



Article

Cystatin C-Based eGFR Predicts Post-Treatment Kidney Prognosis in Patients with Severe Obstructive Nephropathy

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Abstract: A discrepancy between serum concentrations of cystatin C (CysC) and creatinine (sCr) has been reported in patients with acute obstructive nephropathy. However, the usefulness of CysC for predicting the recovery of kidney function in patients with severe obstructive nephropathy remains unclear. We examined the predictability of the estimated glomerular filtration rate calculated with CysC or sCr (eGFR_{cys} or eGFR_{creat}) for the post-treatment recovery of kidney function. We retrospectively collected patients with severe obstructive nephropathy (eGFR_{creat} < 30 mL/min/1.73 m²) whose baseline sCr and CysC were measured between 48 h before and 24 h after the release of urinary tract obstruction (UTO). The primary outcome was recovery from severe eGFR_{creat} depression (i.e., eGFR_{creat} ≥ 30 mL/min/1.73 m²) 7 days after the release of UTO. We calculated the area under the curve (AUC) of the receiver operating characteristic (ROC) curve for the relationship between eGFR_{cys} or eGFR_{creat} and recovery. Thirty-four patients (20 males) with a median age of 76 years were eligible. We identified 20 recovery cases. The AUCs of the ROC curves (95% confidence interval) for eGFR_{cys} and eGFR_{creat} were 0.81 (0.66–0.96) and 0.53 (0.32–0.73), respectively. These results imply cystatin C-based eGFR may help predict kidney prognosis in patients with severe obstructive nephropathy.

Keywords: obstructive nephropathy; urinary tract obstruction; cystatin C; kidney prognosis



Citation: Nakai, K.; Segawa, H.; Yashiro, M.; Yoshii, K.; Kusaba, T.; Matoba, S.; Tamagaki, K.; Hatta, T.; Kado, H. Cystatin C-Based eGFR Predicts Post-Treatment Kidney Prognosis in Patients with Severe Obstructive Nephropathy. *Kidney Dial.* **2022**, *2*, 474–481. <https://doi.org/10.3390/kidneydial2030043>

Academic Editor: Massimo Torreggiani

Received: 7 July 2022

Accepted: 5 September 2022

Published: 9 September 2022

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1. Introduction

Kidney dysfunction characterized by urinary tract obstruction (UTO) is called obstructive nephropathy or obstructive uropathy. UTO increases pressure in the proximal tubules and decreases the hydraulic pressure gradient across glomerular capillaries, which reduces the glomerular filtration rate (GFR) in the kidneys [1,2].

In evaluations of GFR, serum creatinine concentrations (sCr) are generally used as a biomarker to estimate GFR. In obstructive nephropathy, the cessation of urinary flow in the bilateral urinary tracts or solitary urinary tract increases sCr. However, serum cystatin C concentrations (CysC), another biomarker for assessing kidney function, do not increase with sCr in patients with acute obstructive nephropathy, which is also known as postrenal acute kidney injury (AKI) [3–6]. Due to this discrepancy, a high sCr-to-CysC ratio is useful for diagnosing obstructive nephropathy [3,5]. In terms of the relationship between CysC and kidney prognosis, Matsuki et al. reported a relationship between this discrepancy (sCr–CysC) and reductions in sCr after the treatment of obstructive nephropathy [6]. Okuda et al.

also reported that CysC in obstructive nephropathy was correlated with sCr after the release of UTO [3]. Accordingly, CysC may be a marker predicting the post-treatment kidney function in obstructive nephropathy patients. Previous reports have demonstrated the superiority of CysC as a marker of kidney function and as a prognostic marker in the field of chronic kidney disease [7–9]; however, the usefulness of CysC for predicting the post-treatment recovery of kidney function in patients with severe obstructive nephropathy has not yet been demonstrated. Patients with severe obstructive nephropathy sometimes require renal replacement therapy, and the reversibility of kidney function is a matter of great concern for clinicians. If it is possible for clinicians to predict after-treatment kidney function, they may be able to estimate the need for maintenance dialysis or supportive therapy for chronic kidney disease. This estimation is also useful for explaining estimated clinical courses to patients.

We hypothesized that CysC may predict post-treatment recovery from severe estimated GFR (eGFR) depression among patients with obstructive nephropathy. The aim of this study was to assess the predictability of CysC compared to sCr for post-treatment kidney function in obstructive nephropathy.

2. Materials and Methods

2.1. Patients and Measurements

This was a retrospective single-center study to assess the usefulness of kidney biomarkers. Clinical data were collected from the medical records of patients with severe obstructive nephropathy who were admitted to the Omihachiman Community Medical Center in Japan between January 2010 and December 2021. Patients with obstructive nephropathy were initially screened with the insurance disease names of “postrenal failure” or “acute renal failure”. Then, the patients whose CysC had been measured were reviewed further. Each patient’s clinical course was checked in their medical records, and those appropriate candidates for the present study were identified if they met all of the following criteria: (i) diagnosed with obstructive nephropathy by ultrasonography or abdominal CT based on the findings of bilateral hydronephrosis or hydronephrosis in a solitary kidney; (ii) underwent the release of UTO to recover kidney function; (iii) baseline CysC and sCr measured with the same sample between 48 h before and 24 h after the release of UTO; (iv) severe estimated GFR (eGFR) depression defined as eGFR calculated with sCr (eGFR_{creat}) below 30 mL/min/1.73 m² at baseline; (v) admitted to the hospital with a clinical course that was followed. We collected patient data regarding sex, age, etiology of obstructive nephropathy, laboratory data, and clinical course. CysC was measured using colloidal gold immunoassay; sCr was assessed with an enzymatic method.

We calculated eGFR_{cys} and eGFR_{creat} using the following equations: eGFR_{cys} (mL/min/1.73 m²) = (104 × CysC (mg/L)^{-1.019} × 0.996^{age} × 0.929 (if female)) – 8 [10], eGFR_{creat} (mL/min/1.73 m²) = 194 × sCr (mg/dL)^{-1.094} × age^{-0.287} × 0.739 (if female) [11], where eGFR—estimated glomerular filtration rate; eGFR_{cys}—eGFR calculated with serum cystatin C; eGFR_{creat}—eGFR calculated with serum creatinine; CysC—serum cystatin C; sCr—serum creatinine. The normal range of eGFR_{cys} and eGFR_{creat} is ≥60 mL/min/1.73 m².

2.2. Outcomes

The primary outcome was recovery from severe eGFR_{creat} depression within 7 days of the release of UTO. The patients were considered recovering if they were not under dialysis and their eGFR_{creat} exceeded 30 mL/min/1.73 m² as described in a previous study [12]. For example, a patient with an eGFR of 45 mL/min/1.73 m² on the fifth day was considered recovering, and another with an eGFR of 15 mL/min/1.73 m² on the seventh day was not considered recovering.

2.3. Statistical Analysis

Initially, patient characteristics were described. Then, the baseline clinical findings were described and compared between the recovery and non-recovery cases. The Wilcoxon rank-sum test was used for continuous variables, Fisher's exact test—for categorical variables. Logistic regression analysis was performed to examine whether eGFR_{cys} or eGFR_{creat} was associated with recovery from severe eGFR_{creat} depression. Then, ROC curves were used to examine the relationship between the baseline eGFR_{cys} or eGFR_{creat} and the recovery. The AUCs of the ROC curves were calculated. Then, a tentative cutoff point of eGFR_{cys} for distinguishing recovery cases from non-recovery cases was explored.

Statistical analyses were performed using JMP version 14.3.0 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 1078 patients with suspected AKI, including obstructive nephropathy, were screened based on their medical records, 462 of whom had their CysC measured. Thirty-four patients met the criteria and were considered to be appropriate candidates for the present study (Figure 1).

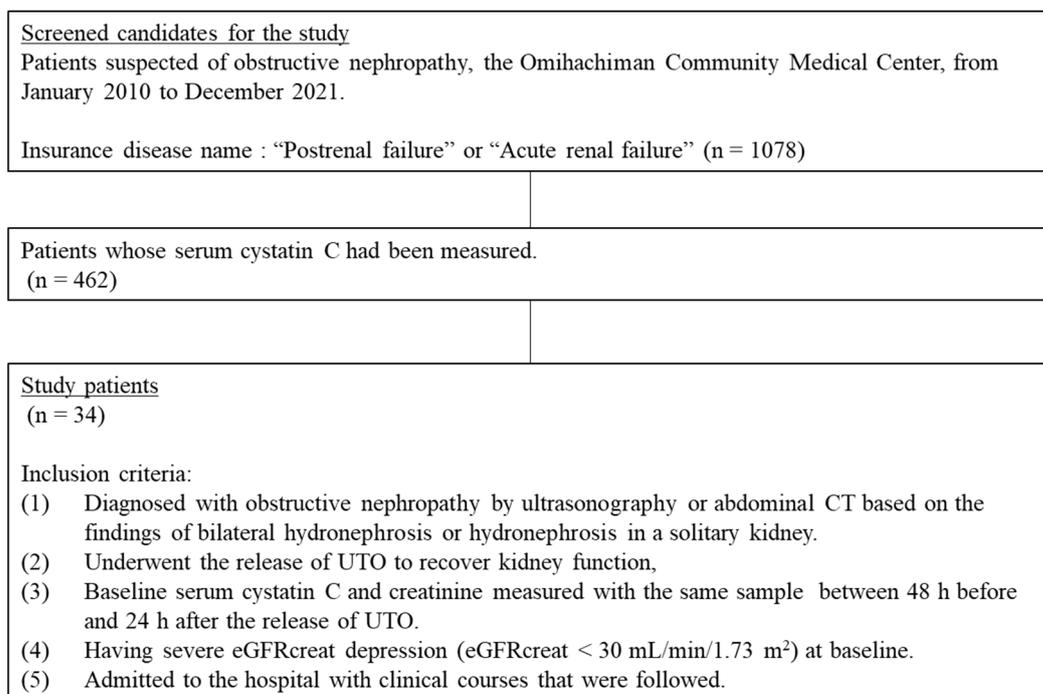


Figure 1. Flow diagram for the inclusion of study patients. Patients with severe obstructive nephropathy admitted to the Omihachiman Community Medical Center in Japan between January 2010 and December 2021 were enrolled. Overall, 34 patients, 20 of whom were male, were eligible for inclusion in this study. UTO, urinary tract obstruction; eGFR_{creat}, estimated glomerular filtration rate calculated with serum creatinine.

3.1. Patient Characteristics

Table 1 shows patient characteristics. Twenty out of 34 patients were male. The median age of the patients was 76 years. The primary cause of postrenal failure was neurogenic bladder ($n = 12$), followed by benign prostatic hyperplasia ($n = 11$).

Table 1. Patient characteristics ($n = 34$).

Sex (male)	20 (59%)
Age (years)	76 (67, 83)
Weight (kg)	58.7 (48.1, 66.4)
Etiology of obstructive nephropathy	
Benign prostatic hyperplasia	11 (32%)
Malignant tumor	7 (21%)
Neurogenic bladder	12 (35%)
Retroperitoneal fibrosis	3 (9%)
Ureteral stone (solitary functional kidney)	1 (3%)

Continuous variables are described as medians (interquartile range); categorical variables are described as n (%).

3.2. Baseline eGFR and Recovery from Severe eGFR_{creat} Depression

Table 2 shows the baseline clinical findings of recovery and non-recovery cases. We identified 20 recovery cases. Among the 14 non-recovery cases, three needed maintenance hemodialysis. Significant differences were observed in eGFR_{cys} ($p = 0.002$) and hemoglobin ($p = 0.004$) between the recovery and non-recovery cases, whereas eGFR_{creat} did not differ significantly ($p = 0.803$).

Table 2. Baseline clinical findings of the recovery and non-recovery cases.

	Recovery * ($n = 20$)	Non-recovery ($n = 14$)	p
Sex (male)	12 (60%)	8 (57%)	1.000
Age (years)	80 (73, 85)	69 (64, 78)	0.069
Weight (kg)	61.0 (49.8, 68.7)	52.3 (44.5, 61.1)	0.336
Etiology of obstructive nephropathy			
Benign prostatic hyperplasia	5 (25%)	6 (43%)	0.521
Malignant tumor	3 (15%)	4 (29%)	
Neurogenic bladder	9 (45%)	3 (21%)	
Retroperitoneal fibrosis	2 (10%)	1 (7%)	
Ureteral stone (solitary functional kidney)	1 (5%)	0 (0%)	
Maintenance hemodialysis	–	3 (21%)	–
Laboratory data			
Serum creatinine (mg/dL)	5.89 (4.74, 8.14)	6.09 (4.53, 10.97)	1.000
Serum cystatin C (mg/L)	1.91 (1.45, 3.05)	3.83 (3.19, 4.17)	<0.001
eGFR _{creat} (mL/min/1.73 m ²)	7 (5, 10)	6 (4, 9)	0.803
eGFR _{cys} (mL/min/1.73 m ²)	31 (14, 40)	13 (9, 14)	0.002
Blood urea nitrogen (mg/dL)	110.1 (53.0, 138.5)	78.8 (55.4, 120.1)	0.877
White blood cells (10 ³ /μL)	9.1 (6.6, 10.6)	7.6 (5.3, 9.3)	0.345
Hemoglobin (g/L)	11.5 (9.4, 13.0)	9.3 (8.3, 9.9)	0.004
Platelets (10 ³ /μL)	221 (175, 341)	167 (134, 215)	0.083
Serum albumin (g/dL)	3.0 (2.8, 3.8)	3.2 (2.8, 4.0)	0.726
Serum sodium (mmol/L)	139 (136, 147)	141 (135, 143)	0.672
Serum potassium (mmol/L)	5.0 (4.4, 6.3)	4.8 (3.4, 5.6)	0.201
Bicarbonate (mmol/L)	17.2 (13.8, 18.4)	17.9 (13.5, 22.3)	0.551
Serum calcium (mg/dL)	8.7 (8.5, 9.0)	8.2 (7.6, 9.0)	0.072
Serum phosphate (mg/dL)	5.5 (3.9, 8.0)	5.1 (3.9, 6.4)	0.619
Serum uric acid (mg/dL)	9.8 (7.2, 14.1)	8.7 (7.6, 9.6)	0.241
C-reactive protein (mg/dL)	8.4 (3.4, 15.2)	4.9 (1.6, 10.6)	0.138

Continuous variables are described as medians (interquartile range); categorical variables are described as n (%). * Recovery from severe eGFR_{creat} depression (i.e., eGFR_{creat} \geq 30 mL/min/1.73 m²) 7 days after the release of UTO. Abbreviations: eGFR, estimated glomerular filtration rate; eGFR_{creat}, eGFR calculated with serum creatinine; eGFR_{cys}, eGFR calculated with serum cystatin C. Note: p -values were calculated using Fisher's exact test for the categorical variables and the Wilcoxon rank-sum test for the continuous variables.

Individual kidney function at baseline and follow-up, timing of sampling, etiology, and interventions are shown in Table S1.

Table 3 shows the association between eGFR_{cys} or eGFR_{creat} and recovery from severe eGFR_{creat} depression using logistic regression analysis. The baseline eGFR_{cys}

was significantly associated with recovery, whereas eGFR_{creat} was not. Figure 2 shows the receiver operating characteristic (ROC) curves of the relationship between eGFR_{cys} or eGFR_{creat} and recovery. The areas under the ROC curves (AUCs) for eGFR_{cys} and eGFR_{creat} were 0.81 (95% confidence interval (CI): 0.66–0.96) and 0.53 (95% CI: 0.32–0.73), respectively.

Table 3. Association between the baseline eGFR_{cys} or eGFR_{creat} and recovery from severe eGFR_{creat} depression ^a ($n = 34$).

	OR (95% CI)	<i>p</i>
eGFR _{cys} (mL/min/1.73 m ²)	1.17 (1.04–1.31)	0.010
eGFR _{creat} (mL/min/1.73 m ²)	1.00 (0.87–1.15)	0.987

Abbreviations: eGFR, estimated glomerular filtration rate; eGFR_{cys}, eGFR calculated with serum cystatin C; eGFR_{creat}, eGFR calculated with serum creatinine; OR, odds ratio; CI, confidence interval. ^a Severe eGFR_{creat} depression was defined as eGFR_{creat} < 30 mL/min/1.73 m².

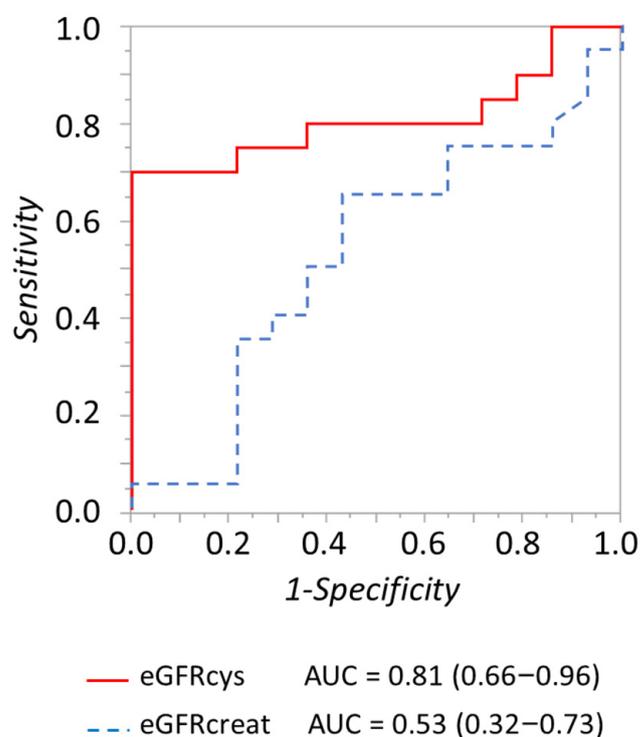


Figure 2. ROC curves of the relationship between eGFR_{cys} (solid line) or eGFR_{creat} (dashed line) and recovery from severe eGFR_{creat} depression defined as eGFR_{creat} < 30 mL/min/1.73 m² in patients with obstructive nephropathy ($n = 34$). The baseline eGFR_{cys} was associated with recovery from severe eGFR_{creat} depression, whereas the baseline eGFR_{creat} was not. Abbreviations: eGFR, estimated glomerular filtration rate; eGFR_{cys}, eGFR calculated with serum cystatin C; eGFR_{creat}, eGFR calculated with serum creatinine; AUC, area under the curve.

Table 4 shows a crosstabulation table between eGFR_{cys} ≥ 25 and recovery from severe eGFR_{creat} depression; eGFR_{cys} ≥ 25 identified recovery cases with a sensitivity of 70% (14/20) and specificity of 100% (14/14).

Table 4. Crosstabulation table between eGFRcys ≥ 25 and recovery from severe eGFRcreat depression ^a.

		Recovery		Total
		Yes	No	
eGFRcys ≥ 25	Yes	14	0	14
	No	6	14	20
Total		20	14	34

Abbreviations: eGFR, estimated glomerular filtration rate; eGFRcreat, eGFR calculated with serum creatinine; eGFRcys, eGFR calculated with serum cystatin C. ^a Severe eGFRcreat depression was defined as eGFR < 30 mL/min/1.73 m².

4. Discussion

In this hospital-based retrospective study, we examined the relationship between eGFRcys or eGFRcreat and post-treatment recovery from severe eGFRcreat depression in patients with obstructive nephropathy. The main result obtained was that the baseline eGFRcys was associated with recovery from severe eGFRcreat depression, whereas the baseline eGFRcreat was not. It is important to note that the reversibility of kidney function in obstructive nephropathy was predicted by eGFRcys, not by eGFRcreat. This is the first study to examine the usefulness of CysC for predicting kidney prognosis in severe obstructive nephropathy patients. Our findings imply that CysC may help predict kidney prognosis in addition to diagnosing obstructive nephropathy. Although further investigation by means of prospective studies is needed, CysC may play an important role in the treatment of obstructive nephropathy.

The mechanism underlying the discrepancy between eGFRcys and eGFRcreat in patients with obstructive nephropathy has been a matter of debate [3,4,6,13]. This discrepancy was recently explained by the degradation of low-molecular-weight proteins in proximal tubules. Cystatin C is reabsorbed and broken down by proximal tubular cells, whereas creatinine cannot be reabsorbed and accumulates in the urinary space [13,14]. In the present study, some patients with obstructive nephropathy had elevated CysC at baseline, and their kidney prognosis was worse than in those without CysC elevations. The reason for this phenomenon may be explained by the residual functions of proximal tubules. Complete UTO increases the intratubular pressure and reduces renal blood flow and GFR in the acute phase [1,2,15,16]. Sustained UTO then leads to interstitial inflammatory infiltration, tubular epithelial cell death, and subsequent tubular atrophy and interstitial fibrosis [2,16–18]. CysC may be absorbed by proximal tubules in the acute phase; however, this absorption may not occur in prolonged obstructive nephropathy because of irreversible structural changes in proximal tubular cells. Further studies on the relationship between tubular changes and CysC are needed to verify this hypothesis.

Based on these results, eGFRcys of 25 mL/min/1.73 m² was suggested as a provisional cutoff point. In the present study, eGFRcys ≥ 25 identified recovery cases with a sensitivity of 70% (14/20) and specificity of 100% (14/14) (Table 4); eGFRcys ≥ 25 was a favorable sign for obstructive nephropathy with severe eGFRcreat depression. However, six out of the 20 patients with eGFRcys < 25 also recovered. This phenomenon may be partly explained by a complication of another curable AKI. These patients received antibiotic therapy other than the release of UTO (patient Nos. 6, 12, 25, 27, 29, and 30 in Table S1). CysC is elevated in patients with prerenal or intrinsic AKI, including septic AKI [19–21]. Therefore, CysC in those patients may have been elevated because of another curable AKI complicated by obstructive nephropathy. The recovery of kidney function is expected in patients with obstructive nephropathy with elevated CysC if it is complicated by a curable AKI. Interpreted with the existing evidence, the discrepancy between Cre and CysC seems to be useful as a marker of favorable kidney prognosis as well as for the diagnosis of obstructive nephropathy. This finding may encourage clinicians to release UTO for severe obstructive nephropathy. The present results cannot be generalized because this was a retrospective study with a small sample size. Further prospective multicenter studies with a large sample size are needed to validate our explanations.

The present study has several limitations. As mentioned before, this was a single-center retrospective study with a small sample size. In addition to the issue of generalizability, the present results may have been affected by selection bias. CysC was often, but not systematically, measured in obstructive nephropathy patients with severe eGFR_{creat} depression. Therefore, some patients whose CysC was not measured for some reason may have been excluded. Furthermore, we were unable to obtain the patients' sCr levels before the development of obstructive nephropathy. Some patients with chronic kidney disease (CKD) complications might have been included among the patients with elevated CysC (acute-on-chronic kidney disease). The predictability of eGFR_{cys} for kidney prognosis in these cases may differ from that in obstructive nephropathy without CKD. In addition, our follow-up period was no longer than 7 days. Since many of our patients were discharged after approximately 7 days, we were unable to follow up for longer outcomes. However, a 7-day follow-up may be reasonable because the recovery of kidney function generally occurs within 7–10 days of the release of the obstruction [22,23].

5. Conclusions

The present study showed that eGFR_{cys} was associated with the post-treatment recovery of kidney function from severe eGFR_{creat} depression in patients with obstructive nephropathy. Cystatin C-based eGFR may help predict kidney prognosis in patients with severe obstructive nephropathy.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/kidneydial2030043/s1>. Table S1. Individual kidney function at baseline and follow-up, timing of sampling, etiology, and interventions for severe obstructive nephropathy patients ($n = 34$, Omihachiman Community Medical Center, 2010–2021).

Author Contributions: Conceptualization, K.N., H.S. and M.Y.; Methodology, K.N., H.S., M.Y., T.K., S.M., K.T., T.H. and H.K.; Formal analysis, H.S. and K.Y.; Investigation, K.N. and H.S.; Resources, K.N., H.S., T.H. and H.K.; Data curation, K.N.; Writing—original draft preparation, K.N. and H.S.; Writing—review and editing, M.Y., K.Y., T.K., S.M., K.T., T.H. and H.K.; Visualization, K.N., H.S. and K.Y.; Supervision, M.Y.; Project administration, H.S. All authors have read and agreed to the published version of the manuscript.

Funding: No funding was received to conduct this study.

Institutional Review Board Statement: The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Board of the Omihachiman Community Medical Center (No. R4-1, 2022).

Informed Consent Statement: Written informed consent for participation in this study was replaced by an opt-out disclosure on the website of the Omihachiman Community Medical Center (<https://www.kenkou1.com/medical-list/dep37> (accessed on 1 July 2022) because this study was performed on the basis of secondhand use of previous medical records.

Data Availability Statement: Not applicable.

Acknowledgments: The authors wish to express their appreciation to Hideyuki Motonaka, Mayuka Yokoe (medical technologists), and Mio Tsurubou (the information management staff at the Omihachiman Community Medical Center) for their contribution to data collection from medical records.

Conflicts of Interest: The authors declare no conflict of interest.

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