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A meta-analysis and systematic review of diagnostic test accuracy found that procalcitonin has a good track record of accurately predicting critical medical conditions and survival in COVID-19 patients.

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ABSTRACT

According to multiple findings, variations in inflammatory biomarkers and white blood cell counts are associated with the course of coronavirus disease 2019 (COVID-19) and can be used as predictive biomarkers. A thorough study and meta-analysis of diagnostic test accuracy (DTA) are advised before adding a component as a diagnostic/prognostic biomarker. We conducted a DTA meta-analysis in order to assess the accuracy of white blood cell counts and inflammatory biomarkers for the prognosis of COVID-19 patient outcomes for the first time.

We looked through the databases of Web of Sciences, Scopus, and MEDLINE/PubMed until August 24, 2020, in an effort to find relevant materials. Using 2x2 tables, bivariate/hierarchical models were used to calculate the summary points and lines of the included research. Critical state and death were taken into account as results.

This study included 13387 patients in total from 28 studies. The inclusion criteria were met by six biomarkers that included leukocytosis, neutrophilia, lymphopenia, elevated C-reactive protein, procalcitonin (PCT), and ferritin. The PCT was the only useful prognostic biomarker for both critical condition and mortality, according to an analysis of the area under the curve (AUCHSROC) (AUCHSROC=0.80 for both conditions). The prognosis of critical condition had a pooled-diagnostic odds ratio of 6.78 (95% CI, 3.65-12.61), and the mortality risk was 13.21 (95% CI, 3.95-44.19). For both circumstances, other biomarkers' accuracies were insufficient (AUCHSROC< 0.80).

Only PCT exhibits good accuracy for prognosticating both critical condition and mortality among the evaluated biomarkers.

It can be regarded as a single prognostic biomarker for unfavourable outcomes in COVID-19. Furthermore, when it comes to death prognosis, PCT is more accurate than critical conditions.

Keywords : *COVID-19; Procalcitonin; Prognosis; Sensitivity and specificity*

INTRODUCTION

In December 2019, Wuhan, the Chinese province of Hubei's capital, reported a number of pneumonia cases with unclear causes. Chinese researchers were able to identify a novel coronavirus from these patients in January 2020; this virus was initially identified as 2019 novel coronaviruses (2019-nCoV) and later dubbed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Ultimately, the World Health Organisation (WHO) dubbed this infectious disease coronavirus disease 2019 (COVID-19) in February 2020. Early in 2020, this virus breaks out as a pandemic, with cases of infection being reported in nearly every nation on earth.

Patients with COVID-19 can have a variety of clinical outcomes, ranging from minimal symptoms to a critical phase that requires hospitalisation in an intensive care unit (ICU), shock, or organ failure and/or require mechanical ventilation, which could ultimately be fatal. Because there aren't enough medical

resources to treat patients in a pandemic, prognostic markers are crucial to these patients' care.

Numerous nations were forced to deal with this predicament due to the pandemic, especially developing nations where access to sophisticated medical testing and equipment is restricted. However, even in cases where they are available, running non-routine laboratory tests—which frequently need time and skilled operators—is impractical due to the high number of infected individuals. Therefore, it would appear necessary to identify common laboratory tests as prognostic biomarkers that can be performed quickly and are accessible in all healthcare facilities.There is a close relationship between viral infections and the human immune system. The degree of the virus-induced illness is thought to be significantly influenced by immune system dysregulation.

Accordingly, since the start of the infection, multiple publications have found variations in inflammatory and white blood cell levels.Acute phase reactants are among the biomarkers that are linked to the severity of the disease as it progresses. Numerous investigations have demonstrated a strong relationship between haematological changes, such as leukocytosis, illness severity, lymphopenia, and neutrophilia. Procalcitonin (PCT) and C-reactive protein (CRP) are the most commonly used and significant inflammatory biomarkers for the diagnosis of pneumonia. They positively correlate with the degree of inflammation and are unaffected by age, sex, physical condition, or co-morbidities of the patient that may cause clinical ambiguity, such as acute heart failure and chronic obstructive pulmonary disease. These tests offer a significant deal of potential as predictive indicators for critical condition and mortality in COVID-19 patients, according to the evidence listed above. But only tests with a high accuracy rate of differentiating between a positive and a negative trait can be used.

Diagnostic test accuracy (DTA) systematic review and meta-analysis are advised in order to determine the accuracy of a diagnostic or prognostic laboratory test. Studies of this kind are used to introduce biomarkers for prognostic and diagnostic purposes. However, there hasn't been a DTA study to date that introduces relevant laboratory tests for predicting mortality and critical condition in COVID-19 patients. In order to ascertain the accuracy of white blood cell counts and inflammatory biomarkers, such as leukocytosis, neutrophilia, eosinopenia, lymphopenia, elevated levels of CRP, PCT, ferritin, and serum amyloid-A (SAA), in a different outcome of COVID-19 patients, a DTA systematic review and metaanalysis was carried out for the first time.

MATERIALS AND METHODS

Search Strategy

The recommended reporting elements for systematic reviews and meta-analyses (PRISMA) statement guided the search approach and article review. We conducted a thorough search on large databases, including MEDLINE/PubMed, Scopus, and Web of Sciences (WOS), until August 24, 2020, in order to locate relevant papers without regard to language limitations. The search terms "Novel coronavirus" or "Novel coronavirus 2019" or "2019 nCoV" or "COVID-19" or "SARSCoV-2" were utilised. Additionally, "severity," "critical," "ICU," "death," "Survivors," "laboratory tests," "inflammation," "white blood cell," "neutrophil," "lymphocyte," "procalcitonin," "C-reactive protein," "ferritin," "eosinophil," or "serum amyloid-A."

To find missing studies, the reference lists of each chosen paper as well as pertinent narrative and systematic reviews on the subject were manually examined. We imported records into Thomson Reuters EndNote (Version X9) in order to remove the duplicate papers.

Study Selection

One of the writers evaluated the titles and abstracts of all the records that were obtained. Based on the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)," different severity levels of COVID-19 patients were divided into 4 groups as follows:

1) Mild: the patient's clinical symptoms were non-existent, and there was no evidence of pneumonia on imaging;

2) Moderate: patients exhibit fever and respiratory symptoms along with radiological findings of pneumonia;

3) Severe: patients who satisfied one of the following criteria: respiratory distress (respiration rate ≥ 30 times/min), oxygen saturation (SpO2) ≤ 93% in the resting state, arterial partial pressure of O2, and the fraction of inspired oxygen (PaO2/FiO2) ratio ≤ 300 mmHg;

4) Critical: patients experience respiratory failure necessitating mechanical ventilation, shock, organ failure, and ICU admission.

The results of "on admission" laboratory tests were the only ones gathered for this study's meta-analysis. The inclusion criteria for this study were as follows: 1) all patients had a diagnosis of SARS-CoV-2 by real-time PCR; 2) clinical characteristics and laboratory test results were categorised according to whether patients were survivors or not; or 3) the type and quantity of abnormal laboratory test results (changes from the local reference range) were evident for each group of studies; 4) at least four studies were required to be found for each laboratory parame-

ter; and 5) the biomarkers' assay methods are quantitative.
Studies that satisfied the following requirements were not accepted: 1) Patients were diagnosed with SARS-CoV-2 infection through non-real-time PCR technique; 2) duplicate publications; 3) reviews, meta-analyses, and case reports; 4) studies that were unable to clearly distinguish between the various groups mentioned; 5) studies that evaluated a single group, such as children or non-survivor patients; 6) studies that were conducted on a specific patient group, such as pregnant women; and 7) qualitative method for evaluating serum biomarkers.

Quality Assessment and Sensitivity Analysis

For the purpose of evaluating the calibre of included research in a systematic review on prognostic test accuracy, no suggested instrument exists.Thirteen As a result, we employed the Newcastle–Ottawa Scale (NOS) instrument, which is suitable for analytical research, such as cohort studies. The methodological quality of the included studies was evaluated using NOS, with a maximum score of 9.15 Three main categories make up this scale: "Selection," "Comparability," and "Outcome." No validation research has provided a cut-off point for classifying studies with "low" bias risk; yet, some studies classify low bias risk studies as having an overall point ≥6, in which case they are classified as "good quality." Studies with an overall point count of 3-5 are classified as "moderate quality," while those with a count of <3 will be classified as "poor" quality.16 As a result, we classified using the same system.Research of "moderate" or "poor" quality limited the scope of the analyses.

Data Extraction

To create 2x2 contingency tables, the data from the included studies were retrieved and computed. Initially, the laboratory tests in all included studies were evaluated, and the proportion or number of results that were outside of the local reference ranges was taken out. Next, for every test that was acquired, the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) of each test were determined.

Data Synthesis and Statistical Analysis

We created separate 2x2 contingency tables for every test based on the retrieved data. For every test, the following metrics were determined: sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR). We took into consideration Pooled-Sensitivity, Pooled-Specificity, Pooled-LR+, Pooled-LR-, and Pooled-DOR for a meta-analysis report of summary points. A threshold effect might influence how these summary points are pooled separately. In order to get around this restriction, we employed a bivariate model that uses a random effect approach to account for the threshold effect as well as the correlation between sensitivity and specificity and between-study heterogeneity.
The area under the curve (AUCHSROC), which is a global measure of test performance, was computed by trapezoidal integration after the hierarchical summary receiver operating characteristic (HSROC) was drawn.The diagnostic (prognostic) accuracy of every laboratory test was indicated by the 11 AUCHSROC value, which has a value range of 0.5 to 1. AUCHSROC is the ideal biomarker for differentiating between positive and negative traits when its value is 1, whereas a value of 0.5 indicates a non-discriminating biomarker. Diagnostic (prognostic) accuracy and AUCHSROC value are correlated in the following ways: 0.90-1 = excellent; 0.80-0.89 = good; 0.70-0.79 = fair; 0.60-0.69 = bad; and 0.50-0.59 = fail.17 We only take into consideration "good" or "excellent" values in the current investigation.(AUCHSROC≥0.80) as clinically useful biomarkers for COVID-19 patient mortality and critical condition prognosis.18 Every biomarker was completed and compiled for reporting, taking into account the 95% confidence interval (95% CI). Stata (Stata Corporation, College Station, TX, USA, version 12.0) and the web-based R software programme, MetaDTA, were used for all statistical analysis.
We used the Moses-Shapiro-Littenberg metaregression method with Meta-Disk 1.4 software to identify confounding variables, such as age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease and other factors. Every report in this meta-analysis was regarded as statistically significant when $p<0.05$.

RESULTS

Study Selection and Quality Assessment

Out of the 3079 initial records, 1367 research were eliminated after the title and abstract were screened, and 1052 studies were eliminated for duplication. At last, 660 studies underwent a full-text evaluation. Three main factors led to the exclusion of the majority of the studies: 1) The quantity or percentage of laboratory test results that were outside of the reference ranges was not disclosed; 2) Critical patients were not segregated from severe type patients; and 3) certain studies only provided data on a subset of patients (for instance, some studies published data on patients who died). In the end, 28 studies met the requirements for qualifying (Table 1 and Figure 1). Of the 28 investigations, 14 evaluated the critical and non-critical outcomes of the laboratory data.Twelve studies and 20–33 evaluated the mortality outcome from the lab.34–45 Two investi-

gations revealed concurrently obtained laboratory results for both outcomes.46, 47 In total, 10388 patients were divided into the survivor/non-survivor group and 2999 patients into the critical/non-critical group. All included studies were rated as "high" quality and obtained a NOS score of at least eight (Table 1). Therefore, no research restriction based on bias risk was carried out. Every study received the maximum number of points in the "Selection" and "Outcome" categories, and variations in point totals amongst studies were associated with the "Comparability" category.

Prognostic Accuracy of Laboratory Tests

SAA and eosinopenia failed to meet the inclusion requirements. Except for ferritin, all other biomarkers under consideration satisfied inclusion criteria in both groups. Ferritin was eligible for assessment in the survivor/non-survivor group even though it did not match the inclusion criteria in the critical/non-critical group. Table 2 and Figure 2 show that of the six evaluated biomarkers, only PCT exhibited "good" accuracy for both critical condition and death prognosis (AUCHSROC=0.80 for both situations). These findings indicate that PCT's prognostic accuracy for both diseases is same. Nevertheless, according to another accuracy summary point, pooled-DOR, PCT is more accurate in predicting mortality than critical condition (pooled-DOR for mortality is 13.21 (95% CI, 3.95-44.19) and 6.78 (95% CI, 3.65-12.61) for critical condition (Table 2). For the prognosis of critical condition, the pooled-sensitivity of PCT was 0.54 (95% CI, 0.29-0.77) and the pooled-specificity was 0.84 (95% CI, 0.76-0.90). Then, for the prognosis of mortality, the pooled-sensitivity and pooled-specificity were, respectively, 0.89 (95% CI, 0.24-0.99) and 0.60 (95% CI, 0.11-0.94) (Figure 2). Leukocytosis and elevated CRP levels had varying accuracy for each group, while neutrophilia and lymphopenia had "fair" accuracy for the prognosis of both critical condition and mortality. For the prognosis of critical condition and mortality, leukocytosis had "fair" and "fail" accuracy, respectively. Additionally, the elevated CRP level had accuracy ratings of "fair" and "fail" for those conditions.

Meta-regression Analysis

In relation to PCT, a meta-regression analysis was carried out to identify potentially confounding variables, such as age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease (Table 3), since the forest plot of sensitivity and specificity suggested heterogeneity. This analysis did not show any source of heterogeneity across covariates in the critical/non-critical group (p>0.05). However, meta-regression analysis revealed that chorionic respiratory illness (p=0.034) contributed to a source of heterogeneity in the survivor/non-survivor group.

DISCUSSION

Numerous research conducted since this infection first surfaced have shown that immune cell numbers and alterations in inflammatory biomarkers are closely correlated with the severity of the illness.5,8 Nevertheless, there was no information available regarding their accuracy for the prediction of various outcomes prior to the current investigation. Therefore, we attempted to ascertain the accuracy of white blood cell counts and inflammatory biomarkers, which have predictive utility for critical condition and mortality of COVID-19 patients, in this DTA meta-analysis for the first time. According to our findings, PCT is the only inflammatory biomarker and change in white blood cell counts that has adequate accuracy for predicting unfavourable outcomes, such as critical condition and death.

Using the NOS tool, we eventually located 28 papers with "high" quality, all of which met our inclusion and search criteria. We did not conduct the study restriction for our analyses since there was little chance of bias for any of the included studies. 2999 individuals were assessed for critical and non-critical outcomes and 10388 patients for death outcomes from these trials.

This is the first report that has assessed this many patients and produced a different conclusion. Useful information on the total white blood cell count, neutrophil count, lymphocyte count, serum CRP level, and PCT in both groups could be extracted. However, the ferritin data was unable to meet the requirements for inclusion in the crucial outcome group.

Moreover, neither SAA nor eosinopenia satisfied the requirements for inclusion in either group. Important positive acute phase reactants in infectious diseases are ferritin, PCT, and CRP.48 Certain pieces of evidence suggest that elevated serum levels of ferritin and CRP are linked to the severity of the disease progression in COVID-19 patients.49,50 Nevertheless, based on our findings, these two biomarkers don't have enough precision for the critical condition diagnosis and death. The levels of these two biomarkers were revealed by the evaluated studies' results in our metaanalysis. elevated in the majority of patients with SARS-CoV-2 infection Various results produce high TP and FP values in Every study that exhibits low sensitivity and high precision. Consequently, the precision of elevated levels of Ferritin and CRP both had inadequate results (AUCHSROC< 0.80).

On the other hand, our findings showed that a higher level of PCT has "good" accuracy for predicting death and critical situ-

ations (AUCHSROC=0.80 for both). In contrast to critical situations, PCT has a higher accuracy for the prognosis of mortality based on its pooled-DOR (Table 2). PCT levels have been demonstrated to rise in COVID-19 patients, and this is more common in those with more severe illness. PCT level has a strong positive link with severity progression in SARS-CoV-2 infected patients, according to the results of two metaanalyses8,49 and has a lot of potential as a predictive biomarker for illness outcome, however its accuracy is unknown.PCT is recognised as a peptide precursor of the hormone calcitonin, which is mostly generated by thyroid cells. Pro-inflammatory cytokines such as TNF-α and IL-6 cause an increase in the serum level of PCT when bacterial infections occur. However, research has indicated that viral or non-infectious inflammations do not cause a significant increase in the serum level of PCT. As a result, patients with more severe SARS-CoV-2 infections who either had bacterial comorbidities or greater levels of pro-inflammatory cytokines tend to exhibit elevations in PCT levels. Prior research findings indicate that alterations in the white blood cell population are a significant factor influencing the severity and prognosis of individuals infected with SARS-CoV-2.5, 8, 49 Increased neutrophil count and total white blood cell counts have been shown to be significantly correlated with the severity of the disease.

Bacterial or fungal comorbidity in a large proportion of SARS-CoV-2 infected patients with poor outcomes is one of the hypothesised explanations for this increase.23–36 Nevertheless, our findings indicate that total white blood cells and neutrophil count are not accurate enough to predict critical condition and death (AUCHSROC<0.80). Lymphoma is another significant biomarker in COVID-19 patients.5,8 In essence, lymphocytes use a rise in viral infection as a marker for the removal of viral pathogens. On the other hand, a drop in lymphocyte count in SARS-CoV-2 infected patients is significant because our comprehension of its mechanism could help us develop a successful treatment plan for COVID-19 patients. Previous research has led to the development of certain theories to explain this occurrence. First, lymphocytes can become directly infected with the virus and die as a result of the expression of SARS-CoV-2 receptors and angiotensin-converting enzyme-2 (ACE-2).51The second theory postulates that COVID-19 patients have higher levels of lymphocyte apoptosis, which is brought on by pro- and inflammatory cytokines.52 Other theories suggest that the destruction of lymphatic organs or lactic acidosis that occurs after COVID-19 could result in a decrease in the number of lymphocytes.36,53 It is still unknown how precisely COVID-19 patients' lymphopenia occurs and how it relates to the severity of the illness. Despite the fact that there is a strong correlation between a lower count and a more severe illness,5,8, our findings showed that lymphopenia has a "fair" accuracy rate for predicting death and critical condition (AUCHSROC=0.75 and 0.71, respectively). In each trial, lymphopenia—a frequent consequence in patients infected with SARS-CoV-2—leads to high TP and FP levels, which are indicative of high sensitivity, low specificity, and inadequate accuracy. We conducted meta-regression analysis to identify possibly confounding factors, such as age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease, because the forest plots of sensitivity and specificity indicated heterogeneity (Table 3). While chorioni respiratory disease contributed to the variability in the survivor/non-survivor group, meta-regression was unable to identify any component that explained the heterogeneity in the critical/non-critical groups. Other tests, such as the serum amyloid-A level and eosinophil count, were unable to achieve the inclusion requirements. It appears that additional research is required to evaluate the predictive accuracy of these tests because of their significant function in the outcomes that were demonstrated to be prognostic in certain studies. Some limitations should be noted in the interim, despite the fact that we conducted this meta-analysis on a large sample size (2999 COVID-19 patients in the critical outcome and 10388 patients in the mortality outcome) and different countries with diverse patient racial backgrounds, which were the most significant limitations of previous meta-analyses. Initially, the majority of the research that were included used retrospective cohorts, which limit their capacity to demonstrate deduce definite causality. Secondly, every potential Cohort studies from China have certain drawbacks. for assessing different patient demographics in different nations. Our findings concluded that PCT has "good" accuracy for predicting critical conditions and death result COVID-19 infected individuals.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus disease 2019–COVID-19. Clin Microbiol Rev. 2020;33(4):1–48.

2. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J I fect Public Health. 2020;13(5):667–73.

3. Nourizadeh M, Rasaee MJ, Moin M. COVID-19 Pandemic: A Big Challenge in Iran and the World. Iran J Allergy Asthma Immunol. 2020;19(S1):1–2.

4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Oca-po E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

5. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis.Med Clin (Barc). 2020;155(4):143–51.

6. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131–4.

7. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020;58(7):1063–9.

8. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-inflammatory parameters in COVID-19 cases: Asystematic review and meta-analysis. Front Med. 2020;7:1–14.

9. Gatsonis C, Paliwal P. Meta-analysis of diagnostic and screening test accuracy evaluations: methodologic primer. Am J Roentgenol. 2006;187(2):271–81.

10. Šimundić A-M. Measures of diagnostic accuracy: basic definitions. Ejifcc. 2009;19(4):203.

11. Lee J, Kim KW, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part II. Statistical methods of meta-analysis. Korean J Radiol. 2015;16(6):1188–96.

12. Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: A practical review for clinical researchers– part I. general guidance and tips. Korean J Radiol.2015;16(6):1175–87.

13. Mathes T, Pieper D. An algorithm for the classification of study designs to assess diagnostic, prognostic and predictive test accuracy in systematic reviews. Syst Rev. 2019;8(1):226.

14. Zhao J-Y, Yan J-Y, Qu J-M. Interpretations of "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)". Chin Med J (Engl). 2020;133(11):1347–9.

15. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2–10.

16. Sabbagh HJ, Hassan MHA, Innes NPT, Elkodary HM, Little J, Mossey PA. Passive smoking in the etiology of non-syndromic orofacial clefts: A systematic review and meta-analysis. PLoS One. 2015;10(3):1–21.

17. Safari S, Baratloo A, Elfil M, Negida A. Evidence-based emergency medicine; part 5 receiver operating curve and area under the curve. Emergency. 2016;4(2):111.

18. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315–6.

19. Freeman SC, Kerby CR, Patel A, Cooper NJ, Quinn T, Sutton AJ. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test accuracy studies: MetaDTA. BMC Med Res Methodol. 2019;19(1):81.

20. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020;5(10):e137799.

21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan,China. Jama. 2020;323(11):1061–9.

22. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB,

et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):E131–4.

23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

24. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364–74.

25. Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine. 2020;21:100331.

26. Li H, Xiang X, Ren H, Xu L, Zhao L, Chen X, et al. Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis. J Infect. 2020;80(6):646–55.

27. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol. 2020;43(7):796–802.

28. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372–4.

29. Chan SSW, Christopher D, Tan GB, Chong VCL, Fan BE, Lin CY, et al. Peripheral lymphocyte subset alterations in COVID-19 patients. Int J Lab Hematol. 2020;1–5.

30. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: A multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201(11):1380–8.