



Diagnosis and Treatment for Mild Cognitive Impairment: A Systematic Review of Clinical Practice Guidelines and Consensus Statements

Ya-Xin Chen^{1†}, Ning Liang^{1†}, Xiao-Ling Li², Si-Hong Yang¹, Yan-Ping Wang^{1*} and Nan-Nan Shi^{1*}

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*Correspondence:

Yan-Ping Wang
wangyanping4816@163.com
Nan-Nan Shi
13811839164@vip.126.com

[†]These authors have contributed
equally to this work and share first
authorship

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¹Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China, ²First School of Clinical Medicine, Shaanxi University of Chinese Medicine, Shaanxi, China

Background: Mild cognitive impairment (MCI) is an important stage between the normal cognitive decline of aging and dementia. The aim of this study was to compare and harmonize the recommendations for the diagnosis and treatment of MCI based on current clinical practice guidelines.

Methods: We searched the PubMed, EMBASE, China National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Periodical Database, and Chinese Biological Medicine Database from their inception date to April 24, 2021 to identify all published guidelines on MCI. The qualities of the eligible guidelines were appraised by two reviewers using the Appraisal of Guidelines for Research and Evaluation II instrument.

Results: Thirteen guidance documents (four guidelines and nine consensus statements) with specific recommendations were included. Nine guidelines and consensus statements covered the screening and diagnosis of MCI. The evaluation of the documents showed that neuropsychological testing and biomarker assessments were the most common recommendations for the diagnosis of MCI. Nine of the 13 guidance documents covered the treatment and management of MCI. The recommendations for the treatment and management were classified into four categories, namely: intervention for risk reduction, pharmacologic interventions, non-pharmacologic interventions, and counseling. Regarding pharmacological interventions, three guidelines recommend no pharmacologic intervention. The use of cholinesterase inhibitors for MCI is contraindicated in three guidance documents, whereas one proposes that cholinesterase inhibitors and memantine should be deprescribed. Ehb761[®], Chinese herbal decoctions, and Chinese traditional patent medicine are recommended in two documents. A total of seven guidance documents recommend non-pharmacological interventions, including physical activity interventions, cognitive interventions, dietary and nutritional interventions, and acupuncture.

Conclusion: An updated search for possible evidence on the diagnosis and treatment of MCI is needed. Potentially effective diagnoses and treatments, either conventional or complementary, and alternative therapies should be highly valued and addressed in correlation with the supporting evidence.

Keywords: diagnosis, guidelines, mild cognitive impairment, therapeutic, systematic review

INTRODUCTION

Mild cognitive impairment (MCI) is regarded as the transitional period between the normal cognitive decline of healthy aging and dementia (1). It is categorized into amnesic and non-amnesic subtypes (2). MCI is one of the most common diseases of the elderly, and it increases the risk of developing dementia (1). According to recent studies, the prevalence of MCI among elderly people in China is 15.5% (3), 13.11% in Greece (4), and 26.06% in South India (5). Moreover, it has been reported that 6–15% of patients with MCI develop Alzheimer's disease (AD) annually, and each patient with AD would spend \$40,000 each year (6). The high conversion rate from MCI to AD places a large financial burden on public health. Thus, it is critical to pay attention to the diagnosis and treatment of MCI.

The first Mayo diagnostic criteria for MCI proposed by Petersen et al. (7) was mainly based on memory problems. The criteria comprised of memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory for the age of the patient, and no signs of dementia (7). However, considering the non-memory problems that can also result in cognitive impairment, Petersen amended the Mayo criteria by adding non-memory criteria (8). Multiple tests, such as the mini-mental state examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Free and Cued Selective Reminding Test (FCSRT), the California Verbal Learning Test, and the Boston Naming Test, have been proposed for screening for MCI. However, no specific accepted test and cutoff score have been recommended for the diagnosis of MCI. This lack of specific standardized tests of assessment cut-off points may influence the accuracy of the diagnosis (8–10). Furthermore, owing to the complexity of risk factors and the lack of clarity in the diagnosis of MCI, it is also difficult to provide specific treatment for patients. Currently, there are no accepted drugs for the treatment MCI (11). However, new management measures for MCI, such as cognitive interventions, exercise, and herbal medicine, are continuously introduced in clinical practice guidelines (12, 13).

Guidance documents, such as clinical practice guidelines and consensus statements, are developed using a systematic method to provide guidance and recommendations for clinicians (14). Guidance documents may focus on different topics, such as screening, diagnosis, or treatment (14). There are several published guidelines and consensus statements for MCI. However, discrepancies exist between the guidelines because of variations in topics and the time-sensitive nature of some of the evidence. Another reason for the variations between the guidelines may be that the guidelines from different countries

are based on different sources and qualities of evidence. Hence, it is necessary to summarize and compare MCI recommendations to enable the clinicians to make more thoughtful clinical decisions and to encourage MCI guideline developers to consider evidence comprehensively. The discovery and evaluation of controversial recommendations is an advantage for future research. Thus, the aim of this study was to systematically review, compare, and harmonize the recommendations for the diagnosis and treatment of MCI in the current clinical practice guidelines.

METHODS

Eligibility Criteria

Clinical practice guidelines and expert consensus were included if they satisfied the following criteria:

- with specific recommendations
- focus on diagnosis and/or treatment of patients with MCI
- not intended for MCI general practice, education, training, certification, and research
- not protocols, abstracts, editorial comments, overview/review articles, and systematic reviews.

Search and Selection

The PubMed, EMBASE, China National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Periodical Database, and Chinese Biological Medicine Database were systematically searched from their inception date to April 24, 2021. The keywords were Cognitive Dysfunction [MeSH] OR MCI [Title/Abstract] OR cognitive impairment [Title/Abstract] OR cognitive disorder* [Title/Abstract] OR cognitive dysfunction* [Title/Abstract] OR neurocognitive disorder* [Title/Abstract] OR cognitive decline* [Title/Abstract] OR mental deterioration* [Title/Abstract] AND Guideline [MeSH] OR expert consensus [Title/Abstract] OR recommendation statement [Title/Abstract]. The keywords mentioned above were adapted and searched in Chinese databases by using corresponding Chinese words; the search strategies are presented in **Supplementary Table 1**. Two authors (YC and NL) independently selected the clinical practice guidelines and consensus statements. The websites including Google Scholar, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, Guidelines International Network, and World Health Organization were also searched for gray literature. The languages were limited to English and Chinese.

Basic Characteristics of the Included Documents and Extraction of Recommendations

The reviewers (NL and YC) extracted the basic characteristics and recommendation content of the included guidelines. The basic characteristics included guideline development information (development group, country, year, and number of guideline versions), guideline scope and content (target population, diagnosis, and treatment), evidence support (systematic search and number of references), grading systems of recommendations (level of evidence and strength of recommendations), and conflict of interest (type of funding).

The included guidelines were reviewed, and the recommendations were extracted. Information on the level of evidence and strength of recommendations for diagnosis (or screening) and treatment (or management) were extracted separately. For guidelines with more than one version but which were developed by the same organization or group, the recommendations on the diagnosis and treatment of MCI were extracted from the most updated version.

AGREE II Assessment

The qualities of the eligible guidelines were independently appraised by two reviewers (YC and XL) using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The results of the assessment were checked by the third author (NL). The AGREE II instrument comprises 23 items organized in six quality domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each of the 23 items is rated on a seven-point scale. A score of 1 indicates “strongly disagree,” whereas a score of 7 represents “strongly agree.” The score of each domain is calculated based on the scores of its specific items (15, 16). Based on the methodology outlined in a previously published paper, we divided the domain scores into three groups: high quality (67–100%), sufficient quality (33–67%), and low quality (0–33%) (17, 18).

RESULTS

Selection of Guidelines

A total of 13 guidance documents with specific recommendations were eligible, including four guidelines (10, 12, 19, 20) and nine consensus statements (13, 21–28). A detailed flow chart of the search and selection is presented in **Figure 1**.

Two documents (12, 24) were developed in the United States, two (21, 28) in the United Kingdom, four (10, 19, 25, 27) in China, one (26) in Canada, one (13) in Singapore, one (20) in Switzerland, and two (22, 23) in Europe. Five of the documents had previous versions (10, 12, 13, 21, 26). Eleven documents (10, 12, 13, 20–26, 28) are directed at MCI populations and three documents (19, 26, 27) are directed at vascular mild cognitive impairment (VaMCI) populations. Recommendations for screening and diagnosis are included in nine documents (10, 12, 13, 19, 22–24, 26, 28), whereas recommendations for treatment and management are included in nine documents

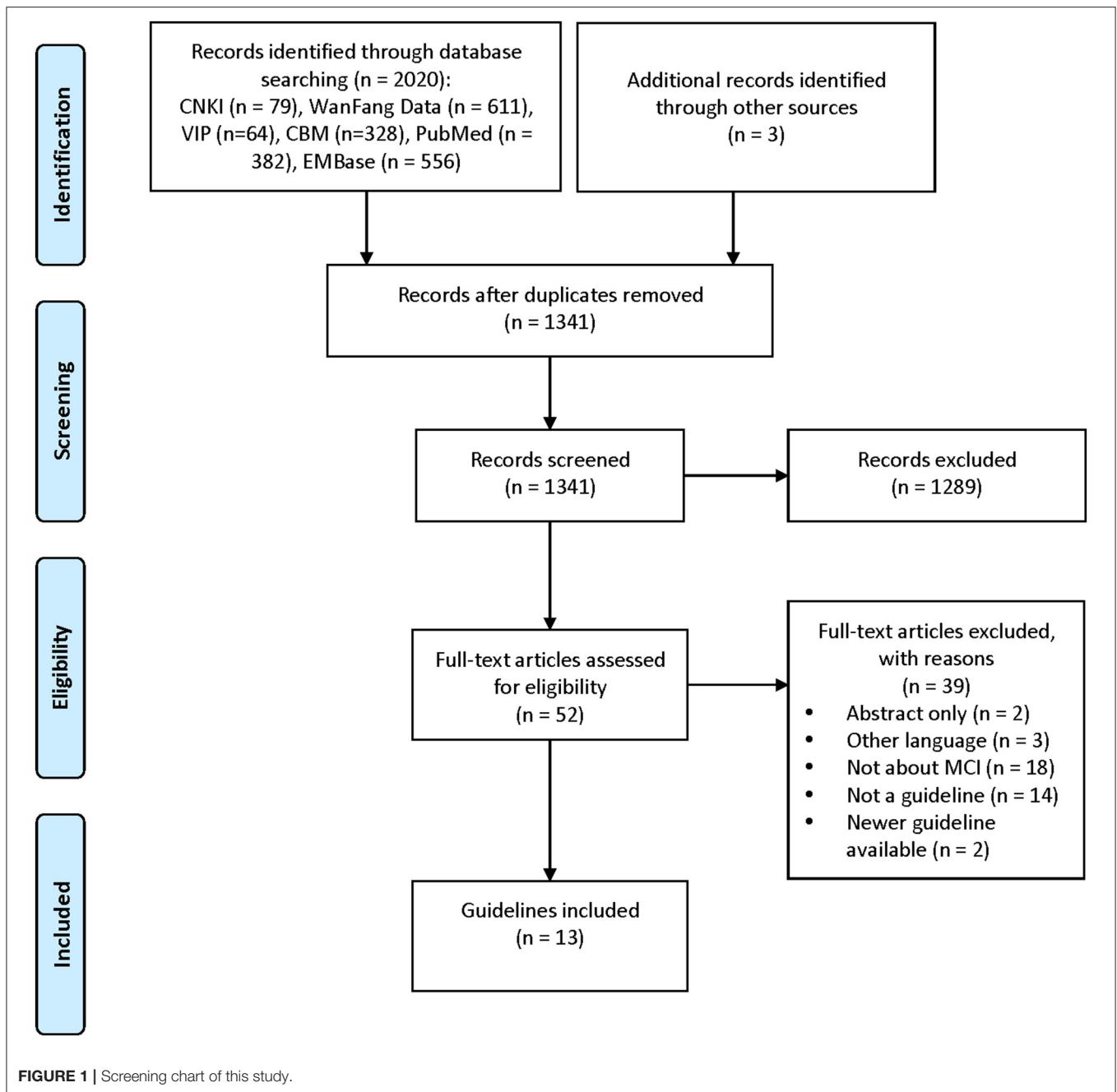
(10, 12, 13, 20, 21, 24–27). Nine documents state that the guideline/statement was developed using a systematic search strategy (10, 12, 19–24, 26). The detailed characteristics of the eligible guidelines and consensus statements are presented in **Table 1**. A summary of the grading systems used in the included guidelines and consensus statements is presented in **Supplementary Table 2**.

Quality Assessment

The scores for each domain of the AGREE II instrument are presented in **Table 2**. The guideline developed by the American Academy of Neurology (AAN) had the highest overall score in the six domains (12). Nine guidance documents (12, 13, 19–24, 26) had high scores in the “scope and purpose” domain (domain 1), whereas four (10, 25, 27, 28) had sufficient scores (domain 1: average, 68%; range, 44–78%). The scores for the “stakeholder involvement” (domain 2) were generally low; all documents scored below 67% in that domain. Eight documents (12, 13, 20, 21, 23, 26–28) had sufficient scores in domain 2, whereas five (10, 19, 22, 24, 25) had low scores (domain 2: average, 37%; range, 22–66%). Two documents (12, 20) had high quality in the “rigor of development” domain, four (13, 22, 23, 26) had sufficient quality, and the others had low quality (domain 3: average, 41%; range, 19–71%). The “clarity of presentation” domain (domain 4) had the highest scores among the six domains (domain 4: average, 74%; range, 47–86%). Ten of the 13 documents were rated as high quality in domain 4 (10, 12, 13, 19–21, 24–26, 28). Overall, “applicability” domain (domain 5) had the lowest scores among the six domains (domain 5: average, 29%; range, 6–48%). Six documents (12, 22–24, 26, 28) were rated as with sufficient quality in domain 5, whereas others were rated as with low quality. Five documents were of low quality in the “editorial independence” domain (domain 6: average 47%; range, 0–92%) (10, 19, 22, 25, 27), two (23, 26) were of sufficient quality, and six (12, 13, 20, 21, 24, 28) were of high quality.

Screening and Diagnosis

Nine guidelines and consensus statements covered the screening and diagnosis of MCI (10, 12, 13, 19, 24, 26, 28). Neuropsychological testing and biomarker assessments are the most recommended tests for the diagnosis of MCI. There was agreement between two guidance documents recommending that standard diagnostic criteria, such as the Vascular Behavioral and Cognitive Disorders Society criteria, Diagnostic and Statistical Manual of Mental Disorders 5, Vascular Impairment of Cognition Classification Consensus Study, or the American Heart Association consensus statement, should be used in the diagnostic process for VaMCI (19, 26). Two guidelines recommend that self-report from patients should not be solely relied on for clinical history but should be supplemented by reports from people familiar with the patient (10, 19). Three guidance documents indicate that clinicians should combine clinical history with neuropsychological testing in the diagnostic process (12, 24, 26). One guideline recommends making a diagnosis of MCI subtype (10). Two guidance documents recommend that clinicians identify the MCI risk factors that are potentially modifiable (12, 28). Seven



documents (10, 12, 13, 19, 24, 26, 28) recommend the use of neuropsychological testing for screening and diagnosis. Three (10, 19, 26) of these seven documents recommend cognitive testing, including assessment using the Modified Mini-Mental State (3MS) examination, the MMSE, the Rowland Universal Dementia Assessment Scale (RUDAS), MoCA, Toronto Cognitive Assessment (TorCA), National Institute for Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN), and FCSRT; three (10, 13, 19) recommend testing activities of daily living and functional assessment, including assessment using the Activity of Daily

Living Scale (ADL), Instrumental Activity Daily Living (IADL) scale, and Functional Activities Questionnaire (FAQ); and one document (10) recommends behavioral and psychological assessment. Three documents (12, 24, 28) do not recommend a specific diagnostic tool, and one guidance document does not recommend cognitive testing for screening asymptomatic adults (26). Three guidance documents (10, 19, 26) propose that a physical examination needs to be conducted for diagnosis and for the prediction of the progression to dementia. Two (10, 26) of these three documents recommend dual-task gait test, while one document recommends the olfactory function

TABLE 1 | Guidelines and consensus statement included in this paper.

Guideline	Institution/Group	Country, territory or area of development	Year	Previous version	Target	Screening and diagnosis	Treatment and management	Number of references	Evidence based	Grading of evidence	Funding type
Tian et al. (19)	Alzheimer's and Related Professional Committees of China Association of Elderly Health Care	China	2016	No	VaMCI	Yes	No	80	Yes	Yes	N/A
Brien et al. (21)	British Association for Psychopharmacology (BAP)	UK	2017	2 (2006, 2011)	MCI	No	Yes	146	Yes	Yes	I
Petersen et al. (12)	American Academy of Neurology (AAN)	USA	2018	1 (2001)	MCI	Yes	Yes	103	Yes	Yes	I
Jia et al. (10)	Cognitive Disorders Professional Committee of Neurologist Branch of Chinese Medical Doctor Association	China	2018	2 (2010, 2015)	MCI	Yes	Yes	22	Yes	Yes	G
Jia et al. (25)	Cognitive Disorders Professional Committee of Neurologist Branch of Chinese Medical Doctor Association	China	2019	No	MCI	No	Yes	24	N/A	Yes	G
Cummings et al. (24)	N/A	USA	2019	No	MCI	Yes	Yes	111	Yes	No	I
WHO (20)	WHO	Switzerland	2019	No	MCI	No	Yes	N/A	Yes	Yes	G
Zhou et al. (27)	State Administration of Traditional Chinese Medicine; Chinese Society of Traditional Chinese Medicine	China	2020	No	VaMCI	Yes	Yes	40	N/A	Yes	G
Ismail and Richard (26)	Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD)	Canada	2020	4 (1989, 1998, 2006, 2012)	MCI, VaMCI	No	Yes	123	Yes	Yes	I
Kandiah and Christopher (13)	Asian Clinical Expert Group on Neurocognitive Disorders (ASCEND)	Singapore	2021	1 (2019)	MCI	Yes	Yes	115	Yes	Yes	P
Dunne et al. (28)	N/A	UK	2021	No	MCI	Yes	Yes	77	Yes	No	N/A
Herukka et al. (22)	N/A	European	2017	No	MCI	Yes	No	51	Yes	Yes	G; I
Nobili et al. (23)	European Association of Nuclear Medicine (EANM) and European Academy of Neurology (EAN)	European	2018	No	MCI	Yes	No	119	Yes	Yes	G; I; P

I, institutional; G, governmental; P, pharmaceutical company; N/A, not applicable.

TABLE 2 | Assessment of guidelines and consensus statements by AGREE II.

Guideline	Domain 1 Scope and purpose (%)	Domain 2 Stakeholder involvement (%)	Domain 3 Rigor of development (%)	Domain 4 Clarity of presentation (%)	Domain 5 Applicability (%)	Domain 6 Editorial independence (%)	Overall (%)
Tian et al. (19)	69	25	29	72	6	0	50
Petersen et al. (12)	77	66	71	86	47	91	92
Brien et al. (21)	69	39	27	86	31	88	58
Jia et al. (10)	61	25	27	69	12	4	42
Jia et al. (25)	44	22	20	77	16	0	33
Cummings et al. (24)	72	33	32	78	35	83	58
WHO (20)	78	61	82	81	40	75	83
Zhou et al. (27)	66	47	19	63	18	0	25
Ismail and Richard (26)	67	50	53	86	42	54	67
Kandiah and Christopher (13)	67	25	45	81	27	71	58
Dunne et al. (28)	61	25	26	81	35	92	50
Herukka et al. (22)	78	25	53	47	48	13	50
Nobili et al. (23)	69	44	53	56	19	46	58
Average	68	37	41	74	29	47	

Green color, 67–100 (high quality); yellow color, 34–66 (sufficient quality); red color, 0–33 (low quality) (18).

test and hearing test (10). Regarding diagnostic radiologic examinations, two documents (12, 19) recommend magnetic resonance imaging (MRI), and three documents (12, 19, 23) recommend positron emission tomography (PET). One guideline recommends the assessment of medial temporal lobe atrophy for the identification of hippocampal atrophy (19). Two guidelines recommend conducting blood tests to exclude other potential diseases (10, 19). Five guidance documents (10, 13, 22, 24, 28) recommend biomarker assessments to help confirm the diagnosis of MCI. Three (10, 22, 28) of these documents recommend cerebrospinal fluid biomarker tests (CSF tau protein and CSF β -amyloid 42), whereas another guideline (12) suggests that there is no accepted biomarker for a definite diagnosis. Three guidance documents recommend follow-up or monitoring the changes in the cognitive status of a patient with MCI (10, 12, 28). The details and levels of recommendations for screening and diagnosis are presented in **Table 3** and **Supplementary Table 3A**.

Treatment and Management

Nine guidance documents covered recommendations for the treatment (10, 12, 13, 20, 21, 24–27). The recommendations for treatment and management were classified into four categories: intervention for risk reduction, pharmacologic interventions, non-pharmacologic interventions, and counseling. Regarding intervention for risk reduction, one guideline (20) recommends that patients reduce or cease harmful drinking, whereas another guideline (12) recommends discontinuing medications that can contribute to cognitive impairment. Seven guidance documents include recommendations for pharmacologic interventions (10, 12, 13, 21, 24, 26, 27). Three guidelines (10, 12, 24) indicate that there is no accepted drug for the

treatment of MCI. Three guidance documents (12, 13, 21) contraindicate cholinesterase inhibitors for the treatment of MCI, whereas one (26) proposes that cholinesterase inhibitors and memantine should be deprescribed. One consensus statement proposes that EHB761[®] can improve the symptoms of MCI (13). One consensus statement recommends Chinese herbal decoction (Guipi decoction, Heche Dazao pills, Huanshaodan, Ditan decoction, and Tongqiao Huoxue decoction) and Chinese traditional patent medicine (FuFangCongRongYiZhi capsule, Tianzhi granules, Yangxue Qingnao granule, and Huanshao capsule) (27). Regarding non-pharmacologic interventions, four guidance documents (12, 13, 20, 26) recommend physical activity interventions, including aerobic exercise; four (12, 13, 20, 25) recommend cognitive interventions; three (20, 24, 27) recommend dietary and nutritional interventions, including a Mediterranean-like diet, Souvenaid, and Chinese medicine dietary therapy; and one (27) recommends acupuncture. Regarding counseling, a guideline proposes that clinicians should discuss prognosis and long-term planning with the patients and their families (12). The details and levels of treatment recommendations are presented in **Table 4** and **Supplementary Table 3B**.

DISCUSSION

Key Findings

As MCI is a transitional stage between the cognitive decline of healthy aging and dementia, its management is critical and requires considerable attention. In this study, we systematically collated MCI guidelines and incorporated

TABLE 3 | Summary of recommendations for screening and diagnosis.

Recommendations	Tian et al. (19)	Herukka et al. (22)	Nobili et al. (23)	Petersen et al. (12)	Jia et al. (10)	Cummings et al. (24)	Kandiah and Christopher (13)	Dunne et al. (28)	Ismail and Richard (26)
Use VAS-COG Society criteria, DSM5, vascular impairment of cognition Classification consensus study or the American Heart Association consensus statement for diagnosis of VaMCI	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Clinical history cannot rely solely on the self-report from patients and should be supplemented by familiar people	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Combining clinical history with neuropsychological testing when making diagnosis	N/A	N/A	N/A	+	N/A	+	N/A	N/A	+
Making a diagnosis of MCI subtype	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Identifying risk factors that are potentially modifiable	N/A	N/A	N/A	+	N/A	N/A	N/A	+	N/A
Use of neuropsychological testing for screening and diagnosis	+	N/A	N/A	+	+	+	+	+	+
Cognitive testing	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Cognitive testing for screening asymptomatic adults	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
3MS examination	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
MMSE	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	+
RUDAS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
MoCA	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	+
TorCA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
NINDS-CSN	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FCSRT	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Activities of daily living testing and functional assessment	+	N/A	N/A	N/A	+	N/A	+	N/A	N/A
ADL	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A
IADL	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
FAQ	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Behavioral and psychological assessment	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Use of physical examination for diagnosis and predicting the progression to dementia	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Dual-task gait test	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	+
Olfactory function test	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Hearing test	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A

(Continued)

TABLE 3 | Continued

Recommendations	Tian et al. (19)	Herukka et al. (22)	Nobili et al. (23)	Petersen et al. (12)	Jia et al. (10)	Cummings et al. (24)	Kandiah and Christopher (13)	Dunne et al. (28)	Ismail and Richard (26)
Use of neuroimaging for diagnosis	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Structural imaging	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MRI	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
MTA scale for identifying hippocampal atrophy	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional imaging	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PET	+	N/A	+	N/A	+	N/A	N/A	N/A	N/A
Use of blood tests for excluding other diseases	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Use of biomarker assessments for helping confirm diagnosis	+	N/A	N/A	N/A	+	+	+	+	N/A
CSF biomarker	N/A	+	N/A	N/A	+	N/A	N/A	+	N/A
Follow-up of MCI patients or monitoring the change in cognitive status	N/A	N/A	N/A	+	+	N/A	N/A	+	N/A

VAS-COG, Vascular Behavioral and Cognitive Disorders; DSM5, Diagnostic and Statistical Manual of Mental Disorders; VaMCI, vascular mild cognitive impairment; MCI, mild cognitive impairment; 3MS, Modified Mini-Mental State; MMSE, Mini-Mental State Examination; RUDAS, the Rowland Universal Dementia Assessment Scale; MoCA, Montreal Cognitive Assessment; TorCA, Toronto Cognitive Assessment; NINDS-CSN, National Institute for Neurological Disorders and Stroke and Canadian Stroke Network; FCSRT, free and cued selective reminding test; MRI, magnetic resonance imaging; PET, positron emission tomography; CSF, cerebrospinal fluid; +, recommended for screening for MCI; -, not recommended for screening in MCI; N/A, not applicable; green, strong recommendation; yellow, moderate recommendation; red, weak recommendation; N/A, not applicable.

the recommendations for review after appraising the qualities of the guidelines. We included a total of 13 MCI guidance documents in this review. The assessment of the guidelines using the AGREE II tool showed that the AAN guideline has the highest methodological quality of all the included guidelines (12). We analyzed the consistency of the recommendations but found some variation among the MCI guidelines.

Some differences were found among the nine guidance documents that include diagnostic recommendations. Neuropsychological assessment is recommended in seven guidelines; however, we noted some inconsistency in the guidelines (10, 12, 13, 19, 24, 26, 28). Three guidance documents do not recommend specific tests (12, 24, 28), whereas others recommend different tests, including MMSE, 3MS examination, MoCA, TorCA, RUDAS, NINDS-CSN neuropsychological protocols, FCSRT, IADL, IADL scale, and FAQ. Among the varied tests mentioned above, NINDS-CSN neuropsychological protocols, FCSRT, ADL, IADL scale, and FAQ are focused on testing deficits in a single cognitive domain (10, 19), while the MMSE and MoCA tests, which are the most common cognitive screening instruments, are used to evaluate multiple cognitive domains (10, 19). Three guidance documents recommend the use of more comprehensive neuropsychological tools for the assessment of multiple cognitive domains in patients with MCI (10, 19, 26). One document (19) states that cognitive assessment should include both a comprehensive test and at least four single-domain tests, while another document (10) states that cognitive assessment should include either a comprehensive test or several single-domain tests. An inconsistency was found regarding whether comprehensive tests and single-domain tests should be used alone or in combination. Moreover, both guidance documents do not clarify which specific test should be used. When choosing which cognitive test to use, clinicians should consider the sensitivity, specificity, and time efficiency of the test (29). The guidelines indicate that the sensitivity of the MMSE is low when it is used alone (10, 26). A transversal study of 229 elderly participants in four medical centers demonstrated that the MMSE has lower sensitivity than the MoCA (30). Three systematic reviews also demonstrated that the sensitivity and specificity of the MoCA are superior to those of the MMSE (29, 31, 32). Hence, the MoCA may be better than the MMSE as a comprehensive neuropsychological screening tool. Moreover, we found that none of the guidance documents included in this review has details of a cutoff score for the diagnosis of MCI. However, a systematic review concluded that the best cutoff point for MoCA score is 24/25 (31). Another systematic review suggested that the influence of education should be considered when using cutoff values (33). In conclusion, there is still no commonly accepted cutoff score for the diagnosis of MCI. Future studies that involve a further evaluation of the diagnostic accuracy of MCI using different tests and clearly defined cutoff values are needed.

There is a controversial question regarding whether the measurement of biomarkers is effective for the detection of progression toward AD in patients with MCI. The biomarkers

TABLE 4 | Summary of recommendations for treatment and management.

Recommendations	Petersen et al. (12)	Brien et al. (21)	Jia et al. (10)	Jia et al. (25)	Cummings et al. (24)	Zhou et al. (27)	WHO (20)	Ismail and Richard (26)	Kandiah and Christopher (13)
Interventions for risk reduction	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A
Interventions for alcohol use disorder	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A
Ceasing medications which can cause cognitive impairment	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pharmacologic interventions	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
No accepted drug	+	N/A	-	N/A	-	N/A	N/A	N/A	N/A
Cholinesterase inhibitors	-	-	N/A	N/A	N/A	N/A	N/A	N/A	-
Cholinesterase inhibitors and memantine should be deprescribed	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A
EHb761® for improving symptoms	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Chinese herbal decoction	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A
Chinese traditional patent medicine	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A
Non-pharmacologic interventions	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Physical activity interventions	+	N/A	N/A	N/A	N/A	N/A	+	+	+
Aerobic exercise	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A
Cognitive interventions	+	N/A	N/A	+	N/A	N/A	+	N/A	+
Dietary and nutritional interventions	N/A	N/A	N/A	N/A	+	+	+	N/A	N/A
Mediterranean-like diet	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A
Souvenaid	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A
Chinese medicine dietary therapy	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A
Acupuncture	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A	N/A
Counseling									
Discussing prognosis and long-term planning topics with patients and families	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

+, recommended for screening for MCI; -, not recommended for screening in MCI; green, strong recommendation; yellow, moderate recommendation; red, weak recommendation; N/A, not applicable.

can be divided into two categories: imaging-based biomarkers and CSF-based biomarkers (34). The imaging-based biomarkers include MRI-based biomarkers and PET-based biomarkers. MRI-based biomarkers contain the hippocampus and entorhinal cortex; PET-based biomarkers mainly contain amyloid PET, tau PET, and fluorine-18-fluorodeoxyglucose (FDG)-PET; CSF-based biomarkers mainly include CSF tau protein, CSF t-tau protein, and CSF β -amyloid peptide ($A\beta_{1-42}$) (35–37). In the present study, six guidance documents covered biomarker assessments; however, they proposed different recommendations (10, 12, 13, 22, 24, 28). Five documents (10, 13, 22, 24, 28) recommend that biomarker assessments may help confirm the diagnosis of MCI and identify prodromal AD in patients with MCI. One (10) of these documents indicates that the CSF tau protein and CSF β -amyloid 42 tests for amnesic MCI (aMCI) are advantageous for screening patients with AD. However, another guideline indicates that there is no accepted biomarker for predicting the progression of MCI (12). Although assessment of biomarker is not recommended in that guideline, the authors state that they have a positive view of the biomarker (12). Only one guidance document recommends using same the cutoff points for CSF biomarkers regardless of apolipoprotein E genotype (22). There are also some contraindications for the application of CSF biomarker test, such as increased intracranial pressure and coagulopathy (22). About imaging-based biomarkers, two documents give the recommendations about the use of FDG-PET to confirm the diagnosis of AD in MCI (19, 23). FDG-PET is also recommended to ascertain the diagnosis of FTL and DLB in MCI (23). The cost benefit of imaging-based and CSF-based biomarkers is another issue worth considering. The Manchester consensus of MCI includes three of 11 recommendations regarding the use of biomarkers for early detection. However, the consensus indicates that the cost utility of biomarkers remains controversial (28).

Variations also exist in the nine documents that include recommendations for the treatment and management of MCI. Three documents do not recommend pharmacological interventions for the treatment of MCI (13, 27). However, Ehb761[®] is recommended in one consensus statement for the improvement of MCI symptoms (13). Ehb761[®] is an extract from the *Ginkgo biloba* plant. A systematic review, which include 21 trials with 2,608 patients, concluded that *G. biloba* may help improve the cognitive function and activities of daily living of patients with MCI (38). Another consensus statement recommends Chinese herbal decoctions and Chinese traditional patent medicine for the treatment of VaMCI (27). A 2-year trial demonstrated that traditional Chinese medicine, such as Bushen capsules, may improve the cognitive performance of patients with aMCI (39). Herb medicine might be a potential treatment for the improvement of MCI symptoms; however, more high-quality evidence is needed to confirm their efficacy. Four guidance documents (12, 13, 20, 26) recommend physical activity interventions for MCI. One (26) of these documents recommends a specific physical intervention, aerobic exercise. A systematic review of randomized control trials indicates

that aerobic and resistance exercises could improve cognitive function (40). Some studies have shown that specific physical activity interventions, such as mind–body exercise, Tai Chi, functional task exercise, and yoga, may significantly improve the MCI symptoms (41–44). The specific physical activity interventions suitable for patients with MCI, the duration of the exercises, and strength of the exercises need to be researched in future studies.

Although guidance on follow-up or monitoring of the changes of MCI patients have been provided by three guidance documents, no detailed information on how to manage it can be determined. As it is worthwhile to clarify how often the patients with MCI should be monitored and what specific assessments the patients should do, this problem needs to be addressed in future guidelines.

In general, most guidelines and consensus statements (seven of 11) included in the present study were of sufficient and low quality. The domain with the lowest score was the “applicability” domain (domain 5). “Applicability” is a key measure of the implementation of a guideline in clinical practice (16). Applicability limitations, lack of description of facilitators and barriers, provision of additional tools, and potential resources may potentially affect health improvement.

Strengths and Limitations

To the best of our knowledge, this is the first paper to summarize the published guideline recommendations for MCI. The main strength of this study is the comprehensive and systematic literature search that was conducted to identify guidance documents related to the diagnosis and treatment of MCI. The guidelines and consensus statements were independently appraised by two reviewers using AGREE II, and the finding on the methodological problems, mainly in the applicability domain, presented as lacking implementation strategies and related application resources, may help in the development of future MCI guidelines. The recommendations were summarized into key recommendations shown in tables, and the consistency of the recommendations and the difference between them were compared.

The limitation of this study is that, although a systematic search strategy was implemented, certain guidelines may have been missed because of language limitations. Moreover, there were no accepted cutoff points for the domain scores of AGREE II. In addition, the fact that we referred to a previous article for the grading of the domain scores might be a matter of dispute (17, 18).

CONCLUSIONS

An updated search of possible evidence for the diagnosis and treatment of MCI is needed. Potentially effective diagnoses and treatments, either conventional or complementary, and alternative therapies should be highly valued and addressed in

correlation with the supporting evidence. The AGREE II and Reporting Items for Practice Guidelines in Healthcare tools can be referred to when developing guidelines.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NL and Y-XC designed the study, developed the analysis plan, analyzed the data, and contributed to the writing of the article. X-LL and S-HY extracted the data and appraised the quality of

eligible guidelines. Y-PW and N-NS revised the manuscript and polish the language. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2021.719849/full#supplementary-material>

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