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Original Article

Association of serum osteopontin with first hospitalization and all-cause mortality after kidney transplantation

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Abstract

Objective: Osteopontin (OPN) is involved in vascular calcification and atherosclerosis. We evaluated the association between serum OPN levels and the first postoperative hospitalization and all-cause mortality in patients who received kidney transplantation (KT). **Materials and Methods:** Seventy KT recipients were enrolled in this study from January to April 2012. The primary end point was first postoperative hospitalization or death. All patients were monitored in the outpatient clinics until June 30, 2017. Serum OPN level was measured by enzyme-linked immunosorbent assay. **Results:** During follow-up (median length, 65 months), 47 first postoperative hospitalizations and 8 deaths occurred. In comparison with serum median OPN levels, serum OPN level was positively associated with KT duration ($P = 0.048$), serum blood urea nitrogen (BUN; $P = 0.043$), and serum creatinine levels ($P = 0.045$) but negatively associated with estimated glomerular filtration rate (eGFR; $P = 0.049$). Hospitalized KT recipients had a higher prevalence of diabetes mellitus (DM) ($P = 0.032$), BUN ($P = 0.002$), and serum OPN level ($P = 0.001$) but lower eGFR ($P = 0.030$) than did patients not hospitalized. KT recipients who died had higher serum level of creatinine ($P = 0.009$) and OPN ($P = 0.001$) but lower eGFR ($P = 0.036$) than did surviving patients. Multivariate Cox analysis adjusted for age, gender, DM, hypertension, eGFR, KT duration, and steroid used showed that serum OPN level was associated with both first postoperative hospitalization ($P = 0.049$) and all-cause mortality ($P = 0.017$). **Conclusions:** Serum OPN level is a potential biomarker for first postoperative hospitalization and all-cause mortality in KT recipients.

Keywords: *All-cause mortality, First hospitalization, Kidney transplantation, Osteopontin*

Introduction

Osteopontin (OPN) is a secreted calcium-binding glycophosphoprotein involved in bone remodeling [1]. Because of its chemotactic properties, OPN promotes cell recruitment into inflammatory sites and is involved in cell attachment and wound healing [2]. Furthermore, OPN can also mediate cell activation, cytokine production, and apoptosis regulation, and, thus, it can augment the development of various cancers [2]. According to some evidence, OPN influences inflammatory processes, atherosclerosis, and vascular calcification [3,4], and is considered an adequate biomarker of vascular remodeling and a predictive factor in cardiovascular disease [4].

Hospitalization after kidney transplantation (KT) has a significant effect on medical costs and affects patient survival. Moghani Lankarani *et al*. reported the causes of hospitalization after KT including surgical complication, infection, graft rejection, and malignancy [5]. The number of infections and surgical complications decreased between the early and late phases after transplantation. The causes of death in KT recipients include infection, coronary artery disease (CAD), cerebrovascular accident (CVA), graft failure, and other unknown reasons [6]. Infection was the major cause of death in the first 5 years after transplantation, whereas cardiovascular disease, including CAD and CVA, dominated during the second 5 years after transplantation. Because KT recipients are surviving longer, attention to risk factors, prevention, and prompt intervention in cardiovascular diseases are essential. There are three main mechanisms of cardiovascular diseases: formation of atheroma, left ventricular hypertrophy, and

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vascular calcification [7]. We aimed to evaluate the association of serum OPN levels with first postoperative hospitalization and mortality in patients after KT.

Materials and Methods

Participants

A total of seventy KT recipients were enrolled in this study, which was conducted between January and April 2012 in the Hualien Tzu Chi Hospital, Hualien, Taiwan. This study had received the approval from the local ethics committee of the institute (IRB 101–144). Informed consent was obtained from all patients before study participation. Participants with acute infection, malignancy, stroke, myocardial infarction, heart failure, or acute allograft rejection at the time of blood sampling and who refused to provide informed consent were excluded from the study. For each participant, systolic blood pressure and diastolic blood pressure were measured three times at 5-min intervals, and all the three readings were then averaged for analysis. Hypertension was defined as systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher; patients who had received any antihypertensive medication in the past 2 weeks were considered hypertensive. Diabetes mellitus (DM) was defined by a fasting plasma glucose level of 126 mg/dL or higher or controlled by oral hypoglycemic medications or insulin [8].

Anthropometric analysis

Body height was measured to the nearest 1.0 cm, and body weight was measured to the nearest 1.0 kg when patients were wearing lightweight clothing and no shoes. Body mass index was calculated as the body weight (in kilograms) divided by height (in meters) squared.

Biochemical determinations

The biochemical determinations were processed as our laboratory routine that had been published before [9-11]. In brief, blood samples (approximately 5 mL) were obtained after overnight fasting and immediately centrifuged at 3000 g for 10 min. In the biochemical analyses, we measured blood urea nitrogen (BUN), creatinine, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, fasting glucose, and albumin level with the use of an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland). We used commercially available enzyme-linked immunosorbent assay to measure serum OPN level (eBioscience Inc., San Diego, CA, USA) and intact parathyroid hormone level (Diagnostic Systems Laboratories, Webster, TX, USA) [12,13]. The estimated glomerular filtration rate (eGFR) was calculated with the abbreviated Modification of Diet in Renal Disease formula. The serum creatinine criteria in the KDIGO guidelines were used for the diagnosis of acute kidney injury.

First postoperative hospitalization and all-cause mortality monitoring

The primary end point was the incidence of first postoperative hospitalization. The reasons of hospitalization were documented. In addition, the number and causes of death during the follow-up period were recorded as the secondary end point. We defined the interval from transplantation to the last outpatient or inpatient chart record, documented mortality, or the last telephone interview (on June 30, 2017) as the follow-up time interval (in months). The event time (from transplantation to hospitalization or death, in months) was not counted until the first postoperative hospitalization or death occurred. One of the investigators (HHY) who was unaware of the patients' baseline characteristics and the study protocol was in charge of each patient's follow-up monitoring.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the collected data for normal distribution. The normally distributed data were expressed as means with standard deviations, and patients' data were compared using the Student's independent *t*-test (two tailed). The nonnormally distributed data (for triglycerides, fasting glucose, BUN, creatinine, intact parathyroid hormone, and OPN level) were expressed as medians and interquartile ranges, and patients' data were compared using the Mann–Whitney *U*-test. Categorical variables were compared using Chi-square test. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) to identify the optimal cutoff value of OPN that predicted first postoperative hospitalization or all-cause mortality in KT patients. We used Kaplan–Meier survival curves with a log-rank test to estimate event-free survival during follow-up on the basis of median OPN concentrations. Univariate and multivariate Cox regression models were used to examine factors associated with first postoperative hospitalization or death. $P < 0.05$ was considered statistically significant.

Results

The demographic, clinical, and biochemical characteristics of the seventy KT recipients are listed in Table 1. A total of 13 recipients (18.6%) had DM, and 26 (37.1%) had hypertension. In patients with OPN concentrations ≥15.53 ng/mL, KT duration lasted longer ($P = 0.048$), serum BUN level was higher ($P = 0.043$), creatinine level was higher ($P = 0.045$), and eGFR was lower ($P = 0.049$) than that in patients with OPN concentrations <15.53 ng/mL. We found no statistically significant difference in age, gender, body mass index, lipid profiles, comorbidity with DM or hypertension, immunosuppressant regimens used, or percentage of KT from deceased donors between the two OPN concentration groups.

After a median follow-up interval of 65 months, 47 first postoperative hospitalizations had occurred. The reasons for hospitalization included acute kidney injury in 21 recipients, infection in 21, cardiovascular disease in 2, and other problems in 3. A total of eight deaths occurred during the follow-up period, and the causes of death included acute myocardial infarction ($n = 1$), sepsis ($n = 3$), malignancy ($n = 1$), and CVA ($n = 3$). Hospitalized patients had a higher prevalence of DM ($P = 0.032$), steroid used ($P = 0.015$), higher serum BUN level ($P = 0.002$), higher OPN level ($P = 0.001$), and lower eGFR ($P = 0.030$) than did those not hospitalized [Table 2]. Furthermore, those patients who died during the follow-up period had higher serum creatinine ($P = 0.009$), higher OPN level ($P = 0.001$), and lower eGFR ($P = 0.036$) than did the surviving patients [Table 3].

Table 1: Clinical features of seventy kidney transplantation recipients according to median serum osteopontin level

Variables	All participants (*n*=70)	Participants with osteopontin<15.53 ng/mL (*n*=35)	Participants with osteopontin levels≥15.53 ng/mL (*n*=35)	*P*
Age (years)	52.10±9.77	50.51±9.62	53.69±9.80	0.176
KT duration (months)	72.56±42.09	62.63±32.90	82.49±48.06	0.048*
Height (cm)	162.37±8.17	163.00±7.98	161.74±8.41	0.523
Body weight (kg)	62.53±12.42	62.29±11.73	62.77±13.25	0.871
Body mass index (kg/m^2)	23.65±4.10	23.45±4.20	23.85±4.05	0.680
Albumin (mg/dL)	4.14±0.48	4.23±0.37	4.04±0.56	0.109
Total cholesterol (mg/dL)	195.94±45.60	190.66±44.88	201.23±46.35	0.336
Triglyceride (mg/dL)	108.00 (79.75-166.25)	117.00 (75.00-167.00)	103.00 (81.00-152.00)	0.814
HDL-C (mg/dL)	51.64±16.04	52.31±15.64	50.97±16.64	0.729
LDL-C (mg/dL)	109.62±39.48	103.73±33.19	115.51±44.62	0.214
Fasting glucose (mg/dL)	93.50 (85.75-110.00)	93.00 (85.00-102.00)	95.00 (86.00-112.00)	0.814
Blood urea nitrogen (mg/dL)	23.00 (17.00-34.50)	21.00 (15.00-30.00)	25.00 (18.00-42.00)	0.043*
Creatinine (mg/dL)	1.60 (1.30-2.10)	1.50 (1.10-2.10)	1.80 (1.50-2.60)	0.045*
Glomerular filtration rate (mL/min)	43. 04±21.73	48.14±22.86	37.94±19.54	0.049*
Intact parathyroid hormone (pg/mL)	115.75 (70.80-166.95)	94.30 (58.60-151.40)	122.50 (75.20-179.80)	0.175
Osteopontin level (ng/mL)	15.53 (9.89-37.63)	9.91 (7.73-12.06)	37.31 (21.62-54.17)	<0.001*
Female (%)	32 (41.7)	18 (51.4)	14 (40.0)	0.337
Diabetes (%)	13 (18.6)	6 (17.1)	7 (20.0)	0.759
Hypertension (%)	26 (37.1)	12 (34.3)	14 (40.0)	0.621
Deceased donor kidney transplant (%)	61 (87.1)	30 (85.7)	31 (88.6)	0.721
Tacrolimus use, *n* (%)	41 (58.6)	24 (68.6)	17 (48.6)	0.089
Mycophenolate mofetil use, *n* (%)	49 (70.0)	26 (74.3)	23 (65.7)	0.434
Steroid use, *n* (%)	27 (81.4)	27 (77.1)	30 (85.7)	0.356
Rapamycin use, *n* (%)	14 (20.0)	5 (14.3)	9 (25.7)	0.232
Cyclosporine use, *n* (%)	16 (22.9)	6 (17.1)	10 (28.6)	0.255

Values for continuous variables were expressed as means±standard deviations and were compared using Student's *t*-test; variables that were not normally distributed were expressed as medians with interquartile ranges and were compared using the Mann-Whitney U-test; values were expressed as numbers (%) and were analyzed using the Chi-square test. *P<0.05 was considered statistically significant. KT: Kidney transplantation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol

According to ROC curve analysis, the AUC for the optimal cutoff value of OPN that was 9.84 ng/mL (sensitivity: 89.36%, specificity: 52.17%) to predicted first postoperative hospitalization was 0.746 (95% confidence interval [CI], 0.627–0.842; P = 0.0003) and the AUC for the optimal cutoff value of OPN that was 40.81 ng/mL (sensitivity: 75.00%, specificity: 85.48%) to predicted all-cause mortality was 0.790 (95% CI, 0.676–0.878; P = 0.002), respectively. Kaplan–Meier analysis showed that the cumulative incidence of first postoperative hospitalization was greater among patients with OPN level >9.84 ng/mL [log-rank P = 0.0007; Figure 1a]. The results of multivariate Cox regressions used to examine serum OPN level associated with first postoperative hospitalization are illustrated in Table 4. We used three models of multivariate Cox regression models: in model 1, the analysis was adjusted for age and gender; in model 2, the analysis was adjusted for age, gender, DM, and hypertension; and in model 3, the analysis was adjusted for eGFR, KT duration, steroid used in addition to the same parameters as in model 2. All the three models showed that serum OPN level was independently associated with postoperative hospitalization in KT recipients [Table 4]. In model 1, the adjusted hazard ratio (aHR) was 1.012 (95% CI, 1.002–1.023; P = 0.018); in model 2, the aHR was 1.014 (95% CI, 1.002–1.025; P = 0.017); and in model 3, the aHR was 1.010 (95% CI, 1.000–1.022; P = 0.049). Kaplan–Meier analysis showed that the cumulative incidence of all-cause mortality was greater among patients with OPN level >40.81 ng/mL [log-rank P = 0.002; Figure 1b]. The same multivariate Cox regression models were used to examine serum OPN level in association with mortality. All the three models showed that serum OPN level was independently associated with all-cause mortality in KT recipients [Table 4]. In model 1, the aHR was 1.030 (95% CI, 1.010–1.050; P = 0.003); in model 2, the aHR was 1.033 (95% CI, 1.010–1.057; P = 0.005); and in model 3, the aHR was 1.032 (95% CI, 1.006–1.059; P = 0.017).

Discussion

In our study, longer KT duration but poorer renal function was noted in recipients with high OPN levels. The KT recipients who were hospitalized had significantly higher serum BUN level, a higher rate of DM, steroid used, higher serum OPN level, and lower eGFR than did those not hospitalized, but there was no significant difference in blood fasting glucose and lipid profile. The KT recipients who died had significantly poorer renal function and higher serum OPN level than did survivors. According to the multivariate Cox regression models, the serum OPN level was significantly associated with first postoperative hospitalization and all-cause mortality among KT recipients.

OPN is an arginine–glycine–aspartate domain-containing extracellular matrix protein that has diverse functions in immune response, cell differentiation, wound healing, and

Table 2: Clinical features of seventy kidney transplantation recipients with or without first postoperative hospitalization

Variables	Participants not hospitalized (*n*=23)	Participants hospitalized (*n*=47)	*P*
Age (years)	50.57±8.10	52.85±10.49	0.362
KT duration (months)	69.13±40.65	74.23±43.11	0.637
Height (cm)	162.83±8.27	162.15±8.20	0.747
Body weight (kg)	61.26±11.92	63.15±12.74	0.554
Body mass index (kg/m^2)	23.00±3.49	23.97±4.37	0.354
Albumin (mg/dL)	4.23±0.34	4.09±0.54	0.256
Total cholesterol (mg/dL)	185.13±36.20	201.24±49.05	0.167
Triglyceride (mg/dL)	102.00 (77.00-142.00)	131.00 (80.00-183.00)	0.247
HDL-C (mg/dL)	51.17±12.55	51.87±17.62	0.866
LDL-C (mg/dL)	107.00±25.76	110.90±44.90	0.701
Fasting glucose (mg/dL)	93.00 (85.00-99.00)	94.00 (88.00-128.00)	0.364
Blood urea nitrogen (mg/dL)	18.00 (14.00-23.00)	26.00 (18.00-41.00)	0.002*
Creatinine (mg/dL)	1.40 (1.00-2.10)	1.80 (1.40-2.10)	0.064
Glomerular filtration rate (mL/min)	51.04±25.21	39.13±18.88	0.030*
Intact parathyroid hormone (pg/mL)	122.50 (63.90-158.80)	108.40 (73.80-169.80)	0.807
Osteopontin (ng/mL)	9.84 (6.44-15.38)	18.84 (11.05-42.32)	0.001*
Female (%)	9 (39.1)	23 (48.9)	0.439
Diabetes (%)	1 (7.7)	12 (25.5)	0.032*
Hypertension (%)	7 (30.4)	19 (40.4)	0.416
Deceased donor kidney transplant (%)	19 (82.6)	42 (89.4)	0.428
Tacrolimus use, *n* (%)	15 (65.2)	26 (55.3)	0.430
Mycophenolate mofetil use, *n* (%)	19 (82.6)	30 (63.8)	0.107
Steroid use, *n* (%)	15 (65.2)	42 (89.4)	0.015*
Rapamycin use, *n* (%)	2 (8.7)	12 (25.5)	0.098
Cyclosporine use, *n* (%)	6 (26.1)	10 (21.3)	0.653

Values for continuous variables were expressed as means±standard deviations and were compared using Student's *t*-test; variables that were not normally distributed were expressed as medians and interquartile ranges and were compared using the Mann-Whitney U-test; values were expressed as, *n* (%) and were analyzed using the Chi-square test. *P<0.05 was considered statistically significant. KT: Kidney transplantation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol

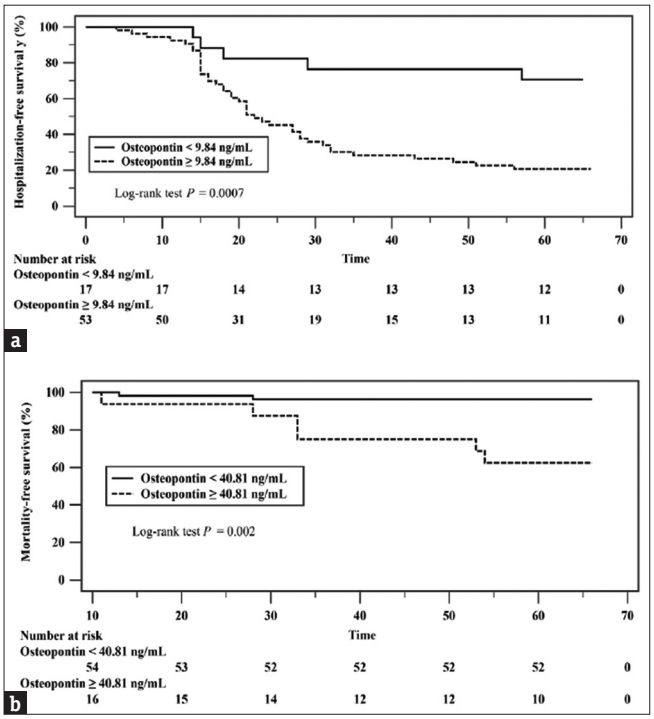

Figure 1: Results of Kaplan–Meier analysis of median serum osteopontin level in relation to (a) first hospitalization and (b) all-cause mortality of kidney transplantation recipients according to the optimal osteopontin concentrations based on the receiver operating characteristic curve with the best sensitivity and specificity pair

tumor genesis [14]. OPN also has a key role in atherosclerosis and is now regarded as an important mediator of vascular calcification. OPN is mainly found in the loop of Henle and distal nephrons in a normal kidney. Upregulation of OPN expression after renal injury has renoprotective actions, such as increasing tolerance of acute ischemia and suppressing nitric oxide synthesis [15]. Results of previous studies implicated the relationship between renal function and OPN [16-18]. Plasma OPN levels increase in a linear manner with declining GFR in patients with chronic kidney disease, which mirrors the severity of renal impairment. OPN might be a mediator of fibrotic processes in chronic kidney disease, and reduced urinary excretion partly results in an increase in circulating OPN.

Yan *et al*. found that plasma OPN level was proportional to the severity of kidney injury and therefore considered OPN an independent indicator of renal damage [17]. Chen *et al*. further demonstrated that higher serum OPN levels or more severe renal function damage was associated with greater severity of coronary artery lesions [18]. Recently, an association between OPN level and metabolic parameters, such as phosphatidylcholine content in the liver, cholesterol level, and HbA1c level, was found in mouse models and in patients with Type II DM [19,20]. Higher OPN level was found to be associated with a decrease in high-density lipoprotein cholesterol in postmenopausal women with Type II DM [20]. However, in our study, we could not find a significant correlation between OPN and lipid profiles.

Table 3: Clinical features of seventy kidney transplantation recipients who survived or died

Variables	Participants who survived (*n*=62)	Participants who died (*n*=8)	*P*
Age (years)	51.61±9.51	55.88±11.59	0.248
KT duration (months)	74.23±43.81	59.63±22.80	0.360
Height (cm)	162.13±7.54	164.25±12.57	0.493
Body weight (kg)	62.00±12.20	66.53±14.26	0.325
Body mass index (kg/m^2)	23.54±4.23	24.50±2.97	0.538
Albumin (mg/dL)	4.16±0.44	3.93±0.76	0.193
Total cholesterol (mg/dL)	197.68±46.37	182.50±39.08	0.379
Triglyceride (mg/dL)	108.00 (79.25-166.25)	102.50 (80.00-167.00)	0.919
HDL-C (mg/dL)	51.76±15.67	50.75±19.93	0.869
LDL-C (mg/dL)	108.66±33.03	117.06±76.06	0.575
Fasting glucose (mg/dL)	94.50 (85.00-110.00)	92.50 (91.25-120.00)	0.904
Blood urea nitrogen (mg/dL)	23.00 (16.75-32.50)	32.50 (19.50-46.25)	0.127
Creatinine (mg/dL)	1.54 (1.20-2.10)	2.80 (1.90-3.50)	0.009*
Glomerular filtration rate (mL/min)	44.98±21.86	28.00±13.95	0.036*
Intact parathyroid hormone (pg/mL)	115.75 (63.63-155.65)	126.00 (74.63-260.58)	0.542
Osteopontin (ng/mL)	15.05 (9.50-32.59)	47.25 (21.58-86.85)	0.001*
Female (%)	30 (48.4)	2 (25.0)	0.211
Diabetes (%)	11 (17.7)	2 (25.0)	0.619
Hypertension (%)	21 (33.9)	5 (62.5)	0.115
Deceased donor kidney transplant (%)	54 (87.1)	7 (87.5)	0.974
Tacrolimus use, *n* (%)	36 (58.1)	5 (62.5)	0.811
Mycophenolate mofetil use, *n* (%)	44 (71.0)	5 (62.5)	0.623
Steroid use, *n* (%)	50 (80.6)	7 (87.5)	0.639
Rapamycin use, *n* (%)	12 (19.4)	2 (25.0)	0.707
Cyclosporine use, *n* (%)	15 (24.2)	1 (12.5)	0.459

Values for continuous variables were expressed as means±standard deviations and were compared using Student's *t* test; variables that were not normally distributed were expressed as medians and interquartile ranges and were compared using the Mann-Whitney U-test; values were expressed as, *n* (%) and were analyzed using the Chi-square test. *P<0.05 was considered statistically significant. KT: Kidney transplantation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol

Table 4: Cox regression for first postoperative hospitalization events or all-cause mortality events of serum osteopontin levels among the seventy kidney transplantation patients

Osteopontin, 1 ng/mL	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
First postoperative hospitalization events	1.012 (1.003-1.022)	0.014*	1.012 (1.002-1.023)	0.018*	1.014 (1.002-1.025)	0.017*	1.010 (1.000-1.022)	0.049*
All-cause mortality events	1.028 (1.010-1.046)	0.002*	1.030 (1.010-1.050)	0.003*	1.033 (1.010-1.057)	0.005*	1.017 (1.006-1.059)	0.017*

CI: Confidence interval, aHR: Adjusted hazard ratio, HR: Hazard ratio, *P < 0.05 by multivariate logistic regression analysis

In the present study, acute kidney injury, infection, cardiovascular events, and other causes accounted for 44.7%, 44.7%, 4.2%, and 6.4%, respectively, of first hospitalizations after KT. In KT recipients, acute kidney injury may occur for several reasons, and most episodes were attributed to urinary tract infection. Other transplantation-specific causes of acute kidney injury included obstruction of vessels to a single functioning kidney, vascular thrombosis, acute rejection or delayed graft function, and drug toxicity [21,22]. Some mediators of acute inflammation, such as tumor necrosis factor-α, interleukin-1β, interleukin-6, and angiotensin II, induced OPN expression [23,24]. Therefore, OPN was regarded as a mediator of systemic inflammatory response syndrome and sepsis. Moreover, Wang *et al*. reported significantly increased serum OPN level in patients with acute cellular rejection of renal allograft, and higher levels of OPN positively correlated with the severity of rejection [14]. Jin *et al*. also found the OPN level on the 7th day after transplantation to be an independent predictor of early acute allograft rejection [25]. Although we did not discuss the detailed causes of acute kidney injury and infection foci in this report, these results may explain our findings that postoperative hospitalization associated significantly with serum OPN levels.

Data from the United States Renal Data System between 1996 and 2014 were analyzed extensively to determine the 1- and 10-year rates of all-cause and cause-specific mortality in KT recipients whose grafts were still functioning when they died [26]. Cardiovascular diseases, infections, malignancies, and unreported causes accounted for 24.7%, 15.2%, 2.9%, and 40.1% of deaths, respectively. The investigators also found that rates of cardiovascular and infection-related mortality declined, but rates of mortality from malignancy did not. Among our patients, one (12.5%) died of acute myocardial ischemia, three (37.5%) of sepsis, one (12.5%) of malignancy, and

three (37.5%) of CVA. Cardiovascular diseases thus accounted for half of the deaths, followed by sepsis and malignancy.

The mechanism of and correlation between OPN level and cardiovascular diseases are well established [2,4]. OPN influences inflammation, atherosclerosis, and vascular calcification via several pathways. As in inflammation, OPN is also overexpressed in several carcinomas and has been implicated in tumor invasion and metastasis because of its pro-tumorigenic or anti-tumorigenic effects [27]. Previous studies had proved the role of OPN in cancer progression by demonstrating enhanced proliferation; motility; and invasion of breast, liver, prostate, colorectal, and lung cancers [28,29]. However, prolonged exposure to immunosuppressants may also aggravate the development of malignancy in KT recipients. In our study, patients who died had significantly higher serum creatinine level than did survivors, which may have been a result of sepsis, and serum OPN level correlated well with other causes of mortality, including cardiovascular diseases and malignancy.

To the best of our knowledge, the present study is the first of its kind in literature to characterize the association between serum OPN level and future hospitalization and death in KT recipients. However, the limitations of this study were that it was an observational, single-center study with a limited number of participants, and the possibility of bias cannot be excluded. Therefore, we tried to explain our observations by the possible mechanisms of the common causes of hospitalization and mortality. Further details about the reasons for hospitalization and mortality in our patients need to be clarified and investigated.

Conclusions

The results of our study showed that the serum OPN level is a biomarker for first postoperative hospitalization and all-cause mortality in KT recipients. We confirmed the association between OPN and renal allograft injury, infection, cardiovascular disease, and malignancy. Further clinical investigation of serum OPN levels in the prognosis of KT recipients can be expected.

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Conflicts of interest

Dr. Bang-Gee Hsu and Dr. Ming-Che Lee, the editorial board members at *Tzu Chi Medical Journal*, had no roles in the peer review process of or decision to publish this article. The other authors declared that they have no conflicts of interest.

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