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Review

Magnesium Depletion Score and Its Potential as an Indicator of Chronic Magnesium Deficiency in Critically Ill Patients

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Abstract

Chronic latent magnesium (Mg) deficiency is a subclinical chronic depletion of Mg body stores. Although this deficiency contributes significantly to morbidity and mortality in critically ill patients, its diagnosis remains difficult because current clinical practice lacks a simple, rapid, and reliable single measurement to detect its presence. The magnesium depletion score (MgDS) is a recently developed scoring system to aid clinical prediction of chronic Mg deficiency. This clinical parameter is easily calculated from several factors: chronic use of diuretics and proton pump inhibitors, alcohol abuse, and kidney disease. These MgDS factors lead to a negative Mg metabolic balance and eventual Mg depletion, primarily due to urinary wasting. The main goal of this review was to investigate the existing literature on the MgDS and consider its potential clinical usefulness as a preliminary indicator of chronic latent Mg deficiency in the critically ill. We searched PubMed to conduct a narrative literature review on the MgDS and its potential use in critically ill patients. The identified references spanned the period from inception in August 2021 through August 21, 2026. We identified 80 relevant papers reporting statistically significant associations between the MgDS and various chronic diseases. These included 77 observational clinical studies, 28 cohort studies (24 prospective and 4 retrospective), 49 cross-sectional studies, and 1 systematic review and meta-analysis. Basic research articles were not found, and case reports were excluded. Most studies used data from the National Health and Nutrition Examination Survey (NHANES). Strong correlations link the MgDS to increased risk of many health conditions, including cardiovascular (17 studies), respiratory (6 studies), neuropsychiatric (11 studies), metabolic (22 studies), urogenital (11 studies), rheumatic (5 studies), and some immune-mediated and age-related diseases (7 studies). These findings confirm that chronic Mg deficiency can lead to a wide range of clinical consequences, chronic conditions, and adverse events. Since its introduction, the MgDS has proved to be a promising clinical indicator of chronic latent Mg deficiency. However, a literature search did not reveal any clinical studies on the MgDS in critically ill patients. After evaluating the advantages and disadvantages of using the MgDS, the authors believe that combining the MgDS with serum total Mg^{2+} and ionized Mg^{2+} levels could provide a valid assessment of Mg^{2+} status and significantly improve detection of negative Mg^{2+} balance associated with various acute and chronic diseases in the critically ill. Moreover, incorporating the MgDS as a prognostic indicator into critical care clinical practice would improve risk stratification and patient management, thereby reducing the adverse health effects of chronic Mg^{2+} deficiency.

Keywords: magnesium depletion score; chronic magnesium deficiency; critically ill

1. Introduction

Magnesium (Mg) is an essential mineral nutrient for living organisms and a crucial electrolyte (Mg^{2+}). In the human body, bones and soft tissues are major storage sites for Mg. Intestinal absorption, renal handling, and tissue uptake and release of Mg^{2+} are regulated by parathormone, calcitonin, and vitamin D. In the blood, total Mg^{2+} (tMg^{2+}) exists in non-filterable (plasma protein-bound) and filterable forms. The filterable fraction comprises complexed, anion-bound Mg^{2+} and the free, unbound, ionized Mg^{2+} fraction (iMg^{2+}). In the kidneys, approximately 70% of circulating Mg^{2+} is filtered by the glomeruli, and most of the filtered Mg^{2+} (up to 96%) is reabsorbed into the bloodstream by the renal tubules. Therefore, healthy kidneys are essential for normal Mg balance. Renal tubular reabsorption of filtered Mg^{2+} is extensive and includes primarily passive, paracellular transport (mediated by claudins: CLDNs, types 2, 10a, 16, and 19) in the proximal tubule and the cortical segment of the thick ascending limb of the loop of Henle, and active transcellular transport mechanisms (mediated by Mg^{2+}-selective ion channels transient receptor potential melastatin, TRPM types 6 and 7) in the distal convoluted tubule. Final fractional excretion of Mg^{2+} (FE_{Mg}) is approximately 4%, leaving only a small fraction of filtered Mg^{2+} to be excreted in the final urine. Hence, proper Mg^{2+} processing by the kidneys is crucial for preventing excessive urinary wasting and maintaining balanced Mg metabolism and adequate Mg status in the body. A balanced diet and tightly

regulated intestinal Mg handling are also required, but Mg homeostasis is still largely controlled by the kidneys [1].

Mg exerts several physiological effects on many, if not virtually all, organ systems. Notably, Mg has an overall calming, stabilizing, and neuroprotective effect across the nervous system, reducing hyperexcitability, anxiety, and depression, while improving sleep quality and cognition. Moreover, Mg helps regulate cardiac function, blood pressure, and arterial wall elasticity, promotes vasodilation and bronchodilation, and helps prevent atherosclerosis and thrombosis. Mg also supports relaxation of myocardial, skeletal, and smooth muscle and helps prevent muscle cramping and preterm labor. Additionally, Mg helps maintain normal neuromuscular excitability, mediates the release and function of various neurotransmitters, exerts immunomodulatory and antioxidant effects, reduces the risk of chronic inflammation, enhances insulin sensitivity, and supports overall metabolic health [2].

Disorders of Mg metabolism more often result in a negative than a positive balance. Negative Mg balance depletes tissue stores more than the extracellular fluid compartment and does so earlier, but the latter is difficult to measure in clinical settings. Intracellular Mg^{2+} depletion can be found, for example, in liver cirrhosis, where a significant decrease in hepatic Mg content can be measured experimentally; however, this requires a prior liver biopsy [3]. Mg deficiency or depletion from the body usually results from prolonged lack of dietary intake, intestinal absorption, tubular reabsorption, and/or bone resorption. The initial phase is often hidden and clinically unmanifested, as it takes a long time for Mg body stores to be significantly depleted. Manifestations depend on the severity of the condition, but mild to moderate Mg deficiency can present with a variety of vague symptoms or no particular symptoms at all. Being seemingly asymptomatic in clinical practice (as no overt presentations draw clinical attention to such a state), chronic latent Mg deficiency is mostly completely disregarded as a health condition [4].

Even when attempting to diagnose it, chronic subclinical Mg deficiency is difficult to detect or evaluate. Based on serum tMg^{2+} and intracellular Mg^{2+} concentrations in red blood cells (RBC), Mg deficiency can be normomagnesemic (type I) or hypomagnesemic (type II), with four distinct consecutive stages of chronic Mg deficiency. Stage 4 is the most severe and is characterized by decreases in both tMg^{2+} and RBC Mg^{2+} [5]. The initial stages are mild to moderate and apparently latent, owing to the absence of noticeable clinical signs and symptoms. At that point, serum tMg^{2+} levels may still be normal or only begin to decrease (initial hypomagnesemia can be latent). Therefore, measuring both tMg^{2+} and RBC Mg^{2+} in stage 1 may yield normal findings, since the first to respond to a developing negative Mg metabolic balance is one of its major body stores—the bone mineral matrix. Unfortunately, even an unmanifested chronic Mg deficiency does not rule out potential links to health risks arising from the insufficiency of many Mg^{2+}-mediated bodily functions. As Mg depletion deepens, signs and symptoms begin to develop. Common manifestations of overt symptomatic Mg deficiency include reduced appetite, nausea, vomiting, fatigue, weakness, muscle cramps, decreased Ca^{2+} and K^{+} levels, worsening insulin resistance, tremors and numbness. Severe presentations may include tetany, ventricular arrhythmias, coronary spasms and epileptic seizures [6].

Several unfavorable factors lead to frequent failure to determine the precise Mg status in a patient and to understand the dynamics of its measurable fractions, including an initial lack of clinical interest in Mg^{2+}, neglect of the frequent shifts between bound and unbound Mg^{2+} fractions (*e.g.*, in acid–base disorders, disorders of plasma proteins, and changes in plasma complexing anions, all common in critically ill patients), and the demanding nature of the diagnostic procedure. Diagnosing and staging Mg deficiency require several clinical laboratory measurements. Additionally, dietary Mg intake can be evaluated; however, this is usually conducted for epidemiological, nutritional, and public health research. Laboratory tests are more convenient in daily clinical practice, yet these tests are not routinely performed and, when available, must be specifically ordered based on clinical suspicion. Finally, the procedure can be time-consuming and unsuitable for urgent conditions and emergency practice.

Nevertheless, to restore lost Mg balance and eliminate the additional health risks associated with Mg deficiency in a patient, the condition must first be properly addressed. Although this type of mineral deficiency is increasingly prevalent worldwide [7], no simple, rapid, single standardized test exists that is both accurate and sensitive enough to determine whole-body Mg status [8]. Therefore, the question of how to test for a negative Mg balance in the body is not easy to answer. A good functional biomarker seems to be lacking [9]. Table 1 lists the most clinically relevant tests currently available.

Table 1. Clinically available tests to detect chronic latent magnesium deficiency in the body.

Measuring serum concentration (level) of total Mg^{2+} (tMg^{2+})
Measuring serum concentration (level) of ionized Mg^{2+} fraction (iMg^{2+})
Measuring intracellular red blood cell (RBC) Mg^{2+} concentration
Measuring 24-hour urinary Mg^{2+} output
Conducting magnesium tolerance test (MTT)
Calculating magnesium depletion score (MgDS)

tMg^{2+}, total Mg^{2+}; iMg^{2+}, ionized Mg^{2+}; RBC, red blood cell; MTT, magnesium tolerance test; MgDS, magnesium depletion score.

Several options are available to assess a potentially negative Mg balance: measuring serum, RBC, or urinary Mg^{2+}; calculating the magnesium depletion score (MgDS);

or performing Mg loading and evaluating the response (testing Mg tolerance). Nevertheless, each of these clinical tools has limitations, further complicating diagnosis. For example, measuring serum Mg^{2+} levels (usually tMg^{2+}, rarely iMg^{2+}) is a common assessment of Mg body status. Although determining tMg^{2+} is the most commonly used and readily available method, it does not reflect Mg content in the tissues and is a poor indicator of total body Mg stores, making this metric unreliable. The normal range for serum tMg^{2+} is 0.70–1.15 mmol/L. Hypomagnesemia (tMg^{2+} <0.70 mmol/L) can present with various symptoms, such as weakness, cramps, or cardiac arrhythmias, although it is usually oligosymptomatic or asymptomatic until tMg^{2+} falls below 0.50 mmol/L [10]. Frank hypomagnesemia is generally a sign of Mg deficiency but does not necessarily imply depleted body stores.

Conversely, normomagnesemia does not exclude Mg depletion. For example, isolated tubulopathies typically cause hypomagnesemia, whereas isolated glomerulopathies can cause hypermagnesemia in advanced renal failure. A combined glomerulo-tubular disorder of kidney function may present without changes in serum Mg^{2+} levels. Thus, progressive chronic kidney disease (CKD) may, at a certain point, result in spontaneous resolution of the initial tubular hypomagnesemia, with a concurrent reduction in the filtered load of Mg^{2+} [1]. Additionally, serum levels of tMg^{2+} do not detect the initial depletion of Mg body stores, as they represent only a minor portion (~1%) of total body Mg content, and their reference ranges are not well standardized. It is now considered that individuals with serum tMg^{2+} <0.85 mmol/L already have low Mg status and should be considered hypomagnesemic and Mg-deficient [11,12].

Physiologically, serum iMg^{2+} is more relevant than serum tMg^{2+}, especially in intensive care unit (ICU) settings, because it reflects the direct, active form of Mg^{2+} in the blood. However, measuring the iMg^{2+} fraction and intracellular Mg^{2+} in RBCs is not part of routine clinical practice, as specific analyzers are not yet widely available [13]. A complementary 24-hour urine collection can also be useful for determining urinary Mg^{2+} output and evaluating Mg balance. Healthy kidneys excrete approximately 100 mg Mg^{2+}/24 h (normal magnesiuria). FE_{Mg} is a useful tool to assess renal Mg^{2+} handling. In patients with hypomagnesemia it helps distinguish between renal Mg^{2+} wasting (FE_{Mg} >4%) and extrarenal cause of Mg^{2+} loss from the body (FE_{Mg} <2%). Finally, the Mg tolerance or loading test is widely considered the most precise and reliable approach for evaluating Mg status in the body. However, its clinical utility is limited by a demanding procedure that requires two separate 24-hour urine collections, one before and one after a 4-hour intravenous Mg loading infusion. The test can reveal normal Mg retention, increased excretion, or Mg deficiency in a patient. Conversely, the newly introduced Mg depletion score (MgDS) offers a simple clinical tool that effectively detects Mg deficiency, is easy to use, and requires no equipment or measuring instruments. It is a fast and inexpensive alternative to the methods described above. However, no single method is considered fully satisfactory, especially for the sensitive population of critically ill patients [6].

The global prevalence of chronic Mg deficiency is high but unknown, as the condition is likely underdiagnosed. Even today, it is rarely considered in clinical practice, often remaining subclinical in ordinary hospital wards and particularly in ICUs. Nevertheless, Mg imbalances are very prevalent in critical illness. In the critically ill, Mg imbalances are a significant adverse factor associated with overall morbidity and mortality and represent an additional risk factor for poor prognosis. Addressing chronic latent Mg deficiency through adequate and timely Mg repletion, while fortifying current treatment protocols, would certainly improve patient outcomes [14]. However, it is difficult to determine who among the critically ill has this latent Mg deficit and therefore carries the associated health risks. Given the high vulnerability of critical care patients and the need for an urgent therapeutic response, faster, more accurate diagnostic procedures are required for this patient population. Quick and reliable diagnosis can be vital, as a profound negative Mg imbalance can lead to overt hyperexcitability, thereby endangering vital body functions such as cardiac action and hemodynamics (causing ventricular tachyarrhythmias and circulatory collapse), respiration (causing dyspnea and respiratory compromise), and others [15].

To obtain an accurate assessment of Mg body status, multiple factors should be considered, including dietary intake, gut health, urinary function, medications, and lifestyle. However, the kidneys are the primary regulators of Mg metabolism, responsible for glomerular filtration of excess Mg^{2+} from the blood and its excretion in urine, while preserving Mg^{2+} through tubular reabsorption when its levels are low. Therefore, compromised renal Mg^{2+} handling is one of the most common pathomechanisms leading to Mg deficiency. Etiologically, excessive renal Mg^{2+} wasting can result from tubulopathies, most frequently acquired (due to toxic, ischemic, or other impairments of normal tubular Mg^{2+} reabsorption) or, rarely, genetic (due to inherited or *de novo* inactivating mutations affecting Mg^{2+} transporters). Given this, we conducted a literature search to determine whether a recently introduced kidney-reabsorption-related clinical parameter, the MgDS, can serve as an indicator of chronic latent Mg deficiency, specifically to detect this condition in seriously ill and critical patients. We found a lack of clinical studies on the MgDS in critically ill patients.

2. Methods

A search was conducted in the PubMed electronic database without filters using the following keywords: magnesium depletion score OR magnesium depletion score AND critical care patients OR critically ill. The literature

search was not time-limited. Language was not restricted, but only English-language publications were found. Articles from the reference lists included clinical studies (cross-sectional, retrospective, and prospective observational cohort studies) and review papers, whereas no basic research articles were found. Selection criteria excluded case reports and conference abstracts. Studies on experimental animals were not excluded; however, only studies concerning the human population were found, including adults and children. After screening the literature, articles of interest were retrieved and examined. We did not conduct a systematic literature search, as this is a narrative review.

This paper does not address the pathogenesis of latent Mg deficiency already present in patients admitted to ICUs, nor does it analyze all potentially relevant etiological factors that could contribute to its development. Rather, this review focuses on the MgDS, a clinical score introduced to estimate Mg deficiency, and on its potential use as a clinical tool for efficiently detecting this condition in the critically ill. Our literature search did not include *hypomagnesemia* as a keyword because it is a transient finding and more likely an epiphenomenon than a true representation of Mg deficiency [16].

We organized the search results into several chapters of this review to address the following questions:

- What is the MgDS (overview, calculation, and interpretation)?

- Is the MgDS associated with the levels of total and ionized Mg^{2+} in serum?

- What is the clinical significance of the MgDS parameter?

- Is the MgDS a reliable indicator of chronic Mg deficiency?

- Why is it important to consider chronic latent Mg deficiency in critically ill patients?

- Is this parameter used for critical patients?

- Can the MgDS indicate chronic latent Mg deficiency in critically ill patients?

Answers to the questions raised are presented as specific results from previously published works identified in the literature search and discussed by the authors. Finally, suggestions from the authors for integrating the MgDS as a diagnostic and prognostic tool into the management of critical care patients are presented.

Consistent formatting of abbreviations for Mg was used throughout the text, with Mg used in the context of a chemical element (concerning its status, homeostasis, balance, imbalance, etc.), and Mg^{2+} when referring to an electrolyte in body fluids or to its electrophysiological, metabolic, and other actions in living systems.

3. MgDS as a Biomarker for Clinical Estimation of Chronic Mg Deficiency

Clinical practitioners usually consider Mg depletion when hypomagnesemia (with or without manifestations) is detected. However, these terms are not synonymous. Since serum Mg^{2+} levels do not accurately reflect Mg deficiency, a new comprehensive scoring system has recently been developed to enable rapid initial assessment of Mg deficiency status, particularly in at-risk individuals. In 2021, Fan et al. [17] introduced the MgDS, a clinical tool based on factors that influence Mg^{2+} absorption, metabolism, and excretion. The Mg depletion score was first used as a novel measure of Mg deficiency in a comprehensive, nationally representative survey study using publicly available datasets from more than 10,000 US adults (National Health and Nutrition Examination Survey (NHANES)), and was validated using the magnesium tolerance test (MTT). The MgDS primarily reflects renal Mg^{2+} reabsorption-related Mg deficiency [17].

This metric predicts the risk of Mg^{2+} wasting (primarily kidney-related), particularly in patients with chronic conditions, by incorporating several lifestyle and health-related factors that influence Mg homeostasis and can lead to negative balance, such as altered kidney function, use of certain drugs, and alcohol use. It is derived by integrating relevant risk factors for Mg depletion: diuretic use, proton pump inhibitor use, estimated glomerular filtration rate, and alcohol consumption exceeding recommended thresholds (alcohol abuse). The goal of introducing this score was to create a more accurate clinical tool for predicting and estimating the severity of Mg deficiency and related disease outcomes, thereby enabling adequate planning of precision-based nutritional interventions. The authors have concluded that the MgDS can serve as a promising new marker for identifying latent Mg deficiency in individuals who may significantly benefit from increased Mg intake to reduce the risk of systemic inflammation and cardiovascular mortality [17]. This methodology has soon been accepted by other authors investigating associations between the MgDS and other diseases.

Several components contribute to the MgDS, and each is assigned a specific number of points. The MgDS typically considers the following factors: current use of diuretics within the last 30 days (1 point), long-term use of proton pump inhibitors (PPIs; 1 point), heavy alcohol consumption (>1 drink/day for women and >2 drinks/day for men; 1 point), mildly reduced kidney function (estimated glomerular filtration rate (eGFR) between 60 and 90 mL/min/1.73 m^2; 1 point) and CKD (eGFR <60 mL/min/1.73 m^2; 2 points) [17]. Since exposure to the factors summarized in the MgDS calculation is chronic, the score reflects chronic depletion, *i.e.*, chronic Mg deficiency in the body. Several reasons can cause an individual to become chronically Mg-depleted. These factors, encompassed by this Mg depletion scoring system, primarily cause insufficient digestive absorption of Mg^{2+} and/or disrupted renal tubular reabsorption of Mg^{2+}, resulting in increased urinary Mg^{2+} wasting; inadequate dietary Mg intake is not directly included. Table 2 lists the factors included in the MgDS calculation and

Table 2. Mechanisms underlying the implicit factors of the magnesium depletion score (MgDS).

MgDS components	Mechanisms responsible for magnesium depletion
PPIs (chronic use)	Impaired Mg^{2+} absorption in the gut (down-regulation of TRPM6)
Diuretics (chronic use)	Increased Mg^{2+} urinary excretion (thiazide and loop diuretics induce down-regulation of TRPM6)
Alcohol (chronic abuse)	Malnutrition, impaired Mg^{2+} absorption in the gut, increased urinary excretion
Reduced kidney function	Increased Mg^{2+} urinary excretion due to insufficient tubular reabsorption of Mg^{2+}

MgDS represents a biomarker used to assess the likelihood of Mg deficiency in an examinee, developed due to a depletion of Mg body stores. It primarily considers major pathophysiological factors that influence kidneys' capability for Mg^{2+} reabsorption. MgDS, magnesium depletion score; PPIs, proton pump inhibitors; TRPM6, transient receptor potential cation channel subfamily M member 6.

the major pathophysiological mechanisms responsible for each. Multiple mechanisms impairing Mg balance often coexist in the same patient.

Calculating the MgDS allows us to approximate the risk of Mg deficiency, with higher total MgDS values indicating a greater risk. The scoring interpretation used in the studies typically categorizes individuals into 3 groups based on their MgDS levels: lower risk (MgDS = 0–1), medium risk (MgDS = 2), or higher risk of Mg depletion (MgDS = 3–5) [17]. Since its introduction, interest in the MgDS has grown, and numerous studies have used this parameter to explore associations with various health conditions and outcomes.

However, it is important to consider whether this new marker, the MgDS, is associated with blood Mg^{2+} levels. Since a positive correlation exists between Mg deficiency, as quantified by the MgDS, and the health risks of several conditions, the MgDS can be reliably used in clinical practice to identify people at risk of Mg deficiency, rather than measuring serum Mg^{2+} levels directly. Namely, more or less routinely measured serum levels of tMg^{2+} represent only a small fraction of the total body Mg. Thus, tMg^{2+} levels may not always accurately reflect overall Mg status and may fail to detect the latent form of chronic Mg deficiency. Unlike tMg^{2+}, the MgDS score offers a more comprehensive evaluation [18]. Normal blood Mg^{2+} levels (both tMg^{2+} and iMg^{2+}) can mask the early widespread Mg deficiency in the body (*e.g.*, in stage 1), but a true parameter of Mg depletion should not [19]. Although our search revealed a number of studies showing that the MgDS is associated with various health conditions, including metabolic syndrome, cardiovascular disease (CVD), and diabetes mellitus (DM), research findings directly comparing the MgDS values with serum Mg^{2+} levels are scarce. One study found that the MgDS parameter had higher predictive performance for Mg deficiency than traditionally measured serum Mg^{2+} levels, suggesting that the MgDS may be a more reliable biomarker of Mg body status [20]. While the MgDS and serum Mg^{2+} levels are both clinically used to assess Mg status, the MgDS may provide a more accurate reflection of Mg deficiency in an individual, especially when serum Mg^{2+} levels remain within the normal range even as total body Mg content decreases [14]. Therefore, the MgDS is a very useful parameter, as it aggregates risk factors for Mg deficiency to better reflect overall Mg status than traditional serum Mg^{2+} tests [21].

The approach for monitoring negative Mg balance using the MgDS was also validated against the Mg loading test (the gold standard for assessing Mg status), demonstrating that the MgDS outperformed traditional serum and urine Mg^{2+} measurements [17,22,23]. Thus, the MgDS offers a more reliable and comprehensive assessment of Mg deficiency by incorporating relevant clinical risk factors and serves as a valuable tool for healthcare providers to evaluate and manage Mg status in cases of Mg depletion. However, the MgDS cannot be used as an indicator of all types of abnormalities in Mg balance, *i.e.*, it is not applicable in cases of Mg excess (hypermagnesemia).

3.1 The Association of MgDS With Various Health Risks

Over the past five years (2021–2026), a series of population-based cross-sectional, prospective, and retrospective clinical studies have used a common methodology with the MgDS, largely drawing on the National Health and Nutrition Examination Survey (NHANES) database [17,20,24]. Indeed, the NHANES database is a large multi-year cross-sectional health database representative of the American population, created for national health surveillance and dietary research. Participants were non-institutionalized US adults from the survey, with data collected on their health and nutrition. Baseline characteristics of study subjects included demographic data (age, sex, race, body mass index), lifestyle factors (smoking, drinking, education), and disease history. Based on their MgDS levels, participants were divided into three groups to estimate the risk of Mg deficiency: none to low risk (MgDS = 0–1), medium risk (MgDS = 2), and high risk (MgDS = 3–5). Appropriate statistical analyses, including multivariate logistic regression and other methods, were performed to examine the independent association between the MgDS and various disorders and to evaluate the predictive performance of the MgDS for several health conditions. Most analyses revealed adverse associations with higher MgDS values. Together, these studies have provided novel epidemiological evidence for the role of MgDS-predicted Mg deficiency in the development of several chronic diseases and disorders.

Our search identified 80 articles, comprising 77 observational studies: 28 cohort studies (24 prospective and 4 retrospective) and 49 cross-sectional studies; one PRISMA systematic review and meta-analysis of observational studies; one Letter to the Editor; and one Author Reply. We classified all studies identified in the literature search by clinical condition into one of 7 disease or disorder groups based on their dominant pathology. The groups are as follows: 1, CVD group; 2, respiratory disease group; 3, neurological and psychiatric disease group; 4, metabolic and endocrine disease group; 5, urogenital disease group; 6, rheumatic disease group; 7, immune-mediated and age-related disease group.

3.1.1 MgDS and CVDs

Since the MgDS was developed, numerous studies have examined its association with CVDs. The first study to develop and validate the MgDS found that this score can predict mortality from CVDs [17]. A stable and significant MgDS–CVD relationship has been confirmed, and higher MgDS values are associated with elevated risk of all-cause deaths and CVD deaths [24]. Specifically, an MgDS $\geq$3 correlates with a high risk of all-cause and cardiovascular mortality [25,26]. Multiple findings support potential mechanisms through which Mg deficiency may deteriorate cardiovascular health. The MgDS may predict long-term outcomes and serve as a promising biomarker for mortality risk stratification in patients with hyperlipidemia [27]. Mg^{2+} is an important modulator of systemic arterial blood pressure regulation; hence, Mg imbalances may negatively affect vascular health. A positive correlation between the MgDS and the risk of developing arterial hypertension has also been confirmed [28]. Higher MgDS values are strongly and independently associated with an increased risk of hypertension [29] and significantly correlate with greater arterial stiffness, an established marker of vascular aging and cardiovascular risk [30,31]. Evaluating mechanistic links between Mg status and arterial hypertension has identified shared molecular pathways, including regulation of vascular tone, oxidative stress response, inflammatory response, endothelial signaling, and extracellular communication, through which Mg deficiency may contribute to the pathogenesis of arterial hypertension [29]. Mg depletion is a significant risk factor for atherosclerotic CVD [32] and for the prevalence of advanced cardiovascular–kidney–metabolic syndrome [33]. In middle-aged and older adults, elevated MgDS levels are independently positively associated with an increased risk of peripheral artery disease [34]. High MgDS also tends to increase the risk of abdominal aortic calcification, especially in individuals with low dietary Mg intake [35]. Higher MgDS can also increase hyperuricemia-related all-cause mortality and cardiovascular mortality in patients with coronary artery disease [36]. Furthermore, the association between even subclinical Mg deficiency and major cardiovascular events is now well known [37]. Mg^{2+} is also vital for proper cardiac health. Chronic Mg deficiency has been shown to affect cardiac morphology and function, potentially contributing to subclinical changes in the heart, particularly those leading to metabolic diastolic cardiomyopathy. Cross-sectional analysis of magnetic resonance imaging (MRI)-derived parameters of alterations in heart structure and function, conducted on German National Cohort participants, has shown that higher MgDS is associated with an increased left ventricular remodeling index, indicating concentric hypertrophy, while serum Mg^{2+} increase correlates with reduced left and right ventricular systolic and diastolic volumes. Hence, the MgDS may serve as an early indicator of cardiac impairment [38]. Finally, increasing MgDS levels can increase the prevalence of congestive heart failure (HF) [39]. In older HF patients, the MgDS may interact with the association between tobacco exposure and depression [40].

3.1.2 MgDS and Respiratory Diseases

Mg-depleted individuals are also more likely to develop certain respiratory conditions, underscoring that Mg is essential for proper respiratory function and, prognostically, for reducing the risk of respiratory disease. A significant positive correlation has been found between higher MgDS values and an increased incidence of chronic obstructive pulmonary disease (COPD) [41,42]. Asthmatics with higher MgDS levels also show a significantly higher risk of all-cause mortality and cardiovascular mortality [43]. Additionally, a strong positive correlation between the MgDS and obstructive sleep apnea (OSA) has been demonstrated [44,45]. In general, a higher MgDS is associated with a higher prevalence of chronic respiratory disease and all-cause mortality [46]. As a novel tool for assessing Mg deficiency status, the MgDS may serve as a promising, cost-effective, and widely applicable prognostic marker for identifying individuals at high risk of COPD, asthma, and OSA. Nevertheless, further studies on the underlying pathophysiological mechanisms linking MgDS and respiratory disorders are still needed. Improving low Mg^{2+} levels could reduce the risk of airway obstruction, while Mg recompense may help mitigate this respiratory burden, improving ventilation and quality of life in these patients.

3.1.3 MgDS and Neurological and Psychiatric Diseases

Studies examining associations between systemic Mg depletion and neurological and psychiatric disorders have found positive correlations between the MgDS and the risk of stroke, depression, poor cognitive performance, and Parkinson's disease. Furthermore, higher MgDS levels are associated with lower survival probabilities in patients with stroke. The MgDS can also serve as an early marker of cognitive decline, as high MgDS is dose-dependently associated with lower cognitive scores and poorer processing speed in older individuals. Since Mg deficiency is a modifiable risk factor and high MgDS is signifi-

cantly associated with an increased likelihood of developing many of the aforementioned neuropsychiatric conditions, the authors conclude that reducing the MgDS may contribute to both their prevention and treatment [47,48,49,50,51,52,53,54,55]. Mg depletion (MgDS ≥2) is also independently associated with an increased risk of chronic pain in adults, and this relationship varies significantly by physical activity level [56]. In patients with extremity injuries, the MgDS is not associated with the development of post-traumatic complex regional pain syndrome type 1 [57].

3.1.4 MgDS and Urogenital Diseases

Studies have also found the MgDS to be positively associated with several urogenital conditions. Mg deficiency is common in patients with CKD, due to impaired Mg^{2+} tubular reabsorption. In patients with CKD, the MgDS is an independent risk factor for all-cause and cardiovascular mortality [58]. In these patients, low serum Mg^{2+} levels are strongly associated with atherogenic dyslipidemia (significantly elevated total cholesterol and low-density lipoprotein), suggesting a link to their significantly increased cardiovascular risk. Since the association between depleted Mg status and lipid alterations increases cardiovascular risk in CKD patients, Mg supplementation might help reduce elevated cardiovascular morbidity and mortality [59]. The MgDS has also been found to be a risk factor for the prevalence of stress, urgency, and mixed-type urinary incontinence [60]. In patients with erectile dysfunction (ED), serum Mg^{2+} levels are significantly lower than in healthy controls, suggesting Mg deficiency may act as a risk factor for ED. However, a novel metric of the MgDS is superior to serum Mg^{2+} alone for ED prediction, as an increase in the MgDS is associated with a higher prevalence of ED [61,62,63]. Furthermore, a positive correlation exists between the MgDS and the risk of an overactive bladder [64,65], and prostate cancer [66], with higher MgDS values significantly associated with higher prevalences of these conditions. Since Mg deficiency has been found to indicate poor general health and nutritional status, several studies have investigated whether it may affect outcomes in cancer patients. A high MgDS value (≥3) is a strong and independent predictor of increased cancer-specific mortality risk among cancer survivors [67]. For example, among endometrial cancer patients, those with an elevated MgDS value were found to experience shorter survival duration [68]. Therefore, monitoring Mg status and managing Mg depletion could help reduce risk and improve treatment of the aforementioned urogenital diseases, as the MgDS affects the clinical outcomes of these patients.

3.1.5 MgDS and Metabolic and Endocrine Diseases

Since the associations between Mg depletion and the development and prognosis of many metabolic diseases and disorders were unclear, several trials using the MgDS methodology were designed and conducted to assess these correlations. Higher MgDS is significantly associated with increased odds of metabolic syndrome and DM in US adults, particularly among those with low dietary Mg intake [20,21]. In patients with type 2 DM, smoking is not an independent determinant of Mg deficiency, as this habit does not independently affect serum Mg^{2+} levels or the MgDS [69]. However, adults with DM and a high MgDS may have an increased risk of all-cause and cardiovascular mortality [70,71]. Diabetic patients with a high MgDS are also more likely to develop certain complications, such as diabetic retinopathy [22,72]. Among patients with type 2 DM, both poor Mg status (MgDS ≥2) and poor blood glucose control (hemoglobin A1c, HbA1c ≥7%) independently increase the risk of diabetic retinopathy, and significant interactions between the MgDS and HbA1c amplify the risk beyond individual effects, particularly among older adults and those with a history of CVD [73]. In patients with diabetic kidney disease, the MgDS serves as a prognostic marker, as higher MgDS values (≥3) significantly increase the incidence of CVDs and all-cause mortality and cardiovascular-cause-specific mortality in these patients [74,75]. The MgDS is also an independent factor associated with sarcopenia in patients with type 2 DM, showing strong predictive potential for its early identification [76]. Furthermore, higher MgDS is significantly positively associated with an increased risk of circadian syndrome, a condition encompassing metabolic syndrome, depression, and sleep deprivation [77]. Additionally, Mg deficiency, assessed using the MgDS, is significantly associated with an increased risk of metabolic dysfunction-associated steatotic liver disease (MASLD) [78,79]. The MgDS is a useful prognostic indicator of mortality in these patients and in those with non-alcoholic fatty liver disease, whose high MgDS values are associated with significantly increased risks of all-cause mortality, CVD mortality, and even cancer mortality [80,81]. A significant positive correlation is also observed between the MgDS grade and the risk of kidney stone formation [82,83,84]. Similarly, high MgDS positively correlates with an increased prevalence of hyperuricemia and gout [85,86,87]. Therefore, Mg deficiency should also be addressed in hyperuricemic patients, as it contributes to the mechanisms underlying hyperuricemia-related diseases. Collectively, these findings provide evidence that Mg is a highly active mineral nutrient with versatile metabolic roles, and that Mg deficiency is a risk factor for many metabolic disorders. Correction of its deficiency could provide long-term health benefits for patients with DM and its complications, steatotic liver disease, hyperuricemia and kidney stones, and help support circadian health. Mg replenishment through dietary intake and supplementation should be incorporated into their treatment strategies to reduce risks, improve prognosis, and prolong survival in these patients.

3.1.6 MgDS and Rheumatic Diseases

Since Mg^{2+} is required to maintain bone mineral density (BMD) and the overall structure and function of the skeletal system, optimizing Mg nutritional status may confer benefits, whereas Mg deficiency may impair patients with rheumatic and orthopedic conditions. However, only a few clinical studies on MgDS in rheumatic diseases have been published to date. Dietary Mg intake is negatively correlated with osteoporosis (OP) in adults, underscoring the need for early screening for OP in individuals with insufficient dietary Mg intake and/or high MgDS [88]. The MgDS exhibits a significant negative effect on hip bone health indicators in older adults, with a higher MgDS associated with greater declines in femoral neck BMD, OP, and subsequent fractures [89]. A study investigating potential links between low body Mg content (indicated by the MgDS) and the development of rheumatoid arthritis (RA) and osteoarthritis (OA) in adults identified a significant graded dose-response relationship between the MgDS and both RA and OA; however, the underlying mechanisms remain incompletely understood [90]. Individuals with OA tend to have higher MgDS values, and the MgDS positively correlates with OA incidence and mortality [18]. Similarly, the MgDS is positively associated with moderate and severe periodontitis [91]. Therefore, severe Mg deficiency significantly affects bone and dental health, but further studies are needed to elucidate the underlying mechanisms.

3.1.7 MgDS and Immune-Mediated and Age-Related Diseases

Finally, Mg deficiency may be relevant to some immune-mediated diseases, such as psoriasis [92], and to age-related disorders, such as frailty. An inverse association is observed between the MgDS and the expression and serum levels of Klotho, a transmembrane protein involved in regulating aging and modulating oxidative stress. Individuals with medium-to-high MgDS values have significantly lower serum levels of the anti-aging protein. Although the underlying mechanisms linking Mg deficiency and aging remain to be elucidated, the authors believe that monitoring the MgDS could help identify individuals at increased risk of developing frailty and accelerated aging. Prompt interventions with appropriate dietary adjustments or Mg supplementation may increase serum Klotho levels, decrease MgDS values, and reduce the risk of all-cause and cardiovascular mortality among older adults [23,93]. Additionally, frailty, a geriatric syndrome of multi-systemic decline in physiological functions, with elevated vulnerability to stressors and increased cardiovascular mortality, is linked to higher MgDS values in frail individuals [94]. Risks of non-melanoma skin cancer and cancer-specific mortality are also higher in individuals with higher MgDS values (≥3), with these associations partly mediated by biological aging [95]. Regarding the association between the MgDS and local inflammation, low pre-operative MgDS values were not predictive of early proliferative remodeling and wound healing following oral surgical extraction of impacted molars in a healthy population [96]. Completing the circle of this literature review, we return to the methodological paper that first introduced this new score and found that it can even predict the risk of systemic inflammation [17]. In summary, Mg-depleted individuals face many associated health risks. Fig. 1 is a schematic representation highlighting the principal associations between MgDS and all disease risks identified in our literature review.

Although cross-sectional clinical studies cannot establish causality, these studies were included in our literature review because demonstrating causation between MgDS-defined chronic Mg deficiency and the diseases examined was not the primary objective of the research. None of the included studies demonstrated Mg deficiency (*i.e.*, high MgDS) as the etiological factor in the pathogenesis of the diseases studied. Instead, studies reported associations between the MgDS and disease risk, incidence, and/or mortality, rather than establishing causal relationships. Higher MgDS consistently predicts worse outcomes (disease prevalence, progression, and mortality) across multiple organ systems, emerging as a promising biomarker for early detection and risk stratification. Supporting evidence typically indicates statistically significant associations between higher MgDS values (>2) and disease risk, as summarized in Table 3 (Ref. [17,18,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96]).

Reviews of studies using the MgDS highlight the importance of Mg^{2+} in several chronic health conditions, suggesting a role for chronic Mg deficiency in their pathogenesis [31,33,41,44,56,62,78,93]. These findings underscore the importance of monitoring and managing Mg status, especially in populations at risk of Mg deficiency and in patients with one or more risk factors for Mg deficiency as included in the MgDS calculation. Individuals with higher MgDS values (≥2) have higher odds of developing numerous adverse health conditions. The MgDS is often used in research and epidemiological studies; however, this metric could also help clinicians identify individuals who might benefit from dietary counseling, supplementation, or additional testing to prevent further worsening of health risks if severe Mg deficiency develops. Timely addressing Mg deficiency through dietary adjustments, supplements, or treatment may help mitigate associated health risks. Present-day knowledge still lacks a full understanding of the pathogenic mechanisms underlying these Mg deficiency-related morbidities. Long-term Mg depletion contributes to a number of adverse health effects; however, it usually acts as a risk factor rather than as the predominant etiology of the disease.

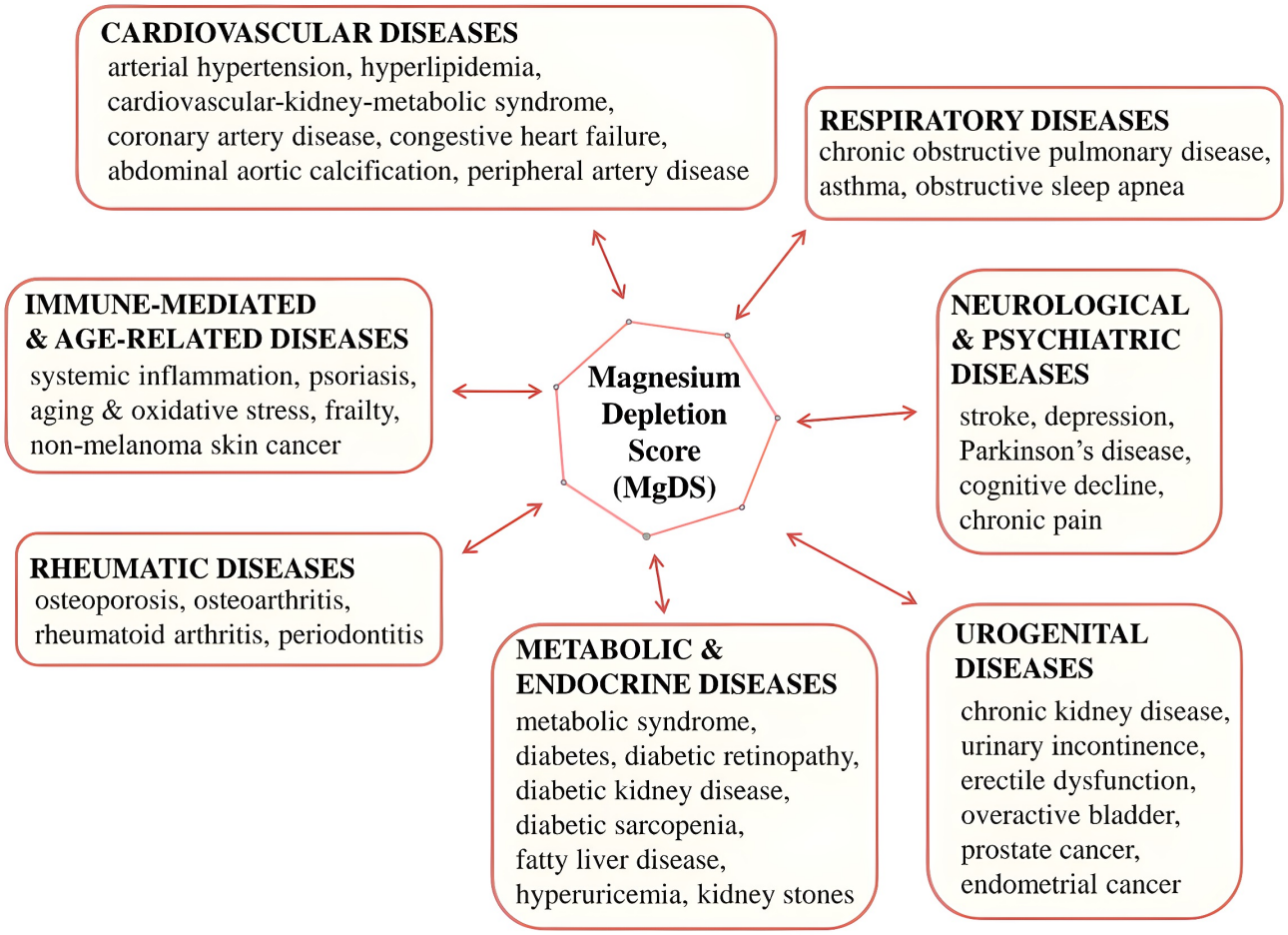

Fig. 1. Many health risks are associated with magnesium depletion. An overview of findings from analyzed clinical studies investigating the associations between magnesium depletion score (MgDS) and different diseases and chronic health conditions is given.

Table 4 lists the most important possible pathophysiological effects and the therapeutic benefits of Mg replenishment.

This table presentation does make Mg seem like a universal remedy or panacea, but as its physiological and pathophysiological roles truly are numerous and versatile, so are its therapeutic roles, typically serving usually as an adjuvant and complementary treatment [2,14,15].

4. Chronic Latent Mg Deficiency in Critically Ill Patients

As a micronutrient mineral and an electrolyte, Mg^{2+} is bioessential for maintaining overall health and well-being and for regulating numerous cellular processes (cell metabolism, membrane transport, cell excitability, cell cycle, etc.) and a range of physiological functions, including heart, muscle, and nerve function, blood pressure regulation, bone health, and blood glucose control. Many pathophysiological conditions and diseases associated with Mg deficiency attest to the multitude of physiological roles that Mg^{2+} plays in the body (Fig. 1). Namely, Mg^{2+} is somewhat unique among other major cations (Na^+, K^+, Ca^{2+}), because it contributes to numerous regulatory and metabolic functions on both the intracellular and extracellular sides of the cell membrane. However, under conditions of insufficient Mg intake, excessive loss from the body, and/or disturbed Mg^{2+} redistribution between body fluid compartments, chronic Mg deficiency can develop and initially remain asymptomatic. If undetected and left unaddressed, chronic Mg deficiency poses significant health risks and is associated with a number of serious health conditions. Acute and severe symptomatic Mg deficiency has a significant impact on vital body functions, posing a serious threat in the critically ill [15].

A number of factors can predispose critical care patients to Mg deficiency, including disease-related increases in renal Mg wasting and other Mg^{2+} losses, decreased Mg^{2+} absorption (*e.g.*, medication-induced), and underlying metabolic and other conditions and comorbidities (*e.g.*, sepsis, inflammation, stress, older age). Other causes of iatrogenic Mg depletion include diagnostic and therapeutic interventions, such as prolonged nasogastric suctioning, and restricted diets (total parenteral nutrition). In the ICU,

Table 3. Key associations between magnesium depletion score (MgDS) and chronic diseases.

Disease category	Key associations	Main outcomes	References
1. Cardiovascular	Higher MgDS linked to arterial stiffness, coronary vasospasm, increased blood pressure and HF development	Predicts CVD mortality, LV remodeling and concentric hypertrophy; increases the risk of CAD and unwanted CV events	[17,24,25,26,27,28,29,30,31,32,33,34,35,36,38,39,40]
2. Respiratory	Higher MgDS associated with COPD, asthma, OSA	Elevates risk of all-cause and CV mortality in asthmatics; prognostic marker for bronchial obstruction	[41,42,43,44,45,46]
3. Neurological & psychiatric	Higher MgDS correlates positively with the risk of stroke, impaired cognition, depression, Parkinson's and chronic pain	Lowers survival in stroke patients; marks a dose-dependent cognitive decline	[47,48,49,50,51,52,53,54,55,56,57]
4. Urogenital	Higher MgDS linked to urinary incontinence, erectile dysfunction, overactive bladder, CKD, prostate and endometrial cancer	Independently predicts mortality in CKD; marks shorter survival in endometrial cancer	[58,59,60,61,62,63,64,65,66,67,68]
5. Metabolic & endocrine	Higher MgDS associated with DM, metabolic syndrome, circadian syndrome, steatotic liver disease, kidney stones, hyperuricemia and gout	Increases the risk of diabetes, diabetic complications and NAFLD; prognostic marker in diabetic kidney disease	[20,21,22,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87]
6. Rheumatic	Higher MgDS linked to OP, RA and OA	Increases the risk of loss in BMD and osteoporotic fractures, OA incidence and mortality	[18,88,89,90,91]
7. Immune-mediated & age-related	Higher MgDS associated with psoriasis, systemic inflammation, skin cancer and frailty	Predicts tendency to develop chronic inflammatory response, frailty and other aging-related changes	[17,23,92,93,94,95,96]

A summary overview of analyzed clinical studies shows that many health risks are associated with Mg deficiency as assessed by MgDS. Cited references are indicated. MgDS, magnesium depletion score; HF, heart failure; CVD, cardiovascular disease; LV, left ventricle; CAD, coronary artery disease; CV, cardiovascular; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; DM, diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; OP, osteoporosis; RA, rheumatoid arthritis; OA, osteoarthritis; BMD, bone mineral density.

Table 4. Major adverse effects related to magnesium deficiency and adequate beneficial effects of magnesium recompense—an overview.

Adverse effects of magnesium deficiency	Beneficial effects of magnesium recompense
pro-oxidative	anti-oxidative
proinflammatory	anti-inflammatory
bronchoconstrictive	bronchodilatory
inducing preterm labor	tocolytic
vasoconstrictive, hypertensive	vasodilative, antihypertensive
coronary vasospasm	vasospasm relieving, anti-ischemic, cardioprotective
arrhythmogenic	antiarrhythmic
cerebral vasospasm	vasospasm relieving, anti-ischemic, neuroprotective
anxiogenic	anxiolytic
depressive	antidepressant
proconvulsant	anticonvulsant
migrenic	anti-migraine
nociceptive	antinociceptive
neurodegenerative	preserving cognition

Mg deficiency is quite common, affecting about half of all patients. ICU morbidity and mortality rates are significantly higher in Mg-depleted than in Mg-balanced patients [97]. Clinical consequences of Mg deficiency are also significant in pediatric patients in critical care [98]. Given its exceptionally high prevalence among critical care patients and the broad clinical relevance of Mg deficiency as a potentially fatal condition, measures are needed to optimize patient outcomes. Closer monitoring of Mg status and vigilance for potential Mg depletion are required in all patients on long-term polypharmacy.

Mg disorders increase the risk of cardiac arrest, acute coronary syndrome, and respiratory failure [99]. Mg deficiency in the body has been linked to a range of chronic diseases, including CVDs, type 2 DM, obstructive respiratory disorders, migraine headaches, mental health issues, and OP. Understanding these health risks associated with Mg deficiency is crucial for appreciating the importance of maintaining adequate Mg balance in the body. However, chronic latent Mg deficiency is not only an independent risk factor for the onset and maintenance of these and many other common chronic non-communicable diseases. In addition to the described MgDS-associated risks, chronic Mg deficiency carries an additional risk of acute exacerbation. Severe acute Mg deficiency, *i.e.*, severe hypomagnesemia, is a well-recognized life-threatening condition in the ICU due to fatal arrhythmias, cardiac arrest, respiratory arrest, neurological emergencies, and refractory electrolyte imbalances it causes [14]. Therefore, in a critically ill patient, a Mg-depleted body status requires timely recognition. However, blood parameters such as Mg^{2+} concentrations in plasma, RBCs, and mononuclear cells cannot accurately detect it, and a response to an Mg-loading test is sometimes not observed [100]. All these reasons led us to question whether using the MgDS as a clinical indicator helps identify chronic latent Mg deficiency in this specific patient population.

4.1 Is MgDS Used to Indicate Chronic Latent Mg Deficiency in Critically Ill Patients?

Physiologically, Mg^{2+} serves as a regulatory cation in excitable membranes. The loss of this regulatory role in chronic latent Mg deficiency significantly affects excitable cells and tissues, leading to low-grade systemic neuromuscular hyperexcitability. This occurs because Mg^{2+} is crucial for normal nerve, muscle, and cardiac function, and its deficiency can lower the membrane threshold potential. Metabolic impairments and weakened immunity, due to decreased antioxidant defenses and proinflammatory responses, also contribute to pathophysiological mechanisms resulting from chronic Mg deficiency, which are unfavorable for the prognosis of critically ill patients, as vital body functions (heart action, circulation, respiration, and nervous system function) could all be affected [15].

Abnormalities in Mg balance are common in critical care patients. Since serum tMg^{2+} levels often do not accurately reflect tissue Mg stores, assessing Mg status by measuring tMg^{2+} is an unsatisfactory method that often yields erroneous and misleading results. In critically ill patients, chronic latent Mg deficiency is likely to be present on admission and to worsen during the ICU stay. Indeed, chronic latent Mg deficiency should not be overlooked, as this condition significantly contributes to the overall health burden and may directly increase the risk of adverse outcomes. Instead, this condition should be detected, estimated, and treated to improve patient prognosis [14].

Our search of the PubMed database identified only three clinical studies that included the keywords *magnesium depletion score* AND *critical care patients* OR *critically ill.* These studies examined associations between the MgDS and COPD [41], depression [48], and kidney stones [82]. Although the literature search identified these studies, none assessed latent Mg deficiency in critically ill patients using the MgDS. Since the score was introduced, no such investigations have been conducted. We found no data on the association between the MgDS and critical care conditions. Therefore, we propose such research for future clinical endeavors. For example, it would be valuable to determine whether an MgDS $\geq$2 correlates with higher all-cause and cardiovascular mortality rates in critical care patients across different ICU departments. This could significantly improve the accessibility of the diagnostic procedure for detecting chronic latent Mg depletion in urgent and intensive clinical practice, thereby optimizing Mg status through dietary and/or pharmacological supplementation. In all patients with preserved kidney function, this could serve as a safe and useful adjunct or treatment for a range of medical conditions, offering significant benefit to critical care patients [101].

4.2 Considerations on MgDS as a Potential Indicator of Chronic Mg Deficiency in Critically Ill Patients

Mg is a crucial electrolyte and micronutrient; however, Mg is frequently overlooked and not evaluated in routine serum electrolyte testing. Despite the many regulatory and physiological functions associated with Mg, this micronutrient remains underappreciated in clinical practice. Although Mg^{2+} is still often neglected in clinical evaluations compared with other major electrolytes, research over the last few decades has significantly increased understanding of its importance. Chronic Mg deficiency is a state of low total body Mg content caused by a prolonged insufficient intake and/or excessive loss from the body. Chronic Mg deficiency is prevalent; however, the true extent remains unknown. Nonetheless, the prevalence of chronic Mg deficiency in the Western world is approximately 10–15%, although rates vary substantially globally [102]. The condition is certainly widespread, particularly among special populations such as postmenopausal women, older

adults, patients with chronic illnesses, cancer patients, patients with malnutrition, kidney patients, and ICU patients. Chronic latent Mg deficiency is the early, clinically silent, subclinical stage of developing Mg depletion. Strong associations have been found between Mg depletion and major chronic diseases (reviewed here), indicating that it contributes, albeit slowly and significantly, to the deterioration of many physiological functions and overall health. We can rightly consider chronic Mg deficiency a leading contributor to non-communicable diseases [7]. If neglected, Mg deficiency can easily aggravate and affect many organ systems, including cardiovascular, respiratory, neurological, psychological, and other functions, as well as metabolism and immunity, thereby increasing overall health risks [11]. Therefore, raising awareness of this condition is a necessity of modern clinical practice. This review paper sheds light on chronic Mg deficiency by focusing on published research on the MgDS, a kidney reabsorption-related score of Mg depletion. This scoring parameter, primarily based on kidney function, reflects the amount of Mg^{2+} that can be lost from the body due to excessive urinary wasting. If this loss increases in magnitude and is not compensated, a state of chronic Mg deficiency will develop over time, and the MgDS will increase. High MgDS has been shown to predict adverse effects.

Preserved kidney function (specifically, tubular reabsorption of filtered Mg^{2+}) is required to prevent urinary wasting of Mg^{2+}. Healthy kidneys are key organs for Mg^{2+} homeostasis. Therefore, a decreasing eGFR is a key component of the MgDS. Alterations in renal capacity to handle Mg^{2+} significantly influence its body status. Notably, CKDs can, on their own, cause moderate Mg depletion, as a significant decrease in eGFR contributes 2 out of 5 points to the MgDS value, even when all other factors are absent (PPIs, diuretics, alcohol). Kidney damage and Mg deficiency stand in a complex, bidirectional relationship, even a vicious circle. The most frequent causes of CKD and end-stage renal disease are diabetic nephropathy and hypertensive nephropathy. Both DM and high blood pressure are strongly associated with the MgDS, in which progressive Mg depletion frequently indirectly worsens kidney function, and progressive kidney failure further deepens urinary wasting of Mg^{2+}. Therefore, it should be a priority to consider Mg depletion whenever eGFR is decreasing and to have Mg status checked in nephrology patients with these and other health issues [102]. Similarly, it would be advisable to use the MgDS as a marker of chronic latent Mg deficiency in critically ill nephrology patients. Finally, patients undergoing dialysis are at an extra risk of Mg depletion. Namely, the Mg^{2+} concentration in current dialysate solutions may be too low (typically 0.50 mmol Mg^{2+}/L), as serum Mg^{2+} levels decline in most patients undergoing routine hemodialysis [103]. Increasing it to 0.75 mmol/L or more appears necessary to prevent post-dialysis negative Mg balance and improve patient outcome [104]. Promotion of better care for kidney health is required due to the heavy overall burden of kidney diseases, which are one of the fastest-growing causes of death globally and were therefore declared a health priority by the 2025 World Health Organization resolution [105].

To our knowledge, this is the second review paper on the MgDS, second only to a recent scoping review by Costello et al. (2025) [106], who found that the MgDS methodology is a promising new tool for the rapid identification of an Mg-depleted nutritional status in a patient; however, the current review represents the first to consider the MgDS in critical care. Our main objective was to review the available literature on the importance of determining and monitoring Mg status in critically ill patients across different clinical conditions, specifically using the MgDS as a clinical parameter to indicate latent Mg deficiency. Hypomagnesemia and negative Mg balance are prevalent among the critically ill and are associated with increased mortality and complications such as lactic acidosis. However, the relationship between Mg status and patient clinical outcome is complex. This review aims to support healthcare professionals in systematically and efficiently approaching patients at high risk of this type of mineral malnutrition and electrolyte abnormality. Efforts to facilitate practical detection of latent Mg deficiency in the critically ill, followed by Mg repletion adequately incorporated into the therapeutic regimen, could certainly improve patient management and outcomes. Since traditional methods to assess Mg deficiency are insufficient for its detection, a new tool has been proposed: the score of Mg depletion, MgDS, designed to indicate Mg deficiency in the body by considering factors such as kidney disease, the use of certain drugs (diuretics and PPIs), and heavy alcohol consumption. Many benefits have been shown to arise from using the MgDS to indicate Mg depletion in clinical practice and, especially, in clinical studies, including an innovative approach through statistical analyses and robust results from many NHANES-based studies. However, certain limitations and criticism regarding methodology have indeed arisen. Concerns exist regarding other relevant factors in the disease history of the patient (*e.g.*, digestive tract issues) and medication history (tetracyclines, bisphosphonates, cisplatin, cyclosporine) that can also significantly lower body Mg content but are not included in the MgDS calculation. Other considerations underscore that we cannot assess whether the MgDS is truly a marker superior to serum Mg^{2+} levels for detecting Mg deficiency, particularly the serum iMg^{2+} fraction, as these are not available in the NHANES database [107,108]. These points should be addressed in the future to improve the methodology of the approach.

This literature review shows that an increase in the MgDS (indicating progressive chronic Mg deficiency) is associated with poor overall health and strongly correlates with a number of disorders (most of which are neither ur-

gent nor critical). While the MgDS has shown promise in chronic conditions such as DM, CKD, and COPD, its utility in critically ill patients remains under investigation. The high prevalence of Mg deficiency among critical care patients and its significant negative prognostic effects prompted us to highlight its underdetection in clinical practice, given diagnostic challenges. Traditional methods such as serum Mg^{2+} levels and the MTT assay are commonly used to assess Mg status. However, these tests have limitations, especially in critical care settings. Total serum Mg^{2+} accounts for only about 1% of total body Mg stores, and its levels can remain normal even when tissue Mg is being depleted; hence, it may not accurately reflect low Mg status of a patient. As for the iMg^{2+} fraction, a promising new biomarker of Mg status in the critically ill, many ICU departments remain without the necessary point-of-care blood gas analyzers equipped with Mg^{2+} ion-selective electrode technology.

Conversely, MTT, the gold standard for assessing Mg body status, is labor-intensive and time-consuming and may not be suitable for all critically ill patients (*e.g.*, those with oligoanuria) [109]. This unfavorable set of circumstances leaves chronic Mg deficiency completely neglected in patients who are controversially at direct risk. Therefore, further research is needed to establish reliable indicators of Mg deficiency in this patient population [16,110].

Since its introduction, the MgDS has been validated for risk assessment and stratification, as well as for associations with various diseases and health conditions. It has been recognized as a more valuable and reliable predictor of Mg depletion than traditional clinical markers. The MgDS is useful for detecting the health risks and burden associated with significant urinary Mg^{2+} loss in otherwise healthy individuals and those with certain morbidities. However, is the MgDS a good indicator of Mg deficiency in critically ill patients? It has been extensively investigated across different patient groups over a short period using comprehensive population databases. Meanwhile, no clinical study has used the newly introduced MgDS parameter to indicate Mg deficiency in the critically ill. This question, in many respects, remains unanswered. For example, higher MgDS is associated with an increased risk of CVD mortality [17], and Mg deficiency in the critically ill (assessed by other means) is also associated with an increased risk of CVD mortality. However, clinical studies are needed to support the use of MgDS in patients in critical care departments, as they are vulnerable and unstable, and their general condition and Mg depletion can easily be exacerbated. The current lack of MgDS research in critically ill patients may be due in part to the fact that it has not yet been clinically validated in this population. Only after validation by a standardized Mg loading test could this score be implemented as an indicator of chronic Mg deficiency in ICU settings.

Another question is whether the MgDS can be applied to all groups of critical care patients, depending on the dominant pathology, and to all people and countries. Results from most studies in this search were drawn from datasets of participants in the NHANES database, which is designed to be representative of the civilian American population. Indeed, Mg is unfortunately often neglected as a micronutrient, with as many as half or more of adults in America and the Western world failing to consume the recommended daily amounts of Mg. Thus, this could be the sole reason for chronic Mg deficiency, but when combined with otherwise low dietary intake, pathophysiologically increased Mg^{2+} loss can seriously deplete body stores [8].

Our search of the PubMed database for Mg deficiency score identified 80 relevant clinical studies, most of which used the NHANES database. This may be another reason no studies were found on the MgDS in critical care patients, as NHANES is a survey that included only non-institutionalized patients. Perhaps this is simply due to the brief period since the MgDS was introduced into clinical research and practice (5 years ago); not a single study on critically ill patients has used this new tool. In any case, there remains insufficient research focus on chronic Mg^{2+} deficiency in the critically ill, even in the Western world. Another dilemma concerns whether these findings can be adequately generalized and extrapolated from the American population to the global population. Most of the published studies we found were conducted using the same database and were based on a single demographic group on a single continent. However, the prevalence of chronic Mg deficiency varies by region and population, as well as by biogeochemical, socioeconomic, demographic, national, racial, and even cultural characteristics (*e.g.*, nutrition, lifestyle). Therefore, it is probably more prevalent in some countries than in others, although reliable and complete registries remain limited in most countries.

Mg deficiency can be of dietary and/or non-dietary origin; however, globally, a substantial portion of the population fails to meet daily intake recommendations, with estimates as high as 31% [111]. For example, in China, as in many countries, the global and regional prevalence of chronic Mg deficiency is only partially established; however, data from the Chinese Nutrition and Health Surveillance indicate that, among multiple micronutrients, Mg is also potentially deficient in Chinese adults. Studies show that a significant portion of the Chinese population in many provinces does not meet the recommended daily intake of Mg, increasing the risk of Mg deficiency. This pattern is particularly prevalent among certain demographics (women more than men, urban residents more than rural residents) and in certain regions of China (southern and western regions are particularly affected due to Mg-deficient arable land), according to environmental health research. Studies also indicate a downward trend over time in dietary Mg intake among adults in China, primarily due to dietary factors (increasing consumption of Mg-depleted processed foods) and soil Mg deficiency (affecting the Mg content of locally

grown foods). This significant decline in Mg intake over the last several decades has led to a corresponding recent increase in the prevalence of Mg insufficiency [112]. In the United States, many people, including children, adolescents, adults, and older adults, do not get enough Mg needed for optimal health from their diet, according to US national dietary surveys [6]. Additionally, the modern-day global trend toward changing dietary habits favors calcium over Mg intake, further contributing to a decline in Mg status. A resulting rise in the calcium-to-magnesium food intake ratio is associated with an increasing incidence of type 2 DM, metabolic syndrome, chronic inflammation-related disorders, OP, etc. [113].

A key point regarding the MgDS is that, when summed, the factors included in the MgDS are chronic in duration (kidney damage, substance use or abuse), and the latent Mg deficiency it can detect and estimate is also chronic. Among these MgDS-associated factors, diuretic-induced Mg depletion is an important one. However, it should be stressed that not all diuretics interfere with Mg^{2+} metabolism, resulting in renal wasting of Mg^{2+}. Potassium-sparing diuretics tend to increase serum and intracellular Mg^{2+} content. In contrast, large doses of loop- and thiazide-type diuretics, given more than once daily for prolonged periods, increase urinary Mg^{2+} excretion and may lead to an Mg^{2+} deficit over time. Mannitol can also cause urinary Mg^{2+} loss due to induced osmotic diuresis [114]. PPI-induced Mg depletion results from long-term PPI use, as PPIs impair intestinal Mg^{2+} absorption via TRPM channels and claudin transporters, creating a negative Mg balance [115]. Chronic excessive intake of alcohol (heavy drinking, binge drinking) depletes Mg from the body through several mechanisms: increasing diuresis, impairing Mg^{2+} absorption from the gut, and potentially damaging the liver and pancreas [116]. However, the kidneys are the primary regulators of Mg balance and Mg^{2+} blood levels; hence, a declining eGFR (indicating reduced kidney function) substantially affects Mg homeostasis. A renal cause of low Mg^{2+} can be confirmed by an elevated fractional excretion of Mg^{2+} (FE_{Mg} >4%) [1].

Thus, this scoring system clinically predicts Mg deficiency by summarizing the most frequent pathophysiological factors that primarily affect renal Mg^{2+} reabsorption. Nevertheless, it is not a comprehensive biomarker of Mg depletion, as it disregards adverse renal Mg^{2+} wasting caused by other drugs, such as certain antibiotics (*e.g.*, aminoglycosides), chemotherapeutics (*e.g.*, platinum-based agents), and immunosuppressive agents (*e.g.*, tacrolimus). These agents are directly tubulotoxic and impair renal Mg^{2+} transport mechanisms, leaving most patients in negative Mg balance. Additionally, some antibiotics, such as tetracyclines and quinolones, when administered orally, can interact with Mg^{2+} in the digestive tract lumen to form insoluble soaps that cannot be absorbed. Another limitation is that the actual calculation of the MgDS does not account for other common pathways of non-renal Mg^{2+} loss. One could consider expanding the MgDS by adding other non-renal-relevant factors to the sum during calculation to increase the sensitivity of the score to latent Mg deficiency in the body. For example, many digestive tract disorders that impair Mg^{2+} absorption from the gut should also be considered (gastric juice hypoacidity, caffeine consumption, chronic diarrhea, malabsorption syndrome, increased loss through gastrointestinal secretions, etc.), as well as skin losses (*e.g.*, in severe burns), and perhaps poor nutritional Mg intake as well. It may be difficult to formulate all this mathematically, but efforts are needed to improve the diagnostics of this subclinical condition. Accordingly, we propose considering more precise terminology and a name for this score that is more appropriate than the current one: renal magnesium depletion score (rMgDS) or urinary magnesium depletion score (uMgDS).

Despite these drawbacks, the MgDS includes some of the most clinically relevant kidney-related factors contributing to this electrolyte imbalance. Indeed, the MgDS can be regarded as a tool for an initial attempt to focus clinical attention on the neglected condition of chronic subclinical Mg deficiency and as an invitation to future methodological improvements. Finally, although acquired causes of renal and/or intestinal Mg^{2+} wasting are more common, rare inherited causes (genetic syndromes affecting Mg^{2+} transport mechanisms in the kidneys and gut) are also possible. Although some improvements are needed, we believe that the MgDS should be implemented in daily clinical practice. Indeed, the MgDS can both help diagnose this mineral deficiency and approximately grade its severity (as a numerical parameter). Knowing the MgDS value of each patient would help stratify the risk of Mg deficiency-related health outcomes. Moreover, the MgDS would facilitate precise statistical analyses in future studies on the not yet fully examined associations between Mg depletion and other health conditions, such as mitral valve prolapse [117] and asthma exacerbations [118]. When planning future research on the MgDS in critically ill patients, multiple ICU departments should be included. Clinical research studies on this topic should encompass critical conditions from different medical fields in both adults and children (coronary units, cardiopulmonary and vascular surgery, neurocritical care, surgical intensive care, liver diseases, renal diseases, obstetrics, pediatric intensive care, etc.) to thoroughly cover patients from all the departments where Mg deficiency prevalence is high [14]. Prospective clinical studies should be designed and conducted to investigate whether the MgDS is useful as a predictor of morbidity and mortality in critically ill patients. Table 5 summarizes and highlights the main points of our considerations of the MgDS as a potentially useful tool for identifying at-risk critical care patients with chronic Mg deficiency.

Finally, since a significant proportion of the population is likely to have chronic latent Mg deficiency, cal-

Table 5. Considerations on the potential use of magnesium depletion score (MgDS) for better diagnosis and treatment of chronic latent Mg deficiency in critical care practice.

Aspects	Details
Systemic importance of magnesium balance	- Magnesium (Mg) is a mineral and an electrolyte (Mg^{2+}) vital for optimal human health. - However, Mg deficiency is often neglected in the clinical practice, including critical care.
Health risks of magnesium depletion	- Severe acute Mg deficiency can vitally endanger a patient. - Chronically low Mg^{2+} levels increase the risks of many non-communicable conditions and worsen the outcomes especially in critically ill patients. - Despite this, chronic Mg deficiency remains an underrecognized health issue in ICU settings.
Magnesium depletion score (MgDS)	- A new composite indicator of depletion of overall Mg body content. - Mainly focuses on kidneys' capacity to reabsorb Mg^{2+}. - Includes chronic use of diuretics, proton pump inhibitors and alcohol, and chronic kidney damage. - Does not directly include data on dietary Mg intake. - Found to be associated with a myriad of versatile adverse health risks resulting from Mg depletion. - High MgDS values suggest a broad comorbidity risk and patient vulnerability to chronic diseases and acute exacerbations.
Research gaps on using MgDS at ICU	- It is unclear if MgDS alone can be a reliable indicator of chronic latent Mg^{2+} deficiency in critical care patients. Clinical studies on using MgDS in these patients are still lacking. - High MgDS is expected to correlate with increased morbidity and mortality risks in ICU patients. Future prospective clinical studies are needed to investigate this.
Potential clinical application of MgDS at ICU	- Screening for Mg deficiency should be a routine measure of patient management at ICU departments. - Incorporating MgDS as a prognostic tool into ICU practice could enhance risk stratification and patient treatment at ICU departments. - Combining MgDS with serum concentrations of total Mg^{2+} and ionized Mg^{2+} fraction could improve diagnostic accuracy of MgDS in detecting chronic Mg depletion.
Final aim	- Therapeutic optimization of Mg status can reduce the adverse outcomes and improve the prognosis in critically ill patients diagnosed with Mg depletion.

MgDS, magnesium depletion score; ICU, intensive care unit.

culating the MgDS and including Mg^{2+} levels in the routine serum electrolyte panel represent a reasonable means of meeting the ongoing need to identify and treat Mg-depleted patients with adequate Mg replacement therapy [119]. Therefore, we believe that when assessing for the development of chronic latent Mg deficiency in a patient, including ICU patients, an ideal approach may be to first screen the patient (especially those on diuretics, PPIs, kidney patients, or heavy drinkers) using the MgDS for risk assessment based on clinical factors, and then, if the MgDS is moderate to high ($\geq$2), to measure, wherever possible, the serum level of iMg^{2+} (as a direct form of active Mg^{2+} in the blood), even when the tMg^{2+} level is normal, whether clinical symptoms suggest Mg^{2+} deficiency or not. This protocol could help uncover hidden Mg deficiency and guide its therapy, especially in patients at high risk or in critical and urgent conditions. The condition is currently underdiagnosed; however, it is normally easy to treat. Repleting Mg stores may help reverse the risks, while maintaining optimal Mg balance to promote health would be the final goal. For example, increased dietary Mg intake inhibits calcification of the abdominal aorta in an experimental animal model; Mg supplementation might also counteract vascular calcification in patients with CKD [120].

The main purpose of this review was to map and summarize the scope and nature of the literature on the evolving topic of the MgDS and to assess its potential applicability in critically ill patients. Overall, our findings suggest that Mg depletion is a relevant, modifiable factor associated with the health burden of several chronic conditions, and that the MgDS may be used to quantify the strength of these associations. The MgDS is a valuable clinical indicator of health risks associated with chronic Mg deficiency, yet its diagnosis remains challenging. However, regarding the potential use of the MgDS in critically ill patients, prospective studies and intervention trials are needed to clarify its value and determine whether lowering the MgDS to improve Mg status in patients at higher risk of Mg depletion can reduce morbidity and improve outcomes.

5. Conclusions

Negative health implications of Mg deficiency are substantial and well established in the literature. However, they still do not receive adequate clinical attention. Many

practical obstacles prevent proper treatment. The diagnosis of Mg deficiency is difficult when it falls within the asymptomatic (*i.e.*, clinically latent) range of presentation. Mg deficiency is usually detected only when hypomagnesemia and its signs and symptoms become evident. However, because Mg^{2+} is a predominantly intracellular cation, the pathobiology of its deficiency is more complex than a simple decline in serum levels would suggest. Substantial depletion of total body Mg content can occur well before that, and normal serum tMg^{2+} is often erroneously interpreted as excluding Mg deficiency.

Regarding this issue, clinicians ought to respond promptly rather than waiting for serum Mg^{2+} levels to drop appreciably. The idea is to actively look for Mg deficiency in the body, as it may not be obvious (subclinical), while bearing in mind the risks of its development. This is particularly important in the critically ill, in whom low total body Mg content poses an additional and unnecessary health risk of developing numerous chronic conditions that contribute to poor outcomes; overall, intensive care management would need to focus more on the Mg status of the patient. This review provides novel insights into the importance of chronic latent Mg deficiency in the critically ill by synthesizing current knowledge of its health implications relevant to this patient population. Some of the major risks for Mg deficiency are collectively summarized in the Mg depletion score presented here.

Practical assessment of Mg status in a patient is challenging, as is the diagnosis of Mg deficiency. Available parameters and functional tests each have specific advantages and limitations, and no single biomarker reliably reflects whole-body Mg status. Combined approaches may improve diagnostic accuracy, particularly for clinical detection and epidemiological research of subclinical Mg deficiency. Currently, the major obstacles include the demanding Mg loading test and the difficulty of estimating total body Mg from serum measurements of tMg^{2+} (which is insufficiently sensitive) and the iMg^{2+} fraction, which is not fully standardized and is not conventionally available owing to the requirement for specialized, high-cost equipment. To address these limitations, the MgDS has been implemented as a pragmatic evaluation tool to predict Mg deficiency by calculating the risk of common nondietary causes of chronic Mg depletion (CKD, chronic alcohol intake, and chronic use of diuretics and PPIs), with values ranging from 0 to 5. Despite its high global prevalence, dietary Mg deficiency is not directly included in the MgDS calculation, but it can certainly further increase the risk of a high MgDS.

This literature review search included studies on the MgDS published from its introduction in August 2021 through August 21st, 2026. The findings show that the MgDS is associated with a variety of chronic diseases and conditions, indicating multiple health risks strongly linked to chronic Mg deficiency. Given that screening for Mg deficiency is not a routine clinical practice, and based on the literature we reviewed, we conclude that practicing physicians should have Mg status checked in all patients with arterial hypertension, coronary heart disease, congestive HF, COPD, sleep apnea, stroke, depression, Parkinson's disease, chronic pain, DM, fatty liver, kidney stones, hyperuricemia, and OP. To facilitate this, it is appropriate to first determine the MgDS as a quick, simple, and informative preliminary measure of Mg deficiency. The list of MgDS-associated conditions is likely to expand in the years to come, as it has been only a few years since the MgDS was introduced. Incorporating the MgDS into routine patient examinations, including those of ICU patients, would improve treatment and outcomes.

Lastly, the MgDS is a prediction, not an exact measure; it is an indicator of probability rather than a definitive confirmation of Mg deficiency. Therefore, the MgDS cannot serve as a diagnostic tool *per se*, but rather represents a valuable metric for the early detection of the condition. This applies to any individual, including a patient, but the MgDS is particularly valuable for the timely management of ICU patients requiring focused, intensive care and treatment without delay. Benefits from using the MgDS in critical care patients stem from its clinical advantages, as well as the very high mortality risk associated with undetected and untreated Mg deficiency that they are likely to carry. 1It is clinically useful to use the MgDS to detect and quantify the severity of Mg depletion (low-grade, moderate, or severe), as this can significantly impact patient outcomes. Although this score represents an empirical and semi-quantitative assessment, it is practical, noninvasive, inexpensive, rapid, easy to calculate, and useful for a practicing clinician to gain initial insight into the state of general Mg deficiency in the body, which is otherwise difficult to measure precisely. High MgDS can effectively identify patients vulnerable to developing various chronic conditions and disorders.

The multiplicity of clinical manifestations of chronic Mg deficiency can be explained by the ubiquitous nature and wide range of physiological functions of Mg^{2+}. Numerous experimental, clinical, and epidemiological data demonstrate that Mg depletion is linked to various health conditions (neurological, psychological, cardiovascular, respiratory, endocrine, metabolic, immunological, digestive, urological, obstetrical, osteoarticular, etc.). In almost every organ system, chronic subclinical Mg deficiency can initiate or exacerbate multiple pathophysiological processes. Relevant examples include cardiac arrhythmias, arterial and pulmonary hypertension, coronary artery and peripheral artery disease, congestive HF, mitral valve prolapse, COPD, asthmatic crisis, epilepsy, migraine and tension headache, neurodegenerative diseases, anxiety, depression, chronic pain, preterm labor, frailty, etc. Elevated MgDS is even associated with adverse health outcomes. Each 1-point increase (out of 5 maximally) in the MgDS value is associated with a higher risk of a number of diseases, including all-cause and cardiovascular mortality in

diabetic patients, stroke risk in CKD, and higher mortality in older adults, etc. Thus, individuals with Mg deficiency status may significantly benefit from dietary Mg supplementation to reduce multiple health risks, some of which are listed in this review.

While the MgDS may serve as a tool for assessing Mg deficiency status in many chronic health conditions, its effectiveness in critically ill and severely endangered patients still requires further validation. As such studies remain limited in the published literature, this review does not meet its first goal: to estimate the MgDS as an indicator of Mg depletion in the critically ill. However, our second goal, to illustrate the long-term health consequences of chronic Mg depletion and to further acknowledge the associated risks, was achieved. Studies on the MgDS have identified this metric as a useful clinical marker of significant Mg depletion. Although there are issues to address regarding the MgDS methodology, the truly valuable clinical implication of the MgDS-chronic morbidity associations is that high MgDS can predict adverse events and that chronic Mg depletion, as indexed by the MgDS, marks a poor prognosis; meanwhile, adequate Mg supplementation may mitigate these risks. Further investigations are warranted to confirm this statement in critically ill patients. However, since clinical studies on MgDS-related mortality risks in critical care patients remain limited, these patients remain a high-risk group. Therefore, we believe that clinicians should continue to rely on established methods and clinical judgment when assessing Mg status in the critically ill, while being aware of its limitations, and simultaneously try to broadly implement this simple test as a quick, readily available asset for estimating chronic latent Mg deficiency in a patient.

In summary, additional research and randomized clinical trials are needed to confirm whether MgDS alone reliably indicates chronic latent Mg deficiency in critical care patients, to investigate whether high MgDS levels are a marker of poor prognosis in the ICU, and to elucidate the underlying mechanisms associated with morbidity and mortality. The goal is to provide an improved, evidence-based clinical decision-making algorithm to support sound assessment and treatment of this condition. Therefore, the authors suggest a procedure to detect and confirm chronic asymptomatic Mg deficiency in critical care patients, including the implementation of a simple, non-invasive MgDS assessment scoring tool. Wherever possible, the MgDS should be considered alongside other Mg^{2+} measurement methods, such as serum levels of tMg^{2+} and iMg^{2+}, to obtain a valid assessment of Mg status and determine whether Mg deficiency is present. Improving diagnostics and identification of Mg-deficient individuals, followed by appropriate Mg repletion through diet and/or supplementation, will help prevent unnecessary Mg-deficiency-related health complications and improve prognosis and survival. To overcome obstacles and improve testing accuracy, we advise using the MgDS and iMg^{2+} combination: calculate MgDS first (to identify individuals likely to be Mg-deficient), then measure iMg^{2+} serum levels (to confirm Mg^{2+} deficiency and tailor treatment). When available to practitioners and researchers, this strategy (yet to be validated) is expected to demonstrate its efficacy in diagnosing chronic latent Mg deficiency compared with the current practice of measuring tMg^{2+} serum levels alone. Although there is currently no research on the MgDS in critical care medicine, we consider this negative finding in the literature search worth publishing. There is still no direct evidence supporting our idea; therefore, the answer to our question, "Could the MgDS be a new indicator of chronic magnesium deficiency in critical care patients?" may remain negative in the future. Theoretical considerations on the topic may motivate future clinical studies to provide or refute such evidence.

Abbreviations

tMg^{2+}, total Mg^{2+}; iMg^{2+}, ionized Mg^{2+}; CLDN, claudin; TRPM, transient receptor potential melastatin; FE, fractional excretion; RBC, red blood cell; MTT, magnesium tolerance test; MgDS, magnesium depletion score; ICU, intensive care unit; NHANES, National Health and Nutrition Examination Survey; PPIs, proton pump inhibitors; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; MRI, magnetic resonance imaging; HF, heart failure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; ED, erectile dysfunction; DM, diabetes mellitus; HbA1c, hemoglobin A1c; BMD, bone mineral density; OP, osteoporosis; RA, rheumatoid arthritis; OA, osteoarthritis; LV, left ventricle; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; rMgDS, renal magnesium depletion score; uMgDS, urinary magnesium depletion score.

Author Contributions

MS: Conceptualization, study design, literature review, original draft preparation, editing, supervision and manuscript revision for important intellectual content. AV: Literature search and screening, manuscript reviewing and editing. KS: Critical review and revision of the manuscript for important intellectual content, analysis data. MB: Literature search, synthesis of evidence and manuscript revision. SS: Graphical processing, analysis data, manuscript reviewing and editing. SL: Data interpretation and critical revision of the manuscript. JNO: Analysis of data, manuscript revision and funding acquisition. All authors revised the content and approved the final manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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