

Supplementary material

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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Country	Center	n
<i>Hungary</i>	First Department of Medicine, Medical School, University of Pécs, Pécs	609
	Szent György University Teaching Hospital of Fejér County, Székesfehérvár	211
	First Department of Medicine, University of Szeged, Szeged	148
	Department of Internal Medicine, University of Debrecen, Debrecen	146
	Bajcsy-Zsilinszky Hospital and Clinic, Budapest, Hungary	12
	Department of Emergency Medicine, University of Szeged, Szeged	10
	Second Department of Medicine, University of Szeged, Szeged	6
	Department of Surgery, University of Debrecen, Debrecen	6
	Markusovszky University Teaching Hospital, Szombathely	6
	Pándy Kálmán Hospital of Békés County, Gyula	4
	Dr. Bugyi István Hospital, Szentes	4
	Csongrád County Health Center, Makó	4
	Dr. Réthy Pál Hospital, Békéscsaba	2
	Buda Hospital of the Hospitaller Order of Saint John of God, Budapest	1
	Heim Pál National Pediatric Institute, Budapest	1
	Second Department of Internal Medicine, Semmelweis University, Budapest	1
<i>Finland</i>	Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki	25
<i>Turkey</i>	Hospital of Bezmialem Vakif University, School of Medicine, Istanbul	20
<i>Russia</i>	Saint Luke Clinical Hospital, St. Petersburg	19
<i>Spain</i>	General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes, Barcelona	14
<i>Croatia</i>	Clinical Hospital Center Rijeka, Rijeka	11
<i>Lithuania</i>	Vilnius University Hospital, Vilnius, Lithuania	5
<i>Romania</i>	County Emergency Clinical Hospital of Targu Mures Hospital, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Targu Mures	2
	Central Military Emergency Hospital "Dr Carol Davila", Bucharest	1
<i>Latvia</i>	Gastroenterology, Hepatology and Nutritional Centre, Pauls Stradins Clinical University Hospital, Riga	2
<i>Japan</i>	Keio University, Tokyo	1
<i>Ukraine</i>	Bogomolets National Medical University, Kiev	1
Total		1272

Table 1 - List of centers
n: patient number

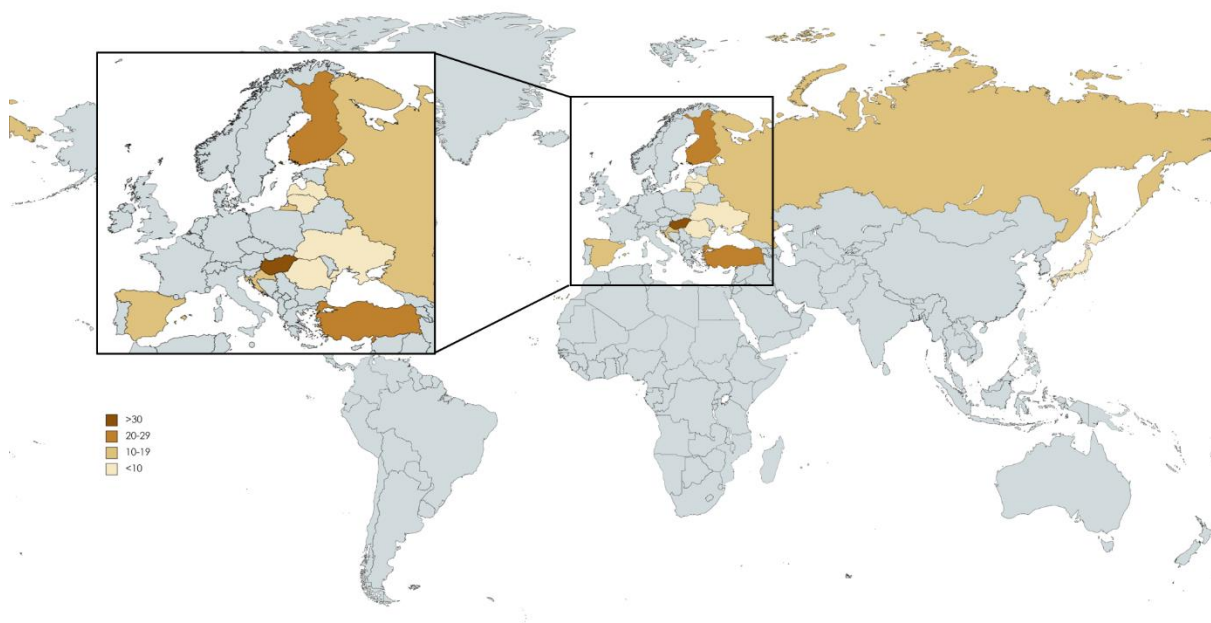


Figure S1 – Map of centers

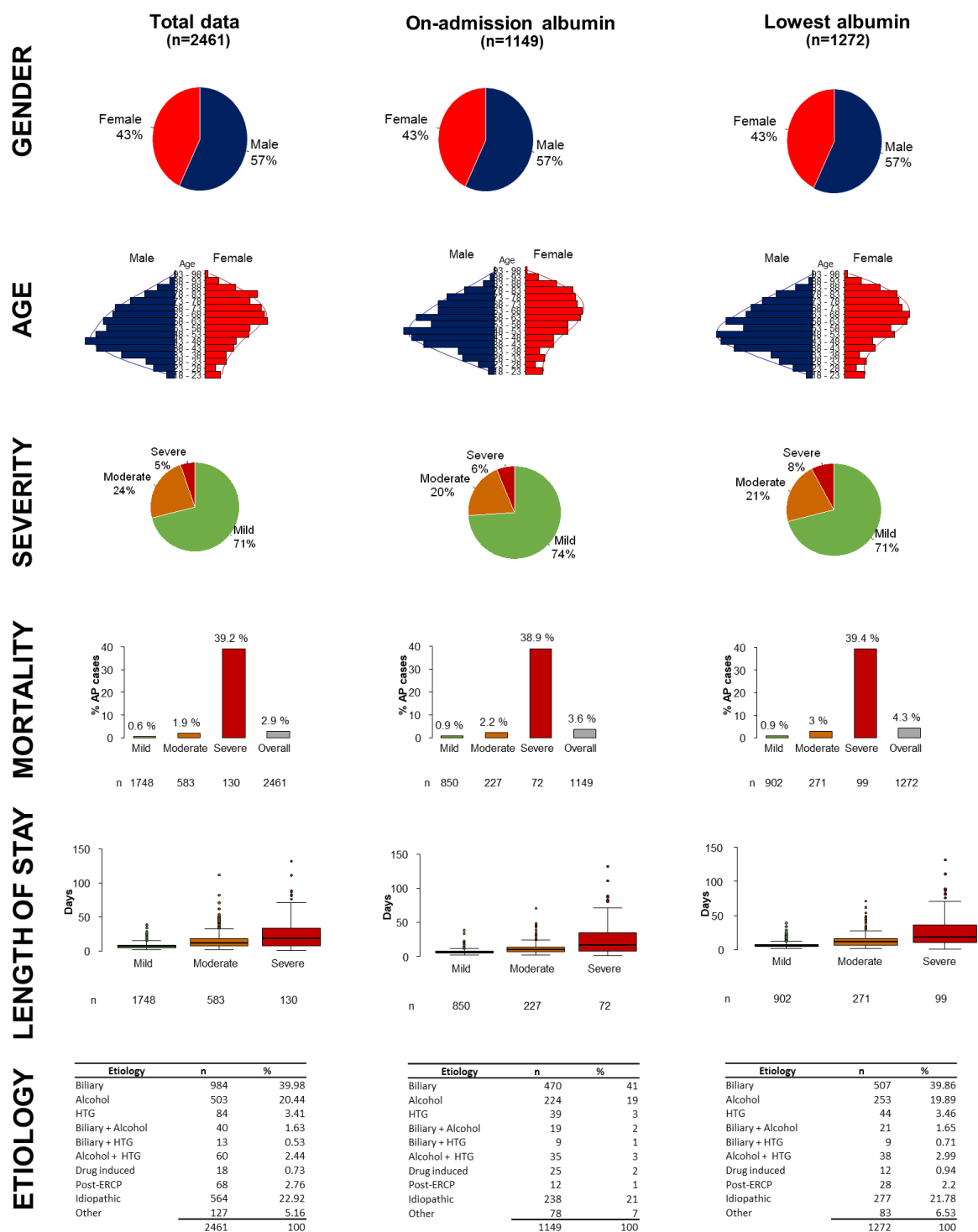


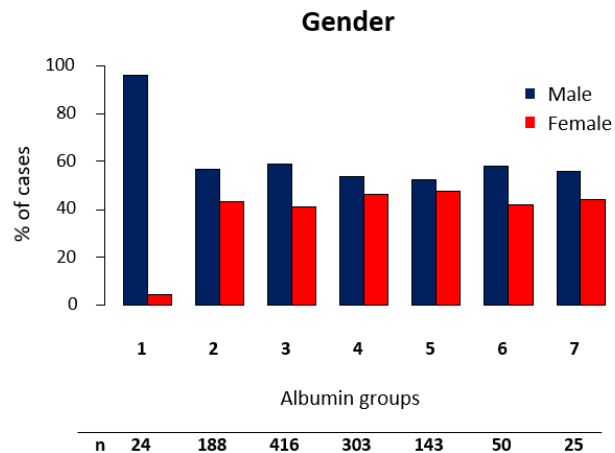
Figure S2 – Representativity of the analysed cohorts

Cohorts were compared to the original (n=2461). The analysed cohorts differed significantly in severity ($p=0.025$ for on-admission and $p=0.005$ for lowest albumin) and length of stay ($p<0.001$ for both cohorts). The lowest albumin cohort also differed in mortality ($p=0.026$).

A

Group	Albumin (g/l)	n	%	Age year (SD)
1	>50	24	2.1%	46.3 (±12.9)
2	49.99-45	188	16.4%	51.2 (±15.1)
3	44.99-40	416	36.2%	55.8 (±16.0)
4	39.99-35	303	26.4%	60.1 (±16.0)
NORMAL Albumin		931	81.0%	56.0 (±16.1)
5	34.99-30	143	12.4%	61.2 (±17.5)
6	29.99-25	50	4.4%	60.6 (±17.6)
7	<24.99	25	2.2%	51.5 (±20.1)
LOW Albumin		218	19.0%	59.7 (±18.0)
TOTAL		1149	100	56.7 (±16.5)

B



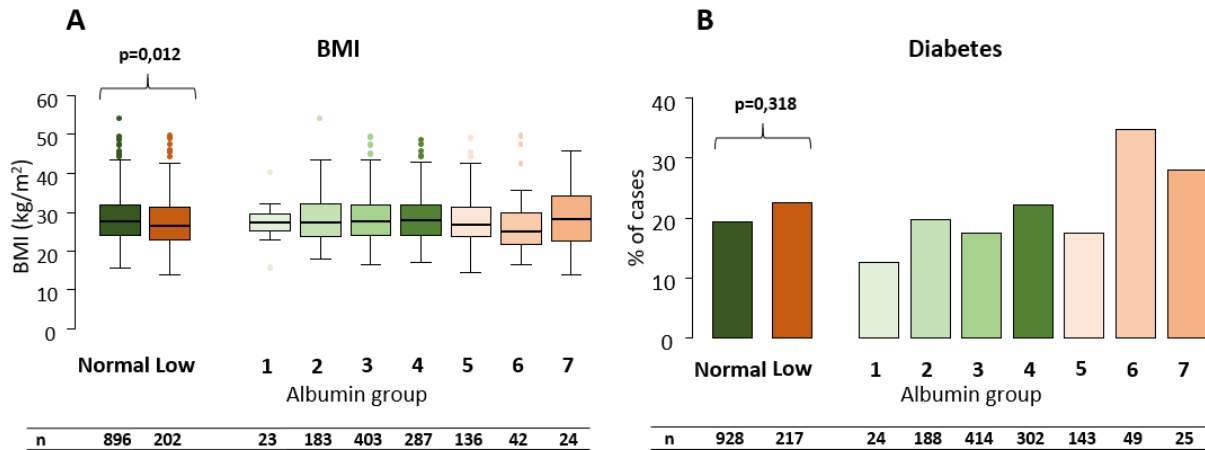
C

Albumin group	n	Biliary (%)	Alcohol (%)	HTG (%)	Post-ERCP (%)	Drug induced (%)	Alcohol + HTG (%)	Alcohol + biliary (%)	Biliary + HTG (%)	Others (%)	Idiopathic (%)
1	24	16.7	58.3	4.2	0.0	0.0	0.0	0.0	0.0	4.2	16.7
2	188	43.6	19.7	2.1	1.6	1.1	3.2	1.6	1.1	6.4	19.7
3	416	41.6	17.1	2.9	1.4	0.7	3.1	1.9	0.5	7.9	22.8
4	303	44.2	18.2	4.3	2.3	1.0	2.6	1.0	0.7	6.3	19.5
Normal Albumin	931	42.2	19.0	3.2	1.7	0.9	2.9	1.5	0.6	7.0	20.9
5	143	37.8	23.8	1.4	5.6	2.1	3.5	2.8	1.4	4.9	16.8
6	50	30.0	28.0	4.0	0.0	2.0	0.0	0.0	2.0	8.0	26.0
7	25	24.0	20.0	16.0	0.0	0.0	16.0	0.0	0.0	4.0	20.0
Low Albumin	218	34.4	24.3	3.7	3.7	1.8	4.1	1.8	1.4	5.5	19.3

n	394	173	32	16	8	28	16	6	66	192
1	0.9	6.1	2.6	0.0	0.0	0.0	0.0	0.0	1.3	1.7
2	17.5	16.1	10.5	12.5	16.7	16.7	16.7	22.2	15.6	15.6
3	37.0	30.9	31.6	25.0	25.0	36.1	44.4	22.2	42.9	40.1
4	28.6	23.9	34.2	29.2	25.0	22.2	16.7	22.2	24.7	24.9
Normal Albumin	84.0	77.0	78.9	66.7	66.7	75.0	77.8	66.7	84.4	82.3
5	11.5	14.8	5.3	33.3	25.0	13.9	22.2	22.2	9.1	10.1
6	3.2	6.1	5.3	0.0	8.3	0.0	0.0	11.1	5.2	5.5
7	1.3	2.2	10.5	0.0	0.0	11.1	0.0	0.0	1.3	2.1
Low Albumin	16.0	23.0	21.1	33.3	33.3	25.0	22.2	33.3	15.6	17.7

Figure S3 – Baseline characteristics of the on-admission albumin cohort

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	



C

Group	AP % (n)	RAP % (n)	CP % (n)
1	41.7 (10)	45.8 (11)	12.5 (3)
2	71.3 (134)	22.3 (42)	6.4 (12)
3	70.2 (292)	24.3 (101)	5.5 (23)
4	77.2 (234)	16.5 (50)	6.3 (19)
NORMAL Albumin	72 (670)	21.9 (204)	6.1 (57)
5	77.6 (111)	15.4 (22)	7 (10)
6	66 (33)	26 (13)	8 (4)
7	80 (20)	12 (3)	8 (2)
LOW Albumin	75.2 (164)	17.4 (38)	7.4 (16)

Figure S4 – Personal medical history

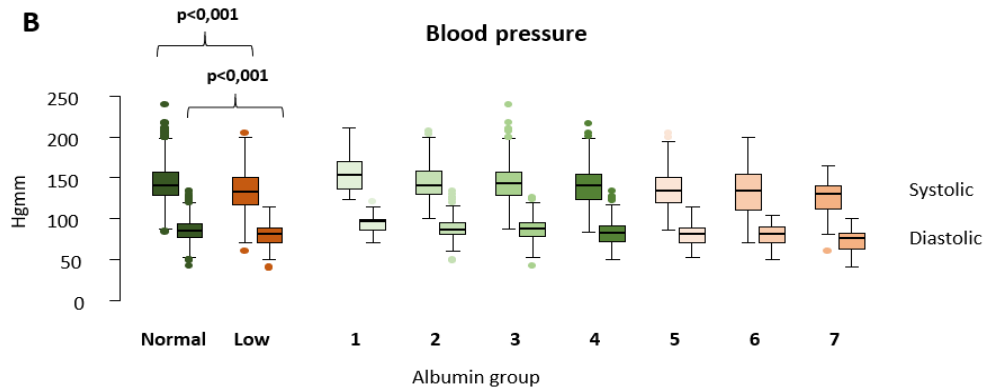
Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

A

Signs and symptoms

Group	Abdominal pain			Nausea % (n)	Vomiting % (n)	Abdominal tenderness % (n)	Abdominal guarding % (n)
	% (n)	Duration hour + IQR (n)	Intensity median + IQR (n)				
1	95.8 (24)	16; 11-25 (15)	8; 6.25-10 (22)	66.7 (24)	58.3 (24)	95.8 (24)	25 (24)
2	99.5 (188)	20; 10-43.25 (134)	8; 6-9 (176)	69.7 (188)	54.8 (188)	90.2 (184)	20.1 (184)
3	98.6 (416)	19; 10-48 (254)	8; 6-9 (397)	67.3 (416)	55 (416)	86.3 (415)	19.3 (414)
4	100 (303)	24; 11- 48 (172)	8; 7-10 (278)	72.4 (301)	57.8 (301)	89.5 (295)	20.1 (294)
Normal	99.2 (931)	21; 10-48 (575)	8; 6-9 (873)	69.4 (929)	56 (929)	88.3 (918)	19.9 (916)
5	95.8 (143)	24; 11.5-48 (80)	8; 6-9 (128)	61.3 (141)	54.9 (142)	90.2 (143)	23.8 (143)
6	91.8 (49)	35; 15-72 (31)	8; 7-9 (34)	66.7 (45)	48.9 (45)	81.6 (49)	28.6 (49)
7	96 (25)	24; 8.7-48 (16)	8; 7-9 (22)	68 (25)	48 (25)	92 (25)	44 (25)
Low	94.9 (217)	24; 12-48 (127)	8; 6-9 (184)	63.2 (211)	52.8 (212)	88.5 (217)	27.9 (217)

B



C

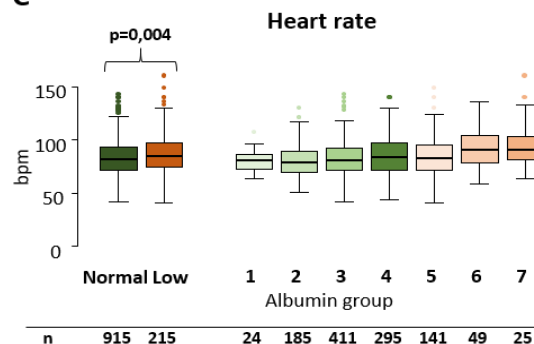


Figure S5 – Signs and symptoms

Diagnostic criteria	NORMAL Albumin	LOW Albumin
	% (n)	% (n)
Pain + Imaging + Enzyme	58.4 (544)	42.7 (93)
Pain + Enzyme	37.8 (352)	43.1 (94)
Pain + Imaging	2.9 (27)	8.7 (19)
Imaging + Enzyme	0.9 (8)	5.5 (12)
Total	931	218

Table S2 – Fulfillment of diagnostic criteria

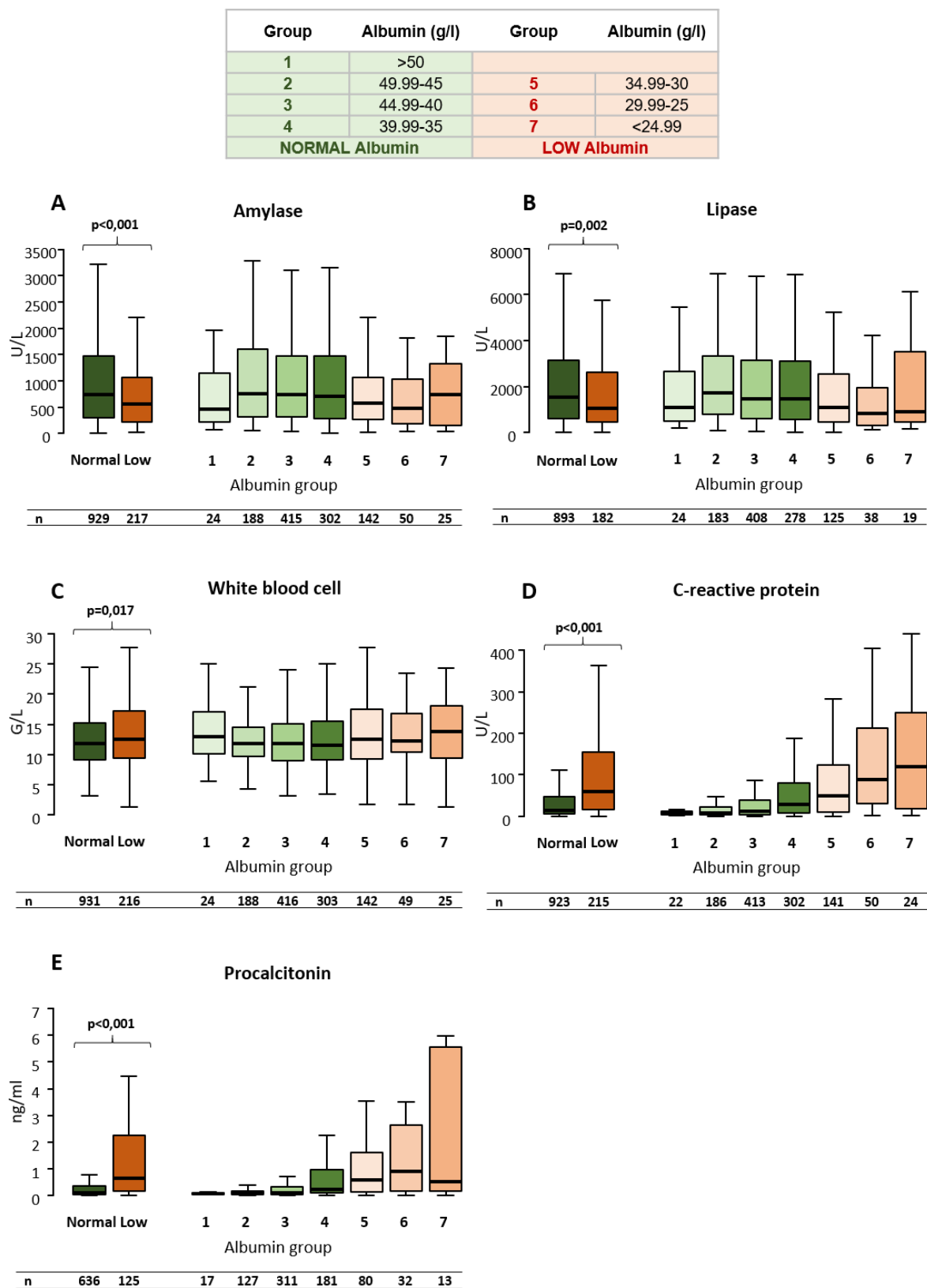


Figure S6 – Pancreatic enzyme levels and inflammatory markers without outliers

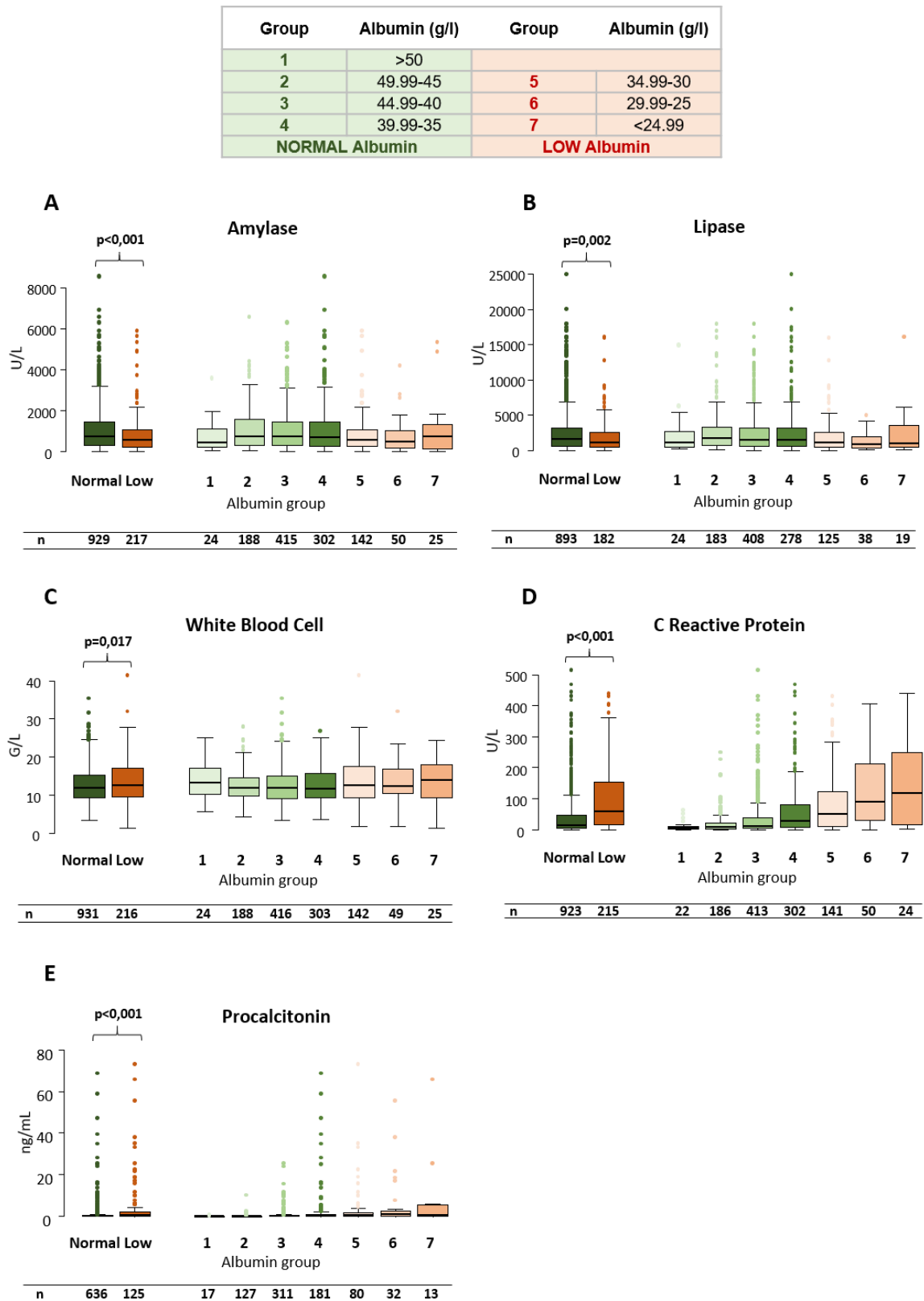


Figure S7 – Pancreatic enzyme levels and inflammatory markers with outliers

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

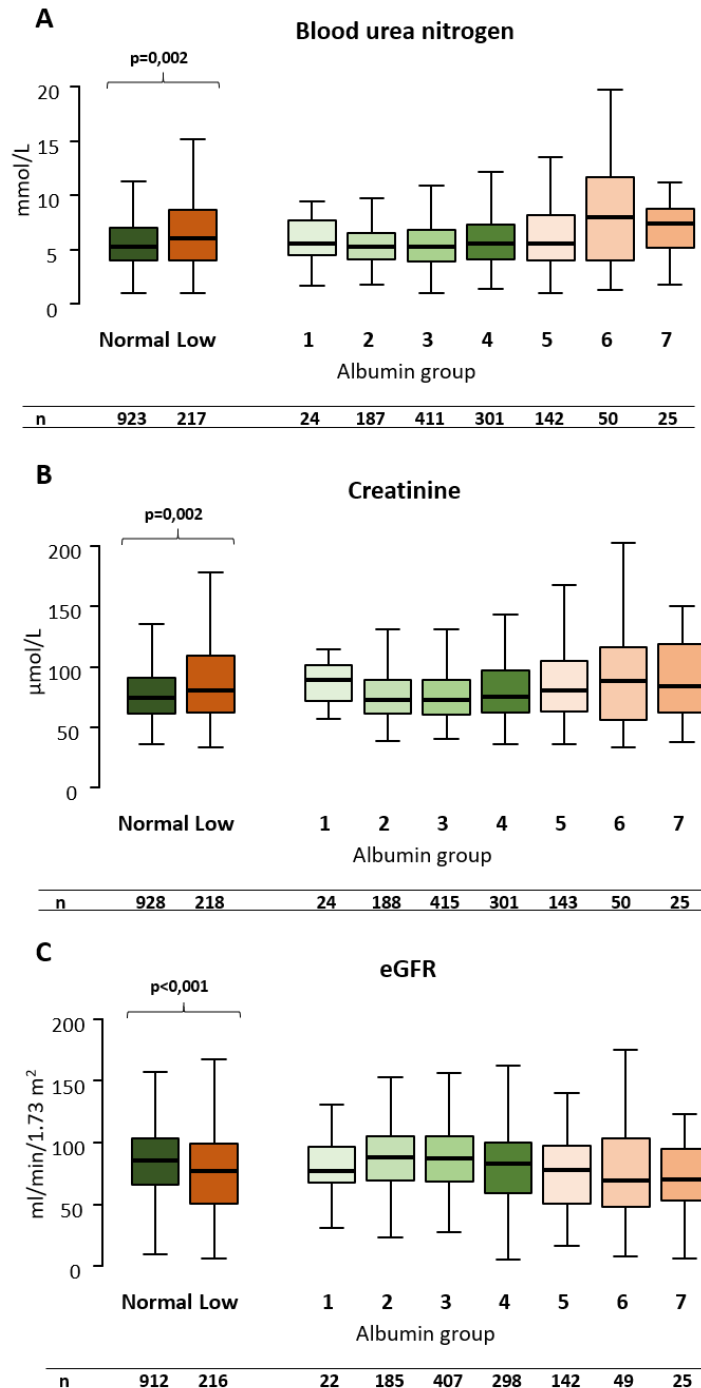


Figure S8 – Laboratory parameters indicating kidney function without outliers

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

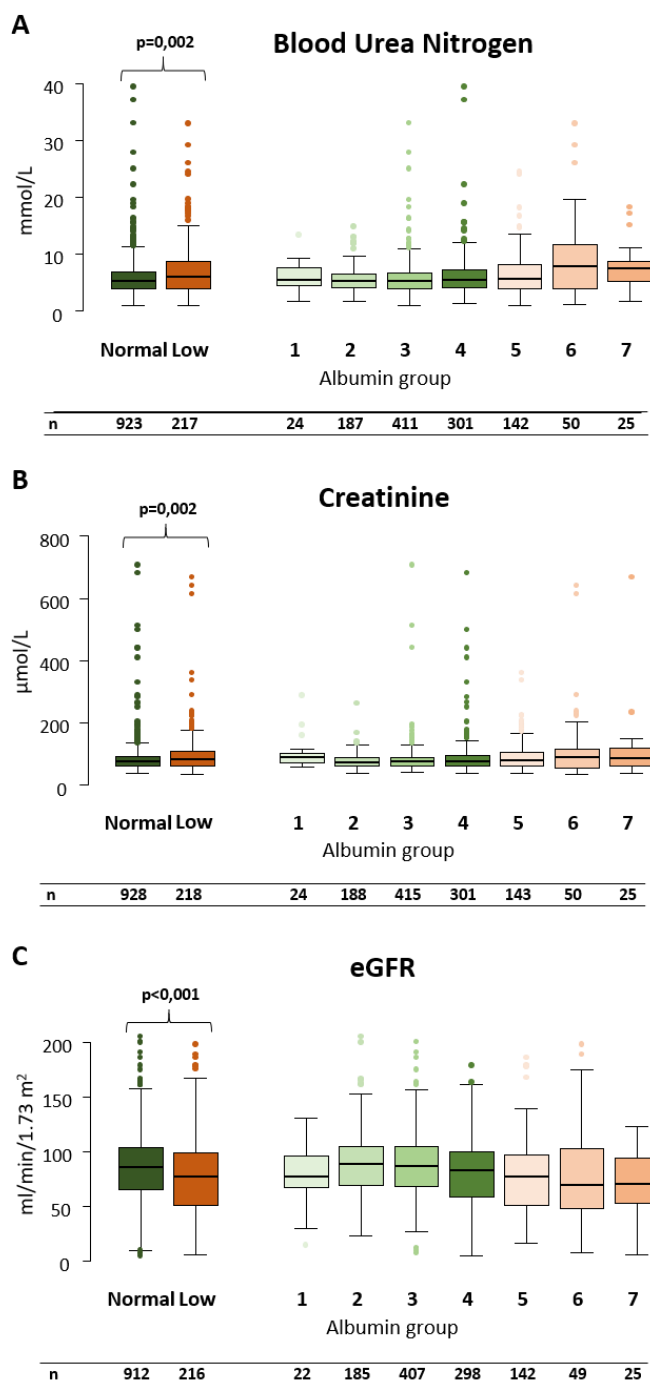


Figure S9 – Laboratory parameters indicating kidney function with outliers

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

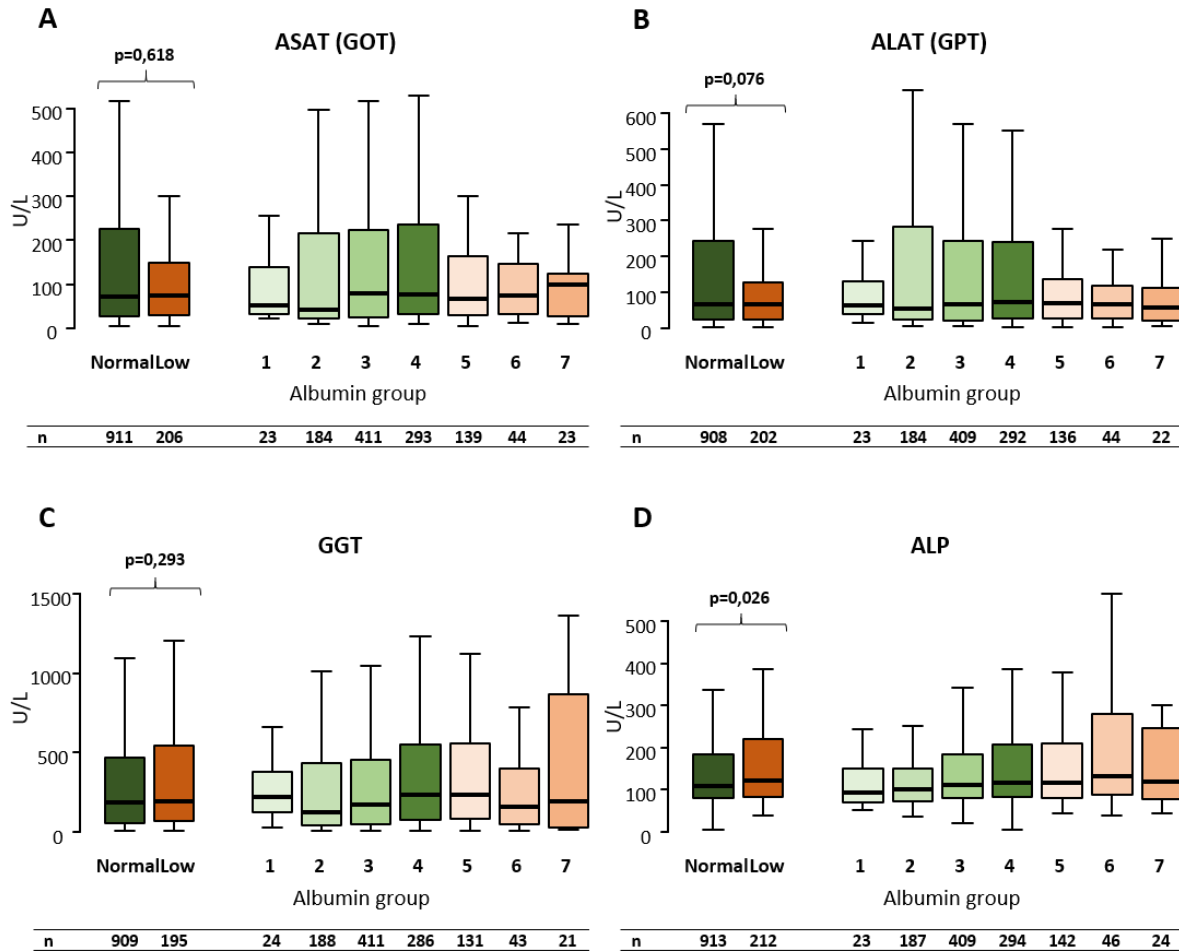


Figure S10 – Laboratory parameters indicating liver function without outliers I.

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

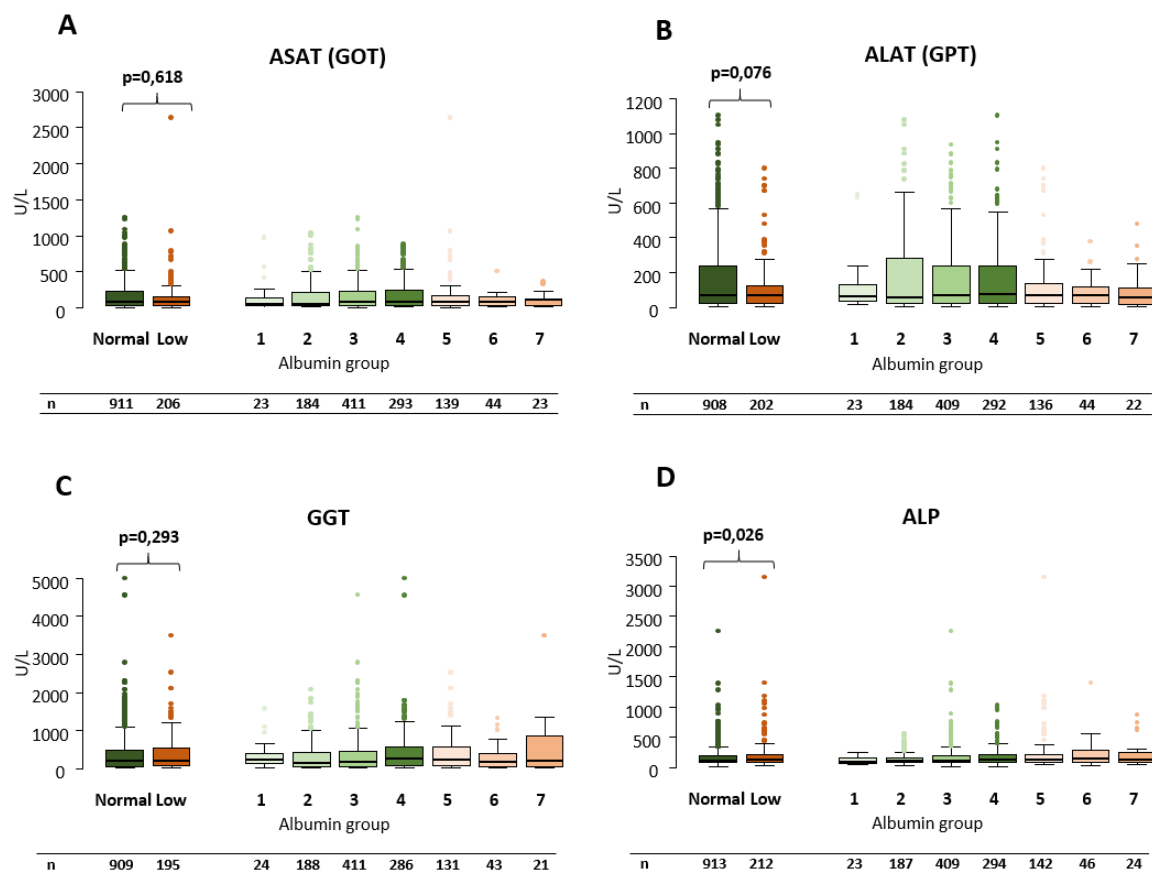


Figure S11 – Laboratory parameters indicating liver function with outliers I.

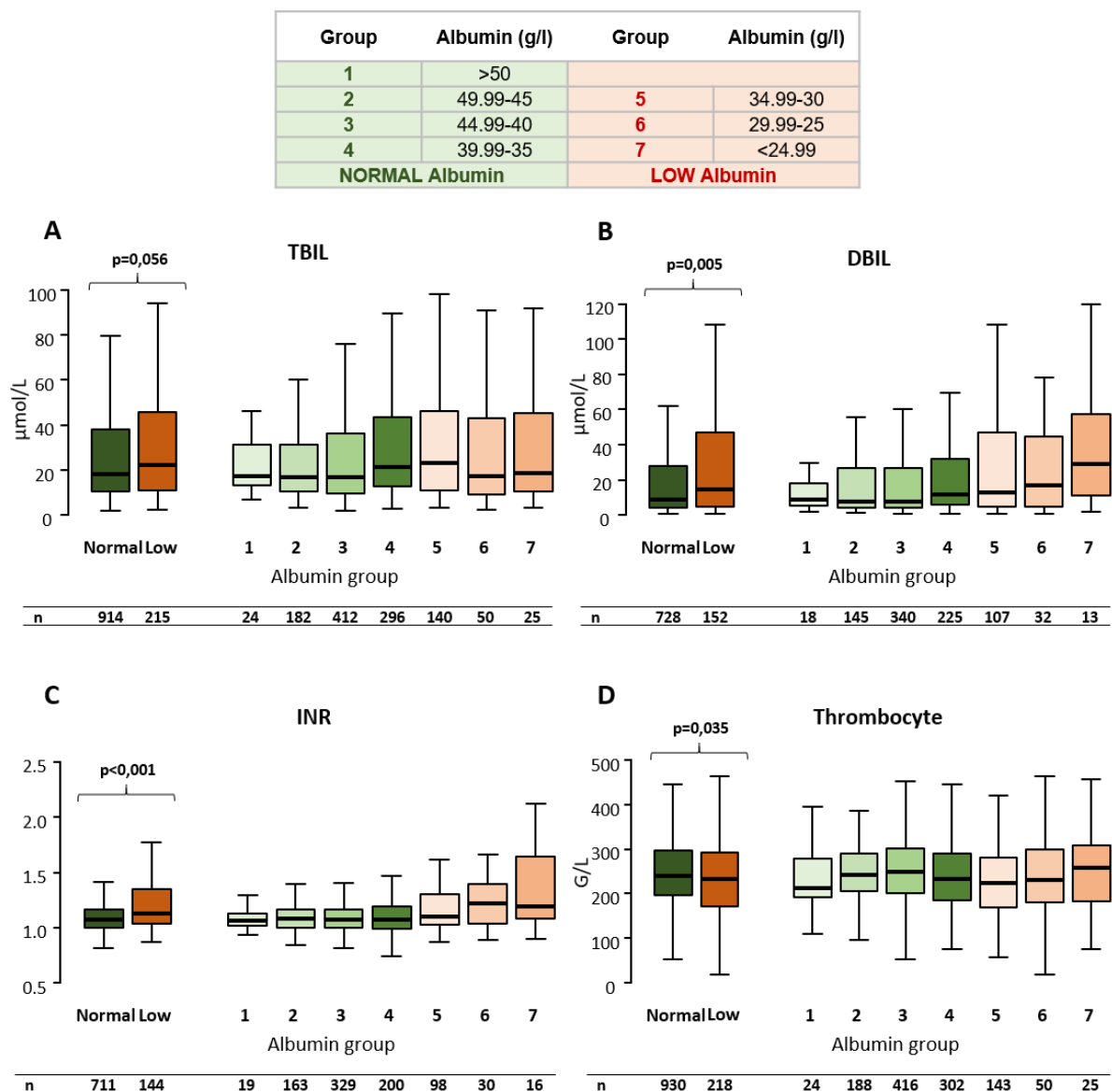


Figure S12 – Laboratory parameters indicating liver function without outliers II.

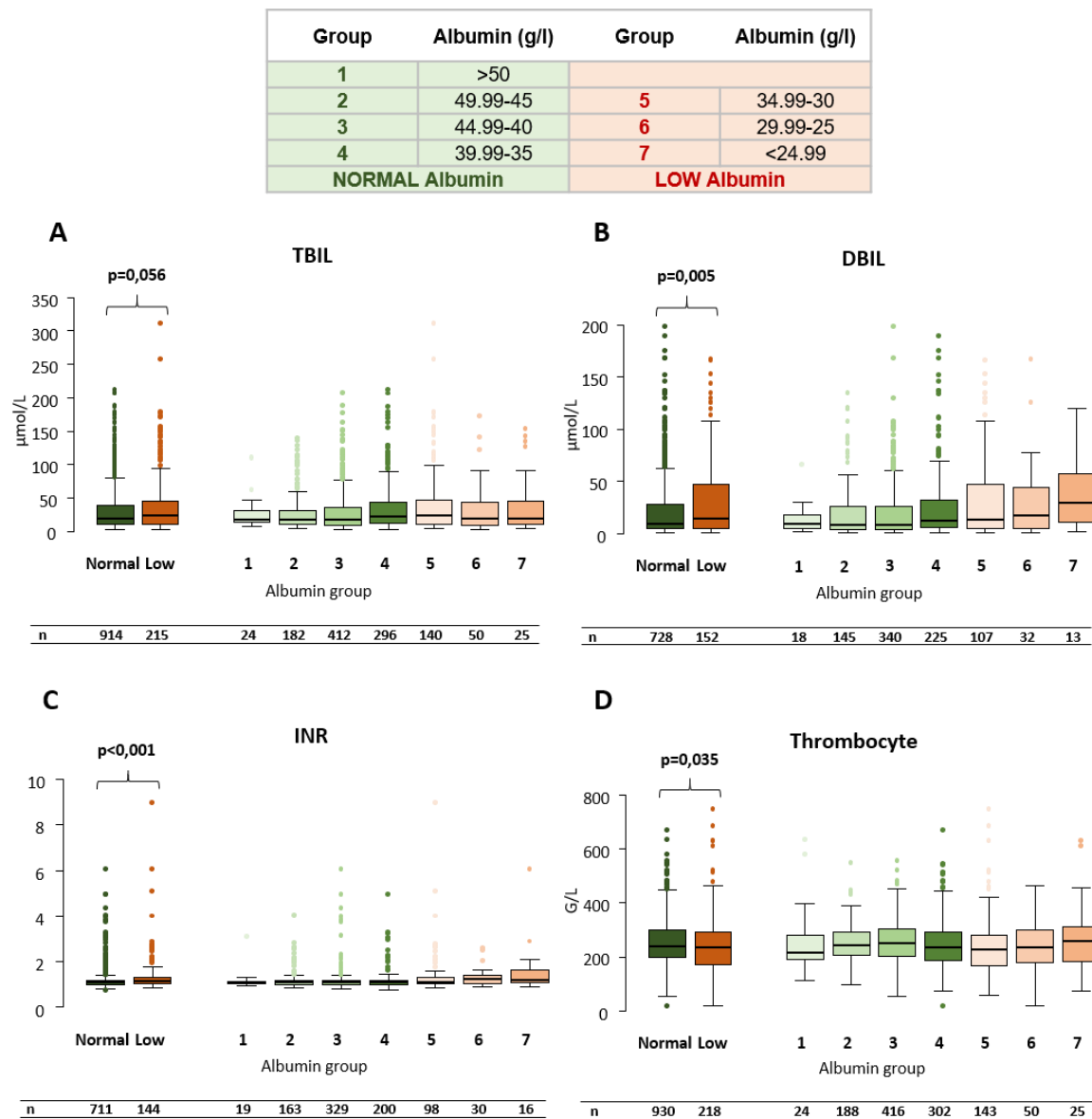


Figure S13 – Laboratory parameters indicating liver function with outliers II.

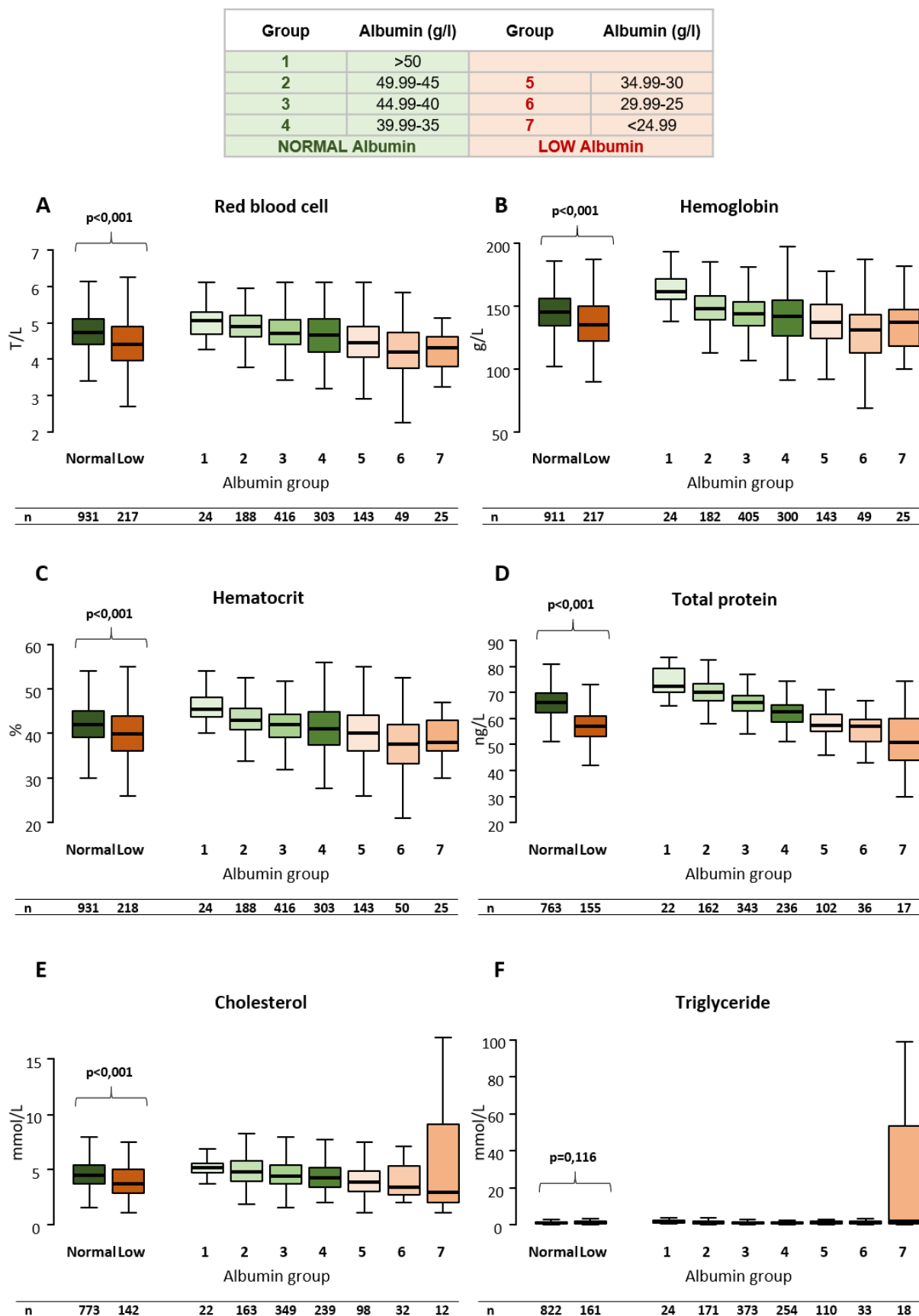


Figure S14 – Haematological parameters and lipid levels without outliers

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

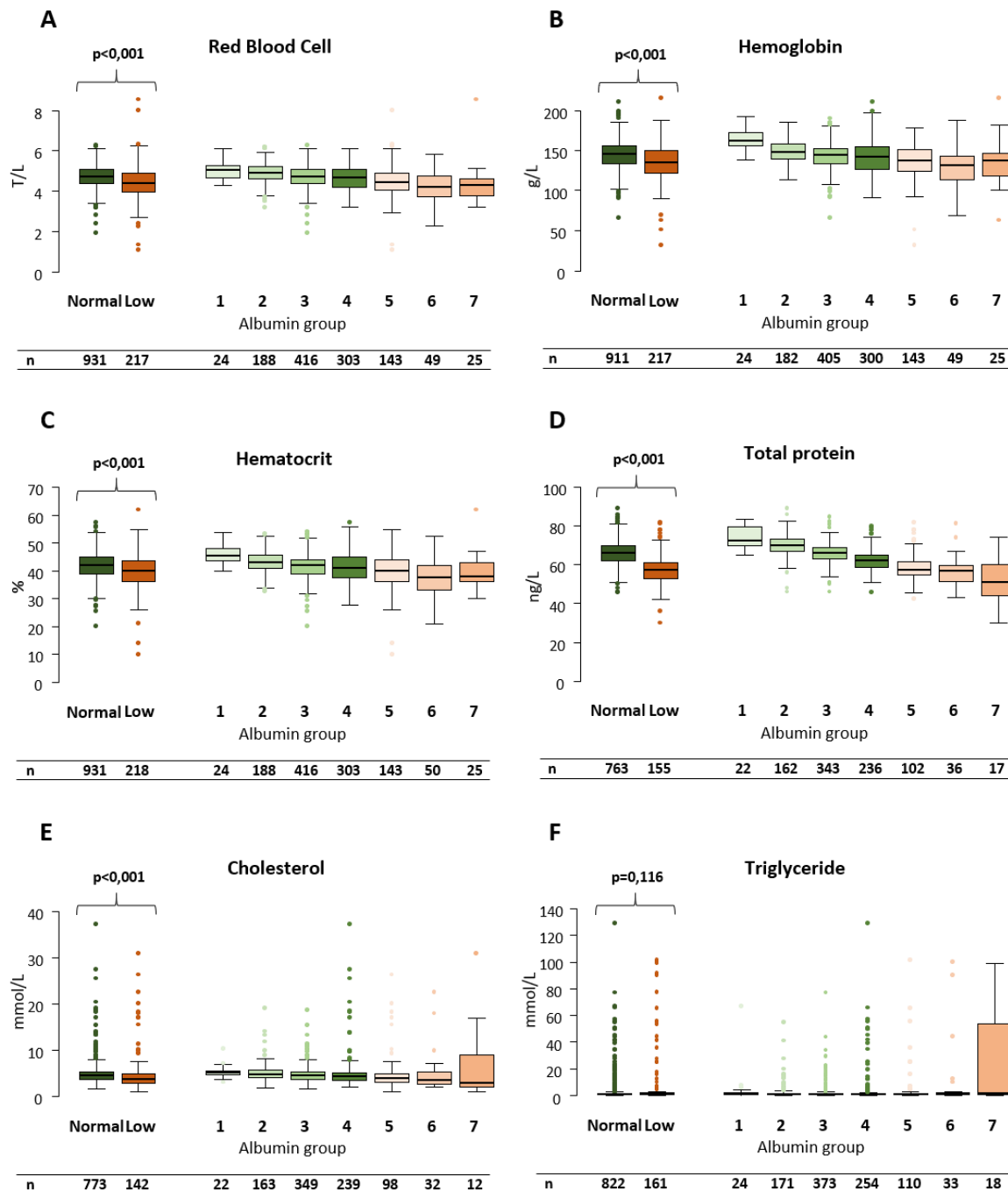


Figure S15 – Haematological parameters and lipid levels with outliers

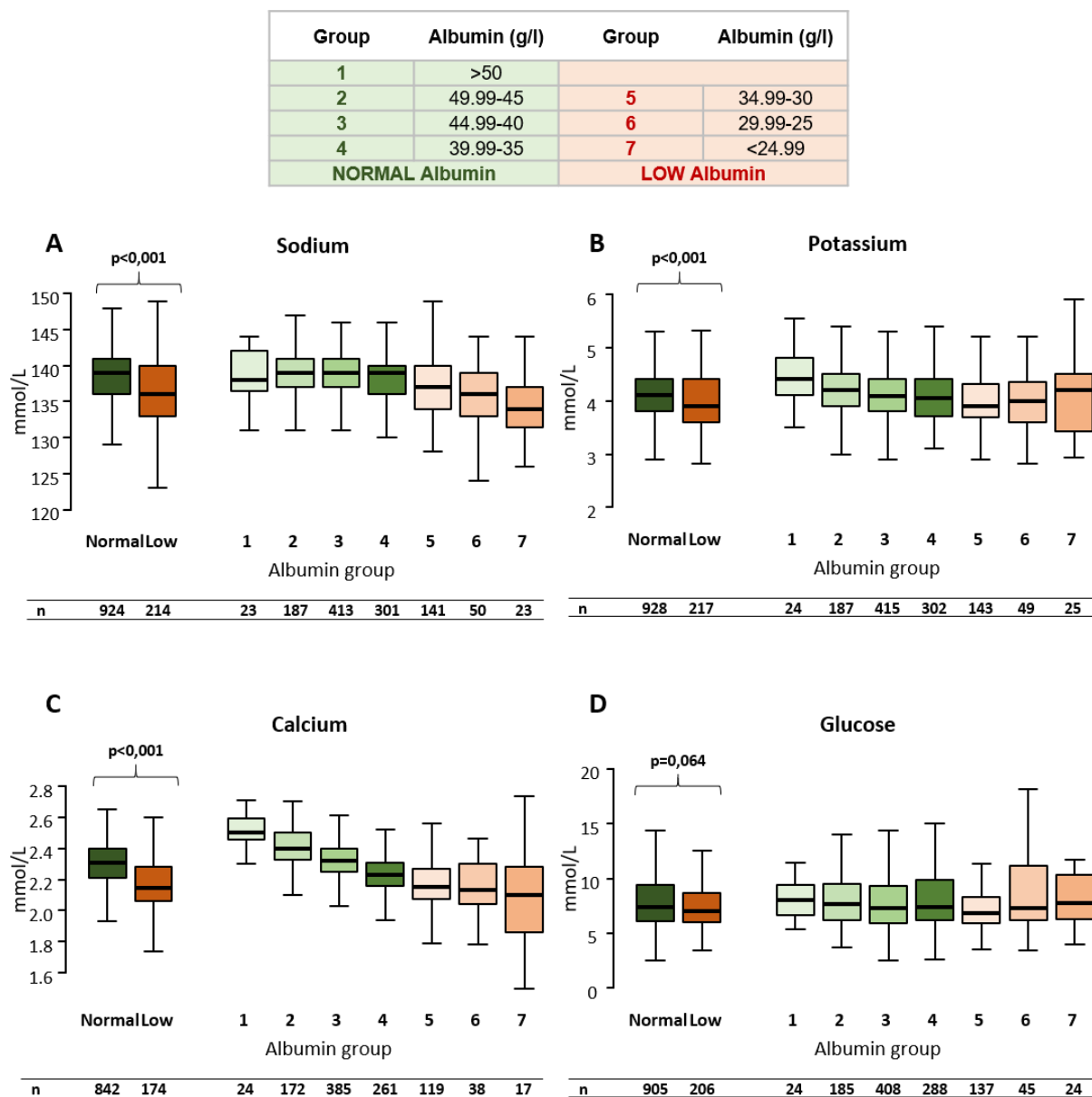


Figure S16 – Ions and glucose levels without outliers

Group	Albumin (g/l)	Group	Albumin (g/l)
1	>50	5	34.99-30
2	49.99-45	6	29.99-25
3	44.99-40	7	<24.99
4	39.99-35		
NORMAL Albumin		LOW Albumin	

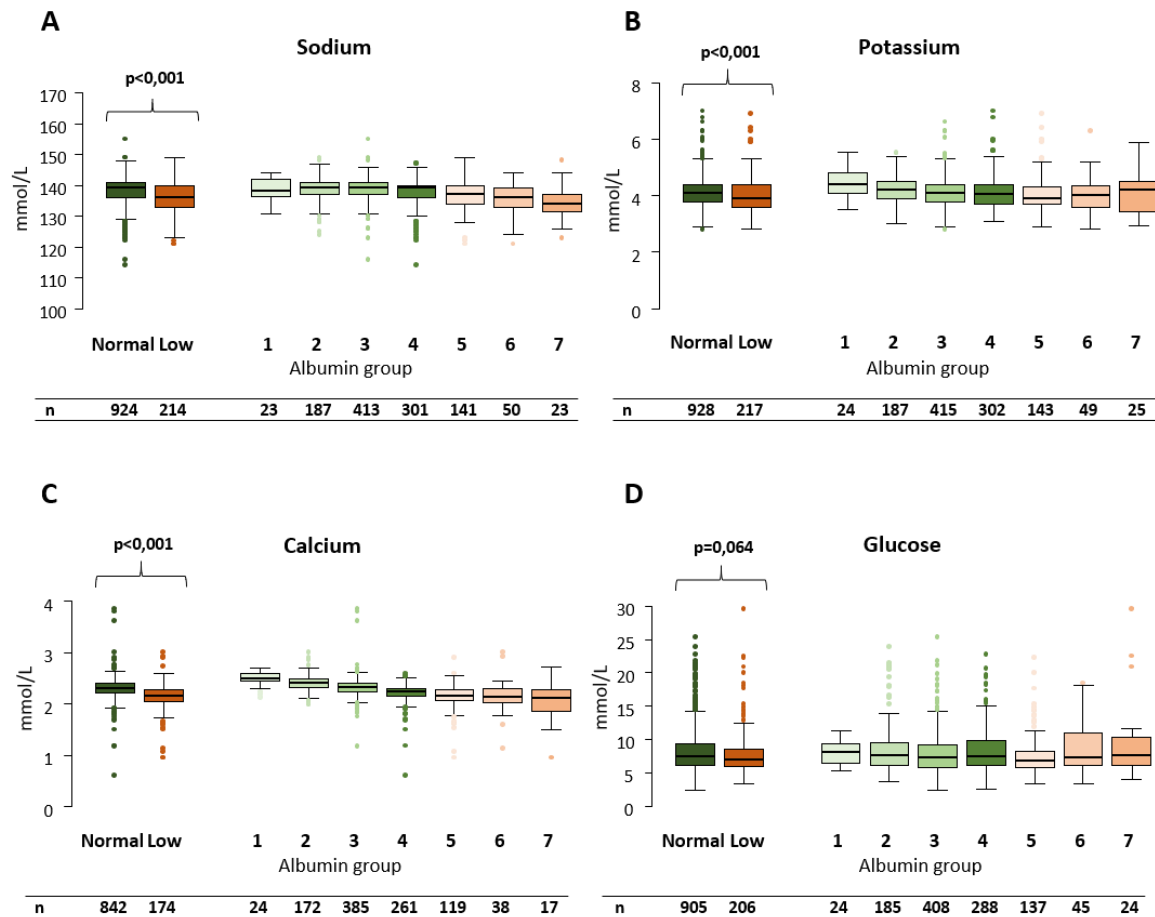


Figure S17 – Ions and glucose levels with outliers

On-admission albumin (n=1149) - mortality						
Predictor		β	SE	OR	95% CI	p
Albumin	<35g/L (v. ≥ 35 g/L)	0.728	0.348	2.070	1.021-4.033	0.036
Age	per years	0.036	0.012	1.037	1.013-1.062	0.003
Gender	female (vs. male)	-0.244	0.368	0.783	0.376-1.607	0.507
Etiology	alcohol (vs. biliary)	0.683	0.549	1.981	0.651-5.755	0.213
	HTG (vs. biliary)	1.836	0.728	6.271	1.271-24.048	0.012
	biliary + alcohol (vs. biliary)	1.029	1.100	2.797	0.145-16.902	0.350
	biliary + HTG (vs. biliary)	-13.032	778.318	-	-	0.987
	alcohol + HTG (vs. biliary)	1.860	0.748	6.422	1.263-25.800	0.013
	idiopathic (vs. biliary)	1.196	0.424	3.308	1.447-7.759	0.005
	other (vs. biliary)	-0.085	0.787	0.919	0.139-3.581	0.914
On-admission albumin (n=1149) - severity						
Predictor		β	SE	OR	95% CI	p
Albumin	<35g/L (v. ≥ 35 g/L)	0.471	0.280	1.602	0.909-2.735	0.092
Age	per years	0.039	0.009	1.040	1.022-1.060	<0.001
Gender	female (vs. male)	-0.190	0.280	0.827	0.475-1.429	0.496
Etiology	alcohol (vs. biliary)	0.525	0.401	1.690	0.760-3.670	0.190
	HTG (vs. biliary)	1.818	0.538	6.160	2.008-17.046	<0.001
	biliary + alcohol (vs. biliary)	0.953	0.801	2.594	0.385-10.416	0.234
	biliary + HTG (vs. biliary)	-13.875	779.136	-	-	0.986
	alcohol + HTG (vs. biliary)	1.384	0.621	3.991	1.040-12.548	0.026
	idiopathic (vs. biliary)	0.580	0.328	1.785	0.928-3.378	0.077
	other (vs. biliary)	-0.526	0.628	0.591	0.137-1.757	0.402

Table S2 – Logistic regression for on-admission albumin cohort

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

p<0.05 was considered statistically significant (highlighted in bold)

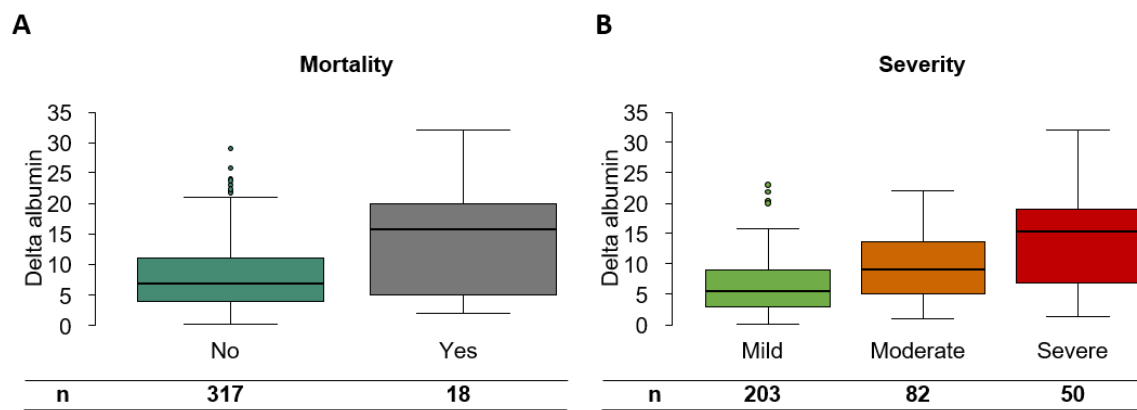


Figure S18 – Albumin loss

Lowest measured albumin (n=1272) – mortality						
Predictor		β	SE	OR	95% CI	p
Albumin	<35g/L (v. ≥ 35 g/L)	1.431	0.319	4.185	2.286-8.039	<0.001
Age	per years	0.040	0.011	1.041	1.019-1.065	<0.001
Gender	female (vs. male)	-0.420	0.327	0.657	0.342-1.241	0.200
Etiology	alcohol (vs. biliary)	0.972	0.499	2.642	0.982-7.060	0.052
	HTG (vs. biliary)	1.433	0.723	4.192	0.855-15.870	0.048
	biliary + alcohol (vs. biliary)	1.867	0.731	6.469	1.303-24.945	0.011
	biliary + HTG (vs. biliary)	-12.872	758.351	-	-	0.986
	alcohol + HTG (vs. biliary)	1.665	0.741	5.283	1.049-20.864	0.025
	idiopathic (vs. biliary)	1.478	0.383	4.385	2.104-9.572	<0.001
	other (vs. biliary)	-0.107	0.785	0.898	0.136-3.482	0.892
Lowest measured albumin (n=1272) - severity						
Predictor		β	SE	OR	95% CI	p
Albumin	<35g/L (v. ≥ 35 g/L)	2.367	0.292	10.664	6.188-19.614	<0.001
Age	per years	0.029	0.008	1.029	1.013-1.047	<0.001
Gender	female (vs. male)	-0.409	0.251	0.665	0.404-1.084	0.104
Etiology	alcohol (vs. biliary)	0.216	0.370	1.241	0.594-2.548	0.559
	HTG (vs. biliary)	0.986	0.513	2.681	0.931-7.113	0.054
	biliary + alcohol (vs. biliary)	0.549	0.698	1.732	0.366-6.155	0.431
	biliary + HTG (vs. biliary)	-13.938	727.870	-	-	0.985
	alcohol + HTG (vs. biliary)	0.883	0.588	2.417	0.701-7.284	0.133
	idiopathic (vs. biliary)	0.641	0.291	1.900	1.072-3.362	0.027
	other (vs. biliary)	-0.378	0.515	0.685	0.224-1.744	0.464

Table S3 – Logistic regression for lowest measured albumin cohort

HTG: hypertriglyceridemia; SE: standard error; OR: odds ratio; CI: confidence interval
p<0.05 was considered statistically significant (highlighted in bold)

	EPIDEMIOLOGY, ETIOLOGY	OVERALL	UPLOADED DATA	%
1	Age	1149	1149	100%
2	Age	1272	1272	100%
3	Gender	1149	1149	100%
4	Gender	1272	1272	100%
5	Etiology	1149	1149	100%
6	Etiology	1272	1272	100%
	<i>Average uploaded data</i>	7263	7263	100%

	SYMPTOMS AND PHYSICAL EXAMINATION ON ADMISSION	OVERALL	UPLOADED DATA	%
7	Abdominal pain	1149	1148	100%
8	Duration of abdominal pain before admission	1149	702	61%
9	Intensity of abdominal pain	1149	1057	92%
10	Nausea	1149	1140	99%
11	Vomiting	1149	1141	99%
12	Abdominal tenderness	1149	1135	99%
13	Abdominal guarding	1149	1133	99%
14	Blood pressure – systolic	1149	1141	99%
15	Blood pressure – diastolic	1149	1118	97%
16	Heart rate	1149	1130	98%
	<i>Average uploaded data</i>	11490	10845	94%

	LABORATORY PARAMETERS ON ADMISSION	OVERALL	UPLOADED DATA	%
17	Amylase	1149	1146	100%
18	Lipase	1149	1075	94%
19	Triglyceride (TG)	1149	983	86%
20	Total cholesterol	1149	915	80%
21	Procalcitonin	1149	761	66%
22	C-reactive protein (CRP)	1149	1138	99%
23	Maximum C-reactive protein (CRP)	1172	1171	100%
24	White blood cell count (WBC)	1149	1147	100%
25	Red blood cell count (RBC)	1149	1148	100%
26	Hematocrit	1149	1149	100%
27	Hemoglobin	1149	1128	98%
28	Thrombocyte	1149	1148	100%
29	Glucose	1149	1111	97%
30	Aspartate transaminase (ASAT)	1149	1117	97%
31	Alanine transaminase (ALAT)	1149	1110	97%
32	Gamma-glutamyl transferase (γGT)	1149	1104	96%
33	Alkaline phosphatase (ALP)	1149	1125	98%
34	Lactate dehydrogenase (LDH)	1149	1085	94%
35	Total bilirubin	1149	1129	98%

36	Potassium	1149	1145	100%
37	Sodium	1149	1138	99%
38	Calcium	1149	1016	88%
39	Albumin	1149	1149	100%
40	Total protein	1149	918	80%
41	Estimated glomerular filtration rate (eGFR)	1149	1128	98%
42	Creatinine	1149	1146	100%
43	Blood urea nitrogen (BUN)	1149	1140	99%
	<i>Average uploaded data</i>	<i>31046</i>	<i>29470</i>	<i>95%</i>

	OUTCOMES	OVERALL	UPLOADED DATA	%
44	Local pancreatic complications	1149	1135	99%
45	Local pancreatic complications	1272	1258	99%
46	Peripancreatic fluid collection	1149	1135	99%
47	Peripancreatic fluid collection	1272	1258	99%
48	Pancreatic pseudocyst	1149	1135	99%
49	Pancreatic necrosis	1149	1134	99%
50	Pancreatic necrosis	1272	1257	99%
51	Diabetes mellitus as complication	1149	1149	100%
52	Diabetes mellitus as complication	1272	1272	100%
53	Organ failure	1149	1149	100%
54	Organ failure	1272	1271	100%
55	Renal failure	1149	1149	100%
56	Renal failure	1272	1270	100%
57	Heart failure	1149	1149	100%
58	Heart failure	1272	1270	100%
59	Respiratory failure	1149	1148	100%
60	Respiratory failure	1272	1269	100%
61	Length of hospitalization	1149	1149	100%
62	Length of hospitalization	1272	1272	100%
63	Severity (mild/moderately severe/severe)	1149	1149	100%
64	Severity (mild/moderately severe/severe)	1272	1272	100%
65	Mortality	1149	1149	100%
66	Mortality	1272	1272	100%
	<i>Average uploaded data</i>	<i>27780</i>	<i>27671</i>	<i>100%</i>

TOTAL	77579	75249	97%
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Table S3 – Data quality for assessed variables

Parameter	Normal vs Low	Normal vs Group 5	Normal vs Group 6	Normal vs Group 7
Figure 1				
Local pancreatic complications – on-admission cohort	0.016	0.553	0.126	<0.001
Peripancreatic fluid collection – on-admission cohort	<0.001	0.0734	0.0052	<0.001
Pancreatic necrosis – on-admission cohort	0.378	1.000	0.314	0.084
Pancreatic pseudocyst – on-admission cohort	0.315	0.393	0.234	1.000
Local pancreatic complications – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Peripancreatic fluid collection – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Pancreatic necrosis – lowest albumin cohort	<0.001	0.020	<0.001	<0.001
Pancreatic pseudocyst – lowest albumin cohort	<0.001	0.005	0.001	<0.001
Figure 2				
Organ failure – on-admission cohort	<0.001	0.880	<0.001	<0.001
Respiratory failure – on-admission cohort	0.051	0.698	0.001	0.019
Heart failure – on-admission cohort	0.088	0.604	0.068	0.040
Renal failure – on-admission cohort	0.004	0.339	<0.001	0.232
Organ failure – lowest albumin cohort	<0.001	0.002	<0.001	<0.001
Respiratory – lowest albumin cohort	<0.001	0.084	<0.001	<0.001
Heart failure – lowest albumin cohort	<0.001	1.000	<0.001	<0.001
Renal failure – lowest albumin cohort	<0.001	0.045	<0.001	<0.001
Figure 3				
Severity – on-admission cohort	0.015	0.755	0.028	<0.001
Mortality – on-admission cohort	0.020	1.000	0.005	0.007
Length of stay – on-admission cohort	0.025	0.592	0.394	0.055
Maximum C-reactive protein – on-admission cohort	<0.001	0.003	0.007	<0.001
Severity – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Mortality – lowest albumin cohort	<0.001	0.784	0.004	<0.001
Length of stay – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Maximum C-reactive protein – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001

Figure S2		
Representativity	Total vs on-admission	Total vs lowest measured
Gender	0.964	0.992
Severity	0.021	0.005
Mortality	0.302	0.026
Length of hospitalization	<0.001	<0.001
Age - Male	0.563	0.324
Age - Female	0.853	0.638
Age - Total	0.591	0.310

Parameter	Normal vs Low	Normal vs Group 5	Normal vs Group 6	Normal vs Group 7
Figure S3				
Age – on-admission cohort	0.005	0.007	0.136	0.431
Etiology: biliary vs non-biliary – on-admission cohort	0.042	-	-	-
Etiology: alcohol vs non-alcohol – on-admission cohort	0.096	-	-	-
Etiology: HTG vs non-HTG – on-admission cohort	0.903	-	-	-
Figure S4				
Obesity (body mass index)	0.012	0.174	0.025	0.915
Diabetes mellitus – on-admission cohort				
AP – on-admission cohort				
RAP – on-admission cohort				
CP – lowest albumin cohort				
Figure 3				
Severity – on-admission cohort	0.015	0.755	0.028	<0,001
Mortality – on-admission cohort	0.020	1.000	0.005	0.007
Length of stay – on-admission cohort	0.025	0.592	0.394	0.055
Maximum C-reactive protein – on-admission cohort	<0.001	0.003	0.007	<0.001
Severity – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Mortality – lowest albumin cohort	<0.001	0.784	0.004	<0.001
Length of stay – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001
Maximum C-reactive protein – lowest albumin cohort	<0.001	<0.001	<0.001	<0.001

Table S4 – Results of statistical comparisons presented on figures