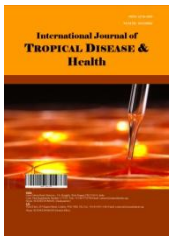

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Progress in the Diagnosis and Treatment of Kawasaki Disease and Other Multi-system Inflammatory Syndromes by Artificial Intelligence

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Purpose: To explore the role of artificial intelligence in distinguishing Kawasaki disease from other multi-system inflammatory syndromes.
Methods: We refer to the existing relevant articles at home and abroad for analysis.
Results: The clinical application of artificial intelligence has played a time-saving and labour-saving role in the differentiation of Kawasaki disease and other multi-system inflammatory syndromes, suggesting that the application of big data in clinical practice can bring new development opportunities for medical treatment.
Conclusion: Kawasaki disease and other multi-system inflammatory syndromes are similar and overlapping in clinical practice, which is difficult to distinguish and easy to misdiagnose and miss diagnose. Artificial intelligence is applied to analyze the above disease data, to achieve the effect of accurate differentiation, timely diagnosis, symptomatic treatment and reduction of complications.

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Keywords: Artificial intelligence; Kawasaki disease; inflammatory syndrome.

1. INTRODUCTION

In December 2019, the first case of the novel coronavirus (COVID-19) was first reported in Wuhan, China [1]. Later, large outbreaks spread globally, and a new syndrome, multisystemic inflammatory syndrome (MIS), with fever and cytokine release after infection with SARS-COV-2, was initially considered to be an atypical form of Kawasaki disease (KD), as most of its clinical symptoms are similar to Kawasaki disease and may also lead to cardiac complications. The difference is that left ventricular insufficiency and cardiovascular shock, coagulopathy and gastrointestinal involvement are more serious in this novel syndrome than in Kawasaki disease. MIS can be seen in both adults and children. Here we will only describe the symptoms that occur in children, which we call pediatric multisystem inflammatory syndrome (MIS-C). Kawasaki disease (KD), previously known as cutaneous mucosal lymph node syndrome, was first reported by TamisakuKawasaki Kawasaki in 1974. The disease is a systemic inflammatory disease with medium-sized vasculitis and is mainly seen in children under 5 years of age [2]. Artificial intelligence (AI) is a technology that integrates advanced brain cognition, big data, cloud computing and machine learning based on modern medical and biomedical theories. Corresponding studies have shown that the multi-system inflammatory syndrome associated with the SARS-CoV-2 pandemic partially overlaps with Kawasaki disease (KD).For example, they all present with fever, rash, mucous involvement, conjunctivitis, erythema/edema of hands and feet, and swollen lymph nodes in the neck [3]. The difference is that the associated lymphocytopenia observed in patients with MIS-C has been compared to the significant neutrophilism and thrombocytosis observed in KD [4]. Other studies have found that the number of related lymphocytes observed in patients with MIS-C is decreased, while the number of neutrophils and platelets observed in KD is significantly increased [5]. In patients with MIS-C tested by deep immunoassay, a significant reduction of lymphocytes was found in a short period, while T cell involvement was more pronounced. Diagnostic biomarkers identified by immune cell profiles of Kawasaki disease and MIS-C may be helpful for early differentiation and diagnosis of these two diseases [2]. With our current knowledge reserve and medical level, KD and MIS-C cannot be judged quickly and accurately, which may make patients in emergency environment or emergency department unable to receive timely and effective symptomatic treatment. We boldly hypothesized whether some modern technologies, such as artificial intelligence, could be used to distinguish these two diseases quickly and effectively. Therefore, the author consulted the literature on this aspect and found that there were very few literatures on the use of artificial intelligence to distinguish and study KD and MIS-C. The study is prospective, and it's worth debating whether using AI to distinguish between diseases can be accurate. It will be a cause for celebration for pediatricians if the research proves to be feasible enough to be applied to the clinic.

2. CONTENT

In the "Research on Knowledge Map Construction of Kawasaki Disease" published on September 10, 2018 by Huang Zhisheng et al., many scholars have done a lot of research but still can't figure out the cause of Kawasaki disease, or even find out whether there is a specific biological marker to diagnose the disease. Therefore, the authors and others prospectively propose that knowledge graph can be an important method for the application of artificial intelligence. However, the establishment of the map needs to collect a variety of knowledge resources related to Kawasaki disease, including clinical guidelines, experimental data, drug knowledge base, medical literature, adverse drug reaction knowledge base, etc. [6]. The research is advanced in that it uses the knowledge map to unify all resources on Kawasaki disease, saving clinicians a lot of time, but the project requires a lot of manpower and effort in the early stages of operation. We boldly assumed that if the relevant information about MIS-C was incorporated into the artificial intelligence technology and compared with Kawasaki disease, whether the two diseases could be accurately distinguished. However, this method only used clinical characteristics to distinguish the two diseases, and only stayed on the surface of the disease without further exploration."AI-guided discovery of the invariant host response to viral pandemics," published on June 11, 2021, fills an earlier gap, The first attempt to define host immune response using artificial intelligence is presented. The authors analyzed transcriptome data sets from more than 45,000 pandemic

viruses, using ACE2 as a "seed" gene to extract 166 genetic markers into host cell receptors. The authors found 166 genetic signatures to be surprisingly conserved across all viral pandemics, including COVID-19, with a subset of 20 genes categorizing disease severity, inspiring the naming of ViP and sViP signatures, respectively [7]. In addition, the precise nature of cytokine storms was defined, the IL15 cytokine and its receptor, IL15RA, were identified as invariant components, and a subset of 20 genes with "severe" ViP characteristics, indicating stress-induced ageing, transcriptional inhibition, DNA damage, and apoptosis, were also shared among various viral pandemics. The authors and colleagues tested their theory by using the BooleanNet algorithm using Boolean equivalent correlation cluster (BECC) [7]. The results of this algorithm can play a guiding role in this pandemic. However, each study has its advantages and disadvantages. This algorithm may lead to over-fitting of some data due to traditional analysis and may lack repeatability when applied to other data sets. Published May 16, 2022, in Nature Communication as "An artificial intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease, an AI-guided approach was proposed to reveal the shared host immune response in Kawasaki disease and multi-system inflammatory syndrome in children. In the context of SARS-CoV-2 infection, the authors developed a computational tool for two genetic signatures to compare the two syndromes, namely ViP and sViP. In addition, 13 transcript features have previously been used to demonstrate the diagnosis of Kawasaki disease. Experiments have demonstrated that KD and MIS-C are in the same continuum of host immune response as COVID-19.Both pediatric syndromes have cytokine storms centred on IL15/IL15RA, suggesting the same proximal pathway of immune pathogenesis. However, there were still differences between ViP and sViP in other laboratory parameters and cardiac phenotypes. To further understand the disease analysis, the author et al through the collection of data for comparison, the characteristics of VIP and SVIP induction observation, found that ① gender does not affect it ② can not predict the treatment response to IVIG ③ in the differentiation of responders and non-responders as good performance but the degree of ViP induction characteristics of responders is lower than that of non-responders. Finally, it was proved that the ability of 20 gene sVIP was superior to 166 gene VIP [8]. Notably, the data collected did not seem to mention differences in age, race, region, or history of other diseases before or at the time of illness. As for age, the answer is given in the study of TongT et al. MIS-C is more common in older children and adolescents [9]. Three conclusions were obtained: (1) The host immune response detected qualitatively by ViP features was similar in KD and MIS-C, and shared an IL15/IL15RA component;② The degree of the host immune response measured quantitatively by ViP characteristic score was stronger in MIS-C than KD.(3) KD and MIS-C induced KD-13 characteristics to similar degrees in two independent cohorts, further supporting the observation of ViP/sViP characteristics that KD and MIS-C share basic aspects of host immune response with each other. Liu Jiayi and other scholars have detailed and interpreted this document from five aspects, making it easier for readers to understand its content [10]. Pediatric multi-system inflammatory syndrome (MIS-C) and Kawasaki disease are both highly inflammatory diseases associated with infectious diseases. PaulTsoukas et al. conducted a further exploration based on the study of Ghosh et al. to further understand whether they are different syndromes or exist in the continuum [11]. Postinfective severe inflammatory syndromes were stratified into subgroups based on the clinical phenotypes identified next to them in a manner independent of infection triggers. It is concluded that these two syndromes have a common host immune response, suggesting a single spectrum of disease. "A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Children," published on October 4, 2022Kawasaki disease in the USA: a retrospective model development and validation study "in which the authors attempt to distinguish KD, MIS-C, and other similar febrile diseases by developing and verifying an AI computational approach. In this literature, the authors et al. developed a deep learning algorithm named KIDMATCH (Kawasaki Disease and Pediatric Multisystem Inflammatory Syndrome) using a retrospective model development and validation study. The algorithm was tested through phases 1 and 2 of internal validation on 1,517 patients with MIS-C, Kawasaki disease, and other febrile diseases; A further 175 MIS-C patients (from different hospitals) were added for external verification. The results showed that MIS-C patients had higher band counts, lower sodium concentrations,

lower platelet counts, higher C-reactive protein, and older age than patients in the other febrile and Kawasaki disease cohorts in the data comparison between the two groups [12]. It is worth considering that this deep learning algorithm is only an initial evaluation. If MIS-C advances to the middle and late stages, this learning algorithm can still evaluate and classify MIS-C and Kawasaki disease or other febrile diseases. In addition, the number of children involved in the study was not large enough and the study area was not broad enough to see whether there would be a difference. In addition, in sensitivity analysis, Kawasaki disease patients with coronary aneurysms and MIS-C patients with decreased left ventricular ejection fraction were tested as characteristic patient subgroups, and the final models were correctly assigned. Raw eigenvalues were extracted from a random sample of the internal validation of the final model and compared with two experienced pediatric infectious disease clinicians with Kawasaki disease expertise to assign diagnoses based on characteristics. The results showed that the algorithm outperformed the two clinicians. This paper presents a novel approach -- a machine learning model -- for screening patients with MIS-C, Kawasaki disease, or similar febrile diseases. This is the first known application of artificial intelligence to help diagnose MIS-C and distinguish it from Kawasaki disease and other febrile diseases. The advantage of this computing is that the required functionality is universally available in most healthcare settings.

Several studies have used clinical and laboratory methods to distinguish MIS-C from Kawasaki disease. Tong et al., through a meta-analysis of clinical features, concluded that respiratory and gastrointestinal symptoms of MIS-C were more common than Kawasaki disease [9,13] possibly due to increased viral load in gastrointestinal tissues. Studies have shown that MIS-C may be a post-infection sequela of COVID-19, while coronavirus is a non-staged plus-strand RNA virus, which can be indicated positive by swabs and stool examination in children [14]. Another study on patients with MIS-C found that gastrointestinal tract involvement was the second most frequently involved organ system after the cardiovascular system [15,16]. A meta-analysis of laboratory features compared to clinical features suggested that MIS-C patients had lower lymphocyte counts, ALT, and ESR levels, higher D-dimer and fibrinogen levels, and higher ferritin levels. Platelet levels in MIS-C were higher than those in Kawasaki disease, but there was no significant difference in neutrophil levels between the two. Analysis of a group of circulating cells may help in early diagnosis and differentiation between the two diseases. These characteristics were also confirmed in the study of AnuradhaRajamanickam et al. [17,18]. In addition, both MIS-C and Kawasaki disease can cause cardiac involvement in patients. Laboratory data from MIS-C show elevated CRP, erythrocyte sedimentation rate, and D-dimer, but no arteriovenous thrombosis. Whether there is any literature that can support this conclusion, the author has not found. But the similarity is its challenge in the clinic and the laboratory. AngelaChun et al. used AI to distinguish MIS-C from typhoid fever in endemic areas. They established an equation to calculate the "MET" score based on demographic, clinical and laboratory characteristics, and the final experimental results showed that only 10 characteristics were enough to distinguish typhoid fever. Whether we can apply the method in this study to the distinction between KD and MIS-C needs further discussion and experimental analysis. Nowadays, there are many methods to distinguish MIS-C from Kawasaki disease at home and abroad, but most of them are based on the clinical characteristics and laboratory test results of the disease. There are few studies on the shared immune response of MIS-C and KD by artificial intelligence. After reading and thinking about relevant literature, the problem that has been solved so far is that we can temporarily distinguish Kawasaki disease, MIS-C and other febrile diseases by some technologies, but whether this technology is mature enough and when it can be applied in the clinic remains to be investigated. In addition, for the pathogenesis of Kawasaki disease and MIS-C, as well as the targeted and effective treatment of MIS-C, we are still unable to accurately answer the question, which requires further in-depth research and a large number of data support. Can we use AI's technique of distinguishing MIS-C from typhoid to distinguish Kawasaki disease from other multi-system inflammatory syndromes? With the development of science and technology and the gradual application of artificial intelligence in clinical practice, the application of artificial intelligence in disease research and treatment will become more and more relevant. The research is obviously feasible, but the challenges it faces are huge, such as collecting sufficient data and specifying them, refining the clinical symptoms, laboratory tests and personal basic data of patients, and the differences in individual genes.

The most important thing is that the preliminary research needs to spend a lot of time, energy and even financial resources to support the research.

3. CONCLUSION

In conclusion, Kawasaki disease (KD) and pediatric multisystem inflammatory syndrome (MIS-C) are both autoimmune hyperinflammatory diseases involving multiple organ systems. It is still a difficult and important task to distinguish immunophenotypes by artificial intelligence method in the diagnosis of these diseases. In order to further explore the pathogenesis and sequelae of Kawasaki disease (KD) and pediatric multi-system inflammatory syndrome (MIS-C), as well as reduce the occurrence of disease complications, reduce the mortality of children, improve the quality of life of children, it has important significance, and is worth further promotion and research in clinic.

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CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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