Severity of SARS-CoV-2 infection and albumin levels recorded at the first emergency department evaluation: a multicentre retrospective observational study

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ABSTRACT

Background The aim of this study was to investigate the association between serum albumin levels in the ED and the severity of SARS-CoV-2 infection.

Methods This is a retrospective observational study conducted from 15 March 2020 to 5 April 2020 at the EDs of three different hospitals in Italy. Data from 296 patients suffering from COVID-19 consecutively evaluated at EDs at which serum albumin levels were routinely measured on patients' arrival in the ED were analysed. Albumin levels were measured, and whether these levels were associated with the presence of severe SARS-CoV-2 infection or 30-day survival was determined. Generalised estimating equation models were used to assess the relationship between albumin and study outcomes, and restricted cubic spline (RCS) regression was used to plot the adjusted dose-effect relationship for possible clinical confounding factors.

Results The mean albumin level recorded on entry was lower in patients with severe SARS-CoV-2 infection than in those whose infections were not severe (3.5 g/dL (SD 0.3) vs 4 g/dL (SD 0.5)) and in patients who had died at 30 days post-ED arrival compared with those who were alive at this time point (3.3 g/dL (SD 0.3) vs 3.8 g/dL (SD 0.4)). Albumin <3.5 g/dL was an independent risk factor for both severe infection and death at 30 days, with adjusted odd ratios of 2.924 (1.509–5.664) and 2.615 (1.131–6.051), respectively. RCS analysis indicated that there was an adjusted dose–response association between the albumin values recorded on ED and the risk of severe infection and death.

Conclusion Albumin levels measured on presentation to the ED may identify patients with SARS-CoV-2 infection in whom inflammatory processes are occurring and serve as a potentially useful marker of disease severity and prognosis.

INTRODUCTION

In February 2020, the novel coronavirus SARS-CoV-2 appeared in Italy for the first time. As of 12 July 2021, 4034 092 people had died worldwide from complications related to SARS-CoV-2 infection.

SARS-CoV-2 infection may trigger a deregulated inflammatory reaction.[1] The involvement of the respiratory system, the most dangerous complication

Key messages

What is already known on this subject
► Patients with suspected SARS-CoV-2 can overwhelm emergency and critical care systems, and methods to prognosticate at the point of access can help mitigate the unpredictable evolution of the disease process.
► Serum albumin decreases during inflammatory processes and has recently been proposed as a prognostic marker for sepsis.

What this study adds
► In this retrospective study from three EDs in Italy, albumin levels recorded on arrival in the ED of patients with SARS-CoV-2 infection were associated with both the severity of COVID-19 pneumonia and short-term mortality.
► Initial albumin levels may serve as a potentially useful marker of disease severity and prognosis in SARS-CoV-2.

of SARS-CoV-2 infection, has led to cases of acute interstitial pneumonia requiring prolonged oxygen therapy and, in some cases, endotracheal intubation and invasive mechanical ventilation.[2 3] Despite the unique involvement of health and research systems worldwide to fight this pandemic, many questions regarding pathology remain to be clarified, and the data to guide clinical judgements remain limited.

The WHO suggests that patients with severe SARS-CoV-2 infection should receive care according to current recommendations for sepsis at first contact with the healthcare system.[4] In sepsis or other critical conditions caused by systemic inflammatory processes, different laboratory markers can help determine the extent of ongoing disease processes and provide some indication of the short-term to medium-term prognosis of patients.[5 6] Among these, serum albumin, a negative acute-phase reactant, has been periodically proposed as a predictor of severity during acute infections because its levels may decrease early, depending on the severity of the inflammatory process.[7 8] The role of hypoalbuminaemia in the initial assessment of patients with sepsis remains the subject of ongoing debate;

however, it is known that the reduction of albumin may be related to the severity of the underlying processes.[9] An early determination of serum albumin levels may provide prognostic information that could be crucial in the management of patients with sepsis in the ED.[10] However, little is known about the role of albumin in estimating the severity of SARS-CoV-2 infection. This preliminary study aims to provide initial data on albumin levels on arrival in ED by patients affected by SARS-CoV-2 infection and how these levels could be related to both the severity of COVID-19 pneumonia and short-term mortality (30-day mortality).

METHODS

Setting and study population

All patients with SARS-CoV-2 infection consecutively evaluated at the EDs of the University Hospital of Verona (Verona, Italy), the General Hospital of Merano (Alto Adige, Italy) and the General Hospital of Bressanone (Alto Adige, Italy) between 15 March 2020 and 5 April 2020 were retrospectively considered for inclusion in the study. Patients infected with SARS-CoV-2 were considered those patients with at least one microbiological sample (nose and throat swabs, bronchoaspirate or antibodies) positive for the virus or clinically suspect patients with a diagnosis of COVID-19 pneumonia established in accordance with the WHO interim guidance.[4]

Laboratory data, albumin measurement and albumin levels

From 15 March 2020, in all three EDs involved in the study, serum albumin levels were added to the panel of blood samples routinely performed on patients with suspected SARS-CoV-2 infection on arrival at the ED. The standard tests were: complete blood count with leucocyte differential, serum electrolyte levels, renal function (including creatinine and Glomerular Filtration Rate (GFR)), liver function, serum albumin and C reactive protein (CRP). Other blood tests (clotting status, other inflammatory tests, arterial blood gas test, etc) were performed at the discretion of the treating ED physician. Analysis of blood samples was performed in the laboratories of the individual facilities; serum albumin levels were measured with Cobas 8000 (Roche Diagnostics) in the ED of Verona, with Alinity ci-series (Abbott) in the ED of Merano and with Dimension Vista 500 (Siemens Healthineers) in the ED of Bressanone.

All three laboratories used the bromocresol green method and the results of the albumin values were provided in g/dL.

Measurements

Serum albumin values were analysed using both categorical and continuous values. In prior literature, an albumin value of less than 3.5 g/dL has been used to indicate a state of hypoalbuminaemia.[7] For descriptive analysis and for survival analysis, we further divided albumin values presented on ED admission (<3 g/dL, between 3 g/dL and 3.49 g/dL and ≥3.5 g/dL).[7–10]

Enrolment

All medical charts of patients with SARS-CoV-2 infection who requested an ED evaluation during the study period were extracted from the electronic ED database. Through manual review of the records by a group of emergency physicians (GT, AB, LC, IK, BM, NP), the diagnosis of SARS-CoV-2 infection was confirmed using the above criteria. Patients in whom serum albumin was not performed (17) were excluded from the patient cohort. In order to investigate the prognostic role of serum albumin in the ED, patients who had been transferred from other hospitals or facilities were excluded. Patients who had already been intubated or patients who required rapid endotracheal intubation immediately on arrival in the ED were also excluded. All anamnestic and clinical characteristics presented by the patients on ED arrival were recorded.

Outcomes

The primary outcome of the study was the presence of severe SARS-CoV-2 infection. As defined by WHO guidelines, infections were defined as severe in cases of fever or suspected respiratory infection, plus one or more of the following: respiratory rate >30 breaths/min, severe respiratory distress or SpO_2 ≤93% on room air.[5]

The secondary outcome of the study was the death of the patient within 30 days of the first ED evaluation. Mortality was reconstructed using death charts or by directly contacting the registry office.

Statistical analysis

No formal sample size calculation was performed but all patients with SARS-CoV-2 infection that consecutively required an ED evaluation during the study period were considered for the study sample size.

Continuous variables were expressed as mean and SD or as median and IQR according to their distribution. The univariate comparisons were performed using Student's t-test, the Mann-Whitney test or the Kruskal-Wallis test, as appropriate. The categorical variables are described as a percentage and number of events out of the total, and comparisons of these variables were performed using Fisher's exact test and the χ^2 test.

In order to verify the prognostic role of albumin and validate its effect on the study outcomes in the presence of possible confounding anamnestic, clinical and laboratory characteristics, multivariate generalised estimating equation (GEE) logistic regression models were used; the dependent variables were the risk of severe SARS-CoV-2 infection or death within 30 days of evaluation in the ED. GEE models with random effects were used since the data were collected from three EDs in order to prevent possible cluster effects. Models have been adjusted for all the variables potential confounding, as well as anamnestic, clinical and laboratory characteristics results associated with their previous univariate analysis. All analyses were considered statistically significant if the two-sided p value was <0.05. The independent association of albumin levels with the different outcomes has been reported in terms of adjusted ORs and their respective 95% CIs.

Subsequently, comparisons between albumin and other inflammatory biomarkers routinely available in the ED were conducted. In addition, multivariate ORs previously obtained using GEEs were compared, evaluating the discriminatory capacity for the two study outcomes by estimating the area under the receiver operating characteristic curve. Analysis of discriminatory capacity was also performed in the subgroups of patients for whom D-dimer (n=155), lactate dehydrogenase (LDH; n=248) and procalcitonin (PCT; n=171) levels were available.

In addition, multivariable restricted cubic spline (RCS) regression models were used to study the potential non-linear dose–response effect between albumin levels and the probability of severe SARS-CoV-2 infection or death at 30 days, using four knots at prespecified locations according to the percentiles of the distribution of albumin. RCS models are very flexible tools for the analysis of the effect of a continuous predictor on an outcome. They extract all available information, producing

more accurate predictions and greater statistical power in identifying dose–response relationships.[11]

Finally, a survival analysis (risk of death within 30 days) among the different patient groups divided by albumin levels measured at ED arrival was conducted using the Kaplan–Meier method, and log-rank tests were used to analyse the differences between patient groups determined by levels of albumin.

All analyses were performed with the statistical software STATA V.14.0 (StataCorp, College Station, Texas, USA).

Patient and public involvement

There was no patient or public involvement in the design, conduct or reporting of this study.

RESULTS

Patients and albumin levels

Records of 313 patients were reviewed; 17 were excluded as they did not have albumin levels, leaving 296 patients diagnosed with SARS-CoV-2 who had albumin levels performed on their arrival in the ED. At least one PCR swab for SARS-CoV-2 was found positive in 82.8% (245/296) of patients, while 17.2% (51/296) received a clinical diagnosis of COVID-19.[4] The mean value of albumin was 3.7 g/dL (SD: 0.5 g/dL). Higher levels of albumin were observed in younger patients, with an average level of 3.9 g/dL (SD: 0.5) in those under 75 years and 3.4 g/dL

(SD: 0.4) in those over 75 years (p<0.001). No difference was observed between male and female patients.

Among the 296 patients in the study, 59.8% (177/296) had an albumin level ≥3.5 g/dL, 30.1% (89/296) had an albumin level between 3 g/dL and 3.49 g/dL and 10.1% (30/296) had an albumin level <3 g/dL (table 1). In addition, lower levels of albumin recorded on ED arrival were associated with higher levels of CRP and liver function abnormalities.

Severity of SARS-CoV-2 infection in patients

Severe SARS-CoV-2 infection was found in 63.2% (187/296) of the patients evaluated. Clinical features of patients associated with severe SARS-CoV-2 infection are reported in table 2.

Patients with severe SARS-CoV-2 infection were older (p<0.001). The anamnestic characteristics associated with the risk of severe SARS-CoV-2 infection were: hypertension (66.8% vs 44%, p<0.001), atrial fibrillation (22.5% vs 11.9%, p=0.030), diabetes mellitus (19.8% vs 6.4%, p=0.002), chronic renal failure (16.6% vs 1.8%, p<0.001), vasculopathy (10.7% vs 1.8%, p=0.005) and previous stroke (12.2% vs 6.1%, p=0.003).

Several laboratory tests performed on arrival in ED were found to be related to the presence of severe SARS-CoV-2 infection. Leucocyte count, kidney function, liver function and CRP were significantly altered in cases of severe infection.

Table 1 Anamnestic and laboratory characteristics of patients divided according to the different levels of albumin recorded at the first evaluation in the ED

Serum albumin levels in the ED	≥3.5/dL	3–3.49 g/dL	<3/dL	P value
Patients, n (%)	177 (59.8)	89 (30.1)	30 (10.1)	
Age, years, median (IQR)	62 (53–75)	75 (69–85)	78 (69–81)	<0.001*
Gender, n (%)				0.015†
Male	105 (59.3)	68 (76.4)	18 (60.0)	
Female	72 (40.7)	21 (23.6)	12 (40.0)	
Clinical history, n (%)				
Ischaemic heart disease	14 (7.9)	14 (15.7)	5 (16.7)	0.096†
Hypertension	92 (52.0)	62 (69.7)	19 (63.3)	0.019†
Chronic heart failure	10 (5.6)	10 (11.2)	6 (20.0)	0.023†
Atrial fibrillation	21 (11.9)	27 (30.3)	7 (23.3)	0.001†
Diabetes mellitus	16 (9.0)	20 (22.5)	8 (26.7)	0.002†
Chronic obstructive pulmonary disease	12 (6.8)	15 (16.9)	6 (20.0)	0.013†
Vascular disease	10 (5.6)	10 (11.2)	2 (6.7)	0.257†
Stroke/transient ischaemic attack history	8 (4.5)	10 (11.2)	5 (16.7)	0.025†
Chronic kidney disease	11 (6.2)	16 (18.0)	6 (20.0)	0.004†
Chronic neurological disease	9 (5.1)	10 (11.2)	4 (13.3)	0.102†
Cancer	23 (13.0)	12 (13.5)	4 (13.3)	0.993†
Comorbidity, n (%)				
At least one chronic disease	114 (64.4)	74 (83.1)	22 (73.3)	0.006†
Two or more chronic diseases	61 (34.5)	61 (68.5)	18 (60.0)	<0.001†
Laboratory findings, median (IQR)				
Haemoglobin (g/dL)	14.1 (12.7–15.2)	13.9 (12.4–15.3)	13.0 (11.7–14.1)	0.008*
Haematocrit (%)	43.0 (39.1–45.3)	42.1 (38.0–45.8)	39.8 (35.9–41.3)	<0.001*
Platelet counts (×1000/µL)	205 (160–261)	198 (144–258)	193 (152–272)	0.560*
Creatinine (mg/dL)	0.9 (0.8–1.3)	1.1 (0.8–1.3)	0.9 (0.7–1.8)	0.012*
Leucocytes (×1000/µL)	6.1 (4.8–8.1)	7.1 (5.2–9.3)	6.7 (5.6–10.9)	0.123*
C reactive protein (mg/dL)	3.9 (1.2–8.7)	8.7 (4.9–15.1)	12.2 (6.9–21.5)	<0.001*
Alanine aminotransferase, U/L	28 (20–41)	34 (23–47)	37 (25–60)	0.050*
Aspartate aminotransferase, U/L	33 (23–47)	39 (28–67)	49 (35–65)	0.004*

*Kruskall-Wallis test.
†χ^2 test.

Table 2 Univariate analysis of anamnestic, clinical and laboratory characteristics recorded on patient arrival in ED and associated with the presence of severe SARS-CoV-2 infection

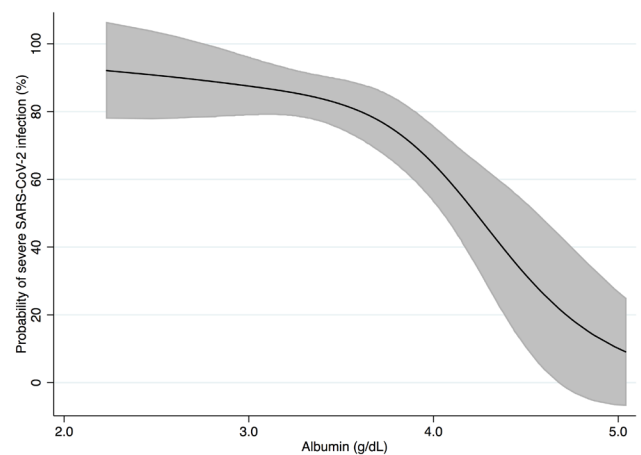|	Non-severe SARS-CoV-2 infection	Severe SARS-CoV-2 infection	P value
Patients, n (%)	109 (36.8)	187 (63.2)	
Serum albumin (g/dL), mean (SD)	4.0 (0.5)	3.4 (0.3)	<0.001*
Serum albumin			
Albumin <3.5 g/dL, n (%)	20 (18.3)	99 (52.9)	<0.001†
Albumin <3.0 g/dL, n (%)	4 (3.7)	26 (13.9)	0.005†
Age, years, mean (SD)	60 (17)	72 (14)	<0.001*
Gender, n (%)			0.379†
Male	66 (60.6)	124 (66.3)	
Female	43 (39.4)	63 (33.7)	
Clinical history, n (%)			
Ischaemic heart disease	11 (10.1)	22 (11.0)	0.706†
Hypertension	48 (44.0)	125 (66.8)	<0.001†
Chronic heart failure	5 (4.6)	21 (11.2)	0.057†
Atrial fibrillation	13 (11.9)	42 (22.5)	0.030†
Diabetes	7 (6.4)	37 (19.8)	0.002†
Chronic obstructive pulmonary disease	7 (6.4)	26 (13.9)	0.056†
Chronic kidney disease	2 (1.8)	31 (16.6)	<0.001†
Vascular disease	2 (1.8)	20 (10.7)	0.005†
Stroke/transient ischaemic attack history	13 (6.1)	10 (12.2)	0.003†
Cancer	11 (10.1)	28 (15.0)	0.286†
Comorbidity, n (%)			
At least one chronic disease	59 (54.1)	151 (80.7)	<0.001†
Two or more chronic diseases	20 (27.5)	110 (58.8)	<0.001†
Temperature on arrival in ED (°C) median (IQR)	37.1 (0.9)	37.5 (0.9)	<0.001‡
Clinical condition on arrival in ED			
Altered mental status, n (%)	3 (2.8)	34 (18.2)	<0.001†
Laboratory findings, median (IQR)			
Haemoglobin (g/dL)	14.3 (13.1–15.4)	13.7 (12.5–14.9)	0.030‡
Haematocrit (%)	43.1 (39.9–46.1)	41.9 (38.1–44.5)	0.042‡
Leucocytes (×1000/µL)	5.61 (4.5–7.3)	6.83 (5.3–9.5)	<0.001‡
Platelet counts (×1000/µL)	215 (171–264)	191 (145–258)	0.042‡
Creatinine (mg/dL)	0.91 (0.7–1.1)	1.0 (0.8–1.3)	<0.001‡
Glomerular filtration rate (mL/min/1.73)	82 (67–94)	64 (45–86)	<0.001‡
C reactive protein (mg/dL)	2.95 (0.9–7.3)	7.8 (4.3–15.2)	<0.001‡
Leucocytes, median (IQR)			
Neutrophil (×1000/µL)	3.69 (2.81–5.15)	5.38 (3.71–7.84)	<0.001‡
Lymphocytes (×1000/µL)	1.21 (0.81–1.77)	0.89 (0.61–1.32)	<0.001‡
Monocytes (×1000/µL)	0.53 (0.39–0.72)	0.45 (0.29–0.68)	0.055‡
Liver function, median (IQR)			
Alanine aminotransferase, U/L	25 (19–39)	35 (24–50)	<0.001‡
Aspartate aminotransferase, U/L	29 (20–39)	41 (31–63)	<0.001‡

*Student's t-test.
†Fisher's exact test.
‡Mann-Whitney test.

The mean value of albumin on arrival in ED for patients with non-severe SARS-CoV-2 infection was 4.0 g/dL (SD: 0.5), and for patients with severe SARS-CoV-2 infection the mean albumin value was 3.4 g/dL (SD: 0.3).

Multivariate analysis (GEE) showed that an albumin value of less than 3.5 g/dL on ED arrival had an adjusted OR (adjusted for anamnestic, clinical and laboratory characteristics associated with the presence of severe SARS-COV-2 infection in previous

Figure 1 Dose–response relationship between the albumin values recorded on patient arrival in the ED and the risk of severe SARS-CoV-2 infection based on a restricted cubic spline model. The model is adjusted for age, comorbidity, temperature, altered mental status, haemoglobin, haematocrit, leucocytes, neutrophil, lymphocytes, kidney and liver function, CRP and platelets. The black line represents pooled probability of severe SARS-CoV-2 infection related to continuous albumin levels and the grey lines indicate the 95% CI.

univariate analyses) of 2.924 (95% CI 1.509 to 5.664, p=0.001) (online supplemental table 1).

When treating albumin as a continuous variable, a non-linear relationship has been observed between albumin values and the risk of severe infection (figure 1). This appears minimal for albumin values above 4.5 g/dL and increases progressively from values below 4.5 g/dL, with a rapid decline between 4 g/dL and 3.5 g/dL, and then stabilisation of the curve for values below 3.5 g/dL. Serum albumin levels entered in the GEE model in continuous form were also found to be an independent risk factor for severe SARS-CoV-2 infection with an adjusted OR of 1.189 for each decrease of 0.1 g/dL (95% CI 1.098 to 1.287, p=0.028) (online supplemental table 1).

Comparison with other biomarkers obtained on ED arrival showed that albumin had a slightly higher discriminatory ability (online supplemental table 2).

Risk of mortality

Among the patients in the study, 18.2% (54/296) of patients died within 30 days of arrival at the ED. The mean albumin level at the ED in patients surviving 30 days was 3.8 g/dL (0.5), and 3.3 g/dL (0.4) in patients who died within 30 days. The anamnestic, clinical and laboratory characteristics associated with the risk of death at 30 days are reported in table 3.

The mortality rate of patients with albumin levels ≥3.5 g/dL, between 3.49 g/dL and 3 g/dL, and <3 g/dL were 7.9% (14/177), 33.7% (30/89) and 33.3% (10/30), respectively (p<0.001). Albumin levels below 3.5 g/dL had an OR of 2.615 (95% CI 1.131 to 6.051, p=0.025) in the adjusted GEE analysis. When expressed as a continuous variable, albumin levels were found to be independent risk factors in the adjusted GEE model, and a reduction of 0.1 g/dL presented an OR for mortality of 1.117 (95% CI 1.007 to 1.238, p=0.036) (online supplemental table 3).

The RCS model reproduced in figure 2 illustrates the dose–response relationship between continuous albumin levels and

Table 3 Univariate analysis of baseline, clinical and laboratory characteristics recorded on ED admissions of patients with SARS-CoV-2 infection distributed according to death within 30 days of ED evaluation

	Alive	Death	P value
Patients, n (%)	242 (81.8)	54 (18.2)	
Serum albumin (g/dL), mean (SD)	3.8 (0.5)	3.3 (0.4)	<0.001*
Serum albumin			
Albumin <3.5 g/dL, n (%)	79 (32.6)	40 (74.1)	<0.001†
Albumin <3.0 g/dL, n (%)	18 (7.4)	12 (22.2)	0.006†
Age, years, mean (SD)	65 (16)	82 (9)	<0.001*
Gender, n (%)			0.876†
Male	156 (64.5)	34 (63.0)	
Female	86 (35.5)	20 (37.0)	
Comorbidity, n (%)			
At least one chronic disease	157 (64.9)	53 (98.1)	<0.001†
Two or more chronic diseases	97 (40.1)	43 (79.6)	<0.001†
Temperature on arrival in ED (°C) mean (SD)	37.3 (0.9)	37.4 (0.9)	0.507‡
Clinical condition on arrival in ED			
Altered mental status, n (%)	18 (7.4)	19 (35.2)	<0.001†
Respiratory rate (breaths per minute) >30	24 (9.9)	20 (37.0)	<0.001†
Oxygen saturation (%) <93%	105 (43.4)	48 (88.9)	<0.001†
Laboratory findings, median (IQR)			
Haemoglobin (g/dL)	14.1 (12.7–15.2)	13.4 (11.9–14.7)	0.094‡
Haematocrit (%)	42.6 (38.9–45.1)	41.0 (36.5–45.1)	0.151‡
Leucocytes (×1000/µL)	6.2 (4.9–8.4)	7.1 (5.1–9.5)	0.250‡
Platelets counts (×1000/µL)	205 (160–266)	173 (137–225)	0.003‡
Creatinine (mg/dL)	0.9 (0.8–1.1)	1.2 (0.9–1.9)	<0.001‡
Glomerular filtration rate (mL/min/1.73)	80 (59–93)	46 (30–68)	<0.001‡
C reactive protein (mg/dL)	5.2 (1.9–10.3)	11.1 (6.5–17.5)	<0.001‡
Leucocytes, median (IQR)			
Neutrophil (×1000/µL)	4.38 (3.15–6.32)	5.98 (3.50–8.35)	0.020‡
Lymphocytes (×1000/µL)	1.07 (0.74–1.50)	0.75 (0.48–1.30)	<0.001‡
Monocytes (×1000/µL)	0.52 (0.34–0.72)	0.38 (0.27–0.62)	0.006‡
Liver function, median (IQR)			
Alanine aminotransferase (U/L)	30 (21–47)	32 (22–43)	0.369‡
Aspartate aminotransferase (U/L)	36 (25–52)	43 (30–63)	0.101‡

*Student's t-test.
†Fisher's exact test.
‡Mann-Whitney test.

Figure 2 Restricted cubic spline (RCS) model of the dose–response relationship between the albumin values recorded on patient arrival in the ED and the risk of short-term death in patients with SARS-CoV-2 infection. The RCS model has been adjusted for age, comorbidity, clinical condition on ED arrival, leucocytes, kidney function and CPR. The black line represents the pooled probability of 30-day mortality linked to continuous albumin levels and the grey lines indicate the 95% CI.

for albumin as a prognostic marker in patients at initial presentation in the ED. Serum albumin level at a threshold of 3.5 g/dL might be most useful in this context, given the discrimination for disease severity and 30-day mortality.

Hypoalbuminaemia is present in several critical medical conditions, especially during deregulated and generalised inflammatory processes.[8 12] For some conditions, hypoalbuminaemia is part of the pathophysiological process of the condition (eg, decompensated liver cirrhosis); in others, it is an epiphenomenon of the damage mechanisms triggered by the pathological condition itself (eg, sepsis).[7 10 12 13] Human serum albumin is a 64 kDa single-peptide-chain protein produced by the liver and released into vessels. It is the main protein component of plasma and plays a crucial role in the regulation of colloid osmotic
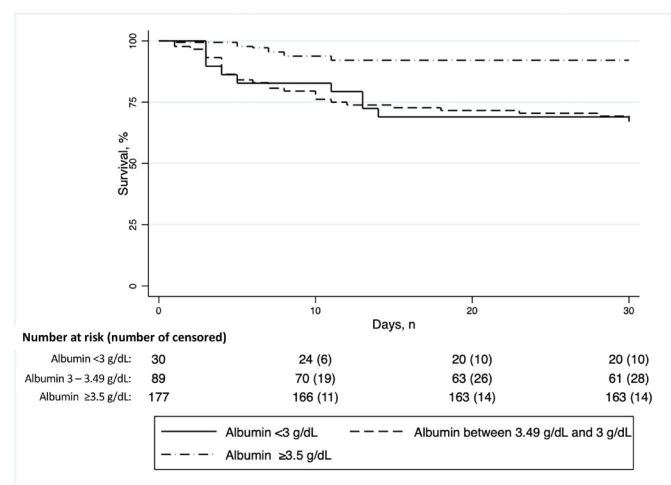
Figure 3 A short-term/medium-term survival analysis after ED evaluation of patients with SARS-CoV-2 depending on the albumin levels recorded at admission. Kaplan-Meier estimates the probability of survival among patients with albumin ≥3.5 g/dL, between 3.49 g/dL and 3 g/dL, and <3 g/dL. Log-rank test p<0.001. Censored patients are reported at the different time intervals.
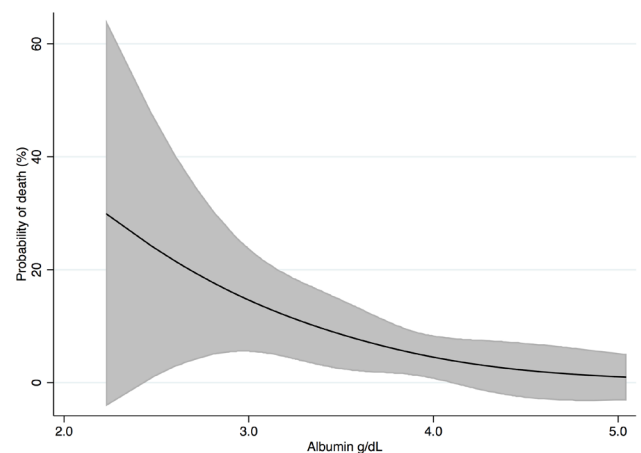
the risk of death at 30 days (figure 2). A higher risk is observed for values below 3.5 g/dL.

Survival was lower with decreased albumin levels, and the log-rank tests for survival functions were statistically significant for the different groups of albumin levels (figure 3; all p<0.001).

Albumin also presented a good discriminatory capacity to predict death at 30 days compared with most of the other biomarkers available at the time of patient evaluation in the ED (online supplemental table 2).

DISCUSSION

This preliminary study of ED patients with SARS-CoV-2 infection revealed that lower albumin levels recorded on patient arrival were associated with both severity of the infection and risk of death at 30 days. Although these are preliminary data collected over a short period of time during the SARS-CoV-2 pandemic in only three EDs, the study seems to suggest a role

pressure.[7] In the vascular system, it usually crosses through the vessel walls and is also distributed in the extravascular interstitial space, with a filtration rate of 5% per hour.[13 14]

In recent years, the role of albumin in patients with sepsis has been discussed. Hoeboer *et al* suggested that albumin levels had a better correlation in patients with severity of the acute respiratory distress syndrome and fever, than other inflammatory markers (CRP and LDH).[15] Microcirculatory dysfunction and increased capillary permeability caused by deregulated inflammatory reactions during infection appear to be related to an early reduction of albumin values.[13 14] Unlike other common inflammatory biomarkers easily obtainable in the ED, such as CRP, PCT and leucocytes, that may not be altered in the first few hours of an infectious process, albumin alteration may already be present at the first assessment in the ED, thereby suggesting the presence of an underlying microcirculatory alteration that has not been clinically identified.[16] Albumin has previously been used in other validated prognostication scores in critically ill patients such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) mortality prediction tool.

Arnau-Barrés *et al* found that albumin levels below 2.6 g/dL presented an adjusted OR of 3.26 (95% CI 1.12 to 9.41, p=0.029) for the risk of 30-day mortality in elderly patients with sepsis and Sequential Organ Failure Assessment (SOFA) ≥2.[10] Yin *et al* confirmed that albumin reduction (<2.9 g/dL) is an independent risk factor for death at 28 days in critically ill patients with sepsis admitted to intensive care units (HR: 2.191, 95% CI 1.023 to 8.714, p=0.045).[17]

Some reports of patients with SARS-CoV-2 have included data on albumin levels. In a cohort of 191 patients hospitalised for SARS-CoV-2 in two Wuhan hospitals. Zhou *et al* revealed that albumin levels were significantly lower in patients who died (2.9 g/dL) than those who survived (3.3 g/dL, p<0.001).[18] Gong *et al* found that in patients with severe SARS-CoV-2 infection albumin was lower compared with the patients with non-severe SARS-CoV-2 infection (3.4 g/dL vs 3.9 g/dL, p<0.01), with levels similar to those reported in the cohort of this study.[19]

The reduction in albumin in patients with severe SARS-CoV-2 infections could be explained by the mechanisms hypothesised for hypoalbuminaemia during sepsis. First, cytokines (interleukin (IL) 1, IL-6 and tumour necrosis factor α) produced by inflammatory processes lead to hypoalbuminaemia both directly, due to the reduction in albumin synthesis, and indirectly due to the increase in hormonal catabolism.[7] During severe SARS-CoV-2 infection, inflammatory processes are elevated, with high levels of inflammatory mediators.[20] Second, in severe inflammatory conditions and when inflammatory deregulation has become systemic, there is an increase in capillary permeability, which may contribute to hypoalbuminaemia due to increased albumin release from the interstice and increased filtration rate.[8 13 21] For these reasons, the reduced levels of albumin measured at a patient's admission may suggest the presence of a large inflammatory reaction, and in more advanced cases, systemic involvement similar to what occurs in sepsis.

Inflammatory biomarkers (eg, CRP, PCT) that are routinely used in ED clinical practice and those that are less commonly used in the initial evaluation of infected patients (eg, LDH, D-dimer) have been tested in the evaluation of the severity of patients with SARS-CoV-2, with contradictory results.[22] Although there was good association, no single biomarker has been able to definitively estimate the medium-term to short-term prognosis (7–30 days), suggesting that summing information from multiple biomarkers may improve their predictive ability.[22] The challenge in using biomarkers in the evaluation of infectious

or septic processes even before the COVID-19 pandemic has been confirmed in this new pathological condition.

More recently, it has been indicated that SARS-CoV-2 may cause a diffuse endothelial inflammatory process with effects on capillary vasomotor capacity, leading to increased vasoconstriction that causes cellular ischaemia, tissue oedema and activation of a pro-coagulant state.[23] These microvascular and thrombotic injuries in the pathogenesis of severe SARS-CoV-2 infection could explain how biomarkers related to altered capillary permeability (albumin) and coagulant homoeostasis (D-dimer) may identify patients with more severe SARS-CoV-2 infection. The serum albumin level, which is easily and quickly obtainable at limited cost at the first patient evaluation, could contribute to the assessment of the severity of SARS-CoV-2 infection in patients and, together with other biomarkers, support the ED physician's evaluation.

This study presents some limitations. First, the retrospective nature of the study exposes it to all of the possible biases associated with this study design. However, the presence of a shared procedure in the three EDs for patients with suspected SARS-CoV-2 should have resulted in appropriate patient selection and allowed patients of different severities to be included in the study. The mortality rate of this cohort was similar to that reported in other Italian studies, suggesting appropriate patient selection.[24] Second, a small quota of enrolled patients presented a clinical diagnosis of COVID-19 that was not confirmed by subsequent microbiological testing. This is consistent with previous studies in which these patients were not excluded from the analyses, and the proportion appears to be comparable.[25] Third, there are no inflammatory (eg, IL-6) or instrumental (CT volumetry) data that are available to estimate the severity of inflammation with albumin values. Fourth, information that could affect baseline values of albumin, such as nutritional status and obesity, were not available. Fifth, the cut-off for the dichotomisation of the albumin value was chosen a priori. While the value of 3.5 g/dL for indicating a condition of hypoalbuminaemia is shared in multiple study settings, lower cut-offs for indicating more severe conditions of hypoalbuminaemia differ among the studies, as they are influenced by setting, population under analysis and therapeutic procedures performed.[7] In particular, the choice of including the cut-off (<3 g/dL) to describe the population and survival was made considering those studies more similar in setting and pathology to the current study as well as the first available reports on patients with SARS-CoV-2 infection.[17 18] For this reason, the multivariate analysis of association with outcomes was performed only on the more consistent cut-off of 3.5 g/dL.

In conclusion, these preliminary data suggest that the serum albumin level in the ED may play a role in the assessment of the severity of SARS-CoV-2 infection and the risk of death at 30 days. Further prospective evaluations are needed to confirm whether serum albumin levels indeed play an important prognostic role in patients with SARS-CoV-2 infections.

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dell'Alto Adige, Bolzano, Italia, approval number 57–2020 and Comitato etico per la Sperimentazione Clinica delle Province di Verona e Rovigo, Verona, Italia, approval number 2577-CESC) and was conducted according to the Declaration of Helsinki regarding the Ethical Principles for Medical Research Involving Human Subjects.

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