A Cost-effectiveness Analysis of Albumin in Septic Shock: A Patient-level Data Analysis

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ABSTRACT

Purpose: Albumin-based fluid therapy in septic shock is a matter of debate and criticism. The aim of this study was to assess the cost-effectiveness of albumin therapy in patients with septic shock.

Methods: A retrospective cohort study was conducted in Imam Khomeini, Sina, and Shariati hospitals on patients with septic shock admitted to intensive care units from March 31, 2016 to September 22, 2017. Data sources were the health information system database and patient medical records. The patients with potential septic shock were identified based on norepinephrine use. Septic shock was confirmed after medical record review based on systemic inflammatory response syndrome criteria, antibiotic use, and fluid therapy. Patients who received albumin in the fluid therapy were compared with patients treated without albumin. The 28-day mortality, life-year gain, and cost-effectiveness were evaluated.

Findings: The addition of albumin had no significant increase in life-year gain (mean difference = 0.67; 95% CI, −2.25 to 3.58). However, the addition of albumin increased the total cost of treatment by US $3846.07 (95% CI, US $2093.46–US $5598.98). The incremental cost-effectiveness ratio calculated based on the mean life-years gained was US$5740.40 per a life-year gained. The net monetary benefit was negative (−355.4; 95% CI, −15,387.61 to 14,676.81), and the probability that the addition of albumin will be cost-effective at a gross domestic product per capita was 40.0%.

Implications: Albumin-based fluid therapy does not improve the 28-day mortality of patients with septic shock. The addition of albumin in the fluid therapy of patients with septic shock was not cost-effective. Both the observational and retrospective nature of the study was expected to introduce bias. We recommend a cost-effectiveness analysis combined with clinical trials to settle the debate once and for all. (*Clin Ther*. 2019;41:2297–2307) © 2019 Published by Elsevier Inc.

Key words: albumin, crystalloids, fluid balance, fluid volume, mortality.

INTRODUCTION

Sepsis is an infectious condition with aberrant and deregulated host responses that inflict multiorgan dysfunction.[1,2] Septic shock is sepsis with refractory hypotension or hyperlactatemia.[3] The Third International Consensus definition for septic shock makes the identification of hyperlactatemia mandatory for the diagnosis.[2] According to an assessment performed on the worldwide burden of

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critical illness, sepsis was a major critical illness in intensive care units (ICUs) (29.5%) and the condition with the highest mortality (25.8%).[4] The mortality rate depends on the setting and severity of the disease. It can reach up to 30% for sepsis, 50% for severe sepsis, and 80% for septic shock.[5] Generally, in the best setups, the mortality had decreased to 20% to 30%.[6] The hospital mortality of septic shock is >40%.[7]

Fluid therapy is a core component of septic shock management. Crystalloids are generally classified as normal saline (0.9% sodium chloride) and balanced solutions. The buffer solution and the chloride content are the main differences in these 2 groups.[8] The use of colloids in fluid therapy is an issue of debate and criticism. Albumin has a better safety profile from all colloids except in patients with traumatic brain injury.[9] Studies came up with contradicting conclusions on the mortality benefit of albumin in sepsis. The Saline Versus Albumin Fluid Evaluation trial and a meta-analysis revealed supporting evidence on the use of albumin in sepsis.[10,11] Similarly, in the Albumin Italian Outcome Sepsis (ALBIOS) trial, albumin-based resuscitation had a 90-day mortality reduction benefit in septic shock, although no survival benefit was observed in severe sepsis.[12] On the other hand, meta-analysis found that albumin has no statistically significant mortality reduction benefit.[13,14] A review by Caironi et al[15] concluded that although recent meta-analysis had a mortality benefit of albumin in patients with septic shock patients, the effect is yet to be confirmed.[15]

Generally, conducting economic evaluations based on patient-level data in conditions of uncertain effectiveness will have a well-pronounced effect on the rational use of medications and health care expenditure containment. The significance of performing cost-effectiveness analysis on medications such as albumin that have a high acquisition cost and can expand the health care expenditure at a minimum use for health policy will never be underrated. Therefore, the aim of this study was to assess the cost-effectiveness of albumin-based fluid therapy in septic shock.

METHODS

Study Area

This retrospective, observational study was conducted in Imam Khomeini Hospital (IKH), Sina Hospital (SH) and Shariati Hospital (ShH), which are among a few of the hospitals in Tehran, Iran, with well-equipped ICUs. The study was approved by the Ethics Committee of Tehran University of Medical Sciences, who waived the need for informed consent because of the observational nature of the study.

Data Sources

The health information system (HIS) database and patient medical records were the data sources for this study. The HIS contains administrative claims and discharge information for all patients managed in the hospitals. The patient information extracted from the database includes age, sex, referral units, date of admission, date of discharge, patient status at the time of discharge, diagnostic and surgical procedures performed, the dose and dates of use for albumin, normal saline, Ringer lactate, hypertonic saline, norepinephrine, epinephrine, dopamine, and dobutamine. The length of hospital stay, length of ICU stays, total cost of treatment, cost of ICU bed, cost of hospital bed, cost of medications, and cost of diagnosis were also extracted from the HIS. Patient medical records were used to extract information on vital signs, Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score, serum creatinine level, platelet count, total bilirubin level, Pao_2, fraction of inspired oxygen, arterial oxygen saturation, Glasgow Coma Score, the type and volume of fluid received, and daily fluid output.

Patient Selection

All potential patients who were suspected to have septic shock were identified based on norepinephrine administration status from the HIS database for patients admitted to ICUs from March 21, 2016, to September 22, 2017. Although the Third International Consensus defines septic shock based on refractory hypotension and a serum lactate level above 2 mmol/L[2] the existing practice in the study area follows the previous definition of septic shock provided by the Surviving Sepsis Campaign,[3] and serum lactate was rarely measured. Therefore, the septic shock was confirmed by patient medical record review based on documented or suspected infection and 2 of the following: temperature <36 °C or ≥38 °C, leukocyte count <4 or ≥12 × 10^9/L, respiratory rate ≥20 breaths/min or mechanical ventilation or heart rate ≥90 beats/min, and

vasopressor infusion despite fluid therapy. The inclusion criteria were as follows: age ≥16 years, septic shock with norepinephrine use, antibiotic therapy on day 1, and duration of ICU stays ≥24 hours. Both patients who developed septic shock before admission to the ICU and after admission to the ICU were included in this study. Patients with incomplete or missing medical records were excluded from the study.

Variables and End Points

The following characteristics were recorded: age, sex, referral units, SOFA score at the time of admission, the type and volume of fluid used for 5 consecutive days after ICU admission, fluid balance for 5 consecutive days after ICU admission, the type and dose of vasopressors and inotropic agents used, length of hospital stay, length of ICU stay, and patient status at discharge. All dopamine doses were converted to equivalent doses of norepinephrine with 100:1 conversion (10 μg/kg/min of dopamine equaled 0.1 μg/kg/min of noradrenaline).[17] Data on all fluids received within 24 hours before norepinephrine administration were recorded, but because of the lower grade of documentation in emergency departments and wards, we did not include these data in the final analyses.

The end points used in the present study were a life-year gain calculated based on all-cause 28-day mortality and the World Health Organization life table by sex and age for the Islamic Republic of Iran.[16] Patients who were discharged from the hospital before 28 days were considered to survive the whole 28 days, and patients who survived the whole 28 days were expected to live the estimated life expectancy by the World Health Organization. Hospital mortality was used as a secondary outcome measure, and the associated life-year gain was calculated to observe an associated significance.

Resource Use and Cost

The cost was identified and calculated based on health care payer perspective. Only direct medical costs were included. Four elements of resource use were measured directly in the study: (1) total cost of treatment, (2) cost of diagnosis, (3) cost of medication, and (4) hospital and ICU bed. In the present study, total cost of treatment was used to mean the total direct medical cost.

The only albumin preparation available in Iran is a vial of 50 mL of 20% albumin, and the mean price of albumin taken from the Food and Drug Administration of Iran market report for 2016 was IRR 1,267,757 or US $39.83 per vial. All the costs were inflated to 2017 costs using the Consumer Price Index of health for 2016 ($100.0) and 2017 ($110.1). The mean exchange rate (IRR 31,823 = US $1) was calculated from the reports of the central bank of Iran and used in the conversion of Iranian rials to US dollars.[17] Because the costs were calculated for a period of >1 year, no discount rate was used.

Statistical Analysis

On the basis of albumin use, patients were divided into 2 groups. Descriptive statistics were expressed as medians with interquartile ranges for continuous variables and the frequency of the total for categorical variables. The Wilcoxon rank sum test was used to compare unpaired continuous data between the groups. The χ^2 test was used for categorical data. The unpaired t test with Welch correction was used to compare unpaired continuous data in cost and life-year gain between albumin and no albumin groups.

Multivariate linear regression, Kaplan–Meier survival estimates, and propensity score matching were used in the analysis in a way to address selection bias and treatment effect. In the multivariate adjustment approach, outcomes and costs were modeled as functions of treatment allocation and observed baseline characteristics in a linear regression modeling framework. A stepwise backward elimination algorithm (at the $P < 0.05$ level of statistical significance) with addition to model (at the $P = 0.049$ level of statistical significance if subsequently proven important) was used to identify covariates significant at 5%. Kaplan–Meier survival estimates with the log rank test were used to assess the differences in the 28-day survival rates between patients with and without albumin use. Multivariate logistic regression was used to determine predictors of mortality for septic shock.

In the propensity score analysis, for each treatment comparison, the probability of treatments (propensity scores) was evaluated as a function of observed covariates. For each comparison, patients in the 2 treatment cohorts were then matched based on these

propensity scores to adjust for observed imbalances and to enable comparison across the matched patient strata. Comparison of outcomes between treatments was performed by the nearest neighborhood propensity score 1-to-1 matching algorithm. The caliper was fixed at 0.2 times the SD of the propensity score.

Cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER), which gives the incremental cost per additional life-year gain from one treatment compared with another. The net monetary benefit (NMB) was calculated from the matched group by taking 1 gross domestic product (GDP) per capita as a willingness to pay for a life-year gain. The probability that albumin-based fluid therapy was going to be cost-effective was calculated based on the number of times the NMB was positive from the total matched group.

RESULTS

The total number of patients who received norepinephrine was 1087 (455 at IKH, 410 at SH, and 222 at ShH). After medical record review only 645 of the total patients were identified as having septic shock based on the inclusion criteria (242 at IKH, 279 at SH, and 124 at ShH) (Figure 1).

The number of patients who received albumin was statistically significantly associated with the age of patients ($P = 0.049$), the hospital in which the patients got the service ($P < 0.001$), the referral unit ($P = 0.029$), and the focus of infection ($P < 0.001$). The length of hospital stays ($P = 0.016$); length of ICU stays ($P < 0.001$); number of patients taking dopamine ($P < 0.001$); amount of epinephrine ($P = 0.004$); fluid received on day 1 ($P < 0.001$), day 2 ($P = 0.003$), day 3 ($P = 0.004$), day 4 ($P = 0.002$), and day 5 ($P = 0.033$); and the in-hospital mortality rate ($P = 0.047$) were significantly different between the albumin and no albumin groups. The 28-day mortality ($P = 0.066$) and hospital mortality ($P = 0.267$) were not significantly different between the 2 groups (Table I). All the baseline characteristics (sex, age, referral unit, focus of infection, mean arterial pressure, serum creatinine level, mechanical ventilation, and the SOFA score) were not significantly different after matching except for the number of patients from each hospital (eTable I).

The Kaplan–Meier survival curve was different for patients treated with and without albumin before matching ($\chi^2 = 8.56$; $P = 0.003$). However, the difference could not be seen after matching ($\chi^2 = 0.86$; $P = 0.353$) (Figure 2).

Before matching, the mean cost of treatment for patients with and without albumin was US $11243.65 and US $7999.90, respectively. The mean life-year gained with the addition of albumin was 13.17 years, whereas it was 9.94 years without albumin. The mean cost-effectiveness ratio was US $853.73 per life-year gained for patients with albumin and US $804.82 per life-year gained for patients treated without albumin. The ICER of the addition of albumin on the fluid therapy regimen in septic shock management was US $1004.26 per life-year gained. Considering the GDP per capita of Islamic Republic of Iran (US $5219.2), the addition of albumin in the fluid regimen of septic shock looked cost-effective (Table II).

After matching, the mean cost of treatment for patients with and without albumin was US $11,954.42 and US $8108.35 respectively. The mean life-year gained in the albumin group was 12.20 years, whereas it was 11.53 years without albumin. The cost-effectiveness ratio was US $979.87 per life-year gained for patients with albumin and US $703.24 per life-year gained for patients treated

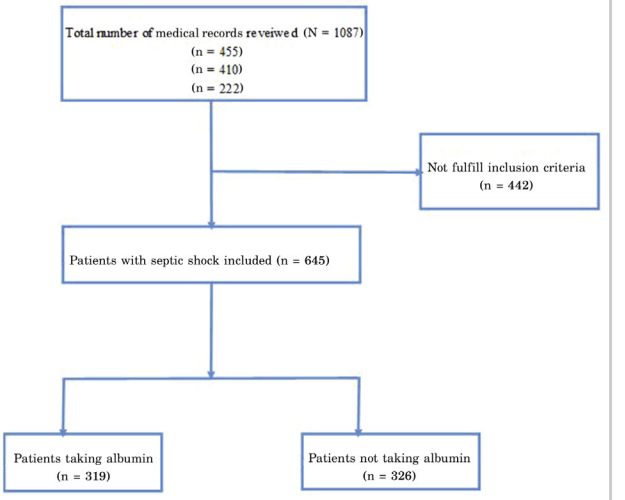

Figure 1. Patient selection. IKH = Imam Khomeini Hospital; SH = Sina Hospital; ShH = Shariati Hospital.

Table I. Baseline characteristics, treatment, and patient outcome between the groups taking albumin and not taking albumin groups before matching.

Variable	Albumin (n = 319)	No albumin (n = 326)	P
Male sex, No. (%)	185 (58.0)	192 (58.9)	0.816
Age, median (IQR), y	61 (45–75)	64 (52–75)	0.049*
MAP, median (IQR), mm Hg	65 (60–70.3)	63.8 (58–69.3)	0.122
ARDS, No. (%)	198 (60.4)	197 (62.1)	0.669
Serum creatinine, median (IQR), mg/dL	1.5 (0.98–2.3)	1.41 (0.95–2.60)	0.881
SOFA score, median (IQR)	11 (9–13)	10 (9–12)	0.094
Mechanical ventilation, No. (%)	253 (79.3)	251 (77.0)	0.477
Hospital, No. (%)			
IKH	134 (42.0)	108 (33.1)	<0.001*
SH	155 (48.6)	124 (38.0)	
ShH	30 (9.4)	94 (28.8)	
Referral unit, No. (%)			
Surgical	102 (32.0)	84 (25.8)	0.029*
Medical	58 (18.2)	79 (24.2)	
Emergency	117 (36.7)	132 (40.5)	
Direct	35 (11.0)	20 (6.1)	
Others	7 (2.1)	11 (3.4)	
Focus of infection, No. (%)			
Pulmonary	45 (14.1)	87 (26.7)	<0.001*
Gastrointestinal tract	97 (30.4)	46 (14.1)	
Urinary tract	23 (7.2)	32 (9.8)	
Blood	36 (11.3)	29 (8.9)	
Osteoarticular	50 (15.7)	55 (16.9)	
Unclear or other	68 (21.3)	77 (23.6)	
Length of hospital stay, median (IQR), d	19 (10–30)	14.5 (7–28)	0.016*
Length of ICU stay, median (IQR), d	12 (6–23)	8 (4–17)	<0.001*
Norepinephrine, median (IQR), mg	112 (56–192)	109 (56–168)	0.264
Epinephrine, No. (%)	121 (37.9)	132 (40.5)	0.506
Dopamine, No. (%)	22 (6.9)	56 (17.2)	<0.001*
Dobutamine, No. (%)	20 (6.3)	10 (3.1)	0.054
Epinephrine, median (IQR), mg	15 (7–32)	10 (6–20)	0.004*
Fluid intake on day 1, median (IQR), mL	3650 (2850–4500)	3125 (2450–3950)	<0.001*
Fluid intake on day 2, median (IQR), mL	3400 (2700–4200)	3100 (2450–3900)	0.003*
Fluid intake on day 3, median (IQR), mL	3200 (2500–4100)	2950 (2300–3600)	0.004*
Fluid intake day 4 (ml)	3150 (2500–3880)	2850 (2100–3600)	0.002*
Fluid intake on day 5, median (IQR), mL	3100 (2500–3900)	3000 (2237.5–3577.5)	0.033*
Fluid balance on day 1, median (IQR), mL	1450 (300–2350)	1275 (300–2150)	0.433
Cumulative fluid balance on day 2, median (IQR), mL	2300 (450–3960)	2250 (150–3750)	0.548
Cumulative fluid balance on day 3, median (IQR), mL	2925 (50–5275)	2162.5 (–150 to 4850)	0.271
Cumulative fluid balance on day 4, median (IQR), mL	2700 (–575 to 6125)	2477 (–625 to 5775)	0.806
Cumulative fluid balance on day 5, median (IQR), mL	2649 (–884 to 6870)	3020 (–1425 to 6900)	0.898
Hospital mortality, No. (%)	184 (57.7)	202 (62.0)	0.267
28-Day mortality, No. (%)	157 (49.2)	184 (56.4)	0.066

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IKH = Imam Khomeini Hospital; IQR = interquartile range; MAP = mean arterial pressure; SH = Sina Hospital; ShH = Shariati Hospital; SOFA = Sequential (Sepsis-Related) Organ Failure Assessment.

* Statistically significant.

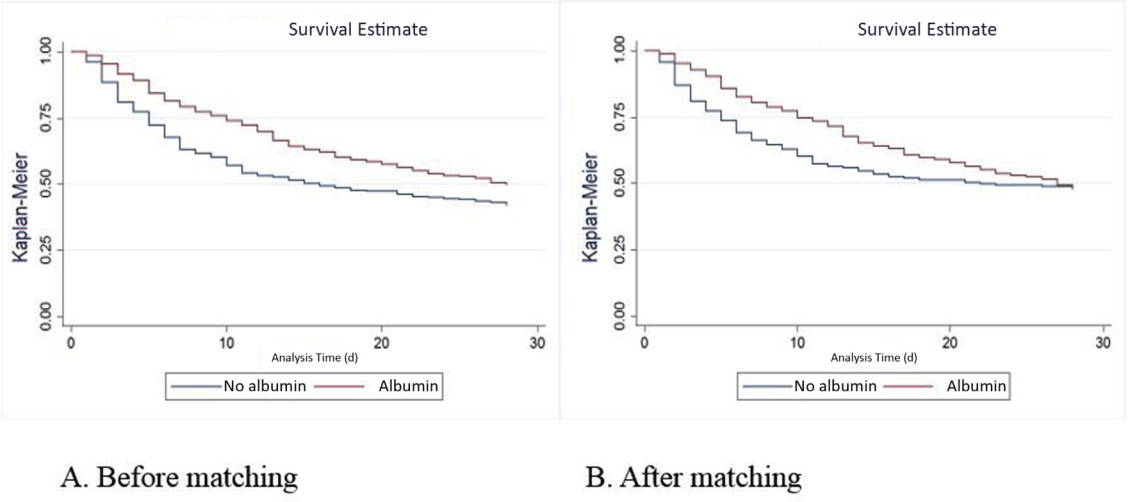

Figure 2. Kaplan–Meier survival curves.

without albumin. The ICER of the addition of albumin on the fluid therapy regimen in septic shock management was US $5740.40 per life-year gained. The GDP per capita of Iran (US $5219.2) is lower than the ICER value; therefore, the addition of albumin in the fluid regimen of septic shock was not cost-effective (Table II). The NMB was −355.4 (95% CI, −15387.61 to 14,676.81). The probability that the addition of albumin will be cost-effective over crystalloids only was only 40.0%. The life-year gained from the albumin group was not statistically different from the no-albumin groups when the life-year gain was calculated based on hospital mortality (life-year gain = 0.54; 95% CI, −2.37 to 3.46; $P = 0.715$). The ICER calculated based on the mean life-year gained from hospital mortality was also not cost-effective (eTable II).

Multivariate regression analysis revealed being treated in SH and ShH decreases the life-year gained. The age of the patient and the SOFA score had an inverse association with the life-years gained. The length of hospital stay had a positive association with the life-years gained. The SOFA score, length of ICU stays, albumin use, and cumulative fluid balance on day 5 had a positive association with the cost of treatment (Table III).

In the logistic regression analysis, the site of care increased the likelihood of 28-day mortality by 4.15 times (adjusted odds ratio [AOR] = 4.15; 95% CI, 2.90–5.93; $P < 0.001$). For each extra 1-year increase in the patient age, the odds of patient mortality increased by 2% (AOR = 1.02; 95% CI, 1.01–1.03; $P = 0.002$). For every extra day in the hospital, the likelihood of 28-day mortality decreased by 8% (AOR = 0.92; 95% CI, 0.90–0.93; $P < 0.001$). However, albumin did not have a statistically significant effect (AOR = 1.18; 95% CI, 0.76–1.84; $P = 0.462$) (eTable III). Albumin did not also have a hospital mortality reduction benefit in the present study (AOR = 1.03; 95% CI, 0.69–1.54; $P = 0.879$) (eTable IV).

DISCUSSION

In the matched analysis, albumin was responsible for 6.4% of the total cost of treatment and 18.4% of the cost of medication. The addition of albumin had no significant increase in life-year gain (mean difference = 0.67; 95% CI, −2.25 to 3.58). However, the addition of albumin increased the total cost of treatment by US $3846.07 (95% CI, US $2093.46–US $5598.98). The ICER calculated based on the mean life-years gained was US $5740.40 per life-year gained. The ICER was higher than the GDP per capital for Iran ($5219.1). The NMB was also negative (NMB = −355.4; 95% CI, −15,387.61 to

14,676.81). The probability that albumin would be cost-effective was only 40%.

Similar studies conducted by decision analytical modeling in the United States and France revealed the cost-effectiveness of albumin-based resuscitation in severe sepsis and septic shock.[18,19] However, these 2 findings could not be considered as supporting evidence in Iran to use albumin in daily practice because the countries' economic status is completely different from Iran.

Albumin takes the largest share in maintaining fluid balance, being responsible for 75% to 80% of colloid oncotic pressure in the basal physiologic state.[20] The endothelial barrier functions normally unless the serum albumin concentration decreased below 10 g/dL.[21] Large-volume resuscitation and positive fluid balance in severe sepsis and septic shock are generally discouraged.[22–24] A total volume of albumin equivalent to a third of the total volume of crystalloids is enough for a similar level of resuscitation.[25] Furthermore, the antioxidant, free radical scavenging, buffer, and antiplatelet aggregation effects give albumin a theoretical advantage over crystalloids in the management of septic shock.[26,27] In the ALBIOS trial, albumin reduced the 90-day mortality of patients with septic shock patients.[12] Nevertheless, all these could not be translated to an overall statistically significant cost-effective 28-day survival benefit in the present study.

Albumin was not associated with a significant 28-day mortality reduction in the ALBIOS trial and Colloids Versus Crystalloids for the Resuscitation of the Critically Ill trials.[12,28] Meta-analysis also revealed no significant effect of albumin-containing fluids on mortality in patients with sepsis of any severity.[13,29] Recently published reviews, on the other hand, reported a statistically significant reduction in mortality with albumin use.[10,30,31] Nonetheless, all these reviews were not head-to-head comparisons of albumin and crystalloids.

Similar studies also found an association between the SOFA score and patient mortality in sepsis.[32–35] Likewise, a prospective observational study identified age as a predictor of 30-day mortality in sepsis.[36] The 28-day mortality difference among hospitals might be explained by the lack of consensus and timing goals across sepsis bundles.[37] The finding of a recently published study that attributes most of the variation in patient outcome to physicians rather than hospitals might actually direct the cause of the 28-day mortality variation among hospitals.[38] However, the institution-based mortality variation in the present study might have been introduced from the way the hospitals were selected and the differences that emanate from the comorbid conditions.

This study was performed based on 2 basic assumptions. First, the different types of crystalloids were expected to be therapeutic equivalents. Second, biopharmaceutical equivalence was assumed among different generic products used in the country. The present study has a few strengths. The observational nature of the study helps in understanding the real practice in the management of septic shock. The use of different analytical techniques from both parametric (t test, propensity score matching, and multivariate regression analysis) and nonparametric (χ^2 and Wilcoxon rank sum tests) was another strength. The assessment of ICER based on the patient-level data provided an insight on the real practice significance. The NMB was calculated on top of the ICER. This study also has limitations. The use of retrospective data introduces a bias in the data collection. The included hospitals were selected purposely, and patients' comorbid conditions were not traced in the present study. This approach will introduce bias and make the observed mortality variation among hospitals less reliable. The central limit theorem was assumed in the use of parametric data analysis. A significant number of patient medical records could not be accessed from the IKH. The data extracted from the HIS might not necessarily mean the patients had received all the medications. Although mortality reduction is the main goal of patient care, organ function improvements are crucial intermediate outcomes that may alter the overall cost of treatment. In the present study, we did not consider the organ-function improvements during hospital stay, which may compromise the result. We used the Surviving Sepsis Campaign guideline to define septic shock because the hospitals included in the present study were defining septic shock according to this guideline in the study period.

CONCLUSION

To the best of our knowledge, this study is the first of its kind in the study area. Albumin use has a statistically significant cost increment without a noticeable life-year gain. The calculated ICER, the

Table II. Cost (in US dollars), effectiveness, and ICER between the groups taking and not taking albumin in unmatched and matched analysis.

Group	Total Cost of Bed	Cost of ICU Bed	Cost of Medication	Cost of Albumin	Cost of Diagnosis	Total Cost	Life-years Gained	Cost-effectiveness	Δ Cost	Δ Life-years Gained	ICER
Unmatched											
Albumin	4115.63	3832.27	3972.65	786.26	1188.84	11243.65	13.17	853.73	3243.75	3.23	1004.26
No albumin	3507.13	3114.05	1851.25	—	991.73	7999.9	9.94	804.82	(1807.93–4679.58)	(0.70–5.75)	
P	0.063	0.027	<0.001	—	0.006	<0.001	0.012				
Matched											
Albumin	4423.86	4172.38	4192.00	769.93	1264.03	11954.42	12.20	979.87	3846.07	0.67	5740.40
No albumin	3579.54	3237.25	1859.34	—	958.68	8108.35	11.53	703.24	(2093.46–5598.98)	(–2.25 to 3.58)	
P	0.033	0.018	<0.001	—	<0.001	<0.001	0.652	0.40			

ICER = incremental cost-effectiveness ratio; ICU = intensive care unit.

Table III. Multivariate regression outcome for life-year gain and cost after matching.

Variable	Coefficient (95% CI)	*P*
Life-year gained based on 28-day mortality		
Hospital		
SH	−5.25 (−7.71 to −2.80)	<0.001*
ShH	−10.38 (−13.84 to −6.93)	<0.001*
Age	−0.50 (−0.56 to −0.44)	<0.001*
SOFA	−0.55 (−0.99 to −0.11)	0.015*
Length of hospital stay	0.23 (0.18−0.27)	<0.001*
Albumin	−0.69 (−1.49 to 2.88)	0.942
Constant	46.36 (40.27−52.46)	<0.001*
Sex	649.48 (42.78−1256.18)	0.036*
Age	−26.46 (−42.59 to −10.33)	0.001*
SOFA	223.81 (103.72−343.90)	<0.001*
Length of ICU stay	280.50 (247.58−313.42)	<0.001*
Length of hospital stay	166.18 (136.46−195.90)	<0.001*
Albumin use	1844.65 (1246.48−2442.82)	<0.001*
Fluid intake day 1	0.46 (0.22−0.69)	<0.001*
Constant	−2569.06 (−4538.39 to −599.73)	0.011*

ICU = intensive care unit; SH = Sina Hospital; ShH = Shariati Hospital; SOFA = Sequential (Sepsis-Related) Organ Failure Assessment.
* Statistically significant.

NMB, and the probability of being cost-effective strongly informed the nonsignificance of albumin use. We cautiously conclude that the addition of albumin in the fluid therapy of severe sepsis and septic shock is not cost-effective in Iran. Finally, piggy-back clinical trials that put the limitations of the present study into consideration could help to identify both the clinical and economic consequence of albumin-based fluid therapy more precisely.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

The following are the supplementary data to this article:

Table I. Baseline characteristics, treatment and patient outcome between albumin and no-albumin groups after matching

Variables		Albumin (n=247)	No albumin (n=247)	P-value
Sex	Male	147(59.51)	145(58.7)	0.855
Age (years)		63(49-77)	63(48-75)	0.768
MAP (mmHg)		65.33(60.33-71)	64.67(58.67-70.33)	0.403
ARDS		148(59.92)	150(50.73)	0.854
Serum creatinine (mg/dl)		1.5(0.97-2.31)	1.4(0.93-2.37)	0.449
SOFA		10(9-12)	10(9-12)	0.950
Mechanical ventilation		193(78.14)	194(78.54)	0.913
Hospital	IKH	76(30.77)	105(42.51)	P=0.002*
	SH	141(57.09)	101(40.89)	
	ShH	30(12.15)	41(16.60)	
Referral Units	Surgical units	85(34.41)	70(28.34)	0.096
	Medical units	43(17.41)	49(19.84)	
	Emergency	85(34.41)	107(43.32)	
	Direct	27(10.93)	15(6.07)	
	Others	7(2.83)	6(2.43)	
Focus of infection	Pulmonary	37(14.98)	60(24.29)	P=0.052
	GIT	76(30.77)	38(15.38)	
	Urinary tract	15(6.07)	20(8.10)	
	Blood	24(9.72)	25(10.12)	
	Osteoarticular	43(17.41)	48(19.43)	
	Unclear/others	52(21.05)	56(22.67)	
Length of hospital stay (days)		20(11-32)	14(7-28)	0.002*
Length of ICU stay (days)		14(6-25)	8(4-16)	P<0.001*
Norepinephrine (mg)		120(56-192)	104(48-160)	0.034*
Epinephrine (mg)		15(7-35)	10(5-20)	0.011*
Epinephrine (n)		90(36.44)	99(40.08)	0.405
Dopamine (n)		17(6.88)	39(15.79)	0.002*
Dobutamine (n)		18(7.29)	8(3.24)	0.044*
Fluid intake day 1 (ml)		3600(2900-4470)	3250(2550-4100)	0.001*
Fluid intake day 2 (ml)		3370(2700-4050)	3250(2550-3900)	0.117
Fluid intake day 3 (ml)		3200(2500-4010)	3000(2300-3650)	0.018*
Fluid intake day 4 (ml)		3137.5(2500-3875)	2902.5(2200-3650)	0.034*
Fluid intake day 5 (ml)		3050(2400-3900)	3050(2425-3633)	0.542
Fluid balance day 1 (ml)		1450(400-2350)	1200(200-2100)	0.132
Cumulative fluid balance day 2 (ml)		2400(750-4050)	1950(-150-3550)	0.027*
Cumulative fluid balance day 3 (ml)		3100(306-5300)	1575(-450-4225)	0.008*
Cumulative fluid balance day 4 (ml)		2825(-500-6075)	1745(-1190-5090)	0.111
Cumulative fluid balance day 5 (ml)		2649(-884-6950)	2315.5(-2100-6375)	0.232
Hospital mortality		146(59.11)	141(57.09)	0.198
28-days mortality		124(50.20)	126(51.01)	0.857

*statistically significant

Table III. Risk factors for 28-day mortality of septic shock patients based on multivariate logistic regression after matching

Variable	AOR	95% CI	P-value
Hospital	4.15	2.90-5.93	P<0.001*
Age	1.02	1.01-1.03	0.002*
Albumin use	1.18	0.76-1.84	0.462
Length of hospital stay	0.92	0.90-0.93	P<0.001*
Constant	0.15	0.06-0.39	P<0.001*

*statistically significant

Table IV. Risk factors for hospital mortality septic shock patients based on multivariate logistic regression after matching

	AOR	95% CI	P-value
Hospital	3.89	2.76-5.48	P<0.001*
Age	1.03	1.01-1.04	P<0.001*
Length of hospital stay	0.98	0.97-0.99	P<0.001*
Albumin	1.03	0.69-1.54	0.879
Constant	0.05	0.02-0.14	P<0.001*

*statistically significant

Table II. Cost (in USD), effectiveness and ICER between albumin and no-albumin groups in unmatched and matched analysis based on hospital mortality

		Total cost of bed	Cost of ICU bed	Cost of medication	Cost of albumin	Cost of diagnosis	Total cost	Life years gained	C/E	Δ cost	Δ life years gained	ICER
Unmatched	A	4115.63	3832.27	3972.65	786.26	1188.84	11243.65	11.99	937.75	3243.75	2.96 (0.44-5.48)	1095.86
	NA	3507.13	3114.05	1851.25	-	991.73	7999.9	9.03	885.93 (1807.93- 4679.58)			
		0.063	0.027	P<0.001	-	0.006	P<0.001	0.012				
Matched	A	4423.86	4172.38	4192.00	769.93	1264.03	11954.42	11.08	1078.92	3846.07	0.54 (-2.37, 3.46)	7122.35
	NA	3579.54	3237.25	1859.34	-	958.68	8108.35	10.53	770.02 (2093.46-5598.98)			
		0.033	0.018	P<0.001		P<0.001	P<0.001	0.715	Probability of cost-effectiveness=0.41			

A-albumin, NA-no-albumin