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Commentary

Potential of artificial intelligence in the diagnosis and prediction of pediatric pneumonia caused by *Mycoplasma pneumoniae*

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Abstract

Mycoplasma pneumoniae pneumonia (MPP) in children has experienced a global resurgence following the COVID-19 pandemic, which has been associated with more severe and/or refractory cases. Simultaneously, macrolide-resistant strains have emerged in recent decades. This new reality has increased the risk to pediatric patients and is testing the healthcare system's response. In this context, artificial intelligence (AI) is emerging as an aid or complement to the work of physicians treating children with MPP. Unfortunately, the scientific evidence regarding the contribution of AI to MPP is still limited. This manuscript compiles the most relevant studies that demonstrate that AI could be successfully applied to support diagnosis, predict severity, and assess the response to certain treatments.

Keywords: Artificial intelligence, Pneumonia, *Mycoplasma pneumoniae*, Children

Introduction

Mycoplasma pneumoniae (MP) is a slow-growing bacterium that has been found in 10 to 40% lower respiratory infections in children, and with outbreaks occurring every 3 to 7 years [1]. First-line treatment includes macrolides such as azithromycin; however, when severe *Mycoplasma pneumoniae* pneumonia (SMPP) is present, it is common to use tetracyclines or quinolones, corticosteroids, or anticoagulants [2]. Between 2023 and 2024, there was a global and simultaneous outbreak of respiratory infections caused by MP, which was more intense in children than those described before the COVID-19 pandemic [3]. In recent years, cases of refractory *Mycoplasma pneumoniae* pneumonia (RMPP) in children have become more frequent, characterized by prolonged fever and clinical-radiological deterioration despite well-managed macrolide therapy for at least 7 days [4]. In addition, since 2000, there has been an increase in cases of macrolide-resistant *Mycoplasma pneumoniae* pneumonia (MRMPP) in children, with prevalences of up to 70–90% in East Asia, which has further complicated the management of this disease [5]. This new reality presents a challenge for the future management of MPP. AI emerges as a tool that could accelerate and deepen knowledge in the diagnosis and treatment of MPP. Machine learning (ML) is the area of AI that has gained the most relevance in respiratory medicine, as it allows for the processing of data to detect patterns and make predictions. However, there are more complex subgroups of ML that have already begun to be used, such as Deep Learning (DL), which solves problems using artificial neurons; Reinforcement Learning (RL), which learns through trial and error with a system of rewards or penalties; and Natural Language Processing (NLP), which allows for the understanding and generation of human language [6]. In pediatric respiratory medicine, and especially in MPP, AI could facilitate the work of physicians by reducing the time spent searching for scientific information, lowering the administrative workload, improving

the analysis of diagnostic images, promoting the development of algorithms for predicting severity or response to treatment, and developing new drugs for MRMPP [7,8].

Prediction in Diagnosis

A recent line of research has focused on using AI to differentiate between MPP and pediatric pneumonias from other causes, including other viral or bacterial pathogens, as well as MPP with or without respiratory coinfection. A retrospective study compiled medical record data from over 7.000 patients diagnosed with childhood pneumonia to design a hybrid automated model capable of transforming, merging, and integrating free-text data with structured numerical records from the medical chart [9]. The model obtained in this study demonstrated good levels of accuracy (Acc), precision (P), recall (R), and F1 score (F1) for differentiating between MPP and pneumonia from other causes [9]. Another retrospective study developed a machine-learning-based model using routinely available laboratory parameters (complete blood count and C-reactive protein) to diagnose pediatric pneumonia. In this study, the Gradient Boosting Decision Tree (GBDT) model performed best, demonstrating high levels of area under the curve (AUC), Acc, specificity (E), sensitivity (S), positive predictive value (PPV), negative predictive value (NPV), and F1 score for differentiating MPP from other causes of pneumonia. C-reactive protein (CRP) and absolute Eosinophils (Eos#) were the blood parameters that contributed the most in the algorithm designed by the GBDT model [10]. A study measured serum cytokine levels in 336 hospitalized children with pneumonia caused exclusively by viruses or by MPP to develop a predictive model that would differentiate between the two groups [11]. The predictive nomogram from this study demonstrated that four factors can achieve high accuracy in predicting MPP: an elevated TNF-α/IL-10 ratio, older age, and lower levels of IL-8 and procalcitonin (PCT). Of these four parameters, the elevated TNF-α/IL-10 ratio was the variable with the greatest predictive impact [11]. ML has also been used to create predictive models for MP in patients with segmental or lobar pneumonia. One retrospective study analyzed clinical data from 630 children with segmental or lobar pneumonia to create a predictive model that could distinguish between MPP and pneumonia caused by other pathogens (non-MPP) [12]. In this study, the Random Forest predictive model performed best in predicting MPP, and the variables that contributed most to this model were: older age, increased platelet count, and increased serum lactic dehydrogenase LDH [12]. A study used data from 769 chest radiographs of children with pneumonia from two hospitals, which were analyzed using deep learning with three neural network models (ResNet50, DenseNet121, and EfficientNetv2-S) to measure their ability to discriminate between MPP and viral pneumonia. All three models achieved good accuracy in diagnosing MPP in the validation tests (Acc over 0.8), but the ResNet50 model had a more stable Acc than the other two models in the training tests [13]. One novel application of ML is radiomics, which involves analyzing large volumes of quantitative radiological data to help make clinical decisions with patients. A retrospective study analyzed high-resolution computed tomography (HRCT) images of 124 pediatric pneumonias with the aim of discriminating between MPP with or without bacterial/viral coinfection (Co-MPP) [14]. In this study, a predictive nomogram model was constructed by integrating clinical-demographic data with HRCT radiomic features (geometric, intensity, and texture features). The integrated nomogram model performed better ($p = 0.004$) in predicting Co-MPP than the model using only clinical data [14].

Prediction of Severe or Refractory Pneumonia

SMPP and RMPP have been the subject of study in recent years. In a single-center retrospective study, the records of 443 children hospitalized for MPP were analyzed to construct different models for predicting SMPP. The best model obtained satisfactory prediction levels (Acc = 0.91, AUC = 0.93). The main variables of the model that predicted SMPP were the number of days of fever and the levels of platelet count, lymphocyte/neutrophil ratio (INL), CRP, LDH, and D-dimer [15]. Another investigation with retrospective data of children hospitalized for MPP designed a model that had a good ability to predict SMPP (AUC = 0.96), and the variables with the best performance were pulmonary auscultation, erythrocyte sedimentation rate (ESR), PCT level, and IL-6 [16]. In a prospective cohort of 597 patients hospitalized for MPP from 1 month to 18 years of age, clinical-demographic and laboratory data were analyzed to build a predictive model of SMPP. The model that best identified SMPP had an AUC= 0.8 and had five variables, such as: the inflammatory protein S100 A8/A9, computed tomography (CT), retinol-binding protein (RBP), platelet large cell ratio (PLCR), and CD4+CD25+T Treg cells [17]. A study in children hospitalized for MPP created a predictive model with three urinary metabolites, such as 3-Hydroxyanthranilic acid (3-HAA), L-Kynurenine, and 16(R)-HETE, with good performance (AUC= 0.91) to predict SMPP [18]. Under some conditions, SMPP can cause damage to other parenchyma, such as the myocardium and liver. A model designed with clinical and laboratory data in children with SMPP showed that alanine aminotransferase (ALT) and MB isoenzyme (CK-MB) were the clinical variables that contributed most to predicting liver and myocardial damage, respectively [19].

A study performed a retrospective collection of clinical-demographic and laboratory data from 219 children to design a model that would allow discrimination between MPP and RMPP. The model achieved a good capacity to predict RMPP (AUC= 0.88), and the clinical variables that best contributed to the model were high fever, increased percentage of neutrophils (N%) in blood count, high LDH, and low albumin [20]. Another retrospective study identified five clinical variables that differentiated between MPP and RMPP in children under 14 years of age: older age, longer duration of fever, lower absolute lymphocyte count (L#), increased serum D-dimer level, and higher scores on pulmonary function imaging, depending on the presence or absence of consolidation and the amount of pleural effusion. This model achieved outstanding discriminatory capacity with an AUC of 0.907 for the development model and 0.96 for the validation model [21]. Another single-center retrospective study analyzed the records of 1332 patients hospitalized for MPP, of whom 9.2% presented with RMPP. The model that performed best in predicting RMPP (Acc = 0.8, AUC = 0.93) incorporated eight variables: longer duration of fever, higher peak fever, macrolide use, increased levels of blood parameters (LDH, N%, and ALT), SMPP, and extensive pulmonary consolidation [22]. In a study of patients under 18 years of age hospitalized for MPP, a deep learning model was used with HRCT images that included identification, segmentation, and volumetric calculation of the pneumonia area. This data was combined with variables that best predicted RMPP, such as longer duration of fever before hospitalization or macrolide therapy before hospitalization, and higher aspartate aminotransferase

(AST) levels, to create a predictive clinical-imaging model of RMPP, which demonstrated better performance than the clinical or imaging models used separately [23].

Plastic bronchitis (PB) is one of the complications of MPP. A multicenter study collected clinical and radiological data from HRCT of 777 children with MPP and pulmonary consolidation. Using this data, a multifactorial mixed model was constructed that accurately predicted which children were at higher risk of developing PB as a complication of MPP [24]. The multifactorial model that achieved the best predictive performance incorporated three variables: pleural effusion, radiomic area of pneumonia, and radiomic area of total lung [24]. A study retrospectively analyzed clinical and laboratory data from 547 children with RMPP who underwent fiberoptic bronchoscopy (FOB). In such a study, a model was built that displayed adequate performance (AUC = 0.81) when predicting BP that included six variables: peak higher body temperature, higher N%, increased absolute platelet count (PLT#), increased IL-6, increased LDH, and pulmonary atelectasis on HRCT [25].

Prediction of Treatment Response

Currently, macrolides are the first choice in the treatment of MPP. Conditions such as poor gastric tolerance or absorption, hypoxia, or severe respiratory failure preclude the use of oral macrolides. In these scenarios, intravenous azithromycin administration becomes a viable option; however, its efficacy and safety have not been fully studied. A recent study used ML to create a pharmacokinetic model to measure the effectiveness of azithromycin in children with bacterial pneumonia. In this study, the area under the plasma concentration-time curve over 24 h (AUC_{0-24}) of intravenous azithromycin was measured, considering the most relevant clinical variables such as age in years, weight in kilograms, dosage in milligrams, and blood ALT level, achieving an accuracy of 90.4%, specificity of 80.4% [26]. The increasingly frequent and uncontrolled use of macrolides in respiratory infections has led to the emergence of MRMPP. A study retrospectively analyzed clinical data from 968 hospitalized children with MPP to design models that would allow discrimination between MRMPP and macrolide-sensitive MPP (MSMPP). The designed model achieved good indicators to predict MRMPP (AUC = 0.8, S = 0.76, E = 0.984), and the clinical variables that contributed the most were the evolution and prehospital use of macrolides and the levels of CRP, albumin/globulin ratio (A/G), interleukin-17 A (IL-17 A), and interferon gamma (IFN-γ) [27]. In children with MPP, related genetic mutations have been identified that could be responsible for the clinical worsening. A single-center study was conducted in children hospitalized for MRMPP to define a predictive model for multilobar consolidating pneumonia with the 23S rRNA A2063G mutation [28]. The model that performed best in predicting MMRPP with the genetic mutation and multilobar consolidation achieved an AUC above 0.9 (training and validation group). The model biomarkers that contributed most to clinical decision-making were, in descending order, CRP, LDH, fibrinogen, PLT, and albumin [28]. With the emergence of MRMPP, the study of molecules capable of inhibiting some immunological pathways activated in MP infection has gained greater interest. Toll-like receptors (TLRs) are part of innate immunity and play a role in recognizing MP infection, but also in amplifying the immune response by stimulating the production of inflammatory molecules. Emerging studies that use ML to collect and analyze data on substances with potential inhibitory biological activity on TLR2 and TLR4 by means of Quantitative Structure-Activity Relationship (QSAR) achieve fine levels of precision, which pave the way for the future search for antimycoplasmal drugs in MRMPP [29,30]. Flexible bronchoscopy (FB) is a procedure that can be used to treat children with MPP who progress with atelectasis or persistent consolidation despite treatment. A retrospective two-center study analyzed and integrated clinical and radiological data in children hospitalized for MPP in whom at least one CT scan was performed during hospitalization [31]. In this study, AI was used to quantitatively analyze CT to integrate it with clinical and laboratory characteristics. With this data, a model was designed that compared patients who required or did not require FB during hospitalization, using the duration of fever in days as the main outcome. Patients who received FB had shorter durations of fever during hospitalization and had a higher proportion of consolidation/atelectasis volume (CAV), pneumonia attenuation (PA), and consolidation-to pneumonia ratio compared to non-beneficiary groups. The model also demonstrated that patients who benefited most from FB were those with CAV combined with elevated PA or lymphocyte counts [31].

Conclusion

AI allows the use of clinical data and laboratory tests to differentiate MPP from infections caused by other factors, such as viruses or coinfections. It also allows differentiation between MPP, SMPP, or RMPP, complications such as PB or extrapulmonary systemic damage. It is even being used in the pharmacokinetics of macrolide treatment, the prediction of MRMPP, new antimycoplasmal molecules, and the selection of patients with a better response to more invasive procedures such as FB. However, most studies are retrospective, which introduces a selection bias that could influence the results. Furthermore, many studies using AI models have been conducted in hospital settings or at a single institution, making it impossible to generalize the findings to the full spectrum of children with MPP. Future research in this field should incorporate more studies in the prehospital setting, limiting models to a few readily accessible and low-cost clinical variables. Furthermore, predictive models for MPP with viral or bacterial coinfection or extrapulmonary manifestations should be expanded.

Conflict of Interest

There is no conflict of interest in this study.

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