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Mild ast elevation as an early sign of COVID-19 severity in a multicenter Madrid cohort

Carlos Fernández Carrillo¹,¹¹, Christie Perelló¹, Elba Llop¹,¹¹, Javier García-Samaniego²,¹¹, Miriam Romero²,¹¹, José María Mostaza³, Luis Ibáñez⁴,¹¹, Rafael Bañares⁴,¹¹,¹², Federico Bighelli⁴, Clara Usón Peirón⁴, Inmaculada Fernández Vázquez⁵, Olga Hernández Castro⁶, Antonio Lalueza⁶, Agustín Albillos⁷,¹¹,¹³, Rosa Malo de Molina⁸, Elena Muñez⁹, Elena Jiménez Tejero¹⁰, José Luis Calleja¹,¹¹,¹⁴

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Author Contributions
C.F.C. performed data acquisition and analysis, contributed to site coordination and was responsible for a first manuscript version; C.P. and E.L. contributed to data analysis and critical revision of the results and the manuscript; J.G.S., M.R., L.I., R.B., I.F., O.H.C., F.B. and C.U.P., were responsible for data acquisition and/or critical revision of the results and the manuscript; A.A., J.M.M., A.L. and P.U. provided important critical revision of the results and contributed to the manuscript; J.L.C. was responsible for the study concept, managed coordination among the sites and gave critical revision of the results and the manuscript. All authors concur with the approval of this manuscript.

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**Keywords:** Alkaline phosphatase. Biomarker. Liver. SARS-CoV. SARS-CoV-2.

**List of abbreviations**

↑, elevated; α-IL6R, tocilizumab; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona-Clinic liver cancer; CI, confidence interval; CK, creatine kinase; COVID-19, coronavirus disease of 2019; CTP, Child-Turcotte-Pugh; CV, cardiovascular; ER, Emergency Room; GGT, gamma glutamyl transpeptidase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCQ, hydroxychloroquine; HCV, hepatitis C virus; ICU, Intensive Care Unit; IFNβ-2b, interferon-beta-2b; INR, international normalised ratio; IQR, inter-quartile range; LDH, lactate dehydrogenase; LN, upper limit of normality; LPV/r, lopinavir/ritonavir; LT, liver transplantation; N/A, not available; NAFLD, non-alcoholic liver disease; NASH, non-alcoholic steatohepatitis; NSAID, nonsteroidal anti-
inflammatory drugs; MELD, model for end-stage liver disease; PPI, proton-pump inhibitors; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Conflict of Interest Statement
The authors have no conflicts of interest to declare. This study did not receive any public or private funds for any of its steps.

ABSTRACT

Introduction: Liver enzyme elevation has been reported for SARS-CoV-2 disease (COVID-19) in heterogeneous cohorts, mainly from China. Comprehensive reports from other countries are needed. We dissect the pattern, evolution and predictive value of such abnormalities in a cohort from Madrid, Spain.

Methods: Retrospective study with prospective 14-day follow-up of 373 patients with confirmed COVID-19 in five Madrid hospitals, including 50 outpatients. COVID-19 severe course was defined as need of mechanical ventilation.

Results: A total of 33.1% hospitalised patients showed baseline AST elevation and 28.5% showed ALT elevation, contrasting with 12% and 8% of outpatients ($P \leq 0.001$). Baseline AST, ALT and GGT levels correlated with LDH and C-reactive protein levels (CRP) ($r \leq 0.598$, $P < 0.005$). AST elevation was associated with other severity markers such as male sex, lymphopenia and pneumonia on X-ray ($P < 0.05$ all). ALP and Bilirubin levels were rarely increased. Patients with elevated baseline AST displayed progressive normalization of this enzyme and increase in ALT and GGT levels. Patients with normal baseline AST showed a flattened evolution pattern with levels in range. Patients with a severe course of COVID-19 showed more frequently elevated baseline AST than those with a milder evolution (54.2% vs. 25.4%, $P < 0.001$). Age, AST and CRP were independent risk factors for a severe course of COVID-19.

Conclusion: Mild liver enzyme elevation is associated with COVID-19 severity. Baseline AST is an independent predictor of severe COVID-19 course, while it tends to normalize
over time. ALT and GGT show late elevation.
INTRODUCTION

In 2019, a new betacoronavirus (SARS-CoV-2) and its disease (COVID-19) emerged in China and has since expanded worldwide, with over 146,000,000 infected and 3,100,000 deceased patients for now.(1-5) Particularly, the Region of Madrid, Spain, has accounted for a substantial part of the nationwide incidence of COVID-19. This was most apparent during the beginning of the pandemic.(6)

COVID-19 is mainly characterized by acute respiratory symptoms that can range from asymptomatic to critical disease.(1,2,7,8) Interestingly, elevation of liver enzymes has been reported as part of the clinical picture in 14-53% of the cases.(1-3,7,9-17) In fact, liver involvement has been previously described for the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus.(10,18) Analogous cell entry mechanisms to SARS-CoV have been described for SARS-CoV-2, and liver infection confirmed in one case.(4,19-21)

Several Chinese cohorts have reported liver enzyme elevation in COVID-19 patients.(1-3,7,9,11-15) However, reports from outside China are almost lacking. The aim of the present work was to characterize the evolution of liver injury in a multicentre cohort of Spanish patients with COVID-19, uncovering the clinical usefulness of liver markers in this context.

Patients and Methods

Patients

We included 373 patients with confirmed COVID-19 in five third-level hospitals in Madrid, Spain, from 11 February 2020 to 20 March 2020. These sites cover more than 2,000,000 residents (Hospital Universitario Puerta de Hierro-Majadahonda, Hospital Universitario La Paz, Hospital General Universitario Gregorio Marañón, Hospital Universitario 12 de Octubre and Hospital Universitario Ramón y Cajal). Study inclusion
was retrospective and follow up was prospective. The selection criteria were i) confirmed symptomatic SARS-CoV-2 infection, and ii) available liver enzymes. SARS-CoV-2 RNA was PCR-detected in nasopharyngeal swab specimens as recommended elsewhere.\(^{(22,23)}\) For control, 50 of the subjects were outpatients with milder COVID-19 who were discharged directly from the Emergency Room. We excluded hospitalised patients with incidental COVID-19 diagnosis, and those below 16 years old. The protocol complies with the Declaration of Helsinki and was approved as consent-waived by the Ethics Committee of the Hospital Universitario Puerta de Hierro-Majadahonda (PI_48-20).

**Variables and outcomes**

De-identified demographic, clinical and analytical data were collected at initial consultation in the Emergency Room (baseline), 7 and 14 days after admission. We considered this length enough for the emergence of the most part of early respiratory complications. For the outpatients, only baseline information was collected. Outcome and liver enzyme peaks were collected at any time point. Liver enzymes included were aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP). The main endpoint was the need of mechanical ventilation (MV) during admission, which in our cohort happened in an Intensive Care Unit (ICU) for almost all the patients.

**Statistical methods**

Variables were described using median (IQR) or n, (%). Comparisons between paired or unpaired, categorical or quantitative variables were performed by Fisher’s exact, Mann-Whitney U or Wilcoxon signed rank tests. Spearman’s rank correlation coefficient was calculated for correlations. Variables with statistical significance and strong clinical meaning were introduced in a binomial logistic regression model to assess the predictive value of AST and other covariates. Collinearity was assessed as previously described,\(^{(24)}\) and the model was step-wise adjusted. Blank values were ignored and results referred to the whole sample size. Two-tailed \(P<0.05\) was considered as significant. IBM SPSS 19 and GraphPad Prism 8 software were used.
Results

Baseline characteristics
A total of 373 patients with COVID-19 was included for this study (Table 1), mainly males (61.9%), with a median age of 67 years (IQR 54 – 78) and a majority of Caucasian ancestry (86.3%). Some 62.2% showed one or more cardiovascular risk factors. Further baseline conditions were not infrequent, with half of the patients (49.9%) on chronic medical therapy.

At baseline, AST, ALT, GGT and ALP levels were abnormally elevated in 30.3%, 25.7%, 24.7% and 2.7% of the patients, respectively (Table 2). Total bilirubin levels were above the upper limit of normality (ULN) in 4.8% of the patients. Still, median elevations were mild (AST, 1.5xULN [IQR 1.2 – 2.1]; ALT, 1.4xULN [IQR 1.2 – 1.9]; GGT, 1.8, [IQR 1.2 – 2.9]; ALP, 1.4xULN [IQR 1.1 – 1.6]; bilirubin, 1.2xULN [IQR 1.1 – 1.8]). AST was concomitantly elevated with ALT or GGT in 18.8% or 13.4% of the patients, respectively.

Baseline differences depending on clinical condition and AST levels
As compared to those patients discharged from the Emergency Room (n=50), the patients admitted to the hospital (n=323) were older, mostly men, had more comorbid conditions and showed radiologic pneumonia more frequently (Table 1). They also exhibited some laboratory features suggestive of more severe COVID-19, such as higher LDH, CRP and CK levels, as well as more lymphopenia. Interestingly, they showed AST and ALT elevation much more frequently (Fig. 1A and Table 2) (33.1% vs. 12% for AST, 28.5% vs. 8% for ALT; P≤0.001 for both), with GGT levels showing a trend (26% vs. 16%, P=0.08). Bilirubin levels were not significantly different and ALP levels were not available for the outpatients. The same associations emerged when assessing these characteristics within hospitalised patients with or without AST elevation (data not shown). In this group, AST levels correlated significantly with LDH and CRP (Fig. 1B) (r=0.585 and r=0.324, respectively; P<0.001 for both).
**Evolution of liver enzymes during hospitalisation**

Even though there were 32 deceases (9.9%) and 83 discharges (25.7%) over the course of hospitalisation, liver enzymes were still available for the remaining 99.7%, 87.6% and 34.5% patients at baseline, the end of the first week, and the end of the second week, respectively. Remarkably, those hospitalised patients with elevated AST at baseline showed a distinctive pattern of liver enzyme evolution (Fig. 2A, left). In this group, AST levels tended to descend from a median of 60 IU/L (IQR 46 – 79) to normality range over the course of admission ($P<0.01$). However, ALT and GGT levels tended to increase over admission up to 72 IU/L (IQR 38 – 109) and 150 IU/L (IQR 72 – 201), respectively ($P=0.081$ and $<0.001$, respectively). This patient profile was more likely to receive multiple treatments such as lopinavir/ritonavir (64.6% vs. 47.6%), interferon-β 2B (37.2% vs. 15.8%) or antibiotics (87.6% vs. 23.9%) ($P<0.001$ for all). On the contrary, hospitalised patients presenting with normal AST showed a flattened evolution pattern, where all these enzymes showed mild variations over time and kept within a normal range (Fig. 2A, right). ALP and bilirubin levels showed no clear tendency in either group.

**AST as a predictor of severity**

A total of 83 hospitalised patients (25.7%) needed MV at any point during the first 14 days of admission. Interestingly, increased AST levels at baseline were present in 54.2% of them, while this only happened in 25.8% of the patients with a milder disease ($P<0.001$) (Fig. 2B). ALT, GGT and bilirubin levels were also more frequently elevated, unlike ALP levels, and increased steadily over the course of admission ($P<0.001$). Furthermore, liver enzyme and bilirubin peak levels during hospital stay were also higher (Fig. 2C).

In order to assess the potential prognostic value of AST, we built a multivariable model including factors previously associated with severity, as well as AST. A model including age, AST elevation and CRP levels showed an AUROC=0.882 for predicting the need of MV anytime during the first two weeks after admission (Table 3). This model classified much better who would not need MV (negative predictive value=94.7%).
Discussion

SARS-CoV-2 infection has explosively spread worldwide, becoming a major global emergency.(5) Spain has been strongly hit by this pandemic, particularly the Region of Madrid.(6) Almost all publications to date on hepatic involvement of COVID-19 include Chinese patients.(1-3,7,9,11-17) In a Spanish cohort, we assessed the most common pattern of liver enzyme elevation at clinical presentation, also defining its evolution and utility for predicting short-term severity.

Around one third of the hospitalised patients showed increased baseline AST, ALT or GGT levels, mildly in general. In agreement with previous reports, the most frequently elevated enzyme was AST (33.1%).(1-3,11-17) AST levels were associated with severity markers such as male sex, radiological pneumonia, and elevated LDH or CRP. Outpatients showed figures that are clearly more benign, also for AST. These findings are in accordance with reports suggesting greater elevations of liver enzymes for severe and critical patients.(1,3,11,12,16,17) Conversely, those severity features that we found to be associated with AST elevation, were compatible with the recently described COVID-19 patient phenotypes B and C.(25) The evolution of liver enzymes over the course of hospitalisation showed two differentiated patterns, similarly to what has recently been described in a Chinese cohort.(15) A first pattern was characterised by progressive normalisation of AST and a parallel increase in ALT and GGT levels. These patients had a worse clinical condition and received more drugs over the course of hospitalisation. These drugs may have accounted, at least partially, for such increases.(9,10,14) In this regard, some histopathological reports show unspecific findings which may overlap with drug-induced liver injury.(11,12) Elevation of liver enzymes has been previously described for lopinavir/ritonavir, although it needed a longer latency period.(26) A hypothetical synergistic effect of lopinavir/ritonavir and SARS-CoV-2 seems plausible. By contrast, those patients presenting with normal AST levels showed a much more flattened and stable pattern. Even though liver enzyme availability was influenced by deceases and discharges, we consider our results robust enough and concordant with Chinese literature.(15)
Finally, we assessed the prognostic value of AST for predicting a severe course of COVID-19 since patients with AST above normality at baseline were 50% more likely to need MV during the first 14 days after admission. A model including age, AST and CRP revealed AST as an independent risk factor for a severe course. Of note, this model predicted much better who would not need MV. This may happen because almost all of our patients receiving MV had been admitted to an ICU first, which is a decision depending on many individual factors.

The power of our models may have been increased by additional markers such as ferritin, D-dimer and interleukin-6, yet, these were not collected. Also, our study was time constrained, thus precluding a mortality analysis and limiting prediction of MV indication. It can be argued that elevated AST may not be fully hepatic. Actually, AST was associated with LDH and CK. Although some extrahepatic contribution cannot be fully excluded, recent findings support liver infection by SARS-Cov-2.(13,21,27) In fact, we found elevated ALT in 25.7% of the patients and there was concomitant AST-ALT elevation in 18.8% of them, similarly to what happened with GGT. On the other hand, comparable liver enzyme elevations and severe hepatitis have been previously described for SARS-CoV.(18,28-30) Cell entry is highly dependent on angiotensin-converting enzyme 2 and TMPRSS2 for both viruses, and these enzymes are expressed by the liver and gallbladder.(4,19,20,31,32)

In conclusion, mild liver enzyme elevation is associated with COVID-19 severity. This elevation is mainly accounted by AST, but also by ALT and/or GGT. Baseline AST is an independent predictor for needing mechanical ventilation, while it tends to normalize over time if elevated. ALT and GGT show multifactorial late elevation.
Acknowledgement

May this manuscript be a tribute to all the healthcare workers, scientists and many other people who are bravely fighting against COVID-19 in the Region of Madrid and all around the World.

References


22. Procedimiento de actuación frente a casos de infección por el nuevo coronavirus (SARS-CoV-2). Gobierno de España, Ministerio de Sanidad, Instituto de Salud Carlos III; 2020 March 30.


<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Hospitalised</th>
<th>Discharged from ER</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=373</strong></td>
<td></td>
<td>n=323</td>
<td>n=50</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>67 (54–78)</td>
<td>71 (59–79)</td>
<td>51 (45–59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age&gt;65</strong></td>
<td>195 (52.3)</td>
<td>164 (58.6)</td>
<td>3 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>231/142</td>
<td>178/102</td>
<td>26/24 (52/48)</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>(61.9/38.1)</td>
<td>(63.6/36.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td>166 (44.5)</td>
<td>139 (49.6)</td>
<td>9 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>77 (20.6)</td>
<td>61 (21.8)</td>
<td>3 (6.0)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>93 (24.9)</td>
<td>79 (28.2)</td>
<td>10 (20.0)</td>
<td>0.232</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>19 (5.1)</td>
<td>18 (6.4)</td>
<td>1 (2.0)</td>
<td>0.328</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>176 (47.2)</td>
<td>147 (52.5)</td>
<td>9 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Chronic lung disease</strong></td>
<td>69 (18.5)</td>
<td>57 (20.4)</td>
<td>5 (10.0)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Active tobacco use</strong></td>
<td>6 (1.6)</td>
<td>5 (1.8)</td>
<td>1 (2)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Previous liver disease</strong></td>
<td>12 (3.2)</td>
<td>11 (3.9)</td>
<td>1 (2.0)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Liver cirrhosis</strong></td>
<td>5 (1.3)</td>
<td>4 (1.2)</td>
<td>1 (2)</td>
<td>0.563</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td>21 (5.6)</td>
<td>13 (4.6)</td>
<td>1 (2.0)</td>
<td>0.703</td>
</tr>
<tr>
<td><strong>On treatment with ≥2 drugs</strong></td>
<td>120 (32.2)</td>
<td>91 (32.5)</td>
<td>10 (20.0)</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>21 (5.6)</td>
<td>16 (5.7)</td>
<td>1 (2.0)</td>
<td>0.486</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonia on chest X-ray</strong></td>
<td>247 (66)</td>
<td>237 (73.4)</td>
<td>10 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AST (IU/L)</strong></td>
<td>32 (23–48)</td>
<td>36 (24–54)</td>
<td>26 (21–36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ALT (IU/L)</strong></td>
<td>25 (18–39)</td>
<td>26 (18–41)</td>
<td>22 (17–32)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>GGT (IU/L)</strong></td>
<td>35 (21–68)</td>
<td>36 (22–70)</td>
<td>30 (19–43)</td>
<td>0.093</td>
</tr>
<tr>
<td><strong>ALP (IU/L)</strong></td>
<td>-</td>
<td>66 (50.8–92.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bilirubin (mg/dL)</strong></td>
<td>0.5 (0.3–0.7)</td>
<td>0.5 (0.34–0.7)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.113</td>
</tr>
<tr>
<td><strong>LDH (IU/L)</strong></td>
<td>262 (207–360)</td>
<td>274 (219–378)</td>
<td>195 (175–222)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>C-Reactive Protein (mg/L)</strong></td>
<td>50.5 (15.8–134.4)</td>
<td>67 (24.1–148.5)</td>
<td>13.7 (5.9–24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CK (IU/L)</strong></td>
<td>81 (53–171)</td>
<td>130 (60–297)</td>
<td>71 (49–109)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Lymphocytes (x10^3/mL)</strong></td>
<td>0.92 (0.64–1.22)</td>
<td>0.91 (0.62–1.2)</td>
<td>1.09 (0.89–1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>264 (70.9)</td>
<td>203 (72.5)</td>
<td>26 (52)</td>
<td>0.022</td>
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<tr>
<td><strong>INR†</strong></td>
<td>1.07 (1–1.15)</td>
<td>1.07 (1–1.16)</td>
<td>0.98 (0.96–1.04)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as median (IQR) or n, (%). *P* values <0.05 are in **bold**.

†Not controlled by anticoagulant treatment.

ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase levels; ALT, alanine aminotransferase levels; AST, aspartate aminotransferase levels; CK, creatine kinase; CV, cardiovascular; ER, Emergency Room; GGT, gamma glutamyl transpeptidase levels; INR, international normalised ratio; LDH, lactate dehydrogenase levels.
Table 2. Liver enzyme elevation at baseline in patients admitted to hospital versus patients discharged from the Emergency Room.

<table>
<thead>
<tr>
<th></th>
<th>Overall n=373</th>
<th>Hospitalized n=323</th>
<th>Discharged from ER n=50</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST&gt;ULN</td>
<td>113 (30.3)</td>
<td>107 (33.1)</td>
<td>6 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT&gt;ULN</td>
<td>96 (25.7)</td>
<td>92 (28.5)</td>
<td>4 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td>GGT&gt;ULN</td>
<td>92 (24.7)</td>
<td>84 (26)</td>
<td>8 (16)</td>
<td>0.076</td>
</tr>
<tr>
<td>ALP&gt;ULN</td>
<td>-</td>
<td>10 (3.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilirubin&gt;ULN</td>
<td>18 (4.8)</td>
<td>18 (5.6)</td>
<td>0</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Data presented as n, (%). P values <0.05 are in bold. ALP was not available for those patients discharged from the Emergency Room.

ER, Emergency Room; ULN, upper limit of normality.
Table 3. Logistic regression model for predicting the need of mechanical ventilation.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Hosmer-Lemeshow P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST &gt; LN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ AST ≤ 2 LN</td>
<td>3.599 (1.558–8.314)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>↑ AST &gt; 2 LN</td>
<td>5.761 (1.816–18.278)</td>
<td>0.002</td>
<td>0.604</td>
</tr>
<tr>
<td>Age &lt; 80 years</td>
<td>8.563 (1.914–18.274)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>CRP levels (mg/L)</td>
<td>1.013 (1.008–1.018)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*P* values <0.05 are in **bold**, excepting the constant.

↑, elevated; CI, confidence interval; CRP, C-reactive protein; LN, upper limit of normality; OR, odds ratio.
Fig. 1. Baseline levels of liver enzymes and associations with relevant parameters. (A) Percentage of patients with baseline elevation of liver enzymes needing admission to hospital vs. those outpatients discharged from the Emergency Room. (B) Correlation of AST levels with LDH levels. \( P \) values were calculated using Fisher’s exact test (A) and Spearman’s rank (B, C), also used for determining \( r \) correlation coefficients. ALT, alanine aminotransferase levels; AST, aspartate aminotransferase levels; Bili, total bilirubin levels; Dis, discharged; GGT, gamma glutamyl transpeptidase levels; Hos, hospitalised; LDH, lactate dehydrogenase; ULN, upper limit of normality.
Fig. 2. Liver enzymes, bilirubin and outcomes. (A) Evolution of liver enzymes over the course of the admission showed normalisation of AST as well as progressive elevation of ALT and GGT for patients presenting with AST elevation (left). Those patients with normal baseline AST levels displayed a flattened pattern of evolution (right). (B) Percentage of patients with abnormal baseline elevation of liver enzymes and bilirubin who needed mechanical ventilation vs. those without mechanical ventilation. (C) Liver enzyme and bilirubin peaks during hospitalisation for patients needing mechanical ventilation vs. those without mechanical ventilation. $P$ values were calculated using Fisher’s exact test (B) and Mann-Whitney U test (D). **$P \leq 0.01$; ***$P \leq 0.001$; $^P=0.081$. ALP, alkaline phosphatase; ALT, alanine aminotransferase levels; AST, aspartate aminotransferase levels; Bili, total bilirubin levels; GGT, gamma glutamyl transpeptidase levels; ULN, upper limit of normality; MV, mechanical ventilation.