



DATABASE

COVID-ONE-hi: The One-stop Database for COVID-19-specific Humoral Immunity and Clinical Parameters



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Abstract Coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, varies with regard to symptoms and mortality rates among populations. **Humoral immunity** plays critical roles

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Protein microarray;
Humoral immunity;
One-stop tool;
Shiny

in SARS-CoV-2 infection and recovery from COVID-19. However, differences in immune responses and clinical features among COVID-19 patients remain largely unknown. Here, we report a database for COVID-19-specific IgG/IgM immune responses and clinical parameters (named COVID-ONE-hi). COVID-ONE-hi is based on the data that contain the IgG/IgM responses to 24 full-length/truncated proteins corresponding to 20 of 28 known SARS-CoV-2 proteins and 199 spike protein peptides against 2360 serum samples collected from 783 COVID-19 patients. In addition, 96 clinical parameters for the 2360 serum samples and basic information for the 783 patients are integrated into the database. Furthermore, COVID-ONE-hi provides a dashboard for defining samples and a one-click analysis pipeline for a single group or paired groups. A set of samples of interest is easily defined by adjusting the scale bars of a variety of parameters. After the “START” button is clicked, one can readily obtain a comprehensive analysis report for further interpretation. COVID-ONE-hi is freely available at www.COVID-ONE.cn.

Introduction

COVID-19 is an unprecedented global threat caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has already caused 209,308,033 infections and claimed 4,393,014 lives as of August 19, 2021 (<https://coronavirus.jhu.edu/map.html>) [1]. However, there is still no effective medicine [2,3] for COVID-19.

Most patients recover via their own immunity, including SARS-CoV-2-specific IgG responses, especially neutralizing antibodies [4–6]. Overall, it is of great interest to decipher SARS-CoV-2-specific IgG/IgM responses at a system level and to correlate antibody responses to clinical parameters.

To understand how the human immune system responds to SARS-CoV-2, we constructed a SARS-CoV-2 proteome microarray containing 18 of the 28 predicted proteins and applied it to characterize IgG and IgM antibodies for the sera of 29 convalescent patients [7]. Recently, we upgraded the SARS-CoV-2 protein microarray, and the new microarray contains 24 full-length/truncated proteins corresponding to 20 known SARS-CoV-2 proteins and 199 peptides fully covering the spike protein [8]. Using this microarray, we screened 2360 serum samples from 783 COVID-19 patients, covering mild, severe, and critical cases. Thus, we compiled a dataset with comprehensive information on SARS-CoV-2-specific antibody responses and rich in clinical parameters.

To share the dataset efficiently, in addition to the related research that we have already published [9–13], we built a database for COVID-19-specific humoral immune responses and clinical parameters, namely, COVID-ONE-hi (www.covid-one.cn), using Shiny. This database contains a comprehensive dataset of IgG and IgM responses to the 24 full-length/truncated proteins corresponding to 20 known SARS-CoV-2 proteins and 199 spike protein peptides from a cohort of 783 COVID-19 patients. To bolster clinical relevance, 96 clinical parameters and basic patient information are also included. COVID-ONE-hi provides search, data analysis, and visualization functions. In particular, COVID-ONE-hi integrates antibody response landscape analysis, correlation analysis, machine learning, *etc.* In the data analysis module, users can easily define sample group(s) of interest by adjusting scale bars, and the sample group can be either one group or paired groups. In-depth analysis is achieved by clicking a single button; optionally, the results can be saved and downloaded as an independent package for further analysis.

To our knowledge, COVID-ONE-hi is the first database for COVID-19-specific humoral immune responses. We believe

that COVID-19 humoral immunity will be of broad interest and will facilitate understanding of immune responses in COVID-19 to combat the pandemic.

Implementation

COVID-ONE-hi is a Shiny (v1.5.0)-based database. Shiny dashboard (v0.7.1) and Shiny BS (v0.61) were used to shape the UI, and the package DT (v0.15) was used to format data tables. For data analysis, dplyr (v1.0.2), tidyverse (v1.3.0), randomForest (v4.6–14), pROC (v1.16.2), and umap (v0.2.6.0) were integrated into Shiny. Pheatmap (v1.0.12) and ggplot2 (v3.3.2) were used to carry out plotting. For the basic environment, the operation system is Ubuntu 20.04 LTS, and the version of R is 3.6.3.

To calculate the rate of antibody response for each protein, the mean plus 2 times standard deviation (SD) of the control serum was set as the cut-off. R was used for most data analysis and drawing, *i.e.*, Pearson correlation coefficient, receiver operating characteristic (ROC), T-test, cluster analysis, and machine learning.

Database content and usage

The database framework and clinical information for the patients

In this study, we collected 2360 serum samples from 783 patients (387 males and 396 females) with an average age of 61.4 years and average onset time of 50 days. Among these 783 patients, there were 369 mild, 309 severe, and 105 critical cases, with 723 cured and 60 dead (**Figure 1A**; **Table 1**, Table S1).

To systematically analyze immune responses to SARS-CoV-2 infection, we screened 2360 serum samples using SARS-CoV-2 protein microarray that contains 24 full-length/truncated proteins corresponding to 20 known SARS-CoV-2 proteins and 199 peptides fully covering the spike protein. Additionally, we analyzed 89 blood parameters for the 2360 serum samples (including complete blood count, blood chemistry study, and blood enzyme tests). Hence, we obtained a comprehensive dataset that contains COVID-19-specific humoral immune responses and clinical parameters.

By combining clinical information, IgG/IgM immune responses, and blood parameters, we established a database (COVID-ONE-hi) that provides a one-stop analysis pipeline for COVID-19-specific humoral immune responses and clinical

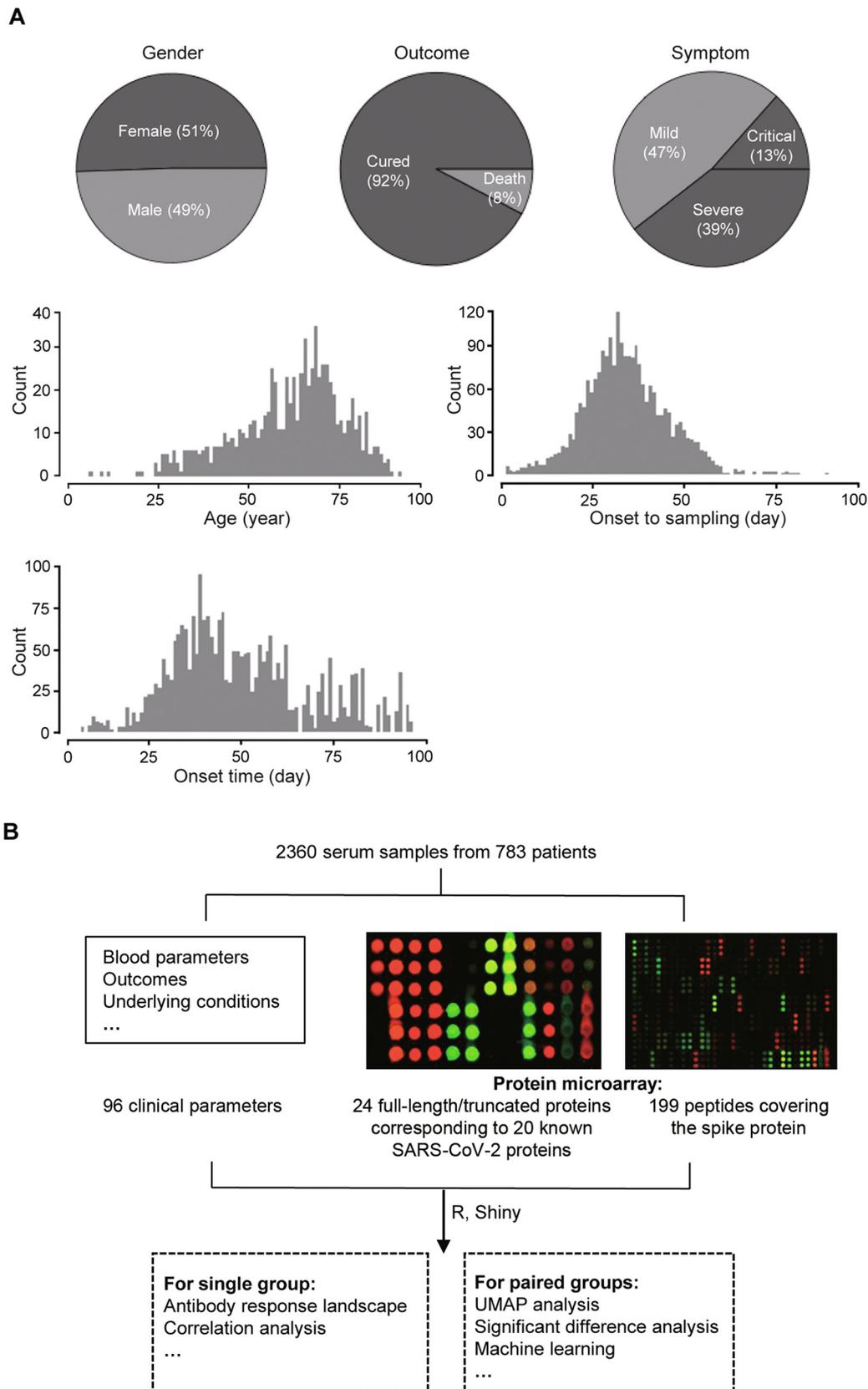


Figure 1 Overview of data resources and functional modules of COVID-ONE-hi

A. Patient information of the study cohort showing the distribution of gender, outcome, severity type, *etc.* **B.** The framework of COVID-ONE-hi. The COVID-ONE-hi, a one-stop database for COVID-19-specific humoral immune responses and clinical parameters, includes 223 protein/peptide antibody responses and 96 clinical parameters from 2360 serum samples collected from 783 COVID-19 patients. Using the Shiny package, COVID-ONE-hi provides single-group or paired-group analysis based on the dataset.

Table 1 The clinical information of involved patients

Group	COVID-19	
Number of patients	783	
Number of serum samples	2360	
Age (year)	61.4 ± 14.5	
Gender	Male	387
	Female	396
Severity/outcome	Mild	369
	Severe	309
	Critical	105
Outcome	Cured	723
	Death	60
Source	Tongji Hospital, Wuhan, China	

parameters (Figure 1B). To help users obtain more COVID-19 serum profiling data, we set up a page on the COVID-ONE-hi website, named “More studies”, to archive other highly related data of COVID-19 serum profiling (protein/peptide microarray/phage display) [14–19]. In addition, a healthy control dataset was added to the “HELP” page, which contains the IgG and IgM responses for 528 healthy people against the 24 full-length/truncated proteins and 199 spike protein peptides (Table S2).

The following three steps are included in the analysis module: users select a set of samples in the panel of patient information and click “START”; COVID-ONE-hi filters candidate samples according to the given parameters; and COVID-ONE-hi conducts analysis and provides results on the webpage.

To demonstrate how to use COVID-ONE-hi for analysis, we provide two cases for single group and paired groups as examples.

Case I: antibody responses and clinical parameters of dead COVID-19 patients

To study the features of dead COVID-19 patients, we selected the “death” parameter of outcome in a single-group analysis module. This cohort contained 392 serum samples from 60 patients (38 male vs. 22 female), with an average age of 69.6 years (Table 2). The IgG response landscape analysis of SARS-CoV-2 proteins showed that the positive rates of S1 subunit of spike protein (S1 protein), N protein, and ORF3b were 95%, 93%, and 87%, respectively, which are consistent with previous studies [20,21] (Figure 2A). Interestingly, NSP7 had a IgG-positive rate of 88%, suggesting that NSP7 may play an important role in COVID-19 (Figure 2A). In addition, the spike peptide S1-45 had the highest positive rate (87%) for the IgM response, indicating that the region including S1-45 may play an important role in IgM immunity (Figure S1).

Correlation analysis of clinical parameters showed that the neutrophil count had negative correlations with the monocyte count and the lymphocyte ratio (Figure 2B). In addition, correlation analysis of IgG responses showed high correlations between S1 IgG response and IgG responses of full-length/truncated N proteins, with S1 IgG response and N-Cter IgG response showing the highest correlation (Figure 2C and D). To study influencing factors of S1 antibody production, we analyzed the correlation between the S1 IgG response and clinical parameters, and found that S1 IgG response correlated with globulin (Figure 2D).

Table 2 Serum sample information of Case I

Group	COVID-19	
Number of patients	60	
Number of serum samples	392	
Age (year)	69.6 ± 10.3	
Gender	Male	38
	Female	22
Severity	Mild	0
	Severe	2
	Critical	58
Outcome	Cured	0
	Death	60
Source	Tongji Hospital, Wuhan, China	

Case II: differences in IgG/IgM immune responses and clinical parameters associated with gender

Previous studies have shown that gender has considerable effect on the severity and outcome of COVID-19 [22,23] and is associated with underlying differences in immune responses to infection [24]. To study differences in IgG/IgM immune responses and clinical parameters between the genders, we defined males as Group 1 and females as Group 2 for severe and critical patients, with 231 males at average age of 64.3 and 183 females at average age of 68.1. Consistent with previous studies [25], males had a higher risk of severe/critical COVID-19 than females (231/387 vs. 183/396, $P < 0.001$) (Tables 3 and 4).

UMAP analysis showed no overall difference in IgG immunity between 387 males and 396 females (Figure 3A). To explore the disease mechanism in the genders, we performed in-depth analyses for antibody responses and blood parameters using COVID-ONE-hi. The antibody response landscape showed that male patients had higher IgG-positive rates than females for ORF9b, RdRp, and NSP1 (Figure 3B). Moreover, longitudinal antibody dynamic analysis showed that males had a stronger ORF9b IgG response during the whole period of symptom onset, with a stronger NSP1 IgG response during the early stage of symptom onset, but had no significant difference in RdRp IgG response compared with females (Figure 3C). ORF9b has been considered a drug target for the treatment of COVID-19 because it suppresses type I interferon responses [26–28]. To explore the relevance between ORF9b antibody responses and COVID-19 severity, we compared ORF9b IgG responses between mild and severe/critical cases in different genders, and the results showed that higher ORF9b IgG response was observed in severe/critical cases than in mild cases in males, whereas no significant difference was observed between mild and severe/critical cases in females (Figure 3D).

To further decipher differences between female and male patients of COVID-19, we employed random forest for machine learning. The results showed creatinine, which is an acute kidney injury marker, to be the most significant factor between males and females (Figure 4A). To explore the relevance between creatinine and gender in COVID-19, we compared the median and dynamic creatinine levels between males and females, and observed that both the median and dynamic creatinine levels in males were significantly higher than those in females (Figure 4B and C). To explore the relevance between creatinine and COVID-19 severity, we

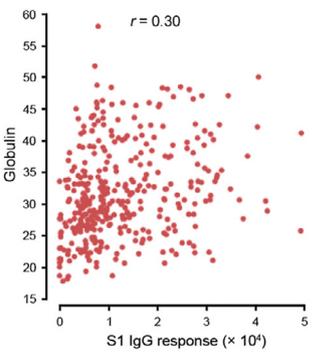
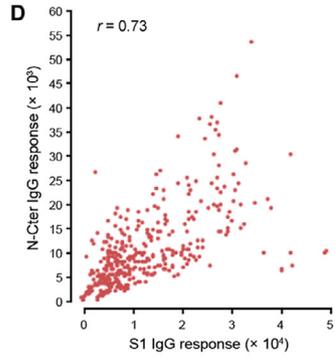
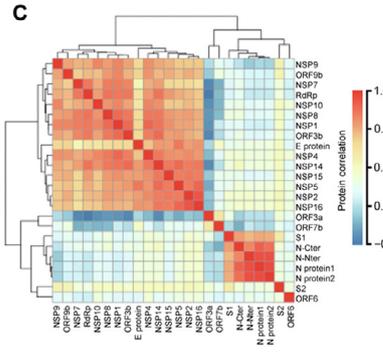
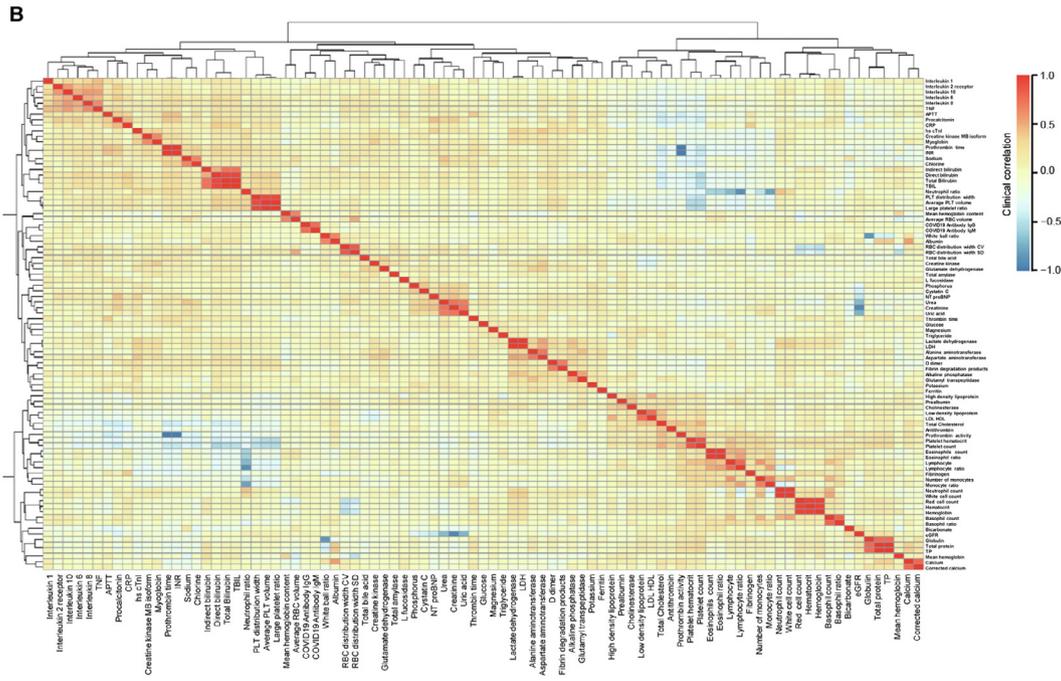
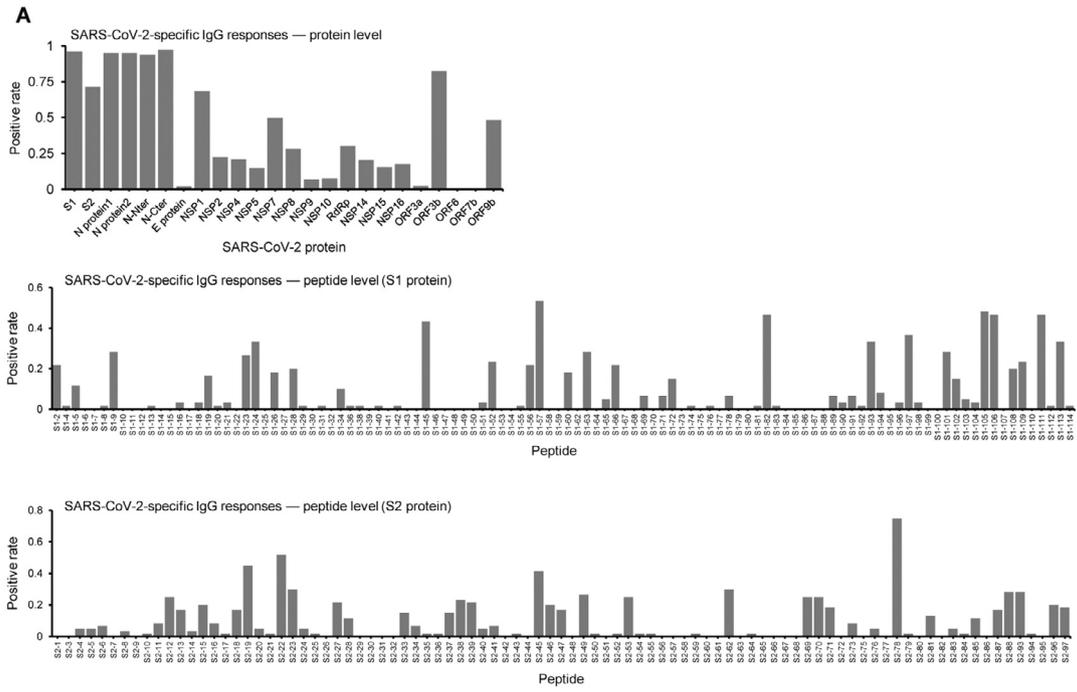


Table 3 Serum sample information of Case II

Group		Group 1	Group 2
Number of patients		231	183
Number of serum samples		949	684
Age (year)		64.3 ± 12.4	68.1 ± 11.9
Gender	Male	231	0
	Female	0	183
Severity	Mild	0	0
	Severe	165	144
	Critical	66	39
Outcome	Cured	193	161
	Death	38	22
Source		Tongji Hospital, Wuhan, China	

Table 4 The binary logistic regression parameter of severity in association with the gender among COVID-19 patients

Gender	Severity				
	β	SEM	Wald χ^2	OR (95% CI)	P
Female	–	–	–	1	–
Male	0.544	0.145	14.180	1.724 (1.298, 2.288)	< 0.001

Note: SEM, standard error of mean; CI, confidence interval.

compared the dynamic creatinine levels between mild and severe/critical cases in males and females, respectively. Similar to ORF9b IgG responses, male patients with severe/critical COVID-19 symptoms had a higher level of creatinine (Figure 4D). Hence, ORF9b antibodies and creatinine are associated with severe/critical symptoms in male COVID-19 patients, which suggests different pathogenesis and complications between male and female COVID-19 patients.

Discussion and perspectives

In this study, we built COVID-ONE-hi, a COVID-19-specific database, using R Shiny. COVID-ONE-hi is based on a comprehensive dataset generated by analyzing 2360 COVID-19 sera using the SARS-CoV-2 protein microarray containing 24 full-length/truncated proteins corresponding to 20 of the 28 known SARS-CoV-2 proteins and 199 peptides completely covering the entire spike protein sequence.

There are several published studies identifying the clinical characteristics, biomarkers, and specific antibody responses of diverse COVID-19 patients (Table S3). To strengthen the credibility of our dataset, we compared SARS-CoV-2-specific antibody responses with other studies at different levels. At the protein level, we analyzed the dynamic response to the S1 and N proteins. The results showed that the responses to S1 and N proteins peaked at 6 weeks after the onset of symptoms for IgG and 4 weeks for IgM, which is consistent with the results of previous studies [18,20] (Figure S2). At the peptide level, we compared IgG recognition of immunodominant regions in the

SARS-CoV-2 spike protein and found that some high response areas that we identified [12] are consistent with those identified by Shrock et al. [14]: aa 25–36, aa 553–588, aa 770–829, aa 1148–1159, and aa 1256–1273. And another hot spot (aa 451–474) was only detected in our study. Regarding antibody diagnosis, Assia et al. [19] achieved an area under the curve (AUC) value of 0.986 for IgG and 0.988 for IgM for the detection of prior SARS-CoV-2 infection when combining N and spike proteins. In our study, the AUC values of the N protein for IgG and IgM are 0.995 and 0.988, respectively, and the AUC values of the S1 protein for IgG and IgM are 0.992 and 0.992, respectively. We also found that S2-78 (aa 1148–1159) IgG is comparable to S1 IgG for COVID-19 patients, with an AUC value of 0.99 for IgG and 0.953 for IgM [11].

To our knowledge, COVID-ONE-hi is the first database for COVID-19-specific immune responses enriched in clinical parameters and has the following features. 1) Universality: COVID-ONE-hi contains 783 COVID-19 patients that have been classified by their medical history (Table S4), and thus will be of broad interest for researchers and clinicians from diverse backgrounds. 2) Accessibility: COVID-ONE-hi provides a one-stop analysis pipeline, by which users can easily obtain meaningful information. 3) Scalability: COVID-ONE-hi is built on the R platform, which is freely accessible, and many modular tools are readily available; thus, we can easily expand and incorporate new analyses for the dataset whenever necessary without changing the overall structure of the database. Nonetheless, there are some limitations for COVID-ONE-hi. For example, it lacks data for convalescent patients,

Figure 2 SARS-CoV-2-specific antibody responses and their correlations with clinical parameters for COVID-19 non-survivors

A. The IgG response landscapes against SARS-CoV-2 proteins (upper), S1 protein peptides (middle), and S2 protein peptides (lower). B. Heatmap showing correlation analysis of blood parameters. C. Heatmap showing correlation analysis of IgG responses against SARS-CoV-2 proteins. D. Scatter plots showing correlations between the S1 IgG response and the N-Cter IgG response / globulin. S1 protein, S1 subunit of spike protein; S2 protein, S2 subunit of spike protein; N protein1, full-length N protein purified by cell-free system; N protein2, full-length N protein purified by prokaryotic system; N-Nter, N-terminus of N protein purified by cell-free system; N-Cter, C-terminus of N protein purified by cell-free system.

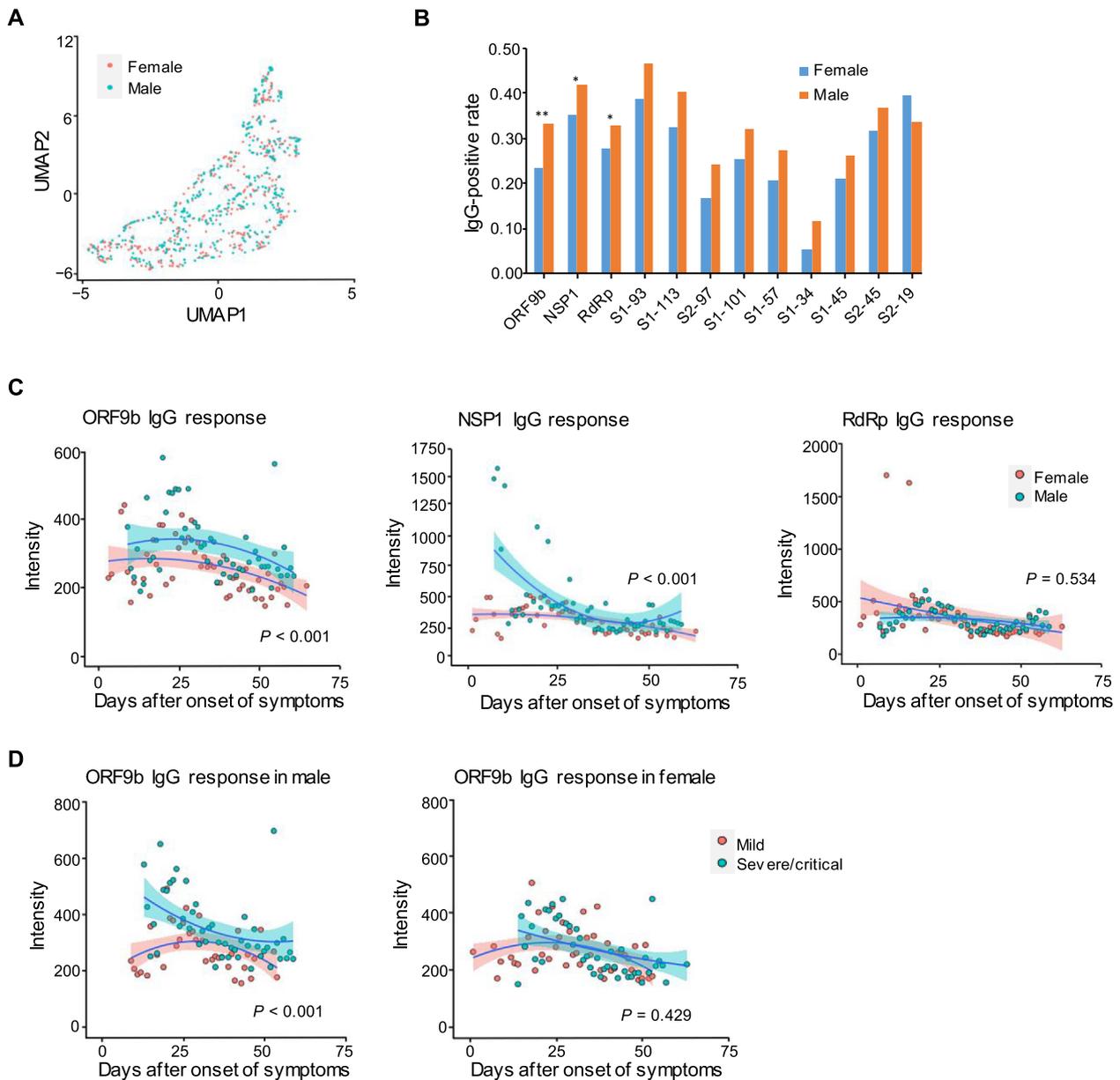


Figure 3 Correlation of the ORF9b IgG response with COVID-19 severity in male patients

A. Scatter plot showing UMAP results for serum samples using IgG/IgM responses to 24 full-length/truncated proteins (corresponding to 20 known SARS-CoV-2 proteins) in gender subgroup analysis. **B.** Histogram showing IgG-positive rates of different SARS-CoV-2 proteins and spike protein peptides in males and females. **C.** Scatter plots showing the dynamic IgG responses of ORF9b (left), NSP1 (middle), and RdRp (right) using longitudinal samples from male and female patients. **D.** Scatter plots showing the dynamic ORF9b IgG response in male (left) and female (right) COVID-19 patients with mild and severe/critical symptoms. P value was calculated by a two-sided t -test. UMAP, uniform manifold approximation and projection.

peptide-level humoral responses to proteins other than S protein, and multicentre samples. In the future, we will analyze the dynamic responses of SARS-CoV-2-specific antibodies using ~ 500 serum samples from ~ 100 COVID-19 convalescent patients. We will also integrate published peptide microarray/phage display-related data [14–16,29] and attempt to update the database covering the whole SARS-CoV-2 proteome at the peptide or amino acid level. In addition, the SARS-CoV-2 protein microarray has already been promoted by CDI Labs (www.cdi.bio) and ArrayJet (www.arrayjet.co.uk), and we anticipate more diverse data for SARS-CoV-2-specific antibody responses from multicentre

samples. We strongly believe that by sharing a large dataset and facilitating data analysis, COVID-ONE-hi will be a valuable resource for COVID-19 research.

Ethical statement

The study was approved by the Ethical Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (ITJ-C20200128). Written informed consent was obtained from all participants enrolled in this study.

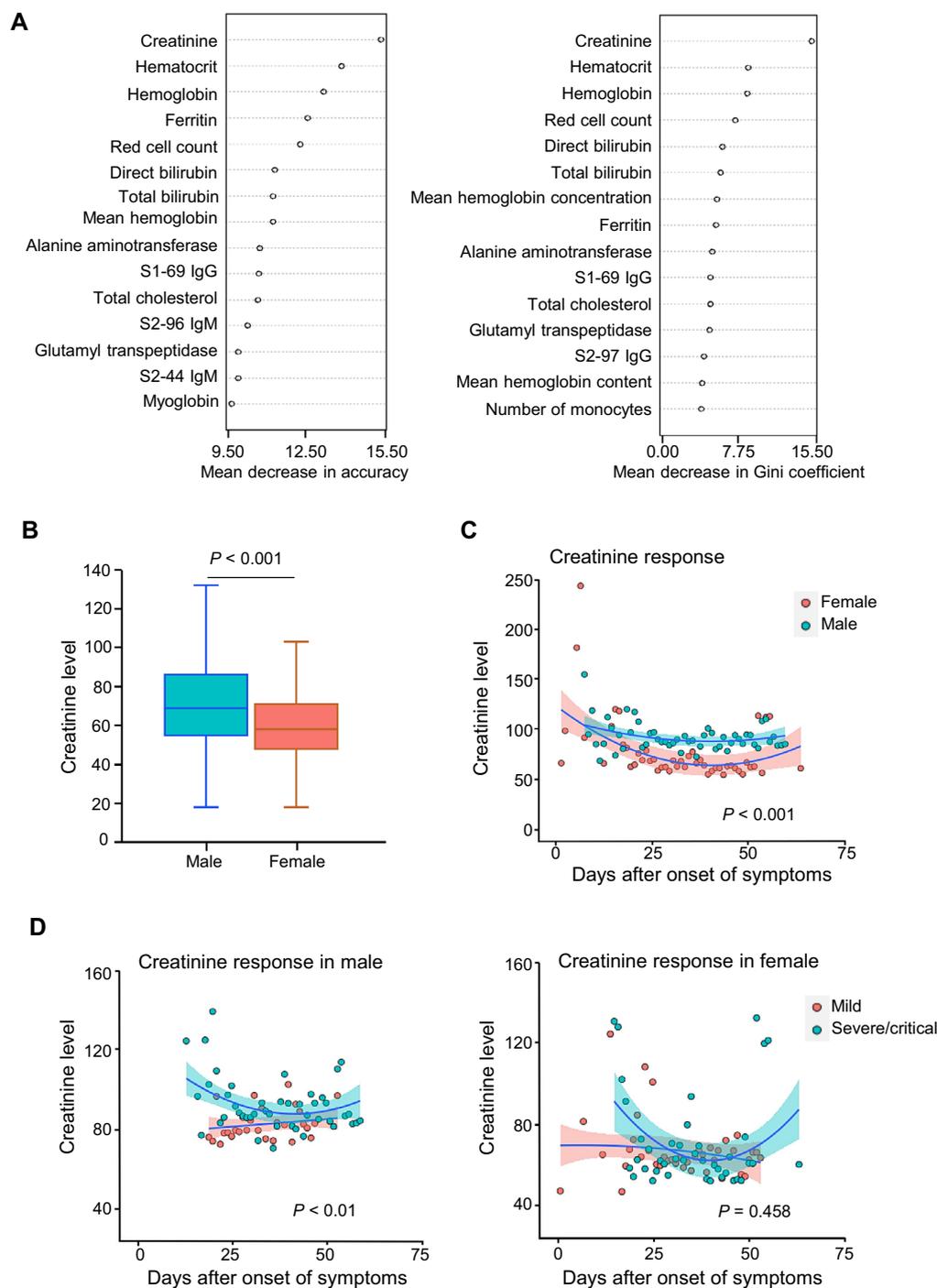


Figure 4 Correlation of creatinine response with COVID-19 severity in male patients

A. The top 15 gender-specific parameters by random forest analysis ranked by the mean decrease in accuracy (left) and Gini coefficient (right). **B.** Boxplot showing the significant difference of median creatinine levels in gender subgroup analysis. **C.** Scatter plot showing the dynamic creatinine levels for male and female COVID-19 patients. **D.** Scatter plots showing the dynamic creatinine levels for male (left) and female (right) COVID-19 patients with mild and severe/critical symptoms. P value was calculated by a two-sided t -test.

Data availability

COVID-ONE-hi is freely accessible at www.covid-one.cn. If users need the raw data of antibody responses or clinical parameters, please contact the corresponding author (taosc@sjtu.edu.cn).

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Competing interests

The authors declare no competing interests.

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Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gpb.2021.09.006>.

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