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Albumin versus standard medical treatment in Brazilian public and private healthcare systems

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HIGLIGHTS

- To assess the economic impact of implementing long-term albumin infusions in patients with cirrhosis and ascites in Brazil
- Incremental cost per cirrhotic patient treated with long-term albumin was estimated based on the rates of complications and healthcare resource utilization from the ANSWER trial and local costs from the public and private healthcare system perspective in Brazil.
- Implementation of long-term albumin could save up to 118,759 BRL and 189,675 BRL per patient treated in the public and private healthcare system setting, respectively.
- Should results from the ANSWER trial translate into real-world effectiveness, addition of albumin to standard medical treatment could lead to improved clinical outcomes and reduced costs.

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ABSTRACT – Background – Cirrhosis is one of the final stages of chronic liver disease. Common causes of cirrhosis include alcoholism and viral hepatitis infections. Cirrhosis can progress from an asymptomatic, compensated phase to decompensation and the appearance of overt symptoms. There is no specific treatment for decompensated cirrhosis. The ANSWER trial positioned long-term albumin infusions as a potential treatment for patients with cirrhosis and uncomplicated ascites. **Objective –** This study assesses the economic impact of albumin infusions following the ANSWER trial regimen in Brazilian patients with decompensated cirrhosis from the public and private healthcare systems perspectives. **Methods –** The incremental cost per patient per year was calculated for standard medical treatment (SMT) plus long-term albumin infusions versus SMT alone. Costs of diuretics and albumin were obtained from *Banco de Preços em Saúde* and the Drug Market Regulation Chamber. Costs for complication and procedures were gathered from the published literature. Costs were transformed to 2021 Brazilian reals (BRL). Incidences of clinical complications and treatments were gathered from the ANSWER trial. Univariate sensitivity analysis was performed by increasing and decreasing all inputs by 20%. **Results –** The cost per patient per year was 118,759 BRL and 189,675 BRL lower for patients treated with SMT and albumin (compared to SMT only) for the public and private healthcare systems, respectively. The additional cost of albumin was offset by reduced complications and treatments (149,526 BRL and 249,572 BRL, respectively). The univariate sensitivity analysis showed cost savings for both healthcare systems in all the scenarios assessed. **Conclusion –** This economic analysis suggests that, if the ANSWER trial clinical outcomes translate into real-world effectiveness, addition of albumin infusions to SMT in patients with decompensated cirrhosis may lead to cost savings for the public and private healthcare systems in Brazil.

Keywords – Liver diseases; costs and cost analysis; human serum albumin; cirrhosis.

INTRODUCTION

Cirrhosis is the end-stage of chronic liver disease. The most common causes of cirrhosis in Brazil are chronic alcoholism, and hepatitis B and C infections[1]. Cirrhosis is characterized by an initial asymptomatic and generally undiagnosed compensated phase that, if untreated, progresses to a decompensated stage generally triggered by the occurrence of a first complication (i.e., ascites, esophageal variceal bleeding, or hepatic encephalopathy)[2]. This first decompensation is followed by subsequent complications, such as, hepatorenal syndrome acute kidney injury (HRS-AKI), spontaneous bacterial peritonitis (SBP) or hyponatremia, among others, that require frequent hospitalizations and pose a significant burden on healthcare systems and patients[2-4].

Decompensated cirrhosis has a poor prognosis, with an estimated 2-year survival from the first decompensation, on average[5]. The Global Burden of Disease study estimated a total of 36,269 deaths and 11.1 million disability-adjusted life years lost due to cirrhosis, with 210,481 prevalent cases of decompensated cirrhosis in 2017 in Brazil[6].

There is no specific treatment for decompensated cirrhosis. Patients are generally managed by treating each individual complication[7,8]. For example, guidelines from the American Association for the Study of the Liver (AASLD) recommend large-volume paracentesis (LVP) combined with hyperoncotic human albumin for tense ascites, fluid restriction for patients with hyponatremia, and sodium restriction for patients with grade 2, 3, refractory ascites, intravenous antibiotics and albumin for SBP, vasoconstrictors in combination with albumin for HRS-AKI, among others[8].

Albumin plays an important role in liver cirrhosis since it is not only reduced in counts, but also dysfunctional due to post-transcriptional modifications[9]. In patients with cirrhosis and ascites, albumin infusions may help mitigate renal sodium retention, arterial underfilling, and portal hypertension and has proved effective in preventing further complications after LVP, in combination with antibiotics for SBP, and added to vasoconstrictors for HRS-AKI[9].

Long-term albumin infusions in patients with decompensated cirrhosis, not associated with specific complications, has been assessed in previous clinical trials with controversial results, probably due to differences in patient population and frequency and dosing of infusions[10-15].

The ANSWER trial assessed the clinical and economic impact of long-term albumin infusions in addition to standard medical treatment (SMT) in patients with decompensated cirrhosis and uncomplicated ascites. Such regimen of albumin infusions managed to significantly reduce 18-month mortality as well as the incidence of liver-related complications resulting in a potentially cost-effective treatment for this patient population[14]. Subsequent economic evaluations from the perspective of the Mexican, Spanish, and English healthcare systems have shown that, should the clinical outcomes of the ANSWER trial translate into real-world effectiveness, addition of albumin to SMT in patients with cirrhosis and uncomplicated ascites may lead to cost savings in these countries[16-18].

While still a matter of continuous debate[8,10,19], evidence assessing the economic impact of albumin infusions in patients with decompensated cirrhosis is still limited. The present study aims to assess the economic impact of implementing long-term albumin infusions in Brazil from the public and private healthcare systems perspectives following the regimen evaluated in the ANSWER trial[14].

METHODS

The present study estimated the incremental cost of illness for patients treated with SMT and albumin following the ANSWER trial treatment regimen (40 g of albumin twice weekly for 2 weeks, and 40 g weekly thereafter) compared to that for patients treated with SMT only, over 12 months.

Clinical and demographic characteristics of the population considered in the economic evaluation were assumed to be that of patients included in the ASNWER trial[14]. The overall cost per patient per year considered: a) liver-related complications (i.e., refractory ascites, SBP, other bacterial infections, hepatic encephalopathy, renal dysfunction, and HRS); b) other healthcare resource utilization (HCRU) (i.e., LVP, non-liver related hospitalizations and follow up visits for albumin infusions); and c) pharmacological treatments (diuretics and human albumin) based on

12-month incidences of complications and frequencies of treatments in the ANSWER trial facilitated by the authors of the trial (TABLE 1)[14,16-18].

TABLE 1. Twelve-month incidence rates of complications and treatments per patient following SMT and SMT + albumin infusions from the ANSWER trial[14,16-18].

Complications / treatments	12-month incidence*	
	SMT	SMT + albumin
Clinical complications		
Refractory ascites	0.57	0.22
Spontaneous bacterial peritonitis	0.35	0.12
Other bacterial infections	0.86	0.64
Hepatic encephalopathy	1.08	0.52
Renal dysfunction	1.08	0.59
Hepatorenal Syndrome	0.20	0.07
Other HCRU		
Large-volume paracentesis	3.50	1.55
Non-liver related hospitalization (days)	1.80	1.40
Follow up visit for albumin administration	0	48
Pharmacological treatments		
Human albumin for regular infusions (g/administration)	0	40
Spironolactone (mg/day)	200	200
Furosemide (mg/day)	40	40

HCRU: healthcare resource utilization; SMT: standard medical treatment.
*12-month rates facilitated by the authors of the ANSWER trial.

Unit costs for each complication, HCRU and treatment were gathered from a literature review and public sources. A detailed list of unit costs and sources is included in TABLE 2. All costs were transformed to 2021 Brazilian reals (BRL) based on inflation rate [1 BRL equals 0.18 United States dollars (USD) on December 31, 2021].

The incremental cost per cirrhotic patient treated with SMT and albumin compared to SMT only was calculated as the difference in cost per patient per year for the two groups (i.e., negative incremental cost means potential savings for the healthcare system when adding albumin to SMT vs SMT). Given that the time horizon for this calculation was 12 months, no discount rate was applied. All costs and assumptions were validated by physicians experienced in the management of cirrhotic patients and in the healthcare system architecture of Brazil.

In order to validate the accuracy of the incremental cost per patient per year estimated herein, a univariate sensitivity analysis was performed by increasing and decreasing by 20% all inputs both from the public and private healthcare systems perspectives. The present study is a cost of illness analysis that

TABLE 2. Unit costs and source from the Brazilian public and private healthcare systems perspectives.

Complications/treatments	Public healthcare system*		Private healthcare system*	
	Cost (BRL, 2021)	Source	Cost (BRL, 2021)	Source
Cost of clinical complications				
Refractory ascites (unit cost)	99,872 BRL	Rodriguez 2021[20]	77,231 BRL	Fonseca 2005[21] Fonseca 2009[22]
Spontaneous bacterial peritonitis (unit cost)	35,885 BRL	Rodriguez 2021[20]	33,436 BRL	Rodiguez 2021[20] Sogayar 2008[23]
Other bacterial infections (unit cost)	4,572 BRL	Osme 2020[24]	5,111 BRL	ANS[25]
Hepatic encephalopathy (unit cost)	103,216 BRL	Rodriguez 2021[20]	263,385 BRL	Fonseca 2005[21]
Renal dysfunction (unit cost)	55,990 BRL	Gouveia 2017[26]	108,478 BRL	Gouveia 2017[26]
Hepatorenal syndrome (unit cost)	142,819 BRL	Rodriguez 2021[20]	69,444 BRL	Rodiguez 2021[20] Sogayar 2008[23]
Cost of other HCRU				
Large-volume paracentesis (unit cost)	793 BRL	Borges de Santana 2014[27]	2,098 BRL	ANS[25]
Non-liver related hospitalization (cost/day)	318 BRL	Schwambach 2020[4]	2,535 BRL	ANS[25] ANAHP[28]
Follow up visit for albumin administration (cost/visit)	153 BRL	Brito 2019[29]	196 BRL	ANAHP[28] CBHPM[30]
Cost of pharmacological treatments				
Human albumin (cost/g)	12.20 BRL	Banco de Preços em Saúde[31]	26.30 BRL	CMED[32]
Spironolactone (cost/mg)	0.006 BRL		0.025 BRL	
Furosemide (cost/mg)	0.013 BRL		0.012 BRL	

HCRU: healthcare resource utilization; ANAHP: National association of private hospitals as per its abbreviation in Portuguese, Associação nacional de hospitais privados; ANS: Brazilian private healthcare system as per its abbreviation in Portuguese, Agência nacional de saúde suplementar; BRL: Brazilian real; CBHPM: Codes for medical procedures classification as per its abbreviation in Portuguese, classificaçao brasileira hierarquizada de procedimentos médicos; CMED: Drug market regulation chamber, as per its abbreciation in Portuguesse, Câmara de regulação do mercado de medicamentos.

utilized only published aggregated data, it did not involve research conducted on humans.

RESULTS

The overall cost per patient per year treated following SMT was estimated at 277,251 BRL and 487,802 BRL from the public and private healthcare systems perspectives, respectively. When albumin infusions were added to the SMT following the ANSWER regimen and assuming similar impacts on HCRU, the cost per patient per year was 118,759 BRL and 189,675 BRL lower than that for patients treated with SMT only from the public and private healthcare systems perspectives, respectively (FIGURE 1). The additional cost derived from albumin infusions administration: 30,767 BRL and 59,897 BRL for the public and private healthcare systems, respectively, was counterbalanced by the reduction in complications (refractory ascites, SBP, hepatic encephalopathy, renal dysfunction and HRS) non-liver related hospitalizations and LVP (149,526 BRL and 249,572 BRL, respectively) (FIGURE 1 and TABLES 3 and 4). Specifically, the major driver for cost reduction was the decrease in the incidence of hepatic encephalopathy (1.08 patient/year vs 0.52 patient/year based on ANSWER) both for the public (-57,388 BRL) and private (-146,442 BRL) healthcare systems analysis (TABLES 3 and 4).

In all scenarios assessed in the sensitivity analysis, when variables included in the economic eva-

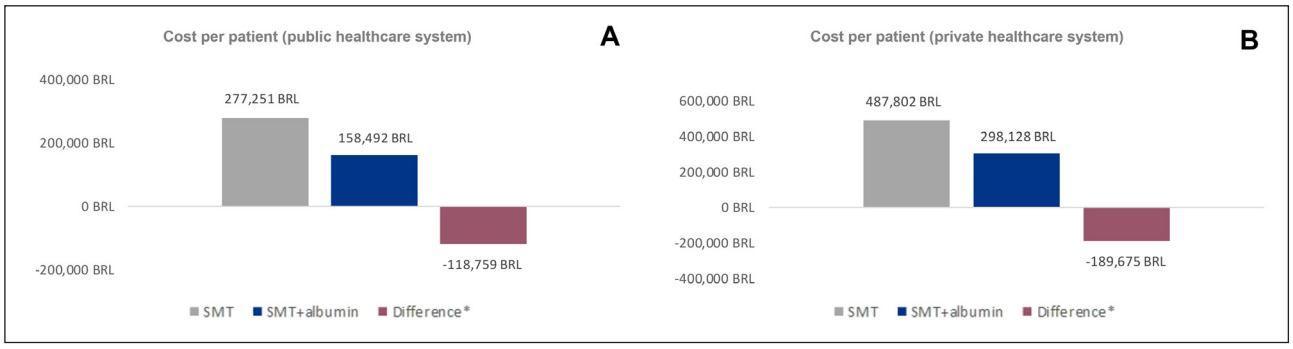

FIGURE 1. Incremental cost per cirrhotic patient treated with SMT + albumin vs SMT from the Brazilian public (A) and private (B) healthcare system perspectives **A:** Cost per patient per year treated with SMT and SMT + albumin and incremental difference from the public healthcare system perspective. **B:** Cost per patient per year treated with SMT and SMT + albumin and incremental difference from the private healthcare system perspective. *SMT + albumin vs SMT: negative values indicate savings. BRL: Brazilian real; SMT: standard medical treatment.

TABLE 3. Average cost per patient treated with SMT and SMT + albumin and incremental difference based on the rates of complications, healthcare resource utilization and pharmacological treatment as per the ANSWER trials and unit costs from table 2 from the perspective of the public healthcare system.

Cirrhosis-related complications	SMT	SMT + albumin	Incremental cost*
Refractory ascites	57,227 BRL	21,872 BRL	-35,355 BRL
Spontaneous bacterial peritonitis	12,560 BRL	4,270 BRL	-8,289 BRL
Other bacterial infections	3,932 BRL	2,945 BRL	-988 BRL
Hepatic encephalopathy	110,957 BRL	53,569 BRL	-57,388 BRL
Renal dysfunction	60,189 BRL	32,922 BRL	-27,267 BRL
Hepatorenal syndrome - type 1	28,421 BRL	9,855 BRL	-18,567 BRL
Large volume paracentesis	2,774 BRL	1,229 BRL	-1,546 BRL
Hospitalization (non-liver-related)	573 BRL	446 BRL	-127 BRL
Total (clinical complications)	276,633 BRL	127,107 BRL	-149,526 BRL
Pharmacological treatment			
Diuretics	618 BRL	618 BRL	0 BRL
Human albumin regular infusions**	0 BRL	30,767 BRL	30,767 BRL
Total (pharmacological cost)	618 BRL	31,385 BRL	30,767 BRL
TOTAL	277,251 BRL	158,492 BRL	-118,759 BRL

*Cost of SMT – cost of SMT + albumin; **Includes human albumin + the cost of visits for albumin administration. BRL: Brazilian real; SMT: standard medical treatment.

TABLE 4. Average cost per patient treated with SMT and SMT + albumin and incremental difference based on the rates of complications, healthcare resource utilization and pharmacological treatment as per the ANSWER trials and unit costs from table 2 from the perspective of the private healthcare system.

Cirrhosis-related complications	SMT	SMT + albumin	Incremental cost*
Refractory ascites	44,253 BRL	16,913 BRL	-27,340 BRL
Spontaneous bacterial peritonitis	11,703 BRL	3,979 BRL	-7,724 BRL
Other bacterial infections	4,395 BRL	3,291 BRL	-1,104 BRL
Hepatic encephalopathy	283,139 BRL	136,697 BRL	-146,442 BRL
Renal dysfunction	116,614 BRL	63,785 BRL	-52,829 BRL
Hepatorenal syndrome - type 1	13,819 BRL	4,792 BRL	-9,028 BRL
Large volume paracentesis	7,344 BRL	3,253 BRL	-4,092 BRL
Hospitalization (non-liver-related)	4,563 BRL	3,549 BRL	-1,014 BRL
Total (clinical complications)	485,831 BRL	236,259 BRL	-249,572 BRL
Pharmacological treatment			
Diuretics	1,971 BRL	1,971 BRL	0 BRL
Human albumin regular infusions**	0 BRL	59,897 BRL	59,897 BRL
Total (pharmacological cost)	1,971 BRL	61,868 BRL	59,897 BRL
TOTAL	487,802 BRL	298,128 BRL	-189,675 BRL

*Cost of SMT – cost of SMT + albumin; **Includes human albumin + the cost of visits for albumin administration. BRL: Brazilian real; SMT: standard medical treatment.

luations (rates of complications and HCRU, doses of pharmacological treatments and costs) were increased and decreased by 20%, the incremental cost resulted in negative values (i.e., indicative of cost savings) both from the public and private healthcare systems perspectives in all scenarios assessed (FIGURE 2).

DISCUSSION

The present economic analysis shows that the implementation of albumin infusions following the ANSWER regimen in Brazil may result in cost savings for the public and private healthcare systems[14], should the clinical outcomes reported in the ANSWER trial translate into real-world effectiveness in patients with cirrhosis and uncomplicated ascites in Brazil. The perception that albumin infusions could result in additional expenditure[8,19] may be compensated by the reduction of costly and frequent complications such as hepatic encephalopathy, refractory ascites and SBP (FIGURE 3)[14].

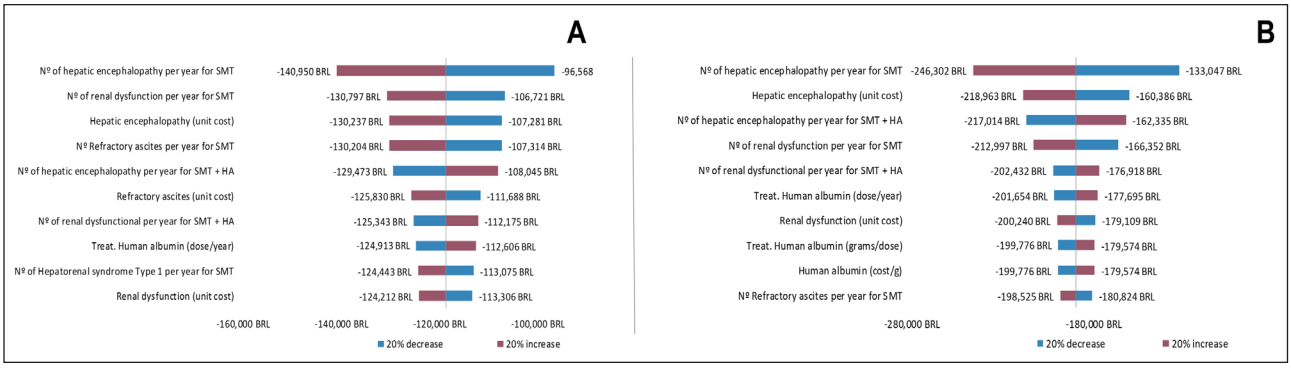

FIGURE 2. Univariate sensitivity analysis showing the 10 variables that would have the highest impact on the incremental cost per cirrhotic patient treated with SMT + albumin (vs SMT) when a 20% increase and decrease is applied following the perspective of the Brazilian public (A) and private (B) healthcare systems. **A:** Tornado diagram presenting the results of a univariate sensitivity analysis of the incremental cost per patient per year treated with SMT + albumin vs SMT from the public healthcare system perspective.
B: Tornado diagram presenting the results of a univariate sensitivity analysis of the incremental cost per patient per year treated with SMT + albumin vs SMT from the private healthcare system perspective.
BRL: Brazilian real; HA: human albumin; SMT: standard medical treatment.

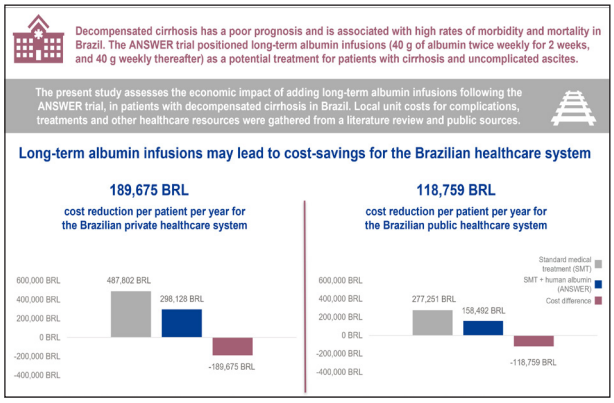

FIGURE 3. Summary of the background, project objectives and main results and conclusions.

Although there is limited evidence on the economic impact of long-term albumin infusions in patients with decompensated cirrhosis, and comparison between studies is challenging due to different methodologies, perspectives and countries, our results seem to be in line with those reported in previous studies[14,16-18].

The ANSWER trial assessed the cost-effectiveness of adding albumin infusions to SMT from the Italian healthcare system perspective showing that patients treated with albumin gained 0.117 quality adjusted life years (QALY) at an incremental cost of 2,488 EUR per year which resulted in an incremental cost-effectiveness ratio (ICER) of 21,265 EUR/QALY which is below the willingness to pay for most healthcare systems in Europe, therefore, albumin infusions resulted in a cost-effective therapeutic strategy when added to SMT (costs reported in 2012 EUR)[14,33].

Previous economic evaluations using similar methods to those described herein assessing the economic impact of albumin in addition to SMT in Spain and in Mexico, also showed cost-savings from both healthcare systems' perspectives[16,17]. Fernandez et al. reported that albumin added to SMT could result in costs savings of 1,377 EUR per patient per year for the Spanish healthcare system (costs reported in 2019 EUR)[17], and Moctezuma et al. estimated a potential cost reduction of 33,417 MXN per patient per year for the Mexican public healthcare system when albumin infusions were added to SMT (costs reported in 2020 MXN)[16].

A discrete event simulation estimated the potential economic impact of adding albumin infusions to SMT from the English National Health Service (NHS) perspective, which also resulted in an estimated potential cost-savings of 264,589 GBP per year when treating 30 patients (i.e., savings of 8,820 GBP per patient per year) (costs reported in 2020 GBP)[18].

Our study has some limitations. For example, clinical outcomes have been directly extrapolated from the ANSWER trial which was conducted in Italy and therefore patient characteristics and treatment patterns may not be fully representative of the Brazilian population. Furthermore, no direct costs for the patient or indirect productivity loss costs have been considered. Future work describing the treatment patterns (i.e., albumin dosing, frequency and duration based on treatment response) and real-world effectiveness may be necessary to confirm our findings.

Liver cirrhosis is a severe condition associated with highly morbidity and mortality[5,6], with limited treatment alternatives that may reduce the costly associated complications[8].

CONCLUSION

The ANSWER trial positioned long-term albumin as a therapeutic approach that may be able to diminish the burden of cirrhosis for patients and healthcare systems[14]. If the ANSWER trial results could be extrapolated to the clinical setting in Brazil, the additional cost of long-term albumin could potentially be offset by the reduction in costly complications, leading to potential cost-savings for public and private healthcare systems in Brazil.

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Authors' contribution

Terra C and Tafla C: validation, investigation, data curation, writing, review & editing; Viayna E: conceptualization, methodology, software, investigation, data curation, writing of original draft, review & editing, supervision; Ayzin L: conceptualization, data curation, writing, review & editing; Fuster C: in-

vestigation, data curation, writing, review & editing; Aceituno S: conceptualization, methodology, software, investigation, data curation, writing, review & editing. All authors critically reviewed the manuscript and approved the final version and its submission to Gastroenterology Archives. All authors agree to be accountable for all aspects of the work.

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Terra C, Viayna E, Ayzin L, Fuster C, Aceituno S, Tafla C. Análise de custos de pacientes cirróticos descompensados recebendo albumina a longo prazo versus tratamento médico padrão nos sistemas de saúde público e privado do Brasil. Arq Gastroenterol. 2023;60(3):356-63.

RESUMO – Contexto – A cirrose representa o estágio final da doença hepática crônica. Causas comuns de cirrose incluem alcoolismo e infecções por hepatite viral. A cirrose pode progredir de uma fase compensada assintomática para descompensação e aparecimento de sintomas evidentes. Não há tratamento específico para cirrose descompensada. O estudo ANSWER demonstrou que a administração de albumina a longo prazo pode representar um potencial tratamento para pacientes com cirrose e ascite não complicada. **Objetivo –** Nosso estudo avalia o impacto econômico da administração de albumina a longo prazo seguindo o protocolo do estudo ANSWER em pacientes brasileiros com cirrose descompensada, sob a perspectiva dos sistemas de saúde público e privado. **Métodos –** O custo incremental por paciente por ano foi calculado para o tratamento médico padrão (SMT) associado a administração de albumina a longo prazo comparado a SMT apenas. Os custos de diuréticos e albumina foram obtidos no Banco de Preços em Saúde e na Câmara de Regulação do Mercado de Medicamentos. Os custos de complicações e procedimentos foram coletados da literatura publicada. Os custos foram transformados em Reais de 2021 (BRL). As incidências de complicações clínicas e tratamentos foram coletadas do estudo ANSWER. Uma análise de sensibilidade univariada foi realizada aumentando e diminuindo todas as variáveis em 20%. **Resultados –** O custo por paciente por ano foi de R$ 118.759 e R$ 189.675 menor para pacientes tratados com SMT e albumina (comparado apenas com SMT) para os sistemas de saúde público e privado, respectivamente. O custo adicional da albumina foi compensado pela redução de complicações e tratamentos (149.526 BRL e 249.572 BRL, respectivamente). A análise de sensibilidade univariada mostrou redução de custos para ambos os sistemas de saúde em todos os cenários avaliados. **Conclusão –** Esta análise econômica sugere que, se os resultados clínicos do estudo ANSWER se confirmarem no mundo real, a administração de albumina associada ao SMT em pacientes com cirrose descompensada pode levar a redução de custos para os sistemas de saúde público e privado no Brasil.

Palavras-chave – Doenças hepáticas; custos e análise de custos; albumina de soro humano; cirrose.

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