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Variability in disease presentation: Diagnostic challenges and emerging solutions

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Abstract

Diagnostic accuracy is often challenged by variability in disease presentation across populations. This study examines the key factors contributing to atypical symptomatology and diagnostic uncertainty. Through a synthesis of current literature, key influences are identified, including genetics, comorbidities, age, sex, social, and environmental determinants of health. Healthcare disparities further complicate diagnosis, particularly in under-resourced settings. Emerging tools such as machine learning and biomarkers offer promise for improving precision but require an inclusive design to prevent the reinforcement of existing healthcare inequities. This paper highlights the need for flexible, patient-centered diagnostic models and policies that account for clinical diversity and promote health equity.

Keywords: Disease variability; Diagnostic error; Atypical symptoms; Machine learning; Precision medicine; Adaptive strategies

1. Introduction

An accurate diagnosis is required for effective medical care and treatment, yet it is often made difficult by the inherent variability in how diseases present across individuals and populations. This variability—driven by many interconnected factors, such as biological, sociodemographic, and environmental factors—can lead to atypical or misleading symptoms. For instance, myocardial infarctions may present without chest pain, especially in women or elderly patients, while autoimmune disorders such as systemic lupus erythematosus (SLE) are notorious for mimicking other conditions.

Global disparities in healthcare access and diagnostic resources further exacerbate these challenges. In low-resource settings, limited access to imaging, laboratory tests, or specialist care may further obscure correct diagnoses. Even in well-resourced healthcare systems, where more advanced diagnostic tools and protocols are available, patients may go undiagnosed due to problems such as accessibility and affordability of healthcare. In recent years, emerging infectious diseases such as SARS-CoV-2 (COVID-19) have proved to pose a great challenge in prevention, diagnosis, and treatment due to the broad spectrum of symptoms that may overlap with common illnesses, as well as the rapid evolution and variants of the disease.

While recent developments in machine learning algorithms to assist with diagnosis are promising, particularly in radiology, they often fail to fully account for the scope of variation seen in real-world patient populations. The increasing push toward personalized/precision medicine shows a growing awareness of the need to account for factors that can cause variability in disease presentation.

The objective of this research is to explore the variability of disease presentation and its effect on diagnosis. By examining key factors contributing to diagnostic complexity, this paper intends to address the need for innovative strategies for improving diagnostic accuracy in the face of clinical uncertainty.

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2. Methodology

A systematic approach was employed to identify relevant literature on the various topics covered. Searches were conducted in academic databases, including Google Scholar and PubMed, using a combination of keywords related to each topic. Preference was given to peer-reviewed publications and studies including clinical data.

The keywords used in the search included terms such as “disease presentation,” “symptom variability,” “atypical symptoms,” “nonspecific symptoms,” “diagnosis,” “diagnostic accuracy,” “diagnostic error,” “misdiagnosis,” “delayed diagnosis,” “genetic predisposition,” “underlying conditions,” “comorbidities,” “age-related differences,” “sex differences,” “sociodemographic factors,” “social determinants of health,” “socioeconomic status,” “regional variation,” “environmental exposure,” “lifestyle factor,” “diagnostic technology,” “machine learning,” “personalized medicine,” and “precision medicine.” Boolean operators (AND, OR) were used to combine search terms across these categories. Additionally, Medical Subject Headings (MeSH) were used in PubMed searches to improve specificity and retrieval relevance. Multiple search iterations were conducted to ensure comprehensive coverage of relevant literature.

Studies were selected based on their relevance to each topic. The selection prioritized the most up-to-date results and studies that presented robust and clearly articulated methodologies. This ensured that the discussion was grounded in current scientific and medical understanding.

For each selected study, relevant information was extracted and organized in a structured format to facilitate synthesis. Key details were documented to provide a clear and coherent analysis. The synthesis method employed in this review follows a narrative synthesis approach, structuring the discussion thematically rather than comparing individual studies. The literature was organized into five main topics: biological and sociodemographic variability, environmental and lifestyle influences, evolving atypical presentations, diagnostic challenges, and current advances in diagnostics and diagnostic technology. Special attention was given to SARS-CoV-2 in evolving atypical presentations as a recent and globally impactful example. This approach ensured a logical progression from fundamental principles to the current landscape, providing a structured and comprehensive summary of the relevant concepts.

3. Results

The synthesis of literature reveals that the variability of disease presentation is a multifactorial problem rooted in a complex interplay of biological, sociodemographic, environmental, and lifestyle factors. This variability leads to significant diagnostic challenges, including atypical presentations that defy classic textbook descriptions. The ongoing evolution of pathogens, exemplified by SARS-CoV-2, further complicates the diagnostic landscape. In response, significant advances in diagnostic technologies, particularly in computational analysis and molecular biology, are being developed to navigate this clinical uncertainty.

3.1. Biological and Sociodemographic Variability

The intrinsic characteristics of an individual, from their genetic code to their existing health status and demographic profile, fundamentally shape how a disease manifests.

3.1.1. Genetic Predisposition

An individual's genetic makeup is a primary determinant of their susceptibility to disease and can significantly alter its presentation. Host genetic factors are key modulators of disease severity, which can explain why some individuals experience disease courses that are more severe or milder than what acquired risk factors alone would predict [1]. These genetic influences can be categorized into two main types. The first is a Mendelian model, where mutations in a single gene, such as *BRCA1* or *BRCA2*, are highly penetrant and confer a strong predisposition to conditions like breast and ovarian cancer. The second is a polygenic model, where the cumulative effect of variations in many genes, each with a small effect, contributes to the risk for common complex diseases like heart disease and diabetes [2]. Polygenic risk scores (PRS) are now being used to quantify this genetic predisposition and have revealed significant molecular heterogeneity responsible for variations in clinical presentation and prognosis, for instance, in different types of diabetes mellitus [3].

3.1.2. Underlying Chronic or Acute Conditions

Comorbidities significantly alter disease presentation and diagnostic accuracy. For instance, elderly patients with myocardial ischemia often exhibit atypical symptoms such as fatigue or dyspnea instead of classic chest pain, particularly when comorbid conditions like diabetes mellitus or dementia are present. Diabetes-associated neuropathy

may blunt pain perception, while cognitive impairments hinder symptom reporting, leading to underdiagnosis or delayed intervention [4]. Similarly, SLE frequently coexists with infections or malignancies, which mimic its symptoms (e.g., fever, rash), complicating differential diagnosis. Viral infections like Epstein-Barr virus can trigger SLE-like autoimmunity through molecular mimicry, further obscuring clinical boundaries [5].

3.1.3. Sociodemographic factors

Racial and ethnic minorities experience higher rates of misdiagnosis due to racial disparities in diseases, systemic inequities in healthcare access and implicit biases. For example, diabetes and cardiovascular disease are more prevalent and severe in non-Hispanic Black and Hispanic populations, yet atypical presentations (e.g., silent ischemia) are often overlooked [6]. Gender also has a significant influence: for example, women with acute coronary syndrome are more likely to present with "atypical" symptoms like nausea or back pain, leading to delayed care compared to men [7]. Socioeconomic status further compounds these challenges; low-resource settings face diagnostic limitations due to limited resources and suboptimal knowledge [8]. In addition, healthcare accessibility varies significantly across geographic and institutional contexts, creating further disparities in timely and accurate diagnosis [9, 10].

3.2. Environmental and Lifestyle Influences

Environmental triggers and lifestyle factors modulate disease phenotypes. Ultraviolet radiation exacerbates SLE flares by promoting apoptosis and autoantigen exposure, while smoking accelerates atherosclerosis, altering cardiovascular symptom profiles [5]. Communities facing systemic disadvantages, such as geographic isolation, pollution, and malnutrition, experience increased susceptibility to infections and chronic diseases [11]. Both industrialized and developing regions grapple with obesity and sedentary lifestyles, which predispose to metabolic syndromes with nonspecific symptoms (e.g., fatigue, weight gain) that mimic other conditions [12, 13].

3.3. COVID-19 as a Case Study in Evolving Atypical Presentations

Initially characterized by respiratory symptoms, SARS-CoV-2 later manifested with gastrointestinal, neurological, and thrombotic complications, varying by age and comorbidity burden. Elderly patients often presented with delirium or functional decline rather than fever, while children developed multisystem inflammatory syndrome (MIS-C), a delayed immune-mediated condition [14-16]. As the pandemic progressed, emerging viral variants introduced additional clinical variability. The Alpha (B.1.1.7) and Delta (B.1.617.2) variants were associated with increased transmissibility and, in some studies, greater severity of illness. In contrast, the Omicron (B.1.1.529) variant, while highly transmissible, often caused milder upper respiratory symptoms but also exhibited enhanced immune evasion capacity, leading to reinfections and breakthrough cases in vaccinated individuals [17].

3.4. Diagnostic Challenges

Diagnostic errors are pervasive, especially in high-stakes settings like intensive care units (ICUs), where cognitive overload and time constraints contribute to inaccuracies. A study of ICU clinicians by Bergl et al. found that attending physicians achieved 77–90% diagnostic accuracy, while junior staff were more prone to errors, though the differences in accuracy were not substantial [18, 19]. These examples from the ICU reveal a broader truth: variability in disease presentation intensifies the risk of diagnostic error in any clinical setting. Incomplete or inaccurate medical histories exacerbate these challenges, as clinicians may miss critical clues (e.g., drug allergies, prior infections) that could redirect them to an accurate diagnosis [20].

3.5. Advances in Diagnostics

In response to the multifaceted challenges of diagnostic variability, recent innovations in computational and molecular technologies have emerged as critical tools to enhance accuracy and reduce disparities.

3.5.1. Machine Learning and Artificial Intelligence

Artificial intelligence (AI) shows promise in mitigating diagnostic variability. For example, algorithms analyzing electronic health records can flag atypical patterns, even when they are subtle [21, 22]. However, current models struggle with underrepresented populations, as training datasets often lack diversity in age, ethnicity, and comorbid conditions [23].

3.5.2. Biomarker-Based Diagnostics

Innovations in molecular diagnostics aim to address phenotypic heterogeneity. In SLE, assays detecting interferon-alpha signatures or anti-dsDNA antibodies improve specificity, while proteomic profiling distinguishes lupus mimickers

like Kikuchi disease [24]. Similarly, point-of-care troponin assays enhance myocardial infarction detection in atypical presentations, though equitable distribution remains a challenge [25].

3.6. Limitations

While this review provides a comprehensive synthesis of disease presentation variability and diagnostic challenges, several limitations should be noted. The narrative approach precludes quantitative meta-analysis of the evidence. Publication bias may skew toward studies with significant or positive findings, and the exclusion of non-English literature could introduce language bias. Additionally, the rapid evolution of diagnostic technologies (e.g., AI tools) means some advances discussed may soon be superseded. These constraints highlight the need for ongoing, methodologically diverse research to validate and refine diagnostic strategies.

4. Discussion

The evidence presented reveals that disease variability stems from complex interactions between biological, sociodemographic, and environmental factors, challenging traditional diagnostic approaches that rely on standardized symptom profiles. This reality demands a fundamental shift in how we conceptualize and implement diagnostic processes across healthcare systems.

The findings underscore three critical needs for improving diagnostic accuracy. First, we must move beyond rigid diagnostic criteria to develop flexible frameworks that account for individual patient contexts, particularly for populations prone to atypical presentations. Second, addressing systemic inequities in healthcare access and clinician training is essential to reduce disparities in diagnostic accuracy. Third, while emerging technologies like AI and biomarker analysis show promise, their development and deployment must prioritize inclusivity to avoid perpetuating existing biases.

The COVID-19 pandemic served as a powerful case study, demonstrating how rapidly evolving diseases can defy initial diagnostic paradigms. This experience highlights the importance of building adaptive diagnostic systems capable of incorporating new evidence in real-time. Such systems should combine technological innovation with human expertise, ensuring that advanced tools complement rather than replace clinical judgment.

Moving forward, healthcare systems should focus on implementing context-aware diagnostic protocols that consider the full spectrum of disease presentations. This requires investments in clinician education about atypical presentations, particularly for high-risk populations, and the development of decision-support tools that account for sociodemographic and environmental factors. Simultaneously, research efforts must prioritize inclusive data collection to ensure diagnostic technologies perform equitably across diverse populations

5. Conclusion

The variability of disease presentation remains one of the most significant challenges in modern medicine, complicating accurate and timely diagnosis across diverse patient populations. This review highlights how biological factors, sociodemographic disparities, environmental influences, and evolving disease patterns collectively contribute to diagnostic uncertainty. While emerging technologies like AI and biomarker-based diagnostics offer promising solutions, their current limitations, particularly regarding equitable implementation, must be addressed to ensure they benefit all patients.

Moving forward, a multifaceted approach is essential. Clinicians must be trained to recognize atypical presentations, especially in high-risk groups, while healthcare systems should prioritize adaptable diagnostic protocols that account for individual variability. Simultaneously, technological innovations must be developed with inclusivity in mind, using representative datasets and ensuring accessibility across resource settings. Crucially, addressing the social determinants of health and systemic inequities in healthcare access will be fundamental to reducing diagnostic disparities.

Ultimately, improving diagnostic accuracy in the face of disease variability requires collaboration across disciplines—from clinical medicine and public health to data science and policy-making. By integrating precision diagnostics with equity-focused strategies, we can work toward a healthcare system that delivers accurate, personalized diagnoses to every patient, regardless of their background or circumstances. The path forward demands both innovation and intentionality, ensuring that advances in diagnosis translate into better outcomes for all.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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