A Novel Triage Tool of Artificial Intelligence Assisted Diagnosis Aid System for Suspected COVID-19 pneumonia In Fever Clinics.

Running title: A Novel Triage Tool for Suspected COVID-19

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Abstract

Currently, the prevention and control of COVID-19 outside Hubei province in China, and other countries has become more and more critically serious. We developed and validated a diagnosis aid model without CT images for early identification of suspected COVID-19 pneumonia (S-COVID-19-P) on admission in adult fever patients and made the validated model available via an online triage calculator. Patients admitted from Jan 14 to Feb 26, 2020 with the epidemiological history of exposure to COVID-19 were included [Model development (n = 132) and validation (n = 32)]. Candidate features included clinical symptoms, routine laboratory tests and other clinical information on admission. Features selection and model development were based on Lasso regression. The primary outcome is the development and validation of a diagnosis aid model for S-COVID-19-P early identification on admission. The development cohort contains 26 S-COVID-19-P and 7 confirmed COVID-19 pneumonia cases. The model performance in held-out testing set and validation cohort resulted in AUCs of 0.841 and 0.938, F-1 score of 0.571 and 0.667, recall of 1.000 and 1.000, specificity of 0.727 and 0.778, and the precision of 0.400 and 0.500. Based on this model, an optimized strategy for S-COVID-19-P early identification in fever clinics has also been designed. S-COVID-19-P could be identified early by a machine-learning model only used collected clinical information without CT images on admission in fever clinics with 100% recall score. The well performed and validated model has been deployed as an online triage tool, which is available at: https://intensivecare.shinyapps.io/COVID19/.

KEYWORDS: Suspected COVID-19 pneumonia; Diagnosis Aid model; Fever Clinics; Machine Learning

Introduction

Since December 2019, the outbreak of novel coronavirus disease (COVID-19; previously known as 2019-nCoV) [1], which causing severe pneumonia and acute respiratory syndrome was emerged in Wuhan, China, and rapidly affecting worldwide[2-5]. Until February 29th, 2020, the total reported confirmed COVID-19 pneumonia (C-COVID-19-P) cases have reached 85,403 in the whole world, including 79,394 in China and 6,009 in other countries globally, and the number of cases is increasing rapidly and internationally[6, 7].

The main reason for the outbreak of infected cases in the early stage of the epidemic was short in ability to rapidly and effectively detect such a large number of suspected cases[8]. Outside Hubei Province, such as in Beijing with a large population, sporadic and clustered cases have continuously been reported. Some other countries and regions, prominently in South Korea, Japan, Iran, etc., are reporting more and more confirmed cases[4, 6, 9, 10]. Currently, epidemic prevention and control outside Hubei province and other countries have become more and more critically serious. Therefore, establishing an early identification method of suspected COVID-19 pneumonia (S-COVID-19-P) and optimizing triage strategies for fever clinics is urgent and essential for the coming global challenge.

The identification of S-COVID-19-P relies on the following criteria: the epidemiological history, clinical signs and symptoms, routinely laboratory tests (such as lymphopenia) and positive Chest computerized tomography (CT) findings[3]. However, clinical symptoms and routinely laboratory tests are sometimes non-specific[2, 3]. Although CT is becoming a major diagnostic tool helping for early screening of S-COVID-19-P, the resources of the designated CT room are relatively limited, especially in less-developed regions and when the influx of patients substantially outweighed the medical service capacities in fever clinics[11, 12]. Moreover, not all

patients with clinical symptoms or abnormal blood routine values need CT examination, besides radiation injury, high cost and other restrictions. Therefore, it is critical to integrate and take the most advantages of clinical signs and symptoms, routinely laboratory tests and other clinical information which available on admission before further CT examination, which would strength the ability of early identification of S-COVID-19-P, improve the triage strategies in fever clinics and make a balance between standard medical principles and limited medical resources.

The increase of secondary analysis in the emergency department and intensive care unit has given feasibility to get 'real time' data from the electronical medical records, thus making them enable for 'real world' research[13, 14]. This term pertains to machine-learning algorithms to analyze specific clinical cohorts and develop models for diagnosis aid or decision support in emergent triage[15]. Such models could be a cost-effective assisted tool to integrate clinical signs and symptoms, blood routine values and infection-related biomarkers on admission for S-COVID-19-P early identification.

The aim of this study was the development and validation of a diagnosis aid model on admission without CT images for early identification of S-COVID-19-P in adult fever patients with the epidemiological history of exposure to COVID-19. The model performance was also compared to some infection-related biomarkers on admission in the general population admitted to the fever clinic. The well-performed model is available as an online triage calculator, and based on it, the optimized strategy for S-COVID-19-P early identification in fever clinics has also been discussed.

Materials and methods

Study design and population: development and validation cohorts

We developed a novel diagnosis aid model for early identification S-COVID-19-P based on the retrospective analysis of a single center study. All patients admitted to the fever clinic of emergency department of the First medical center, Chinese People's Liberation Army General Hospital (PLAGH) in Beijing with the epidemiological history of exposure to COVID-19 according to WHO interim guidance were enrolled in this study. The fever clinic is a department for adults (*i.e.*, aged ≥14 years) specializing in identification of infectious diseases, especially for S-COVID-19-P. We recruited patients from Jan 14 to Feb 9, 2020 as a model development cohort. Meanwhile, we also recruited patients from Feb 10 to Feb 26, 2020 as a dataset for model validation.

The definition of S-COVID-19-P

All recruited patients on admission were given vital signs, blood routine, infection-related biomarkers, influenza viruses (A+B) and chest CT examination. The patients who have the epidemiological history and CT imaging characteristics of viral pneumonia and any other one of the following two clinical signs were diagnosed as S-COVID-19-P, which according to the "Guidelines for diagnosis and management of novel coronavirus pneumonia (The sixth Edition)" published by Chinese National Health and Health Commission on Feb 18, 2020 (6th-Guidelines-CNHHC). The two clinical signs including: 1) Fever and/or respiratory symptoms; 2) Total count of leukocyte was normal or decreased, or lymphopenia ($<1.0\times 10^9$/L).

The definition of C-COVID-19-P

Patients who were clinically identified as S-COVID-19-P, the throat swab specimens from the upper respiratory tract obtained from all patients on admission were maintained in viral-transport medium[3]. Laboratory confirmation of COVID-19 infection was done in four different institutions: the PLAGH, the Haidian District Disease Control and Prevention (CDC) of Beijing,

the Beijing CDC and the academy of Military Medical Sciences. COVID-19 infection was confirmed by real-time RT-PCR using the same protocol described previously[2]. RT-PCR detection reagents were provided by the four institutions.

Data extraction

For each patient, we extracted all data on admission, which included demographic information, comorbidities, epidemiological history of exposure to COVID-19, vital sign, blood routine values, clinical symptoms, infection-related biomarkers, influenza viruses (A+B) test, CT findings, and days from illness onset to first admission. All data were checked and missing data were obtained by direct communication with other two attending doctors (XC and YZ).

Outcomes

The primary outcome is the development and validation of a diagnosis aid model for S-COVID-19-P early identification on admission. The secondary outcome is the comparison of the diagnostic performance between diagnosis aid model and infection-related biomarkers on admission.

Diagnosis aid model and candidate features

For early identification for S-COVID-19-P on admission, a diagnosis aid model was developed which are intended to be used early clinical information based on the availability from patients' medical records. We included following candidate features: 1) 2 variables of demographic information (*e.g.*, age and gender); 2) 4 variables of vital signs (*e.g.*, temperature, heart rate, etc.); 3) 20 variables of blood routine values (*e.g.*, white blood cell count, red blood cell count, hemoglobin, hematocrit, etc.); 4) 17 variables of clinical signs and symptoms [e.g., fever, fever classification (℃ , normal: <= 37.0, mild fever: 37.1-38.0, moderate fever: 38.1-39.0, severe fever: >=39.1), cough, muscle ache, etc.]; 5) 2 infection-related biomarkers (*e.g.*, C-

reactive protein and Interleukin-6); 6) 1 other variable: days from illness onset to first admission (DOA). The complete candidate features list is shown in Table 1.

Features selection and model development

Candidate features were selected based on expert opinion and availability in the medical records. For the model, we compared 4 different algorithms: 1) logistic regression with LASSO, 2) logistic regression with Ridge regularization, 3) decision tree, 4) Adaboost algorithms, and found logistic regression with LASSO achieved overall best performances in testing set and external validation set in terms of AUC and recall score (Table S1). Features selection and model development were performed in the development cohort only and using a logistic regression with Lasso regularization (Lasso regression) which is one of the models that shrinks some regression coefficients toward zero, thereby effectively selecting important features and improving the interpretability of the model[16]. The features selection and model development were performed in Python 3.7. During the model training, we randomly held out 20% of the cohort data as testing set, and then used a 10-fold cross-validation to yield the optimal of LASSO regularization parameter in the training and validation sets. All features were normalized to standard uniform distribution according to the training and validation sets, and then applied this transformation to both held-out testing set as well as external validation set. All computations were achieved by scikit-learn (version: 0.22.1) in python. Random oversampling was performed to construct balanced data on training and validation sets by using imblearn python package (version 0.6.2).

Model validation

After model development, we used the cohort with the epidemiological history from Feb 10 to Feb 26, 2020 for model validation. The model validation was also performed in python.

Features Importance Ranking

Feature importance was performed in the development cohort. The associated coefficient weights correspond to the logistic regression model were used for identifying and ranking feature importance.

Comparison of diagnostic performance among diagnosis aid model and infection-related biomarkers

Lymphocyte count (LYMPH#), C-reactive protein (CRP) and Interleukin-6 (IL-6) were evaluated on admission. Lymphopenia ($<1.0\times10^9$/L) was one of the three diagnostic criteria for S-COVID-19-P according to the 6th-Guidelines-CNHHC. Elevated CRP (>0.8 mg/L) and elevated IL-6 (>5.9 pg/mL) were both important infection-related biomarkers. The diagnostic performance among diagnosis aid model and biomarkers for early identifying S-COVID-19-P was also compared.

The entire workflow is shown in Figure 1.

Statistical Analysis and Performance Evaluation

Continuous variables were expressed as median with interquartile range (IQR) and compared with the Mann-Whitney U test; categorical variables were expressed as absolute (n) and relative (%) frequency and compared by χ^2 test or Fisher's exact test. A two-sided α of less than 0.05 was considered statistically significant. Statistical analysis was performed by R version 3.5.1.

Model performance were evaluated by: 1) the area under the ROC curve (AUC) [17], 2) F-1 score, 3) Precision, 4) Sensitivity (Recall), 5) Specificity. AUC, ranging from 0 to 1, the higher the better, indicates the algorithm's performances. Precision is the fraction of true positive classification among the positive results classified by algorithm; a higher precision indicates an algorithm's result is reliable. Recall is the fraction of true positive classification among all the

true samples, describes the ability of identifying true samples (S-COVID-19-P) among the whole population. F1 score is the harmonic average of precision and recall, higher F1 score indicates better performance. In this study, to avoid missed suspected cases, recall is the most important reference[18]. We considered the model with AUC above 0.80 and recall above 0.95 as the adequate and well-performed model.

Results

Study population: development and validation cohorts

In development cohort, a total of 132 unique admissions with the epidemiological history of exposure to COVID-19 were included from Jan 14 to Feb 9, 2020. 26 patients were clinically identified as S-COVID-19-P according to the 6th-Guidelines-CNHHC and 7 patients out of them were further identified as C-COVID-19-P in Beijing. 10 (38.5%) out of 26 S-COVID-19-P cases were transferred to CDC after the first laboratory confirmation of COVID-19 infection by PLAGH. The left 16 (61.5%) S-COVID-19-P cases were kept hospitalizing for quarantine and further laboratory confirmation of COVID-19 infection. The 7 C-COVID-19-P cases were all belonged to moderate type based on the 6th-Guidelines-CNHHC, so as to no ICU admission and no death occurred. (Table 2)

These S-COVID-19-P cases with a median age of 39.5 (36.3-52.3), 17 (65.4%) were male and the median days of DOA were 2.5 (1.0-4.8). Non-suspected COVID-19 pneumonia (N-S-COVID-19-P) cases with a median age of 33.0 (28.0-40.0), 57 (53.8%) were male and the median days of DOA were 2.0 (1.0-5.0). C-COVID-19-P cases with a median age of 39.0 (37.0-41.5), 5 (71.4%) were male and the median days of DOA were 5.0 (3.5-5.5). (Table 2)

Within 14 days before the onset of the disease, there were 3 (11.5%), 7 (6.6%) and 2 (28.6%) patients had a history of contact with COVID-19 infected patients (laboratory-confirmed

infection) in suspected, non-suspected and confirmed COVID-19 pneumonia cases, respectively. On admission, the median heart rate [107.5 (100.0-116.2) vs 99.5 (89.5-110.0), p=0.035], diastolic blood pressure [89.5 (80.5-96.3) vs 81.0 (75.0-88.0), p=0.014], systolic blood pressure [145.5 (136.2-156.8) vs 134.0 (124.0-143.0), p<0.001] and the highest temperature [37.9 (37.4-38.5) vs 37.4 (36.8-37.8), p=0.006] were much higher in S-COVID-19-P cases than in N-S-COVID-19-P cases. (Table 2)

The most common symptoms at onset of illness were fever [23 (88.5%), 70 (66.0%)], sore throat [15 (57.7%), 43 (40.6%)], and cough [12 (46.2%), 53 (50.0%)) in S-COVID-19-P and N-S-COVID-19-P cases, respectively. However, in C-COVID-19-P cases, muscle ache 6 (85.7%) and headache 5 (71.4%) were also the most common symptoms besides the fever 6 (85.7%), cough 5 (71.4%) and sore throat 5 (71.4%). (Table 2)

The blood routine values of patients on admission showed lymphopenia [lymphocyte count $<1{\cdot}0 \times 10^9$/L; 9 (34.6%), 17 (16.0%) and 1 (14.3%)] and elevated monocyte ratio [monocyte ratio > 0.08; 12 (46.2%), 18 (17.0%) and 4 (57.1%)] in S-COVID-19-P, N-S-COVID-19-P and C-COVID-19-P cases, respectively. Early lymphopenia (p=0.051) and elevated monocyte ratio (p=0.003) were more prominent in S-COVID-19-P than N-S-COVID-19-P cases, but no statistically different between C-COVID-19-P and non-C-COVID-19-P in S-COVID-19-P cases. The ratio of elevated CRP cases on admission was more in S-COVID-19-P cases than N-S-COVID-19-P cases [13(50.0%) vs 29(27.4%), p=0.035], but no statistically significant between C-COVID-19-P cases and non-C-COVID-19-P in S-COVID-19-P cases [6(85.7%) vs 7(36.8%), p=0.190]. The ratio of elevated IL-6 cases on admission was also more in S-COVID-19-P cases than N-S-COVID-19-P cases [16(61.5%) vs 34(32.1%), p=0.007], but no statistically significant

between C-COVID-19-P cases and non-C-COVID-19-P in S-COVID-19-P cases [6(85.7%) vs 10(52.6%), p=0.190]. (Table 3)

On admission, 26 (100%) and 10 (9.4%) patients had positive CT findings in S-COVID-19-P and N-S-COVID-19-P cases, respectively. In S-COVID-19-P cases, multiple macular patches and interstitial changes accounted for 53.8% (n=14) and multiple mottling and ground-glass opacity accounted for 8.5% (n=9). Positive CT findings in 11 (42.3%) S-COVID-19-P cases and 6 (85.7%) C-COVID-19-P cases were obvious in extra-pulmonary zone. (Table 3)

The descriptions and statistics of the development cohort's demographics, baseline and clinical characteristics were summarized in Table 2, the laboratory results and CT findings were summarized in Table 3. Meanwhile, the same details of the validation cohort, a total of 33 unique admissions with the epidemiological history of exposure to COVID-19 from Feb 10 to Feb 26, 2020 were summarized in Table S2 and Table S3.

Features selection

Candidate features and univariable association with S-COVID-19-P are listed in Table S4 from the resulting coefficients of LASSO regularized logistic regression. Therefore, final selected features for model development are including: 1) 1 variable of demographic information (age); 2) 4 variables of vital signs [*e.g.*, Temperature (TEM), Heart rate (HR), etc.]; 3) 5 variables of blood routine values [*e.g.*, Platelet count (PLT), Monocyte ratio (MONO%), Eosinophil count (EO#), etc.]; 4) 7 variables of clinical signs and symptoms [*e.g.*, Fever, Fever classification, Shiver, etc.]; 5) 1 infection-related biomarkers [Interleukin-6 (IL-6)]. The final selected features list was shown in Table 4.

Model performance in development and validation cohort

The diagnosis aid model for S-COVID-19-P early identification on admission performed well in both development and validation cohort according to all evaluation criteria. For the LASSO regularized logistic regression, we introduce LASSO penalty from C = 0.25 to 7.5 with a step size = 0.25 in scikit-learn package and found C = 7.0 achieved optimal performance with respect to the AUC in the validation set. In the held-out testing set, we found AUC = 0.8409, F-1 score = 0.5714, precision = 0.4000, recall = 1.0000 and specificity = 0.727. In the validation set, we found AUC = 0.9383, F-1 score = 0.6667, precision = 0.5000, recall = 1.0000 and specificity = 0.778. (Table S1)

Identifying Feature Importance

We analyzed feature importance from the coefficient weights in the LASSO regularized logistic regression model. The list of feature importance ranking of diagnosis aid model for S-COVID-19-P early identification in development cohort is shown in Figure 2. Note that the top 5 important features that strongly associated with S-COVID-19-P were Age (0.1115), IL-6 (0.0880), SYS_BP (0.0868), MONO% (0.0679), and Fever classification (0.0569).

Comparison of diagnostic performance among diagnosis aid model and infection-related biomarkers

The comparison of diagnostic performance among diagnosis aid model and prominently infection-related biomarkers (lymphopenia, elevated CRP, and elevated IL-6) for early identifying S-COVID-19-P in development cohort was shown in Table 5. The performance of the diagnosis aid model was better than lymphopenia, elevated CRP, and elevated IL-6, respectively, which resulted in AUCs of 0.841, 0.407, 0.613 and 0.599, Recall of 1.0000, 0.346, 0.500 and 0.615.

Online Suspected COVID-19 Pneumonia Diagnosis Aid System

We made the validated diagnosis aid model by LASSO regularized logistic regression algorithm as the "Suspected COVID-19 pneumonia Diagnosis Aid System" which was publicly available through our online portal at https://intensivecare.shinyapps.io/COVID19/.

Discussion

In this retrospective observation, we evaluated the development and validation of a diagnosis aid model based on machine-learning algorithm and clinical data without CT images for S-COVID-19-P early identification. The clinical data comes from the demographic information, routinely clinical signs, symptoms and laboratory tests before the further CT examination. Therefore, in fever clinics under epidemic outbreak, such diagnosis aid model might improve triage efficiency, optimize medical service process, and save medical resources.

From the results in LASSO regularized logistic regression, though some false alarm may exist, the model is able to identify 100% of the suspected cases in both held-out testing set and external validation set. By applying this stringent rule to the clinical diagnosis, it is of our great interest to avoid any missed cases. This suggests that our diagnosis aided system is able to help doctors make decision of suspected cases in a highly reliable manner.

According to the analysis of features selection and features importance ranking, the univariable from the most demographic information, clinical signs, symptoms and blood routine values on admission could not show a remarkable association with S-COVID-19-P, which indicated that they may not be informative and increased the difficulty for early identifying S-COVID-19-P with routinely clinical information. Therefore, it is necessary to integrate all above nonspecific but important features by machine-learning algorithms for secondary analysis and developing cost-effective diagnosis aid models[19, 20].

The infection-related biomarkers, most prominently lymphopenia, elevated CRP and IL-6, played a key role in identifying clinical infections, such as the lymphopenia have been included as one of three diagnostic criteria for S-COVID-19-P based on 6th-Guidelines-CNHHC[3, 21, 22]. In this study, all of these three biomarkers based on the blood routine test on admission could distinguish S-COVID-19-P from the N-S-COVID-19-P well. According to the comparison of diagnostic performance among diagnosis aid model and these biomarkers, the diagnosis aid model significantly outperformed in AUC and Recall than other biomarkers, which highlighting its potential use for clinical triage. Moreover, we also found that the early elevated monocyte ratio in development cohort and the early elevated monocyte count could identify S-COVID-19-P from N-S-COVID-19-P well in this study, which suggested that monocyte ratio or monocyte count would also be a new potentially infection-related biomarker for S-COVID-19-P early identification[22].

Although CT scan was becoming a major diagnostic tool helping for early screening of S-COVID-19-P cases, it could not satisfy every patient when the medical resources insufficient in the epidemic outbreak. From the result of CT findings in development and validation cohort, there were only 10 (9.4%) and 4 (14.8%) N-S-COVID-19-P cases have mild CT findings on admission, which indicated that the triage strategies for CT scans mainly based on fever or lymphopenia need further optimizing[23]. Therefore, it is meaningful to use machine-learning algorithms to comprehensive analyze clinical symptoms, routine laboratory tests and other clinical information before further CT examination and develop diagnosis aid model to improve the triage strategies in fever clinics, which would make a well balance between standard medical principles and limited medical resources.

The developed and validated model performances clearly confirmed that the early identification of S-COVID-19-P in fever clinics could be accurately triaged based only on clinical information without CT images on admission. After features selection, the final developed model based on fewer predictors could perform well according to most evaluation criteria, and also have a better result in further validation. Therefore, the final model based on a small number of features would be likely applicable in most fever clinics.

One of the most effective strategies to control epidemic outbreak was the establishment of an efficient triaging process for early identification S-COVID-19-P in fever clinics[23]. Based on our successful experience in Beijing and well performed 'Suspected COVID-19 Pneumonia Diagnosis Aid System', we have designed the following improved S-COVID-19-P early identification strategies in adult fever clinics (Figure 3). All patients with fever, sore throat or cough, whether there is hypoxia or not, we proposed routinely take the measurements of blood routine, CRP, IL-6 and influenza virus (A+B) test. Then, if the results of the above tests are normal and the patient without any epidemiological history, home quarantine, regular treatment (such as oral antibiotics) and continuous monitoring clinical signs and symptoms are suggested. If not, a rapid and artificial intelligence assisted evaluation of all clinical results will be required based on our 'Suspected COVID-19 Pneumonia Diagnosis Aid System' for S-COVID-19-P early identification, which helping for a decision-support of whether the next CT examination is needed. When the clinical symptoms do not relieve in a few days for home-quarantine patients, they would be required to return for further examination (such as CT scan). Meanwhile, patients with negative CT findings would also be advised to have a home quarantine with regular treatment and continuous monitoring. Therefore, artificial intelligence assisted diagnosis aid system for S-COVID-19-P would take the most advantages of clinical symptoms, routine

laboratory tests and other clinical information which available on admission before further CT examination in order to improve the triage strategies in fever clinics and make a balance between standard medical principles and limited medical resources.

Our current study has several strengths. First, we successfully used machine-learning algorithm to analyze clinical datasets without CT images and develop a diagnosis aid model for early identification of S-COVID-19-P cases in fever clinic, which would become a key method to answer the questions of insufficient medical resources in epidemic outbreak. Second, we integrated most of the routinely available data on admission, including 46 features which would be considered containing the largest number of predictors. Third, we found that the admitted monocyte ratio or monocyte count in blood routine test was more discriminant in S-COVID-19-P cases which might be a new potential infection-related biomarker for early identification. Fourth, we also discussed an optimized triage strategy in fever clinics for early identification of S-COVID-19-P with the help of our new diagnosis aid model which would help to make a balance between standard medical principles and limited medical resources. Fifth, the final model based on a small number of features are likely available in most fever clinics, which has the advantages to increase the possibility of worldwide use and generalizability. Lastly, the developed and validated diagnosis aid model was publicly available as an online triage calculator. This is the first of this method and provides a platform and useful tool for future biomarker and S-COVID-19-P early identification studies in limited resource settings.

Although the diagnosis results are highly reliable according to the recall score, this study may still exist following inevitable limitations. First, we only evaluated lymphopenia, elevated CRP and elevated IL-6, while other biomarkers might be more discriminant. Second, the data size was relatively small based on only a single-center fever clinic, which calls for ‘big data’

analysis depend on multiple-center fever clinics. Third, model was developed and validated for mildly ill patients and with less comorbidities; therefore, more well-performing models would be welcomed for specifically subpopulation. Fourth, since the model was developed and validated in a single-center fever clinic, the performance might vary when evaluated in other fever clinics, particularly if they differ in patient characteristics and COVID-19 prevalence. Therefore, the diagnosis aid model of this study requires further external validation based on different background populations. Fifth, there is a potential risk for misuse of the online calculator. The suited patients and the classification threshold should be taken more consideration so as to make the right choice and decision[24]. Last but not the least, the "Suspected COVID-19 pneumonia Diagnosis Aid System" would only be used as one of the auxiliary references for making clinical and management decisions.

Conclusion

We successfully used machine-learning algorithm to develop a diagnosis aid model without CT images for early identification of S-COVID-19-P, and the diagnostic performance was better than lymphopenia, elevated CRP and elevated IL-6 on admission. The recall score on both held-out testing and validation sets are all 100%, suggest the model is highly reliable for clinical diagnosis. We also discussed an optimized triage strategy in fever clinics for early identification of S-COVID-19-P with the help of our new diagnosis aid model which would make a well balance between standard medical principles and limited medical resources. To facilitate further validation, the developed diagnosis aid model is available online as a triage calculator.

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Author Contributions:

CF designed the study, conducted the data collection, data analysis, data interpretation, and wrote the manuscript. ZH and LL conducted the data analysis, data interpretation, conducted the online calculator, developed the website, and wrote the manuscript. WS, XC, YZ, FZ, XS and YW conducted the data interpretation and reviewed the manuscript. FP, LT, WZ, HC, LZ, and QH conducted the data interpretation and wrote the manuscript. LC, ZZ, JZ, HX and YL reviewed the manuscript. GL, WC, and TL conducted the data interpretation and reviewed the manuscript.

Compliance with Ethical Standards

Data collection was passive and had no impact on patient safety. This study was approved by the PLA General Hospital ethics committee.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Data sharing

The data that support the findings of this study are available from the corresponding author on reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding author, PLAGH and National Health Commission. After publication of study findings, the data will be available for others to request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability to request for our data. The corresponding author, PLAGH and National Health Commission will make a decision based on these materials. Additional materials may also be required during the process.

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Table1: Candidate features for diagnosis aid model

Groups	Candidate features				
Demographic information	Age	Gender			
Vital signs	Temperature (TEM)	Heart rate (HR)	Diastolic blood pressure (DIAS_BP)	Systolic blood pressure (SYS_BP)	
Blood routine values	White blood cell count (WBC)	Red blood cell count (RBC)	Hemoglobin (HGB)	Hematocrit (HCT)	Platelet count (PLT)
	Mean platelet volume (MPV)	Lymphocyte ratio (LYMPH%)	Lymphocyte count (LYMPH#)	Neutrophil ratio (NEUT%)	Neutrophil count (NEUT#)
	Eosinophil ratio (EO%)	Eosinophil count (EO#)	Monocyte ratio (MONO%)	Monocyte count (MONO#)	Basophil ratio (BASO%)
	Basophil count (BASO#)	Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin content (MCH)	Mean corpuscular hemoglobin concentratio (MCHC)	Red blood cell volume distribution width (RDW-CV)
Clinical signs and symptoms on admission	Fever	Cough	Shortness of breath	Muscle ache	Headache
	Rhinorrhoea	Diarrhoea	Nausea	Vomiting	Chills
	Expectoration	Nasal congestion	Abdominal pain	Fatigue	Palpitation
	Sore throat	Shiver	Fever classification (FC)		
Infection-related biomarkers	C-reactive protein (CRP)	Interleukin-6 (IL-6)			
Others	Days from illness onset to first admission（DOA)				

Fever classification: ℃，Normal: <= 37.0; Mild fever: 37.1-38.0; Moderate fever: 38.1-39.0; Severe fever: >=39.1.

Table2: Demographics, baseline and clinical characteristics of 132 patients admitted to PLA General Hospital (Jan 14–Feb 9, 2020) with the epidemiological history of exposure to COVID-19 in development cohort.

	All patients	Non-suspected COVID-19 pneumonia cases	Suspected COVID-19 pneumonia cases	p-value[1]	Non- confirmed COVID-19 pneumonia in suspected cases	Confirmed COVID-19 pneumonia in suspected cases	p-value[2]
Cohort (n)	132	106	26	-	19	7	-
Age, years (median,(IQR))	34.0(29.0-42.0)	33.0(28.0-40.0)	39.5(36.3-52.3)	0.004	40.0(32.5-54.5)	39.0(37.0-41.5)	0.954
Gender (n(%))				0.396			-
Male	74(56.1%)	57(53.8%)	17(65.4%)	-	12(63.2%)	5(71.4%)	-
Female	58(43.9%)	49(46.2%)	9(34.6%)	-	7(36.8%)	2(28.6%)	-
Days from illness onset to first admission, (median,(IQR))	2.0(1.0-5.0)	2.0(1.0-5.0)	2.5(1.0-4.8)	0.974	1.0(1-3.5)	5.0(3.5-5.5)	0.017
Comorbidities (n(%))							
Hypertension	2(1.5%)	2(1.9%)	0(0%)	-	0(0%)	0(0%)	-
Diabetes	2(1.5%)	1(0.9%)	1(3.8%)	-	1(5.3%)	0(0%)	-
Cardiovascular disease	0(0%)	0(0%)	0(0%)	-	0(0%)	0(0%)	-
Chronic obstructive pulmonary disease	3(2.3%)	1(0.9%)	2(7.7%)	-	2(10.5%)	0(0%)	-
Malignancy	0(0%)	0(0%)	0(0%)	-	0(0%)	0(0%)	-
Chronic kidney disease	1(0.8%)	1(0.9%)	0(0%)	-	0(0%)	0(0%)	-
Chronic liver disease	1(0.8%)	1(0.9%)	0(0%)	-	0(0%)	0(0%)	-
The epidemiological history of exposure to COVID-19 (n(%))							
History of sojourn or residence (HSR)	56(42.4%)	48(45.3%)	8(30.8%)	0.263	4(21.1%)	4(57.1%)	0.149
History of contaction with confirmed COVID-19 infected patients (HCCI)	10(7.6%)	7(6.6%)	3(11.5%)	0.412	1(5.3%)	2(28.6%)	0.167

History of contaction with persons who had fever or respiratory symptoms (HCFR)	63(47.7%)	51(48.1%)	12(46.2%)	-	11(57.9%)	1(14.3%)	0.081
Clustering onset	3(2.3%)	0(0%)	3(11.5%)	0.007	3(15.8%)	0(0%)	0.54
Vital sign on admission							
Heart rate, n/min (median,(IQR))	101.5(92.0-112.2)	99.5(89.5-110.0)	107.5(100.0-116.2)	0.035	103.0(97.0-122.0)	110.0(102.5-113.0)	0.885
Diastolic blood pressure, mmHg (median,(IQR))	83.5(75.8-91.0)	81.0(75.0-88.0)	89.5(80.5-96.3)	0.014	91.0(79.5-97.0)	85.0(82.5-90.0)	0.817
Systolic blood pressure, mmHg (median,(IQR))	136.0(125.8-147.2)	134.0(124.0-143.0)	145.5(136.2-156.8)	<0.001	147.0(138.0-157.5)	137.0(133.5-152.0)	0.37
Fever (n(%))	93(70.5%)	70(66.0%)	23(88.5%)	0.045	17(89.5%)	6(85.7%)	-
Highest temperature, °C (median,(IQR))	37.4(36.8-38.0)	37.4(36.8-37.8)	37.9(37.4-38.5)	0.006	37.8(37.5-38.3)	38.5(37.3-38.6)	0.84
<37.1	39(29.5%)	36(34.0%)	3(11.5%)	0.03	2(10.5%)	1(14.3%)	-
37.1–38.0	61(46.2%)	49(46.2%)	12(46.2%)	-	10(52.6%)	2(28.6%)	0.391
38.1–39.0	27(20.5%)	18(17.0%)	9(34.6%)	0.084	5(26.3%)	4(57.1%)	0.188
>39.0	5(3.8%)	3(2.8%)	2(7.7%)	0.255	2(10.5%)	0(0%)	-
Other symptoms on admission (n(%))							
Cough	65(59.2%)	53(50.0%)	12(46.2%)	0.895	7(36.8%)	5(71.4%)	0.19
Shortness of breath	18(13.6%)	17(16.0%)	1(3.8%)	0.197	1(5.3%)	0(0%)	-
Muscle ache	43(32.6%)	32(30.2%)	11(42.3%)	0.343	5(26.3%)	6(85.7%)	0.021
Headache	28(21.2%)	20(18.9%)	8(30.8%)	0.19	3(15.8%)	5(71.4%)	0.014
Sore throat	58(43.9%)	43(40.6%)	15(57.7%)	0.175	10(52.6%)	5(71.4%)	0.658
Rhinorrhoea	28(21.2%)	20(18.9%)	8(30.8%)	0.19	7(36.8%)	1(14.3%)	0.375
Diarrhoea	12(9.1%)	11(10.4%)	1(3.8%)	0.459	1(5.3%)	0(0%)	-
Nausea	4(3.0%)	3(2.8%)	1(3.8%)	-	1(5.3%)	0(0%)	-
Vomiting	3(2.3%)	3(2.8%)	0(0%)	-	0(0%)	0(0%)	-
Chills	37(28.0%)	31(29.2%)	6(23.1%)	0.701	4(21.1%)	2(28.6%)	-
Shiver	18(13.6%)	16(15.1%)	2(7.7%)	0.524	1(5.3%)	1(14.3%)	0.474
Expectoration	39(29.5%)	33(31.1%)	6(23.1%)	0.481	3(15.8%)	3(42.9%)	0.293

Abdominal pain	5(3.8%)	4(3.8%)	1(3.8%)	-	1(5.3%)	0(0%)	-
Fatigue	44(33.3%)	37(34.9%)	7(26.9%)	0.588	4(21.1%)	3(42.9%)	0.34
Palpitation	3(2.3%)	3(2.8%)	0(0%)	-	0(0%)	0(0%)	-
Clinical outcome (n(%))							
Discharged for home quarantine	106(80.3%)	106(100%)	0(0%)	-	0(0%)	0(0%)	-
Hospitalisation for quarantine	16(12.1%)	0(0%)	16(61.5%)	-	16(84.2%)	0(0%)	-
Transferred to Disease Control and Prevention (CDC)	10(7.5%)	0(0%)	10(38.5%)	-	3(15.8%)	7(100%)	-
Death	0(0%)	0(0%)	0(0%)	-	0(0%)	0(0%)	-

Continuous variables were expressed as median with interquartile range (IQR) and compared with the Mann-Whitney U test; categorical variables were expressed as absolute (n) and relative (%) frequency and compared by χ^2 test or Fisher's exact test. A two-sided α of less than 0·05 was considered statistically significant.

COVID-19: 2019 novel coronavirus.

History of sojourn or residence: Within 14 days before the onset of the disease, there was a history of sojourn or residence in the surrounding areas of Wuhan or other confirmed COVID-19 infected case reporting communities.

History of contact with confirmed COVID-19 infected patients: Within 14 days before the onset of the disease, there was a history of contact with confirmed COVID-19 infected patients.

History of contact with persons who had fever or respiratory symptoms: Within 14 days before the onset of the disease, there was a contact history with persons who had fever or respiratory symptoms. The persons come from Wuhan city and its surrounding areas, or come from the community where have reported confirmed COVID-19 infected cases.

p-value[1]: Suspected COVID-19 pneumonia cases compared to Non-suspected COVID-19 pneumonia cases.

p-value[2]: Confirmed COVID-19 pneumonia cases compared to Non- confirmed COVID-19 pneumonia in suspected cases.

Table3: Laboratory results and CT findings of 132 patients admitted to PLA General Hospital (Jan 14–Feb 9, 2020) with the epidemiological history of exposure to COVID-19 in development cohort..

	All patients	Non-suspected COVID-19 pneumonia cases	Suspected COVID-19 pneumonia cases	p-value[1]	Non-confirmed COVID-19 pneumonia in suspected cases	Confirmed COVID-19 pneumonia in suspected cases	p-value[2]
Cohort (n)	132	106	26	-	19	7	-
Blood routine values							
White blood cell count (WBC) ($\times 10^9$ per L; normal range 3.5–10.0)	6.81(5.59-8.37)	6.98(5.71-8.33)	6.09(5.18-8.46)	0.150	6.83(5.33-9.13)	5.15(4.43-5.87)	0.022
Increased	17(12.9%)	14(13.2%)	3(11.5%)	-	3(15.8%)	0(0%)	-
Decreased	2(1.5%)	1(0.9%)	1(3.8%)	0.356	1(5.3%)	0(0%)	-
Red blood cell count (RBC) ($\times 10^{12}$ per L; normal range: male 4.3–5.9, female 3.9–5.2)	4.83(4.43-5.17)	4.88(4.46-5.18)	4.79(4.43-5.10)	0.585	4.82(4.41-5.17)	4.76(4.54-4.97)	0.977
Decreased	3(2.3%)	2(1.9%)	1(3.8%)	0.485	1(5.3%)	0(0%)	-
Hemoglobin (HGB) (g/L; normal range: male 137.0–179.0, female 116.0–155.0)	148.0(133.0-159.0)	147.5(133.2-158.8)	149.0(132.2-159.5)	0.959	149.0(130.5-158.5)	146.0(135.5-156.0)	0.954
Decreased	6(4.5%)	5(4.7%)	1(3.8%)	-	0(0%)	1(14.3%)	0.269
Hematocrit (HCT) (normal range: male 0.4–0.52, female 0.37–0.47)	0.42(0.40-0.46)	0.43(0.40-0.46)	0.42(0.39-0.45)	0.691	0.42(0.39-0.46)	0.42(0.40-0.44)	-
Increased	1(0.8%)	1(0.9%)	0(0%)	-	0(0%)	0(0%)	-
Decreased	14(10.6%)	10(9.4%)	4(15.4%)	0.475	3(15.8%)	1(14.3%)	-
Platelet count (PLT) ($\times 10^9$ per L; normal range 100.0–300.0)	223.0(196.0-258.8)	232.0(206.5-260.2)	196.5(167.2-246.8)	0.046	209.0(184.0-281.0)	171.0(159.5-190.0)	0.083
Decreased	1(0.8%)	0(0%)	1(3.8%)	0.197	0(0%)	1(14.3%)	0.269
Lymphocyte ratio (LYMPH%) (0.2-0.4)	0.25(0.16-0.32)	0.26(0.17-0.33)	0.20(0.11-0.31)	0.114	0.15(0.10-0.24)	0.34(0.27-0.40)	0.002

Increased	14(10.6%)	13(12.3%)	1(3.8%)	0.301	0(0%)	1(14.3%)	0.269
Decreased	46(34.8%)	34(32.1%)	12(46.2%)	0.250	12(63.2%)	0(0%)	0.006
Lymphocyte count (LYMPH#) (× 10^9 per L; normal range 1.0–4.0)	1.66(1.12-2.16)	1.75(1.30-2.22)	1.17(0.86-1.93)	0.014	1.05(0.82-1.59)	1.98(1.26-2.24)	0.064
Increased	2(1.5%)	2(1.9%)	0(0%)	-	0(0%)	0(0%)	-
Decreased	26(19.7%)	17(16.0%)	9(34.6%)	0.051	8(42.1%)	1(14.3%)	0.357
Neutrophil ratio (NEUT%) (0.5-0.7)	0.66(0.58-0.76)	0.65(0.58-0.75)	0.69(0.60-0.80)	0.194	0.77(0.66-0.82)	0.57(0.50-0.65)	0.005
Increased	48(36.4%)	35(33.0%)	13(50.0%)	0.117	12(63.2%)	1(14.3%)	0.073
Decreased	12(9.1%)	10(9.4%)	2(7.7%)	-	0(0%)	2(28.6%)	0.065
Neutrophil count (NEUT#) (× 10^9 per L; normal range 2.0–7.0)	4.36(3.35-6.11)	4.53(3.44-5.96)	4.01(3.22-6.60)	0.466	4.49(3.89-7.04)	3.18(2.85-3.24)	<0.001
Increased	22(16.7%)	17(16.0%)	5(19.2%)	0.770	5(26.3%)	0(0%)	0.278
Decreased	5(3.8%)	3(2.8%)	2(7.7%)	0.255	1(5.3%)	1(14.3%)	0.474
Eosinophil ratio (EO%) (0.01-0.05)	0.008(0.003-0.014)	0.009(0.003-0.015)	0.006(0.002-0.011)	0.139	0.009(0.004-0.013)	0.002(0-0.004)	0.017
Increased	5(3.8%)	5(4.7%)	0(0%)	0.582	0(0%)	0(0%)	-
Eosinophil count (EO#) (× 10^9 per L; normal range 0.05–0.3)	0.05(0.02-0.11)	0.06(0.02-0.12)	0.04(0.01-0.09)	0.131	0.07(0.02-0.11)	0.01(0-0.02)	0.007
Increased	7(5.3%)	7(6.6%)	0(0%)	0.344	0(0%)	0(0%)	-
Monocyte ratio (MONO%) (0.03-0.08)	0.06(0.05-0.08)	0.06(0.05-0.08)	0.08(0.06-0.10)	<0.001	0.08(0.06-0.09)	0.09(0.08-0.11)	0.236
Increased	30(22.7%)	18(17.0%)	12(46.2%)	0.003	8(42.1%)	4(57.1%)	0.665
Monocyte count (MONO#) (× 10^9 per L; normal range 0.12–0.8)	0.45(0.34-0.57)	0.43(0.33-0.57)	0.54(0.43-0.65)	0.040	0.54(0.46-0.65)	0.55(0.34-0.60)	0.572
Increased	9(6.8%)	6(5.7%)	3(11.5%)	0.379	2(10.5%)	1(14.3%)	-
Basophil ratio (BASO%) (0-0.01)	0.004(0.002-0.007)	0.004(0.003-0.007)	0.003(0.002-0.006)	0.064	0.003(0.002-0.006)	0.002(0.002-0.003)	0.185
Increased	6(4.5%)	5(4.7%)	1(3.8%)	-	0(0%)	1(14.3%)	0.269

Basophil count (BASO#) (× 10^9 per L; normal range 0–0.1)	0.03(0.02-0.04)	0.03(0.02-0.05)	0.02(0.01-0.03)	0.019	0.023(0.019-0.033)	0.010(0.009-0.015)	0.03
Increased	2(1.5%)	2(1.9%)	0(0%)	-	0(0%)	0(0%)	-
Mean corpuscular volume (MCV) (fl; normal range: 80-100)	88.00(85.80-90.90)	87.80(85.72-90.60)	89.10(86.78-91.55)	0.239	89.3(86.95-91.50)	88.70(86.00-91.65)	0.977
Mean corpuscular hemoglobin content (MCH) (pg; normal range: 27-34)	30.40(29.57-31.30)	30.15(29.50-31.18)	31.10(30.02-31.40)	0.042	31.00(30.15-31.40)	31.20(30.15-31.55)	0.908
Mean corpuscular hemoglobin concentration (MCHC) (g/L; normal range: 320-360)	343.0(338.0-350.0)	342.0(337.0-349.8)	345.0(342.0-349.5)	0.196	347.0(339.5-350.5)	345.0(343.0-345.5)	0.706
Red blood cell volume distribution width (RDW-CV) (%; normal range:<14.5%)	12.00(11.70-12.43)	12.10(11.72-12.50)	11.90(11.60-12.28)	0.332	11.90(11.55-12.25)	11.90(11.80-12.20)	0.977
Increased	4(3.0%)	4(3.8%)	0(0%)	0.585	0(0%)	0(0%)	-
Mean platelet volume (MPV) (fl; normal range: 6.8-12.8)	10.00(9.50-10.50)	10.05(9.50-10.50)	9.95(9.60-10.47)	0.810	9.80(9.60-10.45)	10.10(9.90-10.40)	0.562
Infection-related biomarkers							
C-reactive protein (CRP) (mg/L; normal range 0.0–0.8)	0.10(0.10-0.98)	0.10(0.10-0.88)	0.75(0.10-1.37)	0.030	0.22(0.10-1.13)	1.26(0.92-1.80)	0.046
Increased	42(31.8%)	29(27.4%)	13(50.0%)	0.035	7(36.8%)	6(85.7%)	0.073
Interleukin-6 (pg/mL; normal range 0-5.9)	2.43(1.50-9.02)	1.50(1.50-6.01)	7.26(4.05-15.56)	<0.001	5.96(3.77-11.38)	15.56(12.73-17.50)	0.148
Increased	50(37.9%)	34(32.1%)	16(61.5%)	0.007	10(52.6%)	6(85.7%)	0.190
CT findings							
Positive findings	36(27.3%)	10(9.4%)	26(100%)	<0.001	19(100%)	7(100%)	-

Multiple macular patches and interstitial changes (MMPIC)	23(17.4%)	9(8.5%)	14(53.8%)	<0.001	10(52.6%)	4(57.1%)	-
Obvious in extra-pulmonary zone (OEZ)	14(10.6%)	3(2.8%)	11(42.3%)	<0.001	5(26.3%)	6(85.7%)	0.021
Multiple mottling and ground-glass opacity (MMGGO)	6(4.5%)	0(0%)	6(23.1%)	<0.001	3(15.8%)	3(42.9%)	0.293
Multiple infiltrative shadow (MIS)	5(0.4%)	1(0.9%)	4(15.4%)	0.005	4(21.1%)	0(0%)	0.546
Pulmonary consolidation	3(2.3%)	1(0.9%)	2(7.7%)	0.099	0(0.%)	2(28.6%)	0.065
Pleural effusion	0(0%)	0(0%)	0(0%)	-	0(0%)	0(0%)	-
Other viruses infection	6(4.6%)	1(0.9%)	5(19.2%)	0.0011	5(26.3%)	0(0%)	0.567
influenza A	3(2.3%)	1(0.9%)	2(7.7%)	-	2(10.5%)	0(0%)	-
influenza B	3(2.3%)	0(0.%)	3(11.5%)	-	3(15.8%)	0(0%)	-

Continuous variables were expressed as median with interquartile range (IQR) and compared with the Mann-Whitney U test; categorical variables were expressed as absolute (n) and relative (%) frequency and compared by χ^2 test or Fisher's exact test. A two-sided α of less than 0.05 was considered statistically significant.

Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.

COVID-19: 2019 novel coronavirus.

p-value[1]: Suspected COVID-19 pneumonia cases compared to non-suspected COVID-19 pneumonia cases.

p-value[2]: Confirmed COVID-19 pneumonia cases compared to non-confirmed COVID-19 pneumonia in suspected cases

Table4: Final selected features for model development

Groups	Final selected features			
Demographic information	Age			
Vital signs	Temperature (TEM)	Heart rate (HR)	Diastolic blood pressure (DIAS_BP)	Systolic blood pressure (SYS_BP)
Blood routine values	Basophil count (BASO#)	Platelet count (PLT)	Mean corpuscular hemoglobin content (MCH)	Eosinophil count (EO#)
	Monocyte ratio (MONO%)			
Clinical signs and symptoms on admission	Fever	Shiver	Shortness of breath	Headache
	Fatigue	Sore throat	Fever classification (FC)	
Infection-related biomarkers	Interleukin-6 (IL-6)			

Fever classification : ℃， Normal: <= 37.0; Mild fever: 37.1-38.0; Moderate fever: 38.1-39.0; Severe fever: >=39.1.

Table 5 Comparison of diagnostic performance among diagnosis aid model and infection-related biomarkers

	Diagnosis aid model	Lymphopenia (<1.0×109/L)	Elevated CRP (>0.8 mg/L)	Elevated IL-6 (>5.9 pg/mL)
AUC	**0.841**	0.407	0.613	0.599
Recall	**1.000**	0.346	0.500	0.615
Specificity	0.727	**0.840**	0.726	0.679
Precisions	**0.400**	0.160	0.273	0.321

Table S1: Comparison of different algorisms

Algorithms/Performance	Cohorts	AUC	F-1 score	Precisions	Recall	Specificity
Logistic regression with LASSO	Development cohort	**0.841**	**0.571**	**0.400**	**1.000**	0.727
	Validation cohort	**0.938**	**0.667**	**0.500**	**1.000**	0.778
logistic regression with Ridge regularization	Development cohort	0.796	0.462	0.333	0.750	0.727
	Validation cohort	0.864	0.571	0.400	**1.000**	0.667
Decision tree	Development cohort	0.580	0.286	0.333	0.250	0.909
	Validation cohort	0.500	0.000	0.000	0.000	**1.000**
Adaboost algorithms	Development cohort	0.500	0.000	0.000	0.000	**0.818**
	Validation cohort	0.790	0.222	0.333	0.167	0.926

Table S2: Demographics, baseline and clinical characteristics of 33 patients admitted to PLA General Hospital (Feb 10–Feb 26, 2020) with the epidemiological history of exposure to COVID-19 in validation cohort.

	All patients	Non-suspected COVID-19 pneumonia cases	Suspected COVID-19 pneumonia cases	p-value
Cohort (n)	33	27	6	-
Age, years (median,(IQR))	38.0(31.0-45.0)	37.0(29.5-42.0)	43.0(39.5-60.0)	0.035
Gender (n(%))				
Male	16(48.5%)	13(48.1%)	3(50.0%)	-
Female	17(51.5%)	14(51.9%)	3(50.0%)	-
Days from illness onset to first admission, (median,(IQR))	2.0(1.0-4.0)	2.0(1.0-5.5)	1.0(1.0-1.75)	0.165
Comorbidities (n(%))				
Hypertension	0(0%)	0(0%)	0(0%)	-
Diabetes	0(0%)	0(0%)	0(0%)	-
Cardiovascular disease	0(0%)	0(0%)	0(0%)	-
Chronic obstructive pulmonary disease	0(0%)	0(0%)	0(0%)	-
Malignancy	1(3.0%)	1(3.7%)	0(0%)	-
Chronic kidney disease	0(0%)	0(0%)	0(0%)	-
Chronic liver disease	0(0%)	0(0%)	0(0%)	-
Vital sign on admission				
Heart rate, n/min (median,(IQR))	100.0(92.0-109.0)	100.0(91.0-106.5)	105.5(97.5-121.0)	0.176
Diastolic blood pressure, mmHg (median,(IQR))	82.0(78.0-87.0)	83.0(78.0-88.5)	80.0(73.3-80.0)	0.175
Systolic blood pressure, mmHg (median,(IQR))	131.0(123.0-141.0)	130.0(120.0-141.5)	133.5(130.0-134.8)	0.608
Fever (n(%))	23(69.7%)	17(63.0%)	6(100%)	0.145
Highest temperature, °C	37.4(36.8-37.8)	37.3(36.8-37.7)	38.7(38.5-38.9)	<0.001

(median,(IQR))				
<37.1	10(30.3%)	10(37.0%)	0(0%)	0.1445
37.1–38.0	18(54.5%)	17(63.0%)	1(16.7%)	0.07
38.1–39.0	5(15.2%)	0(0%)	5(83.3%)	<0.001
>39.0	0(0%)	0(0%)	0(0%)	-
Other symptoms on admission (n(%))				
Cough	13(39.4%)	13(48.1%)	0(0%)	0.06
Shortness of breath	3(9.1%)	3(11.1%)	0(0%)	-
Muscle ache	8(24.2%)	6(22.2%)	2(33.3%)	0.616
Headache	9(27.3%)	6(22.2%)	3(50.0%)	0.309
Sore throat	10(30.3%)	9(33.3%)	1(16.7%)	0.64
Rhinorrhoea	1(3.0%)	1(3.7%)	0(0%)	-
Diarrhoea	5(15.2%)	5(18.5%)	0(0%)	0.556
Nausea	7(21.2%)	4(14.8%)	3(50.0%)	0.093
Vomiting	3(9.1%)	2(7.4%)	1(16.7%)	0.464
Chills	7(21.2%)	3(11.1%)	4(66.7%)	0.011
Shiver	3(9.1%)	2(7.4%)	1(16.7%)	0.464
Expectoration	8(24.2%)	8(29.6%)	0(0%)	0.296
Abdominal pain	1(3.0%)	1(3.7%)	0(0%)	-
Fatigue	9(27.3%)	7(25.9%)	2(33.3%)	-
Palpitation	1(3.0%)	1(3.7%)	0(0%)	-

Table S3: Laboratory results and CT findings of 33 patients admitted to PLA General Hospital (Feb 10–Feb 26, 2020) with the epidemiological history of exposure to COVID-19 in validation cohort..

	All patients	Non-suspected COVID-19 pneumonia cases	Suspected COVID-19 pneumonia cases	p-value
Cohort (n)	33	27	6	-
Blood routine values				
White blood cell count (WBC) (× 10^9 per L; normal range 3.5–10.0)	6.78(5.36-8.62)	6.56(5.31-7.79)	8.89(7.95-9.82)	0.025
Increased	3(9.1%)	1(3.7%)	2(33.3%)	0.078
Decreased	0(0%)	0(0%)	0(0%)	-
Red blood cell count (RBC) (× 10^{12} per L; normal range: male 4.3–5.9, female 3.9–5.2)	4.64(4.16-5.05)	4.74(4.33-5.20)	4.34(4.12-4.61)	0.08
Decreased	2(6.1%)	1(3.7%)	1(16.7%)	0.335
Hemoglobin (HGB) (g/L; normal range: male 137.0–179.0, female 116.0–155.0)	142.0(130.0-151.0)	143.0(133.0-152.5)	131.5(128.0-138.0)	0.088
Decreased	2(6.1%)	1(3.7%)	1(16.7%)	0.335
Hematocrit (HCT) (normal range: male 0.4–0.52, female 0.37–0.47)	0.41(0.37-0.44)	0.42(0.38-0.45)	0.37(0.37-0.38)	0.059
Increased	1(3.0%)	1(3.7%)	0(0%)	-
Decreased	13(39.4%)	8(29.6%)	5(83.3%)	0.025
Platelet count (PLT) (× 10^9 per L; normal range 100.0–300.0)	231.0(200.0-261.0)	231.0(201.5-276.5)	234.0(206.8-242.5)	0.834
Decreased	1(3.0%)	1(3.7%)	0(0%)	-
Lymphocyte ratio (LYMPH%) (0.2-0.4)	0.19(0.14-0.29)	0.22(0.17-0.30)	0.11(0.09-0.13)	0.001
Increased	1(3.0%)	1(3.7%)	0(0%)	-
Decreased	18(54.5%)	12(44.4%)	6(100.0%)	0.021
Lymphocyte count (LYMPH#) (× 10^9 per L; normal range 1.0–4.0)	1.36(1.01-1.87)	1.46(1.21-1.96)	1.00(0.98-1.01)	0.005
Increased	0(0%)	0(0%)	0(0%)	-

Decreased	7(21.2%)	4(14.8%)	3(50.0%)	0.093
Neutrophil ratio (NEUT%) (0.5-0.7)	0.73(0.59-0.78)	0.71(0.58-0.76)	0.78(0.75-0.85)	0.057
Increased	20(60.6%)	15(55.6%)	5(83.8%)	0.364
Decreased	3(9.1%)	3(11.1%)	0(0%)	-
Neutrophil count (NEUT#) (× 10^9 per L; normal range 2.0–7.0)	4.76(3.07-7.01)	4.20(3.02-5.78)	7.29(6.07-8.15)	0.031
Increased	9(27.3%)	5(18.5%)	4(66.7%)	0.034
Decreased	0(0%)	0(0%)	0(0%)	-
Eosinophil ratio (EO%) (0.01-0.05)	0.008(0.003-0.025)	0.008(0.004-0.028)	0.001(0.0003-0.014)	0.129
Increased	4(12.1%)	3(11.1%)	1(16.7%)	-
Eosinophil count (EO#) (× 10^9 per L; normal range 0.05–0.3)	0.05(0.02-0.16)	0.05(0.03-0.16)	0.01(0.003-0.11)	0.146
Increased	4(12.1%)	3(11.1%)	1(16.7%)	-
Monocyte ratio (MONO%) (0.03-0.08)	0.06(0.04-0.08)	0.06(0.04-0.07)	0.07(0.06-0.10)	0.154
Increased	9(27.3%)	6(22.2%)	3(50.0%)	0.309
Monocyte count (MONO#) (× 10^9 per L; normal range 0.12–0.8)	0.38(0.31-0.46)	0.36(0.29-0.44)	0.61(0.55-0.77)	<0.001
Increased	2(6.1%)	0(0%)	2(33.3%)	0.028
Basophil ratio (BASO%) (0-0.01)	0.003(0.002-0.006)	0.003(0.002-0.007)	0.003(0.001-0.004)	0.422
Increased	2(6.1%)	2(7.4%)	0(0%)	-
Basophil count (BASO#) (× 10^9 per L; normal range 0–0.1)	0.02(0.01-0.04)	0.02(0.01-0.04)	0.02(0.01-0.04)	0.91
Increased	0(0%)	0(0%)	0(0%)	-
Mean corpuscular volume (MCV) (fl; normal range: 80-100)	87.10(85.60-89.40)	87.10(85.20-89.65)	87.45(85.80-88.72)	0.944
Mean corpuscular hemoglobin content (MCH) (pg; normal range: 27-34)	30.50(29.50-31.10)	29.90(29.45-31.05)	30.80(30.52-31.90)	0.315
Mean corpuscular hemoglobin concentration (MCHC) (g/L; normal range: 320-360)	348.0(340.0-354.0)	347.0(338.0-353.0)	353.5(347.0-360.0)	0.215

Red blood cell volume distribution width (RDW-CV) (%; normal range:<14.5%)	12.00(11.80-12.70)	12.00(11.80-12.60)	12.25(11.60-14.03)	0.623
Increased	2(6.1%)	0(0%)	2(33.3%)	0.028
Mean platelet volume (MPV) (fl; normal range: 6.8-12.8)	9.90(9.60-10.90)	9.90(9.60-10.90)	10.10(9.68-10.75)	0.743
Infection-related biomarkers				
C-reactive protein (CRP) (mg/L; normal range 0.0–5.0)	0.10(0.10-0.95)	0.10(0.10-0.19)	7.56(2.55-8.41)	<0.001
Increased	9(27.3%)	4(14.8%)	5(83.3%)	0.003
Interleukin-6 (pg/mL; normal range 0.5-9)	1.50(1.50-20.54)	1.50(1.50-1.59)	26.79(21.94-79.94)	<0.001
Increased	10(30.3%)	4(14.8%)	6(100.0%)	<0.001
CT findings				
Positive findings	10(30.3%)	4(14.8%)	6(100%)	<0.001
Multiple macular patches and interstitial changes (MMPIC)	6(18.2%)	4(14.8%)	2(33.3%)	0.295
Obvious in extra-pulmonary zone (OEZ)	0(0%)	0(0%)	0(0%)	-
Multiple mottling and ground-glass opacity (MMGGO)	1(3.0%)	0(0%)	1(16.7%)	0.182
Multiple infiltrative shadow (MIS)	4(12.1%)	0(0%)	4(100.0%)	<0.001
Pulmonary consolidation	3(9.1%)	0(0%)	3(50.0%)	0.004
Pleural effusion	1(3.0%)	0(0%)	1(16.7%)	0.182
Other viruses infection	0(0.%)	0(0.%)	0(0.%)	-
influenza A	0(0.%)	0(0.%)	0(0.%)	-
influenza B	0(0.%)	0(0.%)	0(0.%)	-

Continuous variables were expressed as median with interquartile range (IQR) and compared with the Mann-Whitney U test; categorical variables were expressed as absolute (n) and relative (%) frequency and compared by χ^2 test or Fisher's exact test. A two-sided α of less than 0.05 was considered statistically significant.

Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.

COVID-19: 2019 novel coronavirus.

Table S4: Candidate features and univariable association with S-COVID-19-P

Candidate features	Association and weight
Age	0.1115441
IL-6	0.087957222
SYS_BP	0.086830321
MONO%	0.067880575
Fever_class	0.056941687
Headache	0.052507708
DIAS_BP	0.039076925
HR	0.035209084
MCH	0.01938761
TEM	0.0181481
Fever	0.014057313
Sore throat	0.010200146
WBC	0
LYMPH%	0
LYMPH#	0
Chills	0
MONO#	0
EO%	0
BASO%	0
NEUT%	0
HCT	0
MCV	0
MCHC	0
RDW-CV	0
MPV	0
CRP	0
NEUT#	0
DOA	0
Rhinorrhoea	0
Muscle ache	0
HGB	0

Gender	0
Diarrhoea	0
Cough	0
Palpitation	0
RBC	0
Abdominal pain	0
Vomiting	0
Nausea	0
Expectoration	0
BASO#	-0.004355896
EO#	-0.004700708
Fatigue	-0.00472086
Shiver	-0.006379747
Shortness of breath	-0.006658011
PLT	-0.048908566

Figure legends

Figure 1

The study overview of the Artificial Intelligence Assisted Diagnosis Aid System for Suspected COVID-19 Pneumonia, including (1) Development and validation cohorts, (2) Outcomes, (3) Diagnosis aid model and candidate features, (4) Features selection and diagnosis aid model development, (5) Model validation, and (6) Feature Importance ranking and comparison of diagnostic performance between model and biomarker.

S-COVID-19-P= suspected COVID-19 pneumonia,

Figure 2

Features Importance Ranking. Feature importance was performed in the development cohort. The associated coefficient weights correspond to the logistic regression model were used for identifying and ranking feature importance.

Interleukin-6 (IL-6), Systolic blood pressure (SYS_BP), Monocyte ratio (MONO%), Fever classification (℃，Normal: <= 37.0; mild fever: 37.1-38.0; moderate fever: 38.1-39.0; severe fever: >=39.1), platelet count (PLT), diastolic blood pressure (DIAS_BP), Heart rate (HR), Mean corpuscular hemoglobin content (MCH), Temperature (TEM), Eosinophil count (EO#), Basophil count (BASO#).

Figure 3

Flow chart for improved S-COVID-19-P early identification strategies in adult fever clinics in PLAGH, China.

CRP= C-reactive protein, IL-6= Interleukin-6.

(1) Development and validation cohorts

Model development cohort :
Patients from Jan 14 to Feb 9, 2020

Model validation cohort :
Patients from Feb 10 to Feb 26, 2020

(2) Outcomes

- **The primary outcome** is the development and validation of a diagnosis aid model for S-COVID-19-P early identification on admission.
- **The secondary outcome** is the comparison of the diagnostic performance between diagnosis aid model and infection-related biomarkers on admission.

(3) Diagnosis aid model and candidate features

2 variables of demographic information

4 variables of vital signs and 17 variables of clinical signs and symptoms

20 variables of blood routine values and 2 infection-related biomarkers

1 other variable

(4) Features selection and diagnosis aid model development

◆ **Lasso regression:**
Effectively selecting important predictors and improving the interpretability of the model

Final selected features for model development
1 variables of demographic information
4 variables of vital signs
5 variables of blood routine values
7 variables of clinical signs and symptoms
1 infection-related biomarkers

(5) Model validation

The model validation was also performed in python based on validation cohort .

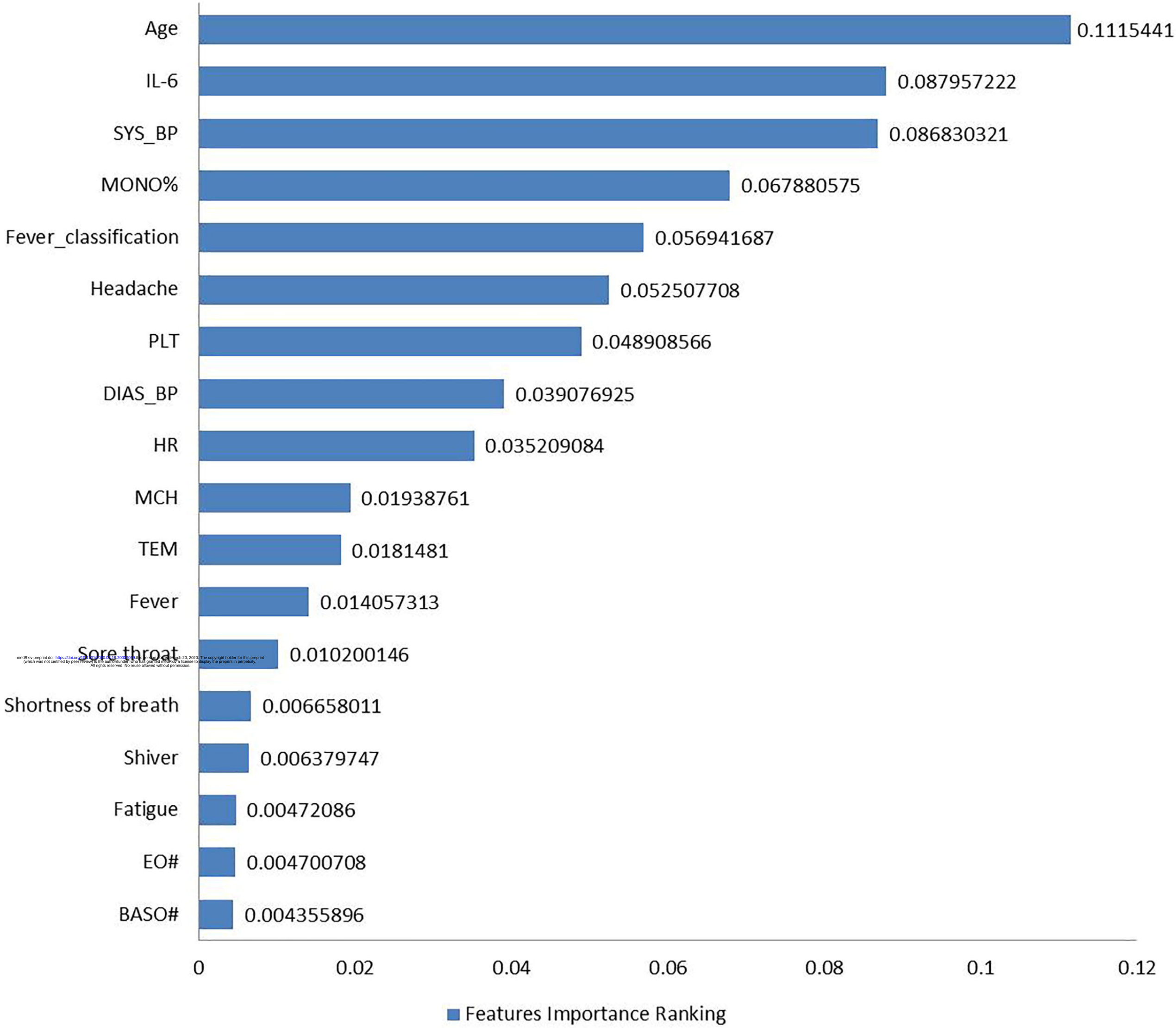
(6) Feature Importance ranking and comparison of diagnostic performance between model and biomarkers

- AUC
- F-1 score
- Precision
- Recall

◆ **Lymphopenia (<1.0×109/L)**

◆ **Elevated CRP (>0.8 mg/L)**

◆ **Elevated IL-6 (>5.9 pg/mL)**



Fever, sore throat or cough

Hypoxia (SPO2 <95%)

Yes

No

Blood routine, CRP, IL-6, influenza virus (A+B)

Negative

Epidemiological history

Positive

Yes

No

Suspected COVID-19 pneumonia Diagnosis Aid System

Negative

Positive

- Home quarantine
- Regular treatment
- Continuous fever, sore throat or cough monitoring

No relief

Negative

Chest CT scan

Positive

Suspected COVID-19 Pneumonia

- Isolated observation or admission to an isolation ward
- Regular treatment

- COVID-19 laboratory test
- ……