Development of network pharmacology in sepsis treatment

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Abstract

So far, sepsis is still a global disease and health problem facing mankind. Due to the complexity of the pathophysiology and pathogenesis of sepsis, the idea that a drug corresponds to a single target - a single disease is no longer suitable for the treatment of complex diseases such as sepsis. The application of network pharmacology to explore the signal network relationship between diseases, targets, and drugs has gradually become a new disease treatment methodology. This effective treatment for disease targets can improve the effectiveness and success of drug therapy, and it is possible to develop from the current treatment of symptoms of complex diseases to the real cure of complex diseases. This paper will discuss the application and discovery of network pharmacology in the treatment of sepsis, to provide a certain scientific theoretical basis for the subsequent basic and clinical research of sepsis treatment.

Development of network pharmacology in sepsis treatment

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Abstract: So far, sepsis is still a global disease and health problem facing mankind. Due to the complexity of the pathophysiology and pathogenesis of sepsis, the idea that a drug corresponds to a single target - a single disease is no longer suitable for the treatment of complex diseases such as sepsis. The application of network pharmacology to explore the signal network relationship between diseases, targets, and drugs

has gradually become a new disease treatment methodology. This effective treatment for disease targets can improve the effectiveness and success of drug therapy, and it is possible to develop from the current treatment of symptoms of complex diseases to the real cure of complex diseases. This paper will discuss the application and discovery of network pharmacology in the treatment of sepsis, to provide a certain scientific theoretical basis for the subsequent basic and clinical research of sepsis treatment.

Key words: Network pharmacology; Sepsis; Signal network; Treatment

Introduce

The concept of sepsis can be traced back to ancient Greece when Hippocrates described it as a dangerous, odorous, and biological body decay [1]. From the establishment of the first sepsis-1 consensus definition in 1991 to the revised sepsis-3 consensus definition in 2016[2], we have a better understanding of the definition, identification, and management of sepsis. Early sepsis identification is the key factor to improve the prognosis of sepsis. Therefore, the sepsis treatment guidelines were revised again in 2021. The guidelines recommend the use of sequential organ failure assessment (qSOFA), national early warning results (News), and modified early warning results (Mews) scoring tools to identify and screen early sepsis[3]. The pathophysiological mechanism of sepsis has a new understanding and change. The systemic inflammatory response caused by infection is no longer simply attributed to sepsis. The occurrence of organ dysfunction will be one of the important factors belonging to sepsis. The incidence and mortality of sepsis in the world are still at a high level. A study counted the incidence and mortality of sepsis in the world from 1979 to 2015 through database retrieval. The report showed that there were about 50 million patients with sepsis in the world, of which about 5 million died of sepsis every year. However, these data were from high-income countries or regions, which could not fully reflect the true incidence and mortality of sepsis in the world but were higher than the current statistics, This is related to data loss and lack in low-income countries or regions[4]. In addition, the major disease-causing death in the pediatric intensive care unit (PICU) is still severe sepsis, with a mortality rate of about 10% -48%[5].

At present, the treatment of sepsis is still based on symptomatic treatment, including empirical antibiotic anti-infection, regulation of coagulation dysfunction, protection of dysfunction of important organs, fluid infusion, and vasopressor drugs to stabilize hemodynamics, but it can not achieve precise treatment [6,7,8]. Sepsis itself is a complex internal molecular mechanism, which has drawn an interconnected and huge disease network (multiple genes, multiple protein functions, and multiple signaling pathways). Just like the complex balance of the human body itself, it is difficult to break the human body's ecological balance only by changing one or several goals. Therefore, we can treat such complex diseases as sepsis, cancer, and cardiovascular diseases through different ways of multi-target diseases.

Network pharmacology shows the complex network relationship of disease target drug function pathway through a biological network, gradually promoting the transformation of the development mode of a single target drug to the overall development mode of the drug[9]. The emergence of network pharmacology is to help us better understand the multiple mechanisms of action of drugs. The use of multi-omics (genomics, transcriptomics, proteomics) theory, combined with powerful database retrieval and computer modeling technology will help us to develop drugs for the treatment of complex diseases and better understand the complex biological mechanisms of diseases, To truly cure such complex diseases as sepsis from the molecular tissue organ organism level [10,11].

1 Network pharmacology

In 2007, Yildirim et al analyzed the relationship between drug targets and disease genes. Although limited by the scarcity of disease and drug databases at that time and the incompleteness of the human protein interaction group spectrum, Hopkins proposed the concept of network pharmacology in November of the same year, and questioned the traditional drug strategy of single drug responding to a single target, believing that the treatment of disease should be carried out in series on multiple nodes [12,13]. With the rapid development of biotechnology and information technology, and the continuous improvement of databases. The reliability and applicability of network pharmacology will also be more powerful[14]. In addition, studies have found that

for similar phenotypes of different diseases, it is often some similar genes that determine their pathological phenotypes. Network pharmacology no longer simply classifies the interaction of each node into the sum of individual parts, but emphasizes the network relevance of each part, so it is also considered the next strategy of personalized treatment. We can build a complex interaction network between disease, target, and drug through huge database screening and computer models, and understand the specific mechanisms and signal pathways between disease and target. As a new research mode of drug discovery and reuse in recent years, network pharmacology has made great progress in the redevelopment and application of traditional Chinese medicine[15,16,17]. In addition, for the treatment of complex diseases such as cancer, diabetes, cardiovascular disease, AIDS, and psychosis, multi-target or combined drug therapy is more effective and less toxic [9]. The method based on network pharmacology has also played a huge role in exploring the molecular mechanism and potential targets of coronavirus disease (COVID-19) in 2019. At the same time, it is a low-cost and efficient strategy and is also used to screen new candidate drugs for COVID-19[18,19,20]. Therefore, as a low-cost, time-consuming, and high-yield drug development method, we should re-examine this web-based drug development.

2 Network pharmacology-related databases and research tools

With the rapid development of network pharmacology, it has made some breakthroughs in drug development and mechanism research. The concept of network pharmacology has only been born more than ten years, but its value and development potential have been paid more and more attention by scholars. These are inseparable from the improvement of various databases and the breakthrough of research tools, which provide important support for the drug development of network pharmacology. There are many kinds of databases and research tools related to network pharmacology, and different databases and tools have different characteristics and functions. The summary is as follows.

Disease target database and its characteristics: Herb(http://herb.ac.cn/), a special traditional Chinese medicine (TCM) high-throughput experiment and reference database connecting the disease target drug interaction relationship, which also provides a tool for target function analysis; Genecards(https://www.genecards.org/), a database about the detailed information of all human gene proteins at present. When predicting disease targets, as long as the input needs to retrieve the disease, all the corresponding prediction targets will be displayed in the form of scoring, and the operation is relatively simple; Diseases(https://diseases.jensenlab.org/Search) database integrating disease gene association information from the existing database has a large amount of data, but the search time is long; The GEO(https://www.ncbi.nlm.nih.gov/geo/) database is the first public storage database of gene expression data (gene chip, high-throughput sequencing). The arrangement of various diseases in the database is very comprehensive, and the acquisition of disease target data needs to be arranged by yourself; Mir2disease(http://www.mir2disease.org/), a database of human diseases related to miRNA, which provides detailed information about the relationship between miRNA and its diseases; OMIM(https://www.omim.org/), which contains the information database of the association between disease phenotypes and pathogenic genes, and provides the connection, composition, structure, and function of pathogenic genes.

Target prediction database of compounds and its characteristics: Stitch(http://stitch.embl.de/)The database mainly provides protein-protein interactions, which are derived from experiments and literature studies; SEA(https://sea.bkslab.org/)In the database of target prediction based on chemical structure formula, the number of prediction targets is usually small. Targetnet(http://targetnet.scbdd.com/), a database based on 623 human protein designs, which can be used to predict the target of any given compound molecular structure formula; Swisstargetprediction(http://swisstargetprediction.ch/)According to the similarity of the molecular structure formula of the compound, the target of the compound can be predicted, which can be carried out in different species (human, rat, and mouse); Drugbank(https://go.drugbank.com/), one of the most powerful and comprehensive drug databases, with comprehensive information of drug targets. The results have been verified by experiments, but the target acquisition cannot be downloaded in batch; Chembl(https://www.ebi.ac.uk/chembl/)The database contains the therapeutic targets of re-

search drugs and approved drugs, and can also quickly obtain the data related to the biological activity of the target. TTD(http://db.idrblab.net/ttd/)It is a database that provides information related to target genes, including biological pathways, functions, diseases, and drugs corresponding to genes; Pharmmapper(http://lilab.ecust.edu.cn/pharmmapper/check.php)The online small molecule drug target prediction platform based on pharmacophore model has more than 7000 receptor-based pharmacophore models, but the retrieval results are time-consuming.

In addition, network pharmacological algorithms and tools are particularly important for mining these databases. Lei[21] et al proposed an algorithm that can effectively predict the association between drugs and diseases-vgaedr, which is based on variational graph automatic encoder and heterogeneous network. At the same time, algorithms such as DeepDR、SCMFDD、BNNR, and GRGMF are also used to predict the relationship between diseases and drugs. As an open-source tool integrating biomolecular interaction networks and states, Cytoscape can visualize protein interaction networks and annotate data, and modularize regional networks to find core nodes [22]. Autodock Vina is software for molecular docking. It evaluates the binding ability of protein molecules to drug molecules through a specific scoring function, predicts the binding conformation and binding affinity, and the accuracy of receptor-ligand binding mode prediction is also reliable, which will provide a certain value for drug screening and development[23]. In addition, discovery studio, a molecular docking software, is also an analysis tool based on computer simulation to screen potential drugs. Its docking efficiency is better than autodock Vina, which is related to the different docking algorithms used by discovery studio.

3 Pathogenesis of sepsis

3.1 Imbalance of inflammatory response

When pathogenic microorganisms and virulence factors invade the body, the body activates the innate immune system through a series of inflammatory reactions to resist pathogen infection. However, when the inflammatory reaction is over-activated, it will cause organ dysfunction and further aggravate the injury. Inflammatory cytokines play an important role in the progression of sepsis and are involved in multiple organ injury in sepsis. At present, most scholars believe that the pro-inflammatory factor TNF- α is not only the "core factor" causing dysfunction and injury of many important organs, but also the initiating factor, and is closely related to IL-1β Play a synergistic effect[24]. IL- 1β As another key inflammatory factor, studies have found that inhibition of IL-1β Expression can reduce hemodynamic and metabolic disorders in severe sepsis[25]. In addition, IL-1β Can promote monocyte chemoattractant protein-1, I-κBα. The synthesis of multiple inflammatory genes, such as MKP-1 and other interleukin-like cytokines, further promotes the spread of inflammatory reaction and causes sepsis-related organ dysfunction[26]. During lipopolysaccharide LPS-induced sepsis, HMGB1 can cause multiple tissue and organ damage through different mechanisms, such as lung, kidney, liver, cardiovascular, and nervous systems[27]. Fu[28] and other researchers believe that HMGB1 is over-regulated in sepsis, and experiments have confirmed that HMGB1 has a protective effect on septic liver injury by targeting HMGB1. When cells are stimulated by pathogenic microorganisms and bacterial products, nuclear factor κ B (NF- κ B) Nuclear translocation and its promoter will be activated, leading to the release of pro-inflammatory factors, including TNF- α、IL-1β. At the same time, these inflammatory factors will further positively feedback and activate NF- κ B. Lead to the imbalance of inflammatory response and then aggravate sepsis.

3.2 Immune macrophages

As an important cell of the innate immune system, macrophages can show different phenotypes and functions when stimulated by external factors, and they are widely distributed in various tissues and organs of the body. Among them, M1 macrophages (classically activated macrophages) are activated and secreted proinflammatory cytokines, which play a central role in the host's defense against infection, while M2 macrophages (alternatively activated macrophages) are involved in the body's anti-inflammatory response and tissue remodeling response by secreting inhibitory cytokines [29]. Hypoxia-inducible factor-1 in sepsis α、Abnormal changes in substances such as 5-adenosine monophosphate-activated protein kinase (AMPK) and succinate

dehydrogenase can regulate the metabolism of immune macrophages, and then directly affect the prognosis of sepsis [30]. A recent study by Kong [31] et al. Showed that the aerobic glycolysis of macrophages could be regulated by targeting GAPDH (a rate-limiting enzyme that regulates the rate of aerobic glycolysis), thereby inhibiting the activation of inflammatory macrophages to play an anti-inflammatory role, and significantly reducing the mortality of septic rats. In addition, inhibiting the abnormal activation of macrophages can regulate the polarization phenotype of macrophages, promote tissue repair and angiogenesis, inhibit pro-inflammatory immune response, and reduce tissue and organ damage. There is evidence that[32], macrophages regulate tissue damage and affect the inflammatory response in the microenvironment, which is related to the release of lipid bilayer-blocking structure (EV). In addition, damaged tissue cells can release ev to activate local macrophages to promote tissue repair.

3.3 Cell pyrosis

Pyrosis is currently defined as a specifically programmed cell death characterized by the release of inflammatory cytokines, which are involved in inflammation and immune response and can be activated by classical pathways dependent on caspase-1 or nonclassical pathways dependent on caspase-4/5/11 [33]. During sepsis, appropriate pyrosis is helpful to resist bacterial infection and reduce the damage to tissues and organs. However, excessive pyrosis will lead to further aggravation of infection and the emergence of multiple organ failure (MODS). IL-18/IL-1 can be reduced by inhibiting the activation of inflammatory corpuscles and regulating the pyrolytic activity of cells β To protect against multiple organ injury in sepsis. In addition, transcription factors are also involved in the regulation of cell death in sepsis, such as NF- ϰ B and nuclear factor red blood cell 2 related factors (Nrf2). Hu [34] et al. Confirmed by animal experiments that after prophylactic glutamine (Gln) supplementation in the septic mouse group, it can increase the cell apoptosis in the early stage of sepsis to enhance the bacterial clearance ability, and can reduce the cell apoptosis and reduce IL-1 in the late stage of sepsis β The release of inflammatory cytokines such as IL-18 can improve organ dysfunction in sepsis.

3.4 Complement system

When the host recognizes the danger signal, the complement system will be activated. Complement can regulate the early innate immune response, which is essential to protect the host from the uncontrolled transmission of invasive pathogens. In the early stage of sepsis, complement-related activated products will increase, such as anaphylactoid toxins C3a, C4A, and c5a[35]. Complement activation products C3a, C5a, and c5b induce anti-microbial response and pro-inflammatory effect through crosstalk with a variety of signal transduction pathways. With the progress of complement activation, continuous production of C5a may lead to congenital immune paralysis, resulting in weakened inflammation and bacterial killing[36]. C5a and C5aR can induce an inflammatory response and participate in multiple organ failures during sepsis. Sommerfeld[37] et al. Found that in the mild to moderate sepsis model, c5ar1 deficient mice had a higher survival rate than the wild group, and the c5ar1 deficient group could also improve liver injury in sepsis. In addition, complement-mediated neutrophil dysfunction, apoptosis, and systemic inflammatory response also affect the progression of sepsis.

4 Network pharmacology - sepsis

The pathogenesis of sepsis is complex and diverse, including pathophysiological processes such as inflammatory reaction imbalance, complement system, necrotic apoptosis, coagulation dysfunction, metabolic immunity, and cell death [38]. Sepsis can be considered a systemic disease, which is caused by the interaction of multiple pathways, genes, and biological networks. The study of a single mechanism or target for complex diseases is no longer the optimal solution. As the human body itself is a complex biological balance system, it is difficult to restore the dynamic balance of the human biological system only by correcting one or several targets[39,40]. Therefore, a new method is needed to understand complex diseases such as sepsis, and the emergence of network pharmacology shows great development prospects. Zhou[41] et al. Found that Xuebijing (XBJ) may treat sepsis by regulating inflammation, immunity, apoptosis, and coagulation. In addition, the experimental results showed that XBJ can reduce IL-1β Level, and protect against sepsis

injury. Li [42]and others, using network analysis, identified 63 main targets of vitamin C (VC) against sepsis from tcmsp, drugbank, disgenet, and other databases, and identified four best core targets of VC against sepsis. GO and KEGG analysis showed that the potential mechanism of VC against sepsis was related to cell response to oxidative stress, immune dysfunction, and inflammatory stress. Lu [43] et al. Used network pharmacology to analyze and screen the key components and antisepsis targets of Xijiao Dihuang Decoction (xjdht). In vivo and in vitro experiments, after evaluating the content of cytokines and signaling pathways, NF- ⋋ B and HIF-1 α Signaling pathway plays an important role in xjdht antisepsis. Fu [44] et al. Screened the pathological targets of sepsis and the pharmacological targets of Dachengqi Decoction with the help of OMIM, genecards, and omicshare databases. The experimental results confirmed that the atmospheric Chengqi Decoction can inhibit the inflammatory factor IL-1β、IL-6 and TNF- α. It can improve sepsis by inhibiting PI3K/Akt signaling pathway.

5 Sepsis - multiple organs

The key inducing factor of sepsis-related multiple organ injury is the uncontrolled persistent inflammatory response, especially for patients with organ dysfunction in the past, which will aggravate the further deterioration of sepsis-related organ dysfunction[45]. When organ dysfunction occurs in hospitalized patients with sepsis, even mild organ injury can cause about 10% of the in-hospital mortality. At present, the SOFA score of sepsis-related organ failure has also been developed. Taking the SOFA score of 2 as the dividing point, the death risk of patients with SOFA scores greater than 2 is 2 to 25 times higher than that of patients with SOFA scores less than 2 [46,47]. At present, the discovery of new bioactive ingredients and the reuse of traditional drugs through network pharmacological methods have shown some effectiveness in the treatment of sepsis with organ dysfunction.

5.1 Lungs

In the intensive care unit (ICU), sepsis is the main indirect cause of ali/ards. In addition, the lung is the first affected and most vulnerable organ in sepsis [48,49]. In severe sepsis, as time goes on, acute lung injury can develop into pulmonary fibrosis, resulting in respiratory failure and death[50]. Yang [51] et al. Predicted the active ingredients and effective targets of Lianhua Qingwen (lhqw) in the treatment of acute lung injury (ALI) caused by sepsis by using the network pharmacological method. Through GO and KEGG, they found that the apoptosis pathway was mainly involved in lhqw's anti-Ali. Further animal experiments confirmed that lhqw could increase the expression of Bcl-2, reduce the release of cytochrome c, and inhibit the overexpression of p53 induced by LPS by reducing the levels of Caspase-3 and caspase-9 in Ali mice, Inhibiting p53 mediated endogenous apoptosis pathway and alleviating sepsis-induced lung injury.

5.2 Kidney

Sepsis kidney injury is closely related to the clinical prognosis of patients. About one-third of patients with sepsis will develop into sepsis kidney injury. The mortality of patients with sepsis kidney injury is higher than that of patients without sepsis kidney injury[52,53]. Yao [54] et al. Discussed the protective effect of saikosaponin d (SA) on sepsis-induced renal injury by using network pharmacology analysis and bioinformatics analysis. The double luciferase reporter gene and chromatin immunoprecipitation (chip) experiments found that SA reduced the expression of apoptosis and inflammatory factors by inhibiting the tcf7/fosl1/mmp9 axis, and ultimately reduced the renal inflammation and apoptosis induced by sepsis, to protect a sepsis-induced renal injury. Tang [55] et al. Found that Astragalus membranaceus and astragaloside IV (as-iv) protect renal tubular injury induced by sepsis by activating Pi3k/akt pathway based on network pharmacology.

5.3 Heart

As one of the main damaged organs during sepsis, the heart can develop into infectious myocarditis when it is infected by the outside world, resulting in cardiac insufficiency and heart failure, which is also one of the main causes of death of hospitalized patients with sepsis in ICU[56]. Other studies have shown that ventricular muscle is inhibited in sepsis, which is manifested as diastolic dysfunction [57,58]. Wang[59] et al.

Preliminarily screened the core target of retinoic acid (RA) against sepsis through network pharmacology, and then established a mouse sepsis model to observe the survival, cardiac function, and antioxidant level of mice. The results showed that RA can improve the survival rate and cardiac function of septic mice, which may be through regulating the PI3K Akt signaling pathway and key gene expression to reduce lipopolysaccharide-induced cardiac dysfunction. Wu[60] et al. Applied network pharmacology to predict the potential target and molecular mechanism of epigallocatechin gallate (EGCG) in the treatment of septic cardiomyopathy. The experimental results showed that EGCG improved myocardial injury in septic cardiomyopathy through anti-inflammatory and anti-apoptotic mechanisms.

6 Network pharmacology - other complex diseases

6.1 Cancer

Cancer is a disease caused by the abnormality of a complex biological network. Some drugs targeting a single target or pathway in the past may not achieve the expected effect in the treatment of some malignant tumors [61]. Therefore, using a system network method to find therapeutic drugs has become a reliable method. This strategy helps to identify the specific signal pathways driving tumor-promoting or anti-tumor signals, and improve drug reuse and development[62,63]. Wu[64]et al. Used weighted gene coexpression network analysis (WGCNA) and network pharmacology to explore the potential mechanism of Compound Kushen Injection (CKI) in the treatment of pancreatic cancer (PC). After molecular docking and experimental verification, they finally found that CDK1, Jak1, EGFR, mapk1, and mapk3 were the core genes regulated by CKI in the treatment of PC. Wo [65] et al. Screened 28 important proteins of four kinds of cancer (bladder cancer, colorectal cancer, liver cancer, and lung cancer) through system biology and computer assistance, and found new drug pathways with multiple target effects through systematic evaluation and analysis.

6.2 Cardiovascular disease

The pathogenesis of cardiovascular disease (CVD) is complex and diverse, and it is also one of the diseases with the highest mortality in the world, including atherosclerosis, arrhythmia, hypertension, and aneurysm[66,67,68]. With the development of medical technology, scholars have gradually realized that the pathogenesis of cardiovascular disease is complex and involves multiple targets[69]. At this time, network pharmacology has been a concern for more and more scholars, and occupies an important position in the mechanism research and drug development of cardiovascular disease treatment. Yu[70] et al. Explored the effects of wild ginseng and garden ginseng on cardiovascular diseases by combining metabonomics and network pharmacology, and found that both kinds of ginseng can pass HIF-1 α/ The vascular endothelial growth factor signaling pathway protects the injured internode vessels, and determines the potential mechanism of different metabolites in CVD. Zhang [71] et al. Discovered Rehmannia glutinosa (RRP) as a new potential herbal medicine against cardiovascular disease through network pharmacology, and put forward new opinions on the molecular mechanism of RRP-mediated anti-atherosclerosis (AS).

6.3 Mental illness

Severe mental illness is a multifactorial disease, with about 4.5% of the population suffering from severe mental illness (SMI)[72]. Depression is a common disease in mental diseases. Zhang [73] and others found that Radix Bupleuri and Radix Paeoniae Alba play an antidepressant role by using metabonomics and network pharmacology research strategies, and found that CYP1A1 and CYP1A2 proteins are the key genes of the drug for antidepressants. Qi [74] et al. Established a network assessment and analysis to determine the signal pathways mainly involved in the targets related to severe mental diseases. Then the experiment confirmed that Coptis extract can improve anxiety-like behavior by improving the survival rate of neurons and inhibiting neuroinflammation.

6.4 New coronavirus pneumonia

At present, COVID-19 is still rampant in many countries around the world and cannot be effectively controlled. Xia[75] et al. Combined with network pharmacology and molecular docking, found that the Lianhua

Qingwen capsule (LQC) has a certain curative effect in patients with COVID-19, and AKT1 may be the therapeutic target of COVID-19. Tao[76] and others, through network pharmacology, revealed that baicalein and quercetin may play a therapeutic role in COVID-19 by regulating a variety of signaling pathways through ACE2. In addition, Liu [77] et al. Screened new candidate drugs for the treatment of COVID-19 based on network pharmacology and transcriptomics methods, and identified 18 separate candidate drugs after screening and analysis, including drugs not previously proposed for the treatment of COVID-19, such as nicardipine, planting, tibial and promethazine.

Conclusion

In conclusion, the application and development of network pharmacology have excavated new insights into the treatment of sepsis, including the treatment mechanism of the disease: the complex network relationship of multi-target, multi-channel, and multi-component, which also makes us a new way of thinking for the drug development and selection of this refractory disease. In addition, it also shows attractive charm in the treatment of complex diseases such as cancer, cardiovascular disease, mental disease, and new coronavirus pneumonia. However, network pharmacology still faces many problems and challenges, such as the lack of uniformity in the diversity of databases, the lack of standardization in data screening, and the poor repeatability and convertibility of data results. Although the development of computer science, genomics, and systems biology may promote the development of network pharmacology in more disease fields, it is still necessary to explore new methods for the treatment of complex diseases such as sepsis.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

Authors contributions

CML formulated the main research plan, CFL collected data and wrote the manuscript. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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