# Novel risk factors for poor outcome in frail cardiac surgery patients

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# Chapter 6

# Pharmacokinetics and analgesic response of morphine and morphine-3-glucuronide in frail older patients undergoing cardiac surgery.

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# ABSTRACT

## Introduction

Acute postoperative pain management is challenging in frail older patients due to their susceptibility to adverse effects of opioids. This study compared the pharmacokinetics (PK) of morphine and morphine-3-glucuronide (M3G) in frail elderly cardiac surgery patients with a general intensive care unit (ICU) population consisting of postcardiac surgery and critically ill patients. Secondly, we studied the analgesic response to a standardized postoperative morphine treatment protocol in the ICU.

## Methods

Using a previously published population model, external validation and simulations were performed to explore differences in PK in frail elderly patients (i.e., ≥ 70 years with Clinical Frailty Scale ≥ 4) versus general ICU patients. For the analgesic response to standardized morphine treatment (2 mg/h), clinically driven dose adjustments were analysed in conjunction with corresponding individual morphine and M3G concentrations, postoperative severe pain (i.e. Numeric Rating Scale (NRS) ≥ 4) and oversedation.

## Results

In total, 237 morphine and M3G concentrations were analysed from 22 frail elderly patients after cardiac surgery. In frail elderly, morphine glucuronidation remained unchanged, morphine clearance through other routes showed a 39% decrease and M3G elimination showed a 43% increase, compared to general ICU patients. These differences result in an increased morphine exposure of approximately 20%. In 4 patients (18%), analgesic response was satisfactory, without requiring dose adjustment due to oversedation or severe pain. 18 patients (82%) experienced oversedation and 11 patients (50%) experienced severe pain at least once. The correlations between morphine concentration or M3G concentration and NRS scores were weak ($r = -0.25$, $p=0.06$ for morphine and $r = -0.07$, $p=0.6$ for M3G).

## Conclusion

In frail older cardiac surgery patients, morphine glucuronidation was similar to general ICU patients, but morphine clearance through other routes was decreased and M3G elimination increased. Analgesic response to standardized morphine treatment varied substantially and was only satisfactory in a minority of patients.

# INTRODUCTION

Moderate or severe postoperative pain after cardiac surgery is associated with complications and risk of chronic pain. Up to one third of older patients experience postoperative pain, especially when frailty is present.[1–4] Optimal dosing of morphine in older surgical patients is difficult due to physiological changes associated with aging and frailty.[2,4–7] These changes may cause altered pharmacokinetics (PK) and pharmacodynamics (PD), leading to poor pain management and side effects, including oversedation or apnoea.[8–13]

Although the PK of morphine and its metabolites are widely studied in the general population, evidence is limited on the PK-PD relationship of morphine in frail elderly following cardiac surgery. Previously, a PK model for morphine and morphine-3-glucuronide (M3G) was developed in a general Intensive Care Unit (ICU) population consisting of cardiac surgery and critically ill patients.[14] For ICU patients with normal creatinine concentrations, a decrease of 76% was estimated in M3G elimination clearance compared to healthy subjects, which results in substantial accumulation of M3G over time.[14]

This study compares the PK of morphine and M3G in frail elderly patients after cardiac surgery to a general ICU population.[14] Additionally, we studied the analgesic response to a standardized morphine treatment using clinically driven dose adjustments in conjunction with morphine and M3G concentrations.

# METHODS

## Study design and population

The Anaesthesia Geriatric Evaluation (AGE) AWARE II study was a single centre, prospective, cohort study in the Netherlands (St. Antonius Hospital, Nieuwegein). Inclusion took place from October 2020 until November 2021. Patients aged ≥ 70 years with a Clinical Frailty Scale ≥ 4[15] undergoing elective open cardiac surgery were eligible to participate. Patients with a contraindication for morphine were excluded. Ethical approval was provided by the local ethics committee before patient recruitment (Medical Ethics Research Committees United (www.mec-u.nl), number R20.015). The study was registered at ClinicalTrials.gov (NCT04696445) and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. This manuscript adheres to the STROBE guidelines.[16]

## Anesthesia and standardized postoperative pain management with morphine

Perioperative care was routinely performed according to local standardized procedures. For intraoperative analgesia, a continuous infusion of remifentanil was initiated after induction of anesthesia and intermittent fentanyl doses were used at predetermined times (i.e., prior to incision of the skin, sternotomy, aorta cannulation, and opening of the pericardium). Doses were determined at the discretion of the attending anesthesiologist, depending on patient characteristics and intraoperative vital parameters. All patients received a loading dose of 10 mg intravenous morphine 30 minutes before the anticipated end of surgery. Postoperatively, all patients stayed in the ICU for one night before being transferred to the general ward for further recovery. On admission to the ICU, a continuous morphine infusion of 2 mg/h was started. Pain was assessed by self-reported Numeric Rating Scale (NRS) for pain (ranging from 0 = no pain at all to 10 = worst imaginable pain).[17] The NRS was scored at least once every 4 hours, except when patients were asleep without evidence of pain. If patients had severe pain (NRS score ≥ 4), additional intravenous bolus doses (2.5 to 7.5 mg) of morphine were administered and/or maintenance doses were increased, based on the discretion of treating physicians. Similarly, in case of anticipated delayed arousal or oversedation, the morphine infusion rate could be reduced or stopped.

## Data collection

Demographics were derived from the electronic health record (EHR), Epic (Epic Systems Corporation, Verona, WI, USA). This included health status, comorbidities, medication history, clinical frailty scale (CFS), previous surgical procedures, laboratory tests. Frailty was categorized according to the CFS into very mild frailty (CFS 4),

mild frailty (CFS 5) and moderate to severe frailty (CFS ≥ 6).[15] To assess the overall burden of comorbidities, the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was calculated.[18] Data on opioid consumption and analgesic response, including use of naloxone, and NRS scores were extracted from the EHR. All data was gathered and managed using the Research Electronic Data Capture (REDCap) system (Vanderbilt University, Nashville, TN, USA).[19]

### Blood sample collection and analysis for pharmacokinetic modelling

In all patients, 2 mL arterial blood samples were drawn at $t$ = 20 – 60, 120, 180, 240, 420, and/or 480 minutes after the first dose of intravenous morphine administered at the end of surgery. In addition, blood samples were collected in case of deviations from the standardized treatment with morphine (i.e. when morphine was decreased or stopped due to oversedation, or increased due to severe pain). The exact timing of each blood sampling was documented. The blood samples were placed in EDTA tubes until separated by centrifugation (4000 rpm for ten minutes) and stored at – 80 °C until analysis. All samples were analysed for serum concentrations of morphine and M3G using high-performance liquid chromatography tandem mass spectrometry.[20] The lower limit of quantification (LLOQ) was 2 µg/L for both morphine and M3G. In total, 11% (14 of 126) of the morphine concentrations and 0.8% (1 of 126) of the M3G concentrations were below the LLOQ; these concentrations were omitted from the PK analysis. The M3G concentrations were expressed as micrograms of morphine base units per L, logarithmically transformed and fitted simultaneously with logarithmically transformed morphine concentrations.



### Sample size

To calculate the sample size of this study, we used the M3G elimination clearance for which a significant difference was seen between the ICU population compared to healthy volunteers as reported in the previously published model.[14] The average M3G elimination clearance and standard deviation was 0.573 (0.313) L/min. The M3G clearance in ICU patients with normal renal function was 76% decreased compared to healthy volunteers. Assuming that these data are normally distributed, the sample size was calculated with a Student's t-test. Using a level of significance of 0.05 and a power of 0.8, 20 subjects were included to be able to detect a 35% difference in M3G clearance between frail elderly and a general ICU population.

### Pharmacokinetic analysis

Population model validation was performed using nonlinear mixed effects modelling software (NONMEM), version 7.4.3 (Icon Development Solutions, Hanover, MD, USA) running under Pirana version 3.0.0 (University of Uppsala, Sweden). The NONMEM

output was analysed using R version 4.1.0 running under Rstudio version 1.4.1717 (R foundation for Statistical Computing, Vienna, Austria).

The previously published population pharmacokinetic model that was used, was developed using 3012 morphine and M3G concentrations from 117 cardiac surgery patients and 18 critically ill patients from the ICU (hereafter referred to as the general ICU population), and 20 healthy volunteers.[14] In this model, a 3-compartment model was used to describe the disposition of morphine and a 1-compartment model for M3G. The schematic representation of the structural model is shown in **Supplementary figure 1**. Morphine clearance was quantified through the formation of the M3G metabolite ($CL_{m,M3G}$) as well as through other routes ($CL_{non\text{-}M3G}$), which includes amongst other unchanged renal elimination and formation of morphine-6-glucuronide. For M3G, a single elimination clearance was quantified ($CL_{e,M3G}$). Log-normally distributed inter-individual variability was quantified for all three clearance parameters as well as for the distribution volume of M3G.

In the current analysis, the previously published model[14] was externally validated in frail elderly undergoing cardiac surgery to assess whether the PK of morphine and M3G was similar to general ICU patients. This external validation was based on the obtained PK parameter values for general ICU patients. Since, contrary to the general ICU patients, our frail elderly patients did not have renal failure, the covariate relationship between serum creatinine concentrations and the M3G elimination clearance was not taken into consideration by fixing all values for creatinine concentration in the elderly at 80 μmol/L. **Supplementary table 1** lists all parameter estimates of the original model of Ahlers et al.[14] Individual post hoc parameter values and predicted morphine and M3G concentrations were then obtained using a Bayesian estimation (i.e., MAXEVAL=0). The obtained output was visually assessed in goodness-of-fit plots for morphine and M3G (observed *versus* population-predicted concentrations and conditional weighted residuals (CWRES) *versus* time and *versus* population predictions). Individual deviations from typical parameter values (i.e., eta-values) were plotted independently versus covariate values, to visualize potential correlations. Then, using a combined dataset of general ICU patients[14] and frail elderly from the current study, deviating values were estimated for frail elderly for each model parameter while keeping the other parameters fixed to the values for general ICU patients, to assess potential differences between frail elderly and the general ICU population. Discrimination between the different models was made by comparison of the objective function value (OFV, i.e., -2 log likelihood). A decrease of 3.84 points in the OFV for one degree of freedom was considered statistically significant, representing a p-value < 0.05. Moreover, the optimized model was assessed by inspection of the aforementioned

goodness-of-fit plots and relative standard errors of the parameters estimates being <50%. Finally, the proportional deviation between the newly estimated parameter values in the optimized model and the original parameter estimates was calculated. To assess the predictive properties of the optimized model in frail elderly, a normalized prediction distribution error (NDPE) analysis was performed using the NDPE package in R. Each observed concentration was visually and numerically compared to 1,000 simulated values.

### Model-based simulations

Simulations using the optimized final model were conducted to illustrate the difference in concentration-time profiles of morphine and M3G upon the applied morphine treatment in frail elderly patients compared to the general ICU population. Using this model, simulations were performed in a typical individual from the general ICU population and a typical frail elderly patient with creatinine levels of 80 μmol/L. Two scenarios were simulated for each typical patient, 1) a 10 mg intravenous bolus dose of morphine, and 2) a continuous 2 mg/h morphine infusion over 72 hours.

### Analgesic response to standardized morphine treatment

To evaluated whether patients received satisfactory morphine treatment, we evaluated the analgesic response at the ICU over time. Analgesic response was considered satisfactory if the morphine infusion rate maintained at 2 mg/h throughout the ICU stay, or was gradually decreased in case of low pain scores. Analgesic response was considered inadequate if; a) the infusion rate was reduced or stopped, due to delayed arousal or when treatment with naloxone was given (i.e. oversedation); or b) the infusion rate was increased, due to severe pain. To assess whether inadequate analgesic response corresponded with the concentrations of morphine and/or M3G in frail elderly patients, the observed concentrations of morphine and M3G were plotted against NRS pain scores. Only NRS pain scores and blood sample collections taken within 90 minutes of each other were included for analysis. The correlation between observed concentrations and NRS was evaluated using the Spearman rank-order correlation coefficient. The Spearman's correlation coefficient was considered weak (0 – 0.3), moderate (0.4 – 0.6) or strong (0.7 – 1). Descriptive statistics of patients characteristics were reported as means with standard deviations (SDs), median with interquartile range (IQR), and proportions. A p-value < 0.05 was considered statistically significant.

# RESULTS

## Population

This study included 22 frail older cardiac surgery patients. Median age was 75 years (IQR 74 – 77). Half of all patients were very mildly frail (CFS 4) and two (9%) patients had moderate to severe frailty (CFS ≥6). Coronary artery bypass surgery and single valve surgery were the most commonly performed procedures (**Table 1**). The median observation period was 22 hours (IQR 18 – 28 hours, range 2 - 74 hours), with a median number of 6 samples per patient. The median length of hospital stay was 7 days (IQR 7 – 10).

**Table 1.** Patient characteristics and data (n = 22 patients)

| **Patient characteristics and data (n = 22 patients)** | |
|---|---|
| Sex, male/female sex | 18/4 (82%/18%) |
| Age, yrs | 75 (74 – 77) |
| Weight, kg | 90 (85 – 107) |
| BMI (kg/m$^2$) | 30 (28 – 34) |
| EuroSCORE II | 1.6 (1.3 – 3.3) |
| Clinical frailty scale | |
| 4 | 11 (50%) |
| 5 | 9 (41%) |
| 6 or more | 2 (9%) |
| Preoperative creatinine concentration (µmol·L) | 97 (82 – 109) |
| Type of surgery | |
| Single CABG | 11 (50%) |
| Single valve | 5 (23%) |
| Aortic surgery | 1 (5%) |
| Combined surgery | 5 (23%) |
| Duration of cardiopulmonary bypass, min | 91 (76 – 99) |
| Cumulative intraoperative fentanyl, µg | 1500 (1500 – 2000) |
| Cumulative intraoperative remifentanyl, µg | 1850 (1450 – 2100) |
| Cumulative morphine administration, mg | 31 (22 – 37) |
| Of which administered as bolus, mg | 10 (5 – 10) |
| Morphine sampling period, hours | 22 (18 – 28) |
| Number of samples (morphine, M3G) | |
| Total | 252 |
| Per patient | 6 (5 – 7) |

*Continuous variables reported as median (IQR), categorical variables as frequency (%).*
*BMI: body mass index; CABG: coronary artery bypass grafting; NRS: numeric rating scale*

## Morphine pharmacokinetics

The analysis was based on 237 morphine and M3G perioperative serum concentrations. Standard goodness of fit plots obtained after fixing all parameters to values of the original model by Ahlers et al[14] showed reasonable accuracy (**Supplementary Figure 2)**. This figure shows that observed morphine and M3G concentrations of the frail elderly fell within the variability observed in the general ICU population, even though some biases could be observed. For the distribution of individual parameters from the typical parameter values (i.e., eta-values), clearance of morphine through other routes ($CL_{non\text{-}M3G}$) and M3G elimination clearance ($CL_{e,M3G}$) showed trends towards decreased and increased values compared to general ICU patients, respectively (**Supplementary Figure 3**).

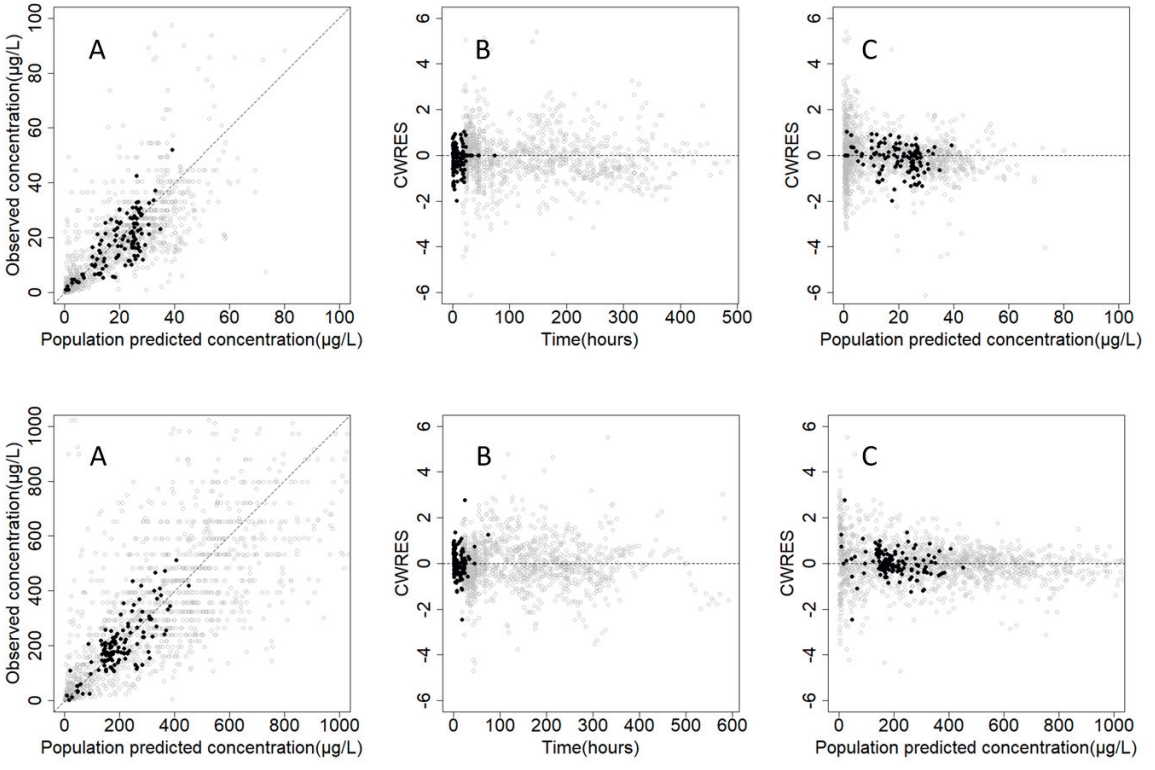
When comparing parameter values for frail elderly patients with the general ICU population, morphine glucuronidation clearance was found to not be statistically significantly different, whereas clearance of morphine through other routes and M3G elimination clearance were different ($p<0.01$). All parameter values are summarized in **Supplementary table 1.** The estimated value for clearance of morphine through other routes and M3G elimination clearance in the optimized model were 0.33 (RSE 13.6%) and 0.0605 (RSE 6.4%), respectively, implying a 39% decrease in clearance of morphine through other routes in frail elderly cardiac patients and a 43% increase for M3G elimination clearance compared to the general ICU population. No statistically significant differences for frail elderly in comparison with general ICU population in any of the other parameters were found.



The optimized model that included adjusted parameter values for morphine through other routes and M3G elimination clearance was found to describe the data of the frail elderly accurately, as confirmed by the goodness-of-fit plots (**Figure 1**). The NPDE analysis confirmed that the optimized model could also accurately predict the typical trend of the concentration profiles in frail elderly patients. However, there was a slight overprediction of the variability of high concentrations for morphine and low concentrations for M3G (**Supplementary figure 4**).

**Figure 2** illustrates the impact of the differences between a typical frail elderly and a typical general ICU patient on the exposure of morphine and M3G based on two treatment scenarios, using the optimized model. The reduced clearance of morphine through other routes in frail elderly increased morphine exposure, which results in an increased steady state concentration with approximately 20% in frail elderly, compared to general ICU patients. The increased morphine exposure also resulted in a higher fraction being metabolized to M3G. This effect is counterbalanced by the increased M3G elimination clearance observed in frail elderly, but does tend to result in decreased M3G exposure upon prolonged treatment.

**Figure 1.** Goodness-of-fit plots for the optimized model consisting of adjusted parameter values for morphine clearance through other routes ($CL_{non\text{-}M3G}$) and M3G elimination clearance ($CL_{e,M3G}$)




(A) Observed concentrations versus population predicted concentrations. The dotted line indicates the line of unity. (B) Conditional weighted residuals (CWRES) versus time. (C) CWRES versus population predicted concentrations. Top row represents morphine concentrations, bottom row morphine-3-glucuronide concentrations. The black dots represent the frail elderly patients, the grey dots represents the general ICU population (i.e., post cardiac surgery and critically ill patients).

## Analgesic response

In 4 patients (18%) analgesic response was satisfactory throughout the follow-up period. In 11 patients (50%) morphine infusion was increased at least once due to severe pain and in 18 patients (82%) morphine infusion was reduced or stopped at least once due to oversedation. Two of these patients (9%) were treated with naloxone. In total 11 patients (50%) experiences both episodes of severe pain and oversedation. **Figure 3** illustrates the observed morphine and M3G concentrations in relation to NRS. The analgesic response to standardized morphine treatment was highly heterogeneous among frail elderly. In addition, the correlations between morphine or M3G concentrations and NRS scores were weak (r = – 0.25, p=0.06 for morphine and r = – 0.07, p=0.6 for M3G).

**Figure 2.** Morphine (left panels) and M3G (right panels) concentrations over time in a typical individual from the general ICU population (purple) and a typical frail elderly patient (green), both with normal creatinin (i.e. 80 µmol/L), after a 10 mg intravenous bolus dose of morphine (top panels) and a 2 mg/h continuous infusion of morphine for 72 hours (bottom panels).

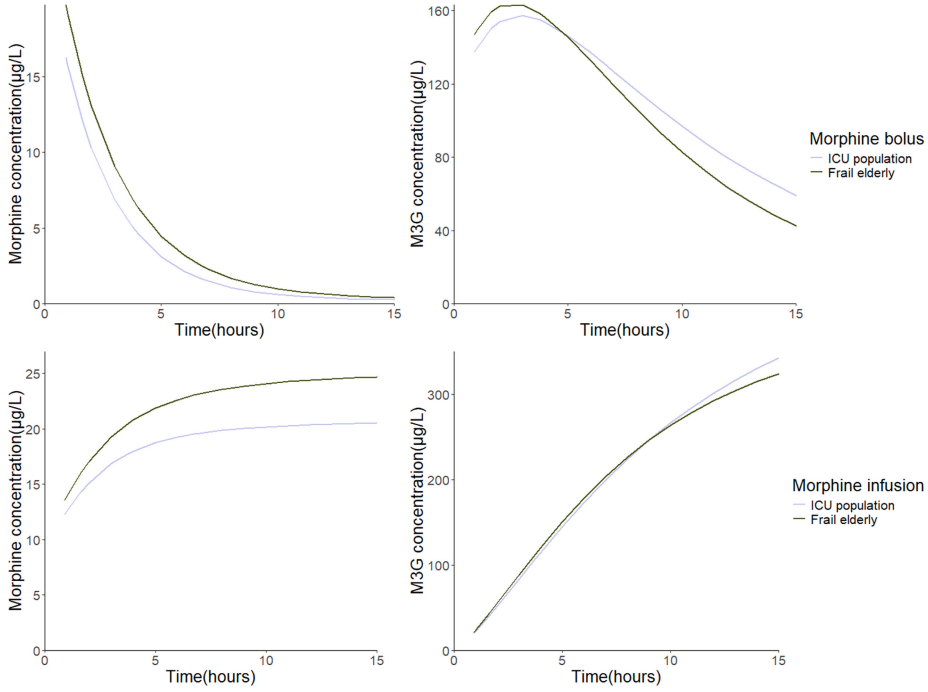
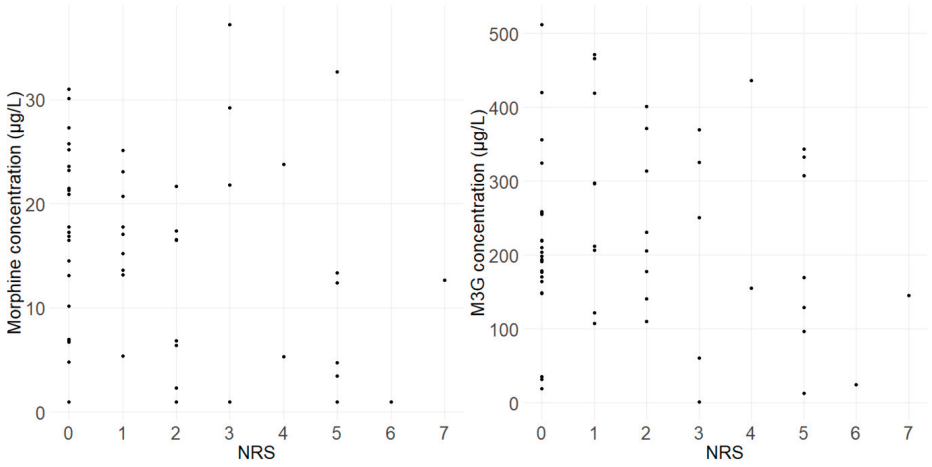


**Figure 3.** Morphine (left) and M3G (right) concentrations with corresponding NRS scores in frail elderly patients.



## DISCUSSION

This study demonstrates that morphine glucuronidation after cardiac surgery in frail elderly is similar to general ICU patients, while elimination of morphine through other routes is decreased and M3G elimination is increased. As a result of these changes, a 20% increased steady state concentration of morphine can be expected. A satisfactory analgesic response was observed in merely one out of five patients, while the vast majority was oversedated. No correlation was found between observed morphine or M3G concentrations and NRS.

A few studies investigated the PK of morphine in non-surgical elderly volunteers (>60 years) and found reduced clearance of morphine and reduced distribution volumes compared to healthy young volunteers, resulting in higher peak plasma concentrations.[21–23] The results of our study showed that glucuronidation clearance was unaffected, elimination clearance of morphine through other pathways was reduced, and M3G elimination clearance was increased. As a result, a standard dosing regimen of 2 mg/h will give about 20% higher concentrations of morphine in frail elderly post-cardiac surgery compared to the general ICU population. In addition, the previous studies concluded that the increased sensitivity of elderly to the analgesic effects of morphine were at least partly due to an altered disposition and that these patients were at increased risk of adverse effects.[21–23] Our study found similar results, as the increased steady state concentration of morphine appeared clinically relevant in our population, because 82% of the patients experienced oversedation. Consequently, one could argue for lowering the infusion rate. However, healthcare personnel should be aware of an increased risk of postoperative pain when applying a lower dose. In our study, standardized pain management with morphine resulted in 50% of patients having severe postoperative pain for which doses of morphine were increased. Elderly patients who suffer from acute postoperative pain are at increased risk to develop chronic postoperative pain, and worse quality of life.[1,10] Given the substantial variation found in analgesic response within frail elderly in this study, it is essential to identify patient variables that are predictive of pain.

The weak correlation between pain scores and morphine concentrations in our study challenges current understandings in postoperative pain management. A previous study in 3.045 patients after various types of surgery (i.e. orthopaedic, urologic, abdominal, gynaecologic, vascular, thoracic, and cervicomaxillofacial), which evaluated the relationship between measurements of pain and morphine requirements during postoperative intravenous morphine titration, demonstrated that a visual analogue scale (VAS) score ≥ 70 predicted the need for a high dose of morphine (>0.15 mg/kg),

with an average dose of 12 ± 7 mg required for pain relief.[24] These results might give an indication of the amount of morphine needed to alleviate pain. In our study, however, the mean cumulative morphine per patient was 31 mg, while still 50% of patients experienced severe pain at some time point during the follow-up period. It should be noted that our population consisted of frail elderly following cardiac surgery, which is a painful procedure. Factors affecting pain relief and possible side effects experienced by the frail elderly patient are multitudinous. They include the pharmacokinetic variation among individuals, the possible effects of active metabolites, development of tolerance, differences in pain physiology and pharmacogenetics, dynamics of pain intensity, as well as psychological and social components.[25] Also, elderly patients may not adequately report pain scores, potentially leading to inadequate pain management. One of the major challenges is to gather quantitative information on all these variables for the development of larger pharmacokinetic models in which various drug and patient properties can be integrated. With such models, the PKPD and ultimately drug dosing of morphine can be predicted for individual frail elderly patients. Therefore, future research should focus on filling in these knowledge gaps to aid in the development of pharmacological models that can ultimately lead to personalized pain management.

This study has some limitations. The study included frail elderly patients with a short duration of morphine administration compared to the reference general ICU population that also evaluated patients with longer ICU stays. This may have restricted the scope of comparison, potentially affecting the generalizability of our findings, although the low values of the relative standard errors of the obtained parameter estimates doe suggest the findings to be adequately supported by the data. Furthermore, the relatively small sample size may have resulted in insufficient statistical power to detect differences between observed morphine and M3G concentrations in relation to NRS.

### Conclusions

In frail older cardiac surgery patients, morphine glucuronidation is similar compared to general ICU patients, while elimination of morphine through other routes is decreased and M3G elimination is increased. Analgesic response to standardized morphine treatment varied substantially and was only satisfactory in a minority of patients. Personalized pain management is essential for older patients to ensure safe and efficient postoperative pain relief.

## ACKNOWLEDGEMENTS

None

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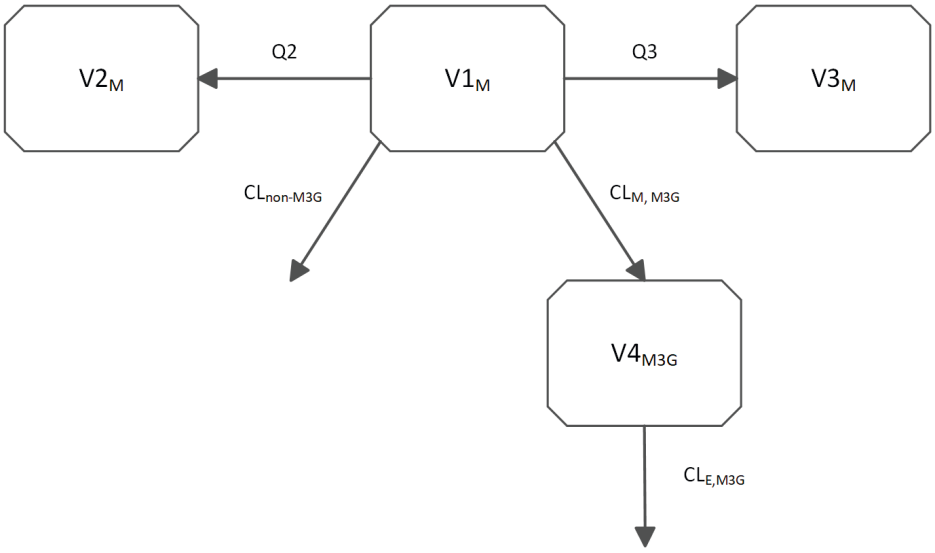
# SUPPLEMENTARY MATERIAL

**Supplementary table 1.** Parameter estimates of the population pharmacokinetic original ICU model (consisting of postcardiac surgery and critically ill patients) and optimized model of morphine and M3G in frail elderly cardiac surgery patients

| Fixed effects | Model of Ahlers et al.[14] | Deviating estimates for frail elderly |
|---|---|---|
| *Morphine* | | |
| $V1_M$ (L) | 17.1 | - |
| $V2_M$ (L) | 88.6 | - |
| $V3_M$ (L) | 399 | - |
| $Q_2$ (L/min) | 1.33 | - |
| $Q_3$ (L/min) | 0.156 | - |
| $CL_{non\text{-}M3G}$ (L/min) | 0.539 | 0.333 (RSE 13.6%) |
| M3G formation ($CL_{m,M3G}$) (L/min) | 0.573 | - |
| *M3G* | | |
| $V4_{M3G}$ (L) | 23 (fixed) | - |
| M3G elimination ($CL_{e,M3G}$) (L/min) | 0.0423 | 0.0605 (RSE 6.4%) |

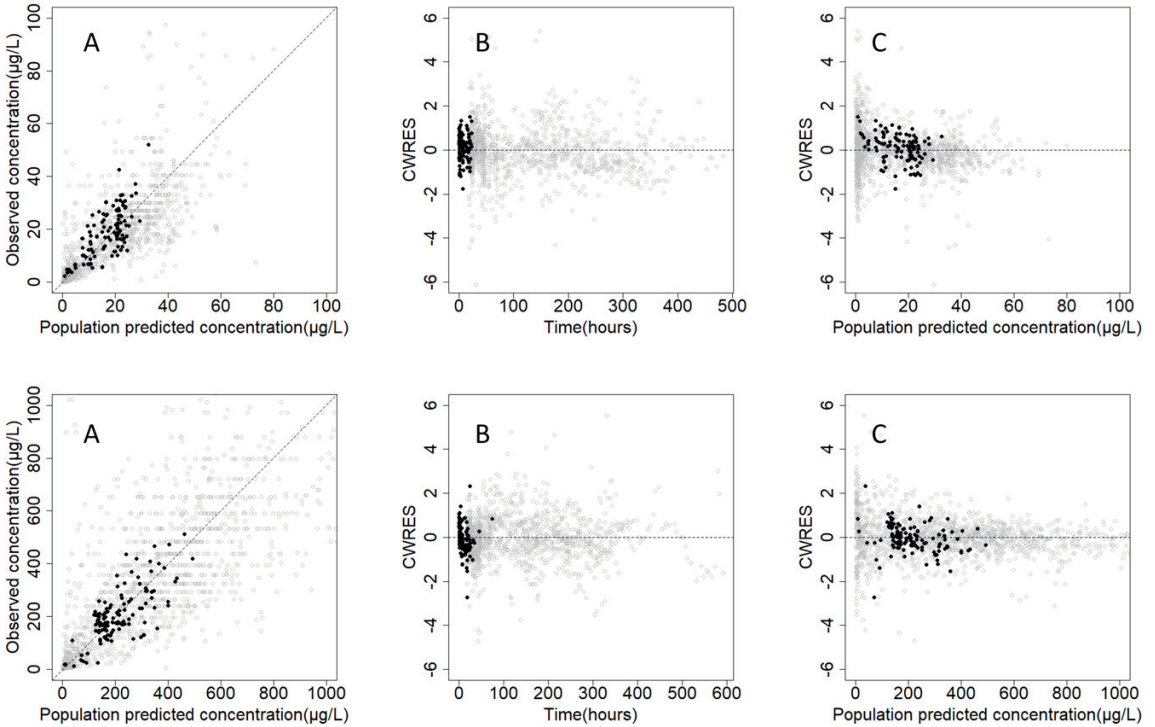
*ICU = intensive care unit; M = morphine; M3G = morphine-3-glucuronide; V1 and V4 = central volumes of distribution for morphine and M3G, respectively, V2 and V3 = peripheral compartments; $Q_2$ and $Q_3$ = inter-compartmental clearances for morphine. $CL_{non\text{-}M3G}$ = morphine clearance through other routes with creatinine concentration of 80 µmol/L; $CL_{m,M3G}$ = M3G formation; $CL_{e,M3G}$ = M3G elimination; - = unchanged compared to Model of Ahlers et al.*

**Supplementary figure 1.** Schematic representation of the population pharmacokinetic structural model of morphine and M3G.



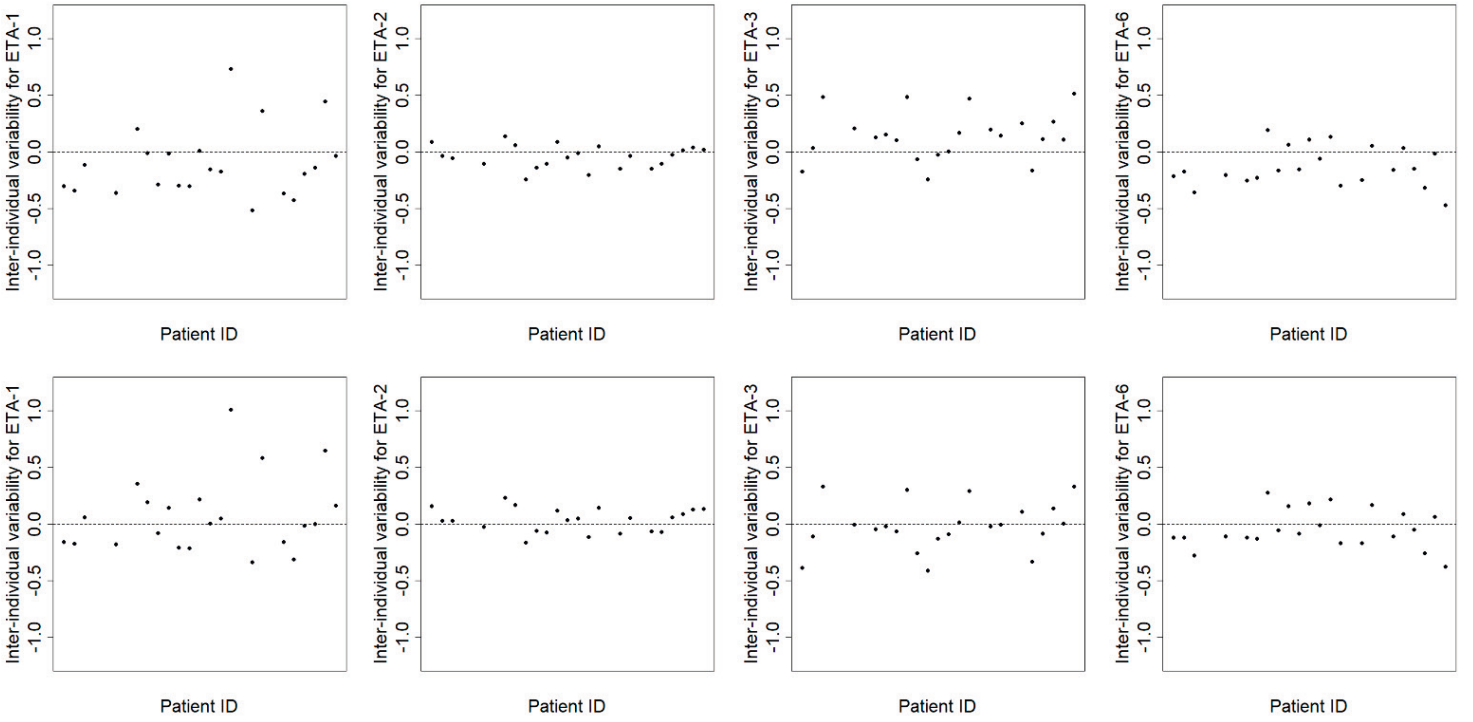

*The dose is administered in the central compartment ($V1_M$).*
*M = morphine; M3G = morphine-3-glucuronide; $V1_M$ and $V4_{M3G}$ = central volumes of distribution of morphine and M3G, respectively; $V2_M$ and $V3_M$ = peripheral volume of distribution of morphine; Q1 and Q2 = inter-compartmental clearances for morphine. $CL_{non\text{-}M3G}$ = morphine clearance through other routes; $CL_{m,M3G}$ = M3G formation clearance; $CL_{e,M3G}$ = M3G elimination clearance.*

**Supplementary figure 2.** Goodness-of-fit plots obtained in a Bayesian re-estimation (i.e., MAXEVAL = 0 fit) with the original model for general ICU patients.



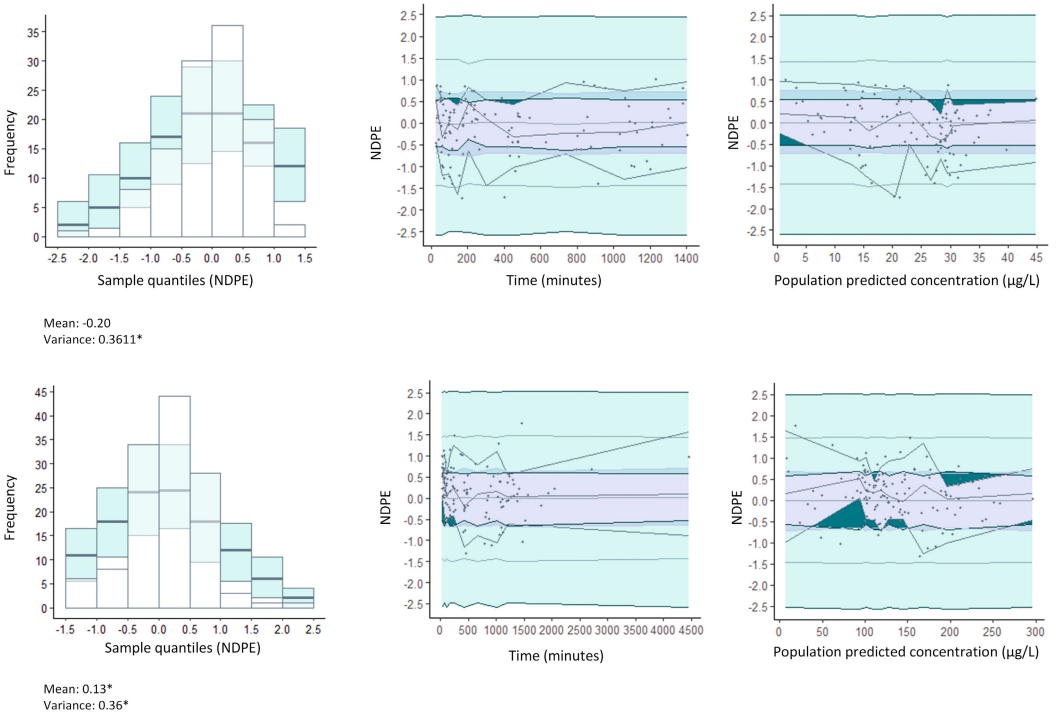

(A) Observed concentration versus population predicted concentration. The dotted line indicates the line of unity. (B) Conditional weighted residuals (CWRES) versus time. (C) CWRES versus population predicted concentration. Top row represents morphine, bottom row morphine-3-glucuronide. The black dots represent the frail elderly patients, the grey symbols represents the general ICU population (i.e., post cardiac surgery and critically ill patients).

**Supplementary figure 3.** Individual deviations from typical parameter values (eta-values) plotted for the Bayesian reestimation (i.e., MAXEVAL = 0 fit) (top row) and optimized PK model for frail elderly patients (bottom row).




From left to right: ETA-1 = $CL_{non\text{-}M3G}$, morphine clearance through other routes; ETA-2 = $CL_{m,M3G}$, M3G formation clearance; ETA-3 = $CL_{e,M3G,}$ M3G elimination clearance; ETA-6 = $V2_{M3G}$, central volume of distribution of M3G. M3G = morphine-3-glucuronide.

**Supplementary figure 4.** Results of the normalized prediction distribution error (NDPE) analysis with the final PK model for morphine (top) and M3G (bottom) in frail elderly after cardiac surgery.




*The histogram shows the NDPE frequency distribution. The green bars indicate a normal distribution. The values for the mean and variance of the NPDE distribution are given below each histogram with * indicating a statistically significant difference of a mean of 0 and a variance of 1 at $p < 0.05$ level as determined by the Student's t-test and the Fisher test of variance. The distribution of NDPE versus time after first dose and NDPE vs. exponent of the concentration are also shown. Symbols represent NPDE values of each observation, the lines represent the 2.5$^{th}$, 50$^{th}$, and 97.5$^{th}$ percentile of the observations and the 95% prediction intervals of these percentiles in the simulated data are represented by the shaded areas.*