Evaluation of Plasma Albumin as a Potential Prognostic Biomarker in Patients with Traumatic SIRS

CRISTIAN MIRCEA NICOLESCU[1,2]*, OVIDIU BEDREAG[3,4], HENRY OSAKWE[1], ALEXANDRU POP[2], LAURA CORINA NICOLESCU[1,2]

[1] County Emergency Hospital of Arad, 1 Victoriei Av., 310158, Arad, Romania

[2] University Vasile Goldis of Arad, 94 Revolutiei Blvd., 310130, Arad, Romania

[3] County Emergency Hospital of Timisoara,156 Liviu Rebreanu Blvd., 300723, Timisoara, Romania

[4] University Victor Babes of Timisoara, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

Hypoalbuminemia occurs in about 90% of critically ill patients admitted in the intensive care unit (ICU), this is caused by an increase in microvascular permeability (capillary and venous wall) as a result of systemic inflammatory reaction (SIRS) and decreased synthesis of hepatic albumin in acute liver response. The aim of this study is to determine the incidence of hypoalbuminaemia in patients with non-septic SIRS (induced by surgical trauma or multiple trauma) and to assess the plasma albumin level as a potential biomarker of severity in the prognosis of these patients. The albumin plasma level of ICU admitted patients were determined every 24h and 48h, patients were continuously monitored for complications. Hypoalbuminemia is probably the cause of prolonged ileus, gastroparesis, sepsis, fistula and acute renal failure). The statistical processing of data consisted in compiling descriptive statistics on values of albumin, highlighting the albumin-age relationship by the regression method. Calculation of mean plasma albumin values for groups of patients without clinical complications, those with clinical complications or with complications and who died and performing the Scheffe(multiple comparison test), correlation tests between albumin value at 48h and APACHE II score (prediction score Of the critical patient) as well as a descriptive analysis taking into account the 3 g / dl albumin value (factor that differentiates mild to moderate hypoalbuminemia in clinical practice) and performing the non-parametric Chi-Square test for validation of statistical analysis.

Keywords; Hypoalbuminemia, Apache II score, sepsis, prolonged ileus, prolonged gastroparesis, sepsis

Albumin is the major plasmatic protein of the body responsible for approximately 60% of total plasmatic protein concentration, synthesis occurs in the liver up to 20 g / day. The pharmacokinetic data of this molecule shows that daily passes through the capillary wall into the interstitial space an amount of approximately 120 g, which doubles under the traumatic-induced inflammatory response conditions, of which about a third returns to the vascular space through lymphatic drainage , the rest accumulating in the digestive mucosa, respectively the skin.

Albumin consists of 585 amino acids, with a molecular weight of 66 kda, microscopic studies describe the presence of 34 cysteine residues linked by bisulfide bridges, which confer stability to this macromolecule, as well as a free -SH group that determines antioxidant activity, some authors considering Albumin as the major extracellular antioxidant of the body.

The main physiological role of albumin is that of the colloid-osmotic pressure determinant, about 80% of the PCO value is due to this albumin molecule; this effect is due to both the molecular weight and the electrical attraction of Na ion (Gibbs-Donnan effect) .

Secondary physiological functions that are still the subject of numerous research are represented by antioxidant function mainly due to free SH, about 80% of plasma thiol interacting with oxygen reagents such as peroxide H2O2 and peroxinite (ONOO) annihilation -l and forming the albumin-sulfenic acid derivative, stabilizing role at the vascular endothelium level by reducing the oxidative stress at this level. Albumin also has the role of a modulator of vascular tonus by binding and inhibiting nitric oxide (NO) produced by vascular endothelium, as well as a possible anti-inflammatory role due primarily to the decrease in the interaction of vascular endothelium with activated neutrophils.

* *email: cristian_ans@yahoo.com*

Experimental part

Materials

After receiving the consent of the ethics committee to conduct hospital clinical trials, 108 patients who underwent major surgery or suffered polytraumatism (these patients developing a SIRS-induced trauma) were initially enrolled in the study. Initial exclusion criteria were associated with pathology that may lead to decreased albuminemia - major hepatic diseases known, kidney disease that associates nephrotic or nephritic syndrome, severe protein-malnourishment (BMI <18) or diarrhea with protein loss. At 48 h after admission to the intensive care unit, 2 patients were excluded from the study because they had liver dysfunction evidenced by elevated transaminases or bilirubin, and a patient with severe hypoalbuminemia of 1.7 g / dl at TI intake and could not be taken into account statistically.

Methods

Determination of albumin is done by dry chemistry methods based on the binding of albumin to the substance pigment under ph acid conditions, which produces the coloration of the solution from yellow to purple, this color change being quantified by spectrophotometry. The underlying reaction for Albuminemia determination is presented below.

Albumin + Bromocresol purple(BCP)----Ph acid-------> Complex BCP-Albumin

In terms of total protein determination, it was based on their bivalent copper reaction, and further measurement by the spectophotometric method of the complex formed, according to the reaction below.

Total Proteine + Cu + 2—OH_———> Complex Prot.-Cu

Both reactions, as well as the determination of transaminases and bilirubin, were done with the Samsung-Labgeo apparatus.

In terms of clinical complications, prolonged ileus due to the absence of intestinal transit at 96 h after surgery in conjunction with abdominal distension and obedience absence of intestinal noise, prolonged gastroparesis was clinically evidenced by the lack of tolerance to food that persists and after 48 h operation, the amount significantly increased by naso-gatric (500 mL aspirated naso-gastric), fistula digestion was evidenced by intolerance to food, the persistence of the drainage liquid containing intestinal and gastric and in some cases the appearance of the sensitivity of the abdominal wall, septic complications was evidenced by laboratory data (leukocytosis, elevated and X-ray evidence of lung inflammation in case of respiratory infection) and clinical data - fever, tachypnea, tachycardia, and in the renal, this complication was seen in the samples increased nitrogen retention.

The APACHE II score was calculated on the basis of internationally standardized criteria, and the statistical tests were performed using Excel.

Results and discussions

The incidence of hypoalbuminaemia as well as the calculation of plasma protein values in the group of patients studied is evidenced by the following descriptive statistics. We can see the averages and deviations of each variable. The calculated media reveals a possible difference between the values over time of albumin or total protein, and these will be validated statistically.

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	105	18	91	65.48	15.693
ALBUMIN	105	3.0	6.0	4.209	.6172
ALBUMIN	105	1.8	4.8	3.370	.5148
ALBUMIN	105	1.6	4.3	3.023	.4925
TOT. PROT.	105	5.0	8.2	6.560	.6646
TOT. PROT.	105	3.3	7.4	5.416	.6424
TOT. PROT.	105	3.0	6.8	5.081	.6008
TGO	105	6	59	24.58	12.907
TGP	105	7	81	30.53	15.882
BIL-D	105	.10	.96	.1776	.15924
BIL-T	105	.10	1.40	.4985	.30043
NEUTROFILE	105	45	92	76.01	10.494

The ANOVA - post hoc test was used to validate the differences between the mean values of albumin.

Test of Homogeneity of Variances

Albumin over the period

Levene Statistic	df1	df2	Sig.
4.642	2	312	.010

ANOVA

Albumin over the period

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	78.021	2	39.010	131.715	.000
Within Groups	92.406	312	.296		
Total	170.427	314			

Differences between baseline albumin at 24 and 48 h are statistically significant, since F (2,312) = 131,715 at a p = <. 001, so we reject the null hypothesis.

In order to see if the differences between the media are also found between the initial and 24, and between 24 and 48 h, etc. the post-hoc Scheffe test was calculated, and the results show that there is a statistically significant difference between all the repeated measurements.

Multiple Comparisons

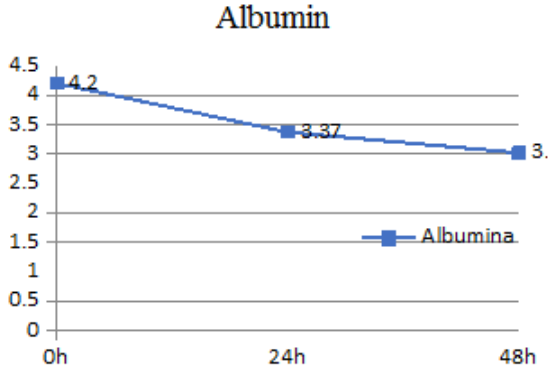
Dependent Variable: Albumina over the entire period

Test Scheffe

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Initial	24 h	.83810*	.07511	.000	.6534	1.0228
	48 h	1.18571*	.07511	.000	1.0010	1.3704
24 h	Initial	-.83810*	.07511	.000	-1.0228	-.6534
	48 H	.34762*	.07511	.000	.1629	.5324
48 h	Initial	-1.18571*	.07511	.000	-1.3704	-1.0010
	24 h	-.34762*	.07511	.000	-.5324	-.1629

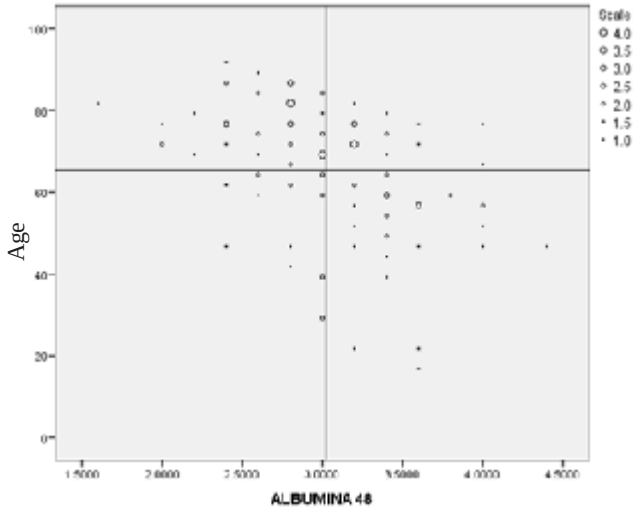
* The mean difference is significant at the 0.05 level.

On the basis of these inferential statistical tests, we notice the decreasing trend in plasma albumin levels in the first 24 h after admission to TI ,which is greater than the following 24 h, according to the schedule.



Initial average value at 0h-4.2g / dL
Average value at 24h-3.37g / dL
Average value at 48h-3.02 g / dL
Albumin normal values 3.5-5.5 g / dL

The increase in plasma albumin variation according to the age of the patients was performed using the linear regression method (albumin - dependent value, and age is the independent value), and is presented in figure.



Calculation of the determinant R2, reveals to what extent the change in albumin value at 48 h is determined by age and the result is 17.9%, being statistically validated.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics			
					R Square Change	F Change	df1	df2
1	.433[a]	.187	.179	.4461085	.187	23.751	1	

a. Predictors: (Constant), AGE

b. Dependent Variable: ALBUMINA

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4.727	1	4.727	23.751	.000[b]
	Residual	20.498	103	.199		
	Total	25.225	104			

a. Dependent Variable: ALBUMINA

b. Predictors: (Constant), AGE

Performing the ANOVA test ,the regression is statistically validated, resulting in an F (1.103) = 23.7 at a p <0.001

In order to verify the statistical hypothesis that low plasma albumin values can be used as a clinically severe prognostic biomarker, the batch was divided into three groups, clinically uncomplicated patients, patients with clinical complications, respectively patients with complications And then death. Calculation of mean albumin values at 48h corresponding to the three groups revealed the following values: 3.33 g / dL - corresponding to the group of 45 patients, 2.88 g / dL - corresponding to the group of 43 patients, 2.54 g / dL –coresponding to the group of 17 patients, These values being statistically validated after the Scheffe test - multiple comparison test, to mention that only the difference between the mean values of albumin at 48h from intake, have statistical significance according to this test.

Post hoc test

Multiple Comparisons

Dependent Variable: ALBUMIN

Test Scheffe

(I) VAR00002	(J) VAR00002	MeanDifference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					LowerBound	UpperBound
1.00	2.00	.4540568*	.0844238	.000	.244337	.663777
	3.00	.7966013*	.1127013	.000	.516636	1.076567
2.00	1.00	-.4540568*	.0844238	.000	-.663777	-.244337
	3.00	.3425445*	.1134177	.013	.060800	.624289
3.00	1.00	-.7966013*	.1127013	.000	-1.076567	-.516636
	2.00	-.3425445*	.1134177	.013	-.624289	-.060800

* The mean difference is significant at the 0.05 level.

Taking into account the plasma albumin value at 48 h as possible predictive factor, APACHE II score correlation tests were performed at the same time as the correlation between age and APACHE II score.

Coefficients[a]

Model		Unstandardized Coefficients		StandardizedCoefficients	t	Sig.	Correlations		
		B	Std. Error	Beta			Zero-order	Partial	Part
1	(Constant)	13.310	3.607		3.690	.000			
	AGE	.127	.026	.398	4.874	.000	.568	.435	.359
	ALBUMIN	-3.964	.829	-.391	-4.782	.000	-.563	-.428	-.352

a. Dependent Variable: SCOR APACHE II

The Pearson partial correlation coefficients are approximately equal to 0.435 in the case of age at a p <0.001 and -0.428 respectively for albumin at 48 h at a p <0.001.

The Beta score(adjusted correlation coefficient) shows how much the correlation between albumin and the APACHEII score is, also between the age and score of APACHEII, when the two factors are calculated together

(albumin, age) in predicting the APACHEII score more precisely:

a.Albumin correlates significantly, from statics point of view $\beta = -391$ to a $p < 0.001$, negatively, suggesting that an increased level of albumin will predict a low APACHE II score.

b.Age correlates significantly, from statistic point of view $\beta = .398$ to a $p < 0.001$, positively, suggesting that with age the APACHE II score may increase.

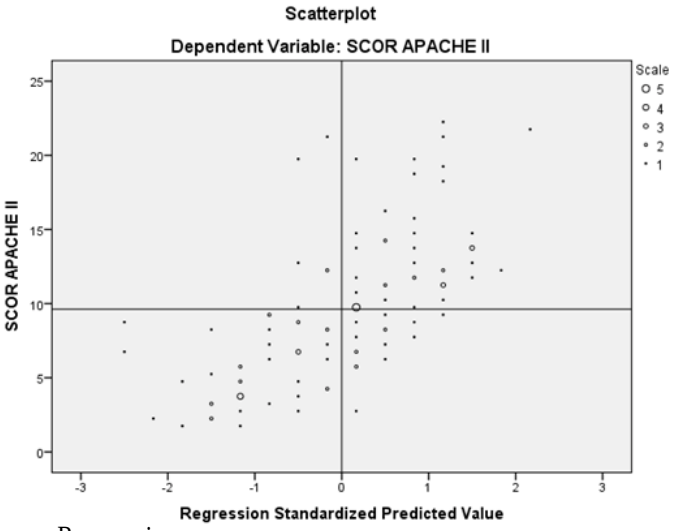
The partial correlation indicates that the consideration of each separate factor (albumin and age) determines the correlation with the APACHE II score. It can be seen that the two variables separately correlate to a higher level than in the case of BETA values, these results are also due to the possibility that the two indicators have a common influence (share variance) in determining the variation of the APACHE II score, thus calculating the covariance and the correlation of the two factors is presented below.

Coefficient Correlations[a]

Model		VARSTA	ALBUMINA
Correlations	VARSTA	1.000	.433
	ALBUMINA	.433	1.000
Covariances	VARSTA	.001	.009
	ALBUMINA	.009	.687

a. Dependent Variable: SCOR APACHE II

The common influence that albumin and the age exerts at 48 h on APACHE II, was revealed by the regression method, it points out how the score (dependent variable) depends on albumin value and age, calculated together as a standardized predictive value (the independent variable)



Regression

Descriptive Statistics

	Mean	Std. Deviation	N
SCOR APACHE II	9.63	4.995	105
AGE	65.48	15.693	105
ALBUMIN	3.022857	.4924931	105

It has been calculated to what extent albumin and age are predictors of the APACHE II score by determining the R2 factor.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	ChangeStatistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.668[a]	.446	.435	3.753	.446	41.102	2	102	.000

a. Predictors: (Constant), ALBUMIN, AGE

b. Dependent Variable: SCOR APACHE II

The determinant R2 reveals how albumin and age predict 43.5% of changes / variation in APACHEII score .Subsequently, the post-hoc ANOVA test was performed to validate the statistical significance of the regression.

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1157.846	2	578.923	41.102	.000[b]
	Residual	1436.669	102	14.085		
	Total	2594.514	104			

a. Dependent Variable: SCOR APACHE II

b. Predictors: (Constant), ALBUMIN, AGE

F (2, 102) = 41.102 at a p <0.001 shows the general prediction model of APACHE II, age and albumin is valid, so we reject the null hypothesis.

Finally, a descriptive analysis was carried out which took into account the 3 g / dL albumin value which differentiates mild to moderate hypoalbuminemia in clinical practice, and is used as trigger for administration of 20% albumin solution. Calculating the frequency of cases without complications, those with complications and those with complications and related deaths, the results were checked by performing the non- Parametric Chi-Square test.

Statistics

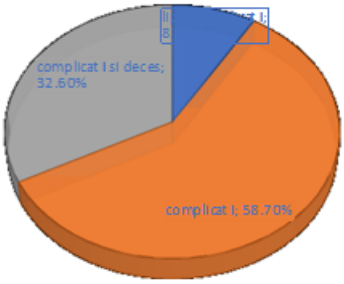
VAR00002

N	Valid	46
	Missing	0

VAR00002

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Without comp	41	69.5	69.5	69.5
	comp	16	27.1	27.1	96.6
	C+D	2	3.4	3.4	100.0
	Total	59	100.0	100.0	

Albumin < 3,0 g/dl



Frequencies

Statistics

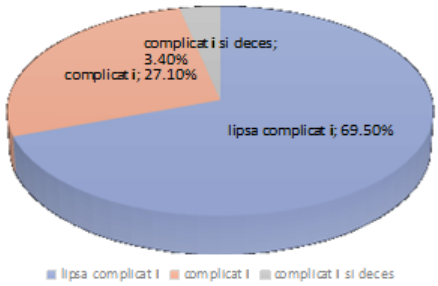
VAR00002

N	Valid	59
	Missing	0

VAR00002

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Without comp	41	69.5	69.5	69.5
	comp	16	27.1	27.1	96.6
	C+D	2	3.4	3.4	100.0
	Total	59	100.0	100.0	

Albumin ≥ 3,0 g/dl



Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Without complications	45	1.9111	.28780	1.00	2.00

VAR00003

	Observed N	Expected N	Residual
1.00	4	22.5	-18.5
2.00	41	22.5	18.5
Total	45		

Test Statistics

	VAR00003
Chi-Square	30.422[a]
df	1
Asymp. Sig.	.000

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 22.5.The test validates de difference between frequencies of patients without comp.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
complications	43	1.3721	.48908	1.00	2.00

Chi-Square Test

Frequencies

VAR00003

	Observed N	Expected N	Residual
1.00	27	21.5	5.5
2.00	16	21.5	-5.5
Total	43		

Test Statistics

	VAR00003
Chi-Square	2.814[a]
df	1
Asymp. Sig.	.093

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 21.5.The test does not validate the difference between frequencies.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Comp + death	17	1.1176	.33211	1.00	2.00

Chi-Square Test

Frequencies

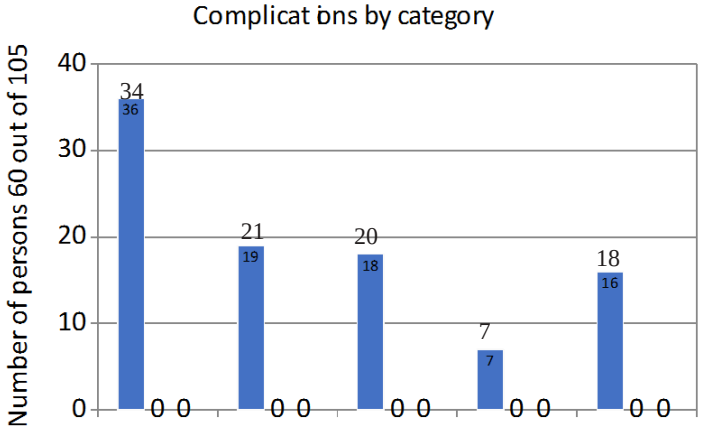
VAR00003

	Observed N	Expected N	Residual
1.00	15	8.5	6.5
2.00	2	8.5	-6.5
Total	17		

	VAR00003
Chi-Square	9.941[a]
df	1
Asymp. Sig.	.002

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 8.5the test validates the difference between frequencies regarding c+d.

Performing the Chi-Square test, we can point out a statistically significant difference between the frequencies



Legend:

1-prolonged Ileus = 34%
2-Infectious complications = 21%
3-Prolonged Gastroparase = 20%
4-Fistula = 7%
5-Acute renal failure = 18%

of lack of complications, namely complications and deaths-related frequencies.

Results and discussions

Previously, we mention that only the statistical significance of this variable (the plasma level of albumin) has been taken into account, and in order to evaluate the clinical significance, which may differ from the statistical one, the place of hypoalbuminemia should be established within the cause- effect relationship.

In other words, the low plasma levels of albumin may be used only as a severe prognostic biomarker, similar to the use of procalcitonin value in the case of sepsis, or may be a contributory factor in the production of complications or even a factor that worsens after the occurrence of these clinical complications .

To determine exactly what is the relationship between the hypoalbuminemia found in these patients and the complications that occur as a result of lowering the plasma albumin and possibly due to this decrease, each complication should be considered, both in terms of etiology, and the effect produced, while taking into account the possible functions of albumin, which is the subject of future studies.

Conclusions

On the basis of statistical tests, we can assert that the statistical hypothesis that the plasma albumin of patients with SIRS induced trauma can be considered as a possible prognostic factor and is verified.

According to the descriptive statistics, all patients under study had a decrease in albumin, and at 48h after admission to TI, the vast majority had plasma levels below 3g / dl, the Scheffe test performed between mean values at 48h, reveals the the lower the albumin value, the higher the rate of complications and the deaths of the patients studied. Correlation tests between this value and the APACHE II score demonstrate a degree of correlation similar to the age of the patients (important criterion in APACHE II score calculation), and in terms of plasma albumin 3g / dl, the non-parametric Chi- Square, validates this value for use in clinical practice as a trigger to administer the 20% albumin solution in order to correct the low plasma levels of albumin.

References

1.*** Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ. 1998, 317: 235-240. 10.1136/bmj.317.7153.235.

2.VINCENT JL: Relevance of albumin in modern critical care medicine. Best Pract Res Clin Anaesthesiol. 2009, 23: 183-191. 10.1016/j.bpa.2008.11.004.

3.VINCENT JL, DUBOIS MJ, NAVICKIS RJ, WILKES MM: Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg. 2003, 237: 319-334.

4.LAXENAIRE MC, CHARPENTIER C, FELDMAN L: Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study. Ann Fr Anesth Reanim. 1994, 13: 301-310. 10.1016/S0750-7658(94)80038-3.

5.*** American Thoracic Society: Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement. Am J Respir Crit Care Med. 2004, 170: 1247-1259.

6.PETERS T: All About Albumin. 1995, San Diego: Academic Press

7.NICHOLSON JP, WOLMARANS MR, PARK GR: The role of albumin in critical illness. Br J Anaesth. 2000, 85: 599-610. 10.1093/bja/85.4.599.

8.FLECK A, RAINES G, HAWKER F, TROTTER J, WALLACE PI, LEDINGHAM IM, CALMAN KC: Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet. 1985, 1: 781-784.

9.JACOB M, BRUEGGER D, REHM M, STOECKELHUBER M, WELSCH U, CONZEN P, BECKER BF: The endothelial glycocalyx affords compatibility of Starling's principle and high cardiac interstitial albumin levels. Cardiovasc Res. 2007, 73: 575-586. 10.1016/j.cardiores.2006.11.021.

10.JACOB M, BRUEGGER D, REHM M, WELSCH U, CONZEN P, BECKER BF: Contrasting effects of colloid and crystalloid resuscitation fluids on cardiac vascular permeability. Anesthesiology. 2006, 104: 1223-1231. 10.1097/00000542-200606000-00018.

11.JACOB M, CHAPPELL D: Reappraising Starling: the physiology of the microcirculation. Curr Opin Crit Care. 2013, 19: 282-289. 10.1097/MCC.0b013e3283632d5e.

12.ROCHE M, RONDEAU P, SINGH NR, TARNUS E, BOURDON E: The antioxidant properties of serum albumin. FEBS Lett. 2008, 582: 1783-1787. 10.1016/j.febslet.2008.04.057.

13.ULLDEMOLINS M, ROBERTS JA, RELLO J, PATERSON DL, LIPMAN J: The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011, 50: 99-110. 10.2165/11539220-000000000-00000.

14.DUBOIS MJ, ORELLANA-JIMENEZ C, MELOT C, DE BACKER D, BERRE J, LEEMAN M, BRIMIOULLE S, APPOLONI O, CRETEUR J, VINCENT JL: Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med. 2006, 34: 2536-2540. 10.1097/01.CCM.0000239119.57544.0C.

15.CAIRONI P, GATTINONI L: The clinical use of albumin: the point of view of a specialist in intensive care. Blood Transfus. 2009, 7: 259-267.

16. MOSHAGE HJ, JANSSEN JA, FRANSSEN JH, HAFKENSCHEID JC, YAP SH: Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. J Clin Invest. 1987, 79: 1635-1641. 10.1172/JCI113000.

17.VINCENT JL, FINK MP, MARINI JJ, PINSKY MR, SIBBALD WJ, SINGER M, SUTER PM, COOK D, PEPE PE, EVANS T: Intensive care and emergency medicine: progress over the past 25 years. Chest. 2006, 129: 1061-1067. 10.1378/chest.129.4.1061.

Manuscript recieved: 15.03.2017