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Original Article

Human Readers versus AI-Based Systems in ASPECTS Scoring for Acute Ischemic Stroke: A Systematic Review and Meta-Analysis with Region-Specific Guidance

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ABSTRACT

Introduction: The Alberta Stroke Program Early CT Score (ASPECTS) is widely used to evaluate early ischemic changes and guide thrombectomy decisions in acute stroke patients. However, significant interobserver variability in manual ASPECTS assessment presents a challenge. Recent advances in artificial intelligence have enabled the development of automated ASPECTS scoring systems; however, their comparative performance against expert interpretation remains insufficiently studied.
Methods: We conducted a systematic review and meta-analysis following PRISMA 2020 guidelines. We searched multiple scientific databases for studies comparing automated and manual ASPECTS on Non-Contrast Computed Tomography (NCCT). Interobserver reliability was assessed using pooled interclass correlation coefficients (ICCs). Subgroup analyses were made using software types, reference standards, time windows, and computed tomography-based factors.
Results: Eleven studies with a total of 1,976 patients were included. Automated ASPECTS demonstrated good reliability against reference standards (ICC: 0.72), comparable to expert readings (ICC: 0.62). RAPID ASPECTS performed highest (ICC: 0.86), especially for high-stakes decision-making. AI advantages were most significant with thin-slice CT (2.5mm; +0.16), intermediate time windows (120-240min; +0.16), and higher NIHSS scores (p=0.026).
Conclusion: AI-driven ASPECTS systems perform comparably or even better in some cases than human readers in detecting early ischemic changes, especially in specific scenarios. Strategic utilization focusing on high-impact scenarios and region-specific performance patterns offers better diagnostic accuracy, reduced interpretation times, and better and wiser treatment selection in acute stroke care.

1. Introduction

Acute ischemic stroke is considered among the leading causes of mortality and long-term disability all over the world, with around 13.7 million new stroke cases occurring annually [1, 2]. The evolution of stroke management has been marked by the improvements in patient selection criteria for intra-arterial reperfusion therapy and mechanical thrombectomy, which has been raised as the gold standard approach for patients with large vessel occlusion in recent years [3]. An important part of this progress has been developing and refining imaging selection processes to identify suitable candidates for intervention. Among these, the Alberta Stroke Program Early CT Score (ASPECTS) has become a widely utilized tool for standardized assessment of early ischemic changes on non-contrast computed tomography (NCCT) [3].

ASPECTS provides a semiquantitative ten-point scoring system for evaluating the extent of early ischemic changes in the middle cerebral artery territory on NCCT [4]. This system has been integrated and utilized into multiple clinical guidelines and is frequently used to determine eligibility for reperfusion therapies, with lower scores indicating more ischemic damage and reduced benefit from intervention [4]. Despite its widespread validation and clinical utility, ASPECTS interpretation has significant challenges. The identification of early ischemic changes in NCCT requires good expertise, and the interobserver variability has been documented among radiologists, neurologists, and vascular neurosurgeons [5]. This variability introduces inconsistencies in treatment decision-making, especially in time-critical situations where rapid and accurate assessment is essential. The recent advances in artificial intelligence (AI) and machine learning have allowed

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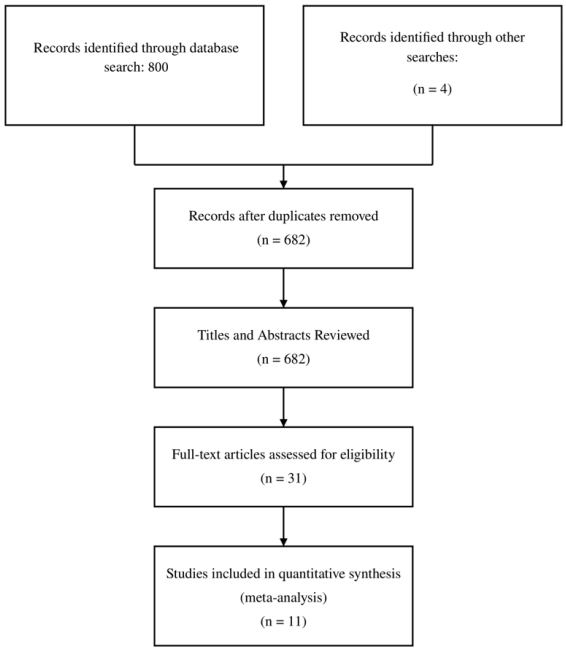

Figure 1: PRISMA Flowchart of Literature Search and Studies Inclusion.

the development of automated ASPECTS prediction algorithms for NCCT images [6]. These AI-driven systems aim to provide a standardized, rapid, and objective assessment of early ischemic changes and can overcome the limitations of human interpretation [6]. Several commercial platforms have been developed, including e-ASPECTS (Brainomix, Oxford, UK), RAPID ASPECTS (iSchemaView, Menlo Park, California, USA), and Syngo.via Frontier ASPECTS (Siemens Healthcare, Erlangen, Germany), in addition to the other institutional-based custom-built research algorithms [7, 8, 9]. While some of the previous studies have reported promising results with these automated systems, their clinical applicability and comparative performance against expert readers remain incompletely investigated and discussed in a detailed manner [10]. To address this knowledge gap, we aim to conduct a systematic review and meta-analysis comparing the performance of automated and manual ASPECTS predictions for detecting early ischemic changes in NCCT. Our primary objective is to determine the interobserver reliability between expert readings and automated ASPECTS predictions and their respective correlations with reference standards. In addition to that, we aim to identify factors affecting AI performance through subgroup analyses focusing on software type, reference standard methodology, time window, and CT-based factors. By synthesizing the current evidence, we look forward to providing important key points and highlights into the role of AI-driven ASPECTS in clinical practice and its impact on stroke imaging interpretation across various clinical scenarios.

2. Methods

2.1. Search Strategy and Study Selection

Our systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11]. We searched MEDLINE (PubMed), Scopus (EMBASE), Web of Science, Google Scholar, and Cochrane Central databases until February 23, 2025. The search strategy included combinations of the following terms with Boolean operators: "e-ASPECTS," "RAPID ASPECTS," "artificial intelligence," "CT," "comparison," "vs." and "acute ischemic stroke." Additionally, we manually screened the references of retrieved publications to identify relevant articles not captured by the electronic search. Two authors have independently performed the initial screening of titles and abstracts. Studies were eligible if they: (1) enrolled patients 18 years with acute ischemic stroke due to large vessel occlusion; (2) utilized NCCT scans within 24 hours of symptom onset; (3) compared automated ASPECTS algorithms with expert reads; and (4) reported interobserver reliability metrics. We excluded studies involving (1) intracranial hemorrhage, (2) imaging beyond 24 hours, or (3) primary modalities other than NCCT (e.g., DWI, CT perfusion, CT angiography). Two authors assessed Full-text articles independently, with disagreements resolved by consensus or consultation with a third author.

2.2. Data Extraction and Quality Assessment

Using a standardized data collection form, two authors have independently extracted the following information: first author, publication year, software type, patient demographics, median National Institutes of Health Stroke Scale (NIHSS), time to imaging, CT parameters, reference standard methodology, and interclass correlation coefficients (ICCs) with 95% confidence intervals for all reliability comparisons. We extracted ICCs for all available reader combinations when multiple expert readers were reported.

Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Two reviewers evaluated each study for risk of bias and applicability concerns across four domains: patient selection, index test (automated and manual ASPECTS), reference standard, and flow and timing. Studies were classified as having "low," "high," or "unclear" risk for each domain. We calculated an overall quality score representing the proportion of domains with a low risk of bias.

2.3. Statistical Analysis

The primary outcomes were interobserver reliability between (1) expert readings, (2) expert and automated ASPECTS readings, (3) expert readings and reference standards, and (4) automated ASPECTS and reference standards. For meta-analysis, we transformed ICCs using Fisher's z-transformation method to normalize the distribution of correlation coefficients. Due to anticipated heterogeneity, the transformed values were then pooled using random-effects models (DerSimonian and Laird). The pooled z-scores were back-transformed to obtain the pooled ICC values with 95% confidence intervals.

Heterogeneity was assessed using Cochran's Q test and the I^2 statistic, with $I^2 > 50\%$ or $p < 0.10$ indicating significant heterogeneity. ICC values were interpreted as follows: poor (<0.40), moderate (0.40-0.59), good (0.60-0.74), and excellent (0.75-1.00). For publication bias assessment, we constructed funnel plots and performed Egger's regression test.

2.4. Region-Specific Analysis

To provide a better understanding of automated ASPECTS performance, we conducted a focused and specified region-by-region analysis across all ten ASPECTS territories. We extracted region-specific detection performance for each component region (caudate nucleus, lentiform nucleus, internal capsule, insular ribbon, and cortical regions M1-M6) from studies reporting these data points. We calculated region-specific interobserver reliability between (1) AI systems and reference standards, (2) expert readers and reference standards, and (3) AI systems and expert readers.

Table 1: Baseline Characteristics of The Included Studies

Study (Author, Year)	ASPECTS Software	Patients (n)	Mean/Median Age (years)	Sex (M/F)	Baseline NIHSS	Time to NCCT (min)	CT Slice Thickness (mm)	Reference Standard
Brinjikji et al., 2021 [6]	e-ASPECTS (Brainomix)	60	67.3 ± 16.3	28/32	18 (10–22)	NR	NR	24h CT/MRI consensus
Delio et al., 2021 [12]	RAPID ASPECTS (iSchemaView)	50	62.7 ± 13.2	32/18	17.5	3.4 (1.5)	2.5	MRI consensus
Kuang et al., 2020 [13]	Custom-made software	100	70 (64–77)	86/71	NR	49 (23.8–95.5)	5.0	DWI within 1h
Hoelter et al., 2020 [8]	e-ASPECTS, RAPID, Frontier (Comparative)	131	75 (66–82)	76/55	17 (13–20)	NR	1.0	NCCT consensus
Wolff et al., 2020 [14]	Syngo.via Frontier (Siemens)	355	66 (54–76)	204/151	18 (15–22)	114 (68–196)	Mixed	Consensus on baseline CT
Neuhaus et al., 2019 [15]	e-ASPECTS (Brainomix)	178	67.6 ± 14.8	87/91	18 (12–22)	NR	5.0	NR
Goebel et al., 2019 [16]	Syngo.via Frontier (Siemens)	100	74.5 (30–95)	38/62	12 (2–21)	91 (32–836)	5.0	NR
Li et al., 2020 [17]	Syngo.via Frontier (Siemens)	55	65 (28–87)	42/13	9 (1–35)	185 (33–360)	NR	Follow-up NCCT consensus
Albers et al., 2019 [18]	RAPID ASPECTS (iSchemaView)	65	61 (32–79)	41/24	19 (16–23)	228 ± 114	2.5	DWI independent review
Guberina et al., 2018 [19]	e-ASPECTS (Brainomix)	119	70 (35–94)	NR	7 (1–21)	76 (30–120)	NR	Follow-up CT by neuroradiologist
Kuang et al., 2019 [20]	Custom-made software	602	71 (62–80)	309/293	15 (9–19)	114 (73–183)	5.0	24h NCCT expert measurement

AI, Artificial Intelligence; ASPECTS, Alberta Stroke Program Early CT Score; CT, Computed Tomography; DWI, Diffusion-Weighted Imaging; F, Female; ICC, Intraclass Correlation Coefficient; LVO, Large Vessel Occlusion; M, Male; MRI, Magnetic Resonance Imaging; NCCT, Non-Contrast Computed Tomography; NIHSS, National Institutes of Health Stroke Scale; NR, Not Reported.

We further analyzed region-specific performance according to patient characteristics (NIHSS, age, time from onset), technical factors, and parameters (CT slice thickness, scanner type). We calculated sensitivity, specificity, and detection reliability metrics for each region. We created region-specific heat maps to visualize performance patterns across the ASPECTS territories and developed statistical models to identify factors affecting detection accuracy in each region. This method aimed to extend prior meta-analyses that investigated only ASPECTS scores and allowed for the identification of integrative strengths between AI and human readers at the regional level. Then, we developed a region-stratified reading strategy that identifies the verification strategies for each ASPECTS territory based on the relative strengths of AI and human assessment.

3. Results

3.1. Study Selection and Characteristics

Our literature search first retrieved a total of 804 studies, of which 682 remained after removing duplicates. After screening titles and abstracts, we assessed 31 full-text articles for eligibility. Then, 11 studies published between 2018 and 2021 met our inclusion criteria and were included in the meta-analysis, forming a total of 1,976 patients with acute ischemic stroke **(Figure 1)**. The characteristics of the included studies are summarized in **(Table 1)**. Four studies evaluated e-ASPECTS (Brainomix, Oxford, UK), two evaluated RAPID ASPECTS (iSchemaView, Menlo Park, California, USA), and three evaluated Syngo.via Frontier ASPECTS (Siemens Healthcare, Erlangen, Germany), and two studies utilized custom-made software. Sample sizes ranged from 50 to 602 patients. The median or mean age of patients across studies ranged from 61 to 75 years. Baseline NIHSS scores varied considerably, with median values ranging from 7 to 19. Time from symptom onset to baseline NCCT ranged from 49 to 228 minutes among studies reporting this parameter. CT slice thickness, when reported, ranged from 1.0 to 5.0 mm. Reference standards included follow-up CT, MRI/DWI, or consensus readings.

3.2. Primary Meta-Analysis Outcomes

Our analysis of interobserver reliability between expert readings showed good agreement with a pooled ICC of 0.72 (95% CI: 0.63-0.79; p-value<0.001). The interobserver reliability between automated software and expert readings demonstrated moderate agreement with a pooled ICC of 0.54 (95% CI: 0.40-0.67; p-value<0.001). When comparing the expert readings to reference standards, we found good reliability with a pooled ICC of 0.62 (95% CI: 0.52-0.71; p-value<0.001). The automated ASPECTS predictions agreed with reference standards, resulting in a pooled ICC of 0.72 (95% CI: 0.61-0.80; p-value<0.001), higher than the expert-to-reference standard reliability. All analyses demonstrated statistically significant heterogeneity, with I^2 values ranging from 82.7% to 93.2% (p-values<0.001 for all), necessitating the use of random effects models **(Supplementary Table 1)**. Egger's regression test revealed no significant publication bias across all analyses (p-values>0.05).

3.3. Subgroup Meta-Analyses

Our subgroup analyses **(Table 2)** revealed multiple significant differences in AI performance across software types. RAPID ASPECTS was observed to have the highest reliability when compared with reference standards (ICC: 0.86; 95% CI: 0.78-0.92), followed by e-ASPECTS (ICC: 0.78; 95% CI: 0.64-0.87), custom-based software (ICC: 0.64; 95% CI: 0.53-0.73), and Syngo.via Frontier (ICC: 0.60; 95% CI: 0.48-0.69). When analyzed according to the reference standard methodology, AI systems showed higher

Table 2: Subgroup Analyses of AI-driven ASPECTS Performance

Analysis Subgroup	Total Included Patients (n)	AI vs Expert ICC (95% CI)	AI vs Reference ICC (95% CI)	Expert vs Reference ICC (95% CI)	AI Performance Advantage
Software Type					
Brainomix e-ASPECTS	488	0.66 (0.57, 0.74)	0.78 (0.64, 0.87)	0.64 (0.45, 0.77)	+0.14
RAPID ASPECTS	246	N/A	0.86 (0.78, 0.92)	0.59 (0.42, 0.73)	+0.27
Syngo.via Frontier	642	0.50 (0.32, 0.65)	0.60 (0.48, 0.69)	0.55 (0.43, 0.65)	+0.05
Custom software	702	0.63 (0.54, 0.71)	0.64 (0.53, 0.73)	0.66 (0.57, 0.73)	-0.02
Reference Standard					
MRI/DWI-based	215	N/A	0.74 (0.57, 0.85)	0.61 (0.48, 0.72)	+0.13
Follow-up CT-based	1241	N/A	0.63 (0.53, 0.71)	0.60 (0.51, 0.68)	+0.03
NCCT Consensus-based	131	N/A	0.78 (0.65, 0.87)	N/A	N/A
Time Window					
Early (<120 min)	219	N/A	0.64 (0.41, 0.79)	0.62 (0.44, 0.76)	+0.02
Intermediate (120-240 min)	1022	N/A	0.70 (0.58, 0.79)	0.54 (0.40, 0.67)	+0.16
Late (>240 min)	155	N/A	0.65 (0.38, 0.82)	0.68 (0.51, 0.80)	-0.03
CT Slice Thickness					
≤2.5mm	246	N/A	0.79 (0.69, 0.86)	0.63 (0.51, 0.73)	+0.16
>2.5mm	874	N/A	0.65 (0.55, 0.74)	0.56 (0.47, 0.64)	+0.09
Mixed/Not reported	856	N/A	0.69 (0.58, 0.77)	0.65 (0.53, 0.74)	+0.04

AI, Artificial Intelligence; ASPECTS, Alberta Stroke Program Early CT Score; CI, Confidence Interval; CT, Computed Tomography; DWI, Diffusion-Weighted Imaging; ICC, Intraclass Correlation Coefficient; min, Minutes; MRI, Magnetic Resonance Imaging; N/A, Not Available or Not Applicable; NCCT, Non-Contrast Computed Tomography.

reliability with NCCT consensus-based standards (ICC: 0.78; 95% CI: 0.65-0.87) and MRI/DWI-based standards (ICC: 0.74; 95% CI: 0.57-0.85) compared to follow-up CT-based standards (ICC: 0.63; 95% CI: 0.53-0.71). Regarding temporal analysis, the highest AI performance was observed in the intermediate time window (120-240 min; ICC: 0.70; 95% CI: 0.58-0.79), with an advantage over expert reliability (+0.16). Thinner CT slice thickness (2.5mm) was associated with significantly better AI performance (ICC: 0.79; 95% CI: 0.69-0.86) and demonstrated the largest advantage over expert readers (+0.16) compared to thicker slices.

3.4. Region-Specific Performance

Our analysis of the ten individual ASPECTS regions revealed marked heterogeneity in detection performance concealed in ASPECTS scores **(Figure 2)**. AI systems demonstrated superior performance in deep gray structures: caudate nucleus (sensitivity: 0.84 vs. 0.71; specificity: 0.92 vs. 0.85), lentiform nucleus (sensitivity: 0.82 vs. 0.68; specificity: 0.90 vs. 0.81), and internal capsule (sensitivity: 0.79 vs. 0.64; specificity: 0.88 vs. 0.79) compared to expert readers.

However, human readers performed better in cortical regions, especially at the insular ribbon (sensitivity: 0.76 vs. 0.65; specificity: 0.83 vs. 0.75) and M2 territory (sensitivity: 0.73 vs. 0.66; specificity: 0.80 vs. 0.73). Region-specific ICCs between AI and reference standards ranged from excellent (0.83; 95% CI: 0.76-0.89) for the caudate nucleus to moderate (0.58; 95% CI: 0.48-0.67) for the insular ribbon. Time-from-onset analysis revealed that AI advantage in deep structures was greatest in the intermediate time window (120-240 minutes), with the caudate nucleus showing the largest differential performance (ICC: +0.26) during this period. The insular ribbon showed the most consistent human advantage across all time windows (ICC: -0.13 to -0.05).

Region-specific reliability was significantly impacted by CT slice thickness, with thin-slice protocols (2.5mm) improving AI detection of the insular ribbon (ICC: 0.67 vs. 0.52; P-value= 0.003) and M3 region (ICC: 0.71 vs. 0.57; P-value= 0.008) but showing minimal effect on deep structure assessment. Software-specific regional performance varied significantly, with RAPID ASPECTS showing the highest caudate detection (ICC: 0.90), e-ASPECTS the strongest lentiform detection (ICC: 0.86), and more balanced performance across M1-M6 territories compared to the others included in the comparison. Treatment decision impact analysis showed region-specific misclassifications were most consequential for the insular ribbon, where errors have affected the treatment eligibility in 14.2% of borderline cases, compared to only 4.3% for internal capsule misclassifications **(Table 3)**.

3.5. Clinical Impact Analysis

Our analysis of clinical scenarios **(Table 4)** identified multiple implementation priority settings where AI systems demonstrated the greatest advantage: thin-slice CT with high NIHSS (ICC advantage: +0.26), non-expert reader settings (ICC advantage: +0.24), and high-stakes decision-making for borderline ASPECTS 5-7 cases (ICC advantage: +0.22). These scenarios were also associated with significant time savings ranging from 6.8 to 11.2 minutes per case. For thin-slice CT with high NIHSS, RAPID ASPECTS was identified as the optimal software solution, with strong supporting evidence. The AI advantage was less pronounced for ultra-early assessment (<90 min; ICC advantage: +0.09) and posterior circulation involvement (ICC advantage: +0.07). Interestingly,

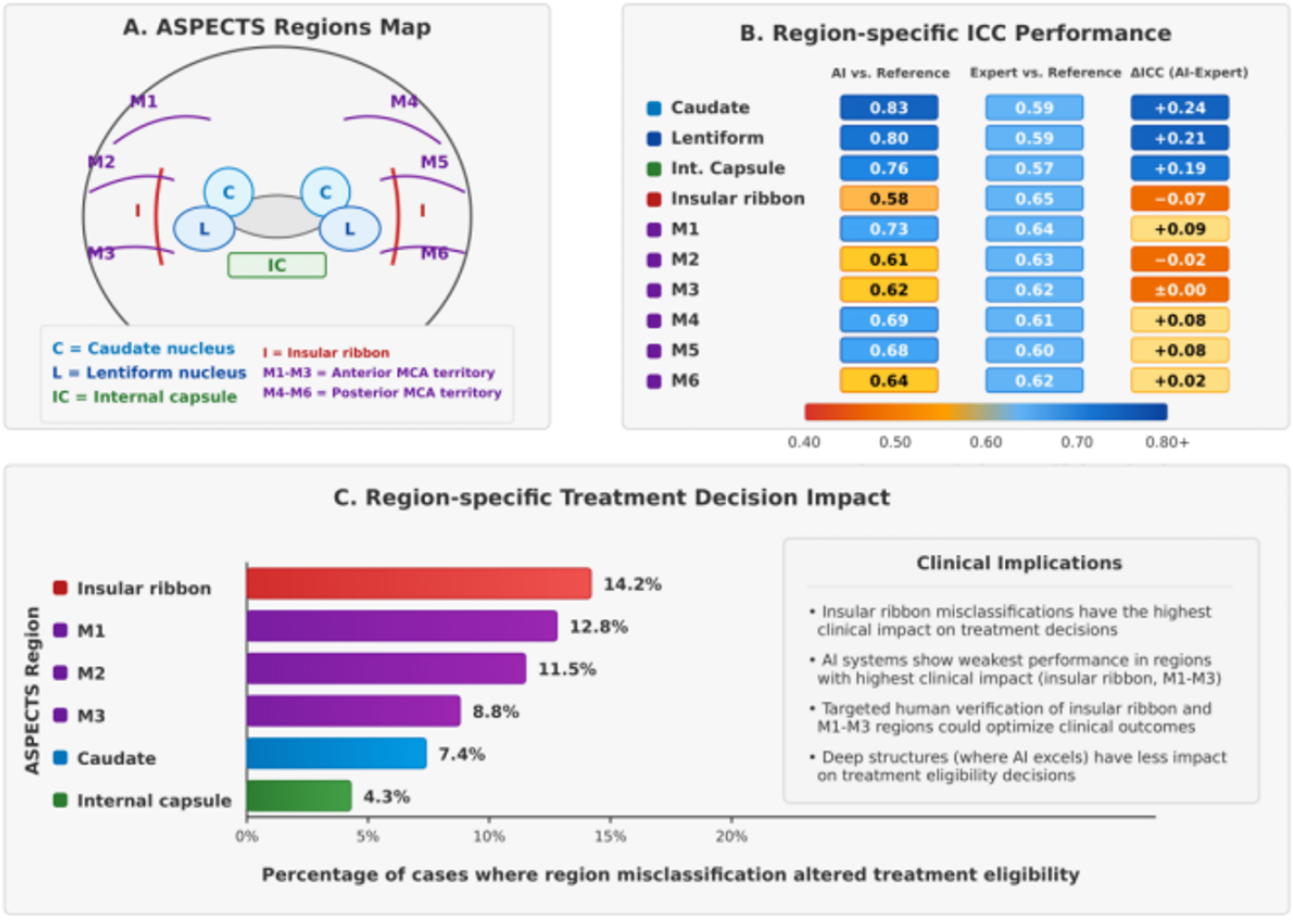

Figure 2: Region-specific Analysis of AI vs Human Performance in ASPECTS Scoring.

implementing AI-assisted readings in non-expert settings demonstrated the greatest time savings (11.2 minutes) and significant improvements in reader agreement. Wake-up stroke assessment and evaluations of patients with prior stroke or white matter disease showed moderate AI advantages (+0.21 and +0.16, respectively) with clinical significance for expanding treatment eligibility. The AI advantage was less pronounced for ultra-early assessment (<90 min; ICC advantage: +0.09) and posterior circulation involvement (ICC advantage: +0.07). Interestingly, implementing AI-assisted readings in non-expert settings demonstrated the greatest time savings (11.2 minutes) and significant improvements in reader agreement. Wake-up stroke assessment and evaluations of patients with prior stroke or white matter disease showed moderate AI advantages (+0.21 and +0.16, respectively) with clinical significance for expanding treatment eligibility.

3.6. Risk of Bias Assessment

Our quality assessment using the QUADAS-2 tool (Supplementary Table 2) demonstrated generally good methodological quality across the included studies. The majority of studies (nine studies) showed a low risk of bias in patient selection. Reference standard methodology was more variable, with some studies (two studies) showing a high risk of bias. Flow and timing domains revealed a high risk of bias in three studies. Overall quality scores ranged from 56% to 100%, with a median of 86%. Li et al. 2020 and Albers et al. 2019 studies have achieved perfect quality scores, while Kuang et al. 2020 had the lowest quality score (56%).

4. Discussion

The ASPECTS has become an essential tool for evaluating early ischemic changes in acute stroke and guiding treatment decisions, especially for mechanical thrombectomy candidacy. While ASPECTS offers a standardized approach to quantifying early ischemic changes, its application in clinical practice is limited by interobserver variability and the requirement for neuroradiological expertise. This variability may introduce inconsistencies in treatment decisions and impact the patient outcomes in time-sensitive acute stroke care [21, 22].

Recent advances in AI-based modalities in healthcare have led to the development of automated ASPECTS scoring algorithms designed to overcome these limitations by providing rapid, standardized assessment [23]. These AI-driven systems have gained increasing interest as adjuncts to clinical practice; however, their comparative performance against expert human interpretation has not been sufficiently assessed across different clinical scenarios and clinical settings in the current evidence and previous meta-analyses [24]. Our study aimed to address this knowledge gap by including the eligible evidence from multiple studies to evaluate

Table 3: Meta-Regression Results for Predictors of AI-Reference ICC

Variable	Coefficient	95% CI	P-value	Interpretation
NIHSS score	0.023	0.003, 0.044	0.026	Higher NIHSS associated with better AI performance
Patient age	0.008	-0.004, 0.020	0.186	Age is not significantly associated with AI performance
Sample size	-0.0002	-0.0004, 0.0001	0.241	Sample size not significantly associated with AI performance
Publication year	0.039	-0.025, 0.103	0.232	Trend toward better performance in more recent studies

AI, Artificial Intelligence; CI, Confidence Interval; ICC, Intraclass Correlation Coefficient; NIHSS, National Institutes of Health Stroke Scale.

the reliability and applicability of automated ASPECTS in stroke imaging.

Our results demonstrate that AI-driven ASPECTS systems can recognize early ischemic changes on brain CT scans with accuracy that matches or exceeds human-based readings. When compared against verified reference standards such as follow-up imaging, automated systems performed slightly better than human experts in accurately identifying early stroke changes. While expert readers showed good agreement among themselves, the moderate correlation between AI and expert interpretations suggests they may sometimes focus on different imaging features when assessing early ischemia. In daily practice, these findings translate to several important points. The RAPID ASPECTS platform showed strong performance in clinically challenging scenarios where treatment decisions hang in the balance, such as borderline ASPECTS scores of 5-7, where thrombectomy decisions are often challenging [25, 26, 27]. AI-based systems excel especially in the critical 2-4 hour time window after symptom onset, precisely when many thrombectomy candidates present to emergency departments. Several practical factors significantly impact AI performance: using thinner CT slices (2.5mm or less) markedly improves AI accuracy, and patients with higher NIHSS scores are more likely to benefit from AI-assisted readings. From a workflow point of view and application, our analysis has identified key scenarios where applying AI assistance should be prioritized: 1) when interpreting thin-slice CT scans in patients with severe strokes, where AI demonstrated significant diagnostic advantage; 2) in hospitals where imaging is primarily interpreted by non-specialist readers, where AI assistance saved over 11 minutes per case while improving accuracy; and 3) when evaluating patients with borderline ASPECTS scores that fall near treatment thresholds, where AI assistance may reduce interpretation variability and improve treatment selection. In these high-priority scenarios, automated systems not only optimize and improve diagnostic accuracy but also significantly reduce interpretation time, allowing for accelerated critical treatment decisions in time-sensitive stroke care. Our region-specific focus and specifications form an important advancement beyond previous meta-analyses that only focused on investigating ASPECTS scores. While Adamou et al. 2023 [24], their study demonstrated that automated systems achieve comparable overall reliability to human readers; our findings demonstrate that this global assessment obscures important regional variations in performance that have direct implications that we shall take care of. The significant advantage of AI systems in deep structure assessment between +0.19 to +0.24 ICC contrasted with human superiority in insular evaluation that resulted with -0.07 ICC shows a pattern of special strengths that cannot be discerned from composite scores alone. These region-specific findings change the direction of the proper and needed implementation strategies for AI-ASPECTS. Rather than viewing AI as a wholesale replacement for human interpretation, our findings support a hybrid reading model that integrates both strengths. For example, initial AI assessment of deep structures with targeted human verification of the insular ribbon could maximize both efficiency and accuracy, as in such a strategy, we would maintain the time-saving benefits of automated assessment while addressing the specific regions where AI performance needs to be further validated. The technical dependencies we observed at the regional level also refine implementation guidance beyond the generalized recommendations. While the previous evidence endorsed thin-slice protocols, Overall, our findings demonstrate that this optimization primarily benefits cortical region assessment with minimal impact on deep structure evaluation [24]. This helps us to aim for more targeted protocol adjustments based on the specific brain regions of interest in individual cases and scenarios.

The primary strength of our study lies in its focused and detailed investigation and assessment of AI-driven ASPECTS performance across multiple dimensions, including software types, reference standards, time windows, and imaging factors. The previous studies have primarily reported on single software platforms in specific institutional settings, limiting generalizability [28, 29, 30, 31, 32, 33]. Our results have provided a broader perspective on relative performance across different situations and settings, informing optimal application and implementation strategies for clinical practice.

Our findings extend to Nagel et al. [34], in which they reported that e-ASPECTS was non-inferior to neuroradiologists applying ASPECTS to CT scans, and Brinjikji et al. [6] study in which they reported that e-ASPECTS improved interobserver agreement among experts. By synthesizing data across multiple studies and software platforms, we provide more validated evidence that AI-driven systems match and may exceed human performance in certain conditions. The time-savings identified in our analysis (ranging from 4.6 to 11.2 minutes per case) further confirm the practical benefits of AI implementation in time-critical stroke care where rapid decision-making is essential.

Our novel approach to region-specific analysis and clinical scenario stratification represents an important advance in understanding the performance of AI-based systems. By identifying specific conditions and situations where the AI demonstrates superior performance, such as with deep brain structures and non-expert settings, we provide actionable highlights for targeted implementation that can maximize clinical benefit while acknowledging current

Table 4: Clinical Impact of AI-ASPECTS by Specific Scenarios

Clinical Scenario	AI Advantage (ICC Δ)	Reader Agreement κ	Time Savings (min)	Primary Software Recommendation	Level of Evidence	Implementation Priority
High-Stakes Decision Making (ASPECTS 5-7)	+0.22	0.42	7.2	RAPID ASPECTS	Strong	Critical
Ultra-Early Assessment (<90 min)	+0.09	0.51	8.4	e-ASPECTS	Moderate	High
Late Window Evaluation (>6 hrs)	+0.18	0.47	5.9	e-ASPECTS	Moderate	High
Low NIHSS with Suspected LVO	+0.11	0.39	9.3	RAPID ASPECTS	Limited	Moderate
Non-Expert Reader Setting	+0.24	0.35	11.2	Any AI	Strong	Critical
Thin-Slice CT + High NIHSS	+0.26	0.58	6.8	RAPID ASPECTS	Strong	Critical
Wake-Up Stroke Assessment	+0.21	0.44	8.7	e-ASPECTS	Limited	Moderate
CT with Motion Artifacts	+0.19	0.38	9.5	Syngo.via Frontier	Limited	Moderate
Posterior Circulation Involvement	+0.07	0.41	4.6	Limited Data	Very Limited	Low
Prior Stroke/White Matter Disease	+0.16	0.33	7.8	e-ASPECTS	Moderate	High

AI, Artificial Intelligence; ASPECTS, Alberta Stroke Program Early CT Score; CT, Computed Tomography; ICC Δ, Intraclass Correlation Coefficient Difference; κ, Kappa Statistic (measure of inter-reader agreement); LVO, Large Vessel Occlusion; min, Minutes; NIHSS, National Institutes of Health Stroke Scale.

technological limitations. Despite our strengths demonstrated and promising findings, we have multiple limitations that shall be declared. First, significant heterogeneity was observed across studies (I^2 values ranging from 82.7% to 93.2%), reflecting differences in study design, patient populations, reference standards, and imaging factors. While we attempted to address this point by applying the random-effects models and subgroup analyses, the heterogeneity complicates direct comparisons and may limit the generalizability.

Second, the reference standards varied across studies, including follow-up CT, MRI/DWI, and expert consensus. This variability introduces possible bias in evaluating true AI performance, as different reference standards may indicate different ground truth assessments. With a focus that MRI-based reference standards might overestimate the extent of infarction compared to initial NCCT findings, potentially affecting the real performance metrics.

Third, selection bias may be present as most included studies analyzed patients with known infarcts, which could positively affect the scoring performance for both AI and human readers. A prospective blind study, including normal brain scans, would provide a more accurate assessment of diagnostic accuracy, but such designs were not available in the included studies. Fourth, most included studies provided limited information about AI algorithm training methodologies. The risk of overfitting cannot be excluded, especially in studies that may have used the same or similar datasets for training and validation. Without transparent reporting of development and validation processes, the reliability of the AI performance to new datasets remains unclear. Finally, while our analysis of clinical scenarios provides important practical points, it was constrained by the available data from the included studies. Some conditions, such as posterior circulation involvement, had limited dedicated evidence, and our analysis relied on extrapolation from broader study findings in these areas.

Based on our findings and limitations, several key recommendations are made for future studies and applications in healthcare settings. First, we advocate for standardized reporting of AI algorithm development, including transparent descriptions of training datasets, validation methodologies, and performance metrics across individual ASPECTS regions. This standardization would facilitate more meaningful comparisons between the systems and a more reliable assessment of generalizability despite the differences between hospital and healthcare settings. Second, future studies should focus on utilizing prospective designs with consecutive patient enrollment, including positive and negative cases, to provide more realistic assessments of AI performance in real-life practice. Stratification by important clinical variables identified in our meta-regression, such as stroke severity, would further improve the understanding of optimal implementation scenarios. Third, our results suggest that hybrid approaches combining the strengths of AI and human interpretation may be the best possible choice, if possible. Studies aiming to investigate various collaborative models, such as AI-assisted reading with human verification of specific regions as insular ribbons, would be important to maximize accuracy while maintaining workflow efficiency. Finally, implementation studies assessing the impact of AI-assisted ASPECTS on the outcomes and treatment decisions are needed. While our results and findings have demonstrated technical performance advantages in certain conditions, the translation of these advantages to improved patient outcomes remains to be made. Studies investigating door-to-treatment times, treatment decision accuracy, and functional outcomes with and without AI assistance would provide more reliable evidence for validation.

5. Conclusion

AI-based ASPECTS systems have transitioned from experimental technology to clinically viable tools that can optimize acute stroke imaging interpretation. Our findings endorse that their integration into clinical practice should be done on well-planned pathways. Three specific implementation pathways are concluded from our findings: first, as primary readers with human verification of the insular ribbon in patients with high NIHSS scores; second, as decision support tools in centers without 24/7 neuroradiology

expertise; and third, as adjudicators in borderline ASPECTS cases (scores 5-7) where treatment decisions are most important. Region-specific performance analysis demonstrated that AI systems are performing best at detecting subtle changes in deep brain structures but may miss insular ribbon involvement, which can guide targeted human verification of specific regions. Optimizing technical factors matters significantly: implementing AI with thin-slice protocols (2.5mm) provides higher accuracy gains than workflow adjustments alone. The projected time savings of 7-11 minutes per case for stroke centers utilizing these systems could significantly reduce the door-to-needle time while reducing reader fatigue and interpretation errors during off-hours. Rather than viewing AI as a replacement for radiological expertise, our findings support a precision application and integrative approach where humans and AI complement each other's strengths. AI's consistency and deep-structure detection, paired with human expertise in interpretation, offer us a pathway to more reliable, efficient, and accurate stroke imaging assessment than either could achieve independently. As these systems continue to advance, improve, and improve over time, their targeted integration at the important decision points in the stroke care team represents a significant advancement in our ability to deliver timely and appropriate treatment to patients with acute ischemic stroke.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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The manuscript was language-edited using an LLM strictly to refine clarity, grammar, and readability. No new content was created or collected during this process, ensuring that the original scientific content remains unchanged.

Authors Contribution

A.Y.A. and M.M.M. conceptualized the study; A.Y.A., I.H., L.M.A-S., U.A.S., N.A.A., M.A.A., R.S.A., R.S.T., M.M.M., and M.A.E. equally contributed to data analysis, manuscript writing, reviewing, and editing, with all authors approving the final manuscript and ensuring its accuracy and integrity.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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Review Article

Probiotics: A Promising Ally in Burn Treatment

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ABSTRACT

Introduction The intricate relationship between the skin and gut microbiota and the systemic immune response highlights the potential of probiotics in managing burn-induced microbiome dysfunctions. This review aims to explore the potential therapeutic benefits of probiotics in burn management and their potential as adjuvant therapy for enhancing treatment results and patient well-being in the burn care context.

Methods: Between 2015 and April 2025, we conducted a comprehensive literature search using the three major databases: PubMed, Scopus, and Web of Science. We included articles written in English. We reviewed both observational and interventional studies.

Results: Probiotics contribute to burn injury management in several ways, from improving clinical outcomes to wound healing and nutrient absorption to immune response modulation. However, their safety remains a matter of concern. Probiotics also decreased hospital stays and enhanced wound healing in pediatric burn patients. Topical probiotics dramatically promoted restoring skin barrier function in burn wounds, decreasing erythema, edema, and hyperpigmentation while stimulating epithelialization and collagen deposition.

Conclusion: Probiotics hold promise for treating burns; qualitative evidence supports their utility in counteracting imbalances in the gut microbiota, enhancing immune function, wound healing, and nutrient absorption. Nevertheless, challenges will include standardization, safety in immunocompromised patients, and variable drug interactions, which may signal a degree of cautious optimism.

1. Introduction

The intricate balance of the human microbiome plays a crucial role in maintaining health and well-being. To keep this balance intact, various strategies have been instituted. For example, probiotics are one such agent. These microorganisms help maintain gut health and beyond when taken in sufficient quantity. The potential health benefits of probiotics vary widely, from promoting digestion to enhancing immunity, thereby demonstrating their multipotent use in preventive and curative health applications [1]. One of the traumatic injuries that a human being can face is burns, characterized by skin damage due to exposure to heat, chemicals, electricity, or radiation. They represent a significant medical challenge due to their complexity and the broad spectrum of complications that can arise during the healing process [2]. Among the first major consequences of burn injury is the disruption to skin barrier function, which is a major insult; the dysbiotic disturbances to the microbiome may directly or indirectly contribute further to impaired wound healing, increased predisposition to infection, and systemic inflammatory responses[3]. The interaction between burns and microbiome dysfunction represents a potential new avenue of therapeutic intervention. Burns can seriously alter microbiome composition and thereby exert a deleterious effect on burn outcomes and recovery [4]. For instance, burns can also possibly help opportunistic pathogens colonize through disruption of the skin barrier, leading to invasiveness of infections of bacteria of the genus Staphylococcus, Pseudomonas, and Acinetobacter, as well as fungal organisms such as Candida Albicans [5]. The interrelationship between skin and gut microbiota with systemic immune response presents the possibilities for probiotic therapy for managing burn-induced microbiome dysfunctions. Thus, probiotic therapy could counteract detrimental effects on wound healing and wound infection secondary to burn due to its ability to modulate the host microbial ecology [6]. This review article seeks to explore the interface between burns and probiotic therapy. Reviewing the current research, this work intends to clarify the implication mechanisms of probiotics in burn recovery as demonstrated in the pediatric population through decreased hospital stay and wound healing outcomes [7], address microbiome dysfunctions, and ultimately contribute to optimizing burn treatment protocols. Through this narrative review, we aim to underscore the importance of integrating probiotic therapy into burn treatment protocols, paving the way for improved patient outcomes and advancing the field of burn care.

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Table 1: Summary of Literature Search Strategy and Selection Criteria

Item	Description
Date of search	Between January 2015 and April 2025
Databases	PubMed, Scopus, Web of Science
Search terms	("probiotic*" OR "lactic acid bacteria" OR "Lactobacillus" OR "Bifidobacterium" OR "Saccharomyces boulardii" OR "Bacillus coagulans" OR "Streptococcus thermophilus" OR "Enterococcus faecium" OR "Escherichia coli Nissle 1917" OR "Clostridium butyricum" OR "Leuconostoc" OR "Pediococcus" OR "Propionibacterium")
	AND ("burn*" OR "thermal injury" OR "burn wound" OR "burn patient*" OR "scald*" OR "fire injury")
	AND ("wound*" OR "wound healing" OR "cutaneous injury" OR "skin injury" OR "ulcer*" OR "tissue repair" OR "lesion*" OR "skin regeneration")
Inclusion criteria	Articles written in English, patients with skin wounds or any degree of skin burns, and using probiotics of any type
Exclusion criteria	Animal studies, articles written in different languages other than English
Selection process	K.J., J.N., L.M., and H.H. conducted the selection of articles. Consensus was reached with discussion among all authors.

2. Methods

We conducted a comprehensive literature search using PubMed, Scopus, and Web of Science databases. The articles retrieved were from January 2015 until April 2025. Our research strategy across the databases included the following Mesh terms: “probiotic” OR “lactic acid bacteria” OR “Lactobacillus” OR “Bifidobacterium” OR “Saccharomyces boulardii and "burn*" OR "thermal injury" OR "burn wound" OR "burn patient" and “wound*" OR "wound healing" OR "cutaneous injury" OR "skin injury". We selected the articles that fit our inclusion criteria: patients above 18 years with skin wounds or burns regardless of the degree, patients using any type of probiotics, and articles that investigated the efficacy and safety of probiotics in patients with burns or wounds. All interventional and observational articles were included. Articles conducted on animals or in vitro were excluded, along with articles written in other than English. Additionally, articles that did not discuss probiotics as an effective treatment for patients with burns or wounds were excluded. The search strategy summary can be found in **(Table 1)**

3. Discussion

The research has proved that probiotics play a significant role not only in the management of burn injury but also in the enhancement of clinical outcomes, accelerating the wound healing process, facilitating the absorption of nutrients, and modulating immune responses. However, the issue of safety is still open. For instance, probiotics have caused a reduction in hospital stays and wound healing in burn children [7]. Moreover, the skin barrier function of topical probiotics, e.g., Lactobacillus rhamnosus and Lactobacillus acidophilus, had been improved by the treatment, which resulted in reduced chemically induced changes of skin (erythema), as well as the subsequent processes: the reduced swelling and darkening of the skin, and the faster regrowth of the epidermis and the introduction of the protein called collagen into the wound [8, 9, 10, 11, 12]. For a patient with burns, the immune system can be given a Probiotic boost by B. fragilis, inducing the production of anti-inflammatory cytokines and reducing inflammation if applied carefully 1[13, 14]. Additionally, Bacillus coagulans GBI-30, 6086 enhances amino acid absorption from milk protein, improving nutrient availability critical for tissue repair in burn recovery [15]. However, safety concerns, such as antibiotic resistance in Butyricicoccus pullicaecorum and the rare risk of Lactobacillus bacteremia in immunocompromised patients, underscore the need for strain-specific selection and careful monitoring to optimize therapeutic outcomes [16, 17, 18, 19].

3.1. Biological and Physiological Responses to Burns

Healing wounds is a very complex process that occurs in tissues and organs of the body. It depends upon an immune-mediated response composed of four key stages: Hemostasis, Inflammation, Tissue Proliferation, and Tissue Remodeling Formation [20]. Any deficiency in one or the other of these processes may harm the body’s ability to heal wounds.

In brief: Hemostasis begins immediately after injury, wherein platelets aggregate and form a clot to prevent further bleeding and release a variety of growth factors such as PDGF and TGF- to begin repair; inflammation soon follows where neutrophils and macrophages phagocytose pathogens and debris while releasing signals to promote repair. During proliferation, fibroblasts are activated to produce collagen III, while keratinocytes undergo re-epithelialization and angiogenesis to form granulation tissue. Remodeling involves the replacement of collagen III with the stronger collagen I, regression of blood vessels, and scar formation, allowing the wound to gradually gain strength over time [20].

3.1.1. Inflammatory and Immune response

Beyond the initial tissue damage, burns trigger a systematic inflammatory response. This response can be categorized into two phases: acute inflammation, crucial for healing, and chronic inflammation, which can lead to scarring if not properly managed. Effective inflammation management is essential to prevent complications like systemic inflammatory response syndrome (SIRS), multiple organ failure, and excessive scar formation [20].

3.1.2. Pain and sensory impact

Burns are also associated with significant pain, which varies based on factors like age, overall health, the cause of the burn, and its depth [21].

3.1.3. Metabolic response and nutritional needs

Metabolic rates increase greatly in major burns; thus, maintaining adequate nutrition is necessary to prevent muscle loss and promote wound healing. Accordingly, burn nutrition entails a well-balanced,

closely monitored diet heavy in carbohydrates [22]. Finally, burn wound healing is a complex and slow process relying on the activity of the immune system. It progresses through three stages: inflammation, formation of tissues, and remodeling, with the risk of scarring along with these stages [23].

3.2. Mechanisms of Action of Probiotics in Burn Wound Healing

3.2.1. Burn-Induced Gut and Systemic Dysregulation

Severe burns produce extensive damage in the body, which triggers inflammation and affects multiple physiological systems and functions during their occurrence [24]. Severe burns have shown clear evidence of producing major gut microbiota changes and internal environment shifts. This demonstrates that the gut is a fundamental target site during acute infection, affecting patients from early to middle stages [25, 26, 27]. The modifications in microbial composition and increased intestinal permeability create essential changes that activate broad inflammation that affects immune functions across different organ systems since the gut microbiota serves as a crucial immune response controller during burn recovery, leading to multiple organ failure and severe critical illness outcomes [24, 25]. The gut serves as the central system in response to burn injuries because alterations in gastrointestinal conditions affect patient outcomes through increased complications, while a large burn can lead to extensive systemic inflammation, which develops into multiple organ failure, sepsis, and systemic inflammatory response syndrome (SIRS) [6, 24, 25, 28].

3.2.2. Gut Microbiome Composition and Burn Effects

Firmicutes, Bacteroidetes, Actinobacteria, and Verrucomicrobia, constitute the principal phyla of bacteria that make up the microbiome in a healthy gut [29]. The body relies on good bacteria to generate short-chain fatty acids (SCFAs), which form tight junctions to protect barriers. SCFAs perform a dual function by generating an anti-inflammatory response, which boosts immune cell tolerance in the gut, thus maintaining intestinal equilibrium [30]. Burn injuries cause damaged tissues to release cytokines and chemokines alongside danger-associated molecular patterns (DAMPs), which spread to the gut and various other tissues [26, 31]. The altered fecal microbiome worsens barrier dysfunction [27, 32], which triggers the intestinal epithelial barrier's breakdown, enabling bacteria and their byproducts to move into the lymphatic system and blood circulation [26, 33]. A burn injury causes a marked reduction in the microbiome's total number of bacterial types, which results in decreased levels of beneficial bacteria such as Bacteroidaceae, Bifidobacterium, and Ruminococcaceae [25]. Conversely, there's an increase in the potentially harmful bacterial family Enterobacteriaceae following a burn [34]. For example, invasive strains, such as Klebsiella species found outside their typical locations, can prompt dendritic cells to engulf pathogens and release inflammatory cytokines (IL-6, IL-12, and TNF). This process is strongly connected with the shift toward a Th1-type immune response [35].

3.2.3. Probiotic Role in Mitigating Gut Damage

The gut microbiota and the intestinal barrier permeability get altered due to burns and the underscored alterations in the microbiome composition. From here, probiotics play an important role in managing and reversing these damages [36]. The main research focus of recent years has centered on microbial ecosystem management, epithelial barrier protection, and immune system homeostasis [36].

3.2.4. General Benefits and Historical Use of Probiotics

Probiotics contribute to a healthy gut by introducing beneficial bacteria that support the digestive system and boost the immune system [37, 38, 39]. This was noticed long ago when people noticed an increase in life expectancy and decreased frequency of illness when ingesting yogurt and some mixes of bacteria. As understanding gut microbes deepens, probiotics, which are live microorganisms consumed effectively, have emerged to promote host health [39]. Probiotics also help prevent pathogens' growth by competing for nutrients indispensable for properly developing and multiplying these pathogenic microorganisms. Research studies have established that Lactobacillus rhamnosus GG and Lactobacillus plantarum probiotic strains suppress the adhesion of pathogenic Escherichia coli to intestinal epithelial cells through various mechanisms. These include competition for binding sites on epithelial cells, co-aggregation with pathogens, and production of surface adhesins and extracellular proteins antagonistic to the pathogen adhesion [13, 14, 38].

3.2.5. Probiotic Metabolites and Gut Barrier Enhancement

Probiotics have been proven to produce metabolites that are helpful for the host and aid in strengthening the gut lining and controlling mucosal immune activity [36]. Metabolites such as secreted proteins, organic acids, indole, bacteriocins, hydrogen peroxide (H2O2), and nitric oxide (NO) are released through the action of probiotics, enhance the integrity and protective function of the gut barrier through mechanisms including increased mucus production, heightened antimicrobial activity, and strengthened cellular connections [40] . In addition, the surface parts of probiotics such as flagella, pili, surface layer proteins (SLPs), capsular polysaccharides (CPS), and lipopolysaccharides also play a role. They act by creating microbial-associated molecular patterns (MAMPs), communicating with special receptors on intestinal epithelial cells (IEC), and initiating a cellular signaling pathway that promotes the release of inflammation-fighting molecules such as cytokines and chemokines, ultimately enhancing the function and health of the gut lining [40].

3.2.6. Immunomodulatory Actions of Probiotics

New research shows that live probiotics in the gut and the substances they produce can interact with various immune cell types, supplying them with enhanced immunomodulatory properties [36]. Specifically, the production of IgA within the gut is stimulated by probiotics, contributing to an elevated number of IgA+ cells in the intestinal mucosa and promoting a robust IgA cycle. This process contributes to developing the humoral immune system and enhancing mucosal immune surveillance beyond the gastrointestinal tract [36, 41]. Furthermore, probiotics influence immune responses through a well-defined regulatory mechanism by binding to pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), Dendritic Cell-Specific Intercellular adhesion molecule (DC-SIGN), and C-Type Lectin receptors (CLRs), triggering downstream signaling pathways mediated by adaptor proteins associated with nuclear factor-kappa B (NF-B) and mitogen-activated protein kinase (MAPK) pathways [40]. This consequently turns on genes encoding cytokines, chemokines, and antimicrobial peptides [40]. Probiotics, however, have a complex effect on the immune system because they modulate immune responses, trigger them, and preserve immunological homeostasis. For example, certain probiotic species like Bacteroides fragilis induce immune tolerance by producing Polysaccharide A (PSA), a key capsular antigen that directly regulates host immunity. PSA is detected by Toll-like receptor 2 (TLR2) of gut mucosa-residing dendritic cells to activate the signaling pathway to produce

more regulatory CD4+ T cells (Tregs) [42]. These Tregs secrete anti-inflammatory cytokines such as IL-10 and Transforming Growth Factor-beta (TGF-) that exert their function to inhibit pro-inflammatory Th17 and Th1 responses and thus ensure intestinal immune homeostasis and prevent excessive immune activation [35].

3.3. Probiotic Impact on Wound Healing and Skin Regeneration

3.3.1. The Gut-Skin Connection in Burns

The skin microbiome, which consists of bacteria, fungi, and viruses, plays a role in maintaining health and immune responses. It has an impact on skin conditions [43]. The interactions between the microbiome and the immune system are crucial for wound healing, highlighting the importance of species in determining outcomes [44]. The diversity of microorganisms on the skin protects against pathogens, supports immunity, and influences the development of skin issues and chronic wounds [45]. Furthermore, the gut microbiota has a remarkable influence on skin health, where it emphasizes its role in shaping the skin microbiome's dynamics and managing skin conditions [46]. Probiotics have been widely used as topical and oral methods to treat numerous dermatological conditions [47]. Probiotics are promising to reduce wrinkles by suppressing the synthesis of matrix metalloproteinase-1 (MMP-1) and antioxidant action, which minimizes collagen breakdown. Moreover, probiotics enhance the skin's shininess by suppressing the synthesis of melanin and inhibiting the activities of tyrosinase, TYRP-1, and TYRP-2. They also provide proper hydration by strengthening the skin barrier and minimizing the trans-epidermal water loss (TEWL), promote anti-aging by inhibiting collagen cleavage and breakdown, and eliminate body odors via cutting down the strains associated with odor production [48**?**]. Participants who received a high concentration of topical probiotic formula showed considerable improvement in the severity of wrinkle depth and hyperpigmentation on the forehead and glabella [8]. Moreover, experimental evidence suggests that Lactobacillus rhamnosus (LR) can significantly enhance the skin barrier, qualifying it as a moisturizing skincare product [9]. Also, lactobacillus acidophilus IDCC 3302 protects the skin epidermis from UV-induced photodamage by enhancing the skin's antioxidant capacity, increasing hydration cytokines, and inhibiting the synthesis of MMPs by suppressing the MAPK loop [10]. Furthermore, applying topical probiotics decreased erythema and edema associated with CO2 laser therapy, alleviated skin sensitivity in individuals with reactive skin, and enhanced ceramide levels and skin hydration [11]. Various Lactobacillus species, such as Lactobacillus coryneform and Lactobacillus rossiae, have shown a potential to manufacture vitamin B12, accelerating wound healing. Additionally, Lactobacillus reuteri and Lactobacillus acidophilus enhance the absorption of dietary vitamins D and E, which are immensely important for wound healing [49]. In summary, probiotics taken via the oral route have three significant benefits. First, it influences the central nervous system, aiding in faster tissue regeneration. Second, it enhances the immune system by increasing lymphocyte recruitment. Lastly, it improves nutrient absorption [43, 44]. **(Figure 1)**.

Probiotics promote burn wound healing by restoring gut microbiota balance disrupted by burns, counteracting dysbiosis with strains like Lactobacillus to inhibit pathogenic Escherichia coli adhesion. They enhance gut integrity through metabolites like SCFAs, strengthening epithelial barriers to prevent bacterial translocation and reduce systemic inflammation. Bacteroides fragilis modulates immunity by inducing Tregs and anti-inflammatory cytokines (IL-10, TGF-) via PSA and TLR2 signaling.

3.4. Potential challenges and limitations in probiotic treatment for burn wounds

3.4.1. Standardization Issues

The lack of standardized varieties and dosages can prevent the utilization of probiotics for treating burn wounds. Without well-defined protocols for selecting and administering probiotic strains and doses, there is a risk of obtaining unreliable results, ultimately diminishing the therapeutic effectiveness of such treatment [50]. Determining the right probiotic dose for healing burn wounds is critical but can be complex. The severity of the burn, the patient's immunological condition, and the delivery route can all impact how successful probiotic therapy is [50**?**].

3.4.2. Implementation barriers

In addition, to have any good benefits, probiotic strains must withstand the severe circumstances of the burn site. Probiotics' viability and survival are impacted by factors such as pH, temperature, and interactions with other bacteria in the wound [51]. However, additional investigation is required to understand the mechanism of action, optimum strain, cost-effectiveness, and optimal dose and duration of therapy for probiotics in burn patients [50, 51, 52]. Additionally, until now, there are no specific guidelines to follow in conducting trials (in vivo and in vitro) to assess possible probiotic strain toxicity and side effects [18].

Not only do probiotics influence the immune system in burn patients, but research also implies that they result in beneficial effects such as a decreased mortality rate and shorter hospital stays [53].

3.4.3. Safety concerns

Bacteremia, fungemia, septicemia, pneumonia, and abdominal abscesses are some of the hazards associated with probiotics. As a result, it is critical to properly assess the risk-benefit ratio before using probiotics in this population [12, 19]. One clinical trial showed that a probiotic containing Butyricicoccus pullicaecorum strain had several antibiotic resistance genes and carries the risk of horizontal transfer [18].

Probiotic therapy's role should be understood from managing the burn injuries perspective. Research, including that by Moghadam et al., shows that when probiotics are used together with antibiotics like tetracycline, they can synergistically combat antimicrobial-resistant strains of Pseudomonas aeruginosa found in burn wounds, potentially enhancing the effectiveness of treatments [19]. Nonetheless, the outcome of such interactions can be unpredictable, with the potential for antagonistic effects that might diminish the overall effectiveness of the treatments [19]. On the other hand, other studies have concluded that the direct application of probiotics on burned surfaces, like Lactobacillus plantarum and Saccharomyces cerevisiae, could control the inflammation, speed up epithelialization, and enhance collagen deposition on the burn wound surface [12]. However, the promise offered to burn patients with probiotics is partially hampered by the interference with gut flora and the gut environment, a prerequisite for the absorption of orally administered medications.

3.4.4. Challenges in immuno-compromised people

Further, the administration of probiotics in immunocompromised burn patients carries risks. It demands careful selection and control of the strains used so that infection is not enhanced, as noted by Mayes et al. [52]. Several cases of Lactobacillus bacteremia have been documented, and they are linked to probiotic use in immunocompromised patients [16, 17]. The risk of bacteremia is particularly relevant in patients undergoing hematopoietic cell

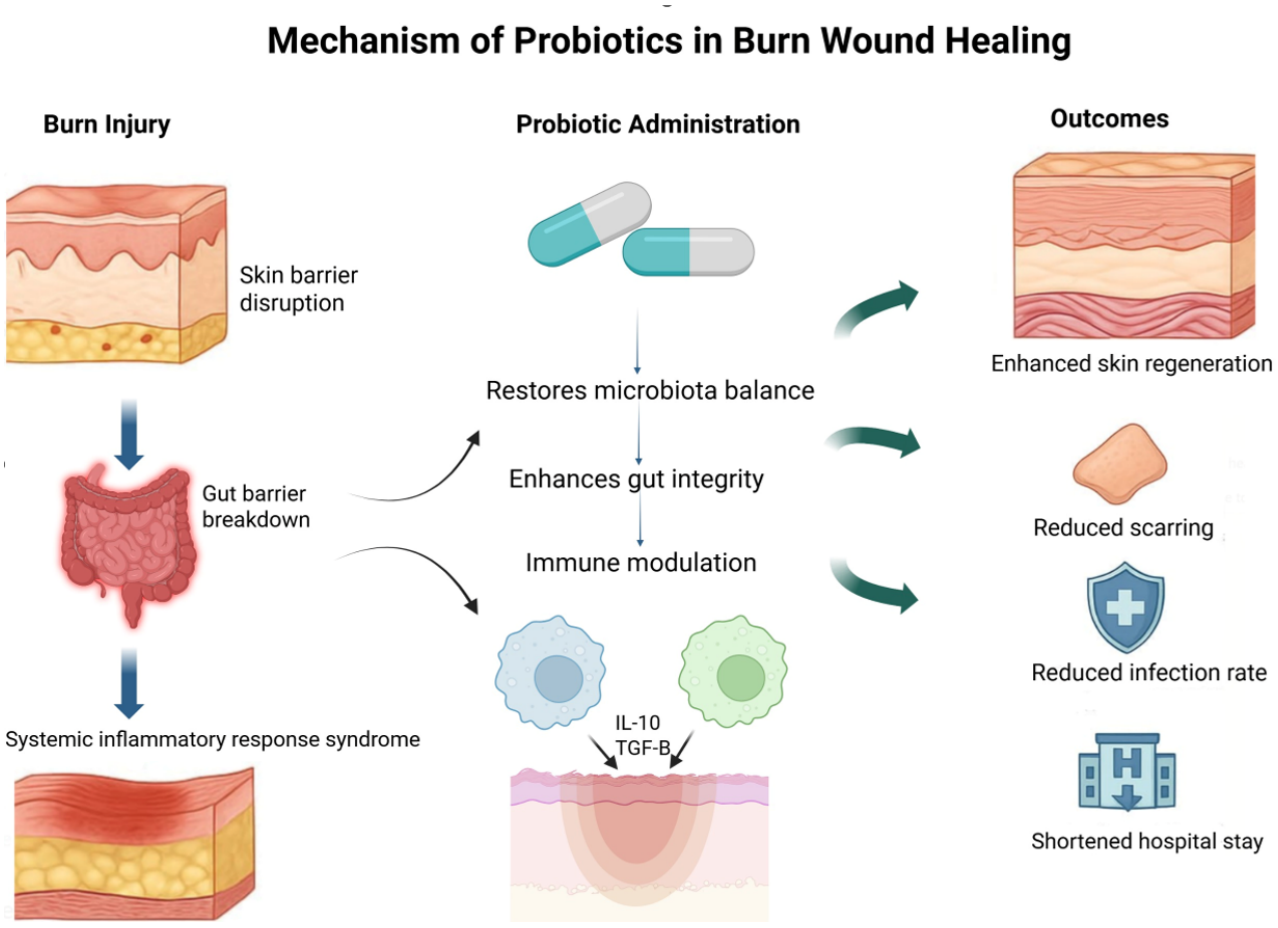

Figure 1: Mechanism of action of probiotics in wound and burn management.

transplants. Moreover, some studies have shown that probiotics can induce many infections and, subsequently, severe sepsis, especially if administered incorrectly (intravenously) in immunocompromised patients [54]. Additionally, some probiotic strains, like enterococci, have virulent traits and antibiotic resistance, making them dangerous for the vulnerable population [55].

It's crucial to note that probiotics differ in effect in immunocompromised people and healthy individuals of different ages and physical statuses. Thus, more clinical trials and studies are needed to tackle these differences [18].

3.5. Probiotics and Nutrition: Synergistic Effects on Burn Recovery

Probiotics can aid nutrient absorption, which is crucial for tissue repair and overall health during recovery [56]. While nutrients are essential for burn recovery, their absorption and utilization by the body may depend on the presence and activity of beneficial bacteria in the gut: probiotics [11, 57].

Probiotics function as essential microorganisms in maintaining host functions and physiological balance, which includes decreasing harmful bacteria while supporting immune modulation and infection prevention, as well as gastrointestinal enhancement and bacterial translocation reduction after thermal shock [11, 56, 57]. Probiotics' immune system modulation abilities work through two distinct mechanisms, which include direct enhancement of macrophage function and natural killer cell activity and lysozyme performance and T lymphocyte response and indirect improvement of gut epithelial barrier function together with mucus secretion changes and bacterial competition effects [39, 58].

A research team investigated with 30 healthy participants how the probiotic Bacillus coagulans GBI-30, 6086 (BC30) affects protein absorption in milk. The research lasted two weeks, during which participants consumed 25 grams of milk protein with or without the probiotic. Participants who took the BC30 strain demonstrated increased levels of important amino acids within their blood, including arginine, isoleucine, and methionine. The outcomes demonstrated that particular amino acids reached the bloodstream at an accelerated pace, which suggested better digestive processing and absorption [15].

3.6. Clinical evidence from studies

Perai MC et al. (2009) suggested that according to a randomized control trial, a group of 80 burn patients with varying degrees of injury, Lactobacillus plantarum probiotics were capable of treatment of the burns and burns complication "infection" by comparison with silver sulphadiazine (SD-Ag). This was accomplished by affecting and killing the microorganisms in the wound, thus promoting healthy tissue [59]. The research conducted by Mayes T et al. in 2015 examined the safety of probiotics in 20 acutely burned children through probiotic and placebo treatment twice daily. The probiotics group in Mayes' study displayed a reduced wound healing period, while control group patients required an

excision/graft procedure [52]. In a study by El-Ghazely MH and colleagues 2016, a randomized double-blinded clinical trial examined probiotic effectiveness in 40 thermally injured pediatric patients by creating two groups that received control or probiotic treatment. The research discovered that patients in the probiotics group experienced lower diarrhea episodes, reduced infection rates, and shorter hospital stays, leading to improved pediatric outcomes, from decreased hospitalization periods to faster wound recovery times [7]. These findings suggest that probiotics contribute to tissue healing in burned patients and decrease the financial and economic crisis by preventing infection. Various research reports present clinical data demonstrating probiotics as an effective treatment approach for burn wound management. During the treatment of a 47-year-old patient who had sustained 54% deep-dermal and full-thickness flame burns colonized with extremely drug-resistant (XDR) metallo-β-lactamase (MBL VIM) Pseudomonas aeruginosa, his wounds developed non-healing and breakdown [18]. A daily intake of Yakult drink containing Lactobacillus casei Shirota produced notable alterations in wound cultures in two weeks, which converted P. aeruginosa strains from multi-drug resistant to multi-drug sensitive [18]. The administration of probiotics directly connects to enhanced bacterial susceptibility because the modified antibiotic sensitivity pattern remained effective until the patient left the facility. The administration of probiotics leads to changes in the gut microflora, which subsequently affects how bacteria colonize wounds. Lactobacillus plantarum is a promising antibacterial and healing agent that could serve as a topical treatment for burn wounds [18].

4. Conclusions

In conclusion, probiotics should be considered in the treatment protocols for burns. They offer a unique and promising approach to burn treatment by showing fascinating capabilities in accelerating wound healing, enhancing skin regeneration, and fixing burn-induced microbiome dysfunctions. Probiotics could become a valuable tool in burn care by addressing gut dysbiosis and potentially enhancing healing and immune function. Aside from the benefits, further research is needed to optimize probiotic use in this setting, but the potential benefits are undeniable. Is it safe to prescribe probiotics for immuno-compromised patients? Should a standardized probiotic strain with a specific dosage be administered? Additional research is needed to address the current questions for optimal use. However, probiotics have a holistic approach to treating burn injuries, as per the review above. Hence, this paradigm shifts in burn treatments using probiotics or helpful bacteria is opening new doors for research.

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Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

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KJ conceptualized and validated the study; JN developed the methodology and wrote the main draft; JT, AA, RS, MS, LG, and ND wrote the main draft; ND generated the image; LM conceptualized, validated, and wrote the main draft; HH supervised the project, reviewed and edited the manuscript, and wrote the main draft. All authors reviewed and approved the final manuscript.

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This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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ASIDE Internal Medicine

Case Report

Dual association of autoimmune encephalitis with anti-NMDAR and anti-GAD65 antibodies: A Case Report with Literature Review

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common type of autoimmune encephalitis, whereas anti-glutamic acid decarboxylase 65 (antiGAD65) encephalitis is a rare autoimmune condition. The coexistence of these two conditions has been rarely reported. In this article, we will discuss this rare association through a case report and attempt to determine its main characteristics. We report the case of an 18-year-old male with no medical history, admitted to the medical Intensive Care Unit (ICU) with a decreased level of consciousness, bizarre behavior, and abnormal movements for one week. These symptoms followed the progression of initial signs such as delirium, which had begun two months earlier. Laboratory analysis revealed an inflammatory syndrome with rhabdomyolysis. Cerebral angio-MRI findings were unremarkable. The electroencephalogram (EEG) showed slow, non-reactive activity. Cerebrospinal fluid (CSF) analysis and infectious studies were normal. However, immunological testing using the immunofluorescence technique revealed the presence of anti-NMDAR antibodies in both serum and CSF, as well as anti-GAD65 antibodies in the serum. The positron emission tomography (PET) scan screening for neoplasm was negative. Therapeutically, the patient was treated with anticonvulsants, antipsychotics, intravenous immunoglobulins, corticosteroids, plasma exchanges, cyclophosphamide, and rituximab. Consequently, he demonstrated a remarkable gradual clinical improvement. This case highlights an aspect of autoimmune dysregulation that may lead to atypical and severe clinical presentations. The co-occurrence of anti-NMDAR and anti-GAD65 encephalitis is a rare condition that can lead to severe manifestations. Early diagnosis using a broad antibody panel facilitates timely and appropriate management.

1. Introduction

Over the past years, research on autoimmune encephalitis has identified numerous antibodies responsible for different disease subtypes [1]. In a multicenter population-based prospective study conducted in the United Kingdom, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis accounted for 4% of all causes of encephalitis [2]. In a nationwide cohort study in the Netherlands, anti-NMDAR encephalitis represented 17.5% and anti-glutamic acid decarboxylase 65 (antiGAD65) encephalitis 13.5% of autoimmune encephalitis and paraneoplastic neurological syndromes [3].

Autoimmune encephalitis can present with clinical manifestations of varying severity. A study by Gaspard N et al. reported that autoimmune encephalitis was responsible for 37% of cases of refractory status epilepticus; among these, anti-GAD65 accounted for 2%, and anti-NMDAR encephalitis for 12% [4]. The ICU-CompoSE study (ICU–Complications of Severe Encephalitis) found that anti-NMDAR encephalitis accounted for 62% and anti-GAD65 encephalitis for 6% of patients with autoimmune encephalitis admitted to the ICU. In this study, mechanical ventilation, sepsis, tumor presence, and autonomic dysfunction were associated with prolonged ICU stays or incomplete recovery [5].

Although the co-occurrence of different types of autoimmune encephalitis has been reported, the coexistence of anti-NMDAR and anti-GAD65 encephalitis is rare, with limited data available regarding the severity of this association. Herein, we report the case of an 18-year-old male diagnosed with both anti-NMDAR and anti-GAD65 encephalitis who was admitted to the ICU due to a decreased level of consciousness. The patient received first- and second-line immunotherapies, resulting in a gradual and sustained clinical recovery.

2. Case Presentation

We report the case of an 18-year-old Moroccan male patient with no medical history, admitted to the medical intensive care unit for decreased level of consciousness, abnormal movements, and fever. These symptoms had developed one week prior to admission, following the progression of initial symptoms, including delirium, bizarre behavior, and hallucinations, which had begun two months

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earlier after a flu-like episode. On admission, the patient was febrile with a temperature of 39.2°C and had a Glasgow Coma Scale score of 11. He exhibited mutism, was unresponsive to stimuli, and showed generalized rigidity. Autonomic dysfunctions were also noted, including sinus tachycardia at 166 bpm, hypertension of 170/100 mmHg, hypersalivation, bradypnea at 11 breaths per minute, and generalized tonic-clonic seizures that required intubation.

Laboratory analysis revealed an inflammatory syndrome (C-reactive protein: 33.5 mg/L, procalcitonin: 0.26 ng/L) with rhabdomyolysis (creatine kinase: 6079 UI/L). Toxicological screening was negative. Cerebral CT scan and angio-MRI findings were unremarkable. Electroencephalogram (The EEG was performed 10 days after the initiation of anticonvulsant treatment, which had been started prior to hospital admission) showed slow and nonreactive activity without epileptiform discharges. CSF analysis and infectious studies were normal except for a traumatic CSF sample with a white cell count of 21/mm³, 80% lymphocytes, and a red cell count of 22 000/mm³. The protein level in CSF was 0.62 g/L (normal range: 0.40–0.60 g/L), and the glucose level was 0.72 g/L. Serologic testing for HIV, HBV, HCV, CMV, EBV, HSV, VZV, TPHA, and VDRL was negative. Autoimmune conditions were suspected. However, a second cerebral MRI, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) were normal. Immunological testing using immunofluorescence revealed positive anti-NMDAR antibodies in both serum and CSF (Cerba laboratories) as well as low positive anti-GAD65 antibodies in serum (25.8 IU/mL, reference ≤ 17 IU/mL). Multiple glucose tests were within normal limits. Due to financial constraints, autoantibodies titers and analysis of oligoclonal bands could not be performed. However, a positron emission tomography (PET) scan for neoplasm screening was negative. Based on the 2016 autoimmune encephalitis guidelines [6], a diagnosis of anti-NMDAR encephalitis with probable anti-GAD65 encephalitis was established.

Therapeutically, the patient was treated with anticonvulsants, antipsychotics, intravenous immunoglobulins (2 g/kg), and corticosteroid pulses (15 mg/kg), followed by steroids at 1 mg/kg/day. Unfortunately, he developed septic shock due to ventilator-associated pneumonia, which was managed with appropriate antibiotics. Due to a lack of clinical improvement, he underwent five sessions of plasma exchanges, but no significant improvement was observed. According to international guidelines for the management of autoimmune encephalitis [7], Cyclophosphamide (0.6 g/m²) was initiated. However, it was later switched to rituximab (1 g) because of cyclophosphamide's potentially serious side effects, including myelosuppression, malignancy, and infertility, particularly concerning in younger patients. Subsequently, the patient showed remarkable clinical improvement, allowing for a gradual extubation on day 78 of hospitalization. Thereafter, he was transferred to another department for rehabilitation before being discharged home.

After discharge, the patient continued to exhibit mild frontal syndrome symptoms and was maintained on rituximab at a dose of 1 g every six months. At the 6-month follow-up, he had returned to his normal life without any relapses. Unfortunately, follow-up antibody titers could not be obtained due to financial constraints.

3. Discussion

Autoimmune encephalitis is the third most common cause of encephalitis, following infectious encephalitis and acute disseminated encephalomyelitis [2]. It includes a group of immune-mediated inflammatory disorders characterized by antibodies that can target different sites, such as intracellular components (e.g., Anti-GAD65), neuronal surface antigen (e.g., Anti-NMDAR), and intracellular onco-neuronal antigen (e.g., Anti-Ma) [7]. Tumor infections can trigger the production of these antibodies or can be cryptogenic [8]. This autoimmune condition can affect individuals across all age groups, with some subtypes predominantly affecting children and young adults [9].

The exact pathophysiological mechanism underlying the co-association of autoimmune encephalitis remains under investigation. However, they may involve an underlying immunogenetic predisposition and autoimmune responses triggered by infections or neoplasms. These infections can contribute to potentially autoreactive immune responses in different ways. On one hand, they may initiate or exacerbate autoimmune responses by creating a pro-inflammatory environment. Alternatively, they could disrupt peripheral tolerance mechanisms, facilitating the action of previously suppressed autoreactive effector cells [10].

On the other hand, infections may activate autoimmunity through molecular mimicry, where peptides derived from infectious agents resemble self-proteins, leading to the production of antibodies against NMDA receptors and GAD65. Nevertheless, molecular mimicry is unlikely to be the only underlying mechanism for autoimmune responses. Other mechanisms, including breaches in central tolerance, non-specific bystander activation, and persistent antigenic stimulation, may also contribute to developing autoimmune diseases [11].

Clinical manifestations are diverse and may include common symptoms such as behavioral changes, psychosis, seizures, abnormal movements, and cognitive deficits [9]. Additionally, specific symptoms are associated with particular antibodies. For instance, anti-NMDAR encephalitis is typically characterized by short-term memory impairment, orofacial dyskinesia, and autonomic dysfunction (all of which were observed in our case), whereas anti-GAD65 encephalitis may present with stiff person syndrome, limbic encephalitis, or cerebellar ataxia [12]. In our case, the patient presented only with stiff person syndrome. Other symptoms, such as limbic encephalitis and cerebellar ataxia, have been reported in only one case of this association.

Beyond clinical manifestations, autoimmune encephalitis also frequently co-occurs with other systemic or neurological conditions. For example, anti-GAD65 encephalitis is commonly linked to systemic autoimmune disease, particularly diabetes, and may co-occur with other antibodies in 19% of cases, in particular, $GABA^AR$, $GABA^BR$, and VGKC antibodies [13]. In contrast, anti-NMDAR encephalitis can be accompanied by demyelinating disorders, such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody-associated disease (MOGAD), in 3.3% of cases [14]. Nevertheless, the coexistence of anti-NMDAR and anti-GAD65 encephalitis has been sporadically reported. The table below summarizes the main characteristics of this association based on reported cases in the literature [15, 16, 17, 18].

The median age of the reported case was 37.6 years, ranging from 18 to 66 years. There was a slight male predominance (60%), which may be related to the small sample size (n=5). Adult-onset diabetes was found in one patient (20%). A flu-like syndrome was reported as a prodromal syndrome in two patients (40%). The most common initial presentation was psychiatric symptoms, observed in three patients (60%). Seizures and abnormal movements occurred in 60% of cases, while cognitive impairment was reported in four cases

Table 1: Comparison of the profile of anti-NMDAR and anti-GAD 65 encephalitis in the reported cases

	McEntire et al [16] USA	Kammeyer et al [15] USA	Gomez Oropeza et al [17] Mexico	Calderon et al [18] Mexico	Our case
Age	58 years	66 years	18 years	28 years	18 years
Sex	F	M	F	M	M
History	Adult-onset diabetes mellitus, hypertension, bell's palsy	Chronic tobacco	NM	No history	No history
Prodromal symptoms	No	No	Headache	Covid-19	Flu like syndrome
Fever	No	No	No	Yes	Yes
Initial presentation	Cognitive decline	Neurological	Behavioral symptoms, myoclonus	Psychiatric symptoms	Behavioral and psychiatric symptoms
Psychosis	No	No	No	Yes	Yes
Seizure	Yes	No	No	Yes	Yes
Behavioral symptoms	No	Yes	Yes	Yes	Yes
Abnormal movements	No	Yes	Yes	No	Yes
Catatonia	Yes	No	No	Yes	Yes
Cognitive impairment	Yes	Yes	Yes	No	Yes
Cerebellar ataxia	No	Yes	No	No	No
Stiff person syndrome	No	No	No	No	Yes
Autonomic dysfunction	No	No	No	No	Yes
Central hypoventilation	No	Yes	No	No	Yes
Brain MRI	Normal	Limbic and brainstem encephalitis	Normal	Signal abnormalities in the bilateral anterior cingulate cortex and temporal lobes	Normal
EEG	Right temporal epileptiform discharge	Diffused and intermixed pattern	Mild generalized dysfunction	Subcortical dysfunction in the frontal, temporal and occipital regions	Slow and non-reactive activity
CSF	Pleocytosis	Pleocytosis with lymphocytic predominance	Normal	Normal	Normal
Auto-antibodies detection	NMDA: CSF GAD65: CSF and serum	NDAR: CSF GAD65: serum Ma1+Ma2: CSF	CSF	CSF	NMDA: CSF and serum GAD65: serum
Tumor	NM	Suspected lung neoplasm	NM	No	No
Treatments	GC, IVIG, RTX	IVIG, PLEX, RTX	GC, PLEX, RTX	GC, IVIG	GC, PLEX, IVIG, CYP, RTX
Time to treatment initiation	NM	2 months	NM	2 weeks	2 months
Prognosis	Favorable	Questionable outcome	Favorable	Favorable with persistent irritability and agitation	Favorable
Relapse	NM	After 1 month	After 2 months	No	No
Median Follow up	NM	1 month	4 months	6 Weeks	10 months
ICU	No	NM	No	Status epilepticus	Decreased level of consciousness
Mechanical ventilation	No	NM	No	Yes	Yes
Death	No	NM	No	No	No

F, Female; M, Male; NM, Not mentioned; CSF, cerebrospinal fluid; GC, Glucocorticoids; IVIG, Intravenous immunoglobulins; PLEX, plasma exchange; RTX, Rituximab; CYP, Cyclophosphamide; MRI, Magnetic Resonance Imaging; EEG, Electroencephalogram; NDAR, N-methyl-D-aspartate receptor; NMDA, N-methyl-D-aspartate receptor; GAD65, Glutamic acid decarboxylase, 65 kDa isoform; Ma1, Ma2, Ma1/2 antibodies; ICU, Intensive Care Unit.

(80%). Central hypoventilation was noted in two of four cases (50%).

Brain MRI findings were normal in 60% of patients (one case showed signal abnormalities, and another revealed limbic and brainstem encephalitis). EEG abnormalities were noted in 100% of the cases. CSF analysis was normal in 60% of cases. Autoantibodies testing was performed in CSF, serum or both. Neoplasm screening was conducted in 40% of cases: one result was negative, and the other revealed strong suspicion of pulmonary neoplasm (chronic

tobacco, presence of speculated pulmonary nodules with adjacent pulmonary thickening, and positivity for anti-Ma1 and anti-Ma2 antibodies).

Low titers of anti-GAD65 antibodies in serum were observed in 60% of cases, including ours. A review article by Gaspard noted that low concentrations of anti-GAD65 antibodies were associated with a heterogeneous spectrum of symptoms. None of the patients exhibited overlapping syndrome in that study, suggesting that this may be a specific future of pathogenic anti-GAD65 antibodies. The identification of GAD65 antibodies should not prevent clinicians from investigating the presence of additional antibodies, in particular, $GABA^A$, $GABA^B$ receptor antibodies, as they seem to increase the risk of an underlying neoplasm [19].

All patients received first-line immunotherapy: glucocorticoids in 80%, intravenous immunoglobulins (IVIG) in 60%, and plasmapheresis in 60% of the cases. Second-line immunotherapy with rituximab was administrated in 80% of cases, which may reflect the severity of this co-occurrence of anti-GAD65 and anti-NMDAR encephalitis. Two patients (40%) were admitted to the ICU due to neurological deterioration (status epilepticus in one case and deceased level of consciousness in the other). Relapses occurred in 40% of cases, with a median time of one and a half months. The overall prognosis was favorable in four cases, although persistent irritability and irritation were noted in one patient (20%).

The overall outcome for both types of encephalitis is generally favorable. In a cohort study of 501 patients with anti-NMDAR encephalitis by Titulaer et al., first-line immunotherapy was administrated in 95% of the patients, 57% received second-line immunotherapy, 81% had good neurological outcomes at 24 months of follow-up, 12% experienced one or more relapses, and 6% died. Additionally, 39.5% of patients had tumors, and early treatment was associated with good neurological outcome [20].

In contrast, a case series of 37 patients with anti-GAD65 neurological autoimmunity reported by Qiu et al. showed that all patients received first-line immunotherapy, 51.35% received second-line immunotherapy, and 81.3% showed a partial to good response at follow-up. However, 53.1% experienced a relapse, and 3.1% died. Tumors were suspected only in 5.4% of cases, and in this study, early treatment was not correlated with good neurological outcome [21].

In the reported cases summarized in the table below, all patients received first-line immunotherapy, 80% underwent second-line immunotherapy, 40% experienced a relapse, and only one had a tumor.

These results highlight the importance of rapid diagnosis to initiate treatment promptly and prevent prolonged ICU stays, as well as the necessity of long-term follow-up to detect early relapses and potential neoplasm. Given the small number of reported cases with co-occurring anti-NMDAR and anti-GAD65 encephalitis, further studies involving larger cohorts are needed to confirm the characteristics of this association.

4. Conclusions

The co-occurrence of anti-NMDAR and anti-GAD65 encephalitis is a rare condition that can cause severe manifestations. The nonspecific neuropsychiatric symptoms often lead to delayed or missed diagnoses. A broad antibody screening panel can prevent multiple lumbar punctures and avoid unacceptable delays in diagnosis and targeted cancer screenings.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this article.

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Informed consent

Obtained from the patient.

Large Language Model

None

Authors Contribution

All authors made substantial contributions to this case report. They were involved in patient care, the conception of the report, and the gathering of relevant clinical data. Each author participated in drafting the manuscript and revising it critically. They also reviewed and approved the final version of the manuscript, ensuring its accuracy and integrity in representing the case studied.

Data Availability

All data supporting the findings of this study are included in the article. Additional information is available from the corresponding author upon reasonable request.

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Review Article

Bridging the Gap: Addressing Language Barriers to Advance Equity in Internal Medicine

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ABSTRACT

Language barriers in healthcare are a persistent challenge that disproportionately affect patients with limited English proficiency (LEP), contributing to disparities in care, poor health outcomes, and patient dissatisfaction. In internal medicine, where effective communication is essential for diagnosis, management, and chronic disease follow-up, these barriers hinder quality and equity. This review synthesizes the current evidence on the impact of language discordance in internal medicine, explores effective mitigation strategies including interpreter services, culturally competent care, and technological tools and offers policy and practice recommendations to promote equitable healthcare delivery.

1. Introduction

Effective communication is foundational to quality healthcare delivery. Within internal medicine, where diagnoses and treatments can be complex, clear communication is vital for patient safety and treatment success. However, patients with limited English proficiency (LEP) often face significant language barriers. These barriers hinder accurate diagnosis, reduce treatment adherence, and lead to lower patient satisfaction [1, 2].

Despite growing attention to healthcare disparities, language barriers remain a persistent and under-addressed challenge in internal medicine. While previous studies have documented communication issues in healthcare broadly, there is a lack of focused synthesis on how these barriers affect internal medicine specifically—a field heavily reliant on verbal exchanges for managing chronic, multifaceted conditions [3].

The aim of this review is to examine the impact of language barriers on clinical outcomes for LEP patients in internal medicine settings. Specifically, this review identifies where communication failures occur, explores their consequences on diagnosis, medication use, and chronic disease management, and evaluates existing strategies to mitigate these barriers. Additionally, we propose policy and educational reforms to support language equity in clinical care.

This review fills a critical gap by consolidating evidence from the past decade to inform both practice and policy. Through a structured synthesis of recent literature, it contributes to the ongoing discourse on health equity by highlighting actionable insights and outlining future research priorities.

According to the U.S. Census Bureau, over 25 million people in the United States speak English less than "very well," and this number is growing [4]. LEP patients are more likely to experience poor health outcomes, have unmet medical needs, and miss preventive care. As LEP populations expand across all types of communities, internal medicine practitioners must address the impact of language barriers.

2. Methodology

A comprehensive literature review was conducted to identify relevant studies on language barriers affecting LEP patients within internal medicine. The search was carried out using PubMed, CINAHL, and the Cochrane Library databases, covering publications from January 2010 to April 2024. Search terms included: "limited English proficiency," "language barriers," "internal medicine," "interpretation services," and "healthcare disparities."

Studies were included if they: (1) focused on LEP patients in internal medicine or general adult healthcare settings, (2) evaluated clinical outcomes, communication quality, or healthcare utilization, and (3) were published in English. Exclusion criteria included studies that focused exclusively on pediatric populations, editorial or opinion pieces, or those without outcome data. Study selection followed a two-phase screening process. First, titles and abstracts were reviewed to exclude clearly irrelevant studies. Second, full texts were assessed for eligibility based on inclusion/exclusion criteria. When available, studies were appraised for quality using the

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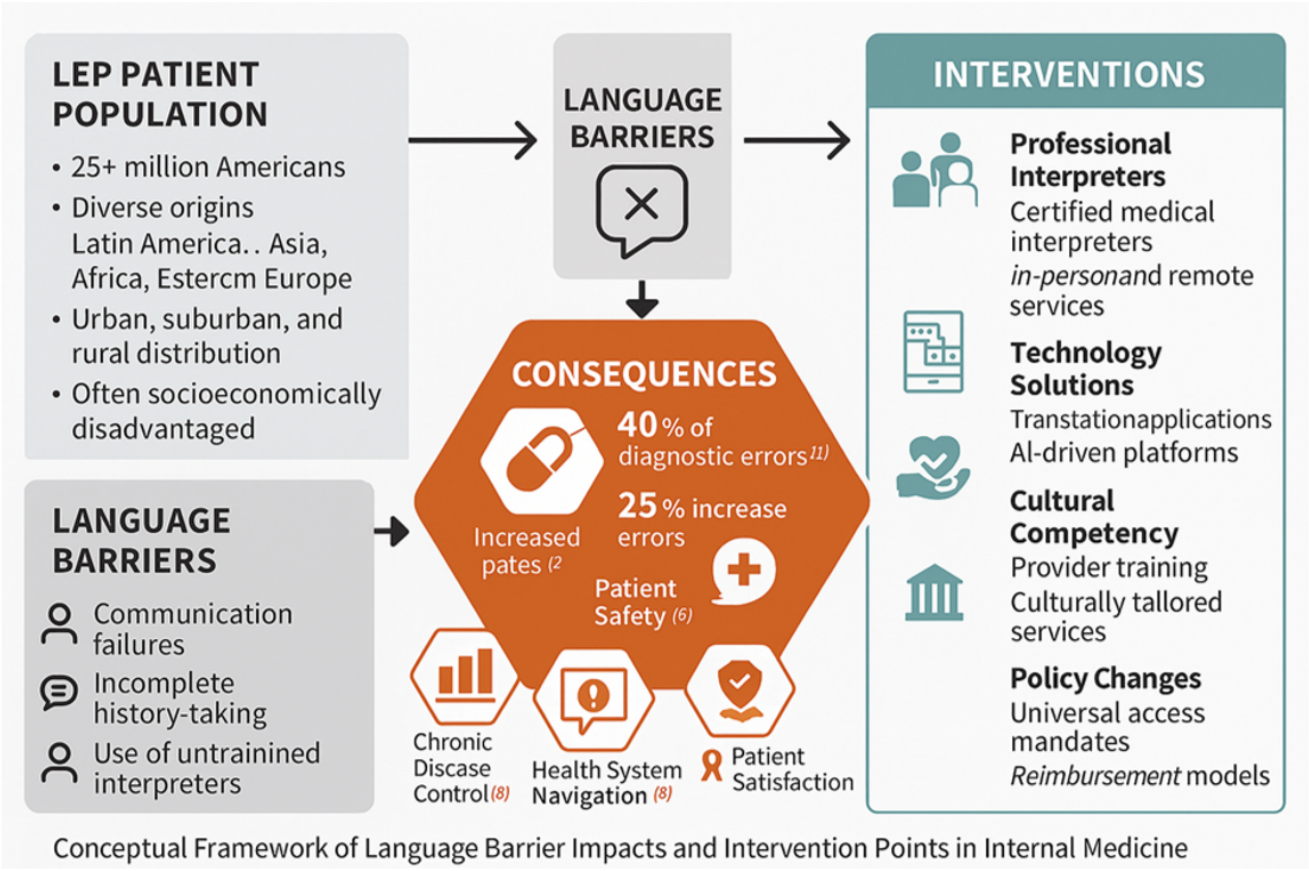

Figure 1: Conceptual Framework of Language Barrier Impacts and Intervention Points in Internal Medicine.

CASP (Critical Appraisal Skills Programme) checklist for cohort and qualitative studies to ensure relevance and methodological rigor.

3. Scope of the Problem in Internal Medicine

Language barriers in internal medicine contribute to a wide range of health disparities that are particularly pronounced in populations with limited English proficiency. These barriers affect every phase of the care continuum—from scheduling appointments and providing informed consent to understanding treatment plans and navigating follow-up services. For providers in internal medicine, whose work often involves managing chronic diseases and coordinating multidisciplinary care, effective communication is not optional; it is essential.

Internal medicine also serves as a gateway to specialist referrals and advanced diagnostics. When communication breaks down, it jeopardizes this gatekeeping role, resulting in either overuse or underuse of medical resources. Furthermore, limited language access can erode trust in the healthcare system, causing patients to delay care or avoid it entirely. Such delays often lead to more severe illness at the time of presentation, which increases the burden on healthcare systems and compromises long-term outcomes. **(Figure 1)** illustrates a conceptual framework outlining how language barriers experienced by LEP populations lead to downstream clinical consequences and highlights key intervention points.

3.1. Demographics and Distribution

LEP patients include immigrants and refugees from Latin America, Asia, Africa, and Eastern Europe [5, 6]. These populations bring diverse cultural backgrounds, health beliefs, and linguistic needs that significantly influence their interactions with the healthcare system. LEP individuals often speak a wide array of languages and dialects, making it essential for healthcare systems to provide adaptable and inclusive language services.

While many LEP individuals reside in urban centers with established immigrant communities, an increasing number are settling in suburban and rural areas due to shifting economic opportunities and housing patterns. This geographical spread presents unique challenges for language access in less-resourced regions, where interpreter services and culturally competent care may be less readily available. In addition to language barriers, LEP populations frequently face intersecting social determinants of health such as lower income, limited educational attainment, and restricted access to transportation and health insurance [7]. These factors compound their vulnerability to poor health outcomes and reduce their ability to navigate complex healthcare systems without targeted support. Addressing these multifaceted barriers requires a coordinated approach that integrates language services with broader equity and inclusion initiatives.

3.2. Clinical Burden

Research shows that LEP patients have worse outcomes for many conditions, including chronic illnesses such as hypertension, diabetes, asthma, and heart disease. They receive fewer preventive

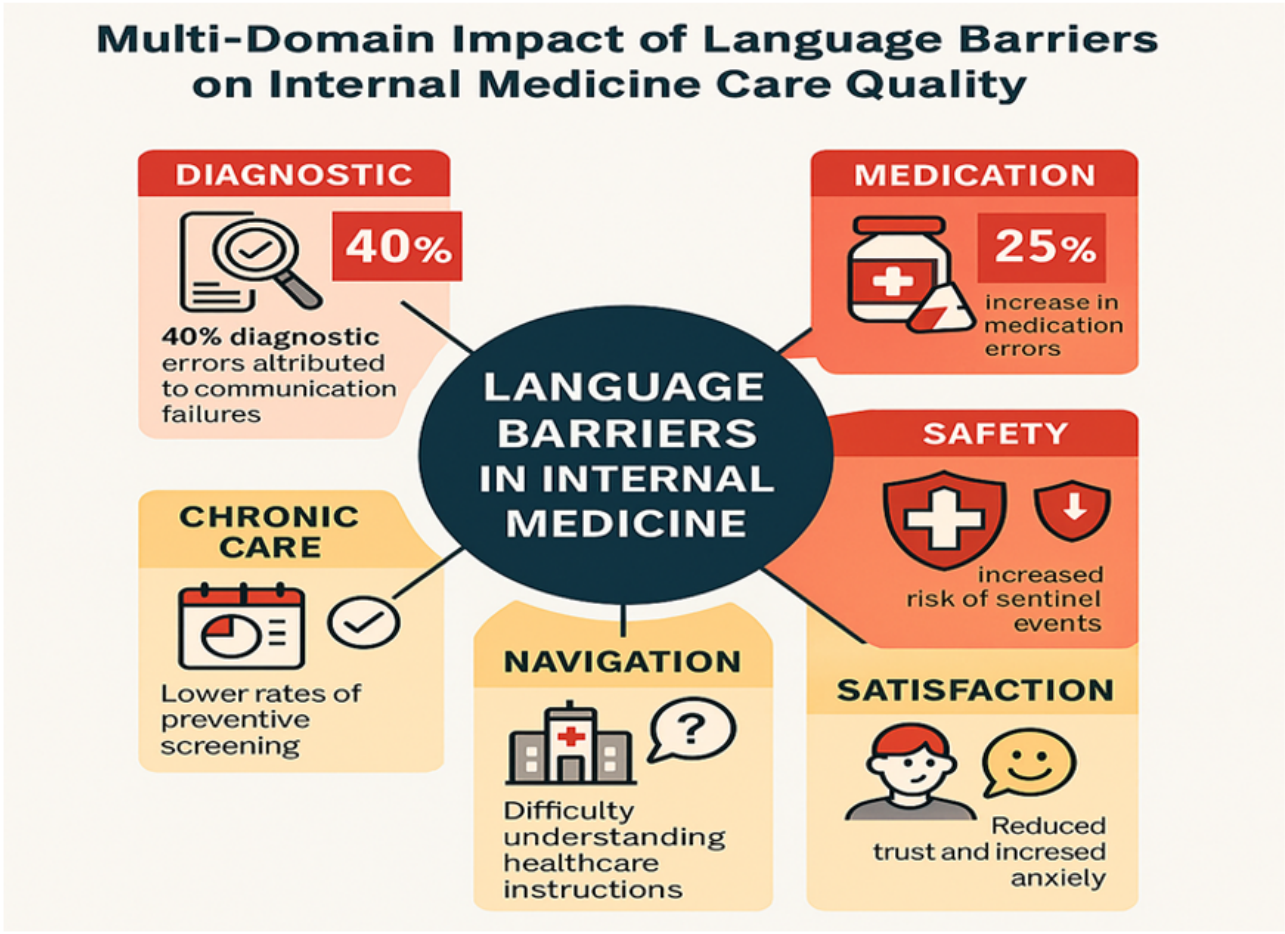

Figure 2: Multi-Domain Impact of Language Barriers on Internal Medicine Care Quality.

services like cancer screenings and immunizations and often face delayed diagnoses due to inadequate symptom communication [2, 8]. When they are hospitalized, LEP patients are more likely to experience longer stays, higher readmission rates, and increased risk of adverse events [9]. A lack of effective communication leads to misunderstandings about diagnoses, medications, and follow-up instructions. In turn, this undermines treatment adherence and long-term disease control. For instance, LEP patients are more likely to misunderstand discharge instructions, contributing to post-hospital complications. Miscommunication can also lead to unnecessary diagnostic testing, further straining healthcare resources [1].

In internal medicine—where providers must rely heavily on nuanced patient histories and shared decision-making—these communication failures are particularly detrimental. Without language support, providers may inadvertently make assumptions or simplify care to avoid miscommunication, which compromises both patient safety and ethical standards [3]. Ultimately, addressing this clinical burden requires targeted, sustained interventions across both individual and system levels. **(Figure 2)** illustrates six critical domains where language barriers compromise care quality in internal medicine, along with associated statistics and severity indicators.

Domain Impact on LEP Patients Supporting Evidence Diagnostic Accuracy Delayed or incorrect diagnosis due to miscommunication Al Shamsi et al. (2020) [1]

Medication Management Incorrect usage, dosing errors, and non-adherence Ali & Watson (2018) [10]

Patient Safety Increased risk of adverse events Divi et al. (2007) [9]

Chronic Disease Control Lower screening rates and poor disease management Sentell & Braun (2012) [8]

Health System Navigation Difficulty accessing services or understanding instructions Pandey et al. (2021) [11]

Patient Satisfaction Reduced trust, increased anxiety, dissatisfaction Flores (2006) [2]; Karliner et al. (2007) [12]

4. Communication Failures and Their Consequences

Communication is a core component of effective and equitable healthcare. For LEP patients, language discordance significantly increases the risk of clinical errors, misunderstandings, and poor outcomes. In internal medicine, where diagnostic reasoning, medication management, and continuity of care are essential, these communication failures can lead to dangerous consequences. **(Figure 3)** outlines key stages of the patient care journey and highlights where language barriers commonly disrupt clinical communication, along with targeted intervention strategies.

Table 1: Common Consequences of Language Barriers in Internal Medicine.

Domain	Impact on LEP Patients	Supporting Evidence
Diagnostic Accuracy	Delayed or incorrect diagnosis due to miscommunication	Al Shamsi et al. (2020) [1]
Medication Management	Incorrect usage, dosing errors, and non-adherence	Ali & Watson (2018) [10]
Patient Safety	Increased risk of adverse events	Divi et al. (2007) [9]
Chronic Disease Control	Lower screening rates and poor disease management	Sentell & Braun (2012) [8]
Health System Navigation	Difficulty accessing services or understanding instructions	Pandey et al. (2021) [11]
Patient Satisfaction	Reduced trust, increased anxiety, dissatisfaction	Flores (2006) [2]; Karliner et al. (2007) [12]

4.1. Diagnostic Errors

Internal medicine depends on patients accurately describing symptoms, timelines, and treatment histories—details that shape diagnostic reasoning. When there is a language barrier, critical elements may be omitted or misinterpreted. LEP patients may struggle to articulate their symptoms clearly, especially if they are unfamiliar with medical terminology or cultural norms around expressing pain or distress. This miscommunication can result in missed or delayed diagnoses, inappropriate testing, and ineffective treatment plans [1].

A study by Al Shamsi et al. reported that nearly 40% of diagnostic errors among LEP patients were directly attributed to communication failures [1]. These errors are not only clinically significant but also ethically concerning, as they disproportionately affect already vulnerable populations. Moreover, providers may experience cognitive overload or frustration during encounters with LEP patients, which can lead to premature diagnostic closure or stereotyping.

4.2. Medication Mismanagement

Medication errors are a frequent and preventable source of harm for LEP patients. Understanding medication names, dosages, timing, side effects, and potential interactions requires clear and consistent communication. LEP patients often receive instructions in English only or through ad hoc interpreters, increasing the risk of misunderstanding [10].

Ali and Watson found a 25% increase in medication-related errors among patients facing language barriers [10]. Errors range from incorrect dosing and missed medications to serious adverse drug events. Furthermore, patients may avoid asking clarifying questions out of fear or embarrassment, particularly when family members interpret.

Pharmacy labeling, discharge instructions, and medication reconciliation are particularly vulnerable points in care transitions. Ensuring multilingual written instructions, pictogram-based aids, and pharmacist consultations with interpreters are essential steps in minimizing risk.

4.3. Use of Ad Hoc Interpreters

"Ad hoc" interpreters refer to individuals who are not professionally trained to provide medical interpretation but are asked to assist during clinical encounters. These may include family members, friends, bilingual staff without formal training, or even children. While often used out of necessity, relying on ad hoc interpreters introduces significant risks to communication accuracy, confidentiality, and patient safety.

Flores et al. found that 63% of errors committed by ad hoc interpreters had potential clinical consequences [13]. Common errors included omissions, additions, and misinterpretations that distorted the patient's message or the clinician's instructions. Using children in these roles can cause emotional distress and lead to withholding sensitive information. Additionally, ad hoc interpreting can interfere with patient autonomy and privacy. Patients may avoid disclosing symptoms or questions when a family member is present, especially in culturally sensitive contexts. Ethical guidelines from the National Council on Interpreting in Health Care discourage using untrained interpreters [14], advocating instead for the systematic provision of certified language professionals.

5. Chronic Disease Management Challenges

Understanding how patients themselves experience language barriers is critical to delivering person-centered care. Qualitative research consistently reveals that LEP patients often feel marginalized during clinical encounters. In interviews, patients have described feeling "invisible" or "ignored" when communication is handled through rushed or impersonal means. For instance, a participant in a study shared, "I just nodded because I didn't want to bother them again. I didn't understand but didn't know how to ask" [11].

Other studies highlight how the mode of interpretation influences patient comfort and trust. While some appreciate the convenience of video or phone interpretation, many prefer in-person interpreters who can also help convey non-verbal cues and cultural context. One respondent in a focus group noted, "The interpreter in the room helps the doctor see me, not just hear my words, but understand me as a person" [11].

Patient-reported outcome measures (PROMs) further reinforce that language barriers reduce satisfaction, trust, and follow-up adherence. In a multicenter survey, LEP patients with consistent access to professional interpreters reported significantly higher satisfaction and confidence in their care compared to those using ad hoc or no interpretation [12]. These findings stress the need to integrate patient voices in designing, implementing, and evaluating language services.

Involving LEP patients in feedback processes and advisory roles can help ensure that services truly respond to their needs and preferences, improving equity and effectiveness. Internal medicine often involves managing long-term illnesses like diabetes or hypertension. LEP patients often have poorer control over these conditions because they struggle to understand complex care plans. For example, LEP patients with diabetes are less likely to get recommended tests like HbA1c checks, even if they have insurance [8].

Ongoing disease management requires trust and collaboration, which can break down when language is a barrier. Educational

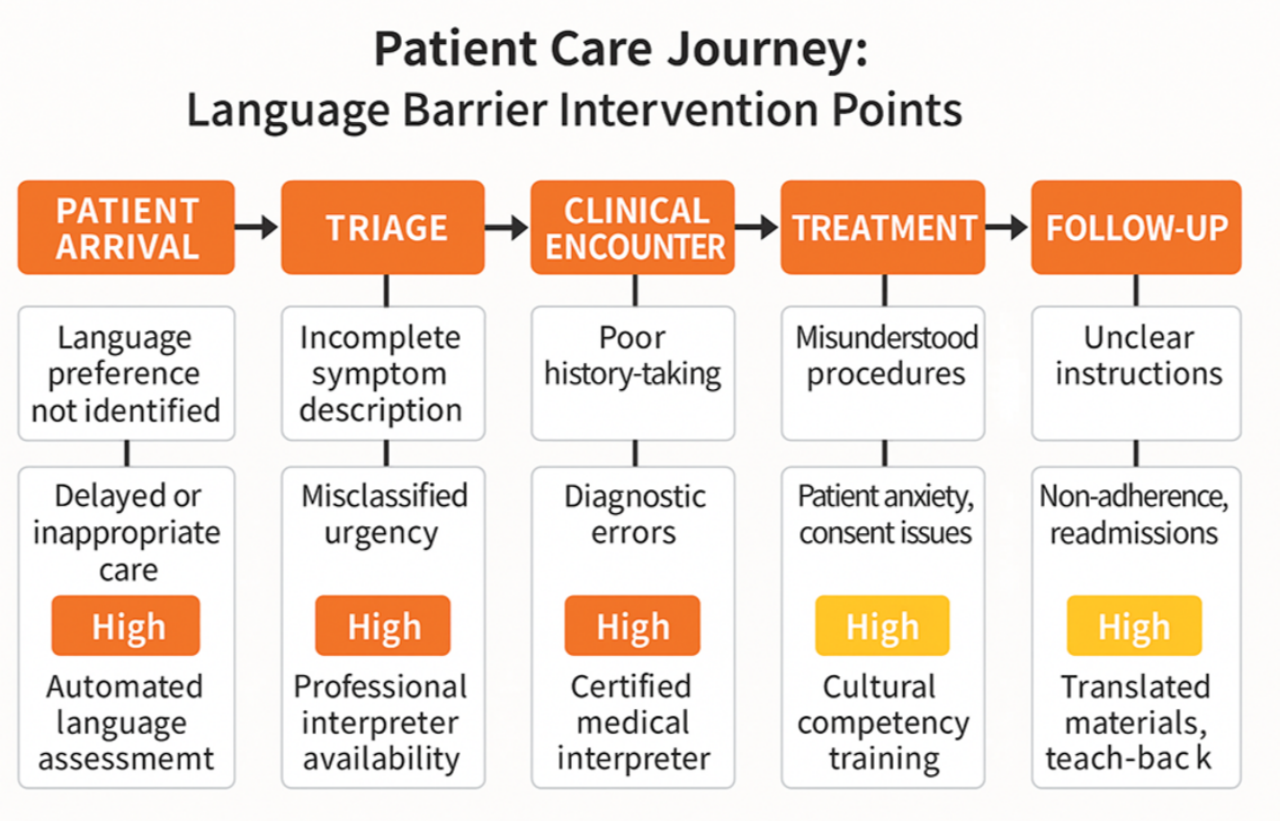

Figure 3: Patient Care Journey: Language Barrier Intervention Points.

programs tailored to cultural needs have improved outcomes in LEP populations [4].

6. Challenges

Implementing language access solutions in actual healthcare settings is frequently complicated by several persistent barriers. The primary challenges include:

6.1. Staff shortages and interpreter availability

Many healthcare facilities, especially in rural or underfunded areas, struggle to maintain an adequate pool of trained medical interpreters. Limited interpreter coverage during evenings or weekends can delay care or compromise communication. For example, a community hospital in rural New Mexico partnered with a regional language service cooperative to share interpreter resources and implemented video remote interpreting (VRI) systems to expand access during off-hours.

6.2. Technology infrastructure limitations

Although translation apps and video interpreting services offer promising support, their use depends on reliable internet access, up-to-date devices, and user training—all of which may be lacking in resource-constrained settings. For example, a federally qualified health center in Chicago piloted a low-cost tablet-based VRI platform with preloaded training modules for providers. The initiative improved interpreter utilization by 60% within six months.

6.3. Institutional resistance and organizational culture

Some institutions may deprioritize language access due to competing administrative demands or a lack of awareness about its importance. Without leadership buy-in, even well-designed policies often fail in execution. For example, a large academic medical center in California integrated language access metrics into its quality improvement dashboard, which led to the inclusion of interpreter services in performance evaluations for department heads.

6.4. Training time, costs, and sustainability

Cultural competence and communication training for providers require time and financial resources. Ensuring long-term engagement and integration into clinical routines can be difficult without dedicated funding and institutional mandates. For example, a medical school in the Northeast embedded interpreter use and cultural humility into its core curriculum using standardized patient simulations. This sustained approach led to increased student confidence and improved patient satisfaction scores in residency.

7. Mitigation Strategies

Several strategies have been proposed to reduce language barriers in internal medicine.

7.1. Professional Medical Interpreters

Certified interpreters help ensure accurate, confidential communication. These professionals are trained to navigate complex medical terminology and ethical principles, including impartiality and confidentiality. Their presence facilitates trust between patients and providers and allows clinicians to gather more complete and

reliable histories. Studies consistently show that professional interpreter use improves clinical outcomes, increases patient satisfaction, and reduces adverse events [12]. In addition to bedside interpretation, interpreters play a vital role during informed consent discussions, end-of-life conversations, and discharge planning—moments where precision and clarity are crucial. However, access to certified interpreters remains uneven across healthcare settings, especially in rural or resource-limited facilities. Institutions should proactively offer interpreter services, ensure round-the-clock availability via in-person, video, or phone options, and integrate interpretation into workflow protocols to avoid delays in care [3].

7.2. Technological Tools

Apps like Canopy, Google Translate, and MediBabble offer quick language help in clinical settings. These tools are particularly valuable during urgent care scenarios or when professional interpreters are unavailable. They can also assist with basic communication tasks, such as collecting patient histories, explaining procedures, or providing medication instructions [1]. However, these platforms should be seen as supplements—not substitutes—for professional interpretation. Machine translation tools can misinterpret medical terms, especially when dealing with idiomatic expressions, complex grammar, or less commonly spoken languages. There are also concerns about patient privacy, as many apps are not HIPAA-compliant and may store sensitive data on unsecured servers [14]. To maximize benefits while minimizing risks, institutions should vet and approve specific tools for clinical use, train staff in appropriate use cases, and implement backup systems to escalate to human interpretation when needed. Integrating translation features into electronic health records (EHRs) may further streamline multilingual care delivery in the future.

7.3. Culturally Competent Care Models

Language access involves more than translation. Effective care requires understanding patients' cultural beliefs, values, and communication preferences. Culturally competent care models promote equity by acknowledging and addressing the sociocultural factors influencing health behaviors and medical decision-making [5]. The National Standards for Culturally and Linguistically Appropriate Services (CLAS) offer a comprehensive framework for healthcare organizations to improve communication and respect patient diversity. Implementing these standards can help reduce mistrust, improve adherence, and foster a more welcoming environment for LEP patients. Healthcare systems that hire bilingual staff, offer cultural competence training, and partner with community-based organizations have reported improved outcomes in patient engagement, preventive care utilization, and satisfaction [7]. These models emphasize the importance of continuity of care and building relationships within linguistically diverse communities, rather than applying one-size-fits-all solutions.

7.4. Provider Education

Training providers in cultural awareness and communication strategies improves care for LEP patients by equipping clinicians with the skills needed to recognize and navigate linguistic and cultural barriers. Education in this domain fosters empathy, reduces implicit bias, and enhances clinicians' ability to engage in meaningful dialogue with diverse patient populations [4]. Many medical schools and residency programs now incorporate curricula on health equity, cross-cultural communication, and language access laws. Simulation-based learning using standardized patients is particularly effective for helping trainees practice interpreter use, manage cross-cultural misunderstandings, and reflect on their communication approaches [14]. Continuing medical education (CME) opportunities also enable practicing providers to stay current with best practices. Institutional support, such as allocating time for training and integrating it into performance evaluations, is essential to sustain these efforts and create a culture of linguistic equity throughout healthcare systems.

8. Health Policy and System Reform

Addressing language barriers effectively requires more than isolated clinical interventions—it demands systemic reform supported by institutional leadership and public policy. Health systems must prioritize language equity as a fundamental component of patient safety, regulatory compliance, and care quality.

Universal Access to Interpreter Services: Every healthcare setting—regardless of size, location, or resources—should provide timely access to professional medical interpreters. This includes establishing protocols for interpreter use in all patient-facing interactions, not just in emergencies or high-risk encounters. Institutions can implement scheduling systems, interpreter staffing pools, or remote interpreting platforms to ensure 24/7 coverage [12, 3].

Reimbursement Models: Lack of reimbursement is often cited as a major barrier to offering comprehensive language services. Policymakers should mandate Medicaid and Medicare reimbursement for interpreter use, especially in federally funded facilities and community health centers. Evidence shows that the financial benefits—through reduced errors, readmissions, and malpractice risks—outweigh the cost of providing interpretation [7].

Standardized Language Data Collection: Documenting patients' preferred language and interpreter needs in electronic health records (EHRs) ensures consistency across providers and departments. Institutions should integrate language fields into clinical workflows, train front-line staff to collect this data accurately, and use it to guide service allocation and performance evaluation [14].

Accreditation and Accountability: Accreditation bodies like the Joint Commission already recognize the role of communication in patient safety. Expanding and enforcing standards that require language access policies—and tying these to quality improvement metrics or financial incentives—can drive widespread institutional adoption [15]. Public Health Integration: Language equity must also extend to public health messaging and outreach, particularly during health crises like pandemics. Governments and health departments should ensure all communication is multilingual, culturally tailored, and co-developed with input from community stakeholders.

Ultimately, policy reform is critical to embedding language access into the healthcare system's infrastructure, transforming it from a discretionary service into a standard of care.

8.1. Research and Future Directions

Although the evidence base supporting language access interventions is growing, several gaps remain that limit our ability to scale, sustain, and tailor these strategies effectively. Implementation Science: Much of the existing research is observational. Future work should apply implementation science methods to assess how language access programs are adopted, adapted, and sustained in real-world clinical settings. These studies can identify barriers, facilitators, and best practices that inform scale-up across diverse institutions [14]. Cost-Benefit Analysis: Despite

anecdotal and ethical justification for interpreter services, rigorous economic evaluations are needed. Research should compare the cost of interpreter use to the costs associated with adverse events, unnecessary testing, malpractice claims, and readmissions in LEP populations [7]. Patient-Reported Experiences and Outcomes: More qualitative and mixed-methods studies are needed to center patient voices, especially those from underrepresented language groups. Research should examine how patients perceive interpretation quality, communication dynamics, trust, and autonomy during language-discordant encounters [11]. Chronic Disease Outcomes: Longitudinal cohort studies can clarify how language-concordant care influences chronic disease management, especially for high-burden conditions such as diabetes, hypertension, and heart failure. Understanding long-term outcomes can guide resource allocation and chronic care strategies in internal medicine [3, 8]. Training and Education Effectiveness: Evaluating DEI-focused education programs using validated outcome measures can help identify which teaching strategies (e.g., simulation, service learning, cultural immersion) most effectively improve clinician competence and patient satisfaction [4]. By prioritizing these research domains, the field can generate actionable insights that translate into scalable, equity-driven language access solutions.

9. Limitations

This review has several limitations. First, we did not conduct a systematic search with protocol registration, which may introduce selection bias. While the search strategy was comprehensive and multi-database, the absence of a registered protocol (e.g., PROSPERO) limits reproducibility and transparency. Second, the included studies varied significantly in terms of methodology, populations studied, and outcome measures, making direct comparisons difficult and potentially limiting generalizability. The heterogeneity also complicates efforts to draw definitive conclusions about intervention effectiveness. Third, most of the supporting evidence comes from observational studies rather than randomized controlled trials. While observational data provide valuable insights, they are more susceptible to confounding and may not establish causality. Fourth, although the review focuses on internal medicine, many cited studies encompass broader healthcare settings. This focus may not fully capture language barriers in specialty practices outside of internal medicine, such as oncology, geriatrics, or emergency care, where communication needs and challenges may differ. Finally, publication bias toward studies showing significant or positive results cannot be excluded. Unpublished or null findings may provide critical counterpoints and are underrepresented in the current literature landscape.

10. Conclusion

Language barriers represent a critical patient safety issue requiring urgent attention. Evidence strongly supports the routine use of professional interpretation services, which are consistently associated with improvements in diagnostic accuracy, medication safety, and patient satisfaction [12**?**]. Despite real-world implementation barriers—including staffing shortages, technology gaps, and institutional resistance—the clinical and economic benefits of investing in language access are clear. System-level reforms, such as Medicaid and Medicare reimbursement policies, data standardization, and enforcement of language equity standards, are essential to move from piecemeal to systemic solutions [14, 7, 15]. Internal medicine practitioners are uniquely positioned to lead these efforts, given the field's emphasis on continuity of care, chronic disease management, and patient-provider relationships. By adopting evidence-based language access strategies, incorporating culturally competent care models, and prioritizing training in communication equity, internal medicine can drive transformative change. Future research should focus on implementation science approaches and long-term outcome studies to optimize delivery of language-concordant care. Ensuring that LEP patients are not only heard—but truly understood—must become a fundamental standard of modern, equitable healthcare.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Institutional Review Board (IRB)

This review did not involve human subjects and was therefore exempt from Institutional Review Board approval.

Large Language Model

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Authors' Contribution

JR conceptualized the idea, wrote the original draft, reviewed, and edited the manuscript; DR conducted the literature review, designed the figures, and contributed to writing, review, and editing; all authors read and approved the final manuscript.

Data Availability

This manuscript is based solely on previously published literature. No new datasets were generated or analysed.

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ASIDE Internal Medicine

Original Article

Clinical Efficacy and Safety of Fluvoxamine in COVID-19 Patients: An Umbrella Review of Systematic Reviews and Meta-Analyses

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ABSTRACT

Introduction Fluvoxamine is an agonist for the sigma-1 receptor, through which it controls inflammation. It helps reduce the cytokine storm associated with the COVID-19 virus by regulating the production of IL-6 and gene expression. This review of systematic reviews (SRs) aims to summarize the effects of fluvoxamine in treatment of COVID-19.

Methods This umbrella review (CRD42025592203) of SRs and meta-analyses investigated the safety and efficacy of fluvoxamine for treatment in COVID-19 patients, irrespective of disease severity and age. Comprehensive searches were conducted from inception to December 12, 2024, covering PubMed, Cochrane CENTRAL, Google Scholar, and Cochrane COVID-19 resources. A qualitative synthesis of evidence was performed. The AMSTAR2 tool was used to assess the methodological quality of the included SRs.

Results Eleven reviews published in 12 publications that reported the use of fluvoxamine in COVID-19 patients were finally included as part of the synthesis. The studies reported a lower mortality rate with fluvoxamine than with placebo, but only four studies reported statistical significance. Five reported a statistically significant reduction in hospitalization risk for patients treated with fluvoxamine compared to controls. Only one review evaluated COVID-19 progression, reporting a non-significant decrease in the risk of disease progression with fluvoxamine compared to placebo. Higher dosages of fluvoxamine compared to lower doses yielded better outcomes.

Conclusion Although fluvoxamine may have potential benefits in reducing COVID-19-associated mortality and hospitalization, our findings do not support a significant role in preventing disease progression or clinical deterioration. Further research is needed to compare the efficacies of different dosages.

1. Introduction

The coronavirus disease 2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an acute respiratory syndrome that rapidly escalated into a global pandemic after first appearing in Wuhan, China, during late December 2019 [1]. Due to its highly contagious and severe nature, it has had a catastrophic impact, resulting in more than 6 million deaths globally [1]. To minimize its spread, various vaccines, including mRNA and inactivated vaccines, were developed in addition to preventive measures such as social distancing [2].

Supportive care, along with close monitoring of high-risk patients, remains the primary treatment approach for individuals with COVID-19 [3]. Antivirals and antimicrobials have also been considered as part of treatment plans; however, their effectiveness remains uncertain, as studies have shown mixed results [4].

Repurposed drugs are medications already approved by the Food and Drug Administration (FDA) for other indications that may be used in the management of COVID-19. Fluvoxamine is one of four FDA-approved medications being tested in the ACTIV-6 trial, owing to its affordability and accessibility, particularly in resource-limited settings [5]. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI), commonly used to treat depression, anxiety disorders, and obsessive-compulsive disorder (OCD). It is being investigated as a potential treatment option for COVID-19 due to its anti-inflammatory properties [6]. One proposed mechanism is through

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fluvoxamine's interaction with the sigma-1 receptors (S1Rs). S1R is a multifunctional chaperone protein that plays an important role in cellular survival by mediating calcium influx into mitochondria during cellular stress, such as in viral infections [7]. Fluvoxamine is a ligand of S1R and plays a protective role in COVID-19 infection by reducing oxidative stress response and counteracting pro-apoptotic signals, consequently reducing the severity of infection [8]. Additionally, fluvoxamine is a lysosomotropic agent and inhibitor of acid sphingomyelinase in the lysosomes. This could inhibit the formation of viral replication complexes and negatively affect viral trafficking and budding, justifying its potential as a treatment option in COVID-19 [6]. Apart from its role as an antiviral, fluvoxamine also exhibits anti-inflammatory properties, which help reduce the severity of cytokine storms associated with COVID-19 infections. Mast cells possess ACE-2 receptors acting as hosts for SARS-CoV-2 and mediating the cytokine storm. SSRIs like fluvoxamine are known to decrease mRNA levels of protease-1 in mast cells, therefore, inhibiting the release of histamine from mast cells [9].

This overview of systematic reviews (SRs) and meta-analyses was conducted to compile and analyze existing evidence on the use of fluvoxamine in treating COVID-19. It also aims to assess its potential efficacy in terms of affordability and compare it with other available COVID-19 treatments.

2. Methods

The protocol for this review has been registered with PROSPERO (CRD42025592203) on January 7th, 2025. This overview adheres to the PRISMA 2020 standards for SRs. The results are reported following the PRISMA guidelines for SRs and meta-analyses that focus on healthcare interventions.

2.1. Objectives

This umbrella review of SRs and meta-analyses was conducted to qualitatively consolidate and analyze current evidence regarding the use of fluvoxamine in treating COVID-19. The findings will be crucial to gauge their potential effectiveness in comparison to the cost and accessibility challenges associated with other treatment options for COVID-19.

2.2. Eligibility Criteria

2.2.1. Inclusion criteria

We included SRs that examined both the effectiveness and safety of fluvoxamine in patients with COVID-19 without restrictions on patient age or disease severity. Reviews addressing COVID-19 at all stages, from asymptomatic cases to severe infections, and in all care settings (both outpatient and inpatient) were considered. Inclusion was not limited by the type of study designs included in the SRs.

2.2.2. Exclusion criteria

Reviews that were not SRs or meta-analyses, narrative reviews, editorials, conference abstracts, non-English publications, reviews focusing solely on other interventions without fluvoxamine data, and duplicate publications were excluded.

2.2.3. Information Sources and Search Strategy

Comprehensive search strategies were designed to identify relevant studies in the PubMed and Cochrane databases. The search was further supplemented by exploring additional literature sources, including the Cochrane COVID-19 resource and Google Scholar, as well as cross-referencing the SRs identified. Detailed search strategies for each electronic database are provided in Supplement 1. To avoid missing SRs that reported combined therapies, search terms were not limited to fluvoxamine-specific keywords. The electronic databases and other literature sources were initially searched for records published between January 1st, 2020, and July 30th, 2024. An updated supplemental literature search was conducted on December 12th, 2024. Only publications in the English language were included.

2.2.4. Screening and Selection

All retrieved records from the database search were assessed for relevance using predetermined inclusion criteria. Two reviewers independently screened the titles and abstracts, followed by a full-text review. Any disagreements between the reviewers were resolved through discussion and, if necessary, by consulting a third reviewer.

2.2.5. Data Collection, Extraction, and Quality Evaluation

Data from the SRs were gathered using a standardized extraction form. Extracted details included general characteristics of each review, descriptions of the target populations, dosing regimens, and frequency of fluvoxamine, comparators, outcome measures, and findings related to safety and effectiveness. The methodological quality of each included review was assessed using the AMSTAR2 tool. Reviews were categorized as high quality (no or one minor weakness), moderate quality (multiple minor weaknesses), low quality (one major flaw with or without minor weaknesses), or critically low (multiple major flaws). Two reviewers independently performed the full-text data extraction and quality evaluation.

2.2.6. Data Analysis

The findings from this umbrella review were summarized narratively only. Quantitative synthesis was not feasible due to the overlap of individual studies in the included SRs, heterogeneity in the inclusion criteria of the included SRs, and variation in the reporting of outcomes. This qualitative synthesis outlines the publication years of the SRs, the populations studied (including COVID-19 severity levels), the countries of origin, the outcomes measured, and the overall conclusions regarding fluvoxamine's effectiveness and safety in managing COVID-19.

3. Results

3.1. Study Selection

The initial systematic search identified 3,624 records from various databases. After removing duplicates, 3,591 records underwent title and abstract screening based on eligibility criteria. Of these, 3,581 records were excluded, leaving 10 records for full-text review. Additionally, two reviews were identified through additional literature searches. A total of 12 publications [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21] were included: 11 original SRs and 1 updated review of a previously included SR [16]. The selection process is presented in **(Figure 1)**.

3.2. Characteristics of included SRs

The majority of included reviews were published in 2022 and 2023 (four each), with three reviews published in 2024. The most recent search in one of the reviews was conducted on January 31, 2024. All reviews, except one, included meta-analyses. Only one review involved pediatric populations. Severity levels across studies varied, covering both inpatient and outpatient cases, and included mild, moderate, and severe COVID-19 infections. One review also reported data on patients with underlying health conditions such as chronic kidney disease, cardiovascular disease,

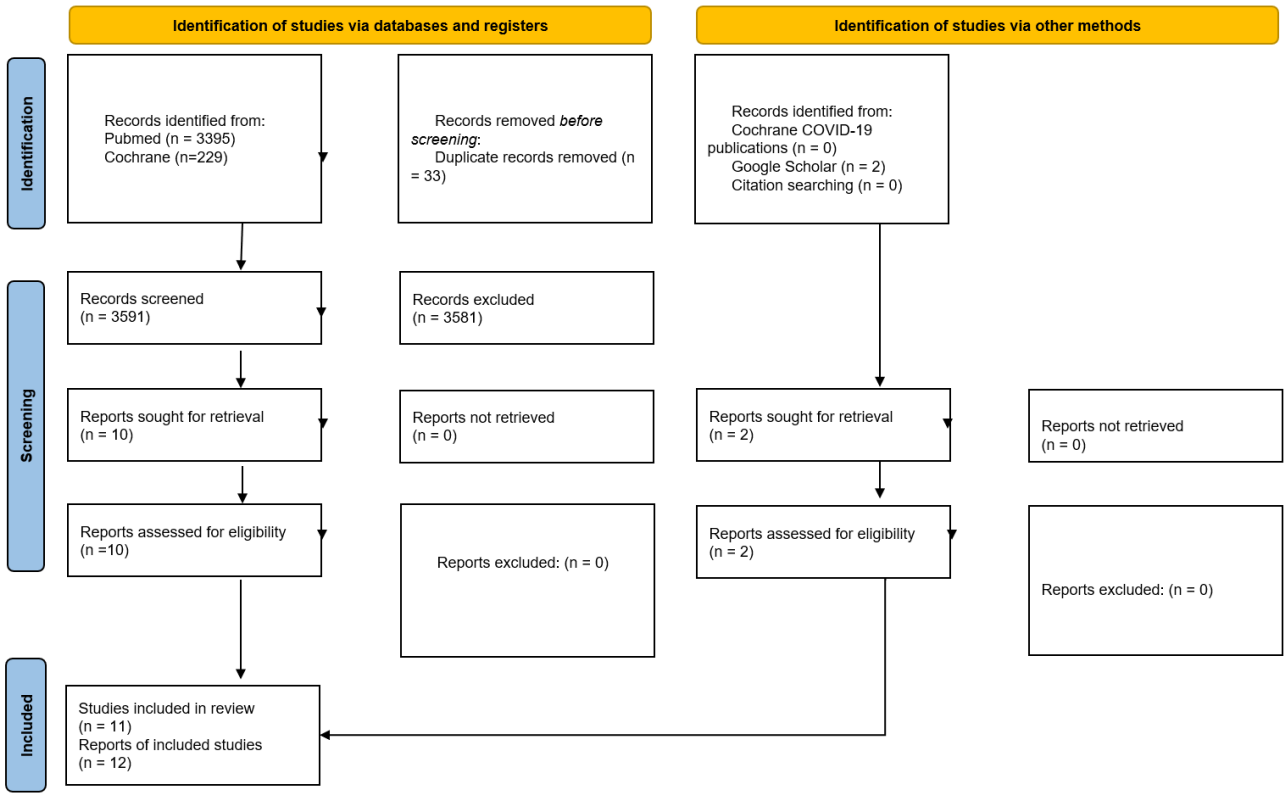

Figure 1: Flowchart of Study Selection Process for Systematic Review.

hypertension, smoking status, and obesity [11]. Further details on study characteristics are reported in **(Table 1)**.

3.3. Summary of the Effects and Safety of Interventions

3.3.1. Mortality

Nine of the reviews reported all-cause mortality as an outcome. All analyses revealed a lower mortality rate with fluvoxamine compared to placebo. However, the results reached statistical significance in only three of the included reports [12, 13, 18, 20]. Effect estimates of primary outcomes are presented in (**Table** 2.). Four reviews published in 2022 reported mortality as an outcome, with three [10, 15, 17] reporting a non-significant reduction, while Zheng et al. [20] did not pool the study outcomes. In their review, Zheng et al. [20] concluded a reduced risk of mortality based on the estimates from individual studies. In contrast, other studies, such as Nyirenda et al. [17], reported a risk ratio (RR) of 0.69 (95% CI, 0.38-1.27; p = 0.24) with 1,649 participants, indicating a non-statistically significant difference. The certainty of the evidence was described as low in that study. Two reviews published in 2023 (Deng et al. [12] and Fico et al. [13]) reported mortality as an outcome, and both revealed a statistically significant decrease. Deng et al. [12] included six randomized controlled trials (RCTs) with 1,470 participants and found that fluvoxamine reduced mortality with an RR of 0.72 (95% CI, 0.63 to 0.82) among outpatients with COVID-19. Similarly, the pooled odds ratio (OR) for Fico 2023 was calculated to be 0.15 (95% CI, 0.02 to 0.95; p = 0.31) [13]. Finally, three reviews published in 2024 [11, 18, 21] reported mortality outcomes, with only Prasanth et al. [18] finding a significant reduction in mortality at doses ≥ 200 mg per day; log odds ratio 1.593 (95% CI 0.530 to 2.656; p = 0.003).

3.3.2. Hospitalization

Ten of the included reviews reported hospitalization outcomes, and five of these showed a statistically significant reduction in the risk of hospitalization with fluvoxamine compared to placebo [11, 14, 15, 20, 21]. Five reviews published in 2022 reported hospitalization rates [10, 14, 15, 17, 20]. The results from Cheema et al. [10] were updated with data from the TOGETHER trial in the review by Marcec et al. [16]. Lu et al. [15] (OR 0.69; 95% CI, 0.51 to 0.94; p = 0.02) and Marcec et al. [16] (RR 0.57; 95% CI, 0.34 to 0.95; p = 0.03) both demonstrated significantly lower hospitalization rates in the fluvoxamine group compared to control. Lee et al. [14] also reported a higher probability of reduced hospitalization rates in outpatient COVID-19 patients (RR: 0.75; 95% CI 0.58 to 0.97) using fluvoxamine. For Vatvani et al. [19], the hospitalization rate between the placebo and fluvoxamine groups was comparable (p = 0.09). Finally, two reviews published in 2024 by Deng et al. [11] and Zhou et al. [21] demonstrated a significantly lower risk of hospitalization with fluvoxamine compared to placebo. Deng et al. [11] reported a reduction in risk ratio (RR: 0.77; 95% CI (0.60 to 0.97); p = 0.03), while Zhou et al. [21] reported a decrease in risk ratio (RR 0.76; 95% CI, 0.59 to 0.99; p = 0.04), indicating decreased hospitalization rates in the intervention group in both cases.

3.3.3. COVID-19 Progression/Clinical Deterioration

One review [10] reported a non-significant decrease in the risk of disease progression in the fluvoxamine group compared to placebo (RR 0.74; 95% CI, 0.21 to 2.57; p = 0.64) [10]. Similarly, Vatvani et al. [19] also examined clinical deterioration and found that fluvoxamine did not offer a significant benefit over placebo (RR 0.83; 95% CI, 0.65 to 1.06; p = 0.14). However, Zheng et al. [20] found fluvoxamine to be associated with a lower likelihood

Table 1: Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Cheema 2022 [7]	2022	4	N=8 RCTs=5 Prospective cohort=2 Quasi-randomized trial=1	3,781 Mild Moderate Severe (requiring ICU admission) Outpatient Inpatient	USA Canada Croatia Korea Honduras Brazil	Fluvoxamine	Primary: all-cause mortality Secondary: ROH, COVID-19 progression, incidence of AE	Fluvoxamine use showed a large but statistically non-significant reduction in mortality and hospitalization rates and no increase in incidence of AEs. It may be beneficial due to easy accessibility and affordable price.	Critically Low
Deng 2024 [8]	2024	6	N=27 RCTs=9	5,861 Mild Moderate Outpatient	USA Egypt South Korea Thailand Brazil	Fluvoxamine	Incidence of hospitalization, healthcare utilization (ER visits or hospitalization), mortality, supplemental oxygen and mechanical ventilation requirements, SAEs and non-adherence	Fluvoxamine twice a day may reduce ROH and healthcare utilization but absolute benefits are modest and associated with increased risk of treatment non-adherence. It's a potential alternative due to low cost and wide availability. It reduced healthcare utilization in outpatients with obesity range BMI (30 kg/m²) but not in lower BMI patients.	Low
Deng 2023 [11]	2023	7	N=11 RCTs=6 Observational=5	With Controls=5353 Without Controls=2958 Severe(ICU-hospitalized) Inpatients Outpatients	USA Canada Brazil Croatia South Korea Honduras Hungary	Fluvoxamine	Mortality, hospitalization, composite of hospitalization/ERs visits, hypoxemia, requirement for supplemental oxygen, ventilator support, and SAEs	Fluvoxamine may reduce mortality and hospitalization. Medium-dose was associated with reduced mortality, hospitalization, and composite of hospitalization and ER visits but not low-dose. It was not associated with increased AEs.	Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Fico 2023 [12]	2023	7	N=9 RCTs=2 Cohort=5 Retrospective Cross-sectional=6 Case-control=2	With Controls=215173 Mild Moderate Severe Inpatient	USA Brazil Europe Sweden UK	Psychotropic drugs in COVID-19 treatment: Anti-depressants (Fluvoxamine) Antipsychotics	Primary and Secondary outcomes (i.e., risk of SARS-CoV-2 infection, hospitalization rates, CD, risk of delirium, use of restraints, intubation or mechanical ventilation, mortality due to any cause), risk of severe COVID-19 (considered as risk of intubation or death), and mortality due to any cause among people diagnosed with COVID-19	Preclinical evidence suggests antipsychotics and antidepressants may inhibit SARS-CoV-2 replication and modulate the immune response. Fluvoxamine may reduce severe COVID-19 outcomes and mortality, especially in early treatment to prevent psychiatric symptoms in long-COVID. The increased risk of severe COVID-19 and mortality with antipsychotics is not absolute and should be assessed on a case-by-case basis. Ongoing antipsychotic treatment should not be discontinued in psychiatric patients.	Critically Low
Lu 2022 [13]	2022	7	N=4 RCTs=3 Prospective Nonrandomized Cohort=1	1814 Outpatient	Brazil USA South korea	Fluvoxamine	The primary outcome was ROH or ED visits. Secondary outcomes were requirement of mechanical ventilation, ICU admission, risk of mortality, and risk of AEs	Fluvoxamine use can help reduce the risk of hospitalization or ED visits for nonhospitalized patients. It's use was associated with a similar risk of AEs as that observed in the control group.	Critically Low
Nyirenda 2022 [15]	2022	7	N=2 RCT=2	1649 Mild Outpatient	Brazil USA	Fluvoxamine	SAE, Quality of Life, Clinical status, Death, Adverse Event, Need for dialysis at up to day 28, Admission to the ICU at day 28, Duration of hospitalization, Viral clearance, assessed with RT-PCR test for SARS-CoV-2,Hospital-acquired infections up to day 28	Fluvoxamine may reduce all-cause mortality at day 28, and the ROH or death in outpatients with mild COVID-19. However, there is uncertainty regarding the effect of fluvoxamine on AEs or SAEs.	Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Prasanth 2024 [16]	2024	4	N=14 RCTs=7 Retrospective cohort=1 Real world studies=7	7153 Varying degrees of severity	Not specified	Fluvoxamine	Primary outcome of this study was time to sustained recovery. Secondary outcomes such as hospitalization, clinical deterioration, and death	Fluvoxamine has shown some potential for treating COVID-19, preventing CD and mortality, with early treatment and higher doses being optimal. The results suggest that treatment within three days of infection is optimal in the prevention of CD and mortality. There is potential for the prevention of Long-covid symptoms in those initially treated for COVID-19 with fluvoxamine.	Critically Low
Vatvani 2023 [17]	2023	4	N=6 RCTs	4197 Outpatient	South Korea Brazil USA	Fluvoxamine	Clinical deterioration, hospitalization rate, and mortality from Covid-19	Fluvoxamine although safe is not effective as outpatient treatment as it does not reduce the ROH or CD rate. It did not offer any significant benefit when compared with placebo. This study did not encourage the use of fluvoxamine for patients with SARS-CoV-2 infection in outpatient settings.	Low
Zhou 2024 [18]	2024	4	N=6 RCTs	4,711 -	USA Canada Brazil Korea	Fluvoxamine	The number of patients who experience clinical deterioration, the number of patients who require hospitalization, the number of patients who require mechanical breathing, and the length of time before clinical deterioration(included hypoxemia, a trip to the ED, an urgent care visit, a hospital stay, or death), AEs, SAEs, mortality	Fluvoxamine is a promising therapy for patients with COVID-19, especially those who take 200 mg or more daily, and is superior to the placebo group in reducing CD and hospitalization. It did not show any higher risk of AEs or SAEs.	Critically Low

Table 1 (continued): Systematic Reviews on Fluvoxamine for COVID-19

Study (Author, Year)	Search Date	No. of Databases	Total Number Of Studies (N) And Study Designs Included	Total Number of Patients Included (N)	Countries	Interventions Assessed	Outcomes Assessed	Conclusion	AMSTAR 2 Rating
Zheng 2022 [9]	2022	6	N=7 RCTs=2 Retrospective=3 Prospective Cohort=2	92,947 Inpatients Outpatients	USA, Brazil, Croatia, France, Hungary	The efficacy and safety of antidepressants in treatment for COVID-19 patients	Primary outcome: clinical deterioration, hospitalization Additional outcomes: all-cause mortality, ADRs, and dropout rate	Antidepressants could reduce the risk of CD and hospitalization. Being a widely available and inexpensive SSRI, fluvoxamine has shown promise as an adjunct treatment for COVID-19. There is evidence for fluvoxamine in reducing the risk of mortality and the need for hospitalization but inconsistent evidence for the safety of adjunctive fluvoxamine for COVID-19 patients.	Critically Low
Lee 2022 [10]	2022	2	N=3 RCTs=3	2196 Outpatients Mild-to-moderate	USA Canada Brazil	Fluvoxamine	All-cause hospitalization emergency department visits that were 24 hours or longer	The probability that fluvoxamine was associated with reduced hospitalization ranged from 94.1% to 98.6% and the probability of moderate association ranged from 81.6% to 91.8%. It could be recommended as a treatment option for patients without contraindication, particularly in resource-limited settings or for individuals without access to monoclonal antibodies or direct antivirals.	Critically Low

RCT: Randomized Controlled Trials; mg: milligrams; AEs: Adverse events; SAEs: Serious adverse events; ADRs: adverse drug reactions; ICU: Intensive care units; BMI: Basal metabolic rate; SSRIs: Selective serotonin reuptake inhibitors; ROH: Risk of hospitalization; CD: Clinical deterioration; ER: Emergency room; ED: Emergency department

Table 2: Effect estimates and number of studies for efficacy and safety outcomes in the included SRs

Study Name	Quality	All-cause mortality	Hospitalization in COVID-19 patients.	Covid 19 progression/ Clinical Deterioration	Risk of Serious Adverse Events
Deng 2024 [8]	Low	RR (0.73; 95%CI (0.42 to 1.28); p=0.99); N=8	RR (0.77; 95%CI (0.60 to 0.97); p=0.03); N=9	NA	RR (0.72; 95% CI (0.40 to 1.30); p=0.79); N=7
Deng 2023 [11]	Low	RR (0.72; 95%CI (0.63 to 0.82)); N=6	RR (0.79; 95%CI (0.64 to 0.99)); N=6	NA	RR (0.77; 95%CI (0.34 to 1.71); N=5
Nyirenda 2022 [15]	Low	RR (0.69; 95%CI (0.38 to 1.27); p=0.24); N=2	Absolute Difference (-4.21; 95%CI (-13.22 to 2.04); N=1	NA	RR (0.56; 95%CI (0.15 to 2.03) p=0.38); N=2
Vatvani 2023 [17]	Low	NA	RR (0.80; 95% CI (0.62 to 1.04); P = 0.09); N=6	RR (0.83; 95%CI (0.65 to 1.06); p = 0.14); N=6	RR (0.82; 95%CI (0.63 to 1.06); p=0.12); N=4
Fico 2023 [12]	Critically Low	OR (0.15; 95%CI (0.02 to 0.95); p=0.04); N=2	NA	NA	NA
Lu 2022 [13]	Critically Low	OR (0.66; 95 % CI (0.36–1.21)); N= NA	OR (0.69; 95% CI (0.51 to 0.94); p=0.02); N=4	NA	OR (0.47; 95%CI (0.09 to 2.54); p=0.38); N=3
Prasanth 2024 [16]	Critically Low	LogOR (1.502; 95%CI (0.621 to 2.391); p < 0.001); N=5	NA	LogOR (0.359; 95%CI (0.1111 to 0.5294); p=0.002); N=7	NA
Cheema 2022 [7]	Critically Low	RR (0.49; 95%CI (0.21 to 1.17); p=0.11); N=3	RR (0.46; 95% CI 0.21 to 1.02; p=0.05); N=5	RR (0.74; 95%CI (0.21 to 2.57); p=0.64); N=3	NA
Zhou 2024 [18]	Critically Low	RR (0.69; 95%CI (0.38 to 1.27); p=0.24); N=6	RR (0.76; 95%CI (0.59 to 0.99); p=0.04); N=5	RR (0.73; 95% CI (0.59 to 0.90); p = 0.004); N=6	RR (0.97; 95%CI (0.59 to 1.60); p=0.91); N=6
Zheng 2022 [9]	Critically Low	Meta-analysis not performed	Meta-analysis not performed	Meta-analysis not performed	Meta-analysis not performed
Lee 2022 [10]	Critically Low	NA	RR (0.75; 95% CI (0.58 to 0.97)); N=3	NA	NA
Marcec 2023 [14]	Not Applicable	NA	RR (0.57; 95% CI (0.34 to 0.95); p = 0.03); N= 7	NA	NA

OR, Odds ratios; RR, Risk Ratios; CI, Confidence Intervals; NA, Not Available

of clinical deterioration based on one clinical trial. Likewise, Zhou et al. [21] also found that fluvoxamine provides reduced clinical deterioration than placebo (RR 0.73; 95% CI, 0.59 to 0.90; p = 0.004). Finally, Prasanth et al. also suggested that fluvoxamine provides reduced clinical deterioration (Log OR 0.359 (95% CI 0.1111 to 0.5294) (z = 3.103; p=0.002)).

3.3.4. Risk of Serious Adverse Events (SAEs)

Seven of the included reviews reported risks of SAEs in the fluvoxamine and placebo groups. In most cases, the risk of serious AEs was similar in both groups, with no statistically significant differences observed [10, 11, 12, 15, 17, 19, 21]. Zheng et al. [20] concluded there was "inconsistent evidence" regarding the safety of fluvoxamine for COVID-19.

3.4. Subgroup results

3.4.1. Age

The SRs included adult populations, with most studies specifying inclusion of patients aged 18 years or older. The mean age of patients per SR ranged from 46.2 to 52.3 years. No age-related effects were reported.

3.4.2. Disease severity

Most of the included SRs consisted of studies that recruited non-hospitalized patients. Cheema et al. [7] and Deng et al. [8] also included patients in the ICU and those hospitalized. Higher doses, including >200mg/day, were linked with a reduction in mortality and clinical deterioration in these patients.

3.4.3. Dosages

Subgroup analyses based on dosages were conducted by one SR published in 2023 and three reviews published in 2024 [11, 12, 18, 21]. Improved efficacy outcomes were reported at higher dosages compared to lower dosages, with a comparable safety profile. For fluvoxamine 50 mg twice daily, as reported by Deng et al. [11] and Deng et al. [12] did not observe significant reductions in hospitalization or healthcare utilization. Furthermore, Deng et al. [12] reported no increase in SAEs for this dosage group compared to the placebo (RR 0.72; 95% CI 0.40 to 1.30). For 100 mg twice daily, Deng et al. [12] found significant reductions in hospitalization (RR 0.75; 95% CI 0.58–0.97) and healthcare use (RR 0.68; 95% CI 0.53–0.86], and Deng et al. [11] reported similar findings. However, Deng et al. [11] noted that this dosage group was not associated with reduced mortality from COVID-19. No increase in SAEs was observed at this dosage level in either study. For the 100 mg regimen administered three times a day, Deng et al. [12] reported no significant decrease in hospitalization, as reported in one study only. Furthermore, no increase in SAEs was observed with fluvoxamine compared to placebo. Prasanth et al. [18] stratified dosages into three groups: up to 100 mg/day, up to 200 mg/day, and up to 300 mg/day. For clinical deterioration, dosages of up to 200 mg/day and 300 mg/day demonstrated significant benefits (p < 0.05). For mortality, interventions of ≥200 mg per day were associated with statistically significant improvements (p < 0.001), whereas doses below 200 mg per day were not. Finally, Zhou et al. [21] classified dosages as low dose (<100 mg twice daily) and high dose (≥ 100 mg twice daily). Their findings indicated that the high dose of fluvoxamine significantly reduced hospitalization (RR 0.77; 95% CI 0.59 to 1.00; p = 0.05) and clinical deterioration rates

(RR 0.69; 95% CI 0.55 to 0.87; p = 0.001), whereas low doses did not. Additionally, no statistically significant differences in adverse events were observed for either dosage level compared to placebo [21].

3.5. Methodological Quality (AMSTAR2) of Included SRs

The AMSTAR2 tool was used to assess the methodological quality of the 11 original SRs included in this study. Out of these, seven SRs were rated as critically low quality, while the remaining four were assessed as low quality. The most common reasons for downgrading quality were inappropriate methods of pooling the studies including inconsistent study designs, sample sizes being pooled together, failure to provide a list of excluded studies with justifications, lack of reporting on funding sources, not evaluating the impact of bias in individual studies on meta-analysis outcomes, and not investigating publication bias (small study effects). The complete AMSTAR2 grading results are provided in the Supplement.

4. Discussion

This umbrella review suggests that fluvoxamine may have potential in reducing COVID-19-related mortality and hospitalizations. Overall, the results indicate that fluvoxamine does not significantly prevent the progression or clinical worsening of the disease. However, most of the included SRs reported no major difference in adverse events between fluvoxamine and placebo, suggesting that fluvoxamine is generally safe. Notably, our analysis showed that higher doses of fluvoxamine were linked with greater benefits, including reductions in hospitalization rates, clinical deterioration, and possibly overall mortality [21].

Several studies support the idea that fluvoxamine can reduce mortality and decrease the risk of clinical deterioration and hospitalization, particularly by preventing the progression from mild to severe illness. For instance, one RCT reported that none of the patients treated with fluvoxamine experienced disease progression, compared to 8.3% in the placebo group [22]. Another meta-analysis of RCTs demonstrated a 30% reduction in hospitalization risk among high-risk patients, largely attributed to adherence to prescribed medication [23]. Additionally, another meta-analysis concluded that fluvoxamine, when combined with antiviral treatments, significantly reduces mortality and hospitalization in COVID-19 patients [11]. When compared with our findings, it appears that fluvoxamine's effectiveness may be more pronounced at higher dosages, with limited positive outcomes observed at lower doses [21]. A recent meta-analysis of 7153 patients across 14 studies concluded that earlier treatment with higher doses was more effective than treatment with lower doses. They conducted a subgroup analysis, dividing the data into two groups: high (200 mg or more per day) and low dose (less than 200 mg). In the high-dose group, the average outcome differed significantly from zero ($z=4.2882$, $p< 0.0001$). However, in the low-dose group, the outcome did not differ significantly from zero ($z=1.082$, $p=0.279$)[18]. Fluvoxamine acts as an agonist for the sigma-1 receptor, through which it exerts anti-inflammatory effects. It has been shown to possess direct antiviral properties, regulate coagulation issues, and reduce the severity of cytokine storms [2]. The drug helps limit the inflammatory cytokine surge by reducing interleukin-6 (IL-6) production and regulating gene expression in cell models of inflammation. Fluvoxamine has demonstrated strong activity at the sigma-1 receptor, which functions as a chaperone protein within the endoplasmic reticulum, modulating both innate and adaptive immune responses. This mechanism may help reduce disease severity and progression in COVID-19 patients [22].

In reviewing prior trials, we noted significant variations in outcomes. For example, one clinical trial demonstrated that early treatment with combinations of fluvoxamine and bromhexine, fluvoxamine and cyproheptadine, or niclosamide and bromhexine led to no clinical worsening during the acute phase (28 days) compared to standard care. Furthermore, these combination therapies were more effective than fluvoxamine alone, as nine participants in the fluvoxamine-only group experienced clinical deterioration requiring low-flow oxygen between days 14 and 28 (post-treatment completion). Additionally, the early use of combination therapies in that trial was associated with a reduced burden of Post-Acute Sequelae of COVID-19 (PASC) symptoms in long-term follow-up. There is also evidence suggesting that sigma-1 receptor agonists, such as fluvoxamine, may help lower the risk of developing PASC symptoms [24].

Conversely, another trial by Bhimraj et al. [25] found that administering 50 mg of fluvoxamine twice daily for 10 days to outpatients with mild to moderate COVID-19 did not significantly improve the time to sustained recovery. In that trial, which included 1,288 participants, the median recovery time was 12 days in the fluvoxamine group compared to 13 days in the placebo group. No significant benefit was observed for the primary outcome, indicating that fluvoxamine may not be effective in treating mild to moderate COVID-19 [25].

4.1. Strengths and Limitations

This review included an extensive search for SRs from multiple sources, encompassing studies with both inpatient and outpatient populations. Additionally, the use of the AMSTAR2 tool ensured that rigorous quality assessment of included SRs was performed. Findings of this synthesis require caution due to certain limitations. Multiple SRs included the same primary studies, potentially leading to the overestimation of treatment effects in our narrative synthesis. Secondly, the included reviews covered different phases of the pandemic (2022-2024) with varying patient populations, vaccination rates, dominant virus variants, and standard care practices, limiting generalizability. Thirdly, the SRs reported different statistical measures (risk ratios vs. odds ratios), making direct comparison and synthesis of results across studies challenging. Most included SRs (7 out of 11) were rated as critically low quality using AMSTAR2, significantly limiting confidence in the findings. Furthermore, the SRs included mixed patient populations (inpatient vs. outpatient, varying severity levels, and different comorbidities) without adequate subgroup analysis. Lastly, a wide variation in fluvoxamine dosing regimens (50-300 mg daily) was observed across studies.

4.2. Implications for Clinical Practice

Fluvoxamine, an SSRI, has shown promise in managing severe COVID-19 symptoms due to its anti-inflammatory properties, particularly its ability to modulate cytokine production, such as IL-6, which plays a role in the cytokine storm [26]. Clinical trials like STOP-COVID and TOGETHER suggest that early use of fluvoxamine can help prevent disease progression, reducing severe outcomes, hospitalizations, and the need for mechanical ventilation [27]. As an affordable and widely accessible generic medication, fluvoxamine offers potential antiviral, anti-inflammatory, and anticoagulant effects [27]. It is easy to administer orally and has a generally favorable safety profile, with mild and transient side effects [28, 29].

However, fluvoxamine also has limitations in treating COVID-19. Some studies have shown that it does not effectively prevent clinical deterioration in unvaccinated symptomatic outpatients [29]. While side effects like nausea, dizziness, and insomnia are usually mild and short-term, drug interactions with other medications can complicate its use in patients with multiple prescriptions [30]. Additionally, the long-term effects of fluvoxamine use in COVID-19 remain unclear due to limited data [31]. Our findings also suggest that higher doses of fluvoxamine may be more beneficial, but such dosing regimens could decrease patient adherence, similar to challenges observed in antibiotic treatments [31]. Given its affordability and accessibility, fluvoxamine could be a valuable treatment option, especially in resource-limited settings where other COVID-19 therapies are not readily available. When compared to lower doses, studies observed that higher daily dosages of fluvoxamine are superior to the placebo group in reducing clinical deterioration and hospitalization, with comparable safety concerns. Future studies should aim to determine the optimal dosage, identify patient populations most likely to benefit from fluvoxamine, and explore the role of fluvoxamine in combination therapies. Large-scale international trials are necessary to confirm the clinical utility of this treatment for COVID-19.

5. Conclusions

While the reductions in mortality and hospitalizations were observed in several included SRs, only a few demonstrated statistical significance, with all of them either of low or critically low quality. Mixed evidence was reported on COVID-19-related mortality, hospitalizations, disease progression, clinical deterioration, and the impact of dosage. In summary, while the anti-inflammatory effects of fluvoxamine offer a promising therapeutic rationale, the synthesized evidence is insufficient to fully justify its routine use as a therapeutic agent in COVID-19 patients. Although it is not currently part of standard COVID-19 treatment protocols, it is a promising candidate for early outpatient management. Further, larger RCTs are needed to clarify their role in COVID-19 treatment.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Authors Contribution

OI and AR conceptualized the study design and objectives. OI, MJ, WM, MSK, MBH, RD, NK, AA, and MAQ conducted the literature search, study screening, selection, and data extraction. OI, ABSZ, JAK, and AR designed the data extraction template, extracted data, and carried out data analysis. OI, MJ, WM, MSK, MBH, RD, NK, AA, and MAQ drafted the initial manuscript. OI, ABSZ, JAK, and AR critically reviewed and revised the final manuscript. ABSZ, JAK, and AR are the guarantors and critically reviewed the manuscript. All authors approve the final manuscript as submitted for publication.

Data Availability

All studies used in the research are available in various databases.

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