Hypoalbuminemia, An Independent Risk Factor for Severity and Mortality Affects One Third of Patients in Acute Pancreatitis: Multicenter Prospective International Cohort Analysis

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Abstract

Introduction The incidence and medical costs of acute pancreatitis (AP) are on the rise, and severe cases still have a 30% mortality rate. We aimed to evaluate hypoalbuminemia as a risk factor and the prognostic value of human serum albumin in AP.

Methods Data of 2461 patients were extracted from the international, prospective, multicenter AP registry of the Hungarian Pancreatic Study Group. Data of patients with albumin measurement in the first 48 hours (n=1149) and anytime during hospitalization (n=1272) was analyzed. Multivariate binary logistic regression and Receiver Operator Characteristic curve analysis were used.

Results The prevalence of hypoalbuminemia (<35g/L) was 19% on-admission and 35.7% during hospitalization. Hypoalbuminemia dose-dependently increased the risk of severity, mortality, local complications, and organ failure and is associated with longer hospital stay. The predictive value of hypoalbuminemia on-admission was poor for severity and mortality. Severe hypoalbuminemia (<25 g/L) was an independent risk factor for severity (OR: 48.761; CI:25.276-98.908) and mortality (OR:16.83; CI: 8.32-35.13). Albumin loss during AP was strongly associated with severity (p<0.001) and mortality (p=0.002).

Conclusion Hypoalbuminemia is an independent risk factor of severity and mortality in AP, and it shows a dose-dependent relationship with local complications, organ failure, and length of stay.

Introduction

Acute pancreatitis is a common gastroenterological disorder, with rising incidence and high medical costs. The commonly used revised Atlanta Classification distinguishes between mild, moderate, and severe disease by the development and duration of organ failure¹. As the mortality rate can reach 30% in severe cases, identifying risk factors and potential therapeutic targets is of utmost importance.

Human serum albumin is the most abundant protein in human serum, with a very diverse role. Although this hypothesis was contradicted by recent data, declining albumin levels during inflammation for long prompted physicians to underestimate its contribution to maintaining homeostasis during inflammation. However, it plays a pivotal role in maintaining the plasma redox state², and its scavenging activity is likely to influence vascular resistance through the regulation of nitric oxide levels³. Furthermore, low albumin levels result in dilution and increased drug clearance, ultimately causing sub-optimal treatment⁴.

Small retrospective cohort studies showed that hypoalbuminemia is an independent risk factor for severe AP and in-hospital mortality in adults and children^{5,6}. Serum albumin was reported to be associated with persistent organ failure and prolonged hospital stay⁷. However, whether albumin is only a marker or there is a cause-effect relationship between hypoalbuminemia and disease severity and mortality should be further evaluated.

While comprehensive analyses are missing on AP patients with hypoalbuminemia and albumin loss in AP, we aimed to evaluate (1) on-admission and in-hospital hypoalbuminemia as a risk factor in AP, (2) the prognostic potential of human serum albumin, (3) whether there is a dose-dependent relationship between albumin level and disease outcomes and (4) the association of albumin loss with severity and mortality.

We found evidence that AP patients with < 25 g/L serum albumin anytime during hospitalization have a 16.8 times higher risk of death and 48.8 times higher risk of severe AP than patients with normal albumin levels. We also pointed out that albumin loss during AP is associated with severity and mortality. These data highlight the unmet need for randomized controlled trials focusing on albumin replacement.

Results

One in every five patients suffering from acute pancreatitis has hypoalbuminemia on admission

Nineteen percent of patients (n = 218/1149) presented with hypoalbuminemia (< 35g/L). 12.4% of patients were admitted with 30-34.99 g/L albumin levels (group 5), whereas 4.4% and 2.2% of patients had 25-29.99 g/L (group 6) and < 25 g/L (group 7) on-admission albumin levels (Supplementary Fig. S3).

Older age, lower body mass index, abdominal guarding, on physical examination and non-biliary etiology are associated with on admission hypoalbuminemia

Hypoalbuminemia was associated with older age (average 59.7 ± 18.0 and 56.0 ± 16.1 years; $p = 0.005$, Supplementary Fig. S3). Males were overrepresented in the analyzed cohort (57%) and all subgroups (Fig. S3). Although biliary etiology was the most frequent in all subgroups, significantly fewer patients had biliary etiology (34.4% versus 42.2%; $p = 0.042$) in the low albumin group, and a tendency of more alcoholic episodes (24.3% and 19%; $p = 0.096$) was seen (Supplementary Fig. S3).

Significantly lower body mass index (average 28.23 and 27.23; $p = 0.012$) was found in the low albumin group compared to the normal albumin group (Supplementary Fig. S4). Diabetes mellitus (22.6% versus 19.3%; $p = 0.318$) and chronic pancreatitis (7.3% versus 6.1%, $p = 0.507$) were overrepresented in patients with hypoalbuminemia, however, fewer patients with hypoalbuminemia had recurrent AP (17.4% versus 21.9%, $p = 0.144$) (Supplementary Fig. S4.).

Considering the signs and symptoms, fewer hypoalbuminemia patients presented with abdominal pain (94.9% and 99.2%; $p < 0.001$) and more with abdominal guarding (27.2% and 19.9%; $p = 0.023$) (Fig. S5). General signs, such as duration and intensity of abdominal pain, abdominal tenderness, nausea, and vomiting, did not significantly differ. Hypoalbuminemia was associated with a dose-dependent increase in heart rate and a decrease in systolic and diastolic blood pressures on admission (Supplementary Fig. S5).

The fulfillment of diagnostic criteria differed significantly ($p < 0.001$) among the low and normal albumin groups on-admission. Low albumin patients were less likely to present with pancreatic enzyme elevation, abdominal pain, and characteristic imaging findings at the same time (42.7% versus 58.4%) (Supplementary Table S2).

On-admission hypoalbuminemia is dose-dependently associated with elevated CRP and PCT levels in AP

The low albumin group had significantly lower serum amylase ($p < 0.001$) and lipase ($p = 0.002$) levels on admission. A dose-dependent C-reactive protein (CRP) ($p < 0.001$) and procalcitonin (PCT) ($p < 0.001$) increase was observed in the lower albumin groups. White blood cell count (WBC) ($p = 0.017$) levels were also significantly elevated in the low albumin group (Fig. S6-7). Concerning laboratory markers of renal function, hypoalbuminemia patients had significantly higher blood urea nitrogen (BUN) ($p = 0.002$) and creatinine ($p = 0.002$) levels and lower estimated glomerular filtration rate (eGFR) ($p < 0.001$) (Supplementary Fig. S8-9). Liver enzymes and total bilirubin levels did not differ between the low and normal albumin groups, but hypoalbuminemia was associated with higher direct bilirubin levels ($p = 0.005$) and a higher international normalized ratio (INR) ($p < 0.001$) (Supplementary Fig. S10-13). Hematological parameters, lipids, ions, and glucose levels are shown in Supplementary Figures S14-17.

On-admission hypoalbuminemia is dose-dependently associated with complications, severity, and mortality in AP

Significantly more patients developed local complications, and organ failure in the low albumin group ($p = 0.016$ and $p < 0.001$, respectively) (Fig. 1–2). Lower albumin levels correlated with a higher rate of peripancreatic fluid collection and respiratory failure ($p < 0.001$ and $p = 0.051$). The rate of pancreatic necrosis, pseudocyst, or heart failure did not differ significantly between the groups.

All types of local complications were significantly more frequent in the low albumin group. A dose-dependent increase was seen in the rate of local complications and peripancreatic fluid collection in both cohorts and in pancreatic necrosis and pseudocyst in the lowest measured albumin cohort. $P < 0.05$ is considered significant. Patients with albumin levels < 35 g/L were included in the low albumin group (groups 5–7).

Significantly more patients developed organ failure in the low albumin group in both cohorts. A dose-dependent increase was seen in the case of all analyses in the lowest measured albumin cohort. Heart failure was dose-dependently increased in the on-admission cohort as well. $P < 0.005$ is considered significant.

Most importantly, hypoalbuminemia was associated with increased mortality ($p = 0.020$), disease severity ($p = 0.015$), and hospital stay ($p = 0.025$) (Fig. 3). Groups 6 and 7 had significantly higher mortality ($p = 0.005$ and $p = 0.007$, respectively) and severity ($p = 0.028$ and $p < 0.001$, respectively) compared to the

normal group. Maximum CRP levels during the course of AP significantly and dose-dependently increased with the degree of serum albumin ($p < 0.001$, Fig. 3).

On-admission hypoalbuminemia is an independent risk factor of severity and mortality, with an odds ratio up to 5.3 for mortality in acute pancreatitis

Age, hypertriglyceridemia-induced (with or without concomitant alcoholic etiology), and idiopathic AP were independently associated with mortality. Severe on-admission hypoalbuminemia proved to be an independent risk factor for mortality with an OR of 3.782 (CI: 1.313–9.462) in group 6 (< 30 g/L) and an OR of 5.256 (CI: 1.389–16.112) in group 7 (< 25 g/L) (Table 1.) Albumin levels were examined with a 35 g/L cut-off in a separate analysis, which found an independent association between hypoalbuminemia and mortality (OR: 2.070; CI: 1.021–4.033; Supplementary Table S1). Age, hypertriglyceridemia-induced AP, and, among the multifactorial etiologies the combination of hypertriglyceridemia and alcohol were independent risk factors of disease severity. On-admission albumin levels < 25 g/L were independently associated with severe AP (OR: 3.620; CI: 1.128–9.978; Table 1).

Table 1

– Multivariate logistic regression analysis on the prognostic role of on-admission hypoalbuminemia in acute pancreatitis

On-admission albumin (n = 1149) - mortality						
Predictor		β	SE	OR	95% CI	p
On-admission albumin level	30-34.99 g/L (vs. ≥ 35 g/L)	-0.108	0.553	0.898	0.259–2.390	0.845
	25-29.99 g/L (vs. ≥ 35 g/L)	1.330	0.496	3.782	1.313–9.462	0.007
	< 25 g/L (vs. ≥ 35 g/L)	1.659	0.611	5.256	1.389–16.112	0.007
Age	per years	0.037	0.012	1.037	0.014–1.063	0.003
Gender	female (vs. male)	-0.222	0.370	0.801	0.383–1.648	0.548
Etiology	alcohol (vs. biliary)	0.669	0.554	1.952	0.636–5.725	0.227
	HTG (vs. biliary)	1.669	0.747	5.304	1.037–21.022	0.025
	biliary + alcohol (vs. biliary)	1.234	1.100	3.436	0.178–20.816	0.262
	biliary + HTG (vs. biliary)	-12.903	783.282	-	-	0.987
	alcohol + HTG (vs. biliary)	1.781	0.768	5.938	1.123–24.693	0.020
	idiopathic (vs. biliary)	1.119	0.427	3.061	1.330–7.223	0.009
	other (vs. biliary)	0.010	0.790	1.010	0.152–3.964	0.990
On-admission albumin (n = 1149) - severity						
Predictor		β	SE	OR	95% CI	p
On-admission albumin	30-34.99 g/L (v. ≥ 35 g/L)	0.029	0.383	1.030	0.457–2.086	0.939
	25-29.99 g/L (v. ≥ 35 g/L)	0.829	0.449	2.292	0.882–5.238	0.065
	< 25 g/L (v. ≥ 35 g/L)	1.286	0.548	3.620	1.118–9.968	0.019

On-admission albumin (n = 1149) - mortality						
Age	per years	0.040	0.010	1.041	1.022–1.061	< 0.001
Gender	female (vs. male)	-0.183	0.281	0.830	0.478–1.442	0.515
Etiology	alcohol (vs. biliary)	0.522	0.420	1.685	0.751–3.673	0.195
	HTG (vs. biliary)	1.712	0.546	5.543	1.776–15.536	0.002
	biliary + alcohol (vs. biliary)	1.056	0.802	2.874	0.426–11.572	0.188
	biliary + HTG (vs. biliary)	-13.792	785.525	-	-	0.986
	alcohol + HTG (vs. biliary)	1.316	0.632	3.727	0.952–11.941	0.037
	idiopathic (vs. biliary)	0.536	0.330	1.709	0.884–3.247	0.104
	other (vs. biliary)	-0.475	0.629	0.622	0.145–1.852	0.450

HTG: hypertriglyceridemia; β : β coefficient; SE: standard error; OR: odds ratio; CI: confidence interval

On-admission albumin levels alone have poor predictive value in AP

On-admission albumin levels have an AUC of 0.615 (sensitivity: 57.6%, specificity: 61.1%) for the severity with a cut-off at 39.3 g/L (Fig. 4). The AUC for mortality was 0.660 (sensitivity: 72.1%, specificity: 53.7%) with a cut-off at 37.0 g/L.

These data prompt that albumin plays a crucial role in the pathophysiology and clinical outcome of AP, however cannot be used as a single biomarker for predicting severity and mortality. Next, we wanted to understand whether albumin loss during the course of AP has any association with the outcome of the disease; therefore, we regrouped our patients based on the lowest measured albumin levels.

One out of three patients suffer from hypalbuminemia in AP during hospitalization, which dose-dependently correlates with disease severity and mortality in AP

The proportion of patients with hypoalbuminemia anytime during hospitalization was 35.7% (454 patients). A significant, dose-dependent increase was seen in the low albumin groups (group 5–7) compared to the normal albumin group regarding the rate of all examined systemic and local complications (Fig. 1–2). The lowest measured albumin levels throughout hospitalization (n = 1272) were

significantly and dose-dependently associated with severity ($p < 0.001$), mortality ($p < 0.001$), length of stay ($p < 0.001$), and maximum CRP values ($p < 0.001$) (Fig. 3).

Moderate and severe AP and mortality is associated with significantly lower albumin levels and greater albumin loss

Albumin loss was analyzed using data from patients with at least two albumin measurements ($n = 335$; Supplementary Fig. S18). Compared to mild cases, patients with moderate and severe AP showed a greater decrease in albumin levels (medians 5.4 vs. 9 and 15.25 g/L; $p < 0.001$ for both comparisons). The comparison of delta albumin between the moderate and severe groups also yielded significant results ($p = 0.003$). Patients who died also lost significantly more albumin during hospitalization (medians 6.7 vs. 15.75 g/L; $p = 0.002$). The median time to the lowest albumin levels from admission was 4 days (IQR: 3–7 days).

AP patients with less than 25 g/L serum albumin have a 16.8 times higher risk of death, and 48.8 times higher risk of severe AP compared to patients with normal albumin levels

Age is an independent risk factor for severe AP and mortality, whereas hypertriglyceridemia-induced and idiopathic AP and the combination of alcoholic and biliary causes are independently associated with mortality (Table 2 and Supplementary Table S2). Hypoalbuminemia below 25–29.99 g/L (OR: 2.912; CI: 1.176–6.893) and below 25 g/L (OR: 16.828; CI: 8.323–35.129) were associated with an increased risk of mortality (Table 2). In a separate analysis, hypoalbuminemia (< 35 g/L) was also an independent risk factor for mortality (OR: 4.185; CI: 2.286–8.039) (Table S3). Furthermore, hypoalbuminemia anytime during hospitalization was associated with a higher risk for severe AP (OR: 10.664; CI: 6.188–19.614), and a gradual increase of odds ratios can be observed in the low albumin groups (OR: 2.359; CI: 1.030–5.240 for group 5; OR: 11.709; CI: 6.038–23.515 for group 6 and OR: 48.761; CI: 25.276–98.908 for group 7).

Table 2
Logistic regression for severity and mortality using the lowest measured albumin cohort

Lowest measured albumin (n = 1272) - mortality						
Predictor		β	SE	OR	95% CI	p
On-admission albumin level	30-34.99 g/L (vs. ≥ 35 g/L)	-0.016	0.531	0.984	0.313–2.621	0.976
	25-29.99 g/L (vs. ≥ 35 g/L)	1.069	0.448	2.912	1.166–6.893	0.017
	< 25 g/L (vs. ≥ 35 g/L)	2.823	0.365	16.828	8.323–35.129	< 0.001
Age	per years	0.043	0.012	1.044	1.021–1.070	< 0.001
Gender	female (vs. male)	-0.352	0.347	0.703	0.352–1.380	0.309
Etiology	alcohol (vs. biliary)	0.909	0.523	2.481	0.880–6.960	0.083
	HTG (vs. biliary)	1.569	0.766	4.803	0.914–19.900	0.041
	biliary + alcohol (vs. biliary)	1.651	0.793	5.215	0.949–22.798	0.037
	biliary + HTG (vs. biliary)	-12.335	786.272	-	-	0.987
	alcohol + HTG (vs. biliary)	1.356	0.793	3.880	0.709–17.009	0.087
	idiopathic (vs. biliary)	1.402	0.402	4.063	1.878–9.181	< 0.001
	other (vs. biliary)	0.213	0.807	1.237	0.182–5.045	0.792
Lowest measured albumin (n = 1272) - severity						
Predictor		β	SE	OR	95% CI	p
On-admission albumin	30-34.99 g/L (v. ≥ 35 g/L)	0.858	0.410	2.359	1.030–5.240	0.036
	25-29.99 g/L (v. ≥ 35 g/L)	2.460	0.345	11.709	6.038–23.515	< 0.001
	< 25 g/L (v. ≥ 35 g/L)	3.887	0.346	48.761	25.276–98.908	< 0.001
Age	per years	0.032	0.009	1.032	1.015–1.051	< 0.001

Lowest measured albumin (n = 1272) - mortality						
Gender	female (vs. male)	-0.332	0.274	0.718	0.417–1.225	0.226
Etiology	alcohol (vs. biliary)	0.093	0.403	1.097	0.492–2.403	0.818
	HTG (vs. biliary)	1.060	0.565	2.885	0.910–8.476	0.061
	biliary + alcohol (vs. biliary)	0.172	0.778	1.188	0.222–5.006	0.825
	biliary + HTG (vs. biliary)	-13.429	753.256	-	-	0.986
	alcohol + HTG (vs. biliary)	0.497	0.657	1.643	0.422–5.688	0.450
	idiopathic (vs. biliary)	0.541	0.320	1.718	0.915–3.218	0.091
	other (vs. biliary)	0.008	0.547	1.008	0.310–2.744	0.988

HTG: hypertriglyceridemia; β : β coefficient; SE: standard error; OR: odds ratio; CI: confidence interval

The lowest albumin values have good and fair predictive value for severity and mortality in acute pancreatitis

The lowest measured albumin levels have higher AUC values: 0.848 for severity and 0.747 for mortality (Fig. 3). The best cut-off values were 31.3 g/L for severity (sensitivity: 82.9%, specificity: 76.4%) and 28.6 g/L for mortality (sensitivity: 89.9%, specificity: 56.1%). The day of the lowest albumin measurement ranged from 1 to 56 days, with a median of 2 days. Most patients only had a single measurement around the time of admission.

Discussion

To date, this is the most comprehensive evaluation of AP patients with hypoalbuminemia, using the largest, prospectively collected, high-quality dataset.

We found that almost one-fifth of patients had hypoalbuminemia on admission (19%), and a further 25% developed hypoalbuminemia during hospitalization, meaning that every third patient was affected.

In our analysis, hypoalbuminemia under 25 g/L anytime during hospitalization was independently associated with a more than 47 times higher chance for severe AP and a more than 16 times higher chance for mortality.

Our findings are in line with results regarding hypoalbuminemia in other diseases. Hypoalbuminemia was a prominent risk factor in community-acquired bloodstream infection with severe sepsis and septic shock⁸. A retrospective analysis from more than 20.000 emergency medical patients' data from Ireland revealed that hypoalbuminemia is independently associated with 30-day in-hospital mortality, with a non-linear relationship between mortality and on-admission albumin levels⁹. Moreover, in a secondary analysis of a prospective cohort, AP patients with multiorgan failure (MOF; n = 18) demonstrated a sharper decline in serum albumin ($P < 0.001$) compared to non-MOF patients (n = 39)¹⁰.

We did not only prove that hypoalbuminemia is a risk factor but showed the dose-dependent association between low albumin levels and severity, mortality, number of patients with any local complications, number of patients developing organ failure, and maximum CRP levels in both analyses (on-admission and lowest measured albumin levels).

These associations can be explained by the numerous physiological functions of human serum albumin. For long, albumin was considered a negative acute-phase protein, with decreasing production giving way to inflammatory cytokines in inflammation¹¹. Serum albumin levels undoubtedly decrease in inflammatory states, which may be due to a shorter half-life and a larger interstitial pool which causes the dilution of albumin¹²⁻¹⁴. Capillary leak consequential to inflammatory processes plays a role in the decline of serum albumin, but it is argued that the escape of albumin to the tissues may be beneficial because of its antioxidant and scavenging activity¹⁵. However, a more than two times higher production rate was observed in critically ill ICU patients; this increased production can still not balance the higher demand. This can be considered as a relative synthetic insufficiency of hepatic function¹⁶.

In our analysis, albumin loss was significantly associated with severity and mortality. However, only 51.7% of patients had albumin measurements at least once, and 13.6% at least twice during their hospitalization in the HPSG database. This highlights how neglected albumin measurements are in AP.

From the clinician's point of view, the decline of serum albumin levels – regardless of on-admission albumin levels - signals clinical worsening and may help identify high-risk AP patients. However, clinicians mostly miss the opportunity to pre-emptively and frequently measure serum albumin, delaying timely intervention.

To date, no clinical trial examined therapeutic albumin administration in AP. As we know, albumin is similarly associated with outcomes in sepsis and septic shock; randomized controlled trials on this field could be a starting block^{15,17}. The controversial results of studies and meta-analyses on this field may be explained by heterogeneous patient populations and the time sensitivity of this treatment¹⁸.

To exploit the potential in therapeutic albumin administration in AP, further, more detailed clinical studies are needed to identify the patient subpopulations benefiting the most from this therapeutical option.

Conclusion

Hypoalbuminemia is remarkably common in AP (seen in 19% of patients on-admission and 35.7% during hospitalization) and an independent risk factor of severity, mortality. Importantly, albumin loss during hospitalization was also associated with severity and mortality, suggesting that routine monitoring of serum albumin is recommended, and albumin administration should be examined as a therapeutic intervention in AP.

Implications for research: Clinical trials assessing the potential benefit of albumin replacement in AP are needed.

Implication for practice: 1) Albumin levels should be measured for all AP patients, 2) Albumin levels should be controlled at least in those patients whose condition is worsening during AP, 3) Albumin administration should be considered at least in those patients with severe hypoalbuminemia (< 25 g/L).

Methods

Study design and definitions

This analysis of an international, prospective, multicenter cohort was done using data from the Acute Pancreatitis Registry of the Hungarian Pancreatic Study Group (HPSG) ¹⁹. Patient data were collected from registry establishment until 31 December 2019 on electronic case report forms and validated using a four-tiered data validation protocol. Contributing centers are shown in the supplementary material (Table and Fig. S1). The registry was approved by the Scientific and Research Ethics Committee of the Medical Research Council (222254-1/2012/EKU) in 2012. It conforms to the Declaration of Helsinki revised in 2013. All participants provided written informed consent. Data collection and validation are detailed by Párniczky et al. ²⁰. The Hungarian Pancreatic Study Group published analyses from the registry, the population of which may overlap with our analyzed cohort ^{20–30}.

Diagnosis of AP was established using the IAP/APA guidelines ³¹, while severity and complications were defined using the Revised Atlanta Classification ¹.

Participants

To answer a post-hoc clinical research question, analyses were performed on patients' data with albumin measurement anytime during hospitalization (lowest measured albumin cohort, n = 1272) and in the first 48 hours of hospitalization (on-admission albumin cohort, n = 1149). The cut-off value between the low and normal albumin group was 35 g/L in both cases, based on the commonly used lower normal value. Subjects were further divided into 7 subgroups (group 1 to 7) using the lowest (n = 1272) or first measured (n = 1149) albumin values.

In the analyses of albumin change, selected patients (n = 335) with at least two albumin measurements were included. Delta albumin was calculated as the difference between the first and lowest measured albumin levels.

Statistical analysis

Descriptive statistics are presented as median with 25% and 75% percentiles (IQR) or mean with standard deviation (SD) for continuous variables and as numbers and proportions for categorical variables.

Chi-squared test or Fisher's exact test were used for the assessment of the relationship between categorical variables. Mann-Whitney U test or Kruskal-Wallis test followed by Dunnett's post hoc test was used to evaluate differences between groups in case of continuous variables.

Multivariate binary logistic regression analysis was performed to identify the risk factors independently associated with severe disease and mortality. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Receiver Operator Characteristic (ROC) curve and Area Under the Curve (AUC) with 95% CI was used to identify the ability of albumin levels predicting mortality or severity of AP (AUC between 0.5–0.6 was considered as fail, between 0.6–0.7 as poor, between 0.7–0.8 as fair, between 0.8–0.9 as good and above 0.9 as excellent). Best cut-offs were calculated by using the Youden index ³².

$P < 0.05$ was considered statistically significant, except for the Kruskal-Wallis test followed by Dunnett's post hoc test, where $p < 0.025$ was considered statistically significant.

All analyses were carried out in R statistical software, version 4.0.2 (R Core Team, 2020, Vienna, Austria), packages: pROC (v. 1.17.0.1) and PMCMRplus (v. 1.9.0.) ^{33,34}.

Representativity

The main characteristics of the analyzed cohorts are in accordance with literature data. However, they differed significantly from the entire cohort ($n = 2461$) in terms of severity, length of stay, and mortality (Fig. S2).

Reporting

We report our results following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, using the provided checklist ³⁵.

Data availability

The full dataset is available upon reasonable request.

Strengths And Limitations

We conducted the most extensive, most comprehensive cohort study on the role of hypoalbuminemia in acute pancreatitis to date. We analyzed high-quality data from a prospective, international, multicentric registry. We identified hypoalbuminemia as an independent risk factor in AP, present in at least every third

patient. We also found a dose-dependent relationship between albumin levels and main outcomes, which was previously not described.

Among the limitations, we must mention the arbitrary classification of albumin levels (except for the low-normal cut-off), the missing data on albumin levels and albumin administration during the hospital stay, and the limited number of albumin measurements during the hospital stay, which could introduce bias. Our analyzed cohorts differed from the total cohort in some aspects, which may signal performance bias, as albumin measurements are more frequently ordered for patients with expected hypoalbuminemia.

Declarations

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Author contributions

KO, PH and AP drafted the concept and interpreted the data. KO wrote the majority of the manuscript. DN and LS performed the statistical analyses. VZ prepared the figures. JB, SG, PS, LC, FI, JH, MP, MV, IT, AM, VS, ERM, SG, PK, RH, BE and ZM all provided a substantial number of enrolled participants. AM, ZS, MI and PJH performed patient enrollment and supervised data quality. NF and OF acted as a radiological supervisor, ensuring data quality. AM and TN provided insight on laboratory markers and contributed to patient enrollment. AS, PH and AP provided methodological and medical guidance and supervised the writing of the article. All co-authors have read and approved the final version of the manuscript.

The authors declare no conflict of interest.

Data availability

The full dataset is available upon reasonable request.

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Figures

Figure 1

Association between albumin level and local complications defined by the Revised Atlanta Criteria in acute pancreatitis. All types of local complications were significantly more frequent in the low albumin group. A dose-dependent increase was seen in the rate of local complications and peripancreatic fluid collection in both cohorts and in pancreatic necrosis and pseudocyst in the lowest measured albumin

cohort. P<0.05 is considered significant. Patients with albumin levels <35 g/L were included in the low albumin group (groups 5-7).

Figure 2

Association between albumin level and organ failures, defined by the Revised Atlanta Criteria in acute pancreatitis. Significantly more patients developed organ failure in the low albumin group in both cohorts. A dose-dependent increase was seen in the case of all analyses in the lowest measured albumin cohort.

Heart failure was dose-dependently increased in the on-admission cohort as well. $P<0.005$ is considered significant.

Figure 3

Association between albumin level and disease severity, mortality, length of stay and maximum C-reactive protein level in acute pancreatitis Severity, mortality, length of stay and maximum C-reactive

protein levels were significantly and dose-dependently associated with hypoalbuminemia in both cohorts. P<0.05 is considered significant.

Figure 4

Receiver operating curves for mortality and severity AUC: area under the curve; best cut-offs are shown in red

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