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Systematic Review of the Implementation of Artificial Intelligence in the Diagnosis of Central Nervous System Infections

Santral Sinir Sistemi Enfeksiyonları Tanısında Yapay Zeka Uygulamaları ile İlgili Sistematik Derleme

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Abstract

Despite the increasing use of machine learning (ML) in the early diagnosis and determination of risk factors of various infections, studies evaluating the use of ML in central nervous system infections (CNSI) are limited. The Scopus, Web of Science, and PubMed databases were searched via Ovid using the keywords "Artificial intelligence" OR "Machine learning" OR "Deep learning" AND "Central nervous system infection" OR "Encephalitis" OR "Meningitis". The last search was performed on July 20, 2022. Studies were selected based on the population, intervention, comparator, outcome(s) of interest, and study design (PICOS). The Joanna Briggs Institute Cohort Studies and Case Control Research Checklist were used to determine the study quality. Studies that included adolescent and adult patients diagnosed with CNSI via cerebrospinal fluid testing or other laboratory examination and imaging methods were reviewed. Five of the 731 identified articles were included. The studies have focused on the role of ML in the following issues: risk factors for developing healthcare-associated ventriculitis/meningitis, assessing treatment failure in patients with spinal epidural abscess (SEA) who were treated non-operatively, prediction of mortality in patients with SEA, differential diagnosis of meningitis, and comparison of differential diagnoses determined using ML methods and that determined by clinicians. Although more studies are needed in this area, ML may soon be used effectively in the diagnosis of CNSI. It is essential to determine the best ML model for each issue. Artificial intelligence applications could potentially contribute to the rapid diagnosis and effective early treatment of diseases.

Keywords: Artificial intelligence, machine learning, deep learning, central nervous system infections, encephalitis

Öz

Farklı enfeksiyonların erken tanısında ve risk faktörlerinin belirlenmesinde makine öğrenmesinin (ML) artan kullanımına rağmen santral sinir sistemi enfeksiyonlarında (SSSE) ML kullanımını araştıran az sayıda çalışma mevcuttur. Literatür taraması; Scopus, Web of Science, Ovid aracılığıyla PubMed veritabanlarında "Yapay zeka" veya "Makine öğrenmesi" veya "Derin öğrenme" ve "Santral sinir sistemi enfeksiyonları" veya "Ensefalit" veya "menenjit" anahtar kelimeleri kullanılarak yapıldı. Son güncelleme 20 Temmuz 2022'de gerçekleştirildi. Çalışmalar popülasyon, müdahale, karşılaştırmalı, ilgilenilen sonuç(lar) ve çalışma tasarımı göre seçilmiştir (PICOS). Çalışmaların kalite kontrolü için Joanna Briggs Enstitüsü Kohort Çalışmaları ve Olgu Kontrol Araştırmaları Kontrol Listesi kullanıldı. Çalışma popülasyonu, beyin omurilik sıvısı testi veya diğer laboratuvar inceleme ve görüntüleme yöntemleri ile SSSE tanısı doğrulanmış adolesan ve yetişkin hastalar olarak tanımlandı. İncelenen 731 makaleden beşi dahil edildi. Çalışmalar aşağıdaki konularda ML'nin rolüne odaklanmıştır: Sağlık bakımıyla ilişkili ventrikülit/menenjit için risk faktörleri, ameliyat olmaksızın sadece medikal tedavi edilen spinal epidural apse (SEA) hastalarında tedavi başarısızlığının değerlendirilmesi, SEA hastalarında mortalitenin öngörülmesi, menenjit ayırıcı tanısı ve ayırıcı tanıda klinisyen kararları ile ML metodlarının karşılaştırılmasıdır. Mevcut literatüre bakıldığında, bu

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Öz

alanda daha fazla çalışmaya ihtiyaç duyulmakla birlikte, ML yakında SSE'de etkin bir şekilde kullanılabilecektir. Her bir konu için en iyi ML modelini belirlemek gereklidir. Yapay zeka uygulamaları, hızlı teşhis ve etkili erken tedaviye katkıda bulunmak için büyük bir potansiyel taşımaktadır.

Anahtar Kelimeler: Yapay zeka, makine öğrenmesi, derin öğrenme, santral sinir sistemi enfeksiyonları, ensefalit

Introduction

The central nervous system (CNS) consists of the brain (brain and cerebellum), spinal cord, optic nerves, and the membranes that cover them^[1]. CNS infections (CNSI) include meningitis/ventriculitis, encephalitis, and brain/spinal abscesses^[1-3]. They can occur spontaneously or as a complication of neurosurgical operations. Bacteremia or viremia may occur due to infections in the regions adjacent to the CNS, such as the mastoid air cells, sinuses, or middle ear, or primary conditions in more distant anatomical regions^[1,3]. Central nervous system infections are diverse, ranging from common to rare, acute to chronic, and benign to fatal. While some infections are self-limiting or recover quickly with modern treatment, others progress relentlessly despite treatment or have no known cure^[4,5]. Rapid diagnosis and aggressive treatment in acute CNSIs provide the best chance of recovery without sequelae and prevent mortality^[1,3,5]. A systematic approach can be followed in patient with suspected CNSI, which includes assessment of risk factors, careful physical examination, neuro-imaging, serological analysis, and modern laboratory testing^[3,5,6]. Early and appropriate anti-infective treatments and critical care may improve patient outcomes^[6].

The Centers for Disease Control and Prevention's criteria for diagnosing CNSIs are as follows^[2]:

- Isolation of the pathogens from the cerebrospinal fluid (CSF), brain or dura, and spinal epidural, or subdural space,
- The patient has at least one (meningitis) or both (intracranial infection) of the following without any other known cause:
 - i. Fever (>38 °C), headache, dizziness, nuchal rigidity, meningeal symptoms, cranial nerve manifestations, altered level of consciousness or confusion, and irritability, or
 - ii. At least one of the following symptoms of a spinal abscess: back pain, focal tenderness, radiculitis, paraparesis, or paraplegia.
- Increased white cell count, elevated protein levels, and/or decreased glucose levels in the CSF; positive antigen test using the CSF, blood, or urine; organisms cultured from the blood; organisms seen on Gram staining of the CSF; radiographic evidence of infection (abnormal findings on ultrasound, CT scan, magnetic resonance imaging, radionuclide brain scan, or arteriogram); or a four-fold increase in the diagnostic single antibody titer (IgM) or matched serum (IgG) for the pathogen.

Clinicians can comfortably interpret and integrate up to four variables at once. However, computers do not share these limitations; they can simultaneously handle a broader range of variables and recognize patterns that the human eye cannot. Therefore, using predictive analytics through artificial intelligence (AI)/machine learning (ML) can improve our ability to identify clinically relevant patterns, including those of infectious diseases^[7-9].

Artificial intelligence applications offer great potential in preventing and controlling infections^[10]. As healthcare information technology systems become more integrated and generate large volumes of data from various sources, AI systems can detect patterns in data, accelerating the detection of outbreaks and providing richer datasets for subsequent analyses. Additionally, AI can support a change in the system state by determining the cost of inaction, modeling solutions by simulating the behavior of different agents within a complex system, and generating analytics using the data collected^[11]. AI is the acquisition of human-specific abilities, such as reasoning, meaning-making, generalization, decision-making, questioning, and learning through past experiences, by computers and computer-assisted/controlled machines. The aim of AI is to create systems using human intelligence. We are in the era of the clinical development of AI, a technology that can greatly enhance and surpass the capabilities of manual procedures and even existing technologies.

In this study, we aimed to systematically review current models that clinically attempted to apply AI techniques in CNSIs and to identify efficient promising methods. In doing so, we aimed to determine whether AI can be used to systematically approach CNSIs, determine differential diagnoses, and predict mortality. Herein, we have presented the current literature systematically based on the evidence available.

Materials and Methods

1. Search strategy

This systematic review was performed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline. The Scopus, Web of Science, and PubMed databases were searched via Ovid using the keywords "Artificial intelligence" OR "Machine learning" OR "Deep learning" AND "Central nervous system infection" OR

"Encephalitis" OR "Meningitis" between 17 June and 20 July 2022.

2. Eligibility criteria

Studies were selected based on the population, intervention, comparator, outcome(s) of interest, and study design (PICOS framework). These criteria are detailed as follows:

Type of population: Studies with adolescent and adult patients with confirmed CNSIs were included.

Type of interventions: Studies where CNSIs were diagnosed by CSF testing or other laboratory examination and imaging (where appropriate) were included.

Type of comparators: There was no restriction regarding the type of comparator used in the study.

Type of outcome measurements: The main outcome of interest were the benefits and risks of AI applications in CNSIs. We aimed to evaluate the use of AI applications in determining the mortality and prognosis of differential diagnoses for CNSIs.

Type of studies: Randomized controlled trials, cross-sectional studies, cohort studies, case-control studies, and case reports, that were published in English between January 1, 2000 and July 20, 2022, and were focused on the application of AI for CNSIs were included in the study.

3. Study selection

Studies were selected based on three steps: the complete titles, summaries, and texts. Studies that did not meet the inclusion criteria during the screening process were excluded. Subsequently, the full text of eligible or potentially eligible articles were independently reviewed by the researchers. Disputes and discussions at every step of the screening process were resolved by consensus. A third-party reviewer was involved in case a consensus could not be reached. Studies that met the inclusion criteria were saved via EndNote (version 20.0; Clarivate, Philadelphia, PA, USA), and the full texts were downloaded. The evaluation of the full texts for inclusion and quality of the studies were performed by the two independent researchers who had assessed the abstracts. The flowchart of the review process is depicted in Figure 1.

4. Data extraction

All authors extracted data independently. Disputes were resolved by consensus after discussing with all the authors. The extracted data included author names, year of publication, study design, country where the study was performed, number of patients, study subject, study purpose, and study results.

5. Quality assessment

The Joanna Briggs Institute (JBI) Cohort Studies and Case Control Research Checklist that was developed by JBI^[12] and translated into Turkish by the researchers were used in this review. The index was used to assess four types of bias: selection, performance, perception, and attrition. The cohort studies quality list included 11 items, and the case control checklist included 10 items. The items were scored one point for "yes" and zero points for "no-uncertain" and "not applicable". A high overall score indicated a high-quality study methodology^[12]. Three of the articles included in the systematic review^[13-15] were evaluated with the cohort studies quality list and two^[16,17] were assessed with the case control checklist. The quality of evidence was determined as medium and high because the answer to more than half of the items was "yes"; these studies were included in the systematic review. In two cohort studies^[14,15], six of the 11 checklist questions were answered "yes", and in one cohort study^[13] nine of the 11 questioned were answered "yes". In two case control studies, six^[16] and seven^[17] of the 10 questions were answered "yes". The general quality score of the studies was 54.5-82%. In addition, the inter-rater agreement (kappa value) was one for both JBI Checklists; a high inter-rater agreement was achieved^[18].

6. Protocol and registration

We have registered the protocol of this review in advance (PROSPERO 2022 CRD42022326064 URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022326064).

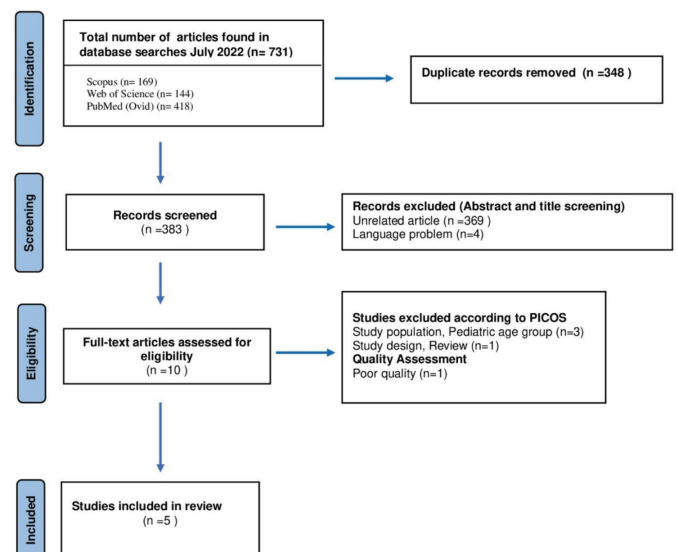


Figure 1. Flowchart of the review process

Statistical Analysis

Inter-rater reliability of the researchers who evaluated the quality of the studies was analyzed using Statistical Package for the Social Sciences (version 22.0; IBM, Armonk, New York, USA). Inter-rater agreement (kappa value) was also analyzed.

Results

1. Search results

A total of 731 studies were identified. Of the 731 studies, 348 were excluded as they were duplicates. After screening the abstracts and titles, unrelated articles (n=369) and articles that were written in a language other than English (n=4) were eliminated. After the full texts were evaluated, four studies were excluded due to the following reasons: the study population belonged to the pediatric age group (n=3) and the study was a review (n=1). The quality of the studies was evaluated by two independent researchers. One study was eliminated due to a low quality score. The flowchart of the review process is presented in Figure 1.

2. Features of the studies

All of the studies included in the systematic review were original research articles. Adolescent and adult patients with confirmed CNSIs were included in the review. The lowest age of the patient included was 14 years. The characteristics and results of the studies reviewed are listed in Table 1.

Executive Summary of AI Implementations for CNS Infections

Machine learning is a broad term used in this field, which refers to recurrent and automatic optimization of statistical models based on the most accurate relevant dataset^[19]. It can be used to find associations between variables by using the present data to predict the prognosis and risk factors and identify the differential diagnoses for the infection. The most frequently used ML algorithms are random forest (RF), artificial neural network (ANN), support vector machine (SVM), and gradient boosting decision tree^[19,20]. Previous studies have used and compared various algorithms to determine the best with the highest performance characteristics, such as sensitivity and specificity^[19].

Despite the increasing use of ML algorithms for the early diagnosis of infections and determining the differential diagnoses, risk factors, and prognosis of the various infections, only a few studies have assessed the role of ML algorithms in CNSIs. Although it has been considered for years that ML could be used in the diagnosis of CNSIs, we determined that the first ML-related article for CNSIs was conducted in Russia by Savins et al.^[13] and was published in 2018. The prospective

single-center study aimed to determine the incidence and risk factors of healthcare-associated ventriculitis and meningitis (HAVM) in high-risk patients in the intensive care unit (ICU). In their study cohort, they evaluated eligible patients who had been cared for in the neuro-ICU for 80 months. Additionally, patients with, and without HAVM were compared. They used RF algorithms and determined that the main risk factors for HAVM were the presence of an external ventricular drainage catheter, CSF leakage, craniotomy, and surgical site infections. They suggested combating the presence and duration of these risk factors to prevent HAVM.

In 2019, two studies investigating the role of ML algorithms in CNSIs were conducted by the same authors; one study had two added authors^[16,17]. Although both studies included patients with spinal epidural abscesses (SEA), one used ML algorithms to predict the mortality of the patients, while the other developed an ML algorithm to predict the risk factors for treatment failure in patients treated medically and not surgically^[16,17]. Karhade et al.^[16], aimed to develop a web application that uses an ML algorithm to predict the mortality of patients with SEA. This retrospective case-control study used five different algorithms, compared them, and determined that stochastic gradient boosting was the best model. They evaluated 1,053 patients with SEA, and 12.7% had in-hospital or 90-day mortality. They determined the risk factors in order of importance as follows: age, albumin level, platelet count, neutrophil-lymphocyte ratio (NLR), hemodialysis, and the presence of malignancy and diabetes mellitus. They also provided the web address of their application for its external validation in other populations (<https://sorg-apps.shinyapps.io/seamortality/>).

Shah et al.^[17] evaluated the risk factors for treatment failure in patients with SEA who were treated non-operatively in the same period as that of the previous study (1993-2016). In this retrospective cohort study, they determined that among the 367 patients who were managed non-operatively, 27% experienced treatment failure. They determined that the elastic-net penalized logistic regression model was the best model; the application is provided at: <https://sorgapps.shinyapps.io/seanonop/>. They determined that the main risk factors associated with treatment failure are the presence of motor and sensory deficits, diabetes mellitus, malignancy, abscess near the thecal sac, or vertebral fracture, and the involvement of three or more vertebrae.

In 2020, Jeong et al.^[15] first attempted to differentiate between viral meningitis (VM) and tuberculosis meningitis (TBM) using ML algorithms. It was an important study because TBM is severe and differentiating it from VM using conventional methods is difficult and time-consuming. It was a retrospective study conducted at five teaching hospitals in Korea, which included 203 patients with a definitive diagnosis of VM (n=143) and those with a probable or

Table 1. Main findings of the studies included in the review

Authors, publication year	Study design	Study period	Country	Number of patients, N	Subject	Objective	Results	Study quality assessment
Savin et al., 2018 ^[13]	An observational, single-center, cohort study	2010-2017	Russia	2286 patients of all ages were included, of which 216 developed HAVM.	Determination of HAVM incidence and risk factors using machine learning methods in patients admitted to the neurology intensive care unit	- To determine the incidence of HAVM in the high-risk patient group - Associated with the incidence of HAVM. Comparing the risk factors that patients are exposed to during their stay in the intensive care unit - Identifying HAVM risk factors with machine learning and regression approaches	- 216 of the 2286 patients developed HAVM. The cumulative incidence of HAVM was 9.45% - The four most important factors associated with the development of HAVM were EVD, craniotomy, superficial surgical site infections after a neurosurgical procedure, and CSF leakage. - The machine learning models performed better than the regression analyses	9/11 (82%)
Mentis et al., 2021 ^[14]	Retrospective cohort study	ND	Greece	Patients ages >14 years (n=1662)	Establishing an algorithm using artificial intelligence for the differential diagnosis of bacterial and viral meningitis	Determining the most appropriate algorithm for determining the differential diagnosis of viral and bacterial meningitis by evaluating the cerebrospinal fluid and laboratory parameters using artificial intelligence approaches (especially machine learning).	- When machine learning algorithms were evaluated by cross-assessment, the optimal algorithm was >95% for viral meningitis and 78% for bacterial meningitis. - Using multiple logistic regression and random forest machine learning algorithms, the best performance was obtained using CSF neutrophil and lymphocyte counts, NLR, albumin, and glucose levels, age, and CRP levels as parameters.	6/11 (54.5%)
Jeong et al., 2021 ^[15]	Retrospective, cohort study	2000-2018	South Korea	203 adult patients. TB meningitis: n=60. Viral meningitis: n=143.	Comparison of the results of machine learning methods and clinician's decisions in differentiating between TB meningitis and viral meningitis	Various machine learning techniques, including deep learning, were used to distinguish between TB meningitis and viral meningitis. These results were compared those obtained based on the clinician's decisions	- Older age, longer symptom duration, lower sodium level, lower CSF glucose level, higher CSF protein level, and CSF ADA positivity were associated with TB meningitis. - The AUC of the artificial neural network model was statistically higher than that of the clinician's.	6/11 (54.5%)

Table 1. Continued

Authors, publication year	Study design	Study period	Country	Number of patients, N	Subject	Objective	Results	Study quality assessment
Karhade et al., 2019 ^[16]	Retrospective, multicenter, case-control study	1993-2016	USA	1053 patients with SEA	Five machine learning algorithms were developed for determining in-hospital and 90-day post-discharge mortality rates in patients with SEAs. The algorithms were evaluated based on discrimination, calibration, overall performance, and decision curve analysis.	- To develop machine learning algorithms for the prediction of in-hospital and 90-day post-discharge mortality rates in patients with SEA - Creating suitable machine learning methods that can be made available as a digital application for the departments involved in the treatment of SEA.	-Of the 1053 patients with SEA, 134 died in the hospital or within 90 days of discharge. -The best performance was achieved by the stochastic gradient boosting model. -Variables used to predict mortality were age, albumin level, platelet count, neutrophil/lymphocyte ratio, hemodialysis, active malignancy, and diabetes.	6/10 (60%)
Shah et al., 2019 ^[17]	Retrospective, case-control study	1993-2016	USA	367 patients with SEA	The use of machine learning methods to predict treatment failure in patients with SEA treated non-operatively	To establish a machine learning algorithm related using factors that could predict the failure of non-operative treatment in patients with SEA	- Ninety-nine (27%) patients experienced treatment failure with non-surgical methods - The elastic-net penalized logistic regression model was determined as the best model. - They determined the factors associated with treatment failure were the presence of motor and sensory deficits, diabetes mellitus, malignancy, abscess near to the thecal sac, or vertebral fracture, and the involvement of 3 or more vertebrae.	7/10 (70%)

HAVM: Healthcare-associated ventriculitis and meningitis, EVD: External ventricular drainage, TB: Tuberculosis, SEA: Spinal epidural abscess, CSF: Cerebrospinal fluid, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio

confirmed diagnosis of TBM (n=60). They used various ML algorithms to differentiate VM from TBM and compared these results with those obtained via the clinical judgment of medical clinicians and infectious disease specialists (with at least 10 years of experience) who used the patients' medical records. The following variables were assessed: age, symptom duration, vomiting, neurologic signs, and symptoms such as confusion, lethargy, cranial nerve damage, and hemiplegia, CSF levels of protein, glucose, and adenosine deaminase, and serum sodium level. They used different ML models, including

naive Bayes (NB), multivariate logistic regression (MLR), RF, ANN, and SVM. They aimed to determine the best model and variables to differentiate VM from TBM more rapidly and accurately. They determined that the ANN model had the highest area under curve value among all the models. Furthermore, they compared the result of this model with that of the clinicians' judgments and concluded that the ANN model had a comparable diagnostic performance with that of an ID specialist and performed better than other non-expert clinicians^[15].

Most CNSIs are fatal. However, several centers experience delays in diagnosing such infections. Thus, ML can be beneficial for such cases. It is challenging to achieve major progress in ML using only research performed by physicians. The cooperation of engineers, software developers, doctors, and basic scientists is also required. Progress in ML may reduce the mortality rate due to CNSIs.

Mentis et al.^[14] used AI for determining the differential diagnosis of VM and bacterial meningitis in a nationwide retrospective study in Greece. They used the National Reference Laboratory data that stored the CSF analysis results of 4339 patients. Of these patients, 1662 were aged >14 years. Of the 1662 patients, 803 had bacterial meningitis, and 824 had VM that were diagnosed using multiplex polymerase chain reaction and conventional methods. They following variables were used to predict the meningitis type using ML algorithms: sex, CSF lymphocyte, and neutrophil counts, CSF NLR, blood soluble urokinase-type plasminogen activator receptor level, blood C-reactive protein (CRP), albumin, and glucose levels, and the CSF lymphocytes to blood CRP ratio. They used three different ML algorithms: RF, NB, and MLR. They concluded that sex, CSF lymphocyte, and neutrophil counts, NLR, and blood CRP, glucose, and albumin levels can predict the meningitis type using ML algorithms. Multivariate logistic regression was the optimum model to predict VM, while RF was the ideal model to detect bacterial meningitis. Therefore, they suggested using both MLR and RF models to optimize the early differential diagnosis of meningitis^[14]. A summary of the main findings of the published studies are presented in Table 1.

Conclusion

Although studies on the use of ML algorithms in CNSIs are limited, the use of AI programs in different medical fields are becoming increasingly common. Machine learning algorithms may be used more effectively for determining CNSIs in the near future. Because rapid diagnosis and early and effective treatment are significant predictors of mortality in CNSIs, the effective use of developing technologies for this purpose will be in the physician's interest. Thus, developing ML algorithms and incorporating them into web-based applications for their use in larger cohorts and during the first presentation to the emergency department will contribute to the rapid diagnosis and effective early treatment of CNSIs by non-expert clinicians as well.

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Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.B., O.K., Design: A.B., O.K., Data Collection or Processing: A.B., B.O.Ö., E.Ö., O.K., Analysis or Interpretation: A.B., B.O.Ö., E.Ö., O.K., Literature Search: A.B., B.O.Ö., E.Ö., O.K., Writing: A.B., B.O.Ö., E.Ö., O.K.

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