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Review

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# Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients?

**Giuliano Ramadori**

Clinic for Gastroenterology and Endocrinology, University Medical Center Göttingen, Göttingen 37075, Germany.

**Correspondence to:** Dr. Giuliano Ramadori, Clinic for Gastroenterology and Endocrinology, University Medical Center Göttingen, Göttingen 37075, Germany. E-mail: giulianoramadori@gmail.com

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## Abstract

The COVID-19 pandemic has led to the greatest worldwide health crisis in decades. The number of infected patients with severe SARS-CoV-2 (COVID-19) disease has overwhelmed the capacity of almost all health care systems around world. Hypoalbuminemia has now been reported in patients with severe disease seeking help in the emergency room because of COVID-19 infection. In the past, hypoalbuminemia was considered to be a negative prognostic marker, not only in patients with chronic liver disease, but also in patients with SARS and MERS infections. Albumin is the major serum protein synthesized by the liver. A low serum albumin level is an ominous clinical sign. Introduction of amino acids to a patient's diet is of fundamental importance to hepatic albumin synthesis in different clinical situations. This highlights the importance of nutritional support during the early phases of COVID-19-infection. Furthermore, albumin synthesis in the hepatocyte is downregulated at a pretranslational level by the direct interaction of the major acute-phase cytokines which are released into the circulation during the cytokine "storm" induced by the viral effects on the lungs. Both mechanisms contribute to severe hypoalbuminemia which, combined with massive fluid losses due to the fever, is responsible for severe hypovolemia and shock commonly observed in patients with COVID-19 in critical care settings.

**Keywords:** Severe acute respiratory syndrome cornonavirus 2, SARS-CoV-2, COVID-19, albumin synthesis, nutrition, acute-phase reaction, cytokines, liver, extrahepatic organs

## COVID-19 INFECTION AND THE CLINICAL RELEVANCE OF HYPOALBUMINEMIA

Severe acute respiratory syndrome, cornonavirus 2 (SARS-CoV-2), formally CoV-19, is a recently recognized RNA-virus which belongs to a larger family of pathogenic human viruses. Severe acute respiratory syndrome

cornonavirus-1 and Middle East respiratory syndrome coronavirus caused primarily pulmonary diseases. HuCoV 229E, 0C43, NL63 and HKU1 are mainly responsible for the common cold, but can also cause lethal nonspecific pneumonias[1]. However, SARS-CoV-2 has a wide range of clinical presentations, with acute respiratory distress syndrome being the often fatal pulmonary complication[2-4].

Most of the publications reporting clinical characteristics for patients with SARS-CoV-2-infection originate from China, many from the city of Wuhan. These publications are descriptive retrospective case series about patients hospitalized with the virus or who died in intensive care units (ICU)[5,6]. The symptoms reported mainly concern the reason for hospitalisation. The spectrum of all symptoms, and key timings from when patients first felt unwell is less well reported[7,8]. In fact, far less is known about the symptomatology at the time of first appearance of the disease in hospitalized patients and in infected persons who remained at home, and who may had even died there.

Parameters indicating liver damage include prothrombin time, serum transaminase and bilirubin levels, acute-phase response markers such as leukocyte count. C-reactive protein, procalcitonin, and several serum cytokine levels have been reported in patients with SARS-CoV-2, together with changes in serum albumin levels[2-5,9,10]. Previous experiences in patients with SARS or MERS suggested that hypoalbuminemia, lymphopenia, a serum CRP level greater than 4 mg/dL, plus elevated lactate dehydrogenase on hospital admission were predictive for pneumonia progressing to respiratory failure[11-14]. Low serum albumin levels have now been found to be an important predictor of progression to severe disease and increased mortality in hospitalised SARS-CoV-2 positive patients of older age[15,16].

## PATHOPHYSIOLOGICAL ASPECTS OF HYPOALBUMINEMIA AND CLINICAL RELEVANCE OF ALBUMIN INFUSION

Albumin is a single chain protein with a molecular weight of 66 kDa made of 585 amino acids which represents more than 50% of the serum proteins and represents an important component of interstitial fluid. The albumin fraction was first separated from the other components of the plasma in 1944 by Edwin Cohn[17], who also appreciated its strong oncotic properties. This characteristic of albumin was also confirmed by Scatchard *et al.*[18] in 1944. Serum albumin levels are used as useful surrogates of liver function[19]. Soon after the fractionation studies, intravenous albumin administration was performed in patients with advanced liver disease. This was done in the United States during the 1940's[21,22] and also in the United Kingdom at the beginning of the 1960's by Wilkinson and Sherlock *et al.*[22].

The beneficial effect of prolonged administration was first demonstrated in a clinical trial by the group of Paolo Gentilini in Florence[23], and more recently by Caraceni *et al.*[24] in Bologna.

The positive diuretic effect of albumin infusion in three patients with liver cirrhosis was published by Patek *et al.*[25]. This finding was subsequently corroborated in a group of ten patients[26,27], showing that albumin infusion in patients with liver cirrhosis and ascites (without spontaneous bacterial peritonitis) increased sodium excretion in the urine, and led to weight reduction and a reduction in diuretics required.

It was shown that repeated daily intravenous administration of albumin was able to avoid the requirement for transjugular stent placement into the portal tract trough the hepatic vein (TIPS)[28]. A similar experience, in a larger patient numbers, was published by Trotter *et al.*[29].

The positive effects of albumin infusion in cirrhotic patients with low levels of serum albumin was shown by Bajaj *et al.*[30] who observed a normalisation in serum sodium concentration in patients with liver cirrhosis and hyponatriemia. Infusion of intravenous albumin solution in decompensated cirrhotic patients was also able to reduce encephalopathic episodes and associated mortality[31].

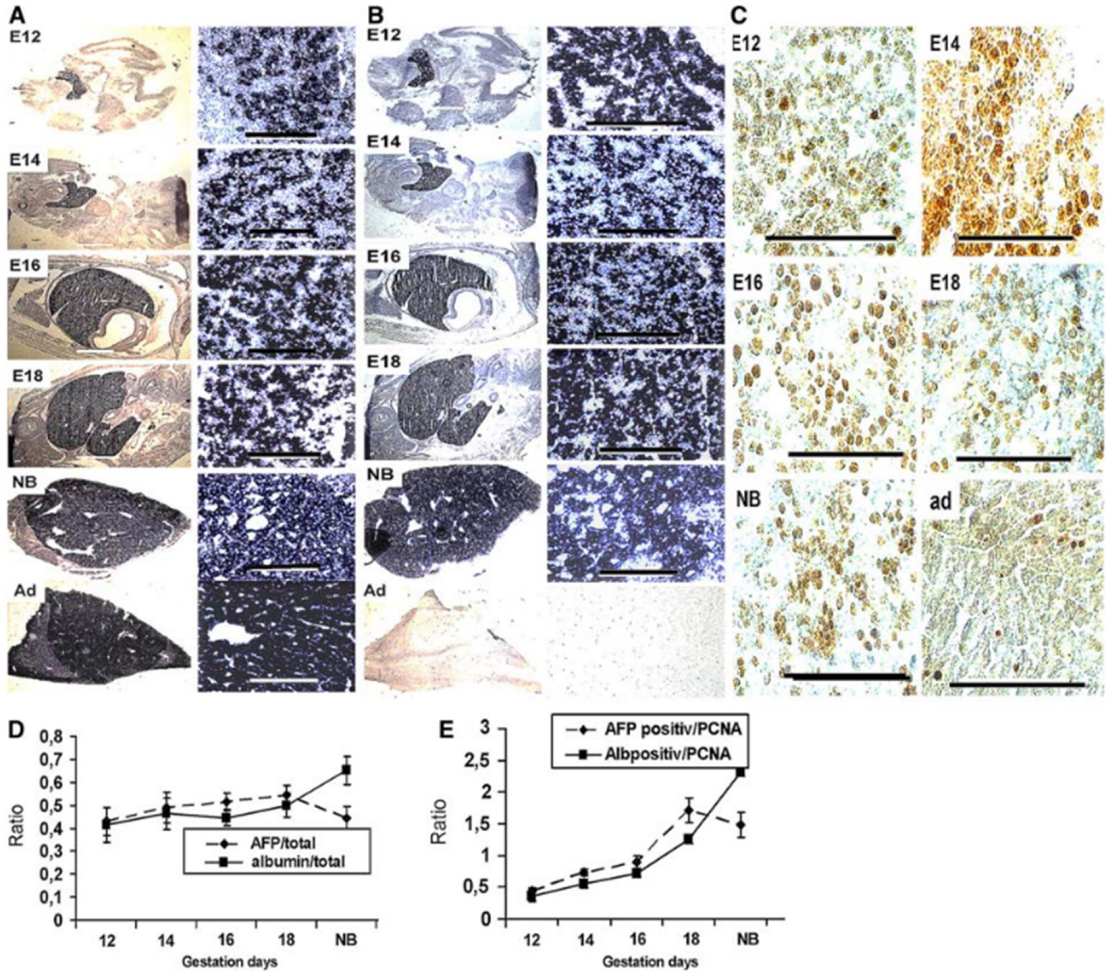


**Fig. 5** Albumin- **(A)** and AFP- **(B)** mRNA-expression in developing liver assessed by in situ hybridization using DIG-labeled antisense RNA probes (Original magnification 50×; 200×, Bars = 100 µm). **(C)** Proliferation of hepatoblasts estimated by the number of cells positively stained for proliferating cell nuclear antigen (PCNA) in developing liver. Immunohistochemical reaction was detected by peroxidase-labeled secondary antibody (Original magnification 400×, bars = 100 µm). **(D)** The ratio of albumin- and AFP-expressing cells to total cells and **(E)** the ratio of albumin- and AFP-expressing cells to $PCNA^+$ cells during liver development. Albumin- and AFP-positive cells were identified by in situ hybridization, and PCNA-positive cells by immunohistochemical staining. The positive cells were counted under microscope using a shaded ocular, and by application of Image J software. Error bars represent S.E.M., $n = 3$. The significance ($P < 0.05$) was analyzed by ANOVA

**Figure 1.** Panel A shows the results of in-situ-hybridisation analysis performed in slices of embrional liver at different stages of developement in NB and Ad rats. The intensity of the reaction demonstrates an abundance of albumin-specific mRNA. NB: newborn; Ad: adult. *Histochem Cell Biol* 2007;128:431-43. (reprinted with permission)[37]

The prognostic importance of serum albumin levels in patients with liver disease is demonstrated by the inclusion of this parameter in the Child-Turcotte-Pugh score, used to assess the prognosis of chronic liver disease, mainly cirrhosis. This score was introduced by surgeons in 1963[32].

In addition, serum albumin level is a key nutritional parameter used to estimate the grade of malnutrition, and to predict survival in patients with liver cirrhosis. Malnutrition is an independent risk factor for transplantation, and improves the prognostic value of the Child-Turcotte-Pugh score, reported by Alberino *et al.*[33].

While administration of albumin in patients with advanced liver disease and hypoalbuminemia is now a standard therapy, albumin administration in critically ill patients with or without liver disease in the ICU is controversial[34-36].

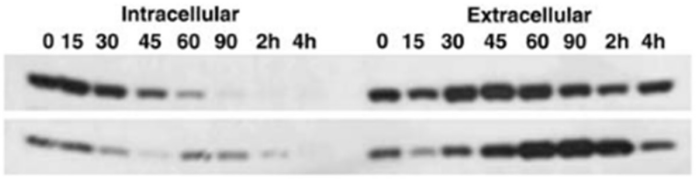


**Fig. 4** Kinetics for albumin synthesis and secretion in hepatoblasts (E14) and adult hepatocytes estimated by pulse chase experiment. The secretion speed in E14 hepatoblasts (upper panel) was comparable with that of the adult hepatocytes (lower panel). At 60 min the apparent increase of labeled albumin protein in the intracellular pool of adult hepatocytes is due to the contamination of the extracellular pool, which dramatically increased at this time point

**Figure 2.** Autoradiograph of a SDS-PAGE-analysis of immunoprecipitates from cell culture supernatants (hepatoblasts and hepatocytes). Radioactively labelled albumin was immunoprecipitated with a specific antibody. The strong speed of the release of the newly synthesized protein is an explanation for the difficulty to detect albumin (as a protein) in the liver sections by using immunostaining techniques. *Histochem Cell Biol* 2007;128:431-43. (reprinted with permission)[37]

The liver is the sole source of serum albumin[37] [Figures 1 and 2] which represents more than 50% of all proteins synthesized in the liver. Under normal conditions albumin synthesis in the hepatocytes is regulated by the amount of proteins reaching the intestine after each meal, and the amount of amino acids transported into the liver through the portal system.

During fasting, reduced albumin synthesis is due to a reduced uptake of amino acids into the hepatocytes[38], which may be in part compensated by using amino acids from muscle proteins.

During acute phase situations, characterised by tissue damage induced by different insults such as trauma, bacterial infection, or viral infections such as SARS-CoV-2, the defence mechanisms of the body concentrate on eliminating the aggressive agent at the site of tissue entry and/or the damaged tissue. The main systemic reactions during the COVID-19 illness are fever, weakness and loss of appetite. In addition vomiting, diarrhea and abdominal discomfort[39], which may be accompanied by loss of taste[40] and loss of smell (anosmia)[41,42], may be also be present. At the beginning of the illness a dry cough and sometimes dyspnoea may be present. The systemic defence reaction may last for a few days and the consequences may not be clinically noted if the person continues to stay home and recovers promptly. If the symptoms last for a week or longer, two major consequences have to be considered: (1) severe fluid losses leading to dehydration and ultimately hypovolaemic shock; (2) reduction in caloric intake which worsens symptoms of weakness, and accelerates a rapid loss in body weight[43].

These changes may be aggravated by the simultaneous intake of antihypertensive medication, including diuretics, as might be encountered in older patients and/or those patients with multiple comorbidities[44].

The systemic reaction, a major component of body defence strategy, is induced by different cytokines that originate the main site of injury, e.g., the lungs. The so called “major acute-phase mediators” are Interleukin-6, Interleukin-1, TNF-alpha, and IFN-gamma, which are all synthesized in different amounts, depending on the quality (organ and damaging agent) and the quantity of tissue damage.

The acute phase cytokines are responsible for the central regulation of body temperature[45], reduction in appetite, and associated adynamia and mental confusion[46].

The reduction of appetite (anorexia) on the one hand, and abdominal discomfort on the other, can also be attributed to the direct action of the cytokines on the intestinal neurons, with alterations in the mobility

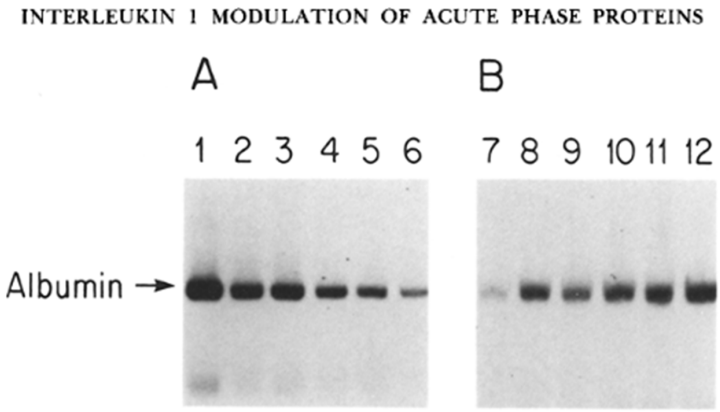


FIGURE 4. Kinetics of mouse recombinant IL-1 inhibition of (*A*) albumin synthesis and kinetics of release, from (*B*) the IL-1 effect. SDS-PAGE (7.5%) of secreted [$^{35}$S]methionine-labeled albumin immunoprecipitated from media of hepatocyte cultures after preincubation with mouse IL-1 (100 U/ml). *A 1*, control (medium alone); *2*, recombinant IL-1 during the 2-h pulse-labelling period; *3*, after 3 h; *4*, after 7 h; *5*, after 12 h; and *6*, after 24 h with recombinant IL-1. *B*, *7*, hepatocytes were pulse-labeled for 2 h, 4 h after washing out recombinant IL-1; *8*, control (no IL-1 preincubation); *9*, 10 h after release from recombinant IL-1; *10*, 10-h control; *11*, 22 h after release from IL-1; *12*, 22-h control.

**Figure 3.** Autoradiograph of a SDS-PAGE-analysis of radioactively labelled albumin from the supernatants of hepatocytes treated with the first recombinant IL-1 for different time lengths (panel A). Panel B demonstrates that the inhibitory effect of IL-1 on albumin synthesis is reversible (kinetic of release of the effect of the cytokine). *J Exp Med* 185;168:930-42. (reprinted with permission)[49]

of the large and small bowel[47,48]. The liver, as the source of the majority of the serum proteins, is the main target of the acute phase cytokines. These cytokines induce pretranslational modification of gene expression through direct interaction with the hepatocytes[49] [Figure 3]. There are positive and negative acute phase proteins[45].

According to the variations of their serum level, the positive acute-phase proteins are defined "major", not because of the volume of their serum level, but because of the magnitude (up to 1.000 fold) of the increase in their serum level.

CRP, Serum Amyloid A, Serum Amyloid P, lactoferrin[50], Lipocalin-2[51], hepcidin[52-55], Interleukin-8[56], and Erythropoietin[57] all belong to the "major" acute-phase secretory protein group, while hemoxygenase-1 belongs to the positive[58] intracellular acute-phase proteins. "Minor" acute-phase proteins are fibrinogen, fibronectin, ceruloplasmin, alpha-1-antitrypsin, complement fraction 3, Factor B, and many others.

As most of the major acute-phase proteins have a low molecular weight, measurement of their serum level may not correspond to a real increase in hepatic synthesis. This is due to the rapid elimination via the urine. Hepcidin was first identified in the urine[59].

Albumin is the main negative secretory acute phase protein [Figure 4][49], whilst ferroportin-1 and hemojuvelin belong to the negative intracellular acute-phase protein group[52-55]. In a rat model, albumin mRNA in the liver was reduced by 50%, while total mRNA was increased by 50%, 2 days after infection with live *Escherichia Coli*[60]. During the 2 days rats ate only 5%-10% of the amount of food consumed prior to injection by the bacteria. This was followed by a further aggravation of the reduction of albumin synthesis[60], further demonstrated in isolated liver perfusion studies[61], and in humans under caloric restriction[62]. The amount of the acute-phase cytokines released into the circulation, and the concentration needed for the systemic appearance of the symptoms and of the metabolic changes, are different in different patients. They may be regulated differently by the drug administered, especially in the acute diseases. However, the response is mainly proportional to the extent of the tissue damage.

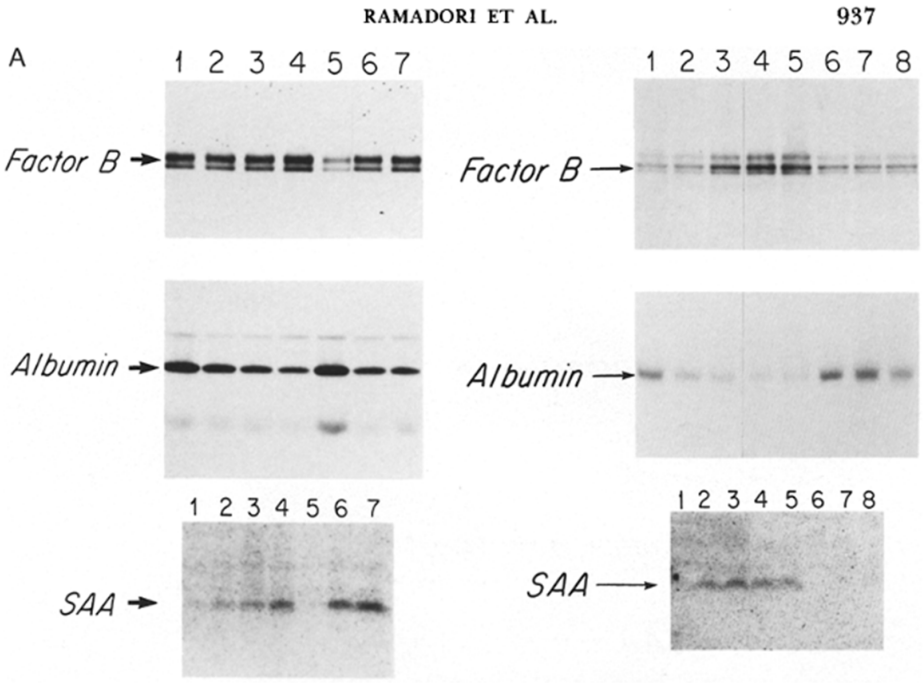


FIGURE 6. *A*, dose-response regulation of factor B, albumin and SAA synthesis by hepatocytes in culture. SDS-PAGE (7.5% for albumin and factor B, 15% for SAA) of extracellular factor B, albumin, and SAA immunoprecipitated from hepatocyte culture media, after a 2-h pulse with [$^{35}$S]methionine. Lanes *1–4*, 0.5, 2.5, 5.0, and 10 U/ml human IL-1, lane *5*, negative control (medium lacking human IL-1), *6* and *7*, 10, and 40 U/ml of mouse recombinant IL-1, respectively. *B*, factor B, albumin, and SAA biosynthesis by hepatocytes in culture; dose-response to mouse recombinant IL-1. SDS-PAGE (7.5% for albumin and for factor B, 15% for SAA) of intracellular factor B, albumin, and SAA immunoprecipitated from cellular lysates after 22-h pulse with [$^{35}$S]methionine. Lane *1*, hepatocytes incubated with medium alone; *2–4*, hepatocytes incubated with medium containing 5, 20, 100 U/ml mouse recombinant IL-1; *5*, 30 U/ml human IL-1; *6*, nontransformed bacterial extract; *7*, medium containing dilution of guanidine hydrochloride; *8*, medium containing 10 μg LPS/ml. Film exposed 2 d for factor B, 24 h for albumin, and 21 d for SAA. The triplet of intracellular factor B represents different stages of glycosylation of the molecule.

**Figure 4.** Autoradiographs of SDS-PAGE-analysis of a biosynthetically, radio-actively labelled major positive acute-phase-protein (SAA), a minor positive acute-phase (factor B) and of the major negative acute-phase protein (albumin) immunoprecipitated from the same sample of supernatant from hepatocyte cultures treated with different amounts of recombinant IL1. Line 5 in panel A and lines 7-9 are negative controls. The relative abundance of the different proteins released into the supernatant is demonstrated by the time of exposure of the film to the filter containing the immunoprecipitated radioactive protein. The shortest time of exposure time was for albumin (24 h) and the longest was SAA (21 days). While synthesis of albumin was inhibited by increasing doses of human recombinant IL-1, synthesis of factor B and of SAA were increased at the same time in the hepatocyte reproducing the process taking place in the liver in vivo during an acute phase situation. It is understandable that the serum concentrations of the acute-phase cytokines produced at extrahepatic sites has to be quite high to induce changes of protein synthesis in the liver until these can become measurable. This is also the case for those proteins whose constitutive gene-expression is almost undetectable, as is the case for SAA or CRP in humans. SAA: serum amyloid A. 1985;162:930-42. (reprinted with permission)[49]

In summary, two main mechanisms act in reducing albumin serum concentration in patients with severe COVID-19-infection: (1) reduction in albumin synthesis due to reduced food intake; (2) inhibition of specific mRNA-synthesis in the hepatocellular nuclei induced by the direct interaction of the cell with the acute-phase cytokines.

The acute-phase cytokines induce up-regulation of gene-expression of several positive hepatic acute-phase proteins, and in extrahepatic organs[63] [Figure 5], but the changes in serum level are influenced by their synthesis in liver cells[45]. This mechanism is not only active in cases of tissue damage caused by bacterial, but also by viral infections[64]. The order of magnitude of variations in the serum level of the acute-phase proteins caused by viral infections is lower than that induced by bacterial infections.

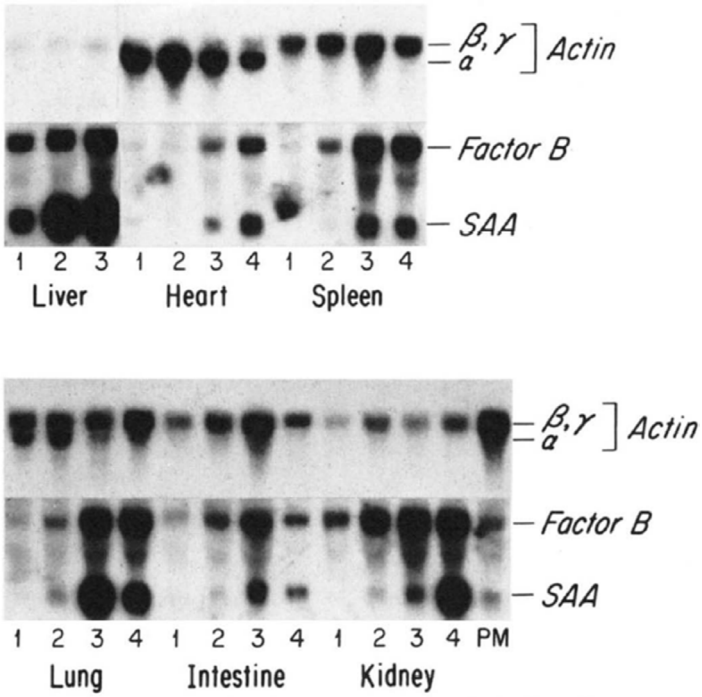


*Figure 1.* In vivo modulation of murine SAA, factor B, and actin gene expression by endotoxin. Animals (C3HeB/FeJ mice) were killed and liver, heart, spleen, lung, intestine, and kidney were taken 16 hr after injection of either saline (*lane 1*) or endotoxin at 1 μg (*lane 2*), 10 μg (*lane 3*), and 100 μg (*lane 4*). *PM* = RNA isolated 2 hr after plating from peritoneal macrophages from five control animals. Fifteen micrograms of total RNA were loaded in each lane. Autoradiograms after exposure to Kodak XAR-5 films at 24 hr for the liver and 6 days for the other organs (SAA- and factor B-specific cDNA probes), and 6 hr exposure for the actin-specific cDNA probe. The signals detected between *lanes 1* and *2* of heart and in *lane 1* of the spleen blots represent nonspecific background. This is one of three experiments that showed similar results. In all of the experiments, a dose-related effect of endotoxin on SAA and factor B gene expression was noted.

**Figure 5.** Autoradiograph of results of analysis of RNA (Northern) from organs of mice treated intraperitoneally with different amounts of *E. Coli* LPS as a model to induce an acute-phase reaction. The filters containing the tissue-RNA were hybridised with radio-actively labelled cDNAs specific for factor B, for SAA and for actin as control. In all organs factor B- and SAA-gene-expression was up-regulated in a dose-dependent manner. The different time of exposure of the x-ray film demonstrate the different abundance of gene-expression of factor B and SAA in the different organs. SAA: serum amyloid A; LPS: lipolysaccharide. *J Immuno*l 1985;135:3645-7. (reprinted with permission)[63]

Physical examination results obtained in hospitalized patients are not reported in the different publications, but most of the patients who were transferred from the emergency room to the ICU will likely have presented with clear signs of exsiccosis, hypotension and eventually malnutrition as testified by the low serum albumin levels. This should be highlighted in the guidelines for the initial supportive management of patients with COVID-19. If not recognized and promptly treated, progression to the second stage of the disease, with deterioration in respiratory function, will likely occur.

Patients suffering from mild disease who presented with normal serum albumin levels, even those who have developed a deterioration, maintained normal serum levels and could be released from the hospital[15,16,65].

Although albumin administration is not recommended in patients with low serum albumin levels being treated in the ICU[35,36], previous positive experiences[66] with repeated administration of 200-400 mL of convalescent plasma showed positive effects in some critically ill COVID-19-patients[67-70]. The positive effect of convalescent plasma infusion could be attributed not only to the COVID-19-specific immunoglobulins, but also to the other components of the plasma e.g., albumin[71].

## DECLARATIONS

### Authors' contributions

The author contributed solely to the article.

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

The author declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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