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Cost-effectiveness of the Surviving Sepsis Campaign protocol for severe sepsis: a prospective nation-wide study in Spain

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Abstract *Context:* Severe sepsis is associated with high mortality and increased costs. The 'Surviving Sepsis Campaign' (SSC) protocol was developed as an international initiative to reduce mortality. However, its cost-effectiveness is unknown. *Objective:* To determine the cost-effectiveness of the SSC protocol for the treatment of severe sepsis in Spain after the implementation of an educational program compared with the conventional care of severe sepsis. *Design:* Observational prospective before-and-after study. *Setting:* 59 medical-surgical intensive care units located throughout Spain. *Patients:* A total of 854 patients were enrolled in the pre-educational program cohort (usual or standard care of severe sepsis) and 1,465 patients in the post-educational program cohort (SSC protocol care of severe sepsis). *Interventions:* The educational program aimed to increase adherence to the SSC protocol. The SSC protocol included pharmacological and medical interventions. *Main outcome measures:* Clinical (hospital mortality) and economic (health-care resource and treatment costs) outcomes were recorded. A health-care system perspective was used for costs. The primary outcome was incremental cost-effectiveness ratio (ICER). *Results:* Patients in the SSC protocol care cohort had a lower risk of hospital mortality (44.0% vs. 39.7%, $P = 0.04$). However, mean costs per patient were 1,736 euros higher in the SSC protocol care cohort (95% CI 114–3,358 euros), largely as a result of increased length of stay. Mean life years gained (LYG) were higher in the SSC protocol care cohort: 0.54 years (95% CI 0.02–1.05 years). The adjusted ICER of the SSC protocol was 4,435 euros per LYG. Nearly all (96.5%) the bootstrap replications were below the threshold of 30,000 euros per LYG. *Conclusion:* The SSC protocol seems to be a cost-effective option for treating severe sepsis in Spain.

Keywords Severe sepsis · Cost-effectiveness analysis · Outcome · Protocol

Introduction

Severe sepsis remains a highly prevalent and lethal syndrome, accounting for one in five admissions to intensive care units (ICUs) and resulting in 30–50% hospital mortality [1–3]. In Spain, an estimated 40,000 cases of severe sepsis and 12,000 sepsis-related deaths occur each year [4, 5]. The Surviving Sepsis Campaign (SSC) protocol was developed as an international initiative to reduce mortality due to severe sepsis and is promoted by several critical care societies [6, 7]. The SSC protocol includes the most up-to-date and advanced therapeutic interventions to be implemented in two bundles: a 6-h resuscitation bundle, including lactate determination, early cultures and antibiotics, and early goal-directed therapy, and a 24-h management bundle, including optimizing glycemia and plateau pressure and considering treatment with corticoids and/or drotrecogin alfa (activated). An international study evaluating the implementation of the SSC protocol showed that the campaign was associated with sustained, continuous quality improvement in sepsis care, and with a reduction in reported hospital mortality rates [8]. In Spain, the SSC protocol was introduced by means of a 2-month educational program. The educational program improved adherence to the SSC recommendations and resulted in a significant reduction in mortality [9].

Severe sepsis is also expensive to treat. In Spain, care of severe sepsis patients costs around 500 million euros annually [10], and in the US the cost exceeds 16 billion dollars each year [11]. The incidence and associated costs of severe sepsis are expected to increase significantly with the aging of the population in developed countries [11]. Therefore, policy makers and clinicians should pay attention to the cost effectiveness of new interventions and/or protocols for severe sepsis; this is especially important for programs that may be implemented at a national level, utilizing performance measures to drive improvement in care. Competitive effectiveness evaluations must also consider cost implications.

This study aimed to prospectively analyze the cost effectiveness, from a health-care system perspective, of the SSC protocol for severe sepsis in Spanish ICUs.

Methods

Overview

We conducted a cost-effectiveness analysis using data from a recent prospective study comparing severe sepsis mortality before and after an educational program in 59 medical/surgical ICUs located throughout Spain [9]. The preintervention cohort included all consecutive patients with severe sepsis admitted to the participating hospitals in the 2 months before the educational program (November–December 2005). The 2-month educational program consisted of training physicians and nursing staff from the emergency department, medical and surgical wards, and ICU in early recognition of severe sepsis and in the treatments included in the SSC protocol (January–February 2006). The postintervention cohort included all consecutive patients with severe sepsis admitted to the participating hospitals during the 4-month period after the implementation of the educational program (March–June 2006). Initial results showed that adherence to the SSC protocol improved and hospital mortality decreased after the educational program [9]. Each participating center's Research and Ethical Review Board approved the study, and patients remained anonymous.

The SSC protocol

The SSC protocol was organized as two 'bundles'. The resuscitation bundle, to begin immediately and to be accomplished within the first 6 h of severe sepsis presentation, included measuring serum lactate, obtaining blood cultures prior to antibiotic administration, administering broad-spectrum antibiotics within 3 h of presentation for emergency department admissions and within 1 h for non-emergency department ICU admissions, and, if appropriate, administration of fluids and implementation of the early-goal directed therapy. The post-resuscitation 'management' bundle, to be accomplished within the first 24 h of presentation, included considering the administration of low-dose steroids, considering the administration of drotrecogin alfa (activated), maintaining glucose control at or above the lower limit of normal but with a median value <150 mg/dl (8.3 mmol/l), and maintaining median inspiratory plateau pressures <30 cm H_2O in mechanically ventilated patients.

Treatment of individual patients varied within the cohorts, and management of patients in the post-educational program cohort did not always comply with the SSC guidelines. Thus, not all patients in either cohort received all the treatments. However, for the purpose of this cost-effectiveness analysis, we designated the pre-educational cohort as the control group (usual or standard care of severe sepsis) and the post-educational program cohort, with a significantly higher adherence to the SSC guidelines [9], as the treatment group (SSC protocol care of severe sepsis).

In both the preintervention and postintervention periods of the study, all ICU admissions from the emergency department or from wards and all ICU patients were actively screened daily for the presence of severe sepsis or septic shock. Patients were systematically identified using a screening tool which included definitions of sepsis and organ dysfunction. When the onset of severe sepsis (time 0) could not be determined, patients were not

included in the study. Severe sepsis and septic shock were defined according to the SSC protocol and consensus definitions [12].

Data collection

The clinical and demographic characteristics of all patients, including age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, diagnosis at admission, and origin of infection, were recorded. Lengths of stay in medical or surgical ward and in ICU were collected for the entire hospital stay. Moreover, compliance with the different elements of the SSC protocol was recorded in the two periods.

Life-years gained and quality-adjusted life years

To derive life-years gained (LYG) we estimated the age and gender-specific life expectancy for each hospital survivor using the data from the 2006 Spanish life-expectancy tables [13]. We then adjusted these life expectancies using the estimated reduction rate for sepsis survivors, 0.51, suggested by Quartin et al. [14]. This approach was recently used to assess the cost-effectiveness of severe sepsis interventions [15–17]. LYGs were discounted at an annual rate of 3%.

Quality-adjusted life years (QALYs) were derived by multiplying LYGs by a utility weight of 0.69. This value takes into account the decrease in quality of life after surviving severe sepsis. Again, this estimate was recently used to assess the cost effectiveness of severe sepsis interventions [17]. This utility weight was obtained from a study of 6-month survivors of severe sepsis using the EuroQol-5D questionnaire [18, 19].

Costs

The Spanish health-care system's perspective was used for costs. Unit cost for emergency visits, surgical and medical ward daily stays, and ICU daily stay were obtained from the Spanish National Health Institute [20]. The unit costs associated with the SSC protocol pharmacological interventions were obtained from the Spanish physician's desk reference [21], and costs associated with materials used in nonpharmacological interventions were obtained from their suppliers. We did not record the resources used in insulin therapy (insulin infusion and blood glucose monitoring), so we decided to apply the average cost per patient reported by Van den Berghe et al. [22] in a cost-effectiveness analysis of insulin therapy (144 euros for intensive therapy and 72 euros for conventional therapy). We assumed that patients who achieved the therapeutic goal recommended in the SSC protocol would use similar resources to patients treated with intensive therapy and that patients who did not achieve the therapeutic goal would use similar resources to patients treated with conventional therapy. The Belgian costs reported by Van den Berghe were converted to Spanish costs using the 2006 Purchasing Power Parities exchange rates [23]. All prices were adjusted to 2006 values using the Spanish consumer price index [24]. We did not include costs incurred after hospital discharge (long-term costs); hence, as no patient stayed longer than 1 year in the hospital, costs were not subject to discounting [25]. The cost of the entire educational program was estimated at 54,270 euros (see Table 1 of the supplementary material). As this cost was negligible compared with the overall costs (less than 0.2% of the total costs of the postintervention cohort), it was ignored for the primary analysis.

Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables and means and standard deviations for continuous variables. To compare variables during the two study periods, independent *t* tests or the chi-squared test were used when appropriate. For the cost and the effectiveness outcomes, we derived 95% confidence intervals for the mean differences between the two periods using bootstrap resampling (2,000 replications) to take into account the skewness of the data [26].

Incremental cost-effectiveness ratios and incremental cost-utility ratios

Cost-effectiveness analysis involves comparing two or more therapeutic options to determine which best maximizes the benefits considering the available resources [27]. This is achieved by calculating the relationship between the costs of a given intervention and its consequences, usually expressed in LYGs, and comparing these costs and consequences with those of another intervention. This relative value is called the incremental cost-effectiveness ratio (ICER), and it expresses the relationship between the incremental average costs and effects of one intervention compared with those of another. Analogously, when the benefits are measured in terms of quality of life and expressed in QALYs, the cost-effectiveness analysis is referred to as cost-utility analysis and the incremental ratio as the incremental cost-utility ratio (ICUR).

Due to the observational design of the study, both the ICER and ICUR numerators (incremental costs) and the ICER and ICUR denominators (incremental effectiveness in terms of LYGs and QALYs, respectively) were

obtained by adjusting multivariable regression models to take into account possible baseline imbalances.

To take into account the skewness of the distribution of cost data, we conducted a modified Parks test to identify the family of generalized linear models that best fitted our cost data [28]. The modified Parks test identified the gamma distribution; therefore, we used multivariable gamma regression models to fit incremental costs. For the analyses of incremental effectiveness (incremental LYGs and incremental QALYs), we fitted multivariable linear regression models. All the multivariable regression models were adjusted for age, sex, APACHE II score, septic shock, location, origin of infection, and intervention. The method of recycled predictions was used to derive mean incremental cost differences between the groups [29]. Moreover, to take into account clustering of patients into centers, the multivariable regression models were fitted using generalized estimating equations with an exchangeable correlation structure [30].

To address uncertainty in the sampling distributions of the ICERs and ICURs, nonparametric bootstrapping was carried out [26]. Thus, 2,000 replications were carried out and plotted in the cost-effectiveness plane, and the proportion falling below the threshold of 30,000 euros per LYG or 30,000 euros per QALY was calculated. This proportion estimates the probability of the SSC protocol being cost effective in Spain [31]. Moreover, net monetary benefit plots and acceptability curves were derived for both LYGs and QALYs.

Finally, the incremental cost per life saved was derived. The numerator of the previous expression was calculated in the same way as for the ICER and ICUR estimates. The denominator was fitted in two steps. First, a logistic regression was fitted where the outcome was patient survivor adjusted for the previous covariates, taking into account the clustering of patients into centers. Second, the method of recycled predictions was used again to estimate the increase in lives saved.

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of our results regarding our assumptions about life expectancy, quality of life, discount rates, and the impact of the time staff spent attending the educational sessions on the costs of the educational program.

Instead of the rate for sepsis survivors of 0.51 that we used in our primary analysis, we applied an even more restrictive rate of 0.39, as suggested by Angus et al. [15]. This approach is also based in the research conducted by Quartin et al. [14], and represents the increased mortality risk in patients with septic shock. In our primary analysis, QALYs were derived by multiplying LYGs by a utility weight of 0.69. However, in a recent study conducted in Finland, the median utility weight derived from EuroQol-5D in 2-year severe sepsis survivors was 0.75 [32]. Hence, we used this value in a sensitivity analysis. In addition, we plotted different possible values for the utility weights versus the associated ICUR estimates. Next, two sensitivity analyses were performed, the first without discounting LYGs and QALYs, and the second discounting LYGs and QALYs at a 5% annual rate.

We also conducted another sensitivity analysis to consider the impact of the costs of the time physicians and nurses spent attending the sessions of the educational program. In the primary analysis, we did not include the costs of staff time in the costs of the educational program, as we considered that the training sessions formed part of ongoing continuing medical education. This approach was adopted in two previous similar studies [17, 33]. However, as others might question this approach, we conducted a sensitivity analysis including the cost of the entire educational program (54,270 euros, see Table 1 of the supplementary material) as well as the costs of the time staff spent attending the educational program.

Subgroup analysis

To explore whether the cost-effectiveness profile of the SSC protocol was homogeneous for different subgroups of patients, we estimated the ICER and ICUR for subgroups according to age, gender and severity measured in terms of APACHE II score in the same way as for the whole sample. For age and severity, we divided the sample into two groups, choosing the median value for each variable as a cut-off.

Results

A total of 2,319 patients fulfilled severe sepsis or septic shock criteria and were included in the study. The mean (SD) age was 62.2 (16.3) years and the mean (SD) APACHE II score was 21.2 (7.7); 60.8% ($n = 1{,}411$) were male, 79.4% ($n = 1{,}842$) had septic shock, and hospital mortality was 41.2% ($n = 956$). The control group included 854 patients and the treatment group included 1,465 patients. The characteristics of patients in both groups were similar (Table 1), with no statistically significant differences in age, sex, or APACHE II score. Adherence to both the resuscitation and management bundles was greater in the treatment group than in the control group (Table 1). Moreover, the mean time to the administration of broad-spectrum antibiotics was 26 min lower in the treatment group (156.0 vs. 129.4 min,

Table 1 Patient characteristics by group

	Control group (n = 854)	Treatment group (n = 1,465)	P
Demographic			
Age, years, mean (SD)	62.4 (16.4)	62.1 (16.3)	0.74
Male	529 (61.9)	882 (60.2)	0.41
Severity			
APACHE II, mean (SD)	21.0 (7.5)	21.3 (7.8)	0.39
Patient location at sepsis diagnosis			0.81
Emergency department	351 (41.1)	613 (41.8)	
Ward	385 (45.1)	641 (43.8)	
ICU	118 (13.8)	211 (14.4)	
Origin of infection			0.002
Pneumonia	329 (38.5)	503 (34.3)	
Acute abdominal infection	248 (29.0)	424 (28.9)	
Urinary tract infection	82 (9.6)	165 (11.3)	
Meningitis	17 (2.0)	56 (3.8)	
Soft-tissue infection	37 (4.3)	49 (3.3)	
Catheter-related bacteremia	19 (2.2)	35 (2.4)	
Other infections	108 (12.6)	170 (11.6)	
Multiple infection sites	14 (1.6)	63 (4.3)	
Organ dysfunction criteria at sepsis presentation			
Hemodynamic	712 (83.4)	1,191 (81.3)	0.21
Respiratory	573 (67.1)	923 (63.0)	0.05
Renal	615 (72.0)	1,076 (73.4)	0.45
Hyperbilirubinemia	164 (19.2)	247 (16.9)	0.15
Thrombocytopenia	213 (24.5)	361 (24.6)	0.87
Coagulation	301 (35.2)	503 (34.3)	0.66
Compliance with SSC protocol[a]			
Resuscitation bundle	45 (5.3)	147 (10.0)	<0.001
Management bundle	93 (10.9)	230 (15.7)	0.001

Values are n (%), unless otherwise indicated
[a] Compliance was measured as fulfilling the requirements of the SSC protocol before it was introduced (control group) and after it was introduced (treatment group)

Table 2 Cost and effectiveness outcomes

	Control group (n = 854)	Treatment group (n = 1,465)	Difference (95% CI)
Length of stay (days)			
ICU	12.5 (15.9)	13.5 (17.7)	1.0 (– 0.4; 2.4)
Ward	10.8 (16.7)	12.6 (18.2)	1.8 (0.4; 3.3)
Total	23.3 (25.1)	26.1 (27.5)	2.8 (0.7; 5.0)
Costs (2006 euros)	16,935 (18,525)	18,671 (20,792)	1,736 (114; 3,358)
LYG[a]	5.44 (6.05)	5.98 (6.11)	0.54 (0.02; 1.05)
QALYs[a]	3.75 (4.18)	4.12 (4.22)	0.37 (0.02; 0.73)
Adjusted ICER	4,435 euros per LYG		
Adjusted ICUR	6,428 euros per QALY		

Values are means (SD), unless otherwise indicated. Deaths are included in length of stay
[a] LYG and QALYs discounted at 3%

$P = 0.003$). These results have been reported and commented on elsewhere [9].

Table 2 shows, among other results, the raw clinical and economic outcomes for the control and treatment groups. The overall mean cost per patient was 18,671 euros in the treatment group and 16,935 euros in the control group. This mean increase of more than 1,700 euros per patient was mainly driven by increased length of hospital stay (Fig. 1).

The risk of hospital mortality was lower in the SSC protocol care group than in the control group (44.0 vs. 39.7%, $P = 0.04$), and mean LYG and mean QALYs were higher in the treatment group: 0.54 years and 0.37 QALYs, respectively (Table 2). The adjusted ICER of the SSC protocol was 4,435 euros per LYG and the adjusted ICUR was 6,428 euros per QALY. Nearly all (96.5%) the bootstrap replications were below the threshold of 30,000 euros per LYG and 95.6% of the bootstrap replications

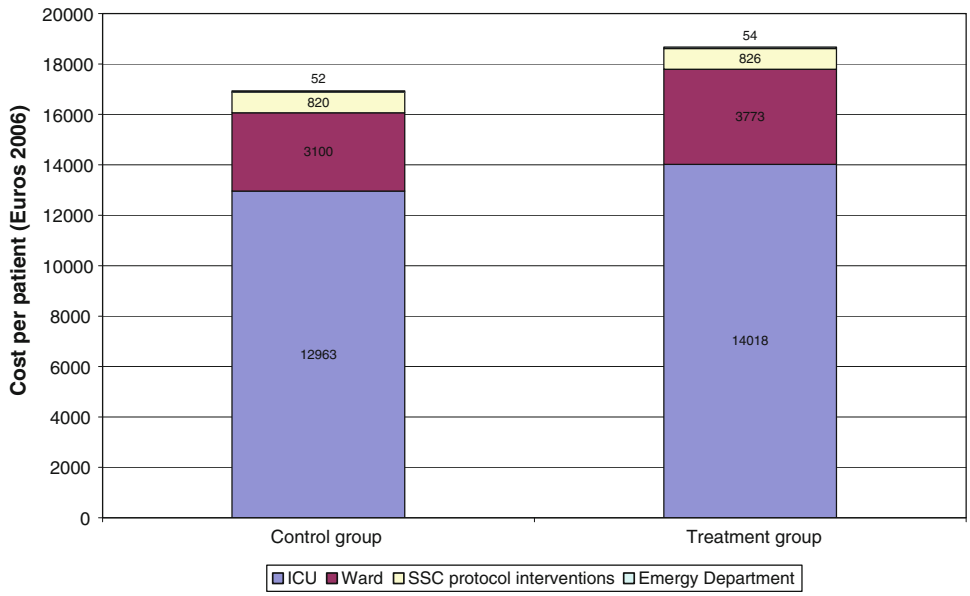

Fig. 1 Distributions of mean costs per patient

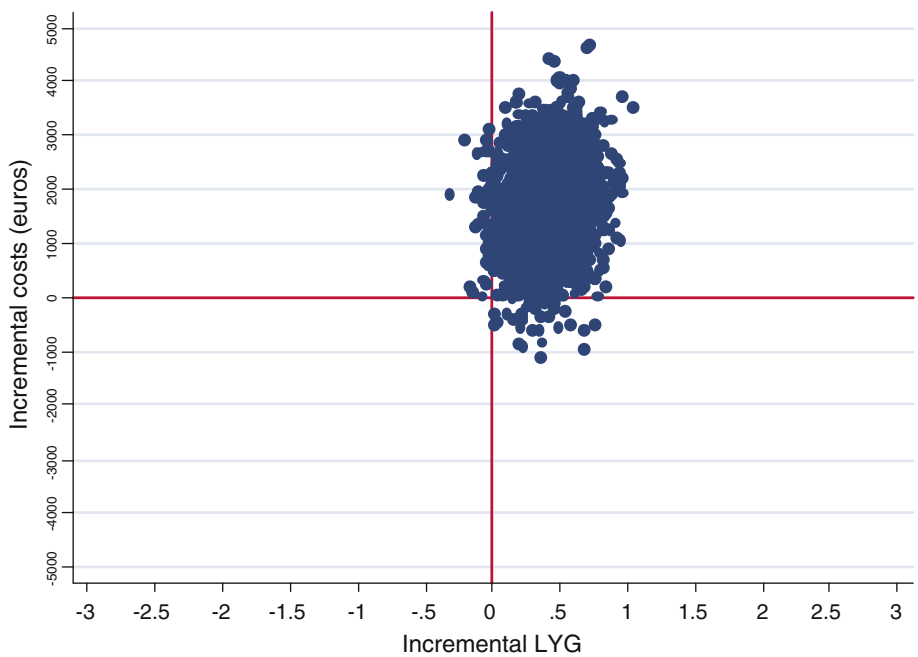

Fig. 2 2,000 bootstrap replications of the total costs and LYG differences between the treatment and the control groups in the cost-effectiveness plane

were below the threshold of 30,000 euros per QALY (Figs. 2, 3). The results of the net monetary benefit plots and the acceptability curves were in the same line (see Figs. 1 to 4 of the supplementary material). Finally, the incremental cost per life saved of the SSC protocol was 48,039 euros.

The results of the sensitivity analyses were highly consistent with the previous findings. For example, for the assumption of a reduction rate for sepsis survivors of 0.39 the ICUR was 8,079 euros per QALY; again this value is clearly below the threshold of 30,000 euros per QALY (see Table 2 of the supplement). And, as can be seen in Fig. 4, only for extremely low values of the utility weight (lower than 0.2) is the ICUR estimate above the usually accepted threshold. Lastly, when the cost of the educational program and the costs of the time physicians and nurses spent attending the educational program were included in the analysis, the ICUR and ICER estimates remained below the usually accepted thresholds (see Table 2 of the supplementary material).

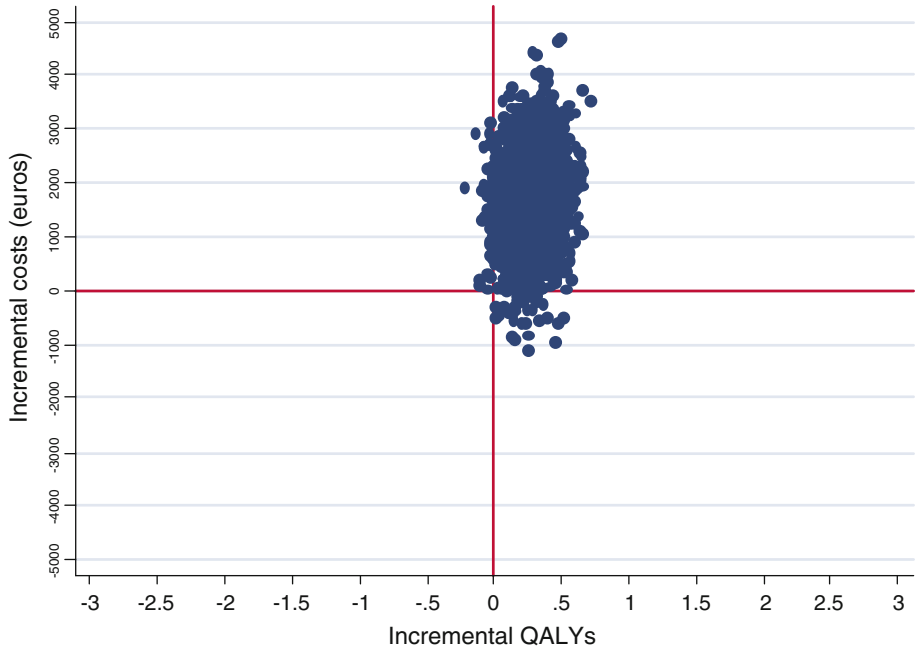

Fig. 3 2,000 bootstrap replications of the total costs and QALY differences between the treatment and the control groups in the cost-utility plane

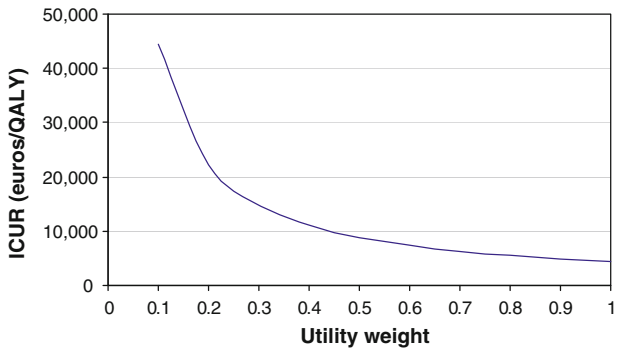

Fig. 4 Sensitivity analysis showing the effects of applying different values of utility weights on the ICUR estimate

The results of the subgroup analysis suggest that the SSC protocol could be less cost-effective for older, more severely affected, and male patients (Table 3 of the supplementary material). However, again, all the values were below the usually accepted thresholds.

Discussion

We analyzed the cost effectiveness of the SSC protocol for severe sepsis, as compared with usual care of the syndrome, in Spain.

The main result of our study was that the reduction in mortality associated with the SSC protocol was accompanied by an increase in costs compared with the standard care for severe sepsis. However, the estimated ICER (4,435 euros per LYG) was significantly lower than the commonly accepted threshold of 30,000 euros per LYG used in Spain [31]. Moreover, our results are in agreement with those of a recent study conducted in the US that showed that a protocol similar to the SSC protocol is a cost-effective alternative to the usual care of severe sepsis with an ICER of 11,274 dollars per LYG (8,906 euros per LYG) [17]. Another similar recent study, also conducted in the US, showed even better results as the sepsis protocol both improved mortality and reduced costs [33]. Nonetheless, these two studies have important limitations. Each was conducted in a single center with relatively small sample sizes, and the first one used a historical control group.

The estimated ICER of the SSC protocol in the present study was better than the estimated ICER for drotrecogin alpha (activated) in Spain (4,435 euros per LYG vs. 13,550 per LGY) [34]. In fact, the ICER of the SSC protocol in Spain compares well with the ICER of many interventions for ICU patients conducted in other developed countries [35] such as drotrecogin alpha (activated) in the US [35] or linezolid compared with vancomycin for the treatment of associated pneumonia due to *Staphylococcus aureus* in the US [35].

The subgroup analysis seems to suggest that there could be some differences in terms of the cost-effectiveness profile of the SSC protocol for age, gender, and severity. Older, male, and more severely affected patients had a worst cost-effective profile than their counterparts. These results could be partially explained by these patients' lower life expectancy. However, as in any post-hoc analysis, these results should be viewed with caution.

Several limitations should be considered when considering the results. First, our study was an observational study and patients were not randomized to groups. Although this is also one of the strengths of the study since it better reflects clinical practice [36], there could be unrecognized differences between the groups that could not be adjusted for in the multivariable analysis and which could therefore have confounded the study results. Second, as patients were not followed after hospital discharge, long-term costs were not included in the analysis. However, other ICU intervention studies have suggested that even when long-term costs are included, the ICER remains below the usually accepted thresholds [15]. Nonetheless, we cannot assume that this applies to the present study. Third, to estimate LYGs and QALYs, we made several assumptions. However, our sensitivity analysis regarding these assumptions produced similar results, reinforcing our primary findings. Fourth, the use of resources associated with insulin therapy was not recorded and we had to use figures from the literature. However, these costs were negligible compared to the overall costs. Fifth, adherence to the SSC protocol, although significantly higher after the educational program, was relatively low. The implementation of other evidence-based tools, such as academic detailing, computerized reminders, or repeated audit and feedback, might have further improved adherence [37]. Nonetheless, better adherence to the SSC guidelines may increase the associated costs. However, it might also reduce mortality due to severe sepsis. Finally sixth, to maintain adherence to the SSC protocol in the long term, additional educational efforts might be necessary, and this could increase the overall costs. However, these costs should not be greater than the costs of the initial 2-month educational program, and these costs were negligible compared to the costs of treating the patients.

Conclusion

In conclusion, the findings of the present study suggest that the SSC protocol is a cost-effective option for treating severe sepsis in Spain. Future research, guided by value of information methods, should be conducted to determine whether these results are similar in other developed countries. As performance measures are introduced for improving the management of critically ill patients, it is essential that ongoing evaluations on the impact of these measures on outcomes and costs are rigorously conducted.

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