Registry, *SIR* Swedish Intensive Care registry, *ICU* Intensive Care unit. Ninety-five patients were excluded because they did not fulfill NQSR inclusion criteria or had no data registered. 230 were excluded since they were not registered in SIR and 195 patients since a different severity score was used in the ICU and they lacked SAPS3 data. For transparency, baseline variables, outcomes and quality of care for the latter two groups minus 14 patients for whom 30-day mortality was not registered are shown in Tables 1 and 2

which differs in men and women. Treatment restrictions and incorrect antibiotics were also deemed important risk factors and possible confounders. In an additional model, infectious diagnoses and Charlson comorbidities not included in SAPS3 were added. A directed acyclic graph shows the hypothesized relationships between different types of variables in our analyses, Online supplement figure e1. Analyses were performed in models with and without treatment in the form of completed sepsis bundles. Mediation of the effects of sex on mortality by bundle fulfillment and SAPS3 score was evaluated using Stata's paramed command. Stata version 15 was used for statistical analysis (StataCorp, College Station, TX).

Results

The final cohort included 2720 patients. Table 1 shows patient characteristics and outcomes and, for transparency, data from 411 patients excluded since they were not registered in SIR or lacked SAPS3 data. Females constituted 44.5% of patients and median age was 68 for both sexes. Men had marginally higher median SAPS3 score—65 vs 64, and higher Charlson score—2.56 (±2.35, mean SD) vs 2.12 (±2.11, mean SD). Higher severity among men was confined to patients under 60—SAPS3 59 vs 55, whereas severity did not differ in the age cohorts 60–69 (SAPS3 63), 70–79 (69), and 80 and over (71). Thirty-day mortality was 25.0% for women and 23.1% for men ($p=0.24$). In those aged 50 and under ($n=453$), mortality was 6% for women and 10% for men ($p=0.13$). At all cutoffs over the age of 50, mortality was higher among women: >50 ($n=2267$) 29 vs 25% ($p=0.05$); >60 ($n=1881$) 31 vs 27% ($p=0.02$); >70 ($n=1175$) 37 vs 31% ($p=0.02$); >80 ($n=479$), 46 vs 38% ($p=0.06$).

Sex and differential care

Table 2 shows crude process of care variables. In the EMS, more men had all vital signs recorded and received IV fluids and oxygen. In the ED, men had complete 1 h sepsis bundles in 41.5% of cases compared to 30.0% in women ($p<0.001$), and shorter time to antibiotics—65 (IQR 30–136) vs 87 min (IQR 39–172) ($p=0.0001$). ICU nursing workload, mechanical ventilation and length of stay were equally distributed.

Figure 2 shows sepsis bundle completion and time to antibiotics stratified according to age, suspected site of infection, comorbidity, SAPS3 score, respiratory rate and body temperature. Men had higher sepsis bundle completion and shorter time to antibiotics in almost all strata, while the reverse did not occur in any stratum.

Table 1 Patient characteristics and outcomes

Characteristic	All patients	Women	Men	Excluded women	Excluded men
Number of patients	2720	1210 (44.5%)	1510 (55.5%)	172	239
Demography					
Age, median, IQR	68, 57–77	68, 56–77	68, 58–77	69, 55–78	69, 58–78
Severity of disease—SAPS3	64, 56–74	64, 55–73	65, 56–75	–	–
Underlying comorbidity					
CCI, median, IQR (Mean, SD)	2, 1–4 (2.37 ± 2.25)	2, 0–3 (2.12 ± 2.11)	2, 1–4 (2.56 ± 2.35)	–	
Focus of infection (% of patients)					
Pneumonia	33.8	30.9	36.1	36.1	35.0
Urinary tract	20.5	21.3	19.9	20.9	20.7
Abdominal infection	11	11.9	10.2	14	13.1
Other focus	21.5	21.9	21.3	15.1	20.7
Unknown ($n = 308$) and missing ($n = 51$)	13.2	14	12.6	14	10.6
Etiology (%)					
Gram-positive, $n = 965$	35	35	35	37	35
Gram-negative, $n = 871$	32	33	31	36	34
Other, $n = 119$	4	4	5	3	3
Unknown, $n = 705$ and missing, $n = 60$	28	27	29	24	28
Vital signs, % of patients and lactate					
BT, °C[a], median, IQR	38.1, 37–39.1	38, 37–39	38.2, 37–39.1	38.2, 37–39	38.2, 37–39
SBP, mm Hg[b], median, IQR	110, 90–131	108, 90–130	110, 90–132	106, 88–133	105, 86–132
SBP < 90 mm Hg	23.1	23.7	22.7	26.1	28.1
RR > 20/min[c]	77.4	74	80	82.1	81.1
Saturation < 90%[d]	26.8	27.9	25.9	33.8	37.8
RLS > 1[e]	25.1	25.2	25	29.7	31.8
PR > 90 bpm[f]	75.6	76.2	75.1	77.6	74.8
Lactate mmol/L, median, IQR[g] median, IQR	3.6, 2.1–5.9	3.7, 2.2–5.9	3.5, 2.5–5.8	3, 1.8–5	3, 1.8–5
Patient outcomes					
30-day mortality, %	24	25	23.1	22.1	22.2
LOS, survivors ICU, hours	54, 26–135	57, 28–140	52, 25–131	–	–
LOS, survivors hospital, days	14, 8–26	15, 8–26	13, 8–25	9, 5–19	9, 4–21

BT body temperature, *CCI* Charlson comorbidity index, *IQR* interquartile range, *LOS* length of stay, *PR* pulse rate, *RLS* reaction level scale (1 = normal, > 1 = affected consciousness), *RR* Respiratory rate, *SAPS3* Simplified Acute Physiology Score 3, *SBP* systolic blood pressure, *SD* standard deviation, *h* hours, *d* days. Excluded patients = patients who were not registered in SIR or who lacked SAPS3 data. Vital signs and lactate measured on ED admittance

[a] Data missing for 290 patients (11%)

[b] Data missing for 69 patients (3%)

[c] Data missing for 210 patients (8%)

[d] Data missing for 107 patients (4%)

[e] Data missing for 479 patients (18%)

[f] Data missing for 79 patients (3%)

[g] Data missing for 755 patients (28%)

Sepsis bundle completion

Figure e2 shows OR for sepsis bundle completion in women compared to men in univariate and different multivariable models, representing available information at successive management decision points in the ED. In the main model, OR for women achieving a completed sepsis bundle, compared to men, was 0.64 (CI 0.51–0.81), adjusted for mode of arrival to the ED, age, vital signs, comorbidities and suspected infectious focus. In an auxiliary analysis, we adjusted for SAPS3 score, which yielded an OR of 0.59 (0.50–0.70). Over all different models, ORs for women achieving a completed sepsis bundle varied within a narrow range of 0.57–0.64.

Subgroup analyses

We observed no statistical support for heterogeneity in the ORs of bundle fulfillment by sex according to

Table 2 Processes of care in women and men

Characteristic	All patients	Women	Men	Women vs men	Excluded women	Excluded men	Excluded women vs men
				p value			*p* value
Number of patients	2720	1210 (44.5%)	1510 (55.5%)		172	239	
Processes of care,% of patients							
EMS							
Arrival in ambulance[a]	80.6	79.7	81.3	0.3	79.3	82.9	0.4
Saturation, SBP, RR, PR all measured and recorded in ambulance	52.4	49.9	54.4	0.02	47.8	46.7	0.8
Oxygen and IV fluids in ambulance	37.7	34.8	40	0.02	23.5	41.2	0.002
Emergency department							
All vital signs measured and recorded in ED	61.8	60.9	62.6	0.37	59.9	59.9	1
Time to AB[b] median, IQR	75 min, 34–150	87 min, 39–172	65 min, 30–136	0.0001	81 min, 46–200	61 min, 25–130	0.003
AB within 1 h	43.6	38.6	47.6	< 0.001	39.7	50.0	0.05
AB within 3 h	80.6	77.1	83.5	< 0.001	73.7	85.9	0.004
Iv fluids within 1 h[c]	82.3	80.9	83.5	0.08	81.3	86.3	0.3
Lactate/BE measured < 1 h	77.4	75.2	79.1	0.02	65.7	76.0	0.02
BC before AB[d]	93.6	91.8	95.1	0.001	94.5	95.4	0.8
Lactate within 1 h	70.4	68.4	72	0.09	60	68.8	0.1
Bundle1h[e]	36.4	30	41.5	< 0.001	31.3	45.4	0.05
ICU					–	–	
Composite NWS median, IQR (mean, SD)[f]	2, 1–3 (2.35 ± 1.14)	2, 1–3 (2.36 ± 1.14)	2, 1–3 (2.35 ± 1.15)	0.84	–	–	
Mechanical ventilation	30.1	29.3	30.7	0.43	–	–	
Incorrect AB	7.5	7.1	7.8	0.49	3.5	4.2	0.7
Treatment limitations 48 h	20.2	20.2	20.2	0.98	12.8	15.2	0.5

AB antibiotics, *BC* blood culture, *BE* base excess, *BT* body temperature, *Bundle1h* completed sepsis bundle within one hour, *EMS* emergency medical services, *ED* emergency department, *IQR* interquartile range, *NWS* nursing workload score, *PR* pulse rate, *RR* respiratory rate, *SBP* systolic blood pressure, *SD* standard deviation. Excluded patients = patients who were not registered in SIR or who lacked SAPS3 data

[a] Data missing for 85 patients (3%)

[b] Data missing for 311 patients (11%)

[c] Data missing for 228 patients (8%)

[d] Data missing for 336 patients (12%)

[e] Complete data missing for 662 patients (24%)

[f] Data missing for 52 patients (2%)

different subgroups of age ($p = 0.42$), body temperature ($p = 0.33$), comorbidity ($p = 0.60$), severity ($p = 0.84$), year of inclusion ($p = 0.15$) or tertiary/secondary hospitals ($p = 0.12$), in models adjusted for mode of arrival to the ED, age, vital signs, body temperature, Charlson score and preliminary focus of infection. The stratum-specific ORs are shown in Online supplement Table e1.

Sex and mortality

Table 3 shows ORs for individual risk factors and from multivariable analyses for 30-day mortality. In crude analysis, the OR for death in women compared to men was 1.11 (CI 0.91–1.36). In multivariable analysis, the OR was 1.28 (CI 1.00–1.64) adjusted for tSAPS3, body temperature, incorrect antibiotics and treatment limitations. The estimated absolute risk difference was 31 (CI 0–62) additional female deaths per 1000 ICU admissions. Addition to the model of treatment in the form of completed sepsis bundles led to the loss of 548 patients due to missing values; the OR estimate remained unchanged at 1.28 (CI 0.97–1.70). There was no association between bundle completion and mortality in either uni- or multivariable

(See figure on next page.)

Fig. 2 **a**, **c**, **e**, **g**, **i** and **k** (left column) shows fraction of patients who achieved a 1-h sepsis bundle stratified by sex and **a** age ($n=2058$), **c** diagnoses ($n=2058$), **e** Charlson comorbidity index ($n=2058$), **g** SAPS3 quartiles ($n=2058$), **i** respiratory rate ($n=1936$), and **k** body temperature ($n=1882$). Figure 1b ($n=2409$), d ($n=2409$), f ($n=2409$), h ($n=2409$), j ($n=2259$) and l ($n=2191$) (right column) were similarly stratified to show time to antibiotics. *Indicates p value < 0.05, ** < 0.01, *** < 0.001 and **** < 0.0001. †Indicates a value between 0.05 and 0.1 and *n.s* indicates non-significant. *AB* antibiotics, *Pneum* pneumonia, *UTI* urinary tract infection, *Abdom* abdominal infection, *Other* other focus of infection, *Unkn* unknown focus of infection, *Ch* Charlson score, *SAPS3* Severe Acute Physiology Score 3, *RR* respiratory rate, *Temp* body temperature

analysis. Further addition of infectious diagnoses and Charlson comorbidities not included in SAPS3 yielded an OR of 1.29 (CI 0.97–1.71). The increase from lower OR in univariate to higher in multivariable analysis is explained by the addition of tSAPS3 which alone increased OR for female death from 1.11 to 1.26 (CI 1.01–1.57). The major contribution was from non-physiologic SAPS3 subscores—OR was 1.22 (0.98–1.52) when vital signs and laboratory SAPS3 subscores were subtracted.

A formal mediation analysis, table e2, Online supplement, showed that the effects of sex on mortality could not be explained by bundle completion; the odds ratio for the indirect effect of being female was 0.99 (CI 0.91–1.07), whereas the direct effect of 1.26 (CI 0.99–1.60) was similar to the total effect of 1.24 (0.97–1.59). The absence of mediation by bundle completion is in line with the result that bundle completion does not decrease mortality. Examining SAPS3 as a mediator, we found evidence of both an indirect and direct effect; the direct effect amounted to 1.25 (CI 1.03–1.51) and the indirect 0.91 (0.85–0.98), quantifying the opposing consequences of female sex—beneficial in terms of disease severity and adverse in terms of other factors. Note that in the analysis considering SAPS3 as a mediator, sex is interpreted as biological sex, whereas in the other analyses sex is interpreted as gender (as observed by healthcare staff), and severity is then considered a confounder.

Adjusted OR for female death did not significantly differ between those who did and did not receive 1-h bundle completion, 1.28 (0.81–2.03) vs 1.29 (0.95–1.77), $p=0.86$, or among those with and without treatment restrictions, 1.42 (0.99–2.05) vs 1.24 (0.94–1.66), $p=0.48$.

Discussion

Main findings

In this nationwide cohort study, we compared management in the EMS, ED and ICU of women and men admitted to an ICU with community-acquired severe sepsis or septic shock. In the ED, a 1-h sepsis bundle was fulfilled 38% more often and median time to antibiotics was 34% faster in men than in women. The findings were consistent in nearly every subgroup, whichever way we stratified data, and in multivariable analyses adjusted for potential confounders. Using models representing successive clinical decision points, we showed consistently around 36–43% lower OR for women achieving a complete 1-h sepsis bundle compared to men regardless of mode of ED arrival, age, vital signs, comorbidities, suspected focus or severity. Small differences favoring men were also found in the EMS, but during ICU stay, no differential management was found concerning nurse workload, mechanical ventilation or ICU length of stay.

After risk adjustment, women had 28% higher odds of death at 30 days, but we found no evidence that the increased mortality was mediated by lower bundle completion. In crude analysis, the mortality difference was most pronounced in patients over the age of 50.

Differential management

A previous study of 340 patients with severe sepsis presenting to the ED [33] identified female sex as one factor among several associated with nonadherence to early goal-directed therapy.

Only one previous study [18, 19], has systematically explored the issue of sex and management of critically ill sepsis patients presenting to the ED. Among 814 patients with severe sepsis or septic shock, it was found that men received antibiotics 20% faster than women (184 vs 153 min, $p<0.001$) [19]. Unlike the present study, it found no significant difference in sepsis bundle completion. The studies differ, however, the previous study was single center, participated in the surviving sepsis campaign (SSC) and had quality assurance teams providing performance feedback. The resuscitation bundle had six elements and a 6-h time frame, whereas the Swedish bundle had just four elements, and a 1-h time frame. The Swedish register is nationwide, multicenter, has no SSC association and only recently has a minority of Swedish hospitals begun to provide regular feedback to physicians regarding time to antibiotics. We believe that our study is representative of the majority of hospitals which are neither SSC associated nor have sepsis quality assurance teams.

Mandated protocols for detection and treatment of sepsis have been associated with improved survival as shown by Seymour [14]. They may also help to equalize management. Seymour found that although 3-h sepsis bundle compliance was higher in men (83.8 vs 81.1%, $p<0.001$), even after introduction of mandated protocols, the relative difference was much smaller than in

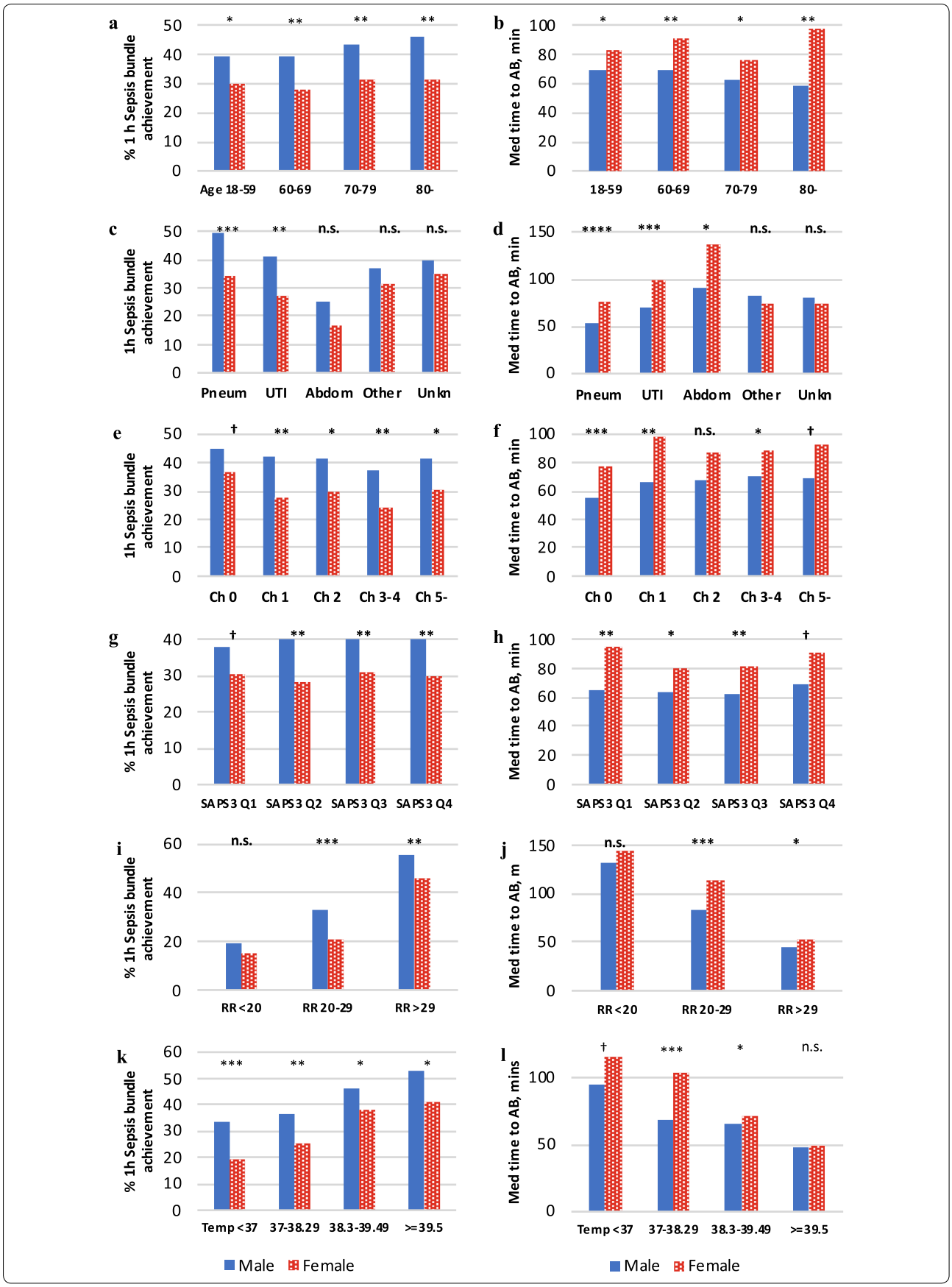
a
% 1 h Sepsis bundle achievement
Age 18-59
60-69
70-79
80-
b
Med time to AB, min
18-59
60-69
70-79
80-
c
1h Sepsis bundle achievement
Pneum
UTI
Abdom
Other
Unkn
d
Med time to AB, min
Pneum
UTI
Abdom
Other
Unkn
e
1h Sepsis bundle achievement
Ch 0
Ch 1
Ch 2
Ch 3-4
Ch 5-
f
Med time to AB, min
Ch 0
Ch 1
Ch 2
Ch 3-4
Ch 5-
g
% 1h Sepsis bundle achievement
SAPS 3 Q1
SAPS 3 Q2
SAPS 3 Q3
SAPS 3 Q4
h
Med time to AB, min
SAPS 3 Q1
SAPS 3 Q2
SAPS 3 Q3
SAPS 3 Q4
i
% 1h Sepsis bundle achievement
RR <20
RR 20-29
RR >29
j
Med time to AB, m
RR <20
RR 20-29
RR >29
k
% 1h Sepsis bundle achievement
Temp <37
37-38.29
38.3-39.49
>=39.5
l
Med time to AB, mins
Temp <37
37-38.29
38.3-39.49
>=39.5
Male
Female
Male
Female

Table 3 Risk factors for 30-day mortality[a]

Characteristic	Univariate analysis ($n=2720$)			Multi-variate analysis[b] ($n=2430$[c])		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Demography						
Sex (female)	1.11	0.91–1.36	0.30	1.28	1.00–1.64	0.05
Age	1.04	1.03–1.05	< 0.001			
Severity of disease						
SAPS3 (per unit increase)	1.07	1.06–1.08	< 0.0001			
tSAPS3 (per unit increase)	1.07	1.06–1.08	< 0.0001	1.06	1.05–1.07	< 0.001
Body temperature, per °C increase	0.78	0.75–0.82	< 0.001	0.82	0.77–0.87	< 0.001
Quality of care						
1 h sepsis bundle achieved	1.06	0.89–1.28	0.51			
Incorrect AB	1.50	1.06–2.12	0.02	1.73	1.13–2.65	0.01
Treatment limitations						
At 48 h	10.30	8.42–12.62	< 0.001	8.06	6.42–10.12	< 0.001

AB antibiotic, *ED* emergency department, *ICU* Intensive Care Unit, *SAPS3* Simplified Acute Physiology Score 3, *tSAPS3* SAPS3 minus points for temperature component of score, treatment limitations: any treatment limitations ordered within 48 h of admittance [a]estimated by GEE logistic regression [b]adjusted for all variables in the column. [c]Minus 290 patients who lacked information on body temperature

our study. Comparison is difficult however, since the study included patients with lower illness severity and for various reasons excluded more than half of patients who were identified from analysis.

In the ICU, we found no evidence of differential management, which contrasts with previous studies which have found less deep venous thrombosis prophylaxis, fewer hemodialysis catheters [9], less invasive mechanical ventilation [9, 20], and shorter LOS [20] in women compared to men. Possible reasons for discrepant results include differences in study sizes, studied variables and case mixes. Concordant with this report, another large Swedish ICU study [10] reported higher nurse workload and longer ICU LOS for men among overall admissions but not in the sepsis subgroup.

Mortality

Previous studies on sex and mortality among critically ill sepsis patients show conflicting results: some found higher mortality among women [9, 21, 22] some in men [20, 34], whereas others reported no difference [18, 24, 25]. One study [10] analyzed SIR for sex-based differences in outcome and use of ICU resources in all ICU admissions from 2008 through 2012, and in subgroups including 9830 patients with sepsis (including postoperative and nosocomial infections). Adjusted OR for 30-day mortality from sepsis for women was 1.17 (CI 95% 1.03–1.33, $p=0.002$). The result was deemed interesting but statistically insignificant (a conservative significance level was set to < 0.001 due to multiple testing), yet is in line with our findings.

We found no association between mortality and sepsis bundle completion. This study was not designed for a thorough scrutiny of all hospital procedures. Therefore, we lack important information needed for a detailed analysis of the mediators of increased odds of death. Nonetheless, it is possible that unequal treatment reflected in sepsis bundle completion and time to antibiotics also affects other aspects of care not captured in our data, which may have contributed to worse outcomes in women.

Strengths and weaknesses

Our study has several strengths. First, it is multicenter, is well powered for detection of treatment imbalances, and draws on information from independent national registers for an unbiased nationwide identification of patients with community-acquired severe sepsis and septic shock. Second, models were adjusted for a wide range of potential confounders. Third, results on treatment imbalances are robust and remain stable in subgroup analyses and in multivariable models. A limitation is that the study reflects only Swedish conditions, but since Sweden is ranked among countries with the lowest gender gap and inequality [35, 36], conditions may plausibly be worse elsewhere. The study suggests inferior care for female patients, but cannot conclusively demonstrate that this is the case. Residual confounding from factors not recorded in the databases cannot be ruled out.

The register does not include information on patients admitted to hospital wards. This may have resulted in selection bias if some women received equal or better treatment in the EMS or ED and thereby avoided ICU

admission. However, to our knowledge, there are no studies suggesting that septic women receive superior EMS/ED care or respond better to treatment than men.

The NQSR is based on routine medical records, likely explaining missingness of complete data, particularly on sepsis bundles in 24% of cases. Missingness has been addressed through careful analysis of existing data and sensitivity analyses. Physiological data used for SAPS3 calculations were complete in 79% of cases. This compares favorably with a general Swedish ICU cohort, in which 59% of patients had complete variables, but for which SAPS3 was nevertheless considered to perform well [37].

SAPS3 is calculated on ICU admittance, up to 24 h after ED arrival, and partly reflects post-resuscitation status—which introduces the risk of adjusting for effects of treatment [38]. However, since omitting the SAPS3 subscores that reflect acute physiological derangement made little difference for the estimates, such a bias likely had a low impact. Even though evaluation of infection was performed by experienced ID specialists, some patients may have been incorrectly diagnosed. Finally, since the NQSR only encompasses hospitals where ID physicians are present, and registration rates vary between centers, it does not capture all eligible patients [26].

Conclusions

Among critically ill patients with severe sepsis or septic shock, women had lower sepsis bundle completion and longer time to antibiotics in the ED compared to men. Differences were pronounced and consistent in subgroups and in analyses adjusted for potential confounders including severity of disease. There were also small differences favoring men in the EMS, but not in the ICU. In adjusted analyses, women had 28% higher odds of dying than men, but the increase was not mediated by lower bundle completion. Further studies are needed to explore underlying causes of the observed differences in treatment and outcome, and to examine their occurrence in a general ED population.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05910-9) contains supplementary material, which is available to authorized users.

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Acknowledgements
Open access funding provided by Karolinska Institute. We want to express our deep gratitude to dedicated colleagues throughout Sweden who painstakingly keep the quality registers up to date.

Author contributions
JSC designed the study, analyzed and interpreted data, wrote the paper, constructed tables and figures and performed literature search. MI contributed to study design, data analysis and interpretation and reviewed the text. AN contributed to data analysis and reviewed the text.

Funding
JSC is supported by Swedish Government Research Grant and Center for Innovative Medicine (CIMED), Karolinska Institute. MI is supported by an investigator grant from the Swedish Government Funds for Clinical Research (ALF).

Compliance with ethics standards

Conflicts of interest
All authors report no conflict of interest.

Ethical approval
The study was performed according to the ethical standards of the 1964 Declaration of Helsinki and was approved by the ethical review board in Stockholm (2015/901-32). Written informed consent was waived.

Publisher's Note

Received: 26 June 2019 Accepted: 19 December 2019
Published online: 23 January 2020

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