Temporal trends in patient characteristics and survival of intensive care admissions with sepsis: A multicenter analysis*

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Objective: **To estimate in-hospital, 1-yr, and long-term mortality and to assess time trends in incidence and outcomes of sepsis admissions in the intensive care unit.**

Design: **A population-based, multicenter, retrospective cohort study.**

Patients: **Patients hospitalized with sepsis in the intensive care unit in seven general hospitals in Israel during 2002–2008.**

Interventions: **None.**

Measurements: **Survival data were collected and analyzed according to demographic and background clinical characteristics, as well as features of the sepsis episode, using Kaplan-Meier approach for long-term survival.**

Main Results: **A total of 5,155 patients were included in the cohort (median age: 70, 56.3% males; median Charlson comorbidity index: 4). The mean number of intensive care unit admissions per month increased over time, while no change in in-hospital mortality was observed. The proportion of patients surviving to hospital discharge was 43.9%. The 1-, 2-, 5-, and 8-yr survival rates were 33.0%, 29.8%, 23.3%, and 19.8%, respectively. Mortality was higher in older patients, patients with a higher Charlson comorbidity index, and those with multiorgan failure, and similar in males and females. One-year age-standardized mortality ratio was 21-fold higher than expected, based on the general population rates.**

Conclusions: **Mortality following intensive care unit sepsis admission remains high and is correlated with underlying patients' characteristics, including age, comorbidities, and the number of failing organ systems. (Crit Care Med 2012; 40:855–860)**

KEY WORDS: intensive care; long-term survival; mortality; outcome assessment; sepsis; septic shock

Sepsis is an ongoing cause of mortality and morbidity. More than a decade ago, a consensus committee of the American College of Chest Physicians and the Society of Critical Care Medicine defined the disorder as the systemic inflammatory response to the presence of infection which, when severe, is accompanied by organ dysfunction or hypotension (1).

Despite the progress in early diagnosis and advanced treatment options (2–4), severe sepsis continues to be a disease with a high mortality rate (5, 6). With the aging of Western populations, the success in treatment and prevention of previously lethal cardiovascular and infectious diseases, and improvements in preventive medicine, the incidence of sepsis and severe sepsis, as a major common pathway for end-of-life events, has increased (6) and is expected to increase further.

Patients with severe sepsis comprise 10%–40% of intensive care unit (ICU) admissions (7). Mortality from sepsis has recently been shown to be decreasing; however, despite sophisticated diagnostic and treatment modalities, severe sepsis mortality remains unacceptably high (8–11). The care of patients with severe sepsis therefore poses a significant economic burden on the healthcare system (5, 12). In the United States, it has been estimated that in-hospital care for these patients requires an average of 20 hospital days, involves ICU admission in more than half of the patients, and results in hospital costs exceeding $16 billion annually (13). Finally, survivors of sepsis face a reduced long-term quality of life (14–18).

Research into the epidemiology of sepsis has traditionally focused on short-term outcome and was conducted mainly in the United States. Contemporary, large, population-based nationwide studies are scarce, and the long-term prognosis of severe sepsis was evaluated only in a small number of studies (17–20).

We conducted a computerized database study of patients hospitalized with sepsis in the ICUs of seven major tertiary hospitals in Israel between January 2002 and December 2008. The study goals

***See also p. 1006.**

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were to estimate in-hospital, 1-yr, and long-term mortality, and to assess time trends in incidence and outcomes of ICU sepsis admissions.

METHODS

The study was approved by the institutional review board of Soroka University Medical Center, Beer Sheva, Israel, and informed consent was waived. The study included all adult patients (aged 18 yrs or older) admitted or transferred to the general, surgical, medical, or respiratory ICU (but not cardiac ICU) and diagnosed with sepsis between January 2002 and December 2008 in seven general hospitals operated by Clalit Health Services ("Clalit"). Clalit is the major health plan in Israel with 4 million enrollees. According to the National Health Insurance Law enacted in 1995, all Israeli citizens and permanent residents are entitled to universal health insurance and are free to choose among one of four health plans, which operate similar to Health Maintenance Organizations in the United States. In addition to offering primary care and ambulatory services, Clalit operates eight general tertiary care hospitals, all of which are teaching hospitals, with approximately 4,400 beds (including adult ICU beds half of which are general noncoronary beds). That represents one third of all acute-care hospital beds in Israel. These hospitals offer inpatient services to all Israeli citizens, regardless of the health plan in which they are enrolled. Of these eight hospitals, seven were included in the present analysis, since one hospital does not have an ICU. For the present study, the central data warehouse of Clalit's hospitals was utilized. The data warehouse collects data from all clinical and administrative data systems, including the admission-transfer-discharge administrative database, operating room database, logistics, imaging, laboratory data, and discharge diagnoses.

Patients diagnosed with sepsis were identified by searching the Clalit's database for admissions with a diagnosis of sepsis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 003.1, 036.2, 038.0–9, 112.5, 785.52, 790.7, and 995.91–92). This definition has been used extensively in population-based and hospital-based studies of sepsis. Furthermore, validation data suggest a sensitivity of 88% (21), and positive predictive values of 89% for confirmed sepsis, and 98% for severe sepsis (22). For the purpose of this study, only the first episode of sepsis that occurred for each patient during the study period was included. For the definition of severe sepsis, ICD-9-CM codes indicative of diagnoses presumed to represent acute organ failure were applied, as described by Martin et al (8). These included codes for respiratory (518.81, 518.82, 518.85, 786.09, 799.1, and 96.7), cardiovascular (458.0, 458.8, 458.9, 785.5, 785.51, 785.59, and 796.3), renal (580, 584, 585, and 39.95), hepatic (570, 572.2, and 573.3), hematologic (286.2, 286.6, 286.9, and 287.3–5), and metabolic (276.2) and neurologic (293, 348.1, 348.3, 780.01, 780.09, and 89.14) organ failure. Patients were classified as having none, one, two, or three or more failing organ systems.

The following variables were collected from the computerized database of Clalit's hospitals: admitting department (ICU, internal medicine, surgery); in-hospital transfers during hospitalization (ICU, internal medicine, other); dates of hospital admission; transfer to ICU and hospital discharge, or alternatively, death; site of infection and organisms identified in blood cultures (according to ICD-9-CM codes); death date; demographics (age, sex, ethnicity); all diagnoses during the index hospitalization as recorded by ICD-9-CM; and Charlson comorbidity index (based on ICD-9-CM codes of chronic diagnoses, presumably diagnosed before admission and listed during hospitalization, automatically calculated within the computerized database). The primary outcomes were in-hospital mortality and long-term survival. Data regarding long-term survival was available only for Clalit's enrollees and retrieved from Clalit's primary care database. For comparison with the general Clalit population, age-specific mortality rates for 2010 were retrieved from the same database.

Statistical Analysis

Data analysis was performed using SPSS version 18 (SPSS, Chicago, IL). Data were summarized using frequency tables for categorical variables and summary statistics (median, mean and SD) for continuous variables. Categorical variables were compared using chi-square tests. Continuous variables were compared using *t* tests or analysis of variance. For continuous variables with a non-normal distribution, comparisons were made using the nonparametric Wilcoxon rank-sum test.

Long-term survival was compared between strata of age, Charlson comorbidity index, and the number of failing organ systems using Kaplan-Meier's method. Log-rank test was used to assess the significance of the difference in survival. Indirect age adjustment was used to compare the observed 1-yr mortality among sepsis survivors to the expected 1-yr mortality based on rates in the general population. p values $<.05$ were considered statistically significant for all comparisons. All reported p values are two sided.

RESULTS

During the study period, 27,516 patients were diagnosed with sepsis. Of these, 1,091 (4.0%) were directly admitted to the ICU, 2,096 (7.6%) were first admitted to an internal medicine ward and later transferred to the ICU, and 1,968 (7.2%) were first admitted to a surgical ward (or the operating room) and later transferred to the ICU. Overall, 5,155 patients were eventually admitted to the ICU and included in the study. These patients comprise 18.7% of the patients with sepsis. The proportion of patients admitted to the ICU among patients with sepsis, severe sepsis, and septic shock were 3.8%, 29%, and 36%, respectively. The rest of the patients were treated in general medical or surgical wards.

Baseline characteristics of the patients are given in Table 1. The patients' median age was 70. Most patients (56%) were male. The most common comorbidities were hypertension (50%), chronic ischemic heart disease (34%), and diabetes (33%). Using ICD-9-CM codes, the site of infection could be identified as pulmonary in 34%, the urinary tract in 12%, soft tissues in 5%, the gastrointestinal tract in 4%, and the peritoneal cavity in 12%. In the rest of the patients (33%), the source of the infection could not be determined from ICD-9-CM codes. Based on the algorithm described by Martin et al (8), 9% had no organ failure, while 31%, 31%, and 30% had one, two, or three or more failing organ systems, respectively (Table 1).

Over time, the number of sepsis-related ICU admissions increased linearly by 37%, from a mean of 49 per month in 2002 to 67 in 2008 (Fig. 1*A*). The R^2 for a linear association between the period of admission and the number of admissions per month was 0.410. During the study period, the number of ICU beds increased only by 5% (from 133 in 2002–2005 to 140 in 2006–2008).

No change was observed during the study period in in-hospital mortality (Fig. 1*B*), which ranged from an average of 53% in 2002 to 55% in 2008. During the study period, the mean age slightly increased (64 in 2002 vs. 67 in 2008, $p = .005$) while the mean Charlson comorbidity index did not change (4.1 in 2002 vs. 4.2 in 2008, $p = .199$). The median hospital length of stay decreased slightly from 24.0 days to 22.5 days ($p = .002$), and the median ICU length of stay remained constant at 8.0 days ($p = .854$).

Data for long-term survival were available for Clalit's enrollees only (n = 3999, 77.5% of patients) and are presented in Figure 2*A*. The proportion of patients surviving to hospital discharge in this

Table 1. Baseline characteristics of intensive care unit sepsis patients, 2002–2008 (n = 5155)

Variable	Patient Characteristic	Mean ± SD or n (%)
Age	Mean	65.5 ± 17.8
	Median	70.3
	Range	18–110
Sex	Male	2904 (56.3%)
Comorbidities	Hypertension	2559 (49.6%)
	Ischemic heart disease	1750 (33.9%)
	Diabetes	1719 (33.3%)
	Congestive heart failure	1255 (24.3%)
	Atrial fibrillation	1352 (26.2%)
	Chronic renal failure	1058 (20.7%)
	Chronic obstructive lung disease	927 (18.0%)
	Cancer	905 (17.6%)
	History of stroke	558 (10.8%)
	Asthma	218 (4.2%)
Charlson Comorbidity Index	Mean	4.1 ± 2.5
	Median	4
	Range	0–14
Pre intensive care unit length of stay (days)	None	1091 (21.2%)
	Mean	4.0 ± 14.3
	Median	1
	Range	0–238
Site of infection[a]	Pulmonary	1727 (33.5%)
	Urinary tract	639 (12.4%)
	Peritoneal cavity	613 (11.9%)
	Soft tissues	254 (4.9%)
	Gastrointestinal tract	222 (4.3%)
	Not stated	2924 (56.7%)
Blood culture	Any positive blood culture	1164 (22.6%)
	Staphylococcus species	403 (7.7%)
	Escherichia coli	163 (3.2%)
	Pseudomonas species	158 (3.1%)
	Klebsiella species	128 (2.5%)
Number of failing systems	0	473 (9.2%)
	1	1580 (30.6%)
	2	1571 (30.5%)
	>3	1531 (29.7%)
Type of failing systems	Respiratory	3606 (70.0%)
	Cardiovascular	2473 (48.0%)
	Renal	2040 (39.6%)
	Metabolic	683 (13.2%)
	Hematologic	572 (11.1%)
	Neurologic	421 (8.2%)
	Hepatic	167 (3.2%)
Septic shock	With septic shock	1797 (34.9%)

[a]Some patients had more than one site of infection.

subgroup was 44%. One-year, 2-, 5-, and 8-yr survival rates were 33%, 30%, 23%, and 20%, respectively. The overall standardized mortality ratio was 2078%, i.e., the observed number of deaths was 21-fold higher than expected, after adjusting for age,

We conducted a landmark survival analysis for Clalit's enrollees surviving the acute sepsis episode (n = 1770, 73% of patients surviving the acute sepsis episode, Fig. 2*B*). The age-standardized 1-yr mortality for out-of-hospital survivors was compared to that of the general population of Clalit enrollees. One-year mortality rates for ages 18–50 was 9% in survivors of sepsis compared to 0.11% in the general population (relative risk = 80). For patients >80 yrs old, it was 42% in sepsis survivors and 4.5% in the general population (relative risk = 9).

We compared long-term survival by age, sex, underlying comorbidities, Charlson comorbidity index, and the type and number of failing organ systems (Figs. 3–5). Long-term mortality (up to 8 yrs) increased with increasing age (from 43% in patients younger than 50 yrs to 94% in those over 80 yrs, $p < .001$, Fig. 3). Mortality was similar among males and females (82% vs. 79%, respectively, $p = .925$) and increased with higher Charlson comorbidity index (from 28% in patients with a score of 0 to 93% in those with a score of 6 or higher, $p < .001$, Fig. 4). When looking at specific underlying diagnoses, hazard ratios ranged from 1.19 for patients with diabetes (95% confidence interval 1.10−1.29), to 1.25 (1.12–1.40) for patients with a previous stroke, 1.26 (1.15–1.38) for cancer, 1.27 (1.18−1.37) for hypertension, 1.29 (1.18−1.39) for congestive heart failure, 1.32 (1.22–1.43) for chronic ischemic heart disease, 1.33 (1.22–1.46) for chronic obstructive lung disease, 1.35 (1.25–1.46) for atrial fibrillation, and reached 1.36 (1.25–1.48) for patients with chronic renal failure (all p values <.001). Patients with asthma had similar mortality rates as the overall cohort (hazard ratio = 0.92, 95% confidence interval 0.76−1.10, $p = .33$). Finally, mortality increased with a greater number of failing organ systems (from 60% in patients with no failing organs systems to 89% in those with three or more failing organ systems, $p < .001$, Fig. 5). Hazard ratios were 1.08 for hematologic failure (95% confidence interval 0.96−1.22, $p = .188$), 1.17 with neurologic failure (95% confidence interval 1.03–1.33, $p = .016$), 1.21 (1.09–1.34, $p < .001$) for metabolic failure, 1.22 (1.01–1.47, $p = .038$) for hepatic failure, 1.26 (1.17–1.36, $p < .001$) for acute renal failure, 1.37 (1.26–1.49, $p < .001$) with respiratory failure, and was as high as 1.46 (1.35–1.57, $p < .001$) for patients with cardiovascular failure.

DISCUSSION

The present study describes the long-term outcome of patients with sepsis in the ICU in seven general hospitals in Israel from 2002 to 2008. The number of ICU admissions with sepsis increased by 37% over these years, while in-hospital mortality remained high and unchanged at approximately 56%. Long-term survival was poor, reaching 33%, 23%, and 20% over 1, 5, and 8 yrs, respectively. For certain subgroups, e.g., those older than 80 yrs, having a Charlson comorbidity index higher than 6, or having three failing systems or more, 8-yr survival was as low as 6%–11%.

The median age of patients in the present study was 70 yrs, much older than in some series (57–62 yrs in the studies by Angus et al [5] and Martin et al [8]), but similar to the range reported by others (9, 19, 23). Most patients (56%) were male, in accordance with some series (5, 19) but not with others (8, 9, 23). Similar to other series (5, 7, 24), the most common sites of infection were the lower respiratory tract, the urinary tract, and

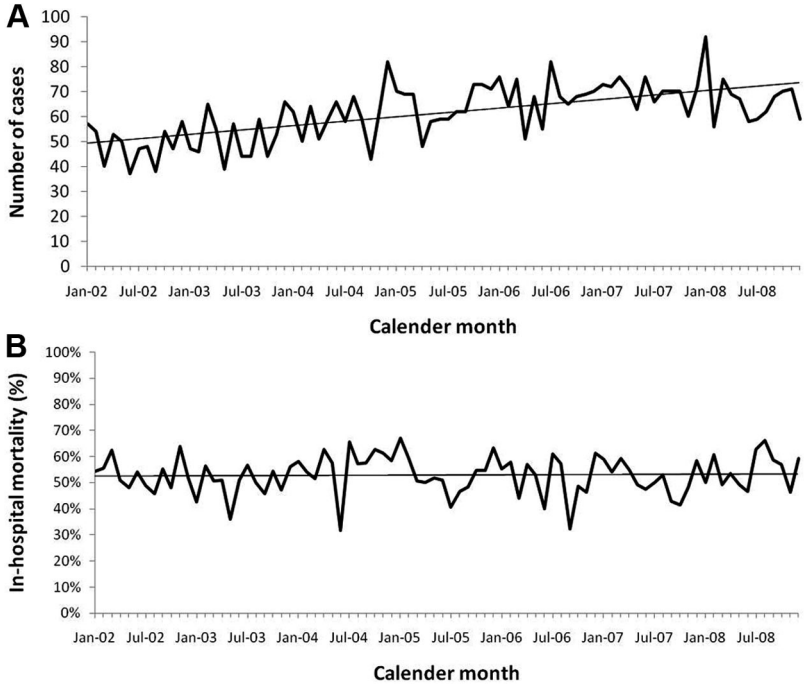

Figure 1. Trends in (*A*) the number of intensive care unit admissions with sepsis (per month), and (*B*) in-hospital mortality, by month, 2002–2008.

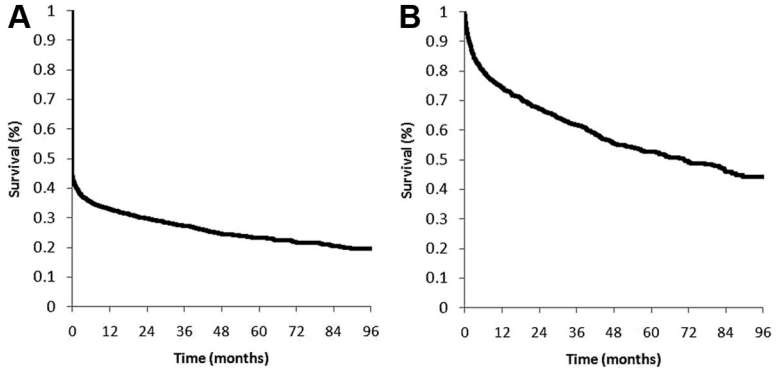

Figure 2. Kaplan-Meier survival plot for (*A*) all patients within Clalit Health Services (n = 3999), and (*B*) out-of-hospital survivors of the sepsis episode (landmark analysis) among Clalit's enrollees (n = 1710), 2002–2008.

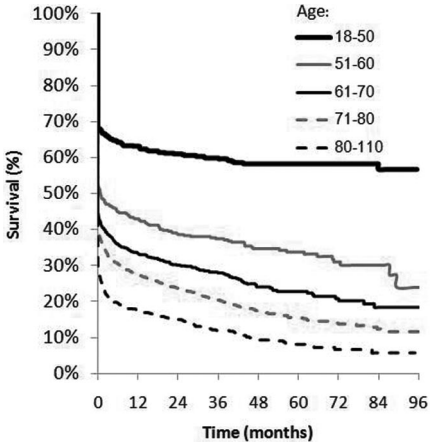

Figure 3. Kaplan-Meier survival plot, by age, within Clalit Health Services enrollees (n = 3999), 2002–2008 ($p < .001$).

the peritoneal cavity. The patients in our study were much more likely to be diagnosed with certain comorbidities when compared with previously reported studies (5, 10, 19, 23–25), including arterial hypertension (50% vs. 24%–35% in previously published series), ischemic heart disease (34% vs. 8%–23%), diabetes mellitus (33% vs. 12%–28%), chronic renal failure (25% vs. 5%–7%), and atrial fibrillation (26% vs. 10%) (5, 10, 19, 23–25).

The percentage of patients having no evidence of organ system dysfunction or one organ system dysfunction in the present study (9% and 31%, respectively) was much lower than previously reported, while those with three or more failing systems (28% of patients in the present study) were much more common than previously reported (5, 8, 19, 26, 27). Martin et al (8) reported that 66%–83% had no evidence of organ system dysfunction and only 0.5%–2% had three or more failing organ systems. Other series (5, 19, 26, 27) focusing exclusively on patients with severe sepsis (i.e., with at least one failing organ system), reported that most patients (58%–81%) had one failing organ system and only 6%–16% had three or more failing organ systems. A possible explanation for these differences is the shortage of ICU beds in Israel, leading to a situation where only the sickest patients are admitted to the ICU. Of note, general medical and surgical wards in Israel treat patients requiring both invasive and noninvasive respiratory support as well as vasopressors (dopamine). It should also be noted that a do-not-resuscitate policy was not supported by the Israeli law at the time of the study and was not a reason for denying ICU admission.

A steady, linear, 37% increase in the mean number of admissions with sepsis per month was noted over the study period. Over that period, the number of ICU beds in hospitals included in the present study increased only by 5%. Health policy planners who look for data to guide resource allocation to optimize the use of ICU beds could use some of the data presented, showing very low long-term survival for patients older than 80 or with a high index of comorbidities.

While some of the increase in the number of sepsis cases is related to the aging of the population, including the rapid increase in the proportion of the very old, this fact alone could not account for the degree of increase noted. The prevalence of comorbidities related to sepsis (e.g., cancer, diabetes) is rising. Similar finding were previously reported in the United States (5, 8, 9, 26), Spain (23), and Israel (28).

The in-hospital mortality in our study (56%) was higher than reported in most other series, ranging from 34% to 43% in series focusing on ICUs (5, 11, 17, 20, 23, 24, 27, 29–34). No change over the study period was observed, in marked contrast with the literature, which clearly shows a trend for decreasing case-fatality rate over time (relative yearly decrease by 2%–5% in several studies) (8–11). Based on the current data, it is impossible to state whether the lack of decrease in the case-fatality rate stems from suboptimal adoption of specific strategies for treating

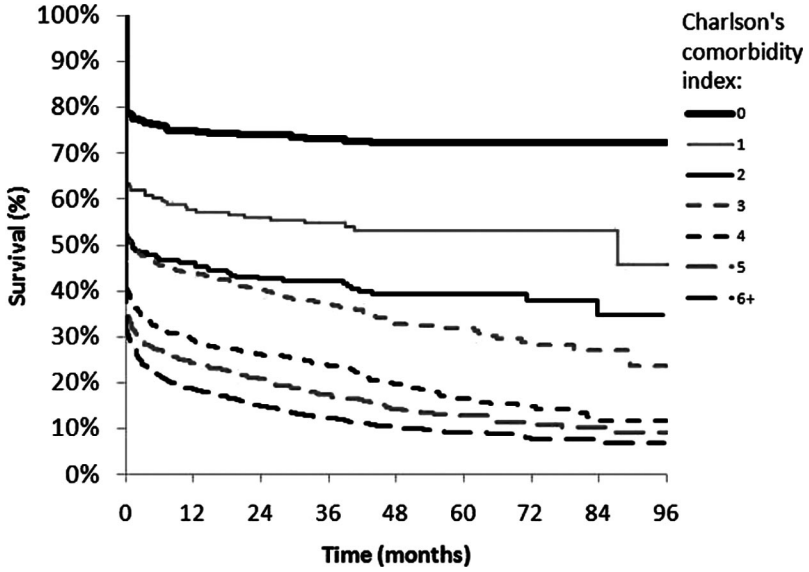

Figure 4. Kaplan-Meier survival plot, by Charlson comorbidity index, within Clalit Health Services enrollees (n = 3999), 2002–2008 ($p < .001$).

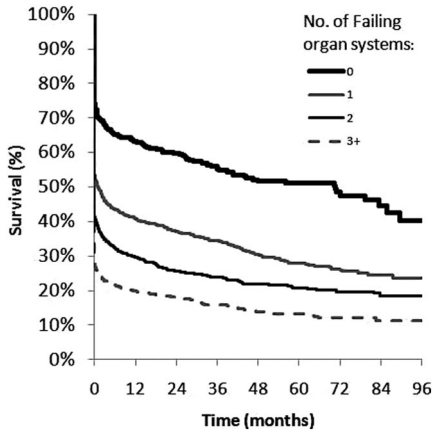

Figure 5. Kaplan-Meier survival plot, by the number of failing organ systems, within Clalit Health Services enrollees (n = 3999), 2002–2008 ($p < .001$).

sepsis (e.g., early goad-directed therapy [3] or recombinant human activated protein C [35]), the general quality of care in the ICU (26), or perhaps the low ratio of ICU-to-general medical beds in Israel, which is estimated at only 3%. This low ratio may lead to admitting only the sickest of the sick to the ICU. Israeli ICUs operate at full occupancy, therefore, admissions to the ICU can be delayed and patients are likely to be discharged too soon for the same reason. There are no step-down units in Israel. This means that the level of care drops precipitously when the patient moves to the general ward. In light of this shortage of ICU beds, the steady case-fatality rate despite the 37% increase in patient load is somewhat encouraging.

Hospital length of stay in the present study is quite long (median: 24 days) and may be related to the delayed discharge of patients with chronic illness, especially chronic critical illness, due to a shortage in long-term care facilities.

One-year mortality was 67%, similar to the previously reported range of 36%–72% (17, 20, 24, 27, 29, 31, 33, 34). One-year mortality for out-of-hospital survivors was 21 times higher than expected based on data from the general Clalit's enrollees' population, after adjusting for age. This emphasizes the long-term sequelae of hospitalization with sepsis, although adjustment was limited by lack of data on comorbidities and underlying diagnoses of the general population.

Few studies reported on the long-term survival of sepsis patients (19, 20). Cumulative mortality reported in the present study is within the range in previously published series (70% vs. 74%–76% at 5 yrs, 80% vs. 82% at 8 yrs following admission) (19, 20). Similar to previous studies, poorer long-term survival was noted with increasing age, higher Charlson comorbidity index, and a greater number of failing organ systems (17, 19, 20).

Several studies have addressed quality of life following sepsis admission (14–18). These patients have been reported to have persisting symptoms, such as dyspnea, fatigue, depression and functional decline (14, 15), work- and daily activities-related difficulties, and overall lower perceived health (15–17). A recently published prospective study (18) reported an increased incidence of new cognitive impairment, worsening of existing cognitive impairment, and an increase in functional disability among survivors of severe sepsis, compared with patients admitted for other reasons. These differences persisted for 8 yrs following sepsis admission. This important aspect lies beyond the scope of the present study.

Our study has several strengths, including the capture of a large percentage of the local population, the long-term follow-up (up to 8 yrs) with virtually no loss to follow-up for Clalit's enrollees, and the large sample size. This study adds to the knowledge base of health planners who are posed with hard choices in a situation where shortage of ICU beds is an issue.

Our study has several limitations relating to the inability to verify diagnostic codes for each case. Data regarding comorbidities and organ system failure were based on ICD-9-CM codes determined from physicians' diagnoses and are of limited precision. There is some potential overlap between the categories of comorbidities vs. organ system failure. Given the shortage of ICU beds, the proportion of patients without organ system failure (9%) might be an overestimate (presumably due to coding errors), these patients were unlikely to be admitted to the ICU. Similarly, the source of the infection could not be identified from ICD-9-CM codes in one third of patients. These difficulties are inherent to the administrative nature of the data. Another limitation is the inability to distinguish between community- and hospital-acquired sepsis, since the precise date of the diagnosis is unavailable; therefore, similarly to the previous studies (36), we do not know if the diagnosis was present at admission or developed during the patient's stay in the ICU. Therefore, we cannot reliably compare the outcome between patients directly admitted to the ICU and those who had delays getting in from the general medical and surgical wards, because we cannot distinguish between late nosocomial sepsis and delayed treatment of community-acquired sepsis. Data regarding severity of disease, such as the Acute Physiology and Chronic Health Evaluation II or Simplified Acute Physiology Score I scores, were not available in this administrative database. We also were unable to assess whether deaths

were related to underlying comorbidities or to the acute event, although when comparing this cohort with the general population, the standardized mortality ratio was significantly elevated. Data regarding the therapies used (e.g., inotropes, vasopressors, antibiotics), timing of therapies, laboratory monitoring, and timing of the diagnosis of sepsis were not available. Laboratory results of central venous oxygen saturation, lactate, and other physiologic parameters (central venous pressure, mean arterial pressure) needed for monitoring the adherence to the goal-directed therapy were not recorded in the database. We were unable to determine whether these parameters were monitored more often over the course of the study and if treatment goals were met, and cannot correlate these with mortality trends.

CONCLUSION

To conclude, the number of ICU admissions with sepsis in Israel is rising. In-hospital and long-term mortality remains high, especially for the elderly and those with significant comorbidities or a larger number of failing organ systems. A severe shortage of ICU beds may be a contributing factor to these outcomes. More answers are needed regarding various aspects of care for patients with sepsis and these could be addressed by a future prospective study we plan to perform.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
2. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
3. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
4. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359–1367
5. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
6. Longo CJ, Heyland DK, Fisher HN, et al: A long-term follow-up study investigating health-related quality of life and resource use in survivors of severe sepsis: Comparison of recombinant human activated protein C with standard care. *Crit Care* 2007; 11:R128
7. Vincent JL, Sakr Y, Sprung CL, et al: Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 2006; 34: 344–353
8. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
9. Dombrovskiy VY, Martin AA, Sunderram J, et al: Facing the challenge: Decreasing case fatality rates in severe sepsis despite increasing hospitalizations. *Crit Care Med* 2005; 33: 2555–2562
10. Martin GS, Mannino DM, Moss M: The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34:15–21
11. van Ruler O, Schultz MJ, Reitsma JB, et al: Has mortality from sepsis improved and what to expect from new treatment modalities: Review of current insights. *Surg Infect (Larchmt)* 2009; 10:339–348
12. Braun L, Riedel AA, Cooper LM: Severe sepsis in managed care: Analysis of incidence, one-year mortality, and associated costs of care. *J Manag Care Pharm* 2004; 10:521–530
13. O'Brien JM Jr, Ali NA, Aberegg SK, et al: Sepsis. *Am J Med* 2007; 120:1012–1022
14. Granja C, Dias C, Costa-Pereira A, et al: Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. *Crit Care* 2004; 8:R91–R98
15. Heyland DK, Hopman W, Coo H, et al: Long-term health-related quality of life in survivors of sepsis. Short Form 36: A valid and reliable measure of health-related quality of life. *Crit Care Med* 2000; 28:3599–3605
16. Hofhuis JG, Spronk PE, van Stel HF, et al: The impact of severe sepsis on health-related quality of life: A long-term follow-up study. *Anesth Analg* 2008; 107:1957–1964
17. Perl TM, Dvorak L, Hwang T, et al: Long-term survival and function after suspected gram-negative sepsis. *JAMA* 1995; 274: 338–345
18. Iwashyna TJ, Ely EW, Smith DM, et al: Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304:1787–1794
19. Weycker D, Akhras KS, Edelsberg J, et al: Long-term mortality and medical care charges in patients with severe sepsis. *Crit Care Med* 2003; 31:2316–2323
20. Quartin AA, Schein RM, Kett DH, et al: Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA* 1997; 277:1058–1063
21. Ollendorf DA, Fendrick AM, Massey K, et al: Is sepsis accurately coded on hospital bills? *Value Health* 2002; 5:79–81
22. Eaton S, Burnham E, Martin G, et al: The ICD-9 code for septicemia maintains a high positive predictive value for clinical sepsis. Abstr. *Am J Respir Crit Care Med* 2002; 165: A471
23. Esteban A, Frutos-Vivar F, Ferguson ND, et al: Sepsis incidence and outcome: Contrasting the intensive care unit with the hospital ward. *Crit Care Med* 2007; 35:1284–1289
24. Sands KE, Bates DW, Lanken PN, et al: Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997; 278:234–240
25. Lee H, Doig CJ, Ghali WA, et al: Detailed cost analysis of care for survivors of severe sepsis. *Crit Care Med* 2004; 32:981–985
26. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007; 35:1244–1250
27. Braun L, Riedel AA, Cooper LM: Severe sepsis in managed care: Analysis of incidence, one-year mortality, and associated costs of care. *J Manag Care Pharm* 2004; 10:521–530
28. Notifiable infectious diseases in Israel: 54 years of surveillance, 1954–2004. Israel Center for Disease Control (2006) Publication No. 245
29. Brun-Buisson C: The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000; 26:S64–S74
30. Granja C, Dias C, Costa-Pereira A, et al: Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. *Crit Care* 2004; 8:R91–R98
31. Puskarich MA, Marchick MR, Kline JA, et al: One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: A before and after study. *Crit Care* 2009; 13:R167
32. Martin CM, Priestap F, Fisher H, et al: A prospective, observational registry of patients with severe sepsis: The Canadian Sepsis Treatment and Response Registry. *Crit Care Med* 2009; 37:81–88
33. Brun-Buisson C, Doyon F, Carlet J, et al: Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. *JAMA* 1995; 274:968–974
34. Rangel-Frausto MS, Pittet D, Costigan M, et al: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995; 273:117–123
35. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
36. Angus DC: The lingering consequences of sepsis: A hidden public health disaster? *JAMA* 2010; 304:1833–1834