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Review

Multifaceted Nutritional Disorders in Elderly Patients Undergoing Dialysis

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Abstract: Advances in medicine have resulted in increased longevity, which has consequently led to unexpected geriatric syndromes, such as frailty and sarcopenia. Patients with end-stage kidney disease, especially those receiving dialysis treatment, often show characteristic reductions in body protein and energy storage, termed protein energy wasting (PEW). Therefore, maintenance of nutritional condition has a key role in defending against both geriatric syndromes and PEW, which share several components in elderly individuals undergoing hemodialysis. To counteract the development of an undesirable condition, nutritional evaluation is indispensable. In addition to simple measurements of body mass index, and serum albumin and creatinine, a composite nutritional assessment including a malnutrition inflammation score is useful, although subjective elements are included and a well-trained examiner is required. On the other hand, the geriatric nutritional risk index and nutritional risk index for Japanese hemodialysis patients (NRI-JH) are objective tools, and easy to use in clinical settings. Undernutrition is closely related to infectious events and the results of an infection are often serious in elderly patients, even those with survival, with large medical costs incurred. Together with appropriate nutritional evaluation, it is necessary to clarify the underlying relationship of PEW with infection for improvement of prognosis in affected elderly individuals.

Keywords: nutrition; protein energy wasting (PEW); sarcopenia; frailty; hemodialysis; end-stage kidney disease (ESKD); chronic kidney disease (CKD)

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1. Introduction

Malnutrition has factors related to both overnutrition and undernutrition [1]. Obesity is a representative overnutrition-related disorder and profoundly linked to various adverse conditions, such as metabolic syndrome, diabetes, cardiovascular disease (CVD), non-alcoholic fatty liver disease, and chronic kidney disease (CKD), etc. [2]. Great efforts have been made to improve poor outcomes induced by overweight and obesity conditions. At the same time, while advances in public health and medical treatments have extended longevity [3], rapid aging has brought on unexpected geriatric syndromes including frailty [4] and sarcopenia [5], with undernutrition rather than overnutrition considered to be the more serious issue related to those conditions.

CKD has become a major health problem throughout the world and known as not only a risk factor for end-stage kidney disease (ESKD), but also for CVD and death. Increased longevity has highlighted the importance of measures needed to protect against CKD development. In addition to primary diseases, such as diabetes and hypertension, aging accelerates structural and functional deteriorations in the kidneys [6,7], resulting in an increased prevalence of CKD and subsequent ESKD in association with aging [8]. In Japan, more than half of current dialysis patients are aged 70 years or older [9]. In patients with advanced CKD and ESKD, a unique nutritional disorder resistant to various interventions has become recognized as a condition termed protein energy wasting (PEW).

Elderly patients undergoing dialysis suffer from both geriatric syndromes and PEW [10–12]. No definitive medication has yet been developed for these conditions, thus improvement of nutritional status is currently the only treatment option available. Generally, energy restriction for diabetes patients and protein restriction in patients with CKD have been accepted as standard diet therapy protocols, although a paradigm shift from restriction to adequate intake has occurred in recent years [12,13]. The present review was conducted to elucidate how to evaluate nutritional status in patients undergoing hemodialysis, primarily elderly, based on considerations of overlapping of PEW, sarcopenia, and frailty in those individuals. In addition, infection as a serious consequence in this population has received focus as a factor for future medical and economic measures.

2. What Are PEW, Frailty, and Sarcopenia?

2.1. PEW

Nutritional derangement in patients with CKD, in particular ESKD, is characterized by wasting (loss of muscle and fat tissues), regardless of the etiology, with multiple mechanisms thought to be involved in this phenotype [14–17]. While an inadequate diet generally induces undernutrition in this population, increased food intake does not always correct wasting. It is considered that the presence of chronic inflammation manifested by increased pro-inflammatory cytokines may be profoundly linked to wasting coupled with endocrine disorders, such as impaired insulin/insulin growth factor-1 signaling. Moreover, metabolic acidosis and uremic toxins exacerbate and accelerate catabolic pathways, increasing the effects of co-morbidities.

To date, many terms have been proposed for this condition, such as protein-energy malnutrition [18], malnutrition-inflammation complex syndrome [19], uremic malnutrition [20], and uremic cachexia [21]. However, those may not adequately cover the common features seen in CKD and ESKD patients, while the most common term, protein energy wasting (PEW), has been proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) [14,22]. Diagnosis of PEW is based on the following four categories: (1) Serum chemistry, such as low serum albumin and low serum cholesterol; (2) body mass, such as low BMI, unintentional body weight loss, and low body fat; (3) muscle mass, such as reduced muscle mass over time and creatinine appearance; and (4) dietary intake, such as unintentional low levels of dietary protein and energy intake (Table 1). Discussion regarding adaptation of the PEW criteria for Asian patients receiving dialysis is presented later in this review.

Table 1. Comparison of NRI-JH with PEW criteria components in dialysis patients [14,23].

PEW Component		NRI-JH Component	Cut-Off Values	Score
Serum chemistry	Albumin < 3.5 g/dL Transthyretin (prealbumin) < 30 mg/dL Total cholesterol < 100 mg/dL	Albumin	Age ≥ 65 → <3.5 g/dL Age < 65 → <3.7 g/dL	4
		Total cholesterol	<130 mg/dL	1
			≥220 mg/dL	2
Body mass	<23 kg/m^2 Unintentional weight loss 5% over 3M or 10% over 6M Total body fat percentage < 10%	BMI	<20 kg/m^2	3

Table 1. *Cont.*

PEW Component		NRI-JH Component	Cut-Off Values	Score
Muscle mass	Reduced muscle mass 5% over 3M or 10% over 6M Reduced mid-arm muscle circumference area Creatinine appearance	Creatinine	Age $\geq$ 65 $\rightarrow$ Male < 9.7 mg/dL Female < 8.0 mg/dL Age < 65 $\rightarrow$ Male < 11.6 mg/dL Female < 9.7 mg/dL	4
Dietary intake	Unintentional low DPI < 0.80 g/kg/day for at least 2M Unintentional low DEI < 25 kcal/kg/day for at least 2M	-	-	

Abbreviations: BMI, body mass index; DPI, dietary protein intake; DEI, dietary energy intake.

2.2. Frailty

Frailty is a vague word originally used to indicate a state in elderly individuals with decreased activities of daily living (ADL) indicating their need for nursing care [24]. However, there is confusion regarding the true meaning and its implications. Apart from impaired ADL, frailty has been used to indicate an age-related state of decreased physiological reserve and increased vulnerability to stressors, resulting in disability, then leading to hospitalization and finally death. Impairment of neurological factors, mechanical performance, and energy metabolism may be involved [25]. Rockwood et al. proposed a frailty index to show accumulation of deficits, such as age-associated disease, non-specific vulnerability, and disabilities [26]. In contrast to an accumulated deficit model, Fried et al. suggested a phenotype model that includes observations of weakness (grip strength), slow gait, unintentional weight loss, low tolerance for physical activity, and self-reported exhaustion, with frailty diagnosed when three or more of those are noted [4].

2.3. Sarcopenia

Sarcopenia is related to anatomical and functional deterioration in skeletal muscle. The term sarcopenia (*sarx* meaning flesh, *penia* meaning loss in Greek) was coined by Rosenberg in the 1980s, and literally meant aging-related loss of skeletal muscle, while some later studies included function of skeletal muscle and physical performance in addition to muscle quantity. As a result, the prevalence of sarcopenia in early reported CKD cases showed great inconsistency, ranging from 4% to 63% [27]. For comparisons among different cohorts, diagnostic criteria with a sense of unity were required. The European Working Group on Sarcopenia in Older People (EWGSOP) was the first to present a definition as well as diagnostic criteria, consisting of muscle mass, muscle strength (handgrip strength), and physical performance (gait speed) [28]. Since the establishment of objective assessments (methods, cut-off values, criteria), research regarding sarcopenia has dramatically progressed. However, another problem to emerge is adaptation of the EWGSOP criteria for non-European populations throughout the world, who show differences in these factors as anthropometric characteristics, ethnicity, and culture. As a result, the Asian Working Group on Sarcopenia (AWGS) proposed criteria for Asian populations in 2014 [29] based on concepts similar to those used by EWGSOP. For the purpose of early detection and treatment of patients with sarcopenia, consensus findings of the EWGSOP and AWGS 2014 criteria have recently been presented as EWGSOP2 [30] and AWGS 2019 [31], respectively.

2.4. Conceptual Overlapping among PEW, Frailty, and Sarcopenia

The concepts of age-related frailty and sarcopenia have developed independently of CKD-accelerated PEW [11]. However, aging deepens the relationships, since these disorders share common components. A comprehensive approach may be required to improve prognosis in elderly patients undergoing hemodialysis.

3. Evaluation of Nutritional Status

The term 'malnutrition' is commonly used to indicate a state of undernutrition, although an evaluation of nutritional status is not easily performed. While nutritional screening and assessment classifications are used, they are confusing and often misunderstood [32]. Nutritional screening is a quicker and more simple to use tool for identification of at-risk subjects, and generally does not require any special techniques. On the other hand, nutritional assessment is performed by trained health-care professionals and provides a nutritional diagnosis, with adequate follow-up of the patient after nutritional intervention. Subjective global assessment (SGA) [33] and malnutrition inflammation score (MIS) [34], as described in the following section, are considered as the gold standard methods. However, in clinical settings in Japan, it is very difficult to perform nutritional assessments including SGA and MIS. Therefore, nutritional screening tools are mainly used, which have both advantages and disadvantages, as noted below.

3.1. Anthropometric Indices

3.1.1. BMI

BMI is a simple anthropometric index to indicate body size. In contrast to overnutrition, a serious health problem in general populations [2], it is well-known that higher BMI is paradoxically correlated to better prognosis in patients with CKD, especially those receiving hemodialysis. This phenomenon has been termed 'obesity paradox' [35] or 'reverse epidemiology' [36]. The inverse association between BMI and mortality is highly consistent, beyond race/ethnicity and geographical area [37,38], suggesting that obesity paradox and reverse epidemiology refer to a universal phenomenon.

Although BMI is a popular and convenient index, there are some points regarding body composition to consider. BMI is influenced by water or solid weight. Apart from nutrition, hydration status in patients receiving dialysis treatment is a critical factor for prognosis. Even when BMI apparently increases, fluid retention is known to be a risk factor for CVD mortality [39]. In contrast, solid mass, including muscle mass and fat mass, is more relevant to nutrition. Unfortunately, separate evaluations of those are very difficult to perform [35]. Furthermore, fat mass is roughly divided into subcutaneous fat, which functions as an energy reservoir, and visceral fat mass, which shows metabolic abnormalities and pro-inflammatory characteristics [40]. Increased waist circumference as a surrogate of visceral fat was found to be associated with all-cause and CV mortality in 537 patients with ESKD [41]. Although it remains controversial whether an increase in fat mass, especially visceral fat mass, may have benefits, maintenance of muscle mass is believed to at least provide an advantage for survival [42].

Additionally, it is recognized that obesity paradox or reverse epidemiology is not always observed, even in patients undergoing dialysis, when BMI alone is utilized without consideration of body composition or age [43,44]. Inconsistent findings may be the result of a discordant contribution of increases in undesirable factors, such as fluid or visceral fat, different follow-up periods, or different modalities used for dialysis.

3.1.2. Measurement of Subcutaneous Fat and Fat-Free Mass

Skinfold measurements to determine subcutaneous fat are useful to estimate body fat mass [45]. The biceps skinfold (front side of mid-upper arm), triceps skinfold (TSF) (back side of mid-upper arm), subscapular skinfold (under the shoulder blade), and suprailiac skinfold (above the iliac crest) are measured. It was found that skinfold thickness was lower in patients on dialysis for 5 years or more as compared to those treated for less than 5 years [46], suggesting that fat mass loss is a time-dependent process. The triceps skinfold is considered to provide the most reliable results, since fluid retention is not often observed in the upper arm in dialysis patients. Although a skinfold caliper is not expensive and measurements are easy to perform with that device, a trained clinician should perform that examination to obtain an accurate result.

Measurements of circumferences with the use of a tape measure, such as of the arm, calf, and waist, can also reflect nutritional status to some degree. Waist circumference is known to be correlated with visceral adiposity, thus it is a critical factor for diagnosis of metabolic syndrome in examinations of general population subjects [47], although its significance in patients undergoing dialysis remains a matter of debate, as noted above. Calf circumference is related to protein storage and used for sarcopenia screening [29], while a recently published work showed the usefulness of calf circumference to discriminate sarcopenia in patients undergoing hemodialysis [48]. Measurement of mid-upper arm circumference (MAC) is easy and simple, and the results are found to be useful as an independent predictor of all-cause mortality in patients receiving hemodialysis therapy [49,50]. Nevertheless, it is also necessary to calculate mid-upper arm muscle circumference (MAMC) combined with TSF, performed with the following equation: MAMC = MAC − (TSF × 3.14) (where MAMC, MAC, and TSF are measured in centimeters) [51], since this can be used to determine muscle tissue reserve. Higher MAMC was shown to be associated with better mental health as well as better survival in hemodialysis patients [52]. Nevertheless, while MAMC has been classically used as an index of muscle mass and calf circumference [53], thigh muscle area assessed by computed tomography, when available, may be better for nutritional evaluation of patients undergoing hemodialysis [54].

3.2. Blood Chemistry Parameters

3.2.1. Albumin

A reduced level of serum albumin has been shown to be a predictor of mortality in patients undergoing hemodialysis [55]. In investigations of other nutritional screening tools, as described below, albumin has been found to be comparable to those in patients undergoing dialysis [56–58].

It is important to note that albumin reflects not only a nutritional disorder but also inflammation. For example, hypoalbuminemia is the result of the combined effects of poor nutritional status and inflammation [59]. Both undernutrition and inflammation reduce protein synthesis, resulting in hypoalbuminemia, while inflammation is associated with protein catabolism [60]. Although a decrease in serum albumin was found to be associated with increased mortality risk in dialysis patients, adjustment for SGA did not decrease that risk, whereas adjustment for inflammation did, suggesting a profound association of the inflammatory process with poor outcome [61]. Therefore, albumin may be more than only an indicator of nutritional status.

A recent study retrospectively examined the association between long-term trajectory of serum albumin and mortality in 421 patients undergoing hemodialysis [62]. In patients who died, serum albumin tended to decrease at 7 to 8 years before death as compared to those who survived, with a difference in albumin trajectory between survivors and non-survivors becoming apparent 3 years before death. This led to the question of whether a change in albumin level is associated with mortality. In association with that, the influence of changes in serum albumin level over time on all-cause or CVD mortality was examined. Time-varying hypoalbuminemia was found to be a predictor of all-cause mortality and CVD death, while an increased albumin level over time was associated with better survival independent of baseline albumin level [63]. In addition, higher dietary protein intake, evaluated using normalized protein catabolic rate (nPCR), which was corrected based on renal urea clearance, during the first 6 months was associated with higher serum albumin level and lower mortality [64]. These findings suggest the importance of periodic measurements of serum albumin.

A number of studies have emphasized various problems associated with an aging society and it is considered that typical guidelines should not be consulted for managing very elderly patients. A recent work examined the association of quality-of-care indicators, including spKt/V, calcium, phosphate, hemoglobin, and albumin, with CVD events and mortality, as those are known to be associated with prognosis in patients receiving hemodialysis. Interestingly, in patients aged 80 years and older, low serum albumin level was the only factor significantly associated with CVD events and all-cause mortality [65]. Albumin measurement may be useful for elderly patients undergoing dialysis treatment.

Although serum albumin level is useful as a nutritional screening tool, it is unclear whether its most diluted concentration during the preparation for hemodialysis is accurate. Therefore, albumin levels before (diluted) and after (concentrated) a hemodialysis session were compared [66]. For prediction of 1- and 5-year mortality, the pre-albumin level was more accurate than post-albumin level. Importantly, among other nutritional factors, such as blood urea nitrogen and BMI, pre-hemodialysis creatinine level, which is described in the following section, was also predictive of mortality.

3.2.2. Pre-Albumin (Transthyretin)

Pre-albumin, also known as transthyretin, is mainly synthesized by the liver according to dietary intake [67] and, when compared to albumin, its half-life is relatively short, thus it is thought to be a more sensitive indicator of nutritional condition than albumin. Reports have noted that serum pre-albumin could be used to predict survival and hospitalization for infection independent of serum albumin in patients undergoing hemodialysis [68,69]. Furthermore, a decrease in serum pre-albumin over time was found to be significantly associated with mortality in patients receiving hemodialysis [70]. Moreover, significant increases in serum pre-albumin as well as albumin were observed in association with oral nutritional supplementation during hemodialysis session over a period of 6 months [71]. These findings suggest that pre-albumin is a good indicator of nutritional status.

3.2.3. Transferrin

Transferrin, a powerful iron chelator that maintains Fe^{3+} in a redox-inactive state and inhibits the generation of free radicals in blood [72], is predominantly expressed in the liver. The synthesis of transferrin increases in association with iron deficiency, although the underlying mechanism is unknown. In the general population, high transferrin levels have been observed in subjects with iron deficiency, pregnancy, or contraceptives use [73], while it is also known to be a surrogate marker of nutritional status and potential indicator of PEW [14]. In clinical settings, serum transferrin level is indirectly evaluated by determination of total iron-binding capacity (TIBC) [74]. TIBC is well correlated to nutritional marker, such as SGA in relation to hemodialysis, with low TIBC in those patients found to be associated with PEW, iron deficiency, inflammation, poor quality of life, and mortality [75]. Therefore, as a component of MIS, TIBC is usually measured, while transferrin can be alternatively used [34].

3.2.4. Creatinine

Serum creatinine is considered to be a surrogate marker of skeletal muscle mass in patients undergoing dialysis [76,77]. Along with albumin, creatinine has been found to be inversely correlated with mortality [50,56]. As compared to other body components, including subcutaneous and visceral fat mass, muscle mass has been shown to be the most critical component of PEW and directly related to sarcopenia [14]. In fact, a lower serum creatinine level was found to be associated with poor prognosis in 119,099 Japanese patients undergoing hemodialysis, although no significant association between BMI and mortality was noted [44]. Furthermore, addition of creatinine to the PEW criteria resulted in more identification in 109 patients on hemodialysis [78].

Low triiodothyronine (T3) syndrome, highly prevalent in patients undergoing dialysis, is characterized by a low free T3 (FT3) level, along with normal concentrations of thyroid stimulating hormone (TSH), the most sensitive and specific test of thyroid function, and free thyrotoxin (FT4) [79]. This syndrome is thought to be a physiologic adaptive response to excessive catabolism, such as PEW and has been reported to be associated with CVD mortality in patients receiving dialysis treatment [80]. We examined the association between low T3 syndrome and clinical factors associated with nutrition and inflammation in 332 hemodialysis patients [81]. The results indicated that serum creatinine, but not albumin or CRP, was significantly associated with FT3/FT4 ratio, a relevant indicator for low T3 syndrome, suggesting that low muscle mass may be a cause of this syndrome. Local T3 generation from T4 occurs in skeletal muscle; therefore, this conclusion is plausible. In addition, serum creatinine may be an indirect marker of dietary protein intake, as creatine levels have been found to be positively associated with nPCR [44].

3.2.5. Lipids (Cholesterol)

Dyslipidemia is caused by a disbalance of lipids, such as high level of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and non-high density lipoprotein cholesterol (non-HDL-C), and established as a cardiovascular risk factor in the general population [82]. However, an opposite association of dyslipidemia with mortality is known in patients with advanced CKD [36,83]. As noted above, an unexpected observation regarding the association between BMI and mortality was reported, and termed 'reverse epidemiology'. More precisely, analysis findings revealed a U-shaped curve between TC and mortality in a cohort of Japanese patients undergoing hemodialysis [84], findings that were then reproduced in the study that developed a nutritional risk index for Japanese hemodialysis patients (NRI-JH) as discussed in detail later [23]. Although these seem to be a contradiction, the key factor to interpret this relationship may be PEW, as an inverse association between low TC and high mortality was found to be mainly due to the presence of PEW. On the other hand, the positive association of high TC with high mortality may reflect atherosclerotic CVD-induced death. Indeed, high non-HDL was shown to be an independent predictor of a CVD event in a study that enrolled 45,390 hemodialysis patients [85]. Nevertheless, while low TC is a good candidate for use as a nutritional marker, biphasic aspects should be also considered.

3.2.6. Other Possible Markers Related to the Immune System

As discussed in detail later, a dysfunction of the immune system consisting of innate and adaptive responses is often observed in patients undergoing dialysis [86]. Neutrophils and monocytes play crucial roles as cellular components in the innate immune system, whereas the complement system promotes and modulates the process through classical, lectin, and alternative pathways. Patients undergoing hemodialysis are known to be affected by problems related to membrane biocompatibility. Adhesion of circulating immunoglobulin (IgG) activates the classical pathway by biding to C1q, while properdin, C3b, albumin, and lipopolysaccharide can stimulate an alternative pathway, as well as activation of the lectin pathway by Ficolin-2. During this process, immune cells including neutrophils are recruited, resulting in leukocytopenia. On the other hand, lymphoid cell lineage, including T cells and B cells function as an adaptive immune system. This dysfunction in dialysis patients may be also profoundly associated with inflammation and nutritional disorder. Unfortunately, these factors are not easily measured. In clinical settings, neutrophil to lymphocyte ratio (NLR) may be useful, as it was reported to be positively related to tumor-necrosis factor α in 61 patients receiving dialysis treatment [87]. In addition, higher NLR was found to be associated with increased risk of cardiovascular and all-cause mortality in 170 incident hemodialysis patients [88], and a significant association between NLR and mortality was confirmed in a large cohort study of 108,548 incident hemodialysis patients [89]. In this study, NLR in addition to serum albumin provided a modest benefit to predict mortality, suggesting that NRL together with albumin may be useful as surrogate indicators of nutritional and inflammatory status.

Furthermore, it has been speculated that a strong association exists among inflammation, immune-deficiency, and nutritional disorder, although the underlying mechanisms are largely unknown. Further studies are necessary to establish immune parameters as nutritional markers.

3.3. Evaluation of Dietary Intake

Dietary evaluation is imperative for nutritional management and four dietary assessment methods are commonly used [90]. (1) The 24-h dietary recall is a rapid and convenient method to gather information about recent food intake, and does not require maintaining a diary [91]. However, this is dependent on the memory and cooperation of the patient. For hemodialysis patients, it should be noted that the food intake pattern differs on dialysis and non-dialysis days [92]. (2) Diet records and diaries are used to gather dietary information over a period of several days, usually three or seven. Dietitians give instruction about how to record that information with the use of a special booklet. Although this method includes a real-time record of food intake beyond 24 h, it relies on compliance by the patient to follow the instructions. (3) For an evaluation of dietary protein intake, nPCR or protein nitrogen appearance (nPNA) can be used [93]. Since most patients receiving hemodialysis treatments do not excrete nitrogen into urine, an increase in serum urea nitrogen between consecutive hemodialysis sessions reflects dietary protein intake. This method is objective and does not require a dietary evaluation. However, nPCR (nPNA) can only evaluate protein intake. It is underestimated whether the patients have residual renal function [64]. (4) A food frequency questionnaire (FFQ) can be useful to estimate long-term dietary intake (weeks to months) and daily intake of many different food items can be calculated with its use. Since an FFQ is convenient when used in a self-administered form, it is a feasible method for large epidemiologic studies. However, at individual levels, under- or over-estimation of food intake can occur. Furthermore, the different diet intake patterns on dialysis and non-dialysis days by hemodialysis patients must be considered. To overcome this limitation, the dialysis-FFQ has been developed, which uses a 3-day record for a dialysis day and two subsequent non-dialysis days, with the data gathering supplemented by a person-to-person dietary interview [94].

3.4. Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) is used to estimate body composition, such as fat-free mass (FFM) and total body water (TBW), which has become established as a portable, inexpensive, and non-invasive method [95–98]. Theoretically, an electric current is not easily conducted through a fat mass, whereas it can be freely transmitted through electrolytes that are abundant in FFM, which includes bone and body cell mass (BCM), with skeletal muscle mass, a major component of the latter. TBW in the human body is comprised of 65% intracellular water and 35% extracellular water, with the proportion of FFM to TBW presumed to be 73% [99]. Using the different levels of conductivity in various body components, the device measures the opposition to a small alternating electric current as it travels through the body. Impedance consists of two components: Resistance (R), caused by total body water, and reactance (Xc), caused by cell membrane capacitance [95–98]. In other words, R represents opposition to electron flow through ionic solutions, while Xc is delay in the flow, which reflects dielectric properties.

Phase angle (PhA), calculated using R and Xc, is a biomarker of cellular health [95,97,98], and seems to reflect cellularity, cell membrane integrity, and distribution of intra-/extra-cellular fluid. Furthermore, PhA is commonly considered to be a predictor for various outcomes in patients receiving hemodialysis [100,101].

For dialysis patients, fluid retention and water shift between intra- and extra-cellular compartments can have profound effects on BIA parameters [98]. Therefore, measurement condition settings are critical. To assess skeletal muscle mass, BIA should be performed following a dialysis session. On the other hand, it is measured both before and after a session to determine dry weight and hydration state.

3.5. SGA and MIS—Comprehensive Nutritional Assessment Tools

As noted previously, SGA is a well-established nutritional assessment tool that is used in a wide range of clinical settings [102,103]. This assessment method is based on medical history and clinical findings. Using SGA as a basis, MIS was developed for patients with CKD and includes BMI, serum albumin, and total iron-binding capacity in addition to seven SGA components [34]. MIS findings were found to be associated with 5-year mortality as well as quality of life in 809 patients undergoing hemodialysis [104], and also shown to effectively identify patients at risk for PEW [105]. However, both SGA and MIS require subjective assessment and evaluation by a well-trained examiner to obtain consistent results.

3.6. Geriatric Nutritional Risk Index (GNRI)

In contrast to SGA and MIS, GNRI is a simple combined nutritional screening tool originally developed for examinations of elderly patients [106]. This objective tool is based on the calculation of only two components, serum albumin and actual to ideal body weight ratio, and its usefulness was examined in 490 patients undergoing hemodialysis. As compared to MIS, used as the reference standard, GNRI was found to be superior as a nutritional tool [107]. Indeed, our group reported that lower GNRI was a significant predictor of all-cause mortality in 490 hemodialysis patients [108]. Subsequently, GNRI findings were shown to be capable of predicting cardiovascular [109] and infection-related [110] mortality. Moreover, a meta-analysis that included 19 studies (10,739 hemodialysis patients) revealed an inverse association between GNRI and all-cause mortality [odds ratio (OR) 0.90, 95% confidence interval (CI) 0.84–0.97, $p = 0.004$ (per one unit increase) and OR 2.15, 95% CI 1.88–2.46, $p < 0.00001$] [111]. Additionally, the results of this analysis showed similar negative associations of GNRI with CVD events and CVD mortality. Together, these findings suggest that GNRI is not only a useful nutritional screening tool but can also be used as a prognosis indicator for patients undergoing hemodialysis treatment.

3.7. GLIM

Apart from PEW, nutritional improvement is a common challenge in a variety of clinical settings, including treatment for conditions, such as cancer, as well as liver and inflammatory bowel diseases. Since a universal evaluation of nutritional status may be required, the Global Leadership Initiative on Malnutrition (GLIM) criteria have been proposed [112]. The main feature is etiology-independent diagnosis for use in various clinical settings that consists of a two-step approach, including an initial screening to identify at-risk status, followed by a second assessment for diagnosis and grading the severity of nutritional disorders. The usefulness of GLIM was investigated in patients undergoing hemodialysis, which showed low levels of agreement, sensitivity, and accuracy as compared to the well-established SGA and MIS [113]. GLIM, SGA, and MIS findings were each shown to be capable of predicting death in crude analysis. However, a more consistent and stronger association was found with MIS and SGA as compared to GLIM with an adjusted model. Therefore, it is suggested that SGA and MIS may be superior to GLIM for evaluating nutritional status in patients with hemodialysis-related PEW.

3.8. NRI-JH

A diagnosis of PEW consists of four categories, as noted previously, although there have been problems with the adaption of these criteria for Asian patients including Japanese. For example, the cut-off value noted for serum albumin is less than 3.8 g/dL. Since the mean level of serum albumin in Japanese patients undergoing dialysis is 3.6 g/d, a more appropriate reference value should be considered [114]. In addition, age and gender are critical factors for cut-off values, such as for creatinine, as they have a relationship with muscle volume. Therefore, Kanda et al. developed a nutritional risk index for Japanese patients, NRI-JH, for predicting 1-year mortality based on data in the Japanese Society for Dialysis Therapy Renal Data Registry [23]. According to the concept of PEW, NRI-JH is calculated based on serum albumin (serum chemistry), serum total cholesterol (serum chemistry), BMI (body mass), and serum creatinine (muscle mass), with considerations for age and gender (Table 1). In this study, nPCR was examined as dietary protein intake (dietary intake), although no clear association with mortality was shown. Based on risk score, patients were divided into three groups: Low-risk: score 0 to 7, Medium-risk: score 8 to 10, and High-risk: score 11 and higher. In addition to 1-year mortality, a recent study showed a significant association of NRI-JH and long-term all-cause mortality in 3046 patients undergoing hemodialysis [115]. Furthermore, NRI-JH was associated with CVD mortality and infection-related mortality in this study.

Although NRI-JH may not be adequate for a full nutritional assessment, it is an objective tool based on practical measurements and the repeated use of this index may be useful for an evaluation of need for nutritional intervention. Furthermore, inclusion of creatinine in NRI-JH may reflect an aspect of sarcopenia as a surrogate marker of muscle mass.

3.9. Functional Evaluation of Skeletal Muscle

Evaluations of both physical function and body composition are necessary for comprehensive management of patients with nutritional disorders. Measurement of muscle strength is one representative approach. Notably, loss of muscle mass and decrease in muscle strength do not always occur simultaneously [11]. Observational studies suggested that a decline in muscle strength could precede a decrease in muscle loss in healthy elderly subjects [116,117]. The most common measurement of muscle strength is handgrip strength, while another is lower extremity (knee extensor) muscle strength. Handgrip strength assessment is also required for diagnosis of sarcopenia. Although the method for determining handgrip strength is simple, there are measurement variations among the presented reports. The inconsistent results may be due to varying posture, different dynameter devices, the hand used for testing, and intervals between the measurement. Therefore, the development of a standard procedure is required [118].

Previous studies have also noted that handgrip strength could be used to predict mortality in patients receiving dialysis [119,120]. More importantly, other reports noted that hemodialysis patients with low muscle strength showed worse prognosis as compared to those with low muscle mass [121,122]. Additionally, a recent meta-analysis of 14 studies demonstrated that lower handgrip strength had a stronger association with all-cause mortality as compared to higher handgrip strength in patients with CKD including ESKD (hazard ratio = 1.99) [123], although this study did not include the muscle mass data. In contrast to handgrip strength, knee extensor muscle strength, measured with a handheld dynamometer, is not commonly used, although it may have a direct link to physical performance [124]. Indeed, decreased knee extensor muscle strength was shown to be strongly associated with mortality in 190 patients receiving hemodialysis treatments [125].

4. Prevalence of PEW, Frailty, and Sarcopenia in Patients Receiving Dialysis

To counteract nutritional and geriatric syndromes, it is indispensable to understand their prevalence rates, as this information is necessary to evaluate the efficacy of possible intervention for patients affected by these syndromes and to allocate necessary health care resources. Although a meta-analysis is desirable, presently only limited data are available since international diagnostic criteria for each disorder have only been recently accepted or not yet reported.

4.1. Prevalence of PEW in Dialysis Patients

The prevalence of PEW in patients receiving dialysis ranges from 20% to 60% [16], as this is dependent on the availability and use of diagnostic criteria. Evidence-based determination of PEW prevalence is required. On behalf of the ISRNM, a meta-analysis was performed to examine the global prevalence of PEW based on results of 90 studies that included 16,434 dialysis patients from 34 countries [126]. For this study, SGA and MIS results were adopted for diagnosis of PEW. The 25th–75th percentile for PEW prevalence ranged from 28% to 54%, although a very high level of heterogeneity was observed among the studies (I^2 = 97%, $p < 0.001$).

4.2. Prevalence of Frailty in Dialysis Patients

In a study of elderly community-dwelling subjects, frailty was noted in 6.9% [4]. However, limited information is available for dialysis patients [127]. Using the above-mentioned validated scoring system [4], frailty in patients undergoing hemodialysis was thoroughly examined with consideration of body composition [128]. As expected, the 30% prevalence of frailty in those patients was significantly higher than the general elderly population. Notably, a lower level of intracellular water, a marker of muscle mass, was strongly associated with frailty [128], which may also be linked to sarcopenia and PEW. Moreover, a recent meta-analysis provided additional information regarding frailty obtained by seven studies of a total of 2604 patients undergoing hemodialysis [129]. In six of those reports, the Fried phenotype scoring system was used for frailty diagnosis. The pooled prevalence of frailty was 46% (95% CI 34.2–58.3) and a high level of heterogeneity was observed ($I^2 = 96\%$, $p < 0.001$). In this study, advanced age, female gender, and presence of diabetes were found to significantly contribute to risk of frailty.

4.3. Prevalence of Sarcopenia in Dialysis Patients

To elucidate factors related to sarcopenia in dialysis patients, a meta-analysis was recently performed using 30 studies published after 2013 that included a total of 6162 patients [130]. Those results showed that the prevalence of sarcopenia was 28.5% (95% CI 22.9–34.1), although the range was quite wide from 4% to 68%. Intriguingly, age was not found to contribute to the prevalence of sarcopenia, suggesting that this population is highly susceptible to muscle disorders related to factors other than aging.

4.4. Overlap between Nutritional Disorders and Sarcopenia

A considerable overlap of PEW, sarcopenia, and frailty is expected, although scant related information is available. The association of sarcopenia, evaluated using the EWGSOP criteria with nutritional status assessed by SGA score in 170 elderly patients receiving hemodialysis in Brazil, was reported [131]. Interestingly, patients with sarcopenia had lower SGA scores, indicating a worse nutritional status. Moreover, the association of sarcopenia, scored according to the EWGSOP criteria and MIS, was examined in 70 hemodialysis patients in Brazil [132]. MIS was significantly associated with each parameter related to sarcopenia except for gait speed. In addition, in two reports from Asia, an inverse association between sarcopenia and MIS was shown in one [133], while this was non-significant in the other [134], even though the EWGSOP criteria were used in both.

Since these studies did not focus on the overlap between sarcopenia and nutritional status, we directly investigated the relationship between nutritional status assessed by NRI-JH and sarcopenia evaluated by the AWGS 2019 criteria in 315 patients undergoing hemodialysis [135]. The prevalence of medium-/high-risk patients was 31.1%, of whom 64.3% were diagnosed with sarcopenia. Importantly, 84.7% patients considered to be medium-/high-risk fell below the cut-off value for muscle strength related to sarcopenia. These results suggest a profound association of nutritional disorder with sarcopenia and a search for common factors related to both conditions may lead to novel interventions.

5. Mortality Related to PEW, Frailty, and Sarcopenia in Patients Undergoing Dialysis

Nutritional disorders and geriatric syndromes are comprised of multifaceted factors, resulting in a variety of outcomes, including cognitive impairment, falls, fractures, vascular access failure, and poor quality of life, as well as CVD and infection events. Among those, all-cause death may be the clearest outcome. However, there are no meta-analysis results available regarding the relationship of PEW and mortality.

As for frailty, it generally seems to be associated with death as compared to other outcomes, regardless of the evaluation method used [136]. A recent meta-analysis showed that patients with frailty undergoing hemodialysis had a greater risk for all-cause mortality as compared to those without frailty (HR 2.02, 95% CI 1.65–2.48) [129].

As compared to a diagnosis of frailty, the criteria for sarcopenia presented by the EWGSOP and AWGS are clear. A recently conducted meta-analysis of eight studies (2117 dialysis patients) that mainly used consensus criteria, such as those of the EWGSOP and AWGS, found that patients with sarcopenia were associated with higher mortality as compared to those without (HR 1.87, 95% CI 1.35–2.59, I^2: 40%) [137]. At the same time, an investigation of the association of sarcopenia with hospitalization or ESKD progression in patients with CKD was conducted, although no definitive conclusions could be made due to the limited number of reports available.

6. Points of Attention for Nutritional Management

6.1. Amino Acids

Amino acids (AAs) are comprised of proteins that are necessary for structure, function including enzymatic activity, and fuel reserve throughout the body, with appropriate quantity and quality required to maintain skeletal muscle mass and function. However, a considerable loss of AAs into dialysate occurs during a hemodialysis session, resulting in a decreased concentration in plasma [138]. Furthermore, hemodiafiltration and hemofiltration can cause additional loss of AAs due to ultrafiltration [139,140]. In patients with three times of weekly hemodialysis session, the annual loss of AAs is estimated to be greater than 800 g/year, resulting in considerable loss of muscle mass [141]. In another study, 20 g of oral protein intake during the hemodialysis session could not compensate for the decline in plasma [138], thus AA supplementation is considered to be essential. Among AAs, leucine is not only a precursor of muscle protein but also a potent stimulator of muscle protein synthesis [142]. Interestingly, a recent meta-analysis showed a significant relationship between leucine supplementation and muscle mass, although there was no clear association of essential AAs with muscle mass, muscle strength, or physical performance found [143]. A balanced and tailored supplementation of AAs, possibly together with exercise as described below, is expected to improve nutritional disorders in affected dialysis patients.

6.2. Exercise

Skeletal muscle is dynamic and distinct from other organs, in which contraction plays a critical role for maintaining homeostasis [11,144]. In addition, physical exercise performed with those muscles has beneficial effects throughout the whole body, including the nervous system, hormones, and cytokines.

Aging is an inevitable risk factor for loss of skeletal muscle mass and function, known as sarcopenia. Elderly patients undergoing dialysis who suffer from both PEW and geriatric syndromes may often suffer from the vicious cycle between low physical activity and sarcopenia, thus intentional physical exercise is highly recommended. In general, aerobic exercise does not have a large effect on muscle hypertrophy. On the other hand, it may improve insulin resistance, a common component of both aging and PEW, resulting in maintenance of skeletal muscle. As compared to the anabolic action of insulin on glucose and lipid metabolism, it is unclear whether insulin has effects on protein synthesis. A recently published study clearly showed that insulin-stimulated protein synthesis in human skeletal muscle [145] in elderly subjects was found to be lower as compared to younger subjects [146]. Interestingly, aerobic exercise improved age-related protein synthesis caused by insulin resistance in the elderly group [147]. Further studies are needed to determine whether aerobic exercise can improve PEW-induced insulin resistance, resulting in protein synthesis in skeletal muscle.

As compared to aerobic exercise, resistance training is recognized to induce muscle hypertrophy and muscle strength. Using CKD model mice, the effects of aerobic as well as resistance exercise on muscle wasting were examined [148]. Although both types of exercise counteracted CKD-induced protein degradation in skeletal muscle, only resistance training improved protein synthesis, suggesting different actions associated with each type. In 23 patients receiving hemodialysis treatments, intervention by resistance training led to muscle hypertrophy, which was comparable in nine healthy subjects [149], although some of the findings reported were inconsistent [150].

In the context of nutritional management for patients undergoing dialysis, the combination of nutritional supplementation and exercise is likely the approach most expected to be used. However, this combined intervention during hemodialysis was found to not always have synergistic effects in hemodialysis patients [15,16,151,152]. A possible explanation for this unexpected observation may be due to inadequate intensity, duration, and/or timing of the performed exercise. In consideration of AA loss during a hemodialysis session, adequate replenishment of AAs is theoretically necessary. In elderly subjects, ingestion of leucin after resistance training resulted in prolonged protein synthesis in skeletal muscle [153]. Future studies should be conducted to establish an appropriate combination of nutritional supplementation and resistance exercise for elderly dialysis patients.

7. Topics of Interest Related to Nutritional Status and Infection

7.1. Infection-Related Outcomes and Medical Costs

Infection is a common cause of death in patients undergoing dialysis, apart from the recent COVID-19 pandemic. In Japan, infectious diseases were shown to be the second leading cause of death in 2018 at 21.3% [154]. Infection-related deaths have been increasing since 1993 and this is expected to be the most common cause of mortality in the near future.

From an economic perspective, hospitalization is a greater problem than death. In the US, the rate of hospitalization for patients undergoing hemodialysis is two times higher and 37% of those patients are re-hospitalized within 30 days of discharge [155], with hospitalization especially common for elderly incidental patients [156]. Among individuals receiving support from Medicare, the US federal health insurance program for those who are aged 65 years or older, younger with disabilities, or with ESKD, patients receiving hemodialysis treatment comprise only 1%, although they account for 9% of Medicare expenditures. Therefore, hospitalization drives up the cost for hemodialysis patients [155].

Among the various causes, infection is a major factor related to hospitalization [157] and infection-related hospitalizations have dramatically increased among patients receiving hemodialysis treatment [158]. The latter report noted that 28% of patients undergoing in-center hemodialysis (Medicare beneficiaries) experienced at least one infection-related hospitalization [158]. Risk factors for hospitalization were found to be higher age, lower serum albumin level, inability to ambulate or transfer, cancer, chronic obstructive pulmonary disease, drug dependence, residence in a care facility, and treatment for other than a fistula.

7.2. Hospitalization for Infection and Resultant Short-Term Outcomes in Patients Undergoing Hemodialysis

Infection is a common cause of hospitalization, thus it is important to understand the consequences of infection-related hospitalization from the viewpoint of both clinical practice and medical economics. Surprisingly, limited data are available regarding the outcomes of these cases. The HEMO study examined whether a higher dialysis dose or use of a high-flux dialyzer membrane resulted in reduced mortality, and examined infection-related hospitalization as a secondary outcome [159]. In this study, 783 (42.4%) of 1846 hemodialysis patients had at least one hospitalization for infection [160]. Among those who were hospitalized, 57.7% had a severe outcome, with 28.6% in the hospital for longer than 7 days and 15.3% treated in the intensive care unit (ICU), while 13.8% died. Older age and lower albumin were shown to be associated with worse outcome. Another study focused on 30-day outcomes after discharge following infection-related hospitalization using the US Renal Data System [161]. Of 140,665 patients, 60,270 (42.8%) experienced at least one hospitalization for infection. Furthermore, of 54,996 who survived the initial hospitalization and were available for a 30-day follow-up examination, 27% were readmitted and survived for 30 days, while 3% were readmitted and then died within 30 days of discharge, and 4% died without hospital readmission. In this study, lower albumin, lower BMI, physical inability, absence of nephrology care prior to dialysis, and non-Hispanic ethnicity were associated with readmission or death without readmission. On the other hand, older age, white race, comorbid conditions, and institutionalization were found to independently contribute to death without readmission. These results indicate a profound link to advance care planning and conservative kidney management, although these topics are beyond the scope of the present report.

7.3. Chronic Critical Illness (CCI)

As emphasized at the beginning of this study, obesity and its related complications including acute myocardial infarction (AMI) have been shown to be severe problems in the US. However, recent medical advances have changed trends in regard to those accompanied by aging. A retrospective study using Medicare data from 1996 to 2008 showed that numbers of hospitalizations for AMI showed a gradual decease, whereas those for sepsis were dramatically increased (2.7 times higher) [162]. As a result, the overall costs of acute hospitalization for AMI and sepsis were USD 3.16 and 15.73 billion, respectively, during that time period. In addition, recent treatment in an ICU has been shown to enable patients with severe illness to survive. Although saving lives is desirable, this situation has also led to the new nebulous term 'chronic critical illness (CCI)' [163,164]. Patients with CCI who tend to have recurrent infections, organ dysfunction, weakness, and/or delirium, frequently require long-term care and remain institutionalized. These reports noted that the annual cost is estimated to more than USD 20 billion.

7.4. Nutritional Disorders and Infection

It is generally accepted that a strong association exists between PEW and infection. Furthermore, a correlation between nutritional resilience and infection-related events in patients undergoing hemodialysis has been described [155]. As noted previously, short-term outcomes after infection-related hospitalization have been found to be poor [160,161]. Some factors noted in the present review were shown to be related to worse outcome, such as older age, lower albumin, and lower BMI. However, long-term outcomes in this population, which are more relevant to clinical and economical countermeasures, are largely unknown.

7.5. Nutritional Disorders and Long-Term Mortality after Hospitalization for Infection

To bridge the gap related to the association of nutritional status and infection-related long-term outcomes, we examined findings of a prospective cohort of 518 patients undergoing hemodialysis to determine whether the GNRI used as a nutritional screening tool could provide results predictive of infection-related hospitalization and subsequent death [165]. Previous reports have noted that lower GNRI was associated with higher all-cause mortality [111] as well as infection-related mortality [110] (Figure 1A). Although no data regarding a direct association between GNRI and short-term mortality after hospitalization for infection are available, lower albumin together with older age or lower BMI has been speculated to be correlated to short-term mortality [97,98] (Figure 1B).

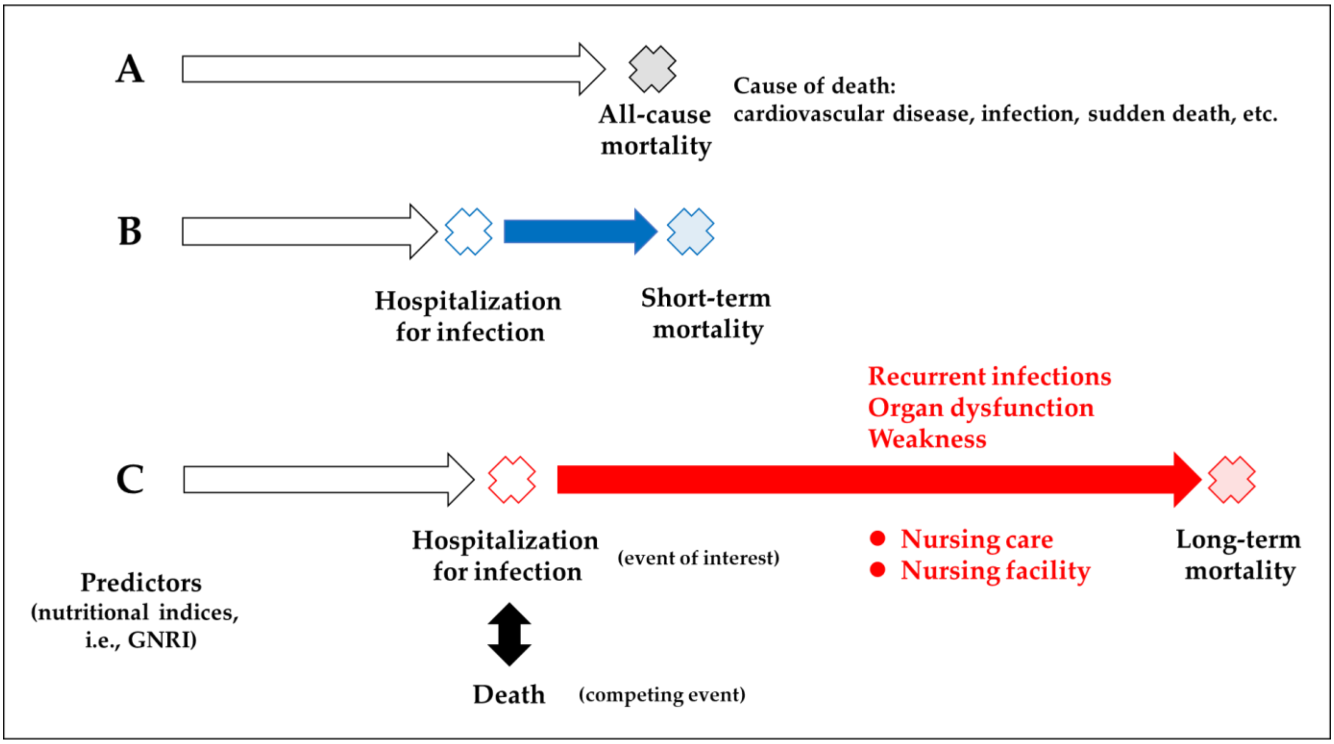

Figure 1. Short- and long-term outcomes after hospitalization for infection.

Our study was the first to show an inverse association of GNRI and all-cause mortality with reproducibility [102]. Therefore, we focused on the association of GNRI with hospitalization for infection. Patients who died are no longer at risk of hospitalization for infection, thus analysis of the multivariable-adjusted association of GNRI with hospitalization for infection was conducted with a Fine-Gray model but not a Cox model, with death as a competing risk factor (Figure 1C) [166,167]. Our prior investigation found that the GNRI was unable to predict hospitalization for infection [102], thus we examined death after hospitalization for infection. On the other hand, it is interesting to note that the GNRI could be used to predict death after hospitalization for infection during the subsequent 2.5-year follow-up period [102], suggesting that baseline GNRI findings can be used for prediction of not only mortality but also long-term death in patients who have been hospitalized for infection.

8. Missing Link among PEW, Immunodeficiency, and Infection

The presence of CKD/ESKD is profoundly associated with a type of immunodeficiency referred to as secondary immunodeficiency related to kidney disease (SIDKD) [168], with aging and malnutrition known to be involved. It is plausible that PEW in elderly patients receiving hemodialysis treatment leads to immunodeficiency, resulting in infection. However, the mechanisms are largely unknown. As described previously, patients with CCI who survive an acute illness often suffer from subsequent recurrent infections. The hallmark traits of CCI are persistent inflammation, immunosuppression, and catabolism syndrome (PICS) [169–172]. Although the trigger for CCI/PICS is critical illness, such as sepsis, common to PEW are subsequent protein catabolism/cachexia, persistent inflammation, and possibly immune suppression. Recent studies have presented findings that suggest involvement of myeloid-derived suppressor cells (MDSCs) as one of the pathogenic factors related to CCI/PICS [169–171]. Furthermore, another recent report showed that increased levels of MDSCs in patients with ESKD were positively associated with infectious events [173]. Additional studies are necessary to better reveal the associations among PEW, immunodeficiency, and infection.

9. Conclusions

Methods for early detection of nutritional disorders will be useful for developing comprehensive intervention strategies for elderly patients undergoing dialysis with the goal of preserving health. An appropriate nutritional status can result in maintaining regular physical activity, which leads to a sense of well-being that can protect from PEW, sarcopenia, and frailty. Additionally, measures against infection are a priority requirement for this population. Elucidation of the underlying mechanisms related to undernutrition, immunodeficiency, and infection should assist in the development of better treatments, resulting in improved prognosis for affected individuals.

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