**SUPPLEMENTARY TABLES**

**Supplementary Table 1.** Summary of Laboratory Predictors of Adverse Outcomes.

|  |  |  |  |
| --- | --- | --- | --- |
| **TEST** | **OUTCOME** | **ASSOCIATION** | **Ref** |
| **Hematologic** | | | |
| Neutrophils | Mortality | high neutrophils: HR 1.08 (1.01-1.17; p = 0.03) | (Wu *et al*., 2020) |
| ARDS | high neutrophils: HR 1.14 (1.09-1.19; p < 0.001) | (Wu *et al*., 2020) |
| Neutrophil  Lymphocyte Ratio  (NLR) | Severe Illness | NLR>3 has worse prognosis  (p = 0.0005) | (J. Liu *et al.*, 2020a) |
| Platelet | Mortality | Thrombocytopenia: OR 5.1 (1.8-14.6) | (Lippi *et al*., 2020) |
| Platelet Lymphocyte Ratio (PLR) | Severe Illness | Higher PLR at peak platelet during treatment was an independent  influencing factor in severe patients (p<0.05) | (L. Chen *et al*., 2020) |
| **Biochemical & Infection-related Indices** | | | |
| Albumin | Disease  progression | Albumin < 40 g/L: OR 7.35 (1.098- 50.0, p=0.003) | (W. Liu *et al*., 2020) |
| Total bilirubin (TB) | Mortality | high TB: HR 1.07 (1.02-1.12; p = 0.003) | (Wu *et al*., 2020) |
| ARDS | high TB: HR 1.05 (1.02-1.08; p = 0.001) | (Wu *et al*., 2020) |
| AST | ARDS | high AST: HR 1.02 (1.01-1.03; p 0 < 0.001 | (Wu *et al*., 2020) |
| Procalcitonin | Mortality | High Procalcitonin: OR 13.75 (1.81- 104.4, p=0.011) | (F. Zhou *et al*., 2020) |
| Hs-Trop-I | Mortality | Trop >28: OR 80.07 (10.34-620.36, p=0.001) | (F. Zhou *et al*., 2020) |
| LDH | Mortality | LDH > 100 U/L: HR 1.30 (1.11-1.52; p = 0.001) | (Wu *et al.*, 2020) |
| ARDS | LDH > 100 U/L: HR 1.61 (1.44-1.79; p < 0.001) | (Philippine Society for  Microbiology and  Infectious Diseases,  2020b; Wu *et al*., 2020) |
| Glucose | ARDS | high glucose: HR 1.13 (1.08-1.19; p < 0.001) | (Wu *et al*., 2020) |
| Creatinine | ARDS | creatine > 10uM: HR 1.05 (1.01-1.10; p = 0.02) | (Wu *et al*., 2020) |
| hs CRP | ARDS | hs CRP >5mg/ml: HR 4.81 (1.52-15.27; p = 0.008) | (Wu *et al*., 2020) |
| CRP | Mortality | CRP 125 mg/L in deaths versus 40 mg/L in survivors | (F. Zhou *et al*., 2020) |
| Disease  Progression | CRP >8.2 mg/dL: OR 10.53 (1.24-34.7, p=0.028) | (W. Liu *et al*., 2020) |
| Ferritin | Mortality | Ferritin >300 ug/L: OR 9.10 (2.04- 40.58, p=0.0038); HR 3.53 (1.52-8.16; p = 0.003) | (F. Zhou *et al*., 2020) |
| D-Dimer | Mortality | D-Dimer > 1 ug/mL: OR 18.42 (2.64- 128.55, p=0.003) | (F. Zhou *et al*., 2020) |
| Mortality | High D-Dimer: 1.02 (1.01-1.04; p = .002) | (Wu *et al*., 2020) |
| ARDS | High D-Dimer: 1.03 (1.01-1.04; p <.001 | (Wu *et al*., 2020) |

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**Supplement Table 2.** Adjusted Estimates for Cytokine Levels and Disease Progression

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cytokine (N)** | **Ill day** | **Without Disease Progression**  Median, ng/mL and Interquartile Range | **With Disease Progression**  Median, ng/mL and Interquartile Range | **p-value** |
| IFN-y (266) | 0 – 3 | 74.17 (-62.13 – 210.47) | 62.85 (-82.19 – 207.89) | 0.39 |
| 4 – 10 | 82.67 (42.32 – 123.01) | 35.16 (-19.53 – 89.84) |
| 11 – 14 | 83.18 (39.01 – 127.35) | 109.34 (47.26 – 171.41) |
| >14 | 102.92 (64.27 – 141.57) | 87.27 (25.46 – 149.08) |
| **p-value** | 0.70 | |  |
| TNF-a (290) | 0 – 3 | 345.13 (-2.15 – 692.41) | 213.53 (-187.01 – 614.06) | 0.18 |
| 4 – 10 | 194.37 (79.24 – 309.49) | 188.95 (32.27 – 345.62) |
| 11 – 14 | 212.10 (91.18 – 333.01) | 237.78 (66.61 – 408.95) |
| >14 | 324.34 (216.76 – 431.91) | 364.00 (189.52 – 538.48) |
| **p-value** | 0.83 | |  |
| IL – 8 (307) | 0 – 3 | 692.53 (-462.18 – 1847.25) | 560.02 (-761.18 – 1881.22) | 0.43 |
| 4 – 10 | 897.58 (492.65 – 1302.51) | 587.06 (20.99 – 1153.12) |
| 11 – 14 | 1259.39 (843.48 - 1675.30) | 864.16 (261.12 – 1467.21) |
| >14 | 1159.20 (777.78 – 1540.62) | 787.70 (163.79 – 1411.61) |
| **p-value** | 0.36 | |  |
| IL-6  (307) | 0 – 3 | 441.50 (-450.32 – 1333.31) | 1402.29 (389.67 – 2414.91) | 0.06 |
| 4 – 10 | 315.07 (24.62 – 605.53) | 397.65 (-5.55 – 800.86) |
| 11 – 14 | 489.44 (188.66 – 790.22) | 534.03 (97.92 – 970.14) |
| >14 | 359.34 (89.03 – 629.64) | 1248.50 (798.47 – 1698.52) |
| **p-value** | 0.03 | |  |
| IL-1B (205) | 0 – 3 | 122.05 (-28.72 – 272.81) | 52.73 (-117.25 – 222.70) | 0.70 |
| 4 – 10 | 67.89 (13.60 – 122.17) | 136.44 (47.69 – 225.18) |
| 11 – 14 | 129.86 (63.35 – 196.37) | 150.08 (46.83 – 253.33) |
| >14 | 136.61 (86.04 – 187.19) | 123.76 (41.56 – 205.96) |
| **p-value** | 0.97 | |  |
| IL – 2  (193) | 0 – 3 | 17.35 (-3.49 – 38.19) | 11.71 (-12.26 – 35.67) | 0.95 |
| 4 – 10 | 8.81 (1.66 – 15.95) | 12.03 (0.74 – 23.32) |
| 11 – 14 | 12.62 (3.85 – 21.38) | 10.04 (-2.69 – 22.78) |
| >14 | 14.23 (6.63 – 21.83) | 11.36 (0.23 -22.48) |
| **p-value** | 0.71 | |  |
| IL-4  (66) | 0 – 3 | 147.99 (5.61 – 290.37) | 158.88 (-53.08 – 370.85) | 0.59 |
| 4 – 10 | 20.26 (-17.94 – 58.46) | 98.11 (9.62 – 186.59) |
| 11 – 14 | 69.93 (14.30 – 125.57) | 59.82 (-28.20 – 147.85) |
| >14 | 57.22 (-0.33 – 114.78) | 67.36 (-10.23 – 144.95) |
| **p-value** | 0.60 | |  |
| **IP-10**  (305) | 0 – 3 | 9872.65 (-1707.03 – 21452.33) | 43532.10 (30336.84 – 56727.37) | **<0.00001** |
| 4 – 10 | 10560.48 (6633.92 – 14487.03) | 21077.02 (15567.53 – 26586.52) |
| 11 – 14 | 6282.21 (2204.15 – 10360.26) | 18827.85 (12964.94 – 24690.76) |
| >14 | 3021.96 (-703.33 – 6747.25) | 2661.90 (-3399.41 – 8723.22) |
| **p-value** | <0.00001 | |  |
| IL – 18  (291) | 0 – 3 | 200.10 (-87.43 – 487.64) | 206.05 (-119.38 – 531.49) | 0.21 |
| 4 – 10 | 190.77 (92.72 – 288.83) | 192.77 (56.98 – 328.55) |
| 11 – 14 | 180.33 (72.45 – 288.20) | 464.28 (315.55 – 613.02) |
| >14 | 212.67 (121.81 – 303.54) | 286.37 (139.55 – 433.20) |
| **p-value** | 0.20 | |  |
| IL-10 (151) | 0 – 3 | 303.64 (18.39 – 588.89) | 88.42 (-147.75 – 324.59) | 0.92 |
| 4 – 10 | 162.01 (65.53 – 258.48) | 130.28 (-1.83 -262.40) |
| 11 – 14 | 119.18 (2.63 – 235.73) | 132.49 (-20.85 – 285.83) |
| >14 | 114.44 (17.66 – 211.23) | 183.53 (30.91 – 336.15) |
| **p-value** | 0.56 | |  |

**Supplement Table 3.** Adjusted Estimates for Cytokine Levels and Mortality

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cytokine (N)** | **Ill day** | **Survivor**  Median, ng/mL and Interquartile Range | **Non-Survivor**  Median, ng/mL and Interquartile Range | **p-value** |
| IFN-y (266) | 0 – 3 | 61.29 (-44.59 – 167.17) | 117.51 (-153.00 – 388.02) | 0.27 |
| 4 – 10 | 73.70 (38.37 – 109.03) | 27.64 (-51.09 – 106.37) |
| 11 – 14 | 79.94 (40.50 – 119.37) | 145.31 (60.96 – 229.66) |
| >14 | 103.76 (-153.00 – 137.97) | 48.61 (-59.68 – 156.90) |
| **p-value** | 0.91 | |  |
| IL – 8 (307) | 0 – 3 | 680.61(-270.27 – 1631.48) | 512.23 (--1580.40 – 2604.86) | 0.91 |
| 4 – 10 | 868.05 (512.22 – 1223.89) | 414.45 (-414.59 – 1243.49) |
| 11 – 14 | 1256.71 (889.48 – 1623.95) | 404.07 (-489.90 – 1298.03) |
| >14 | 1130.22 (788.87 – 1471.56) | 465.00 (-558.68 – 1488.68) |
| **p-value** | 0.21 | |  |
| **IL-6**  (307) | 0 – 3 | 523.47 (-183.69 – 1230.63) | 2454.46 (906.30 – 4002.63) | **<0.00001** |
| 4 – 10 | 321.44 (74.50 – 568.39) | 421.17 (-146.30 – 988.63) |
| 11 – 14 | 414.38 (157.50 – 671.26) | 1014.34 (389.60 – 1639.08) |
| >14 | 329.69 (94.97 – 564.40) | 3037.35 (2320.95 – 3753.76) |
| **p-value** | <0.00001 | |  |
| IL-1B  (205) | 0 – 3 | 90.78 (-33.05 – 214.61) | 85.69 (-171.88 – 343.27) | 0.91 |
| 4 – 10 | 88.38 (38.36 – 138.41) | 78.27 (-45.27 – 201.80) |
| 11 – 14 | 144.11 (84.13 – 204.10) | 91.07 (-59.31 – 241.45) |
| >14 | 137.68 (92.66 – 182.69) | 77.17 (-71.18 – 225.52) |
| **p-value** | 0.54 | |  |
| IL – 2  (193) | 0 – 3 | 14.72 (-3.87 – 33.31) | 15.35 (-14.26 – 44.95) | 0.96 |
| 4 – 10 | 9.60 (3.16 – 16.04) | 10.69 (-6.32 – 27.70) |
| 11 – 14 | 12.29 (4.17 – 20.40) | 9.97 (-5.41 – 25.36) |
| >14 | 13.68 (6.96 – 20.41) | 10.86 (-6.61 – 28.34) |
| **p-value** | 0.89 | |  |
| IL-4  (66) | 0 – 3 | 139.28 (-0.94 – 279.50) | 163.18 (-55.05 – 381.41) | 0.64 |
| 4 – 10 | 31.73 (-4.78 – 68.24) | 80.57 (-61.04 – 222.18) |
| 11 – 14 | 63.54 (10.05 – 117.03) | 67.37 (-30.88 -165.62) |
| >14 | 59.33 (12.25 – 106.41) | 84.79 (-59.82 – 229.41) |
| **p-value** | 0.60 | |  |
| **IL – 18**  (291) | 0 – 3 | 192.59 (-37.41 – 422.59) | 235.05 (-268.43 – 738.53) | **<0.001** |
| 4 – 10 | 180.92 (97.07 – 264.77) | 244.08 (46.92 – 441.25) |
| 11 – 14 | 172.84 (81.39 – 264.30) | 890.36 (668.33 – 1112.40) |
| >14 | 216.73 (137.47 – 296.00) | 385.63 (147.34 – 623.92) |
| **p-value** | <0.01 | |  |
| **IP-10**  (305) | 0 – 3 | 17235.82 (7903.67 – 26567.97) | 57367.50 (36903.53 – 77831.46) | **<0.00001** |
| 4 – 10 | 12193.98 (8803.96 – 15583.99) | 24424.94 (16597.45 – 32252.43) |
| 11 – 14 | 5656.98 (2133.65 – 9180.31) | 36941.07 (28421.85 – 45460.29) |
| >14 | 2605.78 (-658.35 – 5869.92) | 4624.30 (-5141.66 – 14390.26) |
| **p-value** | <0.00001 | |  |
| IL-10  (151) | 0 – 3 | 183.64 (-27.02 – 394.30) | 152.32 (-219.65 – 524.31) | 0.99 |
| 4 – 10 | 159.78 (72.85 – 246.71) | 112.74 (-61.98 – 287.47) |
| 11 – 14 | 112.60 (9.23 – 215.98) | 168.62 (-40.45 – 377.69) |
| >14 | 152.33 (44.61 – 223.28) | 137.39 (-61.31 – 336.10) |
| **p-value** | 0.96 | |  |

**Supplementary Table 4.** AUC calculation for IL-6 and IP-10 in disease progression group of COVID-19 patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Days of Illness** | **IL-6** | | **IP-10** | |
| **AUC** | **95%CI** | **AUC** | **95%CI** |
| 0-3 days | 0.56 | 0.38 - 0.74 | 0.81 | 0.68 - 0.94 |
| 4-10 days | 0.63 | 0.58 - 0.68 | 0.56 | 0.51 - 0.62 |
| 11-14 days | 0.67 | 0.61 - 0.73 | 0.63 | 0.57 - 0.69 |
| >14 days | 0.6 | 0.55 - 0.66 | 0.58 | 0.53 - 0.64 |

**Supplementary Table 5.** AUC calculation for IL-6, IL-18, and IP-10 in nonsurvivors group of COVID-19 patients.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Days of Illness** | **IL-6** | | **IL-18** | | **IP-10** | |
| **AUC** | **95%CI** | **AUC** | **95%CI** | **AUC** | **95%CI** |
| 0-3 days | 0.58 | 0.33 - 0.83 | 0.52 | 0.27 - 0.76 | 0.65 | 0.40 - 0.91 |
| 4-10 days | 0.65 | 0.59 - 0.71 | 0.66 | 0.60 - 0.73 | 0.54 | 0.46 - 0.62 |
| 11-14 days | 0.75 | 0.68 - 0.82 | 0.69 | 0.60 - 0.77 | 0.77 | 0.70 to 0.84 |
| >14 days | 0.75 | 0.68 - 0.82 | 0.62 | 0.52 - 0.72 | 0.66 | 0.59 - 0.74 |

**SUPPLEMENTARY FIGURES**

**Chart

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**Supplementary Figure 1.** Dynamics of serum cytokine levels during the disease course in the general COVID-19 patient cohort. The cytokines were measured in terms of days from illness onset. All samples collected from 400 patients were stratified into four intervals starting from illness onset. The dots represent individual measurement, and the box plots represent medians with interquartile range. The different groups were compared using the Kruskal-Wallis test with Dunn's post hoc test.

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**Supplementary Figure 2.** Dynamics of serum cytokine levels during the disease course in COVID-19 patients based on disease progression. The cytokines were measured in terms of days from illness onset. All samples collected from 400 patients were stratified into four intervals starting from illness onset. The dots represent individual measurements, and the box plots represent medians with interquartile range. The different groups were compared by repeated measures mixed model regression with post hoc test. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001.

Timeline

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**Supplementary Figure 3.** Dynamics of serum cytokine levels during the disease course in COVID-19 patients based on mortality. The cytokines were measured in terms of days from illness onset. All samples collected from 400 patients were stratified into four intervals starting from illness onset. The dots represent individual measurements, and the box plots represent medians with interquartile range. The different groups were compared by repeated measures mixed model regression with post hoc test. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001

Graphical user interface, chart, line chart

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**Supplementary Figure 4.** Average prediction of (A) IL-6 and (B) IP-10 values with 95% CI between those with and without disease progression. The values were adjusted for the treatment received (i.e., tocilizumab or dexamethasone), presence of comorbidities (i.e., chronic kidney disease and diabetes mellitus), and age (cut off at 55 years old). \* *p* < 0.05; \*\* *p* < 0.01; \*\*\* *p* < 0.001.

Graphical user interface, chart, line chart

Description automatically generated

**Supplementary Figure 5.** Average prediction of (A) IL-6, (B) IL-18, and (C) IP-10 values with 95% CI between survivors and non-survivors. The values were adjusted for the treatment received (i.e., tocilizumab or dexamethasone), presence of comorbidities (i.e., chronic kidney disease and diabetes mellitus), and age (cut off at 55 years old). \* *p* < 0.05; \*\* *p* < 0.01; \*\*\* *p* < 0.001.