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Predicting Infections Using Computational Intelligence – A Systematic Review

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ABSTRACT Infections encompass a set of medical conditions of very diverse kinds that can pose a significant risk to health, and even death. As with many other diseases, early diagnosis can help to provide patients with proper care to minimize the damage produced by the disease, or to isolate them to avoid the risk of spread. In this context, computational intelligence can be useful to predict the risk of infection in patients, raising early alarms that can aid medical teams to respond as quick as possible. In this paper, we survey the state of the art on infection prediction using computer science by means of a systematic literature review. The objective is to find papers where computational intelligence is used to predict infections in patients using physiological data as features. We have posed one major research question along with nine specific subquestions. The whole review process is thoroughly described, and eight databases are considered which index most of the literature published in different scholarly formats. A total of 101 relevant documents have been found in the period comprised between 2003 and 2019, and a detailed study of these documents is carried out to classify the works and answer the research questions posed, resulting to our best knowledge in the most comprehensive study of its kind. We conclude that the most widely addressed infection is by far sepsis, followed by *Clostridium difficile infection* and surgical site infections. Most works use machine learning techniques, from which logistic regression, support vector machines, random forest and naive Bayes are the most common. Some machine learning works provide some ideas on the problems of small data and class imbalance, which can be of interest. The current systematic literature review shows that automatic diagnosis of infectious diseases using computational intelligence is well documented in the medical literature.

INDEX TERMS Computational intelligence, expert systems, infection prediction, machine learning, physiological signals, systematic literature review.

I. INTRODUCTION

Infectious diseases are the result of the invasion and multiplication of microorganisms in the body. These microorganisms can be bacteria, viruses, fungi in the form of yeast, or any other microscopic organism. Infections can start anywhere and spread throughout the body. An infection can cause from fever to other health problems depending on the part of the body in which it occurs. There are many different types of infections, and their effect can range significantly: while some infections can remain asymptomatic and have no negligible impact on health, others can put the patient's life on threat leading even to death.

Commonly, microorganisms proliferate fast within the human body, colonizing the affected tissue and beginning the disease's manifestations. In some cases, early diagnosis of an infection can allow medical teams to act quickly, providing a treatment (such as a prescription of antibiotics) that can revert the situation and stop the infection. Even if the outcome of the patient cannot be changed with medical care, early

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identification of infections diseases or their complications can reduce the probability of outbreaks and reduce the cost of medical care.

Medicine has developed a variety of mechanisms for diagnosing infections. Most common techniques involve laboratory techniques, such as blood or urine tests, stool or saliva samples or lumbar punctures. In some cases, more specific tests such as imaging scans or biopsies may be required to be able to properly elaborate a diagnosis. The main drawback of these techniques is that, in most cases, patients only visit the doctor after suffering symptoms, such as fever.

Therefore, the need for automated diagnosis techniques that are able to raise early alarms for some infectious diseases arises. In the best case, infections can be predicted before symptoms appear, enabling for a better treatment and timely isolation if required. In this context, Computational intelligence (CI) can aid the development of diagnosis tools that are able to predict the existence of an infection in patients, and that can be integrated as a part of a clinical decision support system (CDSS) to help medical teams to act accordingly. Some of these tools could only require as input features a set of physiological signals, which in some cases could be retrieved with some wearable devices, allowing for the disease to be detected with some degree of confidence before specific medical tests be performed.

By computational intelligence, we refer to both expert systems and machine learning techniques. In the former, expert knowledge is introduced into the system, e.g. in the form of rules, and the system is able to use this knowledge to provide some decision when data are introduced. In the latter, specific algorithms are used in order to automatically infer a model (e.g. a prediction model) from a labelled dataset, and therefore no explicit expertise is required beyond the labelling of training data.

In this paper, we conduct an analysis of the state of the art in infection prediction, by means of a well-described procedure known as a systematic literature review (SLR). SLRs hold a good prestige when it comes to analyze the body of academic knowledge in complex domains, such as recommender systems [3], Internet of things [79], food-intake monitoring [68], penetration testing in mobile applications [2], big data in healthcare applications [77], or computational intelligence in sports [11].

To do so, relevant research questions are posed and a thorough search procedure is carried out to locate relevant documents that can provide answers to such questions. The purpose of this SLR is to provide an accurate snapshot of the state of the art, describing how machine learning (ML) and expert systems (ES) techniques have been used to tackle the problem of infection prediction, along with the performance attained by different applications. Additionally, some concerns that arise from the machine learning perspective, such as few data availability or the issue of imbalanced data are raised. As a result, this SLR can be useful to researchers aiming at establishing research careers in this domain.

The remainder of this paper is structured as follows: section II enumerates some related works consisting on surveys that overlap to some extent with the problem of infection prediction. Later, section III describes the protocol of the literature review, including the research questions, literature sources, search query, search procedure and filtering criteria. Then, section IV summarizes the execution process of the SLR. Finally, section V analyzes the relevant documents in order to provide answers to the research questions, and section VI provides conclusive remarks about the systematic literature review.

II. RELATED WORK

To the best of our knowledge, there are no other SLRs focusing on the problem of infection prediction by means of automated methods that involve machine learning or other computer science approaches. However, there are some cases of reviews (which might adhere or not to the guidelines of a SLR) that survey papers on disease diagnosis, and whose aim can partially overlap with the objective of the current SLR.

First, van Mourik *et al.* [108] performed a review of automated surveillance methods for healthcare-associated infections. They discussed how existing electronic surveillance systems based on machine learning algorithms provide improvement over manual surveillance methods. One of the findings of this review is that most electronic systems detect infections once they have happened. Authors noted that these systems need to focus on real-time infection detection which is a great challenge in this area.

Esfandiari *et al.* [25] investigated current and future trends of knowledge discovery in medicine. They performed a review research by analyzing previous works along with the medical and data mining issues considered in those papers. Although it includes some relevant materials, the review did not focus on infection prediction.

Luo *et al.* [58] performed a systematic literature review of predictive modeling of bronchiolitis. This review study also included respiratory syncytial virus (RSV), an infection which can be a main cause of bronchiolitis. They reported how machine learning approaches can overcome limitations of predictive modeling. The authors provided some preliminary insights how to cope with open problems and future challenges.

More recently, Bhattacharjee *et al.* [8] conducted a review to analyze recent advancements in the area of sepsis detection on the hospital wards. They discussed advantages and disadvantages of several scoring systems for sepsis detection. In addition, they mentioned and examined several automated sepsis screening tools and their use in general hospital wards. They reported that biomarkers and electronic health records can have a big impact on predicting sepsis in hospital wards according to studies they examined. Finally, they discussed future trends and impact of automated big data approaches for sepsis detection. Ahmadi *et al.* [1] performed a systematic review to search fuzzy logic methods for disease diagnosis from different medical practices.

Finally, Sinha *et al.* [91] performed a review to report the limitations of routine blood culture testing in sepsis diagnosis and analyzed popular sepsis diagnosis technologies. They examined seven molecular technologies that utilize blood samples. They discussed these recent technologies and reported detailed advantages and drawbacks. Furthermore, they analyzed how machine learning methods affect these technologies with the use of electronic medical records. They came to conclusion that combining various diagnostic technologies could improve prediction ability of clinical systems and reduce the risk of wrong antibiotic usage in clinic.

There is an interest in the problem of disease prediction and diagnosis, and computer science constitutes a good approach towards solving this problem. Infections comprise a large set of diseases whose nature makes its early diagnosis of special interest, for example, due to their ability to spread and potential to become epidemic in certain cases. However, we have noticed the lack of systematic reviews focusing on this kind of diseases. As a consequence, there is a need to conduct the current systematic literature review.

III. METHODS

This review was conducted using the guidelines provided by Kitchenham and Charters [48] and in accordance with PRISMA guidelines. Kitchenham and Charters' guidelines were developed for performing SLRs in the field of software engineering, although they were inspired by previous manuals aimed at the medical domain.

In this section, we thoroughly describe the protocol for carrying out the systematic literature review. In order to do so, we first enumerate the research questions that we want to answer through this study, then describe the search strategy followed for retrieving source materials for the SLR, explain the inclusion and exclusion criteria applied over those materials to filter out non-relevant works, and finally describe the process for extracting data for solving such research questions.

A. RESEARCH QUESTIONS

In this research work we want to focus on the prediction of infections using physiological data. For this reason, we have raised the following research question:

RQ1. *Does the literature document methods to predict infections given physiological data?*

While this is our main research question, in case its answer be affirmative, we are also interested on formulating the following subquestions, which enable us to better understand the state of the art of this research field.

RQ1.1. *Which are the infections or types of infections that are susceptible of prediction according to the literature?*

RQ1.2. *Do some of these documented methods involve machine learning?*

RQ1.3. *Do some of these documented methods involve expert systems?*

RQ1.4. *Which are the available data sources for infections prediction?*

RQ1.5. *Which are the most frequently reported performance metrics for infection prediction?*

Again, if the answer to RQ1.2. held true, then we can raise some additional questions that would help us understand how the problem of infection prediction can be tackled by means of machine learning:

RQ1.2.1. *According to the literature, which are the machine learning techniques suitable for infection prediction?*

RQ1.2.2. *According to the literature, which is the impact of few training samples in infection prediction performance?*

RQ1.2.3. *According to the literature, which is the impact of a largely imbalanced dataset in infection prediction performance?*

Many machine learning tasks in the healthcare domain are faced with problems relevant to the size and content of the datasets used. These problems usually emerge in two ways. The first is the fact that large datasets are seldom available in this field. This problem is referred as ''small data'' to indicate the gap between available training data and a complete distribution pattern. When the training data are insufficient to represent an entire population, it becomes more difficult to develop models that generalize in a broad sense. This issue may cause several other problems such as over-fitting, lower accuracy and unfair assessment of the model developed. Another fundamental problem is the imbalanced distribution of classes in the dataset. In the medical field, this problem often arises in binary classification tasks, where there exists a predominant class with the samples in normal/control group and a minority class with diseased or treated samples. This problem is referred as ''imbalanced data''. In this study, we consider these two crucial problems to see how they affect the particular task of infection prediction from physiological data. To this end, we define two research subquestions (RQ 1.2.2 and RQ 1.2.3). These RQs are aimed to identify how small and imbalanced data impact the activities in developing and validating computational models and how these challenges are addresses in the literature. To get an unbiased view of these impacts, relevant keywords are not placed into the search query. Instead, these issues are considered at the data extraction stage after careful reading of full texts of the articles in final SLR repository.

Finally, if the answer to RQ1.3 were affirmative, we could ask one more question to study the ways in which expert systems have been applied to this problem:

RQ1.3.1. *According to the literature, which are relevant reasoning rules for infection prediction?*

B. SEARCH STRATEGY

1) SEARCH TERMS

In order to build the search string, we first identify keywords with some possible alternatives, in order to guarantee the retrieval of an exhaustive set of relevant literature. In this SLR, we only consider papers published in the English language. The keywords for building the core search query, along with their considered alternatives, are the following:

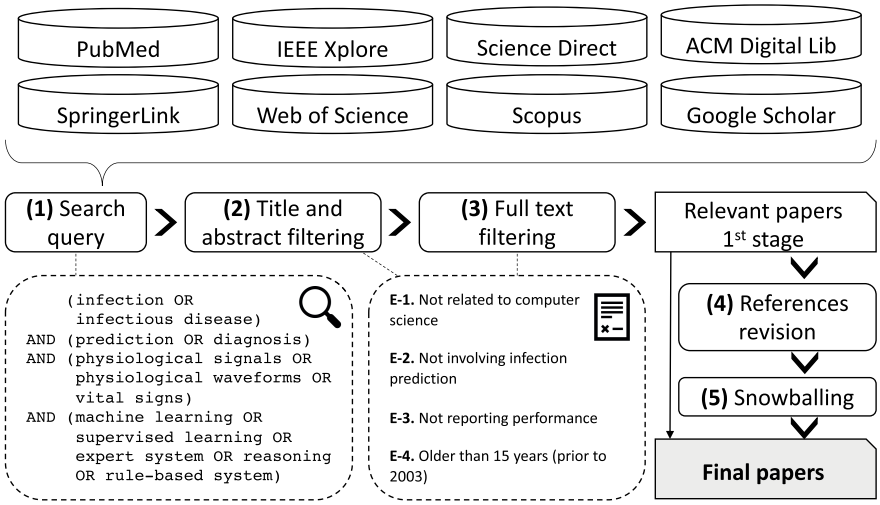

FIGURE 1. Illustration of the search procedure followed for the SLR.

- **Infection**–infectious disease
- **Prediction**–diagnosis
- **Physiological signals**–physiological waveforms, vital signs
- **Machine learning**–supervised learning
- **Expert system**–reasoning, rule-based system

It is noticeable that these alternative to keywords are not necessarily synonyms, but in some cases are reasonable replacements given the object of this SLR. For example, ''supervised learning'' is not equivalent to ''machine learning'', but when considering the problem of prediction, it is a reasonable alternative keyword.

Once these search terms are identified, we build the search query by combining them with different boolean operators. This query is the following:

```
    (infection OR infectious disease)
AND (prediction OR diagnosis)
AND (physiological signals OR
    physiological waveforms OR
    vital signs)
AND (machine learning OR
    supervised learning OR
    expert system OR reasoning OR
    \hbox{rule-based} system)
```

Of course, it is worth realizing that in some cases the query has been adapted to the particular syntax accepted by the different literature resources' search engines.

Additionally, we have considered two more terms aimed towards answering very specific research questions (RQ1.2.2 and RQ1.2.3), and therefore we have not included them in the core query. Instead, we search for these in the retrieved documents in order to find answers to those queries.

- **Imbalanced dataset**–unbalanced dataset, imbalanced data, unbalanced data, imbalanced classes, unbalanced classes
- **Small data**–few training samples, few training instances

2) LITERATURE SOURCES

In order to cover the broadest surface of relevant literature, we have decided to use the following eight literature sources: *PubMed*, *IEEE Xplore Digital Library*, *ScienceDirect*, *ACM Digital Library*, *SpringerLink*, *Web of Science*, *Scopus* and *Google Scholar*.

The criteria for choosing these databases were aimed towards four objectives: (1) covering most of the medical literature, (2) covering most of the computer science literature, (3) covering most papers in journals with an impact factor, (4) being as exhaustive as possible. The chosen databases gather most of the published literature in journals, scientific conference proceedings and book chapters.

3) SEARCH PROCEDURE

In order to select relevant studies, we have adhered to the following procedure:

1) The search query is executed in the search engine of each of the eight literature databases.
2) A first filtering out stage is carried by checking titles and abstracts, in order to quickly remove non-relevant records.
3) A more exhaustive filtering out stage is performed after retrieving and reading full texts. For each excluded document, the reasons leading to its exclusion were documented.
4) The references of each of these works were analyzed to identify further relevant works that had not been found during the first retrieval stage.
5) Snowballing is performed to get access to new literature.

The process is illustrated in Figure 1. After these four steps are carried out, we obtain a set with all documents fulfilling the inclusion criteria, from which we can retrieve the full texts in order to be able to answer the research questions.

C. STUDY SELECTION

In order to carry out filtering stages (2) and (3) in the search procedure, we have established a well-defined set of exclusion criteria. These criteria are the following:

- **E-1.** Papers not related to computer science
- **E-2.** Papers not involving infection prediction
- **E-3.** Papers not reporting results on prediction performance
- **E-4.** Papers older than 15 years old (published in 2003 or earlier)

D. DATA EXTRACTION

The entire search process has been documented, with all records being stored in a reference manager. During the whole process, we have been careful to annotate the exclusion criterion for each excluded paper, as well as the literature source for each of them. Full texts were only retrieved for documents that passed the first filtering stage (title and abstract).

Once a set of relevant records were located and their full texts were downloaded, we designed a form, that was filled for each document, in order to extract the following information:

- Does the paper use machine learning?
- Does the paper use expert systems?
- What machine learning techniques are used in the paper? (if applicable)
- What expert system techniques are used in the paper? (if applicable)
- What features are used for infection prediction?
- What infection(s) does the paper aim at predicting?
- Does the paper mention imbalanced data?
- Does the paper mention small data?
- What performance metrics does the paper report?

With the previous information, we should be able to provide an answer to each of the research questions posed in this systematic literature review.

IV. SYSTEMATIC REVIEW EXECUTION

In this section we summarize the execution of the search process, describing the number of documents retrieved in each phase from each bibliographic source, and how exclusion criteria have filtered out the documents until obtaining a final set of relevant papers.

A. RELEVANT PAPERS (1ST STAGE)

A summary of the execution of the first stage can be found in Figure 2. In all cases, only scientific papers were considered, ignoring other types of resources such as editorials or tables of contents. The figure also displays the different exclusion criteria, both for the first pre-filtering (considering only paper metadata, title and abstract) and for the full text analysis. The figure also points out a few exceptional papers whose full text could not be retrieved by any means. Exclusion criterion E-4 is not shown for the full text analysis, since

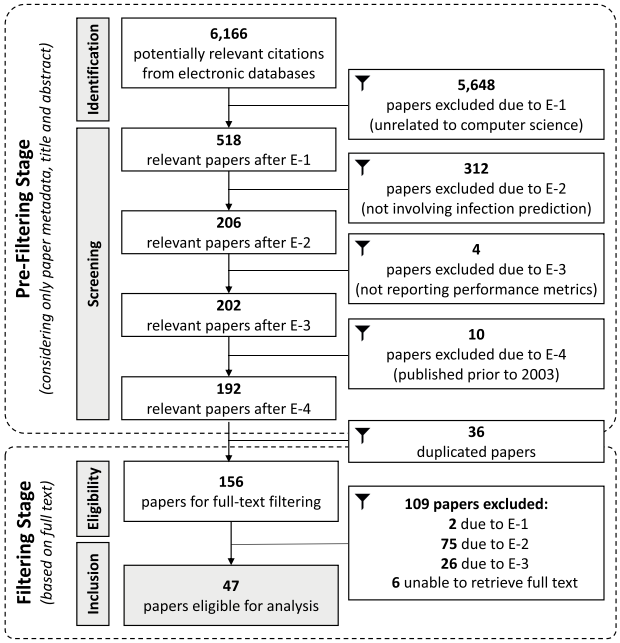

FIGURE 2. Results of the first stage, showing the effect of each exclusion criterion.

it refers to the year of the record, and therefore the filtering was applied earlier.

It can be seen that the most discriminating criterion is E-1, which filters out a large corpora of papers not related to computer science (most of them retrieved from Google Scholar) by simple inspection of the title and abstract: it is easy to identify from such information whether a paper is about computer science or not. Another discriminating criterion is E-2, which is able to filter out almost 400 papers. Criterion E-4 is not particularly helpful, something that can be explained because the object of this research (infection prediction using computer science) is relatively recent, and therefore papers older than 15 years are scarce.

A dataset listing the 47 included papers in the first stage has been publicly released in Mendeley Data [7].

B. RELEVANT PAPERS (2ND STAGE)

In the second stage, we have revised the references from the relevant papers found in the first stage in order to identify additional documents. For these new documents to be considered, they could not be available in our set beforehand and they had to fulfill the inclusion criteria. After completing this process, we found 30 relevant documents. Then, to find more recent papers, we performed forward snowballing, gaining access to other 24 relevant papers. Therefore, the final set of relevant records for the SLR comprises a total of 101 papers.

Figure 3 summarizes the SLR execution process, showing the explicit difference between the two stages.

V. RESULTS AND FINDINGS

After manually reviewing the relevant documents, we are able to provide the following answers to all research questions:

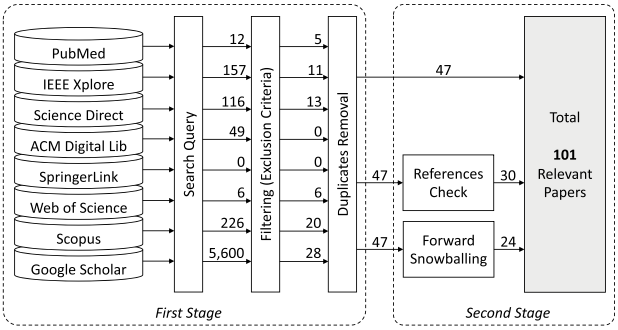

FIGURE 3. Summary of the SLR execution, displaying the number of documents available after every stage.

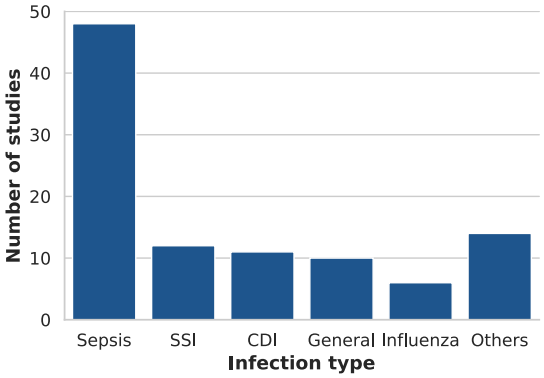

FIGURE 4. Number of documents per type of infection.

RQ1. DOES THE LITERATURE DOCUMENT METHODS TO PREDICT INFECTIONS GIVEN PHYSIOLOGICAL DATA?

The systematic literature review has resulted in a set of 101 relevant documents. Each paper reports one or more computational methods to predict infection from some kind of physiological data. Therefore, the answer to this question is affirmative.

RQ1.1. WHICH ARE THE INFECTIONS OR TYPES OF INFECTIONS THAT ARE SUSCEPTIBLE OF PREDICTION ACCORDING TO THE LITERATURE?

In the literature, 19 different types of specific infectious diseases are reported as susceptible of prediction with computational methods. Six papers target general infections rather than a particular type: they tested their algorithms on several different types.

Figure 4 shows the number of articles in the final SLR repository for each infection type. The most frequent manifestations of infections considered in the context of early prediction by computational methods is sepsis, which is a body's life-threatening response to an infection that can lead to tissue damage, organ failure or even death. Surgical Site Infection (SSI) is the second most frequent type although it does not refer to a specific biological type, but rather indicates any infection that has spread during surgery. *Clostridium difficile infection* (CDI) is the third most common infection addressed in this context. CDI is a bacterial infection that may cause life-threatening inflammation. The influenza infection is addressed in si different studies. Influenza is a viral infection, which is often referred as *flu*. The infection types with a count of lower than three are labeled as others.

The complete list of other infections are as follows: Catheter-Associated Urinary Tract Infection (CAUTI), Healthcare-Associated Infections (HCAIs) (including Central Line-Associated Bloodstream Infection, Central Venous Catheter or Ventilator-Associated Pneumonia), Dengue Fever, Ebola and Marburg Viruses, Malaria, Meningitis and Encephalitis, Methicillin-Resistant Staphylococcus Aureus (MRSA), Upper Respiratory Infection and Urinary Tract Infection.

RQ1.2. DO SOME OF THESE DOCUMENTED METHODS INVOLVE MACHINE LEARNING?

In this context, machine learning refers to any algorithm which attempts to fit a computational model to distinguish between infectious and non-infectious samples given an annotated training data. Some studies address multiple classes, where subtypes of infections are also considered.

In our SLR repository, 66 of the articles propose machine learning methods to predict infection (see Table S2 in the appendix). A framework typically common to all these studies involves two main stages: extracting features from input data and learning a classification model that fits best into the training data.

RQ1.2.1. ACCORDING TO THE LITERATURE, WHICH ARE THE MACHINE LEARNING TECHNIQUES SUITABLE FOR INFECTION PREDICTION?

All methods documented in the literature employ a typical discriminative framework for supervised classification. They differ in the type of classification algorithm used and the feature sets used to feed these classifiers.

Table S1 in the appendix lists all studies involving machine learning methods to predict infection. Some of them report the experimental results with more than one classification algorithm. Most common algorithm is Logistic Regression (LR), which is used in 33 of the studies in total. It is followed by Support Vector Machine (SVM) and Random Forest or Decision Tree methods (RF) with the usage counts of 21 and 18 respectively. Other abbreviations are: Hidden Markov Model (HMM), Linear Discriminant Analysis (LDA), Naive Bayes (NB), K-Nearest Neighbors (KNN), Artificial Neural Networks (ANN), Bayesian Network (BN), Long Short-Term Memory (LSTM), Gradient Boosted Trees (GBT), Contingency Table (CT), Quadratic Discriminant Analysis (QDA), Linear Dynamical System (LDS), Gaussian Process / Gaussian Mixture Model (GP), AdaBoost (AB), Ensemble of Learners (EL), Convolutional Neural Networks (CNN), Topic Models (TM, used for Latent Dirichlet Allocation or its

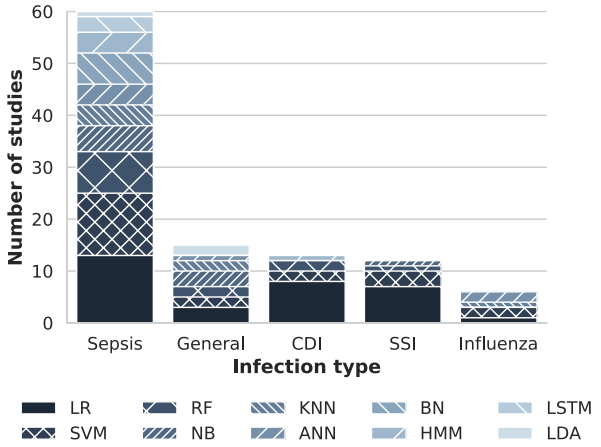

FIGURE 5. Distribution of most common machine learning classification techniques over most common infection types.

variants), Natural Language Processing (NLP[1]) and Linear Regression (LiR).

The preference of classification algorithm may vary according to the infection type being considered. Figure 5 discerns these preferences in the literature, where only the algorithms that are used at least in three studies are plotted. For sepsis prediction, LR and SVM are preferred with similar prevalence. LR is most common in CDI prediction.

Existing studies use several numeric features which are believed to be representative for the infection types under consideration. These features can be grouped into nine sets. Demographics define the personal information such as age, gender etc. Vital signs refer to basic measurements that are routinely monitored to see how well the body is functioning. We consider five vital signs (heart rate, temperature, respiratory rate, pulse oxiometry, blood pressure) as a distinct feature in our analysis since they are most common in all infection types. Lab tests may refer to any kind of lab analysis from blood or urine. The electronic measurements such as Electrocardiograms (ECG) or images obtained from any imaging modality are simply referred as biomedical signals. We use the term "clinical data" to describe any prescriptions, medications or procedures which are employed during examination or treatment of the patients. Logistic data describes any information about the administrative process of the patients, such as hospital entrance time, duration of stay, etc. Microbiology data are all about genotype information such as biomarkers. Risk factors are the features derived from other data to describe the severity of some clinical risks. Some of the studies prefer to use the term of Electronic Health/Medical Records to abstract the features they used. Since they did not specify the features explicitly, we use the term EHR to refer to these category features, although it may include already many of the other feature sets given above. Table S2 in the appendix gives a detailed view of these

[1]Although NLP is an application rather than a technique, the paper allocated to this category provides few details about the actual ML mechanisms used to perform NLP.

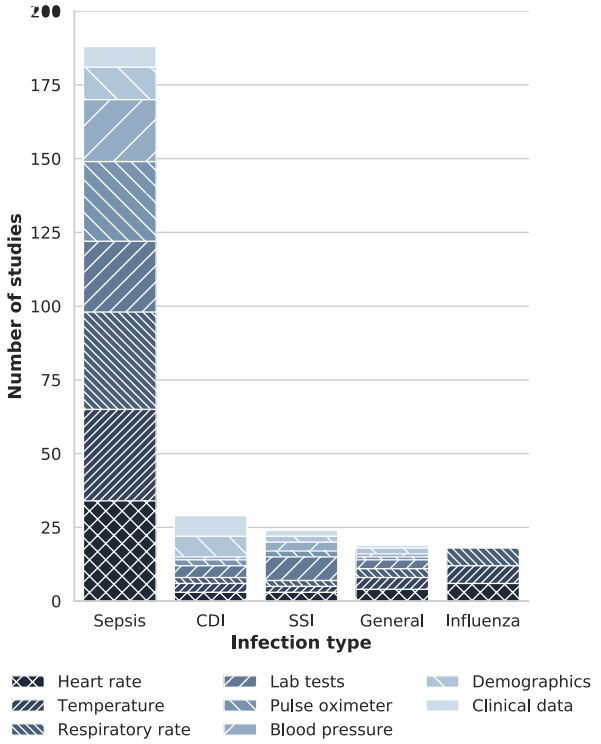

FIGURE 6. Distribution of machine learning features over most common infection types.

features sets used in the articles in our repository. When we simply consider the counts that they are used in collected articles, three vital signs are most common features used for infection prediction: heart rate, temperature, respiratory. Lab tests, demographics and clinical data are also widely used. The feature sets used to feed classifiers also differ based on the infection type (Figure 6).

RQ1.2.2. ACCORDING TO THE LITERATURE, WHICH IS THE IMPACT OF FEW TRAINING SAMPLES IN INFECTION PREDICTION PERFORMANCE?

The small data problem was explicitly mentioned in 30 of the retrieved papers with details given in Figures 7 and 8. Eight of these studies referred the problem as a general limitation imposed in the prediction system without any specific impact. Three particular impacts were revealed: (1) low accuracy, (2) limited generalization and (3) unfair assessment. 11 of the studies either shown or hypothesized that the accuracy of infection prediction diminishes with smaller number of samples in training data. The authors of other 11 articles argued that it is not easy to generalize the model to the entire population due to having a small data set. Three of the papers mentioned the impact of small data in unfair assessment of the model. Unfair assessment in this context refers to the lack of enough resources or proper environment to make a fair comparison between the performances of the computational methods being assessed.

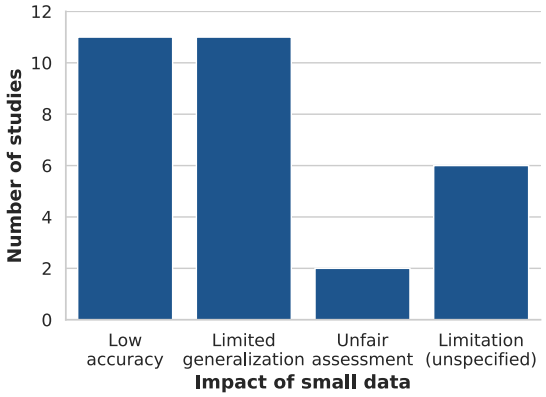

FIGURE 7. Impacts of small data mentioned in the relevant documents.

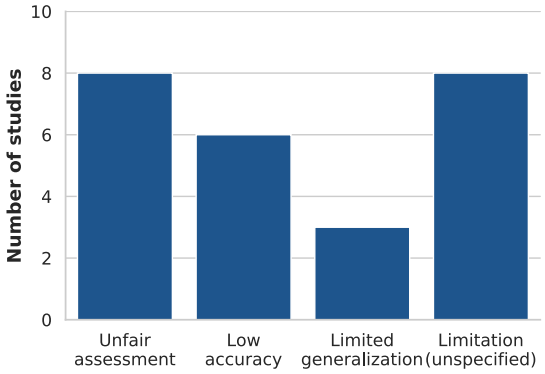

FIGURE 9. Impacts of imbalanced data mentioned in the relevant documents.

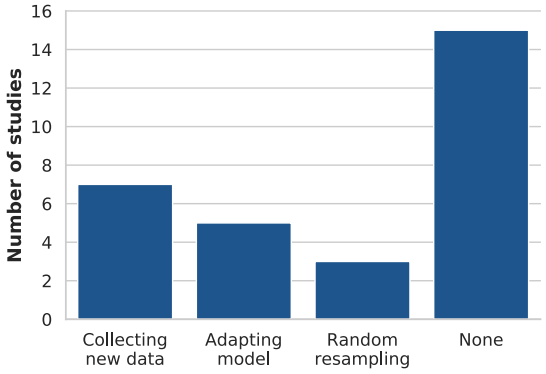

FIGURE 8. Solutions for small data explicitly offered to tackle the problem in the relevant documents.

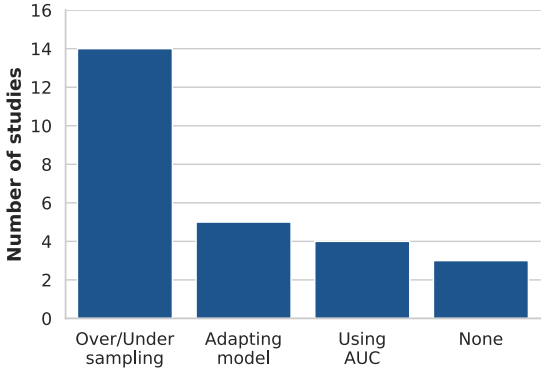

FIGURE 10. Solutions for imbalanced data explicitly offered to tackle the problem in the relevant documents.

In 15 of the papers that mentioned small data problem, no specific solution was offered. Five of the studies reported that they adapted their methods to cope with small training data by adjusting model parameters. For example, Stanculescu *et al.* [93] used a symmetric Dirichlet prior with optimized parameters in their autoregressive Hidden Markov Model to prevent estimates from being too small since the number of samples in their sepsis data is low, Wiens *et al.* [112] proposed a new feature extraction scheme that would fit better for small datasets, and Kam and Kim [43] introduced a new deep learning model with a detailed architecture customized for low dimensional training data. Other three studies used random re-sampling to increase the amount of the training data. The authors of seven papers argued that collecting new data would be the best solution to overcome the negative effects of small data. It should be noted that the counts in the figure do not add up to total number of papers since some of them refer more than one impacts or solutions relevant with the small data problem.

RQ1.2.3. ACCORDING TO THE LITERATURE, WHICH IS THE IMPACT OF A LARGELY IMBALANCED DATASET IN INFECTION PREDICTION PERFORMANCE?

The imbalanced data problem was explicitly mentioned in 26 of the retrieved articles (see Figures 9 and 10). Eight of these studies referred the problem as a general limitation without any specific impact. Same particular impacts were revealed as with the small data problem. According to the results, an unfair assessment of the models developed for predicting infection is the most severe impact of the imbalanced data, which was mentioned in eight of the retrieved articles. The second most frequently mentioned impact is the low accuracy of the resulting model. The authors of these papers determine that conventional methods such as general accuracy metrics are not sufficient to discern the ability of the models under evaluation. In three studies, the authors report that imbalanced data may limit the generalization of the offered model.

Three of the papers that mentioned imbalanced data problem do not offer any specific solution for it. Five of the studies adapted their methods to cope with imbalanced data by adjusting model parameters. For instance, inn CREST [87], the authors assigned a higher misclassification cost to minority class in their modified objective function while learning an SVM model to predict infection, Monsalve *et al.* [69] tailored an ensemble of logistic regression models, where each sub-model was trained from a balanced subset, and Wiens *et al.* [113] used an asymmetric cost parameter to train an SVM from an imbalanced infection data. In 14 of these studies, an over- or under-sampling strategy was applied to balance the distribution of the classes. The authors of four papers did not apply a specific solution, however, employed

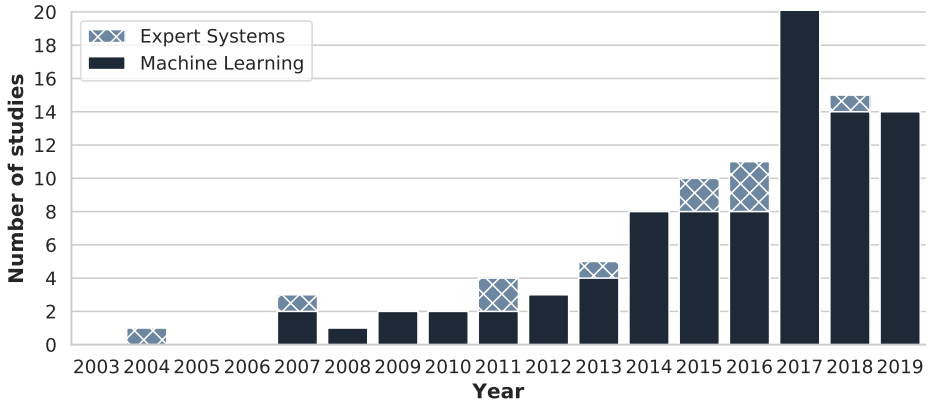

FIGURE 11. Distribution of computational intelligence approaches (ML or ES) over the years of study.

TABLE 1. Main data sources for works in the SLR, along with their source and prevalence.

Dataset	Source	URL	# Documents
MIMIC-III [41]	MIT, Philips, BIDMC (USA)	https://mimic.physionet.org	7
MIMIC-II	MIT, Philips, BIDMC (USA)	https://archive.physionet.org/mimic2/	7
BIDMC [6]	BIDMC (USA)	https://physionet.org/content/chfdb/1.0.0/	2
NHI Res. DB	NHI (Taiwan)	https://nhird.nhri.org.tw/en/	1
Private sources	–	–	84

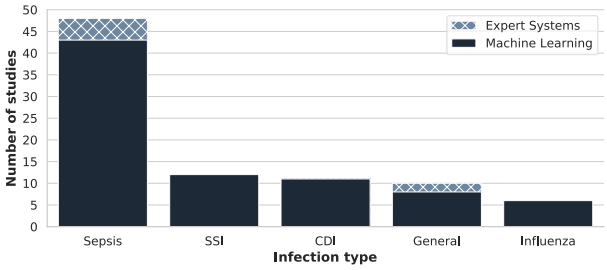

FIGURE 12. Distribution of computational intelligence approaches (ML or ES) over most common infection types.

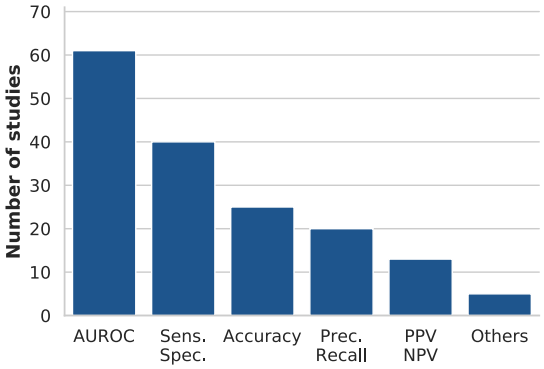

FIGURE 13. Most frequently reported performance metrics in the documents found by the SLR.

a more objective performance evaluation scheme based on the area under ROC (AUROC) curve. In spite of no explicit mention of imbalanced data problem, 61 of the studies in our final SLR repository used an AUROC-based methodology to assess and benchmark their model performance. This means that the imbalanced data problem is considered either in an implicit or explicit way in the majority of the papers that we retrieved on computational infection prediction.

RQ1.3. DO SOME OF THESE DOCUMENTED METHODS INVOLVE EXPERT SYSTEMS?

Expert systems and machine learning are considered to be two ends of a spectrum working to solve classification problems in a different way. Expert systems use if-then-else rules and a logical approach to assign a given sample to one of predefined classes where machine learning methods attempt to build a complex model to distinguish between classes. The rules in expert systems are usually extracted by a domain expert or in a hybrid way that integrates human knowledge with automated reasoning strategies. Some of the documented methods in the literature report the use of expert systems for predicting infection. The count of such articles in our SLR is 11. Figure 11 depicts the use of expert systems and machine learning methods for each calendar year that we include in our SLR study. As shown, there is no specific tendency to prefer either ML or ES method according to publication date. However, ES is preferred for particular types of infections (see Figure 12). The figure suggests that ES can be a convenient alternative to ML techniques for prediction of sepsis. This result may be attributed to the fact that sepsis has some specific guidelines for diagnosis, which make this infection type susceptible to apply rule-based techniques for prediction.

TABLE S1. Machine learning techniques reported in each of the relevant documents.

Document	LR	SVM	HMM	LDA	RF	NB	KNN	ANN	BN	LSTM	GBT	CT	QDA	LDS	GP	AB	EL	CNN	TM	NLP	LiR
Bloch et al. [10]	•	•						•													
Branch-Elliman et al. [12]																				•	
Calvert et al. [13]											•										
Chang et al. [15]	•							•													
Colborn et al. [16]																					•
Danner et al. [17]	•																				
Delahanty et al. [20]											•										
Desautels et al. [21]																	•				
Desautels et al. [22]					•																
Dubberke et al. [23]	•																				
Escobar et al. [24]	•																				
Ghosh et al. [26]		•	•																		
Giuliano [27]	•																				
Guillén et al. [28]	•	•															•				
Gultepe et al. [29]									•										•		
Gultepe et al. [30]			•			•									•						
Gundlapalli et al. [32]																				•	
Gunnarsdottir et al. [33]																					•
Gupta et al. [34]									•												
Hartvigsen et al. [35]	•	•			•																
Hebert et al. [36]	•																				
Horng et al. [37]		•																			
Hu et al. [39]	•																				
Hu et al. [40]	•																				
Hu et al. [38]	•	•			•			•										•			
Kam and Kim [43]										•											
Kamaleswaran et al. [44]	•				•													•			
Ke et al. [45]		•																			
Khoshnevisan et al. [46]	•	•			•	•		•		•											
Kim et al. [47]		•																			
Kocbek et al. [49]	•										•										
Lamping et al. [50]				•																	
Le et al. [51]					•																
Lin et al. [52]										•								•			
Liu et al. [53]					•																
Lo et al. [54]				•																	
López-Martínez et al. [55]								•													
Lu et al. [56]																			•		
Lukaszewski et al. [57]							•														
Mani et al. [59]	•	•			•	•			•												
Mao et al. [61]											•										
Masino et al. [62]	•	•			•	•	•				•				•						
Matsui et al. [63]				•																	

TABLE S2. ***(Continued.)*** **Machine learning techniques reported in each of the relevant documents.**

Document	LR	SVM	HMM	LDA	RF	NB	KNN	ANN	BN	LSTM	GBT	CT	QDA	LDS	GP	AB	EL	CNN	TM	NLP	LiR
Meurer et al. [64]												•									
Mikalsen et al. [65]		•																			
Milechin et al. [66]					•																
Mitchell et al. [67]	•																				
Monsalve et al. [69]																	•				
Mulder et al. [70]	•																				
Na et al. [71]	•																				
Nachimuthu and Haug [72]									•												
Nguyen et al. [73]																					•
Oh et al. [74]	•																				
Parente et al. [75]			•																		
Parreco et al. [76]	•										•							•			
Paxton et al. [78]		•																			
Prasad et al. [80]	•				•								•								
Rabhi et al. [81]	•	•			•	•	•				•							•			
Sanger et al. [82]						•															
Sanger et al. [83]																				•	
Saunders et al. [84]	•																				
Scherpf et al. [85]								•													
Schurink et al. [86]									•												
Sen et al. [87]	•	•			•																
Shashikumar et al. [89]																	•				
Shankar et al. [88]	•	•			•																
Shimabukuro et al. [90]																	•				
Soguero-Ruiz et al. [92]															•						
Stanculescu et al. [93]			•																		
Stanculescu et al. [94]														•							
Strauman et al. [95]								•													
Sun et al. [96]								•													
Sun et al. [97]		•																			
Sun et al. [98]								•													
Sun et al. [99]				•																	
Swiston Jr et al. [100]					•																
Taneja et al. [101]	•	•			•	•										•					
Tanner et al. [102]	•																				
Tou et al. [103]	•				•	•					•										
Tvardik et al. [105]																				•	
van Wyk et al. [109]								•										•			
van Wyk et al. [110]	•	•			•															•	
Ward et al. [111]									•												
Wiens et al. [112]		•	•																		

TABLE S2. *(Continued.)* **Machine learning techniques reported in each of the relevant documents.**

Document	LR	SVM	HMM	LDA	RF	NB	KNN	ANN	BN	LSTM	GBT	CT	QDA	LDS	GP	AB	EL	CNN	TM	NLP	LiR
Wiens et al. [113]	•																				
Yao et al. [114]	•	•		•		•	•						•								
Yee et al. [115]									•												
Binti Mohd Zainee and Chellappan [9]				•																	
Zhang et al. [117]										•											
Zhang et al. [116]											•										

RQ1.3.1. ACCORDING TO THE LITERATURE, WHICH ARE RELEVANT REASONING RULES FOR INFECTION PREDICTION?

A well-known criteria, are the manifestations of the Systemic Inflamamatory Response Syndrome (SIRS). Those were used in two studies for the prediction of Sepsis in an expert system setup [4], [5]. Five of the studies customized their rules with respect to the infection type considered [14], [32], [42], [104], [106]. Two studies deployed fuzzy-logic-based reasoning to soften the boundaries for decision [18], [107]. To predict HCAIs, [19] used a criteria defined by Hospitals in Europe Link for Infection Control through Surveillance (HELICS) program. [60] developed an ontology-driven association rule induction method for classification and applied their method on disease classification including several infections. The studies gathered in the SLR are shown by the end of Table S2 in the appendix, where the previous set of rules can be seen, as well as custom rules and one study applying an Analytical Hierarchy Process (AHP).

RQ1.4. WHICH ARE THE AVAILABLE DATA SOURCES FOR INFECTIONS PREDICTION?

Most of the works surveyed in the SLR rely on private data acquired ad-hoc for the study. In most cases, these data are obtained from pilots in hospitals, clinics or medical centers in different countries over the world. These sources are acknowledged in the *Data* column of Table S2 in the appendix.

Interestingly, some works rely on public data sources, which are more interesting as they can be accessed by other researchers, and can ease reproducibility and benchmarking of the results. The most frequently used public datasets are MIMIC-III and MIMIC-II, followed by far by BIDMC and, in the last place, by the Taiwanese National Health Insurance Research Dataset. The main data sources and their prevalence in the SLR are summarized in Table 1.

RQ1.5. WHICH ARE THE MOST FREQUENTLY REPORTED PERFORMANCE METRICS FOR INFECTION PREDICTION?

The most commonly reported metrics for describing the performance of the infection prediction works surveyed in this SLR are summarized in Figure 13. The most frequent metric was the area under the ROC curve (AUROC), followed by sensitivity and specificity. Accuracy was also a highly reported metric, although it is often not useful by itself, and is most commonly used as a supporting metric. With less frequency, precision and recall (as well as F1 score, which average them) were used, followed by the positive predictive value (PPV) and negative predictive value (NPV).

VI. CONCLUSION

In this paper we have designed and executed a systematic literature review (SLR) to find relevant works where machine learning and expert systems techniques are used for automatic diagnosis and prediction of infectious diseases. This topic is of special interest because accurate early diagnosis allows for the correct application of treatment, increasing the chances of patients' recovery, or in the worst cases enabling authorities to initiate quarantine procedures before the disease spreads.

The results of the SLR has allowed us to provide successful answers to our research questions. Our main RQ involved whether the literature documents methods for predicting infections given physiological data. After executing the SLR, we have found a total of 101 relevant documents, therefore being able to obtain an affirmative response to such question. As a result, this is a very comprehensive survey of the topic, and to the best of our knowledge, it is the first entirely focusing on infection prediction using computational intelligence.

Infection prediction might be a problem too generic since infections comprise a very broad set of diseases, with different symptoms and consequences. For this reason, we wanted to learn about the most common types of infections that were subject of study in the related literature. Given the results of the SLR, we can observe that the most widely studied disease is by far sepsis, followed by *Clostridium difficile infection*. Also, 12 papers focus on surgical site infections, which comprise different types of infections that can be acquired by a patient during and 30 days after surgery.

Additionally, we were interested in knowing whether these papers used machine learning or expert systems to perform such prediction. After carrying out the SLR, we have found that the majority of papers (90) use diverse machine learning techniques to carry out prediction of infectious diseases.

TABLE S2. Relation of the papers studied in the systematic literature review and their taxonomy.

Document	Infection(s)	Objective	Setting	CI Tech.	Data	Features	Performance
Bloch et al. [10]	Sepsis	Infection detection	Hospital care	LR, SVM, ANN	Private own data *(Rabin Medical Center, Israel)*	Temperature, Respiratory rate, Heart rate, Blood pressure	AUROC 0.88, AUCPR 0.936
Branch-Elliman et al. [12]	Catheter-Associated Urinary Tract Infection	Early warning	Hospital care	NLP	Private own data *(The Boston Veterans Affairs Healthcare System, USA)*	EHR, Temperature	Acc. 60%, Sens. 90.9%
Calvert et al. [13]	Sepsis	Early warning	Hospital care	GBT	Public *(MIMIC III)*	Clinical data	AUROC 0.917, Acc. 84.8%, Sens. 79.9%, Spec. 86%
Chang et al. [15]	Hospital Acquired Infection	Surveillance	Hospital care	LR, LDA	Private own data *(Taipei Medical University Wan Fang Hospital, Taiwan)*	Demographics, Clinical data	AUROC 0.969, Acc. 95.04%, Sens. 97.06%, Spec. 96.52%, PPV 90.6%, NPV 99.0%
Colborn et al. [16]	Surgical Site Infection	Infection detection	Hospital care	LiR	Private own data *(University of Colorado Hospital NSQIP Database, USA)*	Laboratory tests	AUROC 0.950, Sens. 83.9%, Spec. 84.2%
Danner et al. [17]	Sepsis	Early warning	Hospital care	LR	Private own data *(Grady Memorial Hospital, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	Chi-Square < 0.0001, Sens. 73.98%
Delahanty et al. [20]	Sepsis	Surveillance	Hospital care	GBT	Private own data *(Tenet Healthcare, USA)*	Lab tests	AUROC 0.97
Desautels et al. [21]	Sepsis	Early warning	Hospital care	EL	Public *(MIMIC III database)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.88, Acc. 80%, Sens. 80%, Spec. 80%
Desautels et al. [22]	Sepsis	Early warning	Hospital care	RF	Private own data *(UCSF Medical Center, USA)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	AUROC: 0.912
Dubberke et al. [23]	CDI	Early warning	Hospital care	LR	Private own data *(Barnes-Jewish Hospital, USA)*	Demographics, Lab tests, Clinical data, Logistic data	AUROC 0.88
Escobar et al. [24]	CDI	Surveillance	Hospital care	LR	Private own data *(Kaiser Foundation Hospitals, USA)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Clinical data	C Statistic 0.605, R^2 -0.1033, Sens. 79.17%, Spec. 32.04%
Ghosh et al. [26]	Sepsis	Early warning	Hospital care	SVM, HMM	Public *(MIMIC II database)*	Respiratory rate, Heart rate, Blood pressure	P-value 0.0014
Giuliano [27]	Sepsis	Early warning	Hospital care	LR	Private own data *(The Project IMPACT data set)*	Temperature, Respiratory rate, Heart rate, Blood pressure	Acc. 78.9%
Guillén et al. [28]	Sepsis	Early warning	Hospital care	LR, SVM, EL	Public *(MIMIC II database)*	Temperature, Respiratory rate, Heart rate, Lab tests	AUROC 0.871, Sens. 64.2%, Spec. 93.6%, PPV 65.1%, NPV 93.3%
Gultepe et al. [29]	Sepsis	Early warning	Hospital care	BN	Private own data *(University of California Davis Medical Center, USA)*	Temperature, Respiratory rate, Blood pressure, Lab tests, Logistic data	Goodness of fit: Loss 15.413
Gultepe et al. [30]	Sepsis	Surveillance	Hospital care	NB, HMM, GP	Private own data *(University of California Davis Medical Center, USA)*	Temperature, Respiratory rate, Heart rate, Blood pressure, Lab tests	AUROC 0.965, Acc. 89.1%, F1 93.1%, Sens. 87.1%, Spec. 100%
Gundlapalli et al. [32]	Catheter-Associated Urinary Tract Infection	Infection Detection	Hospital care	NLP	Private own data *(Veteran Affair Hospital, USA)*	EHR	Prec. 96.5%, Rec. 100%
Gunnarsdottir et al. [33]	Sepsis	Early warning	Hospital care	LiR	Public *(MIMIC II database)*	Respiratory rate, Heart rate, Oxygen saturation, Lab tests	Acc. 75%, Sens. 100%, Spec. 50%
Gupta et al. [34]	Sepsis	Surveillance	Hospital care	BN	Private own data *(Cerner Corporations, USA)*	Clinical data	AUROC 0.84
Hartvigsen et al. [35]	Methicillin-Resistant Staphylococcus Aureus	Early warning	Hospital care	LR, SVM, RF	Public *(MIMIC III Critical Care database)*	Demographics, Logistic data	AUROC: 0.94
Hebert et al. [36]	CDI	Early warning	Hospital care	LR	Private own data *(North Shore University of Chicago Medical Center, USA)*	Demographics, Temperature, Heart rate, Blood pressure, Lab tests, Clinical data	AUROC 0.70
Horng et al. [37]	Sepsis	Early warning	Hospital care	SVM	Public *(BIDMC Dataset)*	EHR, Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	AUROC 0.85
Hu et al. [39]	Surgical Site Infection	Early warning	Hospital care	LR	Private own data *(The University of Minnesota Academic Health Center, USA)*	EHR	AUROC 0.898, Spec. 78.8–98.8%
Hu et al. [40]	Surgical Site Infection	Early warning	Hospital care	LR	Private own data *(The Clinical Data Repository at the University of Minnesota Medical Center, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.935
Hu et al. [38]	Sepsis	Surveillance	Hospital care	LR, SVM, RF, ANN, CNN	Private own data *(Monash Children Hospital, Australia)*	Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	AUROC 0.79, Prec. 76%, Sens. 70%, Spec. 61%
Kam and Kim [43]	Sepsis	Early warning	Hospital care	CNN	Public *(MIMIC II database)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.929
Kamaleswaran et al. [44]	Sepsis	Early warning	Hospital care	LR, RF, CNN	Private own data *(Le Bonheur Children's Hospital, USA)*	Heart rate, Oxygen saturation, Blood pressure	Sens. 76%, Spec. 81%
Ke et al. [45]	Surgical Site Infection	Early warning	Hospital care	SVM	Private data *(Academic Teaching Hospital, Netherlands)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation Blood pressure, Lab tests	MAE 2.7

TABLE S2. ***(Continued.)*** **Relation of the papers studied in the systematic literature review and their taxonomy.**

Document	Infection(s)	Objective	Setting	CI Tech.	Data	Features	Performance
Khoshnevisan et al. [46]	Sepsis	Surveillance	Hospital care	LR, SVM, RF, NB, ANN, CNN	Private data *(Christiana Care Health System, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure, Lab tests	AUROC 0.943, Acc. 87.5%, Prec. 91.5%, Rec. 82.6%, F1 86.8%
Kim et al. [47]	Sepsis	Early warning	Hospital care	SVM	Private own data *(Centricity, General Electric Healthcare, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.95
Kocbek et al. [49]	Surgical Site Infection	INfection detection	Hospital care	LR, GBT	Private own data *(University Hospital of North Norway)*	Lab tests	AUROC 0.967
Lamping et al. [50]	Sepsis	Early warning	Hospital care	LDA	Private own data *(Hannover Medical School, Germany)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Clinical data	AUROC 0.78
Le et al. [51]	Sepsis	Early warning	Hospital care	RF	Private own data *(UCSF Medical Center, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation Blood pressure	AUROC 0.916
Lin et al. [52]	Sepsis	Surveillance	Hospital care	CNN, LSTM	Private own data *(Christiana Care Health System, USA)*	Demographics, Lab data	AUROC 0.94, F1 85.8%
Liu et al. [53]	Hand, Foot, and Mouth Disease	Diagnosis	Hospital care	RF	Private own data *(Guangzhou Women's and Children's Medical Center, China)*	Demographics, Temperature, Respiratory rate, Lab tests	AUROC 0.916, Acc. 91.6%, Sens. 82.4%, Spec. 93.1%
Lo et al. [54]	Urinary Tract Infection	Surveillance	Hospital care	LDA	Private own data *(Taipei Medical University Wan Fang Hospital, Taiwan)*	Lab tests	Acc. 94.65%, Sens. 100%, Spec. 94.61%
López-Martínez et al. [55]	Sepsis	Infection detection	Hospital care	MLP	Private own data *(Cartagena, Colombia)*	Demographics, Clinical data	Acc. 86.7%, F1 81.7%, Prec. 83%, Recall 80.3%
Lu et al. [56]	Upper Respiratory Infection	Surveillance	Hospital care	TM	Public *(National Health Insurance Research Dataset)*	Clinical data	Acc. 32.5%, NDCG 54.7%, MAP 37.5%
Lukaszewski et al. [57]	Sepsis	Early warning	Hospital care	KNN	Private data *(Queen Alexandra Hospital, USA)*	Microbiology data	Acc. 94.55%, Sens. 91.43%, Spec. 80.2%
Mani et al. [59]	Sepsis	Early warning	Hospital care	LR, SVM, RF, NB, BN	Private own data *(Monroe Carell Jr. Children's Hospital at Vanderbilt University, USA)*	EHR	AUROC 0.78
Mao et al. [61]	Sepsis	Surveillance	Hospital care	GBT	Public *(MIMIC III)*, Private own data *(UCSF Medical Center, USA)*	Blood pressure, Clinical data	AUROC 0.96
Masino et al. [62]	Sepsis	Surveillance	Hospital care	LR, SVM, RF, GB, KNN	Private own data *(Children's Hospital of Philadelphia, USA)*	EHR	AUROC 0.87
Matsui et al. [63]	Influenza	Screening	Airport screening	LDA	Private own data *(Japan Self-defense Forces Central Hospital, Japan)*	Temperature, Respiratory rate, Heart rate	Prec. 93%, Sens. 88%
Meurer et al. [64]	General Infection	Surveillance	Hospital care	CT	Private data *(Geriatrics Center and Division of Geriatric & Palliative Medicine University of Michigan, USA)*	EHR	Sens. 14%, Spec. 98%
Mikalsen et al. [65]	Surgical Site Infection	Early warning	Hospital care	SVM	Private own data *(University Hospital of North Norway, Norway)*	Lab tests	F1 80%
Milechin et al. [66]	Pathogen Exposure	Surveillance	Hospital care	RF	Private own data *(US Army Medical Research Institute of Infectious Diseases, USA)*	Respiratory rate, Heart rate, Blood pressure, Biomedical signals	AUROC 0.95 (51h early detection)
Mitchell et al. [67]	Sepsis	Early warning	Hospital care	LR	Public *(MIMIC II database)*	Lab tests	AUROC 0.739, Sens. 57.6%, Spec. 77.3%
Monsalve et al. [69]	CDI	Early warning	Hospital care	EL	Private own data *(University of Iowa Hospitals and Clinics, USA)*	EHR, Demographics, Clinical data, Logistic data	AUROC 0.866, Sens. 82.2%, Spec. 74.8%
Mulder et al. [70]	Surgical Site Infection	Decision support for diagnosis	Hospital care	LR	Private own data *(Amphia Hospital, The Netherlands)*	Demographics, Clinical data	AUROC 0.950, Sens. 98.5%, Spec. 68.7%
Na et al. [71]	CDI	Early warning	Hospital care	LR	Private own data *(University of Houston College of Pharmacy, Beth Israel Deaconess Medical Center, Mater Misericordiae University Hospital, Ireland-USA)*	Demographics, Lab tests	Acc. 72.5%
Nachimuthu and Haug [72]	Sepsis	Early warning	Hospital care	BN	Private own data *(LDS Hospital and Intermountain Medical Center, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.949
Nguyen et al. [73]	Influenza	Screening	Public health emergencies	SVM, LiR	Private data *(Takasaka Clinic, Japan)*	Temperature, Respiratory rate, Heart rate	Prec. 91%, NPV 93%, Sens. 93%, Spec. 91%
Oh et al. [74]	*CDI*	Early warning	Hospital care	LR	Private own data *(University of Michigan Hospitals & Massachusetts General Hospital, USA)*	EHR	AUROC 0.82
Parente et al. [75]	Sepsis	Early warning	Hospital care	HMM	Private own data *(Christchurch Hospital, New Zealand)*	Temperature, Respiratory rate, Heart rate, Blood pressure, Lab tests, Clinical data	AUROC 0.99, Sens. 95%, Spec. 96%
Parreco et al. [76]	Central Line-Associated Bloodstream Infection	Surveillance	Hospital care	LR, GBT, CNN	Public *(MIMIC III database)*	EHR	AUROC 0.722, Acc. 98.6%, Spec. 77.3%
Paxton et al. [78]	Sepsis	Surveillance	Hospital care	SVM	Public *(MIMIC-II Clinical database)*	EHR, Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Clinical data, Logistic data	AUROC 0.7

TABLE S2. ***(Continued.)*** **Relation of the papers studied in the systematic literature review and their taxonomy.**

Document	Infection(s)	Objective	Setting	CI Tech.	Data	Features	Performance
Prasad et al. [80]	Sepsis	Early warning	Hospital care	LR, RF, QDA	Private own data *(Massachusetts General Hospital, USA)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.815
Rabhi et al. [81]	General Infection	Infection Detection	Hospital care	LR, SVM, RF, KNN, GB, NB, CNN	Private own data *(Lyon, Nice, Rouen Hospitals, France)*	Clinical notes	AUROC 0.998, F1 97.7%
Sanger et al. [82]	Surgical Site Infection	Early warning	Hospital care	NB	Private own data *(VU University Medical Center, Netherlands)*	Temperature, Heart rate, Blood pressure, Risk factors	AUROC 0.76
Sanger et al. [83]	Catheter-Associated Urinary Tract Infection	Surveillance	Hospital care	NLP	Private own data *(University of Washington Medical Center, USA)*	EHR, Billing data	Sens. 97.1%, Spec. 94.5%, PPV 66.7%, NPV 99.6%
Saunders et al. [84]	Surgical Site Infection	Surveillance	Hospital care	LR	Private own data *(RAISIN French Institute for Public Health Surveillance, France)*	Demographics, Clinical data, Logistic data	AUROC 0.84
Scherpf et al. [85]	Sepsis	Early warning	Hospital care	RNN	Public *(MIMIC III database)*	Demographics, Clinical data	AUROC 0.81
Schurink et al. [86]	Ventilator-Associated Pneumonia	Decision support for diagnosis	Hospital care	BN	Private own data *(The University Medical Center Utrecht, Netherlands)*	Temperature, Lab tests, Biomedical signals	AUROC 0.846
Sen et al. [87]	CDI	Early warning	Hospital care	LR, SVM, RF	Public *(BIDMC dataset)*	EHR, Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Clinical data	AUROC 0.838
Shankar et al. [88]	Surgical Site Infection	Surveillance	Hospital care	LR, SVM, RF	Private own data *(Dept. of Gastrointestinal Surgery at University Hospital of North Norway)*	Laboratory tests	Acc. 86%, Sens. 68%, Spec. 91%
Shashikumar et al. [89]	Sepsis	Early warning	Hospital care	EL	Private own data *(Emory Affiliated Hospital, USA)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure, Lab tests, Clinical data, Logistic data, Risk factors	AUROC 0.78, Acc. 61%, Spec. 55%, Sens. 85%
Shimabukuro et al. [90]	Sepsis	Surveillance	Hospital care	EL	Private own data *(University of California San Francisco Medical Center, USA)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Logistic data	AUROC 0.952, Sens. 90%, Spec. 90%
Soguero-Ruiz et al. [92]	Surgical Site Infection	Early warning	Hospital care	GP	Private own data *(University Hospital of North Norway, Norway)*	Lab tests	Acc. 83%
Stanculescu et al. [93]	Sepsis	Early warning	Hospital care	HMM	Private own data *(Royal Infirmary of Edinburgh, UK)*	Temperature, Heart rate, Oxygen saturation	AUROC 0.77
Stanculescu et al. [94]	Sepsis	Early warning	Hospital care	LDS	Private own data *(Royal Infirmary of Edinburgh, UK)*	Temperature, Heart rate, Oxygen saturation	AUROC 0.85
Strauman et al. [95].	Surgical Site Infection	Infection detection	Hospital care	ANN	Private own data *(University Hospital of North Norway)*	Blood tests	AUROC 0.91, F1 71%
Sun et al. [96]	Influenza	Screening	Airport screening	ANN	Private own data *(Japan Self-defense Forces Central Hospital, Japan)*	Temperature, Respiratory rate, Heart rate	Sens. 92.3%
Sun et al. [97]	Influenza	Screening	Hospital care	SVM	Private own data *(Nishi-kokubunji Clinic, Ritsu Pediatric Dental Clinic, Japan)*	Temperature, Respiratory rate, Heart rate	Prec. 84.6%, NPV 88.6%, Sens. 81.5%, Spec. 90.7%
Sun et al. [98]	Influenza	Screening	Emergency outpatient unit & airport screening	ANN	Private own data *(Japan Self-defense Forces Central Hospital, Japan)*	Temperature, Respiratory rate, Heart rate	Prec. 79.1%, NPV 97.5%, Sens. 97.1%, Spec. 81.3%
Sun et al. [99]	General Infection	Screening	Airport screening	LDA	Private own data *(Tokyo Metropolitan University, Japan)*	Temperature, Respiratory rate, Heart rate	Acc. 95%
Swiston Jr et al. [100]	Ebola and Marburg Viruses	Surveillance	Hospital care	RF	Private own data *(US Army Medical Research Institute of Infectious Diseases, USA)*	Biomedical signals	AUROC 0.9 (52±14h early detection)
Taneja et al. [101]	Sepsis	Early warning	Hospital care	LR, SVM, RF, NB, GP	Private own data *(Carle Foundation Hospital, USA)*	Temperature, Respiratory rate, Heart rate, Lab tests, Microbiology data	Acc. 81%
Tanner et al. [102]	CDI	Early warning	Hospital care	LR	Private own data *(University Hospitals of Leicester, UK)*	EHR, Demographics, Clinical data, Logistic data	AUROC 0.847, Acc. 96%, P-value <0.001
Tou et al. [103]	General Infection	Decision support for diagnosis	Hospital care	LR, RF, NB, GBT	Private own data *(Zhongshan Hospital, China)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Biomedical signals	AUROC 0.88
Tvardik et al. [105]	General Infection	Decision support for diagnosis	Hospital care	NLP	Private own data *(Lyon, Nice, Rouen Hospitals, France)*	EHR	Acc. 84%, Sens. 83.9%, Spec. 84.2%
van Wyk et al. [109]	Sepsis	Surveillance	Hospital care	ANN, CNN	Private own data *(Methodist LeBonheur Hospital, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure, Lab tests	Acc. 86.1% (1 minute intervals), Acc. 78.2% (10 minute intervals)
van Wyk et al. [110]	Sepsis	Early warning	Hospital care	LR, SVM, RF, NLP	Private own data *(Methodist LeBonheur Hospital, USA)*	Clinical data	F1 67% Sens. 80%
Ward et al. [111]	Sepsis	Prediction of mortality rate	Hospital care	BN	Private own data *(Beilinson Hospital, Israel)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests	AUROC 0.79

TABLE S2. *(Continued.)* **Relation of the papers studied in the systematic literature review and their taxonomy.**

Document	Infection(s)	Objective	Setting	CI Tech.	Data	Features	Performance
Wiens et al. [112]	CDI	Early warning	Hospital care	SVM, HMM	Private own data *(Barnes-Jewish Hospital, USA)*	Risk factors	AUROC 0.79, F1 37%
Wiens et al. [113]	CDI	Early warning	Hospital care	LR	Private own data *(MedStar Health Research Institute, USA)*	EHR, Risk factors	AUROC 0.814
Yao et al. [114]	General Infection	Screening	Mass gathering places & airport quarantines screening	LR, SVM, NB, LDA, QDA, KNN	Private own data *(Japan Self-defense Forces Central Hospital, Japan)*	Temperature, Respiratory rate, Heart rate	AUROC 0.95, Acc. 90.2%, Sens. 93%, Spec. 85.7%
Yee et al. [115]	Sepsis	Early warning	Hospital care	BN	Public *(MIMIC III)*	Demographics, Lab data	AUROC 0.81, PPV 65%, NPV 87%
Binti Mohd Zainee and Chellappan [9]	Dengue Fever	Surveillance	Hospital care	LDA	Private own data *(Pusat Perubatan Universiti Kebangsaan Hospital Canselor Tuanku Muhriz, Malaysia)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure, Lab tests	Acc. 83.3%
Zhang et al. [117]	Sepsis	Early warning	Hospital care	LSTM	Private own data *(Mayo Clinic, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure, Lab tests	AUROC 0.990, Prec. 92.6%, NPV 99.9%, F1 96.1%, Sens. 99.9%, Spec. 96.7%
Zhang et al. [116]	Hand, Foot, and Mouth Disease	Surveillance	Hospital care	GBT	Private own data *(Teaching Hospital in Guangdong, China)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Lab tests, Biomedical signals	AUROC 0.985
Amland et al. [5]	Sepsis	Surveillance	Hospital care	SIRS	Private own data *(Millennium: Cerner Corporation, USA)*	Temperature, Respiratory rate, Heart rate, Blood pressure	Prec. 73%, Sens. 72% (pre alert) Prec. 94%, Sens. 81% (post alert)
Amland and Hahn-Cover [4]	Sepsis	Early warning	Hospital care	SIRS	Private own data *(Millennium: Cerner Corporation, USA)*	Temperature, Respiratory rate, Heart rate, Blood pressure	Prec. 46%, NPV 99%, Sens. 83%, Spec. 92%
Calvert et al. [14]	Sepsis	Early warning	Hospital care	Rules	Public *(MIMIC II database)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	AUROC 0.92
de Bruin et al. [18]	Healthcare-Associated Infections	Surveillance	Hospital care	HELICS	Private own data *(Vienna General Hospital, Austria)*	Lab tests	Prec. 96%, NPV 95%, Sens. 87%, Spec. 99%
de Bruin et al. [19]	General Infection	Surveillance	Hospital care	Fuzzy	Private own data *(Medical University of Vienna, Austria)*	Temperature, Heart rate, Blood pressure, Lab tests	P-value < 0.001
Gundlapalli et al. [31]	Meningitis and Encephalitis	Surveillance	Hospital care	Rules	Private own data *(University Health Care Edinburgh, UK)*	Biomedical signals	AUROC 0.95, Sens. 91%
Jouffroy et al. [42]	Sepsis	Surveillance	Home care	Rules	Private own data *(Paris SAMU Regulation Call Centre, France)*	Demographics, Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	Prec. 41%, NPV 88%, Sens. 92%, Spec. 29%
Mansingh et al. [60]	General Infection	Decision support	Hospital care	Rules	Unreported	Demographics, Lab tests, Clinical data	Conf. 100%, Reliab. 46.39%, Supp. 94.66%, Lift 1.04
Trick et al. [104]	Central Venous Catheter	Surveillance	Hospital care	Rules	Private own data *(Cook County Hospital, Provident Hospital, USA)*	Microbiology data	Prec. 62%, NPV 87%, Sens. 81%, Spec. 72%
Umscheid et al. [106]	Sepsis	Early warning	Hospital care	Rules	Private own data *(The University of Pennsylvania Health System, USA)*	Temperature, Respiratory rate, Heart rate, Oxygen saturation, Blood pressure	Prec. 26%, NPV 94%, Sens. 16%, Spec. 97%
Uzoka et al. [107]	Malaria	Surveillance	Hospital care & screening facilities	Fuzzy, AHP	Private own data *(Hospitals in Nigeria)*	Clinical data	Acc. 80%

The most common machine learning techniques are logistic regression, support vector machine, random forest and decision trees, hidden Markov models, linear discriminant analysis and naive Bayes. The remaining 11 documents used different implementations of expert systems, most commonly custom rule knowledge bases to perform the diagnosis.

Performance reported in this SLR should be taken only as informative, since problems and databases vary across studies, and the latter are in most cases privately hold. However, since a large corpora of works focus on sepsis prediction using the public MIMIC-III database, it is relevant to highlight that the best performance in this case is attained by Kam and Kim [43], who have reported an AUROC of 0.929.

Finally, we were worried about two problems that can be commonly found in the application of machine learning to medical applications: class imbalance and the lack of data. Therefore, we posed two additional questions that we tried to answer during the SLR regarding these two specific issues. From the 101 papers, 30 mentioned the problem of reduced availability of data, and so did 26 papers with the issue of class imbalance. Regarding the former problem, most papers (a total of 15) did not suggest any particular solution, although other papers suggested collecting new data, and to a lesser

extent adapting the model parameters or performing random resampling. As with the problem of class imbalance, most papers suggested the use of over- or under-sampling to tackle this issue, whereas some other papers described solutions which involved adapting the model parameters or using a performance metric that was not affected by this problem, such as the area under the curve (AUROC).

From our SLR, we conclude that automatic diagnosis of infectious diseases is a topic of intensive research, and a field of increasing interest, since more than half of all found papers (a total of 60) were published from 2016 onwards.

As a future line of work, it would be interesting to study how the different features and algorithms used for infection prediction evolve over time, to detect technological trends and advances in the discipline. It could also be useful to study the evolution of peak performance, although this would be a more challenging analysis, given that authors focus on different problems and datasets.

APPENDIX

See Tables S1 and S2.

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