

Assessment of Tumor Markers in Renal Transplant Recipients

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Abstract. *Background/Aim:* Malignant tumors are diagnosed using various methods, including diagnostic imaging methods. The measurement of tumor markers is commonly used because of its noninvasiveness and convenience. Furthermore, it is known that the excretion and metabolism of some tumor markers are affected by impaired renal function. In the present study, we investigated the effect of improved renal function on pre-and post-transplantation changes in tumor marker levels [carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and prostate-specific antigen (PSA)] in renal transplant recipients. *Patients and Methods:* A total of 116 renal transplant recipients, who had not been diagnosed with malignancies between January 2012 and December 2019, were included, and tumor markers were investigated. *Results:* CEA showed a significant decrease after kidney transplantation, regardless of the dialysis type (3.6→2.6 ng/ml, $p<0.001$), while other tumor markers showed a significant increase (AFP: 3.6→3.7 ng/ml; CA19-9: 16.2→19.5 U/ml; PSA: 0.95→1.05 ng/ml; all $p<0.05$). Pre- and postoperative eGFR ratios and postoperative liver function were identified as factors influencing the postoperative CEA and CA19-9 values, while PSA was influenced by the duration of dialysis. No statistically significant factors were found for AFP levels. *Conclusion:* Caution should be exercised when investigating tumor markers in patients with renal dysfunction,

as tumor marker levels may vary depending on the pathophysiology of each patient.

A malignant tumor can be comprehensively assessed and diagnosed through a variety of tests, including various imaging methods and histopathological examinations. Measurement of tumor markers is often performed in clinical practice due to its minimally invasive and convenient diagnostic mechanism. Carcinoembryonic antigen (CEA) is elevated in many carcinomas of epithelial origin, including digestive cancers (colon and stomach), lung, ovarian, and uterine cancer (1). Alpha-fetoprotein (AFP) is predominantly elevated in hepatocellular carcinoma, intrahepatic bile duct cancer, and germ cell tumors (2). Carbohydrate antigen 19-9 (CA19-9) is elevated mainly in pancreatic, colon, lung, breast, and uterine cancer (3). Prostate-specific antigen (PSA) is elevated in prostate cancer (4). Among these tumor markers, CEA and CA19-9 can be elevated because of metabolic and excretory disturbances caused by impaired renal function and the effects of dialysis (5). Therefore, when tumor markers are measured in patients with impaired renal function, it may be difficult to interpret the results. There have been no reports examining the changes in tumor markers before and after renal transplantation. As renal function markedly improves in patients after renal transplantation, we hypothesized that it would be useful to clarify the effect of renal function on tumor markers by comparing the changes in tumor marker values before and after renal transplantation. This study aimed to determine the changes in tumor markers among patients with renal dysfunction undergoing dialysis.

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Patients and Methods

We retrospectively examined changes in the tumor markers CEA, CA19-9, AFP, and PSA before and more than one year after renal transplantation in patients who underwent renal transplantation at Hyogo Prefectural Nishinomiya Hospital between February 2012 and November 2019. We excluded cases in whom tumor markers were not measured before and after renal transplantation, cases with a history of malignancy or development of malignancy less

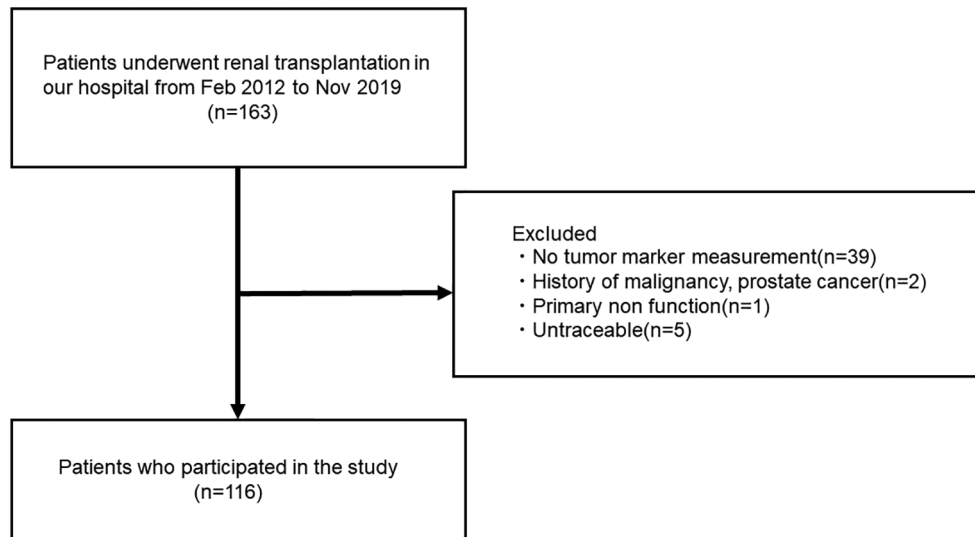


Figure 1. Cohort flow chart illustrating the inclusion and exclusion of participants into this study.

than one year after renal transplantation, cases with primary nonfunction, and cases in which follow-up was impossible. Factors affecting changes in tumor markers were also examined. Immunosuppressive agents included calcineurin inhibitor (CNI) (tacrolimus or cyclosporine), an anti-metabolite drug (mycophenolate mofetil or mizoribine), steroids, and basiliximab, with a protocol of add-on everolimus three months after transplantation. Tumor markers were measured at the same time as the regular follow-up of outpatient visits. This study was reviewed and approved by the Ethics Committees of the Medical Faculty of Hyogo Prefectural Nishinomiya Hospital, approval number: R2-70.

For statistical analysis, the Wilcoxon signed-rank sum test was applied to determine changes in the numerical values of each tumor marker before and after transplantation. In addition, multiple regression analysis was performed to identify factors (age, duration of dialysis, smoking, eGFR ratio before and after surgery, and postoperative ALT level) affecting the change in the value of each tumor marker before and after surgery as the objective variable. JMP ver16.2.0 (SAS Institute Japan Ltd., Tokyo, Japan) was used for all statistical analyses, and a p -value <0.05 was considered significant.

Results

Patient characteristics. The flowchart in this study is shown in Figure 1. Between February 2012 and November 2019, 163 patients underwent renal transplantation, of whom 116 met the eligibility criteria. Overall, 47 cases were excluded (no tumor marker measurement, 39 cases; history of malignancy: two cases; primary non-function: one case; and untraceable: five cases). Patient characteristics are shown in Table I. The median age of the enrolled cohort was 50.5 years (IQR=42-58.3); 41 were women, and 75 were men.

Table I. Patient characteristics.

	N=116
Sex, n(%)	
Female/Male	41 (35.3%)/75 (64.7%)
Age	
Median (IQR)	50.5 (42-58.3)
Renal replacement therapy, n(%)	
HD	66 (56.9%)
PD	10 (8.6%)
Preemptive	40 (34.5%)
Duration of dialysis (month)	
Median (IQR)	47 (8-177)
ABO blood type, n(%)	
Compatible/incompatible	87 (75%)/29 (25%)
HLA mismatch	
Median (range)	3 (0-6)
CNI, n(%)	
Tac/CyA	92 (79.3%)/24 (20.7%)
Antimetabolite, n(%)	
MMF/MZB	112 (96.6%)/4 (3.4%)
Smoking, n(%)	
Yes/No	36 (31%)/80 (69%)
Donor	
Living/deceased, n(%)	100 (86.2%)/16 (13.8%)
Female/Male, n(%)	74 (63.8%)/42 (36.2%)
Age, median (IQR)	56 (49-64)

HD: Hemodialysis; PD: peritoneal dialysis; HLA: human leukocyte antigen; CNI: calcineurin inhibitor; Tac: tacrolimus; CyA: ciclosporin; MMF: mycophenolate mofetil; MZB: mizoribine.

Overall, 66 patients (56.9%) were on hemodialysis (HD), 10 (8.6%) on peritoneal dialysis (PD), and 40 (34.5%) on preemptive kidney transplantation (PEKT).

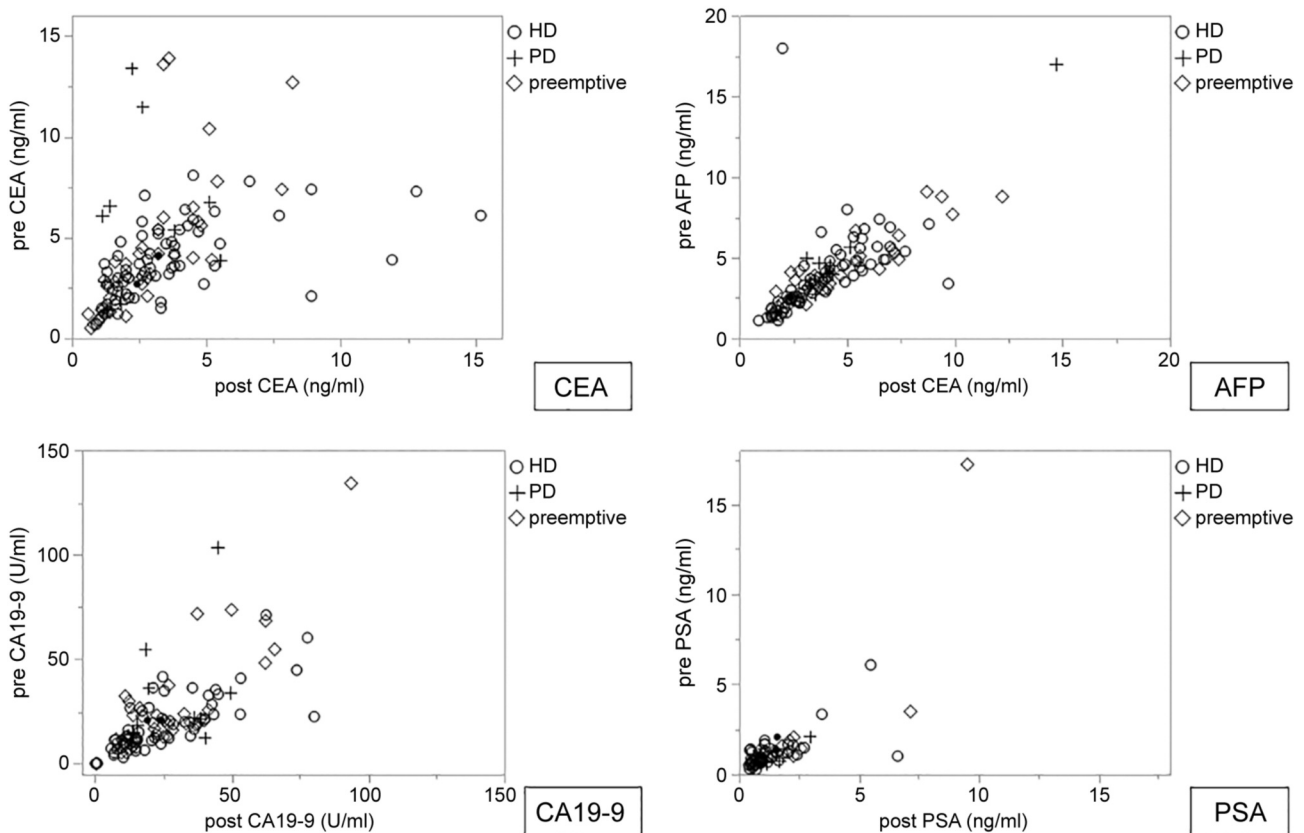


Figure 2. Scatter plots of tumor markers pre- and post-transplantation.

Changes in tumor markers pre-and post-transplantation. Scatter plots of tumor marker values before and after transplantation are shown in Figure 2. Table II shows the changes in tumor marker values pre- and post-transplantation. In the Wilcoxon signed-rank test, CEA showed a significant decrease after transplantation (3.6→2.6 ng/ml). However, other tumor markers showed slightly elevated values following transplantation (AFP: 3.6→3.7 ng/ml; CA19-9: 16.2→19.5 U/ml; PSA: 0.95→1.05 ng/ml). By dialysis type, CEA levels decreased significantly in HD, PD, and PEKT patients. AFP was significantly increased only in PEKT patients, and CA19-9 was significantly increased only in HD patients; however, there were no statistically significant differences in the other markers.

Linear multiple regression analysis for each tumor marker (Table III). Linear multiple regression analysis was performed to identify factors influencing changes in tumor marker values. Regarding CEA, the pre- and postoperative estimated glomerular filtration rate (eGFR) ratio was a factor influencing the values of tumor markers ($p=0.032$), and a higher postoperative ALT level was a significant factor ($p=0.002$). Similar results were obtained for CA19-9, with pre- and postoperative eGFR ratio

($p=0.021$) and postoperative ALT level ($p=0.017$) identified as significant factors influencing the posttransplant values; for PSA, the duration of dialysis ($p<0.001$) was a factor affecting the postoperative values; for AFP, no factors were found to influence the variation in its values.

Discussion

The measurement of tumor markers is minimally invasive and is often used to evaluate malignant tumors; however, the interpretation of reference values is important in renal failure and in dialysis patients. Among the tumor markers examined in this study, CEA and CA19-9 were found to correlate with renal function, as has been reported in the past (5, 6). In our study, the CEA and CA19-9 tumor marker values fluctuated according to the ratio of changes in renal function before and after surgery. In contrast, AFP and PSA levels were significantly elevated pre- and post-transplantation. Notably, eGFR ratio did not emerge as a confounding factor influencing these fluctuations. To the best of our knowledge, this is the first report to evaluate the evolution of tumor markers in patients with end-stage renal failure before and after renal transplantation.

Table II. Tumor markers according to type of dialysis.

	Pre-transplant median (IQR)	Post-transplant median (IQR)	Wilcoxon rank signed test <i>p</i> -value
CEA (ng/ml)			
Total	3.6 (2.2-5.4)	2.6 (1.6-3.9)	<0.001
HD	3.5 (2.3-5.1)	2.8 (1.7-4.1)	0.047
PD	5.8 (2.5-7.9)	2.0 (1.3-4.1)	0.021
Preemptive	3.5 (2.0-5.6)	2.6 (1.4-3.8)	<0.001
AFP (ng/ml)			
Total	3.6 (2.4-4.9)	3.7 (2.4-5.4)	0.020
HD	3.7 (2.5-4.9)	3.8 (2.4-5.4)	0.500
PD	4.3 (3.2-5.2)	3.9 (3.3-4.5)	0.500
Preemptive	3.4 (2.1-4.9)	3.4 (2.3-5.6)	<0.001
CA19-9 (U/ml)			
Total	16.2 (9.4-25.5)	19.5 (11.1-35.8)	0.003
HD	12.3 (7.2-23.7)	16.0 (8.9-30.7)	0.003
PD	21.9 (14.5-41.1)	28.6 (17.6-41.2)	0.090
Preemptive	19.2 (10.8-26.5)	22.2 (11.2-37.3)	0.225
PSA (ng/ml)			
Total	0.95 (0.68-1.38)	1.05 (0.67-1.72)	<0.001
HD	0.85 (0.66-1.31)	0.89 (0.60-1.50)	0.070
PD	0.71 (0.64-2.09)	1.64 (1.14-2.93)	0.310
Preemptive	1.16 (0.69-1.44)	1.08 (0.85-2.10)	0.090

CEA: Carcinoembryonic antigen; AFP: α -fetoprotein; CA19-9: carbohydrate antigen 19-9; PSA: prostate-specific antigen; SD: standard deviation. Statistically significant values are shown in bold.

Table III. Multiple regression analysis in tumor marker.

	Value	β	<i>p</i> -Value	95%CI	VIF
CEA	Age	-0.067	0.579	-0.012-0.006	1.07
	Duration of dialysis	-0.321	0.737	-0.001-4.72 $\times 10^{-5}$	1.03
	Smoking	0.012	0.847	-0.105-0.128	1.11
	eGFR ratio	-0.031	0.032	-0.057-0.003	1.21
	Post-transplant ALT	0.013	0.002	0.006-0.019	1.04
AFP	Age	0.378	0.155	-0.006-0.034	1.03
	Dialysis duration	-0.036	0.937	-0.001-0.001	1.05
	eGFR ratio	-0.126	0.713	-0.062-0.043	1.12
	Post-transplant ALT	-0.221	0.533	-0.021-0.011	1.08
CA19-9	Age	0.222	0.306	-0.008-0.025	1.03
	Dialysis duration	-0.402	0.284	-0.002-0.001	1.05
	eGFR ratio	-0.658	0.021	-0.094-0.008	1.11
	Post-transplant ALT	0.723	0.017	0.003-0.031	1.07
PSA	Age	-0.03	0.853	-0.014-0.011	1.08
	Dialysis duration	1.13	<0.001	0.001-0.002	1.04
	eGFR ratio	0.1	0.541	-0.028-0.053	1.1

Significant values are shown in bold. CEA: Carcinoembryonic antigen; AFP: α -fetoprotein; CA19-9: carbohydrate antigen 19-9; PSA: prostate-specific antigen.

CEA is a broad tumor marker for which even patients with only benign disease often test positive. CEA is also widely known to be positive in smokers (7), but in our study, smoking was not identified as a factor affecting the fluctuation of tumor markers. CEA is also metabolized and excreted in the liver; therefore, an increase in CEA levels may be observed due to impaired liver

function (7). Among the transaminases, ALT specifically reflects hepatic dysfunction; therefore, in the present study, the presence of hepatic dysfunction was evaluated using ALT. The median ALT level was 47 IU/l in 17 patients after transplantation, indicating relatively mild liver dysfunction; therefore, there were no cases of therapeutic intervention (data not shown).

AFP is mainly used as a screening test for hepatocellular carcinoma and is often elevated even in benign liver disease (2). Oberbaue *et al.* reported a significant increase in AFP in patients with elevated transaminase levels compared to those with transaminase levels within the reference range (8), in the present study, there were no factors affecting AFP variation in renal or liver function. The reason for the elevated AFP level in this study is unknown, but we believe it may be due to the effect of taking drugs for hepatic metabolism such as tacrolimus.

Ohira reported that CA19-9 is a tumor marker that tends to be elevated in patients with impaired renal function compared to healthy controls (5). Similarly, Yu *et al.* showed that CA19-9 levels are significantly elevated in patients with impaired renal function (9), but there are also several reports showing no variation in CA19-9 values depending on renal function (10, 11); therefore, no consensus has yet been reached. CA19-9 is elevated in patients with liver dysfunction, such as those with cirrhosis and hepatitis, or obstructive jaundice (10). In this study, improvements in renal function and postoperative ALT levels were found to be factors influencing CA19-9 fluctuations. Contrary to our expectations, based on previous reports, the results revealed a significant elevation in CA19-9 levels rather than a decrease following improved renal function post-transplantation. Multiple regression analysis identified the eGFR ratio and postoperative ALT as factors influencing changes in CA19-9 levels. Judging from the values of the standard partial regression coefficient (Table III), it was inferred that CA19-9 is more strongly influenced by post-transplant liver function, leading to its elevation.

PSA is a tumor marker of prostate cancer. PSA is secreted by the prostate gland; therefore, only men were considered for PSA measurement. Although there are few reports examining the significance of PSA measurement in chronic kidney disease, one prior report (12) showed a significant decrease in free PSA, but no change in total PSA after kidney transplantation. PSA may also be elevated not only in prostatitis and benign prostatic hyperplasia but also in urinary retention or related small arterial infarctions in the prostate gland (13). Furthermore, as daily urine output decreases with the duration of dialysis (14), it is possible that urinary status may contribute to PSA values. Although there were no cases of urinary retention in this study, we cannot rule out the possibility that the increased urine volume after transplantation may have stimulated the prostate gland owing to the effect of urinary drainage, resulting in a slight increase in PSA levels. This could explain the finding that the duration of dialysis in this study was related to an increase in PSA levels after transplantation.

Amiri (15) published a review on the association between chronic kidney disease and tumor markers. That review

stated that CEA was elevated in HD patients. AFP was reported to be unchanged in patients with chronic kidney disease, HD and PD, and renal transplant patients. She reported no significant differences in CA19-9 between the three groups of healthy volunteers, HD patients and renal transplant recipients. However, she also reported that CA19-9 can be elevated in dialysis patients and should be interpreted with caution. She stated that total PSA is a useful marker for screening for prostate cancer after renal transplantation, as free PSA is significantly lower and total PSA remains unchanged after renal transplantation.

Although the cause is unknown, based on the results of renal replacement therapy, CEA showed a significant improvement on all types of dialysis, whereas AFP showed a significant increase only in PEKT patients, and CA19-9 only in HD patients, indicating that tumor markers did not significantly increase in all types of chronic renal failure patients on all types of dialysis. Tumor markers were not significantly elevated in patients with all types of chronic renal failure on any type of dialysis.

For all tumor markers, the possibility that aging itself had an effect on the increase in tumor markers cannot be ruled out, as the data were measured after one year in the same patients as the comparison subjects. However, even if this is discounted, it is necessary to evaluate CEA and CA19-9 in consideration of the changes in tumor markers due to changes in renal function.

Conclusion

The results of this study suggest that caution should be exercised when investigating tumor markers in patients with preoperative renal dysfunction, as tumor marker values may change with improvement in renal function pre- and post-transplantation. It should also be recognized that tumor marker values may change in transplant patients pre- and post-surgery.

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Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

SF conceived the study and wrote the first draft of this manuscript. KY developed the concepts, designed the study, searched the literature, and performed data analysis, manuscript editing and review. SY, TY, and MN performed data analysis and manuscript editing. NF conducted data analysis, manuscript preparation. HK contributed supervision and mentorship.

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