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Outcome of Albumin Infusion in Heart Failure Patients

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Abstract:

Background:Heart Failure (HF) is a major public health burden worldwide. Approximately 5 million Americans, 0.4–2% of the general European population and over 23 million people worldwide are living with heart failure. Like few other chronic disease, low serum albumin is common in patients with heart failure (HF). However, very few studies evaluated the outcome of albumin infusion in different stages of HF. Therefore, the objective of this study is to assess the outcome of albumin infusion in heart failure patients.

Methods:It was a cross-sectional study. A total of 50 cases of chronic heart failure with reduced ejection fraction and NYHA class III or IV with serum albumin level <2.5g/dl who were admitted in CCUwere selected by purposive sampling, from September 2017 to August 2018. 100ml of 20% albumin was infused and serum albumin was measured after 3 days. Then the patients were divided into two groups, Patients who failed to attain serum albumin of 3g/dl(Group A) or Patients who attained serum albumin of ≥3g/dl (Group B). Analysis and comparison for symptomatic improvement of heart failure by NHYA classification and LVEF was done at 10^{th} day after infusion between group A and B.

Result:Among the 50 patients, mean age of patients was 53.64 ± 13.44 years (age range: 26-84 years) with a male-female ratio of 3:2 (60%-male vs 40%- female). Majority patients were previously re-admitted at least two times (40%), 28% were re-admitted once, 16% were re-admitted three times and 4% were re-admitted for four times. Of all, 56% patients presented NYHA class IV and AHA stage D heart failure (56%) and 44% patients presented with NYHA class III and AHA stage C. At day 10 follow up following albumin infusion, overall frequency of following ten days of albumin therapy, in group B, 8 patients (72.7%) among Class III improved to Class I and 3 patients (27.3%) improved to class II. Also, 7 patients (50%), 5 patients (35.7%) and 2 patients (14.3%) among class IV improved to respectively class I, class II and class III. In group A, 3 patients (27.3%) among class III improve to class II and 8 patients (72.7%) remain in class III. Also, 2 patients (14.3%), 5 Patients (35.7%) and 7 patients (50%) among class IV improve to respectively class I, class II and class III. Moreover, statistically significant improvement was noted in ejection fraction of patents irrespective of initial class of heart failure (p<0.001) in group B patients compare to group A (p<0.09).

Conclusion: In this study, the improvement of heart failure was more in patients who attained albumin level of ≥3g/dl.Therefore, in can be concluded that albumin infusion improves both subjective and objective improvement of patients with heart failure.

Keywords:*Heart Failure, Albumin infusion*

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Introduction:

Heart failure (HF), a global health burden, defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder and impairs the ability of the ventricle to fill or eject blood. This can occur either by structural damage or functional abnormalities of the heart (*Hunt., 2005*).[1]

Data shows, in every year per thousand populations 7.2 men and 4.7 women aged 45 or more detected as HF (*Díez-villanueva and Alfonso., 2016; Jan et al., 2012*).[2,3] This increasing trend could be due to progressive aging of the population and also improved survival following cardiac insults, such as myocardial infarction, especially in developed countries (*Metra and Teerlink., 2017; Díez-*

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villanueva and Alfonso., 2016).[2] Whereas, 5 years survival rate was 25% and 38% in men and women, respectively (*Benjamin et al., 2017; Heidenreich et al., 2013; Jan et al., 2012*).[3,4,5]

For practical purpose, the most important distinctions are those between acute and chronic heart failure and between patients with heart failure with reduced (≤40%), mid-range (40-49%) and those with heart failure with preserved (≥50%) left ventricular ejection fraction. *(Ponikowski et al., 2016*).

Besides this common fact, hypoalbuminia is another common finding, prevalence ranging from 18% to 89% (*Ancion et al., 2017; Arques and Ambrosi., 2011*).

There are several hypotheses for the cause of hypoalbuminemia in HF patient of which malnutrition, inflammation and cachexia are worth mentioning. Other causal factors include hem dilution, liver dysfunction, protein-losing enteropathy, increased trans capillary escape rate and nephrotic syndrome (*Araújo et al., 2011*).[6]

Bonilla-palomas et al., (2014)[7] and *Horwich et al., (2008)*[8] in two separate studies showed that low albumin level is associated with higher hospital mortality and can be used a predictor for long term outcome assessment.

Considering the findings of existing literature, it was hypothesized that there may be a link of low albumin level and outcome of different stage of HF patients. However, no study evaluated the relationship of albumin infusion and its outcome in HF patients. The aim of this study was to give albumin infusion in selected symptomatic patient with low albumin level and to see its outcome.

Method

Study design and patients

This cross-sectional study was conducted at the University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Dhaka. Total duration was 1 year from September, 2017 to August, 2018. A total of 50 cases of chronic heart failure with reduced ejection fraction and NYHA class III or IV with serum albumin level <2.5g/dl who were admitted in CCU were selected by consecutive sampling. The protocol was approved by the Institutional Review Board (IRB). Written informed consent was obtained from all study patients after careful explanation of the study procedures.

Study Procedure

The patients who got admitted in the Department of Cardiology, according to the inclusion and exclusion criteria were selected as study population. Detailed history, physical examination, routine laboratory examinations, and echocardiography were done. The diagnosis of heart failure was based on the criteria recommended bythe 2013 ACC / AHA HF guidelines.[9] A total of 50 patients were included in the study. All participants were interviewed meticulously. Before interviewing of the patient, purpose and procedure of the study were discussed with the patients. After getting consent, the patients were asked few questions in four subheading including socio-demographic parameters (age, occupation, living standard, monthly income etc.), about the disease and duration of disease, potential risk factors of aggravation of HF, co-morbid disease.

All symptomatic heart failure (NYHA class III and IV) patients with low serum albumin (<2.5gm/dl) were selected.

At emergency department venous blood samples were collected and patients were all in supine position. Serum albumin was assayed using particle-enhanced immunonephelometric assay on a BN II laser nephelometer (Siemens, Lisbon, Portugal).

An echocardiogram (bed side) was performed using *GE 9* machine to all eligible patients at admission. And patients with systolic dysfunction were included. Severe left ventricular systolic dysfunction corresponded to left ventricular ejection fraction (LVEF) lower than 30%, moderate left ventricular systolic dysfunction to left ventricular ejection fraction (LVEF) between 30-40%.

Patients were treated according to heart failure guidelines by attending physician. Physician treating these acute Heart Failure patients were aware of ongoing Heart Failure registry.

Serum albumin were infused according to the following regimen, 100 ml of 20% albumin daily for 3 days to attain a level of serum albumin concentration ≥3 g/dl. After infusion, serum albumin level was measured by above mentioned method. Then patients were divided into two groups. Group A (who fail to attain serum albumin level ≥3gm/dl) and Group B (who attain serum albumin level ≥3gm/dl). Then analysis of the symptomatic improvement between A and group B according to NYHA functional classification of heart failure and left ventricular ejection fraction (LVEF) by echocardiography at 10 days after infusion.

After completion of the data collection comparison was done between symptoms and left ventricular ejection fraction (LVEF) of patients in group A and group B before

and after infusion. Separate data collection sheet was used for each subject with maintaining confidentiality.

During study period observation for primary end point events medical compliance adverse effects and vital status were evaluated. If any problem, arise in between infusion albumin infusion was stopped. The primary efficacy end point was NYHA functional grading. A standardized questionnaire was used to evaluate symptomatic improvement after infusion. Follow up was done at 10 days after infusion.

Statistical analysis

Data were presented as mean ± SDs for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and as frequencies for categorical variables. Low albumin, or hypoalbuminemia, were defined as the lowest quartile of albumin, ≥3.5 g/dl. Baseline characteristics between patients with and without hypoalbuminemia were compared using independent samples t test, and Ç2 test as appropriate. Data were analyzed using SPSS 23.0 for Windows 10 (SPSS, Inc, Chicago, IL). In all cases significance level was set p value <0.05.

Results:

A total of 50 patients were selected for study. After albumin infusion, the patients were divided into two groups, Patients who failed to attain serum albumin of 3g/dl (Group A) or Patients who attained serum albumin of ≥3g/dl (Group B). Analysis and comparison for symptomatic improvement of heart failure by NHYA classification and LVEF was done at 10th day after infusion between group A and B.

The mean age of patients was 53.64 ± 13.44 years. Minimum age of the patients was 26 years and maximum age of the patients was 84 years. Out of 50 patients majority were from age group 51 to 60 years (48%). The distribution is shown in figure 1.

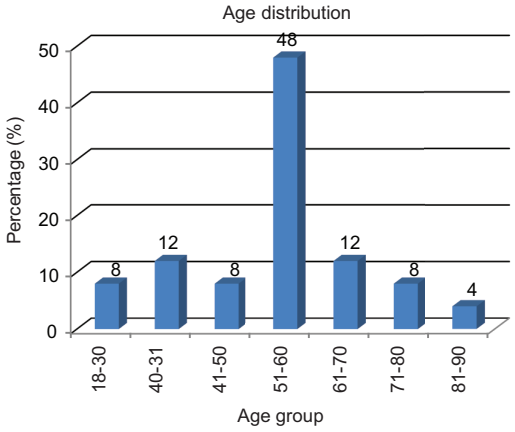

Fig.-1: *Distribution of patients according to their age (n=50).*

Among 50 patients, 60% were male and 40% were female. (figure 2) A male-female ratio of 3:2 was found.

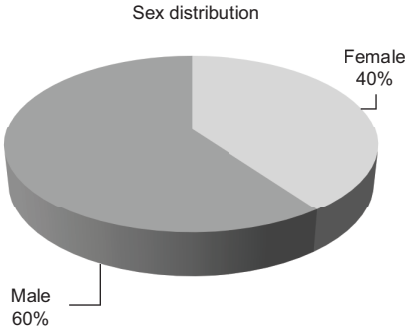

Fig.-2: *Distribution of patients according to sex (n=50).*

Fifty two percent of the study population lived in urban area and 48% lived in rural area. (Figure 6)

Among all study participants, majority patients (48%) were hypertensive, followed in decreasing order by 40% smoker, 28% diabetic, 28% anemic, 24% having dyslipidemia, 16% having atrial fibrillation and 8% having CKD (Table I). The most common clinical presentation was shortness of breath (100%). The most common sign was bilateral basal crepitation (96%). Other features are enlisted in table II.

Table I

Distribution of patients according to personal habit and co-morbid conditions (n=50)

Risk factors	Frequency	Percentage
Smoking habit	20	40
Current smoker	14	28
Past smoker	6	12
Alcohol intake	2	4
Hypertension	24	48
Diabetes mellitus	14	28
Dyslipidemia	12	24
Atrial fibrillation	8	16
CKD	4	8
Anemia	14	28

Table II

Distribution of patients according to clinical presentation. (n=50)

Clinical presentation	Frequency	Percentage
Shortness of breath	50	100
Orthopnoea	54	6S
Paroxysmal nocturnal dyspnea	10	00
Leg odenta	15	56
Raised JVP	10	00
Hypotension	OS	56
Bilateral basal crepitation	48	96

Among all patients, 28% had heart failure for <6 months, 24% had for 7 – 12 months, 28% had for 12 – 24 months and 20% patients had heart failure for >24 months (Figure 3).

Majority patients were previously re-admitted at least two times (40%), 28% were re-admitted once, 16% were re-admitted three times and 4% were re-admitted for four times. Twelve percent patients were not admitted previously (Figure 4).

In this study patients with NYHA class III and IV were included only. Majority of the patients presented NYHA class IV and AHA stage D heart failure (56%), Rest (44%) were NYHA class III and AHA stage C heart failure patients(Table III)NYHA class III patients had mean ejection fraction 40.18±2.78 percent and class IV patients had mean ejection fraction 31.21±5.14 percent (p<0.001) (Table IV)

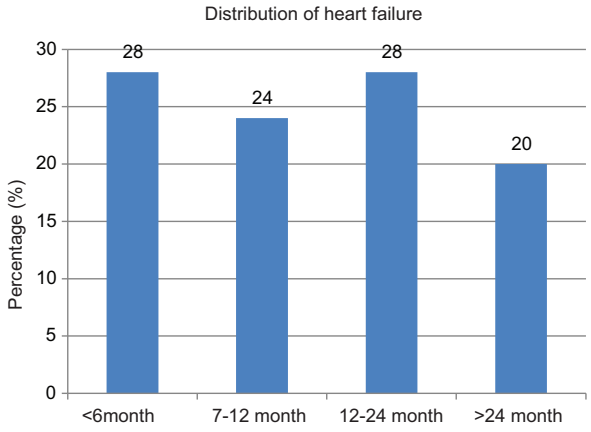

Fig.-3: *Distribution of patients according to duration of heart failure (n=50)*

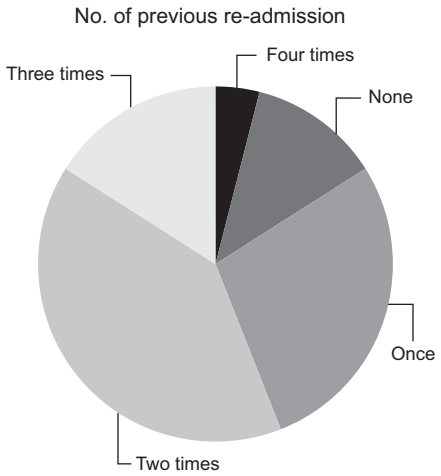

Fig.-4: *Distribution of patients according to number of previous re-admission (n=50)*

Table-III

Distribution of patients according to NYHA and AHA classification of heart failure at admission (n=50)

Classification	Frequency	Percentage
NYHA classification		
Class HI	22	44
Class IV	28	56
AHA classification		
Stage C	22	44
StageD	28	56

Table IV

Ejection fraction of patients at admission(n=50)

Classification		Ejection fraction (%) Mean±SD	P value
NYHA classification	N		
Class III	22	40.18±2.78	<0.001
Class IV	28	31.21±5.14	

Each patient was given 1 bottle (100ml) of 20% albumin each day for 3 days along with diuretics for the management of heart failure. In group A, statistically significant improvement in ejection fraction was not noted irrespective of initial class of heart failure (p<0.09). Ejection fraction of NYHA class III patients improved from 40.18±2.78 to 46.18±3.29. Ejection fraction of NYHA class IV patients improved from 31.12±5.14 to 34.85±4.02(Table V). In group B statistically significant improvement in ejection fraction of patents irrespective of initial class of heart failure (p<0.001) compare to group A. Ejection fraction of NYHA class III patients improved from 40.18±2.78 to 54.54±3.29. Ejection fraction of NYHA class IV patients improved from 31.12±5.14 to 40.85±5.02. (Table VI).

Table-V

Comparison of ejection fraction before and 10 days after IV albumin therapy in group A (n=25)

Classification		Ejection fraction (%) Mean±SD		P value
NYHA classification	N	Before therapy	10 days after therapy	
Class III	11	22	40.18±2.78	0.001
Class IV	14	31.21±5.14	34.85±4.02	<0.09

Table-VI

Comparison of ejection fraction before and 10 days after IV albumin therapy in group B (n=25)

Classification		Ejection fraction (%) Mean±SD		P value
NYHA classification	N	Before therapy	10 days after therapy	
Class III	II	40.18±2.78	54.54±3.29	<0.001
Class IV	14	31.12±5.14	40.85±5.02	<0.001

At admission among 50 patients 44% were NYHA class III and 56% were NYHA class IV patients. Ten days after albumin therapy, in group A, 3 patients (27.3%) among Class III improved to Class II and 8 patients (72.7%) persist in class III. Also, 2 patients (14.3%), 5 patients (35.7%) and 7 patients (50%) among class IV improved to respectively class I, class II and class III.

In group B, 8 patients (72.7%) among Class III improved to Class I and 3 patients (27.3%) improved to class II. Also, 7 patients (50%), 5 patients (35.7%) and 2 patients (14.3%) among class IV improved to respectively class I, class II and class III.

Mean change in ejection fraction before and after albumin therapy were plotted against admission serum albumin level. A positive correlation was noted (r=0.335, p=0.102). This indicates that a higher admission serum albumin level was associated with higher improvement in ejection fraction after albumin therapy along with diuretics (Fig. 5).

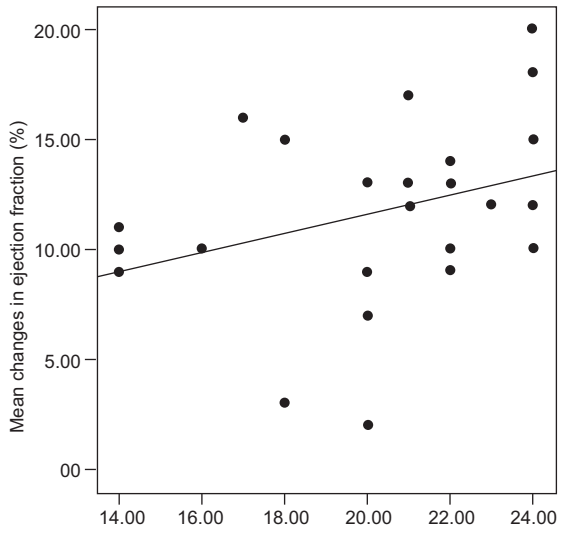

Fig.-5: *Correlation of admission serum albumin level with mean changes in ejection fraction (n=25)*

Discussion:

Total 50 cases of heart failure who had a serum albumin level of <2.5g/dl were included in the study. Mean age of the patients was 53.64±13.44 years. This is similar to a study on socio-demographic profile of heart failure patients admitted in a tertiary care hospital of Bangladesh (*Banerjee et al.,* 2016).[5] They found a mean age of 55±14 years. The mean age of present study was higher than that was found in the study on clinical profile of heart failure patients admitted in a specialized hospital for heart disease. (*Rahman et al.,* 2014)[10] They found a mean age of 46±7 years. Inclusion of children in their study could be the reason for their lower mean age. Other studies involving heart failure patients also showed a mean age around 60 years. In the SOLVD clinical trial (SOLVD Investigators et al., 1991)[11] mean age was 60.7 years. In the digoxin study mean age was 63.4±11 years (Digitalis Investigation Group, 1997)[12]. In RALES study[13] the mean age 822 heart failure patients was 65±12 years. In the ATLAS study[14] the mean age was approximately 63.6±10.3 years. In the study by Kabiruzzaman., et al (2010)[15] the mean age was 54.1±15.3 years. Nieminen et al., (2006)[16]found a mean age of 69.5±12.1 years. This comparative discussion reveals that the mean age of heart failure is lower in Bangladesh in comparison to other western countries.

In this study majority were aged between 51 – 60 years (48%). Similarly, Banerjee et al. (2016)[4] found 42.2% (majority) patients aged between 51 – 60 years. Rahman et al. (2014)[10] found 75% patients aged between 51 – 70 years.

A male prevalence was noted in this study which is similar to the findings of other studies. Sixty percent patients were male and 40% were females. Similarly, Neiminen et al. (2006)[16] found 61.3% male and 38.7% female. Burden of heart failure in a tertiary hospital by Kabiruzzaman., et al (2010)[15] found 71.7% male and 28.3% female in their study. Rahman et al. (2014) had 75% male and 25% female in their study.

In this study 40% patients were smokers including 28% current smokers and 12% past smokers. Smoking is significant risk factor for heart failure. Gopal et al., (2012)[27] ran a prospective cohort to assess the risk of smoking on heart failure. In their study at inception, 54. 8% of participants were non-smokers, 34. 8% were past smokers, and 4% were current smokers. During follow-up (median, 9. 4 years), HF (heart failure) incidence was 11. 4 per 1000 person-years in non-smokers, 15. 2 in past smokers (hazard ratio [HR] vs. non-smokers 1. 33; 95% confidence interval [CI] 1. 01, 1. 76; p=0. 045), and 21. 9 in current smokers (HR 1. 93; 95% CI 1. 30, 2. 84; p=0. 001). So they concluded that

in older adults, both current and past cigarette smoking increase HF risk. Noori et al. (2014)[25]noted that readmission rate was also significantly associated with smoking habit.

In the present study only 4% patients gave history of alcohol consumption. In comparison Banerjee et al., (2016)[5]found 11% patients with history of alcohol consumption.

Among different co-morbid disease, in this study, 48% patients had hypertension, 28% had diabetes mellitus, 24% had dyslipidemia, 16% cases of atrial fibrillation and 8% had chronic kidney disease. Similarly, 45% cases of hypertension, 29% cases of diabetes, 20% cases of dyslipidemia and 9% cases of atrial fibrillationwas found by Rahmanet al., (2014)[10]. Kawashiro et al (2008)[22] found 54.1% cases of HTN, 31.4% cases of DM, 25.7% cases of dyslipidemia, 36.4% cases of atrial fibrillation and 22.8% cases of CKD in their study entitled "Clinical characteristics and outcome of hospitalized patients with congestive heart failure: results of the HIJC-HF registry".[22]

In the present study 28% patients had anemia. In comparison, Kawashiro et al., (2008)[28] found 44.2% cases of anemia.

In this study all patients presented with breathlessness (100%). Among them 68% had orthopnea and 20% had paroxysmal nocturnal dyspnea. Bilateral basal crepitation was noted in 96% patients. Leg edema was noted in 36% patients. Twenty percent patients presented with raised JVP. Hypotension was noted in 56% patients. Similarly, Rahman et al., found 98% cases presenting with breathlessness, 74% having orthopnea, 59% having paroxysmal nocturnal dyspnea, 40% presenting with leg edema and 25% presenting with raised JVP (Rahman et al., 2014).[16] Bilateral basal crepitation was found in 98% patients.

In this study 92% patients were previously readmitted at least once for heart failure. O'Connor noted that more than 70% patients in total get readmitted within 6 months after first episode of heart failure (O'Connor., 2014).[23]

The present study included only NYHA class III and IV patients having serum albumin level <2.5g/dl. Among 50 patients, 28 had NYHA class IV (and AHA stage D) heart failure and 22 patients had NYHA class III (and AHA stage C) heart failure.

Mean serum albumin was significantly higher among NYHA class III patients in comparison to NYHA class IV patients at admission (21.72±2.25 vs. 19.00±3.55, $p<0.05$). This is a unique finding as no similar study was found in the literature. But in one study by Horwich et al., noted that patients with NYHA III and IV were 1.68 times more likely to have hypoalbuminemia than NYHA I and II patients. (Horwich et al., 2008).[8] This corresponds with the finding of this study.

In the present study 20% albumin was given to all patients for three consecutive days along with diuretics. Significant improvement in ejection fraction was found in both NYHA class III and class IV patients those are in group B with serum albumin level>3mg/dl compare to group A where serum albumin level was<3 mg/dl. A case series by Salvatore Paterna et al., (2001)[30]found the similar result. They concluded in their study that albumin infusion in addition to parental loop diuretics in acute heart failure patients showed improved diuresis and return to dry. As baseline albumin was found to be associated with worsening renal function in patients with acute decompensated heart failure receiving continuous infusion loop diuretics (Clarke et al., 2013).[25] A possible mechanism for improvement could be improved loop diuretic efficacy with co-administration of albumin to increase in plasma oncotic pressure and increased diuretic delivery to the nephron.

An additional finding of the present study was the non-significant but positive correlation found between admission serum albumin level and improvement in ejection fraction ($r=0.335$, $p=0.102$). This needs to be evaluated further in large cohort of patients.

Others studies have assessed the predictive significance of admission serum albumin in the outcome of heart failure patients and found that hypoalbuminemia was associated with high mortality in heart failure patients (Horwich et al., 2008; Gopal et al., 2010[21]; Ancion et al., 2017). Therefore, serum albumin infusion in decompensated heart failure of can be of benefit not only in the improvement in the ejection fraction of the patients but also for the decreased hospital re-admissions and increased survivability of patients.

Conclusion:

This study demonstrated that baseline clinical stage of heart failure assessed by both NYHA and AHA criteria improves post albumin infusion. Simultaneous significant improvement of ejection fraction was also noticed in the patients. Besides this, there was a positive correlation between higher baseline albumin levels with subsequent improvement of patients. Therefore, it can be concluded that albumin infusion has a positive role in improvement of symptomatic heart failure patients. However, the findings should be used with caution as the study is

limited to smaller sample size and therefore, further larger cohort study is recommended. Limitations of this study are small sample size and the short follow up period.Therefore, we recommend further larger cohort studies to be carried out with a large sample size to verify the findings of this single center study. We also recommend further research to evaluate if there is a prognostic role of albumin infusion and also weather it improves quality of life in heart failure patients.

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