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ROLE OF ALBUMIN IN INFLAMMATORY RESPONSE IN COVID-19 PATIENTS

Authors

Samorindo Peci[1*], Lorenzo Grillo della Berta[1], Giacomo Caruso[1], Rosjana Pica[2] and Federica Peci[2]

[1]Unità COVID, Ospedale Eugenio Morelli, Sondalo (SO) Italy

[2]Istituto San Celestino, Milano, Italy

***Corresponding author**

Samorindo Peci, Ospedale E. Morelli, Sondalo (SO) Italy; E-mail: info@samorindopeci.it

Email:

Author 1: info@samorindopeci.it

Author 2: lorenzo.grillodellaberta@asst-val.it

1. Abstract

Albumin is the most present protein in plasma. Low serum albumin is common in many inflammatory diseases and it is a significant clinical sign. This study analyzes 50 patients entering the ER of the Morelli Hospital in Sondalo, hospitalized close to the onset of the first COVID-19 symptoms, to evaluate albumin levels in the inflammatory response. The results obtained are noteworthy and open the way for new considerations.

2. Keywords

COVID-19, SARS-CoV-2, Albumin, S-Alb, HSA, C-Reactive Protein, Ferritin, Arterial Blood Gases, Transfusion, Inflammatory Response, Integration.

3. Abbreviations

kDa: Kilo-Dalton; GH: Growth Hormone; IL-6: interleukyne-6; TNF-α: Tumor Necrosis Factor α; Ca^{2+}: Calcium ions; ROS: Reactive Oxygen Species; NO: Nitric Oxide; GMP: Guanosine 5'-monophosphate; EDRF: Endothelium-Derived Relaxing Factor; PAF: Platelet Activation Factor; iNOS: inducible Nitric Oxide Synthase; RNA: Ribonucleic Acid; mRNA: messenger Ribonucleic Acid; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; COVID-19: Coronavirus Disease 2019; HSA: Human Serum Albumin; CRP: C-Reactive Protein; aPTT: Activated Partial Thromboplastin Time; ER: hospital Emergency Room.

4. Introduction

Albumin is the most present protein in the blood, isolated for the first time in egg white. It is a single chain protein with a molecular weight of 66 kDa composed of 585 amino acids which represents more than 50% of the whey proteins and represents an important component of the interstitial fluid [1].

All proteins in the albumin family are water-soluble, moderately soluble in concentrated salt solutions and undergo thermal denaturing. Albumin is commonly found in blood plasma and differs from other blood proteins as it is not glycosylated. Substances containing albumin, such as egg white, are called albuminoids.

Albumin is synthesized by the liver and its production is mainly regulated by the interstitial fluid osmolarity and oncotic pressure in the hepatic extravascular space, but it is also influenced by hormonal factors, in fact insulin, cortisol and GH increase its synthesis, and acute phase cytokines, such as IL-6 and TNF-α, which decrease transcription levels. Once synthesized, it has about 20 days of half-life.

Albumin concentration in blood (albuminemia) is between 3,5 e 5,0 g/dL and is measured by proteins electrophoresis. For children under the age of three, the normal range is wider, 2,9-5,5 g/dL.

Its functions are: (i) maintenance of interstitial fluid oncotic pressure, (ii) thyroid hormones transport, (iii) transport of other hormones, in particular the fat-soluble ones, (iv) free fatty acids transport, (v) non-conjugated bilirubin transport, (vi) several drugs transport (e.g. barbiturates), (vii) competitive bond with calcium ions (Ca^{2+}), (viii) pH buffering.

Albumin isoelectric point is 4,9.

The main and best-studied function of albumin is the maintenance of normal capillary permeability to macromolecules and solutes due to the bond with the interstitial matrix and the sub-endothelial space, which is essential for the stabilization of intravascular volumes. Albumin is important in maintaining the balance of oncotic pressure, that is the osmotic pressure necessary for the correct regulation of water exchanges between the vascular compartment and the interstitial fluid. Due to its high concentration and molecular weight, albumin is responsible for about 70% of the plasma oncotic pressure [2]. The albumin molecule is negatively charged, like the membrane of the renal glomerulus; the electrostatic repulsion therefore normally prevents the passage of albumin into the urine. In nephropathic syndromes this property is lost and consequently the appearance of albumin in the patient's urine is noted. For this reason, albumin is considered an important marker of renal dysfunctions, which appear even after years.

In addition to being the most present protein in blood, albumin is the main vehicle for other proteins transported through it; if it is excreted in the urine (where in normal conditions it is practically absent), the decrease in plasmatic albumin makes it less dissolved and less colloidal, with an oncotic pressure that falls below the limit of 20 mmHg. Moreover, albumin transfers fluids and electrolytes from the vessels to the tissues with generalized edema (usually to the eyelids and extremities in the initial phase, and conspicuous in the abdomen in the higher pressure fall).

Albumin has a strong anti-inflammatory activity thanks to its ability to antagonize the effects of oxidative stress in the body. The importance of this function is confirmed by the fact that when there is a reduction in plasma albumin levels, the cells produce high amounts of oxygen radicals, leading to an uncontrolled activation of the cells until their death. Under conditions of oxidative stress, albumin may undergo irreversible oxidation, which alters antioxidant properties and causes damages to cells and tissues. Interestingly, in this regard, albumin oxidation triggers the "extracellular traps" of neutrophils, through the accumulation of reactive oxygen species (ROS) within the neutrophils, which eventually accumulate in the lungs [3]. In clinical settings oxidative stress and reduced albumin levels are associated with an increased risk of mortality.

Its antithrombotic and anticoagulant action is important: the antithrombotic action of albumin seems to be attributable to the combination of the sulfhydryl groups of albumin and nitric oxide (NO), with the formation of stable S-nitroso-thiol groups, which have a longer half-life compared to NO. These adducts, which prevent the rapid activation of NO, have vasodilatory and anti-aggregating properties, with a mechanism depending on cyclic GMP. Studies conducted in vitro [4] suggest that these adducts are able to exert functions comparable to those exercised by the Endothelium Derived Relaxing Factor (EDRF): (i) significant coronary vasodilations; (ii) less pronounced but significant increase in coronary flow; (iii) a systemic venous and arterial vasodilation; (iv) dose-dependent inhibition of platelets. In addition, the long half-life of the nitroso-thiol groups is responsible for a longer duration of action than other NO-derived vasodilators, such as sodium nitroprusside, nitroglycerin and S-nitrous-cysteine. Albumin interacts with fibrinogen resulting in reduced fibrinogen activity [5].

Several studies suggest that albumin affects blood clotting. Albumin has been shown to carry out an anticoagulant action, due to its ability to bind antithrombin, associated with a greater neutralization of coagulation factor Xa and its inhibitory effect on platelet aggregation [6], which could be partly attributed to its ability to bind arachidonic acid. As a result, cyclooxygenases derived from platelets are deprived of their substrate and cannot form the platelet agonist, thromboxane A2. Moreover, it has been shown that albumin in addition to directly inactivating thromboxane A2, may bind platelet activating factor (PAF) with high affinity [7].

Another mechanism by which albumin may perform its antiplatelet action may be its ability to induce inducible Nitric Oxide Synthase in macrophages (iNOS) in a concentration-dependent way. This induction would lead to a greater formation of the potent platelet inhibitor: nitric oxide (NO). The binding of prostacyclin (PGI2), an inhibitor of platelet aggregation, to albumin prevents its degradation [8]. A greater binding of PGI2 to higher concentrations of albumin could further trigger anticoagulant effects.

A low level of seric albumin is a serious clinical sign. Hypoalbuminemia is common in many inflammatory diseases, since an increased capillary permeability may cause albumin leak into the interstitial space. In the past, hypoalbuminemia was considered a negative prognostic marker, not only in patients with chronic liver disease, but also in patients with SARS and MERS infections [9, 10].

Two main mechanisms operate in reducing serum albumin concentration in patients with severe COVID-19 infection: (i) reduction of albumin synthesis due to reduced food intake - malnutrition; (ii) inhibition of specific mRNA synthesis in hepatocellular nuclei induced by direct interaction of the cell with acute phase cytokines.

Albumin synthesis in hepatocytes is down-regulated by the direct interaction of the main acute phase cytokines released into the circulation during the cytokine storm, induced by the SARS-CoV2 effects on lungs. This mechanism contributes to severe hypoalbuminemia which, combined with massive fluid drops due to fever, is responsible for severe hypovolemia and shock, commonly observed in patients with COVID-19 in intensive care environments [11].

Starting from the assumption that, in any clinical condition, when albumin in blood is below a determined level - which corresponds to <35g/L - the risk of arterial and venous thrombosis increases, the researchers verified these data in COVID-19 patients.

In their investigation, *Huang et al*. found that there is an inverse relationship between albumin level and the risk of death in COVID-19 patients. The authors found that lower albumin levels at admission can predict the outcome of COVID-19 regardless of other known indicators such as lymphocyte counts or comorbidities. The retrospective study revealed that serum albumin levels below 35 g / L at admission independently increased the risk of death from COVID-19 by at least 6-fold [12].

An Italian study showed that patients with COVID-19, especially those with severe or thrombotic complications, had albumin values lower than 35 g/L [13].

The relationship between hypoalbuminemia and reduced survival can have several explanations. First, by acting as an anti-inflammatory and antioxidant protein, albumin can protect against the cytokine storm and subsequent organ failure; in this context, the inverse relationship between serum albumin and troponin levels is interesting, suggesting that albumin may promote some protection against myocardial damage. Second, albumin has anticoagulant properties [14] and inhibits oxidative stress-related coagulation and platelet activation [15].

Therefore, the negative impact of hypoalbuminemia on coagulation activation may be another factor responsible for limited survival; this is suggested at least in part by the discovery of an inverse association between albumin and D-dimer levels, the last one as a recognized marker of thrombotic risk and increased mortality in COVID-19 [13].

However, what was observed by our research group at the Morelli Hospital in Sondalo (SO) was not about the serum albumin levels as a predictor of bad outcome in COVID-19 patients; whereas the incoming patients who had low levels of albumin at the preliminary analyzes.

5. Materials e Methods

To evaluate albumin levels in COVID-19 patients, 50 patients (30 men, 20 women) were examined, hospitalized 3 days (+6 -3) after the onset of symptoms. All patients entering the emergency room underwent hematological investigations. Patients with long hospital stays, patients with signs of malnutrition and patients who showed signs of prolonged fatigue were excluded from the survey. The tests performed at the U.O.C Laboratory of the Morelli Hospital in Sondalo concerned hematology, coagulation, clinical chemistry and immunometric assay.

The data of the 50 patients are shown in Table 1. Normal range of the measured parameters are shown in Table 2.

In other 2 patients, who carried out different analysis during the hospitalization period (January 2021), a drop in the value of S-Alb was found to be less than 20 g/L; therefore it was necessary to undergo a transfusion of human serum albumin (HSA). The transfusion was performed by administering 4 vials of 50 mg/mL HSA over 2 days, for a total of 200 mL.

Patient data are shown in Table 3.

P	*G*	*Age*	*Onset gg/mm*	*Hospital gg/mm*	*pCO_2 mmHg*	*pO_2 mmHg*	*SAO_2 %*	*K^+ mEq/L*	*Na^+ mEq/L*	*Ca^{2+} mmol/L*	*pH*	*Ferritin µg/L*	*aPTT Ratio*	*S/Alb g/L*
1	F	71	09/11	10/11	48	52	89,0	3,1	132	1,03	7,51	512,1	1,23	24,40
2	M	68	30/11	03/12	29	60	94,4	3,5	138	1,15	7,52	1576,2	1,01	27,40
3	F	58	06/11	06/11	28	59	90,3	3,5	132	1,05	7,49	615,6	1,04	29,20
4	M	76	25/11	25/11	31	47	89,2	3,7	134	1,07	7,50	414,4	0,98	24,60
5	M	75	22/12	27/11	30	68	97,0	3,5	132	1,21	7,51	4176,0	0,83	25,40
6	F	70	26/11	27/11	32	65	92,0	3,5	130	1,12	7,48	2320,0	0,89	22,30
7	F	65	28/11	29/11	28	54	91,8	3,6	136	1,13	7,53	2723,0	0,84	23,70
8	M	67	24/11	25/11	34	56	93,1	3,1	135	1,10	7,48	1086,9	1,22	31,90
9	F	66	24/11	24/11	32	54	91,9	4,0	135	1,15	7,52	287,5	0,88	31,20
10	M	59	21/11	25/11	24	60	92,8	4,1	127	1,13	7,49	867,5	1,19	24,70
11	M	63	13/11	15/11	33	59	93,0	3,8	132	1,07	7,48	2163,2	0,84	26,30
12	M	71	21/11	21/11	31	54	90,3	4,5	133	1,15	7,45	1478,4	0,97	28,90
13	M	67	20/11	23/11	35	66	95,1	3,3	156	1,25	7,52	435,4	1,16	27,40
14	F	68	26/11	30/11	40	59	91,8	3,7	140	1,16	7,45	363,5	0,94	24,80
15	F	72	19/11	19/11	43	81	98,0	4,4	134	1,24	7,36	206,5	0,79	20,50
16	M	53	01/12	01/12	39	59	93,2	3,4	134	1,13	7,48	2429,4	0,82	27,80
17	M	54	24/11	30/11	40	50	87,4	3,7	138	1,20	7,41	1229,7	1,07	31,50
18	M	73	22/11	24/11	36	67	95,7	3,5	142	1,07	7,48	1800,7	1,14	33,80
19	F	66	21/11	21/11	38	64	95,0	3,6	136	1,17	7,44	580,0	0,85	28,40
20	F	68	14/10	16/10	37	62	93,0	3,7	138	1,15	7,52	2636,0	1,48	26,40
21	F	63	24/11	25/11	38	41	81,9	4,3	139	1,11	7,50	1358,6	0,85	24,90
22	F	70	22/11	25/11	40	50	86,5	4,4	136	1,11	7,40	108,2	0,94	25,20
23	M	65	17/11	18/11	42	46	84,5	4,9	135	1,15	7,40	1314,5	0,93	27,30
24	M	67	09/11	09/11	33	54	87,6	3,6	131	1,09	7,45	2468,3	0,86	22,10
25	F	62	10/12	12/11	41	45	82,1	4,3	138	1,21	7,41	218,1	0,94	35,90
26	F	53	16/11	17/11	30	55	93,3	3,4	137	1,16	7,52	567,8	1,02	28,70
27	F	73	25/10	27/10	29	53	89,6	4,5	129	1,06	7,47	793,6	0,99	23,80
28	M	60	06/11	07/11	31	57	90,4	3,7	125	1,12	7,48	3417,8	0,94	26,60
29	M	59	01/11	03/11	26	118	100,3	3,8	134	1,10	7,48	111,4	0,82	30,40
30	M	57	21/11	23/11	40	44	83,1	3,7	133	1,11	7,45	466,4	0,97	31,70
31	M	53	12/11	14/11	39	52	89,7	3,9	145	1,15	7,48	211,1	1,45	23,90
32	F	76	15/11	24/11	38	52	90,7	4,2	128	1,12	7,49	814,7	89,0	25,60
33	M	62	23/11	24/11	36	104	99,3	4,1	135	1,16	7,49	1912,5	1,01	32,10
34	F	67	06/11	08/11	42	61	92,2	4,0	135	1,17	7,44	217,8	0,88	36,30
35	M	75	22/11	27/10	40	58	91,1	4,2	131	1,05	7,45	1434,7	0,95	32,20
36	F	58	05/11	07/11	40	82	99,1	3,4	141	1,14	7,48	1928,0	0,86	22,60
37	M	66	01/11	03/11	27	68	95,4	3,8	133	1,12	7,45	899,8	0,84	39,70
38	M	68	21/09	30/10	38	55	90,5	4,1	136	1,09	7,48	1017,1	1,09	25,30
39	M	63	30/10	02/11	34	122	99,4	4,5	138	1,19	7,47	1134,0	0,72	25,50
40	M	66	22/10	23/10	24	61	93,7	3,7	134	1,03	7,52	148,7	1,09	28,10
41	F	73	14/10	16/10	26	66	91,1	3,9	135	1,07	7,53	109,1	1,40	31,20
42	F	70	25/10	29/10	41	59	90,8	4,6	136	1,05	7,40	380,7	1,00	28,80

43	M	72	05/11	08/11	33	71	97,4	3,0	133	1,16	7,50	794,2	0,85	17,20
44	M	72	10/11	12/11	55	129	100,0	4,0	138	1,14	7,52	113,4	0,99	20,10
45	F	52	06/11	10/11	36	83	100,4	3,2	131	1,09	7,50	3825,6	0,89	18,50
46	M	71	04/11	06/11	25	52	87,4	3,3	138	1,10	7,50	2127,2	1,53	18,80
47	M	46	09/11	11/11	37	68	96,4	3,9	136	1,19	7,45	1927,5	0,96	22,30
48	M	68	06/11	12/11	31	60	92,0	4,5	134	1,22	7,45	385,1	1,61	23,60
49	M	72	14/11	16/10	30	52	90,6	3,7	132	1,18	7,46	361,1	0,92	24,20
50	M	59	30/10	03/11	36	96	98,3	3,5	126	0,99	7,45	4302,1	0,97	25,70

Table 1: Data of the 50 patients analyzed at their entrance in the hospital. Onset indicates the day in which patients start feeling COVID-19 symptoms, Hospital indicates the day in which they entered the ER. The abbreviations indicate: pCO_2, partial pressure of carbon dioxide measured in millimeters of mercury (mmHg); pO_2, partial pressure of oxygen; SAO_2, oxygen saturation; K^+, potassium ions; NA^+, sodium ions; Ca^{2+}, calcium ions; aPTT, activated partial prothrombin time; S-Alb, Serum albumin.

pCO_2 mmHg	***pO_2 mmHg***	***SAO_2 %***	***K^+ mEq/L***	***Na^+ mEq/L***	***Ca^{2+} mmol/L***	***pH***	***Ferritin µg /L***	***aPTT Ratio***	***S-Alb g/L***
37-45	80-100	93-97	3,5-5,5	135-145	1,1-1,4	7.38-7.42	F:20-120 M:20-200	<110	35-55

Table 2: Normal range of the measured parameters.

Gender	**Age**	**1st analysis**	**Ferritin ng/mL**	**Fibrinogen g/mL**	**D-Dimer ng/mL**	**aPTT Ratio**	**S-Alb g/L**	**CRP mg/L**
M	95	17/01/2021	1024,8	5,81	1972	1,01	17,3	233
F	95	19/01/2021	328,5	3,86	1678	1,17	16,7	107,6

Table 3: Patient A (man) e Patient B (woman) who received HSA transfusion.

In patients A and B, blood tests were repeated after 5 days.

The research group focused on the values of S-Alb, detected by BCP colorimetric assay, and C-Reactive Protein (CRP), detected by immunoturbidimetric assay, in the 50 patients entering the ER between September and December 2020. A second clinical observation derived from the need to undergo an albumin infusion both in patients A and B.

6. Results and Discussion

The major observation involved 50 patients hospitalized at the Eugenio Morelli Hospital in Sondalo (SO) between September and December 2020. The hospitalization took place a few days after the disease onset to exclude malnutrition from prolonged illness. For this reason, 50 hospitalized patients were examined 3 days (+6 -3) from the onset of the first symptoms (See Materials and Methods).

56% of patients arriving at the ER showed an oxygen saturation value below the normal range; 43% of them had a value of less than 90% of saturation.

Arterial Blood Gases results reveal that:

- in 5 patients a neutral plasma pH value was detected;
- 8 patients showed a normal pO_2 value;
- 1 patient was in an acidosis condition (pH = 7.36);
- 2 patients were in a metabolic alkalosis condition (pH > 7.42 e pCO2 > 45 mmHg);
- 29 patients were in a respiratory alkalosis condition (pH > 7.42 e pCO2 < 37 mmHg) – 58% of the sample.

An abnormal outcome of the blood gas analysis may indicate two situations: (1) the patient does not receive sufficient oxygen, (2) the patient is unable to dispose of an adequate amount of carbon dioxide. In the case of the patients analyzed, most of them arrived at the ER in a condition of respiratory alkalosis; this indicates that the greatest alteration was caused by CO_2. In fact, decreased removal of CO_2 from the lungs creates an accumulation of CO_2 in blood.

In 42 patients (84% of total patients) a condition of hypoxemia was observed, with values below 80 mmHg of O_2; of these, 42,78% (33 patients) had a pO_2 value below 65 mmHg.

The O_2-CO_2 exchange process that occurs in the lungs is closely linked to the blood pH. The plasmatic pH regulation depends on albumin, which acts by regulating the acid-base balance and keeping the pH in the neutral range. In fact, albumin is able, within certain limits, to buffer both temporary increases in plasma acidity, which would tend to lower the pH, and temporary increases in body basicity, which would tend to raise plasma pH [16].

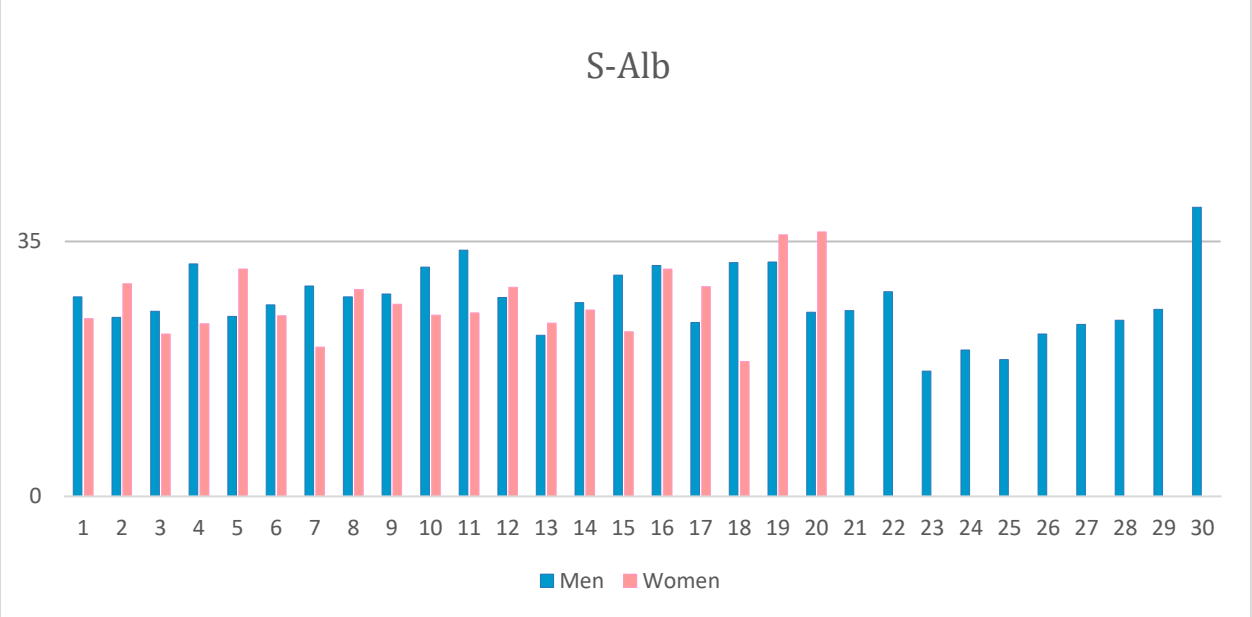
Interestingly, almost all patients who arrived in the ER had a remarkably low albumin value.

5 patients had normal or compensated pH, 4 of them showed S-Alb values between 25,2 – 31,5 g/L, below the normal range. In both patients in metabolic alkalosis condition, an S-Alb value lower than 25 g/L was found. S-Alb values below normal and between 18.5 and 33,8 g/L were observed in 28 patients, out of 29 in

metabolic alkalosis condition.

Considering all patients, in most of them, albumin was found to be below the normal range, which corresponds to 35-55 g/L. As shown in Table 1, in the 50 patients analyzed, albumin values were found in 47 patients (94%) below the normal value, from a maximum of 33,8 g/L to a minimum of 17,2 g/L.

By examining the sample according to gender, it is possible to note that 36% of patients with an albumin deficiency belong to the female gender, while 58% are men. Dividing the sample into 3 age groups (46-55 years, 56-65 years, 66-76 years), 12% belongs to the younger group, 28% to the intermediate group, while 54% corresponds to the older group.

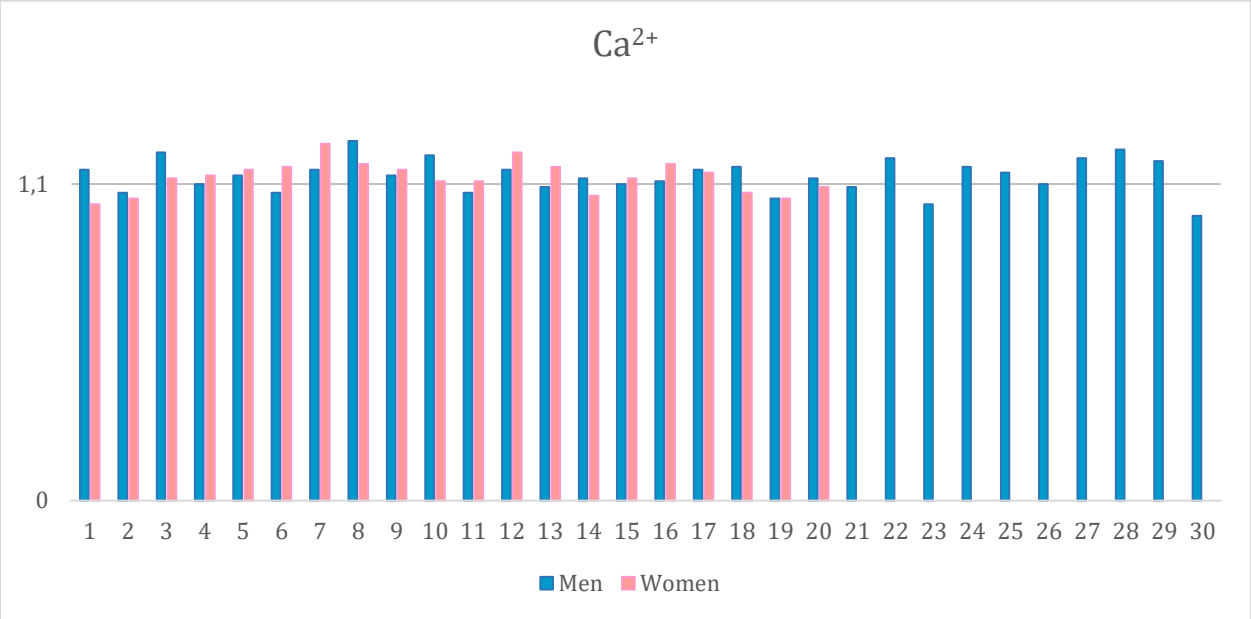


Graph 1: Albumin values in the 50 patients analyzed. 18 women (90%) had S-Alb values below 35 g/L, while in the male sample in 29 men (~97%) the value was below normal.

Albumin has the important role of regulating capillary permeability and the passage of fluids between the vascular compartment and interstitial fluids. A low albumin value causes a lowering of the oncotic pressure, which therefore may not allow fluids, pushed by the osmotic pressure, to re-enter the circulatory stream, generating decompensation.

In the analyzed data, regardless of age, gender, saturation values and other parameters, Ca^{2+} and albumin are related to each other. In fact, one of the functions of albumin is to transport substances in blood. These

include minerals and in particular Ca^{2+} ions. It was observed that 14 patients showed albumin deficiency together with low Ca^{2+} values; in particular 6 women and 8 men had Ca^{2+} values below 1,1 mmol/L (Graph 2).



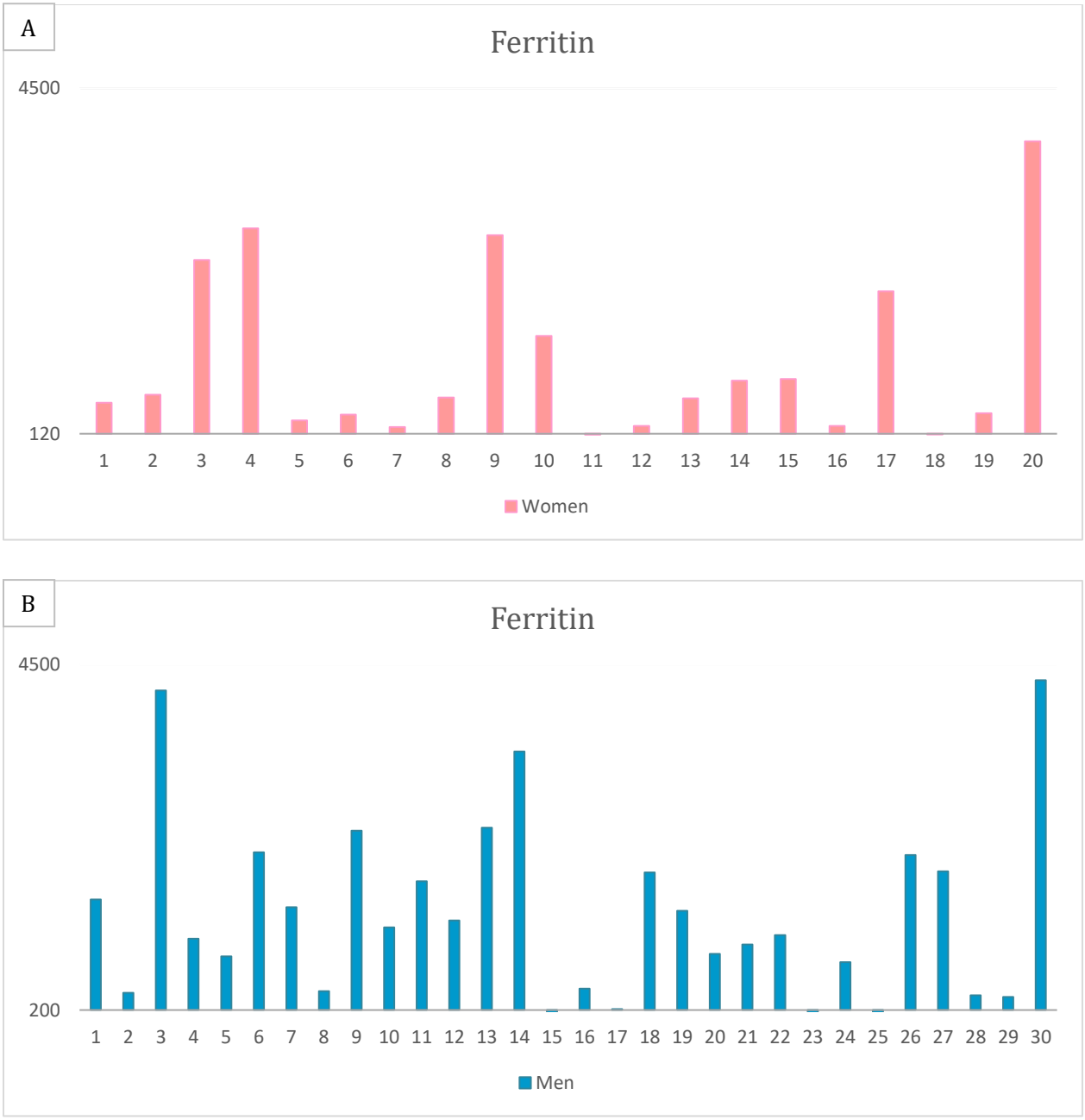
Graph 2: In the analyzed sample, 6 women (30%) and 8 men (26.6%) had Ca^{2+} values lower than 1,1 mmol/L (normal range in Table 2).

Since albumin is also involved in the coagulation processes, the measurement of the activated partial prothrombin time (aPTT) was carried out, which provides with a coagulation index in the analyzed patients. The analysis showed that in only 10 patients the value was above normal range.

It is also necessary to consider the ferritin levels found in the 50 patients entering the ER.

Serum ferritin is a known acute phase reagent, with levels reflecting the degree of acute and chronic inflammation in infectious diseases. Ferritin is also a key mediator of immune dysregulation, especially when extreme hyperferritinemia occurs, through immuno-suppressive and proinflammatory effects, thus contributing to the cytokine storm [17].

Interesting observation concerns the ferritin values detected in our sample. As shown in Graph 3, values are very high in 45 out of 50 patients.



Graph 3: Ferritin values in the 50 analyzed patients. Graph A: in 3 men ferritin value was below the threshold of 200 µg/L; 27 men showed a value above normal (90%). Graph B: 18 out of 20 women (90%) reported a ferritin value above the normal limit of 120 µg/L.

In the 50 patients, only 2 women and 3 men showed normal ferritin levels (10% of women and 10% of men).

On average, in the female sample the ferritin value increased by ~857%, with a minimum out-of-range value of

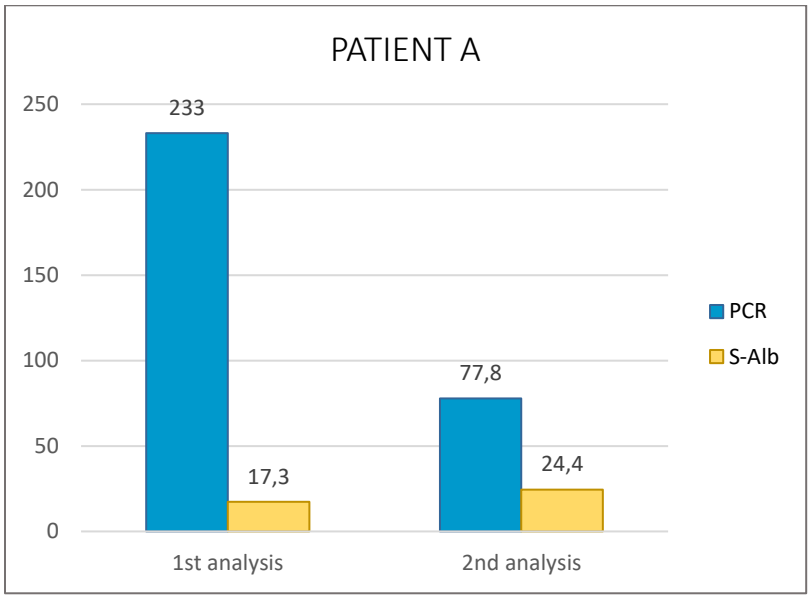
181.5% (217,8 µg/L) and a maximum out-of-range value of 3188% (3826,6 µg/L); in the male population the mean ferritin increased by 703.41%, the lowest value out of the normal range is higher than 105.55% (211,1 µg/L) while the maximum value is equal to 2151% (4302,1 µg/L).

This observation is noteworthy and highlights the body's physiological response to infections. Ferritin is involved in immune regulation and lymphocyte modulation [18]. Therefore, the data show how the body carries out all the mechanisms necessary to face an inflammatory situation.

A second observation on albumin values, carried out in January 2021, derived from the need to undergo two patients to HSA transfusions.

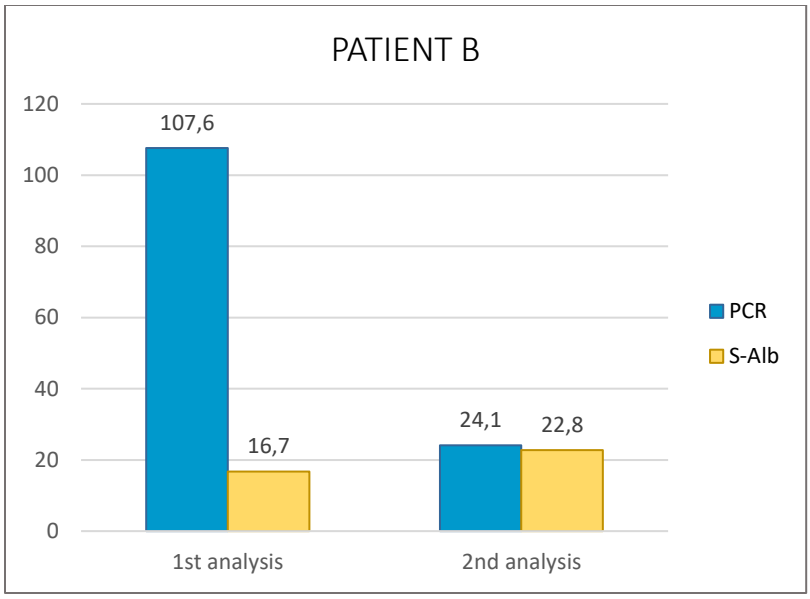
The results that emerged from the analysis carried out on these two patients are relevant and noteworthy.

Analyzing the results of patient A's blood tests (Table 3), an increase in albumin of about 40% was observed after external administration. At the same time, a significant decrease in CRP levels was detected following external administration of HSA. The CRP value, 5 days after the first analysis, went from 233 mg/L to 77,8 mg/L (Graph 4).



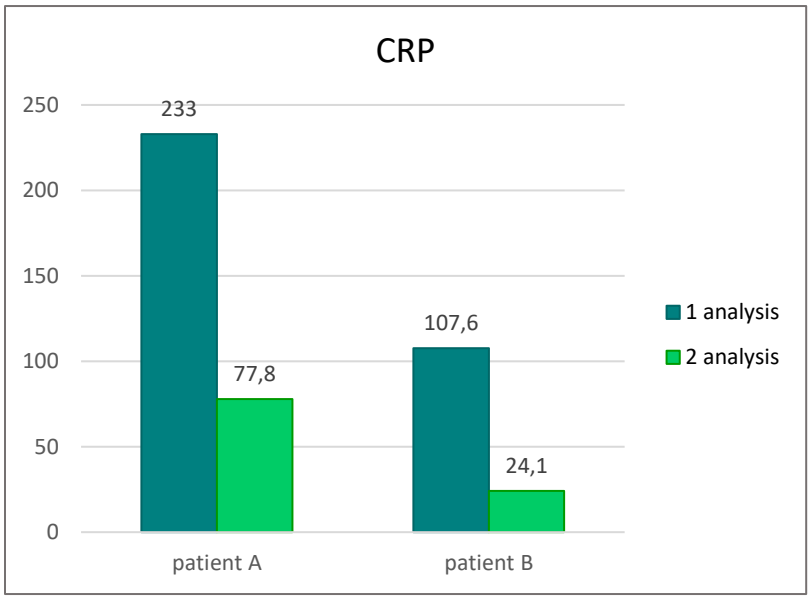
Graph 4: Patient A; the preliminary test carried out on January 17th showed a concentration of 233,0 mg/L of CRP and levels of S-Alb equal to 17,3 g/L. 4 bottles of HSA were administrated in days between January 19th and 20th, 2 bottles of 50 mL per day. The control test on January 22nd shows CRP levels of 77,8 mg/ and S-Alb 24,4 g/L.

In Patient B, the HSA transfusion caused an increase of 36% in S-Alb. Patient B also responded to the increase in albumin with a decrease in the CRP level which dropped from 107,6 mg/L to 24,1 mg/L (Graph 5).



Graph 5: Patient B; the preliminary test carried out on January 19th revealed a CRP concentration of 107,6 mg/L and S-Alb levels of 16,7 g/L. The control test on January 23rd, carried out after HAS transfusion on January 20th, shows CRP levels of 24,1 mg/L and S-Alb of 22,8 g/L.

Both patients, 3 days after HSA administration, reported a decrease in CRP values; in particular patient A had a decrease of 66.6%, while in patient B the CRP value went down by about 77.6% (Graph 6).



Graph 6: Decreased CRP levels in patient A and patient B after HSA transfusion. In patient A the CRP decreased by 66.6%, in patient B the value fell by 77.6%.

Therefore, it is clear that the increase in albumin values caused a decrease in the CRP values.

7. Conclusion

In order to better manage SARS-CoV-2 infection in the acute phase, it is good to know the mechanisms through which the pathogenetic mechanisms responsible for organ damage and the consequent clinical manifestations occur and follow one another.

In view of what emerged from different studies in literature, protein metabolism is severely damaged by SARS-CoV-2 since it targets specific organs: lungs, intestines, eyes, liver, brain, nerves, nose, heart, blood vessels and kidneys. In many patients, important information may be obtained about the alteration of protein metabolism by measuring blood albumin level.

Our study highlighted that almost of all hospitalized patients affected by COVID-19 had albumin values at the entrance to the ER far below normal values.

Albumin works as a transporter of different hormones, fat-soluble vitamins, free fatty acids, and, thanks to the presence of negative charges, it is able to carry positive ions, such as calcium. The albumin, then, modulates the plasma pH by interacting with the endothelium, against which it performs a protective action. If necessary, it is catabolized to supply the amino acids necessary to ensure adequate metabolism and to support a highly stressed organism affected by a hypercatabolic syndrome.

Pharmacological therapies may also undergo metabolic delay in patients whose albumin is reduced.

The role played by albumin in different physiological processes within the human body is undoubtedly very important. Patients who have values of this protein below the normal range are at greater risk of incurring in pathologies and developing complications.

From the second analysis carried out in patients undergoing transfusion with HSA, in fact, it was found that a lowering of albumin values was accompanied by an increase in CRP, which represents an index of inflammation.

If we add to these evaluations the important role of albumin in coagulation and fibrinolysis processes, it is easy to understand that, in a first phase, albumin, present in adequate quantities, helps to limit the action of SARS-CoV-2 at pulmonary level, by regulating interstitial exchanges. In a second phase the albumin deficiency could later be harmful to the body; albumin deficiency in fact predisposes patients with COVID-19 to a greater probability of experiencing thrombotic events, no longer participating in fibrinolytic and inflammatory events.

This clarifies how albumin is important in both phases during SARS-CoV-2 infection. In a first phase, the decrease in albumin allows the inflammatory cytokines to remain confined into the lungs interstitial spaces. In the long term, this kind of congestion leads to the development of inflammatory lung damage, which results in interstitial pneumonia. This phase, if not opposed, can naturally progress into a phase characterized by the inflammatory cytokine storm that may evolve into the highly fatal ARDS (Acute Respiratory Distress Syndrome).

Increasing albumin levels means allowing this protein to facilitate exchanges between fluids and to "decongest" the lung spaces. Thanks to the presence of albumin, the cytokines are able to flow into the interstitial spaces of the whole organism, avoiding accumulation and preventing a cytokine storm in lungs.

An interesting observation concerns the plasma therapy to which COVID-19 patients underwent. The therapy consists in transfusion of hyperimmune plasma, donated by patients recovered from COVID-19, who have developed neutralizing antibodies, and infused directly into the veins of hospitalized patients; this therapy represents an effective strategy used in several hospitals around the world. The method consists in taking 600 cc of plasma from patients recovered from SARS-CoV-2 infection with two negative results in PCR swabs. The sample is adequately treated, obtaining 2 x 300 cc plasma doses [19]. The number of administrations is decided according to the clinical needs of each patients. In the 300 cc of plasma obtained, there are antibodies against SARS-CoV-2 and about 50% of albumin [20], therefore about 150 cc. The amount of albumin transfused in COVID-19 patients through plasma therapy is therefore 3 times higher than with simple serum albumin transfusion (50 mg / ml).

This consideration opens us to a new vision. The inflammatory reaction caused by blocking the virus at the interstitial level is resolved by the increase in albumin, which again allows liquids to permeate into the lung interstices. In this condition, antibodies are able to reach the virus and neutralize it. If this phase were resolved, there would be a high concentration of inflammatory cytokines; also in this case, albumin is useful in reducing the inflammation. Therefore, the usefulness of albumin also affects the immune level, enhancing the antibody response of patients, and the inflammatory scenario.

Moreover, the progress of patients in post COVID-19 phase should not be underestimated.

After SARS-CoV-2 infection, there are long recovery periods. Some patients follow-up at the San Celestino Institute in Milan, certainly showing a natural recovery with an increase in albumin values. Albumin supplementation could have a positive impact on muscular and joint symptoms of Long COVID, reducing painful symptoms and fatigue.

In the future, it would be interesting to evaluate the course of SARS-CoV-2 infection in patients with albumin deficiency and evaluate the supply of albumin provided, in addition to any transfusions, even with dietary supplementation of this protein.

8. Acknowledgements

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9. Conflict of Interest

The authors declare that there is no conflict of interest.

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