Bridging the Lupus Diagnosis Delay: An Analysis and Comparative Study of Systemic Lupus Erythematosus

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Abstract

Across the globe, millions of individuals are affected by an autoimmune disease called lupus. Despite this, there is a lack of a single, definitive diagnostic test. As a result, individuals must undergo numerous tests that point to a plethora of other diseases. Diagnosis can take up to 6 years, causing problems to arise, such as complications from lupus. Our project integrates a mixed-methods approach, using both qualitative and quantitative data, to analyze the problems surrounding lupus. We first researched background information surrounding lupus in order to gain a deeper understanding of the topic. Afterwards, we specifically researched the diagnosis process to recognize the problems with the detection of lupus in the status quo. We then looked into related diseases and their treatments to understand the difficulties that arise in the diagnosis of lupus due to the overlap in symptoms. We also collected information on novel biomarkers currently being tested to be used in the detection process to make it more accurate. Finally, we proposed a model for the accurate diagnosis of lupus, where individuals are categorized into "Lupus" or "Not Lupus" and then undergo testing using biomarkers. We built an AI-assisted decision tree using binary classification to demonstrate the accuracy of the first step of our proposal. We found that the decision tree was able to predict whether individuals had lupus with an accuracy of 92%. As a result, we concluded that our proposal would be able to accurately predict lupus diagnosis and also effectively use biomarkers to prevent individuals from being subjected to an overwhelming number of tests. This would decrease the burden on those already living with a taxing disease, not only on the wallet but also on the mind. In the future, we would like to further investigate and test our model, potentially using larger datasets, in real-life situations to ensure accuracy.

Introduction

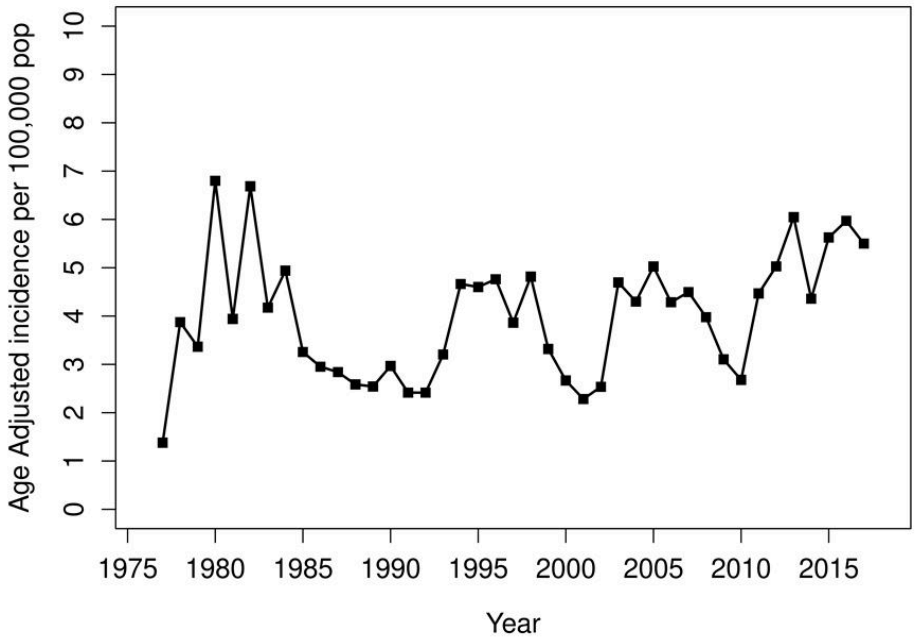
Systematic lupus erythematosus (SLE) is a significant problem within today's society. Nearly 5 million individuals worldwide are affected by this chronic autoimmune disease, which can impact multiple organ systems and lead to the development of serious health complications (*Lupus Facts and Statistics*, 2025). Lupus also creates a substantial burden on both individuals and healthcare systems due to long-term treatment, frequent medical care and associated costs. Despite its prevalence, lupus remains difficult to accurately diagnose. This is primarily because a single definitive diagnostic test does not exist. Symptoms are often individualistic and overlap with those of other autoimmune diseases, as described in detail further in this paper. Frequent misdiagnosis or delayed accurate detection results in many patients experiencing disease progression and harsh symptoms before even receiving appropriate treatment. This project aims to examine the current challenges in detecting lupus, compare related diseases and propose an improved model for easier and more accurate identification. The first aspect of the paper provides background information on lupus and existing diagnostic methods, highlighting the problems present in the status quo. The second aspect explores diseases with similar presentations to identify sources of misdiagnosis and research into any overlaps in treatments or detection methods. The third aspect summarizes recent innovative studies that describe different indicators for detecting lupus. In addition, we propose an enhanced detection model that integrates standardized testing with emerging biological indicators previously mentioned to improve diagnostic accuracy. In short, our project aims to delve deeper into the topic of lupus and present innovative solutions to solve existing problems.

Problem

Lupus is a highly prevalent disease affecting more than 5 million individuals worldwide, though reports may be underestimated due to difficulty in diagnosis (*Lupus Facts and Statistics*, 2025). Even in Canada in 2006, around 1 in 2000 Canadians had SLE (*Musculoskeletal Diseases*, 2006). Not only this, but numbers have been on the rise in the past few years.

Figure 1

Trends in age-adjusted SLE from 1976-2018



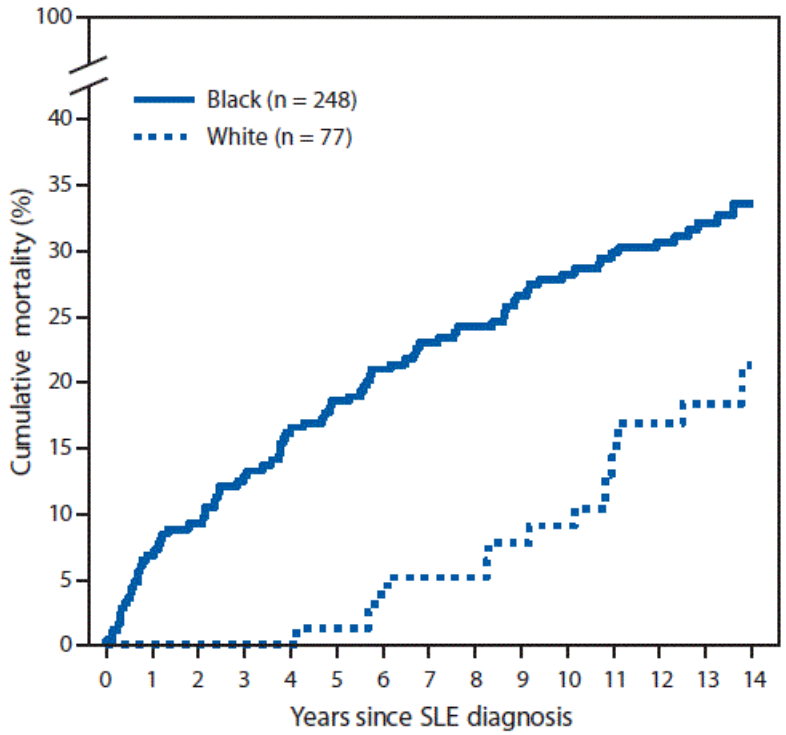
Note. From ACR Meeting Abstracts by Duarte-Garcia et al., *Time Trends in the Incidence of Systemic Lupus Erythematosus: A 40-Year Study.*

The graph above, from Duarte-Garcia et al. (2020), demonstrates the increase in lupus incidence per 100,000 population. As can be seen, the general trend of lupus is on the rise, not at an all-time high, but at a relatively increasing growth. However, there still remains a lack of

standardized testing and accessibility to a majority of the world's population. Diagnosis takes between months and years, with 66% of diagnosed Americans in a survey having been initially misdiagnosed and 55% having to contact four or more healthcare providers in order to receive the correct diagnosis (*Lupus Facts and Statistics*, 2025). Not only this, but the general population is unaware of this problem, with 61% of American surveyors in a survey believing it takes less than six months to diagnose lupus (*Lupus Facts and Statistics*, 2025). Misdiagnosis poses serious dangers to individuals, increasing the mortality rate significantly, as demonstrated by the graph below.

Figure 2

Mortality rate of SLE compared to years since diagnosis



Note. From MMWR. Morbidity and Mortality Weekly Report, *68* by S. Sam Lim, M. D., Charles G. Helmick, M. D., Gaobin Bao, M. P. H., Jennifer Hootman, P., Rana Bayakly, M. P. H.,

Caroline Gordon, M. D., & Cristina Drenkard, M. D. (2019), *Racial Disparities in Mortality Associated with Systemic Lupus Erythematosus — Fulton and DeKalb Counties, Georgia, 2002–2016.*

Figure 2 demonstrates two main ideas. Firstly, the rate of mortality increases over the years of diagnosis, meaning that misdiagnosis and lack of diagnosis are quite dangerous and lethal. Secondly, there is a racial difference between populations, namely African-American and Caucasian individuals. This lack of awareness results in conditions such as anxiety or depression due to feelings of being misunderstood (Izquierdo et al., 2024). Additionally, around 10-15% of individuals with lupus may die prematurely (*Lupus Facts and Statistics*, 2025). Another problem that arises with SLE is the high healthcare costs. In America in 2016, the costs of living with lupus were around $33,223 annually, and overall costs were around $50,000 (*Lupus Facts and Statistics*, 2025). For those with SLE in Alberta in the same year, the average cost was around $7,740 per person for healthcare, compared to non-SLE patients who paid $2,480 (Fatoye et al., 2021).

Figure 3

Healthcare Costs of SLE

Note. From Healio, *Patients with most SLE damage incur ninefold higher costs over a decade. (2019).*

The above image demonstrates that the costs associated with SLE are based on the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI). The SDI is a tool used to measure irreversible organ damage occurring after diagnosis, providing information relating to disease activity and long-term prognosis for individuals. A higher SDI indicates higher mortality rates and, therefore, higher costs, as shown in the image (*Patients with Most SLE Damage Incur Ninefold Higher Costs over a Decade*, 2019.). Patients with an SDI of 5 or higher paid around $189073 for around 10 years, further emphasizing the extreme burdens that are forced upon those with lupus. Comparatively, patients with lower SDI only had to pay $21713, showing the disparity that arises between different severities. Thus, lupus is a taxing condition, not only on the body, but also on an individual's pocket, the government and the overall economy. Due to the existing problems previously mentioned, our project aims to study lupus through a multifaceted approach, researching aspects such as current treatments and novel diagnosis methods. Furthermore, we propose an enhanced

detection model integrating both standardized testing and emerging biological indicators to make diagnosis both cost-effective and accessible.

Method

Scientific research methods can generally be categorized as qualitative or quantitative. Qualitative methods focus on non-numerical data, such as literature analysis, case studies and pattern recognition, while quantitative methods rely on numerical data, including statistics, prevalence rates, and laboratory methods. This project used a mixed-methods approach, integrating quantitative and qualitative data to develop a comprehensive understanding of the challenges associated with diagnosing lupus. The qualitative component of this project involved an in-depth review and analysis of scientific literature and medical reports related to SLE. This included examining common symptoms, misdiagnosis patterns, and limitations of current diagnostic practices. Qualitative comparisons were also made between lupus and other autoimmune diseases with similar clinical symptoms to identify factors that contribute to diagnostic confusion. The quantitative aspects of this research involved analyzing statistical data related to lupus prevalence, misdiagnosis rates, diagnostic delays, and the sensitivity and specificity of commonly used laboratory tests. Data from reputable medical and scientific papers were used to identify trends and gaps in existing diagnostic methods. These numerical findings were then applied to evaluate the effectiveness of current approaches and inform the development of an improved model. This project proposes a multi-stage lupus detection model that relies on both qualitative and quantitative findings to integrate epidemiological risk factors, standard autoimmune testing, and emerging biological indicators. Despite efforts to ensure accuracy and objectivity, certain limitations exist within this methodology, such as relying on

secondary data rather than original clinical experimentation. Additionally, integrating qualitative and quantitative data may introduce challenges in interpreting data. However, multiple sources were cross-referenced and analyzed to minimize bias and ensure that conclusions were supported by credible evidence.

Research

Background Information

Lupus is a chronic autoimmune disorder where the body's immune system attacks itself, causing inflammation and therefore manifesting in a variety of symptoms, some being joint pain, butterfly rashes, fatigue and fever (*Lupus - Symptoms & Causes*, 2025). There are four types of lupus (*Lupus*, 2025). The first is systemic, where the immune system attacks healthy tissue, which occurs in around 70% of individuals with lupus. The second is cutaneous, which affects the skin specifically. The third is drug-induced, which occurs due to high doses of medications. Finally, the fourth is neonatal, where antibodies from a baby's mother affect fetal development, although symptoms in this type typically disappear after six months. The trigger of lupus is unknown, but likely due to a combination of one's genetics and the environment (*Lupus - Symptoms & Causes*, 2025). In general, for autoimmune diseases, immune cells identify healthy cells as foreign cells, triggering the body to attack joints or organs (*Autoimmune Diseases*, n.d.). For example, sunlight, infections and certain types of medications are suspected to be causes of lupus. The mechanism by which sunlight triggers lupus, for example, is quite complex and not entirely understood. The current model proposes that genetic material starts a reaction in individuals that are predisposed to autoimmune conditions. This causes the expression of proteins such as "Ro", which are the targets of antibodies. These antibodies then attract white

blood cells that attack the skin, causing inflammation and rashes (*Photosensitivity, Sun Safety and Lupus*, 2024). Furthermore, since the immune system function is compromised, the dead skin cells are unable to clear out, but rather remain and trigger flares (Kuechle & Elkon, 2007). In a study conducted, around 83% of individuals with lupus reported having sun sensitivity (*Research on Photosensitivity among People with Lupus*, n.d.). One of the major dangers that arises with lupus is the large number of comorbid conditions. Kidney failure, hypertension, inflammation of heart muscles, pregnancy complications, Raynaud's syndrome and an increased risk of infections are just some examples (*Common Diseases That Overlap with Lupus*, 2024). However, due to recent advancements in treatment, individuals may live relatively normal lifespans if accurately diagnosed, an area yet to be further developed. Speed of diagnosis is also a significant concern as individuals must undergo numerous time-consuming and expensive tests, which may all point to different diseases, leading to long waiting times before an accurate diagnosis. To expound on the topic of comorbidities, many individuals living with lupus experience mental health conditions such as depression and anxiety. According to a DASS-42 questionnaire, around 22.1%, 28.7% and 20.3% of patients had varying degrees of depression, anxiety and stress (Dehghan et al., 2023). Additionally, the same study found that around 62% of patients reported living in a degree of distress. The quality of life score for individuals in relation to physical health, psychological health and social relationships was comparatively lower than in normal, healthy adults (Dehghan et al., 2023). As previously mentioned, the high costs of diagnosis and treatments may also contribute to the declining well-being of those living with lupus. Interestingly, lupus also disproportionately affects men and women, with 90% of patients being female (*Men and Lupus*, 2024). This may arise due to the fact that females typically have stronger immune system responses, increasing susceptibility to autoimmune diseases (Kronzer et

al., 2020). In conclusion, lupus is a chronic, incurable autoimmune disease where the immune system attacks the body's own tissues and organs, resulting in inflammation and flares, which typically fluctuate throughout one's life. In summary, lupus poses significant dangers due to comorbid conditions and overall decreased quality of life, which worsen over time without accurate, efficient diagnosis.

Diagnosis and Treatment

As previously stated, diagnosing SLE is challenging due to the absence of a single standardized diagnostic test and the wide variation of symptoms among individuals. As a result, current diagnosis relies on a combination of physical examinations and multiple laboratory tests, which increases the risk of misdiagnosis. Common laboratory examinations include blood tests such as a complete blood count, which measures levels of red and white blood cells, platelets and hemoglobin. These results can indicate abnormalities such as anemia, which may imply lupus (*Anemia*, n.d.). Inflammatory activity is often assessed using the erythrocyte sedimentation rate, which measures how quickly red blood cells settle and may signal lupus or other inflammatory conditions. Kidney and liver function tests are also frequently used, as lupus can impair these organs. Urinalysis plays a particularly important role in detection, as elevated protein or red blood cell levels in urine may indicate lupus-related kidney involvement. Additionally, the antinuclear antibody (ANA) test is commonly used to detect antibodies associated with autoimmune activity; however, because ANA positivity can also occur in other autoimmune disorders, it is not specific to lupus (*ANA (Antinuclear Antibody) Test*, n.d.). In some cases, a kidney biopsy is performed to evaluate tissue damage and confirm lupus nephritis (*Lupus - Diagnosis & Treatment*, 2025). This lack of specificity increases misdiagnosis rates, as lupus is

diagnosed by excluding other diseases through tests that indicate numerous conditions. The diverse detection tests and individuality of lupus result in multiple types of treatments. Treatment varies depending on symptom severity and organ involvement. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed to manage pain and inflammation, though these may cause gastrointestinal bleeding or increase cardiovascular and kidney risks. Antimalarial drugs, such as hydroxychloroquine, are commonly prescribed to reduce disease flares and treat lupus-related rashes and arthritis, despite potential side effects including gastrointestinal discomfort and rare retinal damage. More severe cases of lupus may require corticosteroids or immunosuppressive medications to control inflammation and immune system activity, which can increase the risk of infection or other long-term complications (*Lupus - Diagnosis & Treatment*, 2025). Newer treatments like biologic therapies, such as belimumab, target specific immune pathways but have also been associated with side effects including nausea, infections and mood changes (*Belimumab (intravenous route, subcutaneous route) - Side Effects & Dosage*, 2026). Recent advances in lupus research are improving both diagnosis and treatment, offering the potential for earlier, more precise, and personalized care. Novel diagnostic methods, such as DNA methylation testing, can identify lupus at a genetic level with over 90% accuracy, while advanced blood tests and combined biomarker panels integrate T-cell markers with traditional assays to detect specific lupus subsets and better predict disease flares (*Understanding Your Lupus Care*, 2024). Newer disease activity tests provide a comprehensive immune system assessment to guide treatment decisions more precisely. On the therapeutic side, CAR T-cell therapy is being explored to modify a patient's own T-cells to eliminate the disease-driving B-cells, while targeted biologics aim to improve treatment effectiveness with fewer broad immunosuppressant side effects. Research into reprogramming immune cells and understanding root causes, such as T-cell

imbalances, is also paving the way for treatments that could correct underlying disease mechanisms rather than just manage symptoms (*Car T Cell Therapy for Lupus*, 2024). Lifespans of individuals with lupus and their quality of life are areas of continual improvement, though great strides have been made already. These breakthroughs collectively offer hope for earlier diagnosis, safer and more tailored treatments and, ultimately, more effective long-term management of lupus.

Related Diseases

Several autoimmune and connective tissue disorders share clinical and immunological features with SLE, contributing to the frequent diagnostic overlap and misdiagnosis that arises. Sjögren's syndrome is one of the most common conditions associated with lupus. Similarly, it predominantly affects women and involves immune-mediated tissue damage (*Common Diseases That Overlap with Lupus*, 2024). Diagnosis of Sjögren's syndrome is challenging due to the lack of a single standardized test and often relies on differential diagnosis after ruling out other autoimmune diseases (*Sjogren's syndrome - Symptoms and Causes,* 2022). Common diagnostic tools include blood tests, imaging, biopsies, eye examinations, and urinalysis. The presence of SS-A (Ro) and SS-B (La) autoantibodies is frequently associated with Sjögren's syndrome; however, these antibodies are not disease-specific, as they are also found in lupus patients and, in some cases, healthy individuals (*Sjogren's Syndrome - Symptoms and Causes*, 2022). Raynaud's syndrome is another condition that commonly overlaps with lupus and is characterized by episodes of reduced blood flow to the fingers and toes in response to cold or stress, resulting in colour changes, numbness, and pain. Raynaud's may occur as a primary condition or as a secondary phenomenon associated with autoimmune diseases such as lupus, rheumatoid arthritis,

and Sjögren's syndrome. In lupus patients, inflammation of blood vessels increases sensitivity to environmental triggers, leading to Raynaud's episodes and vasospasms, sudden spasms caused by persistent contractions of a blood vessel, which cause the narrowing of an artery, restricting blood flow and oxygen delivery (*Raynaud's Disease - Symptoms and Causes*, 2024). Rheumatoid arthritis is also frequently considered in the differential diagnosis of lupus due to shared symptoms such as joint pain, swelling, fatigue, and systemic inflammation. Although rheumatoid arthritis primarily targets the synovial lining of joints and often causes joint erosion, lupus-related arthritis may present similarly with less structural damage. In some cases, overlap syndromes such as "rhupus" occur, in which patients exhibit features of both diseases (*Rheumatoid Arthritis - Symptoms and Causes*, 2025). These related diseases and common misdiagnoses are detrimental to the lives of those living with lupus. These shared symptoms, immune pathways, and risk factors, such as genetics, hormones and environmental influences, highlight the complexity of diagnosing lupus and emphasize the need for improved diagnostic models that effectively distinguish between overlapping autoimmune conditions.

Innovative Biomarkers

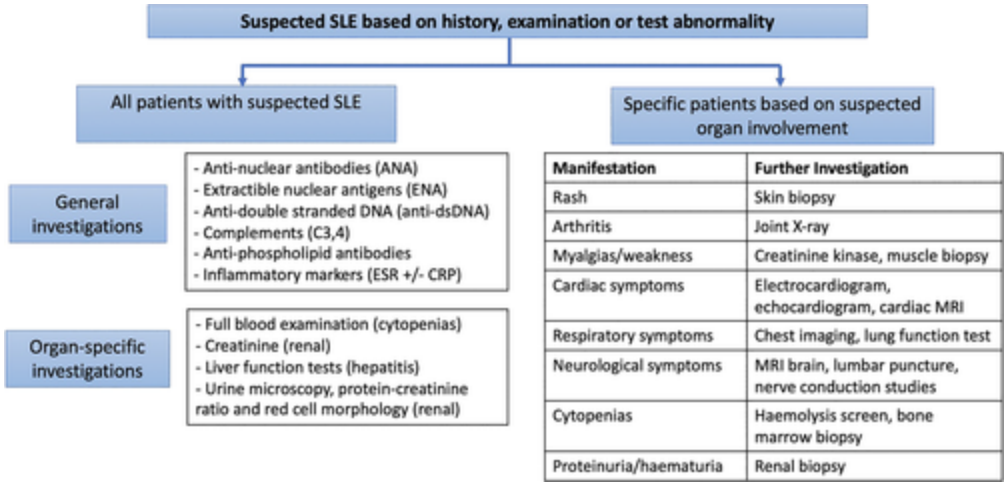
Recently, a trend towards more precise and non-invasive diagnostic measures has been observed, namely, biomarkers. These provide accurate and efficient early diagnosis for diseases such as lupus, where time is of the essence, through recognizing flares or organ damage, for example. There are major biomarkers that have gained popularity recently. Firstly, urinary biomarkers for lupus nephritis (Aragón et al., 2020). Lupus nephritis refers to the serious inflammation of the kidneys caused by SLE, occurring in between 25-60% of SLE patients (Parodis et al., 2025). Urinary biomarkers work in that nearly 70% of proteins present in the urine of lupus nephritis

patients come from the kidneys. Some markers are particular to lupus, such as TWEAK, while others indicate general kidney inflammation. Such biomarkers detect certain proteins, cells or molecules in the urine that are released by the kidneys during inflammation due to lupus nephritis (Guimarães et al., 2022). Specifically, cytokines, chemokines and complement components are often looked for in detection. Cytokines and chemokines are involved in the inflammation of organs like the kidneys, while complement components indicate immune system attacks. For example, inflammation can cause immune cells to release markers such as tumour necrosis factor-like weak inducers of apoptosis (TWEAK) or MCP-1 (Guimarães et al., 2022). Studies have shown that urinary biomarkers can significantly increase the accuracy of diagnosis, with some estimates being as high as 90% (Omer et al., 2024). Urinary biomarkers can be highly efficient while also reducing the requirement for invasive methods like kidney biopsies. Flares and disease activity can be detected earlier, providing factors with an increased timeframe to administer proper treatments, potentially reducing the severity of lupus. Another area of study is serum and blood-based biomarkers (Xu et al., 2025). These work in that they act as “footprints” of an overactive immune system, providing information in relation to the diagnosis and progression of lupus in an individual (Liu et al., 2013). There are numerous mechanisms that can be used. For example, autoantibodies, produced by the body’s own B lymphocytes, attack the body (Liu et al., 2013). These can then be used to check for lupus. One specific type of autoantibody is anti-dsDNA, which is highly specific to lupus (Liu et al., 2013). However, these are not present in all lupus patients, with estimates ranging from 30-80% of individuals having this autoantibody (Keiserman et al., 2013; Matthias et al., 2025). They bind to the DNA, forming structures that then cause damage to the kidneys (Yung & Chan, 2015). High levels of anti-dsDNA indicate active disease and can therefore be used in diagnosis. Complement levels

are another mechanism that is used to diagnose lupus (Haitao et al., 2021). Proteins that are used in fighting infections (part of the complement system) are often present in lower levels during lupus, highlighting their potential to be used in diagnosis (Ayano & Horiuchi, 2023). Other methods include specialized blood tests or inflammatory markers. Finally, Epstein-Barr virus (EBV) biomarkers are another area of promising research. A recent study published in 2025 demonstrated the connection between lupus and EBV (Goldman, 2025). The virus reprograms the immune system, leading to the development of lupus (Younis et al., 2025). Specifically, B cells are reprogrammed to become "hyper", producing antibodies and therefore sending the immune system into a state of overactivity, leading to attacks on healthy tissue. The same study suggested that EBV may be as many as 19 out of 20, or 95% adults worldwide carry the virus (Goldman, 2025). More than the presence, the interactions of EBV in the bodies of those with lupus are essential to consider. EBV is typically dormant, but it occasionally "wakes up" and produces a protein called EBNA2 (Epstein-Barr nuclear antigen 2). EBNA2 plays a crucial role in activating the genes that cause inflammation. Tools such as EBV-seq, a method used to identify and analyze B cells infected with EBV, can also be used to identify lupus (Younis et al., 2025). In summary, numerous detection methods have arisen that aim to utilize innovative biomarkers. Our paper also proposes a similar method in order to make detection more accurate and efficient, and to make diagnosis cheaper and more efficient.

Figure 4

Current Diagnosis Pathway



Note. From Internal Medicine Journal by Connelly, K., & Morand, E. F. (2021). *Systemic lupus erythematosus: A clinical update, 51(8), 1219–1228.*

Figure 4 demonstrates the current detection pathway for SLE. Additionally, the image shows limitations with this process, as there are many overlaps between symptoms and tests administered. For example, an individual may have a positive result for liver function tests, which not only indicates lupus but also indicates hepatitis. This overlap makes it difficult to differentiate between related diseases, overall increasing the rate of misdiagnosis and lack of access to proper treatments. Additionally, this detection model does not include everyone with lupus, as symptoms are very individualistic and not incorporated within the current system.

Data

Table 1

Biomarkers for Lupus Classification

Biomarkers	ACR-1997 Criteria	SLICC-2012 Criteria	EULAR/ACR-2019 Criteria
Proteinuria	Persistent proteinuria > 0.5 g/24 h or >3+, if quantitation not performed	Urine protein to creatinine ratio (or 24-h urine protein) representing 500 mg protein/24 h	Proteinuria > 0.5 g/24 h by 24-h urine or equivalent spot urine protein to creatinine ratio
Urinary casts	Cellular casts may be red cell, hemoglobin, granular, tubular, or mixed	Red blood cell casts	—
Hemolytic anemia	Hemolytic anemia with reticulocytosis	Direct Coombs' test in the absence of hemolytic anemia	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, and positive Coombs' (direct antiglobulin) test
White blood cell count	White blood cell count < 4000/mm^3 on 2 or more occasions; OR Lymphocyte count < 1500/mm^3 on 2 or more occasions	White blood cell count < 4000/mm^3 at least once, in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension; OR Lymphocyte count < 1000/mm^3 at least once, in the absence of other known causes such as corticosteroids, drugs, and infection	White blood cell count < 4000/mm^3
Platelet count	Platelet count < 100,000/mm^3 in the absence of offending drugs	Platelet count < 100,000/mm^3 at least once, in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura immunologic criteria	Platelet count < 100,000/mm^3
Sm antibody	Presence of antibodies to Sm nuclear antigen	Presence of antibodies to Sm nuclear antigen	anti-Sm antibodies
Serologic text for syphilis	False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponemapallidun* immobilization or fluorescent treponemal antibody absorption test	—	—
Antinuclear antibody levels	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome	ANA level above laboratory reference range	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once; testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
DNA antibody	Antibody to native DNA in abnormal titer	Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by ELISA)	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥ 90% specificity for SLE against relevant disease controls
CH50	CH50	Low CH50	—
Complement 3	Complement 3	Low complement 3	Low complement 3
Complement 4	Complement 4	Low complement 4	Low complement 4
Complement 2	Complement 2	—	—
Antiphospholipid antibody	Antiphospholipid antibody positivity	Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant; false-positive test result for rapid plasma regain; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant

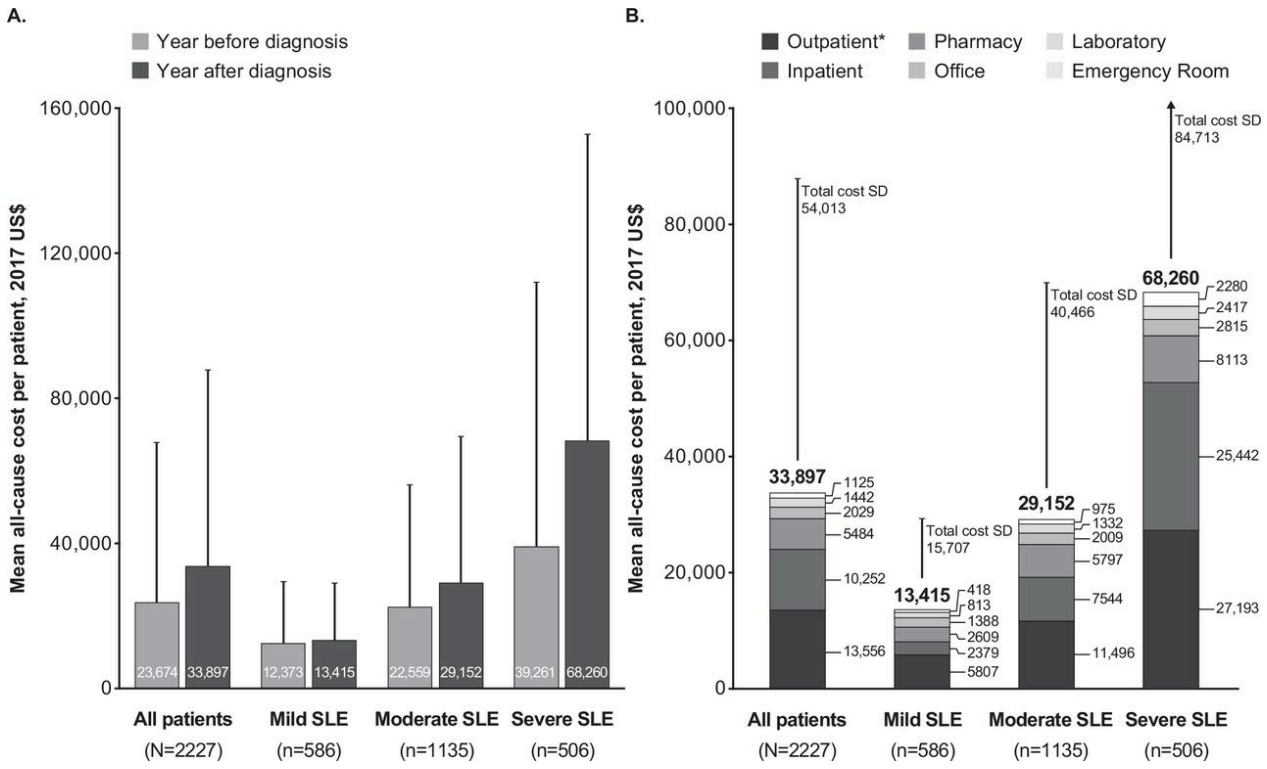
Note. From "Clinical and Immunological Biomarkers for Systemic Lupus Erythematosus" by Yu, Haitao, et al., 2021, Biomolecules, 11(7), *Biomarkers for SLE in the defined criteria of ACR-1997, SLICC-2012, and EULAR/ACR-2019.*

Table 1 illustrates how lupus classification criteria have evolved, reflecting advances in scientific understanding and improvements in diagnostic precision. Earlier criteria, such as ACR-1997, included a broader range of biomarkers, some of which lacked specificity for lupus. Over time, the criteria were refined in SLICC-2012 and further optimized in 2019 EULAR/ACR to emphasize biomarkers with greater clinical relevance and reproducibility. Overall, this progression demonstrates that lupus diagnosis depends on integrating multiple biomarkers rather

than a single definitive test, reinforcing the need for multi-stage detection models to reduce misdiagnosis and diagnostic delays.

Figure 5

Healthcare Costs for Patients After Diagnosis and Varying Severity



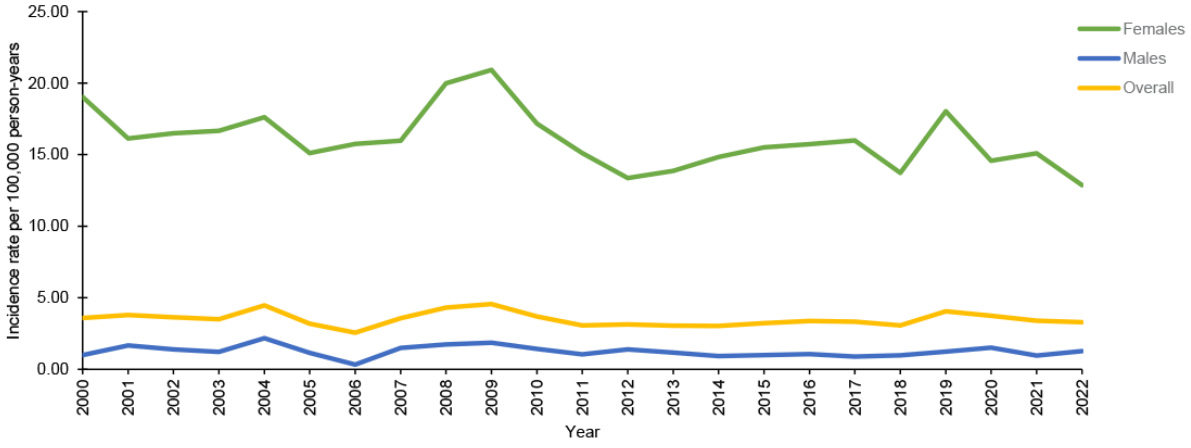
Note. From BMJ Journals by Jiang, M., Near, A., Desta, B., Wang, X., & Hammond, E. (2021, September 14), *Disease and economic burden increase with systemic lupus erythematosus severity 1 year before and after diagnosis: A real-world cohort study, United States, 2004–2015*.

Figure 5 demonstrates the cost per patient of SLE before and after diagnosis in the United States in 2017. The first facet of the graph compares the cost for all patients, patients with mild SLE, patients with moderate SLE and patients with severe SLE. The 2227 patients in the all patients

category, before diagnosis, paid $23,674 USD, while after diagnosis, paid $33,897 USD. This cost includes outpatient, inpatient, pharmacy, office, laboratory and emergency room costs. For patients with mild SLE, before diagnosis, they spent $12,373 USD, and after diagnosis paid $13,415 USD. The majority of this cost was outpatient costs at $5,807 USD, with inpatient costs following at $2,379 USD. Similarly, for patients with moderate SLE, they paid $22,559 USD before diagnosis and $29,152 USD after diagnosis, with outpatient costs being the majority. Finally, for patients with severe SLE, before diagnosis, they spent $39,261 USD, and after diagnosis paid $68,260 USD. Overall, after receiving a diagnosis of SLE at all stages, the costs of treatment increased. Additionally, the majority of costs come from outpatient treatment, such as same-day visits, minor procedures or therapy. Also, depending on the severity of SLE, patients are required to pay more out-of-pocket.

Figure 6

Crude Annual Incidence Rates of SLE by Sex, Active Component Service Members



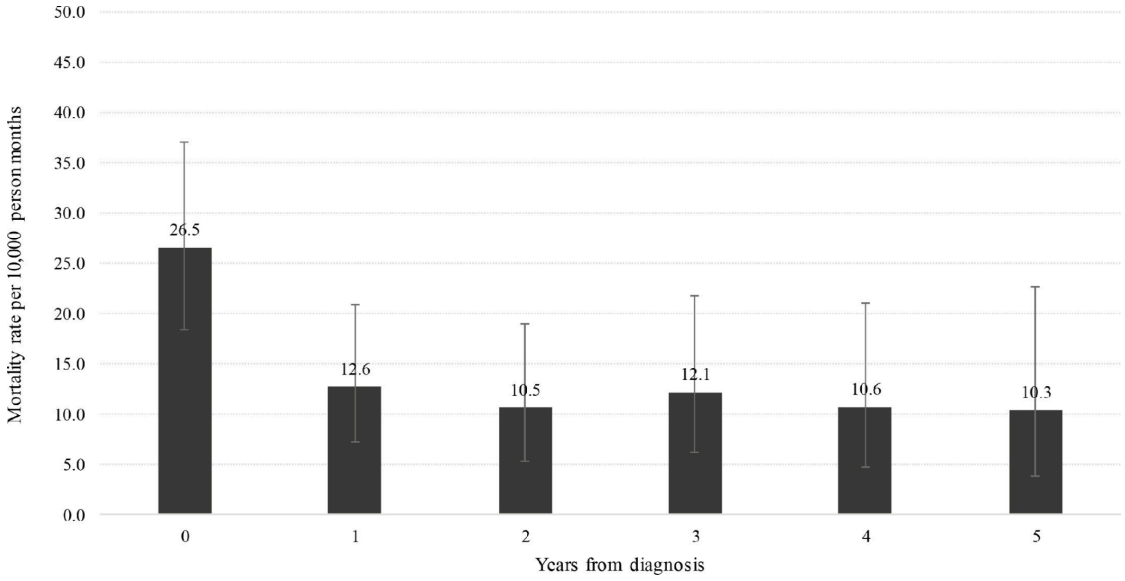
Abbreviation: SLE, systemic lupus erythematosus.

Note. From Military Health System by Denagamage, P., Mabila, S. L., McQuistan, A. A. (2023, December 1), *Trends and Disparities in Systemic Lupus Erythematosus Incidence Among U.S. Active Component Service Members, 2000–2022*.

Figure 6 displays the annual incidence rate of SLE by sex over a 22-year time frame in the United States of America. The incidence rate is the number of cases over a one-year period. In 2000, the incidence rate of females per 100,000 people was around 18.00. While the incidence rate of men per 100,000 individuals was around 1.00. The overall incidence rate per 100,000 individuals was around 4.00. This trend, where the incidence rate of women per 100,00 individuals ranges from 15.00 to 20.00, is consistent from 2000 to 2022. Similarly, for men and the overall incidence rate, the range is from 0.00 to 5.00 over the 22 years. The data shows us that women are more susceptible to crude incidents from SLE. Major peaks of SLE among both sexes were in 2009 and 2019, but ultimately, the number of crude cases had decreased by 2022.

Figure 7

Mortality Rate of Lupus Based on Years After Diagnosis

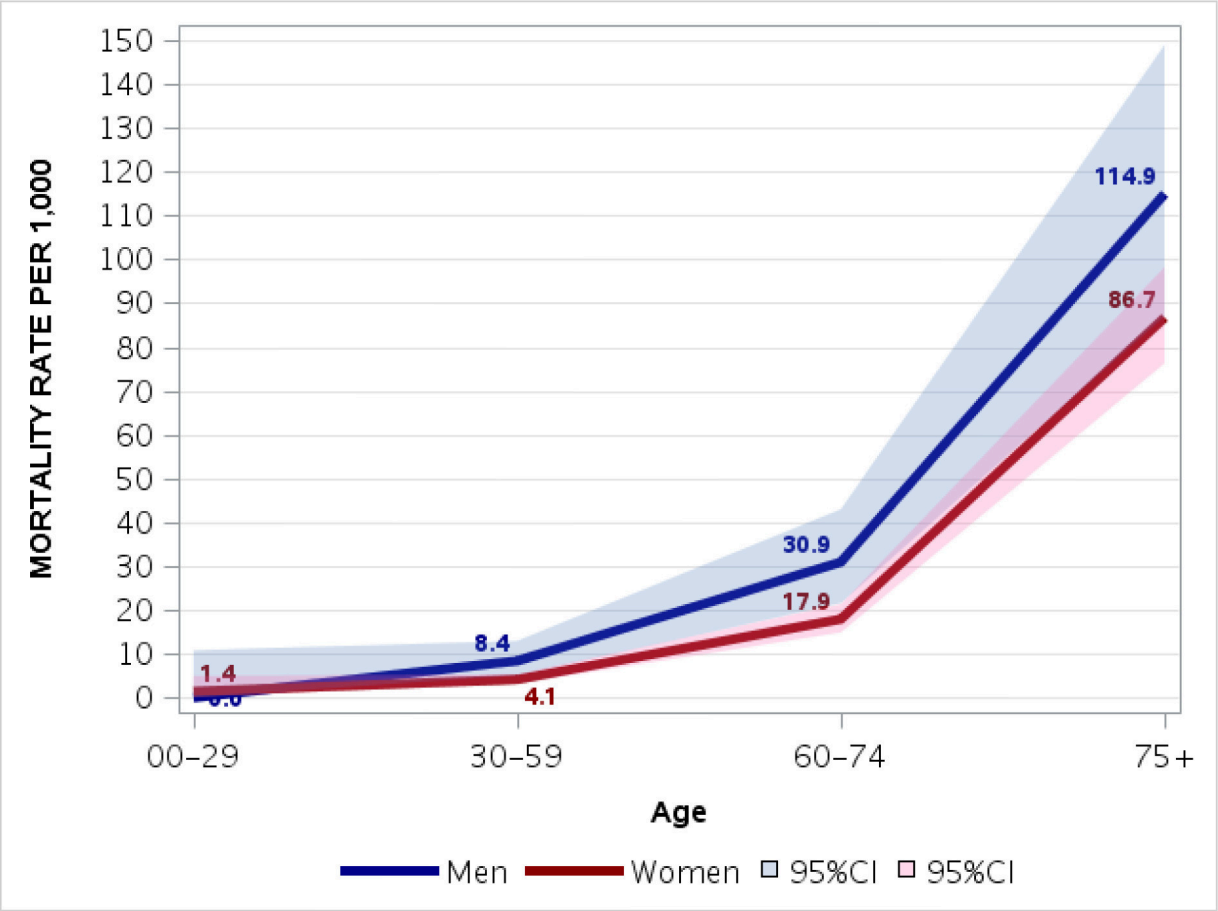


Note. From the European Journal of Internal Medicine by Zen, M., Salmaso, L., & Amidei, C. (2023), *Mortality and causes of death in systemic lupus erythematosus over the last decade: Data from a large population-based study*.

Figure 7 showcases that mortality rates are significantly higher in the first few years after diagnosis and decline in subsequent years. In Year 0, the year of the diagnosis, the rate was around 26.5 per 10,000 person-months. 1 year after diagnosis, the mortality rate reduced to 12.6, then 10.5 in Year 2, 12.1 in Year 3, 10.6 in Year 4 and finally, the lowest, 10.3 in Year 5. Thus, the mortality rate is the highest in the initial year after diagnosis and relatively consistent in the succeeding few years. The confidence intervals indicate some level of variability, but relatively consistent results that do not affect the general pattern. The authors also noted that around 18.2% of deaths arose directly from SLE itself among all cases and around 21.7% in cases that occurred in the first year after diagnosis. As a result, they interpreted that SLE directly impacts the mortality rate. The graph highlights the importance of monitoring newly diagnosed SLE patients, early recognition of the disease and timely treatment.

Figure 8

Mortality Rate of Lupus Based on Sex and Age



Note. From the European Journal of Internal Medicine by Zen, M., Salmaso, L., & Amidei, C. (2023), *Mortality and causes of death in systemic lupus erythematosus over the last decade: Data from a large population-based study*.

Figure 8 demonstrates the mortality rate per 1,000 individuals of SLE based on sex and age. Mortality rate increases sharply for both genders based on age, with older populations being more vulnerable. Interestingly, men had higher mortality rates compared to women in nearly all age categories. For the 0-29 age group, rates are quite low, with men being around 0.6 and women around 1.4. This increases to 8.4 and 4.1, respectively, for ages between 30 and 59. Afterwards, for age groups between 60 and 74, the mortality rate increases further to 30.9 for men and 17.9 for women. Finally, the most vulnerable age group and the age with the highest

mortality rate is 75+, with the rates being 114.9 and 86.7, respectively. In older populations, the gap between the mortality rate for men and women increases sharply compared to younger age groups. The 95% confidence intervals, the shaded portions of the graph, do not affect the observed patterns. This graph emphasizes the high mortality rates associated with lupus and the importance of developing accurate early detection systems.

Figure 9

Proposed Diagnosis Method

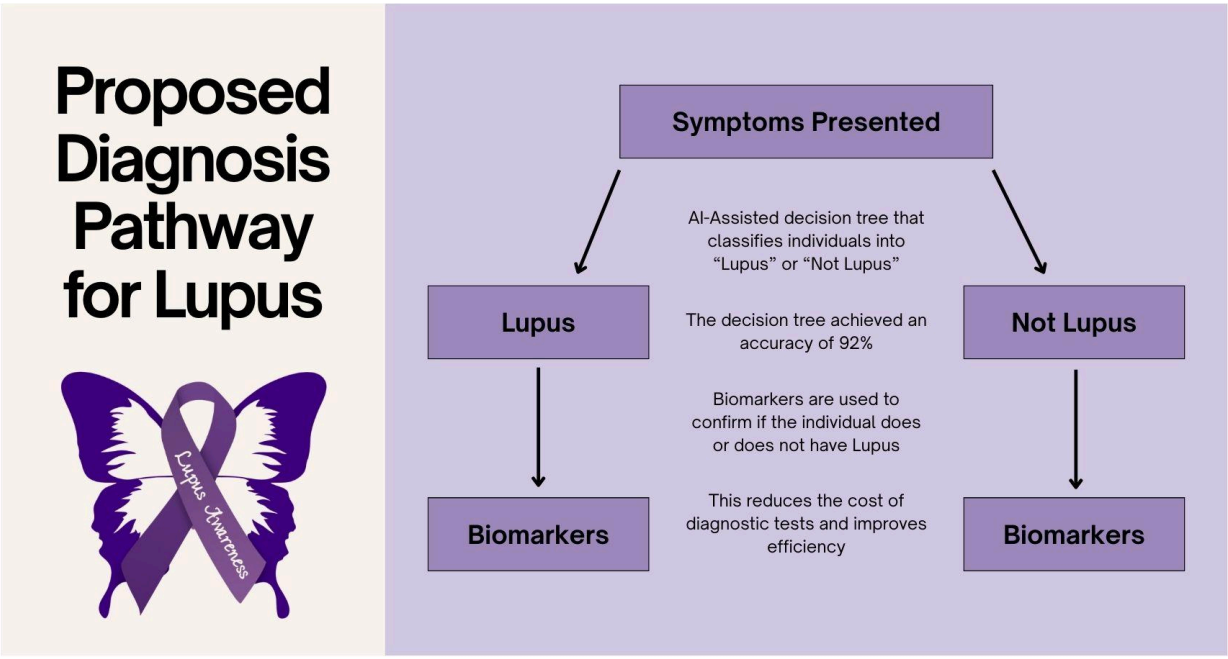


Figure 9 demonstrates our proposed pathway for the detection of lupus. Firstly, individuals visit their doctors after feeling symptoms of lupus, such as butterfly rashes or joint pain. Afterwards, they are divided into two subcategories, "Lupus" and "Not Lupus", by our decision tree, explained further in this section. In both situations, the individuals are then tested for lupus using biomarkers in order to confirm the model's decision. All of this aims to reduce the amount of

time and resources required to accurately diagnose and detect lupus. Finally, after diagnosis, depending on the results, the individuals receive the appropriate treatment needed. To support our findings, we developed an AI-assisted machine learning model that utilizes current data present around lupus and its manifestations to build a decision tree. This would comprise of the first step in our proposal, where individuals are classified into “Lupus” or “Not Lupus”. The dataset used was obtained from Zidoum et al. (2022) which studied lupus symptoms of 219 patients, out of which 138 had SLE and the other 81 had control diseases, in Oman. First, we tried a decision tree regression model, which provided us with an R^2 of 0.46. This means that the model was able to predict only 46% of the variance within the data. As a result, we switched to a binary classification model as we felt it was more appropriate for the dataset. Since the columns were primarily symptom-based, a yes or no type of model seemed suitable for the data. Using the binary classification, we were able to achieve an accuracy of 0.92, or 92%. We set the minimum classification score for lupus to be more than or equal to 10, which is also the EULAR/ACR classification criteria for SLE. This means that the decision tree was able to predict whether an individual did or did not have lupus accurately around 92% of the time. The decision tree primarily used aCL, a type of antibody, and the weightage the authors assigned to Hemolytic Anemia. We found that this supported the first step of our proposal and would provide a gateway to cost-effective and accurate diagnosis of lupus.

Figure 10

Decision Tree Visualization

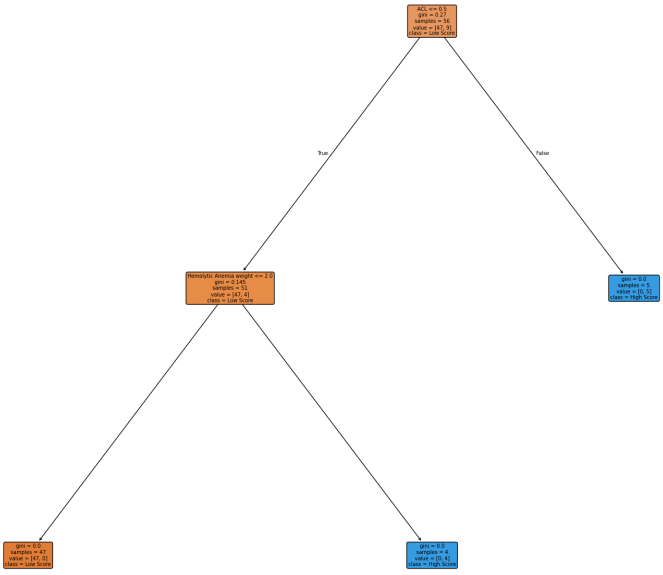


Figure 10 is a visualization of the decision tree previously mentioned. aCL was first analyzed, split into two branches, true and false, based on a score (less than or equal to 0.5 considered as low). The [47,4] shows that the majority of the samples have a low score. In the branch with a high score, the gini was 0.0, demonstrating a perfect classification. Then, the Hemolytic Anemia weight, which was assigned by the authors, was used to further classify individuals into having or not having lupus. A low score was considered as less than or equal to 2 and was used for this classification.

Sources of Error

Efforts were taken to reduce the extent to which sources of error exist. However, we acknowledge there may still be errors due to various reasons. Firstly, an inherent bias exists in selecting examples and statistics to use within our project. Although we aimed to incorporate statistics from various sources across the globe, we realize that some papers may have time

period biases or language biases, for example. We also realize that our ML model for the detection of lupus may have errors due to data quality issues. Although data was gathered from a reputable source, there may still be errors within the data not representative of the population. For example, our dataset was based on a study from Sultan Qaboos University Hospital's Rheumatology clinic in Oman. Despite this, great care was taken to minimize errors within all aspects of our project.

Conclusion

Despite the increasing prevalence of lupus, particularly SLE, within the world's population, the lack of accessibility, diagnosis and awareness remains a significant problem. This paper provides context regarding SLE, compares related diseases to evaluate detection methods and combines novel diagnosis techniques to provide the most effective yet economical option. The findings suggest that a symptom-based approach to diagnosis would be efficient due to reducing the number of tests an individual must endure. Further investigation on this topic, such as conducting studies using our detection pathway proposal, could allow for confirmation of this paper's ideas. In summation, more accurate detection methods can be developed to ensure the proper, quick diagnosis of lupus patients.

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