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# A 9-gene biomarker panel identifies bacterial coinfections in culture-negative COVID-19 cases

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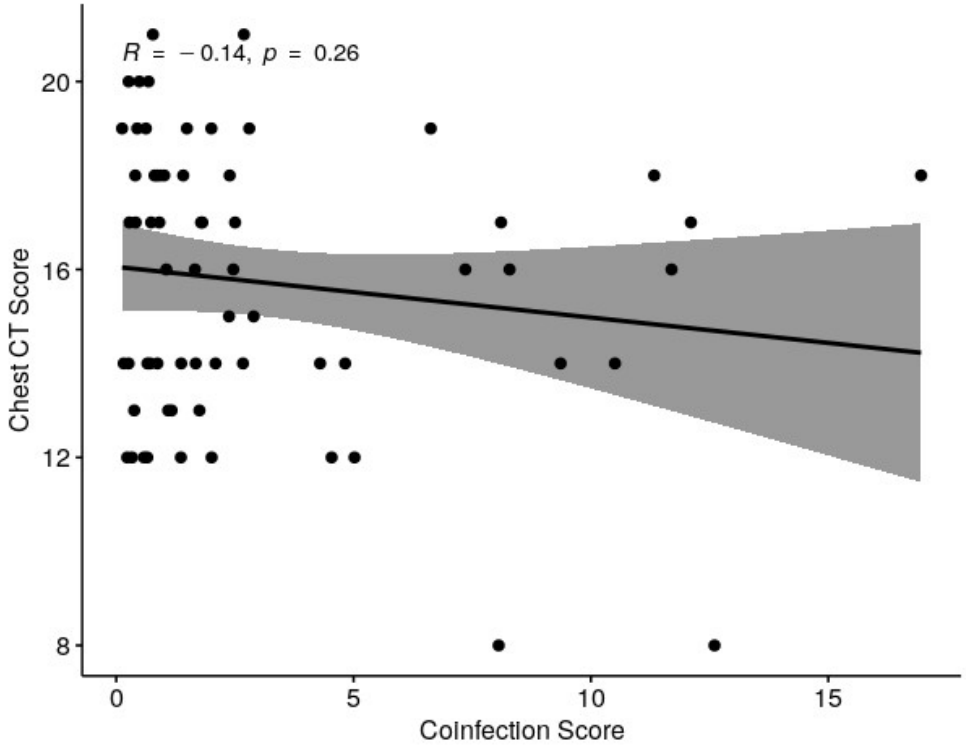
**Supplementary Figure 1:** Correlation between Coinfection Score and COVID-19 severity




Pearson correlation is calculated between the coinfection score and chest CT score (indicative of COVID-19 severity). No association is observed between these two parameters, suggesting that the coinfection score is not dependent upon the severity os SARS-CoV-2 infection and reflects the possible bacterial coinfection.

**Supplementary Table 1:** Description and literature report in the context of bacterial infection and inflammation for the 9-gene panel.

| Gene | Gene Name | Description |
|---|---|---|
| **CR1** | Complement C3b/C4b Receptor 1 | CR1 helps in bacterial recognition by phagocytes and removes pathogen and immune complex coated with complement factors C3b and C4b. This is specially important in case of *S. typhi, M. leprae, F. tularensis* etc. [1-3] CR1 is reported to be increased in bacterial infection. [4] |
| **F5** | Coagulation Factor V | Cofactor for blood coagulation cascade. Coagulation system is perturbed by systemic inflammation [5] as well as bacterial infection or sepsis [6,7]. Mutation in F5 have been linked to susceptibilty to bacterial infection and sepsis. [8] |
| **TLR2** | Toll like receptor 2 | Identifies PAMPs, most commonly on bacteria, sometimes on viruses. [9] TLR2 expression increases in response to LPS stimulation.[10] It has been suggested as a therapeutic target to moderate immune response in bacterial infections.[11] |
| **TLR8** | Toll like receptor 8 | Recognized PAMPs, most commonly viral RNA, also pyogenic bacteria. [12] TLR8 can also recognize URR motifs in bacterial RNA.[13,14] TLR8 can be activated and upregulated by *M. bovis* and *H. pylori*.[15] |
| **MKNK1** | MAPK Interacting Serine/Threonine Kinase 1 | Kinase that plays a role in response to stress and cytokines. Works downstream of MAPK and ERKs. |
| **PFKFB3** | Fructose-2,6-Biphosphatase 3 | Involved in both the synthesis and degradation of fructose-2,6-bisphosphate, a regulatory molecule that controls glycolysis. Linked to HIF1a mediated inflammation. [16,17] It has been implicated in neutrophil activation in sepsis and LPS induced endotoxemia.[18,19] |
| **PPP1R3D** | Protein Phosphatase 1 Regulatory Subunit 3D | Involved in regulation of cell division, metabolism etc. Part of inflammosome and overexpressed in TB [20] and is upregulated in ventilator associated pneumonia.[21] |
| **SH3GLB1** | SH3 Domain Containing GRB2 | Involved in regulating apoptotic pathway. It is |

| | | |
|---|---|---|
| | Like | involved in autophagy and overexpressed in leprosy lesions.[22] |
| **ETS2** | ETS Proto-Oncogene 2, Transcription Factor | Involved in development and apoptosis. Linked to interleukin-12 mediated inflammatory response and can be induced by LPS.[23,24] It is induced in *H.pylori* infection.[25] |

**Supplementary Table 2:** Performance evaluation of clinical parameters individually shows high sensitivity but very limited specificity.

| **Parameters** | **Specificity** | **Sensitivity** |
|---|---|---|
| PCT | 0 | 1 |
| CRP | 0 | 1 |
| ESR | 0 | 1 |
| TLC | 0.5 | 0.97 |
| NLR | 0.5 | 0.97 |

An ideal biomarker should have both specificity and sensivity of 1, meaning all the positive cases are identified as positive and negative cases are identified as negative. Specificity or sensitivity of 0.5 means that the test is equivalent to a random draw. The basic minimum for any biomarker is specificity+sensitivity > 1, and a decent biomarker should have specificity+sensitivity > 1.5. WHO criteria for a triage test biomarker includes a minimum of 0.7 specificity and 0.9 sensitivity. None of the clinical markers cross the threshold of minimum specificity and sensitivity, while the values for some are worse than a random draw. This suggests while the clinical markers perform well in identifying true positives, their performance in identifying the true negative cases are poor.

## Supplementary Reference: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