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RESEARCH ARTICLE

PREDICTING THE SEVERITY OF COVID-19 INFECTION THROUGH THE CONCENTRATION OF C-REACTIVE PROTEIN AS A PRIMARY INFLAMMATORY MARKER

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ABSTRACT

Previous literature studies have reported that clinical presentation and pathology of the novel coronavirus resembled SARS and MERS in regards to the elevated levels of Interleukin-6, through cellular transcription. This study aims to explore the clinical value of C-reactive Protein as a primary inflammatory marker to assess the severity of the disease. Meta-analysis is performed to investigate the association of the clinical manifestation of CRP[1] with disease aggravation in a collective of published clinical findings and evaluate the CRP content as a potential biomarker to predict disease severity. The recent literature databases utilized to study the epidemiology of the SARS-CoV-2 strain and CRP accumulation include PubMed, The Lancet, NCBI[2], Researchgate, and Medscape. In this retrospective cohort study, a clinical index is constructed with the clinical characteristics of 120 RT-PCR[3] confirmed positive patients enrolled from December to February 2020 in China, South Korea, United Kingdom, and France. Calculations for relative weight values of each study and statistical analysis were performed using the inverse variance method. As unabated cytokine storms have correlated with greater risks of chronic lung diseases, CRP blood test as a type of inflammatory marker may serve as a measure of detecting IL-6[4] content in a patient displaying symptoms of COVID-19. Through this study, a definite association between inflammation and severity of Coronavirus was recognized and evaluated. Hence, this study proposes inflammatory markers such as CRP blood test as a guideline for optimal allocation of antibody test kits in the United States where a dearth of these resources exist.

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INTRODUCTION

The emergence of the novel coronavirus disease 2019 (SARS-CoV-2) began in December 2019 (1). Epidemiological evidence traced its origin to the Huanan Seafood wholesale market, and it concluded that the complete gene sequence of the virus showed a significant similarity to those identified in bats (2). The virus was subsequently renamed from 2019-nCov to SARS-CoV-2 due to the high correspondence to the coronavirus of severe acute respiratory syndrome (SARS-CoV), with which it displayed a correspondence of 79% with its sequence (3). Researchers discovered a strong affinity between the disease and human respiratory receptors, implying that it is a global public health threat (4). It displays multiple clinical manifestations, including the common cold, pneumonia, acute respiratory distress syndrome, asymptomatic progression, and even death (5). Since January 2020, the rate of infection has escalated, and the virus has expanded rapidly around the globe, with worldwide cases having surpassed 20 million (6). On March 11, 2020, the World Health Organization declared the disease a pandemic as cases were reported by approximately 195 countries (7). Despite the surge in numbers, many regions of the world are unable to perform mass-testing, due to a lack of testing kits (8). As such, alternative methods of testing are necessary to optimize the allocation of antibody testing kits (9). In countries like the United States, testing has been provided only to severely symptomatic individuals (10). Coronavirus disease 2019 is a novel infectious disease for which there is no currently validated antiviral treatment (11). Though there exist ongoing clinical trials of traditional and western medicines, it is necessary to detect specific clinical characteristics and abnormalities in the patients of the virus (12). C-reactive protein displays elevated expression specifically during inflammatory conditions, such as cardiovascular diseases, rheumatoid arthritis, and infection (13).

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The plasma concentration of C-Reactive Protein, as an acute-phase protein, deviates by a minimum of 25% during inflammatory disorders (13). CRP[1] has been traditionally utilized as a biomarker of cardiovascular conditions and infection as it holds a significant role in inflammatory processes and host responses to infection, including apoptosis, complement pathway, phagocytosis, and the production of cytokines, particularly interleukin-6 (13). Various studies have reported the presence of cytokine storms in COVID-19 infections, which releases proteins, such as Interleukin-6, Interleukin-1, Interleukin-12, and other inflammatory markers (14). C-reactive protein (CRP) levels can be used in the early diagnosis of inflammation and pneumonia, and patients presenting with severe pneumonia have possessed high CRP levels (15). The correlation between CRP level and disease severity is investigated to provide reference for clinical treatment (16). As higher inflammation is often associated with a greater production of pro-inflammatory markers, this research suggests the utilization of C-reactive protein blood tests as a preliminary testing method for the Coronavirus disease (19). In 2016, Zhou and Yang postulated that a type of "cytokine storm" contributed to the high mortality rates associated with prior viral epidemics, including the 1918 H1N1 Spanish flu, 1957 H2N2 Asian influenza, and 1968 H3N2 Hong Kong influenza (17).

It has been reported that elevated levels of CRP can serve as a predictive marker in determining which patients with mild symptoms of the coronavirus disease will progress to a severe case (18). Researchers from the Open Forum Infectious Diseases conducted a study to prove high CRP levels as an indicator of disease aggravation using clinical data from 209 adult RT-PCR[2] patients enrolled in a public health treatment center in Changsha, China, from January 17, 2020, to February 20, 2020 (19). The study concludes that as the levels of CRP elevated before the disease progressed, it could potentially "be a valuable marker to predict the possibility of aggravation of non-severe COVID-19 (in) patients" which can serve as a preliminary distinction within non-severe patients and can allow healthcare workers identify these patients at an early stage for early treatment (20). As such, this research proposes the utilization of C-Reactive Protein inflammatory markers as a guideline for the optimal allocation of COVID-19 antibody testing kits. With the aforementioned trends between infected individuals and CRP content, this study compiles sources and evaluates systematic reviews from various databases to conduct a meta-analysis.

METHODS

Search Criteria: The evaluation of the utilized databases and studies was processed through the Systematic Reviews and Meta-Analyses: The PRISMA Statement. The Lancet Infectious Diseases, Pubmed, ScienceDirect, NCBI, MedRxIV, and Open Forum Infectious Diseases were searched for eligible and credible publications until April 30, 2020. The used search strategy was (((((coronavirus(MeSH Terms)) OR coronavirus infection(MeSH Terms)) OR COVID-19(MeSH Terms)) OR COVID-19 infection(MeSH Terms)) OR ("Coronavirus Infection" OR Coronaviruses OR "Coronavirus Infection Disease 2019" OR "SARS-CoV-2" OR "2019 nCoV Infection" OR "2019 Novel Coronavirus Infection" OR "COVID-19 CRP" OR "Coronavirus CRP" OR "COVID-19 Cytokine" OR "COVID-19 Inflammation" OR covid* OR "nCoV" OR "bat coronavirus")). All editorial, epidemiological, and case-control studies were included in the search, and titles and abstracts of utilized studies were independently screened by All rights reserved. All studies that were deemed potentially eligible were accessed through full-text review. Data from studies published in languages other than English were retrieved by the official translation provided by the same database.

Study Design: To perform the meta-analysis, 17 clinical reviews with the laboratory findings of 120 RT-PCR confirmed positive patients in tertiary hospitals were compiled from literature databases, including Science China (24), The Lancet (27), Frontiers in Medicine (32), Jama Network (33), The New England Journal of Medicine (34), European Urology (26), Journal of Medical Virology Wiley (36), Chinese Journal of Tuberculosis and Respiratory Medicine (37), and Chinese Medical Journal (39). A general guideline for the nomination of studies included in our analysis was the presence of individual data. Specifically, the clinical characteristics of age, gender, and average CRP content (mg/L) pertaining to each patient were obtained to compute variance levels in each study (which was essential to the manual computation of effective weight values). Along with CRP data, other information was obtained from the studies, including the date of publication, country of virus contagion, mean age, gender ratio, and number of patients studied. Individual CRP data was utilized to determine the average CRP content of the selected patients. The data points compiled from the utilized studies were represented in a clinical index constructed of the clinical characteristics and calculated effect sizes. A forest plot consisting of the average CRP values (mg/L) for each study and the grand mean CRP value (mg/L) was constructed to visualize the statistical trend displayed in the meta-analysis.

Calculations

The individual weights values (%) for each study were computed using the inverse-variance method, which allows for minimal variance in the weighted average. Serving as a critical method to perform a meta-analysis, it exhibits the effect size for each study through the following equation:

$$W \quad ht\,V \quad = \frac{1}{SE^2}$$

Where SE refers to the manually calculated standard error values of the study, and Weight Value refers to the effect size of an individual study. Unique weights were computed for each study and converted to relative weights, using the formula:

$$W \quad ht\,\%\,o \quad s \quad A = \frac{W \quad ht\,v \quad o \quad s \quad A}{Si \quad of\,W \quad ht\,v}$$

The resulting percentage summarizes the relative significance of study A in the meta-analysis. For further analysis, the strength magnitude of Study A's relative weight can be compared with the expected relative weight value:

$$E. \quad R \quad W \quad ht\,o \quad s \quad A = \frac{100\%}{n}$$

[1] C-Reactive Protein

[2] Reverse transcription polymerase chain reaction

where n refers to the total number of studies in the meta-analysis. If the calculated relative effect size of study A exceeds the expected value, one can consider the presence of flaws in the methods of other studies within the meta-analysis.

RESULTS

This study constructed a clinical index of 17 studies from regions of China, Korea, France and the United Kingdom. Relative weight values were computed using the inverse variance method and recorded in percentage form. Individual data for 69 male and 51 female were involved, with a mean age of 52.73 years. Data pertaining to each study was represented in a forest plot (figure 1), which included average CRP levels in patients, 95% confidence intervals, and relative weight values.

Additionally, as 17 papers were involved in this study, the expected relative weight for each individual study is computed as follows:

$$E \quad R \quad W \quad ht = \frac{100\%}{17} = 5.88\%$$

This value is uniform across all studies, as the calculation is dependent solely on the total number of studies involved in meta-analysis. The data presented in the forest plot (figure 1) delineates the average CRP values of every study along with their respective upper and lower confidence intervals. We define the line of null effect as the vertical line corresponding to a CRP value of 0. The studies conducted by Lee H, et al., Szabadaos, et al., Lescure et al. and Jin-Wei A, et al. present statistically insignificant results, as their lower confidence intervals exceed the null line. In general, any data point that lies on the left of the null line is statistically insignificant, since negative CRP values are unattainable.

Additionally, three studies that maintained the highest weight values had average CRP contents in the 15 mg/L to 25 mg/L range. These studies included Huijin C, et al., obtaining a value of 23.23 mg/L, Jin-Wei, et al., at a value of 16.51 mg/L, and Zhang M, et al., having a value of 16.28 mg/L. As these three studies included six, seven, and nine patients respectively, one can conclude that the data of all patients gathered closely aligned with the average CRP contents in the study. Boxes were placed around average values, with their relative sizes representing the sample size of a study. Zhang J's study consists of the largest sample size, indicated by the largest box size among others.

Table 1. Clinical Index of all studies, presenting first author, date of publication, country of study, mean age, male-to-female ratio, sample size, average CRP content, and relative weight value

#	Study	Date of Study	Country	Mean age	Male / Female	# of patients	ave CRP (mg/L)	Relative Weight Value (%)
1	Yingxia Liu, et al. [24]	March 2020	China	53.67	8/4	12	41.14	5.31
2	Hyung Ju Lee, et al. [25]	April 2020	Korea	59	3/0	3	66.6	0.26
3	Bernadett Szabados, et al. [26]	May 2020	United Kingdom	64.5	4/0	4	86	0.09
4	Jasper Fuk-Woo Chan, et al. [27]	January 2020	China	74.67	1/2	3	44.9	8.79
5	Huijun Chen, et al. [28]	February 2020	China	31	0/6	6	23.23	41.47
6	Jinping Zhang, et al. [29]	April 2020	China	73	11/8	19	95.4	3.76
7	Heshui Shi, et al. [30]	February 2020	China	48.88	2/2	4	47.35	1.67
8	Francois Lescure, et al. [31]	March 2020	France	47	3/2	5	28	0.59
9	Jin-Wei Ai, et al. [32]	May 2020	China	54.1	4/3	7	16.51	17.61
10	Chenguang Shen, et al. [33]	March 2020	China	54	3/2	5	160.06	0.42
11	Christina Creel, et al. [34]	May 2020	United Kingdom	57	3/2	5	210.2	0.05
12	Lan Zhu, et al. [35]	April 2020	China	45	8/2	10	58.95	3.67
13	Yong Gao, et al. [36]	March 2020	China	45.2	9/6	15	39.37	2.58
14	Zhang Mingqiang, et al. [37]	March 2020	China	35.22	5/4	9	16.28	10.96
15	Yan Bai, et al. [38]	February 2020	China	59.5	1/5	6	85.17	0.20
16	Ren Li-Li, et al. [39]	May 2020	China	53.6	3/2	5	158.8	1.45
17	L. Wang, et al. [40]	May 2020	China	41	1/1	2	105	1.10

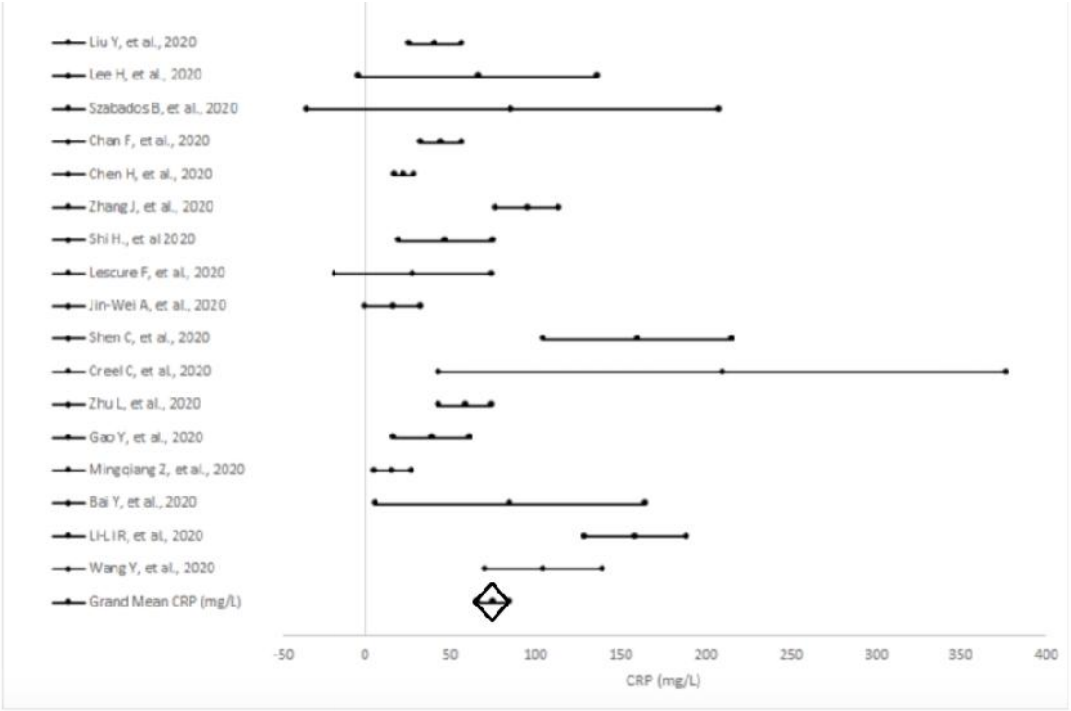

Figure 1. Mean C-Reactive Protein Content of COVID-19 Patients Per Study (mg/L)

The diamond is indicative of the grand mean CRP value at 75.47 mg/L, with average confidence intervals at 66.22 mg/L and 84.71 mg/L for the lower and upper confidence intervals respectively. As effective weight values were computed using the inverse-variance method, studies with a high range in confidence intervals presented lower effective weight values. Graphically, horizontal lines of shorter length corresponded to greater relative weight values. When observing relative weight values and respective box sizes, there exists no definite relationship. This is attributed to the sample sizes of every individual study being less than 20 patients. For example, the study conducted by Zhang J, et al. possesses a relative weight value of 3.76% with 19 patients involved, while the study of Chen H, et al. pertains to a weight value of 41.47% with only 6 patients.

DISCUSSION

With the dearth of COVID-19 antibody testing kits in many regions around the world, an alternative method of testing is necessary. From examining trends in C-reactive protein content within those who are infected with the virus, this paper proposes the usage of inflammatory markers to optimize the allocation of antibody testing kits. Among the studies involved in the meta-analysis, 14 out of 18 presented a range of CRP values that were unhealthy for a human body. The grand mean CRP, an average effective CRP value based on data of all studies, possesses a value of 75.47 mg/L. When accompanied with 95% confidence intervals, its lower and upper intervals lie at values of 66.22 mg/L and 84.71 mg/L respectively. Additionally, Carteron presents evidence of healthy individuals possessing CRP values of < 0.3 mg/L (41). When comparing this quantity with the effective average CRP value presented in the forest plot (indicated by the dotted vertical line), a major discrepancy can be observed, with the effective average CRP content being 66.22 mg/L. This finding is supported by how CRP increases at areas of infection (42).

Furthermore, every study presents a mean CRP value above the healthy threshold, with only four studies presenting lower confidence intervals that achieve healthy CRP values. It is important to note, however, that these four studies' confidence intervals surpass the null line, indicative of a statistically insignificant result. Thus, when considering the latter statistically significant studies, one can conclude that individuals infected with COVID-19 possess abnormal amounts of CRP. When comparing expected relative weight values with the effective weights of all studies, it can be observed that four studies out of 17 exceed this quantity. Furthermore, there exists a large discrepancy between the greatest and lowest relative weight value - further suggesting that certain studies may consist of major flaws.

Implications

Based on the research presented, further alternative methods for antibody testing kits can be explored through consideration of different clinical factors. With the meta-analysis of C-reactive protein content within infected individuals, this research exemplified an observation: those infected experienced high values. However, elevated CRP values are not an observation unique to the infected, as there have been cases wherein uninfected individuals experienced high contents (43). Factors that can be considered include the age, gender, and comorbidities of patients. Once the relationship between these components and COVID-19 presence is clearly defined, a mathematical model can be constructed to predict one's susceptibility to obtaining the virus (based on the cumulation of various factors). With such a system, optimally allocating COVID-19 antibody testing kits can be performed in an accurate and reliable manner.

Declaration of Competing Interest: The authors of this study declare that they each have no conflict of competing interest.

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