**Electronic supplementary material**

**Inflammatory Response and Phenotyping in Severe Acute Respiratory Infection from the Middle East Respiratory Syndrome Coronavirus and Other Etiologies**

Yaseen M Arabi

Dunia Jawdat

Ali H Hajeer

Musharaf Sadat

Jesna Jose

Ramesh K. Vishwakarma

Walid Almashaqbeh

Abdulaziz Al-Dawood

**Table S1:** Summary of missing observations. All the variables with missing values <5% were included in the latent class analysis (LCA) model.

|  |  |  |
| --- | --- | --- |
| **Variables** | **Missing observations** | **% of Missing observations** |
| Age | 1 | 1.00% |
| Body mass index | 3 | 3.00% |
| Heart rate | 2 | 2.00% |
| Temperature | 2 | 2.00% |
| Respiratory rate | 2 | 2.00% |
| Systolic blood pressure | 2 | 2.00% |
| Diastolic blood pressure | 2 | 2.00% |
| Bilirubin | 38 | 38.00% |
| Glucose | 7 | 7.00% |
| Creatinine | 2 | 2.00% |
| Hematocrit | 4 | 4.00% |
| WBC | 4 | 4.00% |
| Platelet | 2 | 2.00% |
| Urine | 9 | 9.00% |
| PaO2/FiO2 | 7 | 7.00% |
| PCO2 mmHg | 22 | 22.00% |
| HCO3 | 22 | 22.00% |
| Plateau pressure | 68 | 68.00% |
| PEEP | 40 | 40.00% |
| Tidal volume | 41 | 41.00% |
| EGF | 0 | 0.00% |
| Eotaxin | 0 | 0.00% |
| GM-CSF | 0 | 0.00% |
| G-CSF | 0 | 0.00% |
| IFN-α | 0 | 0.00% |
| IFN-y | 0 | 0.00% |
| IL-10 | 0 | 0.00% |
| IL-12p40 | 0 | 0.00% |
| IL-12p70 | 0 | 0.00% |
| IL-13 | 0 | 0.00% |
| IL-15 | 0 | 0.00% |
| IL-17A | 0 | 0.00% |
| IL-1β | 0 | 0.00% |
| IL-1ra | 0 | 0.00% |
| IL-1α | 0 | 0.00% |
| IL-2 | 0 | 0.00% |
| IL-3 | 0 | 0.00% |
| IL-4 | 0 | 0.00% |
| IL-5 | 0 | 0.00% |
| IL-6 | 0 | 0.00% |
| IL-7 | 0 | 0.00% |
| IL-8 | 0 | 0.00% |
| IP-10 | 0 | 0.00% |
| MCP-1 | 0 | 0.00% |
| MIP-1β | 0 | 0.00% |
| MIP-1α | 0 | 0.00% |
| TNF-β | 0 | 0.00% |
| TNF-α | 0 | 0.00% |
| VEGF | 0 | 0.00% |

**Table S2:** Complete list of clinical variables included in latent class analysis (LCA) model after data cleaning.

|  |  |  |
| --- | --- | --- |
| **Cytokines** | **Clinical variables** | |
| **Continuous** | **Categorical** |
| IL-1α  IL-1β  IL-1ra  IL-2  IL-3  IL-4  IL-5  IL-6  IL-7  IL-8  IL-10  IL-12P40  IL-12p70  IL-15 IL-17A  IP-10  MCP-1  MIP-1α  MIP-1β  TNF-α  TNF-β  Eotaxin  EGF  G-CSF  GM-CSF  IFN-α  IFN-γ  VEGF | Age  BMI  Creatinine  Hematocrit  Heart rate  Platelets  Systolic blood pressure  Respiratory rate  WBC | Gender  Mechanical ventilation  Inotropes |

**Table S3:** Descriptive fit statistics for latent class analysis (LCA) model.

| **Models** | **AIC** | **BIC** | **aBIC\*** | **Entropy^** | **Number of patients per subphenotype** | | | | | **P-value#** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **1** | **2** | **3** | **4** | **5** |
| LCA-model 2 | 12241.37 | 12566.29 | 12193.30 | 0. 95 | 74 | 42 | - | - | - | 0.03 |
| LCA-model 3 | 11989.10 | 12426.92 | 11924.33 | 0.97 | 9 | 68 | 39 | - | - | 0.47 |
| LCA- model 4 | 11877.69 | 12428.41 | 11796.22 | 0.97 | 8 | 33 | 19 | 56 |  | 0.75 |
| LCA- model 5 | 11791.15 | 12454.76 | 11692.97 | 0.97 | 8 | 34 | 26 | 37 | 11 | 0.74 |

AIC: Akaike information criterion.

BIC: Bayesian information criteria.

\* Sample-size adjusted BIC.

^ Entropy statistic is a summary measure for the quality of the classification. Values close to 1 indicate high classification accuracy, whereas values close to 0 indicate low classification certainty. Entropy statistic value of about 0.8 of higher are thought to be a sign of a useful model.

#Voung-Lo-Mendell-Rubin test to assess whether the number of classes provides improved model fit compared with a model using one fewer class.

**Table S4:** Comparison of additional baseline characteristics and physiological parameters between patients with the Middle East Respiratory Syndrome- severe acute respiratory infection (MERS SARI) and non-Middle East Respiratory Syndrome severe acute respiratory infection (non-MERS SARI) and between patients with subphenotype 1 and subphenotype 2.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **MERS SARI**  **N=40** | **Non-MERS SARI**  **N=76** | **P value** | **Subphenotype 1**  **N= 74** | **Subphenotype 2**  **N= 42** | **P value** |
| Healthcare-associated, non-healthcare worker — no. (%) | 19 (48) | 0 (0.0) | <0.0001 | 11 (15) | 8 (19) | 0.79 |
| Healthcare worker — no. (%) | 10 (25) | 0 (0.0) | 6 (8) | 4 (10) |
| Community-acquired — no. (%) | 11 (28) | 76 (100) | 57 (77) | 30 (71) |
| **Physiological parameters on ICU day 1** — Median (Q1, Q3) | | | | | | |
| Mean arterial blood pressure (mmHg) | 69 (61, 75) | 68 (61, 78) | 0.89 | 69 (62, 83) | 67 (60, 75) | 0.17 |
| PaO2(mmHg) | 76 (65, 89) | 74 (62, 96) | 0.63 | 74 (65, 99) | 74 (56, 88) | 0.26 |
| FiO2 | 0.6 (0.4, 0.7) | 0.5 (0.4, 0.7) | 0.37 | 0.5 (0.4, 0.6) | 0.5 (0.4, 0.8) | 0.91 |
| PaCO2 (mmHg) | 43(36, 50) | 43 (38, 52) | 0.68 | 46 (39, 53) | 41 (37, 46) | 0.11 |
| HCO3 | 23 (22, 27) | 23 (20, 27) | 0.35 | 24 (21, 27) | 22(19, 26) | 0.06 |
| Hemoglobin (g/dL) | 11 (9, 13) | 11 (9, 12) | 0.50 | 11 (10, 13) | 10 (9, 12) | 0.07 |
| Urine output (mL/24 hours) | 1055 (650, 2405) | 1225 (660, 2000) | 0.81 | 1197 (600, 2160) | 1240 (660, 2005) | 0.86 |
| Bilirubin (µmol/L) | 11 (9, 22) | 12 (8, 23) | 0.88 | 11 (7, 14) | 15 (9, 33) | 0.06 |
| International normalized ratio | 1.1 (1.0, 1.4) | 1.2 (1.1, 1.4) | 0.15 | 1.1 (1., 1.3) | 1.2 (1.1, 1.5) | 0.06 |
| Glucose (mmol/L) | 9 (6, 14) | 11 (7, 15) | 0.28 | 11 (7, 14) | 9 (6, 15) | 0.43 |

ICU-Intensive care unit, FiO2: denotes the fraction of inspired oxygen, PaO2: partial pressure of oxygen in arterial blood, PaCO2: partial pressure of carbon dioxide. Continuous variables were compared using Mann-Whitney test and categorical variables were compared using chi-square test.

**Table S5:** Microbiology data of patients with the Middle East Respiratory Syndrome severe acute respiratory infection (MERS SARI) and non- Middle East Respiratory Syndrome severe acute respiratory infection (Non-MERS SARI) and subphenotype 1 and subphenotype 2. Pathogens during the hospital stay are shown with the exception for bacterial pathogens in respiratory samples and in blood cultures that are restricted to the first ±3 days of ICU admission.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **MERS SARI**  **N=40** | **Non-MERS SARI**  **N=76** | **Subphenotype 1**  **N=74** | **Subphenotype 2**  **N=42** |
| **MERS-CoV** | **40 (100)** | **0 (0%)** | **26 (35.1%)** | **14 (33.3%)** |
| **Number of patients with other viruses — no. (%)** | **4 (12)** | **34 (49)** | **25 (40)** | **13 (33)** |
| Influenza |  |  |  |  |
| Influenza A including H1N1 | 0/28 | 16/68 | 10/58 | 6/38 |
| Influenza B | 0/28 | 2/68 | 1/58 | 1/38 |
| Parainfluenza | 0/20 | 1/46 | 1/42 | 0/24 |
| Adenovirus | 1/20 | 2/46 | 3/42 | 0/24 |
| Bocavirus | 1/20 | 0/46 | 1/42 | 0/24 |
| Cytomegalovirus | 1/2 | 4/6 | 3/4 | 2/4 |
| Enterovirus | 0/20 | 0/46 | 0/42 | 0/24 |
| Rhinovirus | 0/20 | 6/46 | 4/42 | 2/24 |
| Respiratory syncytial virus (RSV) | 0/20 | 1/46 | 1/42 | 0/24 |
| Norovirus | 0/0 | 1/1 | 0/0 | 1/1 |
| Human metapneumovirus | 0/20 | 1/46 | 0/42 | 1/24 |
| Humancoronavirus (229E, HKU1, NL63, OC43) | 1/20 | 5/46 | 4/42 | 2/24 |
|  |  |  |  |  |
| **Bacterial pathogens in respiratory samples (± 3 days of ICU admission) — no. (%)** | **3** | **16** | **10** | **9** |
| **Gram positive cocci** |  |  |  |  |
| Streptococcus pneumoniae | 0 | 3 | 1 | 2 |
| Staphyloccocus aureus and MRSA | 0 | 6 | 3 | 3 |
| Others | 1 | 1 | 1 | 1 |
| **Gram negative bacilli** |  |  |  |  |
| Acenatobacter spp | 0 | 2 | 0 | 2 |
| Klebsiella pneumoniae | 1 | 3 | 2 | 2 |
| Pseudomonas Sp | 0 | 3 | 3 | 0 |
| **Other pathogens** |  |  |  |  |
| Legionella pneumophila | 1 | 0 | 0 | 0 |
| Mycoplasma pneumoniae | 0 | 1 | 1 | 0 |
| Chlamydia pneumoniae | 0 | 0 | 1 | 0 |
| Mycobacterium tuberculosis | 0 | 1 | 1 | 0 |

Numerators refer to the number of patients with identified pathogens and denominators refer to the number of patients tested.

**Figure S1:** Comparison of serial measurements for cytokines in patients with Middle East Respiratory Syndrome (MERS SARI), non-MERS severe acute respiratory infection (non-MERS SARI) and healthy control) and and of serial measurements for cytokines in patients with (subphenotype 1 vs subphenotype 2 and healthy control). Day 1 levels in MERS SARI, non-MERS SARI, subphenotype 1 and subphenotype 2 were compared to healthy controls using Mann-Whitney test. The differences between groups with time (group\*time) were tested by repeated measures mixed linear models. Box plots are displayed with medians and quartiles 1 and 3. The distribution of patients in each group over time for all the cytokines is as follows: MERS SARI (D1=36, D3=27, D7=12, D14=9), non-MERS SARI (D1=73, D3=59, D7=35, D14=9), Subphenotype 1 (D1=69, D3=57, D7=30, D14=18), Subphenotype 2 (D1=40, D3=29, D7=17, D14=11) and healthy control (n=10). For all cytokine comparisons, we considered p value <0.0017 to be statistically significant accounting for multiple testing using Bonferroni correction.

|  |  |
| --- | --- |
|  | |
| **MERS vs non MERS-SARI and Healthy control** | **Subphenotype 1 vs Subphenotype 2 and Healthy control** |
| P= 0.03 for between MERS SARI and non-MERS SARI over time  P= 0.001 for between MERS SARI on D1 and healthy controls  P= 0.09 for between non-MERS SARI on D1 and healthy controls | P= 0.51 for between subphenotype 1 and subphenotype 2 over time  P= 0.12 for between subphenotype 1 on D1 and healthy controls  P= 0.05 for between subphenotype 2 on D1 and healthy controls |
| P= 0.46 for between MERS SARI and non-MERS SARI over time  P= 0.55 for between MERS SARI on D1 and healthy controls  P= 0.89 for between non-MERS SARI on D1 and healthy controls | P= 0.02 for between subphenotype 1 and subphenotype 2 over time  P= 0.01 for between subphenotype 1 on D1 and healthy controls  P= 0.0009 for between subphenotype 2 on D1 and healthy controls |
| P= 0.22 for between MERS SARI and non-MERS SARI over time  P= 0.0006 for between MERS SARI on D1 and healthy controls  P= 0.00001 for between non-MERS SARI on D1 and healthy controls | P= 0.24 for between subphenotype 1 and subphenotype 2 over time  P= 0.0001 for between subphenotype 1on D1 and healthy controls  P< 0.0001 for between subphenotype 2 on D1 and healthy controls |
| P= 0.42 for between MERS SARI and non-MERS SARI over time  P= 0.0005 for between MERS SARI on D1 and healthy controls  P= 0.00001 for between non-MERS SARI on D1 and healthy controls | P=0.04 for between subphenotype 1 and subphenotype 2 over time  P= 0.0001 for between subphenotype 1 on D1 and healthy controls  P< 0.0001 for between subphenotype 2 on D1 and healthy controls |
| P= 0.18 for between MERS SARI and non-MERS SARI over time  P= 0.04 for between MERS SARI on D1 and healthy controls  P= 0.27 for between non-MERS SARI on D1 and healthy controls | P=0.006 for between subphenotype 1 and subphenotype 2 over time  P= 0.04 for between subphenotype 1 on D1 and healthy controls  P= 0.62 for between subphenotype 2 on D1 and healthy controls |
| P= 0.86 for between MERS SARI and non-MERS SARI over time  P= 0.003 for between MERS SARI on D1 and healthy controls  P= 0.001 for between non-MERS SARI on D1 and healthy controls | P= 0.04 for between subphenotype 1 and subphenotype 2 over time  P= 0.02 for between subphenotype 1 on D1 and healthy controls  P< 0.0001 for between subphenotype 2 on D1 and healthy controls |
| P= 0.81 for between MERS SARI and non-MERS SARI over time  P= 0.72 for between MERS SARI on D1 and healthy controls  P= 0.03 for between non-MERS SARI on D1 and healthy controls | P= 0.05 for between subphenotype 1 and subphenotype 2 over time  P= 0.75 for between subphenotype 1 on D1 and healthy controls  P= 0.0002 for between subphenotype 2 on D1 and healthy controls |
| P= 0.22 for between MERS SARI and non-MERS SARI over time  P= 0.006 for between MERS SARI on D1 and healthy controls  P= 0.004 for between non-MERS SARI on D1 and healthy controls | P= 0.06 for between subphenotype 1 and subphenotype 2 over time  P= 0.001 for between subphenotype 1 on D1 and healthy controls  P= 0.03 for between subphenotype 2 on D1 and healthy controls |
| P= 0.37 for between MERS SARI and non-MERS SARI over time  P= 0.005 for between MERS SARI on D1 and healthy controls  P= 0.01 for between non-MERS SARI on D1 and healthy controls | P= 0.007 for between subphenotype 1 and subphenotype 2 over time  P= 0.0004 for between subphenotype 1on D1 and healthy controls  P= 0.29 for between subphenotype 2 on D1 and healthy controls |
| P= 0.24 for between MERS SARI and non-MERS SARI over time  P= 0.29 for between MERS SARI on D1 and healthy controls  P= 0.10 for between non-MERS SARI on D1 and healthy controls | P= 0.03 for between subphenotype 1 and subphenotype 2 over time  P= 0.83 for between subphenotype 1 on D1 and healthy controls  P= 0.03 for between subphenotype 2 on D1 and healthy controls |
| P= 0.63 for between MERS SARI and non-MERS SARI over time  P= 0.01 for between MERS SARI on D1 and healthy controls  P= 0.0006 for between non-MERS SARI on D1 and healthy controls | P= 0.21 for between subphenotype 1 and subphenotype 2 over time  P= 0.02 for between subphenotype 1 on D1 and healthy controls  P<0.0001 for between subphenotype 2 on D1 and healthy controls |
| P= 0.24 for between MERS SARI and non-MERS SARI over time  P= 0.0002 for between MERS SARI on D1 and healthy controls  P= 0.0004 for between non-MERS SARI on D1 and healthy controls | P= 0.02 for between subphenotype 1 and subphenotype 2 over time  P<0.0001 for between subphenotype 1 on D1 and healthy controls  P= 0.03 for between subphenotype 2 on D1 and healthy controls |
| P= 0.31 for between MERS SARI and non-MERS SARI over time  P= 0.0002 for between MERS SARI on D1 and healthy controls  P= 0.01 for between non-MERS SARI on D1 and healthy controls | P= 0.54 for between subphenotype 1 and subphenotype 2 over time  P= 0.02 for between subphenotype 1 on D1 and healthy controls  P= 0.0001 for between subphenotype 2 on D1 and healthy controls |
| P= 0.03 for between MERS SARI and non-MERS SARI over time  P= 0.31 for between MERS SARI on D1 and healthy controls  P= 0.70 for between non-MERS SARI on D1and healthy controls | P= 0.18 for between subphenotype 1 and subphenotype 2 over time  P= 0.73 for between subphenotype 1 on D1and healthy controls  P= 0.03 for between subphenotype 2 on D1and healthy controls |
| P= 0.03 for between MERS SARI and non-MERS SARI over time  P= 0.30 for between MERS SARI on D1and healthy controls  P= 0.24 for between non-MERS SARI on D1and healthy controls | P= 0.31 for between subphenotype 1 and subphenotype 2 over time  P= 0.58 for between subphenotype 1 on D1and healthy controls  P= 0.04 for between subphenotype 2 on D1and healthy controls |
| P= 0.59 for between MERS SARI and non-MERS SARI over time  P= 0.77 for between MERS SARI on D1 and healthy controls  P= 0.64 for between non-MERS SARI on D1and healthy controls | P= 0.005 for between subphenotype 1 and subphenotype 2 over time  P= 0.0009 for between subphenotype 1 on D1and healthy controls  P= 0.003 for between subphenotype 2 on D1and healthy controls |
| P= 0.46 for between MERS SARI and non-MERS SARI over time  P= 0.02 for between MERS SARI on D1and healthy controls  P= 0.04 for between non-MERS SARI on D1and healthy controls | P= 0.02 for between subphenotype 1 and subphenotype 2 over time  P= 0.44 for between subphenotype 1 on D1 and healthy controls  P<0.0001 for between subphenotype 2 on D1and healthy controls |
| P= 0.11 for between MERS SARI and non-MERS SARI over time  P= 0.03 for between MERS SARI on D1and healthy controls  P= 0.09 for between non-MERS SARI on D1and healthy controls | P= 0.13 for between subphenotype 1 and subphenotype 2 over time  P= 0.37 for between subphenotype 1 on D1and healthy controls  P= 0.0007 for between subphenotype 2 on D1 and healthy controls |
| P= 0.53 for between MERS SARI and non-MERS SARI over time  P= 0.39 for between MERS SARI on D1and healthy controls  P= 0.05 for between non-MERS SARI on D1and healthy controls | P= 0.59 for between subphenotype 1 and subphenotype 2 over time  P= 0.006 for between subphenotype 1 on D1and healthy controls  P= 0.67 for between subphenotype 2 on D1and healthy controls |
| P= 0.57 for between MERS SARI and non-MERS SARI over time  P= 0.02 for between MERS SARI on D1and healthy controls  P= 0.70 for between non-MERS SARI on D1 and healthy controls | P= 0.29 for between subphenotype 1 and subphenotype 2 over time  P= 0.20 for between subphenotype 1 on D1 and healthy controls  P= 0.42for between subphenotype 2 on D1and healthy controls |
| P= 0.41 for between MERS SARI and non-MERS SARI over time  P= 0.24 for between MERS SARI on D1 and healthy controls  P= 0.91 for between non-MERS SARI on D1 and healthy controls | P= 0.02 for between subphenotype 1 and subphenotype 2 over time  P= 0.004 for between subphenotype 1 on D1 and healthy controls  P= 0.05 for between subphenotype 2 on D1and healthy controls |
| P= 0.15 for between MERS SARI and non-MERS SARI over time  P= 0.005 for between MERS SARI on D1 and healthy controls  P= 0.01 for between non-MERS SARI on D1 and healthy controls | P= 0.009 for between subphenotype 1 and subphenotype 2 over time  P= 0.11 for between subphenotype 1 on D1and healthy controls  P< 0.0001 for between subphenotype 2 on D1and healthy controls |
| P= 0.44 for between MERS SARI and non-MERS SARI over time  P= 0.00003 for between MERS SARI on D1 and healthy controls  P= 0.00001 for between non-MERS SARI on D1 and healthy controls | P= 0.49 for between subphenotype 1 and subphenotype 2 over time  P<0.0001 for between subphenotype 1 on D1and healthy controls  P=0.0002 for between subphenotype 2 on D1and healthy controls |
| P= 0.67 for between MERS SARI and non-MERS SARI over time  P= 0.001 for between MERS SARI on D1 and healthy controls  P= 0.00001 for between non-MERS SARI on D1 and healthy controls | P= 0.62 for between subphenotype 1 and subphenotype 2 over time  P< 0.0001 for between subphenotype 1 on D1 and healthy controls  P= 0.0009 for between subphenotype 2 on D1 and healthy controls |
| P= 0.21 for between MERS SARI and non-MERS SARI over time  P= 0.15 for between MERS SARI on D1 and healthy controls  P= 0.13 for between non-MERS SARI on D1 and healthy controls | P= 0.005 for between subphenotype 1 and subphenotype 2 over time  P= 0.35 for between subphenotype 1 on D1 and healthy controls  P= 0.02 for between subphenotype 2 on D1 and healthy controls |