**Supplementary Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

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**Supplementary Table 1. Demographic characteristics and inflammatory mediators in healthy subjects and patients with compensated cirrhosis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Healthy Subjects**  **(N=40)** | **Patients with Compensated Cirrhosis (N=39)** | **P-value** |
| **Demographic characteristics** |  |  |  |
| Age— year | 52.4 ± 7.28 | 59.6 ± 9.19 | <0.001 |
| Male gender — no./total no. (%) | 14/20 (70.0) | 23/39 (59.0) | 0.407 |
| **Median values for inflammatory mediators (IQR)** |  |  |  |
| TNF-α — pg/ml | 9.0 (6.52- 11.70) | 6.0 (2.85- 9.46) | 0.001 |
| IL-6 — pg/ml | 0.3 (0.30- 0.30) | 2.4 (0.23- 5.59) | 0.007 |
| IL-8 — pg/ml) | 1.6 (0.64- 3.33) | 5.6 (4.14- 12.54) | <0.001 |
| MCP-1 — pg/ml | 337.1 (217.14- 417.05) | 213.7 (154.6- 276.3) | <0.001 |
| IP-10 — pg/ml | 328.4 (234.61- 432.04) | 484.0 (350.2- 905.9) | 0.002 |
| MIP-1ß — pg/ml | 12.5 (6.38- 17.18) | 11.9 (6.59- 30.96) | 0.384 |
| G-CSF — pg/ml | 2.1 (1.80- 11.04) | 9.7 (2.37- 16.33) | 0.084 |
| GM-CSF — pg/ml | 7.5 (7.50- 7.50) | 2.1 (0.63- 6.86) | 0.007 |
| IL-10 — pg/ml | 1.1 (0.40- 1.10) | 2.7 (1.21- 6.72) | <0.001 |
| IL1-ra — pg/ml | 6.5 (2.72- 8.74) | 7.4 (0.75- 61.61) | 0.958 |
| IFNγ — pg/ml | 0.8 (0.80- 5.46) | 4.4 (0.77- 11.10) | 0.258 |
| Eotaxin — pg/ml | 93.5 (54.14- 125.86) | 81.7 (64.28- 107.51) | 0.345 |
| IL-17A — pg/ml | 0.7 (0.70- 2.98) | 0.9 (0.60- 1.67) | 0.822 |
| IL-7 — pg/ml | 1.4 (1.40- 1.40) | 2.6 (1.93- 3.02) | <0.001 |
| HNA2 — % | 1.3 (0.30- 1.93) | 6.7 (5.51- 7.42) | <0.001 |

NOTE: Data are shown as means ± SD or median (range). P values were calculated by unpaired Students’ t-test or Man-Whitney *U* test where appropriate.

IQR denotes interquartile range; TNF, umor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein 1; IP-10, 10 kDa interferon gamma-induced protein; MIP-1ß, macrophage inflammatory protein 1-beta; G-CSF, **granulocyte colony-stimulating factor;** GM-CSF, **granulocyte-macrophage colony-stimulating factor**; IL-1ra, **interleukin-1 receptor antagonist protein**; IFN, interferon; HNA2, human nonmercaptalbumin 2.

**Supplementary Table 2. Clinical characteristics, routine laboratory tests, and inflammatory mediators at enrollment of patients with compensated cirrhosis, patients with acutely decompensated (AD) cirrhosis who were free of ACLF, and patients with ACLF**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Compensated Cirrhosis**  **(N=39)** | **AD Cirrhosis Free of ACLF**  **(N=342)** | **ACLF**  **(N=161)** | **P-value** |
| **Clinical characteristics** |  |  |  |  |
| Age— year | 59.6 ± 9.19 | 57.0 ± 11.53 | 57.3 ± 11.45 | 0.405 |
| Male gender — no./total no. (%) | 23/39 (59.0 ) | 227/342 (66.4 ) | 108/161 (67.1 ) | 0.618 |
| Mean arterial pressure — mm Hg | 100.7 ± 11.89 | 83.9 ± 11.61 | 80.8 ± 13.40 | <.001 |
| Etiology of cirrhosis — no./total no. (%) |  |  |  |  |
| Alcoholic | 8/39 (20.5 ) | 157/321 (48.9) | 90/152 (59.2) | <.001 |
| HCV | 17/39 (43.6 ) | 78/321 (24.3) | 27/152 (17.8) | 0.003 |
| Alcohol + HCV | 0/39 (0.0) | 29/321 (9.0) | 17/152 (11.2) | 0.093 |
| Others | 14/39 (35.9) | 57/321 (17.8) | 18/152 (11.8) | 0.002 |
| **Median values for routine laboratory tests (IQR)** |  |  |  |  |
| Serum albumin — g/dl | 4.0 (3.80- 4.40) | 2.9 (2.50- 3.20) | 3.0 (2.40- 3.40) | <.001 |
| Serum bilirubin — mg/d | 0.9 (0.70- 1.17) | 3.1 (1.60- 6.98) | 6.1 (2.00- 14.37) | <.001 |
| Serum creatinine — mg/dl | 0.7 (0.65- 0.89) | 0.9 (0.70- 1.37) | 2.2 (0.98- 3.04) | <.001 |
| C-reactive protein — mg/L | 0.4 (0.13- 0.70) | 18.0 (6.50- 41.00) | 25.0 (9.70- 50.40) | <.001 |
| International Normalized Ratio | 1.1 (1.07- 1.20) | 1.5 (1.30- 1.76) | 1.7 (1.37- 2.30) | <.001 |
| Platelets — x109/L | 108.0 (72.00- 159.00) | 89.0 (57.00- 136.00) | 76.0 (53.00- 121.00) | 0.049 |
| **Supplementary Table 2. (Continued)** |  |  |  |  |
| White-cell count — x109/L | 4.7 (3.65- 7.11) | 6.3 (4.39- 9.40) | 8.0 (5.30- 12.20) | <.001 |
| **Median values for inflammatory mediators (IQR)** |  |  |  |  |
| TNF-α — pg/ml | 6.0 (2.85- 9.46) | 20.2 (14.45- 29.36) | 29.0 (17.38- 42.83) | <.001 |
| IL-6 — pg/ml | 2.4 (0.23- 5.59) | 24.0 (12.22- 47.78) | 36.7 (13.79- 106.83) | <.001 |
| IL-8 — pg/ml) | 5.6 (4.14- 12.54) | 42.4 (22.30- 83.92) | 84.5 (38.64- 165.10) | <.001 |
| MCP-1 — pg/ml | 213.7 (154.6- 276.3) | 324.3 (229.1- 456.3) | 410.3 (293.9- 690) | <.001 |
| IP-10 — pg/ml | 484.0 (350.2- 905.9) | 988.6 (582.3- 1764) | 1147.0 (651.2- 2123) | <.001 |
| MIP-1ß — pg/ml | 11.9 (6.59- 30.96) | 23.3 (13.85- 37.59) | 26.2 (17.89- 42.55) | 0.001 |
| G-CSF — pg/ml | 9.7 (2.37- 16.33) | 23.5 (12.32- 52.01) | 30.5 (13.85- 81.63) | <.001 |
| GM-CSF — pg/ml | 2.1 (0.63- 6.86) | 5.1 (2.19- 11.02) | 6.8 (3.47- 15.97) | <.001 |
| IL-10 — pg/ml | 2.7 (1.21- 6.72) | 3.8 (1.24- 10.79) | 7.2 (1.90- 25.78) | <.001 |
| IL1-ra — pg/ml | 7.4 (0.75- 61.61) | 11.5 (5.20- 28.35) | 18.7 (8.56- 50.48) | <.001 |
| IFNγ — pg/ml | 4.4 (0.77- 11.10) | 6.4 (2.11- 19.73) | 6.0 (2.32- 23.12) | 0.237 |
| Eotaxin — pg/ml | 81.7 (64.28- 107.51) | 113.8 (84.1- 160.5) | 123.5 (86.6- 177.2) | <.001 |
| IL-17A — pg/ml | 0.9 (0.60- 1.67) | 3.6 (1.60- 11.87) | 4.8 (1.62- 14.90) | 0.001 |
| IL-7 — pg/ml | 2.6 (1.93- 3.02) | 2.8 (1.11- 8.93) | 3.5 (1.62- 11.07) | 0.252 |
| HNA2 — % | 6.7 (5.51- 7.42) | 5.2 (2.65- 9.20) | 11.0 (6.25- 15.15) | <.001 |

NOTE: Patients with acutely decompensated cirrhosis were classified as being free of ACLF or having ACLF according to the EASL-CLIF Consortium criteria 1 2. Data are shown as means ± SD or median (range). P values were calculated by unpaired Students’ t-test or Kruskall-Wallis test where appropriate.

HCV denotes hepatitis C virus; IQR, interquartile range; TNF, umor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein 1; IP-10, 10 kDa interferon gamma-induced protein; MIP-1ß, macrophage inflammatory protein 1-beta; G-CSF, **granulocyte colony-stimulating factor;** GM-CSF, **granulocyte-macrophage colony-stimulating factor**; IL-1ra, **interleukin-1 receptor antagonist protein**; IFN, interferon; HNA2, human nonmercaptalbumin 2.

**Supplementary Table 3. Presence of specific organ dysfunction or organ failure in the patients of the subgroups AD-2 and AD-3. Data are shown as numbers (%).**

|  |  |  |
| --- | --- | --- |
| **Organ function** | **AD-2**  **(N=121)** | **AD-3**  **(N=66)** |
| Renal dysfunction | 61(50.4) | 0(0.0) |
| Cerebral dysfunction | 81(66.9) | 0(0.0) |
| Liver failure | 0(0.0) | 38(57.6) |
| Coagulation failure | 0(0.0) | 12(18.2) |
| Respiratory failure | 0(0.0) | 3(4.6) |
| Circulatory failure | 0(0.0) | 5(7.6) |

**Supplementary Table 4. Clinical characteristics, routine laboratory tests, and inflammatory mediators at enrollment of 342 patients with acutely decompensated cirrhosis who were free of ACLF, according to their outcome (alive or dead) at 90 days**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Alive at 90 Days**  **(N=259)** | **Dead at 90 days**  **(N=55)** | **P value** |
| **Clinical characteristics** |  |  |  |
| Age— year | 57.7 ± 11.50 | 56.6 ± 11.54 | 0.5403 |
| Male gender — no./total no. (%) | 168/259 (64.9) | 36/55 (65.5) | 0.9337 |
| Mean arterial pressure — mm Hg | 84.0 ± 11.86 | 85.4 ± 11.44 | 0.4238 |
| Precipitating events — no./total no. (%) | 31/236 (13.1) | 9/52 (17.3) | 0.4310 |
| Etiology of cirrhosis — no./total no. (%) |  |  |  |
| Alcoholic | 125/246 (50.8) | 23/50 (46.0) | 0.5349 |
| HCV | 58/246 (23.6) | 13/50 (26.0) | 0.7145 |
| Alcohol + HCV | 19/246 (7.7) | 6/50 (12.0) | 0.3992 |
| Others | 44/246 (17.9) | 8/50 (16.0) | 0.7493 |
| **Median values for routine laboratory tests (IQR)** |  |  |  |
| Serum albumin — g/dl | 2.9 (2.59- 3.20) | 2.8 (2.30- 3.20) | 0.1675 |
| Serum bilirubin — mg/d | 2.6 (1.49- 5.67) | 5.2 (2.91- 10.60) | <.0001 |
| Serum creatinine — mg/dl | 0.9 (0.70- 1.28) | 1.0 (0.70- 1.45) | 0.2967 |
| C-reactive protein — mg/L | 15.0 (5.35- 36.30) | 36.5 (18.00- 61.00) | <.0001 |
| International Normalized Ratio | 1.4 (1.24- 1.67) | 1.7 (1.47- 2.03) | <.0001 |
| Platelets — x109/L | 92.0 (58.00- 141.00) | 88.8 (55.00- 122.00) | 0.4115 |
| White-cell count — x109/L | 6.1 (4.10- 8.90) | 8.0 (5.67- 12.56) | 0.0002 |
|  |  |  |  |
| **Supplementary Table 4. (Continued)** |  |  |  |
| **Median values for inflammatory mediators (IQR)** |  |  |  |
| TNF-α — pg/ml | 19.40 (14.14 - 27.33) | 25.35 (17.22 - 32.06) | 0.006 |
| IL-6 — pg/ml | 21.13 (11.72 - 40.71) | 34.14 (17.69 - 80.24) | 0.002 |
| IL-8 — pg/ml) | 37.33 (19.94 - 79.81) | 58.73 (41.69 - 117.82) | <.001 |
| MCP-1 — pg/ml | 323.06 (235.91 - 436.79) | 349.46 (245.99 - 546.44) | 0.196 |
| IP-10 — pg/ml | 972.14 (577.41 - 1722.00) | 1120.00 (580.44 - 1996.00) | 0.565 |
| MIP-1ß — pg/ml | 22.58 (13.92 - 37.50) | 26.25 (15.44 - 45.50) | 0.239 |
| G-CSF — pg/ml | 23.51 (11.70 - 52.24) | 23.79 (15.57 - 46.06) | 0.841 |
| GM-CSF — pg/ml | 4.71 (2.03 - 10.37) | 5.54 (2.57 - 11.91) | 0.121 |
| IL-10 — pg/ml | 3.03 (0.91- 9.75) | 5.93 (1.84 - 16.99) | 0.043 |
| IL1-ra — pg/ml | 10.44 (4.98 - 28.88) | 15.49 (6.35 - 31.87) | 0.116 |
| IFNγ — pg/ml | 6.02 (2.01 - 19.38) | 7.83 (2.78 - 26.79) | 0.370 |
| Eotaxin — pg/ml | 106.75 (77.61 - 152.18) | 137.18 (99.03 - 187.88) | <.001 |
| IL-17A — pg/ml | 3.48 (1.49 - 10.25) | 5.13 (2.21 - 17.41) | 0.030 |
| IL-7 — pg/ml | 2.75 (1.00 - 8.17) | 4.49 (1.63 - 16.41) | 0.041 |
| HNA2 — % | 4.37 (2.38 - 8.17) | 8.35 (5.34 - 11.13) | <.001 |

NOTE: Data are shown as means ± SD or median (range). P values were calculated by unpaired Students’ t-test or Man-Whitney *U* test where appropriate.

Data obtained in 28 patients who received a liver transplant during the 90 days were excluded from this analysis.

HCV denotes hepatitis C virus; IQR interquartile range; TNF, umor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein 1; IP-10, 10 kDa interferon gamma-induced protein; MIP-1ß, macrophage inflammatory protein 1-beta; G-CSF, **granulocyte colony-stimulating factor;** GM-CSF, **granulocyte-macrophage colony-stimulating factor**; IL-1ra, **interleukin-1 receptor antagonist protein**; IFN, interferon; HNA2, human nonmercaptalbumin 2.

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