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Current pharmacological intervention and development of targeting IVIG resistance in Kawasaki disease

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Kawasaki disease is an acute childhood self-limited vasculitis, causing the swelling or inflammation of medium-sized arteries, eventually leading to cardiovascular problems such as coronary artery aneurysms. Acetylsalicylic acid combined with intravenous immunoglobulin (IVIG) is the standard treatment of Kawasaki disease (KD). However, a rising number of IVIG resistant cases were reported with severe disease complications such as the KD Shock Syndrome or KD-Macrophage activation syndrome. Recent reports have depicted the overlapped number of children with SARS-CoV-2 and KD, which was called multisystem inflammatory syndrome. Simultaneously, the incidence rate of KD-like diseases are increased after the outbreak of COVID-19, suggesting the virus may be associated with KD. New intervention is important to overcome the problem of IVIG treatment resistance. This review aims to introduce the current pharmacological intervention and possible resistance genes for the discovery of new drug for IVIG resistant KD.

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Introduction
Kawasaki Disease (KD) was first described as the mucocutaneous lymph node syndrome in 1967 [1]. It is an acute systemic vasculitis and a multi-system disease that can lead to severe complications such as stenosis, thrombosis or coronary artery aneurysms (CAA) which can lead to sudden death [2]. According to the American Heart Association (AHA) guideline, typical diagnostic symptoms and signs for children are fever, bulbar conjunctival infection, chapped lips, strawberry tongue, desquamation and skin peeling, rash, and cervical lymphadenitis [3,4]. Single Intravenous immunoglobulin (IVIG) therapy can reduce the risk of bulging of the artery wall and CAA which can lead to a heart attack [5⁵]. Up to now, combined use of high dose of IVIG and aspirin remains the standard treatment for KD. In fact, about 10–20% of patients did not respond to standard primary treatment and developed resistance to IVIG. Unresponsiveness such as persistent fever after the standard IVIG treatment was considered as resistant KD [6] with increased risk of life-threatening complications such as the Kawasaki Disease Shock Syndrome (KDSS) or KD-MAS (KD-Macrophage activation syndrome) (Figure 1).

In December 2019, a new infectious disease named Coronavirus disease 2019 (COVID-19) pneumonia infected by the new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared and spread rapidly worldwide. On January 30th 2020, the World Health Organization (WHO) has announced SARS-CoV-2 as a health emergency of international concern. By March 11th 2020, the WHO recognized COVID19 as a pandemic. As of June 2020, the number of confirmed cases in the world has exceeded 10 000 000. Recently, many literatures reported the number of SARS-CoV-2 infected children with KD multisystem inflammatory syndrome (MIS-C) has increased sharply. While KD and MIS-C shared some common symptoms such as lymphadenopathy, skin rash, prolonged fever, diarrhea and upregulation of inflammation related protein markers [7,8], recent statistics have shown that the incidence rate of KD-like diseases increased by 30 times after the popularity of COVID-19 [9⁵]. Although without known pathophysiology, the recent increased cases of KD symptoms occurrence in COVID-19 patients have drawn researchers’ attention to the identification of alternate therapeutic drugs and molecular gene targets for both typical or resistant KD [10].

Standard treatment of classical and refractory Kawasaki disease

Intravenous immunoglobulin treatment and resistance in Kawasaki disease

IVIG treatment generally provide its anti-inflammatory effects via neutralization of the infectious antigens or pathogenic autoantibodies, inhibition of tumor necrosis...
Symptoms, complications, possible treatments, and potential resistant target genes of IVIG resistant KD patient.

Aspirin factors (TNF)-α and the release of inflammatory cytokines, and regulation on the function of both B and T cells [11–13]. According to AHA guidelines, patients with persistent fever lasting for 36 hours to a maximum of 7 days after first IVIG infusion is defined as IVIG resistant [4]. Although optimal therapeutic response can be observed when IVIG therapy is administered within 10 days since the symptom existed, or when a high dose of 2 g/kg was administered within 12 hours of symptom onset [4], around 5% of patients who received an appropriate IVIG treatment at an early stage still developed CAA [14].

**Aspirin treatment and resistance in Kawasaki disease**

Single Acetylsalicylic acid (ASA) treatment shows significant anti-inflammatory activity (at a high dose of 30–100 mg/kg/day), anti-platelet activity (at a low dose of 3–5 mg/kg day), and may reduce the risk of vascular thrombosis. ASA combined with IVIG was reported to possess anti-inflammatory and anti-platelet role during different phases of KD [15–17]. However, KD patients who are concurrently affected by influenza or varicella are more likely to develop Reye syndrome if they have taken aspirin for a long time [4]. Aspirin is usually prescribed to reduce the rate of myocardial infarction, stroke, thrombosis or death in patient with a high risk of cardiovascular disease [18*,19*]. However, aspirin resistance was also reported with poor anti-platelet aggregation ability [20]. In fact, aspirin resistance can be defined as two categories. Clinical aspirin resistance usually refers to the failure of aspirin in protecting patients from ischemic cardiovascular events, while in the laboratory, aspirin resistance implies the incomplete inhibition of platelet reactivity [21,22]. Possible causes for clinical aspirin resistance include the activation of alternative pathway for platelet activation, incomplete suppression of thromboxane, inappropriate dosage, and the drug–drug adverse interactions with other medicines such as ibuprofen [4]. Of noted, there is a continuing debate regarding the dosage and side effects of ASA. It was reported that no significant differences in the incidence of CAA and IVIG resistance, and the duration of fever between low-dose and high-dose of ASA [23,24] were observed, therefore, whether high-dose ASA should be used during the acute phase of KD requires further evaluation.

**Treatment of complications of Kawasaki disease**

**Cardiovascular complications and treatments**

Coronary artery disease is the most prominent feature which can further induce CAA, coronary artery stenosis, myocardial infarction, sudden death or even ventricular arrhythmias in KD patients [25]. Chronic use of anti-platelet low-dose ASA (3–5 mg/kg/day) for inhibiting
platelet activation was required in KD patients with persistent CAA [15]. Coronary thrombosis and acute coronary syndrome are more likely to occur in patients with middle sized aneurysms and giant aneurysms [26]. In fact, increasing number of patients with coronary aneurysms associated with KD are entering adulthood, which increase the risk of heart attack caused by progressive arterial stenosis due to aneurysm thrombosis or vascular reconstruction [26]. It is known that endothelial cell damage and inflammation are the two essential processes involved in the coronary endothelial dysfunction of KD. Patients with KD were demonstrated with an increased serum level of pyroptosis-related proteins, including ASC, caspase-1, interleukin (IL)-1β, IL-18, gasdermin D and lactic dehydrogenase when compared with healthy controls [27]. Besides, IL-10 was identified as a negative regulator of cardiac inflammation in a murine model of KD induced by Candida albicans water-soluble fraction [28]. These findings demonstrated that IL-10 supplementation may help to prevent coronary vasculitis and aneurysm formation. Furthermore, atorvastatin therapy which can restore the expression of Krüppel-like factor 4-miR-483, was tested in clinical trial of KD patients and was shown to ultimately suppress the level of connective tissue growth factor and endothelial-mesenchymal transition in endothelial cells which contributed to the coronary artery abnormalities in KD patients [29].

**Kawasaki disease-macrophage activation syndrome and treatments**

Macrophage activation syndrome (MAS), also known as secondary or reactive hemophagocytic lymphohistiocytosis, is characterized by the overactivation and proliferation of T-lymphocyte and well-differentiated macrophages, leading to high mortality rate. It is commonly found in systemic juvenile idiopathic arthritis [30]. The clinical symptoms of MAS were persistent fever, lymphadenopathy, hepatosplenomegaly, hypochromia (anemia, leucopenia, thrombocytopenia), increased C-reactive protein (CRP) expression, low erythrocyte sedimentation rate, lower level of fibrinogenemia, high triglyceridermia expression and significant elevation of serum ferritin leading to multiple organ dysfunction [31,32]. MAS led to an overexpression of proinflammatory cytokines such as interferon (IFN)-γ, IL-1, IL-6, IL-18 and TNF-α, resulting in systemic immune injury [33]. MAS may occur when KD patients showed persistent fever, splenomegaly, thrombocytopenia, hyperferritinemia or IVIG resistance. Early diagnosis and control to the level of cytokine are important to reduce mortality rate of KD-MAS patients [34]. According to the clinical evaluation on patients, corticosteroid, IVIG, cyclosporine and monoclonal anti-TNF are the first-line therapy [35]. Plasmapheresis (PE) are effective alternatives for severe refractory cases [36].

**Kawasaki disease shock syndrome and treatments**

Kawasaki Disease Shock Syndrome (KDSS) is defined as the phenomenon of KD with hemodynamic instability. KDSS usually occurs in the acute phase of KD and is more prevalent in children with atypical KD. The exact mechanism and pathogenesis of KDSS remains unknown [37]. The clinical therapy of KDSS is based on symptomatic treatment. For example, with the early anti-inflammation strategy and maintenance of hemodynamic stability to control systemic inflammatory response, viscera and coronary artery damage, the prevention on the deterioration of multiple organ damage was achieved by using high-dose IVIG therapy combined with glucocorticoid anti-inflammatory therapy as the primary treatment [38]. IVIG plays an essential role in the modulation of KD and KDSS by decreasing the level of inflammatory factors, inhibiting the production of antibody and alleviating the immune response. Although there is no conclusive evidence that children with KDSS are more likely to develop IVIG resistance, based on the IVIG unresponsiveness risk prediction score and the characteristics of an intensified inflammatory response observed in KDSS children, caution should be taken with IVIG resistance in KDSS children [37,39]. The anti-inflammatory effect of glucocorticoid can stabilize lysosomal membrane and strengthen myocardial contractility. Methylprednisolone (MPL), a systemic synthetic corticosteroid [40], can be injected at 20–30 mg/kg for 1–3 days [41,42]. Although only a few cases of vascular and capillary leak were reported in KDSS patients [43], the use of combined clinical therapy of IVIG and vasoactive agents were also reported [44,45]. While noradrenaline is the first choice for vasoactive agents, epinephrine, dopamine and dobutamine can be used according to the state of the disease [46,47]. The strong inflammatory reaction of KDSS may cause IVIG resistance in some cases, consequently increase the risk of coronary artery disease and lead to a massive coronary aneurysm [48].

**Therapies for targeting intravenous immunoglobulin resistance and its complications in Kawasaki disease**

Although the lack of a widely adopted scoring system to predict IVIG resistance and limited available treatments remains the major problems in clinical practice [4], several drug alternatives (Table 1) have been reported [49].

**Corticosteroids**

Corticosteroids are one of the main treatments for various vasculitis and IVIG non-responsive KD patients. Because of its immunosuppressive and anti-inflammatory effect, corticosteroids are usually administered for lowering the risk of CAA in KD. Although the optimal steroid regimen is unclear, intravenous injection and long-term corticosteroids therapy remain one of the treatment choices for resistant KD [50].
Alternate therapies for IVIG resistance in Kawasaki disease

| Medicine                  | Dosage                                      | Mechanistic action                                                                 | Reference |
|---------------------------|---------------------------------------------|-------------------------------------------------------------------------------------|-----------|
| Methylprednisolone        | 20–30 mg/kg, maximum 1 g/day (oral administration) | Blocked inflammatory cytokines which resulted in the immunosuppressive effect       | [42]\(^\text{a}\) |
| Prednisone/prednisolone   | 1–2 mg/kg/day (intravenous injection, oral administration after symptom relief) | Inhibited the transcription of different inflammatory cytokines and promoted the transcription of anti-inflammatory cytokines and proteins | [4,55] |
| Infliximab                | 5 mg/kg (intravenous injection)             | Blocked and inhibited TNF-α, prevented the release of proinflammatory cytokine and interleukin | [4] |
| Anakinra                  | 2–6 mg/kg/day (oral administration)        | Downregulated various IL-18-mediated inflammatory responses, inhibited the binding between IL-1 and the receptor | [4] |
| Canakinumab               | 4 mg/kg (body weight < 40 kg) (oral administration) | Suppressed the inflammation through the neutralization of anti-IL-1β cytokines by another colloid including plasma or albumin from donor | [58]\(^\text{a}\) |
| Plasmapheresis (PE)       | –                                           | Replaced the plasma harboring the inflammatory cytokines that were only eliminated by IVIG | [66] |
| Cyclosporine              | 4–8 mg/kg/day (intravenous injection or oral administration) | Inhibited the calcineurin-NFAT signaling pathway and increased the activity of T cells | [70] |
| Methotrexate              | 10 mg/m²/week (oral administration)         | Inhibited lymphocyte proliferation and as a folic acid antagonist                    | [70] |

**Methylprednisolone**
MPL is the most commonly used corticosteroids to treat KDSS by blocking the rapid immunosuppressive effect from inflammatory cytokines and reducing the risk of electrolytes imbalance. Single intravenous injection of 30 mg/kg can be used in combination with IVIG as a first-line treatment for high-risk KD patients [51]. The AHA recommended using steroids in patients who have failed to response to 2 or more IVIG injections [52]. It was reported that the combined IVIG and steroid therapy for KD was more effective in attenuating the risk of CAA [53]. The use of IVIG combined with MPL on resistant KD patients improved prognosis, and shortened the duration of fever [54].

**Prednisone**
Prednisone has a strong effect on lowering the transcription level of multiple inflammatory cytokine genes, and simultaneously upregulated the level of various anti-inflammatory related proteins [55]. Combined treatment of prednisone with IVIG was reported to reduce the risk of coronary artery abnormalities [56], and is suggested as the treatment of IVIG resistant patients in Japan [57].

**The biologic drugs**
Biologic drugs are important agents for regulating TNF-α or IL-1 which triggered KD-related vasculitis. Owing to the role of TNF-α in the pathogenesis of coronary artery dilation and KD, using TNF-α inhibitors in the treatment of KD is possible [58\(^\text{a}\)]. However, without consolidated evidence about its safety and efficacy on KD treatment, evaluations can only be performed according to the experience of non-KD patients with other diseases using anti-TNF or anti-IL-1 biologic drugs.

**Infliximab**
KD patients demonstrated an increase in TNF-α expression. Infliximab (IFX), a TNF-α monoclonal antibody, exert its anti-inflammatory role via inhibition of TNF-α or soluble TNF-α receptor, lowering the levels of IL-6 or CRP to reduce the severity of vasculitis [4]. It has been reported in many studies to treat refractory KD, and considered as a replacement for the second line treatment in IVIG resistant patients [59\(^\text{a}\),60]. A phase III clinical trial result showed that the combinational treatment of IFX with IVIG can shorten the duration of fever and decrease the level of TNF-α in KD patients [61].

**Anakinra**
Anakinra is a recombinant IL-1 antagonist that competitively inhibits IL-1 and its receptors, thereby downregulating various IL-1 mediated inflammatory responses and IL-1 biological activity [4]. Anakinra may possess anti-inflammatory effects on systemic and coronary artery inflammation in a hypothetical KD model [62]. Of note, there are only a few reports of anakinra being used to treat KD in children.

**Canakinumab**
Canakinumab is a monoclonal antibody that reacts with IL-1β [63]. First phase clinical trials are currently undergoing for its efficacy in various diseases including gout, chronic obstructive pulmonary and coronary heart disease [64]. Unfortunately, a phase II clinical trial on the treatment of canakinumab to KD was withdrawn before recruitment of KD patients, and therefore further investigation is still required.

**Plasmapheresis**
PE can directly reduce the level of inflammatory cytokines and chemokines activated from the bloodstream,
and prevent the occurrence of CAA in KD patients [65]. Colloid was used for the replacement of plasma during PE [66]. Clinical study has reported PE as a treatment for both IVIG and IFX non-responsive KD patients with their fever symptoms relieved, and body temperature restored to normal after treatments [67].

Cyclosporine
As a calcineurin inhibitor, cyclosporine was suggested as a potential treatment to refractory KD via intervening the inositol 1,4,5-trisphosphate 3-kinase C/calcineurin pathway [68]. Besides, cyclosporine can also block the release of cytokine signaling molecule IL-2 and inhibit the differentiation of T cells, therefore attenuating inflammatory status of KD through cell-mediated immunity regulation. Although the efficacy of cyclosporine in the treatment of KD is still controversial, a phase III clinical trial in Japan using both IVIG and cyclosporine was reported effective in treating severe KD [69**].

Methotrexate
Methotrexate (MTX) is used primarily as an anti-cancer and anti-metabolite drug that blocked the synthesis and replication of DNA. Methotrexate is reported to reduce the level of CRP, erythrocyte sedimentation rate and decrease the level of IL-1 and IL-6 in KD [70,71]. In clinical studies, low dose of MTX was reported to improve clinical KD symptoms in resistant KD patients [72,73], suggesting oral administration of MTX might be an effective treatment to refractory KD.

Analysis of possible drug resistance gene of Kawasaki disease
Methodology on bioinformatics analysis
Analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement. Key words are ‘Kawasaki disease’ and ‘resistance’ OR ‘drug resistance’ to access the potential related data in the NCBI Gene Expression Omnibus DataSets database until May 2020. Relevant articles were also cited in this review. Statistical analyses were performed by using the R 3.5.0 software with Biobase and GEOquery package provided by Bioconductor (http://www.bioconductor.org/). 1221 datasets were retrieved in the primary search using the keywords. Consequently, 4 datasets with IVIG responder patient’s data were obtained. In these 4 datasets, 43 cases were involved (14 in the IVIG-responsive group, 21 in the IVIG-resistant patients’ group, 8 in the IFX group). Besides, the data of 46 healthy individuals and 86 KD patients were involved as control. Among the 4 datasets, 2 of them were single IVIG treatment group, and with the gene expression data recorded before and after IVIG therapy in both IVIG resistant and responsive KD patient. While the 3rd dataset included the gene expression level of IVIG-resistant patients after IFX rescue or secondary IVIG treatment, the last dataset included the gene expression profile for KD patients and with healthy individuals as control. A selection was performed according to these 2 criteria: 1. Gene expression data was found in all these 4 studies with no NA (which represents null in r language) value. 2. Expression of genes changes only in IVIG-resistant patients who received IVIG treatments (but not in IFX treatments or KD patients who did not receive treatments). After analysis, out of a total of 197,581 genes data contained in the 4 datasets, 25 genes appeared to be the potential IVIG resistant gene targets (Figure 2) for further investigation.

Potential intravenous immunoglobulin resistance genes
Lymphocyte Antigen 6 Family Member E (LY6E) is a member of human Ly-6 gene family [74]. It was identified as an encoder for stem cell protein markers which are related to the resistance of radiotherapy and the promotion of tumor metastasis in animal models [75]. Knockdown of LY6E led to significant reduction to a series of gene expressions includes ATP binding cassette subfamily G member 2, fibroblast growth factor 7, Nanog homeobox, CD34 molecule, and prostate stem cell antigen which are related to chemotherapy drug resistance [75]. Hence, the high expression of LY6E maybe one of the causes for IVIG resistance in patients. HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 5 (HERC5), also known as CEB1, participates in the ubiquitin-like interferon-stimulated gene 15/Ubiquitin-specific proteases 18 pathways. This pathway is closely related to the infection of hepatitis C virus and resistance to IFN treatment [76]. Since interferon-stimulated gene 15 can stimulate the production of IFN-γ [76,77], which participates in the activation of cellular immune response of IVIG treatments [78], this may further explain the potential relationship between HERC5 and IVIG resistance. In human tumor cells, constitutive indoleamine 2,3-Dioxygenase 1 (IDO1) expression depends on cyclooxygenase-2 upon autocrine signaling [79], while cyclooxygenase-2 was found to be associated with the susceptibility of KD [80]. This may suggest the possible correlation between the IDO1 and IVIG drug resistance in KD patients. With the limitation on the inadequate available data set on resistant KD genes, it is with great anticipation that more precise and accurate targets could be identified if the sample number can be increased. Although the above genes expression matched with the required criteria, more clinical and experimental evidence are required to characterize their roles and effects in resistant KD patients. Based on the meta-analysis results on the possible drug resistance genes of KD, the anti-LY6E antibody which binds to LY6E could be a solution to high LY6E expression [81], HZ-6d, a 7, 11-disubstituted quinazoline derivative that downregulated HERC5 [82], and inhibitors and antibodies targeting IDO1 including indoximod, 4-PI, N3-benzyl derivative, ortho-hydroxyl modifications and
navoximod [83] are also suggested as potential therapeutic agents for resistant KD in further pharmacological evaluation.

**Adjuvant therapies for treating resistant Kawasaki disease**

Current studies have shown that traditional Chinese medicines (TCMs) or natural compounds can be used as an adjuvant therapy for KD [84]. For example, combined IVIG treatment with triptolide reduced the level of intracellular cell adhesion molecule-1 and TNF-α in KD mouse models [85]. In additional to the single use of the IVIG, many clinical reports have described the combinational use of traditional herbal decoction or natural compounds to treat KD and resistant cases. For example, Jiang et al. summarized a list of TCMs prescribed for KD from 1990 to now, and concluded that *Gypsum fibrosum*, *Radix Rehmanniae*, *Lonicera japonica Thunb.*, *Forsythia suspensa* and *Coron Bubali* are the effective herbal medicines commonly prescribed for the treatment of KD [86]. Dan-Shen-Yin is widely used to treat coronary heart disease in clinical practice [87], studies have found that Dan-Shen-Yin reduced infarction size, the level of serum CRP, IL-6, TNF-α and malondialdehyde, and increased superoxide dismutase activity [87], which are closely correlated to the inflammatory level of KD. ‘Qingre Liangxue Decoction’ composed of *Gypsum fibrosum*, *Rhizoma Anemarrhena*, *Lonicera japonica Thunb.*, and other TCMs reduced the level of serum IL-33, TNF-α and platelet count, thus alleviated inflammation and hypercoagulability of KD patients, suggesting that Chinese herbs may play its protective role via reducing inflammatory reaction to protect the myocardium in KD patients [88]. Consistently, many clinical observations have reported the high efficacy of treating KD patients with the modified ‘Qingre Liangxue Decoction’ [89,90]. Furthermore, several traditional anti-inflammatory decoctions including ‘Danshen Shengmaiin Jiawei’ [91], ‘Baihu Decoction’ [92], ‘Qingying Decoction’ and ‘Zhuye Shigao Decoction’ [93] were reported with clinical efficacy in relieving the inflammatory level and clinical symptoms of KD patients. All these clinical application of TCMs in both classical and IVIG-resistance cases of KD still worth further investigation.

responsive patients (GSE16797 and GSE18606 datasets), GSE48498 IVIG column represents the difference of average gene expression before and after second IVIG treatments in IVIG non-responsive patients (GSE48498 dataset), while GSE48498 IFX column represents the difference of average gene expression before and after IFX treatments in IVIG non-responsive patients who showed failure in initial IVIG treatments (GSE48498 dataset). GSE68004 column represents the gene expression difference of KD patients with healthy control used as the baseline from GSE68004 dataset.
Conclusion
Since the first case of KD was reported in 1967, although modification on several major diagnostic criteria of KD have been made, combined IVIG and AAS therapy remains the standard major therapy for KD. With the limitations and side effects of the current combined therapy, such as the prognosis of IVIG resistance and Reye’s syndrome, other factors such as regional and ethnical variation in the epidemiology of KD, pathogenesis and immunological regulation of KD, ambient environment, dietary and genetic factors contributing to KD remains un-elucidated. To this end, many recent works have been focused on the identification of novel susceptibility gene and pharmacological therapy to both typical and resistant KD. On the other hand, consistent with the reported high incidence rate (90%) of new KD cases which were also diagnosed with COVID-19 [94], IgG antibodies of SARS-CoV-2 in KD patients were detected, indicating that the virus was associated with KD. However, MIS-C also has some unique characteristics, such as a higher age of onset with more teenager’s patients, prevalence of abdominal symptom, more signs of heart involvement and macrophage activation syndrome. Although recent study has reported the recovery of a five-year-old child with positive COVID-19 and KD after intravenous IVIG [95], new diagnostic methods to avoid missed or delayed cases of KD during the COVID-19 pandemic is important [96]. With very few studies on COVID-19 and KD, although they may share many similarities, there is insufficient evidence to show the causal relationship between them. In the future, it is anticipated that the relationship between COVID-19 and KD, and also the new pharmacological treatment and adjuvant therapy to KD and MIS-C could be identified.

Author contributions
BYKL and JC conceived and designed the review content; BYKL, RLZ and HHL drafted the manuscript; HHL performed the bioinformatics analysis, designed and drafted the figures and graphical abstract; BYKL, CL, and NI edited and proofread the whole manuscript. RLZ and HHL performed literature search and table preparation. RLZ and HHL are co-first authors and contributed equally to the work. Dr Betty Yuen-Kwan Law and Prof Juan Chen are co-corresponding authors.

Conflict of interest statement
Nothing declared.

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