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Abnormal liver biochemistry constitutes an independent prognostic factor of a less favorable clinical course in patients with COVID-19

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List of abbreviations:

Abnormal liver biochemistry: ALB

Upper limit of normal: ULN.

Baseline abnormality in liver biochemistry: BALB

Global abnormality of liver biochemistry: GALB

Total bilirubin: TB.

Aspartate aminotransferase: AST.

Alanine aminotransferase: ALT.

Alkaline phosphatase: AP.

Gamma-glutamyltransferase: GGT.

Intensive Care Unit: ICU

Confidence interval: CI

Odds ratio: OR

Low molecular weight heparin: LMWH

ABSTRACT

INTRODUCTION: Abnormal liver biochemistry (ALB) is correlated with increased clinical involvement or severity in COVID-19, but its prognostic implications have not been

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studied extensively. Our aim is to determine whether ALB is a risk factor for an unfavorable clinical outcome and involvement.

MATERIALS AND METHODS: Retrospective, single-center study of confirmed COVID-19 cases. Patients with pharmacological hepatotoxicity or liver diseases were excluded. ALB was defined as the elevation of total bilirubin, AST, ALT, alkaline phosphatase and/or GGT above the upper limit of normal. An assessment was first made of the correlation between ALB and the need for hospitalization. This was followed by an assessment of the correlation of hospitalized patients with demographic variables, comorbidities and treatment for COVID-19 and with clinical involvement and outcome. Statistical analysis was performed using age-adjusted multiple logistic regression with a p-value of <0.05

RESULTS: Of 1,277 confirmed cases, 346 required hospitalization, and 302 were included. The prevalence of ALB was higher in hospitalized patients compared to non-hospitalized patients (60.9% vs. 10.3%, p <0.001). Among the hospitalized patients, there was no correlation between ALB and demographic variables, comorbidities or treatment for COVID-19, except for low molecular weight heparin. We found a significant correlation between ALB and moderate/severe COVID-19 involvement and between unfavorable clinical outcomes and elevated total bilirubin. The period of greatest clinical worsening and deterioration of liver biochemistry parameters occurred during the first seven days. There was a significant correlation between ALB and a longer hospital stay and admission to the Intensive Care Unit, but this did not imply higher mortality.

CONCLUSIONS: ALB is correlated with greater clinical involvement and worse clinical outcomes in hospitalized patients with COVID-19.

INTRODUCTION:

COVID-19 has caused a profound health impact and 80,000 deaths in Spain (1). Its primary involvement is respiratory, but ALB is frequent, with an incidence exceeding 50% (2-14). It has a multivariate etiopathogenesis that includes the direct cytopathic effect (15, 16).

A correlation has been described between ALB and greater clinical involvement or severity in patients with COVID-19 (14, 17). However, the prognostic implications of ALB have not been extensively studied and are not included in studies using prognostic predictive models or in clinical guidelines (18, 19).

The aim of our study is to test the hypothesis that, in addition to being correlated with greater clinical involvement, ALB in patients with COVID-19 is an independent risk factor for worse outcomes.

MATERIALS AND METHODS:

Retrospective descriptive study of patients diagnosed with COVID-19 in our center by reverse transcription of the polymerase chain reaction from February 1 to May 15, 2020. The correlation of ALB with the need for hospitalization was assessed, and the study was subsequently continued with hospitalized patients. The following were excluded: persons under 18 years of age, pregnant women, patients with known liver disease, suspected drug-induced liver injury (ALT ≥5 ULN, AP ≥2 ULN or ALT ≥3 ULN + TB ≥2 ULN after introduction of the drug (20)), hospitalization for causes other than respiratory involvement or need for COVID-19 isolation and insufficient analytical data.

Data were obtained by reviewing the patients' electronic health records. The clinical respiratory involvement of patients with COVID-19 was classified as asymptomatic, mild (symptoms with normal physical/radiological examination), moderate (interstitial radiological pattern or pneumonia without respiratory failure) or severe (pneumonia with respiratory failure): SpO2 <93% at ambient air or PaO2/FiO2 <300) (21).

ALB was defined as elevation above our laboratory's ULN of: TB 1.2 mg/dl, AST 35 U/L, ALT 45 U/L, AP 120 U/L and GGT 55 U/L. For TB values of >1.5 ULN, our laboratory determined direct and indirect bilirubin. In the hospitalized group, the presence of these abnormalities at the beginning of hospitalization was termed BALB, and their

presence at any time during the hospital stay was termed GALB. We catalogued the maximum value of each parameter according to the number of times it exceeded its ULN and calculated the ratio between the average maximum values of ALT and AST. We evaluated the changes to liver biochemistry parameters on Days 7 (compared to Day 1) and 14 (compared to Day 7) of hospitalization. This outcome was classified as follows: resolution (normalization of all parameters), improvement (decrease of >15% of the value of the parameters without normalization), worsening (increase of >15%) and maintenance (variations of less than 15%, without normalization).

The clinical outcome was defined according to the first change to the patient's baseline condition; it was considered as worsening if the clinical involvement reached a higher stage, improvement when it changed to a lower stage, and no improvement when it remained the same. The failure of one severely affected patient to improve resulted in his death. The hospital stay, need for transfer to ICU and mortality were recorded.

The demographic variables and comorbidities recorded were: gender, age, previous admittance to a community health center, obesity (BMI >30), diabetes mellitus, arterial hypertension, dyslipidemia and standardized Charlson Comorbidity index. This index measures the impact of comorbidity on mortality based on 19 categories which facilitate the classification of patients into mortality risk groups. Given the risk of including patients with non-alcoholic fatty liver disease, we determined the HSI scores for hepatic steatosis and FIB-4 and APRI for hepatic fibrosis using the transaminase values closest to hospitalization within the previous twelve months for patients with BALB. Treatments used for COVID-19 and their relationship with the onset of ALB in patients without BALB were recorded. Finally, we determined the baseline values of: coagulation (INR), leukocytes, lymphocytes, C-reactive protein, D-dimer, troponin, albumin and ferritin.

The study was approved by our Ethics Committee with a waiver of informed consent. Statistical analysis was performed using SPSS version 15.0. The descriptive study provided the mean and standard deviation. The inferential analysis was parametric in order to avoid deviations from normality and identified a correlation between independent, binary-type variables depending on categorical factors or covariables by means of multiple logistic regression models adjusted for age, with an estimated

power of 93%, to detect ALB proportions of 40% and 60% as significant in two groups with a CI of 95% and p-value of <0.05. For hospital stays, we used a t-test with Welsch's correction and for survival, we used a COX regression model with an age-adjusted Hazard Ratio (HR) and Kaplan-Meyer curves.

RESULTS

Design of the study.

We identified 1,277 patients with COVID-19, 27.1% (346/1,277) of whom required hospitalization. Of the non-hospitalized group, 87 were included and 844 were excluded, the majority (98.7%, 833/844) due to lack of analytical data. From the group of hospitalized patients, 302 were included and 44 were excluded, primarily due to hospitalization for reasons not secondary to COVID-19 (Fig. 1).

Asymptomatic to mild involvement predominated in non-hospitalized patients (97.7%, 85/87) and moderate to severe involvement predominated in hospitalized patients (86.7%, 262/302). The prevalence of ALB in non-hospitalized patients was 10.3% (9/87, CI 95%: 3.95-16.70) while for hospitalized patients, it was 46.4% for BALB (140/302, CI 95%: 40.70-52.00) and 60.9% for GALB (184/302, CI 95%: 55.40-66.40) (Fig. 1). The presence of ALB was correlated with the need for hospitalization (OR = 7.49, CI 95%: 3.62-15.48, p <0.001).

Characteristics of hospitalized patients

Their average age was 69 ± 16 years with no significant differences according to gender. ALB did not exhibit a significant relationship with demographic variables and comorbidities, although previous admission to a community health center and the Charlson Comorbidity index were correlated with the absence of ALB. 98.3% (297/302) required treatment for COVID-19, with no significant relationship observed with any drug, except for LMWH (OR = 2.78, CI 95%: 1.01-7.69, p = 0.049) (Table 1).

We observed a significant correlation between BALB and clinical involvement at diagnosis, indicating that moderate to severe BALB significantly increased the probability of presenting with ALB with respect to asymptomatic to mild BALB (OR = 2.47, CI 95%: 1.14-5.33, p = 0.021; OR = 2.56, CI 95%: 1.15-5.73, p = 0.022). This

relationship was maintained for GALB (OR = 2.12, CI 95%: 1.03-4.36, p = 0.042; OR = 2.65, CI 95%: 1.23-5.69, p = 0.012) (Table 2). The 86.3% (38/44) who did not have BALB, but developed it later, had moderate (47.7%, 21/44) or severe (38.6%, 17/44) baseline involvement.

Elevation was detected in 5.6% (17/302) for TB, 37.3% (107/287) for AST, 20.9% (63/302) for ALT, 8.3% (15/181) for AP and 30.9% (56/181) for GGT. The mean values at diagnosis for AST (42.7 ± 36.4) and GGT (48.2 ± 50.8) were elevated. The maximum elevation (times above their ULN) on average was altered for GGT (2.53 ± 8.28), AST (2.46 ± 5.11) and ALT (2.10 ± 2.98), and the ALT/AST ratio of this average was 0.85. 58.8% (10/17) of patients with hyperbilirubinemia presented with elevations of greater than 1.5 times their ULN, all due to a predominance of direct bilirubin. On Day 7 of changes in the elevation of these parameters, worsening (61.6%, 101/164) predominated, while on Day 14 resolution (28.7%, 33/115) and improvement (35.7%, 41/115) predominated (Fig. 2). No patient exhibited liver failure.

Analysis of the remaining parameters only demonstrated a significant correlation between ALB and ferritin (p <0.001), which was more elevated in patients with ALB (1026.5 ± 1534.1 µg/L vs. 488.5 ± 608 µg/L) (Table 3).

Prognostic implications of ALB

Improvement occurred in 67.9% (205/302) of patients, while 19.5% (59/302) did not improve, and 12.6% (38/302) worsened. Of the last group, 94.7% (36/38) of patients' condition changed from moderate to severe. 97.4% (37/38) of worsening conditions occurred during the first seven days.

BALB was present in 40.5% (83/205) of patients who improved, 42.4% (25/59) who did not improve and 73.7% (28/38) who worsened. GALB was present in 56.1% (115/205) who improved, 54.2% (32/59) who did not improve and 81.6% (31/38) who worsened.

We observed that BALB was significantly related to a lower probability of improvement (OR = 0.48, CI 95%: 0.28-0.84, p = 0.010) and higher probability of worsening/no improvement (OR = 4.88, CI 95%: 2.11-11.30, p <0.001) (Fig.3). Without reaching statistical significance, GALB was correlated with a lower probability of improvement (OR = 0.66, CI 95%: 0.37-1.17, p = 0.155) and a significantly higher probability of

worsening/no improvement (OR 4.24, CI 95%: 1.70-10.60, p = 0.002).

There was a significant correlation between the probability of worsening/no improvement and elevated TB (OR = 1.77, CI 95%: 1.10-2.86, p = 0.019), a non-significant correlation with ALT (OR = 1.36, CI 95%: 0.92-1.99, p = 0.123), and no correlation with AST or GGT. Therefore, each time TB exceeds its ULN, it significantly increases this probability by 77%, and each time ALT exceeds its ULN, it increases it by 36% (non-significant).

The probability of improvement was significantly correlated with no elevation of TB (OR = 0.21, CI 95%: 0.10-0.44, p = 0.001), non-significant correlation with GGT (OR = 0.84, CI 95%: 0.70-1.01, p = 0.067) and AST (OR = 0.79, CI 95%: 0.60-1.03, p = 0.086) and no correlation with ALT (OR = 0.79, CI 95%: 0.60-1.03, p = 0.086). Thus, each time TB exceeded the ULN, the probability of improvement decreased by 79%, and each time GGT and AST did so, it decreased by 26% and 21%, respectively (Fig. 3).

No prognostic influence of baseline albumin or INR was observed, but there was a non-significant correlation between increased ferritin and decreased probability of improvement (OR = 0.99, CI 95: 0.99-1.00, p = 0.019).

14.9% (45/302) required admission to the ICU: 44.4% (20/45) at the time of hospitalization and 55.6% (25/45) during hospitalization. In the first group, we observed a 75% prevalence of BALB (16/20) and in the second group, a 96% prevalence of GALB (24/25). 73.3% (33/45) of those who required the ICU presented with severe involvement, and 24.4% (11/45) with moderate involvement. Admission to the ICU at the time of admission was for lack of improvement in 48% of cases (12/25) and for worsening in 52% (13/25). We found that ALB significantly influenced the need for ICU (OR = 5.28, CI 95%: 1.93-14.50, p = 0.001). Patients with moderate involvement were not more likely to be admitted to the ICU than asymptomatic or mild patients (OR = 2.22, CI 95%: 0.27-18.40, p = 0.459), but those with severe involvement were (OR = 21.40, CI 95%: 2.61-174.70, p = 0.004) (Table 2).

The average length of hospital stay was 17.2 ± 15.3 days, with a median of 12 days and was higher in patients with ALB (19 ± 16.1 vs. 15.7 ± 14.1), with this relationship being significant (p = 0.002). Of the 21.9% (66/302) of patients who died, 45.5% (30/66) had BALB, and 54.5% (36/66) had GALB. The mean survival time was 55.8 ± 5.9 days, with

higher mortality during the first 14 days.

Mortality was non-significantly correlated with moderate baseline involvement (OR = 7.59, CI 95%: 0.93-61.9, p = 0.058) and significantly correlated with severe involvement (OR = 50.9, CI 95%: 6.38-406, p = 0.004). Mortality increased with age (OR = 1.06, CI 95%: 1.03-1.09, p <0.001), especially after 65 years of age, with a 6% added probability of death per additional year.

However, mortality was not significantly related to ALB in the analysis of the logistic regression adjusted for age and involvement (Table 2). Nor did patients with ALB exhibit lower survival in Kaplan-Meyer tables or higher risk of mortality in COX regression (HR = 0.62, CI 95%: 0.37-1.02, p = 0.061).

DISCUSSION

In this study, we found that ALB significantly influences the need for hospitalization, as well as moderate to severe clinical involvement and worse prognosis in hospitalized patients, regardless of their comorbidities and treatment for COVID-19, except for LMWH. The potential of hepatotoxicity with LMWH is less than that of the other drugs used (22) and is described as infrequent and transient (23). Given that this effect does not influence BALB, which has prognostic implications, we consider the impact of the drug on the results to be of little relevance.

Our prevalence of ALB in hospitalized patients coincides with that described in other series which indicate a wide variability, with intervals such as that of the meta-analysis by Wang et al (2.6%-53%)(24) standing out. This variability arises because, unlike ours, other works consider higher cut-off points such as AST/ALT >3 ULN or TB >2 mg/dl (17, 25). Therefore, our study has greater sensitivity.

The parameters most frequently found to be elevated in our study were AST, GGT and ALT, on average without reaching values of ≥3 ULN and with the average maximum elevation of AST levels slightly predominating over that of ALT. Similar results are described by Kulkarni et al (17) and Ghoda et al (26), who note that these elevations are usually mild, even for patients with severe involvement (27, 28).

Like our study, other studies relate ALB with clinical involvement (29, 30). Guan et al (8) and Kumar-P et al (28) describe AST/ALT prevalences of 50-56% in severe patients

and 20% in non-severe patients. On the other hand, as stated by Ampuero et al (31), the assessment of ALB as a predictive factor of worse clinical outcome has not been sufficiently studied. In this meta-analysis, the increases of AST/ALT were specific to worse clinical evolution, and the elevation of AST levels was related to higher mortality.

Similarly, our results demonstrate that the prognosis is significantly worse with elevated TB and, as a trend, with elevated AST. Given that, in our series, the worsening of liver biochemistry and clinical involvement occurred during the first seven days, we recommend close clinical and analytical follow-up during this period, which we believe can be extended to non-hospitalized patients with ALB, without being able to draw conclusions regarding its prognostic impact in this subgroup.

Hyperferritinemia has been associated with increased involvement and mortality (32) and with elevated levels of AST/ALT (33). In our series it was correlated with greater clinical involvement, with a trend toward worse prognosis, so we recommend its determination. However, we did not observe a prognostic relationship with coagulation or albumin, as described by Weber et al (34), probably because, unlike them, we only considered the baseline value and not its maximum change. Finally, we did not observe greater mortality in patients with ALB as described in other studies (8, 17, 31), possibly due to differences in sample size.

The limitation of our study is its small sample size due to being a single-center study with a limited inclusion period. The exclusion of non-hospitalized patients was high, although we obtained significant results. We do not have the TB fractions for elevations between 1-1.5 times their ULN. Finally, we corrected for the impact of under diagnosing non-alcoholic fatty liver disease (35) using the scores, although HSI could not be applied to the entire sample.

The interesting aspect of this study is that it directly assesses ALB as an independent factor of poor prognosis excluding the confounding effect of other etiological factors. We believe that these studies help to identify patients with poorer prognosis at an early stage and are wide applicable.

In conclusion, ALB (especially TB) should be considered as an independent factor for worse clinical outcome. We recommend that it be determined and monitored during

the follow-up of patients with COVID-19, primarily during the first seven days.

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Variable	Category	Prevalence/mean±σ	No ALB (%/mean±σ)	ALB (%/mean±σ)	OR	CI 95%	p-value
Gender	Male	51,3% (155/302)	34,8% (54/155)	62,2% (101/155)	0,69	0,44-1,10	0,122
	Female	48,7% (147/302)	43,5% (64/147)	56,5% (83/147)			
Average age		69,3±16,0	72,8±16,7	67,1±15,2	0,99	0,97-1,01	0,155
Previous admittance to a community health center	No	78,8% (238/302)	33,6% (80/238)	66,4% (158/238)	0,35	0,20-0,61	<0,001
	Yes	21,2% (64/302)	59,4% (38/64)	40,6% (26/64)			
Obesity	No	94% (284/302)	32,3% (51/158)	67,7% (107/158)	0,75	0,27-2,05	0,573
	Yes	6% (18/302)	38,9% (7/18)	61,1% (11/18)			
Diabetes mellitus	No	73,8% (223/302)	36,8% (82/223)	63,2% (141/223)	0,68	0,40-1,14	0,145
	Yes	26,2% (79/302)	46,8% (37/79)	53,2% (42/79)			
Arterial hypertension	No	44% (133/302)	33,8% (45/133)	66,2% (88/133)	0,67	0,42-1,08	0,099
	Yes	56% (169/302)	43,2% (73/169)	56,8% (96/169)			
Dyslipidemia	No	57% (172/302)	36,6% (63/172)	63,4% (109/172)	0,79	0,50-1,26	0,317
	Yes	43% (130/302)	42,3% (55/130)	57,7% (75/130)			
Charlson Comorbidity index		4,59±3,07	5,31±3,23	4,14±2,89	0,88	0,82-0,95	0,001
FIB-4		2,04±1,13	2,19±1,15	1,92±1,10	0,81	0,65-1,00	0,052
APRI		0,37±0,18	0,35±0,17	0,38±0,20	2,34	0,62-9,35	0,205
HSI		36,90±6,15	36,61±6,41	37,12±5,98	1,01	0,96-1,07	0,609
Intravenous Steroids		26,5% (43/162)	62,8% (27/43)	37,2% (16/43)	1,93	0,91-4,08	0,087
LMWH		77,8% (126/162)	69% (87/126)	31% (39/126)	2,78	1,01-7,69	0,049
Lopinavir/ritonavir		53,7% (87/162)	73,6% (64/87)	26,4% (23/87)	0,92	0,46-1,85	0,824
Hydroxychloroquine		83,9% (136/162)	71,3% (97/136)	28,7% (39/126)	1,69	0,60-4,79	0,325
Tocilizumab		5,6% (9/162)	44,4% (4/9)	55,6% (5/9)	3,65	0,93-14,30	0,063
Antibiotic		93,8% (152/162)	71,1% (108/152)	28,9% (44/152)	3,25	0,95-11,60	0,063
Interferon beta-1b		12,3% (20/162)	80% (16/20)	20% (4/20)	0,64	0,20-2,02	0,445

Table 1: Characteristics of the groups of patients with and without ALB and correlation of ALB with demographic variables, comorbidities and treatment. HSI calculated at 52%. σ = standard deviation.

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Table 2: Correlation of ALB with unfavorable clinical events. Asymptomatic to mild involvement and absence of ALB are taken as a reference for the statistical analysis.

Correlation between:	Category	B coefficient	OR	CI 95%	p-value
BALB and need for hospitalization		2,01	7,49	3,62-15,48	<0,001
BALB and clinical involvement	Asymptomatic-mild		1		0,052
	Moderate	0,90	2,47	1,14-5,33	0,021
	Severe	0,94	2,56	1,15-5,73	0,022
GALB and clinical involvement	Asymptomatic-mild		1		0,042
	Moderate	0,75	2,12	1,03-4,36	0,042
	Severe	0,97	2,65	1,23-5,69	0,012
GALB and need for transfer to ICU	No ALB		1		
	ABH	1,66	5,28	1,93-14,50	0,001
	Asymptomatic-mild		1		0,001
	Moderate	0,79	2,22	0,27-18,40	0,459
	Severe	3,06	21,40	2,61-174,70	0,004
GALB and mortality	No ALB		1		
	ALB	-0,29	0,75	0,38-1,47	0,395

Table 3: Correlation of BALB with baseline liver function and inflammatory parameters.

Correlation of BALB with:	p-value
INR	0,739
Albumin	0,181
Leukocytes	0,89
Limphocytes	0,641
D-dimer	0,242
Troponin	0,457
C-reactive protein	0,125
Ferritin	<0,001

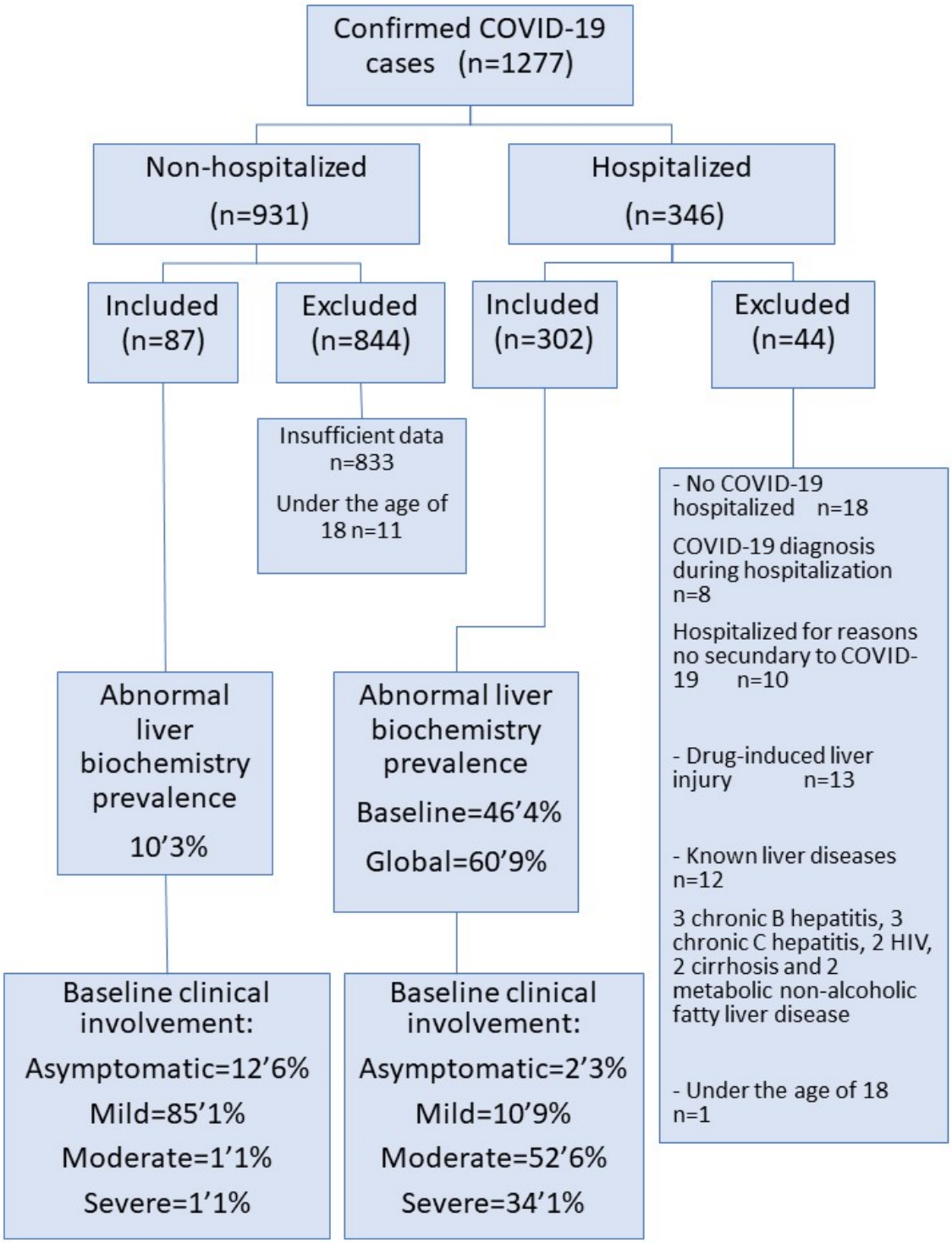

Figure 1: Flow chart of patients, prevalence of ALB and clinical involvement.

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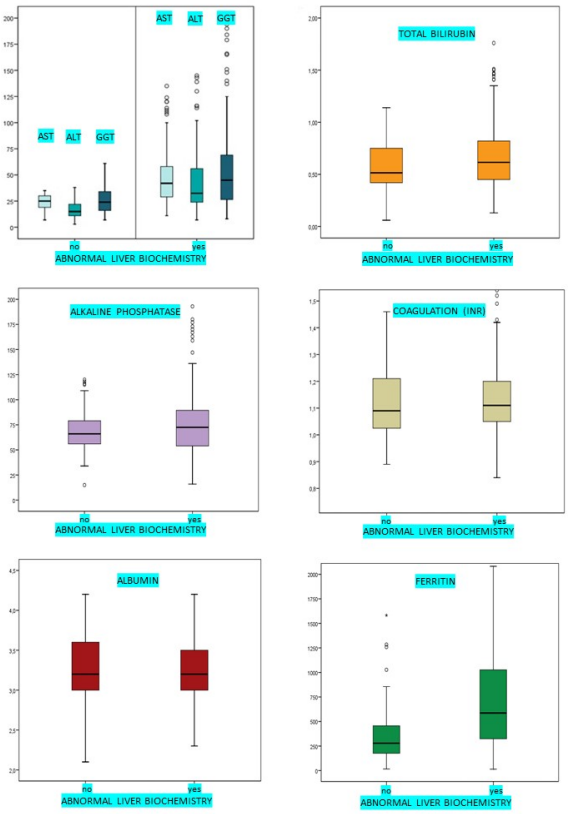

Figure 2.1

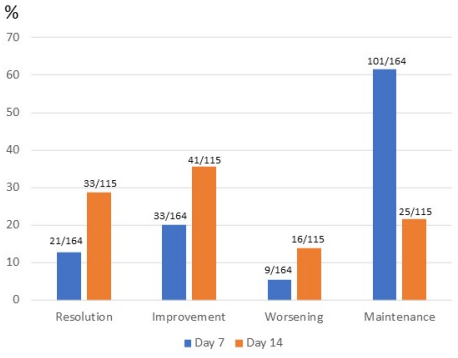

Figure 2.2

Figure 2.1: Diagrams showing the mean values of liver biochemistry parameters in the groups with and without abnormality. Figure 2.2: Graph showing the evolution of ALB on Days 7 and 14 of hospitalization.

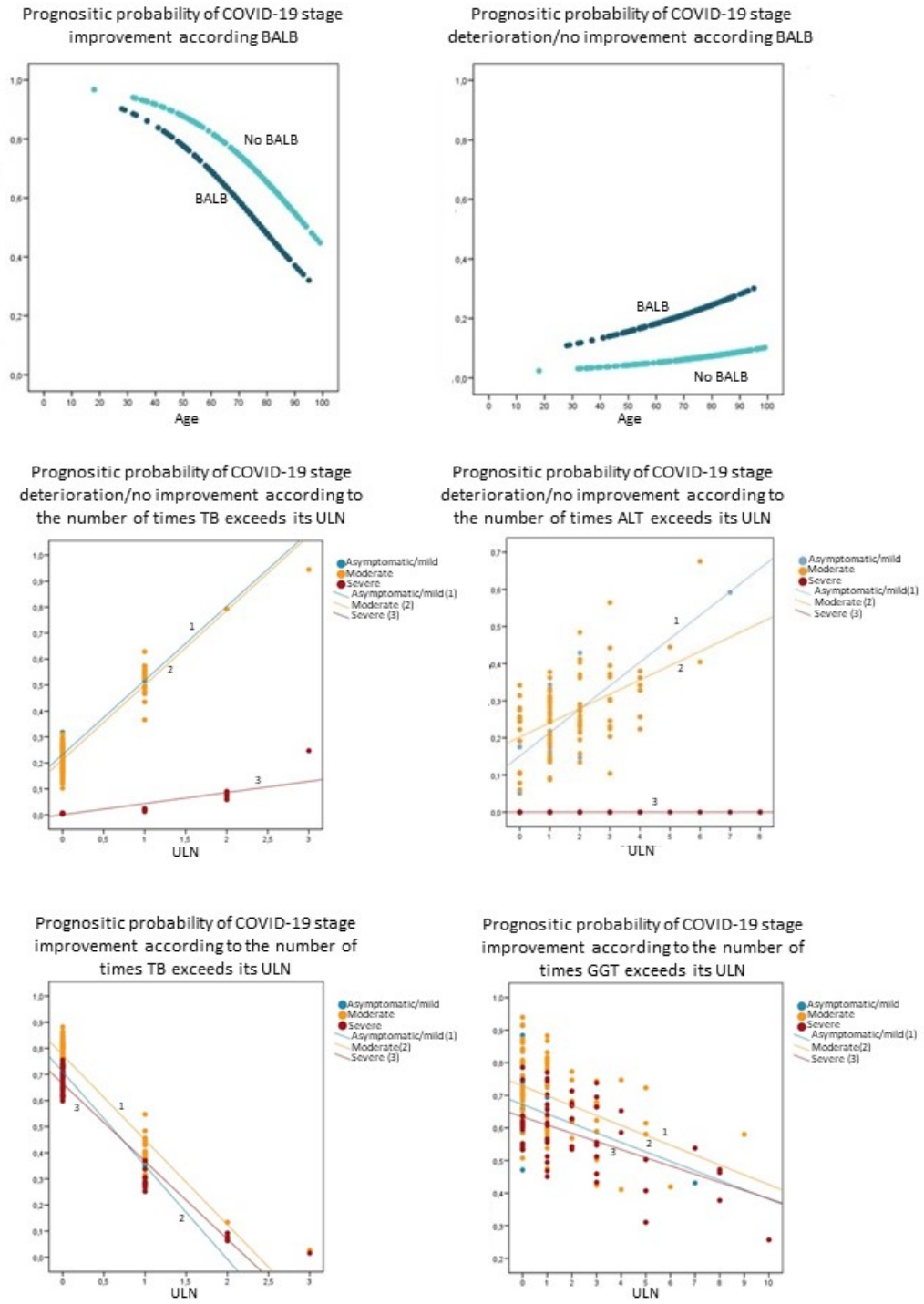

Figure 3: Plots showing correlation of prognostic probability with biochemistry and liver function and inflammatory parameters ($p < 0.05$ for TB only).