Accumulation of Advanced Glycation End Products Independently Increases the Risk of Hospitalization Among Hemodialysis Patients

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ABSTRACT

Objective: To determine the association between AGE accumulation detected by skin-autofluorescence (SAF) and hospitalization among ESKD patients.

Materials and Methods: 196 ESKD patients from two hemodialysis (HD) units in Bangkok were enrolled in this retrospective study from November 2015 to March 2016. Before HD treatment, AGEs were measured with the SAF device on the area with intact skin on the volar surface of the non-fistula arm. The study concluded in December 2020, and the number of and causes of hospitalization were reviewed. A logistic regression model was used to determine the association between SAF level and patient hospitalization.

Results: Of the 196 patients enrolled in the study, SAF was measured in 165 patients with a mean (SD) age of 69.2 (13.0) years. Most of the participants were non-smokers who had hypertension and diabetes and were on high-flux dialyzers. The average weekly spKt/V was 2.1, and the mean (SD) SAF was 3.05 (0.81) AU. The group with high SAF consisted of older patients and had a higher proportion of diabetics and smokers, but this was not statistically significant when compared to the low SAF group. In the multivariable analysis model, SAF greater or equal to 3.05 AU (OR = 2.28; 95% CI, 1.05–4.94; $P < 0.05$) and increased age (OR = 1.05; 95% CI, 1.01–1.09; $P < 0.05$) were associated with an increased risk of hospitalization.

Conclusion: Higher values of age and SAF were independently associated with increased risk of hospitalization among ESKD patients.

Keywords: Hospitalization; skin autofluorescence; advanced glycation end-products; end-stage kidney disease (Siriraj Med J 2022; 74: 305-313)

INTRODUCTION

End-stage kidney disease (ESKD) is recognized as one of the leading non-communicable diseases worldwide. The global prevalence of ESKD patients requiring renal replacement therapy is estimated to be between 4.9 and 7.1 million[1], and the total number of affected patients has been steadily increasing. Progression of chronic kidney disease (CKD) are associated with an increased risk of morbidity, mortality, and decreased quality of life.[2,3] Moreover, ESKD causes a substantial financial burden

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on the patients, and its treatment requires an immense amount of human resources.[4]

Compared with the general population and non-dialysis CKD patients, dialysis patients have higher hospitalization and in-hospital mortality rates.[5,6] With the elevated cardiovascular risk that is related to ESKD, cardiovascular disease (CVD) is the major cause of hospitalization among these patients.[7] Hospitalization of ESKD patients is associated with an increased risk of hospital-acquired infection, malnutrition, depression, and impaired quality of life, and it often results in higher overall costs.[8,9] Strategies for preventing the hospitalization of ESKD patients are yet to be determined.

In the general population, hypertension, diabetes mellitus, dyslipidemia, age, and tobacco use are known risk factors for developing CVD. Non-traditional risk factors contributing to CVD among patients with ESKD include anemia, mineral bone disease from the accumulation of calcium and phosphorous levels, and uremic toxins.[10] In recent times, greater evidence shows markedly increased levels of advanced glycation end-products (AGEs) in ESKD patients, leading to atherosclerosis-one of the established risk factors for CVD.[11]

AGEs are medium-sized uremic toxin molecules[12] that are formed as by-products of non-enzymatic reactions between the glucose and amino groups in proteins and nucleic acids. AGEs can also be formed through the oxidation of lipid-derived intermediates, resulting in advanced lipid oxidation products.[13,14] Moreover, ingestion of processed food and smoking habits are exogenous sources of AGEs. As AGEs are mainly excreted in the urine, AGE accumulation can be found in patients with ESKD. AGEs accumulate in tissues and affect protein structures, leading to the stiffness of tissues and blood vessels. Further, the binding of AGEs to AGE receptors (RAGE) activates the intracellular transduction mechanisms, resulting in cytokine release and oxidative stress. These can cause further tissue damage and accelerate the atherosclerotic process.[15,16] Previous studies have reported that AGE accumulation in tissues is associated with an increased risk of CVD.[17,18] However, to date, the association between AGE accumulation and hospitalization has never been conducted in a formal study.

There are several techniques of AGE measurement. Plasma AGEs are easier to detect, but the plasma levels in patients on dialysis keep fluctuating and is less reliable; this is because dialysis may result in some types of AGEs being removed.[13] Tissue AGEs can be measured via tissue biopsy, but the process is invasive, time-consuming, less specific, and poorly reproducible. Recently, a novel AGE measurement technique with skin autofluorescence (SAF) has been developed. Compared to other methods, SAF is non-invasive and reproducible. The tissue levels measured using this method tend to be more constant and reliable despite the patient undergoing regular dialysis.[18,19] To address the gap in the literature, this study aimed to evaluate the association between tissue AGE accumulation measured by SAF and the incidence of all-cause hospitalization among ESKD patients.

MATERIALS AND METHODS

Participants

We enrolled ESKD patients from Ramathibodi Hospital and Bhumirajanagarindra Kidney Institute Hospital, Bangkok, Thailand. The enrollment period was from November 2015 to March 2016. The participants aged 18-90 years who had received regular chronic hemodialysis (HD) for more than one week, signed the informed consent form, and completed AGE measurements using the SAF device at the enrollment were included in this study. The patients were dialyzed twice or thrice weekly using high-flux HD or hemodiafiltration. Unfractionated heparin was administered as an anticoagulant during HD sessions. Pre-HD blood chemistry was obtained and processed using a standard central laboratory analyzer. Patients hospitalized for elective surgery were excluded. Those participants were followed until December 31st, 2020 when the study concluded.

Ethics

The present study was approved by the Human Research Ethics Committee from the Faculty of Medicine Ramathibodi Hospital, Mahidol University (the approval number MURA2021/1052, dated December 29, 2021) and from Bhumirajanagarindra Kidney Institute Hospital (the approval number Ref. no. 1/2016, dated January 14, 2016).

Study design

This study was a retrospective cohort study. The patients' baseline characteristics, dialysis profiles, and laboratory parameters were collected through interviews and from their electronic medical records. Patient-identifying information was removed. The SAF measurements were performed at the time the participants were initially enrolled between November 2015 and March 2016. Those participants were followed until December 31st, 2020 for hospitalization events.

Measurement of tissue AGEs

Trained nurses were designated to perform AGE measurement as standard instruction. Tissue AGEs were

measured using the skin autofluorescence ultraviolet technique (AGEs reader, DiagnOptics, The Netherlands). The device has been clinically validated and shown to be highly correlated with tissue AGEs that are histologically measured from a skin biopsy.[20] The area with intact skin on the volar surface of the non-fistula arm was examined while the patient was in a seated position. Blemishes and hairy areas were avoided. An additional light source was used for naturally pigmented skin color.[21] Before an HD treatment session, tissue AGEs were measured three times consecutively with the SAF device, calculated using the AGE reader software, and reported in arbitrary units (AU). The mean of the three measurements was used for the statistical analyses. The SAF measurements are nonoperator-dependent, reliable, not fluctuating between pre- and post-dialysis, and highly reproducible.[18,19] To the best of our knowledge, there are no standard criteria for defining high SAF values. Therefore, we divided the patients into two groups, high and low SAF, using the mean SAF from our study as the cut-off point.

Primary outcome of all-cause hospitalization

The term 'Hospitalization' was defined as the event when the patient was hospitalized due to any causes at least once except elective surgery. Multiple rehospitalizations in the same participant would be counted as one.

Statistical analysis

The baseline characteristics of the patients, including their demographic data, underlying diseases, and laboratory results, were reported as mean and standard deviation (SD) or median (interquartile range, IQR) values for continuous variables and as frequencies (%) for categorical variables. Student's *t* test and the Wilcoxon rank sum test were used to compare the means and medians of the two SAF groups, while the chi-square test was used to analyze the categorical variables.

The event of hospitalization was analyzed using a logistic regression model from the time of AGE measurement to the first hospitalization. To test the associations between AGE accumulation and ESKD patient hospitalization, factors that might affect hospitalization were also analyzed using a logistic regression model and reported as odds ratios (OR) with a 95% confidence interval (CI). Variables identified by univariate analysis with *P* value less than .1 were subsequently analyzed using a multivariable analysis model.

A scatter diagram was formed to depict hospitalization, SAF, and any other interesting factors. Two-tailed *P* values less than .05 were considered statistically significant. All the statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp).

RESULTS

Of 196 enrolled, 165 patients met the inclusion criteria and were included in the study, with a mean (SD) age of 69.2 (13.0) years. Most of the patients were non-smokers with hypertension and diabetes. 38% had CVD, and 9% had cerebrovascular disease (CVA). Most of the patients were hemodialyzed using a high-flux dialyzer for 4 hours per HD session. The median dialysis vintage was 21.0 (range 1-41) months, and the mean (SD) weekly spKt/V was 2.1 (0.4). The patients' vascular accesses were 44.2% arteriovenous fistula (AVF), 29.1% arteriovenous graft (AVG), and 26.7% tunneled cuffed catheter (TCC). The mean (SD) SAF level was 3.05 (0.81) AU. There was no significant difference between the characteristics of patients with SAF less than 3.05 AU and those with SAF greater or equal to 3.05 AU. The comorbidities, dialysis profiles, and laboratory parameters were similar for both groups of participants (Table 1).

During the 56-month study period, the total number of hospitalizations was 410. Of 165, 20 patients (12.1% of the cohort) had no hospitalization, and 33 patients (20%) had one hospitalization. The causes of hospitalization (Fig 2) were infection (37.3%), cardiovascular disease (22.2%), stroke (2.2%), and malignancy (1.7%). However, up to 36.6% had no clear documentation regarding the cause of hospitalization. During the follow-up period, 48 patients died while hospitalized; 22 patients (25%) in the low SAF group and 26 patients (33.8%) in the high SAF group. One patient in the low SAF group had died before hospitalization due to infection.

Univariate analysis (Table 2) showed that patient hospitalization was associated with different vascular access types, ages, and SAF levels. When compared with arteriovenous fistula (AVF) or arteriovenous graft (AVG), tunneled cuffed catheter (TCC) was associated with an increased risk of hospitalization (OR = 4.49; 95% CI, 1.02–19.77; $P = 0.05$). Greater patient age was associated with increased hospitalization (OR = 1.05; 95% CI, 1.02–1.08; $P = 0.005$). Further, the risk of hospitalization was higher among patients with SAF greater or equal to 3.05 AU (OR = 4.06; 95% CI, 1.29–12.72; $P = 0.02$). These associations were significant even after adjustments for other covariates. The multiple regression model (Table 2) showed that older age groups and SAF greater or equal to 3.05 AU were independently associated with an increased risk of hospitalization, with ORs of 2.28 (95% CI, 1.05–4.94; $P = 0.04$) and 1.05 (95% CI, 1.01–1.09; $P = 0.01$), respectively. The multiple regression analysis

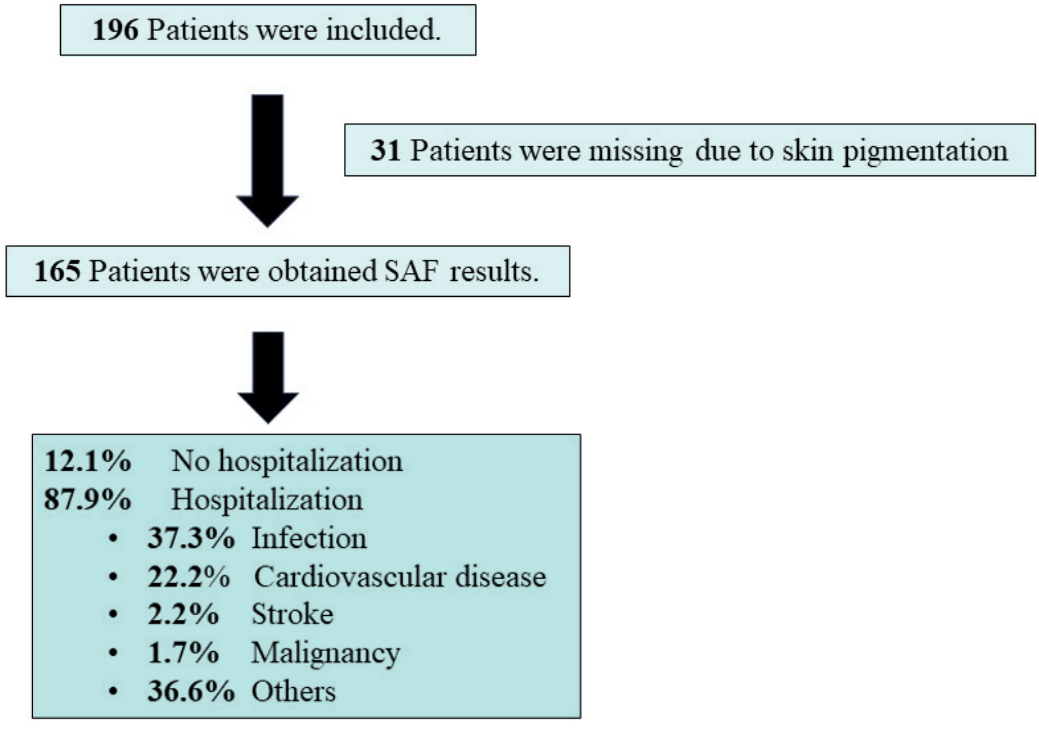
TABLE 1. Baseline characteristics stratified by skin autofluorescence level.

Characteristics	Total (N = 165)	No. (%) SAF < 3.05 AU (n = 88)	SAF ≥ 3.05 AU (n = 77)	*P* value*
Age, mean (SD), y	69.2 (13.0)	68.0 (13.7)	70.4 (12.2)	0.24
Female	96 (58.1)	51 (57.9)	45 (58.4)	0.95
Body mass index, mean (SD), kg/m^2	22.4 (4.3)	22 (4.6)	22.8 (3.9)	0.23
Bodyweight, mean (SD), kg	57.3 (12.4)	56.7 (12.9)	57.9 (11.9)	0.56
Height, mean (SD), cm	159.7 (8.2)	160.4 (8.5)	159 (8.0)	0.27
Hypertension	157 (95)	83 (94)	74 (96)	0.59
Diabetes	95 (57.6)	48 (54.5)	47 (61.0)	0.40
Smoker	32 (19.3)	15 (17)	17 (22)	0.42
Coronary artery disease	54 (38)	28 (32)	26 (38)	0.79
Cerebrovascular disease	15 (9)	8 (9)	7 (9)	0.98
Dialysis vintage, median (IQR), mo	21 (20)	21 (19.2)	27 (21.5)	0.15
Residual urine volume, median (IQR), mL	0 (1100)	0 (1110)	0 (1170)	0.52
Vascular access				0.95
AVF	73 (44.2)	40 (45.4)	33 (42.9)	
AVG	48 (29.1)	25 (28.4)	23 (29.8)	
TCC	44 (26.7)	23 (26.2)	21 (27.3)	
Hemodiafiltration	21 (12.7)	11 (12.5)	10 (13)	0.93
3 times/week dialysis	76 (46)	39 (44.3)	37 (48)	0.63
Time, mean (SD), min	239.2 (4.8)	239.2 (4.9)	239.2 (4.8)	0.98
Hemoglobin, mean (SD), g/dL	11 (1.4)	11 (1.5)	11 (1.3)	0.98
HbA1C, mean (SD), %	6 (5.6)	6 (1.3)	6 (1.1)	0.80
Serum albumin, mean (SD), g/dL	3.7 (0.4)	3.8 (0.4)	3.7 (0.4)	0.40
Serum calcium, mean (SD), mg/dL	9.2 (0.7)	9.2 (0.7)	9.2 (0.7)	0.57
Serum phosphorus, mean (SD), mg/dL	4.6 (1.4)	4.6 (1.4)	4.6 (1.3)	0.90
Serum iPTH, median (IQR), pg/mL	355 (452.9)	382.5 (510.5)	353.0 (366.8)	0.24
Serum B_2-microglobulin, mean (SD), ug/mL	31.2 (10.2)	31.7 (9.7)	30.7 (10.8)	0.57
hsCRP, median (IQR), mg/L	0.16 (0.5)	0.17 (0.51)	0.15 (0.54)	0.63
spKt/V, mean (SD)	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	0.86
nPCR, mean (SD)	1 (0.3)	1 (0.3)	1 (0.3)	0.61

Abbreviations: AVF; arteriovenous fistula, AVG; arteriovenous graft, hsCRP; high sensitivity C-reactive protein, iPTH; intact parathyroid hormone, nPCR; normalized protein catabolic rate, SAF; skin autofluorescence, spKt/V; single-pool Kt/V, TCC; tunneled cuffed catheter.
* Significance threshold, $P < .05$

revealed no association between vascular access type and hospitalization (OR = 2.70; 95% CI, 0.58–12.61; $P = 0.21$). According to our results, SAF is an independent factor associated with the primary endpoint of hospitalization even after adjustment for age and vascular access types.

The AUROC of SAF for prediction of hospitalization was 0.70 (95% CI, 0.566-0.825). The sensitivity was 50.3% and the specificity was 80%. The scatter plot of SAF-stratified hospitalization and age (Fig 3) shows that increased SAF levels in ESKD patients are associated with hospitalization.



196 Patients were enrolled.
31 Patients were unable to obtain complete SAF results.
165 Patients obtained complete SAF results and were included.
Abbreviation: SAF; skin autofluorescence

Fig 1. Flow chart shows that 196 patients were eligible for the study, and SAF was measured for 165 patients.

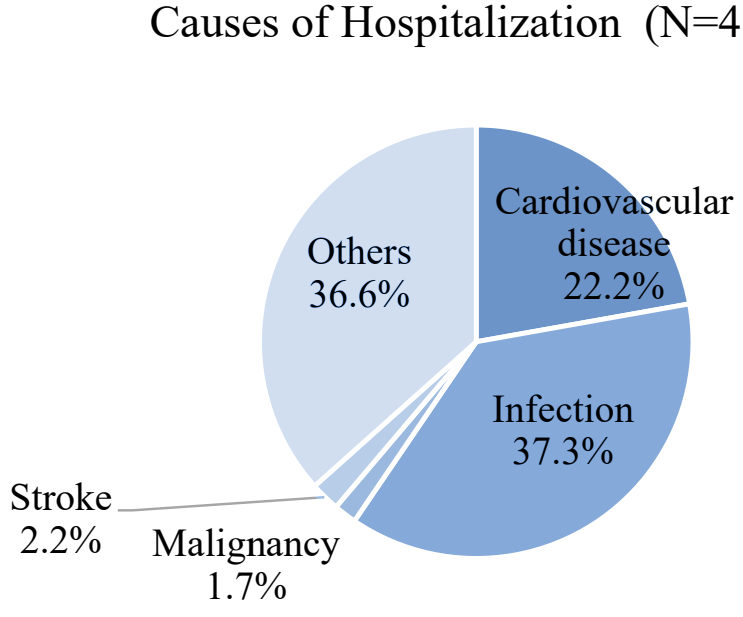


Fig 2. Causes of hospitalization.

TABLE 2. Univariate and multiple logistic regression analyses of factors associated with hospitalization among hemodialysis cohort.

Risk factor	Hospitalization			
	Univariate		Multivariate‡	
	OR (95% CI)	*P* value*	OR (95% CI)	*P* value*
Vascular access				
AVF/AVG	1.00 [Reference]	NA	1.00 [Reference]	NA
TCC	4.49 (1.02–19.77)	0.05	2.70 (0.58–12.61)	0.21
Age	1.05 (1.02–1.08)	0.005*	1.05 (1.01–1.09)	0.01†
SAF ≥ 3.05 AU	4.06 (1.29–12.72)	0.02*	2.28 (1.05–4.94)	0.04†
Female	1.03 (0.44–2.38)	0.95		
Body weight	0.98 (0.95–1.01)	0.22		
Height	0.76 (0.17–3.40)	0.72		
Body mass index	0.94 (0.86–1.03)	0.19		
Hypertension	2.46 (0.62–9.76)	0.20		
Diabetes	1.06 (0.45–2.46)	0.90		
Smoker	0.69 (0.27–1.77)	0.44		
Coronary artery disease	1.32 (0.52–3.34)	0.56		
Dialysis vintage	0.99 (0.98–1.00)	0.25		
Residual urine volume	1.00 (0.99–1.00)	0.24		
Hemodiafiltration	3.73 (0.48–28.92)	0.21		
3 times/week dialysis	0.85 (0.37–1.97)	0.71		
Hemoglobin	0.87 (0.65–1.16)	0.34		
HbA1C	0.90 (0.66–1.22)	0.49		
Serum calcium	1.10 (0.60–2.02)	0.75		
Serum phosphorus	1.06 (0.78–1.44)	0.71		
Serum albumin	0.79 (0.26–2.34)	0.66		
Serum iPTH	1.00 (0.99–1.00)	0.38		
Serum B_2-microglobulin	0.97 (.092–1.01)	0.11		
hsCRP	0.88 (0.59–1.31)	0.53		
spKt/V	1.57 (0.53–4.61)	0.41		
nPCR	1.53 (0.39–5.90)	0.54		

Abbreviations: AVF; arteriovenous fistulae, AVG; arteriovenous graft, CI; confidence intervals, HbA1C; hemoglobin A1c, hsCRP; high sensitivity C-reactive protein, iPTH; intact parathyroid hormone, NA; not applicable, nPCR; normalized protein catabolic rate, OR; odds ratio, SAF; skin autofluorescence, spKt/V; single-pool Kt/V, TCC; tunneled cuffed catheter.

* Significance threshold, $P < 0.05$

‡ Adjusted for age, vascular access, SAF.

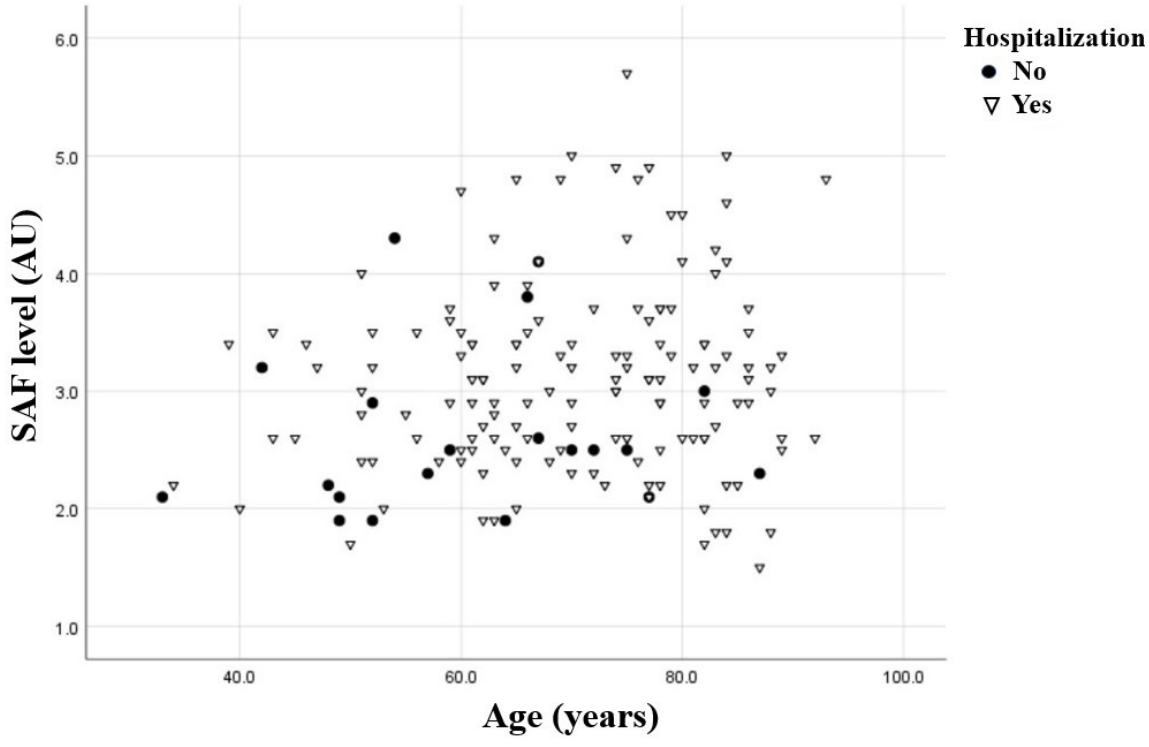


Fig 3. Scatter plot for the hospitalization of ESKD patients stratified by SAF level and age
Abbreviations: ESKD; end-stage kidney disease, SAF; skin autofluorescence.

DISCUSSION

To our knowledge, plasma AGE concentrations fluctuate from one dialysis treatment to another and are affected by dietary intake. In contrast, tissue AGE concentration is relatively constant and likely reflects the chronically elevated plasma AGE level.[22]

SAF measurements, representing tissue AGE accumulation, have been reported to be reliable markers of AGEs and independently associated with overall and cardiovascular mortality among ESKD patients of all ethnicities.[21] Elevated tissue AGEs are associated with advanced age, diabetes, smoking, and inflammatory states. The baseline characteristics of the patients in the present study (Table 1) showed no difference between the higher and lower SAF groups in terms of age, diabetes, smoking status, serum albumin, or CRP, a surrogate marker of inflammation.

The multivariable analysis revealed that SAF level and age are independently associated with hospitalization. The age factor was in agreement with previous studies.[10,23,24] This study reinforces that AGE levels greater or equal to 3.05 AU, measured using SAF, constitute an independent factor associated with an increased risk of hospitalization. While TCC utilization was found to be associated with an increased risk of hospitalization in the univariate analysis model, the effect became statistically insignificant when analyzed in the final multivariable analysis model. This might be due to a preference for using TCC over AVF or AVG in elderly patients with higher risk of CVD or with limited life expectancy.

In this study, the most common causes of hospitalization were infection and cardiovascular disease. Previous studies have indicated that AGE accumulation might increase a patient's susceptibility to infection. Previous observation studies also suggest that AGEs might attenuate the activation of the NLRP3 inflammasome in bone marrow-derived macrophages. Besides, AGEs might dampen innate immune responses, including NLRP3 inflammasome activation and type-I interferon production in macrophages upon infection.[25,26] Therefore, AGEs could impair host NLRP3 inflammasome–mediated innate immune defenses against infection. AGE accumulation not only induces immune system dysregulation but also leads to endothelial dysfunction, arterial stiffness, myocardial changes, and atherosclerosis progression.[27] Previous studies have reported that tissue AGE accumulation measured by SAF is associated with higher prevalence of cardiovascular events, cardiovascular mortality, and all-cause mortality among non-dialysis and dialysis CKD patients.[28] This evidence supports the present study's result of CVD being the second most common cause of hospitalization. Thus, this study emphasizes that high SAF is an independent risk factor for patient hospitalization.

Interestingly, our results showed that the plasma levels of beta-2-microglobulin, one of the middle-molecule uremic toxins similar to AGEs, in the higher and lower SAF did not differ. This discordance between the plasma beta-2-microglobulin level and the tissue AGE level measured by SAF could be from the following reasons. First, plasma uremic toxins could generally be removed with HD more than those accumulated in the tissue.[29] The same principle applies to HD clearance of plasma beta-2-microglobulin compared to tissue AGEs. Second, different kinds of uremic toxins might have different HD clearance properties, even only plasma uremic toxins are considered. Compared to plasma beta-2-microglobulin, plasma AGEs are marginally removed, despite the utilization of a high flux dialyzer or increased dialysate flow rate, given their higher molecular weight of greater than 12 kDa and higher binding affinity to protein. These techniques would not provide any significant effect on the clearance of the solutes.[30-32] Moreover, ingestion of a particular type of food can further increase the accumulation of AGEs whereas beta-2-microglobulin has a lesser correlation with the dietary factor.[33]

Accordingly, measuring AGEs by SAF in ESKD patients may have several clinical applications, including prognosis prediction and possible SAF lowering interventions, such as AGE-rich diet restriction, oral AGE-adsorbent use, or hemodiafiltration. According to our result of the positive association between tissue AGE accumulation and all-cause hospitalization, this may open an avenue for future research in AGE lowering intervention.

To the best of our knowledge, this is the first study that showed the association between AGEs accumulation and hospitalization in ESKD patients. Also, this is the first study that applied SAF to determine dialysis adequacy in Thai populations. Moreover, this study had a long follow-up period to determine study outcome of hospitalization.

However, our study has some limitations. First, this study consisted of a retrospective cohort with a small sample size. Second, since all the participants were of the Asian ethnicity, the results cannot be generalized to the overall population. Third, as the SAF principle is based on the interaction of ultraviolet radiation (UV) irradiation with the AGE chromophore in skin, different skin types may result in different SAF findings. Our study was conducted with Thai patients who normally have Fitzpatrick skin type IV-V, which represents a certain degree of skin pigmentation in response to UV exposure. Thus, our SAF findings may not be applicable to other skin types. Fourth, the SAF cutoff considered was based on the mean SAF value of the study cohort, which may limit the generalizability of results to other ESKD patients. Although classifying the SAF outcome by tertile or quartile is a standard method for non-established cut-off point variable, our study is the early stage with the modest sample size. By this method, the number of sample size in each group is small. Further prospective study in larger number of participants would be appropriate. Last, a large proportion of unidentified causes of hospitalization (36.6%) due to poor documentation in our study might affect the reported outcome.

Although SAF was shown to be an independent risk factor for hospitalization in this study, we can only report an association between increased SAF and hospitalization, not the causality. Nevertheless, our results and AGE measurements by SAF in Thai patients can be considered as preliminary data that would be beneficial for future research.

CONCLUSION

The present study revealed that SAF, as a measurement of tissue AGE deposition, is an independent factor associated with an increased risk of hospitalization.

REFERENCES

1. Lv J-C, Zhang L-X. Prevalence and Disease Burden of Chronic Kidney Disease. Adv Exp Med Biol. 2019;1165:3-15.
2. Thaweethamcharoen T, Sakulbumrungsil R, Vasuvattakul S, Nopmaneejumruslers C. Quality of life and hemoglobin levels of hemodialysis patient at Siriraj Hospital. Siriraj Med J. 2011;63:12-16.
3. Thaweethamcharoen T, Vasuvattakul S, Noparatayaporn P. PUK22 Comparison of Utility Score and Quality of Life Score in Thai Patient Between Twice and Thrice-Weekly Hemodialysis. Siriraj Med J. 2012;64: 94-97.
4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7): e0158765.
5. Mathew AT, Strippoli GF, Ruospo M, Fishbane S. Reducing Hospital Readmissions in Patients with End-stage Kidney Disease. Kidney Int. 2015;88(6):1250-60.
6. Vareesangthip K. Effect of Ultrafiltration Rate in Long Interdialytic Interval Hemodialysis Session versus Average Weekly Ultrafiltration Rate on Mortality Rate and Adverse Cardiovascular Outcomes in Maintenance Hemodialysis Patients. Siriraj Med J. 2020; 72: 391-8.
7. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease. Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-72.
8. Lacson E Jr, Bruce L, Li NC, Mooney A, Maddux FW. Depressive Affect and Hospitalization Risk in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2014;9(10):1713-9.
9. Sorthananusa A, Sitawarin J, Warasompati P, Seetee T, Chirawong P. Assessment of Nutritional Status in Chronic Hemodialysis Patients at the Galayanivadhana Hemodialysis Unit. Siriraj Hosp Gaz. 2005; 57:19-36.
10. Kundhal K LC. Clinical Epidemiology of Cardiovascular Disease

in Chronic Kidney Disease. Nephron Clin Pract. 2005;101(2):c47-52.
11. Peppa M, Raptis SA. Advanced Glycation End Products and Cardiovascular Disease. Curr Diabetes Rev. 2008;4(2):92-100.
12. Kalousová M, Sulková S, Zima T, Deppisch R, Beck W, Bednarova V, et al.Advanced Glycation End Products in Hemodialyzed Patients with Diabetes Mellitus Correlate with Leptin and Leptin/Body Fat Ratio. Ren Fail. 2003;25(2):277-86.
13. Thornalley PJ. Advanced Glycation End Products in Renal Failure. J Ren Nutr. 2006;16(3):178-84.
14. Thornalley P, Rabbani N. Highlights and Hotspots of Protein Glycation in End-Stage Renal Disease. Semin Dial. 2009;22:400-4.
15. Henle T, Deppisch R, Beck W, Hergesell O, Hänsch GM, Ritz E. Advanced Glycated End-products (AGE) During Haemodialysis Treatment: Discrepant Results with Different Methodologies Reflecting the Heterogeneity of AGE Compounds. Nephrol Dial Transplant. 1999;14(8):1968-75.
16. Nongnuch A, Davenport A. The Effect of On-Line Hemodiafiltration, Vegetarian Diet, and Urine Volume on Advanced Glycosylation End Products Measured by Changes in Skin Auto-Fluorescence. Artif Organs. 2018;42(11):1078-85.
17. Meerwaldt R, Lutgers HL, Links TP, Graaff R, Baynes JW, Gans RO, et al. Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. Diabetes Care. 2007;30:107–12.
18. Meerwaldt R, Hartog JW, Graaff R, Huisman RJ, Links TP, Hollander NC et al. Skin Autofluorescence, A Measure of Cumulative Metabolic Stress and Advanced Glycation End Products, Predicts Mortality in Hemodialysis Patients. J Am Soc Nephrol. 2005;16(12):3687-93.
19. Nongnuch A, Davenport A. Skin Autofluorescence Advanced Glycosylation End Products as an Independent Predictor of Mortality in High Flux Haemodialysis and Haemodialysis Patients. Nephrology (Carlton). 2015;20(11):862-7.
20. Jiang J, Chen P, Chen J, Yu X, Xie D, Mei C, et al. Accumulation of Tissue Advanced Glycation End Products Correlated with Glucose Exposure Dose and Associated with Cardiovascular Morbidity in Patients on Peritoneal Dialysis. Atherosclerosis. 2012;224(1):187-94.
21. McIntyre NJ, Chesterton LJ, John SG, Jefferies HJ, Burton JO, Taal MW, et al. Tissue-advanced Glycation End Product Concentration in Dialysis Patients. Clin J Am Soc Nephrol. 2010;5(1):51-55.
22. Yue X, Hu H, Koetsier M, Graaff R, Han C. Reference Values for the Chinese Population of Skin Autofluorescence as a Marker of Advanced Glycation End Products Accumulated in Tissue. Diabet Med. 2011;28(7):818-23.
23. Furuya F, Shimura H, Takahashi K, Akiyama D, Motosugi A, Ikegishi Y, et al. Skin Autofluorescence is a Predictor of Cardiovascular Disease in Chronic Kidney Disease Patients. Ther Apher Dial. 2015;19(1):40-44.
24. Tanaka K, Tani Y, Asai J, Nemoto F, Kusano Y, Suzuki H, et al. Skin Autofluorescence is Associated with Renal Function and Cardiovascular Diseases in Pre-Dialysis Chronic Kidney Disease Patients. Nephrol Dial Transplant. 2011;26(1):214-20.
25. Stinghen AE, Massy ZA, Vlassara H, Striker GE, Boullier A. Uremic Toxicity of Advanced Glycation End Products in CKD. J Am Soc Nephrol. 2016;27(2):354-70.
26. Juliana C, Fernandes-Alnemri T, Wu J, Datta P, Solorzano L, Yu J-W, et al. Anti-inflammatory Compounds Parthenolide and Bay 11-7082 are Direct Inhibitors of the Inflammasome. J Biol Chem. 2010;285(13):9792-802.
27. Birukov A, Cuadrat R, Polemiti E, Eichelmann F, Schulze MB. Advanced glycation end-products, measured as skin autofluorescence, associate with vascular stiffness in diabetic, pre-diabetic and normoglycemic individuals: a cross-sectional study. Cardiovasc Diabetol. 2021;20(1):110.
28. Shardlow A, McIntyre NJ, Kolhe NV, Nellums LB, Fluck RJ, McIntyre CW, et al. The Association of Skin Autofluorescence with Cardiovascular Events and All-cause Mortality in Persons with Chronic Kidney Disease Stage 3: A Prospective Cohort Study. PLoS Med. 2020;17(7):e1003163.
29. Graaff R, Arsov S, Ramsauer B, Koetsier M, Sundvall N, Engels GE, et al. Skin and plasma autofluorescence during hemodialysis: a pilot study. Artif Organs. 2014;38(6):515-8.
30. Gerdemann A, Lemke HD, Nothdurft A, Heidland A, Munch G, Bahner U, et al. Low-molecular but not high-molecular advanced glycation end products (AGEs) are removed by high-flux dialysis. Clin Nephrol. 2000;54(4):276-83.
31. Deluyker D, Evens L, Bito V. Advanced glycation end products (AGEs) and cardiovascular dysfunction: focus on high molecular weight AGEs. Amino Acids. 2017;49(9):1535-41.
32. Srisuwan, W, Charoensri S, Jantarakana K, Chanchairujira T. Increasing Dialysate Flow Rate over 500 ml/Min for Reused High-Flux Dialyzers Do Not Increase Delivered Dialysis Dose: A Prospective Randomized Cross Over Study. Siriraj Med J. 2022;74:152-60.
33. Nongnuch A, Davenport A. The effect of vegetarian diet on skin autofluorescence measurements in haemodialysis patients. Br J Nutr. 2015;113(7):1040-3.