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The characteristics of the older dialysis population—heterogeneity and another type of altered risk factor patterns

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Abstract

The number of older dialysis patients is increasing in many countries. For example, the trend is linked to the increase in the dialysis patients 70 years of age and over in Japan. Older dialysis patients often experience deteriorating physical and psychological functions, and special consideration for older patients has been focused on improving or preventing such deteriorations. On the other hand, from the standpoint of clinical studies, the distribution of clinical parameters, clinical outcomes, and their associations of older dialysis patients differ from those of younger patients. Moreover, they exhibit heterogeneous phenotypes. Health age may be more important than the chronological age in considering older patients. Since the age is the most powerful predictor of survival, clinical interventions might have little benefit on the very old dialysis patients. Therefore, maintaining the quality of life or activity of daily living might surpass survival regarding the goal of management of very old dialysis patients. Above all, individualized management according to the heterogeneity or health age are necessary for the older dialysis patients. Future clinical studies of older dialysis patients are needed for the better understanding of this population.

Keywords: Altered risk factor pattern, Clinical parameter, Clinical outcome, Distribution, Health age, Heterogeneity, Individualized management, Older dialysis population

Background

The older dialysis populations are expanding throughout the world. The increase in the older dialysis population can be attributed to increasing in the population 70 years of age and over in Japan (Fig. 1) [1]. Data from the United States Renal Data System (USRDS) show a similar trend in the dialysis population in the USA [2]. The proportion of older dialysis patients is even larger in other countries. The Dialysis Outcome and Practice Patterns Study (DOPPS) showed that nearly half of the dialysis patients in Belgium are 75 years old or more [3].

The older people have many problems and issues. They experience deteriorating physical function, for example, sarcopenia, protein-energy wasting, frailty, and visual or hearing loss. They experience deterioration of psychological or psychiatric conditions. These conditions relate closely to each other. Frailty can be associated with the impaired cognitive function among end-stage renal disease patients [4] as well as among the general population [5]. They can become a vicious cycle to be broken. They may also suffer from socio-economic difficulties. This malnutrition-cachexia-relating syndrome, or geriatric syndrome, has been reported to associate with worse clinical outcomes [6–9]. The syndrome can include sarcopenia, wasting, and frailty. Sarcopenia focuses on the muscles of the patients, which encompasses muscle mass, strength, and gait speed [10, 11]. Wasting indicates the reduction of visceral proteins, body mass, muscle mass, and dietary intake [12]. Hereinafter, we refer to the reduction of physical component as wasting. On the other hand, frailty is wider meaning and the scope covers psychological, psychiatric, and socio-economic conditions as well as physical conditions [13, 14]. We will refer to the deterioration of the various functions of the patients not limited to physical components as frail or frailty. Withdrawal or withholding of dialysis treatment is a major concern among older dialysis patients.

Older dialysis patients have specific issues from the standpoint of clinical studies or trials. Clinical studies

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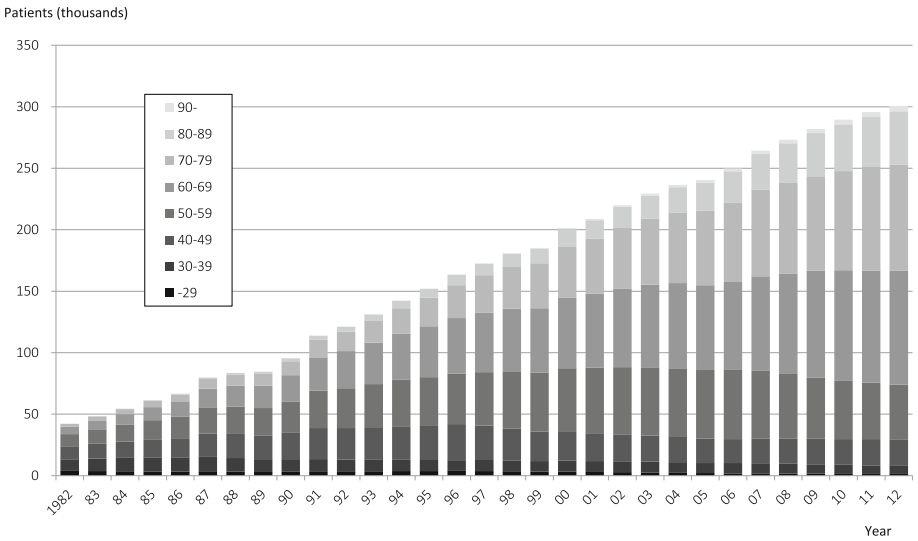

Fig. 1 Trends of the proportions of patients by age group in the Japanese dialysis population. The numbers of dialysis patients have increased over more than the past 30 years. The increase can be attributed to the increase in the number of patients with 70 years of age and over, at least during the past ten years. Adopted from reference [1] with permission

usually attempt to identify associations between certain clinical parameters and outcomes. In this sense, the older population can differ from the younger counterparts in all these parameters which are essential for clinical studies, namely the distribution of clinical parameters, outcomes in both quality and quantity, and the association between clinical parameters and outcomes (Fig. 2). Moreover, there is no consensus definition of the term "older population." Older phenotype might be more important for older patients, and the phenotype can relate to the heterogeneity of the population. In this review, we discuss these issues concerning older dialysis population.

Differences between older and younger dialysis patients

The distribution of clinical parameters

The distributions of clinical parameters sometimes differ across age groups. Figure 3 shows the distributions of several clinical parameters obtained from the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) by age groups [15]. The patients with the low values were prevalent among the older age groups for all parameters presented in this figure.

Fig. 2 Essential components of clinical studies. The aim of observational, clinical studies is to attempt to identify the associations between clinical parameters and clinical outcomes. All these components of clinical studies can differ in their distributions between the older population and the younger population

Extracellular volume status is also known to differ between the older and younger dialysis populations. A study based on the Korean registry investigated the bioimpedance parameters of 90 chronic hemodialysis patients and found that their extracellular water to total body water ratios, which are proxies for overhydration, correlated positively with the ages of the patients. Thus, older patients may be more likely to experience overhydration [16].

On the other hand, these changes in the distribution of clinical parameters have been confirmed by the studies that adjusted for the patient characteristics. Lertdumrongluk et al. investigated chronic kidney disease-mineral bone disorder (CKD-MBD) management across age groups in a cohort of 107,817 patients who were receiving their dialysis treatment at DaVita. They found that the odds of developing hyperphosphatemia were lower in the older population, but the odds of developing hypophosphatemia were higher in the same population. Thus, the distribution of serum phosphate levels can differ across age groups even after adjustments for covariates [17].

Differences in clinical outcomes

Many studies have demonstrated that older dialysis patients are more likely to experience worse outcomes than younger patients. This can be partially based on the shorter life expectancy of the older general population. Figure 4 demonstrates the comparison of the life expectancy between the dialysis population and the general population that was investigated in JRDR database. The result indicates that the older persons in the dialysis and

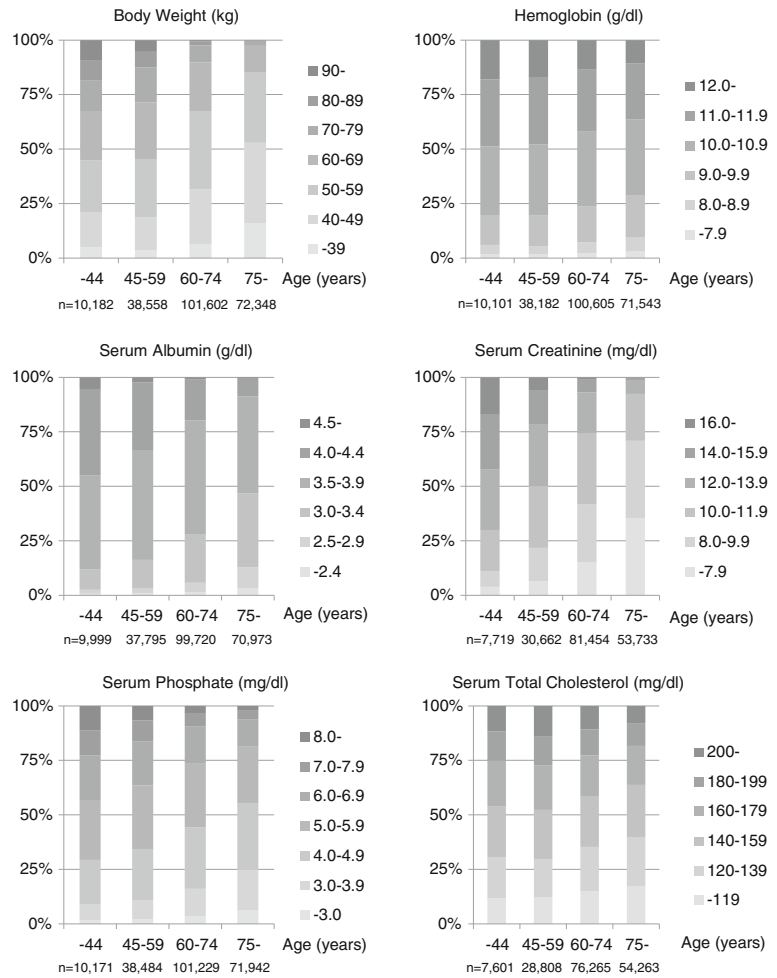

Fig. 3 Distributions of the clinical parameters by age group. The distributions of clinical parameters are shown according to age group. The patients with lower values were more prevalent than younger patients regarding all the clinical parameters shown in this figure. This figure was reproduced from reference [15]

general population experience shorter life expectancy compared to the younger population. Interestingly, the ratios of the life expectancy of the dialysis population to that of the general population were almost 50% irrespective of the age groups of the patients [18]. The fact indicates that the shorter life span of the older dialysis patients is due to the shorter life expectancy of the older general population.

The results of a study that investigated the effects of the older age in the DOPPS cohort showed that the group of patients 75 years of age and over had higher mortality rates than the group under 45 years of age in most of the regions investigated [3]. Moreover, the distribution of the causes of death might also differ across age groups. The proportions of the patients died of cardiovascular disease were smaller in the elderly group except in Japan [3]. JRDR database demonstrated that the proportion of the patients died of cardiovascular disease were almost similar in the elderly patients to the younger patients except for the group of 45–59 years old, while the proportion that died of infection was larger in the older groups (Fig. 5). A similar result was obtained regarding the quality of life (QOL). The older patients might experience poorer QOL than the younger patients, especially based on the physical component summary scores; although, the mental component summary did not differ across the age groups [3]. Regarding QOL, such association can be controversial; several studies demonstrated that the decline in QOL scores among the older dialysis population was slower than the younger patients [19, 20]. Although the associations between the age groups and QOL scores are not uniform and affected by the criteria investigated, many studies demonstrated that age is one of the major determinants of QOL and that the physical functioning in QOL tended to be worse in the older population [21].

These results indicate that the distribution of clinical outcomes or vulnerability to a worse outcome can differ across age groups.

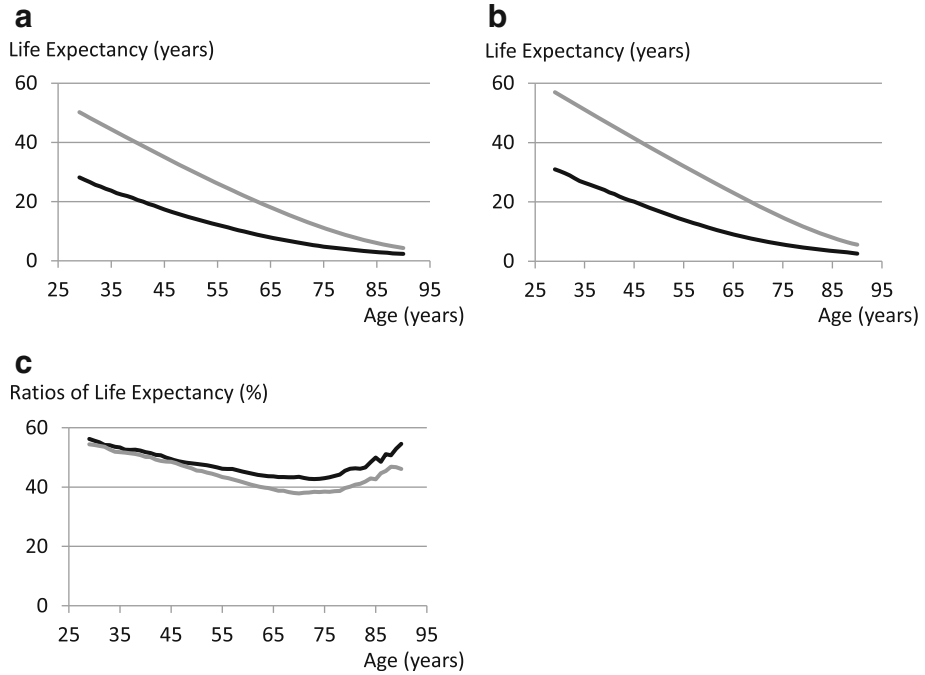

Fig. 4 Life expectancy of the Japanese general population and dialysis population by age. The life expectancy by year were demonstrated among the Japanese general (*gray lines*) and dialysis (*black lines*) population for male (**a**) and female (**b**). The ratios of life expectancy of dialysis patients to the general population by sex (the *black line*, male; the *gray line*, female) were also demonstrated by age (**c**). The ratios were almost uniform and about 50% irrespective of patients' age. This figure was reproduced from reference [18]

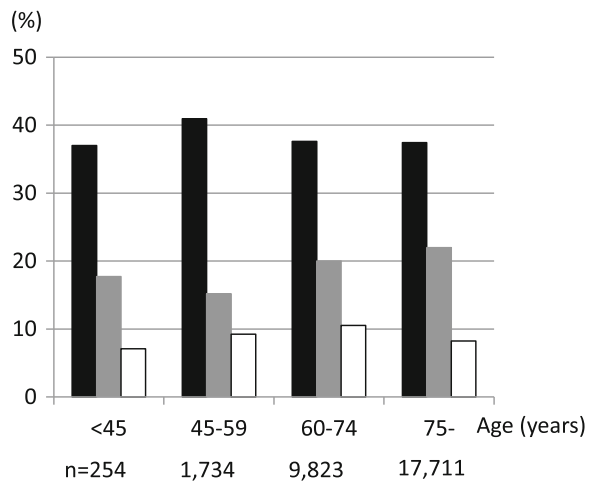

Fig. 5 The breakdown of the causes of death by age groups. The breakdown and proportion of the patients who died of CVD, infection, and malignancy were demonstrated in *black*, *gray*, and *open bars*, respectively. The proportions of CVD as a cause of death were almost equal across age groups except for the group with 45–59 years old. On the other hand, the patients who died of infection were more prevalent in the older patients. Because the patients who died of other causes of death were omitted, the proportions do not sum up to 100%. The figure was produced from the data in reference [15]. CVD, cardiovascular disease

Differences in associations between clinical parameter values and outcomes

The aim of clinical studies is to attempt to identify the association between clinical parameter values and clinical outcomes that can serve as the basis for randomized control trials. Such changes in associations should be considered even in daily clinical practice.

The association between gender and survival may differ across age groups, although somewhat controversial [22]. A study based on the Canadian Organ Replacement Registry investigated associations between gender and all-cause mortality across age groups in a cohort of 28,971 incident chronic hemodialysis patients. This study found that women had survival benefits over men among young patients under 45 years of age, whereas among the older patients 75 years of age and over, women had a lower survival probability than men, even after adjustment for covariates [23]. These results showed that association between gender and survival might differ across age groups.

Hemoglobin (Hb) levels are another example. We investigated the association between Hb levels and survival across age groups in the Japan DOPPS cohort [24] and found differences between the younger group and older group. In the group with Hb levels in the 9–10 g/dl range, only the younger group under 75 years of age had

a higher mortality risk than the group with Hb levels in the 10–11 g/dl range (HR 1.46, 95% CI 1.07–2.00), but the older population in the same Hb levels did not experience worse survival (HR 0.83, 95% CI 0.57–1.21). Moreover, a significant interaction between Hb levels and age groups was found in the group with Hb levels in the 9–10 g/dl range ($p = 0.044$).

This result was confirmed by another study based on the Korean cohort. This study found that only the younger group with Hb levels in the 9–10 g/dl range who were under 65 years of age had a significantly higher mortality risk than the group with Hb levels in the 10–11 g/dl range (HR 4.78, 95% CI 1.81–12.62). On the other hand, the older group did not have a significantly worse outcome (HR 1.80, 95% CI 0.95–3.39); although, the interaction between Hb levels and age groups was marginally non-significant ($p = 0.0526$) [25].

The study mentioned above from DaVita investigated the associations between serum phosphate levels and mortality by age groups [17] and found a J-shaped or U-shaped association between serum phosphate levels and all-cause mortality in the crude models. On the other hand, hypophosphatemia (serum phosphate below 3.5 mg/dl) was associated with higher mortality only in the 65 years of age over group after adjustment for covariates, including for malnutrition-inflammation complex syndrome, while hyperphosphatemia (serum phosphate above 5.5 mg/dl) was uniformly associated with higher mortality risks across all age groups [17].

Another type of altered risk factor patterns

Risk-factor patterns have been reported to change as chronic kidney disease (CKD) stages progress. More specifically, the associations between clinical parameters and outcomes found in the end-stage renal disease (ESRD) population may differ from the patterns observed in early stages of CKD or even in the general population. Such alterations encompass body mass index [26], body height [27, 28], blood pressure [29], and serum cholesterol level [30]. These findings are called "altered risk factor patterns" [31, 32] or "reverse epidemiology" [33]. These altered risk factor patterns can be found in other disease conditions, including congestive heart failure [34], cancer [35], acquired immune deficiency syndrome [36], and even in the older general population [37]. On the other hand, as discussed above, associations between risk factors or clinical parameters and clinical outcomes might change again with advancing age even if the population is confined to ESRD. Such change may be another type of risk factor pattern alterations among patients with kidney disease.

Older populations are heterogeneous

Another problem is that older population is heterogeneous. This fact also relates to the definition of older patients, because the cut-off age for older patients can be ambiguous due to the heterogeneities in the health status among them.

The scheme shown in Fig. 6 illustrates the heterogeneity of older dialysis patients. During the normal aging process, actual or chronological age and age based on health status, i.e., health age, are almost identical. Here, the health age is a conceptual age by which we can consider a patient robust or frail, and the health age can closely relate to the clinical outcomes more than the actual or chronological age. However, the relationship between chronological age and health age can vary among the patients. Patients who are considered frail have a higher health age than their chronological age, while patients who are considered robust have a lower health age than their chronological age. Importantly, the disparities between chronological age and health age become wider in older populations. Moreover, health age may be more closely associated with outcomes than biological age. Thus, patients can be classified as old or young by their health age. Although Fig. 6 is only conceptual, the older dialysis patients are more heterogenic than the younger patients in terms of the phenotypes of wasting or the geriatric syndrome as discussed later. This concept can also be supported by clinical experiences in daily practice. The concept should be confirmed, and the definition of the health age itself should be determined by future investigations.

We performed a preliminary study on heterogeneities in the older dialysis population in the JRDR, the Japanese Registry [38], by comparing the coefficients of variances of clinical parameters with those of the 45–59 years of age groups. The heterogeneities of the clinical parameters indicating "wasting," including creatinine generation rate, serum levels of creatinine, and albumin exhibited large heterogeneities. Therefore, these parameters might relate to the frailty or robustness of the patients.

This study confirmed that the older population is heterogeneous, especially regarding clinical parameters related to wasting. This finding was reinforced by the evidence that protein-energy wasting is closely associated with worse outcomes independent of the patient's age [39–41]. The significance of wasting in considering the well-being or outcomes of the older patients requires further investigation. Activities of daily living (ADL) or comorbidities can be the key issues for an understanding of such heterogeneities among the older patients or the health age. The older incident dialysis patients tend to experience worse ADL assessed by Barthel index [42, 43], and the lower ADL can be associated with the worse outcome [43]. The comorbidities of the patients also relate to the worse outcome even among the elderly patients who undergo dialysis treatments [44–46]. The patients with wasting are vulnerable to complications leading to comorbidities, while the patients with multiple comorbidities

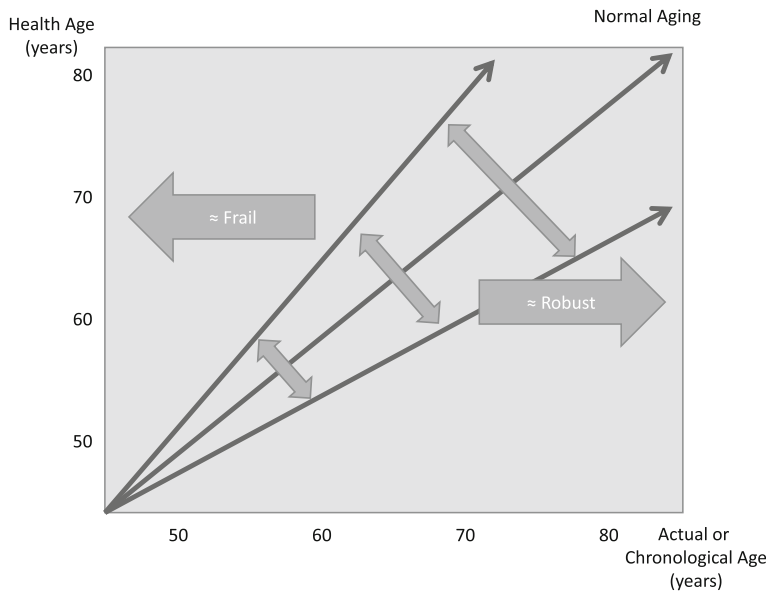

Fig. 6 Scheme of older dialysis patients and heterogeneities. Conceptually, two types of age expression can be considered in a single patient, actual and chronological ages. The chronological age is usually used to determine the age of patients, while health age is a conceptual age and it determines the phenotype of the patients. During the normal aging process, the two ages are identical. Patients are considered frail when their health ages are higher than their actual ages. Importantly, the disparities or the heterogeneities across patients are wider in the older population

often experience wasting conditions. The cause-result relationship between wasting and comorbidities remains unclear because these relationships have been obtained through observational studies. It is possible that interventions against wasting can break the vicious cycle of wasting and comorbidities.

Appropriate goals for the management of older dialysis patients

Age itself is still the most powerful predictor of survival; although, wasting also has a substantial effect on survival. Figure 7 indicates the survival rates by primary diagnoses of the patients [47]. The survival rates were almost identical

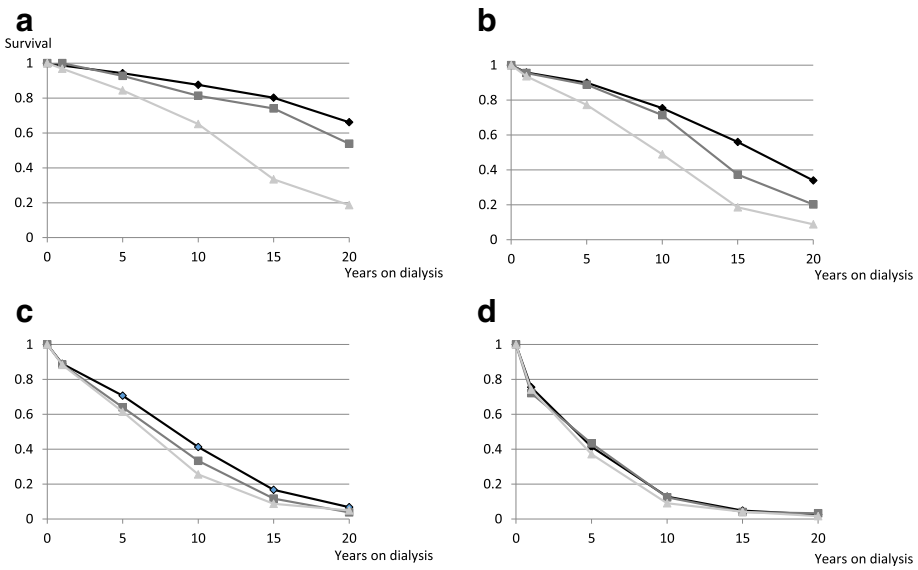

Fig. 7 Crude mortality rates according to primary diagnosis and the age at the start of dialysis. Crude mortality rates are shown according to the primary diagnosis of end-stage renal disease and age at the start of dialysis therapy. The age groups at the start of dialysis therapy were 30–44, 45–59, 60–74, and 75–89 years old in panels **a**, **b**, **c**, and **d**, respectively. Primary diagnoses of glomerulonephritis, nephrosclerosis, and diabetes are shown in *black*, *dark gray*, and *pale gray*, respectively. The differences in survival decreased as the age at the start of dialysis increased. This figure was reproduced from reference [47]

irrespective of the diagnoses, especially among the very old population. This fact suggests that therapeutic interventions on the very old dialysis patients might be of little benefit. Therefore, the goals of the management of such patients could be improving the well-being, QOL, or ADL rather than their survival. Of course, we should prioritize the preferences of patients and their families or caregivers and discuss the goals carefully and comprehensively in decision making.

Conclusions

Older dialysis populations differ from younger dialysis populations in the distributions of their clinical parameters, clinical outcomes, and associations between them. Moreover, there are great heterogeneities within older populations, especially regarding wasting phenotypes, and these heterogeneities require individualized managements. Finally, individualized goals of dialysis management are also necessary, especially for the very old population. However, many points remain to be elucidated regarding the management of older dialysis patients.

Abbreviations

ADL: Activity of daily living; CI: Confidence interval; CVD: Cardiovascular disease; ESRD: End-stage renal disease; CKD-MBD: Chronic kidney disease-mineral bone disorder; DOPPS: The Dialysis Outcome and Practice Patterns Study; Hb: Hemoglobin; HR: Hazard ratio; JRDR: The Japanese Society for Dialysis Therapy Renal Data Registry; JSDT: The Japanese Society for Dialysis Therapy; QOL: Quality of life; USRDS: The United States Renal Data System

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Authors' contributions

NH planned the review, searched the literature, and prepared the article. KN and KT searched the literature and assisted in writing the article. All authors read and approved the final manuscript.

Competing interests

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