

**Table 2**  
Baseline characteristics of the study subjects in both groups.

	Certified for LTCI requirement (n = 536)			Non-certified for LTCI requirement (n = 7527)			P-Value
	Mean	SD	Min–max	Mean	SD	Min–max	
Age (years)	80.8	7.4	66–100	76.7	6.5	65–102	<0.001
Gender (female)	332 (61.9%)	4405 (58.5%)	0.043				
BMI (kg/m <sup>2</sup> )	22.4	3.5	13.8–35.8	22.8	3.2	12.7–39.8	0.073
Frailty checklist (points)	6.5	4.9	0–23	4.3	4.0	0–24	<0.001
Serum albumin (g/dl)	4.2	0.3	3.2–5.0	4.3	0.3	2.6–5.4	<0.001
eGFR (ml/min/1.73 m <sup>2</sup> )	68.5	20.7	22.2–121.3	71.4	17.2	20.3–123.8	<0.001

eGFR quartile and the time to new LTCI service need certification in univariate and multivariate analyses. Multivariate analyses were performed for each covariate and were adjusted for gender, BMI, frailty checklist score, and serum albumin level, factors that are known to be associated with frailty (Levey et al., 2006; Tomata et al., 2011; Yamada, Arai, Sonoda, & Aoyama, 2012). Survival time was defined as the time between enrollment (the date of the baseline measurements) and either the new LTCI service need certification or the end of the follow-up period (March 31, 2011). The data were analyzed using PASW (Windows version 18.0, SPSS, Inc., Chicago, IL). A *P* value <0.05 was considered statistically significant for all the analyses.

### 3. Results

During the 2-year follow-up, 536 subjects (6.6%) became newly certified as needing LTCI services (Table 2). Those who were certified for LTCI need were significantly older ( $80.8 \pm 7.4$  vs.  $76.7 \pm 6.5$ ,  $P < 0.001$ ) and had higher frailty checklist scores ( $6.5 \pm 4.9$  vs.  $4.3 \pm 4.0$ ,  $P < 0.001$ ), lower serum albumin levels ( $4.2 \pm 0.3$  vs.  $4.3 \pm 0.3$ ,  $P < 0.001$ ), and lower eGFR values ( $68.5 \pm 20.7$  vs.  $71.4 \pm 17.2$ ,  $P < 0.001$ ) than those who were not certified. More women than men became certified in this cohort (female: 61.6% vs. 58.5%,  $P = 0.043$ ). However, the BMIs were not different between the two groups ( $P = 0.073$ ) (Table 2). We also examined whether eGFR was associated with BMI, frailty checklist score, or serum albumin level. We found that the subjects with eGFR < 60.0 ml/min/1.73 m<sup>2</sup> were significantly older and had lower BMIs, higher frailty checklist scores, and lower serum albumin levels ( $P < 0.05$ ) (Table 3).

Next, we examined the relationship between each variable and new LTCI need certification. The subjects with BMIs <20.5 exhibited a significantly elevated risk of LTCI service need according to multivariate analyses using a BMI of 22.7–24.7 as the reference (adjusted hazard ratio: 1.41 [95% CI 1.11–1.78]) (Table 4). The mean BMI was  $22.7 \pm 3.3$ , with a range from 12.7 to 39.8; 1975 participants (24.5%) had BMIs <20.5. The subjects with frailty checklist scores >6 had a significantly elevated risk of LTCI service need according to multivariate analyses using frailty checklist scores <2 as the reference (adjusted hazard ratio: 2.24 [95% CI 1.73–2.90]) (Table 4). The mean frailty checklist score was  $4.5 \pm 4.1$ , with a range from 0 to 24; 2042 participants (25.3%) had frailty checklist

scores >6. Participants with serum albumin levels <4.1 g/dl tended to exhibit an elevated risk of LTCI service need according to multivariate analyses using a serum albumin level >4.4 g/dl as the reference (adjusted hazard ratio: 1.25 [95% CI 0.97–1.62]). However, the univariate analysis indicated that subjects with serum albumin levels <4.1 g/dl had an elevated risk of LTCI service need (Table 4). The mean serum albumin level was  $4.2 \pm 0.3$  g/dl, with a range from 2.6 to 5.4; 1722 participants (21.3%) had serum albumin levels <4.1 g/dl.

Fig. 1 shows the Kaplan-Meier survival curves according to new LTCI service need certification, with the subjects stratified into 4 groups according to eGFR quartile. Individuals with eGFR values <60.0 ml/min/1.73 m<sup>2</sup> had a significantly elevated risk of LTCI service need according to multivariate analyses using an eGFR value of 71.4–83.6 ml/min/1.73 m<sup>2</sup> as the reference (adjusted hazard ratio: 1.44 [95% CI 1.12–1.86]) (Table 4). The mean eGFR was  $71.2 \pm 17.4$  ml/min/1.73 m<sup>2</sup>, with a range from 20.3 to 123.8 ml/min/1.73 m<sup>2</sup>; 1963 participants (24.3%) had eGFR values <60 ml/min/1.73 m<sup>2</sup>.

### 4. Discussion

In this study, we found that approximately 25% of adults aged 65 years or over had eGFR values <60 ml/min/1.73 m<sup>2</sup>, which indicates that CKD is common among older Japanese adults. The multivariate analyses demonstrated eGFR values <60.0 ml/min/1.73 m<sup>2</sup> were independently associated with new certifications for LTCI service need. Thus, our data indicate that CKD is a critical marker of frailty in older adults.

According to the multivariate analyses, lower BMIs (less than 20.5), and higher frailty checklist scores (more than 6) were associated with certification for LTCI service need. These results are consistent with those of previous studies (Levey et al., 2006; Tomata et al., 2011; Yamada et al., 2012), which revealed that the subjects with the lowest BMIs had an elevated risk of requiring care and that frailty checklist scores were strongly associated with new LTCI service need certifications (Levey et al., 2006). Thus, it is important to assess nutrition, cognitive function, mood, and ADL for care prevention, and the frailty checklist includes these items.

In terms of nutrition, however, our study failed to demonstrate that serum albumin levels were significantly associated with new LTCI service need certification after adjusting for other frailty-related factors, although the univariate analysis demonstrated that

**Table 3**  
Demographic differences according to eGFR quartile.

	eGFR (ml/min/1.73 m <sup>2</sup> )				P-value	Post hoc				
	Q1: <60.0	Q2: 60.0–71.3	Q3: 71.4–83.6	Q4: >83.6						
Gender (female)	1122 (57.2%)	1153 (54.2%)	1066 (54.2%)	1429 (71.2%)	<0.001	Q2.3 < Q1 < Q4				
BMI (kg/m <sup>2</sup> )	23.1	3.3	22.7	3.2	22.9	3.1	22.4	3.4	<0.001	Q1 > Q4 > Q2.3
Frailty checklist (points)	5.2	4.6	4.0	3.9	3.2	3.6	3.9	3.8	<0.001	Q1 > Q2 > Q4 > Q3
Serum albumin (g/dl)	4.11	0.27	4.16	0.26	4.21	0.25	4.21	0.26	<0.001	Q1 < Q2 < Q3.4

**Table 4**  
Predictors of new LTCI service need certification during a 2-year follow-up period.

		Certified for LTCI requirement		Non-certified for LTCI requirement		Univariate analysis			Multivariate analysis		
		HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI	P-value	
Gender	Female	332	7.0%	4405	93.0%	ref			ref		
	Male	204	6.1%	3122	93.9%	0.88	0.76–1.03	0.11	0.98	0.83–1.17	0.86
BMI	Q1: <20.5	179	9.1%	1796	90.9%	1.53	1.21–1.92	<0.01	1.41	1.11–1.79	<0.01
	Q2: 20.5–22.6	120	5.9%	1915	94.1%	1.00	0.78–1.29	1.00	1.01	0.78–1.30	0.92
	Q3: 22.7–24.7	121	6.0%	1892	94.0%	ref			ref		
	Q4: >24.7	140	6.9%	1900	93.1%	1.13	0.88–1.44	0.35	1.09	0.85–1.39	0.51
Frailty checklist	Q1: <2	91	4.1%	2106	95.9%	ref			ref		
	Q2: 2–3	105	5.5%	1802	94.5%	1.36	1.03–1.80	0.03	1.30	1.30–1.73	0.13
	Q3: 4–6	117	6.1%	1800	93.9%	1.51	1.15–1.99	<0.01	1.41	1.06–1.86	0.01
	Q4: >6	247	12.1%	1795	87.9%	3.04	2.38–3.87	<0.01	2.63	2.05–3.39	<0.01
Serum albumin	Q1: <4.1	167	9.7%	1555	90.3%	1.75	1.36–2.24	<0.01	1.36	1.05–1.75	0.02
	Q2: 4.1–4.2	150	6.7%	2076	93.3%	1.19	0.92–1.53	0.18	1.04	0.81–1.35	0.75
	Q3: 4.3–4.4	140	6.0%	2200	94.0%	1.09	0.84–1.40	0.52	1.01	0.78–1.31	0.93
	Q4: >4.4	101	5.6%	1694	94.4%	ref			ref		
eGFR	Q1: <60.0	191	9.7%	1772	90.3%	1.99	1.55–2.54	<0.01	1.63	1.26–2.09	<0.01
	Q2: 60.0–71.3	142	6.7%	1983	93.3%	1.37	1.06–1.77	0.02	1.25	0.96–1.62	0.10
	Q3: 71.4–83.6	97	4.9%	1871	95.1%	ref			ref		
	Q4: >83.6	128	6.4%	1879	93.6%	1.29	0.99–1.68	0.06	1.17	0.89–1.53	0.26

The multivariate analysis was adjusted for gender, BMI, frailty checklist score, and serum albumin level.

a significantly larger number of subjects in the first quartile were certified as needing LTCI. Furthermore, previous studies have indicated that lower serum albumin levels are associated with future functional decline in older adults (Kalyani et al., 2012; Kane, Shamllyan, Talley, & Pacala, 2012). We assume that this result was caused by our study lacking sufficient power to demonstrate a contribution of low serum albumin to new LTCI service need certifications and by the small number of subjects with malnutrition in this cohort. Nonetheless, CKD was found to be significantly associated with new LTCI service need certification. Therefore, it should be noted that CKD may independently predict new LTCI service need certification in older adults.

We found that the subjects with the highest eGFR values (4th quartile) tended to have a higher risk of new LTCI service need certification, lower BMIs, and higher checklist scores than those in the 3rd quartile, although this difference was not statistically significant. Because eGFR is calculated using serum creatinine levels, a higher eGFR may indicate lower muscle mass, especially in

older adults. Therefore, it should be noted that older adults with elevated eGFR values may be frail. Further research is required to address the role of eGFR in frailty.

Malnutrition is known to be associated with frailty. Several studies have suggested that vitamin D deficiencies are common among patients with CKD (Reuben et al., 2002; Zuliani et al., 2001). Both vitamin D2 and D3 are first converted to 25-hydroxyvitamin D by hepatic vitamin D-25-hydroxylase and are then converted to the active form, 1,25-hydroxyvitamin D, by renal 1 $\alpha$ -hydroxylase (Zuliani et al., 2001). Reduced activation of vitamin D has been associated with the development of hypertension, left ventricular hypertrophy, heart failure, and vascular calcification (Holick, 2007). In addition, vitamin D deficiency has been associated with sarcopenia, falls, fractures, and dementia (Bischoff-Ferrari, 2012; Chonchol, Kendrick, & Targher, 2011; Cozzolino & Ronco, 2011). Therefore, we hypothesized that CKD was a risk factor for new LTCI service need certification.

Two limitations of this study warrant mention. First, we did not collect information about the subjects' comorbidities. Therefore, the effects of comorbidities on the risk of new certifications for LTCI service need remain unclear. Second, the study participants may have had a greater motivation and interest in health issues than the non-participants. Therefore, it is possible that the non-participants had a higher prevalence of CKD and frailty.

In conclusion, this is the first study to demonstrate that CKD is independently associated with new certifications for LTCI service need. In addition, a relatively high percentage of the subjects had moderate to severe CKD (eGFR <60 ml/min/1.73 m<sup>2</sup>). Intervention studies are needed to explore whether treating CKD may delay or prevent new certifications for LTCI service need among older adults.

#### Conflicts of interest

None of the authors have conflicts of interest or financial disclosures.

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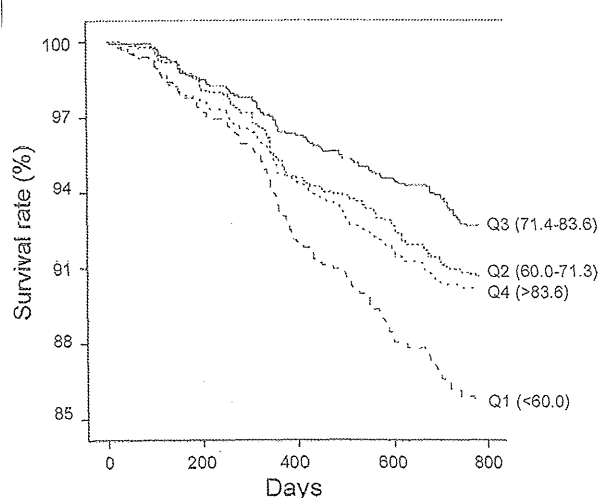


Fig. 1. Kaplan-Meier survival curves for new LTCI service need are shown for 4 groups according to eGFR quartile.

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## 高齢者 CKD における降圧目標は高く設定すべきか？ —Con の立場から\*—

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### はじめに

慢性腎臓病 (CKD) と血圧・年齢の関係を詳細に調査した NHANES III (米国民健康・栄養調査, 1988~1994 年) によると, 60 歳以上の高齢者では高血圧の治療の有無にかかわらず, 血圧と CKD 罹患率には Jカーブ現象がみられる<sup>1)</sup>。すなわち, 収縮期血圧が 120~159 mmHg, 拡張期血圧が 80~99 mmHg で CKD 罹患率が最も低く, それ以下でもそれ以上でも CKD の罹患率は高くなる。

CKD 診療ガイドライン 2009, JSH2009 では CKD の降圧目標として, CKD 進行の抑制および CVD 発症リスクや死亡リスクの軽減の観点から, 130/80 mmHg 未満が推奨されていた。特に尿蛋白が 1g/日以上の場合には, さらに低い 125/75 mmHg 未満を降圧目標にすべきとされていた。また, CKD 診療ガイド 2012 では, 年齢および糖尿病合併・蛋白尿の有無にかかわらず 130/80 mmHg 以下が降圧目標とされた。しかし, 最近の KDIGO-BP ガイドライン<sup>2)</sup>では, 降圧目標は糖尿病合併の有無にかかわらず, CKD 重症度分類の蛋白尿区分が A1 では 140/90 mmHg 以下, A2, A3 区分では 130/80 mmHg 以下とされ, 降圧目標値がやや引き上げられた。また, 2013 年 6 月に欧州高血圧学会/欧州心臓病学会が発表した高血圧管

理ガイドラインでは, 高齢者・糖尿病合併患者を除き 140/90 mmHg 未満に統一された。糖尿病合併高血圧患者は 140/85 mmHg 未満とされ, 高齢者はまず 140~150 mmHg を目標とし, 可能なら 140 mmHg 未満に低下させることが望ましいとされている。最近発表された CKD 診療ガイドライン 2013 では, 糖尿病合併 CKD 患者では 130/80 mmHg 未満, 糖尿病非合併 CKD 患者では A1 区分では 140/90 mmHg 未満, A2, A3 区分では 130/80 mmHg 未満が推奨され, 高齢者では, 腎機能の悪化や臓器の虚血症状がないことを確認しながら緩徐に降圧することが推奨されている。

高齢者の高血圧治療に関する研究は多数存在するものの, 高齢 CKD 患者を対象とした高血圧治療の降圧目標に関する研究はほとんどないのが現状である。KDIGO-BP ガイドライン<sup>2)</sup>でも, 高齢 CKD 患者の降圧管理の項は設けられているものの, 明確な目標値は設定されていない。本稿では, 高齢者および CKD 患者それぞれの高血圧治療の臨床研究を参考に, 「高齢者 CKD における降圧目標は高く設定すべきか」について, Con の立場から, 降圧目標値について考察したい。

### 高齢高血圧患者の降圧治療目標

80 歳以上の高齢者の観察研究 (4,071 名のうち

\* Target blood pressure level for elderly chronic kidney disease patients

key words: INVEST 試験, VALISH 試験, Jカーブ現象

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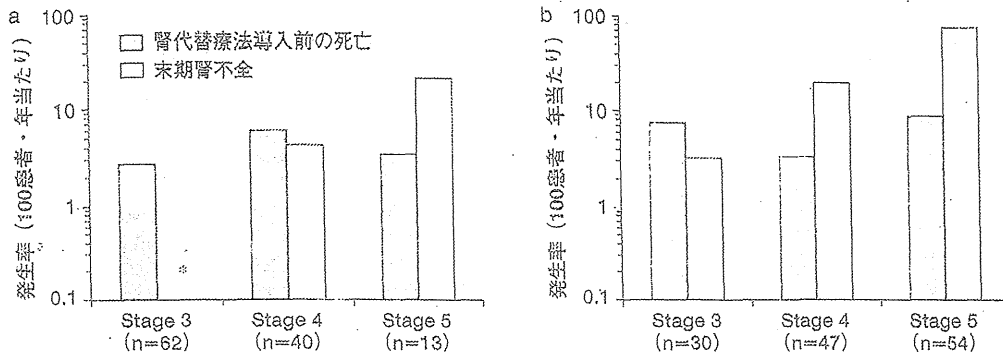


図2 65歳以上のCKD患者におけるイベント発生率の比較  
 a: 高度蛋白尿なし b: 高度蛋白尿あり  
 特にCKD stage 3の患者では蛋白尿の有無により死亡と末期腎不全の発症のリスクが異なる。  
 (文献16)より引用, 改変)

は認められていない。

しかし、蛋白尿を呈するCKD患者においては、厳格降圧が優れているという報告が多い。MDRDのサブ解析<sup>12)</sup>では、尿蛋白0.25g/日以上では厳格降圧群において蛋白尿の増加が抑制され、尿蛋白1g/日以上では腎機能低下速度が抑制された。さらに、MDRD Extension コホート解析<sup>13)</sup>では、厳格降圧群では末期腎不全と死亡のリスクが軽減していた。AASK Extension コホート解析<sup>14)</sup>でも、蛋白尿合併症例(尿蛋白/クレアチニン比>0.22)では、通常降圧群に比して厳格降圧群で腎機能低下速度が抑制されている。また、CKD進展を検討したメタ解析<sup>15)</sup>(11 RCT, 1,860名の非糖尿病CKD患者)では、蛋白尿が1g/日以上の場合には収縮期血圧110~129 mmHgで腎機能進展が抑制されていた。

### 高年齢者CKD患者では降圧目標値を高く設定すべきか?

前述した臨床研究を踏まえて、高年齢者CKD患者の降圧目標値について考察したい。まず、蛋白尿を有する高年齢CKD患者について考察する。高年齢CKD患者においても、蛋白尿が独立して心血管病と関連していることも示されているが、蛋白尿は末期腎不全のリスクでもある。われわれが

65歳以上のCKD患者の予後(腎代替療法導入と導入前の死亡)について検討した観察研究<sup>16)</sup>では、高度の蛋白尿(1g/H以上)を呈さないCKD stage 3の患者の場合、腎代替療法導入のリスクは高くないが、高度の蛋白尿を呈する患者では腎代替療法導入のリスクは死亡のリスクと同等になる(図3)。腎代替療法導入のリスクは、CKDのstageが進行するほど増加する。高齢CKD患者において、降圧による蛋白尿減少が末期腎不全のリスクを軽減できるという明確なエビデンスはないが、MDRD<sup>13)</sup>やAASK<sup>14)</sup>のextensionコホートの結果を考慮すると、1g/日以上の蛋白尿を有するCKD患者では、CKD進展抑制を考慮した厳格な降圧治療が高年齢者でも必要であると思われる。

次に、蛋白尿を呈さない高齢CKD患者の降圧目標値について、高齢高血圧患者を対象とした臨床研究が高年齢CKD患者にもあてはまるかという視点で考察する。高齢CKD合併患者の多くは、蛋白尿が陰性もしくは軽度でGFRが低下した患者であり、その要因は動脈硬化による腎硬化症もしくは虚血性腎症であると推定される。例えば、INVEST研究<sup>4)</sup>が対象とした患者が冠動脈疾患を有する高血圧患者であることを考慮すると、腎硬化症もしくは虚血性腎症に起因する高齢CKD患者においてもINVEST研究<sup>4)</sup>で得られた知見があてはまる可能性が高い。もちろん高齢者では、血

圧の動揺性や過降圧に伴う臓器障害の可能性がある。INVEST 研究<sup>4)</sup>でも過降圧がリスク増大につながる事が報告されており、虚血性心疾患を合併した患者では拡張期圧の低下に注意する必要がある。しかし、INVEST 研究<sup>4)</sup>の結果は post-hoc 解析によるものであり、拡張期圧が低い患者には、陈旧性心筋梗塞や心不全による低心機能/低心拍出状態の患者が含まれていると考えられ、その場合、降圧の程度に関係なく心血管死や心筋梗塞などのリスクが高い可能性があることを踏まえて解釈する必要がある。なお、高齢者 CKD 患者の 5~22%が動脈硬化性腎動脈狭窄症を合併していると報告されており、過降圧は腎灌流圧の低下による急性腎障害をきたす可能性もある。

しかし、高齢者 CKD 患者において降圧目標を一律に高く設定すると、特に蛋白尿を有する患者においては、末期腎不全のリスクが上昇する可能性がある。したがって、高齢 CKD 患者の降圧目標値は CKD 患者と同じ値とし、慎重に徐々に降圧すべきである。腎機能の悪化や臓器の虚血症状がみられる場合は、降圧レベルを個々に高めに設定すべきであるとする。

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