Patient survival, predictive factors and disease course of severe sepsis in Czech intensive care units: A multicentre, retrospective, observational study

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Background. Severe sepsis/septic shock is associated with high mortality. In Central Europe, there is a dearth of information on the prevalence and treatment of severe sepsis. The EPOSS (Data-based Evaluation and Prediction of Outcome in Severe Sepsis) project launched in 2011 was aimed at collecting data on patients with severe sepsis/septic shock.
Methods. The EPOSS study processes data from the EPOSS project database, and is a retrospective, multicentre, observational study. This included all consecutive patients aged 18 and over who were admitted to participating ICUs from 1 January 2011 to 5 November 2013 and met the inclusion criteria of severe sepsis/septic shock. The primary endpoint was to analyse the relationship between in-hospital mortality (either in ICU or after discharge from ICU) and the type and number of fulfilled diagnostic and treatment interventions during the first 6 h after the diagnosis of severe sepsis/septic shock.
Results. The collected dataset involved 1082 patients meeting the criteria of severe sepsis/septic shock. Following data validation, a final dataset of 897 patients was obtained. The average age of the patient group was 64.7 years; mortality at discharge from EPOSS ICUs was 35.5% and from hospital 40.7%. Of the 10 evaluated diagnostic and treatment interventions within the initial 6 hours of identifying severe sepsis/septic shock (i.e. fulfilment of SSC bundles), four or five diagnostic and treatment interventions were administered to 58.4% patients. Combined diagnostic and treatment interventions associated with the lowest in-hospital mortality were: CVP of ≥8-12 mm Hg & MAP of ≥65 mm Hg & Urine output at ≥0.5 mL/kg/h & Lactate of ≤4.0 mmol/L & Initial lactate measured & Antibiotics in the first hour. Lactate at <4 mmol/L and MAP of ≥65 mm Hg remained statistically significant even after adjustment for patient age and APACHE II score. Statistically significantly increased in-hospital mortality was found in patients admitted from general departments (45.7%) or from other ICUs (41.6%), compared to a lower in-hospital mortality of patients transferred from outpatient clinics (26.5%) or Emergency (38.0%). Severe sepsis/septic shock patients transferred from the department of internal medicine were associated with a higher in-hospital mortality (45.1%) than surgical patients (35.5%).
Conclusions. The most effective measures associated with the lowest in-hospital mortality in septic shock patients were CVP of ≥8-12 mm Hg, MAP of ≥65 mm Hg, urine output at ≥0.5 mL/kg/h, initial lactate level of ≤4.0 mmol/L and administration of antibiotics within the first hour.

Key words: severe sepsis, septic shoc, lactate, mortality, assessment

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BACKGROUND

Sepsis, severe sepsis and particularly septic shock - the most severe form of systemic response to infectious insult - are all associated with a high mortality rate of 20-70% depending on patient age, number of failing organ systems and/or comorbidities[1-3] leaving long-term devastating effects in survivors[4]. A number of national epidemiological

studies on patients with severe sepsis/septic shock have been described in the literature[5-8]. In the Czech Republic, there is a dearth of publications on both the prevalence and treatment of severe sepsis[9]. The EPOSS (Data-based **E**valuation and **P**rediction of **O**utcome in **S**evere **S**epsis) project was launched in 2011 with the aim of collecting data on patients with severe sepsis/septic shock and to aid in the evaluation of treatment efficacy[10]. The EPOSS project was conceived as a research project aiming to establish parametric documentation of the treatment of severe sepsis directly in clinical practice and consists of two parts: the EPOSS database (a collaborative programme in which multiple ICUs continuously collect data on severe sepsis) and the EPOSS study (analysis of data gathered in the EPOSS database). This article provides a summary of the results of the EPOSS study. The study assessed compliance with diagnostic and treatment interventions Sepsis Surviving Guidelines during the first 6 hours after the diagnosis of severe sepsis/septic shock. We recorded in-hospital mortality in relation to department from which the patients were transferred to the EPOSS ICU. The study also aimed to identify the most effective combination of diagnostic and treatment interventions related to in-hospital mortality of severe sepsis/septic shock.

METHODS

According to the STROBE statement[11].

Setting and study design

The EPOSS project processes data from the EPOSS project database, and is a retrospective, multicentre, observational study designed to assess both clinical and epidemiological data of ICU patients with severe sepsis in the Czech Republic. The Ethics Committee for Multicentric Trials of the University Hospital in Brno approved the observational study with the need for patient informed consent being waived.

Participants

All patients aged 18 and over who were consecutively admitted to participating ICUs and met the inclusion criteria of severe sepsis/septic shock as defined by the ACCP/SCCM were included[12]. The condition for patient enrolment was meeting the criteria of severe sepsis/septic shock identified either within the first 24-hour stay in EPOSS-ICUs, or within an interval of 24 h prior to admission to EPOSS-ICUs, combined with at least one of the criteria of organ dysfunction or clinical or laboratory signs of hypoperfusion according to "Score to assess
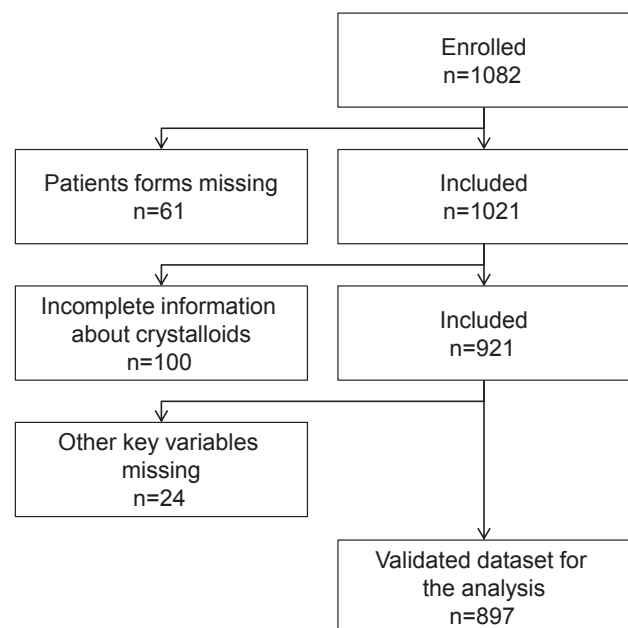

Fig. 1. Flow chart of data validation.

Table 1. Comparison of basic characteristic of patients included and excluded (incomplete data forms) from the analysis.

| | | Patient selection for analysis (n) | | P |
		Included (897)	Excluded (185)	
Gender	Female	342 (38.1%)	82 (44.3%)	0.118
	Male	555 (61.9%)	103 (55.7%)	
Age at enrollment	median (5-95% percentile)	66.0 (21.0; 92.0)	64.0 (35; 84.0)	0.932
Age category	Up to 60 yrs.	295 (33.0%)	65 (39.4%)	0.331
	60-70 yrs	273 (30.5%)	48 (29.1%)	
	70-80 yrs.	193 (21.6%)	34 (20.6%)	
	More than 80 yrs.	133 (14.9%)	18 (10.9%)	
SOFA score	median (5-95% percentile)	10.0 (0.0; 20.0)	10.0 (73.0; 17.0)	0.551
APACHE II	median (5-95% percentile)	25.0 (2.0; 53.0)	28.0 (12.0; 43.0)	0.055
BMI (kg/m^2)	median (5-95% percentile)	27.0 (11.0; 69.1)	27.3 (19.0; 46.0)	0.533
BMI category	<= 20.0	62 (6.9%)	11 (6.9%)	0.315
	20.1-25.0	266 (29.7%)	51 (31.9%)	
	25.1-30.0	314 (35.1%)	43 (26.9%)	
	30.1-35.0	147 (16.4%)	32 (20.0%)	
	35.1+	106 (11.8%)	23 (14.4%)	
In-hospital mortality		365 (40.7%)	70 (37.8%)	0.470

Continuous data is described by median and range and tested using Mann Whitney U test. Categorical variables are described by absolute and relative frequencies and tested by ML Chi square test.

the incidence of organ dysfunction/failure in intensive care units" (SOFA) (ref.[13]). Inclusion criteria were always checked on discharge (even for patients who died in the hospital). Patients with incomplete data in their records were excluded (Table 1), (Fig. 1). Appendix 2 shows participating departments [see Additional file - Appendix 2]. The reference period for patient enrolment in the study was from 1 January 2011 to 5 November 2013. The aim of this article is to summarise data for the first one thousand patients in the EPOSS database. Regarding participation in the study, all ICUs in general, teaching and university hospitals in the Czech Republic were invited to cooperate. Participation by individual ICUs was voluntary. Three types of ICU were recorded in the EPOSS project database: surgical, medical and mixed. In the reference period, the following indicators were monitored in participating ICUs: the number of beds, the total number of patients, in-hospital mortality and the average Acute Physiology and Chronic Health Evaluation II (APACHE II) (ref.[14]) score of all patients in a given institution within the first 24 h of admission.

Data management

The project database was developed and maintained by the Institute of Biostatistics and Analyses, Masaryk University in Brno. Prior to launching the study, representatives of participating centres were trained in entering data into the registry. The project manager communicated electronically with data submitters, and centres involved in the project received a monthly report on the actual number of patients enrolled in the study. Detailed instructions for data entry, as well as the description, professional starting points, organisation and objectives of the project were available to all participants throughout the duration of the study at http://eposs.registry.cz. The Steering Committee continuously coordinated the collection and evaluation of data, and its members were always available to solve any issues.

Patients were monitored until their discharge from the hospital, or until death. Patients' records were used as the data source; data were retrospectively entered in an electronic form and sent to the research database through a web user interface.

The TrialDB application, which was adopted for the EPOSS project, was initially developed by the Centre for Medical Informatics, Yale University School of Medicine (Connecticut, US), and further amended by the Institute of Biostatistics and Analyses of the Faculty of Medicine and the Faculty of Science of Masaryk University (IBA).

The core of the TrialDB data centre is composed of databases administered in the ORACLE 11g system. Such a database is accessed by a web application installed in the application server. The web application is implemented as a package of ASP (Active Server Pages); users may use a current web browser for access, i.e. it is not necessary to install any new software or other accessories. The supported browsers are IE 5.5+, Google Chrome and Mozilla Firefox. Unfortunately, support for rather obsolete browsers is necessary, as they are still broadly used in Czech hospitals.

All the communication between the client application and the server is made via a secured encrypted HTTPS protocol. Only centrally administered and registered users can access the application after entering a correct username and password allocated by the system administrator.

Measurement

Data were collected during the enrolment of patients into the study. An additional file shows this in more detail [see Additional file – Appendix 3].

Urine output was assessed as a goal of ≥0.5 mL/kg/h achieved in the first 6 h, or ≥3 mL/kg/6h respectively. Administration of crystalloid bolus ≥30 mL/kg at MAP≤65 mm Hg was assessed collectively over the first 6 hours. Other diagnostic and treatment goals were evaluated after at least 6 h of treatment.

Outcome Assessment

The assessed primary endpoint was mortality until discharge from the hospital. We analysed the relationship between in-hospital mortality and the type and number of fulfilled diagnostic and treatment interventions in EPOSS ICUs. An evaluation viewpoint of each diagnostic and treatment intervention was whether it was (or was not) fulfilled within the initial period of six hours after the diagnosis of severe sepsis/septic shock (Table 2). The categories of fulfilled diagnostic and treatment interventions were defined on the basis of their interpretation consistency and adequate sample size. The reference cat-

Table 2. The diagnostic and treatment interventions, assessed within the initial 6 h of identifying severe sepsis/septic shock.

Initial lactate measurement (YES/NO)

Taking of blood cultures prior to antibiotics administration (YES/NO)

Administration of broad-spectrum antibiotics during the first hour of identifying severe sepsis/septic shock (YES/NO)

Administration of crystalloid bolus ≥30 ml/kg at MAP≤65 mm Hg (YES/NO)

Measuring and achieving the normalization of lactate at ≤4 mmol/L (36 mg/dL) in the presence of initially elevated levels (YES/NO)

Administration of vasopressors in the event of persistent hypotension MAP≤65 mm Hg, unresponsive to initial fluid resuscitation (YES/NO)

Achieving MAP of ≥65 mm Hg (YES/NO)

Measuring and achieving the target values of CVP≥8 – 12 mm Hg (YES/NO)

Measuring and achieving the target values of $ScvO_2 \geq 70\%$ or $SvO_2 \geq 65\%$ (YES/NO)

Urine output ≥0.5 mL/kg/h (YES/NO)

egory with the highest number of fulfilled components was selected as a reference category with the best survival.

We recorded the following basic patient data: gender (male/female), age at enrolment (years), age category (years), SOFA score, APACHE II, BMI (kg/m²), BMI category, in-hospital mortality.

In pursuing the relationship between in-hospital mortality and the admission source to the EPOSS ICU, we evaluated the sources (outpatient clinic, general ward, ER, other ICU), whether the primary admission was medical or surgical, eventually whether surgical admission was elective, acute or traumatological. From the number of completed interventions in the first 6 h, we assessed adherence to the Sepsis Surviving Guidelines.

Definitions

Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference[12].

Infection was defined in accordance with the International Sepsis Forum Consensus Conference on definitions of infection in the intensive care unit[15].

Severe sepsis/septic shock was defined according to the International Sepsis Forum Consensus Conference on definitions of infection in the intensive care unit[16].

Organ failure was defined according to a (SOFA) score of >2 (ref.[13]).

Patients without any reference to trauma or surgery were defined as "medical". "Surgical" patients were those who underwent surgery within four weeks (at the most) prior to the onset of severe sepsis/septic shock. "Planned surgical" were patients who had undergone a planned operation more than 24 h before the onset of symptoms of severe sepsis/septic shock. "Emergent surgical" were patients with surgery scheduled less than 24 h before the onset of sepsis symptoms. "Traumatological" were patients admitted in direct relation to trauma or complications relating to a trauma in intervals no more than thirty days before the onset of sepsis. Time 0 was defined in accordance with the International Sepsis Forum Consensus Conference on definitions of infection in the intensive care unit[16].

"Admission source" was defined as the place from where the patient was directed for admission to EPOSS ICU (outpatient clinic, ER, ward, other ICU).

Statistical Methods

Patients with incomplete data in key mandatory variables at all time points (108 variables) were excluded from the analysis. The time points were: the moment of fulfilling criteria for severe sepsis/septic shock, and moment after the initial 6 h; the sum of variables at these time points (some or all of them depending on a variable) containing data on Age, Gender, APACHE II, SOFA, BMI, Crystalloids, MAP, CVP, Lactate, Antibiotics, Body temperature, Urine output, ScvO2, SvO2, Norepinephrine, Blood culture provides variables in the database. The selection of variables for the multivariate model was based on two principles: i) variables with a P value <0.1 in univariate analysis were selected for the development

of the multivariate model, ii) redundancy of variables was evaluated and only the most statistically significant variable out of the redundant set of predictors was selected. No replacement of missing values or outliers was performed in order to minimize bias due to changed content of retrospective clinical records. Missing values in mandatory variables were reported in separate tables, and the excluded cases were compared with validated records in order to exclude systematic bias due to data validation. The prerequisites of statistical computations were evaluated using visual inspection of data and normality tests; the redundancy of predictors was evaluated using the analysis of their associations (correlation for continuous variables and contingency table analysis for categorical variables). Standard descriptive statistics were applied to summarize the primary data; continuous variables as means and 95% confidence intervals or median and range; categorical variables by absolute and relative frequencies. Potential predictors of hospital mortality were analysed using logistic regression and risk or protective association was quantified by odds ratios (OR) with corresponding 95% confidence intervals. Multivariate logistics regression was adopted for adjusting univariate results for age and APACHE II, and for defining the final multivariate model. The selection of variables for the multivariate model was based on univariate $P < 0.1$ and redundancy analysis of these preselected predictors. $P \leq 0.05$ was adopted as the level of statistical significance for all analyses and SPSS 21 (IBM Corporation, 2012) was the software used.

RESULTS

Participants

The project was a joint collaboration of 17 ICUs with a total of 220 beds in 12 hospitals. Based on a questionnaire on the long-term global characteristics of these centres, altogether 18,902 patients were admitted during the entire reference period (all diagnoses included). The average patient age was 60.2 years, the average APACHE II score at admission was 20, and the real in-hospital mortality was 11.4% irrespective of diagnosis.

Patients

For the period from 1 January 2011 to 5 November 2013, the EPOSS dataset contained data on 1,082 enrolled patients, and the final validated dataset involved 897 patients. The patient flow is shown in Fig. 1.

Descriptive data

The collected dataset included records of 1,082 patients meeting the criteria of severe sepsis/septic shock. Following data validation, a final dataset of 897 patients was obtained. The average patient age of the group was 66.0 years. Table 3 provides more details on the dataset.

Main results and mortality

All combinations of reported diagnostic and treatment interventions were examined, and the most significant combinations relating to in-hospital mortality were identi-

Table 3. Basic description at enrolment – gender, age, BMI, SOFA and APACHE II.

	Total (n=897)	In-hospital mortality	
		No (n=532) 59.3%	Yes (n=365) 40.7%
Female	342 (38.1%)	202 (38.0%)	140 (38.4%)
Male	555 (61.9%)	330 (62.0%)	225 (61.6%)
Age at enrolment	66.0 (21.0; 92.0)	65.0 (21.0; 92.0)	69.0 (21.0; 92.0)
BMI (kg/m^2)	27.0 (11.0; 69.1)	27.4 (11.0; 62.3)	26.2 (13.1; 69.1)
SOFA score	10.0 (0.0; 20.0)	9.0 (0.0; 20.0)	10.0 (1.0; 20.0)
APACHE II	25.0 (2.0; 53.0)	23.0 (2.0; 53.0)	29.0 (7.0; 51.0)

Continuous data is described by median and range.
Categorical variables are described by absolute and relative frequencies.

Table 4. Combination of the initial 6 h fulfilled diagnostic/treatment interventions as factors associated with in-hospital mortality: CVP≥8-12 mm Hg (CVP), MAP≥65mm Hg (MAP), Urine output≥0.5 mL/kg/hr (Urine output), Blood culture before ATB therapy (Blood), Lactate≤4.0 mmol/L (Lactate), Initial lactate measured (Initial lact), Antibiotics in first hour (Antibiotics), ScvO2≥70% or SvO2≥65% (ScvO2).

	Factor frequency	In-hospital mortality	P
CVP & MAP & Urine output & Lactate & Initial lact & Antibiotics	69 (7.7%)	23.2%	0.003
MAP & Urine output & Initial lact & Antibiotics	44 (4.9%)	56.8%	0.028
ScvO2 & MAP & Urine output & Blood & Lactate & Initial lact	13 (1.4%)	15.4%	0.082
CVP & ScvO2 & MAP & Urine output & Lactate & Initial lact & Antibiotics	11 (1.2%)	18.2%	0.147
MAP & Urine output & Blood & Lactate & Initial lact	20 (2.2%)	25.0%	0.157
MAP & Urine output & Initial lact	24 (2.7%)	54.2%	0.178
CVP & MAP & Urine output & Lactate & Initial lact	20 (2.2%)	55.0%	0.194

Statistical significance is computed for comparison of mortality in the given combination in comparison to the rest of dataset using the maximum likelihood chi-square test
The Table shows the combinations of diagnostic/treatment interventions which achieved a statistical significance or are close to it.

Table 5. Diagnostic/treatment interventions – factor frequency in the initial 6 h, association with in-hospital mortality.

	Factor frequency	In-hospital mortality	OR (95% CI)	P
CVP 8 - 12 mm Hg	265 (29.5%)	37.4%	0.83 (0.61; 1.14)	0.250
ScvO2≥70% or SvO2≥65%	200 (22.3%)	37.5%	1.04 (0.55; 1.96)	0.898
MAP ≥ 65mm Hg	821 (91.5%)	39.0%	0.45 (0.28; 0.73)	0.001
Urine output ≥ 0.5 mL/kg/h	668 (74.5%)	38.3%	0.69 (0.51; 0.93)	0.017
Blood culture before ATB therapy	220 (24.5%)	36.4%	0.99 (0.96; 1.03)	0.686
Lactate ≤ 4.0 mmol/L	560 (62.4%)	34.8%	0.35 (0.25; 0.49)	<0.001
Noradrenaline if MAP < 65mm Hg	66 (88.0%)	62.1%	3.28 (0.75; 14.30)	0.114
Crystalloids ≥ 30 mL/kg if MAP< 65mm Hg	38 (50.7%)	60.5%	1.17 (0.47; 2.93)	0.740
Initial lactate measured	746 (83.2%)	40.8%	1.01 (0.71; 1.45)	0.936
Antibiotics in first hour	524 (58.4%)	39.7%	0.91 (0.69; 1.19)	0.472

Odds ratios and their statistical significance derived using univariate logistic regression model.

fied. Only two of these were statistically significant: CVP ≥ 8-12 mm Hg & MAP ≥ 65mm Hg & Urine output ≥ 0.5 mL/kg/hr & Lactate ≤ 4.0 mmol/L & Initial lactate measured & Antibiotics in first hour (P = 0.003) and MAP ≥ 65mm Hg & Urine output ≥ 0.5 mL/kg/hr & Initial lactate measured & Antibiotics in first hour (P = 0.028), respectively. Table 4 shows the combinations of diagnostic and treatment interventions which were statistically significant or close to it at P ≤ 0.05.

Diagnostic and treatment interventions related to in-hospital mortality which were fulfilled during the first 6 h and which reached statistical significance were: MAP ≥ 65mm Hg (P = 0.001), Urine output ≥ 0.5 mL/kg/h (P = 0.017) and Lactate ≤ 4.0 mmol/L (P < 0.001), (Table 5).

Assessment of the risk of in-hospital mortality adjusted for age and APACHE II showed that only Lactate < 4 mmol/L and MAP ≥ 65 mm Hg were statistically significant (P < 0.001 for both factors), (Table 6).
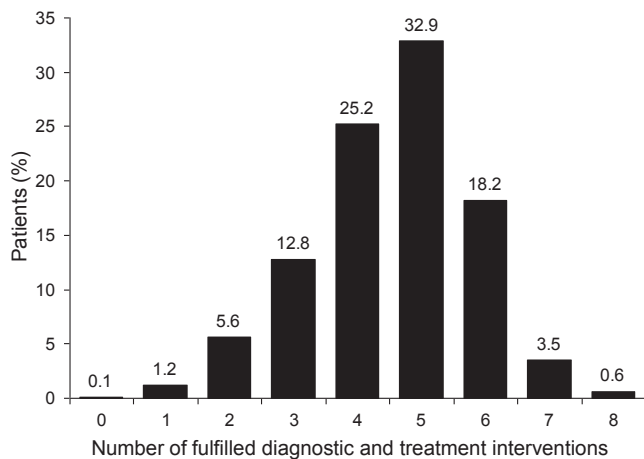
Fig. 2. Number of completed diagnostic and treatment interventions in the initial 6 h.

Of the ten evaluated diagnostic and treatment interventions, 58.1% of patients fulfilled 4-5 and 21.7% of patients achieved 6-7; however, the fulfilment of 8 was only reached in 0.6% of patients, while joint fulfilment of 9 or all 10 diagnostic and treatment interventions was not achieved in any of the patients (Fig. 2).

In-hospital mortality adjusted for age and APACHE II in relation to admission source to EPOSS ICUs: General wards (45.7%), other ICUs (41.6%), outpatient (OPD) clinics (26.5%) and ER (38.0%) respectively (Table 7).

EPOSS ICU mortality was 35,5% (women 36.3%, men 35.0% respectively), mortality at discharge from hospital was 40.7% (women 40.9%, men 40.2% respectively).

Variables with $P < 0.1$ entered the multivariate analysis of factors associated with in-hospital mortality; all these factors with the exception of urine output ≥ 0.5 mL/kg/h remained statistically significant in the multivariate analysis (Table 8).

Table 6. Risk of in-hospital mortality adjusted to age and APACHE II.

	OR	P
CVP 8 - 12 mm Hg	0.88 (0.61; 1.27)	0.494
ScvO2≥70% or SvO2≥65%	1.03 (0.48; 2.22)	0.932
MAP ≥ 65mm Hg	0.36 (0.20; 0.64)	<0.001
Urine output ≥ 0.5 mL/kg/h	0.83 (0.58; 1.19)	0.302
Blood culture before ATB therapy	0.99 (0.95; 1.03)	0.665
Lactate ≤ 4.0 mmol/L	0.34 (0.23; 0.50)	<0.001
Noradrenaline if MAP < 65mm Hg	2.87 (0.42; 19.46)	0.280
Crystalloids ≥ 30 mL/kg if MAP< 65mm Hg	1.29 (0.44; 3.78)	0.643
Initial lactate measured	0.96 (0.62; 1.50)	0.871
Antibiotics in first hour	0.92 (0.67; 1.26)	0.609
Fulfilled 0-3 interventions	2.16 (1.28; 3.64)	0.004
Fulfilled 4 interventions	2.31 (1.50; 3.54)	0.000
Fulfilled 5 interventions	1.61 (1.10; 2.36)	0.015
Fulfilled 6-8 interventions	Reference category of fulfilled components	

Odds ratios and their statistical significance derived using univariate logistic regression model.

Table 7. Admission source, association with in-hospital mortality (adjusted to age and APACHE II).

		Factor frequency	In-hospital mortality	OR (95% CI)	P
Admission (from)	OPD clinic	68 (7.6%)	26.5%	0.58 (0.30; 1.10)	0.094
	General ward	175 (19.5%)	45.7%	1.41 (0.94; 2.11)	0.093
	ER	142 (15.8%)	38.0%	0.81 (0.52; 1.24)	0.328
	Other ICU	512 (57.1%)	41.6%	1.05 (0.77; 1.44)	0.757
Primary admission	Medical	488 (54.4%)	45.1%	1.54 (1.12; 2.10)	0.007
	Surgical	409 (45.6%)	35.5%	0.65 (0.48; 0.89)	0.007
Surgical admission	Elective (planned)	107 (26.2%)	36.4%	0.87 (0.50; 1.52)	0.633
	Acute	267 (65.3%)	34.8%	0.92 (0.55; 1.55)	0.762
	Traumatology	35 (8.6%)	37.1%	2.01 (0.78; 5.14)	0.147
	Severe sepsis/septic shock episode in the last 3 months	96 (10.7%)	42.7%	1.12 (0.73; 1.73)	0.602

Odds ratios and their statistical significance derived using univariate logistic regression model.

Table 8. Multivariate analysis of factors associated with in-hospital mortality.

Variables		OR (95% CI)	P
Age category	Up to 60 yrs.	Reference	
	60-70 yrs	1.261 (0.803; 1.980)	0.315
	70-80 yrs.	1.575 (0.966; 2.568)	0.068
	More than 80 yrs.	2.854 (1.634; 4.984)	<0.001
Primary admission	Medical	0.567 (0.391; 0.823)	0.003
Admission source	OPD clinic	Reference	
	General ward	4.045 (1.717; 9.530)	0.001
	ER	1.887 (0.791; 4.505)	0.153
	Other ICU	2.719 (1.233; 5.995)	0.013
Apache > 30		1.810 (1.232; 2.659)	0.002
MAP ≥ 65mm Hg		0.405 (0.206; 0.798)	0.009
Lactate ≤ 4.0 mmol/L		0.421 (0.267; 0.664)	<0.001
Fulfilled interventions	0-3	1.688 (0.803; 3.548)	0.167
	4	1.841 (1.082; 3.129)	0.024
	5	1.617 (1.067; 2.452)	0.024
	6-8	Reference	

Odds ratios and their statistical significance derived using multivariate logistic regression model.

DISCUSSION

This is the first-ever study describing the outcome of severe sepsis in ICUs in the Czech Republic. In this way, it provides important information on the epidemiology of severe infections in this country. The main result of the study is identification of combinations of effective diagnostic and treatment interventions within the initial 6 hours of diagnosis/treatment of severe sepsis/septic shock in relation to the lowest in-hospital mortality: CVP ≥8-12 mm Hg & MAP ≥65mm Hg & Urine output production ≥ 0.5 mL/kg/h & Lactate ≤ 4.0 mmol/L & Initial lactate measured & Antibiotics in the first hour. Achieving the key values as MAP ≥ 65mm Hg, Lactate ≤ 4.0 mmol/L and Urine output ≥ 0.5 mL/kg/h in the initial 6 hours of identifying severe sepsis/septic shock is statistically significantly associated with lower than the average in-hospital mortality in the patient group. Given the in-hospital mortality, these values can be assessed as protective. Conversely, persistent hypotension - MAP of ≤ 65 mm Hg, and the impossibility of achieving this MAP boundary can be assessed as risk factors of in-hospital mortality. Administering a crystalloid bolus of ≥ 30 mL/kg at a MAP of ≤ 65 mm Hg, as well as vasopressors in the case of persistent hypotension, a MAP ≤ 65 mm Hg, and unresponsive to initial fluid resuscitation, was more prevalent in the deceased than the survivor groups. The result shows that fulfilling important diagnostic and treatment interventions, such as fluid challenge or the support of vasopressors, despite their undeniable therapeutic benefits importance, they did not reduce in-hospital mortality without achieving adequate perfusion pressure. The mere presence of hypotension (MAP ≤ 65 mm Hg) was therefore the major prognostic factor increasing in-hospital mortality. However, the subgroup of patients with hypotension persisting within the initial 6 hours of severe sepsis/septic shock was small (N=75) and difficult to evaluate statistically.

Arterial blood pressure is a major determinant of regional flow, and is often used as an indicator of tissue perfusion but in reality, it is a poor indicator of blood flow. Distribution of flow for a given blood pressure is dependent on the relative values of the resistance in different vascular beds. Regional resistance cannot be assessed in the clinical setting, and hence we are left with blood pressure as a guide to therapy[17].

Some authors recommend rethinking resuscitation endpoints in septic shock patients due to potential vasopressor overuse, and suggest tissue hypoperfusion deterioration be used during over emphasis on blood pressure instead of flow. A three-stage approach to resuscitation endpoints has been proposed: Step One (target minimum MAP 45-50 mmHg to preserve heart and brain perfusion), Step Two (target tissue perfusion-based endpoints irrespective of MAP < 65 mmHg – permissive hypotension), Step Three (target single-organ perfusion) (ref.[18]).

This study found higher in-hospital mortality in patients with severe sepsis/septic shock that developed during hospitalization than in those who were just admitted to hospital with symptoms of severe sepsis/septic shock. The results thus show a higher in-hospital mortality in patients admitted to EPOSS ICUs from general wards (45.7%) or other ICUs (41.6%), in contrast to lower in-hospital mortality in patients admitted from outpatient (OPD) clinics (26.5%) or ER (38.0%). This figure suggests a more serious course of sepsis caused more often by multi-resistant strains of hospital-acquired infections in patients already hospitalized, compared to severe sepsis caused in newly hospitalized patients by community infections. In assessing the differences in mortality rates however, we have to consider the potential influence of differences in sepsis-causative organisms, existing co-morbidities, and the reason for being hospitalized in the first place. We are aware that although some of these were part of the APACHE II score evaluation, the adjustment might not be complete.

The results of the EPOSS study are consistent with the conclusions of the pilot study conducted by Malaska et al.[10]. These results showed the different importance of the diagnostic and treatment severe sepsis interventions in relation to in-hospital mortality. In our group of patients, we found a higher in-hospital mortality (40.7%) than in the compared studies which, however, do not state the input value of APACHE II (ref.[3,19-21]). It is possible that the higher in-hospital mortality we found reflected the severity of patients' conditions (baseline APACHE II in our sample was 25), not only lower fulfilment level for diagnosis and treatment interventions. As expected, we found a statistically significant reduction in in-hospital mortality associated with increase in number of jointly fulfilled diagnostic and treatment interventions. In the group achieving 0-3 diagnostic and treatment interventions, the in-hospital mortality was 47.2%; for 4 and 5 it was 45.3% and 44.0% respectively. In the case of jointly fulfilled 6-8 diagnostic and treatment interventions, the in-hospital mortality decreased to 32.5%. The more treatment interventions were achieved within the first 6 h of treatment, the better was the probability of survival. This finding supports the concept of Sepsis Surviving Guidelines.

Improvements in the outcomes for patients with severe sepsis in relation to fulfilling SSC recommendations were addressed by Castellanos-Ortega et al. These authors reported a significant decrease in mortality within the intervention group compared to the historical group of patients (from 57.3% to 37.5%). An independent predictor of survival was concordance in six and more fulfilled interventions of septic package for the first 6 h[22]. In the present study, only 22.3% of our patients fulfilled six or more diagnostic and treatment interventions. This study has made a new contribution with a combination of factors, where reported studies compared only some diagnostic and treatment interventions[19,20,22,23].

As regards fluids, the current multicentre randomized ProCESS study questioned the importance of EGDT. The study worked with a group of patients with severe sepsis who were initially treated in the ER, i.e. patients newly admitted to hospital, and found no effect of EGDT on in-hospital mortality. This was 21.0% in patients with severe sepsis (EGDT group), 18.2% (protocol-based standard-therapy group) and 18.9% (usual-care group) (ref.[17]). In our study, cases from the ER formed only 15.8% of patients (in-hospital mortality 38%). Recurrence of an episode of severe sepsis/septic shock did not emerge as a significant prognostic factor, as 10.7% of the patients had already had an attack of severe sepsis/septic shock in the past 3 months. This figure, however, increased the average in-hospital mortality by only 1.4% to 42.7%. We do not have a clear explanation for this finding. In fact, we expected that an attack of severe sepsis/septic shock in the past three months would lead to a more significant increase in in-hospital mortality.

SSC recommendations between 2008 and 2012 were modified[9-11,24]. Current SSC guidelines do not follow urine output in the initial 6 h. However, we consider the achieved urine output as an important indicator of adequate renal perfusion, together with an adequately conducted fluid strategy; hence its inclusion here.

A major limitation of this study is that the EPOSS database does not provide data categories fully comparable with SSC. For this reason, the comparison of therapeutic interventions with SSC recommendations can only be general. Other limitations are that the study did not include patients with severe sepsis identified after a 24-hour stay in EPOSS ICUs or within an interval of more than 24 h prior to admission to EPOSS ICUs, or patients who had an attack of severe sepsis but were not admitted to any EPOSS ICU. We do not know what proportion of patients with severe sepsis did not pass through EPOSS ICU. The data may also be biased due to the involvement of only large hospitals and only some of their ICUs. We are also aware of the risk of selection bias: it is possible that EPOSS ICUs admitted patients with a poor prognosis where initial treatment in special ICUs or general wards was unsuccessful. The gradual involvement of centres during the observation as well as the absence of a control group is another drawback of our study. We only evaluated a recent group of patients without being able to assess the trend of the results. The strict validation procedure aimed at obtaining fully verified records for analysis, could lead to selection bias; nevertheless, no statistically significant differences in the key characteristics were found between included and excluded patients (Table 8).

Our study, the most extensive in Central Europe, provides extensive data on the epidemiology and observation of treatment parameters in severe sepsis. Until now, the only available results were those of the Slovak study by Zahorec et al. from 2005, which monitored 121 patients with a reported mortality of 51.2% (ref.[25]). The first descriptive data on epidemiology of sepsis/severe sepsis in patients in the Czech Republic was assembled in 2003 thanks to a prospective, multicenter, one-day observational questionnaire by Cerny et al., which included 327 patients from 53 ICUs. Sepsis was diagnosed in 112 patients (34.2%) and 55 patients (16.8%) met the criteria for severe sepsis[9]. In general features, data from the EPOSS study on in-hospital mortality can be compared to data provided by the FINN study from 2007, for example (the ICU and in-hospital mortality in severe septic patients was 15.5% and 28.3% respectively) (ref.[26]), and more recently, the Intensive Care Over Nations (ICON) audit from 2014 (in-hospital mortality in patients with sepsis was 35.3%) (ref.[27]). The results of our study showed that efforts in this regard need to focus more intensely on active and early identification of patients with sepsis/severe sepsis and the consistent application of interventions that are based on SSC recommendations. It is necessary to promote the use of early SSC intervention also in patients suspected of developing severe sepsis to preclude mainly the development of hypotension. In relation to in-hospital mortality, we primarily showed the importance of interventions related to adequate organ perfusion. The SSC recommended procedures could be profitably used in patients who only tend to meet the criteria for severe sepsis too, although the

onset of severe sepsis is already indicated by laboratory evidence of inflammation.

CONCLUSIONS

The data support the fulfilment of diagnostic and treatment interventions in the early hours after identifying severe sepsis/septic shock. Combined diagnostic and treatment interventions which were fulfilled during the first 6 hours associated with the lowest in-hospital mortality were: CVP of ≥ 8-12 mm Hg & MAP of ≥ 65mm Hg & Urine output at ≥ 0.5 mL/kg/h & Lactate of ≤ 4.0 mmol/L & Initial lactate measured & Antibiotics in the first hour. We recorded lower than average in-hospital mortality with Lactate levels of ≤ 4.0 mmol/L following initial elevation, and a MAP of ≥ 65 mm Hg. The continuing presence of hypotension at MAP ≤ 65 mm Hg, even when adequate initial 6 h fluid resuscitation, was associated with higher than the average in-hospital mortality. Greater in-hospital mortality occurred in patients admitted from general departments or from other ICUs and a lower in-hospital mortality of patients received from outpatient clinics or Emergency. Higher in-hospital mortality in severe sepsis/septic shock patients was found in patients transferred from the departments of internal medicine than in surgical patients.

ABBREVIATIONS

ACCP, American College of Clinical Pharmacy; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, Body Mass Index; CCTN, the Czech Clinical Trial Network; CSARIM, Czech Society of Anaesthesiology, Resuscitation and Intensive Medicine; CSFS, the Czech-Slovak Forum for Sepsis; CSIM, Czech Society of Intensive Medicine; CVP, Central Venous Pressure; EGDT, Early Goal Directed Therapy; EPOSS, Data-based Evaluation and Prediction of Outcome in Severe Sepsis; ER, Emergency; ICU, Intensive Care Unit; MAP, Middle Arterial Pressure; OPD, Outpatient Department; OR, Odds ratio; SCCM, Society of Critical Care Medicine; ScvO2, Central venous oxygen saturation; SOFA, Score to assess the incidence of organ dysfunction/failure in intensive care units; SSC, Sepsis Surviving Campaign; SvO2, Mixed venous oxygen saturation.

Author contributions: RU, MA, VC, VS, MM: manuscript writing; MA, VC, VS, MM, LD, JJ, PSt, RK, JM, PSe: study design; RU, MA, VC, LD, JJ, PSe: analysis and interpretation of data; MA, VC, MM, VS, PSt, RK: drafting the manuscript and revising it critically for important intellectual content; MA, VC, PSe: agreed to be accountable for all aspects of the work in ensuring that queries relating to the accuracy and integrity of the work are appropriately investigated and resolved; MA, PSe: final approval.

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APPENDIX 1

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APPENDIX 2

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APPENDIX 3

When including patients, the following data was registered:
- Age (years)
- Gender (male/female)
- Admission source to EPOSS-ICU (general ward, other ICUs, ER, outpatient clinic)
- Moment of meeting the criteria of severe sepsis
- APACHE II

In forms, at time of 0, 6 hours since identifying severe sepsis, the following data was registered:
- Fluid balance (mL/period of time)
- Administered solutions (mL/period of time), divided into crystalloids, colloids, albumin, plasma and erythrocyte preparations
- Body temperature (°C within the period of time)

- Administration of vasopressors (type and dose in ug/kg/min/period of time)
- Administration of inotropics (type and dose in ug/kg/min/period of time)
- Lactatemia (mmol/L/period of time)
- Urine output (mL/period of time)
- MAP (mmHg in the monitored time)
- CVP (mmHg in the monitored time)
- $ScvO_2$ or SvO_2 (% in the monitored time)
- Time of hemoculture taking (interval from the identification of severe sepsis/septic shock)
- Time of antibiotics administration (interval from the identification of severe sepsis/septic shock)
- Time of discharge from EPOSS-ICU (interval from the identification of severe sepsis/septic shock)
- Time of discharge from the hospital (interval from the identification of severe sepsis/septic shock)
- Time of death (interval from the identification of severe sepsis/septic shock)