5 Frailty in Patients with Pre-dialysis Chronic Kidney Disease: Toward Successful Aging of the Elderly Patients Transitioning to Dialysis in Japan

Yugo Shibagaki

Abstract

Japan has been recognized as having best prognosis of dialysis patients in the world; however, the early mortality of elderly incident dialysis patients is the same as or even worse compared to that in the developed countries in the Western world. One leading reason of this is rapidly growing number of frail aging population among incident dialysis patients.

Frailty in elderly incident dialysis patients was prevalent and severe in degree, and frailty develops in the continuous process. We investigated in pre-dialysis patients of ours to find that physical functional decline is prevalent and develops in early stages in chronic kidney disease (CKD), and mild cognitive impairment is also prevalent in CKD and is associated with physical functioning decline. We demonstrated that even the home-based exercise may improve physical activity and function in elderly CKD patients.

We also pay attention to our routine medical practice if it really helps our patients achieve successful aging. Although recommended in the clinical practice guidelines, protein restriction and intensive blood pressure control, especially in frail elderly with CKD, may not be so effective as in younger counterparts and even be harmful to them. We also need to check how patients face with their reality with illness and how much hope they have.

We just need to pause, look back, and reconsider what we usually do and try our best to think what we can do our best to achieve the successful aging of our elderly patients with CKD.

Y. Shibagaki (✉)
Division of Nephrology and Hypertension, St. Marianna University, Kawasaki, Kanagawa, Japan
e-mail: shibagaki@marianna-u.ac.jp

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Keywords

Frailty · Physical function · Cognitive function · Elderly · Pre-dialysis · Chronic kidney disease · Protein restriction · Target blood pressure · Hope · Successful ageing

5.1 Introduction

Japan has been recognized to enjoy the highest cumulative survival of hemodialysis patients compared to Europe and United States [1, 2]. For example, the cumulative 5-year survival of incident dialysis patients as of 2005 was 59.6% in Japan [3] compared to 35% in United States [4]. I experienced clinical practice in Nephrology both in United States (1999–2002) and in Japan (since 1995) and still cannot feel that Japanese dialysis patients are much happier than those of other countries where survival rate is much lower. Then, what is the problem?

Aging in chronic kidney disease (CKD) and dialysis population has been a common problem worldwide, especially in Japan [5, 6]. Moreover, CKD has been associated with unsuccessful aging [7]. Rowe and Kahn once defined "successful aging" as being multidimensional, encompassing the avoidance of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities [8]. Successful aging in patients with dialysis means they are not only free from disease and disability other than kidney disease but also maintain high physical and cognitive function and continue to engage in social/productive activity. But, are we physicians trying our best to achieve all these elements of successful aging instead of just taking care of diseases?

5.2 Current Status of Dialysis in Japan

As mentioned above, we believed that Japanese dialysis patients enjoy one of the best survival rates in the world. In addition, quality control of dialysis in Japan is superb by rapid technological development and improvement; endotoxin-free dialysate was used in almost all the facilities, and hemodiafiltration (HDF) is offered in more than 10% of all facilities with average single-pool Kt/V of 1.4 in male and 1.6 in female [3]. However, in spite of these improvements in technical quality control in dialysis, annual crude death rate remains flat around just <10% (9.7% in 1992 and 9.8% in 2013) [3]. One of the biggest reasons why crude death rate is not improving is of course rapid aging in dialysis population in Japan. As of end of 2013, age 60 or older accounted for 76.0% and age 75 or older for 30.2% of all prevalent dialysis population (Data from current status of chronic dialysis therapy as of the end of year 2013 by The Japanese Society for Dialysis Therapy), and this number is projected to increase surprisingly and rapidly in year of 2025 with age 60 or older accounting for more than 90% and age 75 or older for 40% of all prevalent dialysis population [9].

Thus, this surprisingly high burden of elderly population seems to be one of the plausible reasons why survival is not improving longitudinally although the survival is still better than those of other countries. However, recently, we doubt that prognosis of elderly incident dialysis patients in Japan is good since many of those patients we took care of died early after initiation of dialysis therapy. So, we investigated the early mortality in incident dialysis patients using large Japanese national registry data in 2007 and surprisingly found that 1-year and 3-month mortality was as much as 30.2% and 15.8% in those aged 80 or more, respectively [10] (Fig. 5.1), which is not superior to or even inferior to other developed countries [11, 12]. Thus, Japanese dialysis patients are not superior in terms of early mortality after dialysis initiation although survival in those who survived a year after dialysis initiation may be better. We then investigated the risk factors of early mortality in Japanese dialysis population and found that functional status was among the most influential factors tightly associated with early mortality with risk ratio of early mortality at 3 months being 3.43 [95% confidence interval (CI) 2.09–5.63] in severe and 2.26 (95%CI 1.37–3.74) in moderate functional impairments compared to mild or no functional impairment [10] (Fig. 5.2).

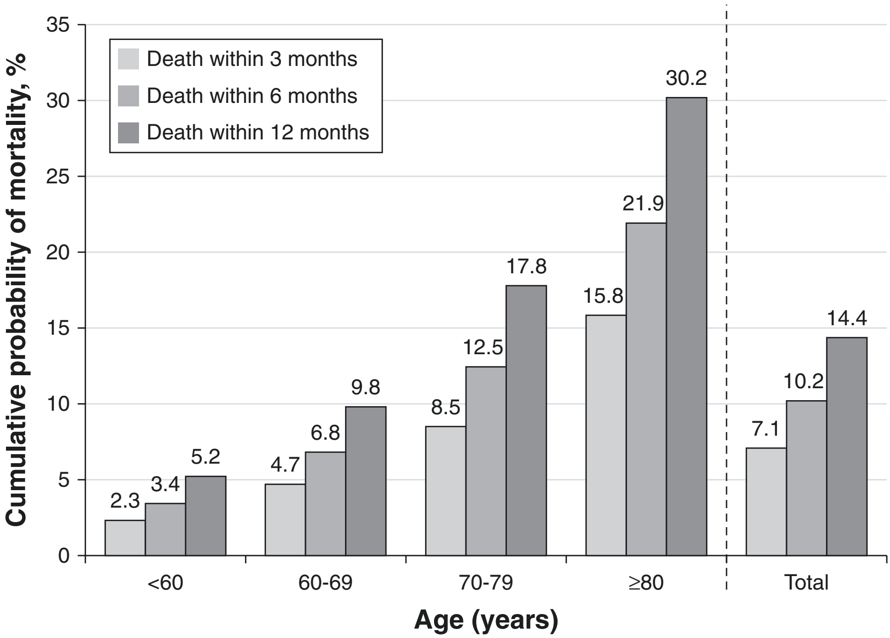

Fig. 5.1 Cumulative probability of early mortality after dialysis initiation by age (n = 33.281). (PMID: 2727061)

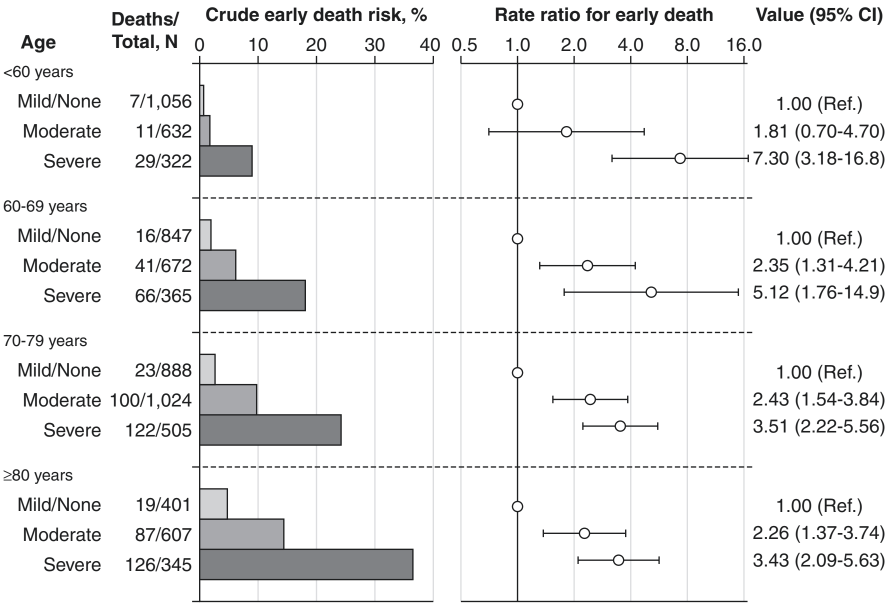

Fig. 5.2 Early mortality risk and the association with functional status at dialysis initiation by age (n = 7.664). (PMID: 27270615)

5.3 Frailty in CKD and Incident Dialysis Patients

Frailty is a physiologic state of increased vulnerability to stressors from decreased physiologic reserves or dysregulation of multiple physiologic systems and is operationally defined by physical and cognitive functional declines, which is associated with poor outcomes [13]. Frailty is very prevalent in CKD and dialysis population, and the prevalence of frailty has been reported to be > 60% in dialysis-dependent CKD patients compared to around 10% in general elderly population and is tightly associated with poor prognosis such as all-cause mortality and morbidities [14].

Thus, many elderly patients who initiated dialysis are frail. As mentioned above, one of the most plausible reasons why early mortality is high in Japanese elderly incident dialysis patients is functional impairment or frailty but why do we Japanese nephrologists initiate dialysis in these population with poor prognosis? One of the biggest reasons is that we tend to ascribe functional impairments to uremia. In fact, we elucidated that Japanese nephrologists consider functional status important in terms of indication to initiate dialysis [15], since we assume that uremia is reversible by dialysis and that is the case with uremic frailty. However, we now know that it is not the case especially in patients with baseline low functional status. Kurella Tamura et al. investigated the trajectory of functional status before and after initiation of dialysis among nursing home residents and found that immediately before initiation, functional status rapidly declined, which seems likely caused by uremia, but the functional decline did not improve but even got worse after initiation and mortality increased [16], indicating that the frailty at initiation of dialysis is more dependent on non-uremic factors than uremia [17].

5.4 Physical Functional Decline in CKD and Incident Dialysis Patients

What are the non-uremic factors leading to sustained decline in functional status after dialysis initiation? One such factor is definitely sarcopenia [17]. We demonstrated that the prevalence of sarcopenia in the dialysis patients taken care of by our facilities (average age of 70.5) by European Working Group on Sarcopenia in Older People [18] was 42.4%, which is much higher than prevalence of 22% in Japanese general elderly population (age 65–89) [19]. Furthermore, the problem in physical functional decline in elderly dialysis patients is that in this population, effectiveness in exercise training is seen in younger population but is inconclusive in the elderly because of lack of trial in this specific population [20]. Regarding why there are few trials addressing this important issue, my impression with elderly dialysis patients is that they are too frail to do the exercise. In fact, our study demonstrated the prevalence of low muscle mass in dialysis patients was 75% [19]. Since physical functional impairment is a continuous process, we hypothesized that even in pre-dialysis, CKD patients have high prevalence of physical functional decline and demonstrated that all indices of physical function decreased according to the progression of CKD with each physical function index significantly lower in CKD stage 4 or 5 patients than CKD stage 2 or 3 patients, and that in multiple regression analysis, kidney function was estimated by glomerular filtration rate (eGFR) and urinary protein, as well as age, female sex, and body mass index were significantly correlated with indices of physical function [21] (Table 5.1). Thus, we must pay more attention to physical function in even early stages of CKD as well as end-stage kidney disease.

Table 5.1 Physical functional parameters by CKD stage. (PMID: 22911116)

Functional measures	CKD G stage				One-way ANOVA	
	2	3	4	5	*F*	*P*
Grip strength (kgf)	35.2 ± 8.7	30.8 ± 10.3	24.0 ± 9.5[a,b]	22.4 ± 7.9[a,b]	8.9	<0.01
Knee extensor strength (kgf/kg)	0.66 ± 0.11	0.60 ± 0.13	0.51 ± 0.15[a,b]	0.47 ± 0.16[a,b]	9.6	<0.01
Single-leg stance time (s)	58.2 ± 7.2	50.6 ± 16.7	31.9 ± 25.1[a,b]	32.2 ± 24.2[a,b]	10.9	<0.01
Maximum gait speed (m/s)	2.2 ± 0.2	2.1 ± 0.4	1.7 ± 0.5[a,b]	1.7 ± 0.4[a,b]	9.6	<0.01

[a]Significantly different compared with the stage 2 group
[b]Significantly different compared with the stage 3 group

5.5 Cognitive Functional Decline in CKD and Dialysis

More recently, CKD and dialysis have also been identified as risk factors for declining cognitive function and dementia, even at moderate stages of CKD [22–24]. Etgen et al. demonstrated in a 2-year follow-up cohort study that odds ratio of developing new cognitive impairment by 6-Item Cognitive Impairment Test was 2.14 in those with moderate-to-severe renal impairment (creatinine clearance <45 mL/min/1.73 m^2) [25]. Poor cognitive function has been linked to poor health literacy, poor medication adherence, worse physical and mental health, greater morbidity and mortality, and may affect healthcare decision-making [22–24]. Therefore, we believe this problem warrants significant attention.

Although moderate to severe, cognitive impairment to the extent with apparent decline in Mini Mental State Examination is often irreversible, but mild cognitive impairment (MCI) is potentially reversible [26], and MCI is also suggested to be prevalent in patients with early CKD [23]. We also demonstrated in elderly CKD patients in our CKD clinic that as much as 62.5% of the elderly (age 65 or older) with pre-dialysis CKD who walk in to our clinic by themselves had MCI and that only physical function (gait speed) was significantly associated with cognitive impairment by multivariate analysis [27]. We further demonstrated that in a 2-year follow-up of our CKD clinic cohort low physical function in addition to low eGFR was associated with lower cognitive function 2 years later (Table 5.2) [28]. These results indicated that cognitive functional decline is highly prevalent in CKD, is tightly associated with physical function, and possibly physical function is the upstream of later cognitive decline.

Table 5.2 Logistic regression models of the impact of the combination of kidney and physical function on cognitive decline over 2 years in older adults with pre-dialysis chronic kidney disease. (PMID 30734184)

			Crude			Adjusted		
	N	*N* with Cognitive decline (%)	OR	95% CI	*P* value	OR	95% CI	*P* value
Group 1	34	7 (20.6)	1	Ref		1	Ref	
Group 2	11	2 (18.2)	0.86	0.15–4.90	0.86	0.56	0.07–4.57	0.58
Group 3	24	7 (29.2)	1.59	0.47–5.33	0.45	1.85	0.49–8.54	0.43
Group 4	15	9 (60.0)	5.79	1.54–21.79	0.009	5.73	1.01–32.52	0.049

Adjusted model is adjusted for age, hemoglobin, proteinuria, and MoCA-J at baseline
Patients with cognitive decline during the 2-year follow-up were defined by %MoCA-J as being in the lowest quartile of all patients
Group 1 = mild-to-moderate impairment in kidney function and high physical function group
Group 2 = mild-to-moderate impairment in kidney function and low physical function group
Group 3 = severe impairment in kidney function and high physical function group
Group 4 = severe impairment in kidney function and low physical function group
OR odds ratio, *95% CI* 95% confidence interval

5.6 Effectiveness and Feasibility of Exercise Training in Elderly Patients with Pre-dialysis CKD

As mentioned earlier, although the effectiveness of exercise in elderly patients with dialysis patients has been inconclusive, since the physical functional impairment in pre-dialysis patients is significantly less prevalent and less in degree, it is possible that exercise training in this population may be effective. However, there are very few trials examining effectiveness of exercise in pre-dialysis CKD, and there are some problems associated with this kind of study. Most of the exercise interventions were conducted center-based, which are not feasible in terms of its cost, availability, broader applicability, and sustainability [29].

Thus, we conducted a randomized controlled pilot and feasibility trial to test the effectiveness of home-based exercise training in 28 patients with CKD stage G3–4 and with average age of 68.7 ± 6.8 years [30]. The exercise group performed home-based aerobic and resistance training exercises without supervision for a period of 1 year after they were instructed how to do it at first visit in the study period. We demonstrated that physical activity by daily steps measured by pedometer significantly increased, and muscle strength (both handgrip and knee extension) was significantly improved only in the intervention group (Table 5.3).

5.7 Does Guideline-Based "Usual Care" Help Elderly CKD Patients to Lead Successful Aging?

Both global and Japanese guidelines in the management of CKD recommend protein restriction and tight blood pressure (BP) control, especially with renin-angiotensin system inhibitors (RASi) in patients with CKD irrespective of age [31, 32]. However, there us few evidences if any to support these recommendations in frail elderly patients with CKD.

Table 5.3 Changes in eGFR, urinary protein, handgrip strength, knee extensor muscle strength after the 12-month period of intervention (vs. control). (PMID 28623895)

	Exercise		Control		
	Baseline	12-month	Baseline	12-month	*P* value
eGFR (mL/min/1.73 m^2)	37.0 ± 10.9	35.1 ± 11.4	41.1 ± 12.2	39.5 ± 12.9	0.93
Urinary protein (g/gCr)	0.9 ± 1.0	1.2 ± 1.7	0.9 ± 1.4	0.9 ± 1.1	0.52
Handgrip strength (kgf)	31.7 ± 7.4	36.4 ± 6.4	35.5 ± 8.8	36.5 ± 9.2	0.01
Change (%)		17.0 ± 16.1		3.4 ± 11.2	0.02
Knee extensor muscle strength (kgf/kg)	0.65 ± 0.17	0.70 ± 0.17	0.66 ± 0.15	0.62 ± 0.13	<0.01
Change (%)		8.2 ± 10.9		−6.0 ± 7.6	<0.01

Values are the mean ± SD unless otherwise noted

Protein restriction has been proved to be renoprotective by metaanalysis [33]. However, its size effect of renoprotection is very small. Moreover, in this meta-analysis, protein restriction was not significantly renoprotective in the elderly [33]. Moreover, is renoprotection the only goal for the very old patients with CKD? Protein restriction is also recognized "safe" as long as adequate calorie (and essential amino acid supplementation) is guaranteed [34]. However, in the real-world setting, many elderly patients with CKD as well as general elderly population living alone or with house-holdwife suffering from functional decline could not adhere to this because of cost and social problems. Their socioeconomic status is often low. In these patients, it is a luxury to prepare low protein diet but with adequate calorie because they cannot cook by themselves or buy the healthy ingredients separately. Actually, it has been shown that caloric intake in elderly patients with CKD was far less than recommended in those who undergo protein restriction (30–35 kcal/kg body weight/day) [35]. Thus, if we advise them to restrict protein in addition to salt intake, they tend to decrease whole amount of foods instead of maintaining calorie intake, leading to protein energy malnutrition with poor prognosis [34]. In addition, in patients with advanced CKD, we showed that muscle strength was positively correlated with protein intake (Fig. 5.3) [36]. Since this observation could not prove causative association, we conducted prospective observational study to elucidate the relation between baseline protein intake and future prognosis (risk of ESKD and mortality) [37]. Surprisingly, those who consume low protein diet, which is recommended in patients with CKD, had significantly worse mortality risk, especially when they are old (Fig. 5.4). Recently, Levine et al. reported in the journal *Cell*

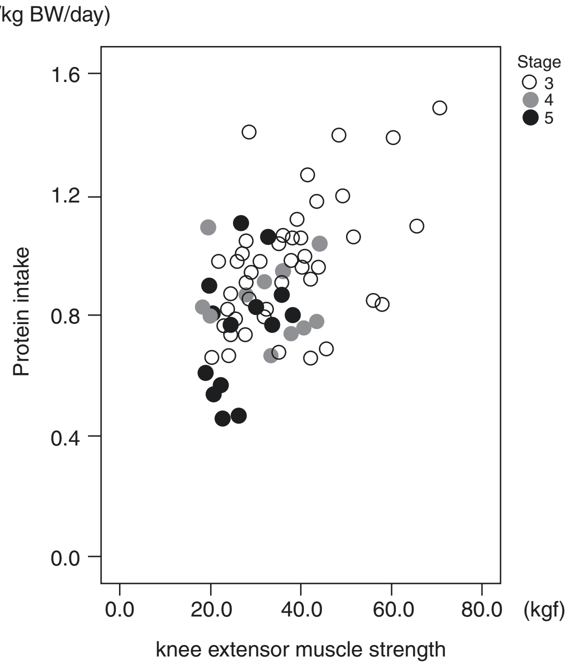

Fig. 5.3 Relation between protein intake and muscle strength in patients with CKD. (PMID: 28258495)

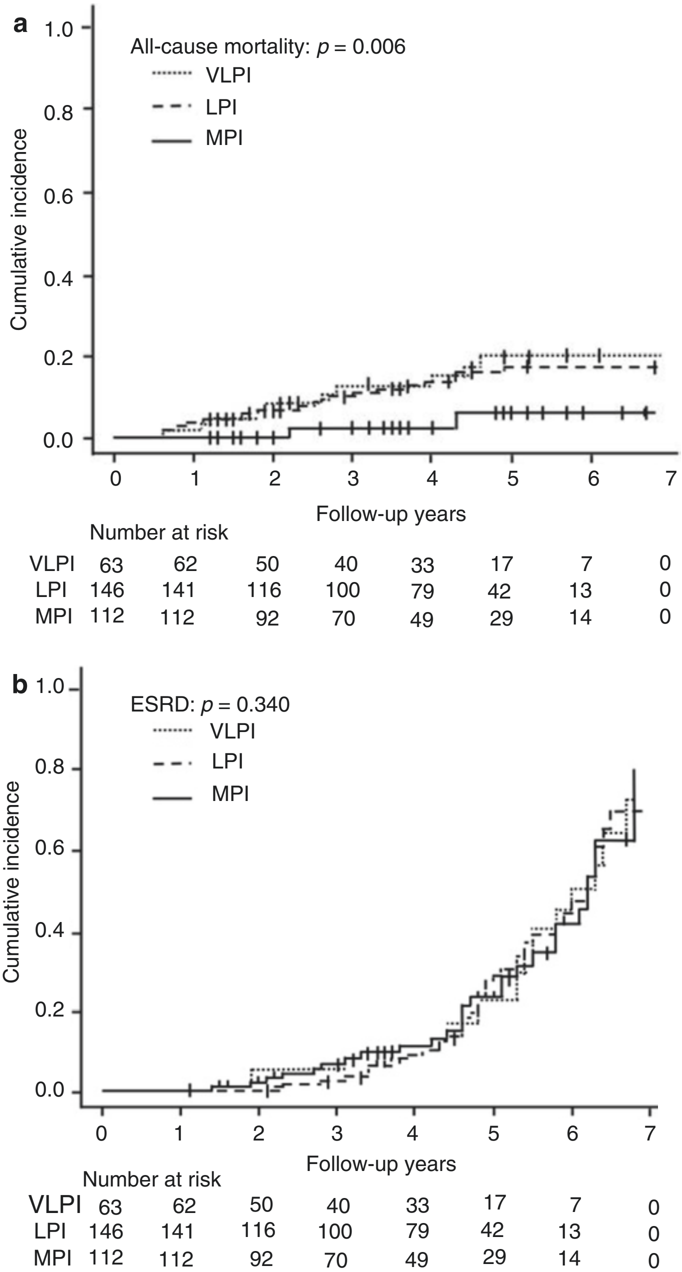

Fig. 5.4 Cumulative incidences (95% confidence interval) of (**a**) mortality and (**b**) end-stage renal disease (ESRD) in the very low protein intake (VLPI), low protein intake (LPI), and moderate protein intake (MPI) groups. (PMID: 30428524)

Metabolism that low protein intake is associated with higher mortality in older population [38]. They investigated the mechanism of this phenomena and speculated by mice experiment that older people cannot maintain anabolism with low protein due to inadequate growth hormone. We found in our patients with CKD that protein intake is significantly and positively associated with muscle strength [36]. Of course, this study is cross-sectional and does not prove the causal relationship between the two factors; however, since the study population is ambulating outpatients walking in to our CKD clinic, it is not plausible to assume they are too physically impaired to eat adequately. So, we assume that low protein intake will lead to lesser muscle strength.

How about strict BP control? Recently, The Systolic Blood Pressure Intervention Trial (SPRINT) reported reduced cardiovascular events by intensive BP control even in the elderly population [39]. However, our feeling of safety of strict BP control in the elderly population does not necessarily get along with the conclusion of SPRINT. In fact, Obi recently reported in a post hoc analysis of SPRINT [40] that intensive BP control did not reduce the cardiovascular outcome but even increased acute kidney injury events in subpopulation with low eGFR (<45 mL/min/1.73 m^2). Several other studies of patients with moderate-to-advanced CKD or coronary artery disease have reported J- or U-shaped relationship, in which low-to-normal BP is associated with higher mortality or morbidities [41–43]. This is especially relevant in elderly with frailty. Odden et al. demonstrated using data from the National Health and Nutrition Examination Survey that elevated but not reduced BP was strongly and independently associated with lower risk of death in patients with slower walking speed [44]. Sink et al. showed in a randomized controlled trial comparing target systolic BP <120 mmHg versus <140 mmHg that risk for syncope, hypotension, and falls are significantly higher in participants with CKD or frailty, especially in the elderly [45].

Interpretation of randomized clinical trials should be cautioned when we apply the results to real-world elderly patients with CKD. O'Hare et al. conducted a simulation study in a retrospective cohort of Veterans Affairs medical centers with more than 370,000 elderly patients aged 70 or older with CKD. She demonstrated that the number needed to treat (NNT) to prevent 1 case of end-stage renal disease (ESRD) ranged from 16 in patients with the highest baseline risk to 2500 for those with the lowest baseline risk and most patients belonged to groups with an NNT of more than 100, even when the exposure time was extended over 10 years and in all sensitivity analyses, indicating we need to use RASi with discretion in patients with short life expectancy considering the risks of RASi such as acute kidney injury and hyperkalemia requiring hospitalizations [46].

In the first place, guidelines may never perfectly address complex patients because this usually requires judgment along with extrapolation of evidence from less complex and often younger populations. Since frail elderly patients with CKD were among the most complex patients with multimorbidities and functional problems, it is hard to apply guidelines since most of them did not discuss the applicability of their recommendations for older patients with multiple comorbidities, nor commented on burden, short- and long-term goals, and the quality of the underlying scientific evidence, nor gave guidance for incorporating patient preferences into treatment plans [47].

5.8 Toward Successful Aging of the Elderly Patients Transitioning to Dialysis

Now, we need to pause, look back, and rethink of what we usually do to our elderly patients with CKD. I understand that most of the conscientious physicians are trying their best to maintain health of their patients. According to the evidence-based guidelines, we often try to put them on food restrictions and lower the BP strictly, and of course with cautions. However, we often miss the fact that successful aging, especially in those with limited life expectancy as in elderly CKD, is not ever achievable without maintaining the rest of the constructs of successful aging, namely maintenance of physical and cognitive function, and keeping social engagement. Intensive treatment tends to interfere with these two important constructs of successful aging even if we are successful in achieving avoidance of progression of disease/disability status. We must not simply add years to life but add life to years.

The approach I have been exploring to achieve successful aging in my patients is to maintain their physical/cognitive function as much as possible to intervene by exercise training at the early stages of CKD. Since the intervention does not need expensive drugs or devices, it is ideal for the coming era of economic downturn in Japan. We also checked the quality of their muscle (physical function) as well as quantity (muscle mass) and if they are not physically fit, we avoid putting them on protein restriction and advise them to do home-based exercise training. I believe that if they improve their physical function, they will maintain cognition and can engage in productive social activities.

The challenge we have now is how we can involve patients with low adherence to these activities. We tend to ascribe their nonadherent behavior to their own characters, but I am sure it is not true. I think they do not have "hope."

Jerome Groopman once stated, hope, unlike optimism, is rooted in unalloyed reality and is the elevating feeling we experience when we see in the mind's eye a path to a better future, which needs to be kept alive in the face of illness [48]. Fukuhara, Kurita, Wakita, and I have been trying to develop the scale of hope in patients with chronic disease, and preliminary results showed that patients with dialysis with higher hope scale felt less burden with adherence to the treatment [49].

5.9 Conclusion

In this era of super-aging society full of frail elderly, we need to pause, look back, and reconsider the way we manage the elderly patients with CKD just by following the guidelines to protect their organs or prolong the life and try our best to achieve the successful aging and maintain their dignity and autonomy.

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