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| **TABLE 1. Baseline characteristics of patients** |
|  | **Cases** **(n=79)** | **Controls (n=58)** | **p value** |
| **Age in years m (IQR)** | 4.1 (1.7-7.5) | 5.2 (2.1-9.3) | 0.193 |
| **Male [no. (%)]** | 62 (78.5) | 36 (62.1) | **0.035** |
| **Genotype [no. (%)]** **SS** **SC** **S*-***thalassemia | 68 (86.1)5 (6.3)6 (7.6) | 52 (89.7)4 (6.9)2 (3.4) | 0.592 |
| **Newborn screening [no. (%)]** | 72 (91.1) | 47 (81) | 0.084 |
| **Parents’ origin [no. (%)]** **Africa** **America** **Other** | 33 (41.8)45 (57)1 (1.3) | 42 (72.4)14 (24.1)2 (3.4) | **0.001** |
| **Complete vaccination status [no. (%)]** | 70 (88.6) | 48 (85.7) | 0.618 |
| **Penicillin prophylaxis [no. (%)]** | 76 (98.7) | 53 (91.4) | 0.084 |
| **Hydroxyurea [no. (%)]** | 39 (49.4) | 33 (56.9) | 0.132 |
| **Vitamin D** **supplementation [no. (%)]** | 77 (97.5) | 56 (96.6) | 0.753 |
| **Splenectomy [no. (%)]** | 8 (10.1) | 4 (6.9) | 0.509 |
| **Central venous catheter [no. (%)]** | 18 (22.8) | 4 (6.9) | **0.012** |
| **Hypertransfusional regimen [no. (%)]** | 9 (11.4) | 2 (3.4) | 0.117 |
| **No. of previous hospital admissions m (IQR)** | 6 (2-10.5) | 5 (2-9) | 0.138 |

 m (IQR) = median (interquartile range). No. = number.

 Variables with significant differences (p value < 0.05) are highlighted in bold font.

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|  **TABLE 2. Characteristics of cases during the febrile episode and differences among study subgroups** |
|  | **All cases (n=79)** | **SBI (n=4)** | **VI (n=41)** | **NPI (n=33)** | **p value** |
| **Clinical presentation**  |
| **Previous days of fever m (IQR)** | 1 (1-1) | 1 (1-2) | 1 (1-2) | 1 (1-1) | 0.459 |
| **Max. temperature m (IQR)** | 38.8 (38.4-39.1) | 39.1 (38.9-39.2) | 38.7 (38.3-39.2) | 38.8 (38.5-39) | 0.430 |
| **Upper respiratory symptoms [no. (%)]** | 49 (62) | 2 (50) | 33 (80.5) | 14 (42.4) | **0.003** |
| **Hemodynamic instability [no. (%)]** | 2 (2.5) | 1 (25) | 1 (2.4) | 0 | **0.012** |
| **Hypoxemia [no. (%)]** | 10 (12.7) | 0 | 4 (9.8) | 6 (18.2) | 0.410 |
| **Laboratory parameters** |
| **Initial hemoglobin g/dl m (IQR)** | 8.5 (7.5-9.5) | 9 (8.4-9.5) | 8.5 (7.4-9.7) | 8.5 (7.5-9.5) | 0.681 |
| **Initial WBC x**$10^{9}$**/L m (IQR)**  | 13.8 (9.7-21.1) | 20.7 (17.6-31.4) | 11.8 (8.9-21.2) | 13.9 (10.9-19.8) | 0.160 |
| **Initial neutrophils x**$10^{9}$**/L m (IQR)** | 8.1 (5.1-13.8) | 16.8 (13.9-26.7) | 7 (3.7-13.3) | 7.8 (6.1-12.5) | **0.039** |
| **Initial CRP mg/dl m (IQR)** | 2 (0.4-5.9) | 9.6 (7.8-15.1) | 1.1 (0.4-3.4) | 3.1 (0.6-6) | **0.007** |
| **Max. CRP mg/dl (n= 56) m (IQR)** | 4 (1.1-10.1) | 13.5 (12.3-17.9) | 3.3 (1-7.2) | 5.2 (1.2-9.4) | **0.047** |
| **Initial PCT ng/ml m (IQR)** | 0.3 (0.2-0.6) | 2 (0.8-2.9) | 0.4 (0.2-0.6) | 0.2 (0.1-0.4) | **0.036** |
| **Max. PCT ng/ml (n= 40) m (IQR)** | 0.5 (0.2-1.4) | 3.1 (1.8-18.9) | 0.6 (0.3-1.3) | 0.3 (0.2-0.5) | **0.031** |
| **Outcome** |
| **Hospital admission [no. (%)]** | 64 (81) | 4 (100) | 29 (70.7) | 30 (90.9) | 0.055 |
| **Antibiotic treatment [no. (%)]** | 76 (96.2) | 4 (100) | 39 (95.1) | 32 (97) | 0.845 |
| **Need for antibiotic change [no. (%)]** | 12 (15.2) | 3 (75) | 3 (7.5) | 5 (15.6) | **0.001** |
| **Final diagnosis of ACS [no. (%)]** | 13 (16.5) | 1 (25) | 5 (12.2) | 7 (21.2) | 0.527 |
| **Final diagnosis of VOC [no. (%)]** | 7 (8.9) | 0 | 1 (2.4) | 6 (18.2) | 0.051 |
| **PICU admission [no. (%)]** | 3 (3.8) | 0 | 1 (2.4) | 2 (6.1) | 0.665 |
| **Total days of fever m (IQR)** | 2 (1-4) | 2.5 (2-4) | 2 (2-3) | 2 (1-4) | 0.749 |
| **Days of admission m (IQR)** | 4 (2-6) | 7.5 (5.5-8.5) | 3 (0.5-5) | 5(2.5-6) | **0.013** |

m (IQR) = median (interquartile range). no. = number. Max. = maximum value during the episode. WBC = white blood count. CRP = C-reactive protein. PCT = procalcitonin. ACS = acute chest syndrome. VOC = vaso-occlusive crisis.

Variables with significant differences (p value < 0.05) are highlighted in bold font.

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|  **TABLE 3. Cytokines values and comparisons among study subgroups** |
|  | **Cases (n=79)** | **Controls (n=58)** | **p value** | **SBI (n=4)** | **VI (n=41)** | **NPI (n=33)** | **p value** |
| **IL-1β** pg/ml | 33 (1.8-242.5) | 29.5 (1.8-212) | 0.861 | 57.9 (1.8-190) | 37 (1.8-289) | 33 (1.8-166) | 0.828 |
| **IL-2**  pg/ml | 6.2 (6.2-6.2) | 6.2 (6.2-6.2) | 0.565 | ND | 6.2 (6.2-6.2) | 6.2 (6.2-6.2) | 0.763 |
| **IL-4**  pg/ml | 2.2 (2.2-85.5) | 2.2 (2.2-91) | 0.509 | 14.6 (2.2-149.5) | 2.2 (2.2-69) | 2.2 (2.2-226) | 0.805 |
| **IL-6**  pg/ml | 0.7 (0.7-0.7) | ND | **0.008** | 163 (70.4-459.5) | 0.7 (0.7-0.7) | 0.7 (0.7-0.7) | **<0.001** |
| **IL-8**  pg/ml | 41 (30-74) | 36 (30-52) | 0.191 | 49 (32.5-68.5) | 44 (30-99) | 38 (30-72) | 0.919 |
| **IL-10**  pg/ml | 0.9 (0.9-73) | 0.9 (0.9-34) | 0.218 | 17.4 (0.9-116.5) | 9.9 (0.9-94) | 0.9 (0.9-58) | 0.561 |
| **IL-12p70** pg/ml | ND | ND | - | ND | ND | ND | - |
| **IL-17a** pg/ml | 4.4 (4.4-266) | 44 (4.4-233) | 0.828 | 53.7 (4.4-263.5) | 4.4 (4.4-248) | 35 (4.4-284) | 0.912 |
| **TNF α** pg/ml | 59.0 (11-112) | 50.5 (23-92) | 0.674 | 24.5 (14-52.5) | 64 (26-156) | 64 (4.9-106) | 0.357 |
| **IFN-γ** pg/ml | 41 (0.4-152) | 34 (0.4-97) | 0.324 | 0.4 (0.4-20.7) | 57 (0.4-203) | 41 (0.4-132) | 0.201 |

ND = Non-detectable in any of the patients of the subgroup.

Variables with significant differences (p value < 0.05) are highlighted in bold font.

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|  **TABLE 4. Diagnostic tests of IL-6 and other significant biomarkers for the prediction of SBI** |
| **Biomarker** | **Cut-off**  | **Sensitivity %**(95% CI) | **Specificity %**(95% CI) | **PPV %**(95% CI) | **NPV %**(95% CI) |
| **IL-6** | 125 pg/ml | 75 (21.9-98.7) | 100 (93.9-99.9) | **PR 5%:** 100 (56.6-100)**PR 10%:** 100 (56.6-100)**PR 15%:** 100 (56.6-100) | **PR 5%:** 98.7 (93.3-99.8)**PR 10%:** 97.3 (86.8-99.5)**PR 15%:** 95.8 (80.6-99.2) |
| **Neutrophils** | 13.8 x10⁹/L | 100 (39.8-100) | 77.3 (66.2-86.2) | **PR 5%:** 18.8 (13.3-26.1)**PR 10%:** 32.9 (24.4-42.7)**PR 15%:** 43.8 (33.9-54.2) | **PR 5%:** 100 (87.8-100)**PR 10%:** 100 (87.8-100)**PR 15%:** 100 (87.8-100) |
| **CRP**  | 7 mg/dl | 100 (39.8-100) | 82.7 (72.2-90.4) | **PR 5%:** 23.3 (15.6-33.2)**PR 10%:** 39.1 (28.1-51.2)**PR 15%:** 50.4 (38.3-62.5) | **PR 5%:** 100 (92-7-100)**PR 10%:** 100 (92-7-100)**PR 15%:** 100 (92-7-100) |
| **Procalcitonin** | 1.3 ng/ml | 75 (19.4-99.4) | 82.7 (72.2-90.4) | **PR 5%:** 18.5 (9-7-32.6)**PR 10%:** 32.5 (18.5-50.5)**PR 15%:** 43.3 (26.5-61.8) | **PR 5%:** 98.4 (92-99.7)**PR 10%:** 96.7 (84.5-99.4)**PR 15%:** 94.9 (77.4-99) |