Impact of the investment deficit for the treatment of chagas disease in Brazil: narrative review

ABSTRACT | Objective: to discuss the impact of the investment deficit for the treatment of Chagas Disease in Brazil. Method: This is a narrative review of the literature conducted in the following databases: SCIELO, LILACS, BIREME and MEDLINE. The final sample consisted of 27 scientific articles published between 2000 and 2020. Results: Brazil is one of the countries with the highest prevalence of patients with the disease, but little progress has been made in research in this area, so as to have a low incentive and investment from governments and the pharmaceutical industry for Chagas Disease, in view of the disease being of slow progression and the diagnosis and treatment are late. Conclusion: it is evident the lack of investment and public policies that make possible the diagnosis and early treatment of the disease with the consequence of a deficit in the quality of life of the patients.
Keywords: Chagas disease; Investments; Therapeutics.

RESUMEN | Objetivo: discutir el impacto del déficit de inversión para el tratamiento de la enfermedad de Chagas en Brasil. Método: se trata de una revisión narrativa de la literatura realizada en las siguientes bases de datos: SCIELO, LILACS, BIREME y MEDLINE. La muestra final consistió en 27 artículos científicos publicados entre 2000 y 2020. Resultados: el Brasil es uno de los países con mayor prevalencia de pacientes con la enfermedad, pero se ha avanzado poco en la investigación en esta área, para tener un bajo incentivo e inversión de los gobiernos y de la industria farmacéutica para la enfermedad de Chagas, considerando que la enfermedad es de progresión lenta y el diagnóstico y tratamiento son tardíos. Conclusión: es evidente la falta de inversión y de políticas públicas que permitan el diagnóstico y tratamiento precoz de la enfermedad con el consiguiente déficit en la calidad de vida de los pacientes.
Palabras claves: Enfermedad de Chagas; Inversiones en Salud; Terapéutica.

RESUMO | Objetivo: discutir sobre o impacto do déficit de investimentos para o tratamento da Doença de Chagas no Brasil. Método: trata-se de uma revisão narrativa da literatura realizada nas seguintes bases de dados: SCIELO, LILACS, BIREME e MEDLINE. A amostra final foi composta por 27 artigos científicos publicados entre o período de 2000 a 2020. Resultados: o Brasil é um dos países com maior prevalência de pacientes portadores da doença, porém pouco se avançou em pesquisas nessa área, de modo a repercutir em um baixo incentivo e investimento dos governantes e da indústria farmacêutica para a Doença de Chagas, tendo em vista a doença ser de progressão lenta e o diagnóstico e o tratamento serem tardios. Conclusão: fica evidente a falta de investimento e políticas públicas que possibilitem o diagnóstico e o tratamento precoce da doença tendo como conseqüência um déficit na qualidade de vida dos pacientes.
Palavras-chaves: Doença de Chagas; Investimentos em Saúde; Terapêutica.

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INTRODUCTION

Chagas' disease (CD) is an infectious disease caused by the flagellated protozoan Trypanosoma cruzi (T. cruzi), popularly known as a grown heart disease, and constitutes a serious public health problem, in addition to one of the most important medical and social problems. which develops a series of peculiarities and consequences for human beings. [1,2] Human CD is transmitted by vector faeces, this being Triatoma infestans (T. infestans), better known as a barber, when the host comes into contact, in addition, it is transmitted orally, throu-

gh the ingestion of contaminated food, blood transfusion or during the pregnancy period, that is, from the infected mother to the fetus. Chagas infection is characterized by two phases, the first being the acute phase that may be evident or not, and the second the chronic phase that accompanies the individual for life, being considered by the World Health Organization (WHO) to be a neglected condition. [3,4]

CD is enzootic in nature, having been present in the Americas for thousands of years. [5,6] In the 1940s, as a result of a series of bioecological and political-social factors, generated by the migration of people from rural areas to large urban centers (rural exodus), man becomes a reservoir of CD, which creates a serious public health problem, demystifying the idea of being a rural disease. [5,7] The discovery and description of human CD in Brazil took place in 1909, in the interior of Minas Gerais, by Ribeiro Justiniano das Chagas, a researcher at the Oswaldo Cruz Institute (FIOCRUZ), being one of the most successful discoveries in biology. However, since then, little progress has been made in the evolution of diagnoses and treatments for this disease. It is believed that the reason for this lack of interest in new research is the fact that this is a disease that mainly affects the low-income population, which has few resources to pay for their treatments. CD has a greater distribution in the American continent, with Brazil reaching 40% of the national territory and the states with the highest case rates are: Minas Gerais, Goiás, Bahia, São Paulo, Acre, Amazonas and Amapá. [8]

The diagnosis of CD occurs, in most cases, through blood tests in the acute phase, and in the chronic phase, specific enzymatic tests are performed, such as the Enzyme-Linked Immunosorbent Assay (ELISA) test. [4] According to information from the Priority Disease Control Project (PCDP) of the National Institutes of Health (NIH) and the World Bank (BM), there is a prevalence of eight to nine million infected people, with Brazil probably between two and three millions of carriers. [9,10] The treatment of CD has been the same for more than 50 years, using only one medication, benznidazole, today, since the use of nifurtimox was suspended due to negative side effects, it is worth considering that studies have shown low efficiency of this medication in the treatment of patients in the chronic phase, being a limited treatment, with

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no progress in research by the pharmaceutical industry for the production of a new chemotherapy since the discovery of the disease. [11,12]

When analyzing the bibliography consulted for the study, it is noticed that little or nothing is said about the improvement in the treatment of CD, neglected evidence about this disease, being characterized as a "poor man's disease" which has its highest epidemiological indexes in the countries underdeveloped. [13] Still, it is emphasized that the lack of incentive on the part of the government affects the quality of life (QOL) of patients with CD, as well as hinders the work of doctors, since the economic reality of their patients does not match the high costs of medications during treatment. [14]

Therefore, this study aimed to discuss the impact of the investment deficit for the treatment of CD in Brazil through a narrative review.

METHOD

This is a descriptive, exploratory, documentary, retrospective study, based on a narrative review of the literature. The search for articles was carried out through the following online databases: Scientific Eletronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), Regional Library of Medicine (BIREME) and Medical Literature Analysis and Retrieval System Online (MEDLINE). The consultation of these databases was taken as an initial criterion for selection. These databases were chosen because they are one of the main sources of scientific publications today and, based on their search system, the following keywords were used: "DC"; "Investimentos em Saúde"; and "Terapêutica".

The following inclusion criteria were adopted to collect the articles: be indexed in the respective databases; have the abstract available for reading

Table 1 – Sampling profile according to the search in SCIELO, LILACS, BIREME and MEDLINE databases.

Descritores	SCIELO		LILACS		BIREME		MEDLINE		TOTAL	
	n	%	n	%	n	%	n	%	n	%
"DC" AND "Investimentos em saúde"	00	0,0	00	0,0	00	0,0	01	0,1	01	0,1
"DC" AND "Terapêutica"	09	0,6	114	6,2	00	0,0	1563	85,9	1686	92,7
Investimentos em saúde AND Terapêutica	00	0,0	02	0,1	00	0,0	129	7,1	131	7,2
"DC" AND "Investimentos em saúde" AND "Terapêutica"	00	0,0	00	0,0	00	0,0	00	0,0	00	0,0
Total	09	0,6	116	6,3	00	0,0	1693	93,1	1818	100,0

Source: Own authorship, 2020.

Table 2 - Profile of the sample after applying the eligibility criteria.

Descritores	SCIELO		LILACS		BIREME		MEDLINE		TOTAL	
	AS	AU	AS	AU	AS	AU	AS	AU	AS	AU
"DC" AND "Investimentos em saúde"	00	00	00	00	00	00	01	01	01	01
"DC" AND "Terapêutica"	09	06	114	10	00	00	1563	05	1686	21
Investimentos em saúde AND Terapêutica	00	00	02	00	00	00	129	05	131	05
"DC" AND "Investimentos em saúde" AND "Terapêutica"	00	00	00	00	00	00	00	00	00	00
Total	09	06	116	10	00	00	1693	11	1818	27

Source: Own authorship, 2020. AS = Selected articles (sampling). AU = Articles Used (sample).

in Portuguese; be available for free to download; be a national or international article; and be published between January 2000 and December 2020. The search resulted in a sample of 1818 articles (Table 1), and, after applying the study's eligibility criteria, the final sample was composed of 27 articles published between 2000 and 2020 (Table 2). Furthermore, a careful reading of all selected articles was carried out in order to guarantee the application of the eligibility criteria. Data collection took place in the first semester of 2020, between April and June of the respective year, by the responsible researcher. For this, a structured form was used as a data collection instrument.

RESULTS

The sample of this study, after selection in the databases (SCIELO, LILACS, BIREME and MEDLINE) and application of the eligibility criteria, was represented in a table according to the following variables: title, author, year of publication, journal, objective and method (Table 3).

Table 3 - Presentation of the study sample, according to the title, author, year, journal, objective and method, after selection in the databases (SCIELO, LILACS, BIREME and MEDLINE) and application of the eligibility criteria (n = 27).

Nº	Título	Autor	Ano	Periódico	Objetivo	Método
1	Utilidade das estratégias de PCR para diagnóstico precoce da reativação da doença de Chagas e acompanhamento do tratamento no transplante cardíaco	Diez et al.[2]	2007	Am. J. Transplant.	Avaliar a incidência de reativação em uma série de pacientes submetidos a transplante cardíaco para o estágio final da cardiomiopatia chagásica.	Estudo ecológico realizado por meio de testes de reativação diagnóstica para a DC.
2	II Consenso Brasileiro em Doença de Chagas, 2015	Dias et al.[3]	2016	Epidemiol. Serv. Saúde	Sistematizar estratégias de diagnóstico, tratamento, prevenção e controle da DC no país, de modo a refletir as evidências científicas disponíveis.	Fundamentou-se na articulação e contribuição estratégica de especialistas brasileiros com conhecimento, experiência e atualização sobre diferentes aspectos da DC.
3	Métodos de diagnóstico para a Doença de Chagas: uma atualização	Alves et al.[4]	2018	Rev. Bras. An. Clin.	Realizar uma atualização sobre os métodos de diagnóstico para a DC.	Utilizaram-se guias, as bases de dados SCIELO, LILACS, e como descritor, DC, cujos artigos foram publicados entre os anos de 1997 e 2017.

4	Análise da soroprevalência da Doença de Chagas em uma cidade do norte de Minas Gerais durante o período de 2012 a 2014	Brasil et al.[5]	2014	Rev. Univ. Vale Rio Verde	Analisar a soroprevalência da DC em uma cidade do norte de Minas Gerais durante o período de 2012 a 2014	Estudo exploratório-descritivo, documental, com abordagem quantitativa, sendo uma investigação retrospectiva dos casos confirmados da DC durante janeiro/2012 a janeiro/2014.
5	Biogeografia, origem e distribuição da domicilia-ção de triatomíneos no Brasil	Forattini[6]	2006	Rev. Saúde Pública	Estimar a influência das modificações ambientais de origem antrópica, objetivando melhor compreensão da situação atual e da eficácia das medidas de controle dos triatomíneos.	Estudo biogeográfico
6	Doença de Chagas: a construção de um fato científico e de um proble-ma de saúde pública no Brasil	Kropf; Azevedo; Ferreira[8]	2000	Ciênc. Saúde Colet.	Analisar dois períodos da trajetória de consolidação e legitimação científica e social da tripanossomíase americana ou DC.	Estudo histórico
7	O futuro do controle da doença de Chagas	Schofield; Jannin; Salvatella[9]	2006	Trends Para-sitol.	Discutir sobre o futuro do controle da DC.	Revisão sistemática
8	Uma revisão crítica sobre a quimioterapia da doen-ça de Chagas	Coura; Castro[11]	2002	Mem. Inst. Oswaldo Cruz	Fazer uma introdução histórica dos fár-macos ensaiados contra a DC a partir de 1912 com os trabalhos de Mayer e Rocha Lima até o uso experimental da nitrofurazona.	Revisão crítica
9	Nanomedicamentos con-tra a doença de Chagas: uma atualização sobre terapêutica, profilaxia e diagnóstico	Morilla; Romero[12]	2015	Nanomed. (Lond)	Discutir sobre a terapêutica, profilaxia e diagnóstico por meio de nanomedi-camentos contra a DC.	Revisão sistemática
10	Tecnologias que empre-gam fármacos antiparasi-tários para tratamento da doença Chagas	Cruz et al.[13]	2016	Rev. Eletr. Co-mun. Inf. Inov. Saúde	Apresentar um mapeamento tecno-lógico dos documentos de patentes relacionadas a tecnologias que empregam fármacos antiparasitários para tratamento da DC, por intermédio do banco de patentes do United States Patent and Trademark Office – USPTO.	Estudo exploratório, documen-tal, retrospectivo, com base em uma revisão sistemática de patentes relacionadas a tecnologias que empregam fármacos antiparasitários o tratamento da DC.
11	Doença de Chagas no Brasil	Vinhaes; Dias[15]	2000	Cad. Saúde Pública	Sumarizar e discutir os dados da Fundação Nacional de Saúde (FNS) sobre o estado atual dos vetores da DC no Brasil.	Estudo histórico
12	Epidemiologia, controle e vigilância da doença de Chagas – 100 anos após sua descoberta	Coura; Dias[16]	2009	Mem. Inst. Oswaldo Cruz	Discutir sobre a epidemiologia, controle e vigilância da DC em 100 anos após sua descoberta.	Revisão sistemática
13	Pesquisas prioritárias sobre doença de Chagas na Amazônia: agenda de curto-médio prazo	Dias et al.[17]	2001	Rev. Soc. Bras. Med. Trop.	Relatar sobre a agenda de curto-médio prazo das pesquisas prioritárias com relação à DC na Amazônia	Relatório técnico
14	Aplicando uma lente de equidade à saúde e mor-talidade infantil: mais do mesmo não é suficiente	Victória et al.[18]	2003	Lancet	Informar sobre as lacunas na mor-talidade infantil entre países ricos e pobres.	Revisão sistemática

15	Mudanças no paradigma da conduta clínica e terapêutica da doença de Chagas: avanços e perspectivas na busca da integralidade da saúde	Dias et al.[19]	2016	Epidemiol. Serv. Saúde	Opinar sobre os avanços e perspectivas na busca da integralidade da saúde tendo em vista as mudanças no paradigma da conduta clínica e terapêutica da DC.	Estudo de opinião
16	Doença de Chagas: uma atualização bibliográfica	Lima; Teixeira; Lima[20]	2019	Rev. Bras. Anal. Clín.	Rever as vias de transmissibilidade, bem como as formas diagnósticas, para a DC.	Revisão bibliográfica
17	Terapia celular na doença de Chagas	Lima; Soares; Santos[21]	2009	Rev. Bras. Hematol. Hemoter.	Discutir sobre a terapia celular na DC à luz da literatura científica.	Revisão sistemática
18	Doença de Chagas: passado, presente e futuro	Ramos Junior; Carvalho[22]	2009	Cad. Saúde Colet.	Abordar sobre o contexto histórico da DC.	Editorial
19	Doença de Chagas aguda no Brasil: série histórica de 2000 a 2013	Brasil[23]	2015	Bol. Epidemiol.	Descrever a DC aguda no Brasil por meio de uma série histórica de 2000 a 2013.	Revisão sistemática
20	A imunização genética induz respostas imunológicas protetoras específicas para antígenos e diminui a gravidade da doença na infecção por Trypanosoma cruzi	Garg; Tarleton[24]	2002	Infect. Immun.	Avaliar a eficácia dos genes ASP-1, ASP-2 e TSA-1 da família trans-sialidase (ts) do T. cruzi como vacinas genéticas.	Estudo ecológico
21	A imunidade tipo 1 fornece proteção mucosa e sistêmica ideal contra um patógeno intracelular invasivo da mucosa	Hoft; Eickhoff[25]	2005	Infect. Immun.	Investigar sobre a imunidade tipo 1 quanto ao fornecimento de proteção mucosa e sistêmica ideal contra um patógeno intracelular invasivo da mucosa.	Estudo ecológico
22	A doença de Chagas está associada a um desfecho ruim no acompanhamento de 1 ano após a terapia de ressincronização cardíaca	Passos et al.[26]	2019	Rev. Assoc. Med. Bras.	Avaliar o prognóstico após terapia de ressincronização cardíaca (TRC) em uma população em que a DC é uma causa freqüente de insuficiência cardíaca (IC).	Coorte retrospectiva realizada entre janeiro/2015 e dezembro/2016
23	Anticoagulação nas manifestações cardíacas da doença de Chagas e acidente vascular cerebral isquêmico cardioembólico	Monteiro et al.[27]	2018	Arq. Neuro-Psiquiatr.	Descrever as características da anticoagulação em pacientes com manifestações cardíacas da DC e comparar os participantes com e sem acidente vascular cerebral isquêmico cardioembólico (AVCIC)	Estudo de coorte retrospectivo com abordagem quantitativa
24	Investigação clínica e manométrica em chagásicos constipados com e sem megacólon	Leite et al.[28]	2019	J. Coloproctol. (Rio J.)	Avaliar os achados da manometria anal (principalmente o Reflexo Inibitório Retoanal) em pacientes chagásicos com constipação crônica, com e sem megacólon, e correlacionar esses achados com dados clínicos e demográficos.	Estudo transversal com abordagem quantitativa
25	Segurança do Ecocardiograma sob Estresse com Dobutamina-Atropina em pacientes com Doença de Chagas	Rassi et al.[29]	2017	Arq. Bras. Cardiol.	Analisar a segurança do Ecocardiograma sob Estresse com Dobutamina-Atropina (EED) em uma população de chagásicos com suspeita clínica de coronariopatia.	Estudo retrospectivo com abordagem quantitativa

| 26 | Doença de Chagas: O que é conhecido e o que deve ser melhorado: uma visão sistêmica | Coura; Borges-Pereira[30] | 2012 | Rev. Soc. Bras. Med. Trop. | Realizar uma ampla revisão sobre o que deve ser melhorado no conhecimento da DC, não somente através da análise dos principais trabalhos publicados sobre os tópicos discutidos, mas em grande parte com base na experiência sobre o assunto, dos últimos 50 anos (1961-2011). | Revisão sistemática |
| 27 | Acometimento cardíaco em Casos de Doença de Chagas Aguda da Amazônia | Barbosa-Ferreira et al.[31] | 2010 | Arq. Bras. Cardiol. | Descrever o acometimento cardíaco em cinco pacientes autóctones da Amazônia com diagnóstico de DC aguda. | Relato de casos |

Source: Own authorship, 2020.

DISCUSSION

Epidemiological characteristics of human CD

T. infestans are wild animals, the forests being their natural habitat, but due to the anthropic actions represented by deforestation and the strong movement of urbanization, man became part of the epidemiological cycle of the disease, becoming a transmitter. [5,15] DC is characterized by reaching an economically vulnerable population, with precarious access to health services, health promotion and disease prevention actions, which are more favorable to illness due to the precarious housing conditions, a greater presence of health problems and exposure to other diseases. [5,15-18]

The level of transmission in households was considered insignificant in Brazil, which gave it a certificate by the Intergovernmental Commission of the Southern Cone, stating that this would no longer be a means of contamination in the country, but it is worth mentioning that there are different species of wild triatomines, where their ability to adapt to households in the northeastern region of the country was evident. [19] The transmission of the disease occurs in several ways: vector transmission, the insect contaminating after biting the man evacuates in the place and the individual ends up scratching the affected region, thus re-

leasing the protozoan into the bloodstream; oral transmission, the individual ingests the food contaminated with the protozoan; vertical transmission (congenital), which the mother transmits to the child; blood transfusion transmission and organ and tissue donation and transplantation (OTDT); and accidental transmission, which happens due to an error in the capture of the barber, breastfeeding, an accident at work with contaminated needles, among others. [3]

For more recent years (Diseases and Notification Information System [SINAN - Sistema de Informação de Agravos e Notificações], 2000 to 2013), with the operational limitation previously indicated, it was found that the form of oral transmission was the most frequent in all years (n=1.08 , 68,9%), followed by vector transmission in 100 cases (6,4%). [3,19] Therefore, the only way to control this transmission is through chemical products used by agents of endemic epidemiological surveillance directly in homes, perches, storerooms and other physical structures close to homes. [3] "CD is divided into two phases: the chronic (late, slow evolution and low parasitemia) and the acute (initial, rapid duration, with high parasitemia and generally self-limited)". [20:104] Its diagnosis is made differently in the two phases. In the acute phase it is done through fresh blood tests, thick drop and smear, the individual may or may not have appa-

rent symptoms, if the professional has a clear suspicion about the disease and the tests are negative, he should request a concentration test (microhematocrit or Strout) whose efficiency can reach 90%. In the chronic phase, where there is already a decrease in parasitemia, the diagnosis must be made exclusively by means of serology "(ELISA with total antigen or semi-purified fractions of the parasite or IFI) and another of high specificity (ELISA, using antigens specific recombinants of T. cruzi)". [20:104]

Difficulties encountered in performing CD treatment in Brazil

Latin American countries, as well as the southern United States, continue to be endemic regions of CD, even with successful interventions in these countries regarding the prevention of the disease. What is observed is that, despite the high expenses incurred in the treatment of the disease, since it causes, in addition to serious heart diseases, digestive diseases in the chronic phase, as well as absence from work and social security costs, it is evident that the greater effort for the control and prevention are not the responsibility of government officials, but of scientists who actively seek to guarantee investments for research in relation to the disease. [3]

CD has a high social impact, relating it to infectious diseases in Latin America where several drugs have been tested for its treatment, since its discovery in 1909.

Among these are: Bismuth, antihistamines, Fuchsin, Amphotericin B, antibiotics , arsenic, among others, but the treatment is still controversial. The cure, in turn, is still very limiting because there is no effective therapy in the chronic phase and due to the absence of a marker that defines the cure for CD. [13,21]

According to the Center for Disease Control and Prevention, in addition to the low effectiveness of nifurtimox in the chronic phase, these existing drugs still cause side effects in patients such as abdominal pain, weight loss, vomiting, allergic dermatitis, in order to cause a lot of discomfort during treatment. It is also important to highlight that, in addition to the different morbidity and mortality profiles, it is costly for public coffers due to the numerous hospitalizations, in view of all the classic symptoms, namely chagasic cardiomyopathy, megaesophagus and megacolon; transplants; absenteeism, that is, the absence of the professional at work due to the excess of medical certificates for the treatment of the disease; retirements; and early deaths. [22]

In addition to the scarcity of medications, factors such as underreporting of the disease are detrimental to the achievement of an early diagnosis, as well as to a more effective treatment in the acute phase of CD. There is also a lack of rapid tests for patients in endemic regions of the disease, lack of screening for diagnosis during prenatal care. [1,23]

Investments to carry out new research for the treatment of human CD

It is known that the investments made in new research for the treatment of CD are still insufficient. Between 1976 and 2014, only 117 patents were filed, with a greater deposit in 2019 with nine patents, which demonstrates that there has not been much progress in treatment since the discovery of the disease. There is now some research being carried out on

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drugs, vaccines, tests for diagnosing prenatal care, but nothing good enough that could be released for use in humans, noting the great lack of interest of the pharmaceutical and government industries. [13]

Research with antiparasitic drugs is a new proposal that is being studied, being a possible alternative for treatment. Another option is the studies carried out for the creation of a vaccine, which had its study started by Brump and since then there is a constant mismatch in the labyrinth of the fateful "immunité partielle", this due to the many specificities that the vaccine has, still not having positive results that would make tests in humans feasible, but this problem does not present impossible obstacles for science, where in the last 20 years researches are being carried out, seeking to develop a deoxyribonucleic acid (DNA) vaccine, which has been showing positive results with regarding the protective immunity of the antigen, as well as under the severity of CD. [13,24]

Another treatment option studied by Hoft and collaborators is the protection of the mucosa, since the greatest transmission nowadays is through the oral route, which seeks to induce mucosal immunity against T. cruzi antigens. [25]

CONCLUSION

The scientific studies found address that the CD provides the patient with a complex condition that affects the sensorimotor malfunction, as well as compromising the biophysiopsychological dimension, negatively affecting the socioeconomic aspects, although it is treatable, but with a late diagnosis. This study could show that CD is neglected by government officials, not being of interest to the large pharmaceutical industries, considering that its prevalence of involvement is in the economically vulneral population, in order to not be able to afford expensive treatments. It is inferred that this lack of in-

terest has lasted for many years, reflecting the increasing worsening of the QOL of patients with CD. Still, many scientific studies are carried out, but most of them do not show the need to improve the treatment of CD, thinking about a better QOL for patients, since they cannot accurately make an early diagnosis of the disease. 🕊

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