



Analysis of mortality risk from Korean hemodialysis registry data 2017

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The End-stage Renal Disease Registry Committee of the Korean Society of Nephrology collects data on the dialysis therapy in Korea through an internet-based registry program and reports it annually. In this article, the method and clinical implications of the mortality hazard ratio analyses of various clinical parameters in the 2017 registry report have been described, with the inclusion of data on four additional parameters. The mortality risk based on clinical parameters was analyzed only for hemodialysis patients. The number of registered patients with laboratory data was 13,943 (8,446 male and 5,497 female patients), and death was reported in 3,139 patients. Analysis of the effects of various clinical parameters on mortality was performed using non-linear Cox proportional hazard model with the R statistics program. For all clinical parameters, univariate and adjusted multivariate hazard ratio analyses were performed. Analysis of the mortality hazard ratio showed that low body mass index, low hemoglobin, low serum albumin, low serum phosphorus, and low urea reduction ratio were associated with a significantly increased mortality risk, whereas paradoxically high serum creatinine levels were associated with low mortality risk.

Keywords: Chronic kidney failure, Dialysis, Mortality

Introduction

The rapid increase in the number of dialysis patients in

the recent decades is associated with an expanding population of the elderly in Korea, the prevalence of diabetes and improved survival of dialysis patients [1–4]. According to the economic growth in the last three decades, dietary habits and living environments have greatly changed, resulting in a rapid increase in the prevalence of diabetes mellitus in Korea [1]. Furthermore, because of the increase in the prevalence of diabetic nephropathy, the number of end-stage renal disease (ESRD) patients has been increasing rapidly, with the rate of increasing being as high as approximately 7% to 10% per year [1–4]. The survival of dialysis patients has improved possibly due to improvements in the dialysis therapy, such as the use of biocompatible dialyzer and erythropoiesis-stimulating agents. However, the increase in the number of long-term dialysis patients as well as dialysis patients with complications has gradually increased the difficulty in the management of dialysis patients, increasing the cost of dialysis.

Identification of the various clinical factors that in-

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crease the mortality risk in complicated dialysis patients could aid in the development of clinical treatment strategies. An analysis of the mortality risk based on various clinical parameters would be most clinically relevant and could provide evidence for clinical treatment guidelines. Thus, an analysis using Cox proportional hazard model was first performed for the Korean Society of Nephrology (KSN) ESRD registry data. In this article, the method and clinical implications of the mortality hazard ratio analyses of various clinical parameters in the 2017 KSN ESRD registry report have been described.

Mortality hazard ratio analyses of various clinical parameters

An internet-based questionnaire for dialysis patient registry is conducted by KSN throughout the year; it includes dialysis center information, as well as a patient’s personal medical information including vascular access for hemodialysis (HD), adequacy performance data, erythropoietin dose, use of phosphate binders, laboratory data, and rehabilitation status. The response rate for the questionnaire including patients’ individual data was 51.9% in 2017 (427 of 823 centers). The mortality risk based on clinical parameters was analyzed for HD patients only. The number of all registered HD patients in Korea from 2007 to 2017 was 87,993; however, the number of registered patients with laboratory data was only

13,943 (8,446 male and 5,497 female patients); death was reported in 3,139 patients, and 8,039 (57.6%) patients had diabetes mellitus.

An analysis of the effects of various clinical parameters on mortality was performed using non-linear Cox proportional hazard model with the statistics program package of “survival”, “rms”, and “survminer” of R project (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). The analysis procedure was processed in R-studio program with CRAN package according to the instructions on R package developer’s web page [5]. All univariate analysis hazard ratio graphs were presented using all clinical parameters as continuous variables on the x-axis. Also, the hazard ratio graphs of various clinical parameters were overlapped with the overall HD patient number distribution bar graph to show the patient number according to each hazard ratio range. The adjusted multivariate hazard ratio with various clinical parameters was also calculated. The first quarter and the third quarter values of clinical parameters were used for stepwise adjusted multivariate analysis.

The mean age of the registered HD patients with laboratory data was 66.2 years, and the mean dialysis duration was 3,276 days. Mean values of other clinical parameters are shown in Table 1.

Age and diabetes mellitus: The mortality hazard ratio of diabetic HD patients was 1.0 at the age of 60 years, which is as expected. The mortality hazard ratio of diabetic HD patients was same as that of overall HD patients at the age

Table 1. Mean values of clinical parameters

Clinical parameter	Value
Age (yr)	66.2 ± 14.1
Systolic blood pressure (mmHg)	144.5 ± 19.9
Diastolic blood pressure (mmHg)	78.1 ± 12.4
Hemoglobin (g/dL)	10.3 ± 1.1
Serum albumin (g/dL)	3.91 ± 0.48
Serum creatinine (mg/dL)	9.43 ± 3.0
Serum calcium (mg/dL)	9.06 ± 0.85
Serum phosphorus (mg/dL)	4.88 ± 1.59
Serum cholesterol (mg/dL)	141 ± 37
Serum uric acid (mg/dL)	6.8 ± 1.8
Parathyroid hormone (pg/mL)	245 ± 228
Hemoglobin A1c (%)	6.8 ± 1.4
Body mass index (kg/m ²)	21.9 ± 3.9
Urea reduction ratio (%)	70.6 ± 6.7
Single pool Kt/V	1.51 ± 0.30

Data are presented as mean ± standard deviation.

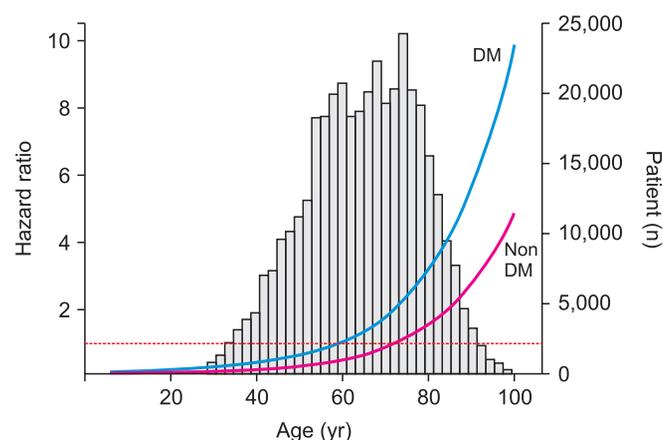


Figure 1. Mortality hazard ratio according to age distribution. Age, as a continuous variable on the x-axis, and the overall hemodialysis patient number distribution bar graph overlapped (right y-axis); horizontal line is at hazard ratio 1.0. DM, diabetes mellitus.

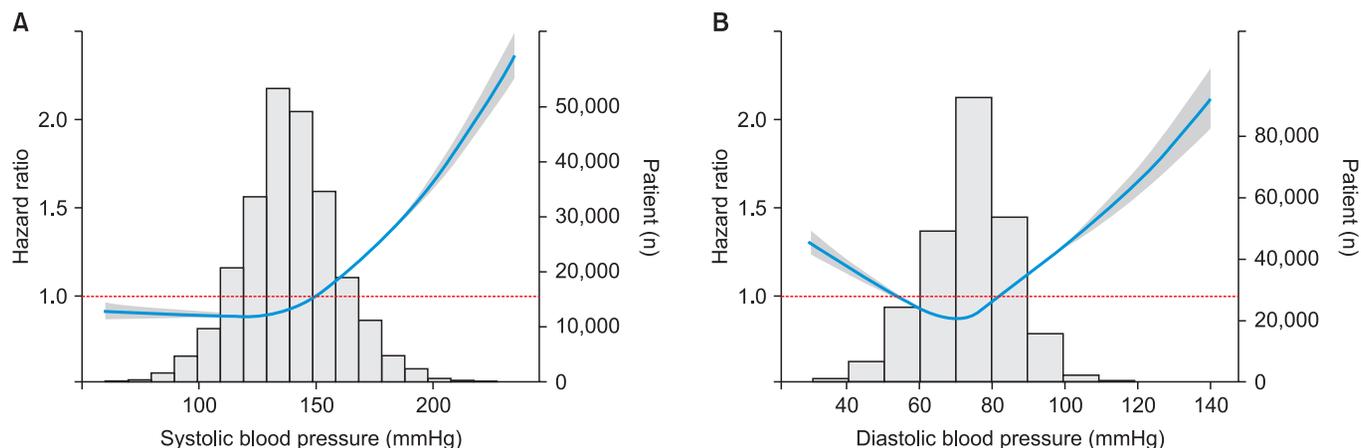


Figure 2. Mortality hazard ratio according to blood pressure distribution. Gray shade around the hazard ratio line represents 95% confidence interval. (A) Systolic blood pressure. (B) Diastolic blood pressure.

of about 60 and same as that of non-diabetic HD patients at the age of approximately 72. Thus, the hazard ratio of diabetic patients was approximately 2.3-fold higher than that of non-diabetic HD patients at the age of 72 (Fig. 1).

Systolic blood pressure: The mortality hazard ratio increased according to systolic blood pressure at levels above 140 mmHg and was only 1.5 at 180 mmHg, but the ratio did not increase at levels below 120 mmHg (Fig. 2).

Diastolic blood pressure: The mortality hazard ratio increased symmetrically in both low and high ranges of diastolic blood pressure. The lowest peak of the mortality hazard ratio was at diastolic blood pressure of 70 mmHg, and the ratio increased, not rapidly, to 1.5 at 110 mmHg. The hazard ratio increased at diastolic blood pressure below 60 mmHg (Fig. 2).

Body mass index (BMI): The mortality hazard ratio obtained according to BMI was somewhat different than expected. The ratio sharply increased when BMI was less than 18 kg/m², but it did not increase when BMI was higher than 25 kg/m², which means overweight or obesity. These results imply that malnutrition is a strong mortality risk factor (Fig. 3). However, because the mean BMI of HD patients was 22.4 ± 3.9 kg/m², which was similar to the BMI range associated with low mortality risk, BMI was clearly not a clinically important parameter.

Hemoglobin: Low hemoglobin concentration was a robust hazard factor, whereas high hemoglobin concentration did not increase the risk. Patients with a hemoglobin concentration of 7 g/dL showed twice the mortality risk compared with overall HD patients. The mortality risk rapidly increased when hemoglobin concentration was

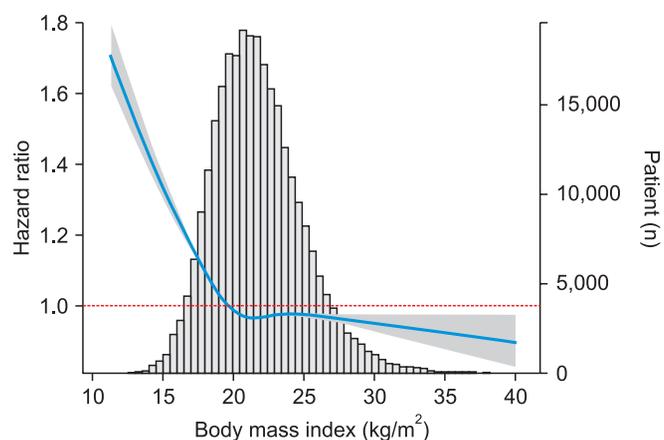


Figure 3. Mortality hazard ratio according to body mass index distribution.

below 10.0 g/dL, and approximately one-third of HD patients exhibited this range. The mean of hemoglobin concentration was 10.4 ± 1.1 g/dL, which was slightly lower than that for low mortality risk (Fig. 4).

Serum creatinine: The mean serum creatinine level for mortality risk was 9.0 mg/dL. The mortality hazard ratio increased in HD patients with low serum creatinine levels, whereas it was low in those with paradoxically high serum creatinine levels. The increased mortality hazard ratio in patients with low serum creatinine levels implies that these patients were diabetic or old aged, with low muscle mass and relative malnutrition (Fig. 5A).

Serum albumin: The mean serum albumin level was 3.9 ± 0.5 g/dL, which was significantly lower than 4.3 g/dL, the level associated with the lowest mortality hazard

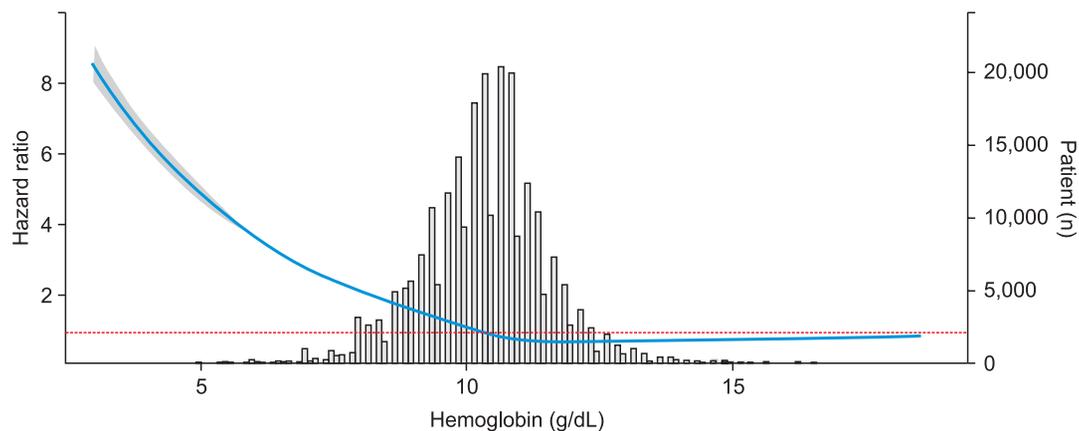


Figure 4. Mortality hazard ratio according to hemoglobin distribution.

ratio. The mortality hazard ratio of patients with serum albumin levels less than 3.0 g/dL sharply increased to more than five times of the overall HD patient. Thus, the low serum albumin levels were the strongest hazard factor. Therefore, it is clinically very important to identify the causes of low serum albumin levels (Fig. 5B).

Calcium: The patient distribution according to calcium levels showed a narrow safety margin, and the mortality hazard ratio was lowest at the level of approximately 9.4 mg/dL. Approximately a quarter of patients had calcium levels of 8.0 mg/dL or less, and the mortality risk below this level was more than twice that for the overall HD patients (Fig. 5C).

Serum phosphorus: The mortality hazard ratio increased in patients with low serum phosphorus levels. Patients with a serum phosphorus level of approximately 3.0 mg/dL had twice the hazard risk, but those with high serum phosphorus levels did not show an increased risk until the level of 10 mg/dL. Although the mean phosphorus level was 4.8 ± 1.6 mg/dL in overall HD patients, the patients with approximately 6 mg/dL of serum phosphorus showed the lowest mortality risk (Fig. 5D). Thus, low serum phosphorus levels presented another hazard factor for mortality in HD patients. Taken together, hazard ratios associated with serum albumin and phosphorus levels show that malnutrition is the most important mortality risk factor in HD patients.

Cholesterol: Patient distribution showed that only few patients had high cholesterol levels and a majority had low cholesterol levels. The hazard ratio according to the cholesterol level was U-shaped. The mean cholesterol level was 141 ± 37 mg/dL; the hazard risk increased above

the level of 230 mg/dL and was lowest at approximately 160 mg/dL (Fig. 5E).

HbA1c: The mean HbA1c of patients in this study was 6%. Patient distribution graph showed that the prevalence of patients with high HbA1c was low, less than approximately 15% of overall HD patients. As expected, patient with high HbA1c (over 9%) had increased mortality risk (Fig. 5F).

PTH: The patient graph of the KSN registry report showed the distribution of parathyroid hormone levels with logarithmic scale x-axis. The mortality risk graph with linear (non-logarithmic) scale x-axis had extremely left-shifted patient distribution. Dialysis patients with high parathyroid hormone levels did not exhibit an increased mortality risk probably because of young age and high phosphorus intake (Fig. 5G).

Serum uric acid: The mortality hazard ratio graph of serum uric acid levels was U-shaped. Patients with low serum uric acid levels were at a higher mortality risk than those with high uric acid levels (Fig. 5H). This finding also exhibited that the mortality risk were reversely correlated with uric acid levels as creatinine levels.

Urea reduction ratio (URR) and single pool Kt/V (spKt/V): The mortality hazard ratio for 70% of URR and 1.5 of spKt/V, which is the 1.2 of a minimum delivered target for dialysis therapy recommendations (The Kidney Disease Outcome Quality Initiative [KDOQI] guidelines for HD), was approximately 1.0. Patients with lower than that point of URR and spKt/V, comprising approximately one-third of overall HD patients, had increased mortality hazard ratio. These findings can provide a clinical evidence for the application of KDOQI guidelines to Korean HD

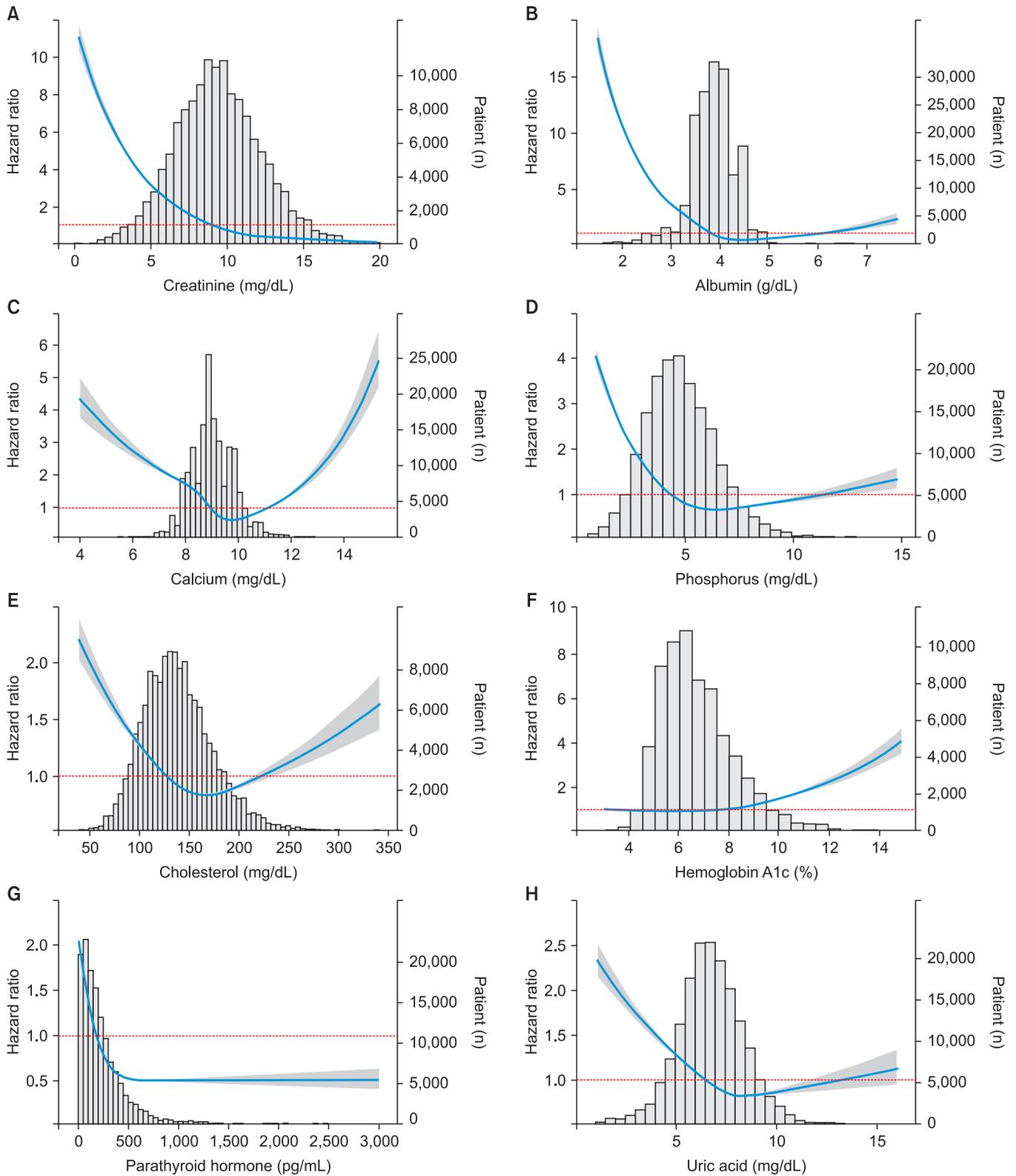


Figure 5. Mortality hazard ratios according to blood biochemical parameters. (A) Serum creatinine. (B) Serum albumin. (C) Serum calcium. (D) Serum phosphorus. (E) Total cholesterol. (F) Hemoglobin A1c. (G) Intact-parathyroid hormone. (H) Serum uric acid.

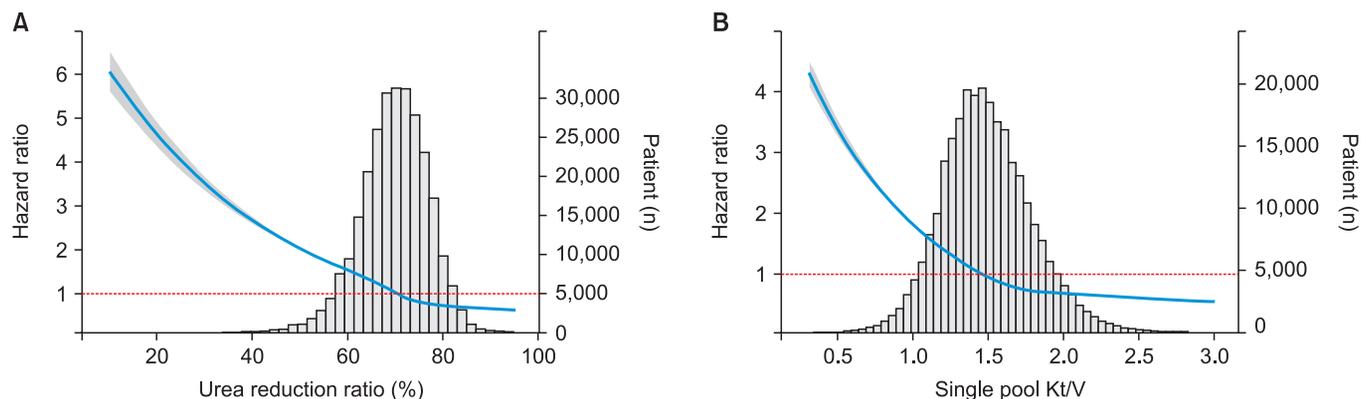


Figure 6. Mortality hazard ratio according to dialysis adequacy. (A) Urea reduction ratio. (B) Single pool Kt/V.

		Hazard ratio								
		0.75	1.00	1.20	1.40	1.60	1.80	2.00	2.20	<i>P</i> (> z)
Age	76 vs. 57								▲	< 0.0001
Systolic BP*	160 vs. 130		▲							0.462
Diastolic BP	90 vs. 70				▲					< 0.0001
Hemoglobin	11 vs. 9.7			▲						< 0.0001
Albumin	4.2 vs. 3.7	▲								< 0.0001
Calcium	9.6 vs. 8.5	▲								< 0.0001
Phosphorus	5.9 vs. 3.8				▲					< 0.0001
Cholesterol	162 vs. 116				▲					< 0.0001
Uric acid*	7.87 vs. 5.8			▲						0.376
PTH	316 vs. 82		▲							< 0.0001
Hb A1c	7.6 vs. 5.7				▲					< 0.0001
BMI	23.8 vs. 19.6			▲						< 0.0001
URR	75.5 vs. 66.2	▲								< 0.0001
spKt/V*	1.724 vs. 1.316				▲					0.063
Female vs. Male			▲							< 0.0001
DM vs. Non-DM						▲				< 0.0001

Figure 7. Adjusted multivariate mortality hazard ratio analyses of various clinical parameters and comparisons of hazard ratio between the third and the first quarter values of each parameter.

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, hemoglobin A1c; PTH, parathyroid hormone; spKt/V, single pool Kt/V; URR, urea reduction ratio.

*The parameters are not statistically significant.

patients (Fig. 6).

Multivariate mortality hazard ratio of various clinical parameters: Hazard ratio analysis with stepwise adjustment of multivariables, including systolic blood pressure (160 vs. 130 mmHg), serum uric acid levels (7.9 vs. 5.8 mg/dL), and spKt/V (1.724 vs. 1.316), did not give significant results due to more strong impact of diastolic blood pressure, urea, and URR, respectively. On the other hand, age, serum albumin levels, and diabetes were robust hazard factors (Fig. 7).

Conclusion

KSN performed ESRD patient registration and presented the 2017 data with mortality hazard ratio based on various clinical parameters. Analysis of the mortality hazard ratio showed that low BMI, low hemoglobin, low serum albumin, low phosphorus, and low URR were associated with a significantly increased mortality risk, whereas paradoxically high serum creatinine and PTH levels were associated with low mortality risk.

Conflicts of interest

The author has no conflict of interest to declare.

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