**Supplemental Digital Content 1.** Comparison of the demographic, clinical phenotypic features, laboratory findings, ECHO and early outcomes in four distinct COVID-19 waves driven by four VOC in South Africa.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Totals** | **Wave 1** | **Wave 2** | **Wave 3** | **Wave 4** | **p Value** |
| **VOC** |  | Ancestral  type | Beta | Delta | Omicron |  |
| **Wave Start date** |  | 3 May 2020 | 8 Nov 2020 | 23 May 2021 | 28 Nov 2021 |  |
| **Cases n (%)** | 129 | 49 (38.0) | 21(16.3) | 43(33.3) | 16(12.4) |  |
| **Age in years median (IQR)** | 6.85 (3.39, 9.28) | 7.37 (3.39, 10.00) | 7.30 (4.17, 7.84) | 6.37 (4.20, 9.11) | 4.93 (2.63, 8.27) | **0.82** |
| **Male: Female** | 69:60 | 25:24 | 12:9 | 23:20 | 9:7 | **0.96** |
| **Black race n (%)** | 66 (51.2) | 32 (65.3) | 12 (57.1) | 14 (32.6) | 8 (50.0) | **0.02** |
| **BMI median (IQR)** | 16 (14, 19.8) | 17 (14.7, 20.0) | 15 (13.5, 20.0) | 16 (15, 19) | 16 (13, 180 | **0.66** |
| **BMI**  **n= 75** | 16 (14, 19.8)  N=75 | 17 (14.7, 20)  N=35 | 15 (13.5, 20)  N=8 | 16 (15, 19)  N=26 | 16 (13, 18)  N=6 | **0.66** |
| **Comorbidity**  **n (%)** | 23 (21.5) | 10/38 (26.3) | 4/17 (23.5) | 5/36 (13.9) | 4 (25.0) | **0.56** |
| **Rash**  **n (%)** | 108 (83.7) | 42 (85.7) | 18 (85.7) | 36 (83.7) | 12 (75.0) | **0.79** |
| **Conjunctivitis**  **n (%)** | 102 (79.1) | 37 (75.5) | 18 (85.7) | 37 (86.1) | 10 (62.5) | **0.21** |
| **Diarrhea**  **n (%)** | 63 (48.8) | 28 (57.1) | 13 (61.9) | 19 (44.2) | 3 (18.8) | **0.03** |
| **Abdominal pain**  **n (%)** | 77 (59.7) | 31 (63.3) | 10 (47.6) | 27 (62.8) | 7 (43.8) | **0.63** |
| **Headache**  **n (%)** | 37 (28.7) | 14 (28.6) | 4 (19.0) | 17 (39.5) | 2 (12.5) | **0.16** |
| **CNS disease**  **n (%)** | 37 (28.7) | 14 (28.6) | 5 (23.8) | 16 (37.2) | 2 (12.5) | **0.31** |
| **Renal (%)** | 38 (29.5) | 14 (28.6) | 5 (23.8) | 17 (39.5) | 2 (12.5) | **0.21** |
| **ICU admission n (%)** | 49 (38.0) | 19 (38.8) | 9 (42.9) | 16 (37.2) | 5 (31.3) | **0.90** |
| **Inotrope required n (%)** | 43 (33.3) | 18 (36.7) | 8 (38.1) | 14 (32.6) | 3 (18.8) | **0.60** |
| **CRP Median mg/L**  **(Normal range <10 mg/L)**  **(IQR) 1** | 213 (127, 302) | 237 (153, 323) | 234 (123, 299) | 196 (107, 284) | 154 (137, 311) | **0.49** |
| **Ferritin Median (IQR)**  **Normal range 7-84 ng/L** | 552 (287, 1020) | 596 (292, 1330) | 638 (364, 835) | 570 (353, 1039) | 255 (200, 550) | **0.16** |
| **Pro BNP Median (IQR)**  **(Normal ranges <450 ng/L** | 3696 (718, 15259) | 5910 (1008, 18465) | 1467 (461, 21820) | 3469 (1699, 15162) | 3995 (423, 12709) | **0.56** |
| **Sodium mmol/L**  **(Normal ranges 136 -145 mmol/L) Median (IQR) 2** | 129 (127, 133) | 129 (127, 131) | 128 (126, 132) | 130 (126, 134) | 131 (127, 134) | **0.34** |
| **<133mmol/L (%)** | 95 (73.6) | 39 (79.6) | 17 (81.0) | 29 (67.4) | 10 (62.5) | **0.35** |
| **Total white cell count cells /mL**  **Normal ranges 3.90 -10.20 X 109/L IQR) 1** | 16.51 (12.01, 23.50) | 16.96 (12.62, 25.47) | 15.90 (12.62, 22.70) | 16.65 (11.12, 22.79) | 16.52 (13.12, 23.31) | **0.87** |
| **Neutrophil count**  **Normal ranges 1.7 -5.0 x 109/L**  **Median (IQR) 1** | 11.74 (7.42, 17.90) | 11.74 (7.80, 18.30) | 12.00 (6.52, 19.39) | 11.50 (6.16, 19.98) | 11.84 (9.26, 15.01) | **0.87** |
| **Lymphocytes Normal ranges 1.90 – 4.30 x 109/L**  **Median (IQR) 2** | 1.25 (0.78, 2.61) | 1.29 (0.80, 2.33) | 0.96 (0.58, 3.12) | 1.27 (0.90, 2.80) | 1.67 (0.68, 2.26) | **0.79** |
| **Platelets**  **Normal ranges 180 - 440 x 109/L**  **Median (IQR) 2** | 193 (144, 296) | 190 (131, 281) | 190 (169, 261) | 193 (155, 290) | 329 (146, 436) | **0.19** |
| **<150 000 (%)** | 37 (28.7) | 17 (34.7) | 5 (23.8) | 10 (23.3) | 5 (31.3) | **0.62** |
| **Raised AST1 (normal ranges 0 – 4 U/L**  **/ALT1 (normal ranges 5 – 25 U/L** | 52 (58/70) | 22 (24/28) | 10 (10/14) | 17 (21/23) | 3 (3/5) | **0.16/0.19** |
| **D-dimer1 (Normal ranges 0.00 – 0.25)** | 2.17 (0.99, 3.72) | 2.22 (1.00, 4.40) | 3.25 (1.31, 4.36) | 2.03 (0.95, 3.31) | 1.98 (0.69, 4.26) | **0.31** |
| **Fibrinogen1**  **Normal ranges 2.0 - 4.0 g/L** | 5.3 (4.3, 6.6) | 5.3 (4.5, 6.3) | 6.1 (4.3, 6.4) | 4.9 (3.9, 7.4) | 5.4 (4.8, 7.8) | **0.80** |
| **Abnormal ECHO any abnormality (%)** | 90/127 (70.9) | 37 (75.7) | 14 (66.7) | 28/42 (66.7) | 11/15 (73.3 | **0.72** |
| **Valvulitis n (%)** | 54/126 (42.9) | 20 (40.8) | 7 (33.3) | 21/41 (51.2) | 6/15 (40) | **0.67** |
| **Coronary artery (%)** | 10/128 (7.8) | 1 (2.0) | 3 (14.3) | 6/42 (14.9) | 0 (0.0) | **0.06** |
| **EF (median)** | 59 (47, 65) | 51 (43, 63) | 64 (46, 68) | 61 (53, 68) | 58 (53, 63) | **0.07** |
| **PCR+ (%)** | 17/128 (13.3) | 8 (38.1) | 2 (9.5) | 4/42 (9.5) | 3 (18.8) | **0.67** |
| **Duration of symptoms before diagnosis** | 4 (3, 6) | 4 (3, 6) | 4 (3, 6) | 4 (3, 7) | 3 (2, 7) | **0.54** |
| **Duration hospitalization** | 7 (6, 10) | 7 (6, 10) | 6 (5, 9) | 7 (6, 9) | 7 (5, 14) | **0.67** |
| **Outcome**  **(No of Deaths)** | 1 (0.01) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (6.3) | **0.12** |
| 1 Highest  2 Lowest  *n* = 129 unless specified  *VOC* variant of concern*, BMI* Body Mass Index*, ICU* intensive care unit*, IQR* Interquartile range; *CNS* Central nervous system, *CRP* C-reactive protein, *Hb* hemoglobin, *WCC* white cell count, *ALT* alanine transaminase, *AST* aspartamine transaminase, *pro-BNP* Pro-brain natriuretic peptide, *LDH* lactate dehydrogenase; *ECHO* Echocardiography, *EF* ejection fraction, *PCR* polymerase chain reaction. | | | | | | |