# Association between systemic exposure of ganciclovir and effect and side effects

*A population pharmacokinetic study*

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Master Thesis
Department of Pharmaceutical Biosciences
45 credits

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# Sammendrag

**Introduksjon:** Cytomegalovirus (CMV) infeksjoner er assosiert med sykelighet og dødelighet hos organtransplanterte pasienter. CMV sykdom behandles med ganciklovir, et nukleosid analog. Ganciklovir blir aktivert ved fosforylering inne i infiserte celler. Dermed kan monitorering av ganciklovir konsentrasjoner være et nyttig verktøy for å forutsi om behandlingen er en sukksess eller ikke. Assossiasjonen mellom ganciklovir AUC og effekt, og oppståtte bivirkningene er et interessant tema å undersøke for å individualisere behandlingsregimen mot CMV infeksjon.

**Metode:** Data fra et studie med 321 organtransplanterte pasienter fra hele verden ble brukt. Disse pasientene var påvist CMV sykdom klinisk og virologisk. Denne studien undersøkte effekten av peroral valganciklovir framfor intravenøs ganciklovir behandling av CMV sykdom. Data for pasienter med fire eller flere ganciklovir plasma konsentrasjonsmålinger ble valgt ut for denne studien. I Pmetrics® ble tids-konsentrasjons kurver estimert ved hjelp av trough plasma ganciklovir konsentrasjoner og en tidligere utviklet modell. Areal under kurven (AUC) ble regnet ut fra disse kurvene. Regresjonsanalyser (logistisk og linjær) ble utført for å finne sammenhengen mellom gancicklovir AUC og effekt og bivirkninger.

**Resultater:** Regresjonsanalysene viste ingen sammenheng mellom systemisk eksponering av ganciklovir og bivirkningshendelser (p-verdi < 0,05). P-verdiene for analysene gjort mellom systemisk eksponering av ganciklovir og effekt var både større enn 0,05 og mindre enn 0,05. Sammenligning av Akaike Information Criterion (AIC) (for logistisk regresjon) og R-squared (for linjær regresjon) indikerte at de statistiske modellene brukt passet mer med dataene som brukte gjennomsnitt AUC for 7 dager før bivirkningene oppstod enn gjennomsnitt AUC for 3 dager før.

**Konklusjon:** Fant ingen sammenheng mellom ganciklovir AUC og bivirkningene i denne studien. Andre risikofaktorene for bivirkningene burde undersøkes nærmere sammen med ganciklovir AUC for å finne andre sammenhenger mellom dem og bivirkninger.

# Acknowledgements

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Foremost, I would like to thank my supervisor, Professor Anders Åsberg. Thank you for your guidance and close supervision during my research. The door to Professor Åsberg's office was always open whenever I ran into a trouble spot or had a question about my research or writing. He consistently allowed this paper to be my own work but steered me in the right the direction whenever he thought I needed it. I have greatly valued your encouragement, advice, funny remarks and constructive comments.

Finally, I must express my very profound gratitude to my parents and to my husband for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Fatima Choudry

May 2017

# Abreviations

| | |
|---|---|
| CMV | Cytomegalovirus |
| QD | Once daily |
| BID | Twice daily |
| PCR | Polymerase chain reaction |
| ADME | Administration, distribution, meatabolism and elimination |
| IT2B | Iterative 2-stage Bayesian |
| NPAG | Non-parametric Adaptive Grid |
| AST | Aspartate aminotransferase |
| ALT | Alanine aminotransferanse |
| IV | Intravenous |
| PO | Peroral |
| AUC | Are under the concentration-time curve |
| AIC | Akaike information criterion |
| HGB | Hemoglobin |
| WBC | White blood cells |
| GFR | Glomerular filtration rate |
| CL | Clearance |
| $V_0$ | Initial volume of distribution |
| $V_P$ | Volume of distribution in the peripheral compartment |
| Q | Intercompartmental clearance |
| PK | Pharmacokinetic |
| Ka | Absorption rate constant |
| SD | Standard deviation |

# Table of Content

# 1 Introduction

## 1.1 Solid-organ transplant patients

### 1.1.1 The risk of infection

In the solid-organ transplant population, the principal causes of morbidity and mortality are infections and rejections. Patients with a solid-organ transplant are at a constant risk of rejecting the allograft. Therefore, they have to go on lifelong immunosuppressants. Along with many other, the downside to this treatment is the risk of infections (1). Cytomegalovirus (CMV) is the most common viral pathogen that causes morbidity and mortality in solid-organ transplant patients (2).

## 1.2 Cytomegalovirus

Opportunistic microbial pathogens that severely affect both allograft and patient survival, and viral pathogens, including CMV, have emerged as the most important microbial agents having deleterious effects on solid-organ transplant recipients (1). CMV is widespread throughout the world. CMV generally causes asymptomatic viral infections in healthy people. However, the immunocompromised get the severe side of the CMV-infections. Solid-organ transplant patients have to use lifelong immunosuppressants, which make them a great target for CMV to cause infections, including pneumonia, hepatitis, retinitis, esophagitis, colitis and congenital infections (3, 4).

Despite all the prophylactic antiviral regimens (See 1.1.3), CMV disease occurs in both patients who have received antiviral prophylaxis and patients who have not (4). Table 1 gives an overview of the frequency of the occurrence of CMV infections in solid-organ transplant patients (5-14).

**Table 1:** Symptomatic CMV infection in solid-organ transplant recipients.

| Organ transplanted | Frequency of CMV disease, first episode (%) | Frequency of CMV disease, including recurrences (%) |
|---|---|---|
| Kidney | 8 – 32 | 9 – 42 |
| Liver | 22 – 29 | 28 – 38 |
| Heart | 9 – 35 | 10 – 39 |
| Kidney-pancreas | 50 | 53 |
| Small bowel | 22 | 22 |
| Heart-lung | 39 – 41 | 43 – 46 |

### 1.2.1 Prevention of infection

The risk of CMV infection and disease after transplantation strongly depends on donor and recipient serostatus. Seronegative recipients from seropositive donors are considered to be the highest-risk group, whereas seropositive recipients of either seropositive or seronegative donor are at moderate risk (15). Antiviral prophylaxis refers to the administration of a regiment to prevent active viral replication. to an entire population (or to the high-risk portion of the population), beginning shortly before or after the transplantation procedure and continuing through the high-risk period; or to a susceptible individual, shortly after high-risk exposure to an active source of infection, to prevent or attenuate the clinical manifestations of the disease.

Generally, the antiviral therapy is applied to different situations (16-18):

1. **Prophylaxis:**

   Seropositive donor/seronegative recipient are well documented to be at high risk for CMV infection. In Norway, CMV prophylaxis is given to every CMV seronegative recipient, where the donor is CMV seropositive (high-risk), and/or if the rejections are steroid resistant (secondary prophylaxis). Valganciclovir, 900 mg QD (once daily) in 3 months, and weekly CMV PCR examination the first six months after the

transplantation. The prophylaxis can be considered for 6 months for severely immunocompromised patients (19).

Prophylaxis is advantageous in that it obviates the need for intensive monitoring for laboratory evidence of viral infection but it involves administration of an antiviral medication to individuals who may never actually be at risk for virus-related consequences (1).

2. **Preemptive therapy:**

   Preemptive therapy refers to the administration of a regimen only when the viral activation has been confirmed but before clinical symptoms or signs of disease have occurred, to prevent progression to disease.

   Preemptive therapy is only undertaken if CMV PCR is positive. The treatment phase includes valganciclovir 900 mg BID until two consecutive CMV PCR are negative, but not shorter than two weeks, followed by weekly CMV PCR monitoring for three months (and every two weeks till 6 months after the transplantation) (19).

### 1.2.2 Antiviral therapy

Antiviral drug therapy is administered once CMV disease is indicated (positive CMV PCR, and bone marrow depression, hepatitis, nephritis, colitis or other organ manifestation of CMV). The treatment phase includes valganciclovir 900 mg BID until two negative CMV PCR, but not shorter than two weeks. The maintenance period varies between one and three months, which includes 900 mg valganciclovir QD, followed by weekly CMV PCR for three months (and every two weeks until six months after the transplantation) (19).

### 1.2.3 Ganciclovir/valganciclovir

Ganciclovir is a nucleoside antiviral drug that inhibits the DNA elongation during DNA replication in herpes viruses (20). Intravenous ganciclovir therapy is indicated for preventative therapy in solid-organ transplant patients, but the impracticality of it and to improve the bioavailability of ganciclovir lead to the development of oral valganciclovir,

which is the valine ester of ganciclovir. The oral bioavailability of ganciclovir is 6 – 9%, whereas the oral bioavailability of valganciclovir is 60%, 10-fold higher. Valganciclovir hydrolyses to ganciclovir after absorption (21).

Mostly, if the patient cannot intake peroral medicine, then ganciclovir 5 mg/kg (prophylactic) and 10 mg/kg (therapeutic) is administered intravenously (19).

### 1.2.4 Side effects of ganciclovir

Ganciclovir is highly effective in preventing and treating CMV disease in solid-organ transplant patients. This has led to widely accepted prophylactic or preemptive use of ganciclovir in CMV seropositive recipients and also in seronegative recipients with seropositive donors, either at the time of engraftment or at first evidence of CMV infection (22). The concentration of ganciclovir equivalent to those achieved clinically (≈ 40 μmol/L) have been shown to inhibit the growth of human bone marrow colony- forming cells *in vitro* (23). The adverse effects induced by ganciclovir therapy are generally of a hematological nature and include thrombocytopenia (low platelet count) and granulocytopenia (decrease in the number of granulocytes). Anemia (decrease in the number of erythrocytes) may also develop with prolonged treatment. The known risk factors for hematological toxicity include low marrow cellularity, hyperbilirubinemia (≥ 6 mg/dL) and elevated serum creatinine (≥ 2 mg/dL) (24).

## 1.3 Population modelling

### 1.3.1 Pharmacokinetics

The fundamentals of pharmacokinetics are crucial in understanding the biological fate of the drug, which are important cornerstones for good drug prescription and development (25). Pharmacokinetics is concerned with the time-course of drug movement through the body. This involves the absorption, distribution, metabolism and elimination (ADME) of drugs and their metabolites (26).

### 1.3.2 Population pharmacokinetics

Population pharmacokinetics is an area of clinical pharmacology that aims at quantitative assessment of typical pharmacokinetic parameters, and the real-life variabilities in drug absorption, distribution, metabolism, and elimination within and between patients (27, 28). The aim is to identify and quantify sources of variability in drug concentration in the patient population. Associations between patient characteristics and differences in pharmacokinetics can then be used to customize individual drug therapy (25).

Traditional pharmacokinetic studies involve healthy volunteers taking the same dose of the drug at fixed times and multiple samples taken at fixed intervals. On the contrary, population pharmacokinetic data are obtained from a population being treated with a drug. These patients are often taking different doses and have blood samples at different times (28). Clinically, population pharmacokinetics approach has the potential to help the selection of the optimum dose for an individual patient (25).

### 1.3.3 Population phamacokinetic models

A primary goal of most population pharmacokinetic modeling evaluations is finding population pharmacokinetic parameters and sources of variability in a population. Other goals include relating observed concentrations to administered doses through identification of predictive covariates in a target population. Population pharmacokinetics does not require “rich” data i.e. many observations and/or subjects, as required for analysis of a single-subject data, nor is there a need for structured sampling time schedules. “Sparse” data i.e. few observations and/or subjects, or a combination, can be used (29).

Population pharmacokinetic modeling involves estimating an unknown population distribution of a drug(s) based on data from a collection of nonlinear models. Statistically, population pharmacokinetic modeling approaches can be classified as either parametric or non-parametric (30).

**Parametric pharmacokinetic modeling**

In parametric population modeling methods, the pharmacokinetic parameters are single point parameter estimates such as measures of central tendency – means, medians, or modes, and measures of dispersion – standard deviations or covariances. A common problem has been to find the best single point estimator of a parameter distribution. The main strength of parametric population modeling methods is that they can separate variability between the various subjects from variability within individual subjects. On the other hand, a significant weakness of most parametric population modeling methods is that they do not have the desirable property of statistical consistency (31).

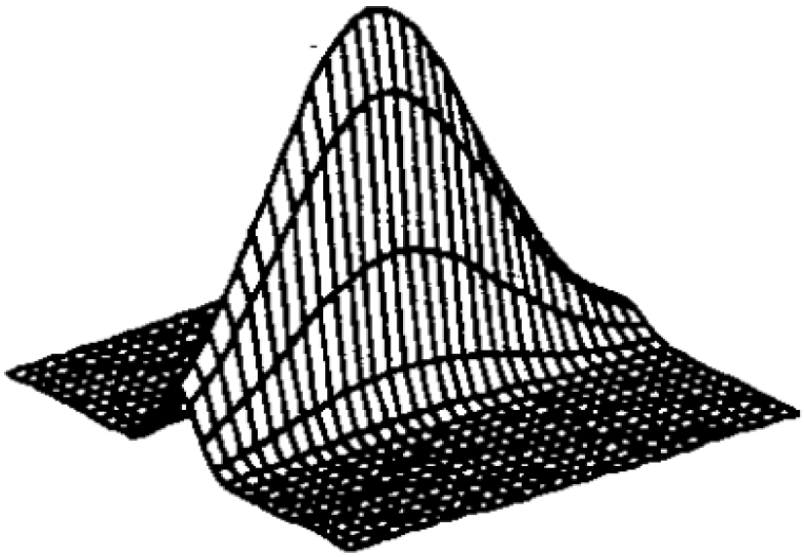

**Figure 1:** Joint density estimated by a parametric method. The axis from the bottom corner toward the left corner is that of V, and the axis toward the right corner is that of K.

**Non-parametric pharmacokinetic modeling**

The most likely parameter distributions in non-parametric population methods are actually found in a discrete, non-continuous, collection of sets of individual parameter values, each of which has a single value for each parameter, along with an estimate of the probability of that particular set of values. There is usually up to one set of parameter values for each subject studied in the population. This approach makes no parametric assumptions (such as normality

or a mixture) about the actual shape of the population parameter distribution. The shape of the population parameter distribution is solely determined by the population raw data itself (32).

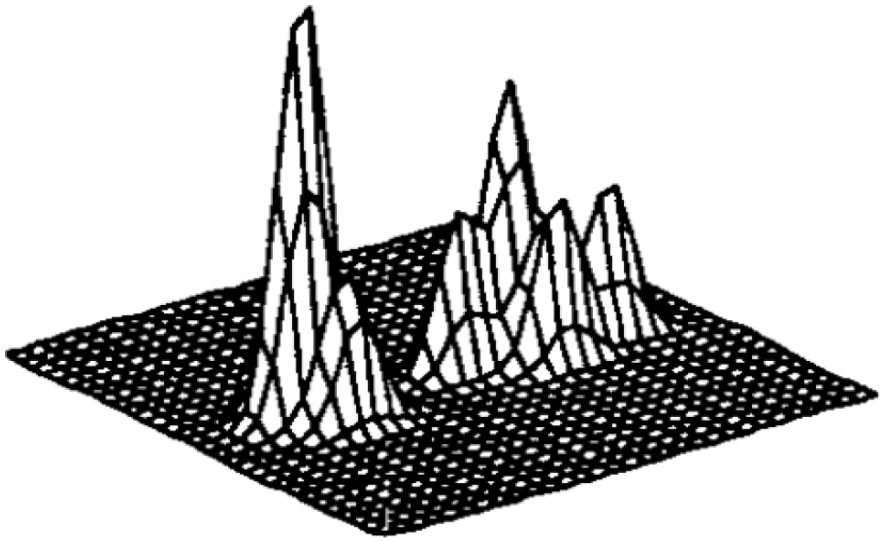

**Figure 2:** Estimated non-parametric joint density obtained with non-parametric expectation-maximization. The axis from the bottom corner toward the left corner is that of V, and the axis toward the right corner is that of K.

### 1.3.4 Pmetrics®

Pharmacometrics, which is incorporated pharmacokinetic and pharmacodynamic modeling and simulation, has revolutionized the drug development process and has the potential to revolutionize individual patient care through a clinical application (33-35).

Pmetrics® is an R package for nonparametric and parametric population modeling and simulation of pharmacokinetic and pharmacodynamic systems to improve therapeutic drug dosing in populations and individuals. Three components are required to be installed when using Pmetrics package: the R/R studio program, Pmetrics package for R/R studio and gfortran (a Fortran compiler). Pmetrics mainly controls three software programs: IT2B (Iterative 2-stage Bayesian), NPAG (Non-Parametric Adaptive Grid) and a semi Monte Carlo simulation software programs (36). The software used in this study is NPAG.

**NPAG: Non-Parametric Adaptive Grid**

NPAG software creates a non-parametric population mixed-effect model consisting of discrete support points, each point having a set of estimates for all the parameters in the

model plus an associated probability of that set of estimates. There can be at most one point for each subject in the study population (36).

Random effects are the values of the model parameters (e.g. clearance) in the population. The error model is the fixed effect, consisting of a polynomial that describes assay variance, along with gamma (multiplier of the assay variance), or lambda (addend to assay variance). These are each estimated as a single value in the population (36).

## 1.4 Aim of the study

The aim of this study is to investigate the association between systemic ganciclovir exposure and the occurrence of adverse effects and its efficacy for the treatment of CMV disease in solid-organ transplant patients.

# 2 Material and method

## 2.1 The patients

The data used was from a study with 321 solid-organ transplant patients from all over the world. These patients had virological and clinical evidence of CMV disease at any time following transplantation, regardless of CMV status (D±/R±) or previous anti-CMV therapy or preventative approaches. Half of these patients were administered intravenous ganciclovir (5mg/kg BID) and the other half oral valganciclovir (900 mg BID) for the first 21 days. Then they were all switched over to the maintenance dose of 900 mg oral valganciclovir QD till day 49.

The patients that were chosen to be included in the study had to have at least four observations (i.e. ganciclovir concentrations) and not be resistant to ganciclovir treatment. Of the 321 patients, 164 made it to the final run of estimating the concentration-time curves for every individual.

## 2.2 Blood samples

Blood samples were drawn on Day 0, 3, 7, 10, 14, 17, 21, 28, 35, 42 and 49 (±1/±2 days).

The collected samples were for:

- CMV viral load and resistance and other viruses
- Safety hematology tests including hemoglobin, hematocrit, white blood cell count including differential count, absolute neutrophil count and platelet count
- Safety serum chemistry consisting of creatinine, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and amylase.
- Some of these were used to measure ganciclovir concentrations

## 2.3 Laboratory assessments

### 2.3.1 CMV virology

Clinical decisions were based on local monitoring of CMV viremia by shell vial culture, antigenemia assay, or accredited DNA/RNA-based assay using the standard method applied at every center.

### 2.3.2 CMV resistance to ganciclovir

The Day 0 sample (pretreatment), Day 21 sample (end of treatment), Day 49 (end of maintenance) and where applicable, the ”treatment failure” sample (collected at the time of treatment failure) were routinely assessed for genotypic changes associated with ganciclovir resistance (for example, mutation at the UL97 locus and the UL54 locus mutation in those showing UL97 mutation).

### 2.3.3 Laboratory safety assessments

The administration of ganciclovir and valganciclovir has certain adverse side effects. Blood samples were drawn not only to measure viral load and ganciclovir concentration but also monitor the side effects and then adjust the patients’ dose according to table 2. The side effects were graded according to their severity, and this grading was further used in the study.

Many other tests were performed and many other items were screened in the study, but the ones mentioned below are those that were used in this study.

**Hematology tests**

These tests included hemoglobin, hematocrit, white blood cell count (absolute neutrophil count) and platelets.

**Table 2:** Grading of severity of adverse events (VICTOR study consolidation 2004).

| **Hematology** | **Grade 1 toxicity** | **Grade 2 toxicity** | **Grade 3 toxicity** | **Grade 4 toxicity** |
|---|---|---|---|---|
| Hemoglobin | 9,5 – 10,5 g/dL | 8,0 – 9,4 g/dL | 6,5 – 7,9 g/dL | < 6,5 g/dL |
| Absolute neutrophil count | 1000 – 1500/$mm^3$ | 750 - 999/$mm^3$ | 500 - 749/$mm^3$ | < 500/$mm^3$ |
| Platelets | 75000 - 99000/$mm^3$ | 50000 - 74999/$mm^3$ | 20000 - 49999/$mm^3$ | < 20000/$mm^3$ |

The grades of severity of the side effects were later used to analyze if the systemic exposure of the drug (AUC) had any association with the occurrence of the side effects.

**Serum chemistry tests**

These tests included creatinine, albumin, total bilirubin, AST, ALT, and amylase. These results were mostly used to adjust the dose accordingly.

Estimated creatinine clearance using the Cockcroft-Gault formula was calculated. Based on the estimated creatinine clearance, the doses of ganciclovir/valganciclovir were adjusted in accordance.

## 2.4 Ganciclovir population model

The pharmacokinetic analysis performed in this study used Pmetrics version 1.5.0. This package was used in R Studio. The software requires two forms of data for the analysis, an input file and a model file.

### 2.4.1 The input file

The input file is an excel format spreadsheet with the data required to describe the population in question. The order, names, and capitalization of the header of the first twelve columns are fixed. The first twelve columns have to be ”Id, evid, time, dur, addl, ii, input, out, outeq, c0, c1, c2 and c3”.

**Table 3:** Description of the row headers in the input file.

| Column | Description |
|---|---|
| ID | An alphanumeric character which identifies every individual. |
| EVID | The event ID field. 0 = observation, 1 = input (e.g. dose) and 4 = reset. |
| TIME | Elapsed time in decimal hours since the first event. |
| DUR | Duration of an infusion in hours. There must be an entry if EVID = 1. 0 if the dose is oral. |
| DOSE | The dose amount. There must be an entry if EVID = 1. |
| ADDL | Specifies the nomber of additional doses to give at interval II. |
| II | Interdose interval and is only relevant if ADDL is not equal to 0. |
| INPUT | Defines which input (i.e. drug) the DOSE corresponds to. |
| OUT | The output value, or the observation (i.e. the drug concentration). |
| C0, C1, C2, C3 | The coefficients for the assay error polynomial for that observation. |

The next columns are the patients’ demographics and covariates defined further in the model file. As the study was randomized, every patient got a patient code, which was their ID in this file. EVID was 0 when only blood was sampled for all the tests (including OUT), whereas it was 1 the rest of the times when the patients were administered a DOSE. The TIME always started with 0. Wherever EVID was 1, the DOSE was given in mg, and if the dose was given

intravenous then the duration of the infusion was given under DUR. When the value of EVID was 0, the OUTEQ was always 1 to indicate which drug was observed (ganciclovir; the only drug in the study), indicating that the row represents an observation and not a dose input. The observed drug (ganciclovir) plasma concentrations were recorded under OUT.

There is a certain way of recording all the data in the input file. For instance, TIME has to be in decimal hours beginning with 0 at the first event. every row must have an entry, and within a given ID, rows must be sorted chronologically in ascending order. The doses in the input file are recorded in milligrams. The ganciclovir concentrations are recorded under OUT in mg/L every time EVID is equal to 0. The gender of every patient was recorded as numeric values under SEX as ”1” for females and ”2” for males so that the R software can recognize it. The values of weight (WT) and height (HGT) were documented in kilograms and centimeters, respectively.

There is no limit to how many covariates we can include in the input file. All the covariates are defined in the model file.

An excerpt of the input file is attached in the Appendix (7.2).

### 2.4.2 Compartment model

In this study, the drug was administered intravenously (ganciclovir) and orally (valganciclovir). Therefore, the compartment model used for this study was the three-compartment model. All the parameters associated with this model were defined in the model file as the primary covariates.

Figure 1 shows a generalized schematic drawing of a three-compartment model, where Ka is the absorption rate constant from compartment 1 to compartment 2, CL is the clearance from the central compartment, Q is the intercompartmental clearance between compartment 2 and 3, and Vc and Vp are the volume of central and peripheral compartments, respectively.

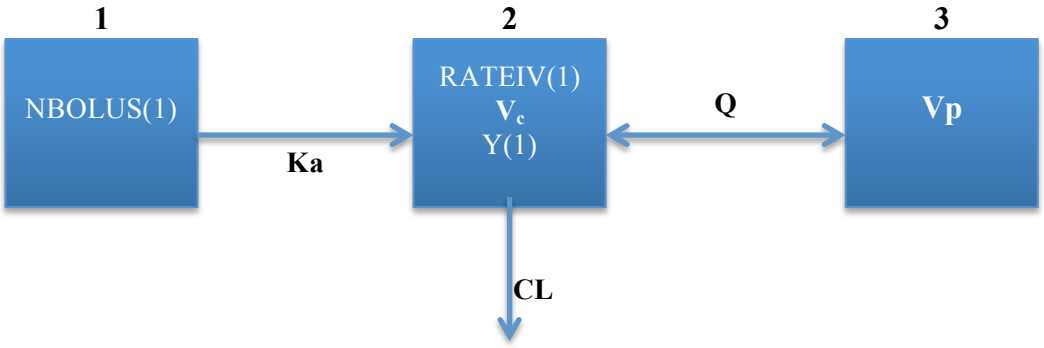


**Figure 3:** The generalized three-compartment model.

### 2.4.3 The model file

The model files are at the heart of all Pmetrics functions. The model file is a text file with eleven blocks, each marked with ”#” followed by a header tag. The model file is the data input file, which contains primary variables (with boundaries defined) and describes every covariate found in the input file. The blocks used in this study were #PRImary variables, #COVariates, #SECondary variables, #INItial conditions, #F (bioavailability), #LAG time, #OUTputs and #ERRor. The primary variables are the parameters that are estimated by Pmetrics. The secondary variables are defined by the equations, given in the model file, that are a combination of the primary variables and covariates.

An already developed population pharmacokinetic model was used in this study (37). This model was used to estimate concentration-time graphs for all the patients included based on the information about dose, covariates, and measured ganciclovir trough plasma concentrations.

The model is technically a three-compartment model but it has an absorption compartment for the doses administered orally and intravenously. Therefore, the compartment model used in this study is practically a two-compartment model with oral absorption.

The model file (37) is attached in the Appendix (7.3).

**Primary variables**

Primary variables are the model parameters that are to be estimated by Pmetrics or are designated as fixed parameters with user specified values. In the model file, the range for the parameter that defines the search space follows the variable name. The format of the limits is *min, max*. A single value will fix that parameter to the specified value.

Table 4 sums up all the primary variables used in the model file used in this study.

**Table 4:** Primary variables defined in the model file.

| Parameter | Definition | Range |
|---|---|---|
| Ka | Absorption rate constant of the oral dose. | 0,1 – 6 |
| $V_0$ | Initial volume of distribution in the central compartment (compartment 1). | 0,1 – 70 |
| $V_p$ | Volume of distribution in the peripheral compartment (compartment 2). | 0 – 350 |
| $Q_o$ | Initial intercompartmental clearance between the central compartment (1) and the peripheral compartment (2). | 0 – 150 |
| $CL_m$ | Clearance for men. | 0,1 – 30 |
| $CL_f$ | Clearance for women. | 0,1 – 30 |
| Tlag | Time delay after an absorbed dose before observed concentration. | 0,01 – 3,2 |
| A2 | Amount of drug in the central compartment (1). | 0 – 10000 |
| GFRcl | A parameter that adjusts glomerular filtration rate (GFR) for it's influence on the clearance. | -5 – 8 |

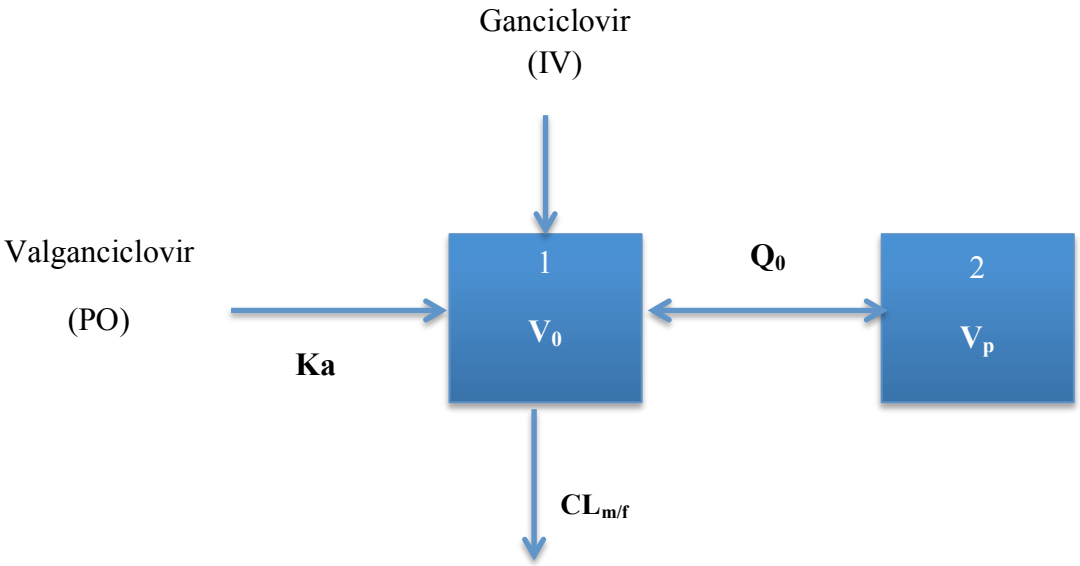


**Figure 4:** The two-compartment model with oral absorption.

### Covariates

Covariates are subject-specific data, such as body weight, height etc., contained in the input file in separate columns after the primary variables. Covariates are applied at each dosing event. The first dose event for each subject must have a value for every covariate in the input file. The covariates can be used in secondary variable equations in the model file (36).

### Secondary variables

Secondary variables are those that are defined by equations that are combinations of primary, covariates, and other secondary variables. If using other secondary variables, they should be defined first.

### Initial conditions

By default, all model compartments have zero amounts of the drug at time 0. This can be changed if necessary. In the model file, only the amount of drug in both compartments was defined at time 0.

### 2.4.4 Population pharmacokinetic estimation

The data was run through the NPAG software to build response files (e.g. concentration-time curves) for the given population model (37), and data input. It is possible from a non-parametric joint density model, i.e. NPAG output, which every point serving as the mean of a multivariate normal distribution, weighted according to the weight of the point. The covariance matrix of the entire set of support points is divided equally among the points.

The function used in the Pmetrics® software was `NPrun()` with `prior = 1`. The NPAG run was run to convergence. This was done through many trial and errors before the perfect parameters for the run were discovered. The final run had 105 independent points (index of starting grid points), the AUC estimation interval was set at 144 hours, the maximum number of NPAG cycles to run was set at 9996, and by using prior = 1, the model was used to estimate individual AUC based on every patient's ganciclovir dose and observation of trough concentrations of ganciclovir. The patients with less than four ganciclovir concentration observations were excluded. The function used was:

```
Nprun("vict19.csv", indpts = 105, aucint = 144, cycles = 9996,
prior = 1, exclude =c(61, 133, 135, 158, 160, 218, 220, 230,
252, 255, 259, 260, 286, 288, 314, 322, 325, 339, 341, 346,
349, 350, 352, 353, 355, 362, 363))
```

### 2.4.5 Area Under the Curve (AUC)

There are several Pmetrics® data objects contained within the Rdata files which are loaded with `PMload()`, making these objects available for plotting and other analysis. Data frames of the class PMpop and PMpost were created by using the function `makePOP()`.

As a parameter of systemic exposure of ganciclovir, AUC was estimated for every individual included in this study. The day-to-day AUC was calculated with the function `makeAUC()`. The hours had to be defined for every day, starting from 0 and increasing by 24 for every day.

The observations incorporated into the dose-time graphs for the 49 days of the study were created using the function:

```
plot(mdata.2, pred = post.2, overlay = F, join = F, pch = 3,
layout = c(3,3), xlim = c(0,1176))
```

The AUC was calculated with 24-hour intervals for every individual throughout the 49 days of treatment and maintenance. There were many individuals that did not have sufficient AUC estimates throughout these 49 days. Those patients were excluded at this point, as their data was insufficient for the analysis. And all patients with average AUC under 10 were also eliminated from this investigation.

The mean $AUC_{3/7\ days}$ before the occurrence of the side effects of interest, were recorded separately and their average was calculated and used in various investigations (analysis 2 and 3).

## 2.5 Regression analyses

The association between systemic exposure of ganciclovir and its efficacy and side effects was investigated with the help of different regression models. The parameters of side effects were the occurrence of the adverse effects, while the parameter for the efficacy was viral eradication.

The data was analyzed using both logistic regression and linear regression. P-value < 0,05 was considered statistically significant (confidence interval 95%).

The significance (p-value) of the independent variable's (ganciclovir AUC) association with the occurrence of the dependent variable (effect and side effects) were recorded. To compare how the data provided fit the regression models, the Akaike interpretation criterion, AIC (for logistic regressions) and R-squared (for linear regressions) were also recorded and compared.

## 2.6 The dependent variables – Effect and side effects

The side effects taken into consideration for this study were hemoglobin (HGB), absolute neutrophil count (WBC) and platelet count (plates). WBC and plates were graded only toxic (Grade 1 or above) or non-toxic (Below Grade 1) or 1 and 0, respectively. Whereas HGB was graded according to table 2, Grade 0 to Grade 4.

To measure the effect, viral eradication was analyzed against ganciclovir AUC. 0 being more than 600 copies/mL plasma (not eradicated) and 1 being viral load less than 600 copies/mL plasma (eradicated).

## 2.7 Analysis 1: Logistic regression – AUC vs. Effect/side effect

There were created two separate data frames for the AUC of Day 0 to Day 20 (treatment period) and Day 0 to Day 48 (treatment and maintenance period). The average AUC was calculated for every patient for both intervals, Day 0 to Day 20 (treatment) and Day 0 to Day 48 (treatment and maintenance), and were recorded in their respective data frames.

The occurrence and severity (in the case of hemoglobin) on the last day of each period (Day 21 and Day 49) was recorded. And the average AUC of both time frames was calculated and recorded. The association between the average $AUC_{3/7\ days}$ and the occurrence of adverse effects on the last days was estimated using a logistic regression model.

Of the 164 individuals, 155 (Day 0 to Day 20) and 68 (Day 0 to Day 48) had AUC readings for all the days in their respective periods. Therefore, only those were investigated.

One round of binary logistic regression was run in R against every side effect separately by using the function:

```
glm.model <- glm(dependent variable ~ mean AUC)

summary(glm.model)
```

Where the dependent variables are the effect and side effects and the independent variable is the mean AUC. The setup of this analysis is summed up in table 5.

**Table 5:** Logistic regression – mean AUC (Day 0 – 20/Day 0 - 48) vs. Effect (VL)/side effect (HGB, WBC, Plates) on Day 21.

| **Side effects** | **Hemoglobin (HGB) 0/1/2/3** | | **Absolute neutrophil count (WBC) 0/1** | | **Platelets count (Plates) 0/1** | | **Viral load (VL) 0/1** | |
|---|---|---|---|---|---|---|---|---|
| **Day** | **21** | **49** | **21** | **49** | **21** | **49** | **21** | **49** |
| **AUC Day 0 to 20** | | | | | | | | |
| **AUC Day 0 to 48** | | | | | | | | |

## 2.8 Analysis 2: Logistic regression – AUC vs. Effect/side effect

Analysis 2 was to investigate the relationship between the mean $AUC_{3\ days}$ and $AUC_{7\ days}$ before the occurrence of the effect and adverse effects and the occurrence or absence of these variables in the individuals that had AUC readings from Day 0 to Day 48 (68 individuals).

Unlike analysis 1 where the effect and adverse effects were only observed on the last day of both periods, the adverse effects were observed throughout the treatment/maintenance span and were recorded on the day they appeared in analysis 2. The patients that did not encounter any adverse effects during the treatment or maintenance periods, their adverse effect status was set to what they had on Day 49.

Functions used in R:

```
glm.model <- glm(dependent variable ~ mean AUC)

summary(glm.model)
```

The outline of the analysis is shown in table 6.

**Table 6:** Logistic regression – mean AUC (3 and 7 days before the occurence) vs. Effect (VL)/side effect (HGB, HGB, Plates) on the day of occurence.

| **Effect/Side effects** | **Hemoglobin (HGB) 0/1/2/3** | **Absolute neutrophil count (WBC) 0/1** | **Platelets count (Plates) 0/1** | **Viral load (VL) 0/1** |
|---|---|---|---|---|
| **AUC 3 days before** | | | | |
| **AUC 7 days before** | | | | |

## 2.9 Log-transforming the data

The average $AUC_{3\ days}$ and $AUC_{7\ days}$ were calculated before the side effects occurred. The adverse effects, for the patients that did not show any sign of adverse effects during the 49 days, were set to the status they had on Day 49.

The number of subjects investigated was 68 that had AUC readings from Day 0 to Day 48.

The mean $AUC_{3\ days}$ and $AUC_{7\ days}$ before the occurrence of the adverse effects were log-transformed in an attempt to make the data less skewed (if skewed) and to find any underlying relationships that could not be gathered from the other analyses.

The log-transformed data was more normally distributed; therefore it was used in the linear regression investigation instead of the regular data.

## 2.10 Analysis 3: Linear regression – logAUC vs. Side effect

The connection between the log-transformed average AUC and the occurrence of side effects (continuous variables) were investigated through linear regression.

Log-transformed mean AUC's$_{3/7\ days}$ relationship with the incidence of the adverse effects was investigated in a linear regression model.

Functions used in R:

```
lm.model <- lm(dependent variable ~ log(mean AUC))

summary(lm.model)
```

**Table 7:** Logistic regression – log(mean AUC) (3 and 7 days before the occurence of the side effects) vs. Side effects (HGB, WBC, Plates) on the day of occurence.

| Side effects | Hemoglobin (HGB) | Absolute neutrophil count (WBC) | Platelets count (Plates) |
|---|---|---|---|
| **logAUC 3 days before** | | | |
| **logAUC 7 days before** | | | |

## 2.11 Statistical regression analyses

In the regression analyses performed, the confidence interval was set at 95%. The p-values were recorded for all the analyses. The AIC-values and multiple R-squared values of the logistic regression and the linear regression, respectively, were compared. AIC is a measure of how fit the logistic model is for the data provided and the lower the value, the better the fit. Multiple R-squared is a statistical measure of how close the data are to the fitted regression line and the higher they are, the better the data fit the regression model.

## 2.12 Plots

Scatterplots were drawn for analysis 3. This was to see the trend in the data graphically if any.

## 2.13 Histograms

Histograms of the continuous variables and the log-transformed variables were plotted, and both were observed how they are distributed.

Both were compared and the data that was more normally distributed was used in analysis 3.

The histograms are attached in the Appendix (7.6).

# 3 Results

## 3.1 Included individuals

The data used in this study was from the VICTOR-study. 164 patients, of 321, were included in this study. The inclusion of these 164 patients was based on they having four or more ganciclovir plasma concentration observations and not being resistant to ganciclovir therapy.

The demographic data of all the individuals is listed in the Appendix (7.1).

## 3.2 Estimated plasma concentration-time curves

The run converged after 9645 cycles. It took 16,27 hours. Figure 5 displays the observation-prediction plot for the data run. The plot describes the correlation between the observed and the predicted values, for both population and individual prediction.

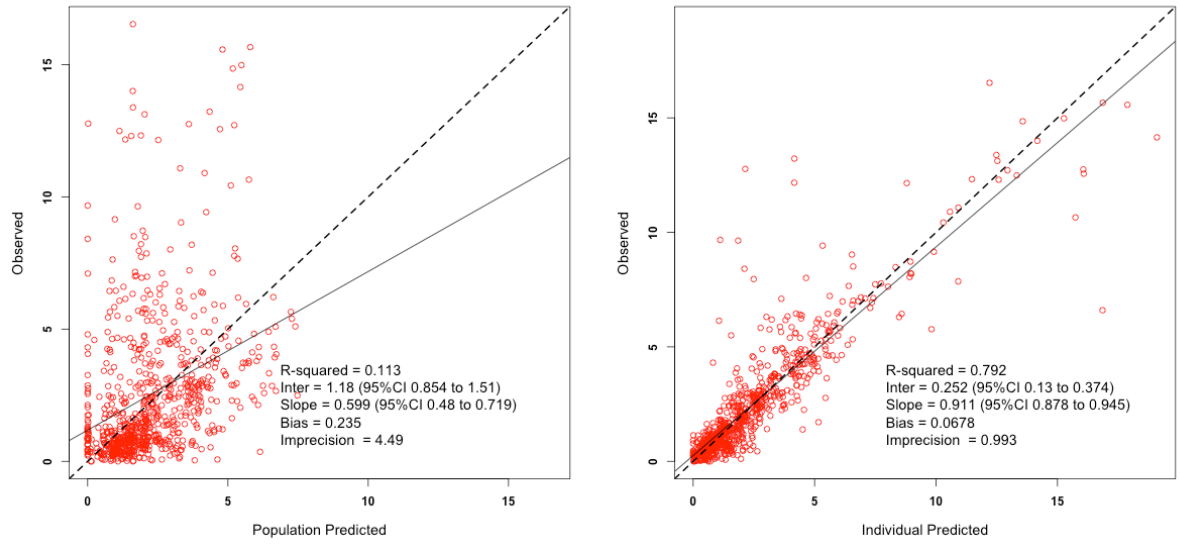


**Figure 5:** Observation-prediction plot. The figure displays the observation-prediction plot for the two-compartment model. The plot describes the correlation between the observed and the predicted values, for both population and individual prediction.

The model (37) was used to estimate individual concentration-time graphs. The average $AUC_{Day\ 0-20}$ was calculated to be 64,97 ± 31,15 mg.h/L (n = 155) and the average $AUC_{Day\ 0-48}$ was 61,04 ± 20,10 mg.h/L (n = 68) for the population estimated. Figure 5 shows a few of the plots. All the plots are attached in the Appendix (7.4).

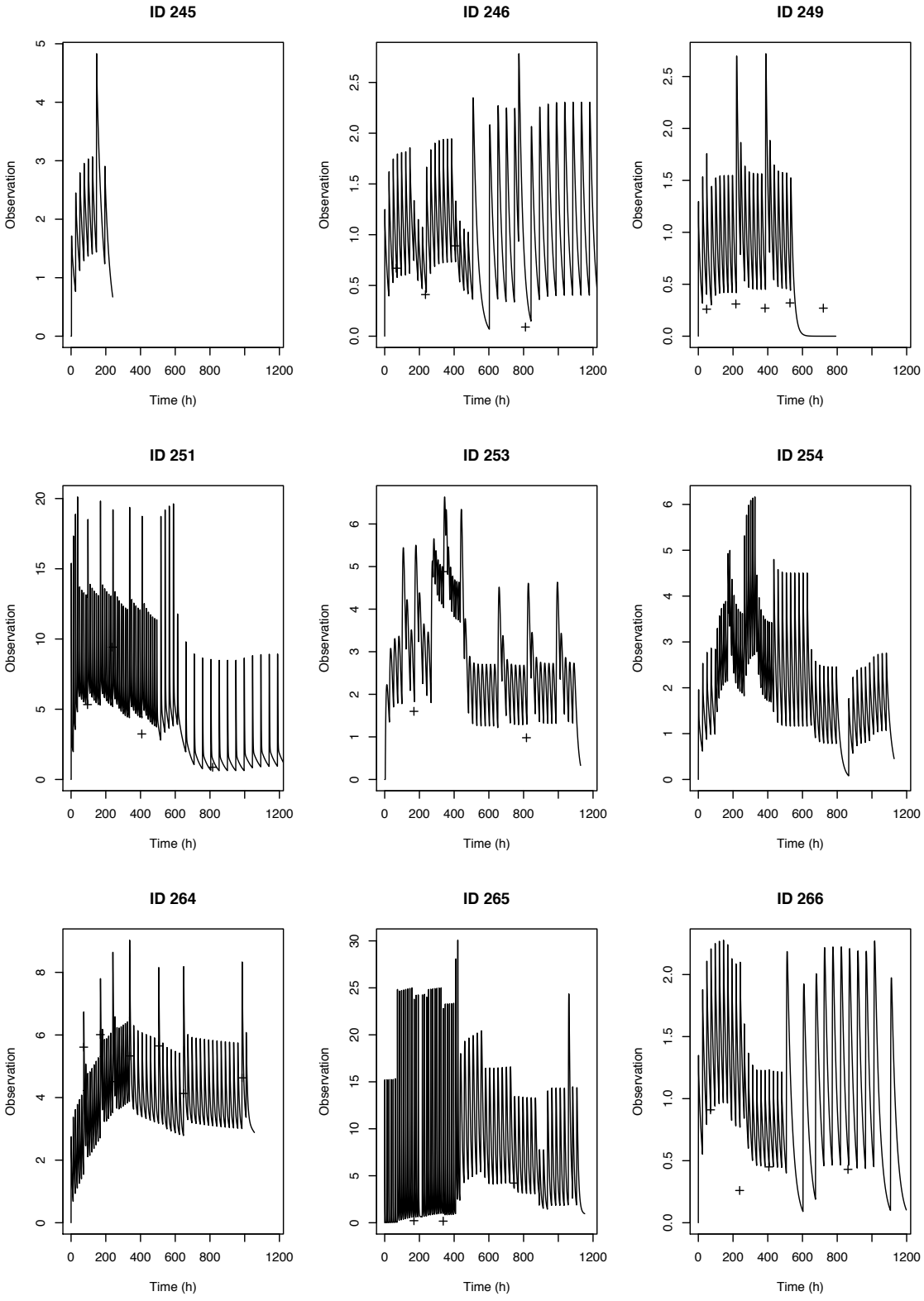


**Figure 6:** Concentration-time graphs of a few individuals from the study. The plots show the concentration of ganciclovir against time. The area under the curve (AUC) is the parameter for systemic exposure of ganciclovir in the patients.

## 3.3 Analysis 1: Logistic regression – AUC vs. effect/side effect

The logistic regression showed that the mean $AUC_{Day\ 0-20}$ and mean $AUC_{Day\ 0-48}$ were insignificant for the adverse effects.

For the efficacy, the mean $AUC_{Day\ 0-20}$ had an insignificant role in viral load eradication. But on the other hand, mean $AUC_{Day\ 0-48}$ was a significant factor for viral load eradication.

The p-values and Akaike Information Criterion (AIC) for every analysis are given in the table below.

**Table 8:** Results of analysis 1 – values from the logistic regression showing mean AUC ± its's standard deviation, p-values and AIC for each set of parameters.

| Effect/side effect | Time period | Mean AUC ± Std. Dev. (mg . h/L) | P-value | AIC |
|---|---|---|---|---|
| **Hemoglobin (HGB)** | **Day 0 – 20** | 64,97 ± 31,15 | 1,00 | 389,00 |
| | **Day 0 – 48** | 61,04 ± 21,10 | 0,10 | 140,04 |
| **White blood cell count (WBC)** | **Day 0 – 20** | 64,97 ± 31,15 | 0,61 | 133,90 |
| | **Day 0 – 48** | 61,04 ± 21,10 | 0,44 | 60,15 |
| **Platelet count (Plates)** | **Day 0 – 20** | 64,97 ± 31,15 | 0,44 | 60,15 |
| | **Day 0 – 48** | 61,04 ± 21,10 | 0,35 | 38,77 |
| **Viral load eraditcation** | **Day 0 – 20** | 64,97 ± 31,15 | 0,26 | 217,42 |
| | **Day 0 – 48** | 61,04 ± 21,10 | 0,04 | 44,19 |

## 3.4 Time of occurrence of the adverse effects

The frequency and the mean time of the occurrences of the adverse effects in the 68 patients investigated are recorded in the table below.

**Table 9:** Time of occurrence of adverse effects.

| Adverse effect | Frequency | Mean time of occurence ± SD (days) |
|---|---|---|
| **Anemia** | 34 | 10,53 ± 4,88 |
| **Leukocytopenia** | 29 | 18,83 ± 12,60 |
| **Thrombocytopenia** | 3 | 23,00 ± 14,42 |

## 3.5 Analysis 2: Logistic regression – AUC vs. effect/side effect

In the 68 patients investigated, 84 cases of successful viral load eradication in the 49 days of treatment and maintenance therapy were also recorded in addition to the adverse effects summed up in table 9.

Table 10 shows the recorded p-values and AIC for the analysis undertaken.

**Table 10:** Results of analysis 2 – values from the logistic regression showing mean AUC ± it's standard deviation, p-values and AIC for each set of parameters.

| Effect/side effect | Systemic ganciclovir exposure | Mean AUC ± Std. Dev. (mg.h/L) | P-value | AIC |
|---|---|---|---|---|
| **Hemoglobin (HGB)** | **3 days before** | 54,16 ± 29,73 | 0,22 | 195,50 |
| | **7 days before** | 54,84 ± 28,26 | 0,30 | 191,88 |
| **White blood cell count (WBC)** | **3 days before** | 50,05 ± 19,90 | 0,51 | 71,64 |
| | **7 days before** | 50,89 ± 17,17 | 0,44 | 71,45 |
| **Platelet count (Plates)** | **3 days before** | 46,07 ± 15,90 | 0,67 | 50,14 |
| | **7 days before** | 48,12 ± 14,77 | 0,45 | 34,17 |
| **Viral load eradication (VL)** | **3 days before** | 60,96 ± 34,52 | 0,28 | 230,08 |
| | **7 days before** | 63,51 ± 34,09 | 0,28 | 242,79 |

## 3.6 Analysis 3: Linear regression – logAUC vs. Side effects

The mean $AUC_{3/7\ days}$ were log-transformed and investigated against the occurrences of side effects through linear regression.

**Table 11:** Results of analysis 3 – values from the logistic regression showing mean AUC ± it's standard deviation, p-values and AIC for each set of parameters.

| Effect/side effect | Time before | Log mean AUC ± Std. Dev | P-value | Multiple R-squared |
|---|---|---|---|---|
| **Hemoglobin (HGB)** | **3 days before** | 4,06 ± 0,49 | 0,86 | 0,00018 |
| | **7 days before** | 4,10 ± 0,47 | 0,56 | 0,0019 |
| **White blood cell count (WBC)** | **3 days before** | 4,04 ± 0,46 | 0,84 | 0,00022 |
| | **7 days before** | 4,08 ± 0,44 | 0,86 | 0,00018 |
| **Platelet count (Plates)** | **3 days before** | 4,04 ± 0,48 | 0,45 | 0,0037 |
| | **7 days before** | 4,09 ± 0,46 | 0,34 | 0,0058 |

## 3.7 Plots

The scatterplots to show the trends between the systemic exposure to ganciclovir and the adverse effects can be found in the Appendix (7.5).

## 3.8 Histograms

All the histograms are attached in the Appendix (7.6).

# 4 Discussion

## 4.1 The patients

The 321-patient study, from which the data for this present study was used, was on the efficacy of the use of oral valganciclovir versus intravenous ganciclovir. This study provided with the most extensive demographics of the patients involved as it was a worldwide study, along with many observations and blood analyses including ganciclovir plasma concentrations, hematological tests, and viral load.

Of these 331 patients, 164 patients were included in this study. All the patients included had four or more observations (ganciclovir plasma concentrations) and were not resistant to ganciclovir treatment.

The concentration-time curves were estimated for every patient with the help of their trough ganciclovir plasma concentrations and the model (37).

## 4.2 The results

The results from all the analyses, that investigate the relationship between systemic exposure of ganciclovir and adverse effects, show p-values higher than 0,05. This indicates weak evidence that the systemic exposure of ganciclovir has significance in the event of an adverse effect.

In a study investigating the efficacy and safety of low-dose valganciclovir for prevention of CMV disease, they found that 450 mg valganciclovir daily is associated with a high degree of hematological toxicity (29,3%). Leukopenia and thrombocytopenia were the most commonly observed adverse effects of low-dose valganciclovir (450 mg/day). This high rate may reflect upon pharmacodynamic drug-drug interactions between valganciclovir and concomitantly administered immunosuppressive agents (e.g. mycophenolate mofetil, tacrolimus) (38).

Whereas in this study, 900 mg valganciclovir (PO) or 5 mg/kg ganciclovir (IV) twice daily (Day 0 – 20), followed by 900 mg valganciclovir (PO) once daily (Day 21 – 48) was administered to the patients. And hematological toxicity found in this population lies at 32,35%.

In a study to investigate the efficacy and toxicity of ganciclovir prophylaxis to prevent CMV disease after allogenic marrow transplant, neutropenia was the only hematopoietic toxicity observed secondary to ganciclovir (30%) (39). In two other random controlled trials, the frequency of neutropenia was not affected by ganciclovir dose (40, 41).

In this study, all of the above mentioned adverse effects were observed. The dose administered in this study was double than what have been investigated before (38). The occurrence of hematological toxicity between 450 mg valganciclovir (29,3%) and 900 mg valganciclovir (32,3%) is not very different. This is showing that the grade of systemic exposure of ganciclovir is not playing any role in the occurrence of the hematological adverse effects.

The results from the logistic regression analysis shows a significant relationship between the systemic exposure of ganciclovir ($AUC_{Day\ 0-48}$) and its efficacy on Day 49 (p-value < 0,05), while the results showno significance (p-value > 0,05) between systemic exposure of ganciclovir ($AUC_{Day\ 0-20}$) and its efficacy on Day 21. The results from the linear regression analysis that investigate the association between systemic exposure of ganciclovir ($AUC_{3\ and\ 7\ days}$) before viral load eradication show p-values higher than 0,05 (not significant). Ganciclovir is accumulated in the infected cells and transformed to its active metabolite ganciclovir-5´-triphosphate (ganciclovir-TP). Thus being unavailable to be measured in the blood samples. Therefore, lower ganciclovir plasma concentrations may indicate a higher accumulation of ganciclovir in infected cells where it inhibits viral replication (23).

## 4.3 Strengths and limitations

The average AUC of the treatment period, and the treatment and maintenance period were calculated and analyzed with the help of binary logistic regression models against the presence or absence of effect or adverse effects at the end of both time periods. This was a very unsure way of analyzing the data, as many times, the adverse effects occurred in the middle of the treatment periods and the ganciclovir dose was adjusted accordingly, so to make the adverse effects disappear. This led to many individuals having no sign of adverse effects on Day 21 and Day 49, making the analysis very weak.

To avoid the problem mentioned above, the occurrences of the side effects were recorded (as categorical and numerical values) on the day they appeared and analyzed with the average

$AUC_{3\ days}$ and $AUC_{7\ days}$ before the day of occurrence of the adverse effects with the help of binary logistic regression model. The rationale behind this was very simple – the immediate systemic exposure of ganciclovir before the occurrences of the side effects would be more logical to analyze.

Looking at the AIC from table 8 and 10, and comparing the AIC for 3 days with the AIC for 7 days for every parameter separately, it indicates that $AUC_{7\ days}$ vs. the side effects data had a relatively better quality of the logistic regression model than $AUC_{3\ days}$ vs. the side effects.

Comparing the R-squared from table 11 for $AUC_{3\ days}$ and $AUC_{7\ days}$ also reinforces that $AUC_{7\ days}$ is a better parameter to conduct a linear regression with than $AUC_{3\ days}$.

Another limitation to this study was the estimation of the systemic exposure of ganciclovir with the help of very few trough concentrations and a population pharmacokinetic model.

The occurrences of the toxic adverse events were maybe not only based on the systemic exposure of ganciclovir but a number of other factors. The solid-organ transplant patients concomitant therapy with immunosuppressants like tacrolimus, mycophenolate mofetil, and others, put them at risk for the same type of side effects (38). Thus we would get a better estimate of how much the AUC of ganciclovir is associated with the occurrence of the side effects if we weigh in the concomitant use of immunosuppressants and the other risk factors, i.e. bone marrow cellularity, hyperbilirubinemia and increased serum creatinine.

## 4.4 Future perspectives

Hematological toxicity is a major concern during ganciclovir therapy. It can cause marrow toxicity, notably neutropenia that could consequently expose immunosuppressed patients to life-threatening infections. Identifying the risk factors for neutropenia in patients treated with ganciclovir is expected to lower the incidence of toxicity and would help to design alternative strategies in high-risk patients (42).

Ganciclovir is a potent inhibitor of viruses of the herpes family, including CMV, which is pathogenic for humans. The primary mechanism of action of ganciclovir is inhibition of the replication of viral DNA, by ganciclovir-TP. This inhibition includes a selective and potent inhibition of the viral DNA polymerase. It is converted by CMV thymidine kinase to a monophosphate, and then to di- and tri- phosphates by the host enzymes. Other nucleotide

metabolizing enzymes may be involved as well. The selective antiviral response associated with ganciclovir treatment is achieved because of the much weaker inhibition of cellular DNA polymerases by ganciclovir-TP. Activity and selectivity are also amplified by the accumulation of ganciclovir-TP in CMV-infected cells (23, 43).

Ganciclovir is most likely to accumulate in lipid bilayers. Accumulation in both bilayers may constitute a reservoir of the drug prior to delivery inside cells through passive diffusion. Ganciclovir is particularly well located in this accumulating region to be actively flushed out by ATP-binding cassette (ABC) transporters. After phosphorylation (activation), ganciclovir-TP is prevented from penetrating back to the lipid bilayer, making it more available to act or accumulate in healthy cells, thus partially explaining the adverse effects observed in this study (42).

This study also showed that the number of days for which the mean AUC was calculated has a big impact on the quality of the regression analyses. Some of the mean $AUC_{3/7\ days}$ calculated were from the very beginning of the regimen. The AUC used in the analysis should be from trough concentrations at steady state, as they are approximately equal. As a rule of thumb, five half-lives after the first dose administered, an individual reaches steady state (44).

The risk factors involved in the hematological adverse effects of ganciclovir apart from high plasma concentration of ganciclovir include bone marrow cellularity, hyperbilirubinemia, increased serum creatinine and the use of concomitant use of immunosuppressants like tacrolimus, and mycophenolate mofetil (45). And these should be factored in to get a clearer picture of how the occurrences of adverse effects can be associated with the systemic exposure of ganciclovir.

# 5 Conclusion

The analyses performed in this study did not show any significant associations of the systemic exposure of ganciclovir with the occurrence of the adverse effects.

There can be many reasons to explain the results. The study might not have been strong enough. Or estimating the AUC was not a good parameter for systemic exposure of ganciclovir.

Other risk factors need to be counted in these models and a multivariate study should be designed. This will help in the development of a more precise model where all the risk factors are weighed and will enable the clinicians to treat the solid-organ transplant patients with low chances of adverse effects and higher chances of effect.

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# 7 Appendix

## 7.1 Patient demographics

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 1 | 1 | 75 | 185 | 58 |
| 2 | 2 | 66 | 170 | 54 |
| 3 | 1 | 85 | 180 | 61 |
| 5 | 1 | 101 | 187 | 66 |
| 8 | 1 | 72 | 172 | 65 |
| 9 | 1 | 62 | 174 | 39 |
| 10 | 2 | 57 | 160 | 56 |
| 11 | 2 | 57 | 160 | 35 |
| 14 | 1 | 82 | 176 | 47 |
| 15 | 2 | 74 | 151 | 46 |
| 16 | 1 | 56 | 168 | 22 |
| 19 | 1 | 60 | 171 | 59 |
| 20 | 2 | 70 | 160 | 68 |
| 21 | 1 | 67 | 171 | 36 |
| 22 | 1 | 53 | 163 | 18 |
| 23 | 2 | 53 | 168 | 40 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 24 | 2 | 53 | 167 | 53 |
| 25 | 1 | 66 | 170 | 53 |
| 29 | 2 | 51 | 148 | 33 |
| 30 | 1 | 56 | 166 | 68 |
| 32 | 2 | 75 | 169 | 25 |
| 34 | 2 | 63 | 154 | 34 |
| 36 | 1 | 52 | 175 | 54 |
| 38 | 1 | 80 | 169 | 56 |
| 40 | 1 | 62 | 180 | 41 |
| 42 | 1 | 63 | 173 | 56 |
| 43 | 2 | 43 | 151 | 27 |
| 44 | 2 | 58 | 157 | 35 |
| 45 | 1 | 100 | 180 | 45 |
| 49 | 2 | 62 | 160 | 43 |
| 52 | 1 | 58 | 174 | 44 |
| 53 | 1 | 77 | 170 | 23 |
| 56 | 1 | 119 | 188 | 70 |
| 57 | 2 | 39 | 165 | 22 |
| 62 | 1 | 76 | 170 | 25 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 63 | 1 | 66 | 175 | 47 |
| 64 | 1 | 73 | 179 | 42 |
| 65 | 2 | 63 | 157 | 57 |
| 68 | 1 | 63 | 170 | 56 |
| 70 | 1 | 62 | 170 | 23 |
| 81 | 1 | 79 | 165 | 60 |
| 90 | 1 | 75 | 174 | 49 |
| 93 | 1 | 50 | 168 | 24 |
| 95 | 1 | 58 | 167 | 46 |
| 97 | 2 | 70 | 155 | 59 |
| 101 | 2 | 49 | 169 | 25 |
| 112 | 2 | 43 | 149 | 19 |
| 115 | 1 | 66 | 176 | 34 |
| 116 | 2 | 58 | 150 | 57 |
| 119 | 1 | 78 | 180 | 29 |
| 121 | 1 | 70 | 171 | 57 |
| 122 | 1 | 72 | 182 | 32 |
| 123 | 1 | 79 | 179 | 39 |
| 126 | 1 | 60 | 155 | 39 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 127 | 2 | 71 | 150 | 63 |
| 129 | 2 | 56 | 164 | 37 |
| 130 | 1 | 73 | 172 | 37 |
| 131 | 1 | 70 | 182 | 60 |
| 132 | 2 | 63 | 152 | 68 |
| 137 | 1 | 65,5 | 164 | 21 |
| 138 | 1 | 51 | 170 | 31 |
| 143 | 2 | 89 | 163 | 40 |
| 147 | 1 | 74 | 187 | 37 |
| 153 | 1 | 60 | 172 | 40 |
| 154 | 2 | 45 | 148 | 27 |
| 156 | 2 | 84 | 165 | 41 |
| 157 | 1 | 71 | 170 | 65 |
| 163 | 2 | 55 | 152 | 40 |
| 166 | 1 | 89,5 | 166 | 55 |
| 168 | 1 | 64 | 162 | 42 |
| 169 | 2 | 76 | 170 | 59 |
| 170 | 1 | 72 | 180 | 22 |
| 171 | 1 | 50 | 165 | 32 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 174 | 1 | 57,5 | 171 | 48 |
| 175 | 1 | 69 | 171 | 36 |
| 176 | 2 | 53 | 166 | 42 |
| 177 | 2 | 72,4 | 158 | 65 |
| 184 | 1 | 51,7 | 172 | 62 |
| 186 | 2 | 53 | 146 | 42 |
| 189 | 2 | 45,1 | 155 | 43 |
| 191 | 1 | 70 | 178 | 43 |
| 193 | 1 | 79,6 | 170 | 60 |
| 196 | 1 | 74 | 175 | 66 |
| 198 | 1 | 106 | 190 | 45 |
| 202 | 2 | 88 | 152 | 54 |
| 203 | 2 | 87 | 166 | 62 |
| 204 | 1 | 129,6 | 169 | 48 |
| 207 | 1 | 80,7 | 158 | 57 |
| 208 | 2 | 78,3 | 158 | 58 |
| 209 | 2 | 70,5 | 158 | 39 |
| 213 | 1 | 45 | 158 | 32 |
| 216 | 2 | 84 | 157 | 50 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 217 | 1 | 52 | 168 | 55 |
| 219 | 1 | 124 | 167 | 56 |
| 221 | 1 | 73 | 158 | 40 |
| 222 | 1 | 74 | 183 | 42 |
| 223 | 1 | 65 | 172 | 55 |
| 224 | 1 | 69 | 164 | 41 |
| 226 | 2 | 68 | 149 | 57 |
| 227 | 2 | 72,2 | 160 | 67 |
| 229 | 2 | 55 | 150 | 64 |
| 231 | 1 | 52 | 156 | 60 |
| 233 | 1 | 70 | 175 | 33 |
| 234 | 2 | 113,6 | 164 | 50 |
| 235 | 1 | 57 | 162 | 33 |
| 236 | 1 | 72 | 167 | 43 |
| 237 | 2 | 68 | 168 | 23 |
| 241 | 1 | 74,9 | 175 | 52 |
| 245 | 1 | 74,8 | 169 | 67 |
| 246 | 2 | 47 | 167 | 39 |
| 249 | 1 | 68 | 164 | 61 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 251 | 1 | 70 | 158 | 61 |
| 253 | 1 | 50,2 | 158 | 43 |
| 254 | 1 | 70,8 | 175 | 40 |
| 264 | 2 | 67 | 159 | 50 |
| 265 | 2 | 56,2 | 159 | 40 |
| 266 | 2 | 61 | 149 | 64 |
| 267 | 2 | 47 | 149 | 40 |
| 268 | 1 | 80 | 175 | 55 |
| 269 | 1 | 84,1 | 163 | 34 |
| 270 | 2 | 63 | 163 | 53 |
| 271 | 2 | 88,6 | 179 | 55 |
| 272 | 1 | 72 | 175 | 43 |
| 273 | 1 | 57 | 160 | 51 |
| 274 | 2 | 67 | 160 | 55 |
| 275 | 1 | 62 | 160 | 49 |
| 278 | 2 | 63 | 178 | 37 |
| 279 | 1 | 95 | 178 | 33 |
| 281 | 2 | 60 | 165 | 54 |
| 282 | 1 | 77 | 178 | 31 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 283 | 1 | 54,7 | 168 | 43 |
| 285 | 1 | 48,2 | 157 | 45 |
| 287 | 1 | 79 | 176 | 57 |
| 290 | 2 | 49 | 164 | 26 |
| 291 | 1 | 70,6 | 180 | 65 |
| 292 | 1 | 57 | 170 | 29 |
| 293 | 1 | 52,5 | 175 | 29 |
| 294 | 1 | 66 | 176 | 43 |
| 295 | 1 | 60 | 170 | 27 |
| 296 | 1 | 70 | 182 | 23 |
| 297 | 2 | 57,5 | 173 | 29 |
| 300 | 2 | 55 | 168 | 39 |
| 304 | 2 | 57 | 166 | 43 |
| 307 | 2 | 55 | 160 | 26 |
| 318 | 1 | 56 | 173 | 72 |
| 320 | 1 | 96,3 | 176 | 62 |
| 324 | 1 | 76 | 176 | 52 |
| 326 | 2 | 66 | 172 | 39 |
| 327 | 1 | 62 | 176 | 35 |

| Patient ID | Gender | Weight (kg) | Height (cm) | Age (years) |
|---|---|---|---|---|
| 329 | 1 | 78,7 | 177 | 66 |
| 332 | 1 | 97 | 186 | 55 |
| 333 | 1 | 131 | 180 | 24 |
| 335 | 2 | 86 | 159 | 33 |
| 337 | 1 | 58,1 | 160 | 32 |
| 338 | 2 | 62 | 160 | 70 |
| 342 | 2 | 70 | 160 | 54 |
| 344 | 2 | 63 | 163 | 29 |
| 345 | 1 | 79 | 184 | 44 |
| 347 | 1 | 85 | 190 | 29 |
| 348 | 1 | 63 | 165 | 34 |
| 351 | 1 | 72 | 173 | 53 |
| 358 | 2 | 708 | 153 | 60 |
| 366 | 2 | 64,6 | NA | 58 |

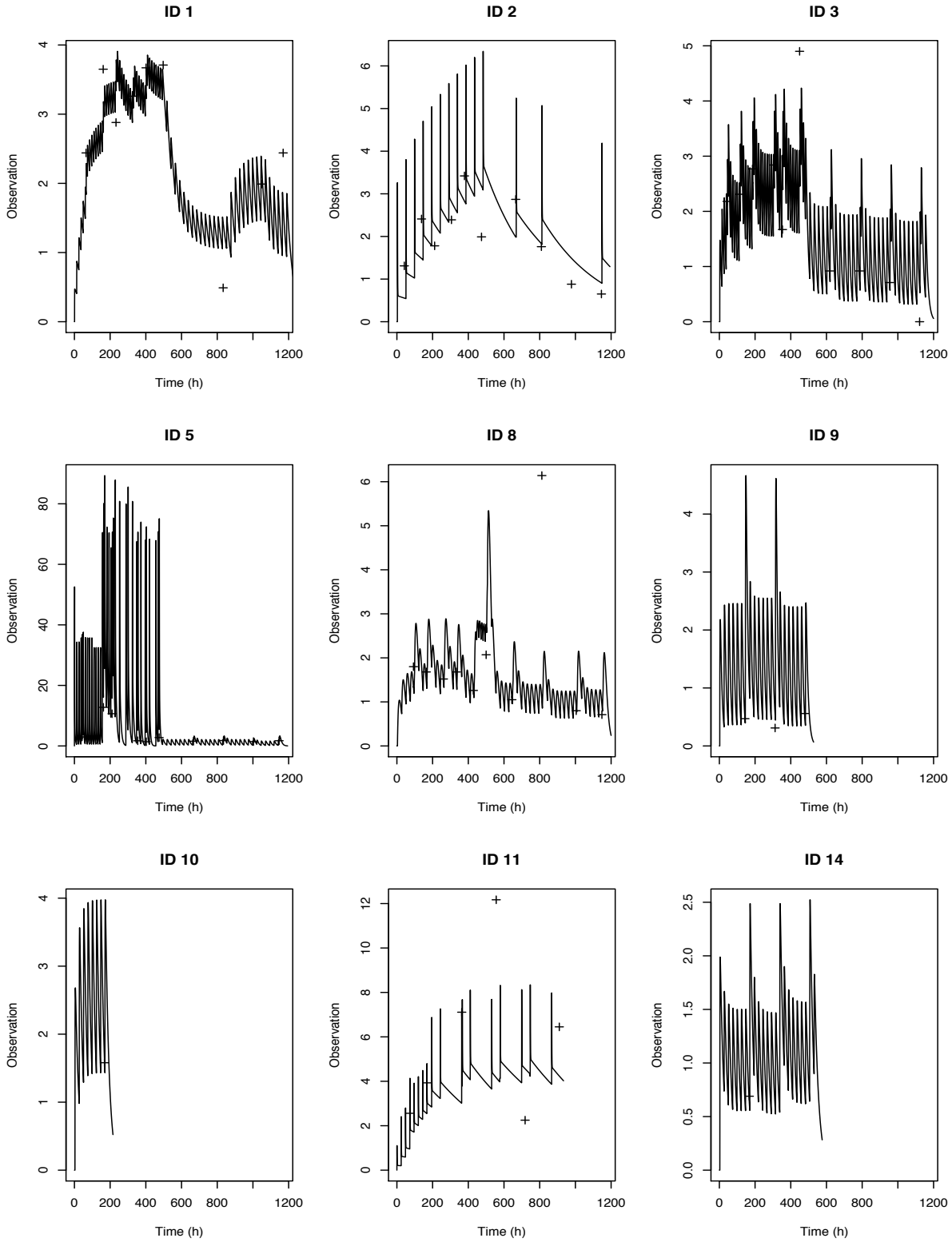
# 7.2 Excerpt of the input file

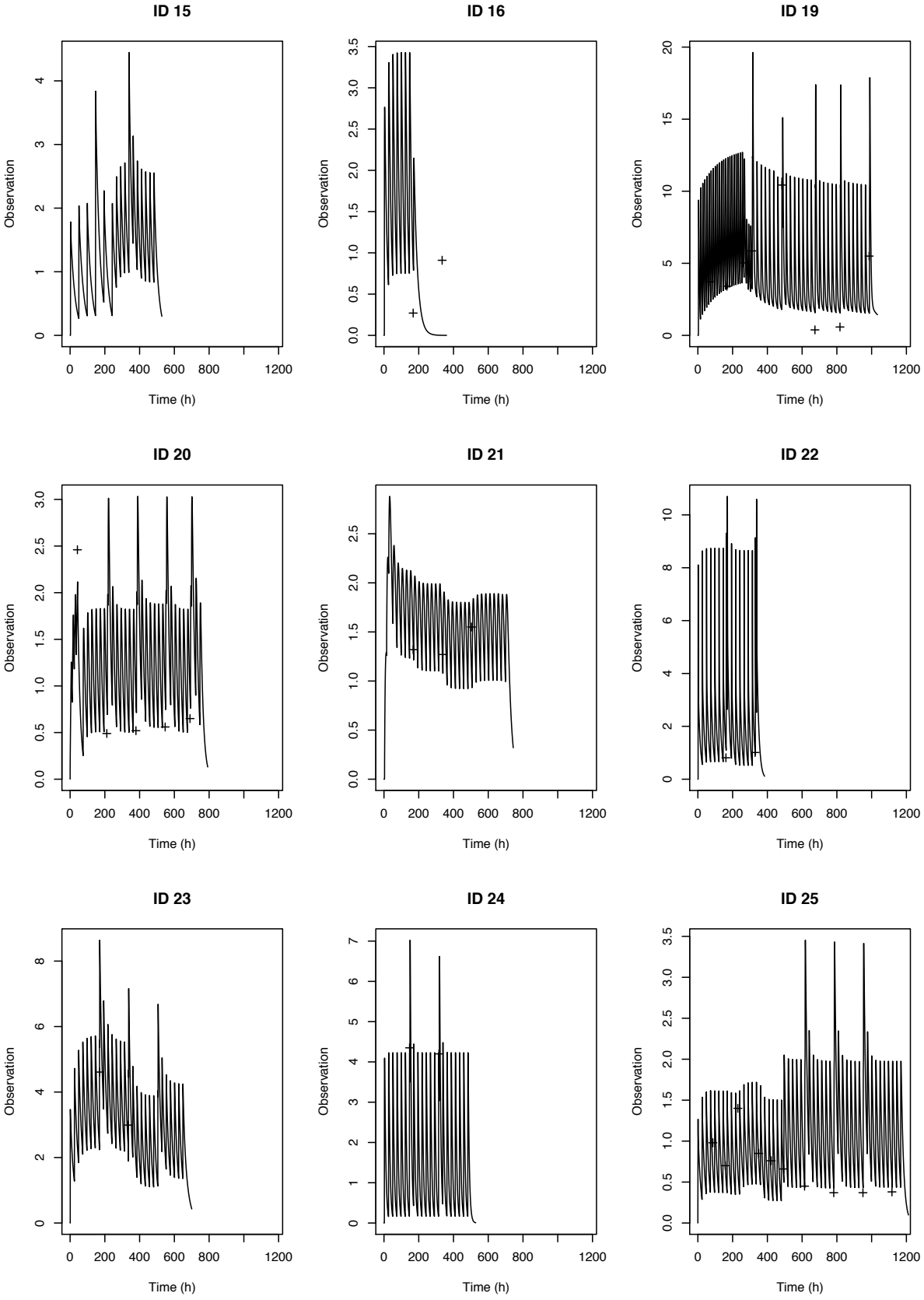
```
POPDATA DEC_11
#ID      EVID     TIME      DUR      DOSE     ADDL  II      INPUT     OUT     OUTEQ    C0       C1       C2       C3       WT       SEX      HGT      ICGCV    CREAT    ALB      HGB      WBC      PLATES   EGFR     AGE      TREAT    GCV
     1        1        0        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1        1       12        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1        1       24        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1        1       36        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1        1       48        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1        1       60        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  48.46       58        1        1
     1 1 65.08                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1 0 65.08                  0         0  .     .       .       1 2.44  .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1       72        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1       84        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1       96        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1      108        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1      120        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1      132        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1      144        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1        1      156        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      131       34        0        0        0  57.7        58        1        1
     1 1 161.25                 0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1 0 161.25                 0         0  .     .       .       1 3.65  .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      168        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      180        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      192        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      204        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      216        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      228        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       36        0        1        0  54.78       58        1        1
     1        1      233        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1 0      233        0         0  .     .       .       1 2.88  .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      240        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      252        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      264        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      276        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      288        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      300        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      312        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1        1      324        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      129       35        0        1        0  57.82       58        1        1
     1 1 329.25                 0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1 0 329.25                 0         0  .     .       .       1 3.26  .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      336        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      348        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      360        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      372        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      384        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1        1      396        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      133       36        0        1        0  56.83       58        1        1
     1 1 401.25                 0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1 0 401.25                 0         0  .     .       .       1 3.67  .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      408        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      420        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      432        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      444        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      456        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      468        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      480        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1        1      492        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      138       37        0        1        0  54.78       58        1        1
     1 0 497.25                 0         0  .     .       .       1 3.71  .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      516        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      540        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      564        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      588        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      612        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      636        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      660        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      684        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      708        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      732        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      756        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      780        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      804        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1        1      828        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      126       39        0        1        0  59.99       58        1        1
     1 0 833.25                 0         0  .     .       .       1 0.49  .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      852        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      876        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      900        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      924        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      948        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      972        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1      996        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1     1020        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1        1     1044        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        74        1      185        0      113       40        0        1        0         66  58        1        1
     1 0 1049.25                0         0  .     .       .       1 1.99  .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1        1     1068        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1        1     1092        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1        1     1116        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1        1     1140        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1        1     1164        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1 0 1169.25                0         0  .     .       .       1 2.44  .       1.       .        .        .        .        75        1      185        0      103       43        0        1        0  74.11       58        1        1
     1        1     1188        0  648.2306129.     .       .       1.      .       1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     1 0      1212        0         0  .     .       .       1       -99     1.       .        .        .        .        75        1      185        0      102       42        0        1        0  74.11       58        1        1
     2        1        0        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      209       33        1        1        0  27.51       54        2        1
     2 0 41.5                   0  1.666666666      0  .     .       .       1 1.31  .       1.       .        .        .        .        66        2      170        0      155       31        0        1        0  38.26       54        2        1
     2        1       48        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      209       33        1        1        0  27.51       54        2        1
     2        1       96        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      209       33        1        1        0  27.51       54        2        1
     2 0      138 1.333333333      0  .     .       .       1 2.41  .       1.       .        .        .        .        66        2      170        0      178       28        1        1        0  33.31       54        2        1
     2        1      144        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2        1      192        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2 0 211.5          1.333333333      0  .     .       .       1 1.78  .       1.       .        .        .        .        68        2      170        0      161       27        1        1        0  37.95       54        2        1
     2        1      240        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2        1      288        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2 0 305.75         1.25      0         0  .     .       .       1 2.39  .       1.       .        .        .        .        67        2      170        0      177       30        1        1        0  34.01       54        2        1
     2        1      336        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      169       37        1        1        0  34.03       54        2        1
     2 0 378.5          1.5       0         0  .     .       .       1 3.42  .       1.       .        .        .        .        64        2      170        0      185       30        1        1        0  31.08       54        2        1
     2        1      384        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      169       37        1        1        0  34.03       54        2        1
     2        1      432        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      169       37        1        1        0  34.03       54        2        1
     2 0      474 1.333333333      0  .     .       .       1 1.99  .       1.       .        .        .        .        64        2      170        0      223       30        1        1        0  25.79       54        2        1
     2        1      480        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      127       38        0        1        0  34.03       54        2        1
     2 1 665.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      209       33        1        1        0  27.51       54        2        1
     2 0 665.5                  0         0  .     .       .       1 2.87  .       1.       .        .        .        .        64        2      170        0      209       33        1        1        0  27.51       54        2        1
     2 1 809.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2 0 809.5                  0         0  .     .       .       1 1.76  .       1.       .        .        .        .        64        2      170        0      159       36        1        1        0  36.17       54        2        1
     2 0 977.75                 0         0  .     .       .       1 0.88  .       1.       .        .        .        .        64        2      170        0      169       37        1        1        0  34.03       54        2        1
     2 1 1145.75                0  324.1153065.     .       .       1.      .       1.       .        .        .        .        64        2      170        0      127       38        0        1        0  34.03       54        2        1
     2 0 1145.75                0         0  .     .       .       1 0.65  .       1.       .        .        .        .        64        2      170        0      127       38        0        1        0  34.03       54        2        1
     2 0 1169.75                0         0  .     .       .       1       -99     1.       .        .        .        .        64        2      170        0      127       38        0        1        0  34.03       54        2        1
     3 1        0        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        85        1      180        0      134       30        1        1        0  62.53       61        1        1
     3 1       12        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        85        1      180        0      134       30        1        1        0  62.53       61        1        1
     3 1       24        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        85        1      180        0      134       30        1        1        0  62.53       61        1        1
     3 1       36        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        85        1      180        0      134       30        1        1        0  62.53       61        1        1
     3 1       43        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 0       43        0         0  .     .       .       1 2.18  .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1       48        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1       60        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1       72        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1       84        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1       96        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1      108        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        82        1      180        0      134       30        1        1        0  59.42       61        1        1
     3 1 114.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 0 114.5                  0         0  .     .       .       1 2.31  .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      120        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      132        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      144        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      156        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      168        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1      180        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        80        1      180        0      142       33        0        1        0  54.7        61        1        1
     3 1 185.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 0 185.5                  0         0  .     .       .       1 2.77  .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      192        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      204        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      216        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      228        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      240        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      252        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      264        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      276        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      288        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1      300        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      153       34        1        1        0  50.14       61        1        1
     3 1 305.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 0 305.5                  0         0  .     .       .       1 2.84  .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 1      312        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 1      324        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 1      336        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 1      348        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      144       32        1        1        0  52.6        61        1        1
     3 1 353.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 0 353.5                  0         0  .     .       .       1 1.67  .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      360        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      372        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      384        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      396        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      408        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      420        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      432        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1      444        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        78        1      180        0      153       33        1        1        0  49.5        61        1        1
     3 1 449.5                  0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 0 449.5                  0         0  .     .       .       1 4.9   .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      456        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      468        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      480        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      504        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      528        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      552        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
     3 1      576        0  324.1153065.     .       .       1.      .       1.       .        .        .        .        79        1      180        0      156       36        1        1        0  49.17       61        1        1
```

## 7.3 Model file

```
#PRI
Ka, 0.1,6
V0,0.1,70
CLm,0.1,30
CLf, 0.1,30
Q0,0,150
Vp0,0,350
Tlag0,0.01,3.2
A2,0,10000
FA0,0.1,1
GFRcl,-5,8

#COV
WT
SEX
HGT
ICGCV
CREAT
ALB
HGB
WBC
PLATES
EGFR
AGE
TREAT
GCV

#SEC
CG = ((140-AGE)*WT*1.23)/CREAT
&IF(SEX.GT.0.D0) CG = 0.85*(((140-AGE)*WT*1.23)/CREAT)
WTc = WT/64
CGc = CG/74
CL = CLm*CGc**GFRcl*WTc**0.75
&IF(SEX.GT.0.D0) CL=CLf*CGc**GFRcl*WTc**0.75
Q = Q0*WTc**0.75
VP = Vp0*WTc
V = V0*WTc
KE = CL/V
KCP = Q/V
KPC = Q/VP

#INI
X(2)=ICGCV*V
X(3)=A2
IF (ICGCV.EQ.0.D0) X(3)=0

#F
FA(1)=FA0

#LAG
TLAG(1)=Tlag0

#OUT
Y(1)=X(2)/V

#ERR
L=10
-0.0045291,0.12022645,0,0
```

# 7.4 Concentration-time curves of the patients in the study

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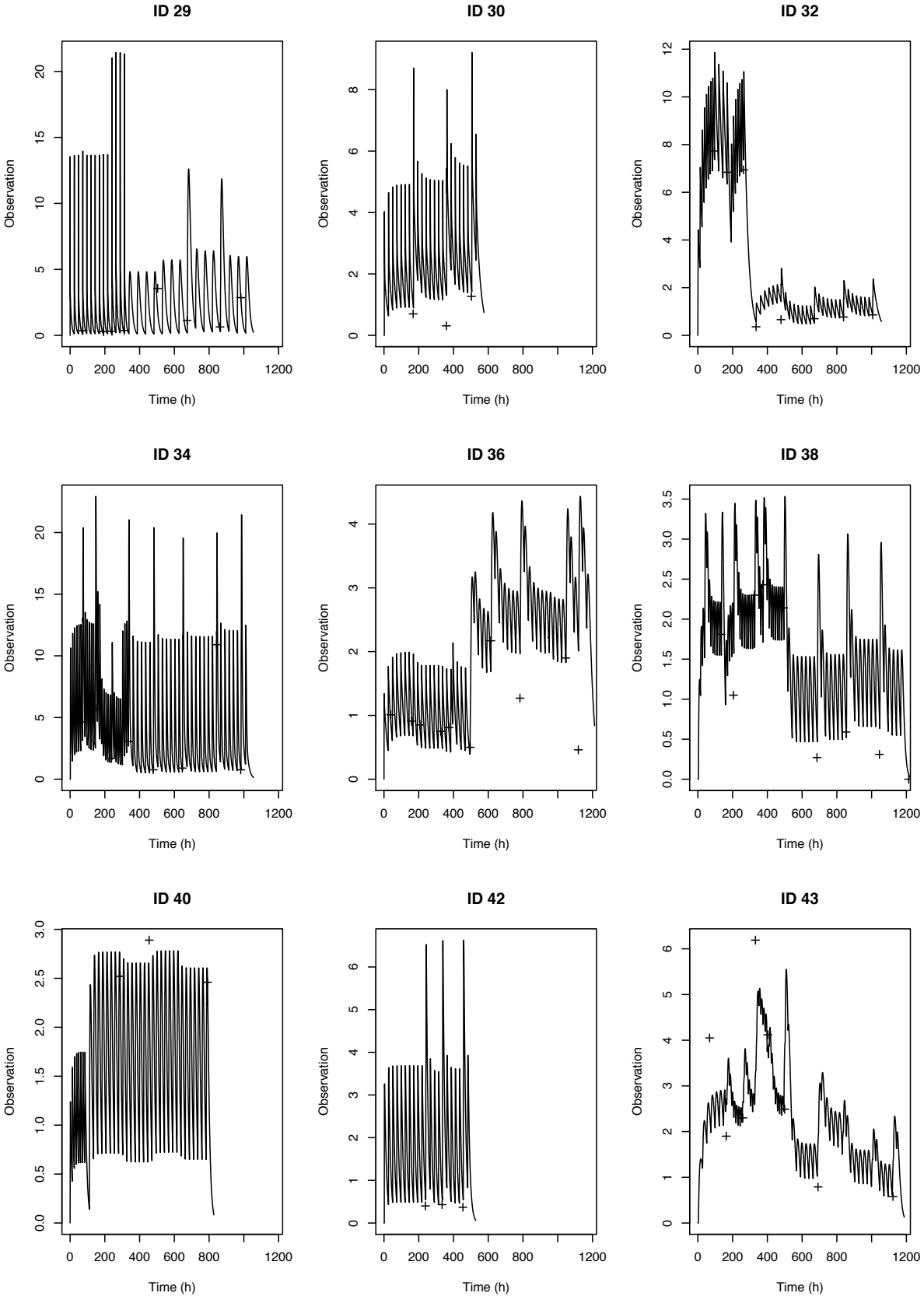
ID 16
ID 19
ID 20
ID 21
ID 22
ID 23
ID 24
ID 25
Observation
Time (h)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ID 30
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ID 34
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ID 38
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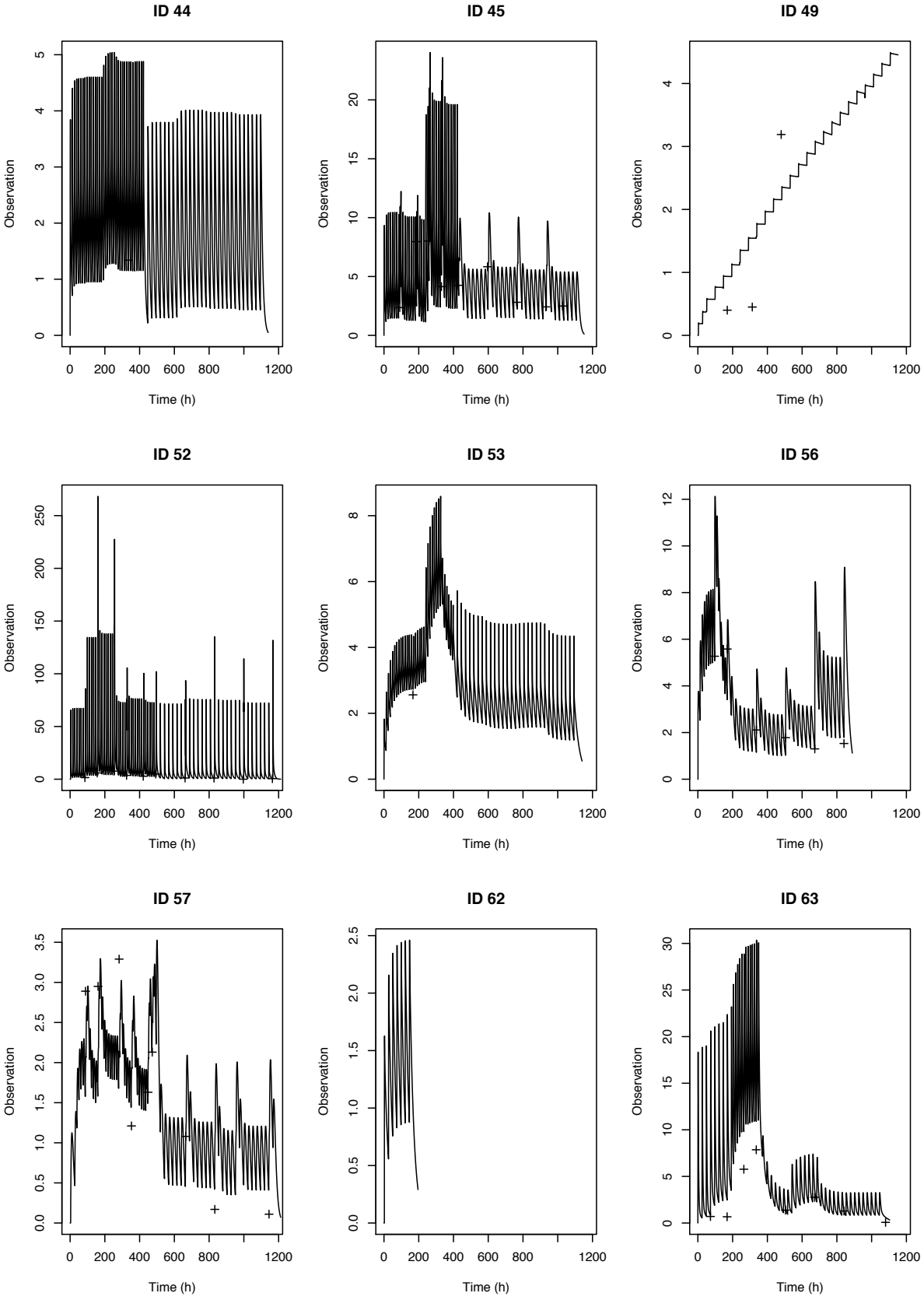
ID 42
ID 43
Observation
Time (h)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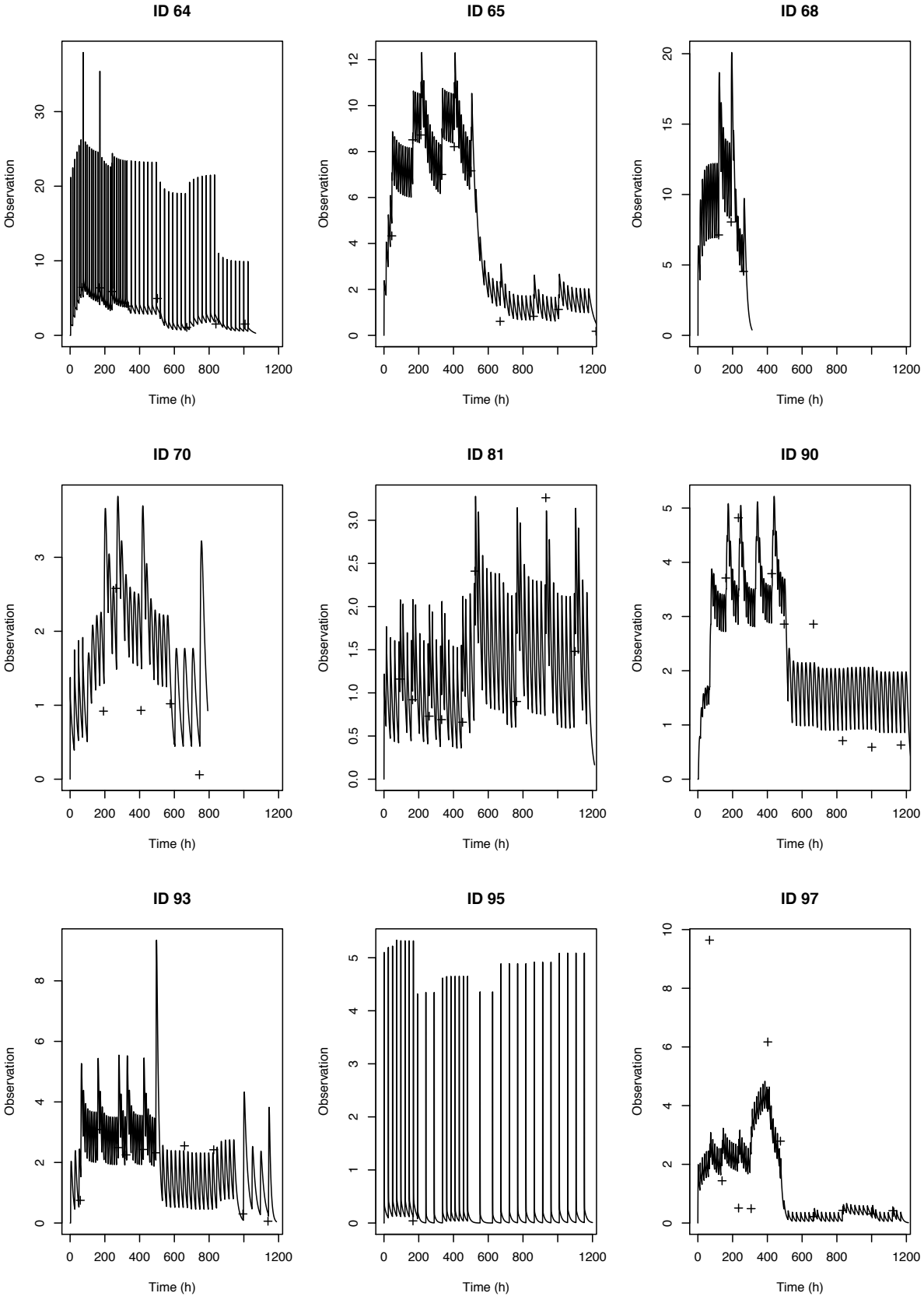
ID 52
ID 53
ID 56
ID 57
ID 62
ID 63
Observation
Time (h)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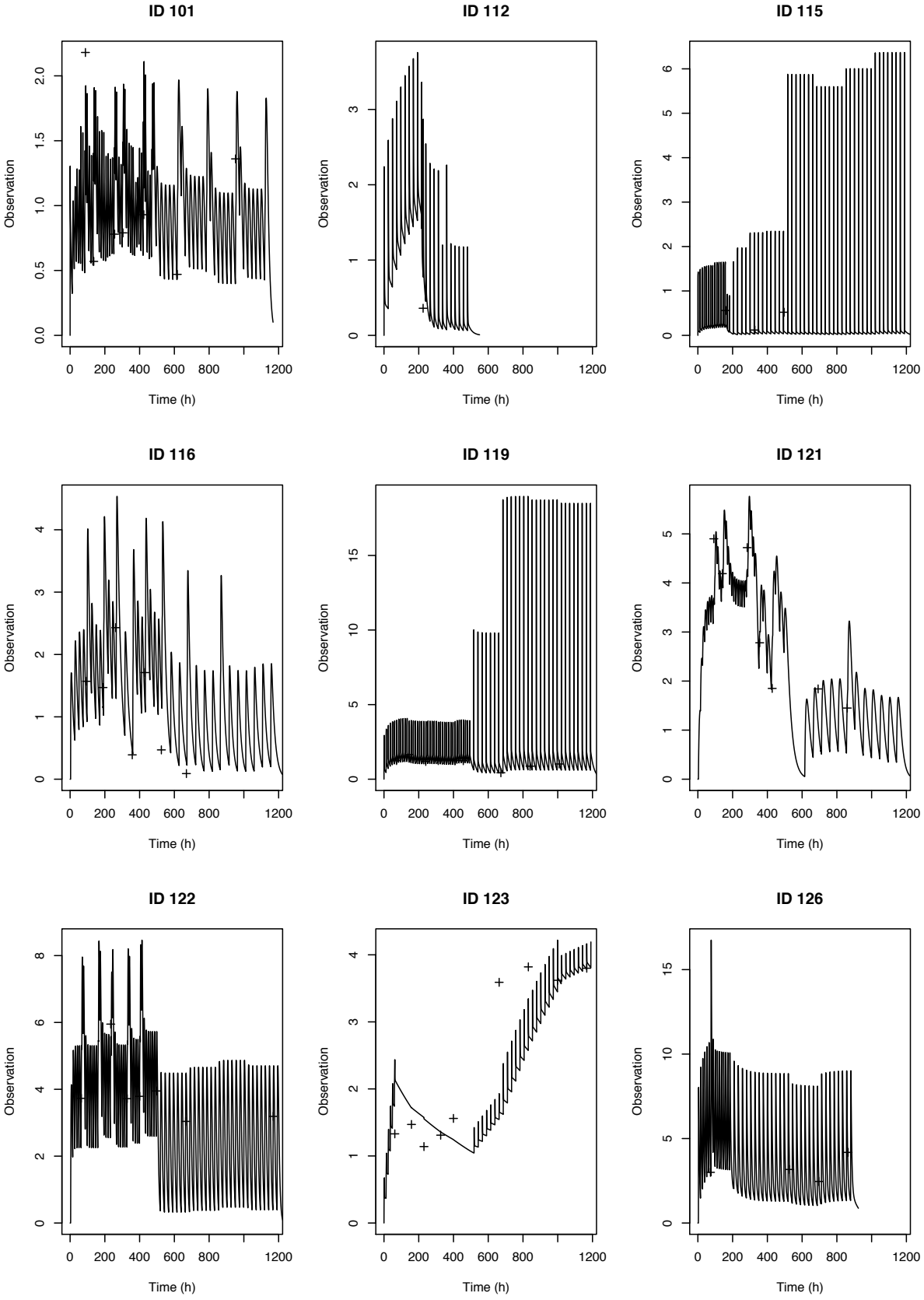
Observation
Time (h)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ID 122
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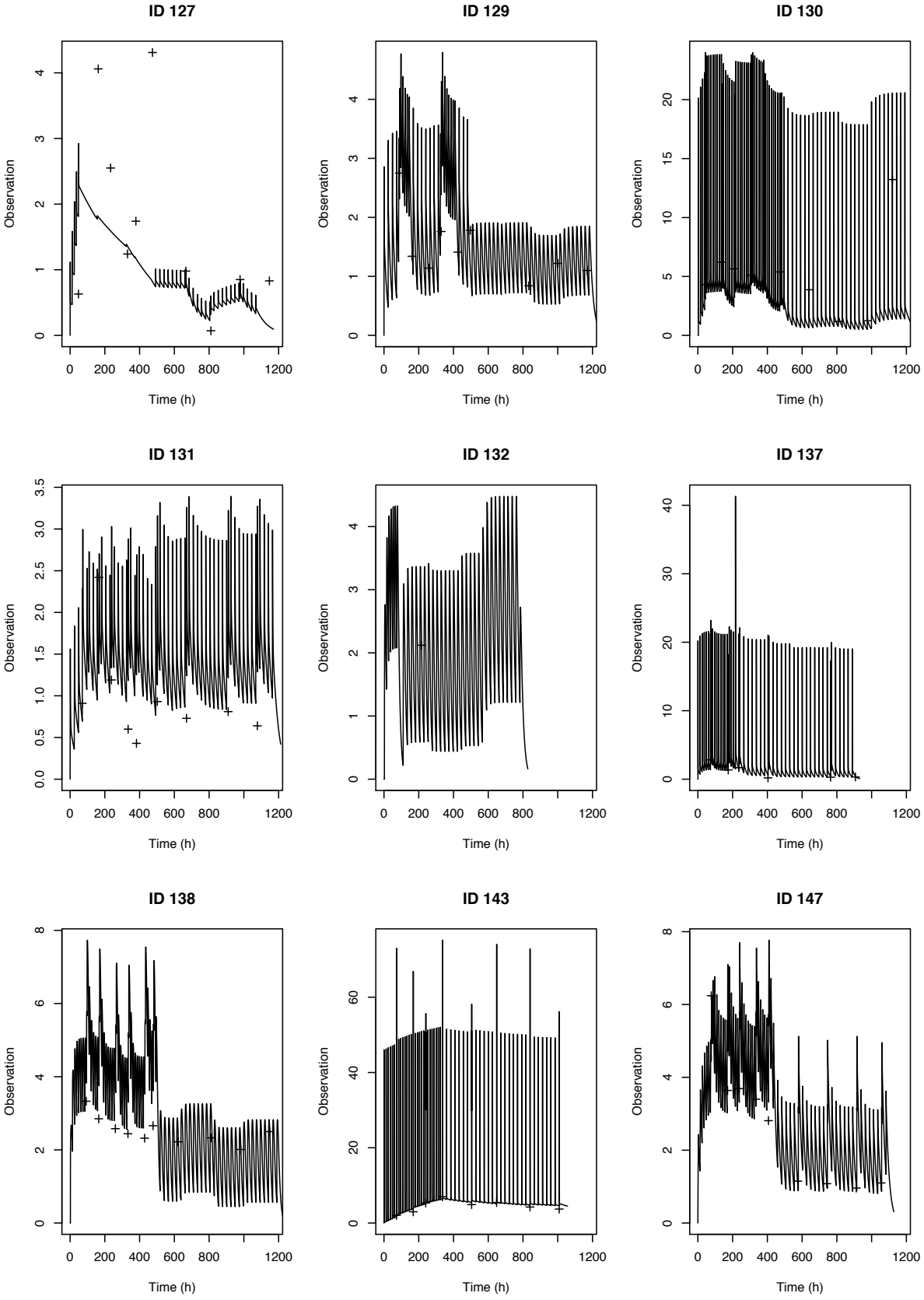
Observation
Time (h)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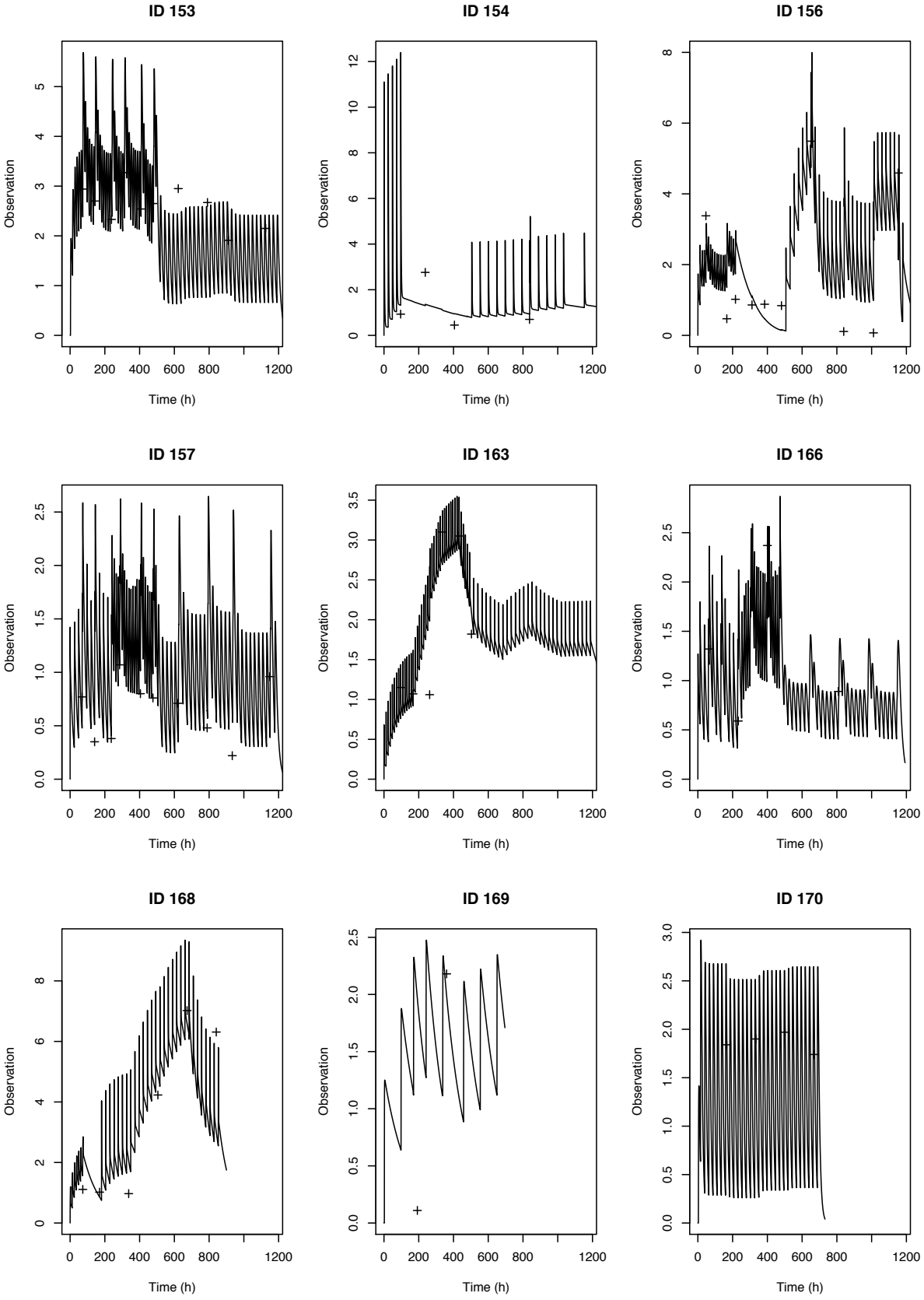
Observation
Time (h)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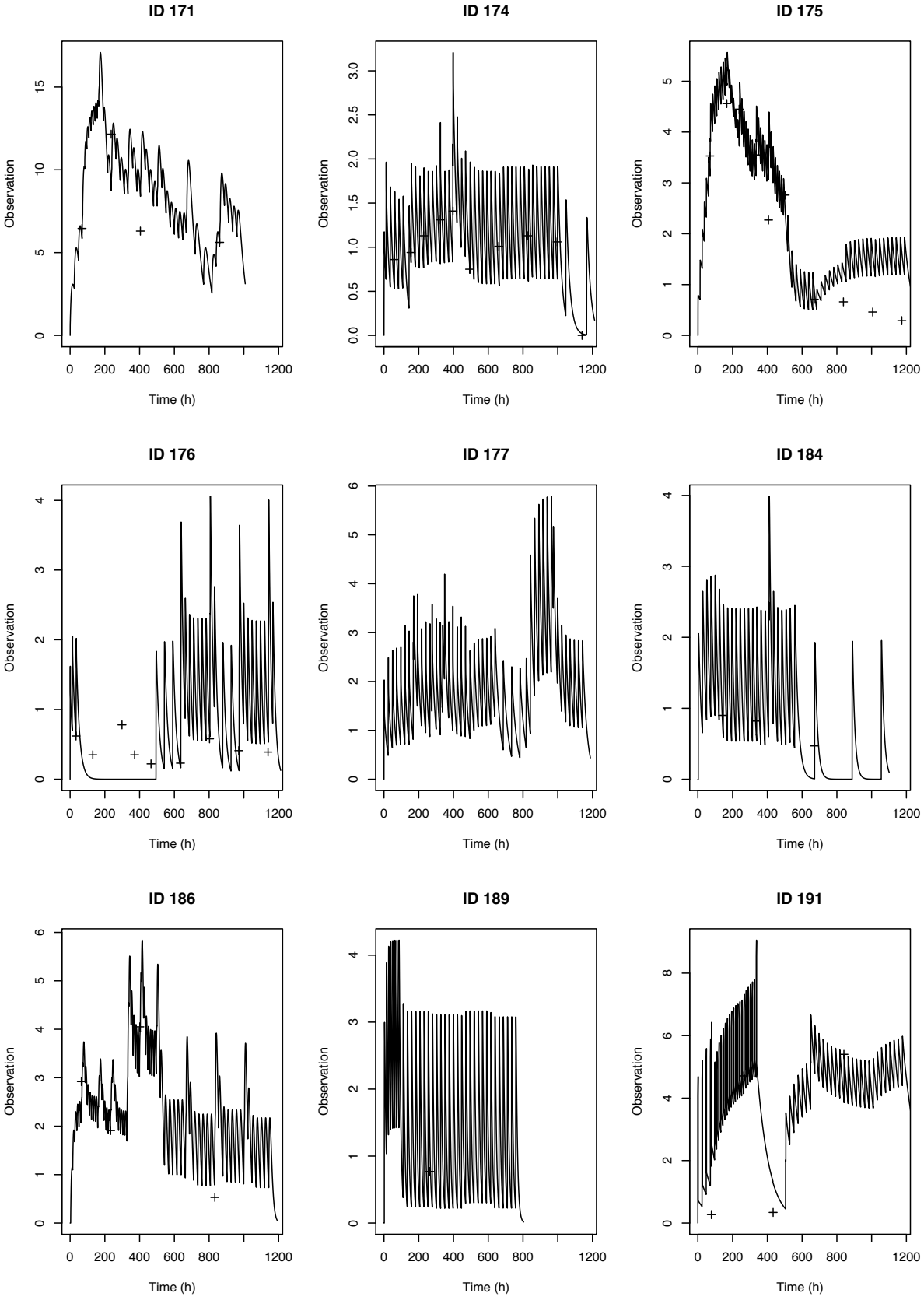
Observation
Time (h)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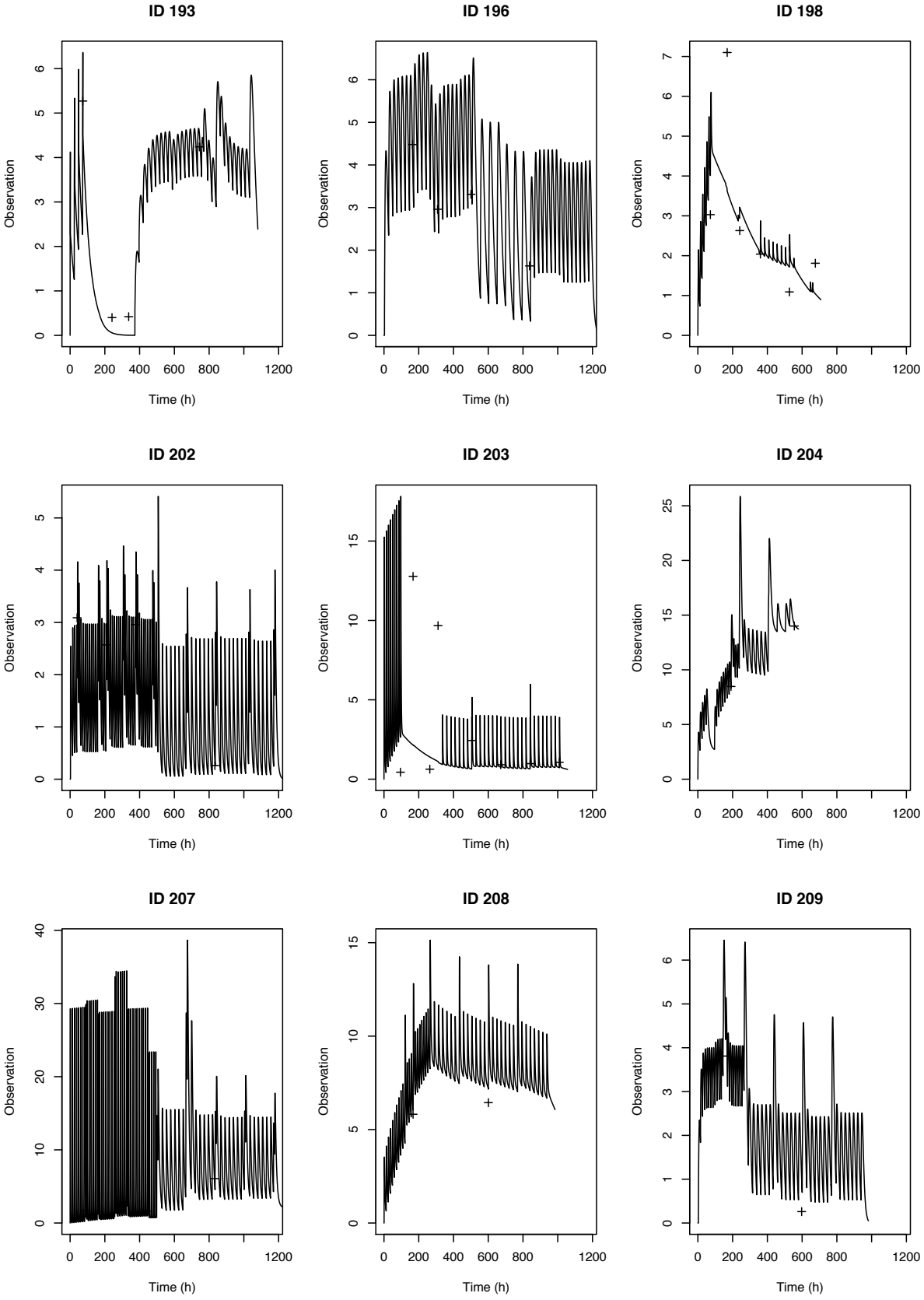
Observation
Time (h)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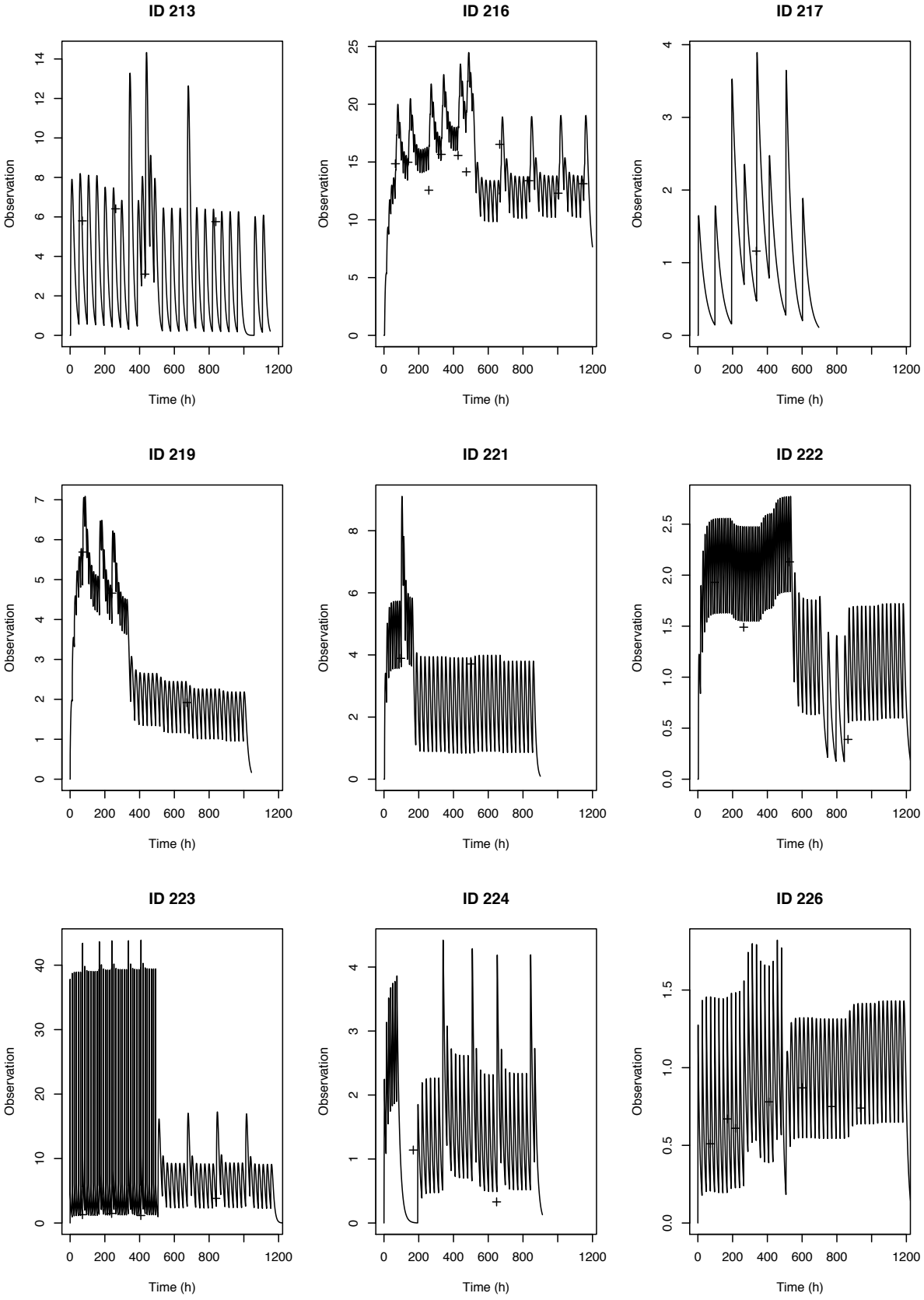
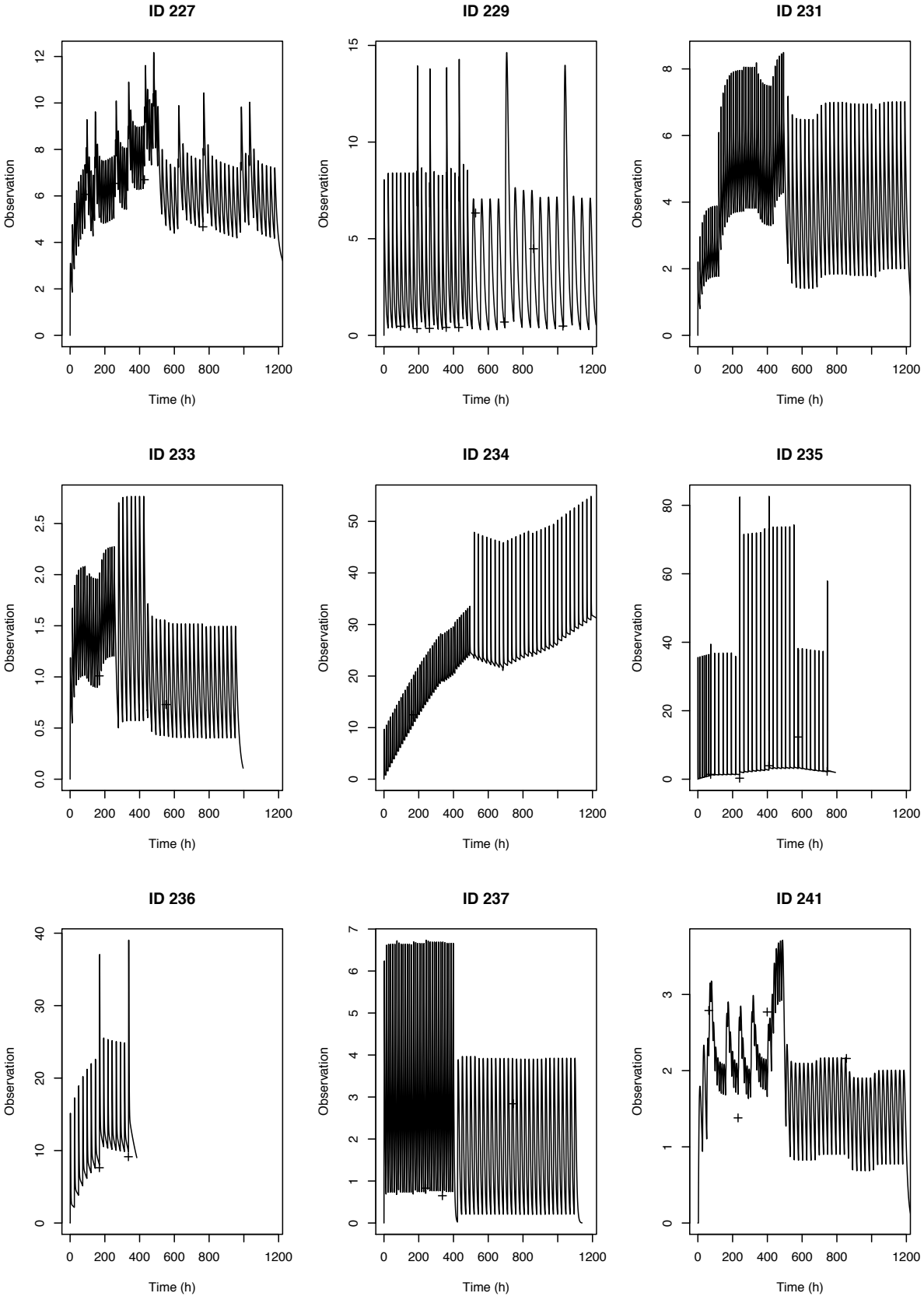
ID 196
ID 198
ID 202
ID 203
ID 204
ID 207
ID 208
ID 209
Observation
Time (h)


ID 213
ID 216
ID 217
ID 219
ID 221
ID 222
ID 223
ID 224
ID 226
Observation
Time (h)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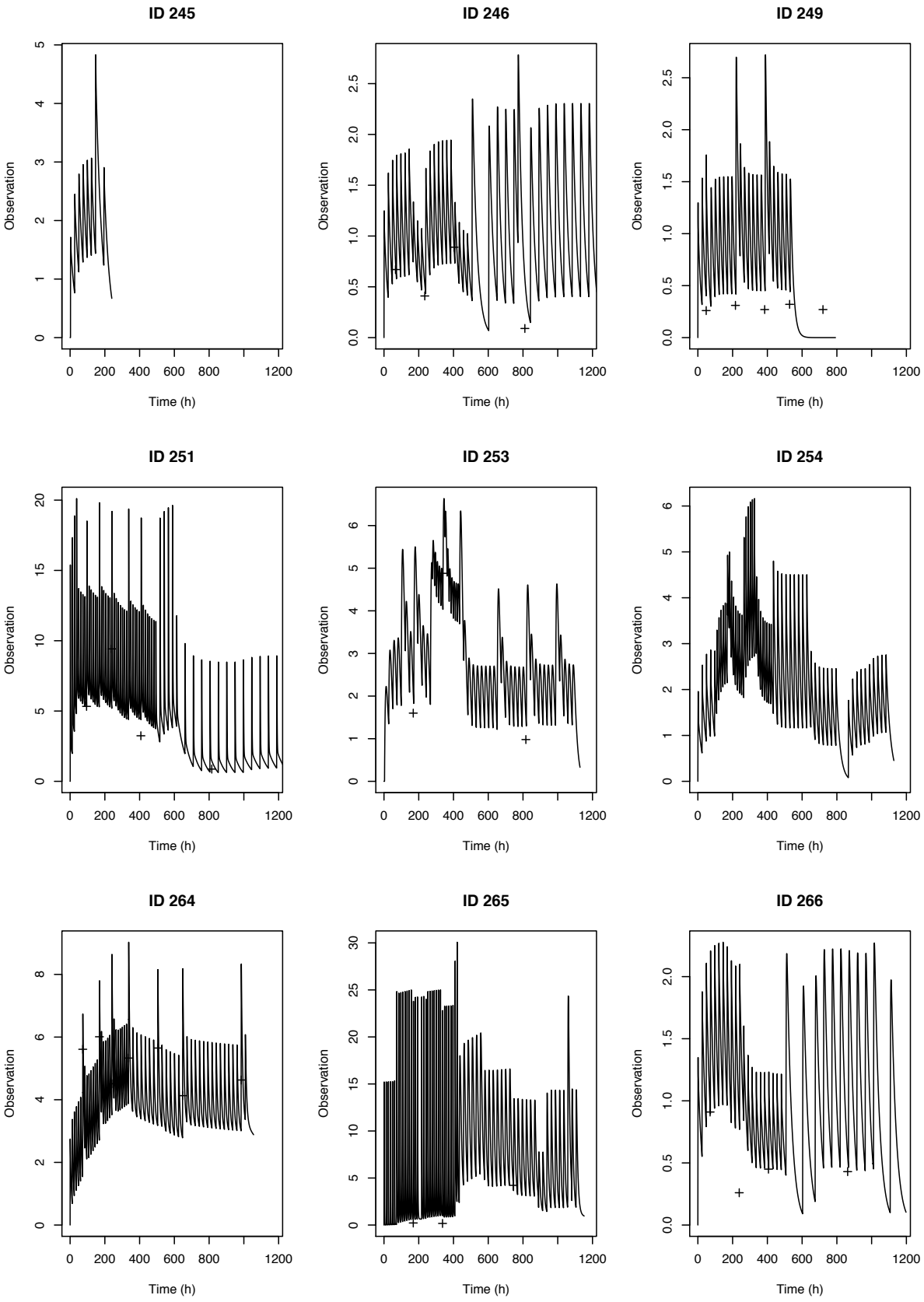
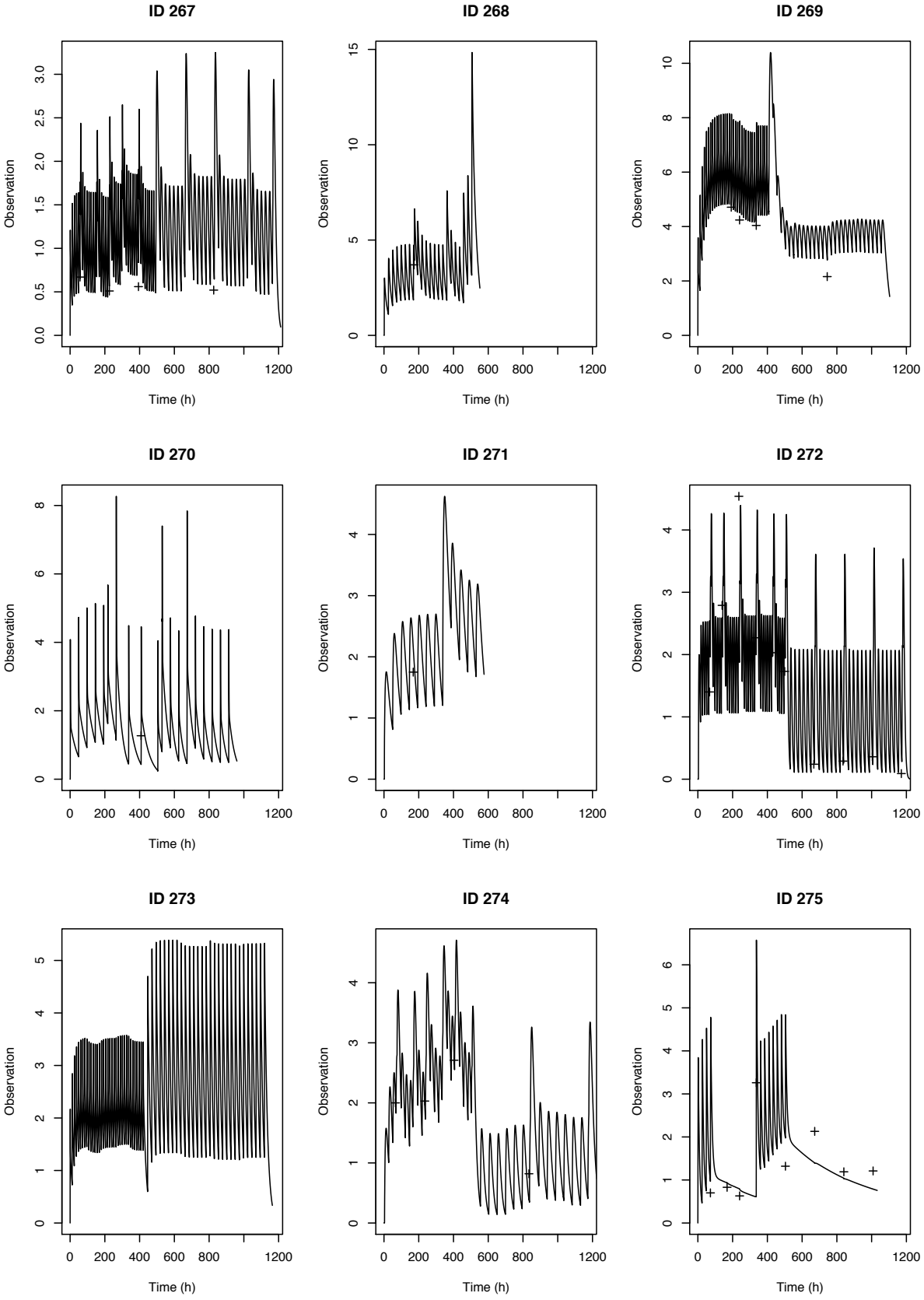
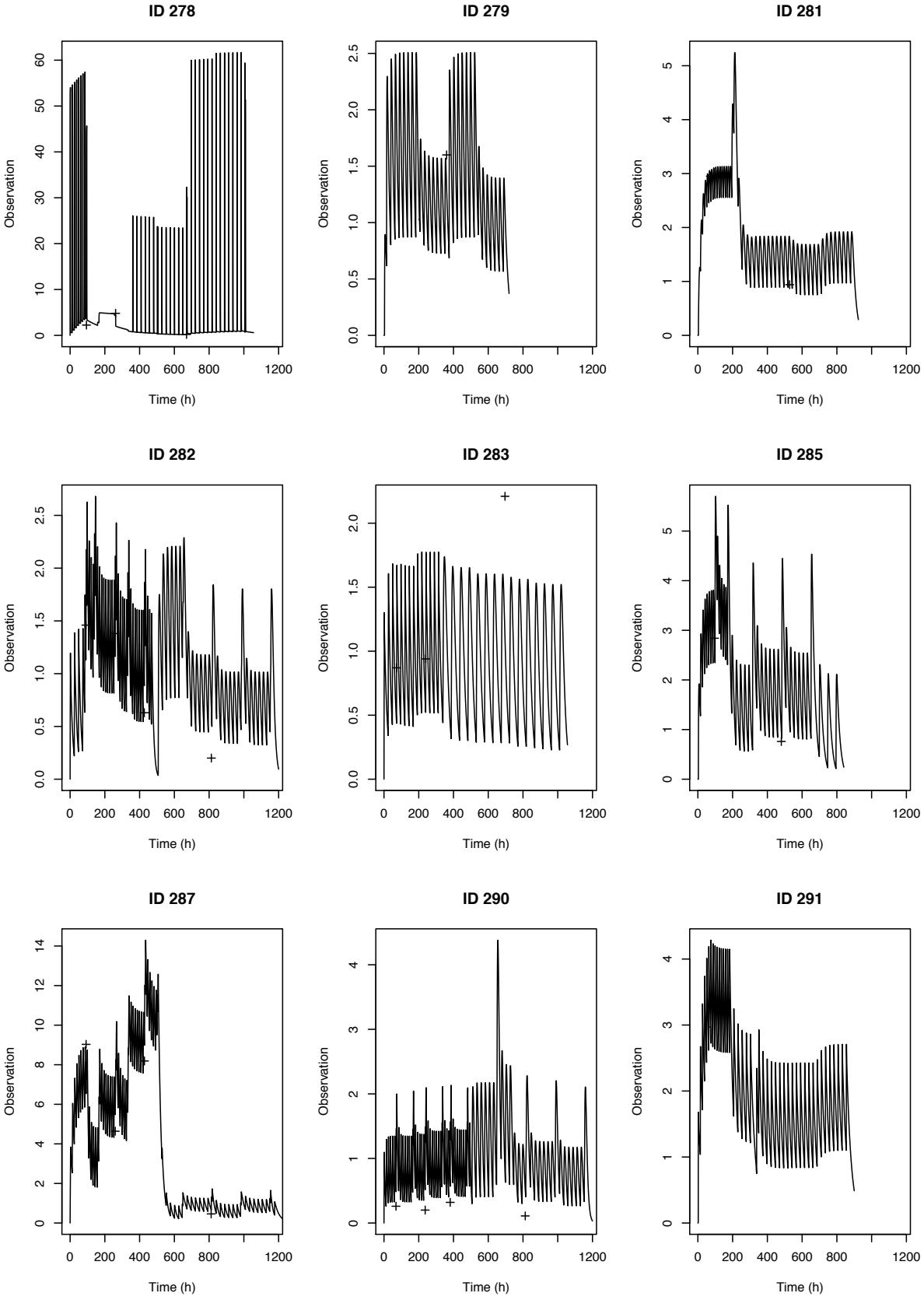
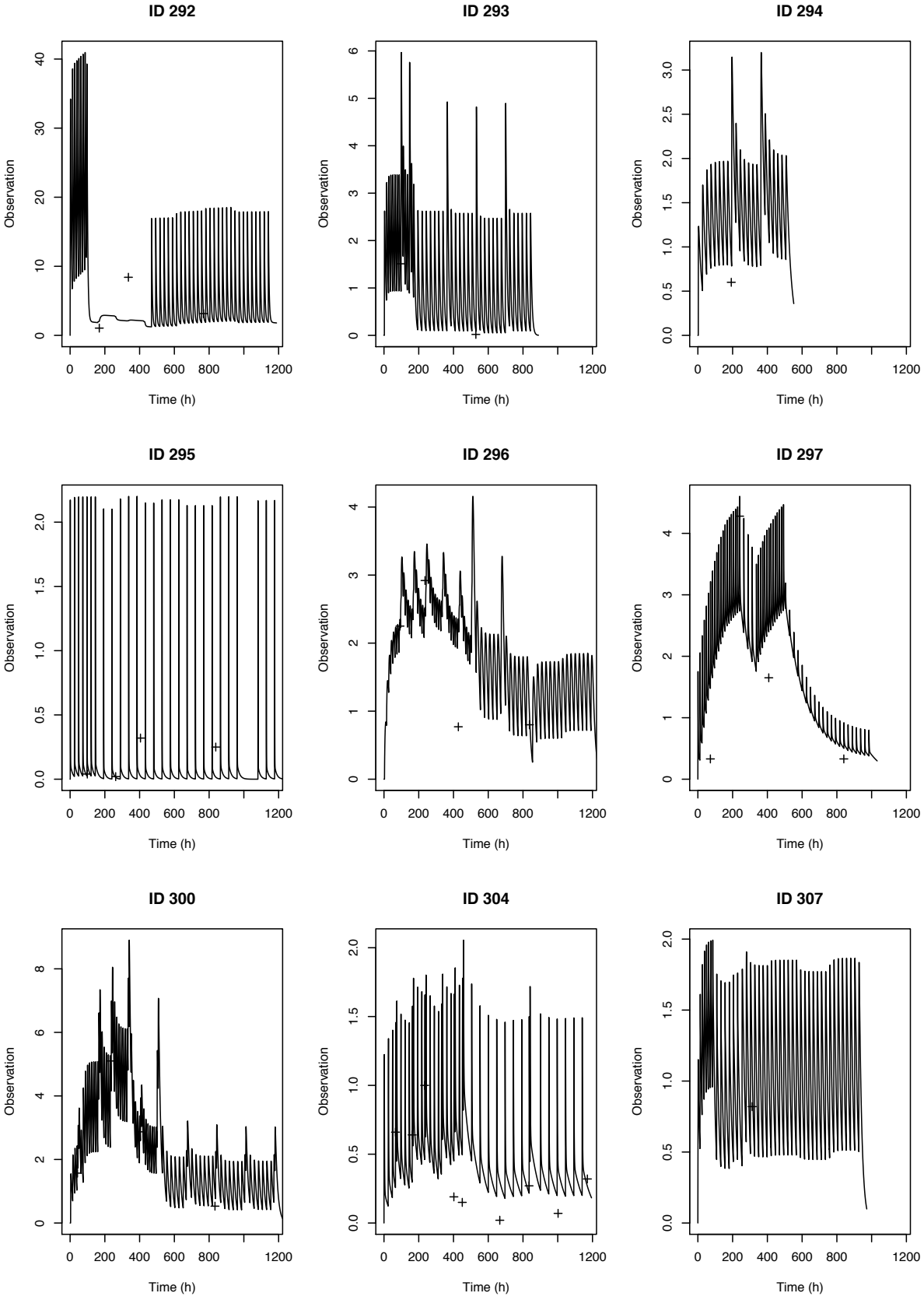
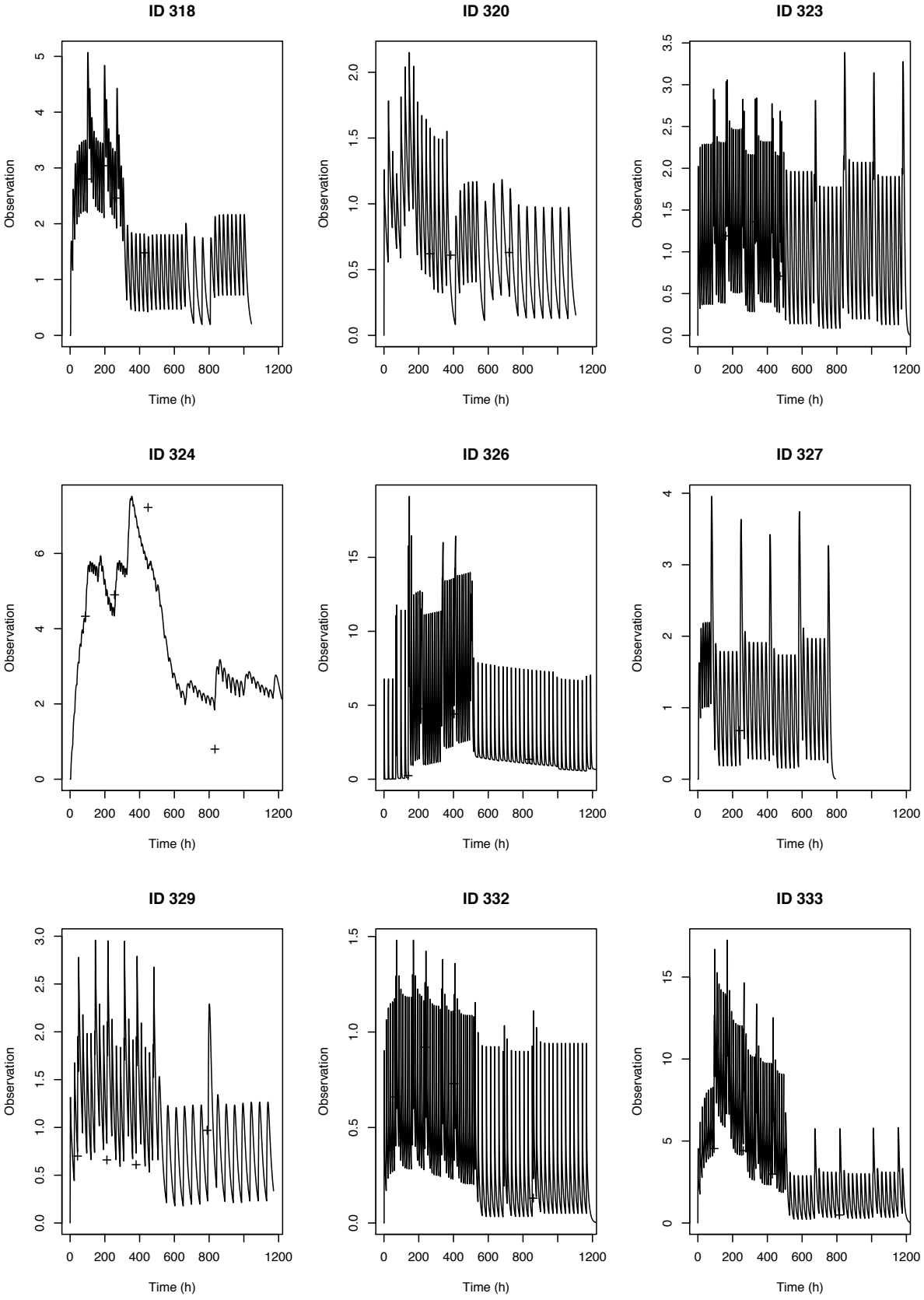
ID 229
ID 231
ID 233
ID 234
ID 235
ID 236
ID 237
ID 241
Observation
Time (h)

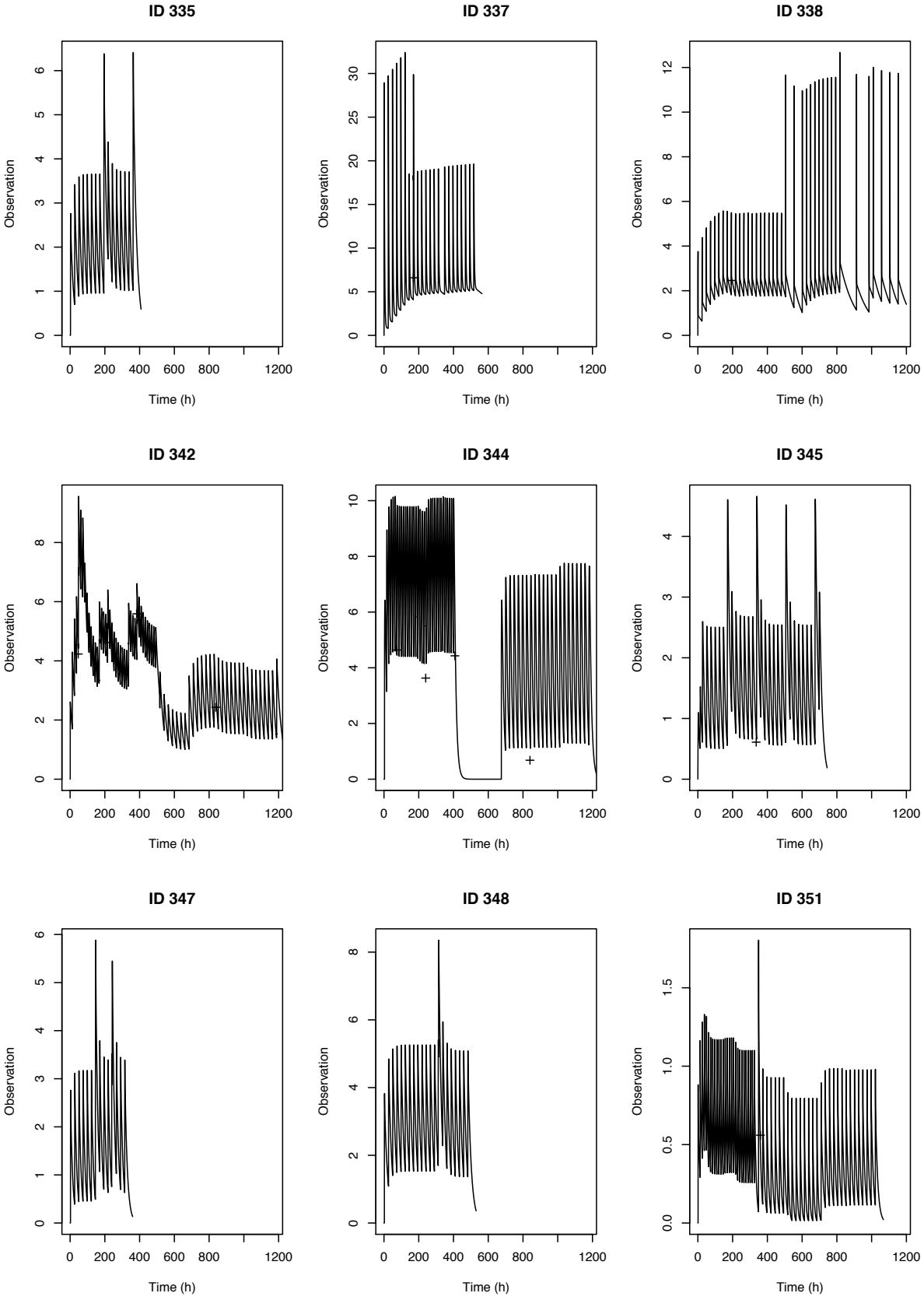

ID 245
ID 246
ID 249
ID 251
ID 253
ID 254
ID 264
ID 265
ID 266
Observation
Time (h)

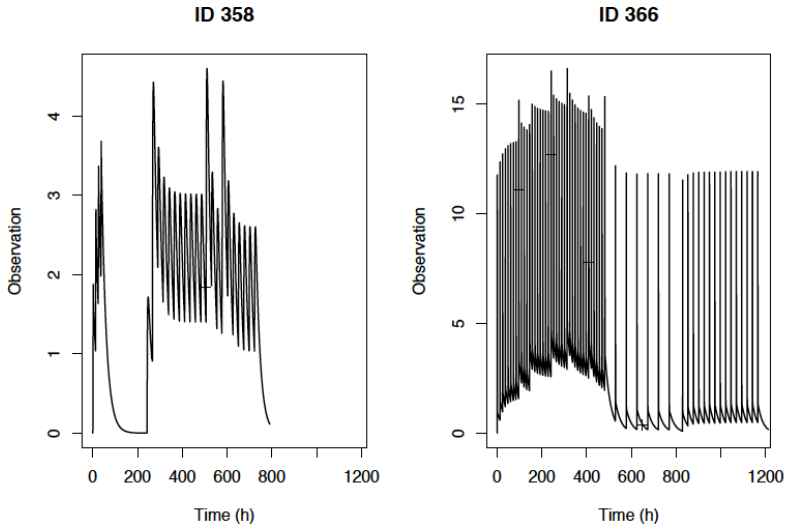

ID 267
ID 268
ID 269
ID 270
ID 271
ID 272
ID 273
ID 274
ID 275
Observation
Time (h)


ID 278
ID 279
ID 281
ID 282
ID 283
ID 285
ID 287
ID 290
ID 291
Observation
Time (h)


ID 292
ID 293
ID 294
ID 295
ID 296
ID 297
ID 300
ID 304
ID 307
Observation
Time (h)


ID 318
ID 320
ID 323
ID 324
ID 326
ID 327
ID 329
ID 332
ID 333
Observation
Time (h)


ID 335
ID 337
ID 338
ID 342
ID 344
ID 345
ID 347
ID 348
ID 351
Observation
Time (h)


ID 358
Observation
0
1
2
3
4
0
200
400
600
800
1200
Time (h)
ID 366
Observation
0
5
10
15
0
200
400
600
800
1200
Time (h)

## 7.5 Plots from analysis 3

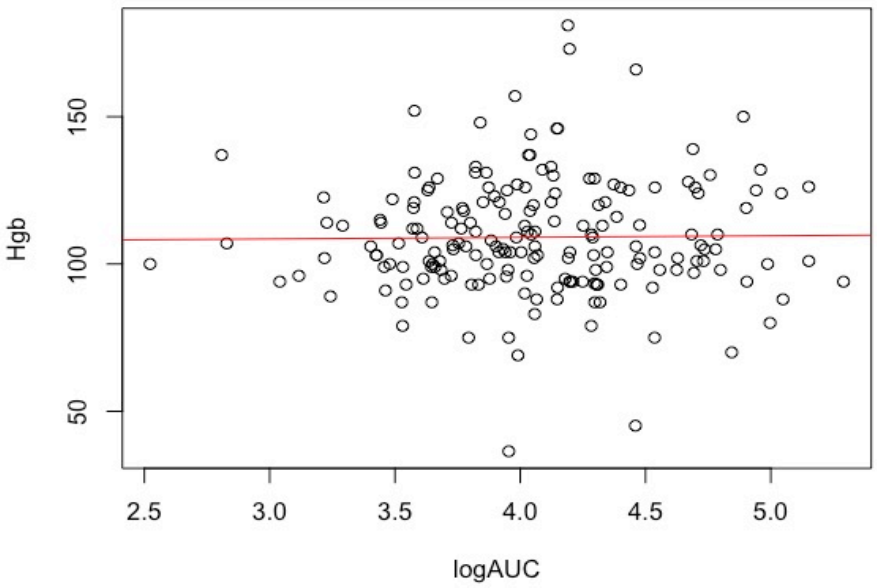



**Figure 7:** Scatterplot $\log AUC_{3\ days}$ vs. Hemoglobin.

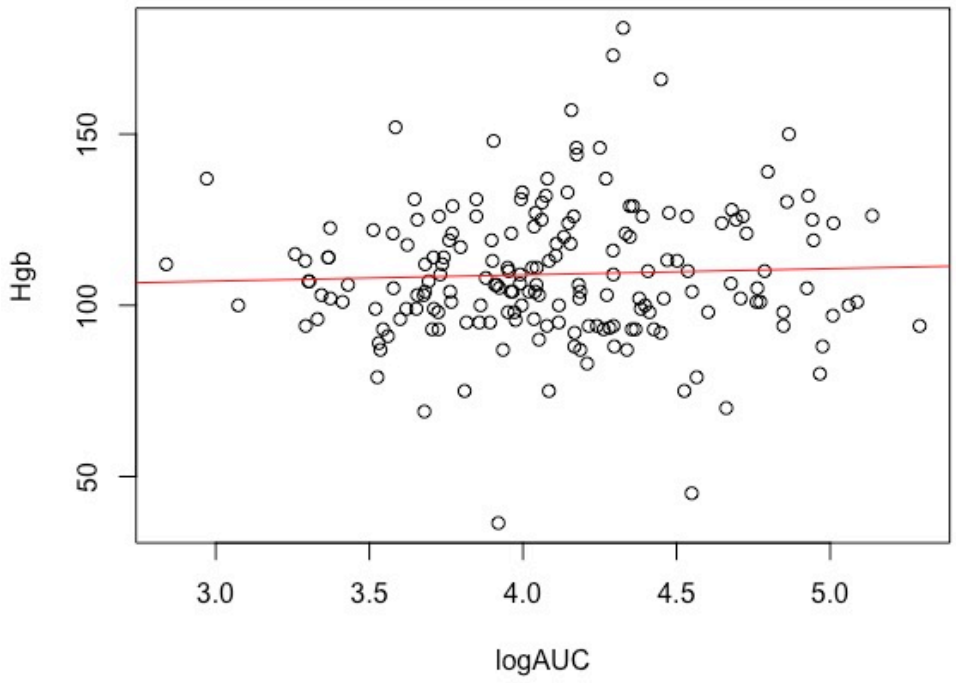



**Figure 8:** Scatterplot $\log AUC_{7\ days}$ vs. Hemoglobin.

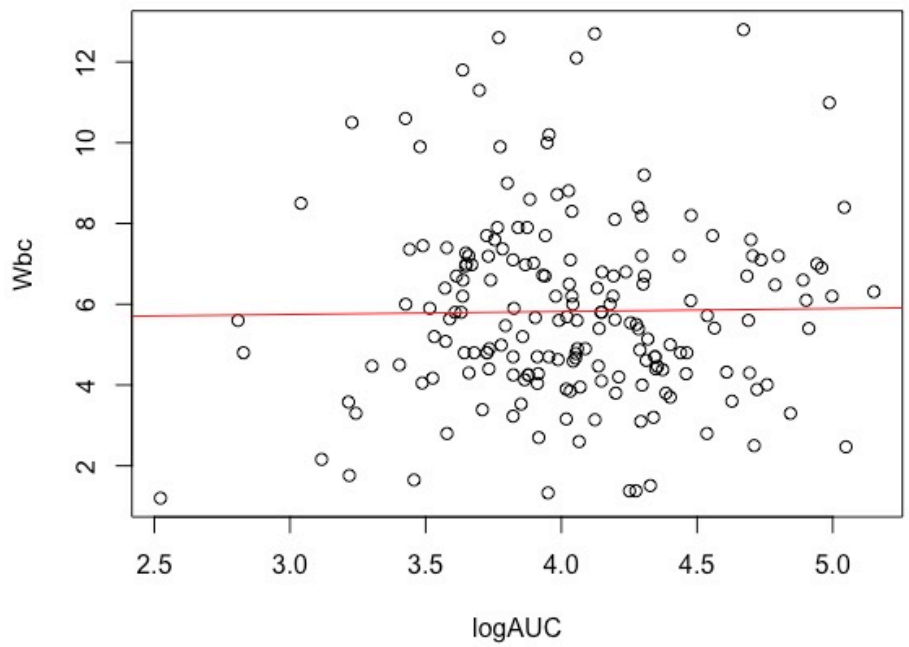



**Figure 9:** Scatterplot $\log AUC_{3\ days}$ vs. White blood cell count.

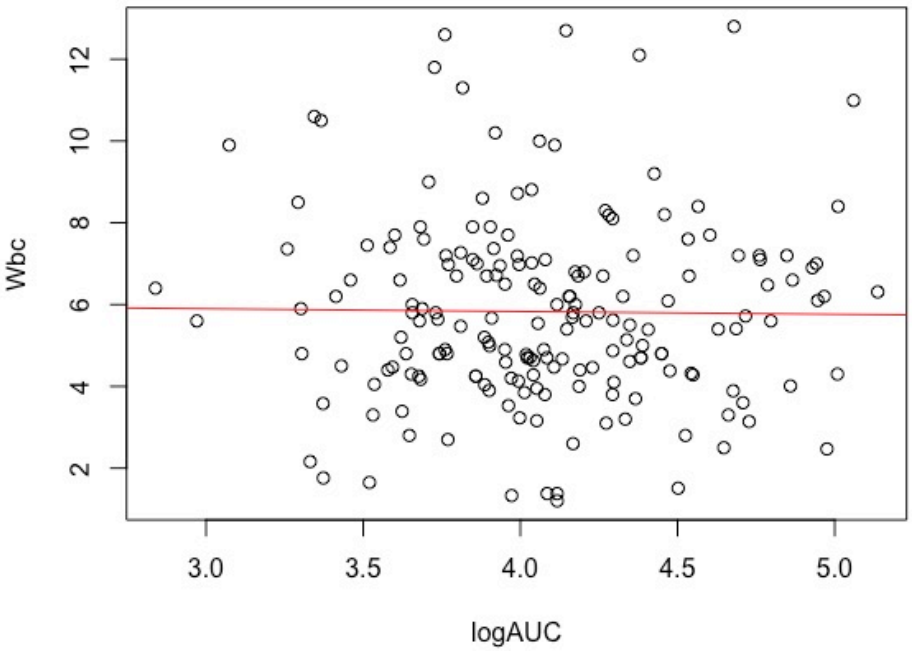



**Figure 10:** Scatterplot $\log AUC_{7\ days}$ vs. White blood cell count.

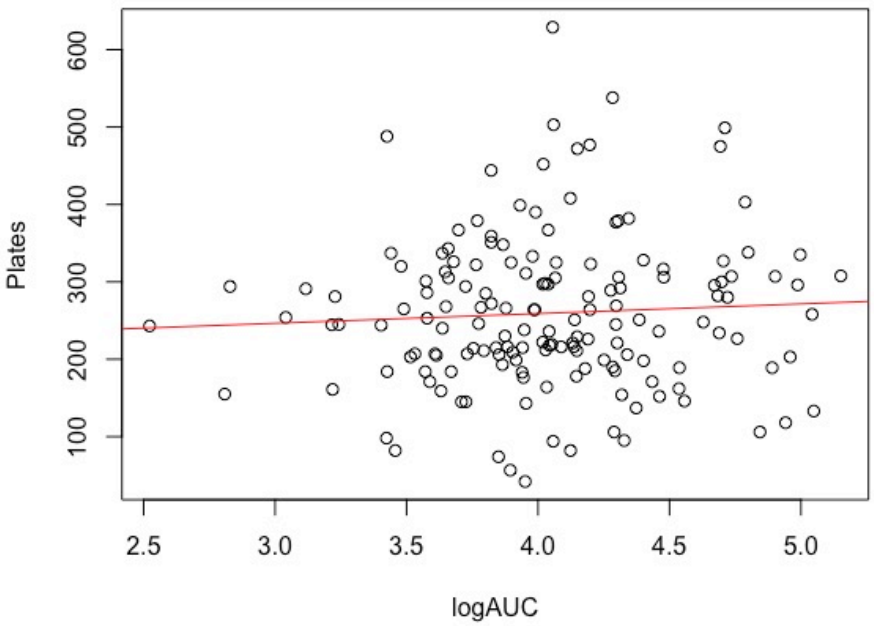



**Figure 11:** Scatterplot $logAUC_{3\ days}$ vs. Platelet count.

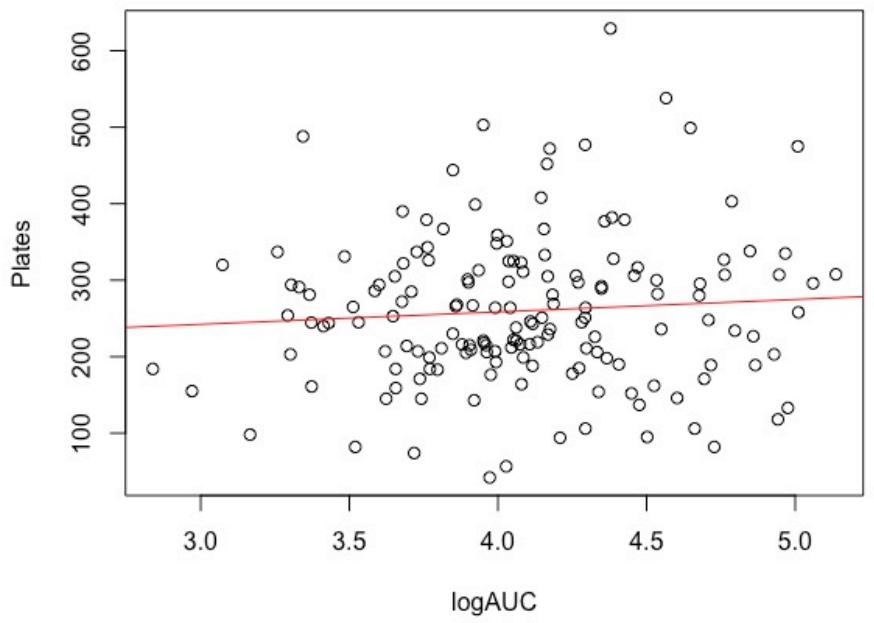
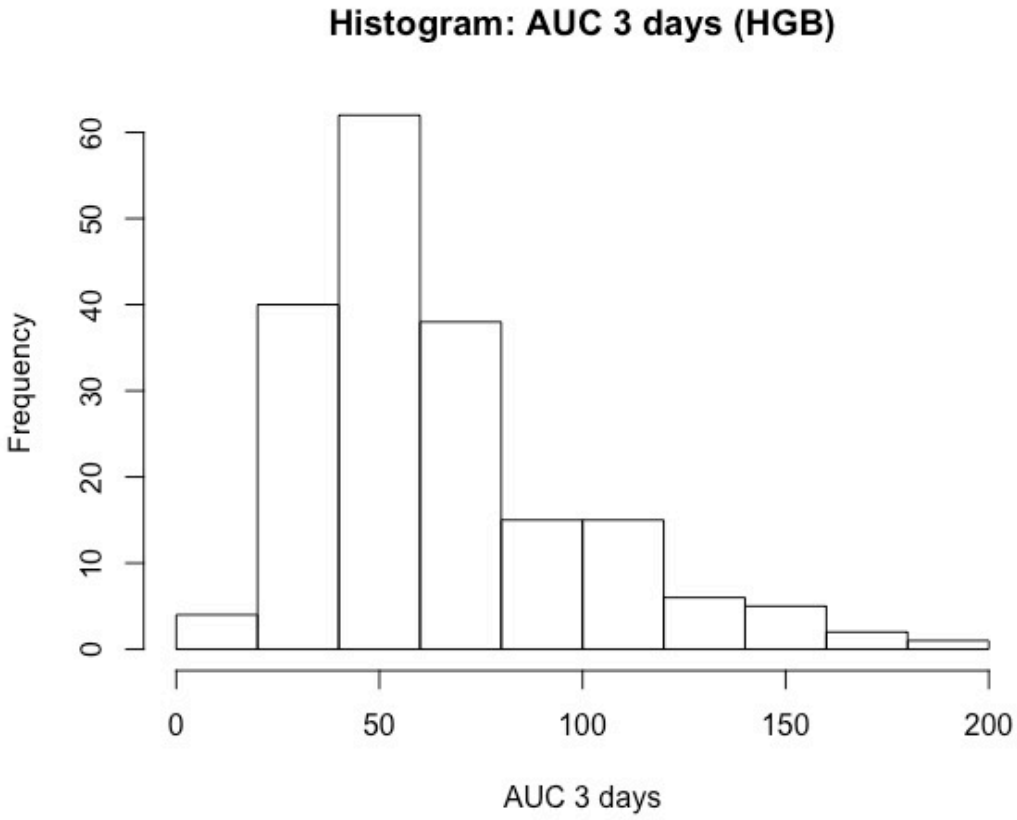
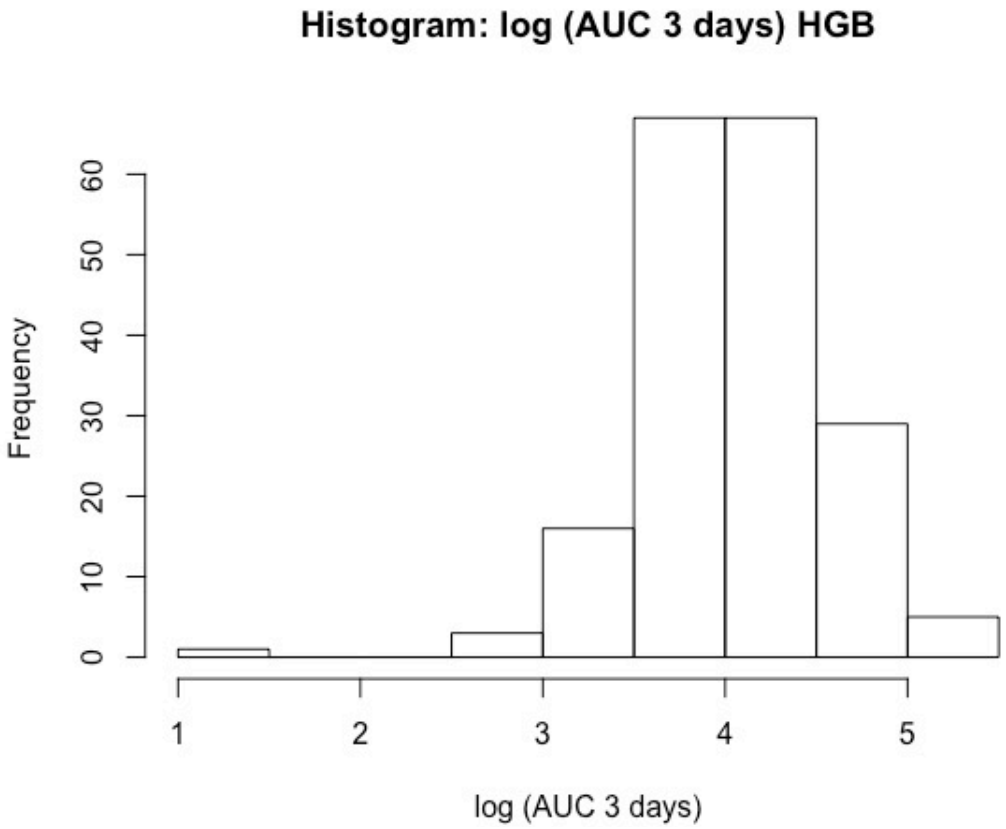
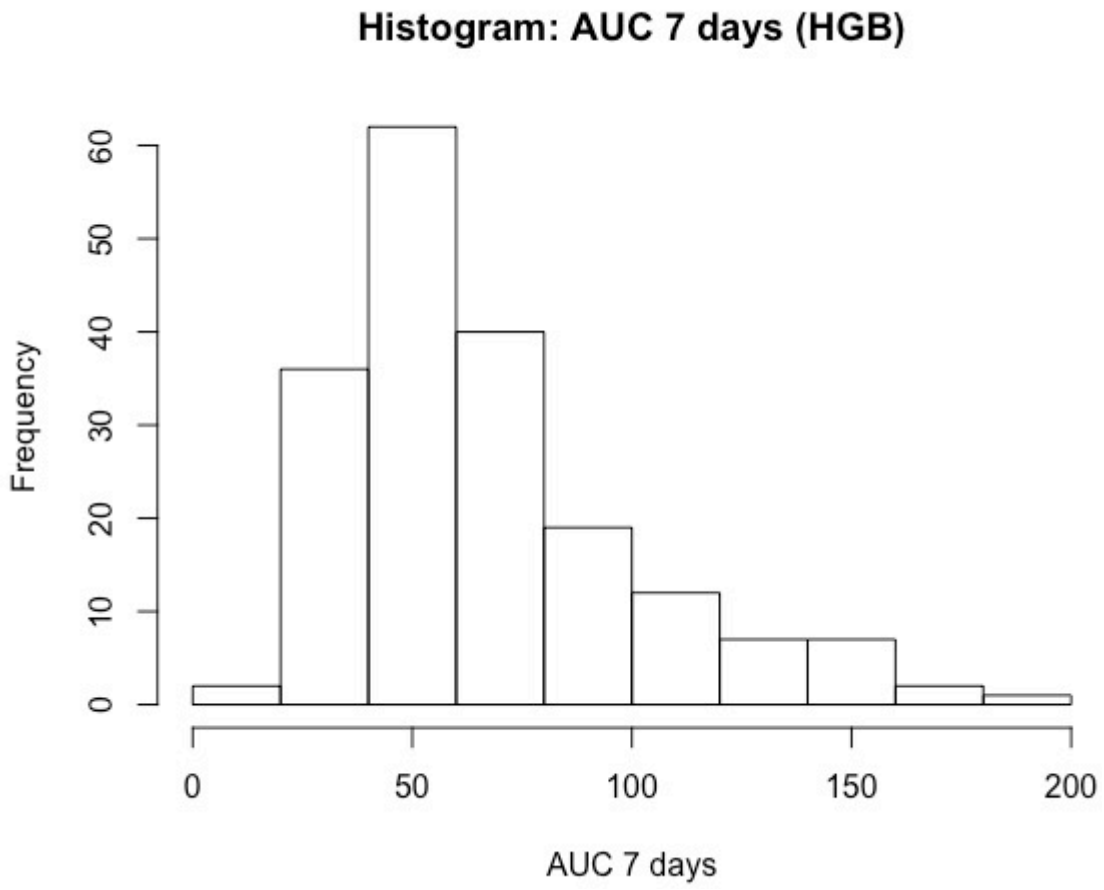


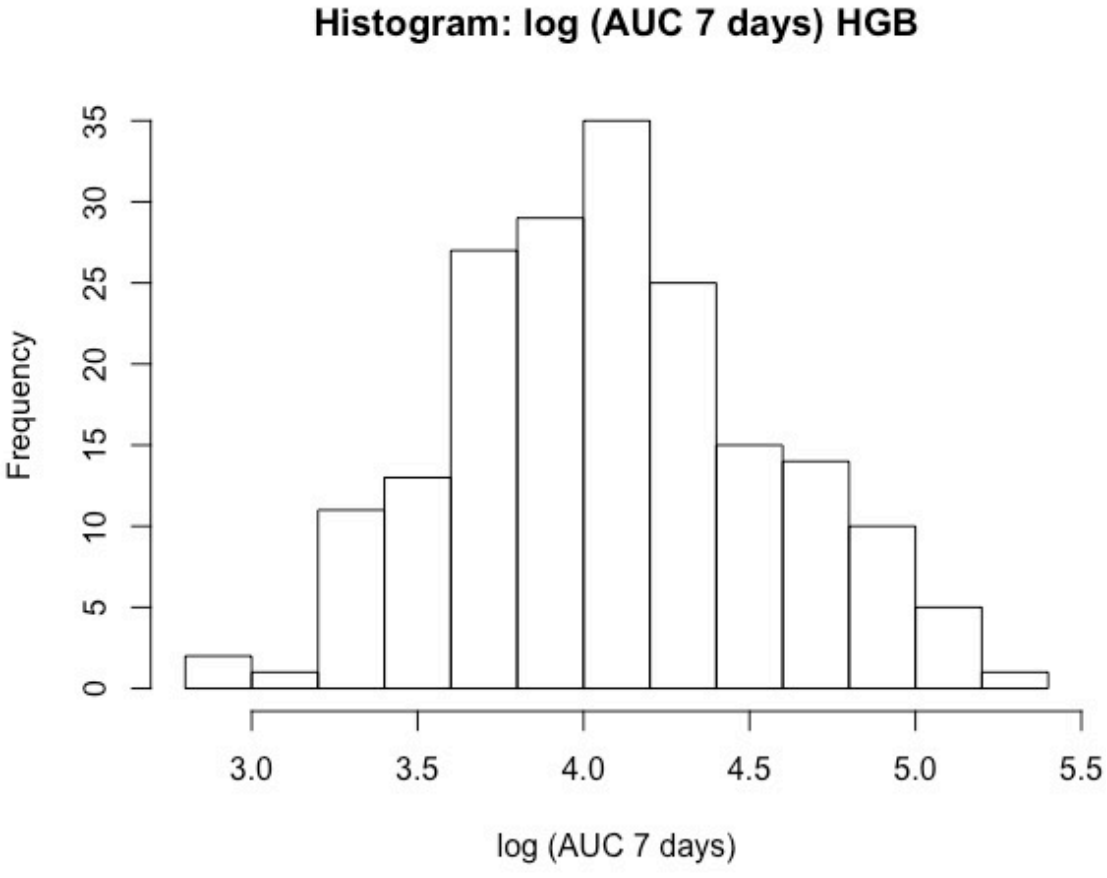

**Figure 12:** Scatterplot $AUC_{7\ days}$ vs. Platelet count.

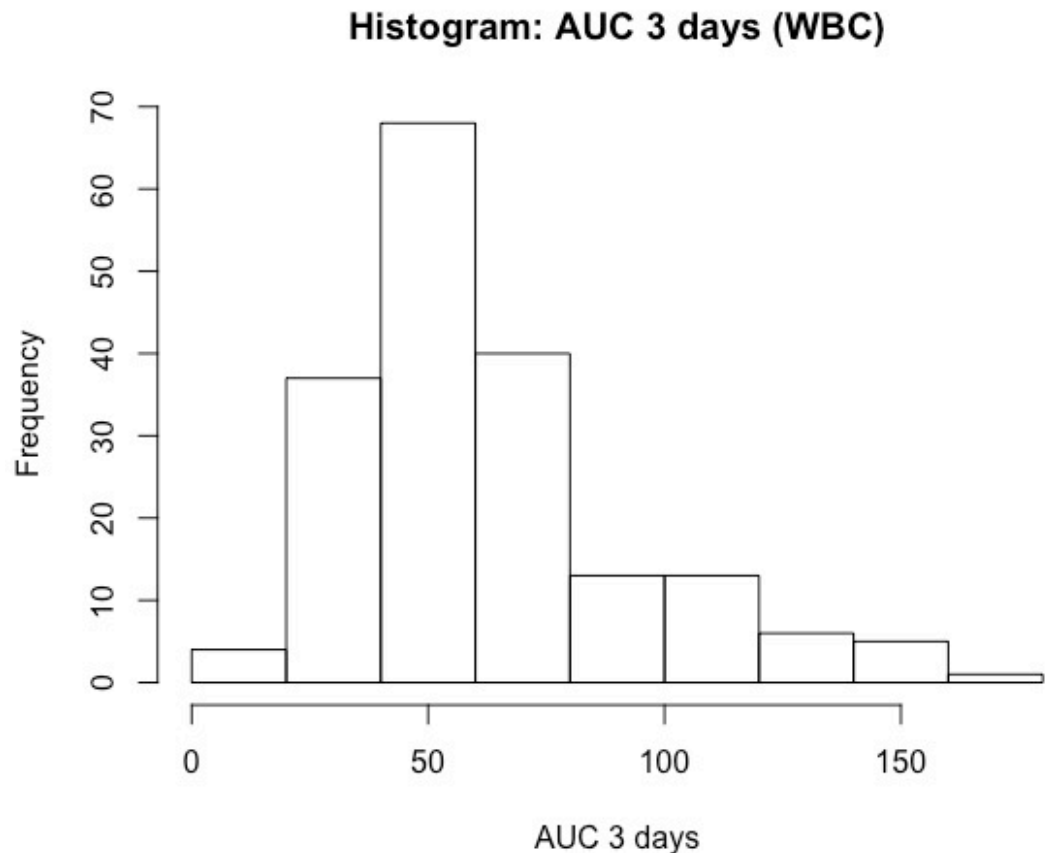
## 7.6 Histograms

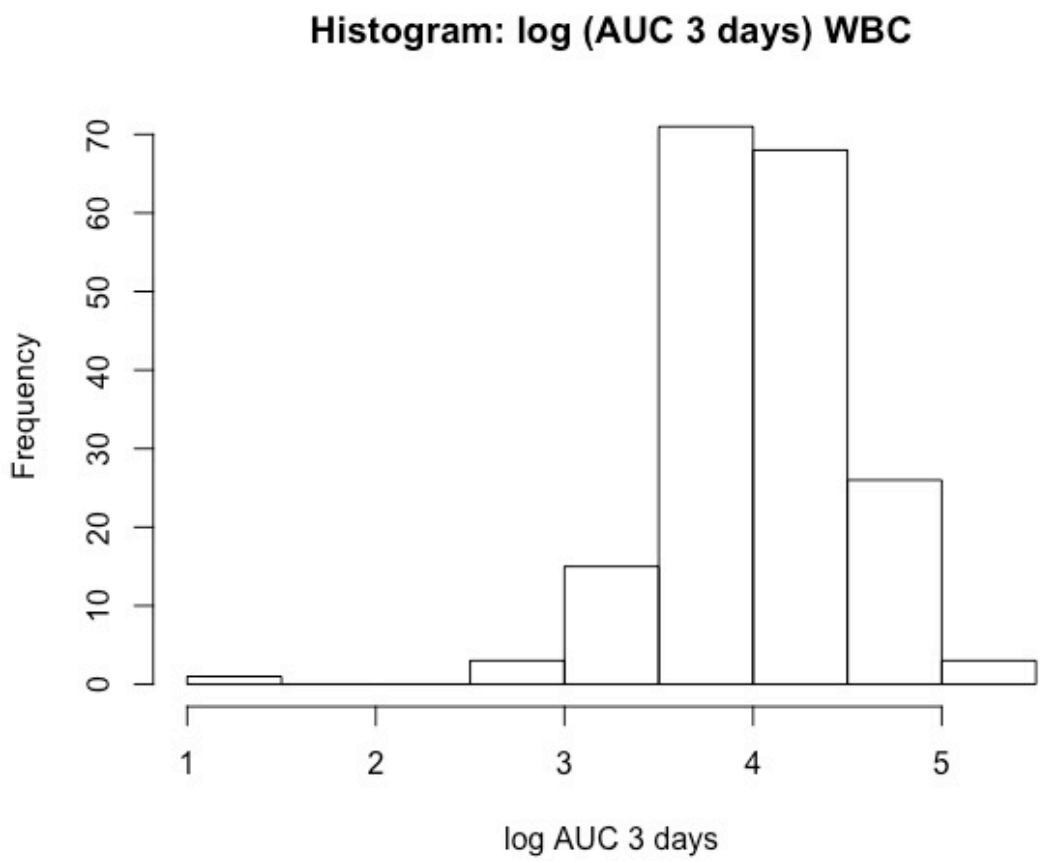


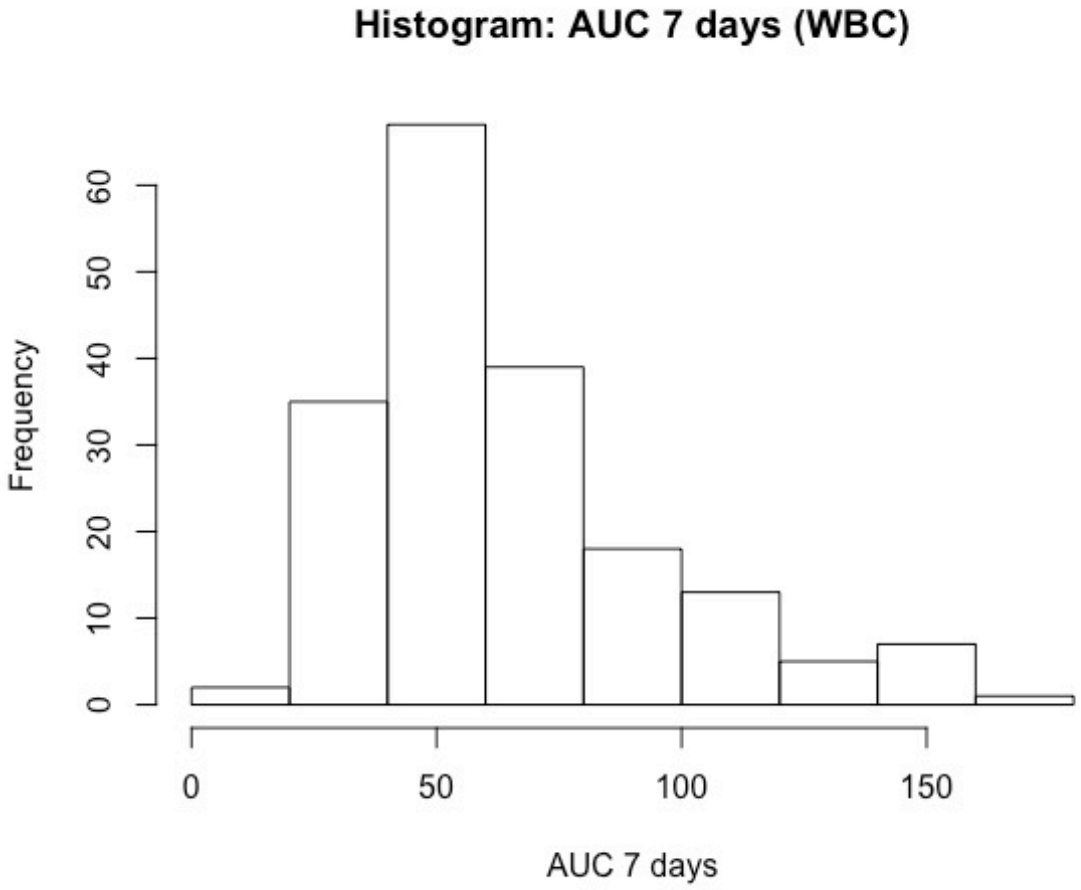



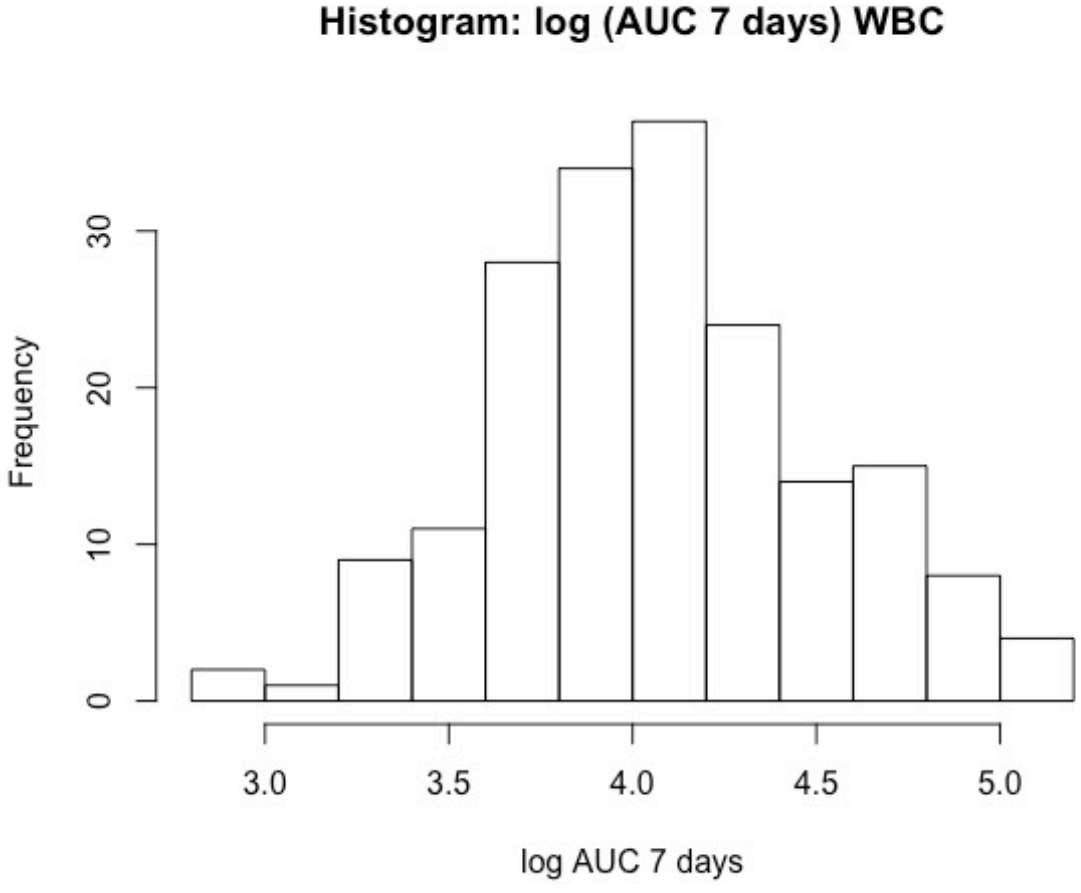

Histogram: AUC 7 days (HGB)
Frequency
0
10
20
30
40
50
60
0
50
100
150
200
AUC 7 days

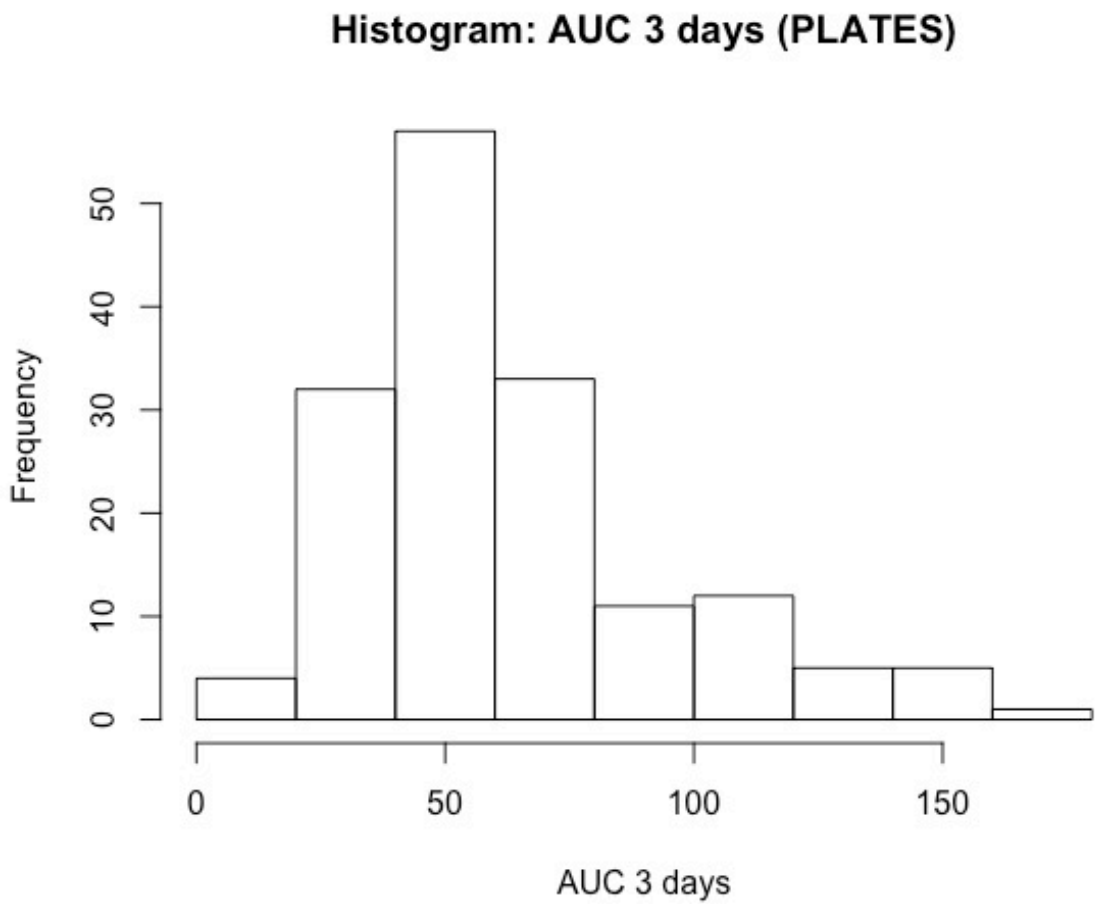

Histogram: log (AUC 7 days) HGB
Frequency
0
5
10
15
20
25
30
35
3.0
3.5
4.0
4.5
5.0
5.5
log (AUC 7 days)

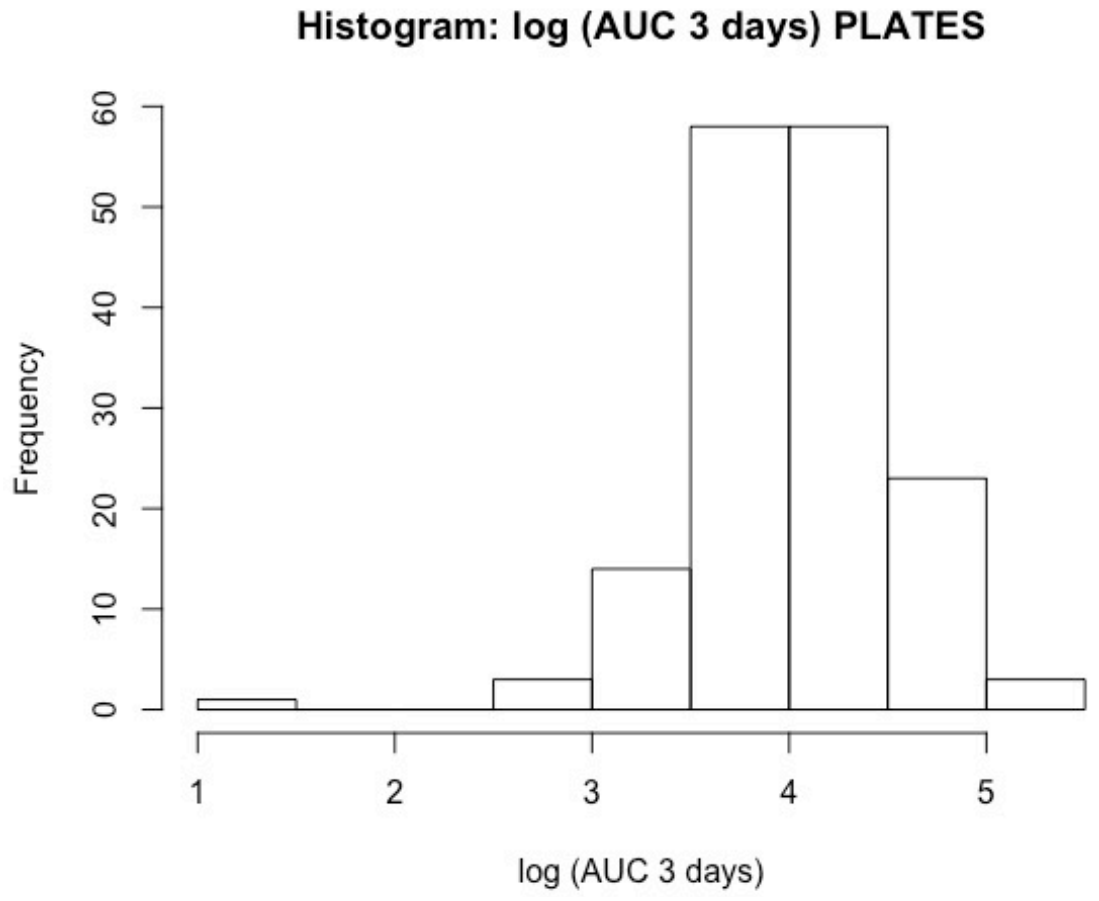

Histogram: AUC 3 days (WBC)
Frequency
0
10
20
30
40
50
60
70
0
50
100
150
AUC 3 days

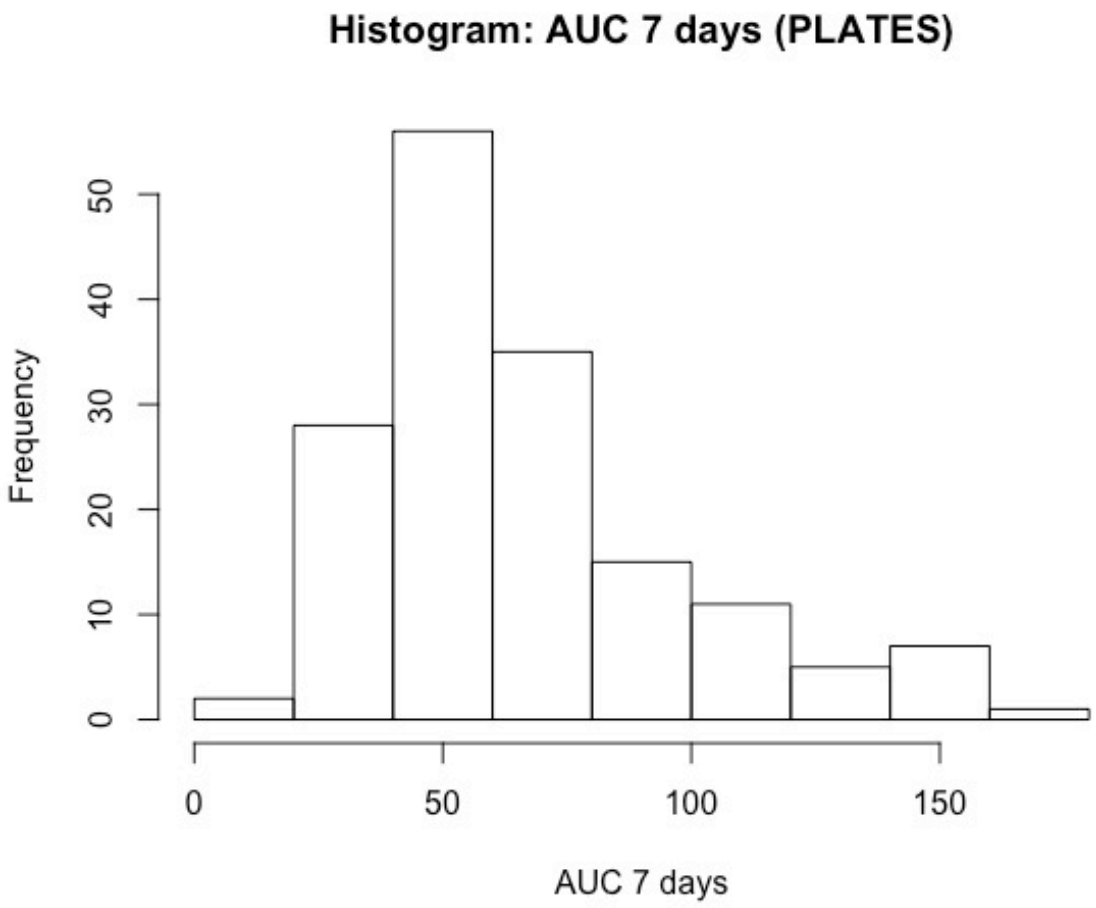

Histogram: log (AUC 3 days) WBC
Frequency
0
10
20
30
40
50
60
70
1
2
3
4
5
log AUC 3 days

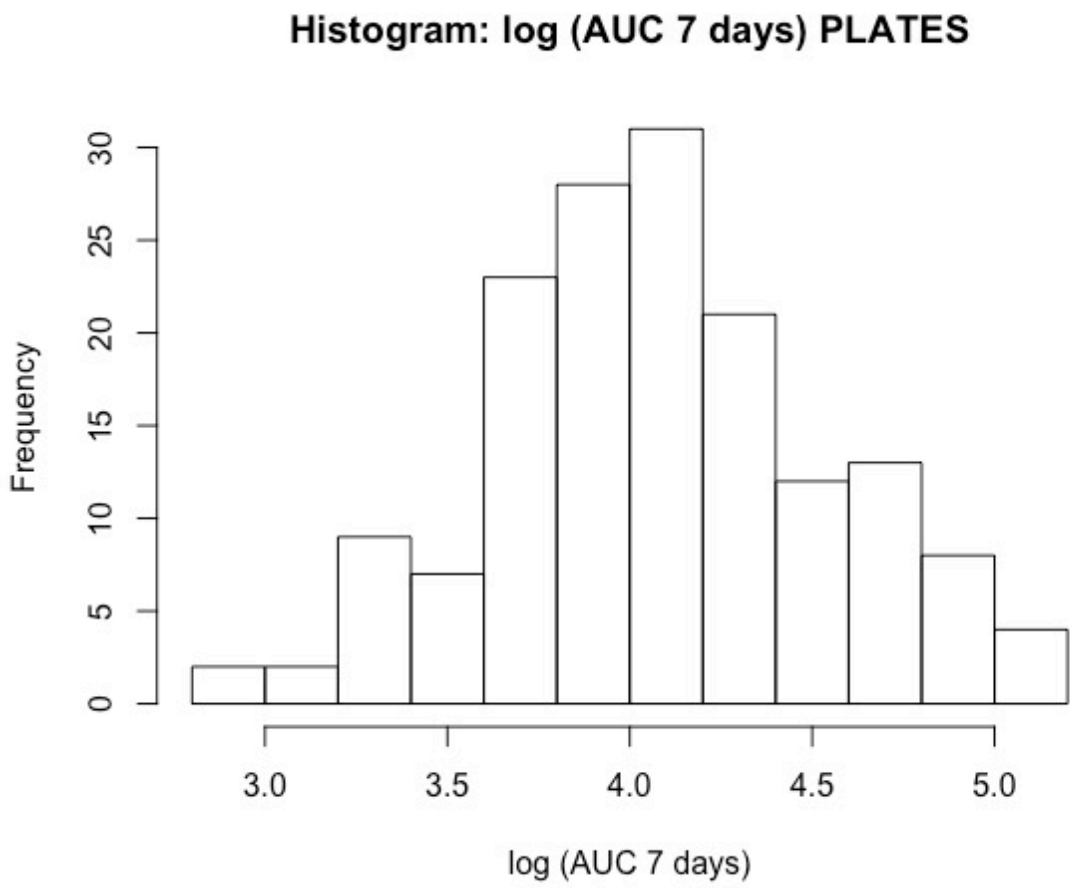

Histogram: AUC 7 days (WBC)
Frequency
0
10
20
30
40
50
60
0
50
100
150
AUC 7 days


Histogram: log (AUC 7 days) WBC
Frequency
0
10
20
30
3.0
3.5
4.0
4.5
5.0
log AUC 7 days


Histogram: AUC 3 days (PLATES)
Frequency
0
10
20
30
40
50
0
50
100
150
AUC 3 days


Histogram: log (AUC 3 days) PLATES
Frequency
0
10
20
30
40
50
60
1
2
3
4
5
log (AUC 3 days)


Histogram: AUC 7 days (PLATES)
Frequency
0
10
20
30
40
50
0
50
100
150
AUC 7 days


Histogram: log (AUC 7 days) PLATES
Frequency
0
5
10
15
20
25
30
3.0
3.5
4.0
4.5
5.0
log (AUC 7 days)