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Models for individualized COVID-19 diagnostic prediction

Modelos para predicción de diagnóstico individualizado de COVID-19

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Abstract:

Since the COVID-19 pandemic, the world has experienced a large incidence of infections in short periods of time, giving rise to waves of contagion caused by the different variations of SARS-COV-2. Health services, as well as personnel, have been overwhelmed, especially in the poorest countries. Currently and after two years, the pandemic continues and according to experts it is here to stay, which highlights the importance of vaccines and methods of detecting the disease, to curb the number of infections and avoid that the pandemic continues to spread and thus the virus continues to mutate. Detection tests have been scarce and expensive for most of the population, so alternative methods to laboratory ones could be a decisive factor so that people can self-isolate before continuing to infect more people. One of the most effective methods have been statistical predictions of the diagnosis of COVID-19 in a patient, based on certain variables. In this article, it was identified that the most common prediction models were developed from logistic regression and machine-learning, which have shown high percentages of predicting test results for COVID-19. The most important predictor variables in the different models developed in various regions of the world were identified and the opportunities, limitations and perspectives of this prediction method are discussed.

Keywords:

COVID-19, individual prediction, prediction models, symptoms, detection

Resumen:

Desde que la pandemia del COVID-19, el mundo ha vivido el gran número de infecciones en periodos cortos de tiempo, dando lugar a las olas de contagio provocadas por las distintas variaciones del SARS-COV-2. Los servicios de salud, así como el personal, se han visto superados, esto especialmente en los países más pobres. Actualmente y después de dos años, la pandemia continua y según expertos llegó para quedarse de forma estacionaria, por lo que hoy más que nunca la importancia de las vacunas y de los métodos de detección de la enfermedad, para frenar el número de contagios y evitar que la pandemia siga extendiéndose y así el virus siga mutando. Las pruebas de detección han resultado escasas y caras para la mayoría de población, por lo que los métodos alternativos a los de laboratorio podría ser un factor decisivo para que las personas puedan autoaislarse antes de seguir contagiando a más personas. Uno de los métodos más eficaces ha sido lo que involucran predicciones estadísticas de diagnóstico de COVID-19 en un paciente, a partir de ciertas variables. En este artículo se identificaron que los modelos de predicción más comunes se desarrollaron a partir de la regresión logística e inteligencia artificial, el objetivo de este trabajo es demostrar los altos porcentajes de predicción de resultado de prueba por COVID-19 de estos métodos alternativos a las pruebas de laboratorio, para mostrar que son confiables como alternativas a ellas, y aplicarlas a la población como método de control de la pandemia de COVID-19. Se identificaron las variables predictoras más importantes en los distintos modelos desarrollados en varias regiones del mundo y se discuten las oportunidades, limitaciones y perspectivas de este método de predicción.

Palabras Clave:

COVID-19, predicción individual, modelos de predicción, síntomas, detección.

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INTRODUCTION

The COVID-19 disease is caused by the SARS-COv-2 virus, which began to spread as a pandemic since 2020, affecting all countries in the world with almost 6 million deaths worldwide until this year.[1,2] This disease has brought a number of subsequent problems, from economic to health problems, revealing how little is known today about viruses, since, although there are already vaccines that are effective in preventing the development of severe COVID-19 by up to 98%, there are still no drugs that cure the disease.[3] However, the fact that people are vaccinated with one or more doses, although they do not prevent infection, does significantly lower the chances of being hospitalized, as well as dying.[4] Here is the importance of continuing to vaccinate as many people as possible. Moreover, although the number of infections has fallen by a large percentage, there are still a large number of infected people worldwide.[2]

Due to the large number of infections, it is of vital importance that detection tests continue to be done for COVID-19 infection, for people to isolate themselves, and by not having contact with other people, contagion can be avoided, especially with the last variant of interest of COVID-19, which caused the most recent wave of infections, and whose symptoms are more like the common cold, so it is more likely that people will become infected even without knowing it.[5]

All this without mentioning that the long-term sequelae are still being studied and that the vast majority of recovered patients have reported, which approach from headaches, psychological problems, to multiple organ failure (varying in each patient, and depending on many factors).[6]

Due to all this, it is of the utmost importance to prevent more people from getting infected, which could be avoided exponentially by increasing the number of tests performed, but because they have been scarce, as well as the medical personnel who apply them, and having such high costs, new detection methods have been developed, among which statistical methods stand out, such as logistic regression models, which through certain variables, are able to satisfactorily predict the result of an individualized test for COVID-19.[7,8]

Because the models for individualized prediction of COVID-19 that have been reported so far are heterogeneous in terms of their composition and performance, as well as the applicability in the time and region in which they were developed, the objective of this work was to analyze the characteristics of the individualized prediction models of COVID-19 that have been reported, identify the main predictor variables, the performance of the models, their limitations and strengths.[9]

VARIANTS OF INTEREST OF THE SARS-COV-2 VIRUS

The mutation of the SARS-COV-2 virus has occurred constantly since its emergence, through the genetic changes it has undergone, also called genetic mutations in which the genome is replicated as there are still a large number of people infected and who continue to infect, the virus acquires new mutations, which are classified according to the World Health Organization (WHO), as variants of interest or not.[2,10] So far 3 variants of interest have been detected because they can cause serious health problems for humans, and in the most serious cases, even death.[11]

The variants of interest are: the original strain, delta and omicron, each of which has caused millions of infections and thousands of deaths around the world.[10]

Although cases have decreased drastically thanks to vaccination in many countries of the world, there is still a significant lag in terms of the least developed countries, so the number of infections worldwide continues to increase.[12]

WAVES OF CONTAGION IN THE PANDEMIC

Since the beginning of the pandemic, in China, in 2019, four waves of contagion have been detected worldwide, which stand out dramatically for the numbers of infections registered until that moment.[13] According to information provided by the WHO and the Centers for Disease Control (CDC) of USA, the first wave was recorded in July-August 2020, the second in January 2021, the third in August of the same year, and the fourth and most recent one, in January 2022.[2,14] Consequently, it is of the utmost importance to continue with sanitary measures and apply a greater number of reliable screening tests, to avoid or mitigate the effects of a possible fifth wave, since health systems are on the verge of collapse, in addition to other ailments have been left aside by the resources that have been allocated to combat the pandemic.

New models for predicting future waves or peaks of contagion are currently being developed, all thanks to the data that has been collected since this new virus emerged.[15]

COVID-19 DIAGNOSTIC STRATEGIES

Currently, millions of screening tests have already been applied for COVID-19, the most reliable has turned out to be the PCR test, with an approximate 90-98% effectiveness in detecting the presence of the virus, followed by the antigen test with an approximate of 82-90% detection efficiency.[16,17] This type of test is followed by laboratory studies that are generally also used to detect the level of severity of the disease in patients, in addition to initially being used to diagnose whether a laboratory test cannot be accessed.[18] However, in view of the high demand for tests, the scarcity and cost of such tests, the time they take, and the lack of medical personnel applying them due to the high risk of contagion when applying them, the development of other types of detection methods has been resorted to, among which statistical methods are applied to try to predict as accurately as possible, the outcome that patients would have for the COVID-19 disease. One of the most effective methods within this category has turned out to be mathematical modeling through logistic regression and artificial intelligence (AI), since they use different independent variables. Although there are variations between the models developed, most model-independent variables include the most frequent symptomatology in infected patients, exposure to the virus, place of residence, and previous medical conditions of the patient.[19] These variables were analyzed separately and then in combinations, to know what the predictor variables for the result of the test for COVID-19 would be.[20-26]

In other words, several previously known independent variables are used to predict the dependent variable, which has shown us a large percentage of success when predicting the result of the test, being able to even compare with the results obtained with the most used laboratory tests, but with less response time, exposure of both patients and staff, and lower cost.

STATICAL PREDICTIONS MODELS FOR COVID-19

There are innovative models for the individualized prediction of the result of the COVID-19 test, developed with statistical methods and that do not require in their variables the result of laboratory analyzes (except for the COVID-19 diagnostic test used as a gold standard to compare the outcome) or physically review patients.[4]

The models that stand out from the others have been those of logistic regression and machine-learning as this is the most used method and that had reported the best results in the various works that were reviewed, and as mentioned above, one of its characteristics. The key is that they don't need laboratory studies to make their predictions.[20-26]

The methods have variations in their population type, sampling method, sample, data collection method, statistical analysis, variables used, and results obtained.[20-26] A comparison analysis of the models was carried out, considering their main characteristics, such as the method of solution of the model, the dependent and independent variables, the population studied, the predictor variables, and the final results.

MODEL OVERVIEW AND ANALYSIS

The models analyzed showed similar structures in terms of research development (Table 1 and Table 2). The information was collected through questionnaires, interviews or databases, with the independent variables previously determined through research that showed which were the risk factors for positive COVID-19 test. Many similar prescribing variables were found, such as the main symptomatology presented by previous confirmed cases (sore throat, fever, cough, headache, changes in smell or taste, difficulty breathing), exposure to the virus by contact with people who were known to be infected, smokers, or recent trips (last two weeks) or co-morbid diseases.[20,21,23,24,26] However, others were not as common, such as gender (women), race (African-Americans) and demographic data (whether or not they live in metropolitan areas or with large percentages of the population) and the level of physical activity they performed.[22,25] Another key point that was considered in only one study is the psychological problems derived from the COVID-19 disease, which could also be determinants as predictive factors (anxiety, depression, insomnia).[27] This was determined for the population and subsequent sample, which in general only required that they have their COVID-19 test, either the PCR or the quick test.[20-26] Having access to patients data before and after the test was useful so they were able to perform a validation phase.[23,25]

After identifying the characteristics of their sample, the most frequent variables in these patients were analyzed, in order to determine which were the predictor variables for the models, as well as to make a combination of them to make the predictions with a greater degree of accuracy.[28] Some studies used one or more predictive or statistical methods, the most common being logistic regression (Table 1), and AI (Table 2).[20-26]

MODEL COMPARISONS

The main variations found in the models, in addition to the type of analysis that was performed, were the independent variables selected for the predictions (Table 1 and Table 2). When a large number of independent variables were reported in various studies, and as they varied at the time they were taken into account for the analyses, it can be considered that there was more or less information about the disease in general, so the researchers decided each one by their own variables. In most models the independent variables were similar, but in other cases they were not. This could explain the difference in the performance of the models, which overall was between 70 and 87% of success effectiveness in positive COVID-19 test.[20-26]

Most of the models were made with samples taken in short periods of time, about one month, and the longest was 4 months.[20-26] In most cases, the investigations were conducted in the United States of America, and all in the year 2020 (Table 1 and Table 2).

ADVANTAGES AND DISADVANTAGES OF MODELS

The models found and analyzed showed effective results (Table 1 and Table 2). However, the diagnostic value of the models is lower than the laboratory results, since there are variants that cannot be controlled, such as the large number of symptoms that the COVID-19 disease has presented, in addition to the fact that these vary from person to person depending on various characteristics that patients present.[29] External factors that contribute to the fact that the results are not more uniform, such as their demographic characteristics and the fact that a large percentage of the population travels due to their daily activities or work, may also affect the predictive value of the models.[20-26] Another factor to consider is that, while research has determined that people have been exposed to the virus by having contact with an infected patient as a highly valuable predictor, many of these patients who may have been exposed do not know it because the other people have not been tested, or did not have the general symptoms.[30]

Some research mentions the fact that one of its limitations is not to give registered follow-up to patients, since having subsequent information from them to be able to reinforce the prediction systems with this data.[20-24,26]

However, and despite all the above, the models analyzed have shown optimal performance when determining the predictor variables, and derived from it, final results above 70% of positive COVID-19 test prediction, some even reaching more than 87% efficacy.[20-26] With this performance, it would be considered that patients analyzed with this type of method could have high certainty of the results, because these percentages can be compared with those of the rapid test for COVID-19, this being one of the most used. Other great advantages to highlight about these methods are their cost, since, in times of pandemic, this type of tests increased their monetary value, increasing the number of people not taking the test.[31] In addition, a shortage of tests has been reported due to the large number of infections recorded, mainly during the waves of contagion, in addition to the lack of medical personnel to apply them due to the possible exposure to the virus, and the time it takes people to perform the test in a laboratory.[31] For these reasons, individualized prediction models based on statistical models and patient symptoms could be more comfortable, cheaper and faster for people.

SYNTHESIS OF THE MAIN CHARACTERISTICS OF THE PUBLISHED MODELS

The results showed mostly models that used statistical or mathematical methods (Table 1), in addition to artificial intelligence (Table 2) to make predictions from certain variables considered and studied by the different authors, which yielded predictor variables for the final prediction model. Most of the research reviewed showed at least 70% effectiveness in predicting outcome, and in the best cases, almost 90% efficacy.[20-26] Therefore, they could be a useful option for more people with symptoms or risk factors to be tested and, if necessary, seek appropriate medical attention.

Most of the models were developed in the US, through electronic surveys or databases of health centers that treated Covid-19 patients, which had the result of their Covid-19 test (PCR, nasopharyngeal or pharyngeal), and almost all considered adult patients, all with the main objective of predicting the result of the positive test for Covid-19, through statistical methods of logistic regression or applying artificial intelligence. The most suitable study designs, mostly cohort, prospective and retrospective, were used as models. The independent variables taken to predict the dependent (Covid-19 test result) were the main ones reported for patients confirmed by the virus, such as the most frequent symptomatology (sore throat, body, headache, changes in smell or taste), co-morbid diseases, exposure to the virus, workplaces, travel, age, gender, race, psychological problems, economic position, among others.[20-26]

Most of these models performed validation stages so that the models could improve or adjust to their first results.[21,23-25]

The development of this research provides the population with new methods to try to stop the infections, and with it, the probability that the virus continues to mutate. In this way, the world could recover little by little from the ravages in all areas that the pandemic has been causing, not to mention that vaccines are still scarce and their annual application has been recommended, despite the fact that a large percentage of the world's population has not been able to receive even the first dose, so today more than ever, the prevention and control of infections is fundamental.[20-26]

OPPORTUNITIES, CONSTRAINTS AND PERSPECTIVE

As already mentioned, the fact that new methods of diagnosing COVID-19 can be developed, of more scope, lower cost and time, that do not expose the health personnel and above all, is faster, which would avoid early detection and that the patient continues to infect people. It turns out to be a solution to various problems caused by the pandemic, especially to try to curb the number of infections and prevent new variants of interest and new waves of contagion from emerging.[20-26]

Some of the limitations reported by the researchers are the variation in symptoms, the displacement of people, and the lack of knowledge of whether they were exposed to the virus or not, this also derived from the lack of tests to detect the virus.[32] In addition, the information used is from 2020, so it is possible to deduce the lack of information that we have today, and which can be considered important for this type of model, such as the symptoms of each variant of interest, which has been shown to be very different from each other, and take into account the vaccination that has been applied as a possible confounding variant to reduce the symptoms, but not to prevent contagion itself.[20-26]

It is essential that new effective and reliable methods for the early detection of the virus continue to be developed, these methods could be of great help for the entire medical system, and in the future for patients, since it has been shown that the virus leaves sequelae in up to 50% of infected patients, depending on the time they were infected and if they had any dose of vaccination.[33]

CONCLUSIONS

The models analyzed proved to be reliable and with less expenditure of resources; however, it is important to incorporate new information that in 2020 was still unknown, in order to have more accurate and reliable models, however, these new methods have great potential, in addition to being able to be applied as a first way to analyze patients, and in this way, if necessary, direct to laboratory tests to those who require it most, and thus be able to optimize medical, personnel and time resources.

Table 1. Comparison of current individualized test prediction models for Covid-19, part 1

Research name/ characteristics	**Smell and taste symptom-based predictive model for Covid-19 diagnosis.[20]**	**Individualizing risk prediction for positive coronavirus disease 2019 testing.[21]**	**Beyond predicting the number of infections: predicting who is likely to be covid negative or positive.[22]**	**Development of an individualized risk prediction model for Covid-19 using electronic health record data.[23]**

Country-region	USA[c]	USA[c]	Iran	USA[c]
Objective	Covid-19 Positive Test Prediction	Covid-19 positive test prediction	Covid-19 Test Result Prediction	Covid-19 Test Result Prediction
Statistical method	Binary logistic regression	Logistic regression	Logistic regression	Logistic regression
Study design	Cohort	Prospective, validation phase: cohort	Not mentioned	Longitudinal cohort
Population	Covid-19 patients in California, USA, who have a PCRa test	Covid-19 patients in Florida, USA	Population in Iran	University of Alabama Patients Tested for Covid-19
Sampling method	Estimation of a proportion	Not mentioned	Not mentioned	Not mentioned
Sample size	145 participants with a positive test for Covid-19 and 157 with a negative test for Covid-19	11672 patients with general characteristics	521 adults with general characteristics	7262 patients admitted to the University of Alabama hospital
Method of obtaining the information	Anonymous surveys via the internet	Registry of patients analyzed for Covid-19, in Cleveland clinic	Primary study through surveys	Database of patients in the health system of the University of Alabama who have been tested for Covid-19
Dependent variable	PCR[a] test result	PCR[a] or nasal test result	PCR[a] test result	PCR[a] test result
Independent variable	Symptoms, demographic information, co-morbidities	Sex, age, symptoms, economic status, race	Sex, age, co-morbidities, active workers, demographics, exercise, depression, anxiety	Age, gender, race, health condition, smoker, addictions, weight
Confusor variant	Myalgia, gastrointestinal problems	Common Symptoms	Gender and age	Age, gender and race
Significance predictors	Changes in smell, unexplained body aches, fever, or chills	Female, African American, elderly, and having been exposed to the virus	Physical activity, workplace, co-morbid diseases	Substance abuse, smoking and co-morbidities
Model Solution Method	Stepwise	Multivariable	Ordination	Linear
Scan time	March-April 2020	April 2020	April 2020	January-June 2020
Validation stage	Not carried out, but considered necessary	Performed with 2295 patients	Not realized	Performed
Results	82% in Covid-19 test result discrimination, 75% correct predictions	The concordance index corrected by bootstrap in the development cohort was 0.863 (95% CI[B], 0.852-0.874). The concordance index in the Florida validation cohort was 0.839 (95% CI[b], 0.817-0.861)	Separate analysis of predictor variables, all showed more than 70% chance of positive Covid-19 test	Time-separated and variant analysis, general analysis with more than 70% prediction efficiency

[a] PCR: polymerase chain reaction, [b] CI: confidence index, [C] USA: United States of America

Table2. Comparison of current individualized test prediction models for Covid-19, part 2

Name of the research/ characteristics	**Machine learning-based prediction of Covid-19 diagnosis based on symptoms.[24]**	**Prediction of individual Covid-19 diagnosis using baseline demographics and lab data.[25]**	**Screening for Covid-19: patient factors predicting positive PCRa test.[26]**
Country-region	Israel	USA[c]	USA[c]
Objective	Covid-9 Positive Test Prediction	Covid-9 Positive Test Prediction	Covid-19 Positive Test Prediction
Statistical method	Machine-Learning	Machine-Learning, baseline data	Logistic regression
Study design	Prospective	Cohort	Retrospective
Population	Patients in Israel tested for Covid-19	Patients from hospitals in the New York metropolitan area	Patients admitted to Rochester, Minnesota clinic
Sampling method	Not mentioned	Stratified sub-populations	Not mentioned
Sample size	51,831 individuals tested (with 4769 confirmed by Covid-19)	31739 adults without a health system	48 positive and 98 negative patients from the Ranchester, Minnesota clinic
Method of obtaining the information	Public information reported by the Minister of Health and Israel	Clinic databases	Questionnaire applied to patients by a nurse
Dependent variable	PCR[a] test and nasopharyngeal test	PCR[a] test	PCR[a] test result
Independent variable	Cough, fever, contact with infected people, sex, age over 60, headache and breathing problems	Demographics, common co-morbidities and laboratory tests, calcium levels, temperature, age, blood tests, smokers, oxygen saturation	Fever, sneezing, respiratory problems, co-morbidities, travel and exposure to the virus
Confusor variant	Headache, shortness of breath and cough	Temperature and blood tests	Fever, chills
Significance predictors	Sex, age over 60 years, exposure to the virus and appearance of at least 5 clinical symptoms	Common co-morbidities and laboratory tests, calcium levels, temperature, age, blood tests, smokers, oxygen saturation	Exposure to the virus and travel to metropolitan areas
Model Solution Method	Decision Tree	Decision tree, random forest, XGBoost multi-tree and logistic regression	Multivariable
Scan time	March-April 2020	April-June 2020	March 2020
Validation stage	Performed with 1000 repetitions (ROC[b])	Realized (ROC[b])	Not realized
Results	87.30% sensitivity, 71.98% specificity, or 85.76% sensitivity and 79.18% specificity	Random forest: 79.10% accuracy, multi-tree XGBoost: 77.66% accuracy, logistic regression: 79.05% accuracy and single-tree XGBoost: 79.37% accuracy	Contact with confirmed cases increases the odds of positive test by 17 times (95% CI[d] 4.6–88.4), and recent trips increases the odds of positive test by 4.7 times (95% CI 1.9-12.7).

[a] PCR: polymerase chain reaction, [b] ROC: operational characteristic of the receptor, [C] USA: United States of America, [d] CI: Confidence indicator

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest with any institution or commercial association of any kind or field. This research was carried out following the corresponding guidelines.

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