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Impaired long-term quality of life in survivors of severe sepsis

Chinese multicenter study over 6 years

Introduction

Conventional 28-day mortality and length of hospitalization after severe sepsis, one of the major life-threatening critical illnesses, have been widely investigated [1, 2, 3]. Severe sepsis can be accompanied by long-term sequelae as it is associated with organ dysfunction. Therefore, whether severe sepsis survivors have an impaired long-term health-related quality of life (HRQOL) is becoming a major concern among healthcare providers and clinical investigators [4]. Several studies have highlighted this issue and suggested that clinical investigations of intensive care unit (ICU) treatment should include long-term follow-up of health-related quality of life (HRQOL) and functional status [5, 6]. Recent research has confirmed this concept and found that HRQOL decreased months or years after ICU hospital discharge [7, 8, 9, 10, 11]. Heyland et al. [8] reported that the HRQOL of patients with resolved sepsis was significantly lower than that of the general U.S. population. Similar conclusions were drawn by Karlsson et al. [10] in a 2-year follow-up study in Finland as well as by Hofhuis et al. [9] in a sequen-

tial measurement of HRQOL from ICU admission to 6 months after hospital discharge in The Netherlands. The same phenomenon was observed in general ICU patients [12, 13, 14, 15]. Up to now most of these studies on HRQOL of sepsis survivors were from North America, Europe and Australia and were confined to a 2-year follow-up after hospital discharge. Little work has been done to assess the long-term HRQOL beyond 2 years in these patients, especially in Asian countries with very different ethnic and socio-cultural backgrounds from western countries [16]. Additionally, the employment status, an important socio-economic indicator reflecting the level of recovery, has been less studied in severe sepsis or general ICU patients. The limited studies available showed that only half of the general ICU patients returned to work 1 year after hospital discharge in European countries [13, 17]. As China is a developing country with a great labor requirement, the employment status after being critically ill has gained increasing attention; however, the number of articles published investigating returning to work of patients after suffering from severe sepsis remains scarce [13, 17, 18]. The pres-

ent study was conducted to systematically assess the HRQOL and employment in survivors of severe sepsis up to 6 years after hospital discharge in a prospectively identified cohort for a better understanding of the long-term outcomes of severe sepsis.

Methods

Study settings and patients

This prospective case-control study was performed at four university hospitals located in Zhejiang province, China. The participating ICUs were all surgical units with 20–35 beds that on average admit approximately 500 patients per year. Study protocols were approved by local ethical committees and informed consent was obtained from all participants. Between January 2003 and December 2008 all adult admissions (age ≥18 years) to these ICUs were screened except for those who stayed in the ICU for less than 24 h for routine postoperative surveillance. Patients diagnosed with severe sepsis either at ICU admission or during the ICU stay were followed and clinical data were collected. Those who survived severe sepsis were ul-

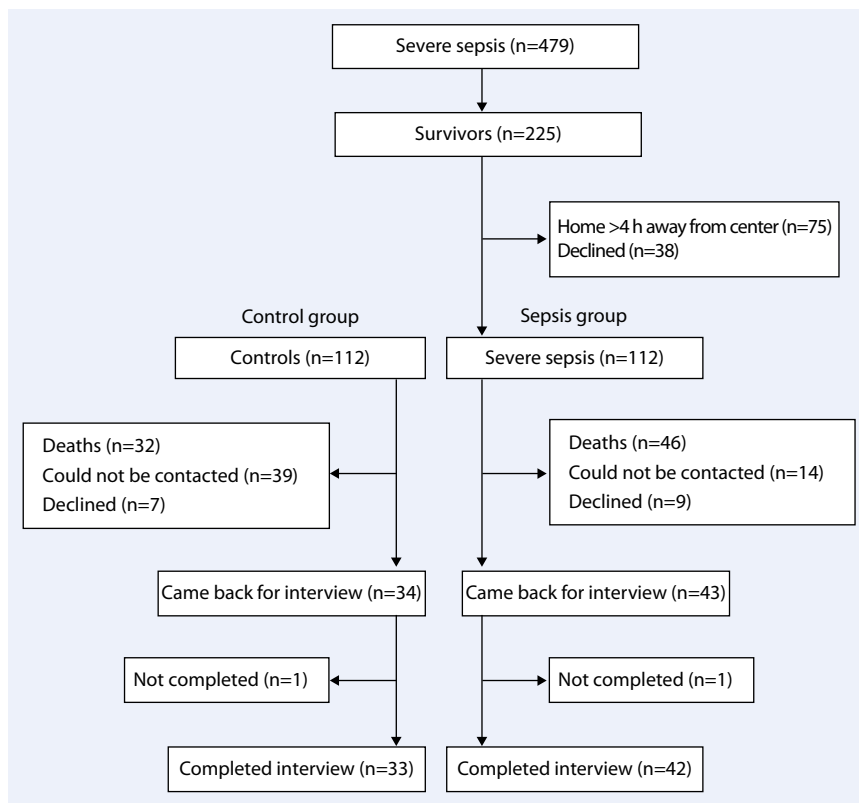


Fig. 1 ▲ Flow chart of study population for quality of life

timately enrolled in the case cohort at ICU discharge. Exclusion criteria included: (1) inability to speak Mandarin Chinese, (2) impaired level of self-awareness or inability to communicate adequately due to severe head trauma or other diseases or injuries involving the central nervous system. Furthermore, patients living in remote locations with a one-way journey to the participating center longer than 350 km (approximately 4 h drive) were also excluded. Once a severe sepsis patient was admitted to the study, an age, gender and Charlson comorbidity index (CCI) matched non-septic critically ill patient admitted to the same ICU was enrolled into the critically ill control cohort. Between August and December 2010 survivors in both cohorts were telephoned to organize in-person interviews at meeting rooms of the respective participating center. If there was no response to the initial telephone call the patients would be called again on another day. If the patient could not be contacted after four attempts or if the telephone number listed was not in service, the primary care physician and the appropriate registry office were consulted. Patients

who could not be traced through any of these ways were considered as the category “could not be contacted”.

Sepsis was defined as infection plus two systemic inflammatory response syndrome criteria according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [19, 20]. Severe sepsis was defined by sepsis plus sepsis-induced acute organ dysfunction (occurring in at least one organ, [19, 20]). Acute organ dysfunction was defined as a sequential organ failure assessment (SOFA) score ≥ 2 [21].

Data collection and follow-up

The following information of enrolled patients was collected prospectively: age, gender, presence of chronic underlying diseases by the CCI [22], severity of illness (acute physiology and chronic health evaluation II, APACHE II, [23]), organ dysfunction score (SOFA, [21]), endotracheal ventilation, length of ICU and hospital stay and employment status. Personal consultation was provided for all participants who attended the in-person in-

terview to complete the SF-36, activities of daily living (ADL) scale by the same trained investigator.

Quality of life, activities of daily living and returning to work

To measure the health-related quality of life, the medical outcomes study 36-item short form health survey (SF-36, copyright 1993, Medical Outcome Trust), a 36-item brief HRQOL questionnaire, was employed [24]. The 36 items are organized in 8 domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Each domain is scored from 0 to 100 with a higher score indicating better HRQOL. The eight domains are clustered to form two higher order scales, physical component score (PCS, including PF, RP, BP, and GH) and mental component score (MCS, including VT, SF, RE, and MH). Calculation of SF-36 domains, physical and mental component scores were in accordance with the standard methods. Population scores on PCS and MCS were standardized at 50. A 5-point difference in the SF-36 score was considered as clinically meaningful [25]. This questionnaire was shown to be reliable and valid in patients who survived sepsis and responsive to small but important changes in HRQOL [26]. The Chinese version of the SF-36 was previously developed and validated, with population norms being established in Hangzhou, Zhejiang province [27]. As the norms were developed nearly 10 years ago and SF-36 is a subjective assessment tool that could be influenced by changing factors, such as socio-economic environment and expectations of life, we also assessed SF-36 was also assessed with age and gender-matched Chinese people in local communities by random sampling. First, one district was selected from every city where the enrolled hospital was located. Second, one community was selected from each district and third, every person in the community had the same probability to be sampled. Among the sampled community residents, age (± 3 years) and gender-matched individuals were enrolled as community controls. The ratio of com-

munity controls to respondents with resolved severe sepsis was 3:1.

The ADL scale was used to assess the daily self-care activities [28]. The Chinese version questionnaire comprises 14 items, 6 of which evaluate physical ADL (e.g. bathing, dressing, toileting, transfer, continence and eating) and 8 of which assess instrumental ADL (e.g. using the phone, doing laundry, mobility, shopping, preparing meals, doing household chores, taking medications and managing finances) with a total score ranging from 14 to 64 and higher scores indicating poorer function in activities.

All of the patients were asked about whether they were employed or not before ICU admission, 1 year after hospital discharge and at the time of the interview. The type of the employment was also documented.

Statistical analysis

Quantitative data were presented as means and standard deviations (SD) or median and interquartile range as appropriate. Qualitative data were reported as N (%). Data were analyzed using SPSS™ 16.0 (SPSS, Chicago, IL). Student's t-test or Mann-Whitney U test was used for comparison of continuous variables and the χ^2 -test for categorical variables as well as one-sample t-tests were used when SF-36 domains were compared with normative data from an age and gender-matched Chinese general population. All these tests were two-tailed and statistical significance was considered when a P value was less than 0.05.

Results

Demographic and clinical characteristics

Between January 2003 and December 2008 a total of 9,356 patients from the participating ICUs were screened. In these individuals, 479 patients were diagnosed as having severe sepsis among which 225 patients (47.0%) survived and were discharged to home. A total of 75 patients were excluded from the follow-up study because of living in remote locations (>4 h drive to the participating hospitals) and

Anaesthesist 2013 · 62:995–1002 DOI 10.1007/s00101-013-2257-8
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Impaired long-term quality of life in survivors of severe sepsis. Chinese multicenter study over 6 years

Abstract

Objectives. The present study was undertaken to evaluate the long-term health-related quality of life (HRQOL) as well as the employment status in survivors of severe sepsis up to 6 years afterwards.

Material and methods. From January 2003 to December 2008 a total of 112 severe sepsis and 112 age, gender and Charlson comorbidity index-matched non-septic critically ill patients from 4 university hospital intensive care units (ICU) were enrolled in the study and 126 age and gender-matched community residents were interviewed as the community control group.

Results. A total of 66 (58.9%) severe sepsis and 80 (71.4%) non-sepsis critically ill patients survived during the long-term follow-up time. Between August and December 2010 a total of 75 patients including 42 survivors of severe sepsis and 33 critically ill controls completed the face-to-face interview. There were no differences in the long-term HRQOL in terms of Short-Form 36 crite-

ria between severe sepsis and non-sepsis critically ill survivors. However, when compared with the community controls, HRQOL in survivors of severe sepsis showed a significantly and clinically meaningful decrease, with a lower physical functioning ($p=0.016$), vitality ($p=0.037$), role-emotional ($p=0.043$), mental health ($p=0.038$) and mental component scores ($p=0.042$). In addition, the criteria returning to work at 1 year and at the time of interview in severe sepsis survivors were similar with those in critically ill survivors (60.5% vs. 70.0%, $p=0.41$ and, 71.1% vs. 76.7%, $p=0.602$).

Conclusions. The HRQOL in survivors of severe sepsis was impaired even up to 6 years after hospital discharge.

Keywords

Employment status · Critically ill · Follow up studies · Questionnaire · Matched case control study

Verminderte Langzeitlebensqualität Überlebender nach schwerer Sepsis. Chinesische Multizenterstudie über 6 Jahre

Zusammenfassung

Hintergrund. Die vorliegende Studie untersucht die langzeitgesundheitsbezogene Lebensqualität („long-term health-related quality of life“, HRQOL) von Überlebenden einer schweren Sepsis innerhalb von 6 Jahren. Untersucht wurde auch die Wiedereingliederung in das Arbeitsleben.

Material und Methoden. Im Zeitraum von Januar 2003 bis Dezember 2008 wurden 112 Patienten mit schwerer Sepsis (Sepsis-Score) und 112 kritisch kranke, nichtseptische Patienten (angepasst nach Alter, Geschlecht und Charlson-Komorbiditätsindex) in die Studie einbezogen. Die Patienten stammten allesamt von Intensivstationen 4 chinesischer Universitätskliniken. Als Kontrollgruppe dienten 126 Bewohner, angepasst nach Alter und Geschlecht, der näheren Umgebung.

Ergebnis. Nach 6 Jahren lebten noch 66 Patienten mit schwerer Sepsis (58,9%) und 80 kritisch kranke, nichtseptische Patienten (71,4%). Insgesamt wurden zwischen August und Dezember 2010 75 Patienten (42 Überlebende einer schweren Sepsis und 33 ehemals kritisch kranke, nichtseptische Patienten) persönlich befragt. Zwischen septischen und nichtseptischen Patienten fand sich kein

Unterschied in der HRQOL, bezogen auf den Short-Form 36. Im Vergleich zur lokalen Kontrollgruppe war die HRQOL der Überlebenden einer schweren Sepsis signifikant und klinisch bedeutend reduziert. Es zeigten sich insbesondere eine reduzierte körperliche Funktionsfähigkeit ($p=0,016$), eine verminderte Vitalität ($p=0,037$), Abweichungen von der emotionalen Rollenfunktion ($p=0,043$), vermindertes psychisches Wohlbefinden ($p=0,038$) und eine Veränderung des Mental Component Score ($p=0,042$). Der Anteil der Patienten, die nach einem Jahr in das Arbeitsleben zurückkehrten, war zum Zeitpunkt der Befragung in der Gruppe der schweren Sepsis und der nichtseptisch kritisch kranken Patienten ähnlich hoch (60,5 vs. 70,0%, $p=0,417$; 71,1 vs. 76,7%, $p=0,602$).

Schlussfolgerung. Die HRQOL nach schwerer Sepsis ist auch 6 Jahre nach Krankenhausentlassung deutlich reduziert.

Schlüsselwörter

Beschäftigung · Kritisch Kranke · Fragebogen · Follow-up-Studie · Angepasste Fallkontrollstudie

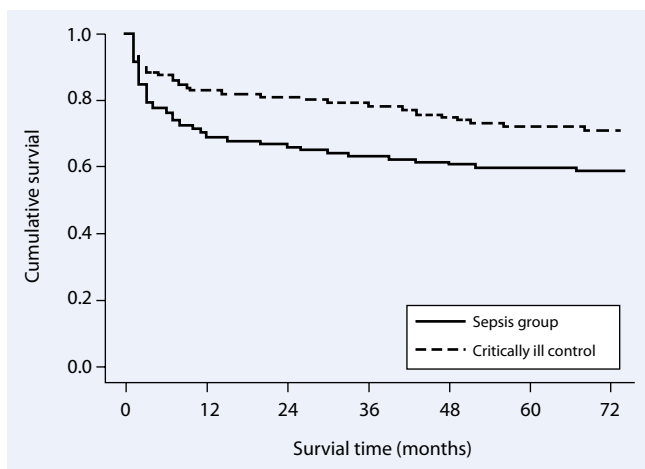


Fig. 2 ◀ Kaplan-Meier survival curve of the sepsis group and critically ill group

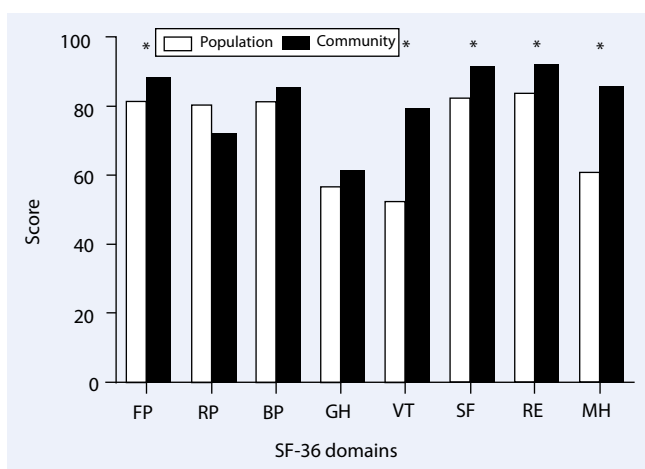


Fig. 3 ▲ Comparison of eight domains in the short form-36 (SF-36) between population norms and community control group. The SF-36 score of population are adjusted by age and gender of the sepsis respondents. Data are shown as mean. * $p < 0.05$. BP bodily pain, GH general health, MH mental health, PF physical functioning, RE role-emotional, RP role-physical, SF social functioning, VT vitality

another 38 cases declined participation. Hence, a total of 112 patients were enrolled into the sepsis group. In addition 112 age, gender and CCI-matched non-septic critically ill survivors were enrolled into the critically ill control group. Between August and December 2010 all these patients were contacted via telephone and asked to attend the participating hospitals for in-person interviews. At the time of the telephone call 78 patients in the 2 groups were deceased, 53 could not be contacted and 16 declined to participate in the study. Ultimately, consent for an in-person interview were obtained from 77 survivors and 75 (42 in the sepsis group and 33 in the critically ill control group) completed the interview. The characteristics of recruitment and retention, death and loss to fol-

low-up during the study period are shown in **Fig. 1**. The respondents had a mean age of 51.30 ± 18.39 years with a male proportion of 73.3%, which was not significantly different from those excluded or lost from the follow-up study ($p = 0.27$). Survivors had similar demographic characteristics when compared with non-survivors (average age 53.03 ± 17.36 years vs. 56.99 ± 18.94 years, $p = 0.12$, gender: male 71.0% vs. 68.6%, $p = 0.64$). The survival data within 6 years after discharge of both sepsis and critically ill groups are shown in **Fig. 2** and baseline characteristics of the sepsis group and critically ill control group are presented in **Tab. 1**. No significant differences were noted regarding age, gender, number of comorbidities, responding time or employment

status between the two groups. However, the sepsis group was associated with higher APACHE II scores ($p = 0.017$), mechanical ventilation rates ($p = 0.001$), longer median length of stay (LOS) in hospital ($p = 0.001$), LOS in ICU ($p < 0.001$) and mechanical ventilation times ($p < 0.001$). The sites of infection and distribution of various microorganisms in the sepsis group are shown in **Tab. 2**. A group of 126 community residents was enrolled as a community control group with a mean age of 55.46 ± 13.41 years, of whom 76.2% were male. No significant differences were found in age, gender and CCI between the sepsis group and the community control group.

Health-related quality of life

A total of 75 patients were assessed with the SF-36 questionnaire, including 42 severe sepsis survivors and 33 critically ill controls. The mean response time (from hospital discharge to the date of interview) of severe sepsis and critically ill controls was 39.68 months and 36.85 months, respectively.

Among the eight domains of SF-36, no statistically significant differences were noted between the sepsis group and the critically ill control group. However, compared to the community control group, the sepsis group had statistically and clinically meaningful decreases in the PF ($p = 0.016$), VT ($p = 0.037$), RE ($p = 0.043$) and MH ($p = 0.038$) domains of SF-36. When compared with the population norms, severe sepsis survivors demonstrated a statistically and clinically meaningful decrease only in the RP domain ($p = 0.021$). Interestingly, in VT and MH, two domains contributing to MCS, the sepsis group had even higher scores than the population norms (both $p < 0.001$). Detailed results of the SF-36 questionnaire are presented in **Tab. 3**.

With regard to PCS and MCS, sepsis patients and the critically ill controls had very similar scores; however, MCS in the sepsis group was significantly lower than that of the community control group ($p = 0.042$).

Furthermore, the long-term HRQOL of the population norms was found to be significantly lower than that of the com-

Tab. 1 Main demographic and clinical characteristics of the sepsis group compared with the critically ill control group

	Sepsis group (n=42)	Critically ill control group (n=33)	p-value
Age (years)	53.07±17.36	47.00±18.17	0.145
Gender (male; n, %)	32 (76.2%)	23 (69.7%)	0.528
Response time (months)	39.68±14.82	36.85±15.38	0.422
CCI ≥1 (n, %)	20 (47.6%)	14 (42.4%)	0.654
Employment status before ICU admission (n, %)	38 (90.5%)	30 (90.9%)	0.95
APACHE II	18.35±6.80	13.70±6.51	0.017
SOFA	5.97±3.49	4.44±2.04	0.101
Organ dysfunction (n, %)			
– Cardiovascular	14 (33.3%)	9 (27.3%)	0.57
– Respiratory	22 (52.4%)	12 (36.4%)	0.17
– Renal	12 (28.6%)	9 (27.3%)	0.90
– Hematologic	9 (21.4%)	5 (15.2%)	0.49
– Neurologic	23 (54.8%)	16 (48.5%)	0.59
LOS in hospital (days)	40.00 (25.75–70.25)	29.00 (20.50–40.00)	0.001
LOS in ICU (days)	10.50 (5.00–15.25)	5.00 (3.00–6.00)	<0.001
Mechanical ventilation (n, %)	35 (83.3%)	16 (48.5%)	0.001
Duration of mechanical ventilation (days)	3.00 (1.00–8.25)	0.50 (0.00–2.00)	<0.001

Data are show as mean ± SD or median (quartile), unless otherwise indicated. *APACHE II* acute physiology and chronic health evaluation II, *CCI* Charlson comorbidity index, *ICU* intensive care unit, *LOS* length of stay, *SOFA* sequential organ failure assessment.

Tab. 2 Sites of infection and distribution of various microorganisms in the sepsis group

	Sepsis group (n=42)
Site of infection, (n, %)	
– Lungs	31 (73.8%)
– Abdomen	20 (47.6%)
– Blood	7 (16.7%)
– Urinary tract	6 (14.3%)
– Multisite ^a	20 (47.6%)
– Others	8 (19.0%)
Pathogen type in cultures (n, %)	
– Gram positive alone	3 (7.1%)
– Gram negative alone	14 (33.3%)
– Mixed organisms ^b	20 (47.6%)
– Other	1 (2.4%)
– No pathogen	4 (9.5%)

^aMultisite infection refers to infections present in more than one site per patient. ^bMixed organisms refers to infections that were considered to have more than one type of organism per patient.

Activities of daily living and returning to work

At the time of the in-person interview, 33 (78.6%) of the severe sepsis respondents and 26 (78.8%) of the critical illness respondents had no or minor physical complaints, 9 severe sepsis and 7 critically ill controls had a major functional impairment, including 5 severe sepsis and 3 critically ill controls who required daily assistance. There were no significant differences between the sepsis group and the critically ill control group.

Before ICU admission, 38 (90.5%) of the severe sepsis respondents and 30 (90.9%) of the critical illness respondents were employed full-time or part-time. Among these patients, 23 (60.5%) severe sepsis survivors and 21 (70.0%) critically ill controls had returned to work 1 year after discharge. At the time of the interview, 27 (71.1%) severe sepsis and 23 (76.7%) critically ill controls had returned to work

(**Tab. 4**).

munity control group in PF ($p < 0.001$), VT ($p < 0.001$), SF ($p < 0.001$), RE ($p = 0.015$) and MH ($p < 0.001$). Details are presented in **Fig. 3**.

Tab. 3 Comparison of eight domains of the short form-36 (SF-36) between sepsis group, critically ill control group, community control group and population norms

	Sepsis (n=42)	Critically ill controls (n=33)	p-value ^a	Community controls (n=126)	p-value ^b	Population	p-value ^c
Physical functioning	79.12±21.22	83.18±27.30	0.471	88.39±13.69	0.016	81.56±18.09	0.461
Role-physical	64.40±43.21	68.18±40.64	0.701	72.46±40.39	0.340	80.45±21.91	0.021
Bodily pain	79.44±18.18	80.15±18.60	0.868	85.59±18.93	0.105	81.40±19.31	0.489
General health	61.63±20.37	64.97±22.76	0.509	60.94±21.48	0.872	56.42±19.59	0.109
Vitality	71.12±18.90	72.27±19.08	0.798	78.73±15.05	0.037	52.40±20.78	<0.001
Social functioning	83.61±24.48	83.73±25.29	0.984	91.31±14.54	0.079	82.62±17.87	0.799
Role-emotional	78.57±39.52	76.76±39.53	0.844	91.53±23.65	0.043	83.82±32.65	0.395
Mental health	77.40±20.31	77.70±19.67	0.950	85.15±13.49	0.038	60.67±22.83	<0.001

The short form-36 (SF-36) scores of population are adjusted by age and gender of the sepsis respondents. Data are shown as mean ± SD.^aSepsis vs. critically ill control. ^bSepsis vs. community control. ^cSepsis vs. population.

Tab. 4 Employment status of the sepsis group compared to the critically ill control group

	Sepsis group (n=42)	Critically ill control group (n=33)	p-value
Employment status before ICU admission (n, %)			0.95
– Full-time	31 (73.8%)	25 (75.8%)	
– Part-time	7 (16.7%)	5 (15.2%)	
– Retired	1 (2.4%)	1 (3.0%)	
– Unemployed	3 (7.1%)	2 (6.1%)	
Current employment status (n, %)			0.73
– Full-time	17 (40.5%)	15 (45.5%)	
– Part-time	10 (23.8%)	8 (24.2%)	
– Retired	2 (4.8%)	3 (9.1%)	
– Unemployed	13 (31.0%)	7 (21.2%)	

Discussion

The present study evaluated the HRQOL of severe septic survivors up to 6 years afterwards with a mean follow-up of 38.43 months after hospital discharge, providing pivotal information that supplemented the findings of previous clinical investigations [8, 9, 10, 11, 29]. To the best of our knowledge, this is also the first prospective, multicenter, follow-up study documenting the post-discharge HRQOL in patients surviving severe sepsis in China. Patients with resolved severe sepsis had comparable long-term HRQOL to age and gender-adjusted critically ill controls but lower than that of community residents.

The HRQOL is an important patient-centered outcome measure in the critical care setting, which could help health-care providers to have a better understanding of patients' prospects as well as policy makers to a better consideration of the cost-effective ratio of certain interventions or therapeutic management. The SF-36 questionnaire, which has been

adopted in the present study, is the most widely used generic health status instrument to assess the HRQOL and has demonstrated good reliability in various ICU settings. Furthermore, the SF-36 was validated in the general population of China in 2002 [27].

In the present study no significant differences were detected between the sepsis respondents and non-septic critically ill patients in HRQOL by using the SF-36 questionnaire. This finding confirms the results of most previous studies which documented that the survivors of severe sepsis had a similar HRQOL to other critically ill patients [7, 11]. Oeyen et al. [30] demonstrated that long-term HRQOL depended largely on the diagnostic category and patients with severe sepsis, severe trauma and acute respiratory distress syndrome had the worst reductions in HRQOL. Therefore, the present results can mostly be attributed to the fact that severe sepsis and non-septic critically ill controls were both critically ill patients who required an intensive

level of care, as well as the inclusion criteria of critically ill patients which were age, gender and CCI-matched with severe sepsis. Furthermore, it was found that the long-term HRQOL of the sepsis group was significantly lower than that of the community control group, although it was comparable to that of the age and gender-adjusted population norms. Notably, population norms of the Chinese SF-36 were evaluated nearly 10 years ago and therefore it might not be appropriate to use these norms today as there are remarkable differences in HRQOL between the population norms and community controls in the current study. The current findings were in concordance with major previous publications, which suggested a multi-dimensional decrement in the post-discharge HRQOL of severe sepsis patients [8, 9, 10, 11, 29]. They also indicate that, like other critical illnesses although the HRQOL of patients with resolved severe sepsis improved over the years, the recovery would still be incomplete in the long term and HRQOL could not achieve the level of the general population [9, 30, 31]. Recently, Cuthbertson et al. assessed severe sepsis patients 5 years after discharge in Scotland and reported a lower QOL in all domains of SF-36 when compared to the present study. These results indicate a relatively poor recovery of severe sepsis survivors in the study of Cuthbertson et al. [32], which is not surprising as these patients had more severe illnesses and were older than the patients in the current study. A comparison of the present paper with previous studies in severe sepsis is shown in **Tab. 5**.

Tab. 5 Comparison of the characteristics of sepsis survivors in the present paper with previous studies

Study	Country	Age (Years)	Gender (Male, %)	APACHE II score	Follow-up time (months)	QOL assessment		Major finding
						Instrument	Method	
Present study	China	53.07±17.36	76.2	18.35±6.80	39.68±14.82	SF-36	Face to face	Survivors of severe sepsis have a similar HRQOL compare with non-septic critically ill patients
Hofhuis et al. [9]	The Netherlands	66 (57–74)	56.7	20 (15–24)	6	SF-36	Telephone	Survivors of severe sepsis have a decline of HRQOL during ICU stay and a gradual improvement during the 6 months after ICU discharge
Granja et al. [7]	Portugal	52 (38–66)	64.0	17 (13–21)	6	EQ-5D	NA	Survivors of severe sepsis have a similar HRQOL compare with non-septic critically ill patients
Heyland et al. [8]	Canada	62±13.7	53.3	22.47±6.04	16.6±10.6	SF-36	Telephone	HRQOL of survivors of sepsis is lower than general population
Karlsson et al. [10]	Finland	58.60±15.8	73.1	22 (17–28)	17(16–18)	EQ-5D	Mail	QOL of severe sepsis is lower than before critical illness
Korosec Jagodic et al. [11]	Slovenia	64.4±13.5	49	15.5±6.4	24	EQ-5D	Telephone	HRQOL of sepsis was similar with non-septic critically ill patients
Cuthbertson et al. [32]	United Kingdom	58 (45–67)	53	23 (17–28)	60	SF-36, EQ-5D	Telephone	QOL of severe sepsis was lower than population norms and similar to other critically ill cohorts

Data are show as mean ± SD or median (quartile), unless otherwise indicated *APACHE II* acute physiology and chronic health evaluation II, *EQ-5D* European quality of life-5 dimensions, *LOS* length of stay, *NA* not available, *SF-36* the medical outcomes study 36-item short form health survey.

Returning to work, one of the most commonly accepted non-biological markers for health status has been regarded as an important long-term outcome after critical illness in previous studies. In the present study, the proportion of patients who worked prior to ICU admission was higher than previous studies reported in general ICU patients [13, 18]. The percentage of patients returning to work by the time of interview was close to the percentage in ICU trauma patients in a 5-year follow up study by Ringdal et al. [17]; however, the percentage of those returning to work after 1 year was higher than previous studies which showed that 57% of trauma patients and 55% of general ICU patients returned to work 1 year after hospital discharge [13, 18]. These results could be attributed to differences in value systems and socio-cultural backgrounds between western countries and China. As China is a developing country with great labor requirement, returning to work as soon as possible is imperative for patients to guarantee the household income. Otherwise, Chinese people always worked longer than the official retirement age as there are many privately owned enterprises in rural areas. The present results showed an improvement

of working abilities over the years; however, it still did not revert to the normal level, similar to the HRQOL described above, which confirmed previous reports and indicated that the employment status indeed reflects the level of QOL to some degree [13].

Several limitations in the present study should be acknowledged. First of all, the sample size of the study was not large; however, in the present study, almost all the patients lost to the study were those who moved to unknown locations with changed telephone numbers, which could be ascribable to the cross-nation population flow in China, especially the flow of hundreds of millions of migrant laborers. As previous studies always used telephone or mail to assess the HRQOL, the present study chose the face-to-face interview in order to get a more accurate evaluation of the patients. The case numbers were further reduced as some of the patients were living too far away to participate in the in-person interviews. However, the response rate was comparable with some previous studies concerning HRQOL in severe sepsis, such as the study by Karlsson et al. [10]. Secondly, the baseline HRQOL of patients prior to ICU admission was not assessed in the pres-

ent study. This was due to the fact that the self-assessment of HRQOL by the patients was usually difficult during the emergency procedures and the unstable levels of consciousness at ICU admission. Furthermore, the consistency between baseline HRQOL evaluated by patients and that evaluated by proxy remains controversial [29]. The agreement is moderate especially in the area of psychological well-being [29]. In an attempt to minimize this potential limitation, some important and objective baseline factors, such as the number of comorbidities before the episode of sepsis were provided in this study instead. Thirdly, the present study did not observe the time course of HRQOL in severe sepsis patients from hospital discharge to the time of interview. This should be approached in future studies.

Conclusion

In summary, this multi-center, follow-up study indicated that survivors of severe sepsis still had impaired quality of life even up to 6 years after hospital discharge, which would enrich the data pool of the long-term outcomes of severe sepsis.

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Acknowledgements. This research was supported by the National Science Fund for Distinguished Young Scholars from National Natural Science Foundation of China (30825037), Changjiang Scholar Program of China, Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents and the Research Project of Education Bureau of Zhejiang Province (Y200908925, Y200909678).

Compliance with ethical guidelines

Conflict of interest. K. Zhang, X. Mao, Q. Fang, Y. Jin, B. Cheng, G. Xie, H. Li, L. Yu, T. Zhu, H. Wang, X. Liu, Y. Zhang, Y. Jin, N. Zhang, T. Lou and X. Fang state that there are no conflicts of interest. All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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