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Potential diagnostic tools for intensive care unit acquired weakness: A systematic review

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ABSTRACT

Background: Intensive care unit-acquired weakness is a prevalent complication among critically ill patients, associated with heightened mortality rates, extended durations of mechanical ventilation and hospital stays, as well as diminished mobility and unfavorable prognoses. Early diagnosis of intensive care unit-acquired weakness and identification of its subcategories are essential for early implementation of targeted interventions and care strategies. Nevertheless, there remains a significant gap in the availability of widely accepted, accurate, and user-friendly diagnostic tools for intensive care unit-acquired weakness.

Objective: The aim of this research was to conduct a comprehensive review of pertinent studies on diagnostic tools for intensive care unit-acquired weakness in critically ill patients, summarizing their diagnostic efficacy and constraints to aid healthcare professionals in choosing suitable diagnostic tools for intensive care unit-acquired weakness.

Methods: The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement were utilized to direct the literature search, bias risk assessment and data extraction. The search databases included PubMed, Web of Science, EMBASE, Cochrane Library, and CINAHL. The search period was from the inception of the database to 1 July 2024. Different types of risk bias assessment tools were used for different types of studies. Due to the heterogeneity of the data, solely a narrative synthesis of the intensive care unit-acquired weakness diagnostic tool was performed in this study.

Results: A total of 38 observational studies were included in the study. In the included studies, the gold standard for intensive care unit-acquired weakness diagnosis include the Medical Research Council score, muscle biopsy and electrophysiologic testing, potential diagnostic tools include the manual muscle test, electrophysiologic testing, imaging, serum inflammatory markers, neuromuscular ultrasound, and other parameters. In various studies, the diagnostic accuracy of intensive care unit-acquired weakness diagnostic tools has been inconsistent, with each tool possessing its own set of advantages and disadvantages. At present, no single tool is available for the definitive diagnosis of intensive care unit-acquired weakness, necessitating the combined use of multiple methods, each with inherent limitations. Manual muscle test is inexpensive and straightforward to perform, but it requires the patient to be conscious and cooperative. Muscle

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biopsy is invasive and rarely utilized. Electrophysiological testing can help differentiate whether intensive care unit-acquired weakness is caused by neural or muscular alterations, thereby aiding in the classification of its subtypes. However, it is moderately invasive, costly, and operator-dependent. Other diagnostic modalities, such as imaging and respiratory parameters, are under ongoing investigation.

Conclusions: The diagnostic tools available in intensive care unit-acquired weakness are varied, each with its own strengths and limitations. This study summarizes the current evidence on potential diagnostic tools for intensive care unit-acquired weakness and identifies possible future directions for these diagnostic tools.

Registration: PROSPERO Registration Number CRD42024573139.

What is already known about this topic?

- Intensive care unit-acquired weakness, a consequence of severe illness, can be categorized as either critical illness polyneuropathy, critical illness myopathy, or a combination of both, depending on the origin of the disease.
- Intensive care unit-acquired weakness is the main reason for extending mechanical ventilation duration, prolonging intensive care unit admission, escalating hospitalization expenses, boosting mortality rates, and diminishing the quality of life for patients post-critical illness.
- The most common diagnostic tool for intensive care unit-acquired weakness diagnosis is Medical Research Council score, yet its application is limited to alert and cooperative patients, frequently resulting in diagnostic and treatment delays.

What this paper adds?

- This review summarizes the existing diagnostic tools for intensive care unit-acquired weakness, including established gold standards and emerging diagnostic methods, and summarizes the diagnostic accuracy of these tools.
- Based on the mechanism of intensive care unit-acquired weakness, this study points out the advantages and limitations of existing diagnostic tools, introduces some novel diagnostic tools and improved methods, and offers insights for follow-up diagnostic tool development and future research.

1. Introduction

Intensive care unit acquired weakness (ICU-AW) was defined as clinically recognized weakness and inability to move against resistance in critically ill patients without a plausible etiology other than critical illness (Elkalawy et al., 2023). ICU-AW is not simply disused muscle atrophy caused by prolonged immobilization, but nerve and muscle injury that occurs after acute and critical illness. It is characterized by symmetrical involvement of the extremities, greater impact on proximal muscles than distal muscles, reduced or unchanged deep tendon reflexes, varying degrees of impact on respiratory muscles, and generally unaffected facial and extraocular muscles (Le Stang et al., 2024). Although the term ICU-AW is still commonly used, it has been recognized that this severe weakness occurs in critically ill patients regardless of care setting, not exclusively in the ICU. Therefore, in recent years, the term critical illness weakness (CIW) has been considered more appropriate (Latronico et al., 2023). However, for consistency and familiarity, this study continues to use ICU-AW.

The prevalence of ICU-AW ranges from 25 % to 100 %, and it often leads to longer duration of mechanical ventilation and ICU stay, increased hospital costs, higher mortality, reduced quality of life after discharge, and even disability in critically ill patients (Chen and Huang, 2024; Le Stang et al., 2024). ICU-AW can manifest within 3–5 days of ICU admission and may persist for months to years after discharge, making early diagnosis and intervention crucial for critically ill patients (Maramattom, 2022).

We believe that a comprehensive understanding of the pathogenesis of ICU-AW is crucial for developing diagnostic tools. Unfortunately, the pathophysiological mechanisms and diagnostic criteria remain poorly understood (Sapra, 2021). The etiology may be related to inflammatory status, multiple organ dysfunction syndrome, hyperglycemia, multiple organ failure, prolonged mechanical ventilation, length of ICU stay, aminoglycoside use, prolonged sedation, and other risk factors (Yang et al., 2022). Additionally, multiple pathophysiological mechanisms are thought to contribute to the development of ICU-AW, including reduced muscle and nerve excitability, loss of myosin, enhanced proteolysis, anabolism/catabolism ratio, and increase pro-inflammatory cytokines (Habr et al., 2020).

ICU-AW is classified into three subcategories based on its origin, whether myogenic or neurogenic: critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness polyneuromyopathy (CIPNM) (Tortuyaux et al., 2022). CIP is a distal axonal sensory-motor polyneuropathy affecting limb and respiratory muscles, characterized by symmetrical limb involvement with greater proximal than distal muscle weakness, while facial muscles are typically spared. CIM is a primary myopathy that is not secondary to muscle denervation, showing similar clinical features to CIP, such as ventilator weaning difficulty and flaccid limbs, but with normal sensation. CIPNM represents the coexistence of both conditions (Latronico and Bolton, 2011). In general, CIM is considered to be more common, appear earlier, and have a better prognosis than CIP, so early differential diagnosis is of clinical significance (Gonzalez

Marrero et al., 2020). Currently, there are three hypotheses about the pathogenesis of CIM: decreased membrane excitability, decreased calcium release from the sarcoplasmic reticulum and selective decrease in myosin protein (Tankisi et al., 2021). There are also three main hypotheses about the mechanism of CIP: decreased circulation of local axonal survival factors, alteration to the microvasculature to the axons of peripheral nerves and dysfunction of voltage gated sodium channels (Cheung et al., 2021; McClafferty et al., 2020). Since the mechanisms of CIM,CIP and CIPNM have not been clearly defined and unified, how to diagnose and differentiate them as early as possible has become a major problem.

"An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults" published in 2014, states that there is no consensus approach to diagnose ICU-AW, including how or when to make a diagnosis, the most common diagnostic tools were physical examinations (84 % of studies), electromyogram (EMG) (90 % of studies), and nerve conduction studies (NCS) (84 % of studies) (Fan et al., 2014). For patients with adequate cognitive function, manual muscle testing at the bedside can be used to diagnose ICU-AW. However, for those unable to cooperate due to coma, delirium, or other reasons, specific neurophysiological examinations or, when necessary, muscle biopsies are recommended. It is important to note that each of these diagnostic tools has limitations, particularly in distinguishing between CIP, CIM, or their coexistence (Latronico et al., 2023).

This study conducted a systematic review of the literature, synthesized the current diagnostic tools for ICU-AW, and comprehensively assessed the diagnostic accuracy of various tools, thereby providing a theoretical foundation for early clinical diagnosis of ICU-AW.

2. Methods

2.1. Search strategy

This study was conducted under the guidance of The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021). And the study protocol was registered and published on 06 August 2024 on the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute for Health Research under the ID CRD42024573139.

Population, Exposure, Comparison, Outcomes and Study design (PECOS) eligibility criteria were used to develop a search strategy, including adult critically ill patients (P), diagnostic tools for CIM, CIP, CIPNM, or ICU-AW (E), critically ill patients without ICU-AW (C), ICU-AW (O), cohort studies, case-control studies and cross-sectional studies (S). Adult critically ill patients are defined as individuals with life-threatening conditions or severe injuries requiring urgent medical intervention, whether in the ICU or other clinical settings. We use the combination of MESH terms and key terms to search the relevant literature systematically, including (intensive care unit acquired weakness OR ICU-acquired weakness OR ICU-AW) AND (biopsies OR electrophysiologic OR computer tomography OR magnetic resonance imaging OR scale OR score OR ultrasonography OR imaging OR assessment OR diagnosis OR measurement). We conducted our search on PubMed, Web of Science, EMBASE, Cochrane Library, and CINAHL databases. The search period was from the inception of the database to 1 July 2024.

2.2. Selection process

The literature search was conducted by the first author, and the preliminarily searched literature was imported into NoteExpress 4.0 for deduplication and screening. Two reviewers (CX&YHL) independently read the titles and abstracts of the deduplicated literature, and initially excluded the literature with inconsistent content. After that, the two reviewers read the full text of the literature, and conducted the final literature screening according to the inclusion and exclusion criteria. If there is disagreement in the literature selection process, another reviewer (YBG, YQW or BRH) with rich evidence-based experience will be included for discussion.

2.3. Eligibility criteria

Inclusion criteria include: (1) the study participants were critically ill patients, aged $>$ 18 years, with or without ICU admission; (2) the studies focuse on ICU-AW diagnostic tools; (3) outcomes included ICU-AW and its three subcategories, CIM,CIP and CIPNM; (4) the gold standard for diagnosis is the accepted Medical Research Council (MRC) score, biopsy and electrophysiologic testing; (5) observational studies, including cohort studies, case-control studies and cross-sectional studies; (6) literature written in English or Chinese.

Exclusion criteria include: (1) only the ICU-AW assessment tool was explored and its diagnostic value was not reported; (2) non-observational studies, such as interventional studies and animal experiments; (3) duplicate literature; (4) full-text was not available; (5) grey literature, conference abstracts, dissertations, case reports and secondary analyses of preexisting data.

2.4. Data extraction and synthesis

Data extraction was performed blindly by two reviewers. Study characteristics such as authors, years, countries, population, sample sizes, reference test, index test, and other relevant information from studies that met the inclusion criteria, were extracted and recorded in excel sheets. Due to inconsistencies in diagnostic tools, timing of diagnosis, and outcomes, resulting in too much heterogeneity in data for meta-analysis, this review used a narrative synthesis approach to the included studies. The testing methods, observational parameters, diagnostic thresholds, and diagnostic accuracy metrics, including consistency assessments, area under the receiver operating characteristic curve (AUC-ROC), sensitivity, specificity, and other related indicators, were extracted from the included studies.

2.5. Study risk of bias assessment

Two reviewers independently assessed the quality and risk bias of the studies that met the inclusion criteria. Cohort studies and case-control studies were evaluated using the Newcastle-Ottawa scale (NOS), and studies with NOS score >5 were considered methodologically high quality to be included (Wang et al., 2019). Cross-sectional studies were assessed using an adapted version of the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies (Vatovec and Voglar, 2024). Considering that a certain number of diagnostic accuracy studies were included in the eligible studies, we used the recommended tool for diagnostic studies, Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2), and managed it using RevMan 5.3 (Arruzza et al., 2022). QUADAS-2, a revised version of the original QUADAS tool released in 2011, consists of two main components: risk of bias and applicability concerns. The risk of bias assessment includes four items: (1) patient selection, (2) index test, (3) reference standard, and

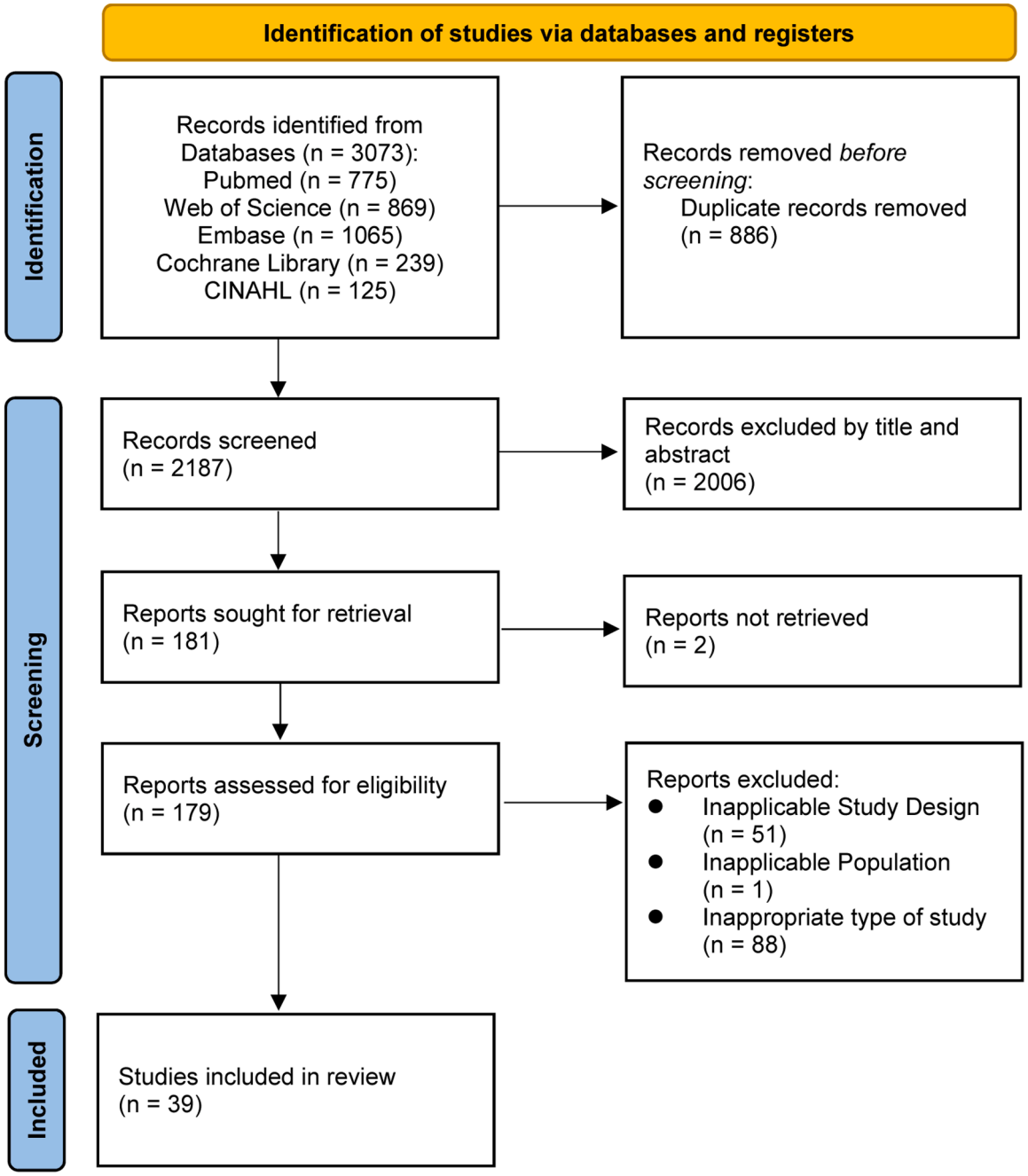

Fig. 1. Flow diagram of selected studies according to the PRISMA guidelines.

Table 1
The quality evaluation results of cohort studies.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Raghig et al., 2010	Hough et al., 2011	Tzanis et al., 2011	Hermans et al., 2012	Connolly et al., 2013	Wieske et al., 2014	Moss et al., 2014	Wieske et al., 2015	Parry et al., 2015	Kelmenson et al., 2018	Bragança et al., 2019	Schmidt et al., 2019	Mitobe et al., 2019	Patejdl et al., 2019
Selection														
1) Representativeness of the exposed cohort	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2) Selection of the non exposed cohort	1	1	1	1	1	1	0	1	1	1	1	1	1	0
3) Ascertainment of exposure	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4) Demonstration that outcome of interest was not present at start of study	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Comparability														
1) Comparability of cohorts on the basis of the design or analysis	1	2	2	2	2	2	1	1	1	2	2	1	2	1
Outcome														
1) Assessment of outcome	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2) Was follow-up long enough for outcomes to occur	1	1	1	0	1	1	1	1	0	0	1	1	1	1
3) Adequacy of follow up of cohorts	1	1	1	1	1	1	1	1	0	0	1	1	1	1
Quality scores	8	9	9	8	9	9	7	8	6	7	9	8	9	7

(4) flow and timing. The applicability concerns assessment covers three items: (1) patient selection, (2) index test, and (3) reference standard (Whiting et al., 2011). This tool helps evaluate the quality of diagnostic accuracy studies by identifying potential biases and assessing the applicability of the studies to specific research contexts.

3. Results

3.1. Search results

In the initial electronic databases search, a total of 3073 studies were retrieved. After software deduplication, 2187 studies were obtained. After manual screening of titles, abstracts and full texts, 39 studies were eventually included. The flow chart for screening studies in accordance with PRISMA guidelines is shown in Fig 1.

3.2. Methodological quality of the studies

There were 39 observational studies that met the inclusion criteria, including 35 cohort studies, three case-control studies, and one cross-sectional study. The eligible studies in this study were evaluated using the corresponding quality evaluation tools, and the quality evaluation results of 35 cohort studies are shown in Table 1. The NOS score of the study of Tran et al. (2020) was 3, <5, and therefore excluded. The other 34 included studies were of acceptable quality, with a mean NOS score of 7.82. The quality of the three case-control studies was acceptable, with a mean NOS score of 6.33, as shown in Table 2. Witteveen et al. (2017) as the only cross-sectional study, its evaluation criteria were eight items, among which the item 3 “Was the exposure measured in a valid and reliable way?” and item 7 “Were the outcomes measured in a valid and reliable way?” are “Not applicable”, item 6 “Were strategies to deal with confounding factors stated?” is “Unclear”, the remaining entries are “Yes”. In addition, methodological evaluation of the risk of bias and applicability concerns of 25 diagnostic studies in the eligible studies was also performed, as shown in Fig. 2.

3.3. Study characteristics

After excluding the studies that failed to pass the quality assessment, 38 studies remained. The included studies comprised 33 prospective studies, four retrospective studies, and one cross-sectional study, covering the period from 2010 to 2024. The researchers were from 20 different countries, with the highest number of studies ($n = 10$) conducted in China. The sample sizes ranged from 10 to 212 participants. Among the studies, 11 studies focused on the differential diagnosis of ICU-AW subcategories, CIM, CIP, or CIPNM. The reference tests and index tests used for diagnosis, along with other detailed characteristics, are presented in Table 3.

3.4. Diagnostic gold standard

The “gold standard” diagnostic tool is defined as one that accurately detects the presence or absence of a disease with high sensitivity and specificity, supported by rigorous validation and broad acceptance in the medical community. Since ICU-AW develops from the physical symptoms of limb paralysis in critically ill patients, its diagnostic gold standard has not yet been unified. The most widely used gold standard, or reference test, in the 38 included studies was the MRC (Medical Research Council) score, which was used as a reference test in 32 studies (Attwell et al., 2022; Braganca et al., 2019; Chen and Huang, 2024; Connolly et al., 2013; Daste et al., 2023; Ding et al., 2022; Elkholy et al., 2024; Haijun et al., 2020; Hermans et al., 2012; Hernandez-Socorro et al., 2021; Hough et al., 2011; Jung et al., 2020; Kelmenson et al., 2018; Klawitter et al., 2022; Li et al., 2020; Maramattom, 2022; Mitobe et al., 2019; Moss et al., 2014; Naoi et al., 2022; Paolo et al., 2022; Parry et al., 2015; Patejdl et al., 2019; Tzanis et al., 2011; Wieske et al., 2014, 2015; Witteveen et al., 2017; Xie et al., 2020; Yang and Chen, 2022; Yuan et al., 2021; Zeng et al., 2023; Zhang et al., 2021, 2024). The manual muscle test is a highly reliable method of assessing strength, and the MRC muscle strength scoring system is the most

Table 2
The quality evaluation results of case-control studies.

	1	2	3
	Tankisi et al., 2021	Hernández-Socorro et al., 2021	Maramattom 2022
Selection			
1) Is the case definition adequate?	1	1	1
2) Representativeness of the cases	1	1	1
3) Selection of controls	0	0	0
4) Definition of controls	1	1	1
Comparability			
1) Comparability of cases and controls on the basis of the design or analysis	1	1	1
Exposure			
1) Ascertainment of Exposure	1	1	1
2.) Same method of ascertainment for cases and controls	1	1	1
3) Non-response rate	0	1	0
Quality scores	6	7	6

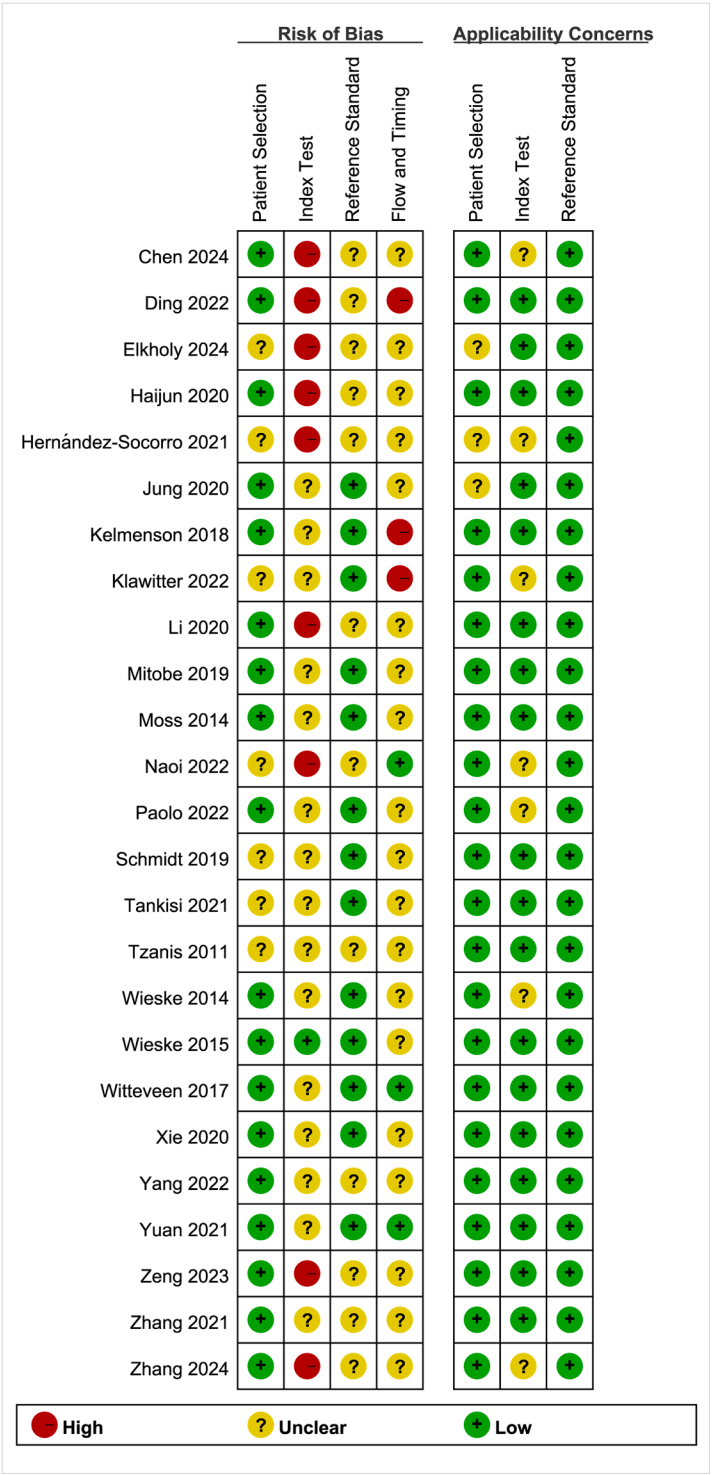

Fig. 2. Critical appraisal of diagnostic studies.

commonly standardized algorithm (Ciesla et al., 2011). The MRC scoring system performs a bilateral test of six specified muscle groups movement (upper limbs: wrist flexion, forearm flexion and shoulder abduction, lower limbs: ankle dorsiflexion, knee extension and hip flexion) in patients who are conscious and cooperative (Elkholy et al., 2024). Muscle strength is scored on a scale of 0 (no visible contraction) to 5 (normal power), and the MRC sum score (MRCss) of 60 with an average score of < 4 or a total score of < 48 is considered to be weakness. In 32 studies, five studies (Hernandez-Socorro et al., 2021; Naoi et al., 2022; Wieske et al., 2014, 2015;

Table 3
Characteristics of the included studies.

Study (year)	Country	Type of Study	Type of ICU-AW	Population	Sample Size (n)	Reference test	Index Test
Raghig et al., 2010	Canada	Retrospective observational cohort study	CIP, CIM and CIPNM	ICU patients	10	Muscle biopsy	EMG
Hough et al., 2011	United States of America	Prospective observational cohort study	ICU-AW	Critically ill patients (at least 18 years, at least 3 days of mechanical ventilation)	30	MRCss < 48	MRC score
Tzanis et al., 2011	Greece	Prospective observational cohort study	ICU-AW	ICU patients	74	MRCss < 48	Maximal inspiratory pressure
Hermans et al., 2012	Belgium	Prospective observational cohort study	ICU-AW	Critically ill patients who had been treated in the surgical or medical ICU for at least 7 days	121	MRCss < 48	Handgrip dynamometry
Connolly et al., 2013	United Kingdom	Prospective observational cohort study	ICU-AW	ICU patients (patients 18 years of age and older who had been invasively ventilated for 48 or more hours)	94	MRCss < 48	MRC score
Wieske et al., 2014	Netherlands	Prospective observational cohort study	ICU-AW	ICU patients	212	Mean MRC score < 4	Easily Available Parameters (highest lactate, treatment with any aminoglycoside and age)
Moss et al., 2014	United States of America	Prospective observational cohort study	CIPNM	ICU patients	64	MRCss < 48, NCS and EMG	NCS
Wieske et al., 2015	Netherlands	Prospective observational cohort study	ICU-AW	Newly admitted critically ill patients who were mechanically ventilated for 2 days	40	Mean MRC score < 4	NCS
Parry et al., 2015	Australia	Prospective observational cohort study	ICU-AW	Adult patients (> 18 years) with critical illness who were mechanically ventilated for >48 h	60	MRCss < 48	A new collapsed four-point MRC scale and handgrip dynamometry
Bragança et al., 2019	Brazil	Prospective observational cohort study	ICU-AW	Adult patients (18 years or older) requiring at least 5 days of critical care	45	MRCss < 48	Handgrip dynamometry
Schmidt et al., 2019	Brazil	Prospective observational cohort study	CIPNM	Septic patients who required mechanical ventilation for at least 5 days	50	EMG	MRC score, handgrip dynamometry, maximal inspiratory pressures, maximal expiratory pressure
Mitobe et al., 2019	Japan	Retrospective observational cohort study	ICU-AW	Adult sepsis patients	31	MRCss < 48	Skeletal muscle index measured by abdominal computer tomography scans
Jung et al., 2020	Korea	Prospective observational cohort study	CIP	Patients who were ≥18 years old and were dependent on mechanical ventilation for ≥21 days	41	MRCss < 48 and NCS	Simplified NCS
Xie et al., 2020	China	Prospective observational cohort study	ICU-AW	ICU patients who required mechanical ventilation therapy	92	MRCss < 48	Plasma growth differentiation factor-15 level, erector spinae muscle cross-sectional area loss
Tankisi et al., 2021	Denmark	Prospective observational case control study	CIM	Critically ill patients	58	NCS and EMG	Muscle velocity recovery cycles
Yuan et al., 2021	China	Prospective observational cohort study	ICU-AW	ICU patients who were mechanically ventilated	104	MRCss < 48	Erector spinae muscle cross-sectional area Loss Ratios measured by chest computer tomography

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Table 3 (*continued*)

Study (year)	Country	Type of Study	Type of ICU-AW	Population	Sample Size (n)	Reference test	Index Test
Rodriguez et al., 2022	Switzerland	Prospective observational cohort study	CIM	Adult critically ill patients admitted to the ICU due to COVID-19 related acute respiratory distress syndrome requiring mechanical ventilation	31	NCS, EMG and muscle biopsy	Muscle velocity recovery cycles
Maramattom 2022	India	Retrospective observational case control study	ICU-AW	Patients with a diagnosis of CIM or Guillain-Barre syndrome	15	MRCss < 48	Muscle magnetic resonance imaging
Hirose et al., 2022	Japan	Prospective observational cohort study	CIM	ICU patients	31	NCS	Excitation-contraction coupling time
Inan et al., 2022	Turkey	Prospective observational cohort study	CIM or CIPNM	Acute stroke patients aged≥18 years	24	NCS	Multimodal assessment: electrodiagnostic testing, histopathology, and assessment of respiratory complex activities
Attwell et al., 2022	Switzerland	Prospective observational cohort study	CIM and CIP	ICU patients who either had septic shock or who developed septic shock during ICU stay and who had invasive ventilation for ≥ 72 h	18	MRCss < 48 and NCS	NCS
Daste et al., 2023	France	Prospective observational cohort study	ICU-AW	Patients with acute respiratory distress syndrome due to COVID-19	25	MRCss < 48	Shoulder-girdle magnetic resonance imaging
Witteveen et al., 2017	Netherlands	Cross-sectional observational study	ICU-AW	ICU patients who were mechanically ventilated for ≥48 h	71	Mean MRC score < 4	Neuromuscular ultrasound
Kelmenson et al., 2018	United States of America	Prospective observational cohort study	CIPNM	Patients from the medical, cardiac, surgical, and neurosurgical ICUs	95	MRCss < 48 and NCS	NCS, muscle ultrasound
Patejdl et al., 2019	Germany	Prospective observational cohort study	ICU-AW	Adult ICU patients	20	MRCss < 48	Muscular ultrasound, inflammatory biomarkers
Haijun et al., 2020	China	Prospective observational cohort study	ICU-AW	ICU patients who were mechanically ventilated	41	MRCss < 48	Muscle ultrasound
Li et al., 2020	China	Prospective observational cohort study	ICU-AW	ICU patients who were mechanically ventilated for ≥24 h	45	MRCss < 48	Muscle ultrasound
Hernández-Socorro et al., 2021	Spain	Prospective observational case control study	ICU-AW	ICU patients who needed prolonged mechanical ventilation and were expected to have an ICU stay longer than seven days	43	Mean MRC score < 4 or EMG	Shear wave elastography, superb microvascular imaging, contrast-enhanced ultrasound
Zhang et al., 2021	China	Prospective observational cohort study	ICU-AW	Patients aged ≥ 18 years with an anticipated ICU stay of at least 2 days	37	MRCss < 48	Muscle ultrasound
Ding et al., 2022	China	Prospective observational cohort study	ICU-AW	ICU patients with sepsis	99	MRCss < 48	Muscle ultrasound, plasma monocyte chemoattractant protein-1
Klawitter et al., 2022	Germany	Prospective observational cohort study	ICU-AW	ICU patients with a Sequential Organ Failure Assessment score ≥ 8 on three consecutive days	38	MRCss < 48	Muscular echogenicity
Paolo et al., 2022	Italy	Prospective observational cohort study	ICU-AW	Patients 18 years of age and older mechanically ventilated with an expectation of ICU stay ≥72 h	50	MRCss < 48	Muscle ultrasound

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Table 3 (*continued*)

Study (year)	Country	Type of Study	Type of ICU-AW	Population	Sample Size (n)	Reference test	Index Test
Naoi et al., 2022	Japan	Retrospective observational cohort study	ICU-AW	ICU patients who were mechanically ventilated for >48 h	25	Mean MRC score < 4	Muscular echogenicity
Yang and Chen, 2022	China	Prospective observational cohort study	ICU-AW	ICU patients	62	MRCss < 48	Muscle ultrasound
Zeng et al., 2023	China	Prospective observational cohort study	ICU-AW	ICU patients	40	MRCss < 48	Muscle ultrasound
Elkholy et al., 2024	Egypt	Prospective observational cohort study	CIM	Septic patients	40	MRCss<48, NCS and EMG	Muscle ultrasound
Zhang et al., 2024	China	Prospective observational cohort study	ICU-AW	ICU patients who were mechanically ventilated	75	MRCss < 48	Handgrip dynamometry, diaphragm ultrasound
Chen et al., 2024	China	Prospective observational cohort study	ICU-AW	ICU patients	86	MRCss < 48	Muscle echogenicity, plasma inflammatory factors (serum interleukin-6, procalcitonin)

ICU-AW: intensive care unit acquired weakness; CIP: critical illness polyneuropathy; CIM: critical illness myopathy; CIPNM: critical illness polyneuromyopathy; MRC: Medical Research Council; MRCss: MRC sum score; NCS: nerve conduction studies; EMG: electromyogram.

Witteveen et al., 2017) used a mean MRC score < 4 as the diagnostic threshold, and the remaining 27 studies used an MRCss < 48 as the diagnostic criteria. In addition to the MRC score, of the remaining six studies, one study (Raghig et al., 2010) used muscle biopsy as the gold standard, two study (Hirose et al., 2022; Inan et al., 2022) used NCS, one study (Schmidt et al., 2019) used EMG, one study (Tankisi et al., 2021) used a combination of NCS and EMG, one study (Rodriguez et al., 2022) used a combination of NCS, EMG and Muscle Biopsy. Besides, three studies (Attwell et al., 2022; Jung et al., 2020; Kelmenson et al., 2018) used MRCss < 48 and NCS as reference tests. Two studies (Elkholy et al., 2024; Moss et al., 2014) employed MRCss < 48 in combination with NCS and EMG, while another study (Hernandez-Socorro et al., 2021) used mean MRC score < 4 or EMG as reference tests.

3.5. Potential diagnostic tool

In this review, a "potential diagnostic tool" refers to the index test under investigation in the study, which shows promise in diagnosing a condition but has not yet demonstrated the same level of diagnostic accuracy as the gold standard and may require further validation before it can be widely used. Of the included studies, two studies (Connolly et al., 2013; Hough et al., 2011) performed an inter-observer agreement examination of MRC score. Schmidt et al. (2019) investigated the diagnostic validity of MRCss with EMG as the reference standard. Parry et al. (2015) introduced an innovative four-point scale for the MRC score and validated its inter-rater reliability. However, it has seen limited use and therefore will not be discussed further. Compared with MRC scoring system, handgrip dynamometry is a much simpler method for measuring muscle strength. Two studies (Braganca et al., 2019; Hermans et al., 2012) explored inter-observer agreement between handgrip dynamometry and MRC score, and three study (Parry et al., 2015; Schmidt et al., 2019; Zhang et al., 2024) investigated the diagnostic value of handgrip dynamometry in ICU-AW.

In terms of electrophysiological tests, there are five studies (Attwell et al., 2022; Jung et al., 2020; Kelmenson et al., 2018; Moss et al., 2014; Wieske et al., 2015) that have analyzed the use value of NSC in ICU-AW diagnosis, and one study (Raghig et al., 2010) explores the differential diagnosis of EMG in ICU-AW. Hirose et al. (2022) also used a novel electrophysiological approach to diagnose CIM, which was excitation-contraction coupling was studied by recording motor related potential. Another new electrophysiology technique, a method to assess muscle excitability in vivo by recording muscle velocity recovery cycles, has also been shown to be an alternative to diagnosing CIM by Tankisi et al. (2021) and Rodriguez et al. (2022).

Imaging also plays a significant role in ICU-AW diagnosis. Erector spinae muscle cross-sectional area loss ratio measured by computer tomography and skeletal muscle index measured by abdominal computer tomography scans have also been tried to diagnose ICU-AW. In addition, two studies (Daste et al., 2023; Maramattom, 2022) investigated the use of muscle magnetic resonance imaging and shoulder-girdle magnetic resonance imaging in the diagnosis of ICU-AW.

Among the diagnostic tools, ultrasound technology has received the most attention from researchers. A total of 17 studies (Chen and Huang, 2024; Ding et al., 2022; Elkholy et al., 2024; Haijun et al., 2020; Hernandez-Socorro et al., 2021; Kelmenson et al., 2018; Klawitter et al., 2022; Li et al., 2020; Naoi et al., 2022; Paolo et al., 2022; Patejdl et al., 2019; Witteveen et al., 2017; Xie et al., 2020; Yang and Chen, 2022; Zeng et al., 2023; Zhang et al., 2021, 2024) investigated ultrasound methods such as muscle ultrasound, neuroultrasound, and diaphragm ultrasound in the diagnosis of ICU-AW, which will be described in detail later.

Finally, since systemic diseases involving peripheral muscles also affect respiratory muscles, the study of Tzanis et al. (2011) has investigated the application of maximal inspiratory pressure as a surrogate parameter in the diagnosis of ICU-AW. Schmidt et al. (2019) not only studied maximal inspiratory pressure, but also validated the efficacy of maximal expiratory pressure as a diagnostic

tool.

In addition to single diagnostic tool mentioned above, there are a number of studies that have explored the role of comprehensive measures in the diagnosis of ICU-AW and its associated subcategories. Wieske et al. (2014) used easily available parameters as the index test for ICU-AW, such as highest lactate, treatment with any aminoglycoside and age. Two studies have suggested the use of a combination of muscle ultrasound and inflammatory biomarkers for the diagnosis of ICU-AW (Chen and Huang, 2024; Patejdl et al., 2019). The Inan et al. (2022) conducted a multimodal assessment of ICU-AW using electrodiagnostic tests, histopathological analysis, and respiratory complex activities evaluation. Zhang et al. (2024) explored a diagnostic modality that combines handgrip dynamometry and diaphragm ultrasound.

3.6. Diagnostic accuracy

Manual muscle testing includes MRC scoring system and handgrip dynamometry. Regarding the MRC scoring system, in the study of Hough et al. (2011), the observers showed good agreement on the diagnosis of ICU-AW for 93 % of participants ($n = 30$), with a kappa value of 0.76 (95 % confidence interval [CI] 0.44-1.00). Hermans et al. (2012) reported good agreement (kappa $= 0.68 \pm 0.09$) for identifying patients with an MRCss < 48 and excellent agreement (kappa $= 0.93 \pm 0.07$) for diagnosing "severe weakness" defined as an MRCss < 36 in a study of 75 patients. The study by Connolly et al. (2013) also confirmed that the MRCss inter-observer agreement is good, and the kappa value for diagnosis of ICU-AW was 0.60 (95 % CI 0.25-0.95). In addition, Parry et al. (2015) used the previously developed gender-based cut-off for handgrip dynamometry, < 11 kg (kg) for males and <7 kg for females, has a sensitivity of 0.88 and a specificity of 0.80 for the diagnosis of ICU-AW. And Bragança et al. (2019) also used this threshold and demonstrated a high degree of agreement between handgrip dynamometry and MRC criteria (100 % accuracy; Kappa $= 1$). In the study by Schmidt et al. (2019), EMG was used as the reference test, with handgrip dynamometry cut-off values set at < 4 kg for females and < 7 kg for males, achieving sensitivity and specificity above 0.85. In the study by Zhang et al. (2024), grip strength < 13.2 kg for males and < 9.5 kg for females were the optimal critical values, and their sensitivity and specificity were both greater than 0.7.

In terms of electrophysiological tests, Moss et al. (2014) used a combined peroneal and sural nerve amplitude test as an alternative to the detection of bilateral NCS of six nerves, which had a sensitivity of 100 % (95 % CI 100 %−100 %) and a specificity of 81 % (95 % CI 71–91 %) for the diagnosis of ICU-AW. Good discriminative power was found by Wieske et al. (2015) for the extensor digitorum brevis peroneal compound muscle action potential (CMAP) amplitude (AUC: 0.80 95 % CI 64–96 %), and the ulnar sensory nerve action potential (SNAP) amplitude had excellent discriminative power (AUC: 0.93 95 % CI 84–100 %), they have good sensitivity and specificity whether used alone or in combination. Kelmenson et al. (2018) used the most accurate cut-off range of peroneal nerve and sural nerve reported by Moss et al. (2014) (0.65 mV for peroneal and 4μV for sural, pointed out that the sensitivity and specificity of peroneal motor nerve in diagnosing CIP were 94 % and 91 %, while the sensitivity and specificity of sural sensory nerve were 100 % and 42 %. Tankisi et al. (2021) used a method developed by Z'Graggen and Bostock (2009) to assess muscle excitability in vivo by automatically record muscle velocity recovery cycles, which was measured by direct muscle stimulation and electromyographic needle recording. Muscle velocity recovery cycles and frequency ramp parameters show abnormal muscle fiber membrane characteristics with up to 100 % sensitivity and specificity for the diagnosis of CIM. Rodriguez et al. (2022) validated the diagnostic accuracy of muscle velocity recovery cycles on day 10 of ICU admission for CIM with 90 % in critically ill COVID -19 patients with acute respiratory distress syndrome (sensitivity 100 %; specificity 71.4 %).

In terms of diagnostic imaging, Mitobe et al. (2019) using the skeletal muscle index (cm^2/m^2) at ICU admission by dividing the cross-sectional area (cm^2) of the skeletal muscle at the level of the third lumbar vertebra (L3) by the square of the patient's height (m^2) on computer tomography was used to assess ICU-AW, when its threshold is 44.1 cm^2/m^2, The sensitivity was 78.3 % and the specificity 25.0 %. Yuan et al. (2021) analyzed the cross-sectional area of the erector spinae muscle corresponding to the the 12th thoracic vertebra by computer tomography, and found that on the 7th day of ICU admission, when the optimal cut-off value of erector spinae muscle cross-sectional area loss was 4.14 cm^2, the sensitivity and specificity were 85.42 % and 67.86 %, respectively; when the optimal cut-off value of erector spinae muscle cross-sectional area loss rate was 11.5 %, the sensitivity and specificity were 89.58 % and 73.21 %, respectively. Maramattom (2022) employed magnetic resonance imaging to distinguish between patients with CIM and those with Guillain-Barre syndrome. When magnetic resonance imaging showed muscle involvement on short tau inversion recovery imaging, the result was considered CIM-positive, with a sensitivity of 100 % and a specificity of 85.7 %.

In terms of other diagnostic tools, considering that the plasma growth differentiation factor-15 is one of the important regulators of protein synthesis/catabolism balance, Xie et al. (2020) speculated that it may be able to distinguish between ICU-AW and non-ICU-AW patients. In this study, plasma growth differentiation factor-15 demonstrated an AUC of 0.904, an optimal cut-off value of 1722 pg/ml, with a sensitivity of 94.0 % and a specificity of 71.1 %. Tzanis et al. (2011) investigated the diagnostic accuracy of maximal inspiratory pressure for ICU-AW, identifying cut-off points of 36 cmH_2O and 40 cmH_2O, with sensitivities of 88 % and 84.6 % and specificities of 76 % and 90.9 %, respectively. Besides, Schmidt et al. (2019) uniquely used maximal expiratory pressure, recommending a cut-off of 34 cmH_2O, achieving 80.8 % sensitivity and 90.9 % specificity, and reported an MIP of 40 cmH_2O with a sensitivity of 84.6 % and specificity of 90.9 %. Wieske et al. (2014) used three easily available parameters as an early prediction model for ICU-AW, and its AUC was 0.71, which had good discriminative performance, but lacked external validation. This review summarizes the testing methods, observational parameters, diagnostic thresholds, and diagnostic accuracy of each diagnostic tool from the included studies, as detailed in Table 4.

The diagnostic accuracy of ultrasound technology is discussed in more detail in the following section.

In addition to the studies mentioned in Result 3.5, some included studies did not show the diagnostic accuracy, but pointed out the value of reference tests in the diagnosis of ICU-AW. Inan et al. (2022) evaluated ICU-AW in stroke patients by electrodiagnostic testing,

Table 4
Summary of diagnostic accuracy of included studies.

Diagnostic tools	Testing methods	Observational parameters	Diagnostic threshold	Diagnostic accuracy
Manual muscle Testing	MRC scoring system	MRC sum score	48	kappa 0.60–0.76
			40	AUC 0.97; sensitivity 89.3 %; specificity 95.5 %
			36	kappa 0.93
	Handgrip dynamometry	Handgrip strength	4 kg for women and 7 kg for men	sensitivity 88.2–100 %; specificity 90.9–100 %
			7 kg for women and 11 kg for men	AUC 0.73–0.89; sensitivity 72–100 %; specificity 45–92 %; kappa 1
			9.5 kg for women and 13.2 kg for men	AUC 0.88–0.93; sensitivity 79–92 %; specificity 77–83 %
Electrophysiological tests	NCS	The compound muscle action potential amplitude and duration of single or multiple nerves, sensory nerve action potential amplitude and the presence of abnormal spontaneous activity	Not unified	AUC 0.69–0.93; sensitivity 47.1–100 %; specificity 42–91 %
	Direct muscle stimulation	Muscle velocity recovery cycles	Not unified	AUC 0.60–0.91; sensitivity 47.1–100 %; specificity 30.8–100 %
Imaging	Abdominal computer tomography scans	Skeletal muscle index	44.1 cm^2/m^2	AUC 0.75; sensitivity 78.3 %; specificity 25.0 %
		Muscle cross-sectional area loss ratio	Not unified	sensitivity 85.42–89.58 %; specificity 67.86–73.21 %
	Magnetic resonance imaging	Magnetic resonance imaging muscle hyperintensities	Muscle short tau inversion recovery imaging	sensitivity 100 %; specificity 85.7 %
Ultrasound	Nerve ultrasound	The thickness and cross-sectional area of multiple nerves	Not unified	AUC 0.51–0.67
	Muscle ultrasound	The thickness and cross-sectional area of multiple muscles	Not unified	AUC 0.51–0.82; sensitivity 46.7–87.1 %; specificity 48.8–80.8 %
		Muscle thickness and cross-sectional area loss ratio	Not unified	AUC 0.68–0.89; sensitivity 36.5–90.5 %; specificity 46.2–100 %
		The global mean Heckmatt score	Not unified	AUC 0.79–0.88; sensitivity 70.7–100 %; specificity 57–84.8 %
		Muscle grayscale level calculation using automated histogram analysis	74	AUC 0.76; sensitivity 69.2 %; specificity 75.0 %
		Change in rectus femoris pennation angle	Not reported	AUC 0.82
	Shear wave ultrasound elastography, superb microvascular imaging, contrast-enhanced ultrasound	Shear wave elasticity, maximum and minimum contrast-enhanced ultrasound, muscle thickness and area, subcutaneous tissue thickness	Not unified	AUC 0.50–0.99; sensitivity 61.5–96 %; specificity 52.9–100 %
Other diagnostic tools	Serum biomarkers	Plasma growth differentiation factor-15	1722 pg/ml	AUC 0.9; sensitivity 94 %; specificity 71.1 %
		Plasma monocyte chemoattractant protein-1	206.3, 410.9, 239.5 ng/L	AUC 0.73–0.89; sensitivity 64–87.1 %; specificity 54.4–96.1 %
	An unidirectional valve method	Maximum inspiratory pressure	36 cmH2O; 40 cmH2O	sensitivity 88 %–84.6 %; specificity 76 %–90.9 %
		Maximum expiratory pressure	34 cmH2O	AUC 0.94; sensitivity 80.8 %; specificity 90.9 %

(*continued on next page*)

Table 4 (*continued*)

Diagnostic tools	Testing methods	Observational parameters	Diagnostic threshold	Diagnostic accuracy
Combined diagnostic tools	Easily available parameters	Highest lactate, treatment with any aminoglycoside and age	Not reported	AUC 0.71
	Muscle echogenicity combined with plasma inflammatory factors	The global mean Heckmatt score, serum interleukin-6 and procalcitonin	Not reported	AUC 0.89
	Handgrip dynamometry combined with diaphragmatic ultrasound	Grip strength value combined with diaphragmatic excursion or thickening fraction	Grip strength value 9.1 kg; diaphragmatic excursion 2.23 cm; thickening fraction 28 %	AUC 0.90–0.95; sensitivity 84–88 %; specificity 81–88 %

MRC: Medical Research Council; AUC: area under the curve; NCS: nerve conduction studies.

histopathology, and assessment of respiratory complex activities, then discovered the CMAP amplitude of vastus medialis and the CMAP duration of abductor digiti minimi is closely related to ICU-AW and may aid in early diagnosis. Daste et al. (2023) concluded that ICU-AW had a greater impact on the proximal upper limb, and observed specific magnetic resonance imaging findings of the shoulder girdle in patients with COVID-19-related ICU-AW discharged from hospital for one month. Bilateral, peripheral muscular edema-like magnetic resonance imaging signals of the shoulder girdle were found in 92 % of patients. This suggests that shoulder magnetic resonance imaging may help clinicians distinguish between critical illness myopathy and other more serious diagnoses. Ding et al. (2022) explored plasma monocyte chemoattractant protein-1 of sepsis patients admitted to ICU at day 1, 4, and 7, which proved to be of certain value for the diagnosis of ICU-AW.

3.7. Ultrasound for ICU-AW diagnosis

Most studies have chosen to use ultrasound to observe the thickness and cross-sectional area of multiple muscles or nerves. Witteveen et al. (2017) utilized quantitative neuromuscular ultrasound to assess ICU patients with and without ICU-AW at the time of awakening (median 7-9 days after ICU admission), results showed lower diagnostic accuracy for all muscular and neurological parameters, with AUC values ranging from 51.0 % to 68.0 %. Haijun et al. (2020) concluded that flexor carpi radialis thickness, rectus femoris (RF) thickness, and tibialis anterior thickness had diagnostic value for ICU-AW, with AUC and 95 % CI of 0.742 (0.582-0.866), 0.787 (0.631-0.899), and 0.817 (0.665-0.920), respectively, but thickness of biceps brachii (BB) has no diagnostic value for ICU-AW. Zhang et al. (2021) used ultrasound to measure the muscles of BB, vastus intermedius (VI) and RF, the results showed that on the 10th day after ICU admission, the changes of thickness and cross-sectional area of RF on the right side and the changes of thickness of VI on both sides had good AUC values, ranging from 0.734 to 0.888. Li et al. (2020) explored the application of quadriceps femoris thickness and cross-sectional area in ICU-AW diagnosis in more detail, and the results were as follows: on the 3rd day after ICU admission, the optimal cut-off value of rectus femoris cross-sectional area (RFcsa) atrophy rate for discrimination of ICU-AW was 6.0 %, with a sensitivity of 66.7 % and a specificity of 77.8 %; on the 5th day, the optimal cut-off value of RF thickness atrophy rate was 14.5 %, with a sensitivity of 77.8 % and a specificity of 66.7 %; on the 7th day, the optimal cut-off value of VI thickness atrophy rate was 19.9 %, with a sensitivity of 70.6 % and a specificity of 87.5 %. Zeng et al. (2023) also suggested that the bedside ultrasound quantitative evaluation of lower extremity muscle is helpful for the early diagnosis of ICU-AW, and the AUC was the highest at 0.844 when the cut-off value of thickness loss rate of RF was 18.5 % on the 7th day of ICU admission. Ding et al. (2022) used ultrasound to measure thickness and cross-sectional area in RF and VI of septic patient population, and the results showed that thickness of RF had diagnostic value for ICU-AW on the 7th day of ICU admission, with an AUC of 0.688 (95 % CI 0.526–0.849), a sensitivity of 66.7 %, and a specificity of 68.4 % at a cut-off of 0.41 cm. Moreover, the study results of Xie et al. (2020) showed that when the RFcsa loss was the optimal cut-off value of 0.25 cm^2, the AUC was 0.873, the sensitivity was 88.0 %, and the specificity was 80.0 %, while when the optimal cut-off value of RFcsa decline rate was 12.75 %, the AUC was 0.886, and the sensitivity was 84.0 %. The specificity was 84.0 %. The study by Yang and Chen (2022) also confirmed that RFcsa atrophy rate contributes to the diagnosis of ICU-AW, in their study, when RFcsa atrophy rates were 15.82 % and 8.49 % on day 3 and 5, the AUC was 0.870 and 0.827, respectively. The effectiveness of ultrasound monitoring of respiratory muscles is also being explored. Zhang et al. (2024) explored the diagnostic value of grip strength, ultrasound measured diaphragmatic excursion, and diaphragm thickening fraction in ICU-AW. When the diaphragmatic excursion $<$ 2.23 cm cut-off was used, the sensitivity was 87.1 % and the specificity was 48.8 %, and when the diaphragm thickening fraction $<$ 28 % cut-off was used, the sensitivity was 71 % and the specificity was 74.4 %.

The global mean Heckmatt score (MHS) is a qualitative method for assessing muscle echogenicity measured by ultrasound with four grades, which is calculated by averaging all Heckmatt scores of each single muscle in every participant. The MHS was used by Kelmenson et al. (2018) to quantify muscle echogenicity, with a muscle echogenicity score of at least grade II for any muscle as diagnostic criteria, and a sensitivity of 82 % (95 % CI 48–98 %) and specificity of 57 % (95 % CI 43–70 %) for diagnosing possible CIP. Klawitter et al. (2022) used the MHS at day 10 of ICU admission to identify ICU-AW patients, with the optimal cut-off value of 2.2, sensitivity of 86 %, and specificity of 60 %. The study of Chen et al. (2024) evaluated muscle echogenicity in 8 limb muscles, including bilateral BB, bilateral brachioradialis, bilateral RF, and bilateral tibialis anterior. The results showed that the AUC was 0.838, the sensitivity was 70.7 %, and the specificity was 84.8 % when the optimal cut-off value of the global Heckmatt score was 12 on day 7. In the study of Elkholy et al. (2024), When at least two tested muscle MHS showed grade II-IV, the ultrasonographic muscle architecture was considered abnormal, and compared with EMG, the sensitivity and specificity of the diagnosis of CIM were 100 % and 75 %. In

addition to the above studies using MHS to quantify muscle echogenicity, Naoi et al. (2022) conducted a retrospective study using software to perform grayscale histogram analysis to calculate muscle echogenicity and showed that the cut-off level for muscle echogenicity of the upper arm to predict ICU-AW was 74.00, the specificity was 75.0 %, and the sensitivity was 69.2 %, while the utility of muscle echogenicity in the lower leg was controversial in comparison.

Because severe systemic inflammatory responses may be associated with the development of ICU-AW, inflammatory biomarkers are also thought to be able to help diagnose ICU-AW (Li et al., 2024). Patejdl et al. (2019) only demonstrated that the combination of muscle ultrasound and inflammatory biomarkers may be helpful in diagnosing ICU-AW and predicting the long-term prognosis of critical illness, but did not validate its diagnostic effect in ICU-AW alone. Chen et al. (2024) showed that the combined use of the global total Heckmatt score, Serum interleukin-6 and procalcitonin could help improve the diagnostic accuracy of ICU-AW.

With the development of ultrasound technology, Hernández-Socorro et al. (2021) used three new ultrasound methods to evaluate the quadriceps RF muscle with shear wave elastography, superb microvascular imaging, contrast-enhanced ultrasound to explore its application value in diagnosing long-term critical patients with ICU-AW, detailed diagnostic accuracy is presented in Table 4. The results showed that these three methods could not only observe muscle thickness and cross-sectional area, muscle stiffness and muscle perfusion were also observed, thus helping to diagnose ICU-AW by assessing the muscle quantity and quality wasting process. The change in pennation angle of ultrasound detection is also being explored for ICU-AW diagnosis. According to Paolo et al. (2022), both quadriceps and respiratory muscles suffered quality loss during the first week of mechanical ventilation in ICU patients. The change in pennation angle between day 7 and day 1 can best diagnose ICU-AW, and its AUC is 0.82 (95 % CI 0.69-0.95).

3.8. Timing of diagnosis

The included studies had different timings for the diagnosis of ICU-AW, some of which used multiple time points for index tests, and some studies did not have a clearly defined time point for diagnosis.

3.9. Cost of diagnosis

The use of the MRC score to assess ICU-AW does not require additional cost to the patients, but generally requires 15–30 min for healthcare professionals to test 12 muscles (Hermans et al., 2012). In contrast, handgrip dynamometry is a simple and quick tool that takes just a few minutes to screen for the presence of ICU-AW (Parry et al., 2015). Performing a comprehensive electrophysiological examination of multiple nerves to diagnose ICU-AW is expensive and time-consuming, typically taking up to 90 min to complete, but single nerve conduction can provide significant time savings, requiring only approximately 5 to 10 min (Moss et al., 2014). Although the implementing EMG does not take a long time, but it is expensive, moderately invasive, requires the patient to remain awake and cooperative, and requires a qualified professional to perform the procedure (Schmidt et al., 2019). Similarly, muscle biopsies are invasive, expensive, painful, and require a professional technician to perform. Furthermore, ultrasound also requires the operator to have certain qualifications, but in contrast, ultrasound is rapid, repeatable, and non-invasive.

4. Disscussion

4.1. Methodology

Methodologically, since the object of this study is a diagnostic and evaluation tool for ICU-AW and does not involve intervention measures, all 38 literatures included after literature quality evaluation are observational studies. It is worth mentioning that since 25 of the observational studies were also diagnostic studies, we also used the diagnostic study-specific quality assessment tool QUADAS-2 to assess their risk of bias and applicability. Therefore, the quality of the included studies is good, and it has certain scientificity and credibility.

In terms of study design, some studies (Braganca et al., 2019; Connolly et al., 2013; Hermans et al., 2012; Hough et al., 2011; Parry et al., 2015) evaluated the inter-observer consistency of potential diagnostic tools with existing gold standards, while some studies (Attwell et al., 2022; Daste et al., 2023; Hirose et al., 2022; Inan et al., 2022; Patejdl et al., 2019; Raghig et al., 2010) only explored the feasibility and relevance of index tests, and the remaining studies explored the diagnostic effectiveness of index tests compared to reference tests. The index test for diagnosing ICU-AW was based on ROC curve analysis. It is generally considered that an AUC value between 0.90 and 1 is excellent, between 0.80 and 0.90 is good, between 0.70 and 0.80 is fair, between 0.60 and 0.70 is poor, and below 0.60 is failed (Wieske et al., 2015). On the other hand, some studies made a general diagnosis of ICU-AW, while others subdivided its subtype, distinguishing between CIM,CIP or CIPNM.

Moreover, the incidence of ICU-AW varies among critically ill patients. In the included studies, mechanically ventilated ICU patients were the most commonly studied group, followed by patients with sepsis or multiple organ dysfunction syndrome, and critically ill patients with COVID-19. This variation can be explained by the underlying pathophysiology. Sepsis or multiple organ dysfunction syndrome is thought to induce weakness through complex pathophysiological mechanisms involving severe inflammatory responses, microcirculatory disturbances, cellular changes, metabolic alterations, and electrical imbalances (Elkholy et al., 2024). The high prevalence of neuromuscular diseases in COVID-19 patients may be related to multiple risk factors for ICU-AW, rather than COVID-19 infection alone (Bax et al., 2021). Furthermore, there is an interrelationship between mechanical ventilation and ICU-AW, though the underlying mechanisms remain unclear. It is also important to note that it remains uncertain whether the results of observational studies in these specific populations can be generalized to the broader population of critically ill patients.

4.2. Potential diagnostic tools for ICU-AW

Clinical, electrophysiological, imaging, and histological approaches have been used to diagnose ICU-AW (Tzanis et al., 2011). To date, the most common diagnostic modalities for ICU-AW include MRC score, NCS, EMG, direct muscle stimulation, neuromuscular ultrasound, and muscle/nerve biopsy. The results of this review indicate that due to differences in study populations and reference tests, the diagnostic accuracy of current ICU-AW diagnostic tools varies across studies. Nevertheless, each diagnostic tool demonstrates its potential in diagnosing ICU-AW and its subtypes.

ICU-AW was named based on the clinical observation of limb weakness in critically ill patients. As a result, the most commonly used diagnostic method for ICU-AW became the assessment of limb muscle strength, primarily using the MRC strength scale. In order to simplify the evaluation process and save time, the handgrip dynamometry method was developed as a more efficient alternative. In this systematic review, both manual muscle testing methods, handgrip dynamometry and the MRC score, demonstrate good diagnostic efficacy. They are non-invasive, inexpensive, and easy to implement. However, a common limitation is that they can only be applied to awake and cooperative patients. Furthermore, limb evaluation may be hindered in cases of trauma, burns, or medical treatments involving devices. Due to these constraints, many critically ill patients are not diagnosed early, leading to missed opportunities for early intervention. Additionally, while handgrip dynamometry is faster and more user-friendly, it exhibits significant variability across gender and age groups. The optimal cut-off value for this method still requires further investigation and external validation in future studies.

As awareness of ICU-AW grows, more researchers recognize the importance of identifying its subtypes. The current differential diagnosis of the subtypes of ICU-AW, CIM and CIP, must be performed by routine nerve conduction studies, electromyography, and muscle biopsy, which can also be verified in Table 3 (Tankisi et al., 2021). The accepted diagnostic criteria for CIP proposed in previous studies are: (1) MRCss < 48; (2) CMAP amplitudes < 80 % of the lower limit of normal in ≥ 2 nerves without conduction block; (3) SNAP amplitudes < 80 % of the lower limit of normal in ≥ 2 nerves (Jung et al., 2020). CIM is characterized by a reduction in muscle membrane excitability, accompanied by an increased duration of CMAP amplitude, as well as a preferential loss of myosin and its associated proteins (Marrero et al., 2020). CIM defines that when the MRCss is <48 in critically ill patients, CMAPs were of low amplitude together with an increased duration, with a normal sural SNAP (Attwell et al., 2022). Certainly, before applying these diagnostic criteria, non-neuromuscular causes of limb weakness, such as cardiopulmonary diseases or medication side effects, should be excluded (Latronico and Bolton, 2011). Due to the long time required for complete NCS and the presence of environmental electrical interference or venous or arterial ducts that impede nerve contact, NCS is not always possible on bilateral nerves, so many researchers have attempted to explore other electrophysiological diagnostic methods (Moss et al., 2014). Jung et al. (2020) attempted to explore a simplified diagnostic criterion for CIP, with NCS performed on the motor and sensory nerves in combination with the MRC sum score, but its diagnostic accuracy has not been confirmed. On the other side, although Attwell et al. (2022) validated the feasibility of the peroneal nerve test and sural SNAP for the early detection of CIP and CIM in the screening of patients with septic shock and mechanical ventilation for >72 h, clinical, NCS, and EMG differentiation between CIP and CIM is sometimes difficult. NCS and EMG also have limitations, complete electrodiagnostic testing is expensive, moderately invasive, operator-dependent, limited by edema, coagulopathy, electrical interference, and complete EMG examination requires alert and cooperative patients (Elkholy et al., 2024; Tzanis et al., 2011). Furthermore, since critical illness neuropathy and myopathy may co-exist, it is often difficult to differentiate these using electrophysiological studies alone, or to determine which predominates in a given patient (Raghig et al., 2010). It is also worth noting that, prolonged neuromuscular blockade due to non-depolarizing neuromuscular blockers in critically ill patients must be considered in differential diagnosis (Bax et al., 2021).

Direct muscle stimulation has also been rapidly developed in recent years. In addition to the studies by Tankisi et al. (2021) and Rodriguez et al. (2022) mentioned above, muscle velocity recovery cycles obtained by direct muscle stimulation have good diagnostic accuracy. Hirose et al. (2022) use The excitation-contraction coupling time to detect reduced muscle membrane excitability in the early stage of CIM. Motor related potential was recorded using an accelerometer attached to the base of hallux after tibial nerve stimulation, and excitation-contraction coupling time was measured from the latency difference between soleus CMAP and motor related potential. This study showed that 87.5 % of patients with CIM had excitation-contraction coupling impairment on the 3 day after admission to the ICU, suggesting that it may be a parameter that predicts the development of CIM.

Imaging diagnostic tools are still being explored. The imaging diagnostic tools included in this study are based on the observation of skeletal muscle area and mass, but there is no unified standard.

Detection of nerve and muscle changes early in the course of illness will aid in our understanding of the biology and pathophysiology of ICU-AW to help with diagnosis (Bunnell et al., 2015). Previous studies have shown that neuromuscular changes can occur at a very early stage, even before electroneurographical changes can be observed by sonography (Bulinski et al., 2022). Coupled with the fact that ultrasound is cheap, fast, and repeatable, ultrasound has become the most highly regarded diagnostic tool for ICU-AW. The included 17 studies exploring ultrasound as a diagnostic tool observed skeletal muscle, respiratory muscle, nerve and blood vessel, most of the observational indicators were cross section and diameter, and a few were echogenicity and pennation angle. In muscle, RF is the most widely studied and thought to reflect ICU-AW, followed by VI. Besides, Hernández-Socorro et al. (2021) are the only studies that used superb microvascular imaging and contrast-enhanced ultrasound to visualize blood vessels to probe muscle perfusion. Although ultrasound has been shown to be helpful in the diagnosis of ICU-AW, no two studies have identified the same diagnostic criteria due to individual differences and inconsistent observation subjects and time points. Therefore, a large sample size multi-center study should be conducted in the future.

4.3. Selection of diagnostic tools for ICU-AW

The diagnosis of ICU-AW is undoubtedly challenging, not only due to limitations in diagnostic techniques but also because of its underlying pathophysiology. The development of ICU-AW is a dynamic process, during which both histological and electrophysiological characteristics evolve. The difficulty in determining the specific stage of the condition contributes to the diagnostic challenge. For example, in the early stages of CIM, the loss of myosin precedes a decrease in muscle membrane excitability. During recovery, electrophysiological studies show an increase in CMAP amplitude and normalization of duration, while muscle biopsies reveal a reduction in necrosis and the gradual restoration of myosin filaments. Due to these differences in temporal patterns, all diagnostic criteria should be regarded with caution (Latronico and Bolton, 2011; Marrero et al., 2020).

Each of the diagnostic tools mentioned in this review has its advantages and disadvantages. Muscle biopsy is expensive and invasive. Due to its practicality and low cost, most ICUs prefer to use manual muscle test (Hermans et al., 2012). However, Richmond Agitation and Sedation Scale between -1 and 1 is a prerequisite for manual muscle test, as most patients in the ICU often fail to perform muscle strength assessment due to persistent coma and delirium (Hough et al., 2011). In order to ensure the attention and comprehension of muscle strength assessment in ICU patients, the daily interruption of sedation should be recommended. Furthermore, as a simple and quick method of muscle strength assessment, handgrip dynamometry not only requires the patient to be awake and cooperative, but also requires the patient to have antigravity strength in the elbow and wrist, and age, weight and gender may affect the threshold. In addition, if you want to distinguish CIP from CIM, it is currently necessary to rely on electrophysiological examination or muscle biopsy, and the patient's condition and economic situation should be fully considered before use. Imaging diagnostic methods have not been widely used and validated, so their applicability and credibility should be carefully considered when used. After weighing the pros and cons, qualitative and quantitative muscle ultrasound is increasingly used to assess neuromuscular atrophy and architecture changes in critically ill patients (Elkholy et al., 2024). Nevertheless, the use of ultrasound is still lacking in standard and uniform, so clinical health professionals should consider the ultrasound, manual muscle test, electrophysiology or muscle biopsy results comprehensively when diagnosing ICU-AW. Other novel diagnostic techniques, such as serum inflammatory markers, are also being explored, and it is expected that these tools will enable early diagnosis of ICU-AW for the benefit of critically ill patients in the future.

In an ideal scenario, the diagnosis of ICU-AW should begin with manual muscle testing to assess the presence of limb weakness, followed by an analysis to determine whether the weakness is attributable to critical illness. At this stage, it is crucial to exclude non-neuromuscular causes. Subsequently, electrophysiological tests, muscle or nerve biopsies should be employed to investigate the origin of the weakness, distinguishing between CIP, CIM, and CIPNM. However, clinical practice often presents various challenges, such as patients being unable to cooperate with the tests or the unavailability of certain diagnostic tools. Additionally, identifying ICU-AW before the onset of weakness is also one of the key goals that researchers continue to pursue.

4.4. Implications for practice and future research

Early diagnosis is critical to understanding the incidence and etiology of ICU-AW, providing care and interventions, and improving prognosis (Hough et al., 2011). This study summarized the studies on the diagnosis of ICU-AW from 2010 to 2024 through a systematic literature search. We summarize in detail the observational methods and diagnostic accuracy of potential ICU-AW diagnostic tools in the included studies. Furthermore, we discuss the advantages, limitations, and applicable contexts of each diagnostic tool, and offer a recommended process for clinical health professionals in selecting the most appropriate diagnostic tools for ICU-AW diagnosis. Finally, this review provides guidance for advancing the development of new diagnostic tools or the standardization of existing ones.

4.5. Strengths and limitations of this review

The strength of this review lies in the use of standardized methods to summarize potential diagnostic tools for ICU-AW and their diagnostic accuracy, providing evidence for clinical implementation and intervention. The limitation is that we were not able to perform quantitative analyses due to the diversity and heterogeneity of potential diagnostic tools. Furthermore, we focused only on clinical phenomena, without statistical outcome measures, follow-up outcomes, and survivor quality of life.

5. Conclusion

There is growing recognition that ICU-AW is associated with increased mortality, prolonged treatment, impaired function at discharge, and an increased financial burden on healthcare facilities and patients. How to diagnose ICU-AW early and intervene has become a major problem. Focusing on the critically ill patient population, this systematic review summarizes the pathogenesis, gold standard, potential diagnostic tools, and diagnostic efficacy of ICU-AW, and identifies the strengths and limitations of these diagnostic tools. In the future, we should develop simple, low-risk and high diagnostic accuracy tools for critically ill patients with the credible gold standard as the control, and at the same time carry out external verification to formulate scientific and unified diagnostic thresholds.

Data availability

The retrieval data of this systematic review can be obtained from the corresponding author.

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CRediT authorship contribution statement

Chen Xin: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Yubiao Gai:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Lili Wei:** Writing – review & editing, Formal analysis. **Yanqiu Wang:** Validation, Methodology, Formal analysis. **Yuhong Luo:** Visualization, Resources, Data curation. **Binru Han:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Supplementary materials

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