

Systematic Review

Albumin Usage in Iran

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Background: Human albumin is an expensive therapy with inappropriate use in many clinical conditions. Inappropriate use of albumin imposes a substantial economic burden on the healthcare system and society. Drug use evaluation (DUE) is one method of assessing the appropriateness of drug use which has been powered by increasing concern about the cost-effectiveness of drugs. The objective of this study is to systematically review the appropriateness of albumin utilization in Iranian hospitals.

Methods: We searched the PubMed, MEDLINE, EMBASE, SCOPUS, and Google Scholar for articles in English and SID, Magiran, Medlib, and Irandoc for articles in Persian from 1997 to 2018. Studies on the DUE of albumin in Iranian hospitals were included in this study. Articles conducted outside Iran, editorials, letters and review articles were excluded.

Results: In total, eight studies were selected for the final review. The majority of the papers were conducted in Tehran. In most studies, the highest albumin consumption was related to the intensive care unit. The most frequent reasons for prescribing albumin were edema, hypoalbuminemia, volume expansion after heart surgery, ascites, cardiac surgery and cirrhosis. Of the studies included, five studies evaluated the costs of drug use.

Conclusion: Our findings show that inappropriate use of albumin imposes a relatively high additional cost on the society. The included studies show that the percentage of inappropriate use of albumin is relatively high in Iran and this abuse is an essential problem in Iranian hospitals. Prescription based on standard guidelines could improve rational use of albumin and lead to savings in treatment costs.

Keywords: Albumins, Drug utilization review, Health expenditures, Review

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Introduction

Inappropriate use of drugs is one of the major problems in health care systems.¹⁻⁴ Drugs should be prescribed based on valid guidelines and the clinical requirements of patients.⁵ Recently, drug use evaluation (DUE) studies are increasingly used as an effective method for assessing the appropriateness of drug use in treatment of patients.⁶ DUE is one way of improving the cost-effectiveness of drugs which is used to optimize drug costs through improvement of rational use of drugs.⁷⁻⁹ The World Health Organization (WHO) addressed drug utilization as the marketing, distribution, prescription and use of drugs in a society, considering its consequences: medical, social, and economic.¹⁰ DUE is especially important for expensive and high consumption drugs with limited therapeutic guideline.¹¹ Albumin is an expensive drug with vast clinical utilizations such as plasmapheresis, paracentesis, extensive burn, spontaneous bacterial peritonitis and nephrotic syndrome.¹² However, inappropriate use of albumin has become an issue of controversy in the health

care system.^{13,14} Since albumin imposes an additional economic burden on the healthcare system, DUE for this drug is very necessary. Several DUE studies of albumin in Iranian hospitals have been published in the medical literature in recent years.^{15,16} However, there has been no systematic review to assess these DUEs of albumin.

Aim of the Review

The aim of this study is to conduct a systematic literature review of the “Evaluation of Albumin Utilization in Iran”. We reviewed the published information on reasons for albumin prescription, the percentage of inappropriate use of albumin and its costs. This review will facilitate better utilization of albumin and help to improve decision-making.

Material and Methods

A systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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statement.¹⁷The objective of this study was to systematically review the use of albumin with respect to clinical and economic outcomes in Iranian hospitals. In this systematic review, we searched the PubMed, MEDLINE, EMBASE, SCOPUS, and Google Scholar for articles in English and SID, Magiran, Medlib, and Irandoc for articles in Persian from 1997 to 2018. We also manually searched the reference lists of the obtained articles. The search strategy was: (“Serum Albumin” OR “Albumin, Serum” OR “Plasma Albumin” OR “Pharmaceutical Preparations” OR “Preparations, Pharmaceutical” OR “Pharmaceutic Preparations” OR “Preparations, Pharmaceutic” OR “Pharmaceutical Products” OR “Products, Pharmaceutical” OR “Pharmaceuticals” OR “Drugs”) AND (“Drug Utilization Review” OR “Evaluation, Drug Utilization” OR “Drug-Use Review” OR “Drug Use Review” OR “Drug-Use Reviews” OR “Reviews, Drug-Use” OR “Review, Drug Utilization” OR “Drug Utilization Reviews” OR “Reviews, Drug Utilization” OR “Utilization Reviews, Drug” OR “Utilization Review, Drug” OR “Drug Utilization Evaluation” OR “Drug Utilization Evaluations” OR “Evaluations, Drug Utilization” OR “Utilization Evaluation, Drug” OR “Utilization Evaluations, Drug” OR “Review, Drug-Use” OR “Review, Drug Use”) AND (Iran OR “Islamic republic of Iran”). Citations were integrated into EndNote 8 and duplicates were then automatically deleted. Two independent reviewers (JJN and AS) reviewed the other articles. We included English and Persian articles reporting on DUE of albumin in Iran. Articles performed outside Iran, editorials, letters and review articles were excluded. Using a data extraction form, we conducted an evaluation

of the eligible studies. For each article included in the final review, data on study population and sample size, study settings, the greatest prescription of albumin in terms of hospital wards and reasons for prescription, the percentage of inappropriate use of albumin, the most frequent reason for inappropriate use of albumin and cost of albumin were extracted. The correct and appropriate usages were defined as prescription corresponding to the accepted indications. In the included studies, indications for defining appropriate use of albumin were extracted from the most up to-date and comprehensive evidenced-based guidelines.^{18,19} This process was performed independently by two authors (JJN and AR).

Results

Figure 1 shows the procedure of literature search. After screening the titles and abstracts, 48 records were identified through database searching and 2 additional records were identified through other sources. After the deletion of duplicates (n = 17), 33 records remained. The full texts of these records were reviewed. Finally, 25 articles were excluded because they did not meet the eligibility criteria for the review. Eight studies were suitable for inclusion in this systematic review.^{15,16,20-25}

Quality Assessment

In order to assess the quality of the articles, a checklist prepared by the Joanna Briggs Institute (JBI) was used.²⁶ The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers were evaluated based on

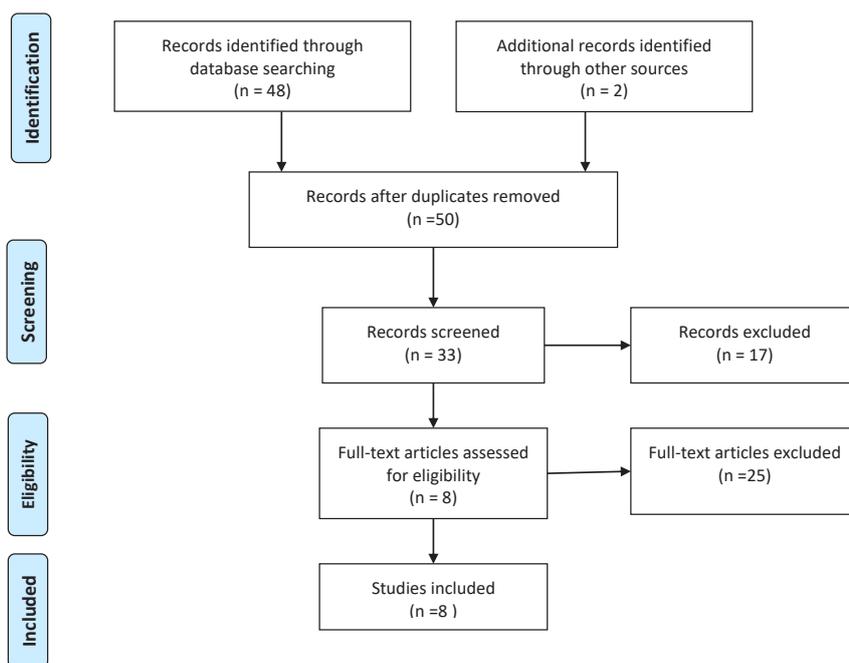


Figure 1. PRISMA Flow Diagram of the Selection Process Used to Identify Studies for Inclusion in This Review.

data relevance and methodological rigor. The results of quality assessment are presented in Table 1.

General Characteristics

The general characteristics of eligible articles are shown in Table 2. These studies had been conducted during 2011–2017. Of the eight selected articles, four (50%) were conducted in Tehran^{15,16,22-24}; the three remaining studies were performed in Mashhad,²⁵ Tabriz²⁰ and Mazandaran.²¹ There was no article about the evaluation use of albumin in other provinces of Iran. In most studies (n = 6), the highest albumin prescription was recorded in the ICU.^{16,20-24} In two studies, most albumin prescriptions pertained to the burns ward and the internal ward.^{15,25} The results from this study show that the percentage of inappropriate use of albumin is between 36–95% in Iran, indicating a high prevalence of irrational use of albumin. On the other hand, in five studies, the irrational use of albumin was reportedly more than 70%.^{15,16,20,22,23} An overview of albumin prescriptions with respect to reasons

for administration showed that the most frequent reasons for prescribing albumin were edema, hypoalbuminemia, volume expansion after heart surgery, ascites, cardiac surgery and cirrhosis (appropriately and inappropriately). Among the included studies, five studies evaluated the costs of drug use.^{15,20,21,23,25} These studies showed that inappropriate use of albumin imposed a relatively high additional cost on the society.

Table 3 shows the percentage of inappropriate prescription of albumin with respect to reasons for prescription. Seven studies reported these results. For example, all albumin prescriptions for plasmapheresis were appropriate in different studies.^{15,16,20,22}

Discussion

To our knowledge, the present study is the first systematic review of albumin use evaluation in Iran. The main purpose of this systematic review was assessment of the inappropriate use of albumin and its costs. The number of albumin use evaluation studies in Iran was limited. This

Table 1. JBI Critical Appraisal Checklist Applied for the Included Studies

Author Name/Year	Sample was representative?	Participants were appropriately recruited?	Sample size was adequate?	Study subjects and the setting were described?	Data analysis was conducted?	Objective, standard criteria were reliably used?	Appropriate statistical analysis was used?	Confounding factors/ subgroups/ differences were identified and accounted for?	Subpopulations were identified using objective criteria?
Shafiee ²⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ala ²¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kazemi ²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jahangard-Rafsanjani ¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Farsad ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Talaszaz ²⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zolfagharian ²⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Foroughinia ¹⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. General Characteristics of the Included Studies

Author	Year	Setting	Sample Size	Wards with Most Albumin Use	Percentage of Inappropriate Albumin Use	The Most Frequent Reason for Albumin Prescription	The Most Frequent Reason for Inappropriate Albumin Prescription	Overall Cost	Cost of Inappropriate Albumin Use
Shafiee ²⁰	2016	Tabriz	210 patients	ICU and surgery	76.2%	Edema	Hypoalbuminemia	\$369 268	\$274 607
Ala ²¹	2015	Mazandaran	100 patients	ICU	37%	Hypoalbuminemia	—	\$25 868	\$4904
Kazemi ²²	2013	Tehran	120 patients	ICU	%95	Edema	Intractable edema	—	—
Jahangard-Rafsanjani ¹⁶	2011	Tehran	135 patients	ICU-open heart	74.8%	Cardiac surgery	Cardiac surgery	—	—
Farsad ²³	2016	Tehran	300 patients	ICU	93.7%	Ascites and edema	Hypoalbuminemia	—	\$259 612.5
Talaszaz ²⁴	2012	Tehran	69 patients	ICU	36.2%	Cardiac surgery	Hypoalbuminemia and nutritional suppose	—	—
Zolfagharian ²⁵	2017	Mashhad	50 patients	Burns ward	62%	—	—	—	\$17 477
Foroughinia ¹⁵	2017	Shiraz	110 patients	Internal ward	87.3%	Cirrhosis	Nephrotic syndrome without hypoalbuminemia	\$48 928	\$42 920

ICU, intensive care unit.

Table 3. Percentage of Inappropriate Prescription of Albumin with Respect to Reasons for Prescription

	Shafiee ²⁰	Kazemi ²²	Jahangard-Rafsanjani ¹⁶	Farsad ²³	Talasaz ²⁴	Zolfagharian ²⁵	Foroughinia ¹⁵
Edema	62.9%	100%					100%
Hypoalbuminemia	100%		100%		36.2%	19.35%	100%
Nutritional support	100%		100%		24.4%	48.39%	
Nephrotic syndrome	0%	0%	0%				96.2%
Plasmapheresis	0%	0%	0%				0%
Paracentesis	50%	0%	11.7%				
Pleural effusion	100%						
Liver failure and hepatic resection	0%						
ARDS	0%						
Shock and dehydration and alkalosis	50%						
Cardiac failure		00%1	95.8%				
Acute normo-volumic shock		100%					100%
Hemorrhagic shock			0%				100%
Non-Hemorrhagic shock			0%				100%
Cirrhosis							65.5%
Hepatorenal syndrome							50%
Cerebral ischemia/brain tumor							100%

systematic review found eight articles that assessed the pattern of albumin use.^{15,16,20-25} The included studies on DUE for albumin were performed in only four province of Iran. No evidence was identified on albumin utilization in other provinces. Most of these scientific works were performed in Tehran. A likely reason for the high number of albumin use evaluation studies in Tehran could be the abundance of hospitals in the capital of Iran. In the eligible articles on albumin use evaluation in Iranian hospitals, the percentage of inappropriate use of albumin varied from 36% to 95% in different hospitals. These results could be due to variation in the settings of studies and methods used for reporting albumin consumption. Table 3 shows the percentage of inappropriate prescription for each reason. This classification was not reported in two studies. The most frequent reason for appropriate albumin prescription pertained to plasmapheresis. Different studies showed that all albumin prescriptions for plasmapheresis were appropriate.^{15,16,20,22} One of the most common reasons for irrational prescription of albumin was hypoalbuminemia. Three studies indicated that 100% instances of albumin therapy due to hypoalbuminemia were inappropriate but two studies indicated that this figure was lower than 40%.^{15,16,20,24,25} A serum albumin level <3.5–4 g/dL is defined as hypoalbuminemia.²⁷ However, in many studies, it has been shown that doctors do not pay enough attention to serum albumin levels. Also, some studies have revealed that albumin prescription in hypoalbuminemic patients has no certain consequence on mortality or morbidity.²⁸ According to the guidelines, albumin can be prescribed only in cases where the serum albumin level is less than 2.5 g/dL.^{18,19} Then, in several guidelines, hypoalbuminemia is not an appropriate indication for the prescription of albumin. Kazemi et al showed in

their study that in many cases, doctors did not have any estimate of serum albumin levels before prescription of albumin.²² Jahangard-Rafsanjani et al showed that serum albumin level was more than 2.5 g/dL for all patients and the prescription of albumin for hypoalbuminemia was irrational.¹⁶ Shafiee et al reported that most patients with serum albumin levels >3.5 g/dL received albumin.²⁰ Foroughinia et al found that 87% of albumin prescriptions were inappropriate. In their study, nephrotic syndrome without hypoalbuminemia was the most frequent reason for irrational use of albumin. The results of their study showed that only 13.6% of patients had an albumin serum level <2 g/dL.¹⁵ Nutritional support was another reason for inappropriate prescription of albumin. Regarding albumin prescriptions for nutritional support, two studies indicated that 100% of these prescriptions were inappropriate.^{16,20} Several guidelines state that albumin could be prescribed for patients with malnutrition in the following conditions: patients with diarrhea (>2 L/day), serum albumin level <2 g/dL, diarrhea not resolved by short-chain peptides or elemental formulas, and in cases where other reasons for diarrhea have been excluded. In the study conducted in Tabriz, none of the patients receiving albumin fulfilled these criteria. Jahangard et al showed that cardiac surgery was the most common reason for inappropriate prescription of albumin.¹⁶ Several guidelines have recommended albumin therapy as the last alternative, after crystalloid solutions and non-protein colloids, for volume expansion following open-heart surgery.^{18,19} Jahangard et al demonstrated in their study that non-protein colloids were not used at all. The included studies showed that inappropriate use of albumin imposed a relatively high additional cost on the society. Of the included studies, five studies evaluated the costs of drug use. For example, Foroughinia et al found

that about 88.6% of total costs for albumin prescription were inappropriate. In their study, the additional costs of inappropriate use of albumin amounted to US\$42920.¹⁵

One of the limitations of this review is the heterogeneity across studies. In addition, the number of eligible papers was not large enough for a meta-analysis. Furthermore, in this study, we only reviewed English and Persian articles reporting on DUE of albumin in Iran, which means that we have left out studies which have been performed outside Iran.

The results show that the percentage of inappropriate use of albumin is relatively high in Iran and physicians should change their pattern of albumin prescription. As a result, adherence to standard guidelines, especially for albumin prescription, could minimize the irrational use of albumin and lead to savings in treatment costs. Moreover, training workshops for physicians on how to use these criteria and elucidating the most problematic inappropriate reasons for prescription seem essential. Therefore, it is necessary to perform another DUE after the educational program on introducing and implementing appropriate guidelines in order to evaluate the impact of these interventions on reduction of albumin use.

Authors' Contribution

JJN and AR contributed to the study rationale and design, and performed the systematic review. JJN prepared the draft of the manuscript. All authors commented on the manuscript and approved the final version.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Ethical Statement

Not applicable.

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