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IMPROVING CLINICAL DECISION USING THE DIAGNOSIS, SIGN AND SYMPTOMS OF PARASITIC DISEASES USING A NETWORK APPROACH

MELHORAR A DECISÃO CLÍNICA USANDO O DIAGNÓSTICO, SINAIS E SINTOMAS DE DOENÇAS PARASITÁRIAS USANDO UMA ABORDAGEM EM REDE

MEJORA DE LA DECISIÓN CLÍNICA UTILIZANDO EL DIAGNÓSTICO, SIGNOS Y SÍNTOMAS DE ENFERMEDADES PARASITARIAS UTILIZANDO UN ENFOQUE EN LA RED

ABSTRACT

Historically, the diagnosis has a central role and impacts in the number of medical errors, which have increased in the last decade. Usually the diagnosis of parasitic diseases requires the demonstration of presence or absence of an actual or previous infection. We believe that the network community model can improve the understanding of the disease relationship. It could help to differentiate the signs and symptoms, or even diagnostic methods, which is often related by different medical sub-disciplines.Network parameters, such as: modularity and topology were evaluated, according to the algorithm described by Csardi and collaborators in 2010 and a hierarchical clustering analysis using the Network distance was performed. Also, we employed an optimization protocol to define the optimal number of clusters. The frequency of each variable and the description of connections were measured by bar graphs on the R platform. Chi Square was performed and the p value considered significant will be $p < 0.05$. By applying a complex multivariate methodology, we were able to identify associations between parasitic diseases. We have identified 3 major clusters with distinct parasite composition, diagnosis methods and sign and symptoms. The clusters present here can drive to the specific use of one diagnosis class or investigate a set of specific symptoms that help the clinician decision. The novel information could help in the improvement of new diagnosis protocols, which leads to better diagnosis performance whereas can reduce the time and diagnosis cost.

KEYWORDS

Network. Medicine. Parasitology.

RESUMO

Historicamente, o diagnóstico tem papel central e impacto no número de erros médicos, que aumentaram na última década. Geralmente o diagnóstico de doenças parasitárias requer a demonstração da presença ou ausência de uma infecção real ou prévia. Acreditamos que o modelo de comunidade em rede pode melhorar a compreensão da relação doença. Pode ajudar a diferenciar os sinais e sintomas, ou mesmo métodos de diagnóstico, que muitas vezes são relacionados por diferentes subdisciplinas médicas. Parâmetros de rede, tais como: modularidade e topologia foram avaliados, de acordo com o algoritmo descrito por Csardi e colaboradores em 2010 e foi realizada uma análise de agrupamento hierárquico utilizando a distância de rede. Além disso, empregamos um protocolo de otimização para definir o número ideal de clusters. A frequência de cada variável e a descrição das conexões foram medidas por gráficos de barras na plataforma R. Foi realizado o Qui Quadrado e o valor de p considerado significativo será $p<0,05$. Aplicando uma complexa metodologia multivariada, conseguimos identificar associações entre doenças parasitárias. Identificamos 3 grupos principais com composição parasitária, métodos de diagnóstico e sinais e sintomas distintos. Os agrupamentos aqui apresentados podem levar ao uso específico de uma classe de diagnóstico ou investigar um conjunto de sintomas específicos que auxiliam a decisão do clínico. As novas informações podem ajudar no aprimoramento de novos protocolos de diagnóstico, o que leva a um melhor desempenho do diagnóstico, ao mesmo tempo em que pode reduzir o tempo e o custo do diagnóstico.

PALAVRAS CHAVES

Network. Medicina. Parasitologia

RESUMEN

Históricamente, el diagnóstico tiene un papel central e impacta en el número de errores médicos, que se han incrementado en la última década. Por lo general, el diagnóstico de enfermedades parasitarias requiere la demostración de la presencia o ausencia de una infección actual o previa. Creemos que el modelo de comunidad en red puede mejorar la comprensión de la relación entre enfermedades. Podría ayudar a diferenciar los signos y síntomas, o incluso los métodos de diagnóstico, que a menudo están relacionados por diferentes subdisciplinas médicas. Se evaluaron parámetros de red, tales como: modularidad y topología, según el algoritmo descrito por Csardi y colaboradores en 2010 y Se realizó un análisis de agrupamiento jerárquico utilizando la distancia de red. Además, empleamos un protocolo de optimización para definir el número óptimo de grupos. La frecuencia de cada variable y la descripción de las conexiones se midió mediante gráficos de barras en la plataforma R. Se realizó Chi Cuadrado y el valor de p considerado significativo será $p < 0,05$. Mediante la aplicación de una metodología multivariante compleja, pudimos identificar asociaciones entre enfermedades parasitarias. Hemos identificado 3 grupos principales con distinta composición de parásitos, métodos de diagnóstico y signos y síntomas. Los grupos presentes aquí pueden conducir al uso específico de una clase de diagnóstico o investigar un conjunto de síntomas específicos que ayuden a la decisión del médico. La nueva información podría ayudar a mejorar los nuevos protocolos de diagnóstico, lo que conduce a un mejor rendimiento del diagnóstico y puede reducir el tiempo y el costo del diagnóstico.

PALABRAS CLAVE

La red. Medicamento. Parasitología.

INTRODUCTION

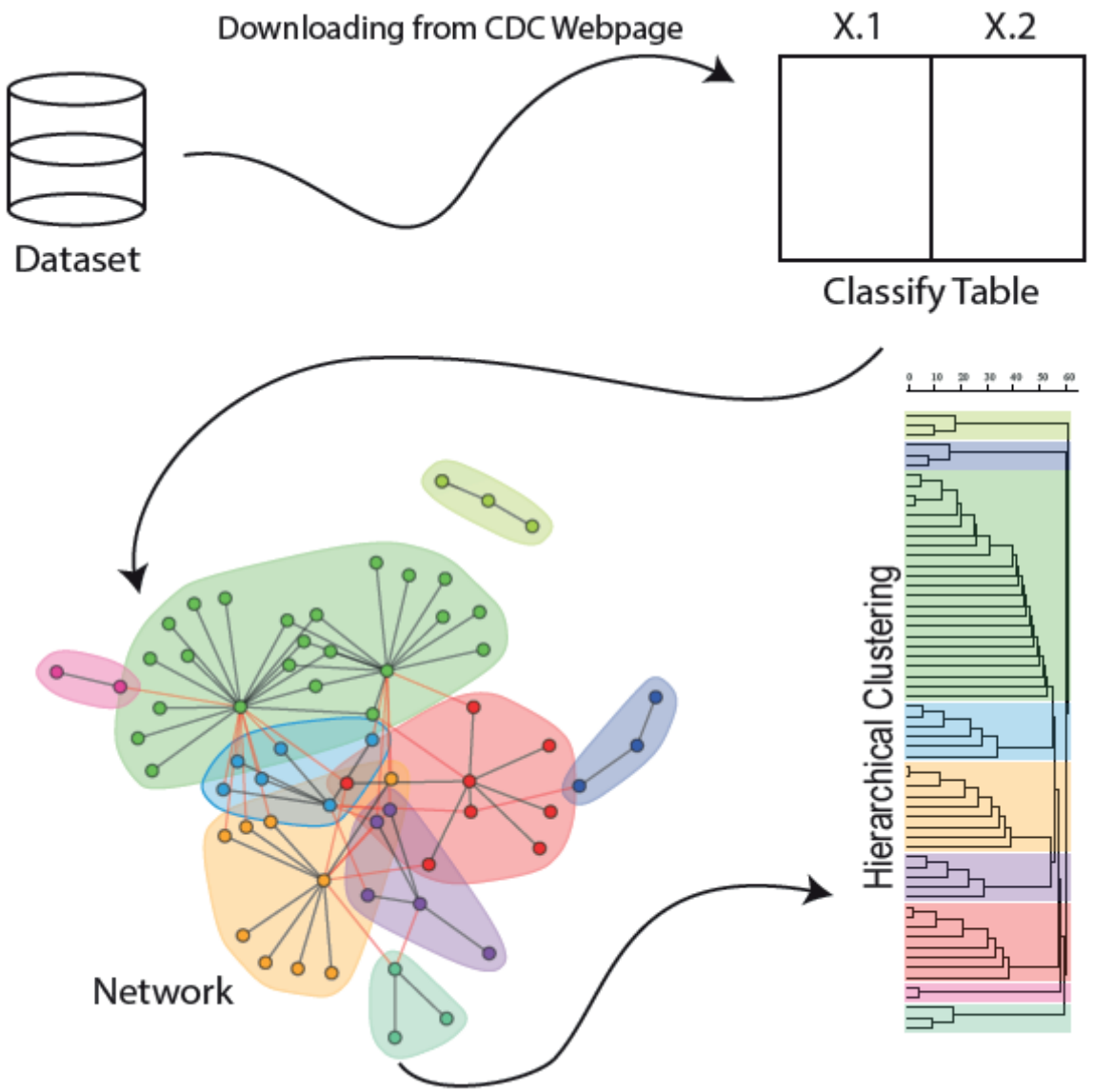
Medicine is composed of three major axes: (i) The diagnosis, which consists in classifying the disease [1]; (ii) The prognosis, focused on predicting the patient progression or possible outcome of a disease or treatment (iii) and cure the patient [2]. Historically, the diagnosis has a central role and impacts in the medical errornumbers, which have increased in the last decade [3,4],[5]. Usually, the parasitic disease diagnosis requires the demonstration of presence or absence of an actual or previous infection.However, the clinical manifestation is not enough for disease identification. This occurs because several infections can occur simultaneously, due to the asymptomatic manifestations [6]. The diagnosis procedure depends on the signs and symptoms[7]. New diagnosis methods were proposed, following technological advances, replacing, and overcoming the old methods in costs/benefits and speed[6]. However, the validation of a new diagnosis method lacks information [8]. Several methods use indirect products resulting from the response against the etiological agents to perform the diagnosis [9] which are results of all the biological systems crosstalk[10]. At the genomic level, that response is complex due to approximately 25,000 genes encoding countless numbers of variants, which produce a huge amount of interactions with several different layers of the transcriptional and protein systems [11,12]. This plethora of molecules potentially has trillions of interactions which impacts differentially each biological system[13,14].

The investigation of biological interaction influence is complex and requires employing systems biology or network medicine methodologies.[15]. Network medicine is based on a series of advances in network theory, which provides information on biological interactions in general [16]. Studies show that the biological networks are not random compared with technological or social networks and are also characterized by a set of organizing principles.These characteristics allow us to investigate relevant questions using fundamental properties, such as the network topology, degree and betweenness centrality [13],[14]. We are able to evaluate the connections between diseases and related variables, that leads to a complex web of interaction[17]. We suppose that the network community model can improve the understanding the relationship between the disease, signs and symptoms, or even diagnostic methods, which is often related by different medical sub-disciplines. Moreover, the aim of this approach is help to understand why certain groups of diseases arise with the same characteristics, but it is diagnosed by different forms and provide new insights to manage the parasitic diseases.

METHOD

The diagnosis criteria were retrieved from the Center of Disease Control (CDC) medical literature database. The signs and symptoms from each disease were used as input for network analysis of human parasitic diseases. The disease list and the etiologic agent list (https://www.cdc.gov/parasites/index.html) were downloaded in a UNIX system [18]. All the etiological in CDC agents list were collapsed by genus. After downloading, the data was organized on a 'classification table", corresponding to the name of the etiologic agent in one column and the sign, symptoms and diagnosis method in another column. This table represents the association of these variables with the etiologic agent and that can be transformed in a network using the R platform (R 3.6.2, R Foundation, Vienna, Austria) [19] [20]. Network parameters, such as: modularity and topology were evaluated, according to the algorithm described by Csardi and collaborators in 2010 [21] and a hierarchical clustering analysis using the Network distance was performed [22]. Also, we employed an optimization protocol to define the optimal number of clusters [23]. The frequency of each variable and the description of connections were measured by bar graphs on the R platform[24]. Chi Square was performed, and the p value considered significant will be $p < 0.05$ (Figure 1).

Figure 1. Data analysis protocol: Dataset was accessed and downloaded from CDC webpage and etiologic agents, diagnosis methods and sign and symptoms were organized in a classification table and transformed in a network to analyze the modularity depicted in hierarchical clustering diagram.



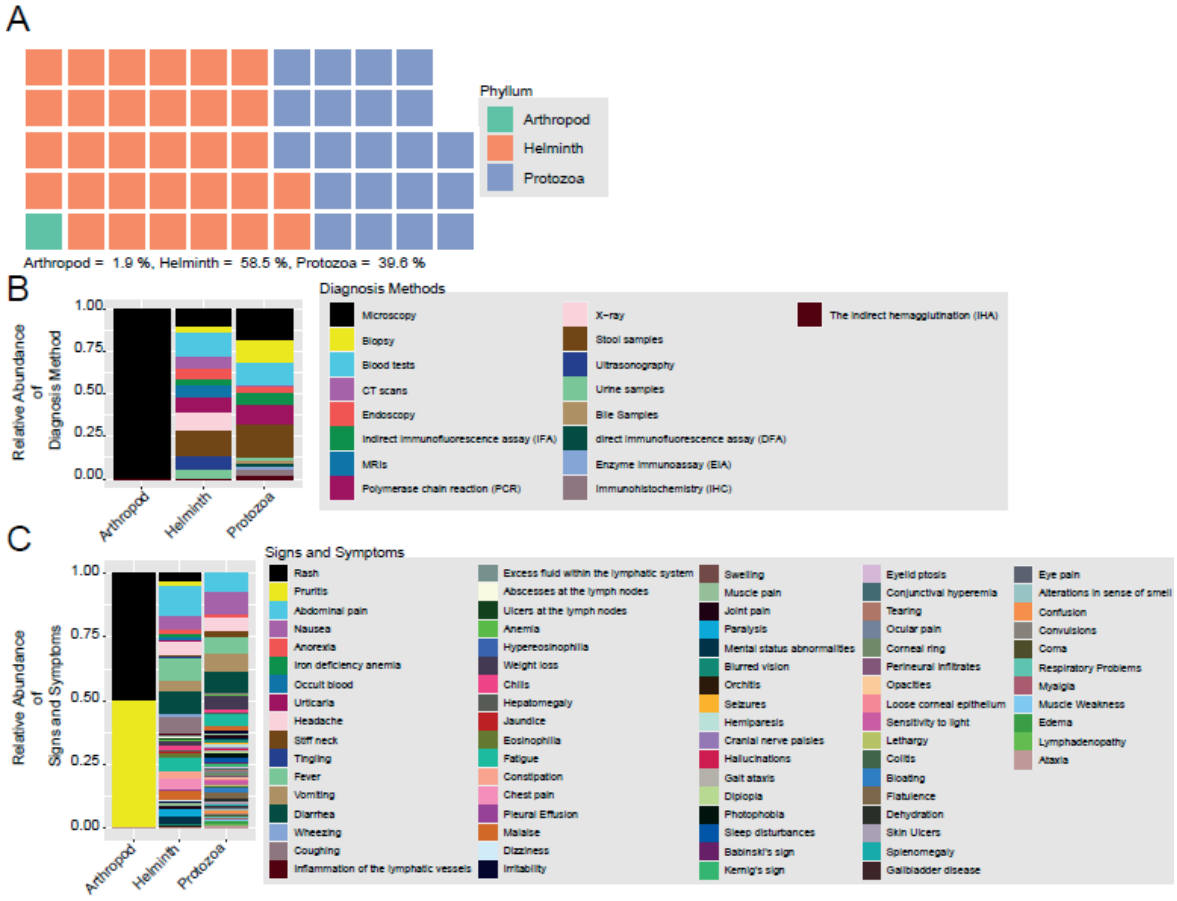
Results

Description of dataset

A total of 53 Etiologic agents of parasitic disease were retrievedfrom CDC webpage. From these,21are described as a protozoa phylum and it is representing 39.6% of a total etiological agent, 31 occurrences of

helminthes representing 58.5%, and only 1 (1.9%) was signed as Arthropod (Figure 2A). These 53 agents were kept resulting in 81 signs and symptoms and 18 methods of diagnosis associated with them. Describing these numbers, the most frequent diagnosis method between all etiologic agents were; Stool samples with 30 occurrences, microscopy with 24 and blood tests with 24. Also, we review the signs and symptoms, and abdominal pain was the most present with 34 occurrences, Diarrhea with 29 and fever with 27.The proportion of diagnosis methods between the phylum, the arthropods had only microscopy as a diagnostic method, helminthes and protozoa have several methods enrolled, however without statistical difference (Figure 2B). The arthropod group only had lice as a represent, because presents only two sign and symptoms, rash and pruritis, however the helminthes and protozoa have several sign and symptoms addressed without statistically significant between the phylum (Figure 2C).

Figure 2. Description of used dataset. A. Frequency of etiologic agent by Phylum. Arthropod, Helminth and Arthropod depicted by colors green, orange and blue respectively. B. Relative abundance of the diagnosis methods and C. sign and symptoms.



Network Analysis

After accessing the parasitic disease information and filter the occurrences by the genus in the classify table, the distance between the variables were calculated and with these distances, we built a network and analyze its topology. This analysis revealed a complex network topology with 3 clusters communities, below.

The cluster 1 are composed by 11 Signs and symptoms (Malaise, Mental status abnormalities, Paralysis, Chest pain, Pleural Effusion, Fatigue, Wheezing, Blurred vision, Coughing, Eye pain and Gallbladder disease); 11 etiologic agents (Echinococcus sp, S. haematobium, S. haematobium, S. japonicum, Dirofilariasp, Schistosoma mansoni, S. mekong, S. intercalatum, Ascaris sp, Toxocaraasp and Microsporidiosissp) and 6 diagnosis methods (Endoscopy, MRIs, CT scans, Ultrasonography, X–ray and Urine samples) ;

Cluster 2 are composed by 24 Signs and symptoms (Myalgia, Muscle Weakness, Edema, Respiratory Problems, Lethargy, Sensitivity to light, Alterations in sense of smell, Confusion, Stiff neck, Orchitis, Ataxia, Lymphadenopathy, Sleep disturbances, Fever, Coma, Convulsions, Headache, Tingling, Chills, Joint pain, Muscle pain, Swelling, Splenomegaly and Skin Ulcers); 14 etiologic agents (Sarcocystissp, Babesia sp, Balamuthia mandrillaris, Naegleria fowleri, Onchocerca volvulus, Wuchereriabancrofti, Trypanosoma sp, Paragonimussp, Plasmodium sp, Angiostrongylussp, Trichinella sp, Loa loa, Toxoplasma sp and Leishmania sp) and 5 diagnosis methods (Immunohistochemistry (IHC), Indirect immunofluorescence assay (IFA), Polymerase chain reaction (PCR), Biopsy and Blood tests) (Figure 3 and Figure 4);

Cluster 3 are composed by 44 Signs and symptoms (Occult blood, Iron deficiency, anemia, Urticaria, Anorexia, Nausea, Flatulence, Bloating, Abdominal pain, Weight loss, Colitis, Dehydration, Diarrhea, Hypereosinophilia, Anemia, Vomiting, Constipation, Pruritus, Rash, Ulcers at the lymph nodes, Inflammation of the lymphatic vessels, Excess fluid within the lymphatic system, Abscesses at the lymph nodes, Diplopia, Kernig's sign, Conjunctival hyperemia, Ocular pain, Hemiparesis, Tearing, Seizures, Cranial nerve palsies, Hallucinations, Gait ataxia, Photophobia, Babinski's sign, Eyelid ptosis, Corneal ring, Perineural infiltrates, Opacities, Loose corneal epithelium, Hepatomegaly, Jaundice, Eosinophilia, Irritability and Dizziness); 28 etiologic agents (Iodamoebabutschlii, Chilomastixsp, Necator americanus, Ancylostoma duodenale, Endolimax nana, Blastocystis hominis, Cyclospora sp, Giardia lamblia, Taenia sp, Dientamoeba fragilis, Trichuris trichiura, Balantidium coli, Cryptosporidium sp, Capillariaphilippinensis, Anisakiasis sp, Gnathostomasp, Diphyllobothrium sp, Cystoisospora belli, Opisthorchis sp, Sarcoptesscabiei, Dipylidium caninum, Strongyloidesstercoralis, Entamoeba sp, Brugiasp, Acanthamoeba sp, Fasciola sp, Clonorchiasissp and Hymenolepis nana) and 5 diagnosis methods (Stool samples, direct immunofluorescence assay (DFA), Bile Samples, Microscopy, The indirect hemagglutination (IHA) and Enzyme immunoassay (EIA)) (Figure 3 and Figure 4).

The distribution of diagnosis methods, signs and symptoms and etiologic agent between the cluster depicted the richness between these variables and it does not differ significantly from each other (P Value = 0.2149 of chi square test), meaning the composition between diagnosis methods, signs and symptoms and etiologic agent did not differ in proportion of information (Table 1).

Figure 3. The Knowledge Network of the etiologic agents associated with sign and symptoms and diagnostic methods from CDC webpage. The nodes of the graph represent one of these categories. The edge represents the association between then and the node red color represents the diagnosis method.

Figure 4. Identifying the topological modules of the Network. A. The topology of the network correspondsto a hierarchicaltree that quantifies the relation between the different modules identified in the(B) The First Cluster,(C)Second Clusterand (D) The third Cluster.

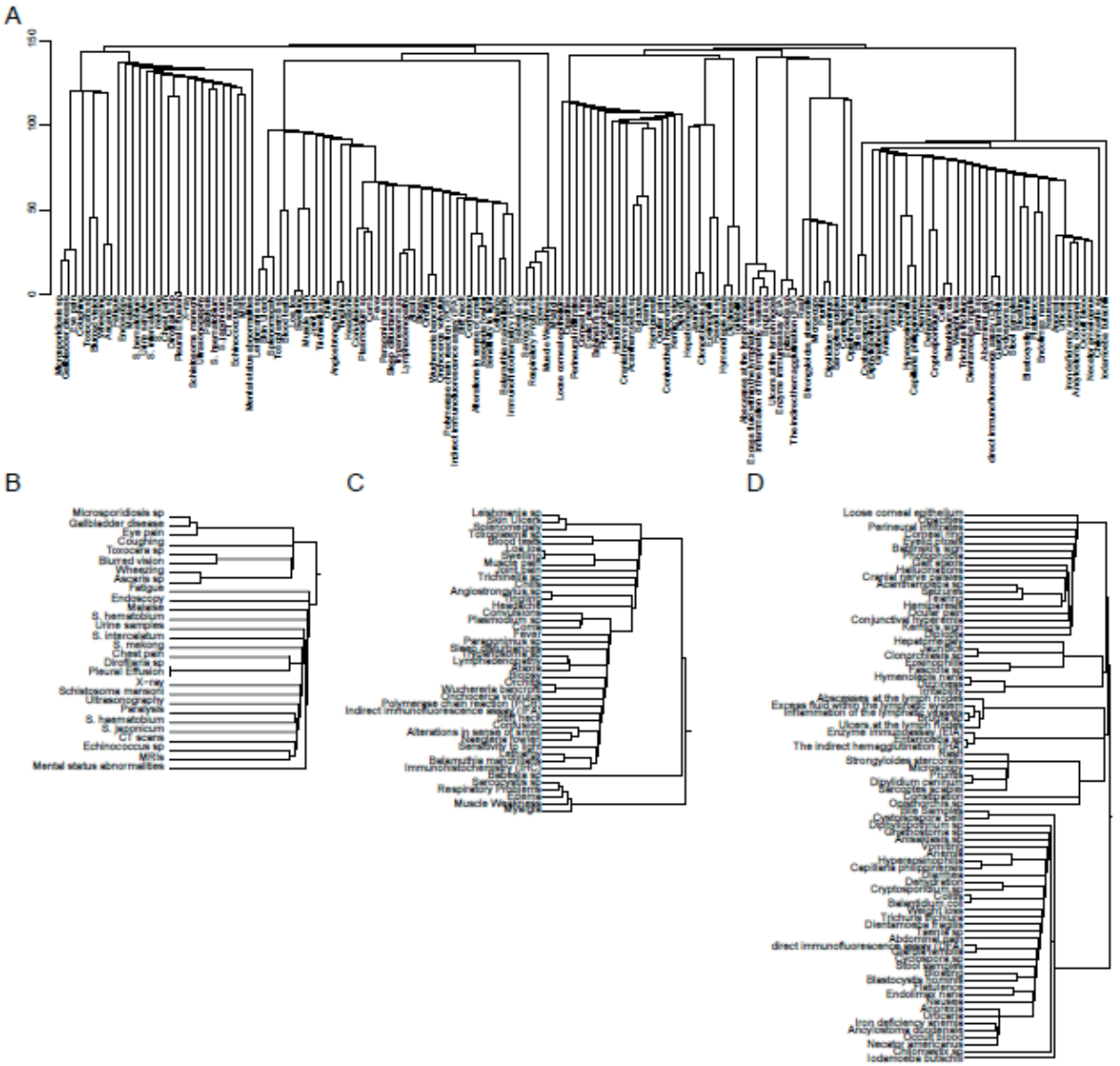


Table 1. Difference of optimized cluster composition.

	Cluster 1	Cluster 2	Cluster 3	P Value
Diagnosis Method, (%)	6 (21.4)	5 (11.6)	5 (6.5)	0.2149
Sign and Symptom, (%)	11 (39.3)	24 (55.8)	44 (57.1)	
Etiologic Agent, (%)	11 (39.3)	14 (32.6)	28 (36.4)	

Discussion

The Network Community model allowed the disease patterns identification, based on the relationship between signs and symptoms, diagnostic methods, and the etiologic agent of each parasitic disease. This provides interesting insights about the how the biological factors are involved in the sickness development process. We also evaluated the frequency of etiologic agents. The majority (90%) of all diseases described in the CDC database are caused by protozoa and helminths. It is not surprising, since around 77.9% of all parasitosis worldwide are caused by these phylums, which makes these two the most prevalent etiological agent to infect the human species [25]. Regarding the diagnosis, the parasite identification on the feces is the most used method. This is commonly accompanied by microscopy and together they have an excellent predictive value for determining intestinal etiological agents [26]. We observed abdominal pain the most common symptom and it was associated with presence of protozoa and helminths in feces. This was also related with (i) fecal-oral route, (ii) active penetration of the skin by larvae, and (iii) vector arthropods.[27]. Abdominal manifestations are commonly observed in parasitic diseases although this symptom is usually considered nonspecific [28]. No association between the parasitic disease and symptoms frequency and severity was previously observed [29] nevertheless symptoms are poorly studied and it is commonly reported in first medical contact [30,31].

Using an unsupervised network analysis, we accessed the communities' structure to discover the clusters arrangement and reveal a hidden information that is not easy to detect due to the network complexity [32]. The optimization of the communities uses the hierarchical clustering analysis resulted from network topology and selects the best number of clusters to explain the network distribution [33,34]. The optimization has identified3 major clusters, with the first cluster mainly Schistosomiasis followed by Microsporidiosissp, toxocarasp, Echinococcus sp, ascaris sp and dirofilaria sp. All these parasites observed in this cluster present a pulmonary phase during the disease cycle [35]. These parasites are commonly diagnosed in countries with high prevalence of these diseases [36]. However, the symptoms have a wide spectrum with a nonspecific clinical manifestation and poor radiologic finding [37]. The patient's detailed travel history and immunosuppression are the major evidence that leads to respiratory parasite--infection investigation [38]. This cluster has few diagnosis methods associated: urine samples, X-ray, ultrasonography, endoscopy, CT scans and MRIs, that are commonly between the parasites [35]. The second cluster is composed with parasites diagnosed by immunologic tests, biopsy, and molecular diagnosis. The detection and diagnosis of parasite infections rely on several laboratory methods in addition to clinical symptoms, clinical history, travel history, and geographic location of patients [39]. Therefore, development of the immunologic tests and the molecular tests are associated with: (i) the access of expert microscopists [40]; (ii) the speed of the diagnosis and (iii) the disease prevalence that has a low number of requests mainly in a not endemic area [41]. This cluster provides a diversity of diagnosis methods to be applied and improves these parasites diagnosis efficacy. The Third cluster is composed of parasites diagnosed by stool samples and could be nominated as gastrointestinal clusters. Although showing high prevalence, these parasites are neglected, showing low research interest and lower new diagnosis methods development [42]. The Signs and symptoms of intestinal parasites are generally weakness, nutritional impact, decreasing absorption of micronutrients, loss of appetite, weight loss, and intestinal blood loss and possibly evolving to anemia [43]. Due to the wide variety of intestinal parasites, a description of the symptoms rarely is sufficient for diagnosis. Instead, medicine recommends an active search in stool samples for the parasites [44] This study is the first study to apply a network approach in the panorama of parasitic disease using the etiologic agent information, the sign and symptoms and the diagnosis methods. although there are several limitations and the first is the absence of experimental validation of the clusters we are proposing.

Conclusion

This study applied a novel complex multivariate method, to describe the associations between parasitic diseases, sign and symptoms and diagnosis methods. We have identified 3 major clusters, without differences in the composition, but it can improve the time required to reach the final diagnosis and new diagnosis protocols, which leads to better diagnosis performance and could help the clinician decision.

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