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Original Article

Long-term quality of life after sepsis and predictors of quality of life in survivors with sepsis

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ABSTRACT

Purpose: To evaluate the quality of life among survivors after sepsis in 2 years, comparing with critical patients without sepsis and the general people, analyze the changes and the predictors of quality of life among septic survivors.

Methods: This prospective case-control study screened the intensive care unit (ICU) patients in Tianjin Third Central Hospital from January 2014 to October 2017, and the Chinese general population in the previous studies was also included. According to inclusion criteria and exclusion criteria, 306 patients with sepsis were enrolled as the observation group, and another 306 patients without sepsis in ICU during the same period, whose ages, gender and Charlson Comorbidity Index matched with observation group, were enrolled as the control group. At 3 mo, 12 mo, and 24 mo after discharge, the Mos 36-item Short Form Health Survey (SF-36), the Euroqol-5 dimension (EQ-5D), and the activities of daily living (ADL) were evaluated in face-to-face for the quality of life among survivors.

Results: There were 210 (68.6%) septic patients and 236 (77.1%) non-septic critically ill patients surviving. At 3 months after discharge, the observation and control groups had the similar demographic characteristics (age: 58.8 ± 18.1 years vs. 57.5 ± 17.6 years, p = 0.542; male: 52.0% vs. 51.4%, p = 0.926). However, the observation group had higher acute physiology and chronic health evaluation II (APACHEII) scores, higher sequential organ failure assessment (SOFA) scores, longer hospital stay, and longer ICU stay than the control group did (p < 0.05). There were no significant differences in the eight dimensions of the SF36 scale, the EQ-5D health utility scores, and the activities of daily life scores between septic survivors and non-septic survivors (p > 0.05). In addition, compared with the quality of life of the Chinese general population (aged 55-64 years), the quality of life of septic patients were significantly lower at 3 months after discharge (p < 0.05). Comparing the quality of life of the ill patients who had been discharged at 3 mo and 24 mo, the general health improved statistically (p = 0.000) and clinically (score improvement > 5 points). Older age (OR, 1.050; 95% *Cl*, 1.022–1.078, p = 0.000), female (OR, 3.375; 95% *Cl*, 1.434, -7.941, p = 0.005) and longer mechanical ventilation time (OR, 3.412; 95% *Cl*, 1.413, 8.244, p = 0.006) were the risk factors for the quality of life of septic survivors.

Conclusion: The long-term quality of life of septic survivors was similar to that of non-sepsis critically ill survivors. After discharge, the general health of sepsis improved overtime. Age, female and mechanical ventilation time (>5 days) were the predictors of the quality of life after sepsis.

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Introduction

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Sepsis is a systemic inflammatory response syndrome caused by infection,¹ which is one of the most common diseases in the intensive care unit (ICU). An epidemiological study estimated that there were 4,857,000 septic patients, 1,265,000 patients with

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severe sepsis and septic shock in China per year, the annualized mortality rate of sepsis was 79/100,000. According to this, there would be 4,025,000 survivors of sepsis every year.²

The long-term prognosis of the patients with sepsis is of great concern to the patients, their families, health care workers, and health care decision makers. The study showed that survivor among sepsis patient had the increasing long-term mortality. decreasing quality of life and mounting health care costs, due to the long-term neuropsychiatric damage, physical dysfunction, residual inflammatory reaction, and impaired immune function, which maked sepsis a "hidden public health problem".³ Other studies also depicted a higher mortality rate and the impaired quality of life in a longer period after sepsis.^{4–6} Currently there has been only two studies on long-term quality of life of sepsis patients in China, although there were many survivors.^{7,8} One study evaluated the quality of life in survivors of severe sepsis over 6 years. However, it had a small sample size.⁷ The other study used only one questionnaire to evaluate the quality of life by telephone interview, which may lead to the inaccurate results.⁸

The purpose of this study was to evaluate the quality of life of septic patients within 2 years after discharge. We used multiple questionnaires to measure the quality of life from multiple per-spectives, and followed up survivors by face-to-face to improve the quality of the investigation. In addition, the study analyzed the changes and the risk factors of the quality of life, providing references for the treatment and rehabilitation of sepsis.

Methods

Study subjects

This was a prospective case-control study that screened the ICU patients of Tianjin Third Central Hospital from January 1, 2014 to October 31, 2017. The general population of China in the previous studies were also included.^{9,10}

Inclusion criteria

Sepsis was defined in accordance with the 2001 septic criteria issued by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM) and the American College of Chest Physicians (ACCP). Patients with sepsis were considered as observation group; patients of non-sepsis who were similar in age, sex, and Charlson Comorbidity Index (CCI) with septic patients during the same period served as the control group. The general population included had similar ages with ICU patients.

Exclusion criteria

Age \leq 18 years old; ICU stay \leq 24 h; patients from other places except Tianjin; patients with other diseases that significantly affect the quality of life, such as head injury with sequelae, Alzheimer's disease, severe fractures, etc.

Ethics

This study was approved by the Ethics Committees of Tianjin Third Centre Hospital. Written informed consent was obtained from all patients included in the study.

Questionnaires

Three scales were used in this study: the Mos 36-item Short Form Health Survey (SF-36), the Euroqol-5 dimension (EQ-5D), the Activities of Daily Living (ADL). The SF-36 scale includes 8 dimensions, each dimension scores from 0 to 100 points. The higher score, the better quality of life is, and a 5-point or more difference in the SF-36 score was assessed as clinically meaningful.¹¹

Follow-up and data collection

At 3 months, 12 months, and 24 months after discharge, we contacted the survivors included in the follow-up to appoint home or hospital visits. We recorded the number of patients who died after discharge; we considered those who did not answer the phone for five times on different days and had wrong phone number as out of touch: we regarded those who did not accept the visits for three times on different days as rejection. Reviewed the medical records of patients and collected the following information: age, gender, CCI (Charlson Comorbidity Index), the number of comorbidities (the number of diseases in the Charlson Comorbidity Index), acute physiology and chronic health evaluation II (APACHE II) score within 24 h of admission to the ICU, sequential organ failure assessment (SOFA) score and organs with acute dysfunction (defined as SOFA>2), hypoxemia (defined as blood oxygen saturation <90%) and hypotension (defined as mean arterial pressure<60 mmHg), treatment of mechanical ventilation and continuous venous-venous hemofiltration. Two trained researchers completed all the above issues.

Statistical analysis

The continuous data were presented as mean \pm standard deviation or median with the 25th and 75th percentile. Comparisons between the two groups were performed using the Student *t*-test (normal distribution) or the Mann-Whitney *U* test (non-normal distribution). Comparisons of quality of life between two time points used paired *t*-test (normal distribution) or Wilcoxon (W) test (non-normal distribution). For categorical variables, comparisons between groups used chi-square test (with large samples) or Fisher exact test (with small samples). The binary logistic regression analysis was used to analyze the risk factors of quality of life. We assumed statistical significance at *P* < 0.05. Statistical analyses were conducted in SPSS 21.0.

Results

Demographic and clinical characteristics

As shown in Fig. 1, there were 210 (68.6%) of sepsis and 236 (77.1%) of non-sepsis critically ill patients surviving at discharge respectively, the in-hospital mortality rate of sepsis was significantly higher than that of the non-sepsis was (p = 0.018). At 3 months after discharge, the observation and control group had the similar demographic characteristics (age: 58.8 ± 18.1years vs. 57.5 ± 17.6 years old, p = 0.542, male: 52.0% vs. 51.4%, p = 0.926) and some clinical characteristics (p > 0.05). However, the observation group had higher APACHEII scores (p = 0.000), higher SOFA scores (p = 0.047) than the control group did (Table 1).

Therapies according to guidelines were given to patients with sepsis and other different non-sepsis diseases, although survivors in the control group were admitted for different reasons, with most frequent being postoperative surveillance, acute heart failure, gastrointestinal bleeding, acute kidney injury, obstetric critical illness, trauma.

Quality of life

Compared to the control group and the general population

The quality of life of the follow-up survivors is shown in Tables 2–4. Within 2 years after discharge, there were no statistically significant differences in the scores of SF-36 except vitality (VT) and in the scores of EQ-5D between the observation and





control group (p > 0.05). In the 24 months after discharge, the observation group had better daily activities (p = 0.016) than the control group did. Compared with the quality of life of the Chinese general population (aged 55–64 years),^{9,10} the quality of life of sepsis and non-sepsis survivors were significantly lower at 3 months after discharge (p < 0.05). At 24 months, sepsis and non-sepsis survivors scores of physical functioning (PF), role physical (RP), and social functioning (SF) than the general population did (p < 0.05), in addition, non-sepsis survivors had a lower scores of bodily pain (BP), vitality (VT), mental health (MH), and the health utility scores (Figs. 2 and 3).

Changes in quality of life

Comparison with the quality of life among survivors who completed three follow-ups between 3 months and 24 months after discharge (Tables 5 and 6), the multiple domains of SF-36, health utility, and activities of daily living of sepsis survivors increased significantly (p < 0.05), only general health (GH) improved significantly in clinic (score improvement>5 points). In the control group, the scores for PF (physical functioning) (p = 0.008), BP (bodily pain) (p = 0.002), GH (general health) (p = 0.005), and VT (vitality) (p = 0.000) also increased, but there were no clinically significance (score improvement < 5 points).

Risk factors

In order to determine the predictors of the quality of life after sepsis, we defined the quality of life as poor when the EQ-5D health utility scores was less than the median of 0.89 at 3 months after

Table 1

Characteristics of study patients at 3 months after discharge.

Variable	Sepsis	Non-sepsis	Statistics	р
	(n = 125)	(n = 140)		
Age, years	58.82 ± 18.07	57.48 ± 17.56	0.611	0.542
Male sex, n (%)	65 (52.0)	72 (51.4)	0.009	0.926
CCI	2.0 (1.0-3.5)	2.0 (1.0-3.8)	-0.187	0.852
With comorbidities, n (%)			1.924	0.860
0	21 (16.8)	29 (20.7)		
1	41 (32.8)	39 (27.9)		
2	27 (21.6)	35 (25.0)		
3	22 (17.6)	20 (14.3)		
4	11 (8.8)	13 (9.3)		
5	3 (2.4)	4 (2.9)		
APACHEII	19.01 ± 7.33	14.75 ± 6.15	5.089	0.000
SOFA	7.58 ± 3.18	5.43 ± 3.40	5.307	0.000
Type of organ dysfunctions, n (%)				
respiration	112 (89.6)	111 (79.3)	5.268	0.022
coagulation	31 (24.8)	29 (20.7)	0.629	0.428
liver	22 (17.6)	15 (10.7)	2.606	0.106
cardiovascular	59 (47.2)	18 (12.9)	37.784	0.000
central nervous system	25 (20.0)	19 (13.6)	1.971	0.160
renal	30 (24.0)	23 (16.4)	2.366	0.124
With organ dysfunctions, n (%)			31.228	0.000
0	2 (1.6)	17 (12.1)		
1	31 (24.8)	55 (39.3)		
2	46 (36.8)	50 (35.7)		
3	33 (26.4)	12 (8.6)		
4	11 (8.8)	6 (4.3)		
6	2 (1.6)	0 (0.0)		
Hypoxemia, n (%)	36 (28.8)	29 (20.7)	2.332	0.127
Hypotension, n (%)	28 (22.4)	22 (15.7)	1.928	0.165
CVVH, n (%)	57 (45.6)	25 (17.9)	23.786	0.000
Hospital stay, days	25.0 (16.0-35.0)	18.0 (12.0-25.8)	-4.382	0.000
ICU stay, days	10.0 (5.5–16.0)	7.0 (5.0–12.0)	-1.990	0.047
Duration of MV, days	5.0 (1.5–9.0)	4.0 (1.1–7.0)	-1.639	0.101

CCI = Charlson comorbidity index, APACHE II = acute physiology and chronic health evaluation II, SOFA = sequential organ failure assessment, CVVH = continuous venous-venous hemofiltration, MV = mechanical ventilation.

Table 2

Comparison of quality of life between sepsis and non-sepsis at 3 months.

Quality of life	Sepsis (<i>n</i> = 125)	Non-sepsis ($n = 140$)	Statistics	р
Physical functioning	63.88 ± 24.54	67.71 ± 23.88	-1.288	0.199
Role physical	54.40 ± 32.54	58.21 ± 32.91	0.918	0.359
Bodily pain	66.71 ± 20.69	68.14 ± 19.92	0.727	0.468
General health	57.40 ± 17.28	57.43 ± 17.96	-0.012	0.991
Vitality	66.12 ± 17.98	61.61 ± 18.66	2.000	0.047
Social functioning	65.46 ± 22.57	67.50 ± 24.03	0.912	0.362
Role emotional	68.00 ± 31.22	65.95 ± 31.35	-0.627	0.530
Mental health	70.03 ± 16.52	70.06 ± 14.45	-0.013	0.989
Health utility scores	0.89 (0.78, 1.00)	1.00 (0.78, 1.00)	0.562	0.574
Activities of daily living	100.0 (90.0–100.0)	100.0 (90.0-100.0)	-0.31	0.757

Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health are 8 dimensions of the SF-36 scale, each dimension scores were presented as mean \pm standard deviation. Health utility score was the score of EQ-5D scale and activities of daily living was the score of ADL scale, which were presented as median with the 25th and 75th percentile.

discharge. Univariate and multivariate analysis were performed in turn using binary logistic regression. The results are shown in Table 7: older age (*OR*, 1.050; 95% *CI*, 1.022–1.078, p = 0.000), female (*OR*, 3.375; 95% *CI*, 1.434–7.941, p = 0.005) and prolonged mechanical ventilation time (>5 days) (*OR*, 3.412; 95% *CI*, 1.413–8.244, p = 0.006) were independent risk factors for the quality of life of septic survivors.

Discussion

This study mainly assessed the quality of life of septic survivors within two years after discharge, and analyzed the changes and risk factors of quality of life. Firstly, the study found that the sepsis survivors whose age, sex, CCI -matched non-sepsis critically ill survivors during the same period had the similar quality of life, although the sepsis had a more serious condition (with higher APACHEII scores and SOFA scores), longer hospital and ICU stay, and higher in-hospital mortality rate. This suggested that the patients with sepsis recovered as well as or better than the patients with other critical illness did. It may attribute to the irreversible factors affecting quality of life in non-sepsis critically ill patients, which needs further research to confirm. However, the quality of life among survivors suffered from sepsis and non-sepsis critical ill decreased compared with the general population with similar age. This is a common manifestation of "post intensive care syndrome" (PICS), or the result of their own pathophysiological response, or

Table 3

Comparison of quality of life between sepsis and non-sepsis at 12 months.

Quality of life	Sepsis ($n = 103$)	Non-sepsis ($n = 112$)	Statistics	р
Physical functioning	66.07 ± 23.81	67.99 ± 24.82	-0.579	0.563
Role physical	58.50 ± 31.61	60.04 ± 32.96	0.384	0.701
Bodily pain	67.38 ± 21.10	69.12 ± 20.66	-0.610	0.543
General health	59.30 ± 19.26	59.59 ± 18.55	-0.111	0.912
Vitality	65.78 ± 18.91	63.39 ± 19.32	0.910	0.362
Social functioning	67.91 ± 23.78	68.97 ± 24.72	0.550	0.582
Role emotional	70.87 ± 31.55	63.69 ± 32.44	-1.758	0.079
Mental health	71.79 ± 16.76	71.34 ± 14.74	0.210	0.835
Health utility scores	0.89 (0.78, 1.00)	1.00 (0.78, 1.00)	1.348	0.178
Activities of daily living	100.0 (90.0, 100.0)	100.0 (90.0, 100.0)	-0.533	0.594

Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health are 8 dimensions of the SF-36 scale, each dimension scores were presented as mean \pm standard deviation. Health utility score was the score of EQ-5D scale and activities of daily living was the score of ADL scale, which were presented as median with the 25th and 75th percentile.

Table 4

Comparison of quality of life between sepsis and non-sepsis at 24 months.

Quality of life	Sepsis ($n = 72$)	Non-sepsis ($n = 80$)	Statistics	р
Physical functioning	68.96 ± 22.04	67.31 ± 24.98	0.431	0.667
Role physical	60.07 ± 34.77	59.69 ± 35.24	-0.042	0.967
Bodily pain	71.15 ± 20.78	68.54 ± 21.33	0.764	0.446
General health	61.99 ± 20.16	58.45 ± 18.93	-1.021	0.307
Vitality	66.46 ± 19.94	62.56 ± 19.39	1.220	0.224
Social functioning	69.79 ± 23.05	68.44 ± 24.28	0.053	0.958
Role emotional	75.47 ± 33.09	69.17 ± 33.03	-1.585	0.113
Mental health	72.86 ± 16.15	71.65 ± 14.56	0.486	0.627
Health utility scores	1.00 (0.87, 1.00)	1.00 (0.78, 1.00)	3.095	0.213
Activities of daily living	100.0 (100.0, 100.0)	100.0 (90.0, 100.0)	-2.409	0.016

Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health are 8 dimensions of the SF-36 scale, each dimension scores were presented as mean \pm standard deviation. Health utility score was the score of EQ-5D scale and activities of daily living was the score of ADL scale, which were presented as median with the 25th and 75th percentile.



Fig. 2. Comparison of quality of life between sepsis survivors and the general population. GP = the general population, PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health.



Fig. 3. Comparison of quality of life between non-sepsis survivors and the general population. GP = the general population, PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health.

Table 5 Changes in quality of life of sepsis patients who finished three follow-ups.

Sepsis	At 3 mon $(n = 72)$	At 24 mon $(n = 72)$	Statistics	р
Physical functioning	65.42 ± 23.52	68.96 ± 22.04	3.197	0.002
Role physical	59.03 ± 32.85	60.07 ± 34.77	-0.561	0.575
Bodily pain	66.85 ± 20.51	71.15 ± 20.78	3.780	0.000
General health	55.86 ± 18.03	61.99 ± 20.16	-5.367	0.000
Vitality	63.82 ± 18.53	66.46 ± 19.94	2.753	0.008
Social functioning	65.56 ± 21.35	69.79 ± 23.05	-2.142	0.032
Role emotional	73.15 ± 28.33	75.47 ± 33.09	-0.172	0.863
Mental health	71.39 ± 16.64	72.86 ± 16.15	1.480	0.143
Health utility scores	0.89 (0.86, 1.00)	1.00 (0.87, 1.00)	-2.553	0.011
Activities of daily living	100.0 (95.0, 100.0)	100.0 (100.0, 100.0)	-2.346	0.019

Table 6

Changes in quality of life of non-sepsis patients who finished three follow-ups.

Non-sepsis	At 3 mon $(n = 80)$	At 24 mon $(n = 80)$	Statistics	р
Physical functioning	65.13 ± 25.63	67.31 ± 24.98	2.718	0.008
Role physical	56.56 ± 34.39	59.69 ± 35.24	-1.733	0.083
Bodily pain	66.46 ± 20.72	68.54 ± 21.33	3.199	0.002
General health	56.93 ± 19.43	58.45 ± 18.93	-2.797	0.005
Vitality	60.38 ± 19.89	62.56 ± 19.39	3.946	0.000
Social functioning	68.13 ± 25.38	68.44 ± 24.28	-0.224	0.823
Role emotional	67.50 ± 32.69	73.75 ± 32.13	-2.239	0.025
Mental health	69.90 ± 14.33	71.65 ± 14.56	2.902	0.005
Health utility scores	1.00 (0.72,1.00)	1.00 (0.78,1.00)	-2.168	0.030
Activities of daily living	100.0 (90.0,100.0)	100.0 (90.0,100.0)	-1.384	0.166

both of the above reasons, which also needs further research to confirm.

Granja and coworkers¹² drew a similar conclusion using the EQ-5D to assess the long-term quality of life after severe sepsis and septic shock. Zhang and colleagues⁷ used the SF36 to conduct a multicenter study in China. The study showed that severe sepsis survivors performed as well as the non-sepsis survivors did, worse than the general population in PF (p = 0.016), VT (p = 0.037), MH (p = 0.038), role emotional (RE, p = 0.043) did. However, the number of people who completed questionnaires in the study was relatively small.

Secondly, the study found the significant increase in general health (GH) at 24 months after discharge. It suggested that the quality of life of sepsis survivors may improve over time after discharge. Hence, early and aggressive treatment, comprehensive care should be given to the patients with sepsis to get a better recovery.

Table 7	
Logistic regression analyses of predictors for quality of life of sepsis survivors.	

Variables	References	Measures	Univariate	Univariate			Multivariate		
			OR	95% CI	р	OR	95% CI	р	
Age (yrs)			1.044	(1.021, 1.068)	0.000	1.050	(1.022, 1.078)	0.000	
Gender	Male	Female	2.614	(1.267, 5.394)	0.009	3.375	(1.434, 7.941)	0.005	
CCI			1.360	(1.094, 1.692)	0.006	_	_	_	
With comorbidities (n)	0	≥ 2	3.230	(1.128, 9.251)	0.029	_	_	_	
Duration of MV (d)	<5.0	\geq 5.0	2.074	(1.013, 4.248)	0.046	3.412	(1.413, 8.244)	0.006	

CCI = Charlson comorbidity index, MV = mechanical ventilation, <math>OR = odds ratio, CI = confidence interval.

The study also demonstrated that older age, female and longer mechanical ventilation time (>5 days) were the risk factors for the quality of life of sepsis survivors. This result was in accord with the previous study.⁴ It was interesting that Brown and colleagues^{13,14} also depicted that older age and female were associated with worse quality of life in patients with acute respiratory distress syndrome (ARDS). The older age of our study population (average age > 50 years) may lead to the poor quality of life for women. The absence of protection from sex hormones deteriorated immune function, meanwhile unfavorable inflammatory mediator regulation in older female may contribute to the worse prognosis.¹⁵ Additionally, we observed that women were more vulnerable compared to men after the critically illness, which may cause women prone to the worse quality of life. However, these hypotheses need to be confirmed in large, prospective studies. Mechanical ventilation is one of the most important supportive treatments in the ICU, but prolonged mechanical ventilation time was associated with worse quality of life. This may be related to increasing sedation or analgesic use, muscle weakness, and ventilator-associated lung injury resulting in prolonged treatment of mechanical ventilation. It suggests that the appropriate time of mechanical ventilation may improve the long-term quality of life of sepsis patients. To date, the predictors for the long-term quality of life after sepsis were not identified clearly, it may be associated with the underlying disease of the patients before hospitalization, during hospitalization and after discharge. However, our study did not analyze the situation after discharge, it requires further investigation.

The SF36 and the EO-5D were recommended in the 2002 Brussels Roundtable¹⁶ and they were also used in many previous studies. The SF-36 scale is the most widely used assessment tool for quality of life in the world, its reliability and validity have been validated in critically ill patients.^{17,18} Moreover, the reliability and validity of the Chinese version have also been verified.¹⁹ The EQ-5D scale is a general assessment tool for health status,²⁰ and it was used in multiple studies about sepsis.^{4,5,8} This study used the Chinese version of the questionnaire and the Chinese utility values.²¹ We also used the ADL scale, which is a reliable scale for assessing the independence and functional status of daily activities.^{22,23} The decline in daily activity may lead to a worse quality of life,²⁴ therefore, this scale can help us further understand the subjects' health status. Using these three scales at the same time can not only help us understand the quality of life of patients from many aspects, but also the results can be mutually verified, increasing the reliability of the study. This study has some limitations. Firstly, we did not obtain the quality of life before admission. Because of the urgent conditions at admission, this was also a problem that most studies encountered. Secondly, most patients who participated in the follow-ups had better physical and mental state, so this study may overestimate the quality of life of sepsis. In the future, we can interview patients by face-to-face and telephone, to increase the subjects for more comprehensive information.

In summary, the quality of life of sepsis survivors is fair within 2 years after discharge, which is similar to the quality of life of nonsepsis survivors, although it is still worse than the quality of life of the general population in China. After discharge, the general health of sepsis patients improved significantly over time. Older age, female, and longer time of mechanical ventilation (>5 days) are the risk factors for the quality of life after sepsis. This study provides a reference for further treatment, rehabilitation and long-term prognosis of sepsis.

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