ORIGINAL PAPER

Prediction of CD4+ T lymphocyte count in HIV patients from their total leukocyte count and previous CD4+ counts

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Abstract

Introduction: CD4+ T lymphocyte count is a high-cost para-clinical test, essential for follow-up of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients. For this test, various methodologies have been developed to allow estimating the evolution of this cell line in a more cost-effective way, giving the possibility for large number of patients to better control their immune status. Aim of the study was to confirm the predictive capacity of a methodology based on set theory, probability theory, and mathematical patterns, to predict the evolution of CD4+ T lymphocyte count in patients with HIV/AIDS.

Material and methods: Mathematical patterns identified in a previous study were applied to predict CD4+ T lymphocyte counts in ranges of clinical interest, in para-clinical follow-ups of 90 HIV-infected patients from previous studies' databases of the Insight Group.

Results: The global success probability of 93.33% was obtained for the evaluation of 5 dynamics. Leukocyte ranging below 4,000/ml^3 and 3,000/ml^3 were associated with less than 570 CD4+/µl, with the probability of success of 0.923 and 1, respectively.

Conclusions: The clinical applicability of the methodology developed for the prediction of CD4+ T lymphocyte count in patients with HIV/AIDS was confirmed without using statistical measures, while minimizing costs and resources.

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Key words: hemogram, set theory, probability, HIV/AIDS.

Introduction

Infection by human immunodeficiency virus (HIV) is a disease that currently affects people living around the globe. Sub-Saharan Africa is one of the countries with the highest number of HIV-infected cases in the world, where acquired immunodeficiency syndrome (AIDS) was recorded as one of the main causes of deaths, with approximately 1.3 million cases [1]. According to epidemiological reports, in Latin America, the incidence of this virus is lower than in other continents; it has a low-level-controlled epidemic [2]. Between 1983 and 2009, countries, such as Colombia, reported 71,653 HIV cases, with a prevalence rate of 0.7% [2].

HIV infects several cell lines, which are important for the regulation and function of immune system, such as CD4+ T lymphocytes, macrophages, dendritic cells, and other populations to a lesser extent [3]. There are laboratory

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tests that can be used to study parameters in general, or different populations and sub-populations of blood cells, as is the case of complete blood count, which is widely used in clinics. However, CD4+ T lymphocyte count is performed by various methods, e.g., flow cytometry, allowing for monitoring of the disease and treatment [3]. This technique suggests a higher cost and, therefore, lesser availability in health services in developing countries [3].

There is an association between total white blood cell count per cubic millimeter and CD4+ T cell count, suggesting that individuals with a total white blood cell count of less than 1,500 cells, for the most part, tend to have fewer than 500 CD4+ T cells per cell microliter [5]. In multiple studies, predictive approaches were developed relating to the evolution of CD4+ T lymphocyte count, according to certain parameters [6-9], and considered necessary to reduce the costs associated with treatment and follow-up of HIV/AIDS-infected patients, thus, increasing the accessibility of this methods to healthcare services [6-9]. CD4+ T cell count prediction is challenging, partially because the approach to the problem is based primarily on clinical and statistical perspectives [6-8].

Over time, different mathematical and physical theories have been developed, allowing for various solutions at the experimental, clinical, and epidemiological levels. Such is the case of the Zipf-Mandelbrot law, which became a tool for making predictions in different fields of medicine [10]. One of the most important things that this law established is that the physiology of immune system can be characterized by means of a statistical fractal dimension [10].

This can be achieved by considering the difference in fractal dimensions of mathematical behavior of the specific T repertoire against the Poa p9 allergen and the Th2 pattern, in the presence and absence of interferon [10]. This fact may have general implications for immunology [10]. Rodríguez [11] developed a predictive theory to establish the binding or non-binding state of all theoretical, natural, and synthetic peptides to HLA class II.

Other mathematical theories described relationships between elements based on various properties, including the membership relationship defined in the set theory. This proves that by means of operations, such as union and intersection, it is possible to differentiate particular elements [12]. Using the probability theory, it is possible to estimate possible occurrence of an event in a numerical range (0-1), considering the frequency of repetitions of evaluated event with respect to the total number of possible events in a probability space [13]. This theory was recently applied to predict the count of LT-CD4+/µl in HIV patients from the count of leukocytes and lymphocytes obtained from complete blood count, with accuracy percentages greater than 80% for 5 ranges measured out of a total of 8 ranges.

Based on this methodology, an original method was developed to predict the CD4+ T lymphocyte count using the probability theory and set theory. This methodology was employed in 135 clinical samples. Subsequently, the belonging of each sample to previously defined sets [14] was analyzed, evaluating the lymphocyte count in 9 ranges using the probability theory. On the other hand, the mean square deviation was also calculated to determine if the evaluated event presented a loading in its probabilities, that is, if it was an event that was not equiprobable. When performing these calculations, it was possible to establish that a not equiprobable phenomenon was analyzed, which allowed predictions to be made based on the probability theory. When evaluating the results, it was found that the accuracy of methodology, expressed in terms of probability, reached values of 1, with total leukocytes in a range of less than 4,000. On the other hand, it was observed that ranges greater than 5,000 had probabilities between 0.57 and 0.83 [15]. Previous values were calculated independently of the viral load, pharmacological history, sex, etc.; in this way, it was possible to abstract the behavior of evaluated variables from the same values it takes, generating a simplifying abstraction, which would allow the decrease of high-cost of para-clinical requirements to monitor follow-up of HIV/AIDS patients.

Considering all of the above, the present work aimed to confirm the clinical applicability of the methodology developed by Rodríguez *et al.* [14], using the identification of mathematical patterns for the LD-CD4+ count of 80 HIV-infected patient samples.

Material and methods

Population

Records of 90 patients were obtained from databases of previous studies of the Insight Group, and included total leukocyte count and CD4+ lymphocytes, while other variables were excluded.

Definitions

Probability

Probability is a dimensionless mathematical measure of the likelihood of an event occurring. Given an experiment that presents several possible results or events, the relative frequency of a particular event is the quotient between the number of times that result occurs with respect to the total number of repetitions [13].

$$P(A) = \frac{\text{Number of times that event occurs}}{\text{Total repetitions of all events possible}}$$

The values of probability are between 0 and 1: if the value is zero, it means that the event will not happen, if the value gets closer to 1, the occurrence of the event is more and more likely to occur, and if it is 1, it means that the event will happen.

Set

A set is the meeting in a whole of well-defined and differentiable objects, which are called its elements. The elements denote the relations of membership to the sets, that

is, if an element '*a*' is an element of the set A, the relation of membership of $a \in A$ exists, otherwise, if '*a*' is not an element of *A*, it denotes $a \notin A$. In the same way, relationships were established between the sets that define operations between them. The set theory is a mathematical theory that enables differentiating particular elements from general rules by performing fundamentals, such as union, intersection, difference, and symmetric difference, complying with a series of axioms, which define mathematical relationships between the elements [12].

Process

The methodology of this study was designed in a previous work [14], in the context of theoretical physics, selecting the number of leukocytes and CD4+ lymphocytes per cubic microliter, to find essential mathematical proportions that allow predictions evaluation. Five groups of possible dynamics for CD4+ T lymphocyte counts were established to make the predictions:

1. Dynamics, in which all the sequence records show CD4+ lymphocyte values > 500.
2. Dynamics, where all the records of sequence present values of CD4+ lymphocytes between 200 and 500.
3. Dynamics, in which all the sequence records show CD4+ lymphocyte values < 200.
4. Dynamics, where the sequence records show values of CD4+ lymphocytes > 500 and between 200 and 500.
5. Dynamics, in which some of the sequence records show CD4+ lymphocyte values < 200 and others show values between 200 and 500.

Based on these dynamics, predictive parameters were applied to determine clinically significant ranges, where patients' CD4+ T lymphocyte count will be found in the next para-clinical control.

Predictive parameters

For dynamic 1, in the following measurements, when populations of leukocytes ≥ 3.7 are present thousands/mm^3, the associated CD4+ populations will be > 500 cells/mm^3.

For dynamic 2, if in the following measurements the leukocyte values are greater than 4,000/mm^3, the CD4+ population will be between 200 and 500 cells/mm^3.

For dynamic 3, when the leukocyte values are between 2,000 and 3,000/mm^3, in the following measurement, the CD4+ population will be less than 200 cells/mm^3.

For dynamic 4, when the leukocyte values are between 3,000-3,900/mm^3 and the next leukocyte measurement is also in that range, the CD4+ values will be greater than 500 cells/mm^3 or will be between 200 and 500 cells/mm^3.

For dynamic 4, if the measure that presents a CD4+ value between 200 and 500 cells/mm^3 also presents a value of leukocytes ≥ 4,000/mm^3, and the measurement with a CD4+ value > 500 cells/mm^3 also shows a leukocyte value ≥ 3,700/mm^3, and if the following measurement shows a leukocyte value ≥ 4,000/mm^3, then the CD4+ values will be between 200 and 500 cells/mm^3 or will be greater than 500 cells/mm^3.

For dynamic 5, if the value of leukocytes of the measure that presents CD4+ is greater than 200 cells/mm^3 and is less than 3 cells/mm^3, and for the measurement that presents a CD4+ value between 200 and 500 cells/mm^3 and has a leukocyte value ≥ 4,000/mm^3, if in the following measurement there is a leukocyte value between 4,000 and 6,000/mm^3, the CD4+ value will be between 200 and 500 cells/mm^3, but if the leukocyte value is > 6,000/mm^3, the CD4+ value < 200 cells/mm^3 may occur.

Finally, the probability of success was calculated for each of the afore-mentioned criterion using Equation 1, and for all cases analyzed with the five dynamics, Equation 2 was applied, as follows:

$$P = \frac{\text{Number of subjects whose dynamics were correctly predicted}}{\text{Total number of cases associated with a dynamic}} \quad \text{Eq. 1}$$

$$P = \frac{\text{Number of subjects whose dynamics were correctly predicted}}{\text{Total number of registered cases}} \quad \text{Eq. 2}$$

Results

The described methodology was applied to 90 patients, with 74 patients presenting 158 records and 12 patients presenting 36 records. The minimum and maximum values of CD4+ lymphocyte counts ranged from 28 to 1,223, while values for the absolute leukocyte counts ranged from 2,200 to 19,740 (Table 1).

Predictive result

Two counts of the total leukocytes and CD4+ T lymphocytes of the 100 cases evaluated were taken into account to establish whether they presented any of the following dynamics:

(a) Both have a CD4+ population > 500 and leukocytes ≥ 3.7.
(b) Both have a CD4+ population between 200 and 500, and at least one of the leukocyte measurements shows values greater than or equal to 4.
(c) Both have a CD4+ population < 200, and leukocyte measurements between 2, 3, and 9.
(d) One of the measurements shows CD4+ > 500, and the other CD4+ between 200 and 500, and one of the measurements shows CD4+ between 200 and 500 and the other shows CD4+ < 200.

1. In case (a), the greatest probability is that in the following measurements, when presenting leukocyte populations ≥ 3.7, the associated CD4+ populations will be > 500.
2. In case (b), it is most likely that if the leukocyte values are greater than 4 in the following measurements, the CD4+ population will be between 200 and 500.

Table 1. Leukocytes/ml^3 and CD4+/ml^3 values corresponding to 23 of the 90 patients evaluated

No.	Total leukocytes First sample	CD4+ count First sample	Total leukocytes Second sample	CD4+ count Second sample
1	1,058	5,300	980	6,020
2	1,000	7,800	692	8,730
3	983	7,900	838	6,630
4	982	7,300	970	8,000
5	906	6,200	980	7,140
6	879	7,900	896	6,700
7	879	8,800	543	8,520
8	866	8,500	802	7,760
9	776	7,500	968	7,690
10	729	5,700	603	8,060
11	721	10,160	782	7,440
12	681	3,833	1,124	8,610
13	674	7,200	651	8,910
14	674	7,200	651	8,910
15	649	6,400	620	6,860
16	748	5,600	806	6,200
17	646	4,600	647	6,800
18	611	7,600	611	6,300
19	768	6,700	771	8,200
20	666	5,600	660	5,000
21	37	3,400	28	3,500
22	71	2,200	238	4,100
23	49	2,400	57	4,320

3. In case (c), it is most likely that when presenting a leukocyte value between 2 and 3 in the next measurement, the CD4+ population will be less than 200.
4. In case (d) and if the white blood cell (WBC) values are between 3, 3, and 9, and the next WBC measurement is also in that range, then the CD4+ values will be greater than 500 or between 20 and 500.
5. In case (d) and if the measurement with a CD4+ value between 200 and 500 also has a leukocyte value ≥ 4, and the measurement with a CD4+ value > 500 also has a leukocyte value ≥ 3.7, then if the next measurement shows a WBC value ≥ 4, then CD4+ values are more likely to be between 200 and 500 or greater than 500.
6. In case (e) and if the leukocyte value of the measure that presents CD4+ < 200 is less than 3, and for the measure that presents a CD4+ value between 200 and 500 has a leukocyte value ≥ 4, and if in the following measurement there is a value of leukocytes between 4 and 6, it is most likely that the CD4+ value is between 200 and 500, but if the value of leukocytes is > 6, it may be that the value is CD4+ < 200.

Table 2. Success percentage for each defined dynamic, according to the established mathematical patterns

Dynamic No.	No. of individuals who met defined mathematical patterns	No. of individuals who did not meet defined mathematical patterns	Hit percentage
1	55	2	96.49%
2	14	3	82.35%
3	5	0	10.00%
4	8	0	100.0%
5	2	1	66.66%

The probability of success for each specified dynamic ranged from 66.66% to 100%, with an average rate of 93.33% (Table 2). The sensitivity and specificity results of 99% were obtained.

The values of leukocytes/ml^3 were between 2,200 and 19,740, and those of CD4+/µl were between 28 and 1,223 (Table 1).

Discussion

This is the first work, where a confirmation of the predictive capacity/clinical applicability of the methodology developed from the theory of probability and ensembles was carried out, to predict CD4+ count with data from the count of leukocytes and CD4+ T lymphocytes of 90 HIV/AIDS patients, reaching a percentage of success equal to or greater than 93.33% for 5 of the 9 ranges measured. This confirms the predictive capacity of this methodology.

In this work, the predictive capacity of the methodology developed by Rodríguez was confirmed. Moreover, a greater number of patients was employed than in the original study, and similar percentages of success were obtained in the different groups of possible values of CD4+ T lymphocytes. This confirmed that there is an underlying mathematical order in the variation of total leukocyte and lymphocyte counts, which was determined by applying both the set theory and probability theory.

Conversely to other studies, the present work demonstrated that it is possible to predict the CD4+ T lymphocyte count using only historical values of the total leukocyte count and CD4+ count. Previously, various methodologies evaluated other factors to estimate the evolution of white line counts, including hemoglobin values, CD8+ T lymphocyte count, age, sex, medications use, etc.

Different investigations concluded that the prediction of CD4+ from the total lymphocyte count did not have a high percentage of accuracy [9, 16, 17]; however, in this work, it is shown that using the set theory, it is possible to

develop an effective prediction, which allows the methodology to be applied clinically. Over the years, the WHO has made antiretroviral treatment more affordable in areas, where adherence to treatment was difficult, mostly due to economic reason, to be successful [1]. Despite the efforts made, alternatives are required that enable recognizing the evolution of the immune response of each patient, with which clinical and therapeutic behaviors can be adopted.

Due to the high complexity and high-cost of this technique, its implementation in some developing countries, especially in Africa, is not simple [16]. Countries, in which HIV/AIDS has the greatest impact on public health, have been shown to have fewer resources to access high-quality diagnosis and treatment [4]. Alternatives, such as CyFlow, aim to reduce costs in flow cytometry with simplified tools [4]. However, since the complete blood count has better global coverage and is a widely known technique, it aims to become a very useful test in patients with HIV and, although it cannot differentiate lymphocyte sub-populations, can be considered having a therapeutic approach at each moment of the disease evolution in HIV-infected patients.

In order to predict the behavior of CD4+ lymphocytes, various types of methods were developed. From epidemiological point of view such, one of them determined the distribution of the number of CD4+ in sero-negative patients and survival rates after treatment, seeking to predict a change for the decrease in CD4+ T lymphocytes in sero-positive patients. The model was applied to different population groups and individuals, and obtained predictive values greater than 75% accuracy related to the real value of T4 lymphocytes [7, 19].

A cross-sectional study constructed a series of values made up of combined total T lymphocyte counts and hemoglobin, as factors of indirect influence for the prediction of CD4+ lymphocytes < 200 cells/mm^3. A comparison was made with the deduction based solely on lymphocytes, resulting in an increase in sensitivity but not in specificity in male patients, while in female patients, sensitivity did not change while a decrease in specificity was observed [9].

There are models, such as that proposed by Singh and Mars, which are based on machine learning to determine dynamic algorithms, where the viral load and the number of weeks since the first CD4+ T cell count have an accuracy of up to 83% compared with the actual value [8]. In the context of dynamic systems, a descriptive but not predictable model of the dynamics of immune response against HIV was developed, showing graphically the CD4+ T lymphocytes, CD8+ T lymphocytes, activity of B lymphocytes and antibodies, and the evolution of viral load [20]. The method developed in this study is based on individual values for each patient, but it is widely applicable, avoiding the limitations of epidemiological variables or variations in the viral genotypes.

In order to stage the disease and have a therapeutic guide in each patient, other methodologies used neural networks to determine the viral load based on the genotype, clinical information, or changes in viral sequence, to determine the degree of resistance to treatment [21, 22, 24]. These studies were purely experimental, and it was not possible to obtain generalization of the results [15]; whereas in the present work, the opportunity of physical-mathematical thinking to specify solutions for clinical application was evidenced. A similar prediction was recently developed, in which the ability of mathematical perspective for effective predictions in the clinic was confirmed; although the predictions of both works are similar.

Many studies found an acausal pattern for different medical phenomena in areas, such as immunology [11], diagnosis of pre-neoplastic and neoplastic lesions of the cervix [25], prognosis of epidemics, e.g., dengue and malaria [26], diagnosis of fetal heart diseases [27], neonatal in the prediction of sepsis occurrence [28], and adults [29, 30]. Recently, a method based on the set theory and dynamical systems for the prediction of mortality rate in ICU patients was developed and applied [31]. As in this work, these investigations reveal the underlying physical and mathematical order of medical phenomena, which allow for practical applications.

Conclusions

This research is designed in the context of theoretical physics, selecting only two variables: the number of leukocytes (thousands/mm^3) and CD4+ lymphocytes (cells/ mm^3), with high sensitivity and specificity, which allow predictive diagnosis. This would allow for effective monitoring of CD4+ lymphocyte counts over time in HIV-infected patients.

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