LEILI NOZADDIZAJI

İSTANBUL ÜNİVERSİTESİ SAĞ. BİL. ENST.

YÜKSEK LİSANS TEZİ

İSTANBUL-2021

← Adınızı soyadınızı giriniz

Tez kabul edildikten sonra yapılan **sabit ciltte sırt yazısı**
bu şablona göre yazılacak. Yazılar tek satır olacak
Cilt sırtı yazıların yönü yukarıdan aşağıya
(sol yandaki gibi) olacak .

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← Tez, Yüksek Lisans'sa, YÜKSEK LİSANS TEZİ;
Doktora ise DOKTORA TEZİ ifadesi kalacak

← Tez Sınavının yapılacağı yılı yazınız

T.C.
İSTANBUL ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ

(MASTER THESİS)

A SYMPTOM BASED CLINICAL DECISION SUPPORT SYSTEM FOR EARLY DIAGNOSIS OF BEHCETS DISEASE

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İTHAF

Dedicated to my supportive family

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CONTENT

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Anti-Endothelial Cell Antibodies	AECA
Anti–Glomerular Basement Membrane Disease	Anti-GBM
Anti Neutrophil Cytoplasmic Antibody	ANCA
Antineutrophil Cytoplasmic Antibody Associated Vasculitis	AAV
Behçet Hastalığı	BH
Behcet's Disease	BD
Central Nervous System	CNS
Clinical Decision Support System	CDSS
Cogan's Syndrome	CS
Cryoglobulinemic Vasculitis	CV
Decision support system	DSS
Electronic Health Record	EHR
Electronic Medical Records	EMR
Eosinophilic Granulomatosis with Polyangiitis	EGPA
Gastro Intestinal	GI
Giant Cell Arteritis	GCA
Granulomatosis with Poly Angiitis	GPA
Heat Shock Protein 65	HSP 65
Human Shock Protein	HSP60
Hypocomplementemic Urticarial Vasculitis	HUV
IgA Vasculitis	IgAV
Interleukin 12 receptor Beta	IL-12B2
Interleukin 23 Receptor	IL23R

International Study Group	ISG
Kawasaki Disease	KD
Large Vessel Vasculitis	LVV
Major Histocompatibility Complex	MHC
Medium Vessel Vasculitis	MVV
Microscopic Polyangiitis	MPA
Naïve Bayes' Classifier	NBC
National Center for Biotechnology Information	NCBI
National Library of Medicine	NLM
Natural Killer T	NKT
Osteo Arthritis	OA
physician Order Entry	CPOE
Polyarthritis Nodosa	PAN
Rheumatoid Arthritis	RA
single organ vasculitis	SOV
Small Vessel Vasculitis	SVV
stationary Linear Stochastic System	LSS
Support Vector Machines	SVM
Systemic Vasculitis	SV
T Regulatory	Treg
Takayasu Arteritis	TAK
The International Criteria for Behcet's Disease	ICDB
Variable Vessel Vasculitis	VVV
Weight Coefficients	Wk

ABSTRACT

Nozaddizaji, L . (2021) A symptom based decision-support system for early diagnosis of Behcet's disease, Istanbul University, Institute of Health Science, Department of genetics, MSc thesis. Istanbul

Behcet's disease (BD) is an inflammatory disorder that belongs to the systemic vasculitic syndromes and affects all types of vessels and sizes. BD in Turkey has the highest incidence among other countries (between 20 upto 420 per 100,000 people). Since no definitive test is available for BD, general basis for detection of this disorder is looking for physical manifestations. As time progresses the symptoms get worse, Therefore, early detection of the disease is important and could make patients' condition less painful. Nowadays, several studies with focus on developing clinical decision support system for early diagnosis of various diseases have been performed. In this thesis, we intended to work on a pre-diagnosis method of Behcet's disease and develop a mathematical model based on Bayes' theorem and conditional probability for patients, who are suspicious of BD. By performing the model in MATLAB program, we created a clinical decision support system that is able to detect BD cases based on physical symptoms. Our proposed system was able to detect BD cases with high frequency and also could exclude cases with diseases other than BD. We believe, this model could provide support for people in early diagnoses of Behcet's disease and help refer them to the proper expert.

Key words: Behcet's disease, symptom, decision support systems, clinics, early diagnosis

OZET

Nozad Dizaji, L. (2021). Behçet hastalığının erken teşhisi için semptom temelli bir karar destek aracı. İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, Genetik ABD. Yüksek Lisans. İstanbul.

Behçet hastalığı (BH), sistemik vaskülitik sendromlara ait olan ve her tür damarı ve boyutu etkileyen enflamatuar bir hastalıktır. Türkiye'de BH, diğer ülkeler arasında en yüksek insidansa sahiptir (100.000 kişi başına 20 ila 420 vaka). Hastalığın teşhisi için kesin bir test olmadığından, teşhis fiziksel belirtilere dayanmaktadır. Zaman geçtikçe fiziksel semptomlar kötüleşmekte ve şiddetlenmektedir. Bu nedenle, hastalığın erken teşhisi önemlidir ve BH hastalarının yaşam kalitesini artırabilmektedir. Günümüzde çeşitli hastalıkların erken teşhisi için klinik karar destek sistemi geliştirmeye odaklanan çeşitli çalışmalar yapılmaktadır. Bu tezde, Behçet hastalığının ön tanısında kullanılmak üzere BH şüphesi olan hastalar için Bayes' teoremine ve koşullu olasılığa dayalı bir matematiksel model geliştirmeyi amaçladık. Modeli MATLAB programında gerçekleştirerek, BH vakalarını fiziksel semptomlara göre tespit edebilen bir klinik karar destek sistemi oluşturduk. Bizim önerdiğimiz sistemin, BH vakalarını yüksek sıklıkta tespit edebildiğini gösterdik. Geliştirdiğimiz model ile ayrıca BH dışındaki hastalıkları olan vakaların dışlanabildiği gösterilmiştir. Böylelikle, geliştirdiğimiz bu model ile Behçet hastalığına erken teşhis konularak, uygun uzmanlara yönlendirilmesine katkı sağlanabileceği düşünülmektedir.

Anahtar Kelimeler: Behçet hastalığı, semptom, karar destek sistemleri, klinik, erken tanı

1. INTRODUCTION AND PURPOSE

Behcet's disease (BD) is classified under the systemic vasculitic disorders that affects all types of vessels (arteries and veins) and sizes (small, medium, large), whose aetiopathogenesis is unknown. BD is identified with four major symptoms: oral and genital ulcers, skin lesions and ocular lesions. Additional symptoms include vascular, gastrointestinal and neurological involvement (1). It is believed that genetic factors, infectious agents and immunological processes play roles in the BD manifestation (2,3). BD is a disorder that can involve several organs and systems. Since no definitive test is available for BD, general basis for detection of this disorder is looking for physical manifestations (4).

In the past few decades, with the development of technology, several clinical decision support systems have been introduced for helping physicians in the process of making decisions about a disease (5).

In this study, we aim to create a stationary linear stochastic system model based on Bayes' theorem and naïve Bayesian classifier rule and propose a reliable clinical decision support system for early diagnosis of BD. This CDSS-tool is established with relevant historical data gathered from symptoms of patients suffering from Behcet's syndromes.

Symptoms are defined through precise classification of sets of properties, which are mutually exclusive and complete sets in order to precisely define the disease under consideration. By executing the model in MATLAB programming environment, we will create a decision support tool that is able to detect BD cases. The system requires symptoms of suspicious cases. It registers the availability of a symptom by means of yes or 1 and the absence of a symptom via no or 0 as input and compute the chance of the pertinent illness in the subject as output. If the patient matches with a comprehensive CDSS tool, they will have a chance of early detection of their condition and be directed to rheumatologist. Our proposed system would be beneficial, for family physicians and internists to guide patients in the early stages of the disease. Also, aforementioned tool would be an advantage for patients to reduce the time of diagnosis, prognosis, energy and cost of treatment.

2. GENERAL INFORMATION

2.1. Systemic vasculitis

Vasculitis refers to the inflammation of blood vessels. The inflammatory process will lead to the destruction of vessels, which are observed as fibrinoid necrosis or cell death (4). Vasculitis can affect the whole organ or only a single artery. It belongs to a wide group of heterogeneous diseases, effects of which, are observed in blood vessels regardless of their size and type (6). Jennette et al. described different types of vessels in which symptoms of vasculitis could be non-specific and changeable (Figure 2-1) (7).

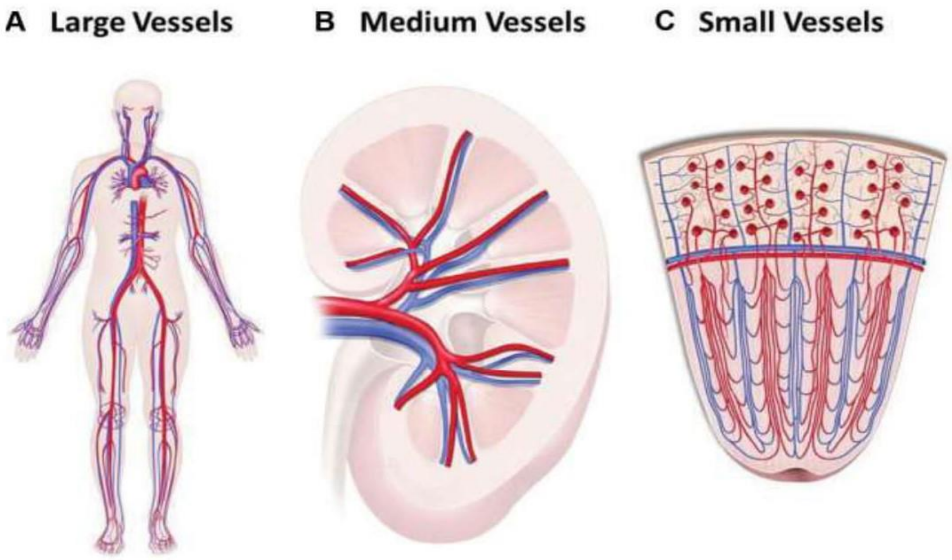

Figure 2-1 : Variations of vessels involved in vasculitis

"Types of vessels that are defined as large vessels (A), medium vessels (B), and small vessels (C) in the Chapel Hill Consensus Conference nomenclature system (7) and involved in vasculitis. The kidney is used to exemplify medium and small vessels. Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intraparenchymal arteries, arterioles, capillaries, venules, and veins" (7).

Since vasculitis is not a specific disease and the disease can change, the clinical diagnosis is very difficult. Vasculitis' initial symptoms may vary. It could be lung involvement, pneumonia, asthma, or a system or organ infection like sinusitis or arthritis (8). If the vasculitic destruction process affects only one organ it is named a single organ vasculitis (SOV) . On the other hand, some of them affect different organs and systems and are called systemic vasculitis (SV). Systemic vasculitis can be primary or secondary. Primary

vasculitis is the type of vasculitis having little or no information on the etiology of occurrence. Thus when disease manifests without a recognizable etiology or causation, it will be identified as primary vasculitis. If it occurs to be caused of a second factor like infection, drug abuse, cancer or connective tissue disorders, it will be considered as secondary vasculitis (9). Therefore, the names for vasculitides was adopted by the "2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides", which represents different vasculitis and their subgroups as outlined in Table 2-1 (7).

Primary systemic vasculitis had been sub categorized regarding the size of the vessel involved in the disease. In addition, in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, various vessel vasculitis have been added to the primary systemic vasculitis (Table 2-1) (7).

Table 2-1: Vasculitides adapted by "2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides" (7).

Large vessel vasculitis (LVV)	Takayasu arteritis (TAK) Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)	Polyarthritis Nodosa (PAN) Kawasaki disease (KD)
Small vessel vasculitis (SVV)	**Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV)** Microscopic polyangiitis (MPA) Granulomatosis with polyangiitis (Wegener's) (GPA) Eosinophilic granulomatosis with polyangiitis (Churg Strauss) (EGPA) **Immune complex SVV** Anti–glomerular basement membrane (anti-GBM) disease Cryoglobulinemic vasculitis (CV) IgA vasculitis (Henoch-Scho¨nlein) (IgAV) Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Variable vessel vasculitis (VVV)	Behcet's disease (BD) Cogan's syndrome (CS)
Single-organ vasculitis (SOV)	Cutaneous leukocytoclastic angiitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis Others
Vasculitis associated with systemic disease	Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Others
Vasculitis associated with probable etiology	Hepatitis C virus–associated cryoglobulinemic vasculitis Hepatitis B virus–associated vasculitis Syphilis-associated aortitis Drug-associated immune complex vasculitis Drug-associated ANCA-associated vasculitis Cancer-associated vasculitis

2.1.1. Large vessel vasculitis (LVS)

2.1.1.1. Takayasu arteritis (TAK)

TA is a granulomatous vasculitis, which often happens in individuals younger than 50. It mainly targets the aorta and its main branches such as pulmonary and coronary arteries (7). Stenosis, occlusion, and aneurysm of large elastic arteries are the characteristic of the disease (10).

2.1.1.2. Giant cell arteritis (GCA)

GCA is arteritis, often granulomatous and usually targets the aorta and/or its major branches with a tendency for carotid and vertebral arteries. Giant cells have been detected in biopsy specimens from GCA patients. The onset starts after the age of fifty. The age of the onset of vasculitis helps to distinguish between GCA and TA (7).

2.1.2. Medium vessel vasculitis (MVV)

2.1.2.1. Polyarthritis Nodosa (PAN)

PAN is a systemic necrotizing vasculitis mainly targeting medium arteries, which middle-age and older individuals are more prone to have. Among other vasculitic diseases, PAN is rare and its prevalence is hard to determine. All the organs except lungs could be attacked by PAN. Tissue ischemia or hemorrhage, peripheral nervous system and skin disorders, gastrointestinal tract and kidney ailments, orchitis and hearing loss are the most common symptoms of this disease (11).

2.1.2.2. Kawasaki disease (KD)

KD is arteritis that mostly affects medium arteries. It usually happens in infants and young children. High fever for more than 5 days, bilateral conjunctival injection; erythema of the oropharynx with red, cracked lips and ‘strawberry tongue’; edema and erythema of hands and feet; erythematous rash; and non-suppurative unilateral cervical lymph node enlargement are the characteristics of KD (12).

2.1.3. Small vessel vasculitis (SVV)

SVV are classified according to the presence or paucity of vessel wall immunoglobulin in to two classes: Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and immune complex small vessel vasculitis. ANCA are

antibodies against antigens present in the granules of neutrophils or lysosomes of monocytes (5).

2.1.3.1. ANCA-associated vasculitis (AAV)

They are necrotizing vasculitis, with few or no immune deposits, mostly affecting small vessels like capillaries, venules, arterioles, and small arteries. Microscopic polyangitis (MPA), granulomatosis with polyangitis (Wegener's) (GPA), eosinophilic granulomatosis with polyangitis (Churg- Strauss) (EGPA) belong to this category (7).

Granulomatosis with Polyangitis (Wegener's) (GPA)

GPA is necrotizing granulomatous inflammation, which mostly affects the upper and lower respiratory tract. It also targets small to medium vessels such as capillaries, venules, arterioles, arteries, and veins. Necrotizing glomerulonephritis, ocular vasculitis and pulmonary capillaritis with hemorrhage are common (7). Sinonasal, pulmonary, upper respiratory tract and renal involvements are the most frequent clinical manifestations appear in GPA (13).

Eosinophilic granulomatosis with polyangitis (Churg-Strauss) (EGPA)

EGPA is abundant in eosinophil. Also, ANCA is present in 40–60% of these patients. EGPA typically establishes three subsequent phases: the allergic phase, identified with asthma, allergic rhinitis, and sinusitis, the eosinophilic phase, in which the eosinophilic organ infiltrations (e.g., lungs, heart, and gastrointestinal system) is the most in pathological findings, and the vasculitic phase, described by purpura, peripheral neuropathy, and constitutional symptoms (13).

2.1.3.2. Immune complex small vessel vasculitis

In immune complex SVV, vessel walls possess deposits of immunoglobulin and/or complement. It targets small vessels and barely affect arteries despite ANCA-associated vasculitis. Anti-glomerular basement membrane (anti-GBM) disease, cryoglobulinemic vasculitis (CV), IgA vasculitis (Henoch-Schonlein) (IgAV), hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) belong to this category (7).

Anti–glomerular basement membrane (anti-GBM) disease

Anti-GBM disease is vasculitis that targets glomerular capillaries, pulmonary capillaries, or both, and classified as an immune complex disease because of the formation of immune complexes comprised of autoantibodies in the basement membrane of glomerular and pulmonary capillaries. Lung involvement leads to pulmonary hemorrhage, and renal involvement leads to glomerulonephritis with necrosis and crescents (7).

Cryoglobulinemic vasculitis (CV)

CV occurs because of the presence of cryoglobulin-containing immune complexes in the body, which in turn leads to the systemic inflammatory process. It mostly affects small vessels and the following symptoms would be fatigue, arthralgia, purpura, ulcers, neuropathy and/or glumeronephritis (14).

IgA vasculitis (Henoch-Schönlein) (IgAV)

IgA1 is the dominant immune deposit in IgAV. Abnormal IgA deposits in vessel walls are the defining pathophysiologic feature of the disease. It mainly affects small vessels such as capillaries, venules, or arterioles. Skin and gastrointestinal tract are involved in IgAV and arthritis is frequent in the disease (7).

Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

HUV (anti-C1q vasculitis) is vasculitis which It affects small vessels such as capillaries, venules, or arterioles, and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are the characteristics of HUV (7).

2.1.3.3. Variable vessel vasculitis (VVV)

VVV can affect vessels with all sizes (small, medium and large) and all types (arteries, veins, and capillaries). In CHCC 2012 Behcet's disease and Cogan's syndrome included in this category (7).

Behcet's Disease (BD)

BD affects all types and sizes of vessels. It mainly identified with oral ulcers, genital ulcers, skin lesions and ocular lesions (7).

Cogan's syndrome (CS) vasculitis

CS is characterized by invading several organ involvement and vascular inflammation such as ocular inflammatory lesions, inner ear disease and vasculitic involvement such as arteritis including small, medium, or large arteries, aortitis, aortic aneurysms, and aortic and mitral valvulitis (7).

2.2. Behcet's disease (BD)

BD is one of the systemic vasculitic diseases that affects all types of vessels (arteries and veins) and sizes (small, medium, large), whose etiopathogenesis is unknown. BD is identified with four major symptoms: oral ulcers, genital ulcers, skin lesions and ocular lesions. Additional symptoms include vascular, gastrointestinal and neurological involvement (15). In 1937, Hulusi Behcet, a Turkish dermatologist of Istanbul University, recognized 3 dominant manifestations (oral aphthae, genital ulcerations, recurrent uveitis) and arranged them in such a clinical entity that helped name it as the "triple symptom complex" (16). The "2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides", defined BD as a variable vessel vasculitis, whithin primary systemic vasculitis category (7).

2.2.1. Epidemiology

BD is more frequent in areas alongside the "Silk Road", which was an old route for ancient trades. These areas are Mediterranean countries like Turkey and Iran, which expand to the East Asia such as Korea and Japan. According to the several surveys, Turkey has the highest incident among other countries (between 20 upto 420 per 100,000 people). In addition, the frequency of the disease in Asian part of Turkey is more widespread than the European part (17). After Turkey, Iran, Israel, northern China, and Korea have the maximum rate of this disease. Table 2-2, depicts the countries with high prevalence of BD (18). United Kingdom, Spain, Sweden, Portugal, and the United States, ranging from 0.3 to 6.4 per 100,000 persons, are countries that have a lower frequency (19,20). Although the prevalence of this disorder is high, it should be considered that other vasculitic disorders such as Polyarthritis Nodosa, Microscopic Polyangitis, Wegener's granulomatosis, and Churg–Strauss syndrome are frequent as BD as well (17). It seems that environment plays a might be a factor in having the disease. Studies have shown that people, who moved from their country to a region where the prevalence of BD is low, have lower chance of getting the disease. For instance, Turkish people, who migrated from Turkey to Germany, were less infected by BD than Turkish people who

continued to live in Turkey (16,21). A research conducted in Germany, which studied epidemiological features of BD in Germany and in Europe showed that permanent residents of Turkish people in Germany have a considerably lower prevalence than Turkish people in Turkey (22). In 60% of BD patients, *HLA-B*51* is recognized, which is regarded as BD susceptibility gene (23). In addition, *HLA-B*51* is observed more commonly in the Middle and the Far East compared to other regions (15). BD can involve people of all age groups, but the occurrence in populations under the age of maturity and ove13r 60 years old are unusual. The incidence usually starts in ages more than 30 years old (17). Some of the symptoms of BD differ from the others because of the regional differences. For example, gastrointestinal syndromes are more common in patients residing in the East Asia, contrary to Turkey and in the Middle East (24). Another example is about the Pathergy test, which is rare in patients from north Europe and the United States (25). “The pathergy phenomenon is a non-specific hyper-reactivity in response to minor trauma” (17).

Table 2-2: Countries with the highest number of cases of BD per 100,000 people

Country	**Cases per 10^5**
Turkey [Istanbul (urban)]	420
Israel (Druze)	146.4
Northern China	110
Iran	80
Korea	30.2
Japan(Hokkaido)	22
Saudi Arabia	20
Iraq	17
Morocco	>15
Egypt	7.6

2.2.2. Etiopathogenesis

The etiopathology of BD is yet to be fully understood, however the assumption is that it is an auto immune mechanism is activated because of microbial agents or environmental factors in a person with genetic susceptibility. Below describes these three components that play roles in the onset of BD (26,27).

2.2.2.1. Genetic factors

As described previously, the regional distribution of BD is not consistent and it is seen more frequent alongside the Silk Road, clustered especially in Turkey and Japan. Also, as mentioned before, about 60% of people diagnosed with BD, are positive for *HLA-B*51* gene . Therefore, carriers of *HLA-B*51* allele are determined to be susceptible to developing BD (28). *HLA-B*51* is located in the MHC (major histocompatibility complex) locus, on chromosome 6p (21). Common variants of the IL-10 and interleukin 23 receptor *(IL23R)* and interleukin 12 receptor beta *(IL-12B2)* genes are also related to BD pathology. IL-23 is a proinflammatory cytokine that activates the reproduction of Th17, increases the accumulation of inflammatory cytokines, which leads to expression of IL-23 p19 mRNA in patients who manifest erythema nodosum-like skin lesions in their disease. IL-10 is an anti-inflammatory cytokine that prevent the cytokines with proinflammatory roles. In addition, the upregulation of the CD4(+) CD25(+) T regulatory (Treg) cells by IL-10 in the Behcet's mouse models alleviate the inflammatory manifestations. Therefore, IL10 and IL23R/IL12B2 region could be possible agents responsible in the BD pathology (29,30).

2.2.2.2. Infectious agents

In 1937, Hulusi BEHCET proposed microorganism association with BD for the first time (21). It is believed that herpes simplex virus-1 and Streptococcus sanguis are the main infectious agents that lead to this illness. The association of streptococcal agent and BD is proposed based on two evidences: First, by detecting Some infections such as tonsillitis and tooth decays in Behcet's patients which give rise the condition of BD. The second, antibacterial treatments are effective in mucocutaneous and arthritic symptoms of BD (31).

HSV type 1 DNA and serum antibodies in BD patients are detected in higher percentage than healthy control group. HSV DNA has been observed in the genital and intestinal ulcers. Other viral agents such as hepatitis C virus, parvovirus B19,

cytomegalovirus, Epstein-Barr virus, and varicella zoster virus, could be effective as well (21).

However, there is no study that can support the idea that only one specific infectious agent is responsible for the BD pathology. Anyhow, there is a well-constructed theory among experts explaining high homology between microorganism antigens and human proteins. For instance, heat shock protein 65 (HSP 65), which is extracted from Mycobacterium, has high homology with human protein (HSP60) and therefore this cross-reaction triggers the immune response (21).

2.2.2.3. Immunological theory

It is believed that auto immune processes affect blood vessels particularly on the endothelial cells, which lead to the presence of vasculitic manifestations (15).

Anti-endothelial cell antibodies (AECAs) have been observed in BD and other vasculitis. Also, a relation between the presence of these antibodies and the pathogenesis of the disease have been recognized (32). AECAs are antibodies that bind to endothelial cells and trigger them to produce more cytokines (18). Cytokines are proteins that regulate the host immune system's responses towards infections, inflammation and trauma. Some kinds of these cytokines could act as pro-inflammatory elements and worsen the host's condition (33).

Subpopulations of T cells have been observed to be markedly involved in the BD pathogenesis. They include: γδT cells and cytotoxic T cells, Th1 T cells, Tregs and Th17 cells (34). Studies have discovered that the changing balance of T cells, in particular the proliferation of Th1 and Th17 cells and decreased regulation by Tregs, play a major roles in BD pathogenesis (35).

Natural killer T (NKT) cells are another group of cells that increase during the disease. Several studies underlined increased NKT cells in the peripheral blood and BD lesions, within the active phases of the illness in particular. They control immune responses towards the cytokines' proliferation (36).

IL-8 is a chemokine, which is reported in BD lesions with active oral and neurological symptoms. High levels of IL-8 can trigger the immune responses to change the endothelial cells, which lead to skin lesions and disease activity (37).

Furthermore TNFα, INFγ, and IL-12 have been found in oral and genital ulcers, and gastrointestinal lesions of BD (38).

Neutrophil abnormalities are observed in BD frequently. Neutrophils have major roles in the innate immune system and their up-regulation mostly triggered by T cells. The involvement of neutrophils in BD lesions are fully accepted so much so that it is been suggested to categorize BD as neutrophilic vasculitis. In Figure 2-2, the pathogenic process of BD is summarized (15).

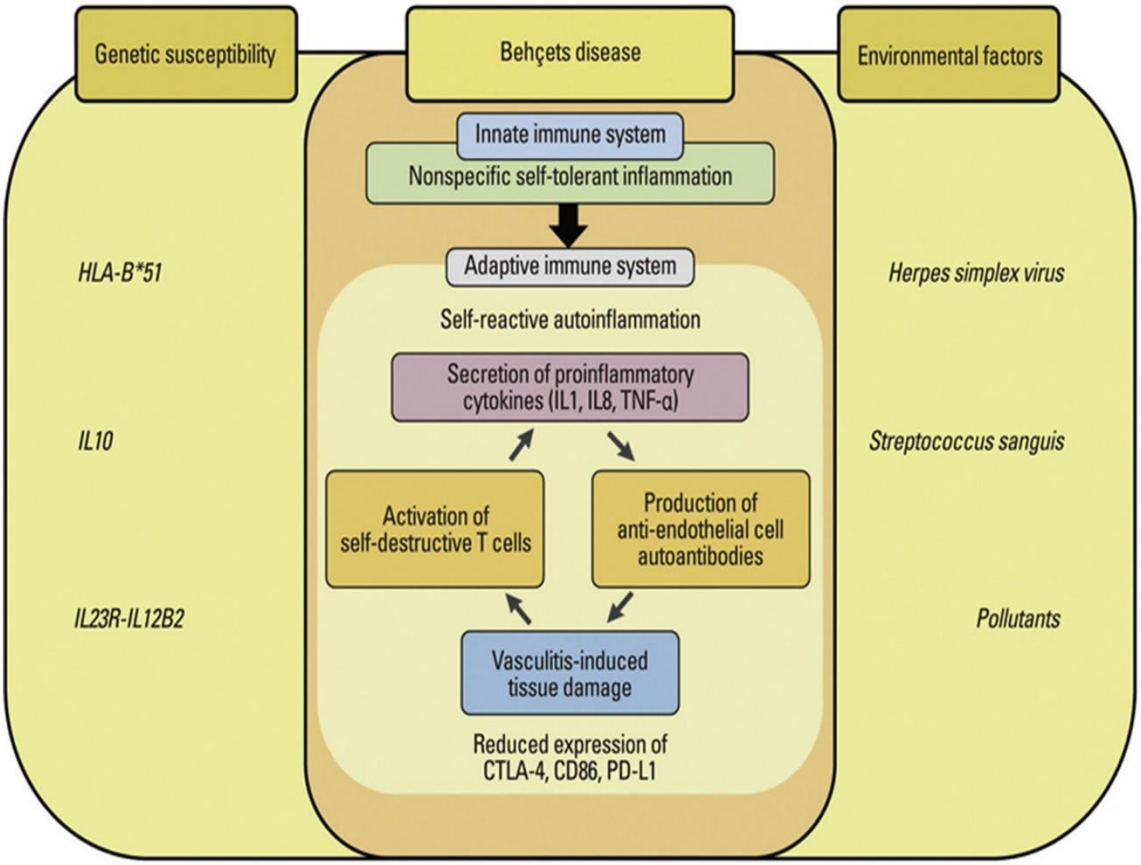

Figure 2-2: Behcet's disease pathogenesis

Environmental factors, such as infectious agents or pollution, in patients with backgrounds of genetic susceptibility trigger the disease (18).

2.2.3. Clinical findings

Behcet's is a disorder that can involve several organs and systems. Since there is no definitive test to detect the disease, general basis for detection of this disorder is looking for physical manifestations (5). The clinical findings include : various skin and mucosal lesions, uveitis which could lead to blindness, a vast spectrum of central nervous system

(CNS) abnormalities, vessel disease, musculoskeletal and gastrointestinal (GI) problems. The first clinical manifestations are as follows: oral and genital ulcers; ocular lesions; papulopustular skin lesions; erythema nodosum; and arthritis. One or two of these symptoms may appear when the disease initiate. This process is intensified and gets worse as the time passes (17).

2.2.3.1. Mucocutaneous findings

Oral ulcers

Oral ulcers have the highest frequency of manifestation as they appear almost in all of the patients (98%) (39). However, about 1 to 3 percent of patients might not have oral ulcers and present other symptoms of Behcet's. It is very hard to recognize the initiation of these ulcers and sometimes they get confused with aphthous ulcers. However, they are more abundant than the former. They mostly present as erythematous, which progress to the raised and round ulcers with mostly 1 to 3 cm in diameter in 48 hours (15). Oral ulcers in Behcet's present in three shapes : minor, major, or herpetiform aphthous (17).

Minor aphthous

The most frequent types are minor aphthous ulcers. They are shallow, oval, round and and have a radius smaller than 5 mm. In these ulcers, a grey-white pseudo membrane is bounded with a thin erythematous inflammatory halo. Mucous membranes of the lips, gingiva, cheeks, and tongue are the loci of these types of ulcers. The palate, tonsils, and pharynx are usually freed of these ulcers. In herpetic forms the skin portion of lips are involved with these ulcers. Minor ulcers cover almost 90% of all oral ulcers in BD. The alleviation usually takes 15 days and no scars remains. They make eating hard for the patients (17).

Major aphthous

The second form of aphthous ulcers are called major scars, which are observed less than minor types. They are between 1 to 3 cm in diameter, grey-white color and could be present in different parts of the oral mucosa. Unlike minor ulcers, they are painful and leave scars after healing. Sometimes these ulcers make swallowing difficult, which are followed with innutrition deficiency and probable death of the patients (40).

Herpetiform aphthous

Herpetiform aphthous ulcers are the rare types, which appear as multiple ulcers in 2-3 mm in diameter around oral cavity. They don't leave scars and heal fast (41).

Genital ulcers

Genital ulcers usually are considered as pustules and papules at the initiation of the disease and then they turn into ulcers. The form of these ulcers are round or oval and they are more prone to getting infected than oral ulcers. In males, the region of formation for these ulcers is scrotum and they manifest as scars. They are larger and deeper than oral ulcers, and are less likely to get healed. In females, ulcers are seen more in the labiaes and less in the cervical region. Most of the time, they have no sign unless they get infected. Hence, in suspected patients, gynecological examination should be performed. Genital ulcers usually alleviate in 10 to 30 days (42).

Other skin lesions

Other skin lesions include erythema nodosum, papulopustular lesions and other lesions. Erythema nodosum-like lesions are present in half of the BD cases (43). They might not be recognizable from idiopathic or other disease-related erythema nodosum, but usually they are deeper (43). The acne-like lesions of BS (papulopustular lesions) are observed in the face, upper chest, and upper back, and also on the legs and arms, which are less common regions for the presence of acne. Other lesions include ulcers, Sweet's syndrome (Gomm-Button), and pyoderma gangrenosum (44).

Pathergy test

Pathergy test is a diagnostic approach, which is applied with a 20 gauge needle into the skin of the forearm. If a papule or pustule appear on the skin after 48 hours, then the Pathergy reaction is positive. It should be noted that the wound heals normally (44). In Pathergy test, the intensity of reaction is higher in males compared to females (45). Pathergy test is used frequently in the Middle East. However, the positive reaction declines outside the Middle East, Far East, and the Mediterranean regions. In addition, research propose that the amount of Pathergy has been reduced during the time and it has postulated that the sharper needles reduce the traumatic skin reactions. The reproducibility of Pathergy has been restricted because of intra- and inter-observer variation. In addition, the scope of the reaction might vary at different times for the same patient (44).

2.2.3.2. Eye manifestation

Eye manifestation is one of the most important and vital symptoms of BD with respect to fatality and frequency. Ocular involvement is one of the significant reason for the loss of vision within the Mediterranean region, Middle East, and Far East. In a survey performed among different parts of Turkey, Behcet's is the most prevalent diagnosis among patients, who suffer from uveitis (46). Eye involvement is common in the initiation of the disease. It happens in both eyes in 70% to 80% of patients, engaging posterior uvea more than anterior uvea (47,48).

Ocular manifestation usually presents as retinal vasculitis and hypopyon pan uveitis, which might aggravate or alleviate during the process of inflammation (49) (Figure 2-3).

Hypopyon is a pile of inflammatory cells, which appear as a layer in the front region of iris (Figure 2-4). It is present in almost 20% of BD patients with eye disease (44). About half of the patients with the mentioned problem lose their vision after a few month. Retinal vasculitis can be seen as patches of fluorescein flows alongside the vessels, retinal exudates, hemorrhages, cytoid bodies or white patches; venous thrombosis, papilloedema; and the macular disease (44).

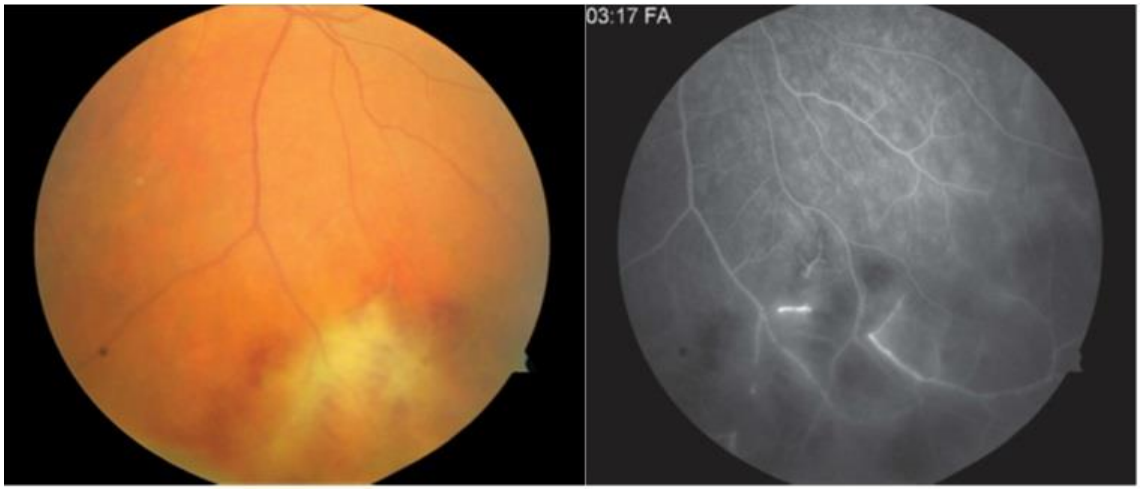

Figure 2-3: eye involvement in a BD patient

"Retinal vasculitis with associated hemorrhage and retinitis in a patient with Behcet's disease" (left) and "Fluorescein angiography of same area revealing hyper fluorescence along involved vessels, indicating active vasculitis" (right) (50).

Figure 2-4: Hypopyon uveitis

Inflammatory cells, which appear as a layer in the front region of the iris (44).

2.2.3.3. Vascular manifestations and cardiac involvement

Effects of Vasculitis in BD can be seen in all vessels regardless of their size, including venous and arterial structures. Venous are more commonly involved than arterial. About 30 percent of BD patients experience venous thrombosis, while arterial disease occurs only in 3-5 percent of the cases (51). Also, it is more dominant in males. Deep veins of the lower extremity are the regions that venous thrombosis occur (60-80%). Other sites include some big vessels of heart (*vena cavae*), cerebral venous sinuses in cranial cavity and other veins. It can involve pulmonary artery, non-pulmonary artery and central venous during different courses of the disease, too (52).

Vascular disease in BD is recurrent. In a retrospective study, the recurrence rate was reported to be 23% and 38% over 2 and 5 years, respectively. Also, lower extremity deep vein thrombosis was the most detected symptom (53). Chronic repetitive thrombosis of the lower extremities can cause symptoms like erythema, dermatitis, hyperpigmentation, and skin ulcers (52).

Cardiac involvement occurs rarely in 1%–6% of the BD patients. It consists of pericarditis, myocarditis, endocarditis (54). Aneurysms and/or thrombosis of the coronary arteries along with hemorrhage, myocardial infarction and unexpected death have been observed in BD cases with cardiac involvement (15).

2.2.3.4. Musculoskeletal manifestations

Arthritis or arthralgia has been observed in almost 45 percent of BD cases (15). These characteristics usually come before other symptoms of BD (15). Arthritis usually occurs in large joints like knees, ankles, elbows, and wrists. However, it can affect some small joints too. Arthritis usually does not damage the affected regions and they would heal after some days or weeks (55).

2.2.3.5. CNS disease

It affects 20-40 percent of BD cases (56). Neurological involvement in BD consists of two types: parenchymal (Neurobehcet's disease) and non-parenchymal (cerebral vascular thrombosis and aneurism) lesions. Parenchymal lesions usually initiate abruptly. Headache, meningitis or meningoencephalitis, hemiplegia, or cranial nerve palsies are its symptoms. In addition, psychiatric problems such as character disorders, impairment of memory and dementia could happen (15). The other type includes dural sinus thrombi which causes intense headaches. Parenchymal lesion in BD patient with neurological problems is more frequent than non- parenchymal type (about 75%) (17).

2.2.3.6. GI manifestation

The frequency of GI in BD patients vary from 1% to 30%, because their symptoms are similar to other GI inflammatory disorders. The disorder's symptoms include nausea, anorexia, abdominal pain, and diarrhea that could be bloody sometimes. Perforation of the intestine could happen also. Transverse colon, ascending colon and esophagus are the regions that inflammation can occur. However, ileocecal is the region that is affected more than other parts of gastrointestinal tract (57).

2.2.3.7. Other manifestations

Amyloidosis

Amyloidosis has been seen in BD patients with very low frequency. Its morbidity rate is about 50% (58). The disorder would be related to the nephrotic syndrome or proteinuria. It is postulated that the disease has been associated with large vessel vasculitis and arthritis (59).

Periodontal disease

The accumulation of plaque and periodontal index scores in BD cases are more than healthy control groups (60).

Orchitis and epididymitis

They tend to occur repetitively. The swelling of epididymitis could be painful or painless. They could remain for few days to weeks. Orchitis' attacks are painful and mark both testicles (61).

Inner ear involvement

Inner ear involvement consists of two types: hearing loss and disequilibrium. Several research reports have shown the frequency of hearing loss as 12–80% (15).

2.2.4. Diagnosis/Classification Criteria for Behcet's Disease

In 1990, scientists of France, Iran, Japan, Tunisia, Turkey, UK, and USA gathered to develop criteria from an international study group (ISG) in diagnosing Behcets' disease. ISG criteria comprises of five characteristics: oral aphthosis and genital aphthosis, skin manifestations, which include pseudo folliculitis and erythema nodosum. The fourth is ocular manifestations. They are anterior uveitis, posterior uveitis, and retinal vasculitis. The last criterion is the positive Pathergy test. According to these criteria, the manifestation of oral aphthous is obligatory. Two out of other 4 other symptoms should be present to define a case as BD (62). However, when the mentioned diagnostic criterion was performed in each individuals' country, the results had low sensitivity. Because in this classification, variations of BD symptoms were not accepted.

In 2006, The International Criteria for Behcet's Disease (ICBD) were presented to the International Conference of Behcet's Disease in Lisbon (Portugal). The conference is held by twenty-seven different countries of the world. Considering various parts of the world, both in and out of the silk road countries, proved that this study can confirm the variability of manifestations, which can be carried out in any country with different backgrounds. The ICBD criteria added vascular manifestations as the sixth item of the criteria with the involvement of superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, and aneurysm. According to the ICBD, each genital aphthous lesions and eye lesions are considered to be two points and other four items

have the value of one point (Table 2-3). A patient with the point of three or more is considered as BD (63).

Table 2-3: International Criteria for Behcet's Disease

Signs/symptoms	points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	1
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1

2.2.5. Manifestations of BD with approximate % prevalence

Frequency of clinical symptoms of BD are presented in the Table 2-4 as percentages (16), which are resulted from several studies including the criteria suggested by International Study Group for Behcet's Disease. In this table, symptoms are classifed under two major and minor symptoms groups. Major features occur frequently, and minor features are the ones with rarely occurrence and it is not related to the intensity of a symptom. In addition, it should be noted that the prevalence of symptoms in different countries are not equal (16).

Table 2-4: Prevalence of Behcet's disease symptoms

Major symptoms	**Prevalence%**
Recurrent oral ulceration	98%
Recurrent genital ulceration	80%
Inflammatory eye disease including uveitis ± hypopyon and retinal vasculitis	50%
Skin lesions	80%
Erythema nodosum	47%
Folliculitis/acneiform lesions	51%
Hyperirritability − Pathergy	60%

Minor symptoms	
Arthritis (arthralgia)	45%
Vasculitis including large vessel vasculitis, aneurysm formation and arterial/venous thrombosis	16%
Gastrointestinal lesions	12%
Neurological lesions	15%
Epididymitis	8%
Family history	20%

2.3. Decision making and medical decision making

A decision is choosing a certain course of action to solve a problem after elaboration and assessment of the problem at hand (64).

The decision maker can make a decision in regard with the evidence of the available data during the decision making process. One can attain data by observing the present state of the problem or by searching through the history of the problem. The people responsible for diagnosis must have adequate knowledge and experience in the issue. This become even more important if the issue were in the field of medicine where no mistake is acceptable. In addition, a decision maker should consider all possible options and choices in the situation and select the best of them. Medical decision making could be considered as a process for deciding the best treatment strategy, and for the diagnostic purpose of the disease, which is obtainable by various physical findings and diagnostic tests (65).

2.4. Clinical decision support system (CDSS)

Decision support system (DSS), is a structure where the a criteria is used to evaluate specific conditions necessary to form correct decisions. Based on studies done in this field, about 15% of the DSS research is in the medical area (66).

Clinical decision support systems (CDSS) are tools that help making medical decision by using patients' data which in turn provide patient-specific evaluations or recommendations. CDSS needs quantified biomedical information, data sets made up of

indvidial datapoints, and a reasoning or deduction strucutre to bring useful information for clinicians (67).

Nowadays, several articles about various CDSSs which are used in the clinical practice and routine, is accessible with a simple PubMed database query. The search strategy for PubMed was "clinical Decision Support Systems," and totally 17,079 papers were found from 1987 to February 2021. As shown in Figure 2-5, papers related to CDSSs have been increasing by time.

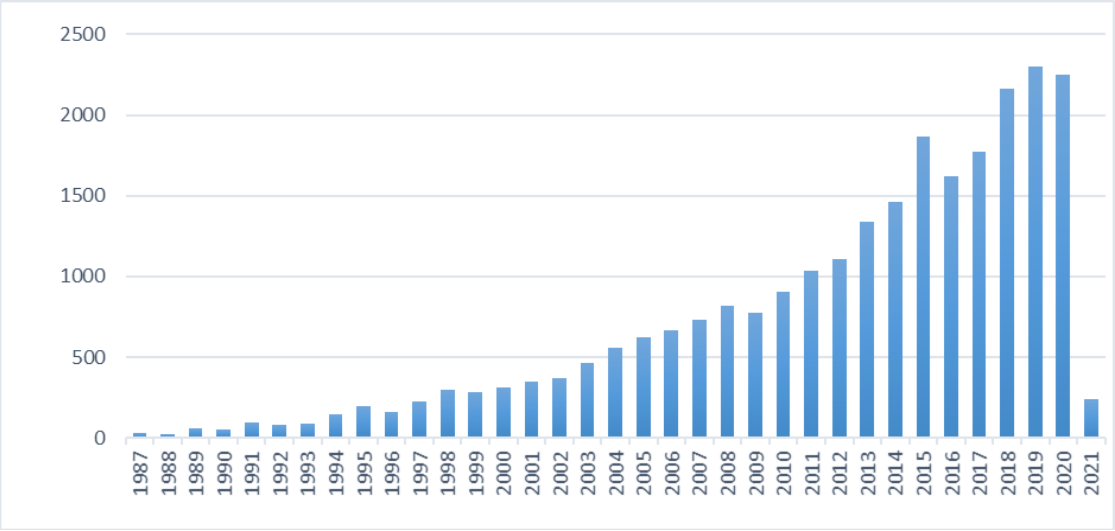

Figure 2-5: Number of articles of CDSS from 1987 to 2021

Annual distribution of the number of articles on CDSS registered in PubMed database and published between 1987 and 2021 (obtained from PubMed search).

2.4.1. Types of CDSS

CDSS features must be defined and categorized to comprehend the importance and function of this system. These characteristics are mostly based on system's function, model of advice output, communication method, decision making scheme within the system and the user interface (68).

2.4.1.1. System's function

Two sorts of this system are available. The first one determines 'what is true?' which focuses on diagnostic function. Data of this system is fixed data, which is put by a user and then advice is given by the system. Websites like Diagnosaurus® or WebMD®

are the examples of this function (69,70). WebMD symptom checker is presented in Figure 2-6 (70). The second one goes further and addresses the question “what to do?” it can tell us which test should be ordered for better differential diagnoses or which drugs should be given to the patient. However, available CDSSs now can do two functions at the same time, first determine the diagnosis and then advise for test orders and drug prescription.

2.4.1.2. Model of advice output

There are passive and active systems in this category. In passive advice the user must press a button or request to access the information from the system while in active type the system itself deal with data and process information (71). Active systems generate alerts to inform clinicians about the actions needed to apply or actions must be avoided. However, excessive alerts have become a big challenge in this field.

2.4.1.3. Communication method

In these systems, CDSS become an advisor, first asks questions about the diagnosis and then determine the medication and right dose or let the user determine the dose in the system and then generates alerts if the given dose is wrong (72).

2.4.1.4. User Interface

With the help of processing power, electronic health record (EHR) integration and computer portability the CDSSs are now fast, easy to access and use. User Interface is still a good method to classify CDSS describing EHR integration or overlay, keyboard or audio interaction and advice using of pop-up screens, audio signals or text.

2.4.1.5. Decision making scheme within the system

These models include problem-specific flowcharts designed for computer programs use which are the simplest model. More complex models are Bayesian models (73,74), artificial neural networks (75), support vector machines (SVM) (76) and artificial intelligence (77). These models help calculate and predict the disease, choose the best treatment and interventions.

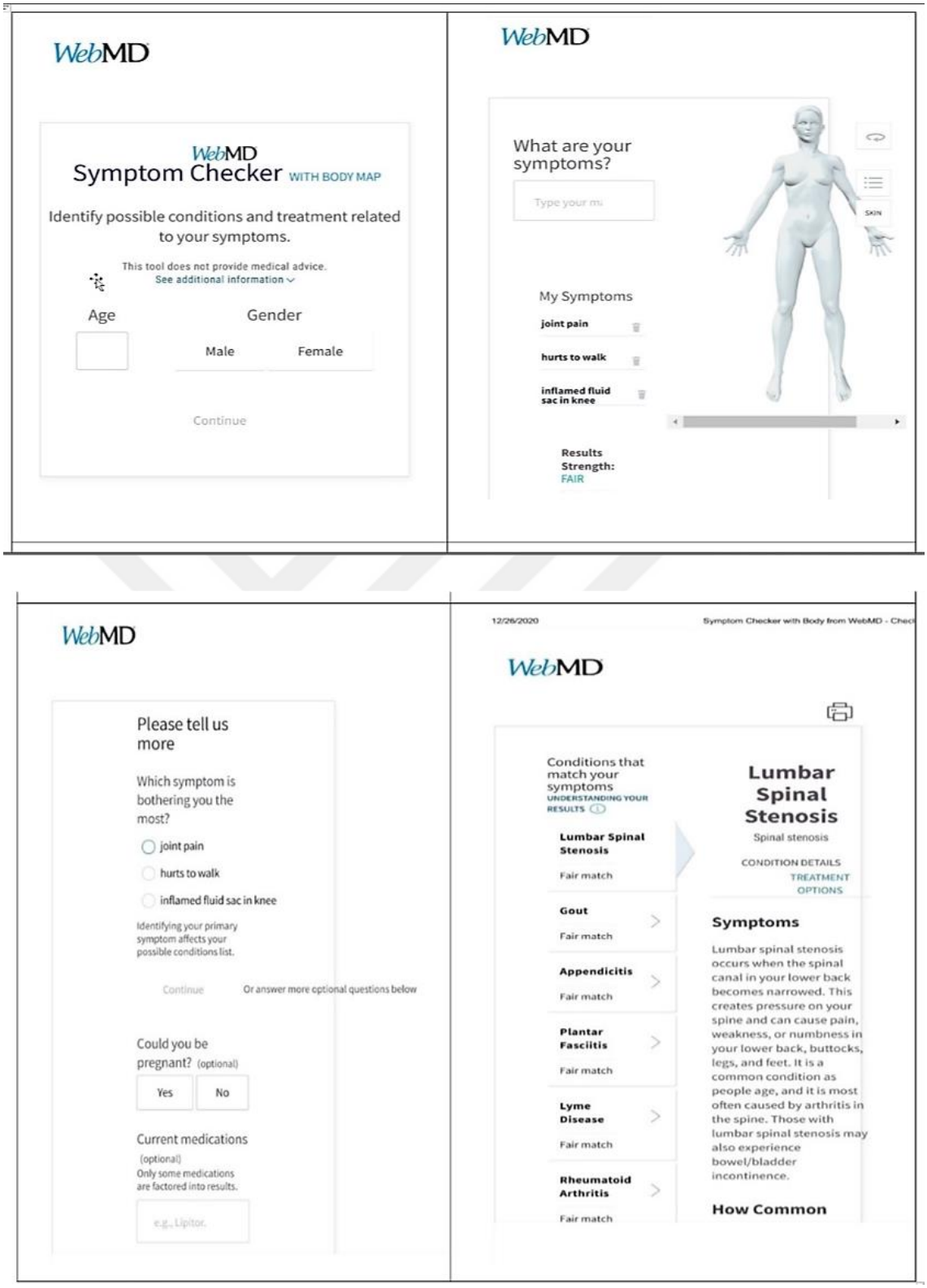

Figure 2-6: WebMD symptom checker

This tool identifies possible conditions and treatment according to the available symptoms. In this website, first the age and gender is requested in the boxes. Then, the location of ache or disease involvement in the body should be identified. When the processes are done, system asks about symptoms, person's current health condition and drug treatments. Finally, it provides possible diagnosis of the disease and suggests treatment options.

2.4.2. Advantages of CDSS

We are facing with vast amount of clinical data including EHR, disease entries, patient surveys and exchange of already available datasets, which are accumulating quickly. However, improving patient care is not necessarily guaranteed by digitalization alone. For example, various research show that although computerized physician order entry (CPOE) systems have reduced some errors, they also have generated novel errors instead (78,79,80). Therefore, a precise clinical decision support is needed for utilizing EHR and CPOE. At the present, healthcare practitioners do not have the knowledge to whether a patient's data is available in the EHR or face challenges like how to obtain data from the patients and not having enough time to analyze the datasets. However, CDSS is capable of addressing above issues (72). In addition, the system can record and consider subtle changes in a patient's condition at all stages and analyze data in regard to that changes. The final aim of CDSS is to assist doctors in difficult and challenging medical situations and diagnosis of various diseases (68).

2.4.3. Real-life instances and relative research of clinical decision support system

Since CDSS can stimulate human thinking, there are many clinical support systems which have been built for various diseases for the purpose of decision support. These systems have been used for Dental education (81), Ventilator treatment (82), Cancer Diagnosis (83), Cancer Treatment (84), Diagnosis of heart diseases (85) and Heart Failure (86), Diagnosis of neuromuscular disorders (87) Respiratory pattern analysis (88) and many more. One good example applied in the field of CDSS, is named DXplain. This system was built in Massachusetts General Hospital for the purpose of diagnosis in general medicine. DXplain uses laboratory results, clinical findings and symptoms as input, and could help physician to make decisions (89). Also, the system recommends further tests analysis and explains every differential diagnosis detail by detail. Therefore, it could be utilized in several hospitals for the purpose of clinical education of medical students and medical consultation (90). Another reliable CDSS is HEPAXPERT-III: It is a knowledge-based CDSS developed as a successor to HEPAXPERT I and II. HEPAXPERT-III can interpret the serologic tests for Hepatitis A, B, C and D viruses. It automatically connects to the hospital laboratory information system and generates interpretive reports on serologic findings such as analysis of probable viral infection , immunity, stage of illness, treatment, and virality rate (91).

2.5. Data mining and its advantages

Nowadays, many hospitals are well equipped with a health care information system which can provide and save information of all patients. These systems usually are capable of performing simple statistical analysis. For instance, they can address questions like “What is the average age of patients who have heart disease?” , “How many surgeries had resulted in hospital stays longer than 10 days?”, “Identify the female patients who are single, above 30 years old, and who have been treated for cancer” (92). However, these kinds of analysis are not satisfactory since valuable knowledge is waiting to be found in the vast amount of data in these systems. These systems should be able to infer patients’ information and answer advanced questions like “Given patient records, predict the probability of patients getting a heart disease.” (92). “Data mining is a very useful technique in this field. It is the nontrivial process of identifying valid, novel, potentially useful and ultimately understandable pattern in data with the wide use of databases and the explosive growth in their sizes. Data mining refers to extracting or mining knowledge from large amounts of data. Data mining is the search for the relationships and global patterns that exist in large databases but are hidden among large amounts of data” (92). There are various types of algorithms that create models in data mining. Commonly utilized approaches include Neural Networks, Fuzzy Logic, Decision Trees, Bayesian Classifiers, Support Vector Machines, Genetic Algorithms and Hybrid System (93).

2.5.1. Bayes’ theorem

Bayes’ theorem has been named after Thomas Bayes J (1702-1761). This simple formula determines all modern artificial intelligence (AI) systems for probabilistic inference (94). In this formula, a conditional probability is calculated in which the probability of an event occurring given the probability of another event that has happened beforehand. If B stands for the dependent event and A is the outcome that has already occurred, Bayes' theorem is expressed below (94):

$$\text{Prob}(B|A)=(\text{Prob}(A|B))/(\text{Prob}(A)) \qquad (2\text{-}1)$$

2.5.1.1. Applying Bayes’ theorem

This rule has become very useful in practice especially in the field of medical diagnosis. It helps to obtain the unknown probabilities from other known probabilities. In order to explain Bayes’ theorem, Russel et al. (94), describes it as follows:

"For example, A doctor knows that the disease meningitis causes the patient to have a stiff neck, 50% of the time. The doctor also knows some unconditional facts: the probability of a patient having meningitis is 1/50,000, and the probability of any patient having a stiff neck is 1/20.

Letting S be the proposition that the patient has a stiff neck and M be the proposition that the patient has meningitis, we have

$P(S|M) = 0.5$

$P(M) = 1/50000$

$P(S) = 1/20$

$P(M|S) = P(S|M)P(M) / P(S) = 0.5 \times 1/50000 / 1/20 = 0.0002$

Therefore, the probability of patients with a stiff neck who have meningitis is 2 in 1000" (94).

2.5.2. Naïve Bayes' classifier (NBC)

NBC is a data mining technique for classification with basis of the Bayes' theorem. By giving a set of input data, the algorithm creates models that predict the posterior probability of each class. This classifier, has two assumptions: All the attributes and features are independent from each other and the importance of the attributes is equal. These assumptions make the computation easier and because of that it is called Naïve (95). NBC has been a reliable technique offering high accuracy among other machine learning techniques (96).

3. MATERIAL AND METHOD

3.1. Data derivation

The optimum method to provide data is to extract them from relevant literature review, expert opinion and data gathered from real patients. However, regarding the restrictions of the Covid-19, we were unable to obtain data from 2 former sources and only data from the literature was extracted. PubMed and National Center for Biotechnology Information's (NCBI) National Library of Medicine (NLM) catalog were utilized to search the following keywords: "Behcet's disease review", "Behcet's disease symptoms", "Behcet's disease clinical findings", "prevalence of Behcet's symptoms and vasculitis". The years literature searched were between 2000 and 2021. Extracted data includes all the manifestations of BD patients according to its criteria and in the form of prevalence.

3.2. A multi- dimensional stochastic-model to predict Behcet's disease

The model that will be axplained has been adapted from Yarman et al. (97). According to the mathematical-modelling point of view, a specific disease, like "A", may be related with a random variable X or equally a random set X. For instance, if X is the set of the members which have the disease "A" for sure, then we can find the probability P(X) of a person to be a member of that set (95,98,99). Disease "A" could be described as the combination of some physical symptoms designated by { A1, A2, … , AN} where the integer N designates the total number of symptoms, which build up the disease "A".

Random variables { X1, X2, … , XN} may be considered as the mutually exclusive sets, which are related with the physical symptoms { A1, A2, … , AN}, respectively. More clearly, Xk could be a set made up with the members who owns the symptom "Ak ". At this point, we can compute the conditional probability P(X|Xk) for a person having the disease "A" while possessing the symptom "Ak ".

Conditional probabilities P(X|Xk) are essential factors to evaluate the probability P(X) for a case who has the disease "A". In order to assess conditional probabilities, we may choose a sample set XS that has total number of NS members who for sure own the disease "A". Then, we form a training set XT from the sample set XS as follows:

According to Figure 3-1 (97), let each independent set {XT ∩ Xk ; k = 1,2, . . , N} is formed on the patients of XS, who surely possess the disease "A" with symptom

Ak with total number of nk patients. In this case, total number of members of the training set XT is given by

$$N_T = \sum_{k=1}^{N} n_k \qquad (3\text{-}1)$$

In this regard, the training set XT is constructed on the union of the intersection-sets XT ∩ Xk such that

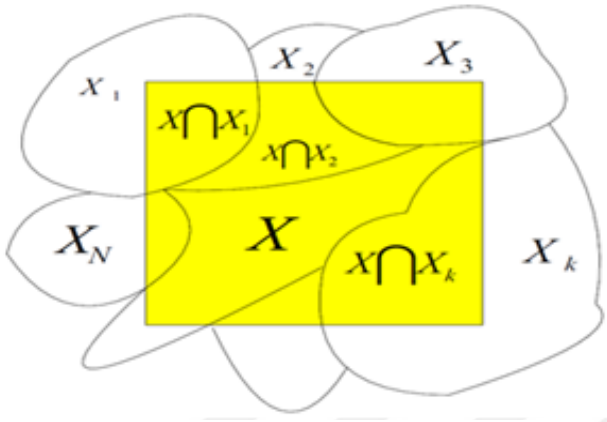

Figure 3-1: Event X = (X ∩ X1) ∪. . .∪ (X ∩XN)

The random set X may be described by means of mutually exclusive random sets {x1,x2,…,xn} (97).

In regard with the above foundation, the probability of having the disease "A" for each member of XT is unity (i.e. P(X) = 1). In addition, for each member of Xk probability of P(Xk) = 1, because all the members of Xk have the symptom Ak. Now, conditional probability P(X|Xk) may be approximated utilizing the frequency count fk = nk/NT such that

$$P(X|Xk) = P(X \cap Xk)/\ P(Xk) = \lim NT \to \infty\ nk\ /NT \cong nk\ /NT = fk \qquad (3\text{-}3)$$

In this regard, by analyzing clinical datasets of BD cases, and by employing a multi-dimensional stochastic linear model, it is possible to compute the probability of having the disease. Patients who have BD, are considered as the members of an event set X. Here, the random set X may be defined with mutually exclusive random sets {X1, X2, … , XN} as shown in Table 3-1 (97).

Table 3-1: Constructing XT with total number Nk members

$XT \cap X1$ $n1$	$XT \cap X2$ $n2$	$XT \cap X3$ $n3$	…
…	…	…	$XT \cap XN$ nN

In figure 3-1, event-set X is constructed with N- mutually exclusive sets Xk such that

$$X = (X \cap X1) \cup (X \cap X2) \cup \dots \cup (X \cap XN) \quad (3\text{-}4)$$

In this case, probability of having the event X is given by

$$P(X) = P(X \cap X1) + P(X \cap X2) + \cdots + P(X \cap XN) = \sum_{k=1}^{N} P(X \cap XK) \quad (3\text{-}5)$$

Also, while event Xk occurs, conditional probability of having event X is given by

$$P(X|Xk) = \frac{P(X \cap Xk)}{P(Xk)} \quad (3\text{-}6)$$

Therefore,

$$P(X \cap X_K) = P(X \mid X_k) \cdot P(X_k) \quad (3\text{-}7)$$

In this point, we designate the conditional probability P(X|Xk) by wk

Then,

$$P(X) = \sum_{k=1}^{N} wk\ P(Xk) \quad (3\text{-}8)$$

When event X occurs; P(X) must be equal to one, which in turn makes all P(Xk) equal to one. Therefore, , $\sum_{k=1}^{N} Wk$ must add-up to one. Therefore,

$$W_{sum} = \sum_{k=1}^{N} Wk = 1 \quad (3\text{-}9)$$

According to the article which described the above formula, “the above equation can be expressed as a theorem” (97).

3.2.1. Theorem on Conditional Probabilities

If an event X is constructed with N-mutually exclusive complete-events X1, X2, … , XN as shown in Figure 3-1, then the sum of conditional probabilities wk = P(X|Xk) must be equal to one such that

$$\sum_{k=1}^{N} Wk=1 \quad (3\text{-}10)$$

3.2.2. Utility Score or Probability of Occurrence

Let y = P(X). Let Xk = P(Xk). Then, we say that y is the utility score of the random event X, which describes the probability of occurrence for event X.

3.2.3. Outcome of a Stationary Linear Stochastic System

The random variable y is called the outcome of a stationary Linear Stochastic System (LSS) which is described by

$$y= \sum_{k=1}^{N} Wk.Xk \quad (3\text{-}11)$$

3.2.4. Inputs and the Output of LSS

In LSS, xk is called the independent random input variables, whereas y is called the random output variable of LSS.

3.2.5. Parameters of LSS

In LSS, wks are called the system parameters. They are predicted on the occurred event X by using the conditional probabilities wk = P(X|X).

In fact, if the set X = (X ∩ X1) ∪ (X ∩ X2) ∪ … ∪ (X ∩ XN) is complete, the system parameters wk specifically determine the probability of occurrence for the random event X.

3.2.6. Weight Coefficients (w_k)

By equation (3-11), the outcome y = P(X) is the weighted sum of the random inputs Xks. By considering that, the system parameters wks of LSS are also called weight coefficients which perform on the random-input variables Xks.

With regards to the above bases and descriptions, we can now recommend a mathematical modeling for predicting the Behcet's disease.

3.3. Applying LSS Model for BD

BD could be defined with LSS as shown in Figure 3-2 (97). The wks are the system parameters that performs on inputs wks with employing equation $y=\sum_{k=1}^{N} Wk.Xk$ (3-11). And they will be predicted by calculating a training set XT as

$$P(X|Xk) = P(X \cap Xk)/ P(Xk) = \lim_{NT\to\infty} nk/NT \cong nk/NT = fk \quad (3\text{-}3)$$

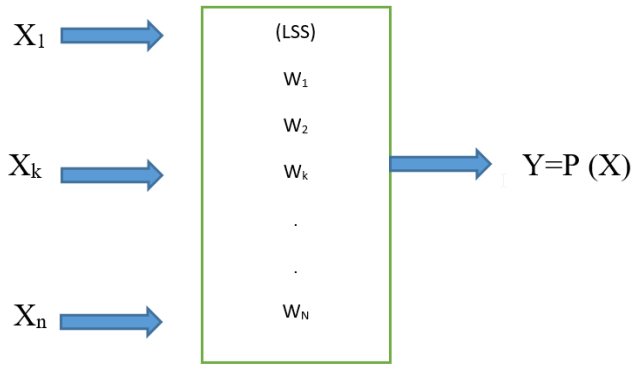

Figure 3-2: LSS for BD

In order to utilize this model, the symptoms of BD are considered mutually exclusive attributes, that have been observed in BD cases. Mentioned symptoms were fully explained in Table 2-4. For example, the first symptom we mentioned was recurrent oral ulceration and it could be related with a random event set X1 which was formed by members which share that particular attribute (i.e. A1) and so on. Some symptoms can be listed as below:

Recurrent oral ulceration (attribute A1→X1)

Recurrent genital ulceration (attribute A2→X2)

Inflammatory eye disease (attribute A3→X3)

Behcet's disease includes 13 symptoms with pertinent frequencies. LSS parameters can be measured by forming a sample set XS comprised of NS=100 cases that have distinct attributes definitivly. For example, the frequency in attribute A1 or recurrent oral ulcer is 98%, which means that out of 100 people, 98 person possess this symptom. Or 80 out of 100 people have recurrent genital ulceration attribute. The complete list of symptoms and their associated frequencies (nk) of the sets ($XT \cap Xk$) are listed in Table 3-2, in which, the training set XT is designated as the total number of NT which equals to 1. By considering the parameters {wk; k=1,2,…,13} calculated in Table 3-2, a test of diagnosis for Behcet's disease can be applied through employing a utility function described by equation 3-10 such as follows:

$$P(X)= \sum_{K=1}^{N} Wk.P(Xk) \qquad (3\text{-}12)$$

In this point, P(Xk) is associated with attribute Ak. Therefore, if a person possess the attribute or symptom Ak, then P(Xk)=1 and if the person does not possess the attribute, then P(Xk)=0.

Table 3-2: Event set and predicted wk

Event Sets	**Descriptions $Ak \rightarrow Xk$ (symptoms)**	**members (nk) in the sample set XS with attribute Ak**	**Weight Coefficients wk=P(X|Xk)=nk/NT**
$X \cap X_1$	Recurrent oral ulceration	98	0.168
$X \cap X_2$	Recurrent genital ulceration	80	0.137
$X \cap X_3$	Inflammatory eye disease including uveitis ± hypopyon and retinal vasculitis	50	0.085
$X \cap X_4$	Skin lesions	80	0.137
$X \cap X_5$	Erythema nodosum	47	0.080
$X \cap X_6$	Folliculitis/acneiform lesions	51	0.087
$X \cap X_7$	Hyperirritability – Pathergy	60	0.103
$X \cap X_8$	Arthritis (arthralgia)	45	0.077
$X \cap X_9$	Vasculitis including large vessel vasculitis, aneurysm formation and arterial/venous thrombosis	16	0.027
$X \cap X_{10}$	Gastrointestinal lesions	12	0.020
$X \cap X_{11}$	Neurological lesions	15	0.025
$X \cap X_{12}$	Epididymitis	8	0.013
$X \cap X_{13}$	Family history	20	0.034
NT=Total number of BD cases in the Set XT		Nt= 582	Sum=1

3.4. Setting a threshold

We set our threshold for 50%, which signifies the presence of BD in the case. If yielded result is above the threshold, BD is detected in the patient. Otherwise, BD does not exist in the person.

3.5. Web programming

Web programming is the final step of constructing the clinical decision support system. This program is constructed to help run the self test by family practitioners and medical doctors, which propels them to the early detection of BD. In this point, more recent data from suspected patients is entered and the system processes these data according to aforementioned model we have created. Finally, the output of the system will be dealing with prediction of possessing the disease and making decision about the patient. The program has been written in MATLAB environment and developed according to the algorithm in Figure 3-3.

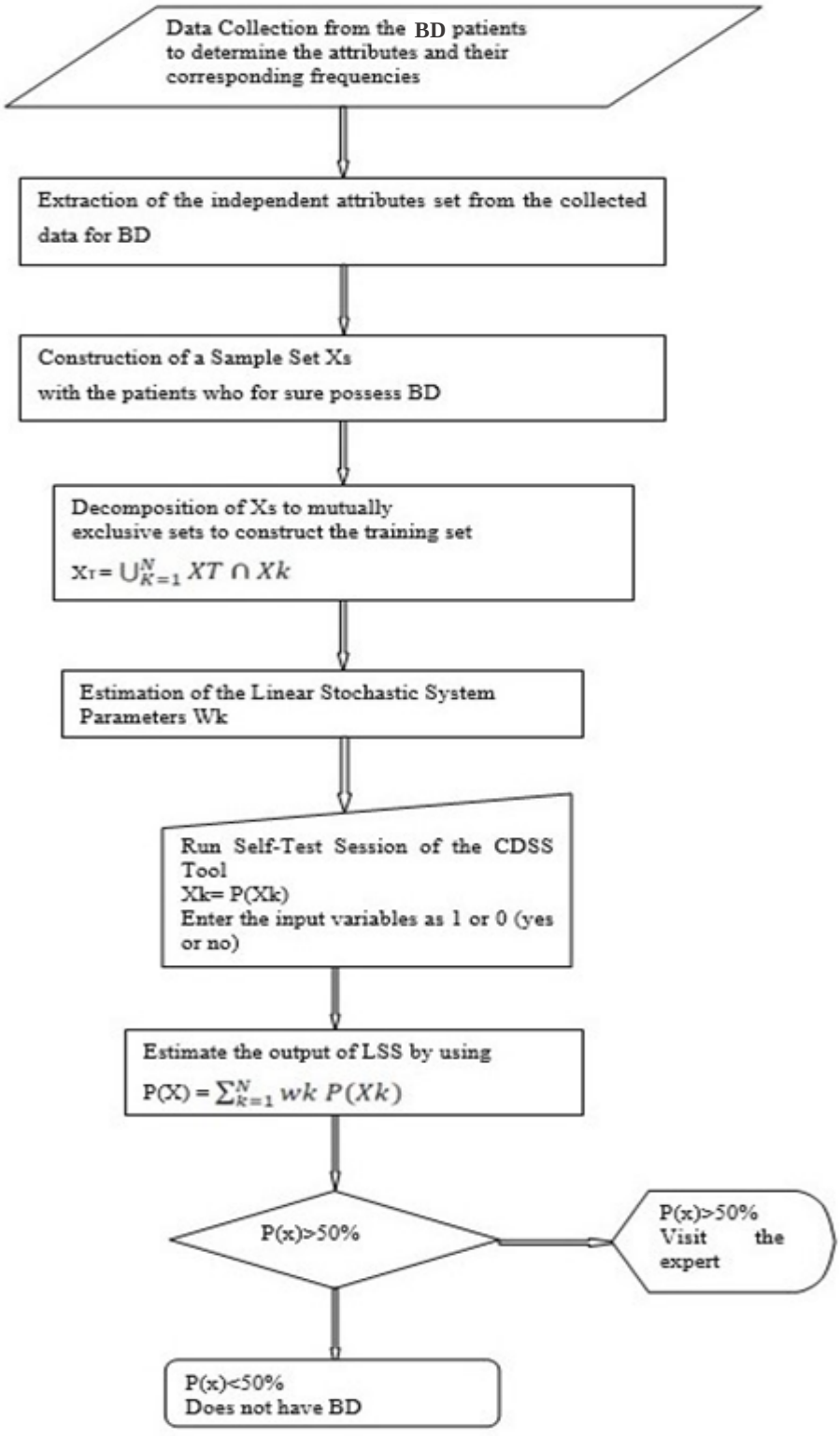

Figure 3-3: The algorithm of test

Work flow of developing a CDSS for BD disease. If the output shows results above 50%, the patient should visit the expert. (adapted from Yarman et al.)(97).

3.5.1. Steps in MAT LAB

In the first step, we loaded the real row data in MATLAB program. Real row data is the frequencies of different symptoms of Behcet's disease:

load 'real_row_data'

Second step is to normalize the row data. Normalization is one of the preprocessing techniques in data mining which turn all data in a specific range of numeric scale like a range between 0 and 1 (100).

([C_N, xmax] = BEH_Normalization(real_row_data)

Next step is finding the weight of each variable or symptom in our data

[W_Ln] = BEH_Augmented_Weight_Matrix(Xmn)

Then, we input new data which belongs to a suspicious person , to find out about the probability of having the Behcet's disease.

load 'inputs'

After normalizing the new data, with the help of if/else statements, system can make decision about the person's condition.

if any(X_wLn2 > limit)

disp('Behcet's disease symptoms have been detected in the patient. Please Visit an Expert!')

max_value=max(X_wLn2);

disp('Frequency of the disease :%'),disp(max_value*100)

else

disp('This case does not have Behcet's disease.')

Steps of operation in MATLAB is depicted in Figures 3-4, 3-5, 3-6 and 3-7.

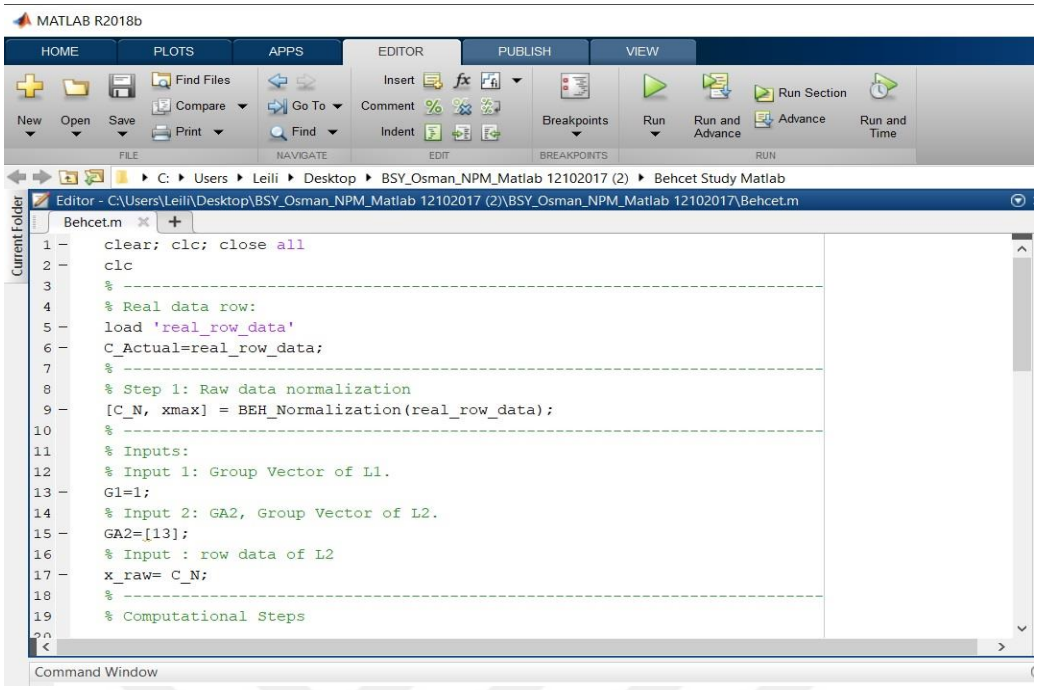

Figure 3-4: Operations in MATLAB step 1

In this step real row data is loaded

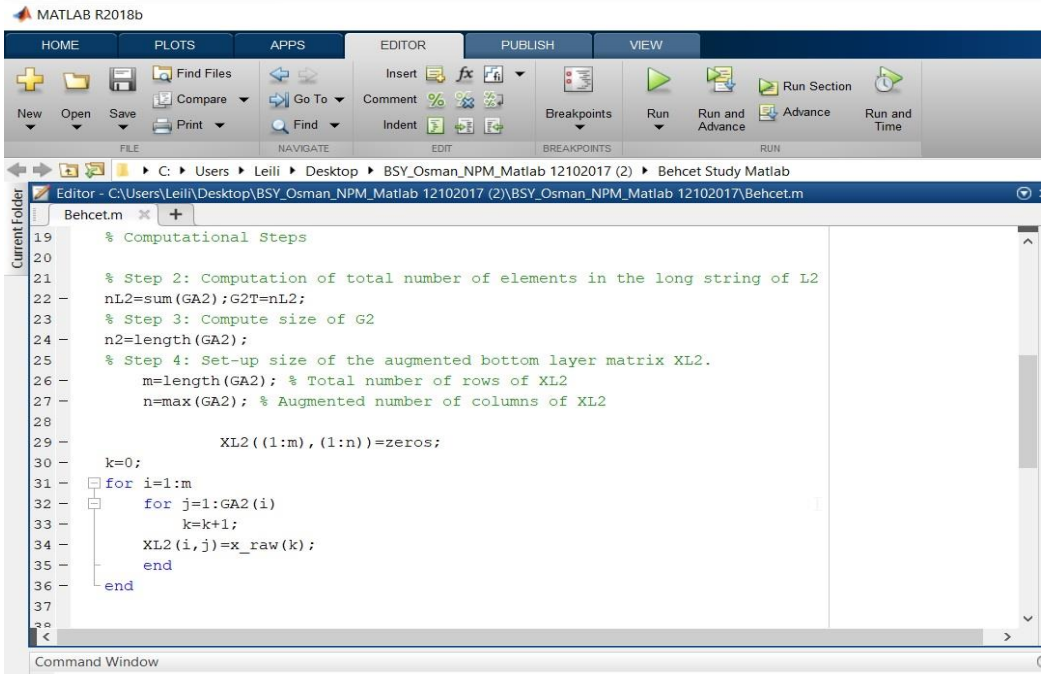

Figure 3-5: Operations in MATLAB step 2

In this section computional steps are performed.

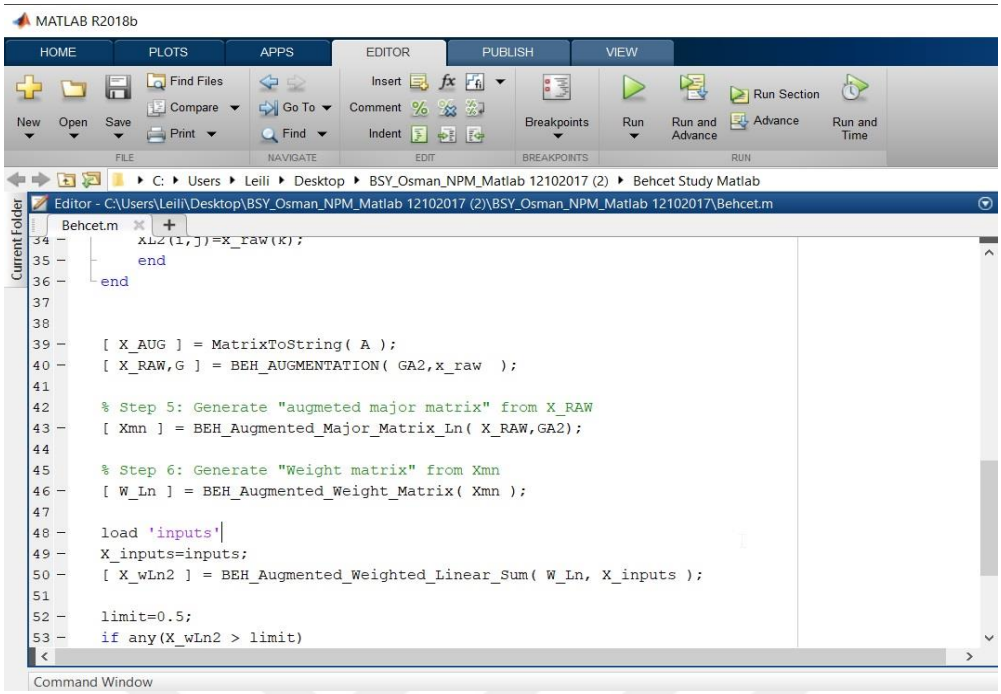

Figure 3-6: Operations in MATLAB step 3

weight of each variable is calculated and threshold is set.

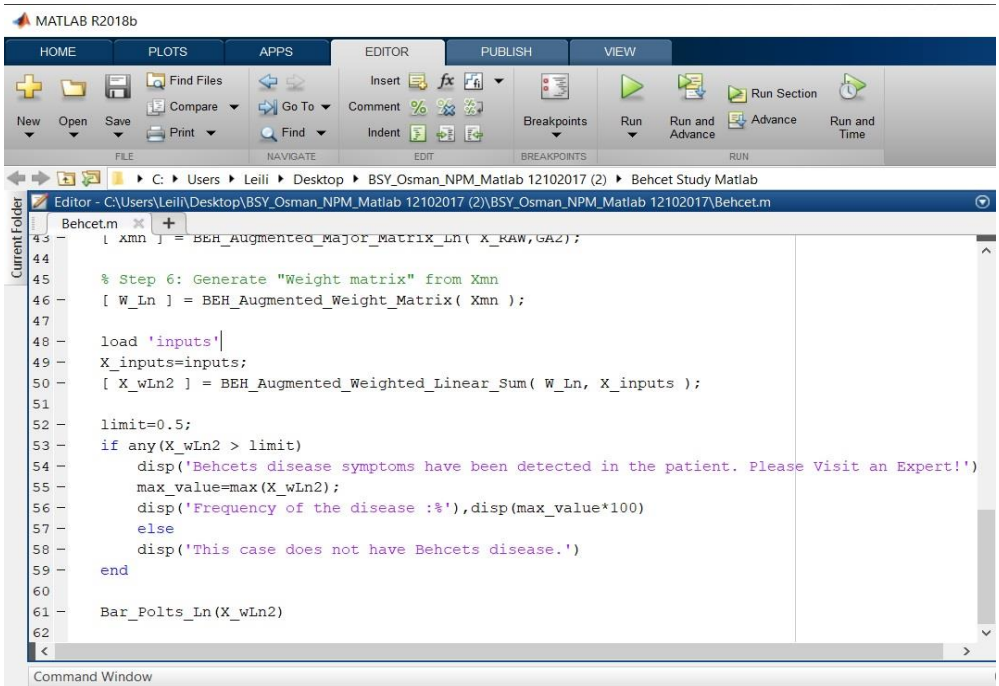

Figure 3-7: Operations in MATLAB step 4

By loading a patient's symtoms as input, system can make decision about the patient's condition.

3.6. Evaluation of the model

We performed 4 different case evaluations to test our developed model. In this regard, two case reports of BD and two case reports from diseases other than BD, which have similar manifestions to BD were selected. For cases number 1 and 2, PubMed was used to search the literature entering these key terms: “Behcet’s disease clinical findings”, “Behcet’s disease case report” and the years of publications were selected from 2000 to 2021. Selected cases included all physical signs and symptoms of BD reported in the literature (101,102).

For the case report number 3 research gate was used to derive data from the literature. The research key words was “acute sever ulcerative colitis case report” and reports published between 2000 and 2021 were scanned. Among these, the one chosen for case report number 3 was picked, because the patient’s disease is named acute sever ulcerative colitis, which belongs to the inflammatory bowel disease and its symptoms are similar to BD manifestations (103). Both disorders have non-specific gastrointestinal manifestations and similar extra intestinal involvements (16). In this case report, a male patient at the age of 44 visited a healthcare facility. Some of his symptoms were diarrhea with blood, arthralgia in large joints (elbow and knee), skin rash and some extra intestinal involvement such as erythematous nodular lesions in the lower limbs (103). According to these manifestations, there is similarity between patient’s symptoms and BD symptoms, therefore, by using these common symptoms, we tried to check our model and test whether it is able to rule out the disease from BD or not.

Data of case report 4 was gathered by using PubMed and the key words used to search for the reports were “sweet syndrome case report", and years were selected between 2000 to 2021. The disorder is called sweet syndrome (Gomm-Button) and has common symptoms with BD. It is an acute dermatologic disorder and afflicted patients manifest tender plaques or nodules, fever, arthralgia, eye manifestations, headaches, and in few cases, oral or genital lesions (104). In this case report, one male patient of the age 51 had been refered to an otolaryngologist with pain in his tongue and throat. Some of the symptoms of this case were overlapped with BD symptoms. Aphthous ulcerations in oral and oropharyngea region, and raised inflammatory lesion on tongue were diagnosed during examination. The patient also suffered from swollen ankle, hand, and wrist.

Erythematous papules and macules were present on his face, neck, and extremities (104). We put the patient’s manifestions in our model and checked its detectibility.

4. RESULTS

4.1. Case study 1

Table 4-1 depicts a person's symptoms or attributes, the weight coefficient and utility function. In this table, a person's BD symptoms has been gathered and listed as below. According to the research, the case has BDs for sure (101). Therefore, we can evaluate our model with the prior knowledge. Our algorithm also confirmed the case as having BD (Table 4-1).

Table 4-1: Result of diagnosis test for case study 1

Attributes	**Event Sets**	**Descriptions $Ak \rightarrow Xk$**	**Weight Coefficients wk=P(X|Xk)=nk/NT**	**P(X)**	**$W_k.P(X_k)$**
A_1	$X \cap X_1$	Recurrent oral ulceration	0.168	1	0.168
A_2	$X \cap X_2$	Recurrent genital ulceration	0.137	1	0.137
A_3	$X \cap X_3$	Inflammatory eye disease	0.085	1	0.085
A_4	$X \cap X_4$	Skin lesions	0.137	1	0.137
A_5	$X \cap X_5$	Erythema nodosum	0.080	1	0.080
A_6	$X \cap X_6$	Folliculitis/acneiform lesions	0.087	0	0
A_7	$X \cap X_7$	Hyperirritability − Pathergy	0.103	0	0
A_8	$X \cap X_8$	Arthritis (arthralgia)	0.077	0	0
A_9	$X \cap X_9$	Vasculitis	0.027	0	0
A_{10}	$X \cap X_{10}$	Gastrointestinal lesions	0.020	0	0
A_{11}	$X \cap X_{11}$	Neurological lesions	0.025	0	0
A_{12}	$X \cap X_{12}$	Epididymitis	0.013	0	0
A_{13}	$X \cap X_{13}$	Family history	0.034	0	0
	Result of the test		Sum=1		0.607

4.2. Case study 2

Another case report was studied that was diagnosed with BD (102). The patient's symptoms are presented in Table 4-2.

Table 4-2: Result of diagnosis test for case study 2

Attributes	**Event Sets**	**Descriptions $Ak \rightarrow Xk$**	**Weight Coefficients wk=P(X|Xk)=nk/NT**	**P(X)**	**$W_k.P(X_k)$**
A_1	$X \cap X_1$	Recurrent oral ulceration	0.168	1	0.168
A_2	$X \cap X_2$	Recurrent genital ulceration	0.137	1	0.137
A_3	$X \cap X_3$	Inflammatory eye disease	0.085	1	0.085
A_4	$X \cap X_4$	Skin lesions	0.137	1	0.137
A_5	$X \cap X_5$	Erythema nodosum	0.080	0	0
A_6	$X \cap X_6$	Folliculitis/acneiform lesions	0.087	0	0
A_7	$X \cap X_7$	Hyperirritability – Pathergy	0.103	1	0.103
A_8	$X \cap X_8$	Arthritis (arthralgia)	0.077	1	0.077
A_9	$X \cap X_9$	Vasculitis	0.027	1	0.027
A_{10}	$X \cap X_{10}$	Gastrointestinal lesions	0.020	0	0
A_{11}	$X \cap X_{11}$	Neurological lesions	0.025	0	0
A_{12}	$X \cap X_{12}$	Epididymitis	0.013	0	0
A_{13}	$X \cap X_{13}$	Family history	0.034	0	0
	Result of the test		Sum=1		0.737

This person has 74% chance of having the Behcet's disease. And the yielded percentage is above the threshold, therefore, he is highly recommended to visit an expert immediately.

4.3. Case study 3

Here, a case report from a different study rather than BD is selected. Symptoms of this case is similar to BD (103). We put the attributes of the case study in our model and tested how it predicted the disease (Table 4-3).

Table 4-3: Result of diagnosis test for case study 3

Attributes	**Event Sets**	**Descriptions $Ak \rightarrow Xk$**	**Weight Coefficients wk=P(X|Xk)=nk/NT**	**P(X)**	**$W_k.P(X_k)$**
A_1	$X \cap X_1$	Recurrent oral ulceration	0.168	0	0
A_2	$X \cap X_2$	Recurrent genital ulceration	0.137	0	0
A_3	$X \cap X_3$	Inflammatory eye disease	0.085	0	0
A_4	$X \cap X_4$	Skin lesions	0.137	1	0.137
A_5	$X \cap X_5$	Erythema nodosum	0.080	1	0.080
A_6	$X \cap X_6$	Folliculitis/acneiform lesions	0.087	0	0
A_7	$X \cap X_7$	Hyperirritability – Pathergy	0.103	0	0
A_8	$X \cap X_8$	Arthritis (arthralgia)	0.077	1	0.077
A_9	$X \cap X_9$	Vasculitis	0.027	0	0
A_{10}	$X \cap X_{10}$	Gastrointestinal lesions	0.020	1	0.020
A_{11}	$X \cap X_{11}$	Neurological lesions	0.025	0	0
A_{12}	$X \cap X_{12}$	Epididymitis	0.013	0	0
A_{13}	$X \cap X_{13}$	Family history	0.034	0	0
	Result of the test		Sum=1		0.314

As the result shows, the output of the model is 0.314 which is under the threshold. Also we can conclude that although the symptoms were similar to Behcet's, the model could differentiate it from BD.

4.4. Case study 4

This case is also reported from a study with a disease other than BD (104). Yielded result shows 0.382 which is under the threshold. In this case also, our model could predict the diagnosis properly (Table 4-4).

Table 4-4: Result of diagnosis test for case study 4

Attributes	**Event Sets**	**Descriptions for the attributes $Ak \rightarrow Xk$**	**Weight Coefficients wk=P(X|Xk)=nk/NT**	**P(X)**	**$W_k.P(X_k)$**
A_1	$X \cap X_1$	Recurrent oral ulceration	0.168	1	0.168
A_2	$X \cap X_2$	Recurrent genital ulceration	0.137	0	0
A_3	$X \cap X_3$	Inflammatory eye disease	0.085	0	0
A_4	$X \cap X_4$	Skin lesions	0.137	1	0.137
A_5	$X \cap X_5$	Erythema nodosum	0.080	0	0
A_6	$X \cap X_6$	Folliculitis/acneiform lesions	0.087	0	0
A_7	$X \cap X_7$	Hyperirritability – Pathergy	0.103	0	0
A_8	$X \cap X_8$	Arthritis (arthralgia)	0.077	1	0.077
A_9	$X \cap X_9$	Vasculitis	0.027	0	0
A_{10}	$X \cap X_{10}$	Gastrointestinal lesions	0.020		0.020
A_{11}	$X \cap X_{11}$	Neurological lesions	0.025	0	0
A_{12}	$X \cap X_{12}$	Epididymitis	0.013	0	0
A_{13}	$X \cap X_{13}$	Family history	0.034	0	0
	Result		Sum=1		0.382

Operations of predicting Behcet's disease and making decision about them in MATLAB program for 4 case studies are presented below in Figures 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7 and 4-8.

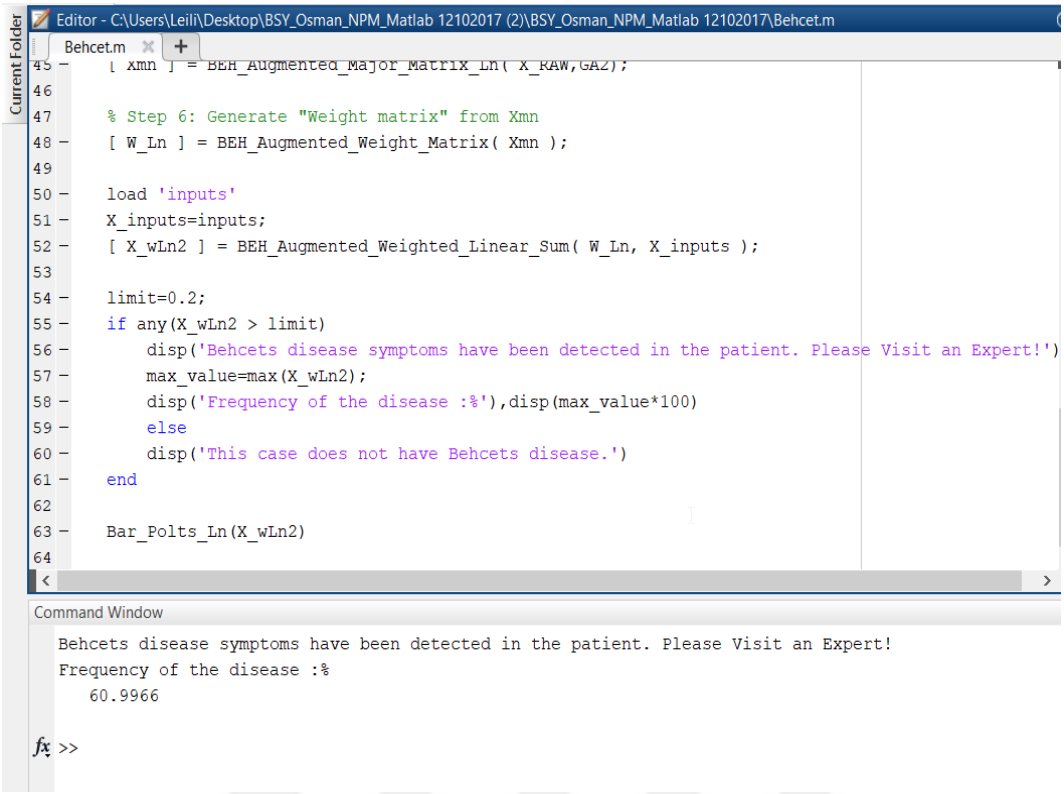

Figure 4-1: Prediction of BD in case study 1

The test result predicts BD with the probability of 61, and it suggests the user to visit an expert.

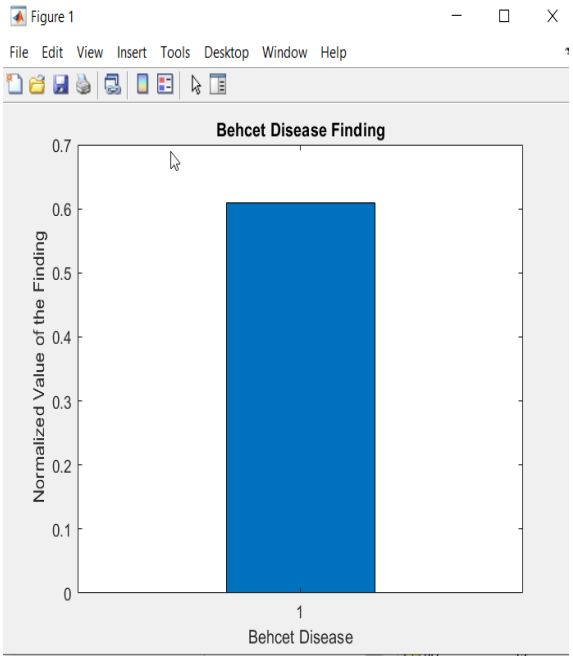

Figure 4-2: bar plot for case 1

The bar plot depicts frequency of finding Behcet's in the case study 1 (60.99%).

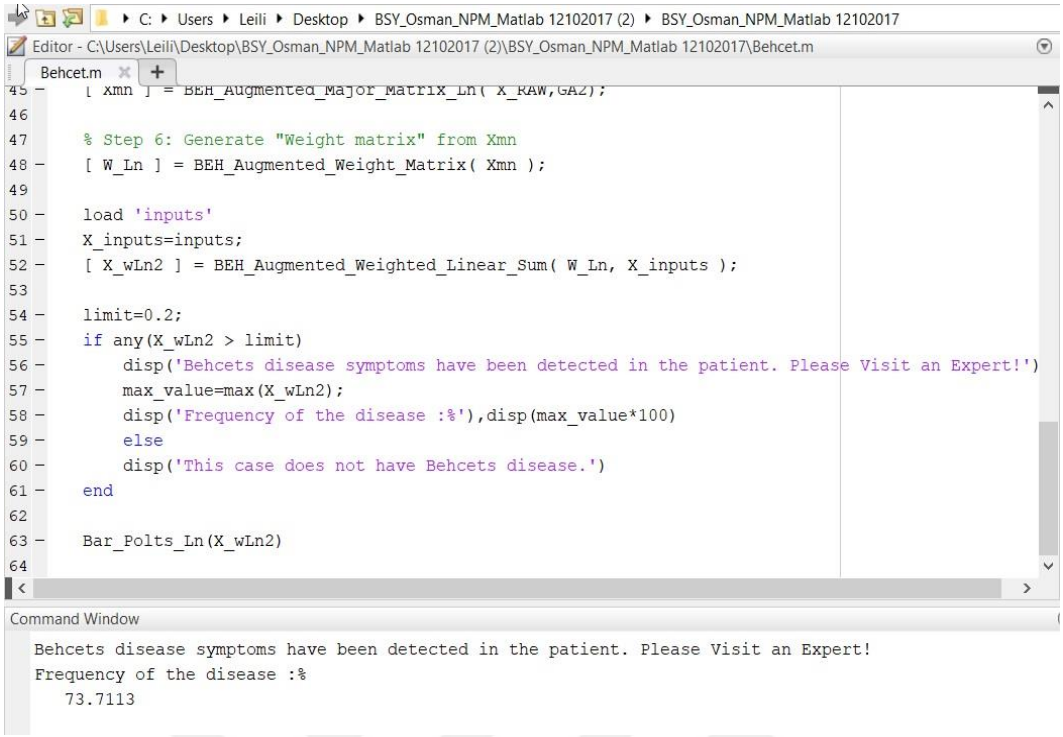

Figure 4-3: Prediction of BD in case study 2

The test result predicts BD with probability of 74%, and it suggests the user to visit an expert

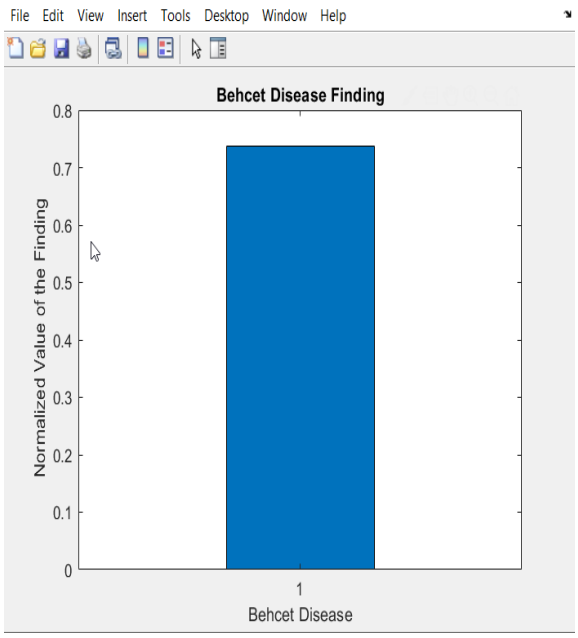

Figure 4-4: Bar plot for case 2

The bar plot depicts frequency of finding Behcet's in the case study 2 (73.71%).

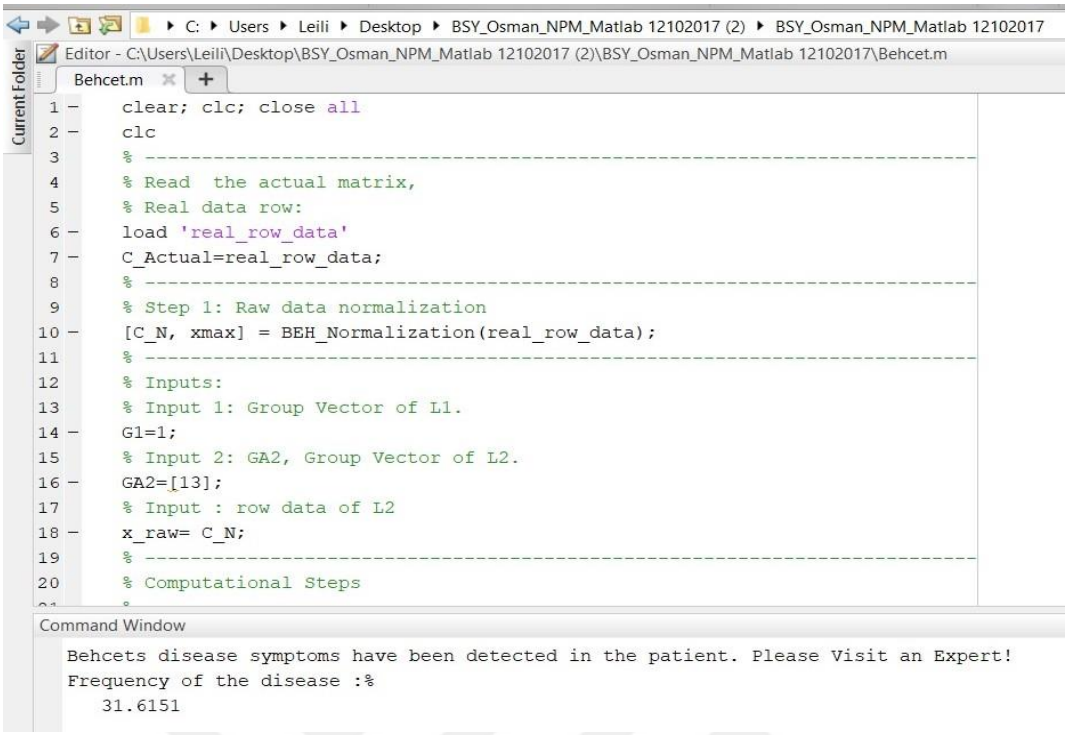

Figure 4-5: Prediction of BD in case study 3

The system predicted possessing BD as 32 percent and suggests that there is no need to visit the expert. Since case study does not have BD, our model predicted accurately

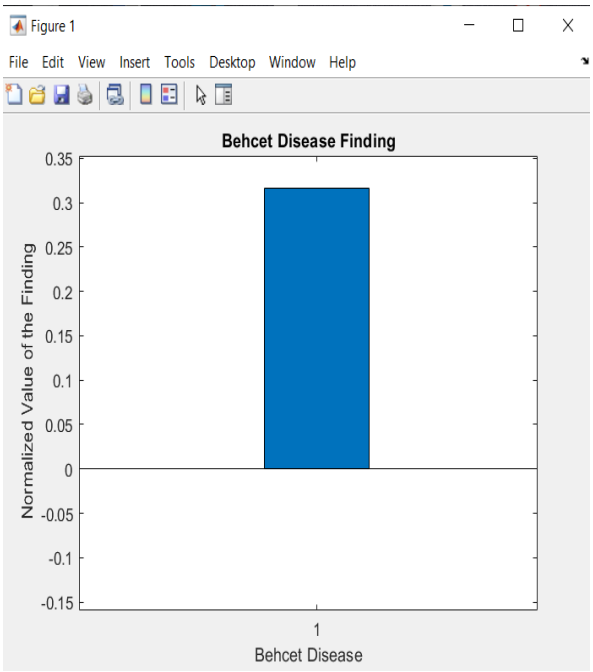

Figure 4-6: Bar plot for case 3

The bar plot depicts frequency of finding Behcet's in the case study 3 (31.61%).

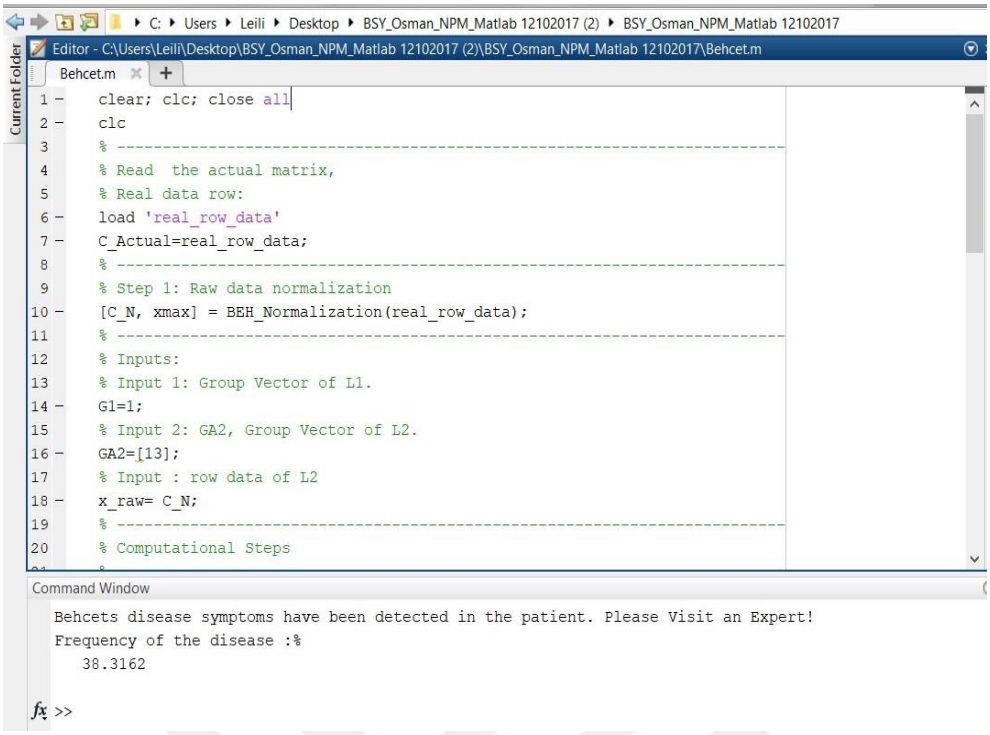

Figure 4-7: Prediction of BD in case study 4

The system predicted possessing BD as 38 percent and suggests that there is no need to visit the expert. Since case study does not have BD, our model predicted accurately.

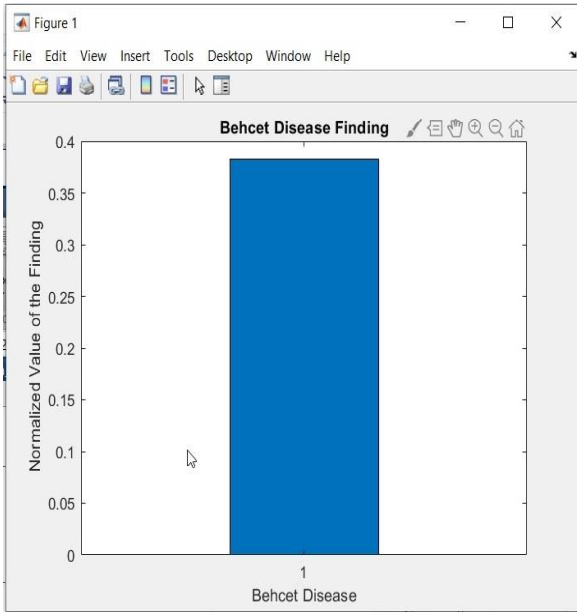

Figure 4-8: Bar plot for case study 4

The bar plot depicts frequency of finding Behcet's in the case study 4 (38.31%).

5. DISCUSSION

Behcet's disease is an inflammatory disease that belongs to primary systemic vasculitic diseases. Various organs and arteries are affected by it and as time progresses, the symptoms get worse. It is prevalent in countries alongside the silk road with remarkable frequency in Turkey (between 20 to 420 cases per 100,000 population). Detection of BD is mostly revovles on the physical signs which are oral and genital ulcers, skin lesions and ocular lesions.

Clinical decision support systems are web based programs that have been utilized for medical decisions in early diagnoses and prediction, treatment, practice and prognosis. Several CDSSs have been designed with several machine learning methods and studied for different diseases.

Symptom checkers base their differential diagnosis on the information entered by the user. Most of them use simple decision tree model. By using text book knowledge and given symptoms, differential diagnosis are presented to the user. Nowadays, advanced symptom checkers like symptomate.com use chat bots for electronic diagnosis (105). However, a survey demonstrated that only one-third of the cases were diagnosed accurately (106).

To date, SVMs and random forest methods have been used frequently in the rheumatology field for disease recognition and classification (105). Lin et al. (107) proposed a system for detecting rheumatoid arthritis (RA) from electronic medical records (EMR). More than 2500 clinical notes and laboratory values were trained and then evaluated on a data set more than 2000 notes. By using a text analysis tool, the system derives key words such as synovitis, pain or stiffness as input variables. Extracted terms in addition to clinical and laboratory information, help system to detect RA patients. According to the study, AUC score of SVM was 0.831 and concluded that its detectability results is similar to human performance (107).

Another study used random forests technique to detect RA patients among clinical codes in an EMR. By training more than 15000 data sets with random forests, they detected eight 8 features in relation to the diagnostic codes for RA. By evaluating the model on more than 5000 testing sets, they achieved 92% accuracy (108).

Machine learning methods also could be used for prediction of disease progression. In 2018, a study in the Netherlands used different machine learning methods (random forests, logistic regression and k-nearest neighbor models) to achieve the best performance for detecting flares in RA patients (109). The definition of a flare was given as “an increase swollen joint count or an increase in medication from the last visit” (105). Input variables included demographic, laboratory and medication and clinical data of 314 patients. The best performance was achieved by a random forest, which could identify flares with AUC score of 0.8 (109).

Over the last decade, deep learning has been used widely for image processing of musculoskeletal radiology (105). In clinical practice, automatic image interpretation is helpful in identifying lesions or regions of high interest by heat maps. In a study by Brahim et al. (110), with tibial texture analysis, they detect osteoarthritis (OA) on 1024 knees in the OA primary dataset and achieved 83% accuracy.

In the future, systems with various machine learning methods could assist rheumatologists to find the best patient-specific treatment option. CDSS will perform better if more data is available to support the rheumatologist in disease prediction and treatment options.

Mentioned studies are some instances of CDSS in the field of rheumatology performed between 2010 and 2021. However, no CDSS has been developed for BD diagnosis to date. Therefore, we decided to use a model based on Bayes’ theorem for our CDSS. Bayesian model has demonstrated a high diagnostic accuracy in CDSS studies for heart disease, renal failure and rheumatic diseases (111,112,113). It is simple and understandable, easy to build, and fast in achieving results.

In this study, we extracted historical data of BD patients from the literature and created a Stationary Linear Stochastic model which was tested with our data in MATLAB program. The data obtained from the literature includes all the major and minor symptoms of BD. Then we derived data of two BD cases from other studies, and entered the symptoms to check how the system works. Yielded results were 61% and 74%, which means the proposed model could predict the disease correctly. In addition, we entered data from 2 disorders other than Behcet’s and checked the model to see how it predicts. Yielded results were 32% and 38%, which means that the model could exclude them from BD. In this regard, if a person was suspicious about his health condition and can put his

symptoms in the algorithm we developed, then he could obtain a prediction for early diagnosis of BD, which could direct him to seek medical consultation . Also, it could become handy for family doctors and general physicians to direct symptomatic cases to the specialist more accurately.

There are a few BD candidate genes reported in the literature (including *HLA* and non-*HLA* genes) other than the most common BD associated allele (*HLAB*51*) that is mentioned in this thesis (114). Since BD is not a single gene disorder, meaning that there are multiple genes involved in BD onset (29,30), and that there is no genetic testing established to diagnose BD, we did not include genetic aspect calculation in our model with an attempt to avoid bias. If we were to take into account the alleles so far associated with BD, we would have been eliminating any potential BD genes that have not been identified, yet. And therefore this incomplete set of genes would create error in our model.

Considering these facts, when a complete set of genetic variants involved in BD diagnosis is identified, it can be incorporated in our model. This way we believe that our model will serve to provide a more accurate diagnosis in the future.

In the current study, we concentrated on the mathematical modelling and algorithmic structure of the decision making process. Although the algorithm has been constructed so far, due to the lack of real patient data, the performance of the system has not been assessed. However, a similar study done with the same algorithm and model (97) , has yielded high accuracy of the system.

In the future work, we can expand our training data by extracting real data of patients in hospitals, experts' opinion and literature, to assess system's accuracy. Also, since it is easy to use and understandable and, if the system is performed with a user friendly application on mobile phones, general practitioners and suspicious people can use it as an assisting tool to guide them to the proper expert as fast as possible.

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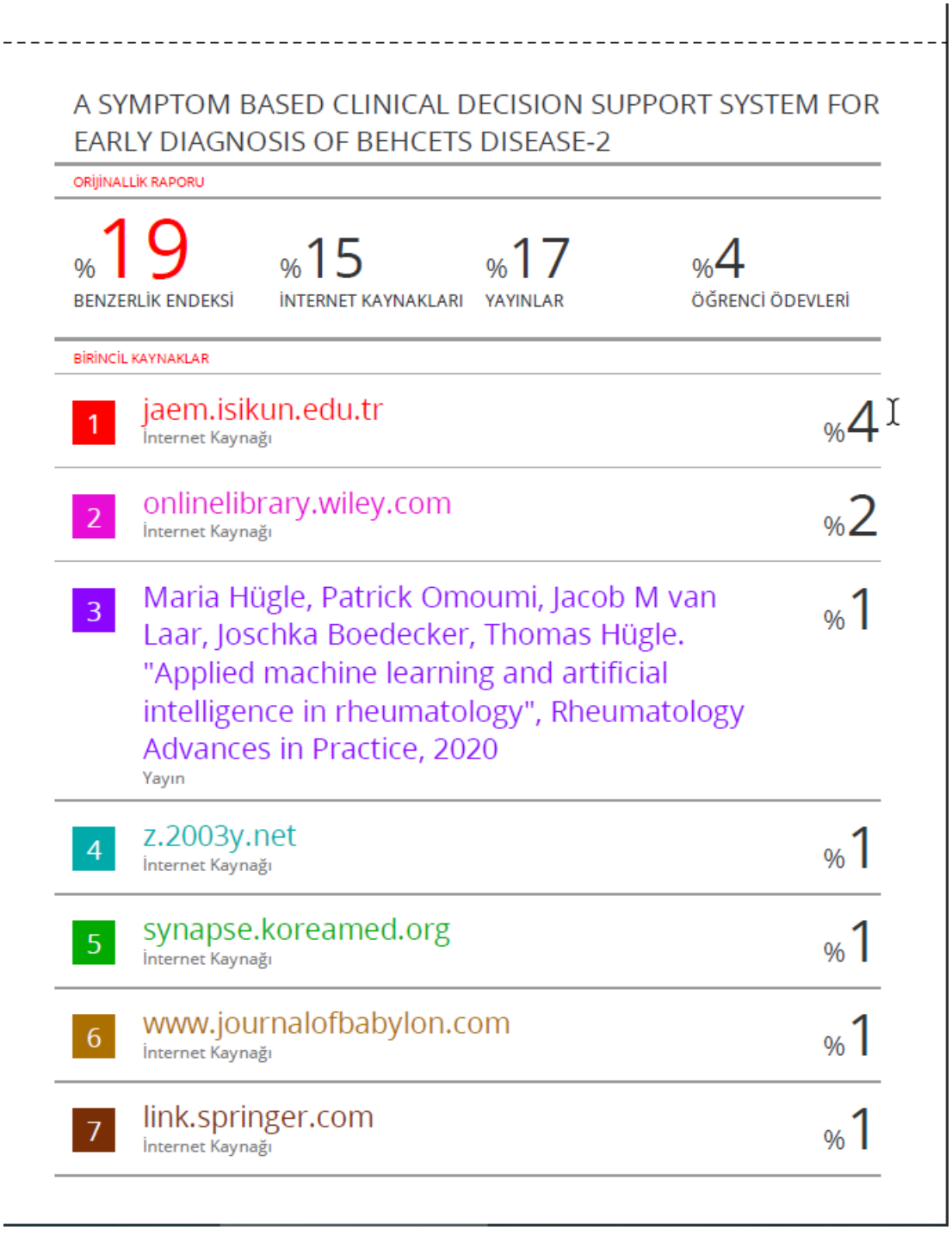

A SYMPTOM BASED CLINICAL DECISION SUPPORT SYSTEM FOR EARLY DIAGNOSIS OF BEHCETS DISEASE-2

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