



Trust Me, I'm Artificial Intelligence - The Roles of AI in Rheumatoid Arthritis



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Rheumatoid arthritis (RA) is a systemic autoimmune pathology associated with a chronic inflammatory process leading to damage in joints and extra-articular organs, including the heart, kidney, lungs, digestive system, eye, skin, and nervous system¹. Patients with RA commonly suffer from persistent pain, fatigue, and various physical and psychosocial impacts². With the recent technological advancement, the roles and applications of artificial intelligence (AI) have grown in the medical field. For instance, AI has been suggested to improve the diagnostic process of RA, optimise treatment protocol, and to be used in drug development³. In a recent interview, Dr. Yeung Wan Yin Winnie, Specialist in Rheumatology, highlighted the disease burden of RA and shared her opinions on the potential roles of AI in managing RA.

People at Increased Risk of Rheumatoid Arthritis

Patients with RA often experience a reduced quality of life in several domains, such as physical health, level of independence, environment, and personal beliefs, compared with the healthy population³. Moreover, the disease also incurs a substantial socioeconomic burden on the patients, their families, and society⁴. The global prevalence of RA ranges between 0.3% and 1.0%, whereas that reported in Hong Kong was 0.35%⁵.

RA affects patients of all ages, but the ages between 35-50 appear to be the peak⁵. Although the exact cause of RA is yet to be fully understood, Dr. Yeung outlined that genetic, hormonal, and environmental factors may play significant roles in initiating the disease. For instance, a family history of first-degree relatives having RA would increase the risk by 2- to 3-fold⁶. Moreover, Järvinen and Aho (1994) reported that the concordance rate in monozygotic twins is approximately 15-20%⁷. Dr. Yeung added that individuals having specific shared epitopes of the human leukocyte antigen (HLA), such as HLA-DRβ1 *0401, *0404, or *0405, are at an increased risk⁸.

Interestingly, while the risk of RA is 3 times higher in females and the difference diminishes in older age groups, sex hormones thus possibly affect the risk of RA⁵. Besides, rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies (anti-CCP) are associated with the progression of

joint destruction in RA patients and are useful for diagnosing RA⁹. Dr. Yeung highlighted that tobacco smoking is a well-known environmental risk factor for RA. A meta-analysis by Di Giuseppe *et al.* (2014) demonstrated that cigarette smoking increases the risk of RA development by 26% in those who smoked 1-10 pack-years and 94% in those with more than 20 pack-years compared to never-smoker¹⁰.

Rheumatoid Arthritis - A Real Medical Challenge

RA primarily affects the lining of the synovial joints and can cause progressive disability. Common clinical manifestations of RA include arthralgia, swelling, redness, and limited range of motion in joints symmetrically¹¹. "Typically, the symptoms occur in smaller joints such as fingers and toes," Dr. Yeung noted. Other systemic symptoms of RA include morning stiffness of the affected joints for more than 30 min, fatigue, fever, and weight loss¹¹.

Uncontrolled RA would result in both synovial and systemic complications. "Unrelenting RA is characterised by uncontrolled inflammation with consequent damage to cartilage and bone of joints leading to joint deformity," according to Dr. Yeung. The classic examples of joint deformities associated with RA include Boutonniere deformity and Swan neck deformity in fingers¹¹. In considering the systemic impacts, RA-associated inflammation and damage may occur in the skin leading

to rheumatoid nodules and vasculitis. RA can also trigger interstitial lung disease, pleuritis and pleural effusion. Moreover, RA would result in complications in the heart, e.g., pericarditis and pericardial effusion, and eyes, e.g., episcleritis and scleritis, as well⁵.

Apart from pathophysiological complications, RA contributes to various psychosocial consequences. "Some patients may be depressed, while others may experience anxiety," Dr. Yeung noted. Indeed, the prevalence of depression among RA patients is 2-3 times higher than in the general population. A meta-analysis reported 16.8% of RA patients would develop major depressive disorders¹². Dr. Yeung explained that the patients might worry about the impacts of RA on their lives and sleep quality. Remarkably, she added that fibromyalgia would also worsen patients' emotions.

● Mitigating the Adverse Impacts of RA

RA is a long-term, progressive inflammatory and systemic disease. Currently, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend RA should be managed from 2 perspectives: symptomatic treatment (NSAIDs and GCs) and disease-modifying management (DMARDs)¹. In addition, non-pharmacological interventions are required to maximise therapeutic success.

While physical exercises are beneficial for RA patients, Dr. Yeung particularly recommended swimming and water-based exercises. "The risk of joint damage associated with swimming is low, and the exercise is particularly suitable for overweight patients, especially in Summer," she stated. Given joint pain would increase the likelihood of disuse and hence muscle atrophy, muscle-strengthening exercises help relieve the loading of joints. Moreover, physical exercises would reduce the cardiovascular risk among RA patients, regardless of type.

Diet is one of the factors governing our health. Notably, a systematic review of human prospective studies by Forsyth *et al.* (2018) reported that Mediterranean diet would significantly reduce pain and increase physical function in RA patients¹³. Subsequent commentary by Badsha (2018) suggested that Mediterranean diet shows anti-inflammatory effects due to the protective properties of omega-3 polyunsaturated fatty acids and vitamins, and by influencing the gut microbiome¹⁴.

Apart from physical exercises and diet, patient education is essential to improve the person's life as much as possible despite the disease. "Patients should learn self-care abilities

to cope at home with the varying symptoms caused by RA," Dr. Yeung advised. She added that effective patient education enables patients to seek help and relieve anxiety. Because of the increased risk of psychological complications among RA patients, psychological intervention is a crucial component in ensuring the psychological well-being of RA patients. Of note, a recent systematic review by Slagter *et al.* (2022) demonstrated that mind-body therapies such as meditation, yoga, and mindfulness improved RA patients' vitality, functioning, and mental health and symptoms related to disease activity¹⁵.

As the primary weapons countering RA, the efficacy of pharmacological interventions has been evaluated in previous studies. For instance, it has been reported that over 60% of RA patients achieve a good response after 12 months of treatment when following the EULAR guidelines for treatment¹⁶. Despite the promising efficacy, in considering the safety profiles of RA medications, Dr. Yeung noted that infections are a main concern for patients considering DMARDs. A meta-analysis by Singh *et al.* (2015) indicated that biologic DMARDs are associated with an increased risk of serious infections compared to traditional DMARDs, with an absolute increase in serious infections by 6 per 1,000 cases¹⁷.

● AI – A New Member of the Multidisciplinary Team

AI refers to a wide range of interdisciplinary approaches enhancing machine capabilities. Since AI is getting more sophisticated and promises to improve the diagnostic process in healthcare, the technology is expected to help reduce diagnostic time, provide cost-effective improvements, and support decision-making in clinical settings.

Dr. Yeung noted that facilitating the analysis of imaging data is one of AI's potential roles in managing RA. "While X-ray and ultrasound are commonly applied to diagnose RA, certain observations such as joint effusions and subchondral cysts might not be indicative for RA. With machine learning, AI might precisely estimate the likelihood of RA and other diseases with similar imaging features," she commented. She opined that the progress of machine learning is far more rapid than human learning and that computers can generate analysis by summarising millions of image data which is impossible for humans. In this regard, Stael (2020) reviewed that AI can be an alternative to visual scoring. Given that automation is allowed, image data analysis with AI would be less time-consuming, more objective, and consistent, and at a lower cost. Practically, less staff training would be required¹⁸.





Another application of AI in rheumatology is the analysis of biomarkers. Dr. Yeung outlined that the diagnosis of RA-associated interstitial lung disease (RAILD) requires evaluation of the patient's medical history, clinical characteristics, laboratory indicators, high-resolution computed tomography (HRCT), pulmonary function test (PFT), and even lung biopsy. Nonetheless, the present assessment tools, including chest X-ray, HRCT, and PFT, may not be optimal for all patients. In contrast, blood biomarkers would be useful in RAILD diagnosis.

The application of AI in the analysis of biomarkers was demonstrated in a recent trial by Qin *et al.* (2022) involving 153 RA patients with RAILD. Blood biomarkers were identified among the profiles of the patients by using machine learning classifiers and probe correlations between the markers and the characteristics of RAILD. The results suggested that the levels of Krebs von den Lungen-6 (KL-6), D-dimer, and tumour markers, such as carbohydrate antigen (CA) 19-9, greatly aided RA-ILD identification¹⁹.

"AI and human analysis are complementary in developing diagnosis and treatment protocols for RA patients," Dr. Yeung expressed.

Beyond Clinical Management

Besides clinical management, Dr. Yeung suggested some potential applications of AI beyond the management of diseases. For instance, while many medical records worldwide have been digitalised, the development of global electronic health records (EHRs) would provide important real-world data. Remarkably, Dr. Yeung noted that a substantial proportion of current EHRs focuses on Caucasians though there are reports on ethnic minorities. Accordingly, AI facilitates capturing an almost complete variety of patients, leading to more generalisable results. Through machine learning, AI allows clinicians to leverage a large amount of heterogeneous clinical data for clinical algorithms, testing, and validation²⁰.

Currently, drug discovery is primarily hypothesis-driven, whereas the chance of successfully developing a medication that can be approved for clinical use is modest. Designing and optimising a compound with well-balanced biochemical activity, selectivity, and physical properties is challenging. In this regard, AI-based modelling technology for ligand and structure-based *de novo* drug design focusing on multi-parametric optimisation and AI-driven synthesis planning is

expected to shorten the timeframe for drug development and probably at a lower cost.

The Multidisciplinary Team in RA Care

Dr. Yeung emphasised that the role of a multidisciplinary team is crucial for the holistic care of RA patients. Physicians play a core role in making the appropriate diagnosis and providing timely treatments. She further highlighted the importance of understanding the patient's overall conditions, such as diabetic status and bone quality. Besides, both physicians and rheumatology nurses have the role of educating patients about the disease, the treatments, and, importantly, how to live with the disease. Moreover, the parts of physiotherapists and occupational therapists are vital in the rehabilitation of patients. In cases of severe joint deformity and pain, orthopaedic surgeons will evaluate the condition and perform surgery if necessary. Given that RA contributes to the psychological burden, clinical psychologists and psychiatrists are also involved in managing RA. On the other hand, local non-governmental organisations (NGOs) provide information and support to RA patients.

Dr. Yeung mentioned that AI would help physicians in accurate diagnosis and prognosis for RA patients. However, it is unlikely that AI will replace physicians in providing care for patients. She noted that AI could not perform data processing if no clinical and research data were provided by clinicians at the initial stage. Thus, human analysis is vital in the development of AI algorithms. Of importance, doctor-patient interaction is an essential component in the holistic management of RA. "Patients expect the care provided by doctors and other healthcare professionals, which AI or computers cannot replace," Dr. Yeung noted.

To conclude, AI will provide extensive benefits in clinical management and drug discovery for RA and other diseases. It also facilitates optimisation in the operation of the healthcare system. Instead of replacing the role of clinicians, AI will more likely emerge as a new member of the multidisciplinary team, improving patient outcomes.



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