**Supplementary Methods**

**Statistical Analysis**

The primary outcome of this study was the diagnostic performance of IMX-BVN-2 bacterial and viral scores when using adjudicated infection status established by the expert panel. Performance metrics include the area under the receiver operating characteristic (AUROC), nominal likelihood ratios for each band, and the percentage of subjects that were allocated to those bands.

To generate the bands, diagnostic thresholds were set in the training set to match pre-specified criteria so that the IMX-BVN-2 bacterial and viral scores would be separated into four results interpretation bands each. The thresholds were set so that the lower-band of each score targeted a likelihood ratio (LR) of 0.05, and the upper-band of each score targeted LR of 10 in the training data. The performance of the candidate classifiers, including the likelihood ratios, was evaluated and compared using the validation set. Once the best classifier (IMX-BVN-2) was selected, the thresholds and weights were locked and applied to this study’s data without further modification. The selected cutoffs were 0.096, 0.317, and 0.537 for the bacterial score, and 0.075, 0.288, and 0.502 for the viral score.

Although Procalcitonin (PCT) was used for the adjudication process, we also assessed its performance for predicting the presence vs. absence of bacterial infections and viral infections using the same performance metrics as used for IMX-BVN-2. For segmenting PCT scores into results interpretation bands, we used cutoffs which were predefined by others1: <0.1 μg/L, 0.1-0.25 μg/L, 0.25-0.5 μg/L, and > 0.5 μg/L.

To evaluate whether the IMX-BVN-2 scores are affected by factors other than infection status, linear regression modeling was used to check for variables that are statistically significant predictors of either the bacterial or viral IMX-BVN-2 scores. We tested two linear regression models using the IMX-BVN-2 bacterial and viral scores as outcome variables and with age, consensus adjudication, and controls for severity (qSOFA, lactate, mortality) as predictor variables.

All statistical analyses were performed on R version 3.6.1.

**Linear Regression**

We used two linear multiple regression models to assess whether IMX-BVN-2 bacterial and viral scores were impacted by any of several patient characteristics. For both IMX-BVN-2 bacterial and viral scores, age had a small but statistically significant coefficient, indicating that older individuals tended to have slightly higher bacterial and lower viral scores, even when correcting for infection adjudication. The bacterial score also tended to increase with higher lactate levels.

**Supplementary Table S11.** Linear Regression with IMX-BVN-2 Bacterial Score as Dependent Variable

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Coefficients: | Estimate | Std. Error | t | P |  |
| (Intercept) | 0.0254 | 0.0819 | 0.31 | 0.757 |  |
| Bacterial Infection Presence (CA) | 0.235 | 0.0577 | 4.06 | 7.24E-05 | \*\*\* |
| Viral Infection Presence (CA) | -0.124 | 0.0440 | -2.79 | 0.00590 | \*\* |
| Age | 0.00241 | 0.00103 | 2.34 | 0.0207 | \* |
| qSOFA | 0.0328 | 0.0197 | 1.67 | 0.0978 | . |
| 30-Day Mortality | -0.00421 | 0.0560 | -0.0700 | 0.944 |  |
| Lactate | 0.00365 | 0.00108 | 3.38 | 0.000905 | \*\*\* |
| Immunocompromised | 0.0760 | 0.0424 | 1.80 | 0.0750 | . |
| Male | -0.0428 | 0.0335 | -1.28 | 0.203 |  |

**Supplementary Table S12.** Linear Regression with IMX-BVN-2 Viral Score as Dependent Variable

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Coefficients: | Estimate | Std. Error | t | P |  |
| (Intercept) | 0.5716 | 0.0744 | 7.68 | 1.12E-12 | \*\*\* |
| Bacterial Infection Presence (CA) | -0.194 | 0.0525 | -3.70 | 0.000291 | \*\*\* |
| Viral Infection Presence (CA) | 0.319 | 0.0400 | 7.97 | 2.08E-13 | \*\*\* |
| Age | -0.00337 | 0.000938 | -3.59 | 0.000424 | \*\*\* |
| qSOFA | -0.0133 | 0.0179 | -0.744 | 0.458158 |  |
| 30-Day Mortality | 0.0832 | 0.0542 | 1.54 | 0.126639 |  |
| Lactate | -0.00112 | 0.000982 | -1.14 | 0.2552 |  |
| Immunocompromised | -0.0563 | 0.0386 | -1.46 | 0.146438 |  |
| Male | 0.0548 | 0.0304 | 1.80 | 0.073475 | . |