

Effect of depression on progression to end-stage renal disease or pre-end-stage renal disease death in advanced diabetic nephropathy: A prospective cohort study of the Diabetes Study from the Center of Tokyo Women's Medical University

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ABSTRACT

Aims/Introduction: This study aimed to determine the effect of depression on the progression to end-stage renal disease (ESRD) and pre-ESRD death in patients with advanced diabetic nephropathy.

Materials and Methods: This single-center prospective cohort study enrolled Japanese patients with type 2 diabetes and advanced diabetic nephropathy. The total Patient Health Questionnaire-9 score was used to evaluate depression at baseline and classified patients into: no, mild and severe depression groups. The outcomes were ESRD, defined as initiation of renal replacement therapy, and pre-ESRD death. The relationship between the severity of depression and these outcomes was analyzed using a competing risks model, defining each outcome as the competing risk of the other outcome.

Results: Of the 486 patients with a mean estimated glomerular filtration rate of 37.1 ± 21.1 mL/min/1.73 m², 345 were men. During the median follow up of 4.4 years, 164 patients progressed to ESRD and 50 died. The cumulative incidence function of ESRD was significantly higher in the severe depression group (Gray's test, $P = 0.003$). The ESRD risk increased by 12.4% and 45.1% in patients with mild and severe depression, respectively, compared with those without depression, although these differences did not reach statistical significance in the multivariate subdistribution hazard model ($P = 0.450$ and 0.161 , respectively). The cumulative incidence of death was similar for the study groups.

Conclusion: Depression potentially has a weak impact on progression to ESRD, however, the presence of comorbidities might have the possibility to reduce the effect of depression on the renal outcome in patients with advanced diabetic nephropathy.

INTRODUCTION

The frequency of depression in patients with diabetes has been shown to be 20–30%, depending on the assessment tools and the patient's background¹. In a cross-sectional study from Japan², approximately one-third of Japanese patients with diabetes experienced mild-to-severe depressive symptoms, assessed

by the Patient Health Questionnaire-9 (PHQ-9). Furthermore, there is a close relationship between depression severity and the complications of diabetes², especially the progression of diabetic nephropathy³. We have previously reported in a cross-sectional study that the incidence and severity of depression was significantly increased with progression of the stage of nephropathy, with the mean adjusted depression scores exceeding the diagnostic criteria for depression after advanced diabetic

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nephropathy³. In contrast, recent cohort studies^{4,5} have reported the effect of depressive symptoms on the progression to end-stage renal disease (ESRD) only in patients with an earlier stage of diabetic nephropathy, but this association has not been examined, thus far, among patients with advanced diabetic nephropathy.

We therefore carried out this single-center prospective cohort study to clarify the effect of depressive symptoms and its severity on hard renal outcomes, including the progression to ESRD or pre-ESRD death, in patients with type 2 diabetes and advanced diabetic nephropathy.

MATERIALS AND METHODS

Patients

The present single-center prospective cohort study enrolled Japanese patients with type 2 diabetes showing advanced diabetic nephropathy. Inclusion criteria were as follows: Japanese patients with type 2 diabetes aged ≥ 30 years who were admitted to and/or regularly visited the Diabetes Center of Tokyo Women's Medical University with an advanced stage of diabetic nephropathy defined as a urinary albumin-to-creatinine ratio (UACR) ≥ 300 mg/g and/or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², who had not received any renal replacement therapy, and had participated in the first survey of the Diabetes Study from the Center of Tokyo Women's Medical University (DIACET) initiated in October 2012 and completed all nine items in the PHQ-9 questionnaires.

The present study was approved by the Tokyo Women's Medical University Ethics Committee and was carried out in accordance with the Helsinki Declaration in 1995 (as revised in Fortaleza, Brazil, October 2013). All the patients provided informed consent to participate in the study.

DIACET and PHQ-9

The protocol of DIACET has been described previously^{2,3}. Self-administered questionnaires on health status including glycemic control, medications, diabetes-related complications (e.g., retinopathy, neuropathy, clinical visits for heart diseases, stroke and foot gangrene) and the items from the PHQ-9⁶ were distributed to eligible patients at regular outpatient visits or during hospitalizations between October 2012 and February 2013. The questionnaires were collected by postal mail, or retrieved at the subsequent outpatient visit or during the hospitalizations.

The PHQ-9, comprising nine items with regard to the frequency of depressive symptoms, was used to evaluate the presence and severity of depressive symptoms⁶. The PHQ-9 consists of 'somatic items' (e.g., sleep disturbance, fatigue, appetite changes, concentration difficulty and psychomotor agitation/retardation) and 'non somatic items' (e.g., depressed mood, lack of interest, feelings of worthlessness and suicidal ideation)^{7,8}. Each item instructed respondents to choose one of the following frequencies during the 2 weeks: 'not at all', 'several days', 'more than half of the days' or 'nearly every day', corresponding to a score of 0, 1, 2 and 3 points, respectively. Based

on the total score of all questions (0–27), patients were assigned to the following three groups by the severity levels of depression as no, mild or severe depression (0–4, 5–9 and ≥ 10 points, respectively). The Japanese version of the PHQ-9 showed adequate validity and reliability by Muramatsu *et al.*⁹

Extraction of baseline characteristics and laboratory data

Laboratory data were obtained for the 30 days before and after the distribution of the questionnaire. Serum and urinary creatinine levels were measured using an enzymatic assay, and urinary albumin was measured using immunoturbidimetry to calculate the UACR (mg/g). The eGFR (mL/min/1.73 m²) was calculated based on the formula: $eGFR = 194 \times \text{serum creatinine level (mg/dL)}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ in women})$. Glycated hemoglobin was measured by high-performance liquid chromatography. Blood pressure was measured with a validated oscillometer at rest with the patient in a sitting position. Age, sex, diabetes type, duration of diabetes, body mass index (BMI), and use of pharmacotherapy for diabetes, hypertension and dyslipidemia were confirmed by reviewing the patients' electronic medical records.

Follow up and end-points

Patients were followed up until 31 October 2020. The end-point was progression to ESRD, defined as the necessity of dialysis or pre-emptive renal transplantation, and pre-ESRD death.

Statistical analysis

Continuous data are expressed as arithmetic means and standard deviations, or geometric means and 95% confidence intervals, with the distribution of the data. Categorical data were expressed as the actual frequencies and percentages. Among three groups classified by the severity of depression according to the PHQ-9 scores (no, mild or severe depression), the Jonckheere–Terpstra tests were used to compare continuous data, and Cochran–Armitage tests used were for binary data.

For the time-to-event analysis, a competing risks model was used, rather than conventional Kaplan–Meier estimates and Cox proportional hazard models, as ESRD and pre-ESRD death hampered the observations of the other event^{10,11}. The cumulative incidence function of ESRD and pre-ESRD death were stratified by the severity of depression and compared using Gray's test. Univariate and multivariate subdistribution hazard models were constructed to calculate the crude and adjusted hazard ratios (HR) and 95% confidence interval of mild and severe depression for ESRD and pre-ESRD death with 'no depression' as the reference.

For the multivariate analysis of the subdistribution hazard model, the following candidate variables were used: age, sex, BMI, duration of diabetes, use of oral antidiabetic medications, injectable medications (insulin preparations and glucagon-like peptide-1 receptor agonists), antihypertensive medications, antilipemic medications, eGFR, logarithmically transformed UACR, glycated hemoglobin, retinopathy, neuropathy, heart diseases,

stroke and foot gangrene. We analyzed the results of renal outcomes with adjustment of proteinuria (albuminuria) as a covariate rather than stratifying with proteinuria. The explanatory variables were selected when the *P*-value for the HR was <0.10 in each univariate analysis. Multicollinearity was verified by the variance inflation factor (VIF) and confirmed when the VIFs were more >3.0¹². Applying the rule of thumb, we stipulated that the number of explanatory variables had to be less than one-tenth of the number of events. For continuous variables, the HR per 1-unit increase of standard deviation was calculated.

Furthermore, we carried out the analysis for the effect of depression on ESRD and pre-ESRD death using the PHQ-9 score as a continuous variable, instead of the depression category. Treating the scores as continuous variables, the association between the total score and all the items of the PHQ-9 was assessed by the Pearson's correlation coefficient. Before the sensitivity analysis, the multicollinearity among the items was verified by the VIF¹². The totaled score or each item was input as an explanatory variable, and adjusted HR was estimated for ESRD and pre-ESRD death. For continuous variables, the HR per 1-unit increase of standard deviation was calculated.

RESULTS

Baseline patient characteristics

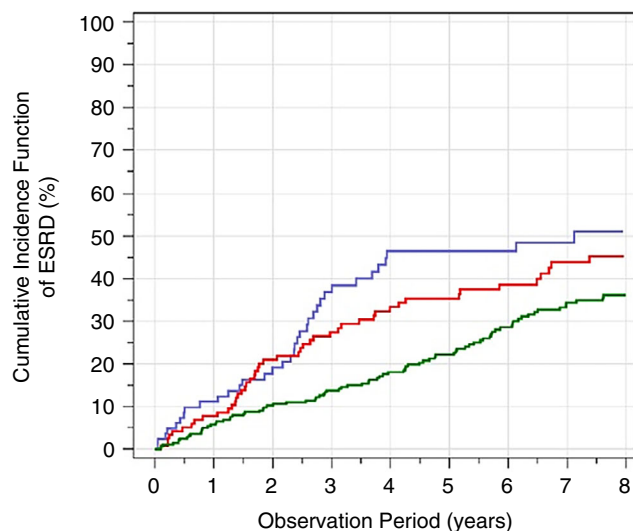
The present study cohort included 486 patients (mean age 67 ± 12 years), comprising 345 men and 141 women, who met the inclusion criteria. The mean ± standard deviation eGFR was 37.1 ± 21.1 mL/min/1.73 m² and the geometric mean value of the UACR was 730.3 mg/g. There were 419 patients (86.2%) with macroalbuminuria and 413 patients (85.0%) with eGFR <60 mL/min/1.73 m². Based on the PHQ-9 scores, 284 (58.4%), 119 (24.5%) and 83 (17.1%) patients had total PHQ-9 scores of 0–4, 5–9 and ≥10 points, indicating no, mild and severe depression, respectively.

Table 1 shows the clinical characteristics among the three study groups. Patients with more severe depression were significantly younger (Jonckheere–Terpstra trend test, *P* = 0.010), and their mean BMI was significantly higher (*P* = 0.002). The total scores, and both 'somatic items' and 'non-somatic items' of the PHQ-9 were incrementally associated with more severe depression (*P* < 0.001). There were no significant trends with regards to sex, duration of diabetes, systolic or diastolic blood pressure, alcohol consumption or smoking status. However, statistically significant trends toward a higher rate of peripheral neuropathy (*P* < 0.001), greater UACR (*P* = 0.045) and lower eGFR

Table 1 | Clinical characteristics and laboratory findings among patients classified according to PHQ-9 scores

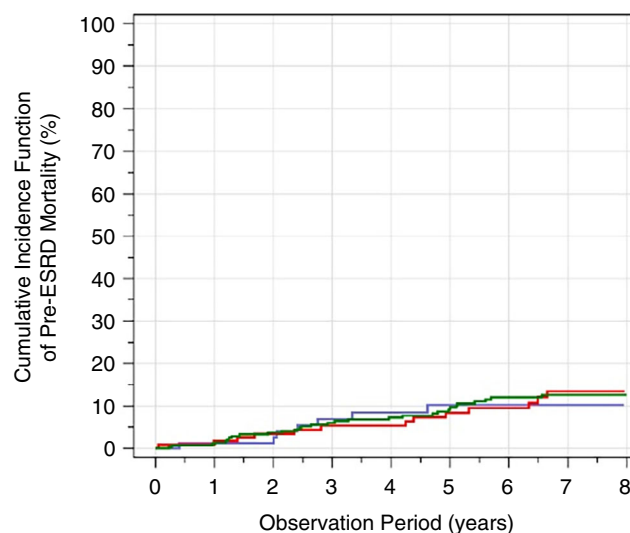
PHQ-9 scores	0–4 (<i>n</i> = 284)	5–9 (<i>n</i> = 119)	≥10 (<i>n</i> = 83)	<i>P</i> for trend
Age (years)	68 ± 12	64 ± 13	66 ± 13	0.010*
Men (%)	74	67	65	0.061
Diabetes duration (years)	19 ± 11	20 ± 11	21 ± 12	0.135
BMI (kg/m ²)	24.7 ± 3.8	26.6 ± 4.5	25.7 ± 4.6	0.002**
Systolic blood pressure (mmHg)	140 ± 21	137 ± 23	142 ± 20	0.692
Diastolic blood pressure (mmHg)	72 ± 12	71 ± 13	75 ± 12	0.541
Oral antidiabetic agents (%)	69	65	71	0.909
Injectable medications (%)	59	73	70	0.016*
Antihypertensive agents (%)	77	83	87	0.040*
Lipid-lowering agents (%)	52	58	59	0.214
HbA1c (%)	7.5 ± 1.3	7.6 ± 1.7	7.5 ± 1.7	0.795
eGFR (mL/min/1.73 m ²)	38.7 ± 19.3	35.2 ± 22.9	34.3 ± 23.8	0.001**
UACR (mg/g)	650.0 (551.2–766.6)	866.1 (692.9–1082.6)	826.9 (588.9–1161.1)	0.045*
PHQ-9 total score	1.6 ± 1.5	6.8 ± 1.4	13.6 ± 2.9	<0.001**
Somatic item's score	1.4 ± 1.3	4.8 ± 1.5	8.4 ± 2.3	<0.001**
Non-somatic item's score	0.2 ± 0.6	2.0 ± 1.5	5.2 ± 2.2	<0.001**
Smoking (%)	19	22	21	0.643
Alcohol (%)	31	29	30	0.760
Neuropathy (%)	66	83	89	<0.001**
Retinopathy (%)	64	71	69	0.280
Clinical visit for stroke (%)	5	3	6	0.978
Clinical visit for heart disease (%)	22	25	22	0.898
Clinical visit for gangrene (%)	1	2	4	0.123

Binary and continuous data are presented as the percentage and mean ± standard deviation or geometric mean (95% confidence interval). The trends of continuous and binary data were examined by the Jonckheere–Terpstra trend and the Cochran–Armitage trend tests, respectively. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PHQ-9, Patient Health Questionnaire-9; UACR, urinary albumin-to-creatinine ratio. **P* < 0.05 among three groups in trend. ***P* < 0.01 among three groups in trend.



Number at Risk by Severity of Depression								
Severe	83	69	57	36	28	23	21	17
Mild	119	103	83	70	62	54	44	32
No	284	253	226	199	169	146	116	97

Figure 1 | The cumulative incidence of end-stage renal disease (ESRD) among patients classified according to the severity of depression. The cumulative incidence of ESRD was estimated by the cumulative incidence function and compared using the Gray's test, with death as a competing risk. Green, red and blue lines in the figure indicate no depression ($n = 284$), mild depression ($n = 119$) and severe depression ($n = 83$) groups, respectively.



Number at Risk by Severity of Depression								
Severe	83	69	57	36	28	23	21	17
Mild	119	103	83	70	62	54	44	32
No	284	253	226	199	169	146	116	97

Figure 2 | The cumulative incidence of pre-end-stage renal disease (ESRD) death among patients classified according to the severity of depression. The cumulative incidence of pre-ESRD death was estimated by the cumulative incidence function and compared using the Gray's test, with ESRD as a competing risk. Green, red and blue lines in the figure indicate the no depression ($n = 285$), mild depression ($n = 119$) and severe depression ($n = 83$) groups, respectively.

($P = 0.001$) were observed, along with an increased use of injectable drugs ($P = 0.016$) and antihypertensive agents ($P = 0.040$) among patients with more severe depression. No significant trends were observed in the frequencies of clinical visits for heart disease, stroke or gangrene (Table 1).

Cumulative incidence function of ESRD and pre-ESRD death according to depression severity

During a median observational period of 4.4 years (range 0.1–8.0 years), 164 patients (33.9%) progressed to ESRD and 50 (10.3%) died before reaching ESRD. Figure 1 shows that the cumulative incidence function of ESRD was significantly higher in the groups with more severe depression (Gray's test: $P = 0.003$). The cumulative incidence function of pre-ESRD death was not significantly different ($P = 0.939$; Figure 2).

Effects of depression severity on ESRD or pre-ESRD death

In the unadjusted subdistribution model, the likelihood of ESRD increased by 49.7% ($P = 0.028$) and 90.3% ($P = 0.002$) in patients with mild and severe depression, respectively, compared with those without depression (Table 2). For the fully

adjusted model, the following 10 variables were selected based on the univariate analysis with P -value < 0.10 in each, and incorporated into the subdistribution hazard model for ESRD: age, use of oral antidiabetic medications, injectable medications, antihypertensive medications, antilipemic medications, presence of retinopathy, presence of neuropathy, glycated hemoglobin, logarithmically transformed UACR and eGFR. None of these variables had a VIF ≥ 3.0 , indicating that the presence of multicollinearity among the variables was unlikely. In the multivariate subdistribution model, the increased risk of ESRD was reduced to 12.4% ($P = 0.555$) and 45.1% ($P = 0.101$) in patients with mild and severe depression, respectively, but without statistical significance.

In the univariate subdistribution model, no increased mortality risk was observed in patients with mild or severe depression, compared with those without depression. For the multivariate model, the following five variables were selected based on the univariate analysis with P -value < 0.10 in each and incorporated into the subdistribution hazard model: age, duration of diabetes, BMI, use of antihypertensive medication and logarithmically transformed UACR. None of these variables had a VIF ≥ 3.0 . Similar to the univariate model, the multivariate model did not

Table 2 | Adjusted hazard ratios of mild and severe depression for end-stage renal disease and pre-end-stage renal disease death

	Unadjusted			Fully adjusted		
	HR	95% CI	P-value	HR	95% CI	P-value
ESRD						
Mild depression	1.497	1.045–2.145	0.028	1.124	0.763–1.656	0.555
Severe depression	1.903	1.269–2.855	0.002	1.451	0.930–2.265	0.101
Death						
Mild depression	1.008	0.529–1.922	0.980	1.732	0.880–3.411	0.112
Severe depression	0.852	0.372–1.947	0.703	1.141	0.482–2.698	0.765

Mild and severe depression were defined based on a Patient Health Questionnaire-9 total score of 5–9 and ≥ 10 points, respectively. Risks of mild and severe depression for end-stage renal disease (ESRD) and pre-ESRD death are shown as unadjusted and adjusted hazard ratios (HRs) estimated by the subdistribution hazard model. The HRs of mild and severe depression were calculated with 'no depression' as the reference. The following variables were incorporated into the fully adjusted model of ESRD: age, oral antidiabetic medications, injectable medications, antihypertensive medications, antilipemic medications, presence of retinopathy, neuropathy, glycosylated hemoglobin, estimated glomerular filtration rate and logarithmically transformed urinary albumin-to-creatinine ratio. The following variables were incorporated into the fully adjusted model of pre-ESRD death: age, duration of diabetes, body mass index, antihypertensive medication and logarithmically transformed urinary albumin-to-creatinine ratio. CI, confidence interval.

yield any differences in mortality risk among the three patient groups.

Effects of the PHQ-9 scores on ESRD or pre-ESRD death

When the PHQ-9 score was treated as a continuous variable, the total score showed more strong association with 'somatic items' than with 'non-somatic items'. The total score was relatively associated with 'fatigue', 'depressed mood' and 'lack of interest' (Table S1). Among all the items of the PHQ-9, no multicollinearity was observed on ESRD and pre-ESRD death ($VIF < 3.0$). Then the adjusted subdistribution model was carried out, with each item input as an explanatory variable, and the result of the model showed that the risks of ESRD were not statistically increased along with each item's score except for 'sleep disturbance' (Table 3). The each risk of ESRD per 1 score increase in total, somatic, and non-somatic item of PHQ-9 was also statistically insignificant after adjusted for covariates. Only 'sleep disturbance' significantly increased the risk of ESRD by 17.7% ($P = 0.029$) in the adjusted sub-distribution model. For all the items, no increased mortality risk was observed (Table 3).

DISCUSSION

The present single-center prospective cohort study aimed to clarify the association between the presence and severity of depression and a risk of progression to ESRD or pre-ESRD death in patients with type 2 diabetes and advanced diabetic nephropathy. The cumulative incidence function of ESRD in the univariate analysis differed significantly among the patients classified according to the severity of depression, although the statistical significance disappeared after adjustment for several independent covariates. The impact of depression on pre-ESRD death was not significant in univariate and multivariate analysis.

The results of the present study were inconsistent with those of previous studies among non-dialysis chronic kidney disease

(CKD) patients^{13–15}, showing the significant effect of depression on the composite events of ESRD and death. One of the reasons for this discrepancy might be explained by the differences in the method of survival analysis. A competing risk might have been prevalent in the CKD population^{16,17}. In this regard, progression to ESRD and pre-ESRD death compete with each other, because pre-ESRD death completely hinders any observation of the progression to ESRD, as does the ESRD progression to pre-ESRD death¹⁷. Conventional survival analyses, including the Kaplan–Meier method and Cox proportional hazards model that were used previously, treated competing events as non-informational censored data, presumably causing an overestimation of the cumulative incidence of the primary event of interest^{16,17}. To overcome these issues, we used a competing risk model to evaluate the effect of depression severity on progression to ESRD and pre-ESRD death.

The Pathway Study, one of the previous studies examining the association between diabetes and depression, also used a competing risk model, and found that patients showing severe depression, defined as a PHQ-9 ≥ 10 points, were associated with an 85% increased risk of ESRD⁴. However, that study investigated patients with earlier stages of diabetic nephropathy, with a mean eGFR ≥ 60 mL/min/1.73 m². In contrast, we studied patients with advanced stages of diabetic nephropathy, with a mean eGFR of 37.1 mL/min/1.73 m² and a geometric mean UACR of 730.3 mg/g, which indicated a higher risk of ESRD¹⁸. Indeed, despite a shorter observation period (4.4 years vs 8.8 years) in this study, a higher proportion of patients progressed to ESRD than in the Pathway Study (33.9% vs 2.2%). Therefore, the attenuated effect of depression on ESRD was unlikely to be due to reduced statistical power.

Given the potential mechanisms of the impact of depression on kidney function in patients with diabetes, the effect of comorbid depression on renal function might be less

Table 3 | Estimated effect of all the items of Patient Health Questionnaire-9 on end-stage renal disease and pre-end-stage renal disease death

	Adjusted for ESRD			Adjusted for death		
	HR	95% CI	P-value	HR	95% CI	P-value
Total score						
PHQ-9 total score	1.023	0.988–1.060	0.199	1.028	0.975–1.084	0.303
Somatic item's score	1.046	0.990–1.105	0.111	1.057	0.970–1.152	0.208
Non-somatic item's score	1.027	0.955–1.104	0.477	1.033	0.919–1.162	0.584
Each item						
Somatic item						
'Sleep disturbance'	1.177	1.017–1.363	0.029	1.195	0.935–1.528	0.154
'Fatigue'	1.062	0.894–1.261	0.496	1.214	0.899–1.640	0.205
'Appetite changes'	1.160	0.973–1.383	0.098	0.930	0.663–1.305	0.676
'Concentration difficulty'	1.099	0.907–1.331	0.334	1.198	0.878–1.635	0.254
'Psychomotor agitation/retardation'	0.951	0.734–1.233	0.706	1.180	0.810–1.718	0.389
Non-somatic item						
'Depressed mood'	0.915	0.741–1.129	0.407	1.181	0.853–1.634	0.316
'Lack of interest'	1.123	0.899–1.403	0.308	1.078	0.723–1.609	0.712
'Feeling worthlessness'	1.099	0.926–1.304	0.278	1.015	0.700–1.474	0.936
'Suicidal ideation'	1.214	0.941–1.566	0.136	1.031	0.497–2.137	0.935

Risks of increasing the score of the Patient Health Questionnaire-9 are shown as adjusted hazard ratios (HR) estimated by the subdistribution hazard model for end-stage renal disease (ESRD) and pre-ESRD death with totaled score or each item input as an explanatory variable. For the scores, the HR per 1-unit increase of standard deviation was calculated. The following variables were incorporated into the adjusted model of ESRD: age, oral antidiabetic medications, injectable medications, antihypertensive medications, antilipemic medications, presence of retinopathy, neuropathy, glycosylated hemoglobin, estimated glomerular filtration rate and logarithmically transformed urinary albumin-to-creatinine ratio. The following variables were incorporated into the adjusted model of pre-ESRD death: age, duration of diabetes, body mass index, antihypertensive medication, and logarithmically transformed urinary albumin-to-creatinine ratio. CI, confidence interval.

pronounced in the advanced, rather than early, stage of diabetic nephropathy. Several potential mechanisms have been implicated in the association between depression and diabetic complications^{19,20}, and the effects of these mechanisms might affect renal function from early-stage diabetic nephropathy^{4,5}. In regard to maintained renal function, a greater decline of eGFR was shown in patients with diabetes and depression than those without depression⁵. In contrast, we investigated patients who already had decreased eGFR and macroalbuminuria. It is likely that these patients had a substantially higher baseline risk of ESRD due to severe kidney function impairment and complications, including hypertension and microvascular and macrovascular complications, to ensure that the contribution of depression might be smaller.

The result that the depression severity was strongly associated with 'somatic items' of the PHQ-9, and of which, 'sleep disturbance' particularly showed an increased risk of ESRD should be noted. Previous studies of patients with CKD also suggested the association between sleep disturbances and poor renal outcomes^{21,22}. The symptom reported as 'sleep disturbance' in the present study might not have been attributed solely to depression, because sleep problems (e.g., sleep apnea syndrome) were reported by patients with advanced diabetic nephropathy²³. However, sleep disturbance is likely to be the first and only symptom of depression that the person is aware of, and persistent sleep disturbance is most likely due to

depression²⁴. Therefore, it could not be denied that depressive symptoms shown as sleep disturbance might have a potential effect on the progression to ESRD.

The lack of associations between severe depression and mortality in the present study was inconsistent with the results of previous studies of patients with CKD²⁵ and diabetes²⁶. The most likely explanations for the discrepancy might be the differences in the mortality rate and cause of death. The mortality rate was lower in Japanese patients with diabetes than those of other ethnicities, reducing the statistical power. Although we were unable to obtain information on the cause of death in the present study, a recent Japanese study of 45,708 patients with diabetes showed that deaths from malignant neoplasms were increasing, whereas those from cardiovascular diseases were decreasing²⁷. From another point of view, there might be a possibility that the associations between severe depression and mortality were modified by antidepressant use, because a recent study showed that antidepressant use reduced total death in patients with diabetes and depression²⁸. Furthermore, the competing risks model underestimating the cumulative incidence function of death might have failed to provide a meaningful statistical analysis. Differences in the serious comorbidities of patients with earlier and advanced stages of diabetic nephropathy might also explain this discrepancy.

The present study had several strengths. We were able to collect a comprehensive clinical dataset of confounding factors

from a study sample specifically comprising patients with advanced nephropathy. Furthermore, we were able to compare the independent effects of depression with eGFR and UACR, both of which are the most important clinical manifestations of diabetic nephropathy. Depressive symptoms were analyzed in detail using all the items of PHQ-9 in the present study^{6–8}, and we were able to find that one of the depressive symptoms shown as ‘sleep disturbance’ might have potential effects on the progression to ESRD.

The present study had several limitations. First, because of its observational design, we were unable to determine a causal relationship between the severity of depression and the outcomes. Second, the DIACET study^{2,3} was voluntary, and depression was assessed using a self-administered questionnaire. This study showed a high participation rate (92.2%)², but patients, such as those with highly severe depression, patients in poor condition and dementia patients, who had difficulties in answering the questionnaire, might have been excluded. Therefore, the frequency and severity of depression could have been underestimated. Third, we were unable to evaluate the effect of antidepressant use on the progression to ESRD or death, because the data of antidepressants was not collected and the frequency of antidepressant use was unclear. The various effects of antidepressants on outcomes, such as death and cardiovascular events, have been reported in patients with diabetes^{28,29}, and they should also be assessed on renal outcome. However, the Pathway Study reported that depressive symptoms itself was strongly associated with the progression to ESRD, even after adjusted with antidepressant use in patients with earlier stages of diabetic nephropathy⁴, so that the present study had the meaning to clarify the effect of depressive symptoms and its severity on renal prognosis in those with advanced diabetic nephropathy. Fourth, the PHQ-9 questionnaire reported high sensitivity and low specificity in patients with diabetes³⁰, thus far, depression might have been overestimated.

In addition, the PHQ-9 is useful only for screening purposes. An interview with a psychiatrist is necessary to obtain an accurate diagnosis of depression. Finally, the present study was carried out in a single center for the care of patients with diabetes, thereby limiting the generalizability of the results to all patients with diabetes. Thus, heterogeneity, which was not able to be ascertained, in the effect of depression on diabetic nephropathy and other CKD, might have existed. Multicenter studies are required to confirm the generalizability of the findings of the present study.

In conclusion, the effects of depression on the progression to ESRD and pre-ESRD death were considered weak in patients with type 2 diabetes presenting with advanced diabetic nephropathy. Compared with the results of univariate analysis suggesting the possible effect of depression on the progression to ESRD, the results that a statistical significance disappeared after adjustment with several independent covariates in multivariate analysis indicated that the presence of serious comorbidities was strongly associated with a higher risk of renal

outcome, and might reduce the effect of depressive symptoms and its severity on the renal prognosis in patients with advanced diabetic nephropathy.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Association between the total score and all the items of the Patient Health Questionnaire-9.