



# Objective impacts of tadalafil on storage and voiding function in male patients with benign prostatic hyperplasia: 1-year outcomes from a prospective urodynamic study

Yoshihisa Matsukawa<sup>1</sup> · Shun Takai<sup>1</sup> · Tsuyoshi Majima<sup>1</sup> · Yasuhito Funahashi<sup>1</sup> · Naoto Sassa<sup>1</sup> · Masashi Kato<sup>1</sup> · Tokunori Yamamoto<sup>1</sup> · Momokazu Gotoh<sup>1</sup>

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## Abstract

**Purpose** To investigate the 1-year effects of tadalafil on storage and voiding function in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (LUTS/BPH) based on a urodynamic study.

**Methods** In a one-armed, prospective study, 105 untreated outpatients with LUTS/BPH received 5 mg tadalafil every day for 12 months. Subjective symptoms and objective findings on voiding and storage functions, obtained through urodynamic studies that included cystometry and pressure flow study, were evaluated before, at 3 months, and at 12 months of treatment.

**Results** The analysis included 94 patients with a mean age of 70.7 years and a mean prostate volume of 44.5 mL. Subjective symptom parameters of LUTS were significantly ameliorated after 3 months, and progressively improved until study conclusion. Similarly, monitoring of storage and voiding functions revealed significant improvements after 3 months that continued to improve until 12 months. In 49 patients who revealed detrusor overactivity during cystometry at the baseline assessment, uninhibited detrusor contractions disappeared in 15 (30.6%) patients after 3 months ( $p = 0.02$ ), and in 22 (44.9%) after 12 months ( $p < 0.001$ ). Mean maximum flow rate significantly increased by 2.9 mL/s during the 12-month treatment ( $p < 0.001$ ), whereas mean bladder outlet obstruction index significantly decreased from 59.5 at baseline to 45.7 at 3 months ( $p = 0.001$ ), and to 42.9 at 12 months ( $p < 0.001$ ).

**Conclusions** Tadalafil significantly improved storage and voiding functions, along with LUTS, in patients with LUTS/BPH during a 1-year treatment.

**Keywords** Benign prostatic hyperplasia · Lower urinary tract functions · Urodynamics · Long term · PDE5 inhibitor

## Introduction

In several countries, current guidelines on the treatment of benign prostatic hyperplasia (BPH) recommend the use of  $\alpha_1$ -adrenoceptor antagonists ( $\alpha_1$ -blockers) or phosphodiesterase 5 (PDE5) inhibitors in patients presenting with lower urinary tract symptoms (LUTS) suggestive of BPH (LUTS/BPH) [1–3].

Treatment with  $\alpha_1$ -blockers reportedly improved not only subjective symptoms but also lower urinary tract

(LUT) functions such as storage function and bladder outlet obstruction (BOO) [1–4]. PDE5-inhibitors are also known to relieve LUTS in BPH patients [1–3, 5–7]. Tadalafil, the only PDE5-inhibitor approved for patients with LUTS/BPH, is predicted to improve LUTS and LUT functions by the following mechanisms: (1) relaxation of the smooth muscle tone of the prostate and bladder neck due to increased nitric oxide/cGMP signaling [8], (2) increased blood perfusion to the lower urinary tract organs [9, 10], (3) inhibition of afferent nerves activity such as C-fibers [3, 11], and (4) suppression of inflammation by decreasing Rho-kinase activity [12, 13]. However, in placebo-controlled clinical trials, tadalafil reportedly failed to improve objective parameters for voiding functions such as urinary flow rate, although it provided a beneficial effect on subjective symptom improvement [14, 15].

✉ Yoshihisa Matsukawa  
yoshi44@med.nagoya-u.ac.jp

<sup>1</sup> Department of Urology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

PDE5-inhibitors have a short history of usage in patients with LUTS/BPH, and, compared with  $\alpha$ 1-blockers, there is less evidence regarding their efficacy in these patients. Specifically, few studies have focused on the objective effects of PDE5-inhibitors such as tadalafil on both storage and voiding functions using a urodynamic study. We previously reported that a short-term tadalafil treatment of 12 weeks significantly improved both storage and voiding functions, besides amelioration of LUTS [16]. However, there has been no report to evaluate the effect of tadalafil on storage and voiding function longer than 12 weeks. It should be meaningful in clinical practice to clarify whether tadalafil improves the LUT functions for long term or not. On these backgrounds, we prospectively evaluated the 1-year efficacy of tadalafil monotherapy on voiding and storage functions in patients with LUTS/BPH, using urodynamic study.

## Materials and methods

We conducted a single-center, open-label, prospective study in accordance with the ethical principles of the Declaration of Helsinki. The ethics committee of the Nagoya University Graduate School of Medicine approved the protocol (IRB approval number: 2015-0106). All participants provided written informed consent before enrollment. The study was registered at <https://center.umin.ac.jp> as UMIN000017925.

The study included treatment-naïve men who visited our hospital with a chief complaint of both storage and voiding LUTS between June 2015 and March 2016. The inclusion criteria were as follows: total international prostate symptom score (IPSS)  $\geq 8$ ; IPSS-quality of life (QOL) score  $\geq 3$ ; prostate volume (PV)  $\geq 25$  mL as determined by transabdominal ultrasonography; maximum urinary flow rate ( $Q_{\max}$ )  $< 15$  mL/s at voided volume of  $\geq 100$  mL; residual urine  $< 150$  mL; age  $\geq 50$  years. Patients were excluded if they had received oral treatment with  $\alpha$ 1-blockers, anticholinergic agents, 5 $\alpha$ -reductase inhibitors, antidepressants, anti-anxiety agents, sex hormone agents, nitroglycerin, amyl nitrite, or isosorbide dinitrate. Medical conditions for exclusion were neurogenic bladder dysfunction, bladder calculi, active urinary tract infection, severe cardiac disease, renal dysfunction (serum creatinine level  $\geq 2$  mg/dL), and/or hepatic dysfunction (aspartate and alanine aminotransferase concentrations more than twice the normal values). To ensure that only cancer-free patients were included, prostate biopsy was performed in all patients who had prostate-specific antigen levels  $> 4$  ng/mL and had never received prostate biopsy.

Patients who satisfied all the inclusion and exclusion criteria received tadalafil (5 mg/day) for 12 months. To monitor subjective symptom severity and QOL in patients, IPSS, IPSS-QOL, overactive bladder (OAB) symptom scores

(OABSS), and BPH impact index (BII) were measured before, at 3 months, and at 12 months of treatment. The same schedule was implemented to evaluate LUT functions by subjecting patients to UDS, which included uroflowmetry, cystometry, and pressure flow study (PFS). First desire to void (FDV), maximum cystometric capacity (MCC), and detrusor overactivity (DO) were assessed as parameters of storage function.  $Q_{\max}$ , post-void residual urine volume (PVR), detrusor pressure at  $Q_{\max}$  (Pdet $Q_{\max}$ ), and bladder outlet obstruction index (BOOI) were determined as parameters of voiding function. BOOI was calculated according to the following formula:  $\text{Pdet}Q_{\max} - 2Q_{\max}$ . Patients were diagnosed with obstruction if BOOI was  $> 40$ , equivocal if BOOI was 20–40, and unobstructed if BOOI was  $< 20$ , according to the International Continence Society (ICS) nomogram [17, 18]. Disappearance of DO was defined as no apparent uninhibited detrusor contraction on cystometrogram during filling phase. One author, YM, performed the cystometry and PFS according to the standard methods defined by the ICS [17, 18]. Two members, ST and YF, who were not involved in conducting UDS, analyzed de-identified UDS data.

We calculated the required sample size based on previous studies [19, 20] and a clinical relevant change in BOOI of 15 was adopted. The expected mean change (standard deviation) for the change of BOOI from baseline was assumed to be 20 (15). The sample size required to determine this change was 85 when the two-sided alpha level and power were assumed to be 5 and 85%, respectively. Given 20% of ineligible patients, the target sample size was determined to be at least 105 patients. Patients were excluded from the analysis if they discontinued treatment due to adverse reactions, or if urodynamic assessment data were not collected until 12 months of treatment.

All statistical values were presented as mean  $\pm$  standard deviation. The Wilcoxon signed-rank test and the McNemar test were utilized to evaluate changes in subjective symptoms and objective findings. All tests were two-sided, and  $p < 0.05$  was considered statistically significant. Statistical analysis was performed using SPSS software (IBM, Armonk, NY, USA).

## Results

Out of 105 patients, five (4.8%) discontinued treatment due to adverse reactions that included headache ( $n = 2$ ), erection problems ( $n = 2$ ), and dizziness ( $n = 1$ ). In addition, two patients developed urinary retention during the study period, and four were not subjected to PFS after treatment initiation. Therefore, the analysis included 94 patients with a mean age of 70.7 years (range 51–83) and a mean PV of 44.5 mL (range 25–108 mL). All study participants were Japanese. The distribution of symptoms at baseline was

**Table 1** Patient characteristics at baseline

<i>n</i> = 94	Mean ± SD	<i>n</i>
Age (years)	70.7 ± 7.5	
50–59		9
60–69		28
70–79		47
80–		10
Prostate volume (mL)	44.5 ± 16.2	
≥ 25–< 40		49
≥ 40–< 60		29
≥ 60		16
PSA (ng/mL)	3.4 ± 3.1	
< 4.0		63
≥ 4.0		31
IPSS	19.0 ± 5.9	
≥ 8–< 20 (moderate)		48
≥ 20 (severe)		46
BOOI	59.5 ± 30.9	
BOO (–)		7
BOO (±)		16
BOO (+)		71
DM incidence rate	20.2%	
DM (+)		19
DM (–)		75
HT incidence rate	60.6%	
HT (+)		57
HT (–)		37
HL incidence rate	36.2%	
HL (+)		34
HL (–)		60

DM diabetes mellitus, HT hypertension, HL hyperlipidemia, PSA prostate-specific antigen, IPSS international prostate symptom score, BOOI bladder outlet obstruction index

BOO (+): BOOI > 40, BOO (±): 20 < BOOI ≤ 40, BOO (–): BOOI ≤ 20

as follows (Table 1): 46 (48.9%) patients with IPSS ≥ 20 (severe subjective symptoms); 63 (67.0%) with OAB (total OABSS ≥ 3, urinary urgency ≥ 1 per week); 71 (75.5%) with BOO (BOOI > 40, based on PFS); 57 (60.6%) with hypertension (under pharmacotherapy); 34 (36.2%) with hyperlipidemia (under pharmacotherapy); 19 (20.2%) with diabetes.

The changes in subjective symptoms and QOL are summarized in Table 2. The treatment caused significant improvements in IPSS, OABSS, IPSS-QOL, and BII within 3 months and, even stronger, within 12 months, resulting in overall reductions of mean scores by 6.9 (36.3%), 2.0 (31.3%), 1.9 (38.8%), and 3.2 (42.1%), respectively. The improvements included significant reductions in the IPSS sub-scores for voiding and storage and the OABSS-urgency sub-score. By applying the diagnostic criteria of the OABSS for the entire 12-month period, the number of patients diagnosed as OAB decreased significantly from 63 to 31. In addition, significant reductions in IPSS-total and IPSS-voiding scores were observed during the first 3 months, and further significant improvements were observed until after 12 months in these parameters.

Table 3 summarizes changes in all urodynamic parameters. The storage function parameters such as FDV and MCC improved after 3 months of treatment, and further improvement was documented after 12 months. Moreover, DO disappeared significantly in 15 patients (30.6%) after 3 months, which increased to 22 patients (44.9%) after 12 months with a significant improvement (Fig. 1a).

As for voiding functions,  $Q_{\max}$  significantly increased over 3 months, with an increase of 2.9 mL/s over the entire 12 months. PVR also improved gradually, and a significant decrease was observed after 3 and 12 months. PVR was decreased by 27 mL after 12 months compared with the baseline value. Additionally, the significant decrease in Pdet- $Q_{\max}$  at 3 months continued further until 12 months, resulting in a reduction of 10.9 cm H<sub>2</sub>O at treatment termination. BOOI also improved significantly at 3 and 12 months, with a decrease in score by 16.6 at study end (Fig. 1b). At baseline,

**Table 2** Changes in subjective symptoms and quality of life

	Baseline Mean ± SD	Month 3 Mean ± SD	Difference in mean change from baseline	<i>p</i> value	Month 12 Mean ± SD	Difference in mean change from baseline	<i>p</i> value
IPSS	19.0 ± 5.9	13.6 ± 6.4	– 5.4	< 0.001	12.1 ± 5.7*	– 6.9	< 0.001
IPSS-voiding	11.2 ± 4.4	8.1 ± 4.6	– 3.1	< 0.001	7.0 ± 4.1*	– 4.2	< 0.001
IPSS-storage	7.8 ± 2.9	5.5 ± 2.8	– 2.3	< 0.001	5.1 ± 2.5	– 2.3	< 0.001
IPSS-QOL	4.9 ± 0.9	3.3 ± 1.4	– 1.6	< 0.001	3.0 ± 1.2	– 1.9	< 0.001
OABSS	6.4 ± 2.9	4.7 ± 2.8	– 1.7	< 0.001	4.4 ± 2.4	– 2.0	< 0.001
OABSS-urgency score	2.3 ± 1.3	1.5 ± 1.2	– 0.8	< 0.001	1.4 ± 1.2	– 0.9	< 0.001
BII	7.6 ± 2.7	4.9 ± 3.2	– 2.7	< 0.001	4.4 ± 2.6	– 3.2	< 0.001

IPSS international prostate symptom score, QOL quality of life, OABSS overactive bladder symptom score, BII benign prostatic hyperplasia impact index

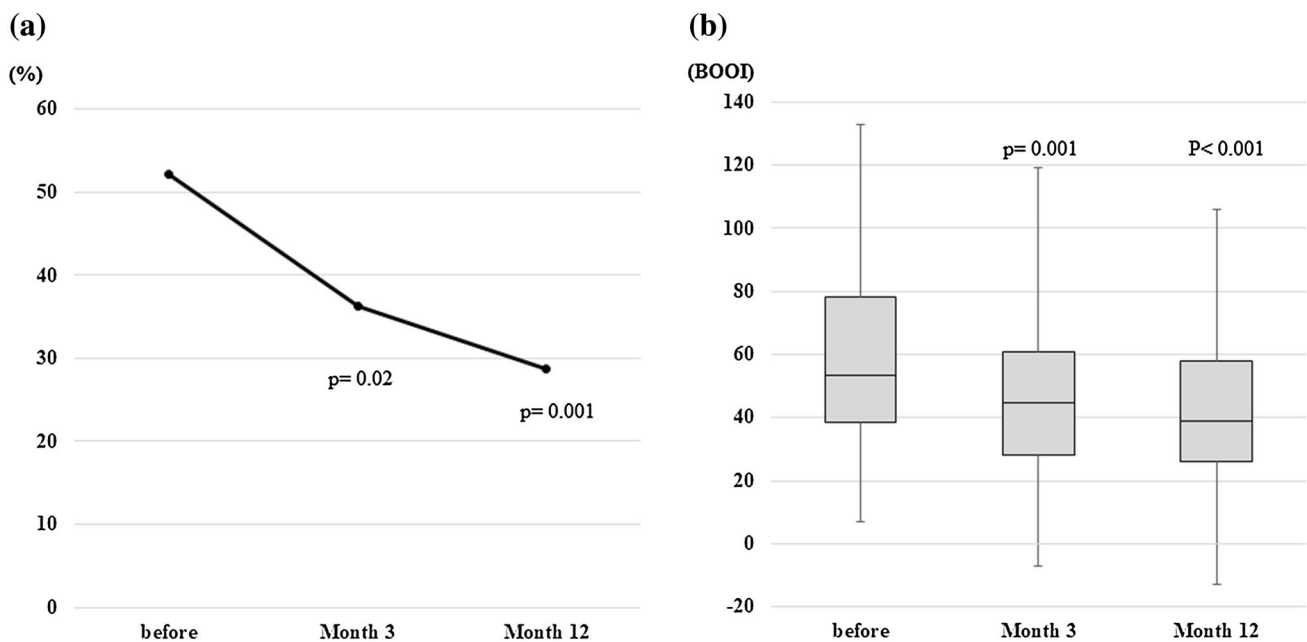
\**p* < 0.01 vs month 3

**Table 3** Changes in urodynamic parameters

	Baseline Mean $\pm$ SD	Month 3 Mean $\pm$ SD	Difference in mean change from baseline	<i>p</i> value	Month 12 Mean $\pm$ SD	Difference in mean change from baseline	<i>p</i> value
FDV (mL)	134 $\pm$ 60	152 $\pm$ 58	+ 18	0.04	159 $\pm$ 57	+ 25	0.004
MCC (mL)	245 $\pm$ 98	264 $\pm$ 90	+ 19	0.16	277 $\pm$ 92	+ 32	0.02
$Q_{\max}$ (mL/s)	7.2 $\pm$ 3.5	9.2 $\pm$ 3.8	+ 2.0	< 0.001	10.1 $\pm$ 4.0 *	+ 2.9	< 0.001
Pdet $Q_{\max}$ (cmH <sub>2</sub> O)	73.9 $\pm$ 28.5	64.1 $\pm$ 24.5	- 9.7	0.01	63.0 $\pm$ 19.3	- 10.9	0.002
PVR (mL)	70 $\pm$ 70	50 $\pm$ 47	- 20	0.02	43 $\pm$ 45	- 27	0.002
BOOI	59.5 $\pm$ 30.9	45.7 $\pm$ 28.2	- 13.8	0.001	42.9 $\pm$ 23.3	- 16.6	< 0.001
DO	49/94 (52.1%)	34/94 (36.2%)	Improvement rate 30.6%	0.02	27/94 (28.7%)	Improvement rate 44.9%	0.001

FDV first desire to void, MCC maximum cystometric capacity,  $Q_{\max}$  maximum flow rate, Pdet $Q_{\max}$  detrusor pressure at  $Q_{\max}$ , PVR post-void residual urine, BOOI bladder outlet obstruction index, DO detrusor overactivity

\* $p < 0.01$  vs month 3



**Fig. 1** **a** The incidence of DO after tadalafil administration: the incidence of DO decreased significantly from 52.1% (before administration) to 36.2% (month 3), and 28.7% (month 12). **b** Change of BOOI before, at 3 months, and at 12 months of tadalafil administration

71 patients (75.5%) had BOO (BOOI > 40), which decreased to 44 patients (46.8%) after 12 months, showing a substantial improvement ( $p < 0.001$ ).

## Discussion

This was the first study to evaluate the objective effects of tadalafil at a 5-mg daily dose, administered in clinical practice, on storage and voiding functions in patients with LUTS/BPH, for the longer term than 3 months. Although Dmochowski et al. reported the urodynamic short-term (3 months) effects of tadalafil in a placebo-controlled

study [21] and several studies have reported the significant improvement in subjective symptoms of LUTS during intermediate-term tadalafil monotherapy, there was no report on the long-term objective effects of tadalafil until our study. We showed that tadalafil caused significant improvements in storage and voiding functions that continued to improve after 3 months (short-term) until 12 months (intermediate-term).

After 12 months of tadalafil treatment, mean Pdet $Q_{\max}$ ,  $Q_{\max}$ , and BOOI improved significantly by 10.9 cm H<sub>2</sub>O, 2.9 mL/s, and 16.6, respectively. Although the lack of similar studies makes it impossible to compare our data with the published literature, we previously reported the 1-year effects of an  $\alpha$ 1-blocker, silodosin, recommended as the first

choice for LUTS/BPH treatment, and showed a mean Pdet $Q_{\max}$  change of  $-12.6$  cm H<sub>2</sub>O ( $p < 0.001$ ), a mean  $Q_{\max}$  improvement of  $1.8$  ml/s ( $p < 0.001$ ), and a mean BOOI change of  $-16.2$  ( $p < 0.001$ ) [20]. When comparing the two studies, the ameliorating effect is almost equal, and tadalafil is likely to have an equivalent efficacy regarding the improvement in voiding functions such as  $Q_{\max}$  and BOO. In addition, besides the significant improvement of bladder capacity, the incidence of patients with disappearance of DO was 30.6% after 3 months, which increased to 44.9% after 12 months with a significant difference. Our findings on the 1-year effects of tadalafil will provide evidence-based guidance for clinicians in selecting a therapeutic strategy for patients with LUTS/BPH.

There are some discrepancies in the literature regarding the effect of tadalafil on  $Q_{\max}$ ; significant improvement was reported in a placebo-controlled clinical study [22], whereas others reported that tadalafil did not improve  $Q_{\max}$  significantly [14, 15]. Although  $Q_{\max}$  is regarded as an objective parameter for BOO, it depends on voiding volume and bladder contractility. A pressure flow study needs to be implemented for evaluating the change in BOO accurately. Dmochowski et al. reported that tadalafil treatment had no significant effect on voiding functions such as  $Q_{\max}$ , Pdet $Q_{\max}$ , and BOOI [21]. However, a limitation of the study was the low proportion of patients with BOO at baseline; at 34%, it was possible that the effect of tadalafil on BOO could not be evaluated accurately. In our study, 71 (75.5%) patients had BOO based on PFS (BOOI  $> 40$ ). These differences in patient background at baseline between the two studies might explain the different results of tadalafil on voiding functions.

In the present study, BOOI significantly improved by 27.9% (from 59.5 to 42.9) after 12 months of tadalafil administration in whole patients. However, in 23 patients without BOO at baseline (BOOI  $\leq 40$ ), Pdet $Q_{\max}$  and BOOI changed from 45.6 and 26.6 to 47.1 and 23.3, respectively, demonstrating no significant improvement. On the other hand, in these patients without BOO at baseline, mean IPSS, OABSS, and BII significantly improved from 20.2, 6.6, and 8.5 to 13.1 ( $p < 0.001$ ), 4.9 ( $p < 0.001$ ), and 5.0 ( $p < 0.001$ ), respectively, after a 12-month treatment period. It was interesting that the discrepancy between the improvement in subjective symptoms and objective findings with tadalafil was observed in patients without BOO at baseline. Although we were unable to determine the precise reason for this discrepancy, one plausible hypothesis can be discussed. Recently, Osman et al. reported that not only BOO but also detrusor underactivity (DU) was common causes of LUTS and DU was present in 9–48% of men undergoing urodynamic evaluation for non-neurogenic LUTS [23]. Tadalafil was considered to be effective in the improvement of LUTS for patients with DU, by increasing blood perfusion to the

pelvic organs. In a rat model of chronic bladder ischemia which resulted in detrusor overactivity and fibrosis of the bladder wall; Nomiya et al. reported that treatment with tadalafil protected bladder function and morphology [24]. In our 12-month tadalafil study, mean bladder contractility index significantly improved from 92 to 107 ( $p = 0.04$ ) in 23 patients without BOO at baseline. Although further studies are needed to evaluate the effect of tadalafil for patients with LUTS caused by DU, tadalafil is considered to improve LUTS by ameliorating BOO in patients with BOO, and by increasing bladder contractility in patients with DU.

A limitation of the present study is the lack of a placebo control. Therefore, placebo effects cannot be excluded regarding changes in subjective symptom and UDS parameters. However, these effects were likely minimal on the evaluation of urodynamic parameters, which were the primary endpoints. In addition, the habituation effect could play a role in repeated urodynamic examinations. However, the influence of the effect was negligible in other studies using a placebo [21], and we concluded that the effect did not cause a major problem in the objectivity of this study either. Another limitation is the 12-month study period that needs to be extended by additional follow-up examinations of the study participants. Hence, multi-year studies are further needed to assess the long-term effects of tadalafil on bladder function, and BOO.

## Conclusions

The treatment with tadalafil for 12 months significantly relieved storage and voiding functions, along with LUTS, in patients diagnosed with LUTS/BPH. Monitoring the parameters of LUT function, such as bladder capacity, DO,  $Q_{\max}$ , and BOOI, revealed that beneficial effects of tadalafil treatment observed at 3 months continued to improve until 12 months.

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**Author contributions** YM: Protocol/project development, Data management, Manuscript writing/editing. ST: Data analysis. TM: Manuscript writing. YF: Data analysis. NS: Data management. MK: Protocol/project development. TY: Protocol/project development. MG: Protocol/project development, Manuscript editing.

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.



**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee of the Nagoya University Graduate School of Medicine approved this study protocol (IRB approval number: 2015-0106).

**Informed consent** Informed consent was obtained from all individual participants included in the study before enrollment. The study was registered at <https://center.umin.ac.jp> as UMIN000017925.

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