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SHORT REPORT

Comparison of creatinine-based equations for estimating renal function for digoxin dose adjustment in patients with atrial fibrillation and heart failure

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Abstract

The aim of this study was to determine an appropriate equation for estimating renal function to dose regulate the serum digoxin trough concentration to a target of <0.9 ng/ml in patients with atrial fibrillation (AF) and heart failure (HF). All patients received 0.125 mg oral digoxin daily. The estimated glomerular filtration rate by the Modification of Diet in Renal Disease ($eGFR_{MDRD}$) equation deindexed based on body surface area had the highest correlation with digoxin trough concentrations ($r = -0.450$) compared to the Cockcroft-Gault equation ($r = -0.415$) or deindexed eGFR based on the Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation ($r = -0.416$). The median digoxin trough concentrations were 0.60, 0.77, 0.97 and 1.30 ng/ml in patients with a deindexed $eGFR_{MDRD} \geq 60$, 45–59, 30–44 and < 30 ml/min, respectively. The deindexed $eGFR_{MDRD}$ is an appropriate equation for digoxin dose adjustment in patients with AF and HF.

KEYWORDS
atrial fibrillation, digoxin, equation, glomerular filtration rate, heart failure, therapeutic drug monitoring

1 | INTRODUCTION

Digoxin inhibits membrane-bound alpha subunits of sodium-potassium ATPase, which increases the intracellular calcium concentration and myocardial contractility and modulates neurohormonal abnormalities in patients with heart failure (HF).[1] Digoxin also increases parasympathetic tone (vagomimetic effect) in the atrioventricular node and slows atrioventricular conduction.[1] Previous clinical trials have shown that digoxin has a neutral impact on mortality but reduces in-hospital admission in patients with HF, and this effect is also demonstrated in patients with combined atrial fibrillation (AF) and HF.[2] Recent guidelines recommend oral digoxin as a second-line treatment for rate control of AF in patients with HF, especially HF with reduced left ventricular ejection fraction.[3] However, digoxin has several adverse drug effects, and its use is limited in clinical practice despite its beneficial effects.

Abbreviations: AF, atrial fibrillation; BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; MDRD, Modification of Diet in Renal Disease; OATP, organic anion transport polypeptide.

Digoxin has a narrow therapeutic window and complex pharmacokinetics with large variability due to elimination via the kidneys through glomerular filtration and tubular secretion, and therapeutic drug monitoring using serum digoxin concentration is recommended; a target serum digoxin concentration of ≤0.9 ng/ml is recommended for patients with HF.[1,4] In practice, physicians should adjust the dosing schedule based on the patient's renal function.[4,5]

Renal function is generally assessed using serum creatinine levels and creatinine-based equations such as the Cockcroft-Gault formula,[6] the Modification of Diet in Renal Disease (MDRD) formula,[7] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[8] There have been studies on digoxin clearance and renal function indices in some patient groups; the use of the MDRD equation can lead to an overestimation of renal function compared with the Cockcroft-Gault equation in older patients,[9] and for obese patients, the deindexed MDRD equation based on body surface area (BSA) is recommended for estimating renal drug clearance.[10] This issue may cause errors in drug dosage adjustment, especially for patients with severe renal dysfunction. However, it remains unclear which index of renal function is most appropriate for reflecting digoxin clearance for patients with AF and HF.

This study aimed to examine the appropriate equation for estimating renal function for digoxin dose adjustment in patients with AF and HF.

What is already known about this subject

- It is recommended that patients with heart failure be managed at low serum digoxin concentrations to avoid adverse events.
- Creatinine clearance by the Cockcroft-Gault formula has traditionally been used as an index of renal function for the dose adjustment of digoxin.
- The appropriate equation to estimate glomerular filtration rate (eGFR) for dosing adjustments in patients with renal dysfunction remains controversial.

What this study adds

1. In patients with atrial fibrillation and heart failure, eGFR by the Modification of Diet in Renal Disease (MDRD) formula, deindexed by body surface area, had the highest correlation with serum digoxin concentration among creatinine-based equations.
2. Deindexed eGFR by the MDRD formula will be appropriate as an index of renal function for digoxin dose adjustment in patients with atrial fibrillation and heart failure.

2 | METHODS

2.1 | Patients

This study consisted of 187 Japanese patients with AF and HF aged >18 years who received oral digoxin at a daily dose of 0.125 mg; these patients were obtained from a cohort study of 391 patients who were taking oral digoxin at Tokyo Women's Medical University Hospital between January 2008 and December 2016. HF stage C or D disease was diagnosed on the basis of the American College of Cardiology Foundation/American Heart Association criteria.[11] Patients who were receiving methyldigoxin, patients whose trough concentration of digoxin was not measured, patients who had undergone renal replacement therapy or patients who had received concomitant potent P-glycoprotein inhibitors (verapamil, diltiazem, and amiodarone) were excluded from this analysis. The study design and data collection have been described in detail elsewhere.[5] The study protocol was approved by the institutional review boards of Tokyo Women's Medical University and Jikei University.

2.2 | Data collection and renal function equations

We reviewed the electronic medical charts to collect demographic data (sex, age, height, body weight, body mass index, and BSA), clinical laboratory data (serum creatinine), and detailed data on digoxin (dosing schedule, trough concentration, and digoxin intoxication). We also reviewed the occurrence of digoxin intoxication, which was defined as any event associated with symptoms and/or suggestive of arrhythmias that resolved after the discontinuation or decreased dose of digoxin or a decrease in serum digoxin concentration. Digoxin intoxication was categorized as cardiac rhythm disturbance, gastrointestinal symptoms, and others.

Serum digoxin trough concentration was measured at 6 h after the last administration and was regarded as the steady-state concentration at least 5 days after digoxin administration.[1,4] Until November 2016, serum digoxin concentration was assayed using the COBAS TDM system (Roche Diagnostics K.K) by the kinetic interaction of microparticles in a solution. The detection limit of this assay was 0.3 ng/ml. The standard curves for digoxin were linear from 0.3 to 5.0 ng/ml. After that, the serum digoxin concentration was measured using the Nanopia TDM system (SEKISUI MEDICAL CO., LTD) by latex coagulating nephelometry. This assay had a detection limit of 0.05 ng/ml. The standard curves for digoxin were linear from 0.2 to 5.0 ng/ml.

Renal function equations were calculated based on creatinine clearance (CLcr) using the Cockcroft-Gault equation, the estimated glomerular filtration rate using the Japanese version of the MDRD formula ($eGFR_{MDRD}$), BSA using the deindexed eGFR (deindexed $eGFR_{MDRD}$), the estimated glomerular filtration rate using the Japanese version of the CKD-EPI formula ($eGFR_{CKD\text{-}EPI}$), and BSA using the deindexed eGFR (deindexed $eGFR_{CKD\text{-}EPI}$) as follows:

$$CL_{cr}\ (\mathrm{ml/min}) = \frac{(140 - \mathrm{Age}) \times \mathrm{Body\ weight}}{72 \times \mathrm{Serum\ creatinine}} \times 0.85\ (\text{if female})$$

$$eGFR_{MDRD}\ (ml/min/1.73m^2) = 194 \times Serum\ creatinine^{-1.094} \times Age^{-0.287} \times 0.739\ (if\ female)$$

$$deindexed\ eGFR_{MDRD}\ (ml/min) = eGFR_{MDRD} \times \frac{BSA}{1.73}$$

CKD-EPI (female sex and serum creatinine level ≤0.7 mg/dl)

$$eGFR_{CKD-EPI}\ (ml/min/1.73m^2) = 144 \times \left(\frac{Serum\ creatinine}{0.7}\right)^{-0.329} \times 0.993^{Age} \times 0.813$$

CKD-EPI (female sex and serum creatinine level >0.7 mg/dl)

$$eGFR_{CKD-EPI}\ (ml/min/1.73m^2) = 144 \times \left(\frac{Serum\ creatinine}{0.7}\right)^{-1.209} \times 0.993^{Age} \times 0.813$$

CKD-EPI (male and serum creatinine level ≤0.9 mg/dl)

$$eGFR_{CKD-EPI}\ (ml/min/1.73m^2) = 141 \times \left(\frac{Serum\ creatinine}{0.9}\right)^{-0.411} \times 0.993^{Age} \times 0.813$$

CKD-EPI (male and serum creatinine level >0.9 mg/dl)

$$eGFR_{CKD-EPI}\ (ml/min/1.73m^2) = 141 \times \left(\frac{Serum\ creatinine}{0.9}\right)^{-1.209} \times 0.993^{Age} \times 0.813$$

$$deindexed\ eGFR_{CKD-EPI}\ (ml/min) = eGFR_{CKD-EPI} \times \frac{BSA}{1.73}$$

2.3 | Statistical analysis

The statistical software utilized was JMP Pro 16 (SAS Institute). A two-tailed $p < .05$ was regarded as statistically significant. Continuous data are presented as the mean ± standard deviation for normally distributed data and the median [interquartile range] for nonnormally distributed data. Categorical data are presented as numbers (%). Spearman rank correlation was used to examine the correlation between digoxin trough concentration and the indices of renal function. We summarized digoxin trough concentration in four categories by the highest correlated index (≥60 ml/min, 45–59 ml/min, 30–44 ml/min, and < 30 ml/min) using a violin plot.

3 | RESULTS

The clinical characteristics of the patients in this study are summarized in Table 1. The median digoxin trough concentration was 0.75 [0.52–0.99] ng/ml. There were 25 (13%) patients who experienced trough digoxin concentrations >1.2 ng/ml. Digoxin intoxication was observed in 7 (4%) patients, including cardiac disturbance ($n = 2$), gastrointestinal symptoms ($n = 3$), and xanthopsia (yellow vision) ($n = 2$).

Spearman rank correlation revealed that the deindexed $eGFR_{MDRD}$ had the highest inverse correlation with digoxin trough concentration compared to serum creatinine level, CLcr, $eGFR_{MDRD}$, $eGFR_{CKD-EPI}$, and deindexed $eGFR_{CKD-EPI}$ (Figure 1). The median digoxin trough concentrations were 0.60 [0.41–0.81] ng/ml, 0.77 [0.52–0.96] ng/ml, 0.97 [0.75–1.27] ng/ml and 1.30 [1.10–1.75] ng/ml in patients with a deindexed $eGFR_{MDRD}$ ≥60 ml/min, 45–59 ml/min, 30–44 ml/min and < 30 ml/min, respectively (Figure 2). The proportion of patients with serum digoxin trough concentrations ≥0.9 ng/ml was the highest in the group with a deindexed $eGFR_{MDRD}$ <30 ml/min (8/9, 89%) compared with those with a deindexed $eGFR_{MDRD}$ of 30–44 ml/min (18/32, 56%), 45–59 ml/min (26/75, 35%) and ≥ 60 ml/min (14/71, 20%).

TABLE 1 Patient characteristics

Variables	$n = 187$
Demographic data	
Female, *n* (%)	77 (41)
Age, years	67 ± 13
Body weight, kg	58 ± 15
Body mass index, kg/m^2	23 ± 5
Body surface area, m^2	1.6 ± 0.2
Clinical background	
LVEF, %	43 ± 12
NYHA class II/III/IV, n	156/22/9
Underlying heart disease	
Coronary artery disease, *n* (%)	26 (14)
Nonischemic cardiomyopathies, *n* (%)	44 (24)
Valvular disease, *n* (%)	28 (15)
Hypertensive heart disease, *n* (%)	13 (7)
Congenital heart disease, *n* (%)	16 (9)
Others, *n* (%)	60 (32)
Atrial fibrillation	
Permanent/persistent, *n* (%)	152 (81)
Paroxysmal, *n* (%)	35 (19)
ICD/pacemaker, *n* (%)	21 (11)
Clinical laboratory data	
Serum creatinine, mg/dl	0.87 [0.71–1.01]
CLcr, ml/min	66.2 ± 29.9
$eGFR_{MDRD}$, ml/min/1.73 m^2	62.7 ± 18.5
deindexed $eGFR_{MDRD}$, ml/min	57.8 ± 18.5
$eGFR_{CKD-EPI}$, ml/min/1.73 m^2	65.1 ± 15.8
deindexed $eGFR_{CKD-EPI}$, ml/min	60.1 ± 17.0

Note: Values are number (%) or mean ± standard deviation or median [interquartile range].

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association.

4 | DISCUSSION

The present study showed that the deindexed $eGFR_{MDRD}$ has the highest correlation with digoxin trough concentration among

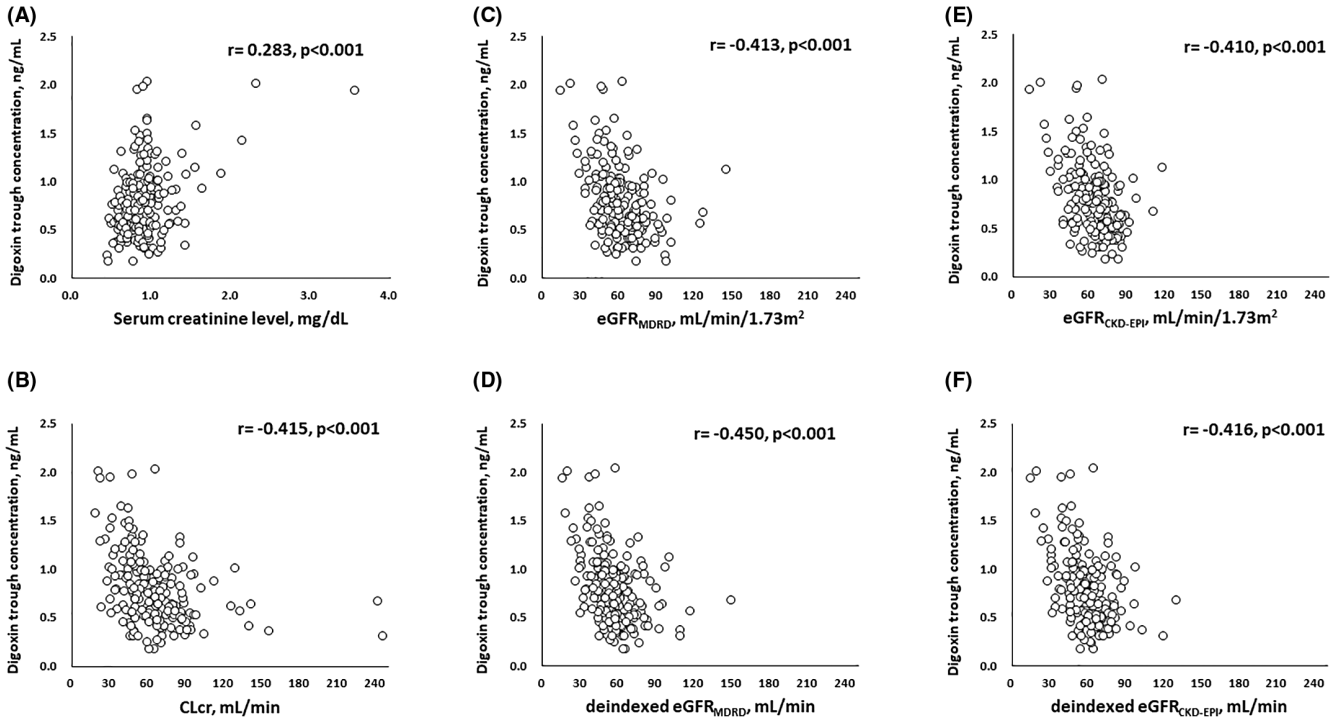

FIGURE 1 Spearman rank correlation between digoxin trough concentration and serum creatinine (A), creatinine clearance (CLcr) using the Cockcroft-Gault equation (B), estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula ($eGFR_{MDRD}$) (C), deindexed $eGFR_{MDRD}$ (D), estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula ($eGFR_{CKD\text{-}EPI}$) (E), and deindexed $eGFR_{CKD\text{-}EPI}$ (F).

creatinine-based equations of renal function in Japanese patients with AF and HF who received 0.125 mg daily of oral digoxin. The main limitation of using serum creatinine and CLcr is that there are many factors that can affect the metabolism of creatinine from creatine in the muscle and the rate of the secretion of creatinine in the renal tubules. Creatinine is affected by muscle mass, which changes with age, sex and ethnic group. There are also factors that can affect the production and secretion of creatinine. The eGFR is corrected for body surface area in mL/min per 1.73 m^2 to compare glomerular filtration rate (GFR) between individuals by reducing as much as possible the differences that result from differences in body size. The eGFR is widely used in practice because it can be calculated easily if only patient sex, age and serum creatinine level are known. However, it has not been shown whether these standardized indices are suitable for dose adjustment. Because standardized indices do not reflect individual body size, these indices are biased for the obese population and very elderly individuals. For this reason, a deindexed eGFR that is not adjusted for BSA is recommended, but it does not provide accurate data.

Our results indicate that body size plays an important role in determining digoxin clearance. Indeed, the accuracy of digoxin trough concentration predictions was better when total body weight was used rather than ideal body weight. Digoxin has a large volume distribution (4–8 L/kg) and is distributed mainly in skeletal muscles.[4] Therefore, our findings support that renal function and body size (as a surrogate for muscle mass) are contributing factors to the pharmacokinetics of digoxin.

The mechanism underlying digoxin elimination by the kidneys mainly corresponds to not only glomerular filtration but also secretion related to P-glycoprotein and organic anion transport polypeptide (OATP) 4C1.[12] We previously demonstrated that digoxin clearance is significantly associated with CLcr and the coadministration of amiodarone, which is known to inhibit P-glycoprotein.[5] In this study, however, the deindexed $eGFR_{MDRD}$ showed a moderate correlation with digoxin trough concentration despite the highest correlation coefficient value. Previous studies have not suggested a clear relationship between glomerular filtration and many types of drugs that are secreted by the proximal tubule of the kidneys.[13] In patients with renal impairment, GFR and proximal tubular secretion may not decrease in parallel. A study using a physiologically based pharmacokinetic model showed that digoxin was most successful in predicting a decrease in clearance when the decrease in proximal tubular cell count or OATP4C1 abundance was proportional to the decrease in GFR and that predicted proximal tubular concentrations of digoxin were associated with changes in OATP4C1 transporter expression.[12] These facts suggest the need for biomarkers indicative of renal tubular function in addition to GFR.[13] However, there are currently no biomarkers of renal tubular function available for clinical use, which limits the prediction of digoxin renal clearance.

Creatinine-based GFR equations were developed from different cohorts.[14] The $eGFR_{MDRD}$ was developed in a cohort consisting of patients with chronic kidney disease.[7] It is known that these equations cannot provide accurate estimates of GFR for the specific

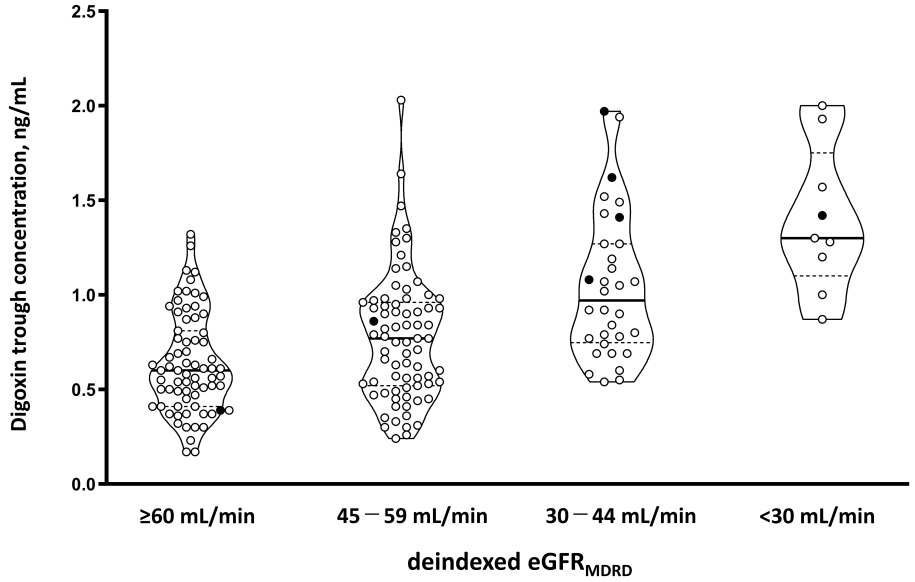

FIGURE 2 Violin plot of digoxin trough concentration by the deindexed estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula ($eGFR_{MDRD}$).Opened circles are points for patients without digoxin intoxication. Closed circles are points for patients with digoxin intoxication.

conditions/patients in clinical practice.[14] The appropriate equation to estimate GFR for dosing adjustment in patients with renal dysfunction remains controversial.[15] Douling et al. reported the superiority of CLcr over $eGFR_{MDRD}$ or $eGFR_{CKD\text{-}EPI}$ for drug dose adjustment in elderly patients.[9] $eGFR_{MDRD}$ or $eGFR_{CKD\text{-}EPI}$ may overestimate GFR because these equations do not reflect individual body weight (loss of skeletal muscle mass) in elderly patients. However, our study included patients with HF younger than the elderly population in Douling's study (mean age: 67 ± 13 vs. 81 ± 6 years). Furthermore, some HF patients had relatively high fluid volume (due to sodium retention and/or volume overload), and body weight may not necessarily reflect decreased skeletal muscle mass. On the other hand, Bouquegneau et al. reported that CLcr overestimates GFR in the obese population.[10] Our study did not include any obese patients with a body mass index >30 kg/m^2 but showed that the distribution of CLcr was larger than those of deindexed $eGFR_{MDRD}$ or $eGFR_{CKD\text{-}EPI}$. CLcr might partly overestimate GFR in patients with HF whose weight is also affected by factors other than skeletal muscle mass.

Patients with HF often have coexisting renal impairment.[3] Although there are limitations in assessing renal function as an excretory organ of drugs in this population, this study found that the deindexed $eGFR_{MDRD}$ is the most appropriate index related to serum digoxin trough concentration in Japanese patients with AF and HF taking digoxin with the current indication among the creatinine-based equations used in clinical practice.

4.1 | Study limitations

There were several study limitations that should lead researchers to interpret these findings with caution. First, this study was a retrospective observational study with a small number of subjects. Unknown confounding factors and bias could be present. Second, we could not completely confirm adherence to medications. Third, cystatin-C was identified as an additional marker of renal function. However, this dataset did not include data on cystatin-C levels. Fourth, hemodialysis patients were excluded from this analysis. We should not overgeneralize these findings to this patient subgroup. Fifth, we could not evaluate the genotype of P-glycoprotein, which affects digoxin pharmacokinetics. Finally, there were few data on outliers (e.g., body mass index >30 kg/m^2).

5 | CONCLUSIONS

This study showed that the deindexed $eGFR_{MDRD}$ based on BSA has the highest correlation with serum digoxin trough concentration among creatinine-based equations. In therapeutic drug monitoring of digoxin in Japanese patients with AF and HF, the deindexed $eGFR_{MDRD}$ may be a valuable indicator to adjust digoxin dosage according to individual renal function. Further studies will be needed to confirm the utility of the deindexed $eGFR_{MDRD}$.

AUTHOR CONTRIBUTIONS

M.S. and T.S. conceived and designed the study. T.H. and T.S. collected and organized the patient data from the patient files. M.S., T.H. and S.S. analyzed the data. T.H. and T.I. contributed to interpretation of the data. T.H. and T.S. were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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This research received no grants from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

ETHICAL APPROVAL

The protocol was approved by the Institutional Review Boards of Tokyo Women's Medical University (2020–0117) and Jikei University (32–209 [102909]) in view of the retrospective nature of the study, and all the procedures being performed were part of routine care. The study received ethical approval for the use of an opt-out approach to consent. This study was conducted in compliance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour and Welfare and the Declaration of Helsinki.

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