

## Assessing Physicians' Knowledge about International Guidelines of Albumin Use in Patients with Liver Cirrhosis

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### ABSTRACT

**Background:** Hepatocellular function is compromised in liver cirrhosis patients, and albumin production is decreased.

**Objective:** The aim of the current study was to evaluate clinicians' understanding of the International Guidelines-supported evidence-based indications for using human albumin (HA).

**Patients and methods:** A survey was conducted on specialized Gastroenterology Physicians at Al-Rajhi Liver Hospital and other Hospitals in Assiut, who regularly treat patients with liver cirrhosis. The study was carried out between October 2020 and December 2021. Physicians' knowledge was assessed using Tool I then re-evaluation was done to determine the effect of designed evidence-based indications (Tool II) for HA use on Physicians.

**Results:** There was statistically significant higher mean knowledge score at the post test compared to baseline ( $7.6 \pm 0.9$  compared to  $3.6 \pm 1.8$ , respectively). Regarding knowledge score categories, good knowledge of Physicians statistically increased from 52.4% at the baseline to 100% at the post test. There was statistically significant higher mean difference in function of HA knowledge score in academic doctors ( $3.9 \pm 1.7$ ) compared to nonacademic doctors ( $2.7 \pm 1.9$ ). There was statistically significant higher mean difference in function of HA knowledge score in doctors with experiences  $\geq 5$  years ( $4.0 \pm 1.6$ ) compared to doctors with experiences  $< 5$  years ( $3.3 \pm 1.9$ ).

**Conclusion:** The level of knowledge to function and the International Guidelines of albumin use in patients with liver cirrhosis significantly increased in the post test especially among nonacademic doctors and fresh graduate doctors.

**Keywords:** Human Albumin, Liver cirrhosis, Ascites, Hepato-renal Syndrome.

### INTRODUCTION

Patients with liver cirrhosis produce fewer albumins and have altered hepatocellular function, which in severe cases can decline by 60-80%<sup>(1)</sup>. A further decline in protein levels is caused by the retention of water and salt as well as the sequestration of circulating albumin in extracellular space and ascetic fluid<sup>(2,3)</sup>.

Even while some trials have shown that routine long-term albumin infusion improves decompensated cirrhosis<sup>(4)</sup>, it is not advised. As a plasma expander, albumin is more costly than crystalloids and has been associated with major negative effects<sup>(5,6)</sup>. The aim of the current study was to evaluate clinicians' understanding of the International Guidelines-supported evidence-based indications for using human albumin (HA).

### PATIENTS AND METHODS

A survey was conducted on specialized Gastroenterology Physicians at Al-Rajhi Liver Hospital and other Hospitals in Assiut, who regularly treat patients with liver cirrhosis.

The physicians were interviewed at various national meetings between October 2020 and December 2021.

The survey was carried out (in English) using two tools:

**Tool (I)** consists of two parts:

- *Part (1)*: Demographic data about the physicians such as age, sex, job category, and years of experience.

- *Part (2)*: Physicians' knowledge about general information of albumin prescription and functions, mechanism of action of albumin in liver cirrhosis and potential clinical indications for albumin.

**Tool (II)**: Developed evidence-based HA usage indications backed by global recommendations. It contains general information on the use and function of albumin as well as its mode of action in liver cirrhosis,

assessing the effect of the worldwide guidelines-designed evidence-based indications for utilizing HA on doctors' knowledge after one month using **Tool I**.

Total score of physician's knowledge about functions of HA, the score was created by asking 8 questions about function of HA. Total score of a doctor's awareness of worldwide recommendations for using human albumin in cirrhotic patients.

**Ethics Approval:** This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Assiut University (ClinicalTrials.gov NCT04242979). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

**Statistical Analysis:** The Statistical Package for Social Sciences (IBM-SPSS) version 26.0 was used to analyze the data. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and McNama r test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Quantitative variables were described as mean and standard deviation (SD) or median and range. The Kruskal-Wallis test was used to evaluate differences between quantitative variables for more than two groups, whereas Mann-Whitney U test was used to analyze differences between two independent groups. The association between knowledge score, age, and years of experience was determined using Spearman's correlation. When evaluating the internal consistency or reliability of scale item scores using Cronbach's alpha, a value of 70 or more is regarded as appropriate. P value  $\leq 0.05$  was considered to be statistically significant.

**RESULTS**

**Table 1** summarizes the sociodemographic characteristics of the participants.

**Table (1): Sociodemographic characteristics of the study sample.**

Variable	(N=168)	%
<b>Age (Years)</b>		
< 30 years	69	41.1
30 to <40 years	90	53.6
≥40 years	9	5.4
<b>Mean ± SD (range): 31.7 ± 5.5 (25 - 63)</b>		
<b>Gender</b>		
Male	127	75.6
Female	41	24.4
<b>Place of work</b>		
Academic hospital	123	73.2
Nonacademic hospital	41	24.4
Private practice	4	2.4
<b>Years of experience</b>		
< 5 years	112	66.7
≥ 5 years	56	33.3
<b>Median(range) : 4 years (1 - 40)</b>		
<b>Job categories</b>		
Residents	38	22.6
Specialists	26	15.5
Assistant Lecturers	100	59.5
Lectures and Professors	4	2.4
<b>Specialty</b>		
Tropical Medicine and Gastroenterology	121	72.0
Internal Medicine	29	17.3
Surgery	18	10.7

Data were presented by frequency and % or mean and SD, median (range).

**Baseline knowledge of Physicians about functions of human albumin:**

About 78.0% knew that HA is the main circulating protein in healthy individuals, 69.0% knew that HA synthesized by hepatocytes and released into the circulation, 62.5 % knew that HA is the main modulator of fluid distribution.

**Baseline knowledge of Physicians about International Guidelines of human albumin uses in patients with liver cirrhosis:**

About 62.5 % of the participants knew the presence of hypoalbuminemia per se is not an indication for the prescription of HA, 72.6% knew when the incidence of post paracentesis circulatory dysfunction (PPCD) increased.

**Table (2): Comparison of Physicians' correct knowledge about functions of human albumin pre and post.**

Variable	Pre (N=168)	Post (N=168)	P- value*
HA. is the main circulating protein in healthy individuals (Yes) <sup>#</sup>	131 (78%)	151 (89.9%)	<b>0.002</b>
HA synthesized by hepatocytes and released into the circulation (Yes) <sup>#</sup>	116 (69%)	157 (93.5%)	<b>&lt;0.001</b>
Total half-life of HA in healthy young adults (12 to 19 days) <sup>#</sup>	20 (11.9%)	168 (100%)	<b>&lt;0.001</b>
HA the main modulator of fluid distribution and accounting for about 70-80% of the plasma oncotic pressure (Yes) <sup>#</sup>	105 (62.5%)	152 (90.5%)	<b>&lt;0.001</b>
Albumin bind to and transport endogenous and exogenous compounds (Yes) <sup>#</sup>	131 (78.0%)	168 (100.0%)	<b>&lt;0.001</b>
Albumin has the action of modulation of the inflammatory and immunological responses (Yes) <sup>#</sup>	106 (63.1%)	168 (100.0%)	<b>&lt;0.001</b>
Albumin has antioxidant activity (Yes) <sup>#</sup>	136 (81.0)	151 (89.9)	<b>&lt;0.001</b>
Albumin has the action of preservation of the functional integrity of the microcirculation (Yes) <sup>#</sup>	116 (69.0%)	155 (92.3%)	<b>&lt;0.001</b>
<b>Total score</b>			
▪ Mean	3.6 ± 1.8	7.6 ± 0.9	<b>&lt;0.001</b>
▪ Median (range)	5 (0 - 6)	8 (5 - 8)	
▪ Mean difference (post-pre)	3.9 ± 1.9		
<b>Knowledge score categories</b>			
▪ Good knowledge	88 (52.4%)	168 (100%)	<b>&lt;0.001</b>
▪ Poor Knowledge	80 (47.6%)	0 (0.0%)	

**Total score of physicians' knowledge of the use of human albumin in patients with liver cirrhosis according to international recommendations (Table 3):** There was statistically significant higher percent of correct answers of all 20 questions about International Guideline of HA uses in patients with liver cirrhosis in the post test compared to the baseline (P value <0.05).

**Table (3): Physicians' correct knowledge about International Guidelines of human albumin uses in patients with liver cirrhosis pre and post.**

Variable	Pre (N=168)	Post (N=168)	P-value*
The presence of hypoalbuminemia per se is not an indication for the prescription of HA (Yes) <sup>#</sup>	105 (62.5%)	152 (90.5%)	<0.001
When the incidence of post paracentesis circulatory dysfunction (PPCD) increased (If > 5 L of ascites are removed) <sup>#</sup>	122 (72.6%)	151 (89.9%)	<0.001
Correct dose of used HA (per L of ascites removed) to prevent PPCD (6-8 g) <sup>#</sup>	0 (0.0%)	88 (52.4%)	<0.001
Non-oncotic properties contribute to the effects of HA in the prevention of PPCD (Yes) <sup>#</sup>	106 (63.1%)	168 (100%)	<0.001
Correct time for the HA administration to prevent PPCD (After large volume paracentesis) <sup>#</sup>	136 (81%)	151 (89.9%)	0.012
If albumin is not available, how could you compensate for paracentesis (colloid only) <sup>#</sup>	0 (0.0%)	20 (11.9%)	<0.001
HA used (with antibiotics) for prevention of renal failure after spontaneous bacterial peritonitis (SBP) (Yes) <sup>#</sup>	131 (78%)	147 (87.5%)	0.021
Non-oncotic properties contribute to the effects of HA in the \Prevention of renal failure after SBP (Yes) <sup>#</sup>	108 (64.3%)	154 (91.7%)	<0.001
Dose of Albumin to prevent renal failure after SBP (1.5 g /kg body weight at diagnosis, and 1 g/kg on the 3rd day of diagnosing SBP) <sup>#</sup>	0 (0.0%)	103 (61.3%)	<0.001
HA used for diagnosis of hepatorenal syndrome (HRS) (Yes) <sup>#</sup>	134 (79.8)	168 (100%)	<0.001
Dose of HA used in treatment of HRS (1g/kg / day for 2 days) <sup>#</sup>	0 (0.0%)	15 (8.9%)	<0.001
HA used for Treatment of type I HRS (Yes) <sup>#</sup>	126 (75%)	156 (92.9%)	<0.001
Correct dose for Treatment of type I HRS (1 g/kg at diagnosis and 20-40 g/day in association with vasoconstrictors) <sup>#</sup>	96 (57.1%)	148 (88.1%)	<0.001
In which type of cirrhotic patients is it mandatory (High risk patients (bilirubin >4 mg/dL and serum creatinine >1 mg/dL) <sup>#</sup>	92 (54.8%)	142 (84.5%)	<0.001
Non-oncotic properties contribute to the effects of HA in the Treatment of HRS (Yes) <sup>#</sup>	123 (73.2%)	156 (92.9%)	<0.001
HA used for Treatment of hyponatremia (Yes) <sup>#</sup>	124 (73.8%)	155 (92.3%)	<0.001
Cut of used in treatment of hyponatremia (<125 mmole/l) <sup>#</sup>	116 (69%)	144 (85.7%)	<0.001
HA used with antibiotics in non-SBP bacterial infections (No) <sup>#</sup>	138 (82.1%)	162 (96.4%)	<0.001
HA used for treatment of hepatic encephalopathy (no) <sup>#</sup>	133 (79.2%)	168 (100%)	<0.001
HA used for Treatment of septic shock in cirrhotic patients (Yes) <sup>#</sup>	126 (75%)	168 (100%)	<0.001
<b>Total score</b>			
▪ Mean	11.2 ± 2.8	16.3 ± 1.9	<0.001
▪ Median (range)	12 (2 - 16)	16 (9 - 19)	
<b>Knowledge score categories</b>			
▪ Good knowledge	93 (55.4%)	166 (98.8%)	<0.001
▪ Poor Knowledge	75 (44.6%)	2 (1.2%)	

Data were presented by frequency and % of correct answers. \* McNamar test was used to compare proportion of knowledge among physician at the baseline and posttest, the significant was when P value <0.05. \* Wilcoxon sign test was used to compare mean knowledge score at the baseline and post-test. <sup>#</sup> Correct answer of physician knowledge was referenced to the recent Guidelines of albumin use in patients with liver cirrhosis

**Factors associated with Physicians' knowledge (table 4):** There was statistically significant higher mean difference in knowledge score regard function of HA in academic doctors (3.9±1.7) compared to nonacademic doctors (2.7±1.9).

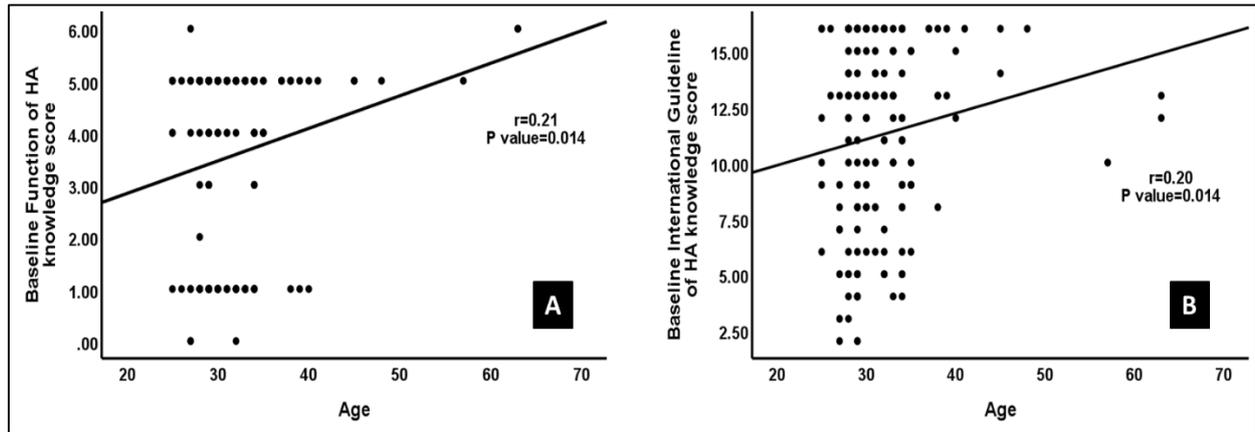
**Table (4): Factors associated with Physicians' knowledge about function of human albumin and International Guideline use in patients with liver cirrhosis at the baseline.**

Variables	Baseline	
	Function of HA knowledge score	HA knowledge score of International Guideline
<b>*Age categories</b>		
▪ < 30 years	3.4 ±1.9	<b>10.3±4.7</b>
▪ 30 to <40 years	3.5±1.8	<b>11.7±3.5</b>
▪ ≥40 years	4.8±1.5	<b>13.8±2.2</b>
<b>P-value*</b>	0.05	<b>0.033</b>
<b>**Gender</b>		
▪ Male	3.5±1.9	11.3 ±4.0
▪ Female	3.8 ±1.7	10.9 ±4.2
<b>P-value*</b>	0.377	0.550
<b>**Place of work</b>		
▪ Academic	<b>3.9±1.7</b>	<b>12.3±3.6</b>
▪ Nonacademic	<b>2.7±1.9</b>	<b>8.5±4.1</b>
<b>P-value*</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
<b>**Year of experiences</b>		
▪ < 5 years	<b>3.3±1.9</b>	<b>10.8±4.2</b>
▪ ≥ 5 years	<b>4.0±1.6</b>	<b>12.2±3.6</b>
<b>P-value*</b>	<b>0.018</b>	<b>0.035</b>
<b>*Job categories</b>		
▪ Residents	3.7±1.8	11.1±4.2
▪ Specialists	3.9 ±1.5	12.0 ±3.8
▪ Assistant Lecturers	3.4 ±1.9	11.1 ±4.0
▪ Lectures and Professors	4.0 ±2.0	11.3±5.7
<b>P-value*</b>	0.691	0.776
<b>*Specialty</b>		
▪ Tropical Medicine	3.6±1.8	11.1 ±2.8
▪ Internal Medicine	3.1±1.9	10.6±2.4
▪ Surgery	3.8 ±1.8	12.9±3.2
<b>P-value*</b>	0.268	0.137

\*Kruskal Wallis test. \*\* Mann Whitney U test.

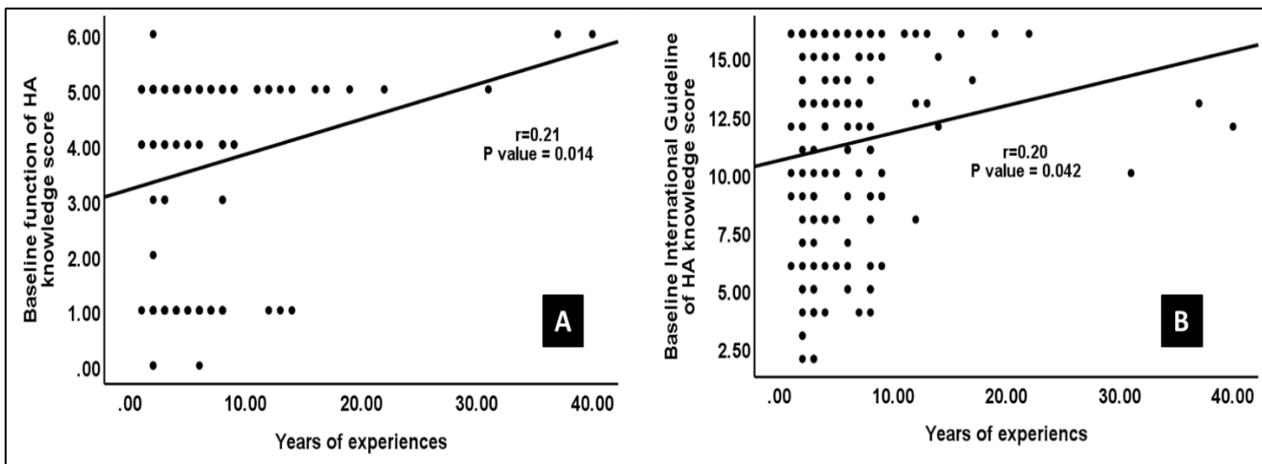
**Correlation between age and Physicians' knowledge at the baseline assessment:**

There was significant positive mild correlation between age and Physicians' knowledge score regarding function of HA (r=0.21, P-value 0.014) (Figure 1A), and Physicians' knowledge score regarding International Guideline of HA (r=0.20, P-value 0.014) (Figure 1B).



**Figure 1:** **A)** Scatter diagram for correlation between age and Physicians’ knowledge about function of HA at the baseline assessment. **B)** Scatter diagram for correlation between age and Physicians’ knowledge about International Guideline use in patients with liver cirrhosis at the baseline assessment.

**Correlation between years of experiences and Physicians’ knowledge at the baseline assessment:** There was significant positive mild correlation between years of experiences and Physicians’ knowledge score regarding function of HA ( $r=0.21$ , P-value 0.014) (Figure 2A), and Physicians knowledge score regarding International Guideline of HA ( $r=0.20$ , P-value 0.042) (Figure 2B).



**Figure 2:**

**A)** Scatter diagram for correlation between years of experiences and Physicians’ knowledge about function of HA at the baseline assessment. **B)** Scatter diagram for correlation between years of experiences and Physicians’ knowledge about International Guideline use in patients with liver cirrhosis at the baseline assessment.

**Factors associated with improvement of Physicians’ knowledge (Table 5):**

Age group <30 years old had significantly increased mean knowledge score difference, followed by age group 30- <40 years old and age group ≥40 years old ( $5.8\pm4.0$ ,  $4.7\pm2.9$ , and  $3.3\pm2.5$ , respectively; P-value 0.045). Nonacademic doctors had significantly increased mean knowledge score difference than academic doctors ( $6.7\pm3.7$  compared to  $4.5\pm3.6$ , respectively; P-value <0.001).

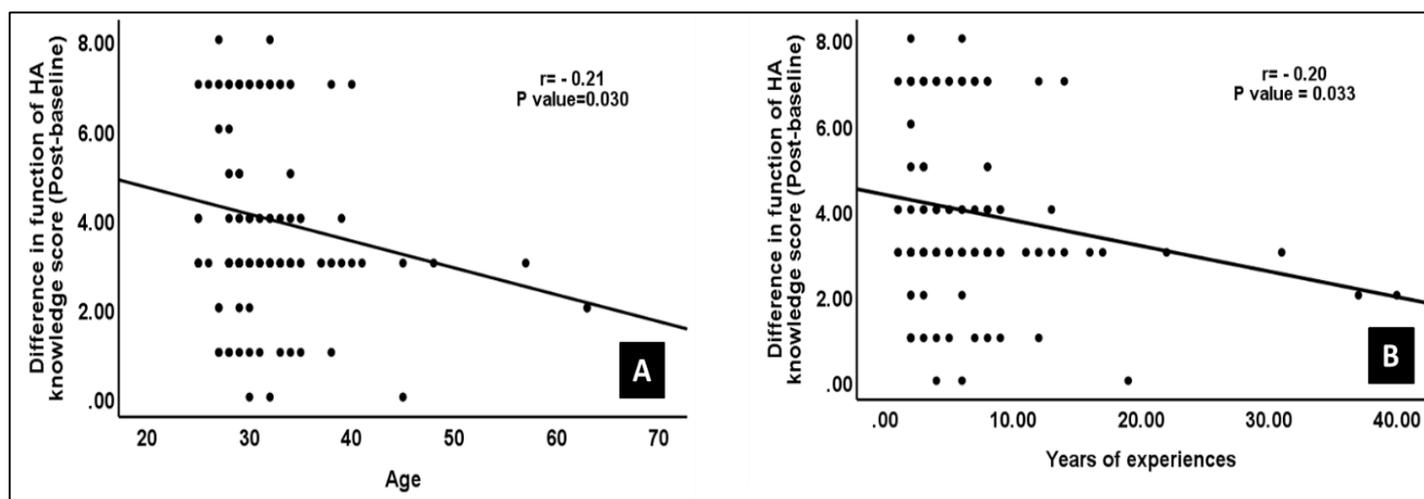
**Table (5): Factors associated with improvement of Physicians' knowledge.**

Variables	Knowledge difference (post-baseline)	
	Function of HA knowledge score	HA knowledge score of International Guideline
<b>*Age categories</b>		
▪ <30 years	4.1 ± 1.9	5.8 ± 4.0
▪ 30 to <40 years	3.9 ± 1.9	4.7 ± 2.9
▪ ≥40 years	2.9 ± 1.8	3.3 ± 2.5
<b>P-value*</b>	0.198	0.045
<b>**Gender</b>		
▪ Male	4.0 ± 1.9	5.0 ± 3.4
▪ Female	3.8 ± 1.9	5.3 ± 3.5
<b>P-value*</b>	0.539	0.618
<b>**Place of work</b>		
▪ Academic	3.8 ± 1.9	4.5 ± 3.6
▪ Nonacademic	4.5 ± 2.1	6.7 ± 3.7
<b>P-value*</b>	0.007	0.001
<b>**Year of experiences</b>		
▪ < 5 years	4.2 ± 2.1	5.4 ± 3.6
▪ ≥ 5 years	3.6 ± 1.7	4.4 ± 2.9
<b>P-value*</b>	0.044	0.037
<b>*Job categories</b>		
▪ Residents	3.9 ± 1.9	5.0 ± 3.8
▪ Specialists	3.6 ± 1.8	4.5 ± 3.3
▪ Assistant Lecturers	4.2 ± 2.0	5.2 ± 3.3
▪ Lectures and Professors	3.5 ± 2.5	5.8 ± 4.6
<b>P-value*</b>	0.556	0.803
<b>*Specialty</b>		
▪ Tropical Medicine	3.9 ± 1.9	5.1 ± 3.4
▪ Internal Medicine	4.34 ± 2.2	5.5 ± 3.5
▪ Surgery	4.2 ± 1.8	4.1 ± 3.5
<b>P-value*</b>	0.491	0.364

\*Kruskal Wallis test. \*\*Mann Whitney U test.

**Correlation between age and years of experiences and Physicians' Knowledge difference (post-baseline):**

There was significant negative mild correlation between age and Physicians' knowledge difference score regarding function of HA ( $r=-0.21$ , P-value 0.030) (**Figure 3A**). Also, there was significant negative mild correlation between years of experiences and Physicians' knowledge difference score regarding function of HA ( $r=-0.20$ , P-value 0.033) (**Figure 3B**).



**Figure 3: A)** Scatter diagram for correlation between age and Physicians' knowledge difference (post-baseline) about function of HA. **B)** Scatter diagram for correlation between years of experiences and Physicians' knowledge difference (post-baseline) about function of HA.

## DISCUSSION

To the best of our knowledge, this is the first study in our region that aims to gauge physicians' familiarity with the clinical situations for which HA usage is supported by research. We also sought to ascertain the effect of disseminating the developed evidence-based indications on clinicians' knowledge. These objectives were accomplished by designing the evidence-based indications for the use of HA in accordance with International Guidelines.

Our study included 168 participants across Assiut hospitals. The Physicians were categorized according to their age, gender, specialty, years of experience, job categories and place of work. They were personally interviewed and their knowledge about HA use in patients with liver cirrhosis was evaluated through a questionnaire at the start of the study then after 1 month of distributing the designed evidence-based indications for HA use (supported by the International Guidelines) on them.

According to this study, no significant difference in knowledge score regard function of HA according to age, gender, job categories and specialty. There was significant higher mean difference in knowledge score regard function of HA in academic doctors ( $3.9 \pm 1.7$ ) compared to nonacademic doctors ( $2.7 \pm 1.9$ ). Moreover, there was significant higher mean difference in knowledge score regard function of HA in doctors with experiences  $\geq 5$  years ( $4.0 \pm 1.6$ ) compared to doctors with experiences  $< 5$  years ( $3.3 \pm 1.9$ ).

Moreover, there was significant higher mean knowledge score in doctors with experiences  $\geq 5$  years ( $12.2 \pm 3.6$ ) compared to doctors with experiences  $< 5$  years ( $10.8 \pm 4.2$ ). However, there was no statistically significant difference in Physicians' knowledge about International Guideline regard gender, job categories and specialty.

In contrary, in European survey done by **Caraceni et al.** <sup>(7)</sup>, reported that 78% (consistent with our study) and 86% of participants concur that modification of inflammatory/immune responses, binding, and transport are pertinent for cirrhotic patients, respectively. For antioxidant activity, the proportion drops to 52%, and for endothelial function and coagulation regulation, it drops to 39%.

Interestingly, there was statistically significant higher percent of correct answers of all 8 questions in our study about functions of HA in the post test compared to the baseline (P-value  $< 0.05$ ). Moreover, there was statistically significant higher mean knowledge score at the post test compared to baseline ( $7.6 \pm 0.9$  compared to  $3.6 \pm 1.8$ , respectively). Good knowledge of physicians statistically increased from 52.4% at the baseline to 100% at the post test.

Among evidence based indications, it was found that, only 63.1% of participants concur that HA is recommended for PPCD prophylaxis, 72.6% of them

has the knowledge that incidence of PPCD increase if more than 5 L ascites removed but none of them knew correctly the dose of albumin. About 64.3% of participants prescribe albumin to prevent renal failure after SBP but none of them knew the correct dose.

Unlike other studies which showed more adherence of the Physicians to the International Guidelines for albumin use in patients with liver cirrhosis, where 92%, 87.8%, 95% of their participants respectively, agree with the International Guidelines in using HA for prevention of PPCD after large volume paracentesis (LVP) <sup>(8,9,10)</sup>.

On the other hand, **Garioud et al.** <sup>(10)</sup> found that, the participants do not follow the International Guidelines considering dose of albumin for prevention of PPCD after LVP (if more than 5 L ascites removed) and about 84.6% of their participants use fixed dose of albumin, 67.4% use 20 gm per 3 L ascites removed and 16.8 % use 20 gm per 2 L ascites removed, 94% use albumin for prevention of renal failure after SBP.

Moreover, the study done by **Caraceni et al.** <sup>(7)</sup> showed that almost all participants (97%) prescribe albumin at dose 6 g/L, 97% use albumin in renal failure after SBP and about 60-80% of them use recommended dose, 93% prescribe albumin in diagnosis and treatment of HRS and about 60-80% of them use the recommended dose.

It's interesting to note that more than half of the physicians we spoke with in our survey believe HA treatment is beneficial for diseases for which there isn't strong scientific proof such as sever hyponatremia (73.8%), septic shock in LC (75%), less than one third assume that HA is used in non SBP bacterial infections and hepatic encephalopathy. Also we noted that about 76.8% of the Physicians followed EASL Guidelines, 16.7% followed AASLD Guidelines and about 6.5% prescribe albumin according to their personal experience.

In this study, according to correlation between age and Physicians' knowledge score regarding function of HA, and Physicians knowledge score regarding International Guideline of HA, there was significant positive mild correlation [ $r=0.21$ , P-value 0.014 and  $r=0.20$ , P-value 0.014, respectively].

In contrast, there was significant negative mild correlation between age and Physicians' knowledge difference score regarding function of HA ( $r=-0.21$ , P-value 0.030). Also, there was significant negative mild correlation between years of experiences and Physicians' knowledge difference score regarding function of HA ( $r=-0.20$ , P-value 0.033).

## CONCLUSION

In our study, the scientific character of the questionnaire, the personal request to participate, and the specific interest in studies related to albumin usage in patients with cirrhosis may all have contributed to the

physicians' high response rate in the post-test. The researcher also provided many reminders.

**Competing interest:** Not applicable.

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