output: pdf_document: default html_document: default

start end N auclast cmax tmax half.life

0 24 150 1080 [76.3] . . .

0 Inf 150 . 107 [65.9] 3.00 [1.00, 6.00] 7.75 [4.17]

Table 2: auclast, cmax, aucinf.obs: geometric mean and geometric coefficient of variation; tmax: median and range; half.life: arithmetic mean and standard deviation; N: number of subjects (continued below)

aucinf.obs
.
1260 [86.1]

```r
# Obtaining subject-level NCA results
param_table <- as.data.frame(results)

head(param_table)
```

```
## # A tibble: 6 x 6
##   Subject start   end PPTESTCD   PPORRES exclude
##     <int> <dbl> <dbl> <chr>        <dbl> <chr>
## 1       1     0    24 auclast   382.     <NA>
## 2       1     0   Inf cmax       34.0    <NA>
## 3       1     0   Inf tmax        1      <NA>
## 4       1     0   Inf tlast      24      <NA>
## 5       1     0   Inf clast.obs   5.30   <NA>
## 6       1     0   Inf lambda.z    0.0829 <NA>
```

```r
#aggregating the data from original dataset to add 'Gender' and 'Dose' level to the subject-level NCA r
data_grouped <- data %>%
  group_by(ID) %>%
  summarize(Dose = first(Dose), Gender = first(Gender))

# left join aggregated data to param table by = c('Subject' = 'ID'))
param_table <- param_table %>%
  left_join(data_grouped %>% select(ID, Dose, Gender), by = c('Subject' = 'ID'))

head(param_table)
```

```
## # A tibble: 6 x 8
##   Subject start   end PPTESTCD   PPORRES exclude  Dose Gender
##     <int> <dbl> <dbl> <chr>        <dbl> <chr>   <int> <chr>
## 1       1     0    24 auclast   382.     <NA>     5000 Male
## 2       1     0   Inf cmax       34.0    <NA>     5000 Male
## 3       1     0   Inf tmax        1      <NA>     5000 Male
## 4       1     0   Inf tlast      24      <NA>     5000 Male
## 5       1     0   Inf clast.obs   5.30   <NA>     5000 Male
## 6       1     0   Inf lambda.z    0.0829 <NA>     5000 Male
```

```
#pivot PPTESTCD and PPORRES columns

data_wide <- param_table %>%
  pivot_wider(names_from = PPTESTCD, values_from = PPORRES)

#adding the Clerance and Volume parameters to NCA subject level parameter table

data_wide <- data_wide %>%
  mutate(
    CL = Dose / aucinf.obs,             # Clearance
    Vd = CL / lambda.z                  # Volume of distribution
  )

# View the reshaped dataset
head(data_wide)
```

```
## # A tibble: 6 x 22
##   Subject start   end exclude  Dose Gender auclast  cmax  tmax tlast clast.obs
##     <int> <dbl> <dbl> <chr>   <int> <chr>    <dbl> <dbl> <dbl> <dbl>     <dbl>
## 1       1     0    24 <NA>     5000 Male      382.  NA      NA    NA     NA
## 2       1     0   Inf <NA>     5000 Male       NA   34.0     1    24      5.30
## 3       2     0    24 <NA>     5000 Male     1199.  NA      NA    NA     NA
## 4       2     0   Inf <NA>     5000 Male       NA  100.      2    24     32.9
## 5       3     0    24 <NA>     5000 Male      459.  NA      NA    NA     NA
## 6       3     0   Inf <NA>     5000 Male       NA   53.9     3    24      2.34
## # i 11 more variables: lambda.z <dbl>, r.squared <dbl>, adj.r.squared <dbl>,
## #   lambda.z.time.first <dbl>, lambda.z.n.points <dbl>, clast.pred <dbl>,
## #   half.life <dbl>, span.ratio <dbl>, aucinf.obs <dbl>, CL <dbl>, Vd <dbl>
```

```
# Summary statistics for AUCLAST, CMAX, TMAX, and other NCA parameters
summary_stats <- data_wide %>%
  group_by(Dose, Gender) %>%
  summarize(
    median_auclast = median(auclast, na.rm = TRUE),           # Median AUCLAST
    median_cmax = median(cmax, na.rm = TRUE),                 # Median CMAX
    median_tmax = median(tmax, na.rm = TRUE),                 # Median TMAX
    q1_auclast = quantile(auclast, probs = 0.25, na.rm = TRUE), # 25th Percentile AUCLAST
    q3_auclast = quantile(auclast, probs = 0.75, na.rm = TRUE), # 75th Percentile AUCLAST
    median_tlast = median(tlast, na.rm = TRUE),                 # Median TLAST
    median_half_life = median(half.life, na.rm = TRUE),         # Median Half-Life
    median_CL = median(CL, na.rm = TRUE),                     # Median Clearance
    median_Vd = median(Vd, na.rm = TRUE),                     # Median Volume of Distribution
    n = n_distinct(Subject)                                   # Number of Distinct Subjects
  )
```

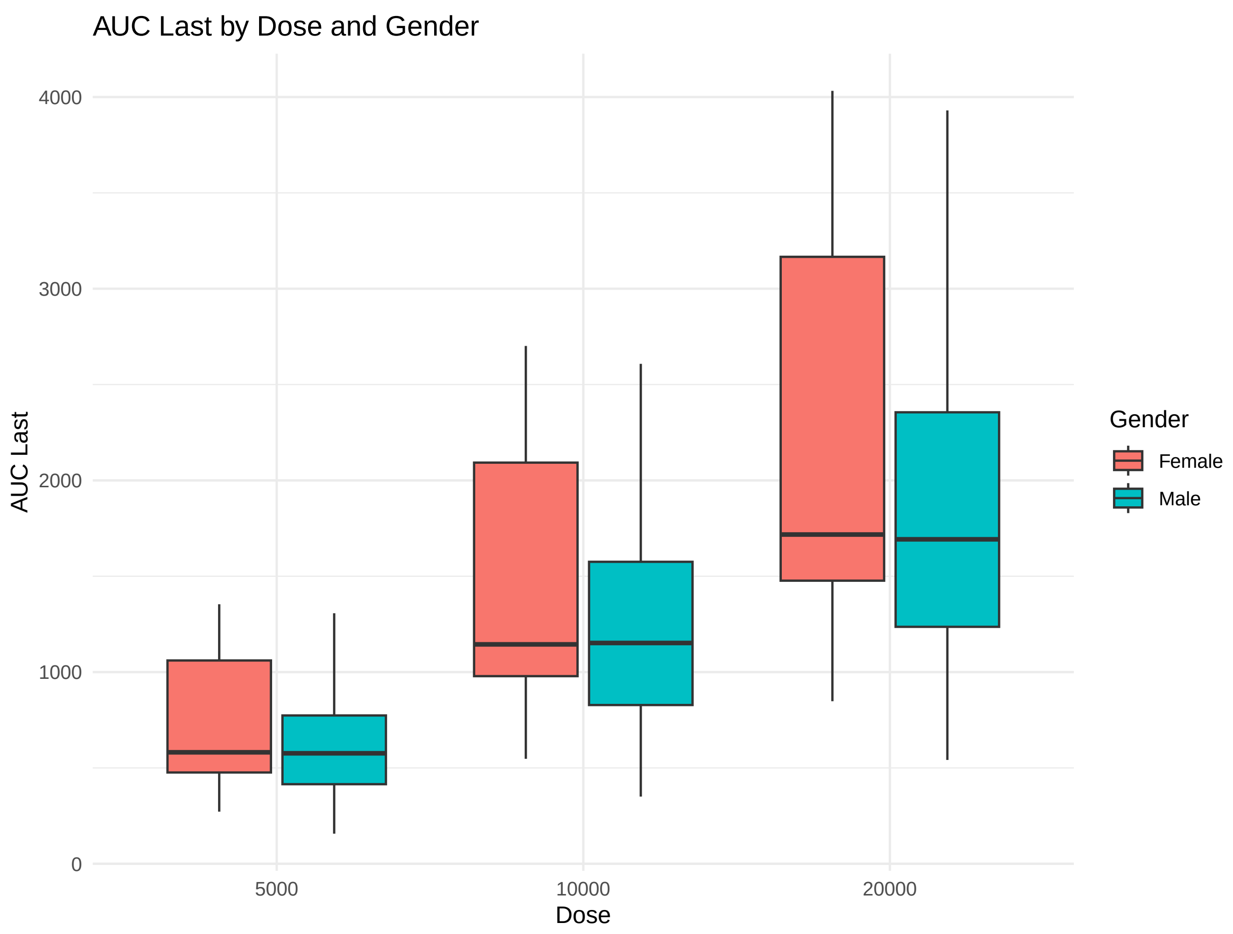
```
## ‘summarise()‘ has grouped output by ’Dose’. You can override using the
## ‘.groups‘ argument.
```

```
print(summary_stats)
```

```
## # A tibble: 6 x 12
## # Groups:   Dose [3]
##    Dose Gender median_auclast median_cmax median_tmax q1_auclast q3_auclast
##   <int> <chr>           <dbl>       <dbl>       <dbl>      <dbl>      <dbl>
## 1  5000 Female           581.        51.6           2       476.      1060.
## 2  5000 Male             576.        58.5           3       415.       774.
## 3 10000 Female          1145.       105.            3       979.      2093.
## 4 10000 Male            1152.       114.            3       828.      1575.
## 5 20000 Female          1718.       157.            3      1477.      3166.
## 6 20000 Male            1693.       173.            3      1236.      2355.
## # i 5 more variables: median_tlast <dbl>, median_half_life <dbl>,
## #   median_CL <dbl>, median_Vd <dbl>, n <int>
```

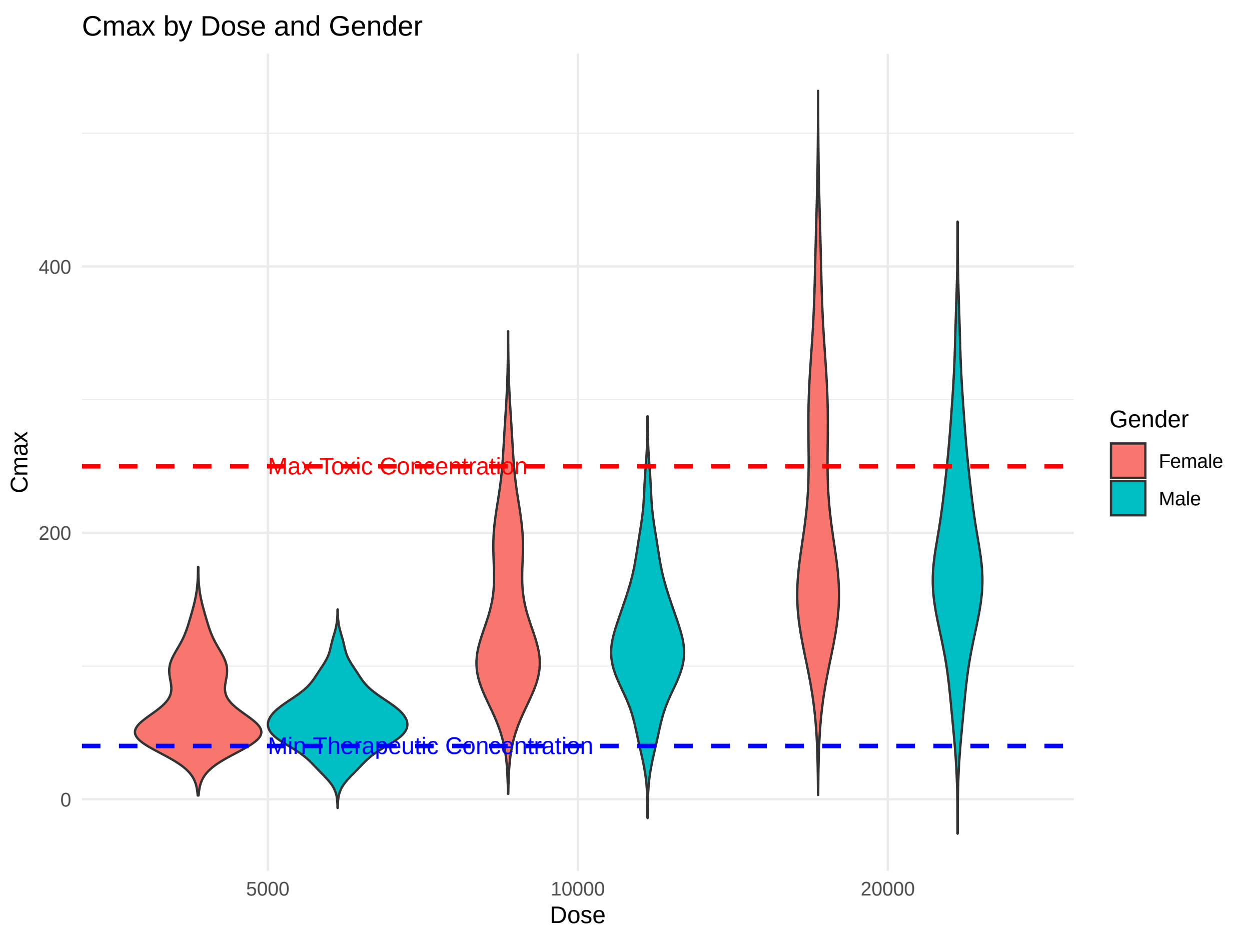
```
#Dose Gender median_auclast median_cmax median_tmax q1_auclast q3_auclast median_tlast
#<int> <chr>           <dbl>       <dbl>       <dbl>      <dbl>      <dbl>        <dbl>
#1  5000 Female           581.        51.6           2       476.      1060.           24
#2  5000 Male             576.        58.5           3       415.       774.           24
#3 10000 Female          1145.       105.            3       979.      2093.           24
#4 10000 Male            1152.       114.            3       828.      1575.           24
#5 20000 Female          1718.       157.            3      1477.      3166.           24
#6 20000 Male            1693.       173.            3      1236.      2355.           24


#BOX PLOT of median AUCLast by Gender
ggplot(data_wide, aes(x=factor(Dose), y=auclast, fill=Gender)) +
  geom_boxplot() +
  labs(title="AUC Last by Dose and Gender", x="Dose", y="AUC Last") +
  theme_minimal()
```

```
## Warning: Removed 150 rows containing non-finite outside the scale range
## (‘stat_boxplot()‘).
```



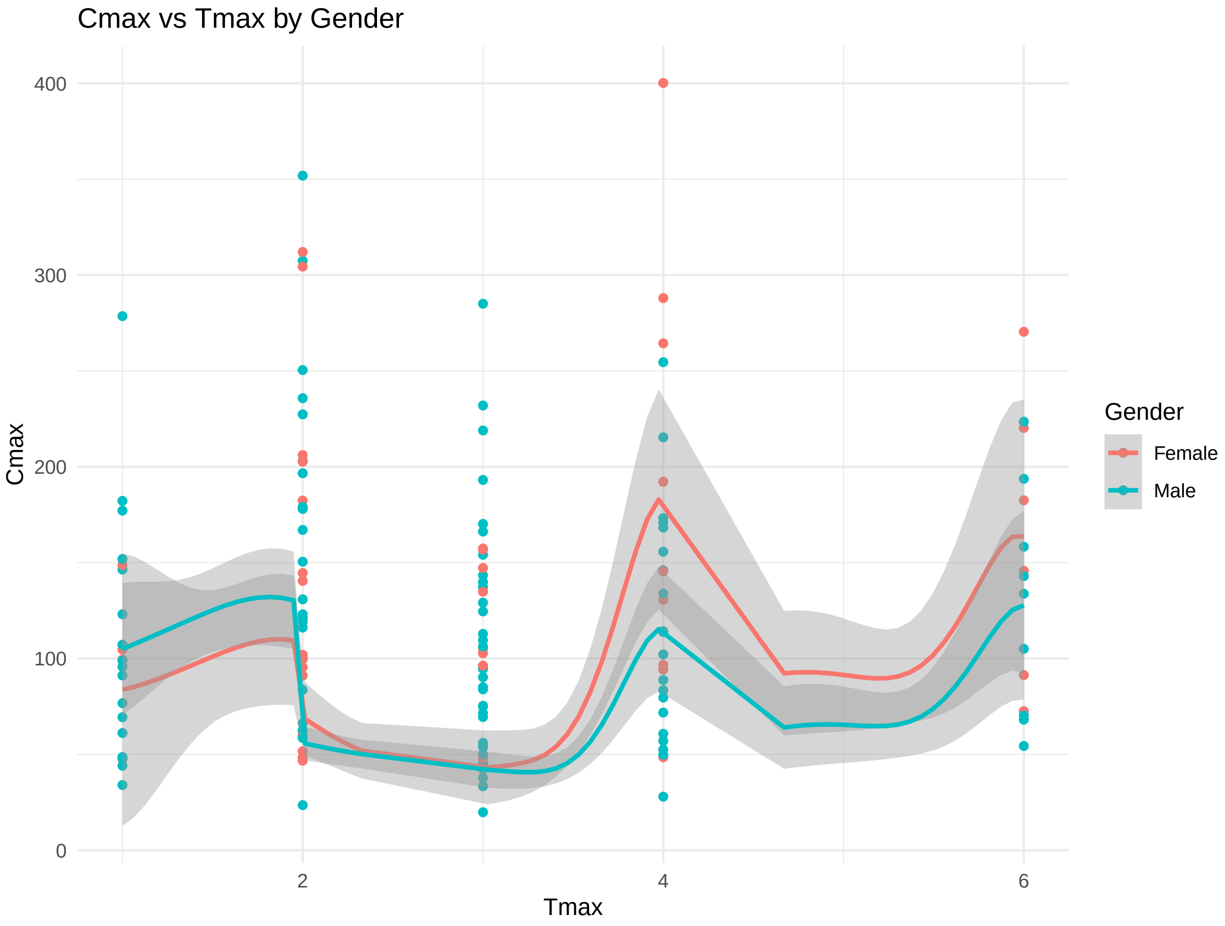
```
#Violin PLOT of median Cmax by Gender MEC and MTC lines
min_therapeutic_concentration <- 40  # theoretical value for MEC
max_toxic_concentration <- 250  # theoretical value for  MTC

ggplot(data_wide, aes(x = factor(Dose), y = cmax, fill = Gender)) +
  geom_violin(trim=FALSE) +
  labs(
    title = "Cmax by Dose and Gender",
    x = "Dose",
    y = "Cmax"
  ) +
  theme_minimal() +
  geom_hline(yintercept = min_therapeutic_concentration, color = "blue", linetype = "dashed", size = 1.
  geom_hline(yintercept = max_toxic_concentration, color = "red", linetype = "dashed", size = 1.0) +
  annotate("text", x = 1, y = min_therapeutic_concentration + 0.5,
           label = "Min Therapeutic Concentration", color = "blue", size = 4, hjust = 0) +
  annotate("text", x = 1, y = max_toxic_concentration + 0.5,
           label = "Max Toxic Concentration", color = "red", size = 4, hjust = 0)
```

```
## Warning: Removed 150 rows containing non-finite outside the scale range
## (‘stat_ydensity()‘).
```



```
#scatterplot of Cmax vs Tmax by Gender
ggplot(data_wide, aes(x=tmax, y=cmax, color=Gender)) +
  geom_point() +
  geom_smooth(method="loess",formula = y ~ splines::bs(x, 3), se=TRUE) +# have chosen the loees fitting
  labs(title="Cmax vs Tmax by Gender", x="Tmax", y="Cmax") +
  theme_minimal()
```

```
## Warning: Removed 150 rows containing non-finite outside the scale range
## (‘stat_smooth()‘).

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : pseudoinverse used at -0.015775 -0.015775 -0.028086

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : neighborhood radius 4.0106

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : reciprocal condition number 1.0517e-47

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : There are other near singularities as well. 12.734
## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : pseudoinverse used at
## -0.015775 -0.015775 -0.028086

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : neighborhood radius
## 4.0106

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : reciprocal condition
## number 1.0517e-47

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : There are other near
## singularities as well. 12.734

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : pseudoinverse used at -0.01405 -0.015397 -0.06381

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : neighborhood radius 4.5929

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : reciprocal condition number 3.4904e-46

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : There are other near singularities as well. 18.437

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : pseudoinverse used at
## -0.01405 -0.015397 -0.06381

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : neighborhood radius
## 4.5929

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : reciprocal condition
## number 3.4904e-46

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object)), : There are other near
## singularities as well. 18.437
## Warning: Removed 150 rows containing missing values or values outside the scale range
## (`geom_point()`).

## Warning: Removed 40 rows containing missing values or values outside the scale range
## (`geom_smooth()`).
```



```
############# NCA analysis considering also Age

# dose data with Age
dose_data_Age <- data %>%
  filter(Time == 0) %>%  # Only keep rows where Time == 0 (corresponding to dosing)
  group_by(ID) %>%       # Group by each subject ID
  summarize(
    Subject = first(ID), # Unique subject identifier
    Time = first(Time),  # Dosing time (usually 0)
    Dose = first(Dose),
    Gender = first(Gender),
    Age = first(Age)
  )

print(dose_data_Age)
```

```
## # A tibble: 150 x 6
##       ID Subject  Time  Dose Gender   Age
##    <int>   <int> <dbl> <int> <chr>  <int>
##  1     1       1     0  5000 Male      56
##  2     2       2     0  5000 Male      45
##  3     3       3     0  5000 Male      51
##  4     4       4     0  5000 Female    47
##  5     5       5     0  5000 Female    51
##  6     6       6     0  5000 Male      41
##  7     7       7     0  5000 Male      56
##  8     8       8     0  5000 Male      57
##  9     9       9     0  5000 Female    47
## 10    10      10     0  5000 Male      60
## # i 140 more rows
```

```
#creating Dose object
dose_data_Age_obj <- PKNCAdose(
  dose_data_Age,
  Dose ~ Time | Age + Subject
)

# Concentaration data with Age

Conc_data_Age <- data %>%
  select(ID, Time, Conc, Age, Gender) %>%
  rename(
    Subject = ID,
    Concentration = Conc
  )
head(Conc_data_Age)
```

```
##   Subject Time Concentration Age Gender
## 1       1 0.00      0.000000  56   Male
## 2       1 0.25      8.612809  56   Male
## 3       1 0.50     19.436818  56   Male
## 4       1 1.00     34.006699  56   Male
## 5       1 2.00     30.228800  56   Male
## 6       1 3.00     31.299610  56   Male
```

```
#creating Concentration object
Conc_data_Age_obj <- PKNCAconc(
  Conc_data_Age[!is.na(Conc_data_Age$Concentration), ],  # Filter rows where concentration values are n
  Concentration ~ Time | Age  + Subject                # Formula: Concentration as a function of Time,
)

#creation of the PK object
PK_object_Age <- PKNCAdata(
  data.conc = Conc_data_Age_obj,  # Concentration-time object
  data.dose = dose_data_Age_obj          # Dosing object
)

#obtaining overal results for PK_object as AUC last, Cmax, tmax, halflife
results_Age<-pk.nca(PK_object_Age)
```

```
## ===============>--------------- 49% | ETA: 1s ===============>---------------
## 49% | ETA: 1s ========================>------ 79% | ETA: 1s
## ========================>------ 81% | ETA: 1s ===========================>----
## 85% | ETA: 0s ===========================>--- 89% | ETA: 0s
## ============================>-- 93% | ETA: 0s ==============================>-
## 97% | ETA: 0s
```

```
pander::pander(summary(results_Age))
```

Table 3: auclast, cmax, aucinf.obs: geometric mean and geometric coefficient of variation; tmax: median and range; half.life: arithmetic mean and standard deviation; N: number of subjects (continued below)

start	end	Age	N	auclast	cmax	tmax
0	24	56	9	869 [62.0]	.	.
0	Inf	56	9	.	87.6 [65.4]	3.00 [1.00, 4.00]
0	24	45	9	1120 [89.0]	.	.
0	Inf	45	9	.	126 [61.7]	2.00 [2.00, 3.00]
0	24	51	18	939 [70.7]	.	.
0	Inf	51	18	.	92.7 [74.5]	3.00 [2.00, 4.00]
0	24	47	9	1590 [59.3]	.	.
0	Inf	47	9	.	119 [61.1]	4.00 [2.00, 4.00]
0	24	41	9	1450 [108]	.	.
0	Inf	41	9	.	106 [89.0]	4.00 [2.00, 6.00]
0	24	57	3	812 [61.2]	.	.
0	Inf	57	3	.	78.4 [57.8]	3.00 [3.00, 3.00]
0	24	60	3	310 [69.6]	.	.
0	Inf	60	3	.	44.6 [64.6]	3.00 [2.00, 3.00]
0	24	48	9	944 [83.7]	.	.
0	Inf	48	9	.	106 [52.7]	1.00 [1.00, 6.00]
0	24	59	3	646 [61.1]	.	.
0	Inf	59	3	.	88.0 [60.2]	1.00 [1.00, 1.00]
0	24	55	12	1300 [74.8]	.	.
0	Inf	55	12	.	117 [68.2]	3.00 [1.00, 3.00]
0	24	54	9	794 [60.8]	.	.
0	Inf	54	9	.	114 [68.4]	2.00 [1.00, 3.00]
0	24	50	9	1440 [67.6]	.	.
0	Inf	50	9	.	124 [59.5]	3.00 [2.00, 4.00]
0	24	53	12	1250 [69.1]	.	.
0	Inf	53	12	.	119 [79.5]	3.00 [2.00, 6.00]
0	24	38	3	831 [59.2]	.	.
0	Inf	38	3	.	83.1 [57.7]	2.00 [2.00, 3.00]
0	24	58	6	869 [54.9]	.	.
0	Inf	58	6	.	110 [52.0]	2.00 [2.00, 2.00]
0	24	40	3	2300 [60.2]	.	.
0	Inf	40	3	.	131 [63.7]	6.00 [6.00, 6.00]
0	24	42	3	1360 [56.9]	.	.
0	Inf	42	3	.	131 [61.3]	3.00 [3.00, 3.00]
0	24	52	6	865 [63.1]	.	.
0	Inf	52	6	.	120 [55.7]	3.00 [1.00, 4.00]
0	24	61	3	2450 [59.7]	.	.
0	Inf	61	3	.	240 [61.4]	4.00 [4.00, 4.00]

start	end	Age	N	auclast	cmax	tmax
0	24	46	9	1100 [61.5]	.	.
0	Inf	46	9	.	91.8 [51.0]	4.00 [2.00, 6.00]
0	24	49	3	845 [62.3]	.	.
0	Inf	49	3	.	80.6 [60.9]	4.00 [1.00, 4.00]

half.life	aucinf.obs
.	.
6.85 [2.19]	965 [63.3]
.	.
10.3 [9.02]	1430 [121]
.	.
5.66 [2.06]	1020 [72.4]
.	.
11.3 [2.77]	2110 [63.4]
.	.
10.1 [3.51]	1870 [127]
.	.
5.51 [0.965]	867 [64.1]
.	.
6.07 [2.23]	334 [77.3]
.	.
7.88 [4.02]	1080 [96.6]
.	.
4.92 [0.171]	669 [61.4]
.	.
7.86 [2.16]	1490 [77.3]
.	.
4.80 [2.84]	842 [63.9]
.	.
8.76 [4.41]	1780 [80.4]
.	.
9.25 [4.59]	1550 [65.4]
.	.
10.9 [3.41]	1050 [65.7]
.	.
3.45 [0.781]	883 [55.1]
.	.
10.3 [0.292]	3080 [60.9]
.	.
5.56 [1.75]	1460 [51.4]
.	.
5.07 [3.10]	933 [69.2]
.	.
6.05 [0.379]	2670 [61.0]
.	.
10.6 [4.70]	1410 [75.6]
.	.
7.18 [0.371]	924 [62.9]

```r
# Obtaining subject-level NCA results
param_table_Age <- as.data.frame(results_Age)

head(param_table_Age)
```

```
## # A tibble: 6 x 7
##     Age Subject start   end PPTESTCD   PPORRES exclude
##   <int>   <int> <dbl> <dbl> <chr>        <dbl> <chr>
## 1    56       1     0    24 auclast   382.     <NA>
## 2    56       1     0   Inf cmax       34.0    <NA>
## 3    56       1     0   Inf tmax        1      <NA>
## 4    56       1     0   Inf tlast      24      <NA>
## 5    56       1     0   Inf clast.obs   5.30   <NA>
## 6    56       1     0   Inf lambda.z    0.0829 <NA>
```

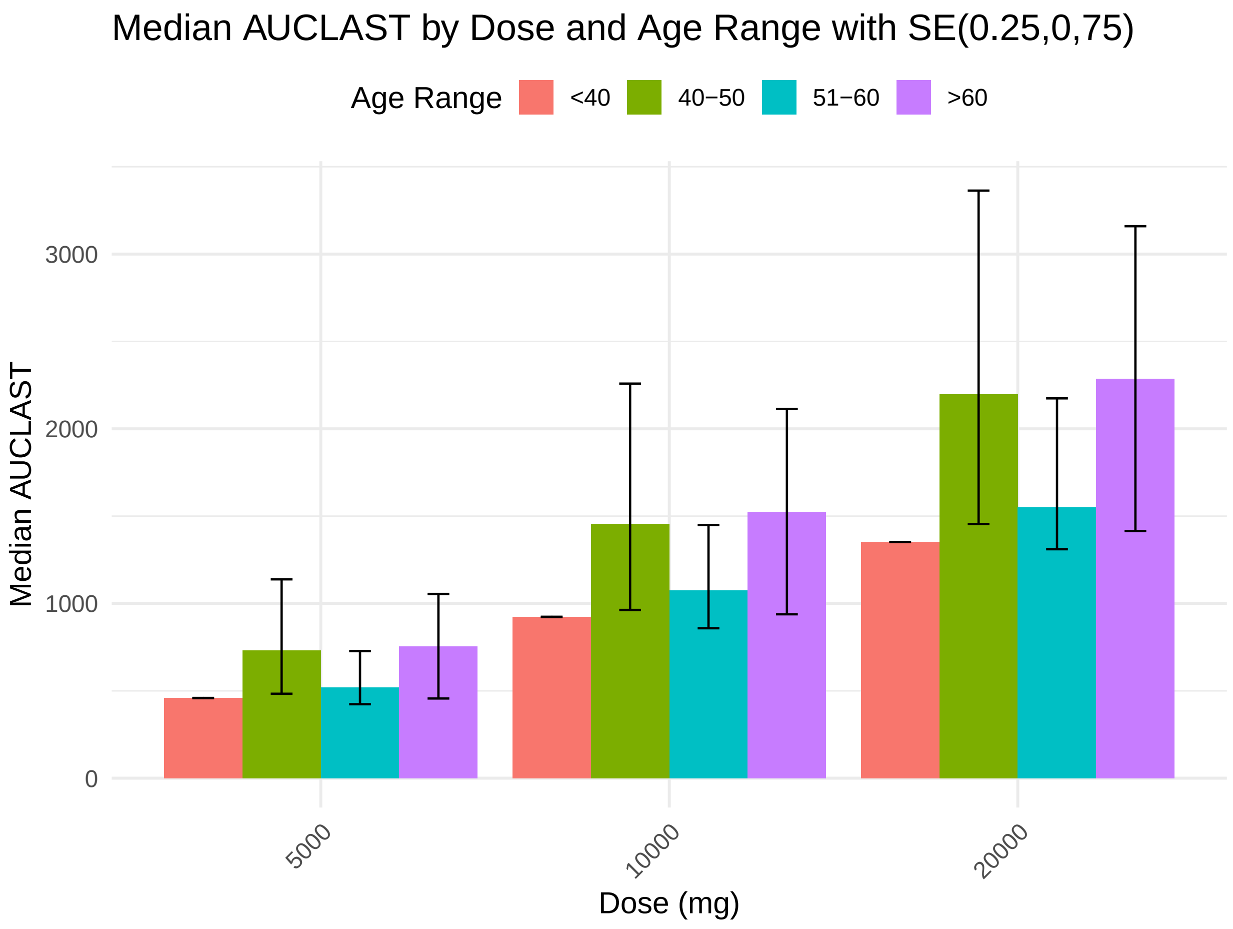
```r
#it seems that adding Age to the Dose and ConcentraTION AS GROUPING factor did not affect calculation o

# left join aggregated data to param table by = c('Subject' = 'ID')) to add Dose
param_table_Age <- param_table_Age %>%
  left_join(data_grouped %>% select(ID, Dose), by = c('Subject' = 'ID'))

#pivot PPTESTCD and PPORRES columns

data_wide_Age <- param_table_Age %>%
  pivot_wider(names_from = PPTESTCD, values_from = PPORRES)

#adding the Clerance and Volume parameters to NCA subject level parameter table

data_wide_Age <- data_wide_Age %>%
  mutate(
    CL = Dose / aucinf.obs,            # Clearance
    Vd = CL / lambda.z                 # Volume of distribution
  )


# Add Age Range to Dataset
data_wide_Age <- data_wide_Age %>%
  mutate(
    Age_Range = cut(
      Age,
      breaks = c(0, 40, 50, 60, Inf),  # Define intervals (e.g., 0-40, 40-50, etc.)
      labels = c("<40", "40-50", "51-60", ">60"),  # Labels for ranges
      right = FALSE  # Include left endpoint, exclude right endpoint
    )
  )
# create summary table that has the same column as previous table but with Age grouping
summary_stats_Age <- data_wide_Age %>%
  group_by(Dose, Age_Range) %>%
  summarize(
    median_auclast = median(auclast, na.rm = TRUE),           # Median AUCLAST
    q1_auclast = quantile(auclast, probs = 0.25, na.rm = TRUE), # 25th Percentile AUCLAST
    q3_auclast = quantile(auclast, probs = 0.75, na.rm = TRUE), # 75th Percentile AUCLAST
    median_cmax = median(cmax, na.rm = TRUE),                 # Median CMAX
    median_tmax = median(tmax, na.rm = TRUE),                 # Median TMAX
    median_tlast = median(tlast, na.rm = TRUE),                 # Median TLAST
    median_half_life = median(half.life, na.rm = TRUE),         # Median Half-Life
    median_CL = median(CL, na.rm = TRUE),                     # Median Clearance
    median_Vd = median(Vd, na.rm = TRUE),                     # Median Volume of Distribution
    n = n_distinct(Subject)                                   # Number of Distinct Subjects
  )
```

```
## ‘summarise()‘ has grouped output by ’Dose’. You can override using the
## ‘.groups‘ argument.
```

```
print(summary_stats_Age)
```

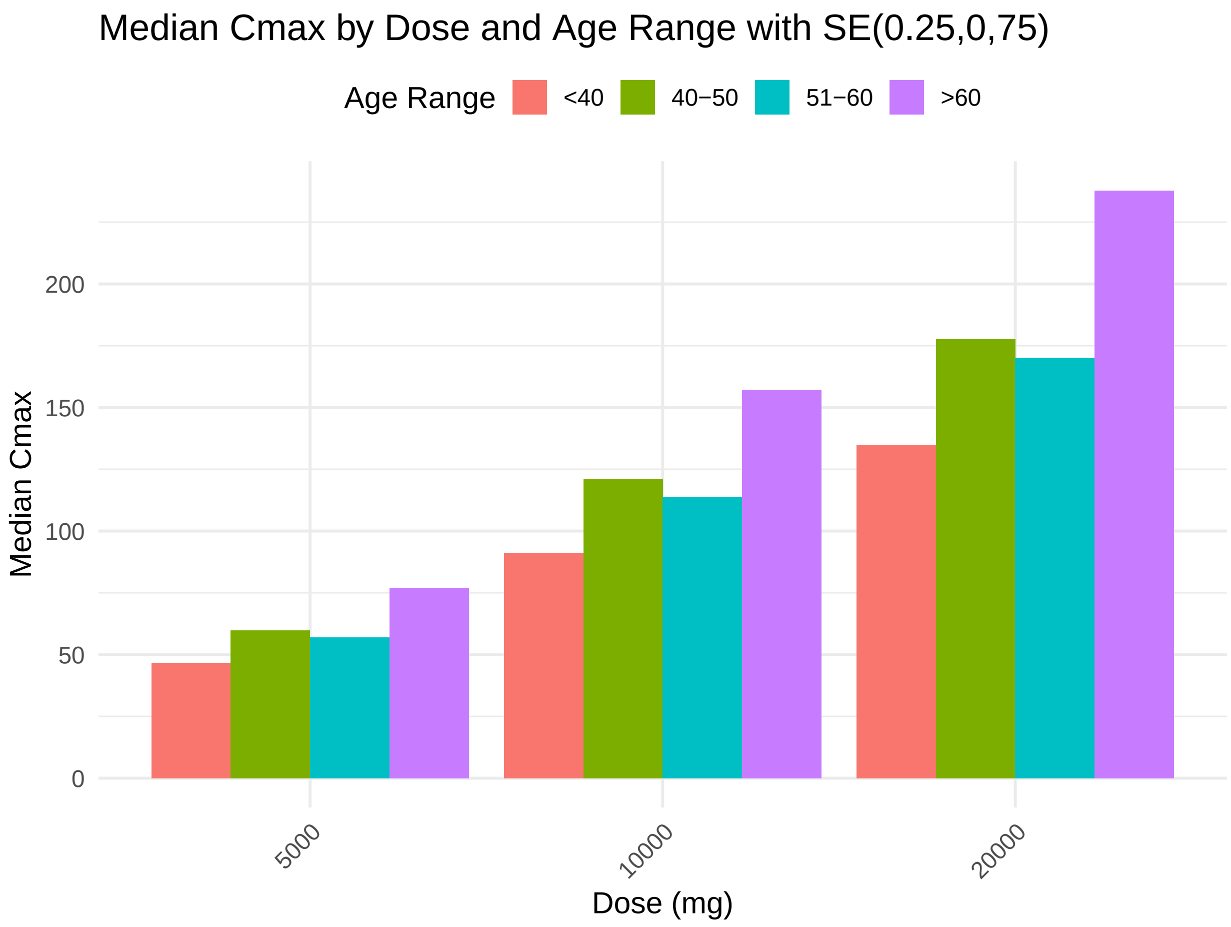
```
## # A tibble: 12 x 12
## # Groups:   Dose [3]
##     Dose Age_Range median_auclast q1_auclast q3_auclast median_cmax median_tmax
##    <int> <fct>              <dbl>      <dbl>      <dbl>       <dbl>       <dbl>
##  1  5000 <40                 459.       459.       459.        46.7         2
##  2  5000 40-50               732.       483.      1138.        59.8         3
##  3  5000 51-60               519.       423.       728.        57.0         3
##  4  5000 >60                 755.       456.      1055.        77.1         3
##  5 10000 <40                 923.       923.       923.        91.1         2
##  6 10000 40-50              1455.       963.      2259.       121.          3.5
##  7 10000 51-60              1074.       858.      1449.       114.          3
##  8 10000 >60                1526.       938.      2114.       157.          3.5
##  9 20000 <40                1352.      1352.      1352.       135.          3
## 10 20000 40-50              2197.      1455.      3363.       178.          3.5
## 11 20000 51-60              1550.      1310.      2174.       170.          3
## 12 20000 >60                2287.      1414.      3160.       238.          3.5
## # i 5 more variables: median_tlast <dbl>, median_half_life <dbl>,
## #   median_CL <dbl>, median_Vd <dbl>, n <int>
```

```
# the computation of

#Median AUCLAST by Dose and Age Range with SE(0.25,0,75)
ggplot(summary_stats_Age, aes(x = factor(Dose), y = median_auclast, fill = Age_Range)) +
  geom_bar(stat = "identity", position = position_dodge()) +
  geom_errorbar(aes(ymin = q1_auclast, ymax = q3_auclast),
                position = position_dodge(0.9), width = 0.25) + # Error bars
  labs(
    title = "Median AUCLAST by Dose and Age Range with SE(0.25,0,75)",
    x = "Dose (mg)",
    y = "Median AUCLAST",
    fill = "Age Range"
  ) +
  theme_minimal(base_size = 14) +
  theme(
    axis.text.x = element_text(angle = 45, hjust = 1), # Rotate x-axis labels for better readability
    legend.position = "top"                           # Move legend to the top for better layout
  )
```



Median AUCLAST by Dose and Age Range with SE(0.25,0,75)

```r
#Median Cmax by Dose and Age Range with SE(0.25,0,75)
ggplot(summary_stats_Age, aes(x = factor(Dose), y = median_cmax, fill = Age_Range)) +
  geom_bar(stat = "identity", position = position_dodge()) +
  labs(
    title = "Median Cmax by Dose and Age Range with SE(0.25,0,75)",
    x = "Dose (mg)",
    y = "Median Cmax",
    fill = "Age Range"
  ) +
  theme_minimal(base_size = 14) +
  theme(
    axis.text.x = element_text(angle = 45, hjust = 1), # Rotate x-axis labels for better readability
    legend.position = "top"                           # Move legend to the top for better layout
  )
```


Median Cmax by Dose and Age Range with SE(0.25,0,75)
Age Range
<40
40−50
51−60
>60
Median Cmax
0
50
100
150
200
5000
10000
20000
Dose (mg)