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Population pharmacokinetics of milrinone in patients undergoing cardiovascular surgery with cardiopulmonary bypass

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Abstract

Background

Milrinone, a selective phosphodiesterase III inhibitor with both positive inotropic and vasodilatory effects, is widely used during cardiovascular surgery. However, limited information is available on the pharmacokinetics (PK) of milrinone in patients undergoing cardiovascular surgery with cardiopulmonary bypass (CPB). CPB may alter the PK of many drugs through hemodilution, altered protein binding, hypothermia, and changes in organ perfusion. This study aimed to develop a population pharmacokinetic (PPK) model of milrinone and evaluate the influence of renal function on PK parameters in patients undergoing cardiovascular surgery with CPB.

Methods

This prospective observational single-center study included adult patients who received intravenous milrinone during cardiovascular surgery with CPB between October 2021 and March 2022. Plasma milrinone concentrations were measured at 0.5, 2, 12–24, and 24–36 h after the initiation of administration and quantified using liquid chromatography-tandem mass spectrometry. PPK analysis was performed using nonlinear mixed-effects modeling. Candidate covariates included age, sex, body weight, creatinine clearance (Ccr), serum albumin, CPB priming volume, and cell saver volume. Their effects on the clearance (CL) and volume of distribution (V) were evaluated. Model performance and stability were assessed using goodness-of-fit diagnostics and bootstrap validation.

Results

A total of 61 patients and 229 plasma samples were included in the analysis. The one-compartment structural model with a proportional error model provided the best fit to the observed data. Covariate analysis identified Ccr as a significant covariate influencing CL. Bootstrap validation generally supported model stability, although uncertainty remained in the estimation of some parameters. The final model was described as follows: CL (L/h) = $2.26 \times Ccr^{0.48}$, V (L) = 13.32.

Conclusions

This study developed a PPK model of milrinone use in patients undergoing cardiovascular surgery with CPB, and identified renal function as a factor influencing CL. These findings suggest that renal function may be important when determining milrinone dosing in this population, although further external validation is required.

Background

Myocardial dysfunction is a risk factor for postoperative mortality [1]. Cardiopulmonary bypass (CPB) is often employed to support severe cardiopulmonary dysfunction during these surgeries [2]. In such cases, pulmonary vasodilators, inotropic agents, and vasopressors are often required to facilitate separation from CPB and to maintain adequate cardiac output [3]. Among these agents, milrinone, a selective phosphodiesterase III inhibitor, exerts both positive inotropic and vasodilatory effects by increasing intracellular cyclic AMP levels without elevating the heart rate or myocardial oxygen consumption [4]. During surgery, milrinone has been shown to improve cardiac function and promote weaning from CPB [5–8]. Additionally, patients with impaired cardiac function before CPB may develop low cardiac output syndrome after CPB, and milrinone may be beneficial for such patients [9]. These pharmacological properties make milrinone a common choice for cardiac surgery involving CPB, particularly for coronary artery bypass and valve replacement surgeries [10].

However, CPB is known to alter the pharmacokinetics (PK) of various drugs by reducing plasma protein binding and impairing renal or hepatic clearance due to decreased organ perfusion and hypothermia [11, 12]. A previous study demonstrated that CPB may increase the volume of distribution (V) and reduce the clearance (CL) of tranexamic acid [13]. Furthermore, high concentrations (exceeding 500 ng/mL) have been reported to be associated primarily with systemic hypotension caused by excessive vasodilation [14], potentially increasing the risk of adverse effects such as ventricular tachycardia, atrial fibrillation, and thrombocytopenia. Therefore, understanding the PK of milrinone in patients undergoing cardiovascular surgery with CPB is clinically important.

Although milrinone is widely used, its population PK (PPK) in patients undergoing cardiovascular surgery with CPB remains poorly characterized. Most previous studies have focused on patients with congestive heart failure [15], neonates [16], or children [17, 18] without CPB. Thus, these PPK models may not be applicable to patients undergoing cardiovascular surgery with CPB. Moreover, milrinone is primarily eliminated by renal excretion [19, 20]. In healthy adults, milrinone has a volume of distribution of 0.32 L/kg, a plasma clearance of 18–24 L/h, and an elimination half-life of 48–56 min [21]. In congestive heart failure, the volume of distribution is slightly increased, whereas plasma clearance is reduced. Prolonged elimination half-life and reduced plasma clearance have also been reported in patients with chronic renal failure. Therefore, a PPK model of milrinone that incorporates renal function is required. This study aimed to develop a PPK model of milrinone and evaluate the influence of renal function on PK parameters in patients undergoing cardiovascular surgery with CPB.

Methods

Study design

This prospective, observational, single-center study included adult patients who received intravenous milrinone during cardiovascular surgery with CPB at Nagoya University Hospital between October 2021 and March 2022. Patients receiving hemodialysis and those who did not undergo CPB were excluded. CPB was performed using an S5 perfusion system (LivaNova, Italy). The pump flow rate was set to 2.4–

2.6 L/min/m², and a target mean blood pressure was also set. Patient characteristics and perioperative information, including sex, age, body weight (BW), CPB usage, milrinone dose, and administration schedule, surgical method, CPB priming volume, and cell saver volume, were collected using an electronic medical record system (HOPE/EGMAIN-GX; Fujitsu, Tokyo, Japan). Serum creatinine (CRE) and albumin (ALB) levels were obtained before cardiovascular surgery. Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault formula. Preoperative and postoperative CRE and ALB levels were compared using the Wilcoxon signed-rank test. Statistical analyses were performed using IBM SPSS Statistics version 31 (IBM Corp., Armonk, NY, USA). The infusion rate was adjusted within the range of 0.1–0.5 μg/kg/min at the discretion of the attending anesthesiologists.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the Nagoya University Hospital Bioethics Committee (approval number 2021 − 0231). Written informed consent was obtained from all the patients prior to cardiovascular surgery.

Sample preparations

Blood samples were collected at 0.5, 2, 12–24 h, and 24–36 h after initiation of milrinone administration. The samples were centrifuged at 3,000 rpm (round per minute) for 5 min at room temperature to separate the plasma. All plasma samples were stored at − 80°C until analysis. For sample preparation, 300 μL of 1% formic acid in acetonitrile (FUJIFILM Wako Pure Chemical Industries, Ltd., Osaka, Japan) was added to 100 μL of each plasma sample and vortexed for 2 min. The mixture was applied to an InertSep Phospholipid Remover column (GL Sciences Inc., Tokyo, Japan) for solid phase extraction and centrifuged at 3,000 rpm for 5 s. The obtained extract was diluted with 0.1% formic acid in acetonitrile, and 100 μL of the diluted sample was mixed with 25 μL of a 1,500 ng/mL internal standard (IS). Olprinone (Eisai Pharmaceutical Co., Ltd., Tokyo, Japan), which has a chemical structure similar to that of milrinone, was used as the IS. Milrinone was purchased from Takata Pharmaceutical Co., Ltd. (Saitama, Japan).

Liquid chromatography-tandem mass spectrometry analysis

Plasma milrinone concentrations were measured using ultra-performance liquid chromatography (UPLC)-tandem mass spectrometry (Waters ACQUITY UPLC® System; ACQUITY TQD). Chromatographic separation of milrinone and the IS was performed using a CORTECS® C18 + column (100 × 2.1 mm, 2.7 μm, Waters) maintained at 40°C. Separation was performed by gradient elution using eluents A and B, consisting of 5 mM ammonium acetate (FUJIFILM Wako Pure Chemical Industries, Ltd., Osaka, Japan) and methanol (FUJIFILM Wako Pure Chemical Co. Ltd., Osaka, Japan), respectively. The gradient program was as follows: 75% eluent A (linear gradient, v/v) at 0 min, 15% eluent A from 2.5 to 4 min, and

75% eluent A at 6 min. The total run time was 6 min, with a flow rate of 0.2 mL/min and an injection volume of 20 μL. Samples were analyzed in positive ion mode by multiple reaction monitoring. The multiple reaction monitoring transitions were m/z 211.85 to 228.79 for milrinone and m/z 304.73 for the IS.

PPK analysis methods

In this study, PPK analysis was performed using a methodology similar to that used in our previous study [13]. The PK model was constructed using Phoenix NLME software version 8.7.0 (Certara, Princeton, NJ). PPK parameters and variability were estimated using the first-order conditional estimation with the extended least-squares method (FOCE-ELS).

Building base model

One-, two-, and three-compartment PK models were tested to fit the PPK data. The Base model was selected depending on the-2 log likelihood (-2 l,l,).,diagnostic plots, relative standard error(RSE) of parameter estimates, and numerical stability of the model, including the bootstrap success rate.

Structural models with one, two, and three compartments were evaluated, assuming first-order elimination from the central compartment.

Interindividual variability (η) in the PK parameters was modeled using an exponential random-effects model as follows:

$P_i = P \times \exp(\eta_i)$

where P_i is the PK parameter value for the i-th individual, P is the typical population value of the PK parameter, and η_i represents the interindividual variability. The η_i values were assumed to follow a normal distribution with a mean of 0 and variance of ω^2.

A proportional residual error model was used to describe the residual variability (ε), as follows:

$C_{pij} = Cpred,_{ij} \times (1 + \varepsilon_{ij})$

where C_{pij} represents the observed plasma concentration at time point j for the i-th individual, and $Cpred,_{ij}$ represents the model-predicted concentration at the same time point. The residual error (ε_{ij}) was assumed to follow a normal distribution with a mean of 0 and variance of σ^2.

Covariate model development

The effects of age, sex, BW, Ccr, preoperative ALB levels, CPB priming volume, and cell saver volume on PK parameters were evaluated using stepwise covariate modeling. If the addition of a covariate to the

model resulted in a decrease of -2 l.l. greater than 6.635, the covariate was considered to significantly influence the model parameters (χ^2 test, 1 degree of freedom, $p < 0.01$).

Final model development and evaluation

The final model was selected by incorporating the covariate that resulted in the greatest decrease in − 2 l.l. from the one-compartment base model. Goodness-of-fit was assessed using scatter plots of the actual plasma milrinone concentrations versus population predicted concentrations (PRED), the actual plasma concentrations versus individual predicted concentrations (IPRED), conditional weighted residuals (CWRES) versus PRED, and IPRED versus individual weighted residuals (IWRES).

To evaluate the stability of the final model, bootstrap analysis was performed using 500 resampled datasets generated from the original dataset. Bootstrap runs with return codes of 1–3 were considered successful. The mean, relative standard error (RSE), and 95% confidence intervals (CI, 2.5–97.5%) of the bootstrap parameter estimates were calculated and compared with the final model estimates.

Results

Patient demographics and measured plasma concentrations

A total of 61 patients (42 males and 19 females) were included in this study. Patient characteristics are summarized in Table 1. The mean ± standard deviation (SD) values for age, BW, preoperative ALB, postoperative ALB, preoperative CRE, postoperative CRE, and Ccr were 66.9 ± 11.9 years, 63.9 ± 12.5 kg, 2.82 ± 0.37 g/dL, 2.85 ± 0.40 g/dL, 1.00 ± 0.34 mg/dL, 0.97 ± 0.25 mg/dL, and 68.5 ± 29.7 mL/min, respectively. The mean CPB priming volume was 1,132 ± 143 mL, and the mean cell saver volume was 231 ± 396 mL. ALB levels differed significantly before and after surgery, but CRE levels did not.

Table 1
Patient profiles used in the population pharmacokinetic analysis of milrinone

Parameter	No. or Mean (± SD)	Range	*p* value
Subjects	61		
Sex (male/female)	42/19		
Age (yrs)	66.9 (11.9)	26–84	
Body weight (kg)	63.9 (12.5)	41.7–90.8	
Preoperative ALB (g/dL)	2.82 (0.37)	1.6–3.6	< 0.01[a)]
Postoperative ALB (g/dL)	2.85 (0.40)	1.6–3.8	
Preoperative CRE (mg/dL)	1.00 (0.34)	0.52–2.33	0.236[a)]
Postoperative CRE (mg/dL)	0.97 (0.25)	0.43–1.53	
Creatinine clearance (mL/min)	68.5 (29.7)	13.6–187	
CPB priming volume (mL)	1,132 (143)	809–1,409	
Cell saver volume (mL)	231 (396)	0–1,941	
Surgical method			
CABG	7		
Valve	32		
Vascular	10		
CABG + Valve	4		
CABG + Vascular	1		
Valve + Vascular	5		
Other	2		

Creatinine clearance was estimated using the Cockcroft-Gault formula. SD, standard deviation; ALB, serum albumin; CRE, serum creatinine; CABG, coronary artery bypass grafting. a) Preoperative and postoperative CRE and ALB levels were compared using the Wilcoxon signed-rank test.

Blood samples for plasma concentration measurement were collected at 0.5, 2, 12–24 h and 24–36 h after initiation of milrinone administration (Fig. 1). A total of 229 plasma samples were obtained for analysis, with most of the measured concentrations being below 100 ng/mL.

PPK analysis

Model selection was based on the evaluation of the compartmental structure and the residual error model (Table 2). Structural models with one, two, and three compartments were compared. The − 2 log-likelihood (-2 *l.l.*) values were − 1295.7053 for the one-compartment model, -1355.273 for the two-compartment model, and − 1354.889 for the three-compartment model. However, the two-compartment model showed a statistically significant lower − 2 *l.l.* compared to the one-compartment model (Δ-2 *l.l.* = -59.568, $P < 0.01$), it resulted in poor precision of parameter estimates, with relative standard errors (RSEs) for clearance (CL) and volume of distribution (V_2) exceeding 100% (126.37% and 219.41%, respectively). Furthermore, no clear visual improvement was observed in the goodness-of-fit plots.

During the development of the base model, additive, proportional, and combined residual error models were evaluated. The proportional residual error model provided the best fit, and the one-compartment model with this error structure was selected as the final structural model. The results of covariate analysis are presented in Table 2.

Table 2
Summary of population pharmacokinetic analysis of milrinone

Model No.	Details	-2 l.l.	Decrease in -2 l.l.	*p* value
Structural model				
1	1-compartment model	-1295.7053	—	—
Covariate model (based on Model 1)				
2	Add Ccr on CL in model 1	-1306.310	-10.605	< 0.01
3	Add BW on CL in model 1	-1300.2729	-4.5676	NS
4	Add preoperative ALB on CL in model 1	-1295.7171	-0.0118	NS
5	Add BW on V in model 1	-1300.5385	-4.8332	NS
6	Add preoperative ALB on V in model 1	-1295.7987	-0.0934	NS

Model selection was based on changes in − 2 l.l. between the compared models. Covariate models 2–6 were compared with model 1. A decrease in − 2 l.l. greater than 6.635 was considered statistically significant ($p < 0.01$). Decrease values are shown only when the tested model had a lower − 2 l.l. than the corresponding comparison model. -2 l.l., -2 log likelihood; BW, body weight; CL, clearance; V volume of distribution; ALB, serum albumin; Ccr, creatinine clearance; NS, not significant.

Although cardiopulmonary bypass (CPB) priming volume and cell saver volume were tested as covariates, they did not result in a significant decrease in -2 *l.l.* and were thus deemed unsuitable. A model incorporating creatinine clearance (Ccr) as a covariate for clearance (CL) significantly improved the goodness-of-fit compared with the base model. Therefore, *the CrCL level* was incorporated as a covariate for clearance in the final model.

The parameter estimates, %RSE, and 95% CI for the final PK model are summarized in Table 3. The estimated values of CL, and V were 1.90 L/h, and 13.27 L, respectively. The final model incorporating the effect of Ccr was expressed as follows: CL (L/h) = $2.26 \times Ccr^{0.48}$, V (L) = 13.32.

Bootstrap analysis was performed to evaluate the stability of the final model. All 500 bootstrap replicates were successfully completed (success rate, 100%). The bootstrap mean estimates for V and the effect of Ccr on CL were close to the corresponding final model estimates. The bootstrap mean estimate for CL was higher than the final model estimate (2.26 vs. 1.90 L/h). All final model parameter estimates, including CL, were within the corresponding 95% CI obtained from the bootstrap analysis.

Table 3
Parameter estimates and bootstrap results for milrinone population pharmacokinetic model

Parameters	Final model		Bootstrap (n = 500)		
	Estimate	RSE (%)	Mean	95% CI	RSE (%)
CL (L/h)	1.90	45.79	2.26	0.72–5.92	68.10
V (L)	13.27	10.80	13.32	10.59–16.15	10.98
Ccr on CL	0.48	14.79	0.48	0.20–0.72	28.06

RSE, relative standard error; CI, confidence intervals; CL, clearance; V, volume of distribution; Ccr, creatinine clearance.

The goodness-of-fit diagnostic plots for the final model are shown in Fig. 2. The scatter plot of the observed milrinone concentrations versus PRED showed that the data points were generally distributed around the line of identity (Fig. 2(a)). The scatter plot of observed concentrations versus IPRED demonstrated closer agreement than that of PRED, indicating improved individual prediction (Fig. 2(b)). In the CWRES versus PRED plot, most values were distributed within ± 2, indicating no evident bias (Fig. 2(c)). The IWRES versus IPRED plot showed no apparent bias in the distribution of residual errors (Fig. 2(d)). Overall, the goodness-of-fit plots for the final model indicated no clear systematic bias in the structural or residual error models.

Discussion

In this study, we developed and evaluated a PPK model of milrinone in patients undergoing cardiovascular surgery with CPB. Few studies have evaluated the PPK of milrinone in this clinical setting. Although two-compartment [15] and three-compartment [14] models have been reported for milrinone, a one-compartment model was selected in the present study. Milrinone was administered by continuous low-rate intravenous infusion without a loading dose, and the limited number of early sampling points provided insufficient information to reliably characterize the distribution phase. The final model identified

Ccr as a significant covariate for CL, suggesting that renal function is a relevant factor influencing milrinone clearance in this patient population.

A one-compartment model with a proportional error structure adequately described the observed plasma milrinone concentrations (Table 2). Overall, the goodness-of-fit diagnostics supported the adequacy of the final model for describing the observed plasma milrinone concentrations. The bootstrap mean estimate for CL was higher than the corresponding final model estimate, although this estimate remained within the corresponding 95% CI obtained from the bootstrap analysis. This difference may partly reflect the limited sample size and sparse perioperative sampling. To the best of our knowledge, only two previous studies have examined the PPK of milrinone in adult patients undergoing cardiovascular surgery with CPB, and both have reported that a three-compartment model provides a good fit. Bailey et al. reported that a central-compartment volume of 102 mL/kg, a volume of distribution of 1,698 mL/kg, and an elimination clearance of 1.88 mL/kg/min, corresponding to approximately 6.52 L, 108.5 L, and 7.21 L/h, respectively, for a patient weighing 63.9 kg (the mean BW in our study) [14]. Butterworth et al. described the PK of milrinone using a three-compartment model comprising a central compartment and peripheral distribution compartments, reporting the following values for adult patients with a median body weight of 72–88 kg: V1 = 11.1 L, V2 = 16.9 L, V3 = 363 L, CL1 = 0.067 L/min (equivalent to 4.02 L/h), CL2 = 1.05 L/min, and CL3 = 0.31 L/min. In the present study, the estimated CL for a representative patient with a Ccr of 60 mL/min was approximately 16.1 L/h, and V was estimated to be 13.32 L. Although the PK parameter estimates differed across studies, direct comparison of individual compartmental parameters should be interpreted with caution because of differences in model structures, CPB equipment and conditions, patient characteristics (e.g., lower mean BW), types of surgery, dosing regimens, and sampling schemes.

In healthy adults, the volume of distribution has been reported to be 0.32L/kg [21]. In this study, the estimated volume of distribution was 13.27L, corresponding to approximately 0.21 L/kg based on the mean body weight of 63.9 kg recorded in the study cohort. Therefore, the apparent volume of distribution in the surgical population included in the present study is lower than that reported for healthy adults. Although direct comparisons are limited by differences in study populations and model structures, the distribution volume estimated in the present study appears to differ from that reported in healthy adults. These differences may reflect CPB-related physiological changes, including altered protein binding, hypothermia, hemodilution, and changes in organ perfusion. Additionally, unlike previous studies, our analysis incorporated Ccr as a covariate, allowing characterization of the influence of renal function on clearance. Therefore, our model may support the development of individualized, renal function–based dosing regimens for patients undergoing cardiovascular surgery with CPB. CPB and perioperative clinical conditions may also affect PK through changes in ALB and renal function. However, in the present study, no significant perioperative changes were observed in ALB or CRE levels, and ALB was not retained as a significant covariate in the final model. Taken together, these findings suggest that, among the evaluated covariates, renal function represented by Ccr was the most relevant factor influencing milrinone clearance.

Most plasma concentrations measured in this study were below 100 ng/mL, which is lower than the commonly reported effective plasma concentration (100–400 ng/mL) [22]. Milrinone was administered intraoperatively without a loading dose because of concerns regarding hypotension and arrhythmias. Given that these adverse events are considered dose-dependent, low-dose continuous infusion without a loading dose may be clinically reasonable in the perioperative setting. Consistent with this approach, the Comprehensive Heart Failure Practice Guidelines from the Heart Failure Society of America recommend starting milrinone at a low dose of 0.1 μg/kg/min and titrating to 0.2–0.3 μg/kg/min to achieve symptomatic improvement [23]. Additionally, several reports suggest that the concentration required for clinical efficacy during cardiovascular surgery may be lower than the threshold reported in patients with chronic congestive heart failure [7, 22]. Therefore, although the dosing regimen used in this study (0.1–0.5 μg/kg/min without a loading dose) may reduce the risk of dose-dependent adverse effects, it may also result in relatively low plasma exposure, particularly in patients with preserved renal function. Based on the final model, milrinone clearance was influenced by renal function, suggesting that Ccr may need to be considered when determining the milrinone dose during cardiovascular surgery with CPB. In particular, low-dose administration without a loading dose may not maintain the plasma concentrations within the commonly reported effective range in patients with preserved renal function. Conversely, patients with reduced renal function may be at an increased risk of milrinone accumulation. Thus, the present model may be useful for predicting milrinone exposure under different renal function scenarios and may support individualized dose selection in this population.

This study had several limitations. First, it was a single-center study with a limited sample size, which may limit its generalizability. Second, the dosing regimen of milrinone varied among patients, as the infusion rate (0.1–0.5 μg/kg/min) was determined at the discretion of the attending anesthesiologists. In some patients, intraoperative or postoperative hypotension and arrhythmia resulted in early discontinuation of milrinone, limiting the collection of planned plasma samples. These factors may have influenced the parameter estimates. Third, PK sampling was constrained by the perioperative setting, which may have contributed to the uncertainty in some of the model parameters. In addition, CPB-related factors that may influence drug disposition, such as CPB duration, temperature management, and ultrafiltration, were not evaluated as covariates and may have contributed to unexplained variability. Fourth, pharmacodynamic endpoints, such as hemodynamic response, hypotension, arrhythmias, and clinical outcomes, were not incorporated into the model. Finally, although bootstrap analysis and goodness-of-fit diagnostics generally supported the adequacy of the final model, no external validation was performed. Therefore, further multicenter studies with larger cohorts, richer PK sampling strategies, and external validation are warranted to confirm the robustness and clinical applicability of the present model. Despite these limitations, the present study provides limited evidence on milrinone PPK in patients undergoing cardiovascular surgery with CPB and suggests that renal function is relevant to milrinone clearance in this setting.

Conclusions

We developed a PPK model for milrinone use in patients undergoing cardiovascular surgery with CPB. The final model was described as follows: CL (L/h) = $2.26 \times Ccr^{0.48}$, V (L) = 13.32. Ccr has been identified as an important covariate of CL, suggesting that renal function may influence milrinone clearance in this population. These findings suggest that renal function should be considered when determining milrinone dosing in patients undergoing cardiovascular surgery with CPB. The present model may support individualized dosing strategies for milrinone, although further validation in larger multicenter cohorts is required.

Abbreviations

ALB
Serum albumin
BW
Body weight
CABG
Coronary artery bypass grafting
Ccr
Creatinine clearance
CI
Confidence intervals
CL
Clearance
CPB
Cardiopulmonary bypass
CRE
Serum creatinine
CWRES
Conditional weighted residuals
IPRED
Individual predicted concentration
IWRES
Individual weighted residuals
PK
Pharmacokinetics
PPK
Population pharmacokinetics
PRED
Population predicted concentrations
RSE
Relative standard error

SD
Standard deviation
V
Volume of distribution
− 2 l.l.
-2 log likelihood

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethics committee of Nagoya University Hospital (Nagoya, Japan, approval number 2021-0231). Written informed consent was obtained from all patients before cardiovascular surgery.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

OW, TN, TT and YM designed the study. OW and TT recruited patients. OW performed the data acquisition. OW and YM performed analyses. OW, TN, and YM interpreted data. OW and TN prepared the draft and OW, TN and YM edited the manuscript. TI, MM, SY, KY, KN, HM, and HI supervised the study. All the authors have read and approved the final version of the manuscript.

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Figures

Figure 1

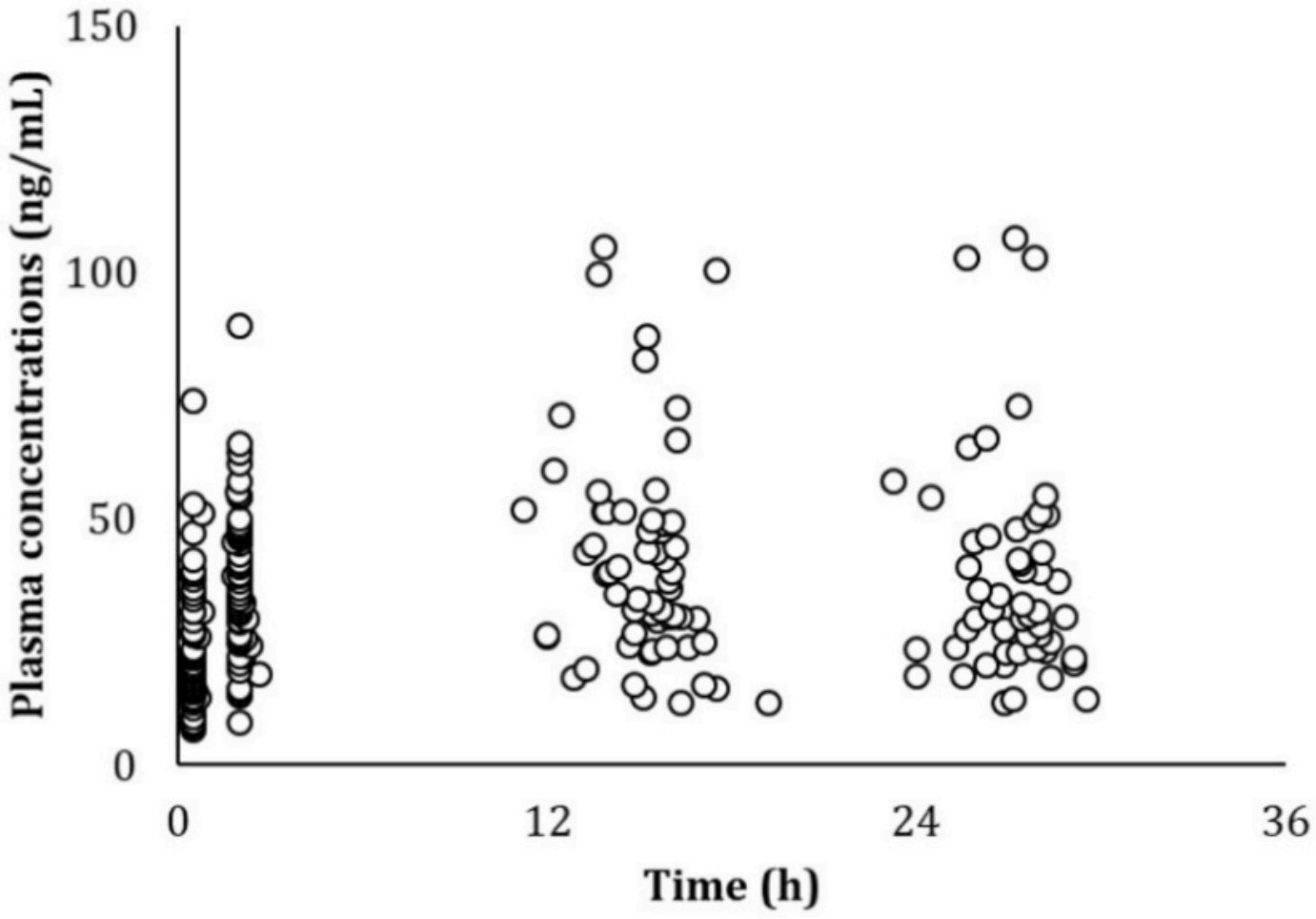


Figure 1

The actual plasma milrinone concentrations. The horizontal axis indicates the time after the first administration.

Figure 2

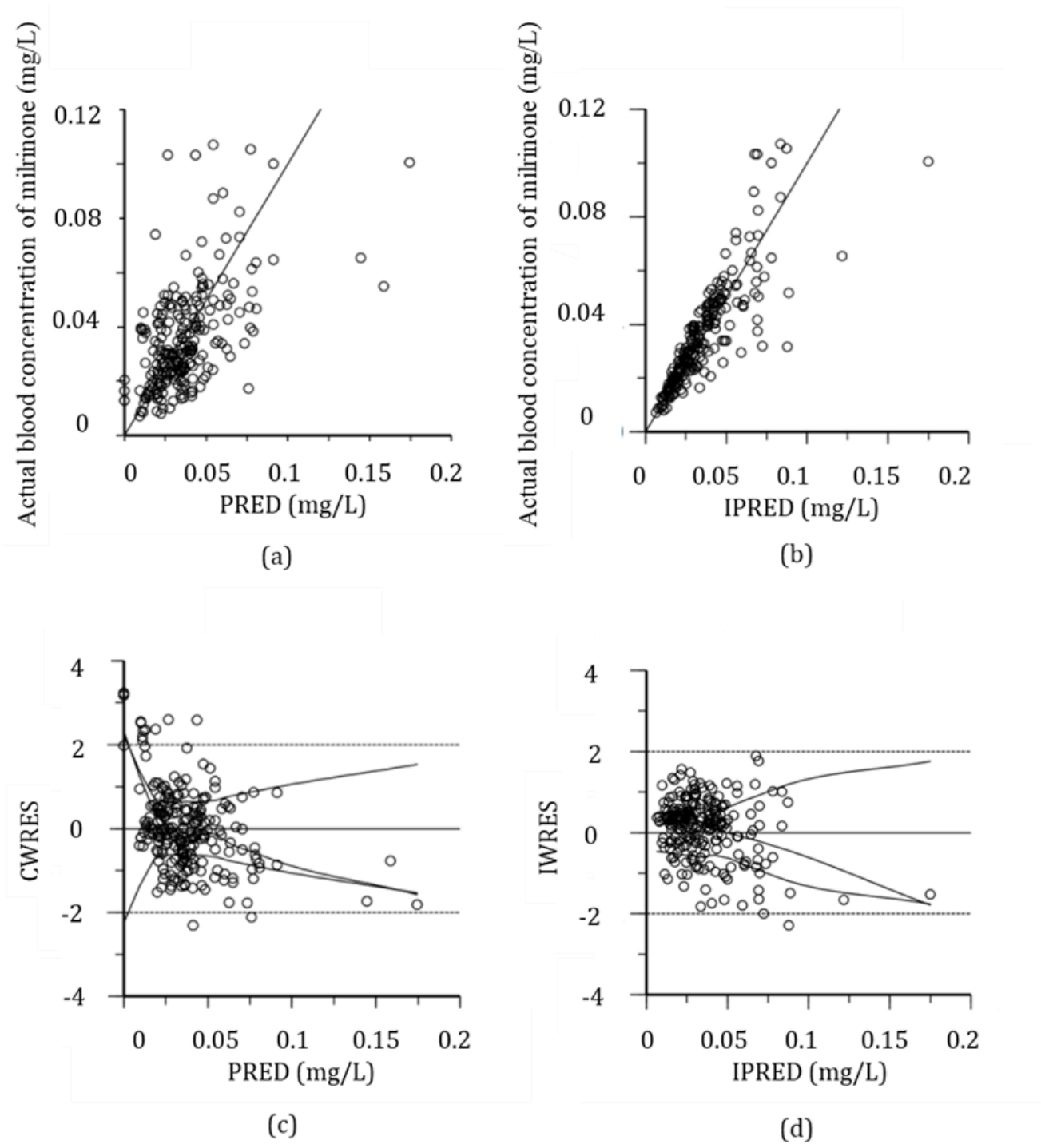


Figure 2

Diagnostic goodness-of-fit plots of the final model. (a) Actual plasma concentrations of milrinone versus PRED. (b) Actual plasma concentrations of milrinone versus IPRED. (c) CWRES versus PRED. (d) IWRES versus IPRED. In (c) and (d), the curves symmetrically centered around y = 0 represent locally weighted scatterplot smoothing (LOESS) lines fitted to the absolute values of the residuals. In contrast, the asymmetrical curves represent LOESS lines fitted to the raw residuals. PRED, population predicted

concentrations; IPRED, individual predicted concentrations; CWRES, conditionally weighted residuals; IWRES, individual weighted residuals.