A Systematic Literature Review of Machine Learning Applications for Community-Acquired Pneumonia

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Abstract. Community acquired pneumonia (CAP) is an acute respiratory disease with a high mortality rate. CAP management follows clinical and radiological diagnosis, severity evaluation and standardised treatment protocols. Although established in practice, protocols are labour intensive, time-critical and can be error prone, as their effectiveness depends on clinical expertise. Thus, an approach for capturing clinical expertise in a more analytical way is desirable both in terms of cost, expediency, and patient outcome. This paper presents a systematic literature review of Machine Learning (ML) applied to CAP. A search of three scholarly international databases revealed 23 relevant peer reviewed studies, that were categorised and evaluated relative to clinical output. Results show interest in the application of ML to CAP, particularly in image processing for diagnosis, and an opportunity for further investigation in the application of ML; both for patient outcome prediction and treatment allocation. We conclude our review by identifying potential areas for future research in applying ML to improve CAP management. This research was co-funded by the NIHR Leicester Biomedical Research Centre and the University of Leicester.

Keywords: Community acquired pneumonia, Machine Learning, CAP prediction, CAP outcome prediction, CAP treatment

1 Introduction

Pneumonia is a respiratory condition that represents a worldwide public health concern, since it involves high mortality, affects Intensive Care Unit (ICU) capacity, and results in high costs for health systems [1]; with annual costs for care and management of €2.5 billion in Europe and $9.5 billion in the United States [2, 3].

Community acquired pneumonia (CAP) occurs when infection is transmitted outside hospitals and in people over the age of 16. CAP management comprises diagnosis, severity prediction, and treatment with or without hospital and/or

ICU admission. Individuals are diagnosed using X-rays to identify "shadowing clusters" in the lungs. If admitted, Hospital-based severity assessment generally employs standardized scoring systems evaluating severity based on patient's symptoms and signs - for instance CURB65, PSI, ADROP. Assessments include baseline physiological observations as well as biochemical and haematological tests. CAP treatment may be delivered on general respiratory wards or involve ICU care, and most importantly involves pathogen directed antibiotic therapies and also other measures [1].

Machine Learning (ML) and Artificial Intelligence (AI) have been successfully applied to respiratory medicine conditions. For instance, Angelini et al. discussed the detection of pulmonary tuberculosis from radiographs, and identification of pathologically enlarged intrathoracic nodes from computed tomographies (CTs) [4]. Complementary, Chumbita et al. briefly discussed whether ML can be employed to improve CAP management [5].

This paper presents a structured review of peer-reviewed literature of ML applied to CAP management, classifying studies and results with the aim of identifying areas that may benefit from further research. The paper is structured as follows: in Section 2, we set out the approach used to carry out our review; Section 3 presents the papers that meet the review criteria and their clinical classifications; and in Section 4, findings of our review are discussed along with our conclusions and potential further study.

2 Methodology

The review was carried out using the methodology of Petersen et al. [6], and following the PRISMA statement checklist for systematic reviews in healthcare science [7]. The steps taken included: i) define the research questions (RQ) (Section 2.1); ii) define search terms and screen results (Section 2.2); and iii) classification and extraction of information (Section 2.3).

2.1 Research Questions

A total of five research questions were proposed:

1. What ML and data-based approaches have been employed to support CAP management? Identifies main clinical outputs where ML has contributed to CAP management.
2. What kind of data and features have been used and which sources studied? Evaluates relevance of data used in studies and consequently the generalisation and validation of those studies.
3. What statistical and AI approaches have been tested? Maps the extent, and complexity of ML techniques applied to CAP.
4. How have the AI models been assessed and compared? Enables performance assessment of algorithms and models used in literature, thus enabling definition of state-of-the-art in the domain.
5. What is the level of interpretability that models have reached? Lack of interpretability is regarded as a limitation for use of models in clinical settings.

2.2 Searching and screening

A comprehensive search was performed using three major scholarly international libraries—PubMed, ScienceDirect, and Web of Science. The search term is given in Figure 1, and only articles published in peer reviewed conferences or journals between January 1990 and June 2020 were considered. This period gathers the main articles in the field.

("artificial intelligence" OR"data science" OR "machine learning" OR"adaptive models") AND ("severity" OR "outcome" OR "mortality" OR "prediction" OR "diagnosis") AND ("pneumonia")

Fig. 1. Searched terms in scholarly international libraries

Articles were screened for inclusion or exclusion in two stages. In the first stage they were considered based on title, keywords, and abstract. Then, Articles were screened based on full content. Those that addressed any phase of CAP management using ML or adaptive models (not necessarily AI) were included. Those where content is not novel research (reviews, case reports, opinions etc), or relate to respiratory disease that is not pneumonia, or do not present adaptive/AI models were excluded. Articles primarily relating to COVID-19 were also excluded.

2.3 Classification and data extraction

Included articles were subjected to classification considering both clinical utility and ML output. Four categories were considered: *diagnosis* (presence of the disease in patients), *outcome prediction* (severity, course of disease, and mortality), *ICU admission prediction* (ICU outcomes), and *treatment* (predicted treatment for specific patients). For each study we extracted the following information:

Data: Our study considered the analysis of types of data (such as images, text, time series, tabular); the size of data sets (number of records); and the data source. These considerations are necessary as ML models use data to calculate hyper parameters that determine patterns between features and target values that are then used to classify new data.

Algorithms The study considered different classifications of algorithms including relational models: Causal Probabilistic Networks, Markov Chains, Bayesian networks, logistic regression (LR), Decision Trees, Random Forest (RF), Support Vector Machines (SVM), rule based heuristics. And non relational models: Boosting methods, Neural Networks (NN), Convolutional NN (CNN), Generalised Additive Models (GAM).

Performance: The study considered different performance measurements including precision, sensitivity, specificity, F1 and mainly AUROC curves that present variation of trade-off between sensitivity and specificity depending on decision threshold.

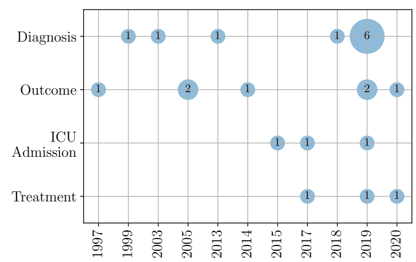

Fig. 2. Year and clinical contribution

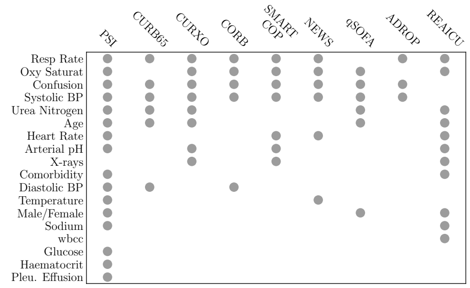

Fig. 3. CAP scoring and features

3 Results

Initial searching found 578 articles—201 in PubMed, 239 in Science Direct, and 138 in Web of Science. First stage screening reduced this to 94, and second stage, to 23 articles that were deemed relevant. Classification is shown in Figure 2: 10 on diagnosis, 7 on outcome prediction, 3 on ICU admission prediction, and 3 on treatment. CAP specific data was used in 15, the other 8 were not specific about the type of data although their approach suggested it may be CAP specific.

The majority of studies were published from 2017 onwards with the earliest in 1997 (Figure 2)—indicating significant previous and recent interest in the area. In terms of the types of data (Figure 4), hospital admissions data was the most frequent (12), followed by chest X-ray images (6), time series of electronic health records (EHR) (2), text medical reports (2), and statistical meta-data (1). In terms of size, four studies used data sets with fewer than 1000 samples, four greater than 20000, and the rest an intermediate size. Moreover, features employed were mostly associated to data relevant to CAP severity scores such as oxygen saturation, respiratory rate and those presented in Figure 3.

In terms of techniques, the most common were relational algorithms. CNN and DL algorithms were mainly used for classification of image diagnosis. Studies involving NN presented before 2012 (5) were simpler than those after (2)—fewer hidden layers and without regularisation methods. Most of the studies (13) use AUROC for performance and accuracy measurement.

3.1 Diagnosis

Diagnosis is the primary topic of ten articles, seven of which focus on image classification ([8–14]), and three apply the model to clinical data([15–17]).

Two established datasets were identified as primary sources for these studies. These consist of ChestX-Ray14 from Kaggle (112,120 frontal chest X-ray images from 30,085 patients[10]) and CheXpert (a set of chest X-rays for automated interpretation of different chest conditions, labelled by radiologists [18]).

Models were mainly directed to identify shadowing clusters in lungs, with results defined as a diagnosis classification. These image processing studies are the most recent corresponding to those published between 2018 and 2020 in Figure 2.

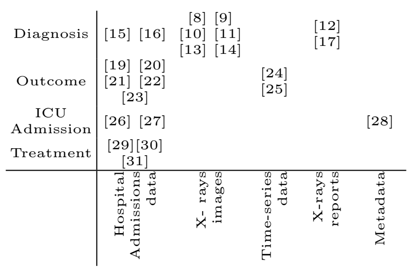

Fig. 4. Distribution of articles

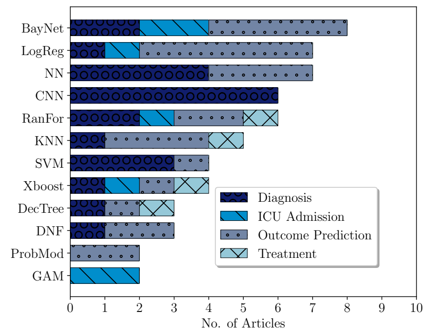

Fig. 5. Frequency of algorithms

Knok et al. implemented a VGG16 CNN with 94% accuracy using ChestX-Ray14, also fine-tuned the network using a drop-outs technique in the final three dense layers [9], although this model would benefit from further evaluation as the validation set was small and unbalanced (532 images and 73% as health lungs). Varshni et al. used different CNN architectures (XCeption, VGG16-19, ResNet50, DenseNet121-169) as feature extractors, with classification performed using relation methods (SVM, Naïve Bayes, KNN and RF) resulting in a total of 24 models tested [10]. In this work, the best AUROC reported was 0.8 using a DenseNet169 ensemble with a SVM classifier. Vijendran et al. reported a NN employing online sequential learning with an accuracy of 92% for the same dataset [13].

CheXpert was used to interpret real-time chest images for different lung conditions reporting an AUROC of 0.9 for pneumonia diagnosis, 0.88 for pleural effusion and 0.79 for multilobar anomaly [12].

Alternative models have exhibited less accuracy. O'Quinn et al. pre-process data to balance the number of positive and negative samples, resulting in an accuracy of 72% [11]. A comparison of CNN and classic classifiers reports CNN with the best performance at 84% [14]. While an accuracy of 83% was obtained by identifying affected regions of the lungs on the image [8].

DeLisle et al. describe studies that evaluate text data and assess their models with recall, precision, and specificity using a heuristic incorporating EHR reports to diagnose acute respiratory disease [15]. Additionally, Chapman et al. present statistical frameworks that analyse X-ray reports to predict CAP, the best of which is a Bayesian Network [17].

3.2 Outcome Prediction

CAP scoring systems and features are depicted in Figure 3 and are used as a benchmark for ML models to predict mortality or severity. Studies of clinical outcome prediction have utilised relational algorithms [19–21]. LR and single layer networks have been used to greater effect, showing the promise that ML, and more complex models, may deliver [21].

In more recent articles, rules-based models were proposed to predict 90-day mortality, with a highest AUROC reported of 0.78 [24]. In another study, the SepsisFinder model was developed in and predicted 30-day mortality and bacteraemia [22]. At 0.811, the AUROC reported for this model is higher than that reported for PSI (0.799) and CURB65 (0.75), although a comparison with other ML models is not presented. Shimzizu et al. developed three models to assess the risk of in-hospital mortality: XGBoost, LR, and RF with AUROCs of 0.88, 0.84 and 0.83, respectively [23].

Use of Markov Chains based on qSOFA scores for time series analysis produces an outcome prediction matrix [25]. Although the authors note that it is limited as it does not consider systematic implications of the disease. Nevertheless, this study is the most advanced in terms of predicting evolution of the disease over time.

3.3 ICU Admission prediction

Hospital admissions have been studied based on the likelihood of readmission to ICU. In one study, decision trees based on Bayesian models complementing CURB65 were used to determine whether a patient should be treated as an outpatient or ICU patient [28]. Unfortunately the use of metadata from another study meant that direct comparisons could not be drawn, since results were the variance analysis of the model (ANOVA) rather than the validation of it. Possible re-admissions to hospitals have been considered using LR, RF, Boosting, and GAM reporting an AUROC of 0.78 [26, 27]. The benefit of the GAM model is that it can also evaluate interactions between features.

3.4 CAP Treatment

Treatment is a relevant area with few reported studies. Konig et al. created decision trees determining best use of antibiotic combination therapy involving macrolides. It is important to note that although macrolides therapy can be beneficial for CAP management, it is also associated with cardiovascular toxicity. However, results of this study suggest significantly reduced mortality (27%) when utilised based on their model[29].

Khajehali et al. considered clinical factors affecting admission state and prediction of length of stay. Their model involved imputation of missing values. Bayesian boosting produced the best result in this study with an accuracy of 95.17%—they also reported use of Meropenem as antibiotic to reduce length of stay in patients admitted with CAP [30].

Aetiology (whether the disease is viral or bacterial) was studied using 43 clinical and 17 biological features [31]. Relevance of the features was assessed using LR and predictions were made using an RF classifier on a dataset of 93 samples. This work did not include validation using larger datasets, or evaluation relative to other models.

4 Discussion and Conclusion

This section considers the results of our review relative to the questions presented in Section 2.

RQ 1: The main classification or prediction approaches of ML for CAP are: diagnosis, mortality prediction, hospital admission status, and treatment. Diagnosis is the area that has received most attention from an ML perspective particularly analysis of X-ray imaging. There has been limited focus on treatment prediction, lack of studies offering support for intervention and antibiotic selection represents a gap in the field and could prove to be a rewarding area for the application of deep ML models to stratified treatment.

RQ 2: A number of the studies used relatively small datasets (12 with fewer than 3000 samples), mostly from hospital admissions. Non-image based studies included from 7 to 160 data features, with the most relevant presented in (Figure 3). There is a lack of time-series data, and few studies reported management of missing values or dirty data. Another common issue uncovered in our study concerns the size, reproducibility and scalability of data sets used for evaluation including distribution and characteristics of data, which vary widely. A clear state-of-the-art approach appears not to have emerged yet.

RQ 3: Most studies employed relational algorithms—LR, RF, Bayesian Networks—as shown in Figure 5. Bayesian networks were mostly naive, implying independence of features, which is unlikely to have clinical utility. Poor LR performance has shown many non-linear dependencies, and unbalanced data in CAP data.

For outcome prediction and ICU admission prediction, NNs have been used, although architectures do not go over three hidden layers. There is certainly scope for further study in this area as Deep Learning and ensemble models have previously been shown to offer benefits in other clinical applications [1, 4, 5]. There may also be opportunities to exploit transfer learning in this area, or other emerging models such as recurrent NN. At this stage the most promising technique would depend on the research question and data available.

Only one study suggested a fine-tuning process [9]. This group presented the evolution of training and validation sets to identify when the model identified general patterns of data, rather than specifics of training set (overfitting).

RQ 4: AUROC curves are the generally accepted method of reporting and comparing performance of binary classification models, although in some cases accuracy, sensitivity, and specificity are used. This can create issues when drawing comparisons.

RQ 5: Interpretability is as important as performance in clinical settings. Most studies reported typically consider performance without considering this or clinical availability. Typically, due to their nature relational and statistical models exhibit more interpretability than non-relational and DL models.

In summary, this is the first systematic review studying ML applied to CAP. It followed guidelines in both the engineering and clinical domains enabling it to take an interdisciplinary view. There is also an overlap between CAP and other acute respiratory and non-respiratory diseases that may provide further insights. Although the article search was wide and structured, it is possible that other studies—such as those published in libraries that were not included—have been missed.

There are still a lack of key criteria to enable proper assessment, suggesting the field is still in an exploratory stage and further research is required. Classification employed in our study have enabled us to identify some areas that will benefit from further research in terms of clinical processes. Firstly, validation of models for interpretation of diagnostic images. Secondly, the use of time-series and the application of DL to hospital admissions data for mortality and disease progression prediction. Thirdly, research into the application of DL on the predicted effectiveness of interventions and treatment—an area in which there is still paucity of published work, but evidence of clinical demand.

Finally, an increasingly helpful trend in the literature is the reporting of results that follow the TRIPOD checklist [32]—a method of reporting multi variable prediction models that is commonly adopted in medical sciences but less so in DL/ML communities. Although this checklist still presents gaps — for instance standardised metrics, greater adoption of this checklist would facilitate a like-for-like comparison and evaluation of models from different studies.

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