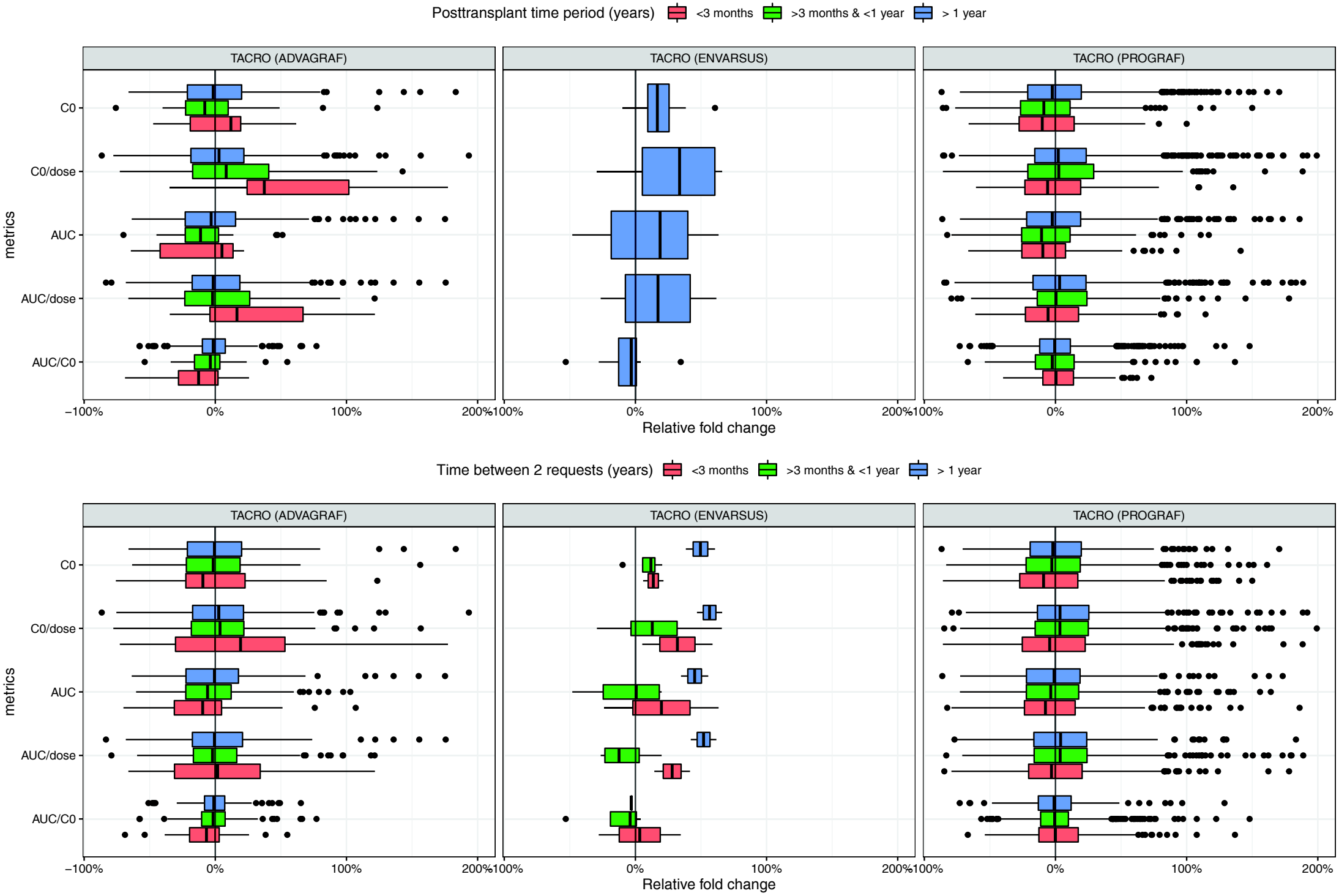
Figure S1

Boxplots of relative intraindividual variations of the metrics of interest censored beyond −100% and +200%, depending on the posttransplant period (A) and the time elapsed between 2 instances (B) (categorized) per formulation type.



Can the Area Under the Curve/trough level ratio be used to optimize tacrolimus individual dose adjustment?

jbw

2022-08-16 15:17:38

Original Analysis filtering out the AUC and C0 outliers

Loading of packages

```
library(tidyverse)
library(tidymodels)
library(skimr)
library(lubridate)
library(patchwork)
library(plotly)
```

Modification done on the csv to transform . in , for c1, T1, c2, t2 etc…

```
tac<-read_csv2("C:/Users/woillp01/Desktop/mobilite_toulouse/tac_auc_c0/auc_c0_ratio/Modele_choisi_tacro_011107_011119.csv",n
a = c(".", "NA", "", "NC"))
tac <- tac %>% separate(Taux_residuel, c("c0", "unit_c0")," ",convert = TRUE) %>%
  separate(Cmax, c("cmax", "unit_cmax")," ",convert = TRUE) %>%
  separate(Valeur_AUC, c("AUC", "unit")," ",convert = TRUE) %>%
  separate(Poso_mini, c("poso_reco_bas", "unit_reco_bas")," ",convert = TRUE) %>%
  separate(Poso_max, c("poso_reco_haut", "unit_reco_haut")," ",convert = TRUE) %>%
  separate(Date_validation, c("date_validation", "heure_validation")," ", convert = TRUE) %>%
  mutate(
    c0 = as.numeric(gsub("\\,", ".", c0)),
    cmax = as.numeric(gsub("\\,", ".", cmax)),
    AUC = as.numeric(gsub("\\,", ".", AUC)),
    poso_reco_bas = as.numeric(gsub("\\,", ".", poso_reco_bas)),
    poso_reco_haut = as.numeric(gsub("\\,", ".", poso_reco_haut)),
    AUC_0_24 = ifelse(Type_demande == "TACRO (PROGRAF)",AUC * 2, AUC),
    ID = str_c(Nocentre,Nom,Prenom,sep="_"),
    Methode =fct_recode(Methode,"H.P.L.C" = "AUTRE -> precisez commentaire"),
     Date_naissance = dmy(Date_naissance),
    Date_dosage = dmy(Date_dosage),
    Date_greffe = dmy(Date_greffe),
    date_validation = dmy(date_validation),
    age = as.numeric((Date_dosage - Date_naissance)/365.25),
    Dose_matin = as.numeric(Dose_matin),
    Dose_soir = as.numeric(Dose_soir),
    Dose_j = Dose_matin + Dose_soir,
    Delai_post_greffe = Delai_post_greffe/365.25,
    C0_obs = case_when(
  T1 == 0 ~ C1,
  T2 == 0 ~ C2,
  T3 == 0 ~ C3,
  T4 == 0 ~ C4,
  T5 == 0 ~ C5,
  T6 == 0 ~ C6,
  T7 == 0 ~ C7,
  T9 == 0 ~ C9,
  TRUE ~ 0),
  AUC_dose = AUC_0_24/Dose_j,
  c0_dose = ifelse(C0_obs != 0, C0_obs/Dose_j, NA),
  AUC_c0 = ifelse(C0_obs != 0, AUC_0_24/C0_obs, NA)
    ) %>% mutate_if(is.character, factor) %>%
  filter(Tt_associe != "Ciclosporine",
         Tt_associe != "Everolimus",
         Methode == "H.P.L.C",
         Methode_calcul != "NM",
         Type_greffe == "Greffe renale",
          Dose_midi == 0,
         Type_demande != "TACRO",
         ID != "999_XXX_XX",
         C0_obs >0,
         AUC_c0 <700,
         Date_greffe>1980-01-01) %>%
dplyr::select(-Dble_adaptation, -Valideur, -Fonction_valideur, -Demandeur, -email_demandeur, -Complement_greffe, - Commentai
re_centre, -Commentaire_valideur, -Comprimes, -Dose_complementaire,
       -Nb_prise,-Nb_pic, - Tmax, -Poso_AUC45, -Valeur_mini_AUC, -Valeur_max_AUC,     -Nb_prise_conseille,-Motif,-Commentair
e_Motif, -"Switch_Prograf_>Advagraf" , -Muco,-unit_reco_haut,-unit_reco_bas,  -Prograf_depuis_au_moins_1_semaine, -Clairance
_apparente, -Volume_de_distribution_apparent, -Log, -T8,              -C8, -T10, -C10, -Nom, -Prenom,-Nocentre,-Date_naissan
ce,-Type_greffe,-Methode, -unit, -unit_c0, -unit_cmax, -Dose_matin, -Dose_midi, -Dose_soir,  -Plage_AUC, -heure_validation,
       -C1, -T1, -T2, -C2, -T3, -C3, -T4,-C4, -T5, -C5, -T6, -C6, -T7, -C7, -T9, -C9, -Methode_calcul)


## we keep at least 2 requests per patient
tac_multi <- tac %>% group_by(ID) %>% filter(n() > 1) %>% dplyr::select(ID, everything()) %>% arrange(ID,Date_dosage)

# modification of aberrant transplantation date by the median value for each patient
date_greffe_mediane <- tac_multi %>% summarise(date_greffe_mediane = median(Date_greffe))
tac_multi <- tac_multi %>% left_join(date_greffe_mediane, by = "ID" ) %>%
  mutate(Delai_post_greffe = ifelse(Date_greffe == date_greffe_mediane,(Date_dosage - Date_greffe)/365.25,(Date_dosage - dat
e_greffe_mediane)/365.25)) %>% filter(Delai_post_greffe>0.005, between((as.numeric(Date_dosage - date_validation)), -31, 31
))# filter time post transplant > 1 day (>0.005)


# lag and time between request calculations
tac_multi <- tac_multi %>%
```

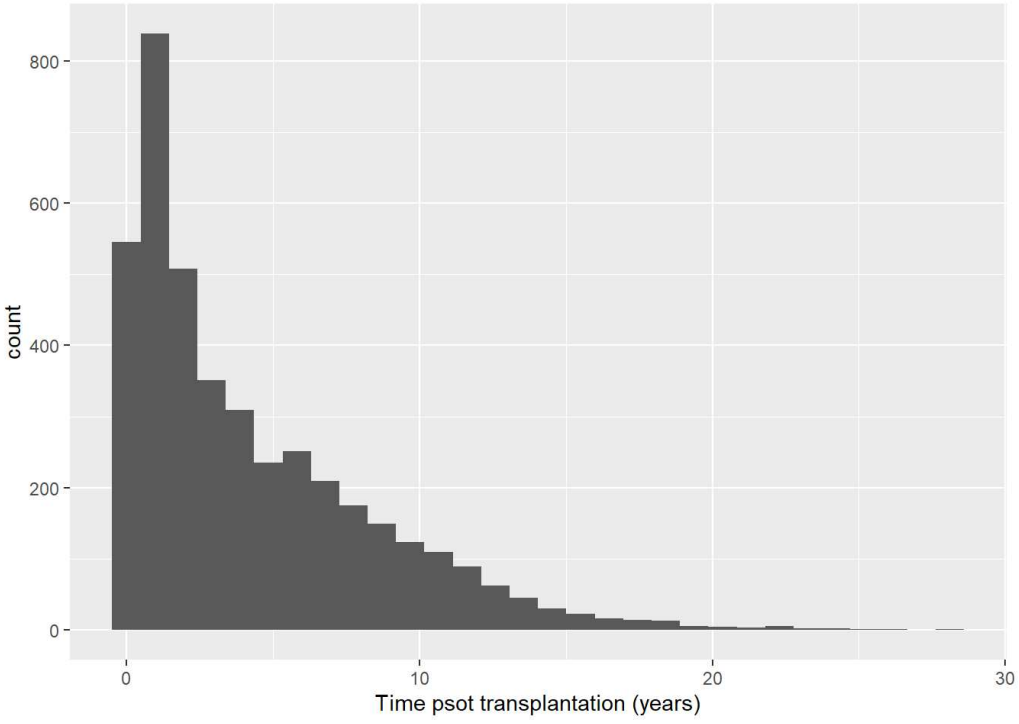
```
  mutate(
    lag_id = lag(ID),
    AUC_prec = ifelse(ID==lag_id,lag(AUC_0_24),0),
    cmax_prec =  ifelse(ID==lag_id,lag(cmax),0),
AUC_dose_prec =  ifelse(ID==lag_id,lag(AUC_dose),0),
AUC_c0_prec =  ifelse(ID==lag_id,lag(AUC_c0),0),
  c0_prec =  ifelse(ID==lag_id,lag(C0_obs),0),
c0_dose_prec =  ifelse(ID==lag_id,lag(c0_dose),0),
delai_prec =  ifelse(ID==lag_id,lag(Delai_post_greffe),0),
poso_reco_bas_prec =  ifelse(ID==lag_id,lag(poso_reco_bas),0),
poso_reco_haut_prec =  ifelse(ID==lag_id,lag(poso_reco_haut),0),
c0_prec =  ifelse(ID==lag_id,lag(C0_obs),0),
delai_entre_visite = Delai_post_greffe - delai_prec,
variation_rel_AUC = ((AUC_0_24 - AUC_prec) / AUC_prec),
variation_rel_AUC_dose = ((AUC_dose - AUC_dose_prec) / AUC_dose_prec),
variation_rel_c0 = ((C0_obs - c0_prec) / c0_prec),
variation_rel_c0_dose = ((c0_dose - c0_dose_prec) / c0_dose_prec),
variation_rel_AUC_c0 = ((AUC_c0 - AUC_c0_prec) / AUC_c0_prec)
) %>% filter(delai_entre_visite>0)
```

Every prograf AUC has been transformed to AUC0-24 by multiplying by 2 the prograf AUC0-12h.Daily dose corresponds to the sum of morning and evening dose for prograf

Filtering out aberrant values for Time post transplantation and histogram

Removal of time post transplantation > 33 years

```
tac_multi <- tac_multi %>% filter(Delai_post_greffe < 33)#2019-1986
ggplot(tac_multi, mapping = aes(x = Delai_post_greffe)) +
   geom_histogram()+ labs( x = "Time psot transplantation (years)")
```



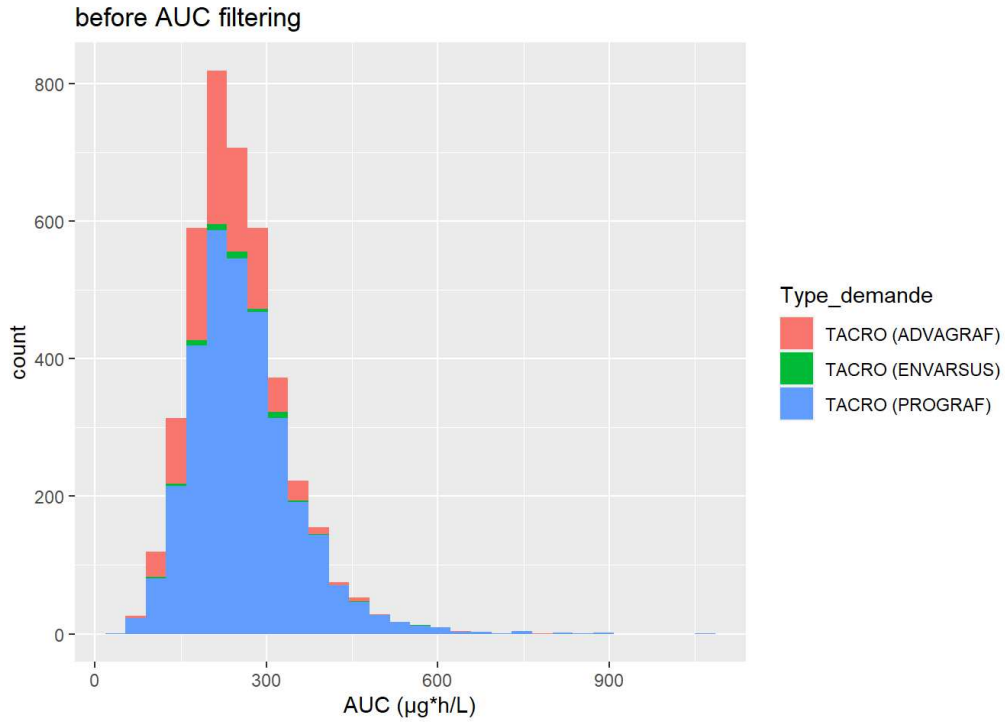
Filtering out aberrant values for AUC and histogram

Removal of > mean+/- 1.96 SD = [80-430]

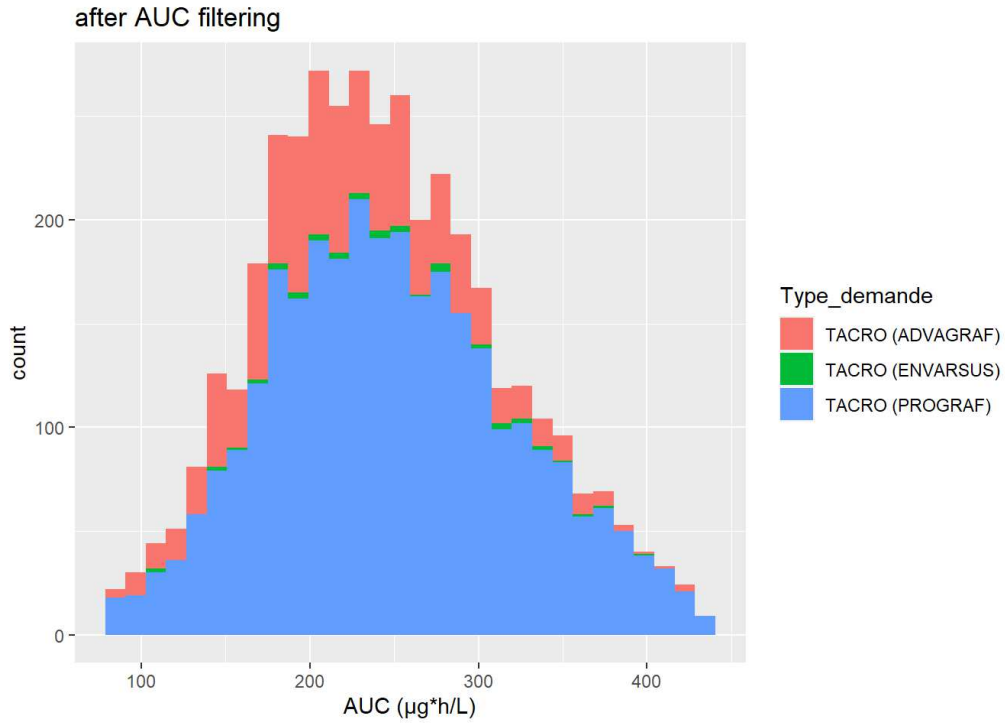
```
#before filtering
tac_multi %>% ungroup() %>% summarise(mean_AUC = mean(AUC), sd_AUC = sd(AUC_0_24),quantiles_AUC = quantile(AUC_0_24, c(0.05,
0.5, 0.95)), q = c(0.05, 0.5, 0.95))
```

```
## # A tibble: 3 x 4
##   mean_AUC sd_AUC quantiles_AUC     q
##      <dbl>  <dbl>         <dbl> <dbl>
## 1     153.   91.5           134  0.05
## 2     153.   91.5           240  0.5
## 3     153.   91.5           412  0.95
```

```
ggplot(tac_multi, mapping = aes(x = AUC_0_24, fill = Type_demande)) +
   geom_histogram()+ labs(title = "before AUC filtering", x = "AUC (µg*h/L)")
```




```
#after filtering
# tac_multi <- tac_multi %>% filter(AUC_0_24 < 517)
tac_multi_non_auc_filtered <- tac_multi
tac_multi <- tac_multi %>% filter(between(AUC_0_24,80,430))
ggplot(tac_multi, mapping = aes(x = AUC_0_24, fill = Type_demande)) +
   geom_histogram()+ labs(title = "after AUC filtering", x = "AUC (µg*h/L)")
```



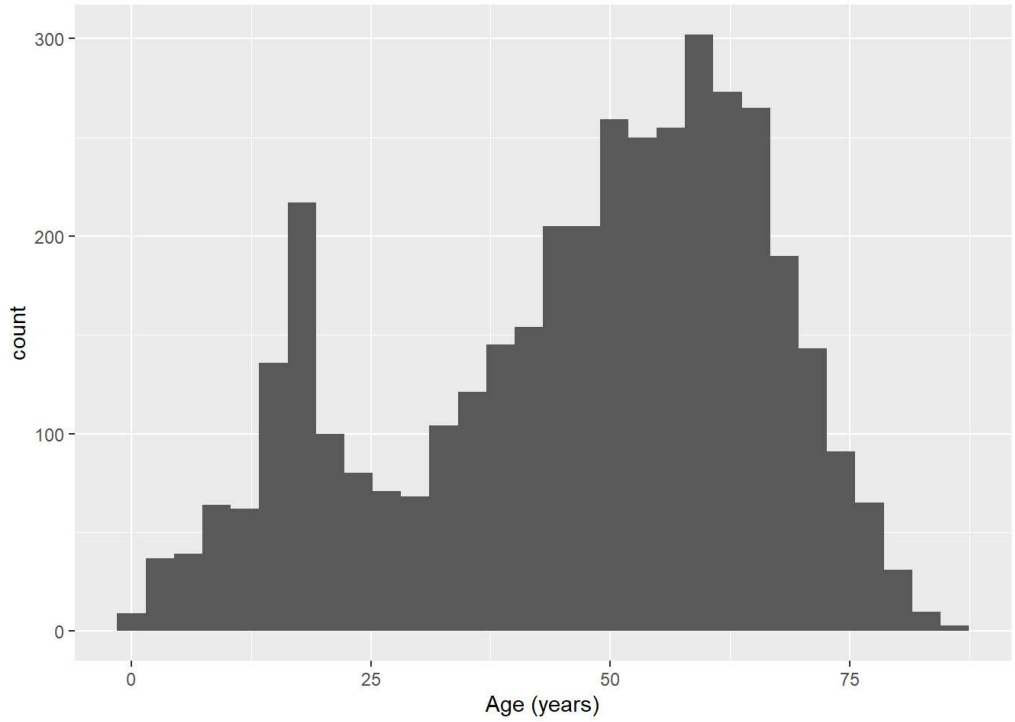
```
tac_multi  %>% ungroup() %>% summarise(mean_AUC = mean(AUC), sd_AUC = sd(AUC_0_24),quantiles_AUC = quantile(AUC_0_24, c(0.05
, 0.5, 0.95)), q = c(0.05, 0.5, 0.95))
```

```
## # A tibble: 3 x 4
##   mean_AUC sd_AUC quantiles_AUC     q
##      <dbl>  <dbl>         <dbl> <dbl>
## 1     148.   71.0           134  0.05
## 2     148.   71.0           236  0.5
## 3     148.   71.0           374  0.95
```

Filtering out aberrant values for age and histogram

Removal of age > 100 years

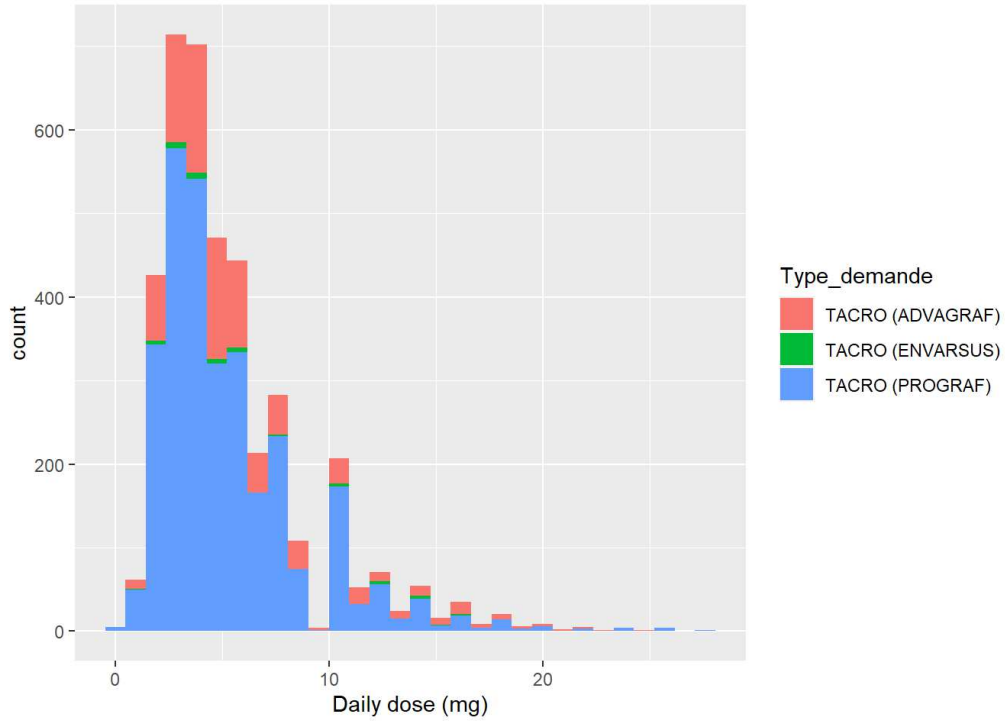
```
tac_multi_non_auc_filtered <- tac_multi_non_auc_filtered %>% filter(age < 100)
tac_multi <- tac_multi %>% filter(age < 100)
ggplot(tac_multi, mapping = aes(x = age)) +
   geom_histogram()+ labs( x = "Age (years)")
```



Filtering out aberrant values for daily dose and histogram

Removal of daily dose > 40 mg

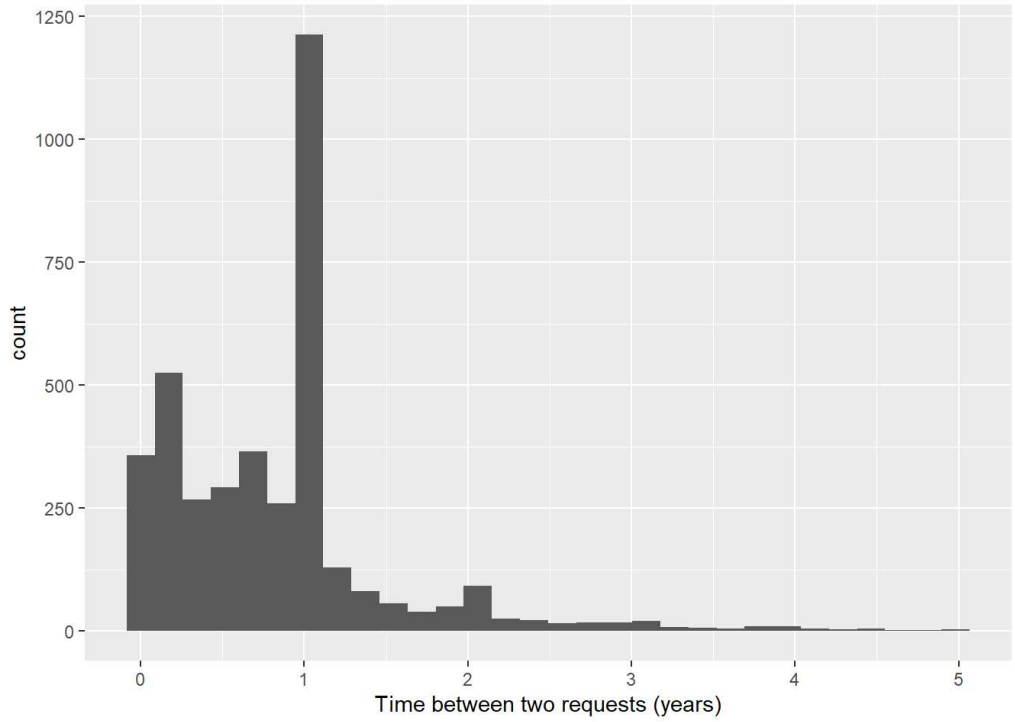
```
tac_multi_non_auc_filtered <- tac_multi_non_auc_filtered %>% filter(Dose_j < 40)
tac_multi <- tac_multi %>% filter(Dose_j < 40)
ggplot(tac_multi, mapping = aes(x = Dose_j,  fill = Type_demande)) +
   geom_histogram()+ labs( x = "Daily dose (mg)")
```



Filtering out aberrant values for time between two consecutive requests and histogram

Removal of time between 2 consecutive requests > 5 years

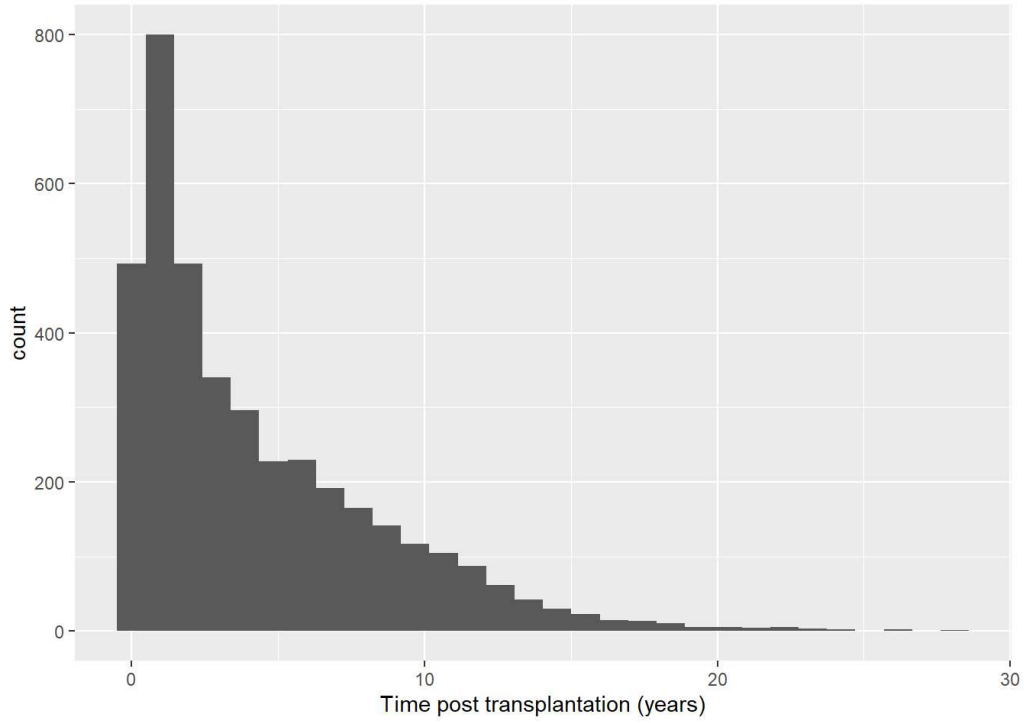
```
tac_multi_non_auc_filtered <- tac_multi_non_auc_filtered %>% filter(delai_entre_visite < 5)
tac_multi <- tac_multi %>% filter(delai_entre_visite < 5)
ggplot(data = tac_multi, mapping = aes(x = delai_entre_visite)) +
  geom_histogram()+ labs( x = "Time between two requests (years)")
```



Histogram of Time post transplantation

No value removed

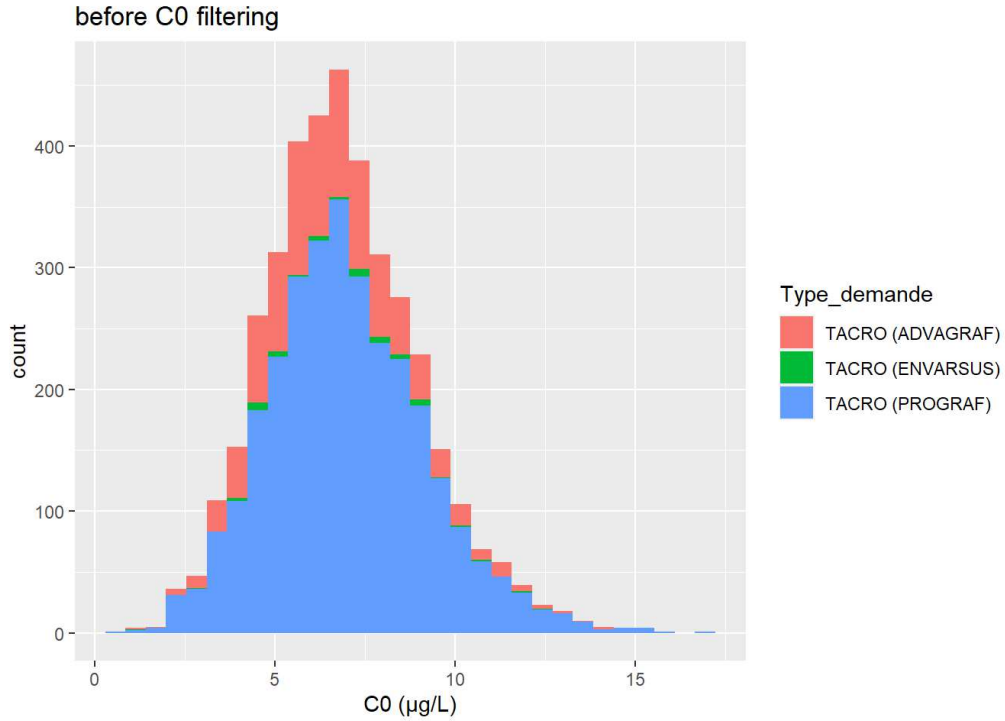
```
ggplot(data = tac_multi, mapping = aes(x = Delai_post_greffe)) +
  geom_histogram()+ labs( x = "Time post transplantation (years)")
```



Histogram of c0

Removal of C0 > 1.96*SD [2.18-12.14]

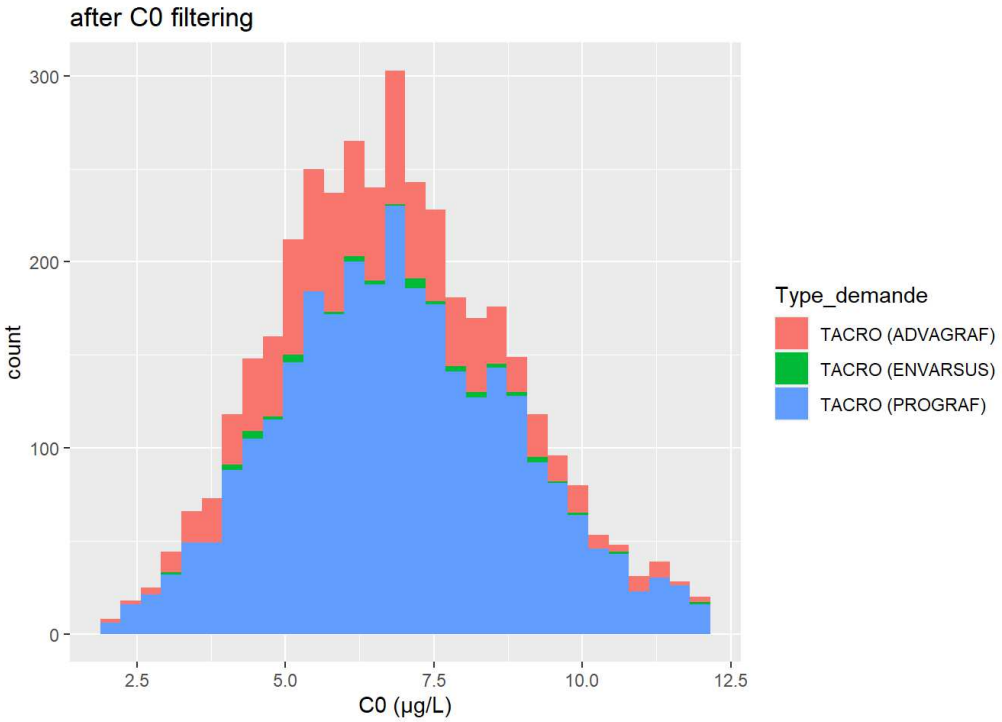
```
# before c0 filter
ggplot(tac_multi, mapping = aes(x = c0, fill = Type_demande)) +
   geom_histogram() + labs(title = "before C0 filtering", x = "C0 (µg/L)")
```




```
tac_multi %>% ungroup() %>% summarise(mean_c0 = mean(c0), sd_c0 = sd(c0),quantiles_c0 = quantile(c0, c(0.05, 0.5, 0.95)), q
 = c(0.05, 0.5, 0.95))
```

```
## # A tibble: 3 x 4
##   mean_c0 sd_c0 quantiles_c0     q
##     <dbl> <dbl>        <dbl> <dbl>
## 1    6.90  2.14         3.63  0.05
## 2    6.90  2.14         6.76  0.5
## 3    6.90  2.14        10.7   0.95
```

```
tac_multi_non_auc_c0_filtered <- tac_multi_non_auc_filtered

# After filtering
# tac_multi <- tac_multi %>% filter(c0 < 20)
tac_multi <- tac_multi %>% filter(between(c0,2.18,12.14))
ggplot(tac_multi, mapping = aes(x = c0, fill = Type_demande)) +
   geom_histogram()+ labs(title = "after C0 filtering", x = "C0 (µg/L)")
```




```
tac_multi %>% ungroup() %>% summarise(mean_c0 = mean(c0), sd_c0 = sd(c0), quantiles_c0 = quantile(c0, c(0.05, 0.5, 0.95)), q
= c(0.05, 0.5, 0.95))
```

```
## # A tibble: 3 x 4
##   mean_c0 sd_c0 quantiles_c0     q
##     <dbl> <dbl>        <dbl> <dbl>
## 1    6.82  1.96         3.75  0.05
## 2    6.82  1.96         6.74  0.5
## 3    6.82  1.96        10.3   0.95
```

Ranking of visits

```
tac_multi <- tac_multi %>% arrange(ID,Delai_post_greffe) %>% mutate(rank_visite = row_number())

tac_multi_non_auc_c0_filtered <- tac_multi_non_auc_c0_filtered %>% arrange(ID,Delai_post_greffe) %>% mutate(rank_visite = ro
w_number())
```

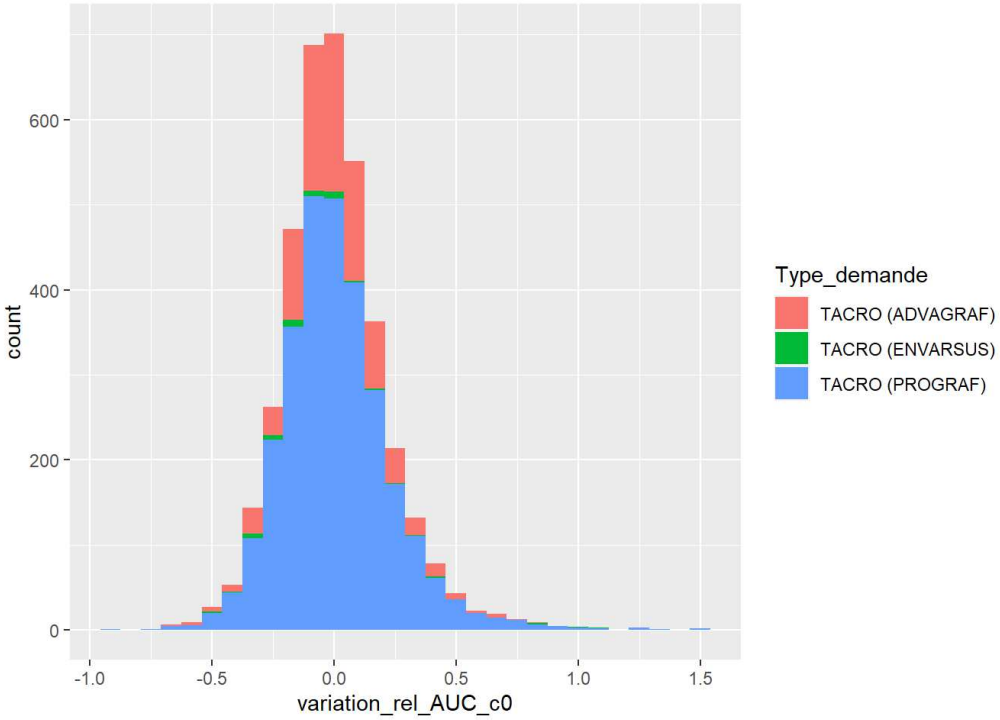
Proportion of patients having at least one AUC/C0 excluded due to AUC or C0 filters

```
visite_perid_filtered <- tac_multi %>% group_by(ID) %>% summarise(n_f = n())
visite_perid_nonfiltered <-tac_multi_non_auc_c0_filtered %>% group_by(ID) %>% summarise(n_nf = n())
left_join(visite_perid_nonfiltered,visite_perid_filtered) %>% mutate(diff_visite = if_else(n_nf - n_f>0,1,0),diff_visite = r
eplace_na(diff_visite,0)) %>% summarise(mean(diff_visite>0))
```

```
## # A tibble: 1 x 1
##   `mean(diff_visite > 0)`
##                     <dbl>
## 1                   0.129
```

Histogram relative variations of AUC

```
ggplot(tac_multi, mapping = aes(x = variation_rel_AUC_c0, fill = Type_demande)) +
   geom_histogram()
```



Summary of data after filtering

```
skim(ungroup(tac_multi))
```

Data summary

Name	ungroup(tac_multi)
Number of rows	3827
Number of columns	39
_____	
Column type frequency:	
Date	4
factor	5
numeric	30
_____	
Group variables	None

Variable type: Date

skim_variable	n_missing	complete_rate	min	max	median	n_unique
date_validation	0	1	2009-08-14	2019-10-31	2016-01-14	1829
Date_greffe	0	1	1986-11-22	2019-08-03	2011-10-05	1422
Date_dosage	0	1	2009-08-14	2019-10-31	2016-01-12	1867
date_greffe_mediane	0	1	1986-11-22	2019-08-03	2011-08-18	1187

Variable type: factor

skim_variable	n_missing	complete_rate	ordered	n_unique	top_counts
ID	0	1.00	FALSE	1325	32_: 42, 32_: 26, 32_: 23, 32_: 20
Tt_associe	0	1.00	FALSE	3	MMF: 3213, Nea: 589, Cor: 25, Cic: 0
Type_demande	0	1.00	FALSE	3	TAC: 2924, TAC: 858, TAC: 45, TAC: 0

skim_variable	n_missing	complete_rate	ordered	n_unique	top_counts
Diabete	1966	0.49	FALSE	2	NON: 1733, OUI: 128
lag_id	0	1.00	FALSE	1325	32_: 42, 32_: 26, 32_: 23, 32_: 20

Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
Nodemande	0	1	80627.42	24166.74	23226.00	61967.00	83693.00	100621.50	119406.00	
Delai_post_greffe	0	1	4.37	4.23	0.02	1.00	3.00	6.87	28.13	
cmax	0	1	17.14	7.21	3.61	11.98	15.77	20.80	66.53	
c0	0	1	6.82	1.96	2.18	5.41	6.74	8.14	12.11	
AUC	0	1	147.24	60.02	40.00	105.00	134.00	175.50	428.00	
poso_reco_bas	5	1	3.65	2.89	0.25	2.00	3.00	4.50	30.50	
poso_reco_haut	6	1	4.62	3.76	0.50	2.50	3.50	5.50	43.50	
AUC_0_24	0	1	241.73	68.34	80.00	192.00	236.00	288.00	430.00	
age	0	1	46.86	19.14	0.95	34.01	50.83	61.71	86.93	
Dose_j	0	1	5.61	3.57	0.40	3.00	5.00	7.00	28.00	
C0_obs	0	1	6.87	1.98	2.00	5.40	6.80	8.20	14.00	
AUC_dose	0	1	57.51	38.10	4.93	34.24	49.20	71.33	815.00	
c0_dose	0	1	1.71	1.26	0.09	0.91	1.43	2.17	22.00	
AUC_c0	0	1	36.01	7.67	11.52	30.83	34.50	39.64	89.29	
AUC_prec	0	1	270.41	96.65	56.00	206.00	256.00	320.00	1076.00	
cmax_prec	0	1	19.43	8.99	3.35	12.96	17.44	23.95	75.06	
AUC_dose_prec	0	1	57.85	43.80	7.83	33.65	48.67	71.33	1084.00	
AUC_c0_prec	0	1	36.91	12.16	11.52	31.16	35.08	40.41	560.00	
c0_prec	0	1	7.54	2.74	0.10	5.75	7.20	8.90	34.10	
c0_dose_prec	0	1	1.68	1.26	0.10	0.88	1.40	2.14	22.00	
delai_prec	0	1	3.53	4.04	0.01	0.31	1.99	5.65	25.91	
poso_reco_bas_prec	4	1	3.64	3.07	0.50	2.00	3.00	4.50	38.50	
poso_reco_haut_prec	4	1	4.68	4.15	0.50	2.50	3.50	5.50	55.00	
delai_entre_visite	0	1	0.85	0.70	0.00	0.31	0.88	1.01	4.98	
variation_rel_AUC	0	1	-0.02	0.38	-0.86	-0.27	-0.07	0.15	2.96	
variation_rel_AUC_dose	0	1	0.08	0.46	-0.92	-0.18	0.02	0.24	6.56	
variation_rel_c0	0	1	0.01	0.81	-0.87	-0.26	-0.07	0.19	43.00	
variation_rel_c0_dose	0	1	0.12	0.70	-0.88	-0.19	0.03	0.28	28.33	
variation_rel_AUC_c0	0	1	0.01	0.22	-0.94	-0.13	-0.01	0.12	1.48	
rank_visite	0	1	3.40	3.69	1.00	1.00	2.00	4.00	42.00	

Table 1 for the article

	Overall
n	3827
Tt_associe (%)	
Corticoides	25 (0.7)
MMF	3213 (84.0)
Neant	589 (15.4)
Delai_post_greffe (median [range])	3.00 [0.02, 28.13]

	Overall
cmax (median [range])	15.77 [3.61, 66.53]
c0 (median [range])	6.74 [2.18, 12.11]
AUC (median [range])	134.00 [40.00, 428.00]
poso_reco_bas (median [range])	3.00 [0.25, 30.50]
poso_reco_haut (median [range])	3.50 [0.50, 43.50]
Type_demande (%)	
TACRO (ADVAGRAF)	858 (22.4)
TACRO (ENVARSUS)	45 (1.2)
TACRO (PROGRAF)	2924 (76.4)
Diabete (%)	
NON	1733 (45.3)
OUI	128 (3.3)
NA	1966 (51.4)
AUC_0_24 (median [range])	236.00 [80.00, 430.00]
age (median [range])	50.83 [0.95, 86.93]
Dose_j (median [range])	5.00 [0.40, 28.00]
C0_obs (median [range])	6.80 [2.00, 14.00]
AUC_dose (median [range])	49.20 [4.93, 815.00]
c0_dose (median [range])	1.43 [0.09, 22.00]
AUC_c0 (median [range])	34.50 [11.52, 89.29]
AUC_prec (median [range])	256.00 [56.00, 1076.00]
cmax_prec (median [range])	17.44 [3.35, 75.06]
AUC_dose_prec (median [range])	48.67 [7.83, 1084.00]
AUC_c0_prec (median [range])	35.08 [11.52, 560.00]
c0_prec (median [range])	7.20 [0.10, 34.10]
c0_dose_prec (median [range])	1.40 [0.10, 22.00]
delai_prec (median [range])	1.99 [0.01, 25.91]
poso_reco_bas_prec (median [range])	3.00 [0.50, 38.50]
poso_reco_haut_prec (median [range])	3.50 [0.50, 55.00]
delai_entre_visite (median [range])	0.88 [0.00, 4.98]
variation_rel_AUC (median [range])	-0.07 [-0.86, 2.96]
variation_rel_AUC_dose (median [range])	0.02 [-0.92, 6.56]
variation_rel_c0 (median [range])	-0.07 [-0.87, 43.00]
variation_rel_c0_dose (median [range])	0.03 [-0.88, 28.33]
variation_rel_AUC_c0 (median [range])	-0.01 [-0.94, 1.48]
rank_visite (median [range])	2.00 [1.00, 42.00]

	Overall
n	3827
Tt_associe (%)	
Corticoides	25 (0.7)
MMF	3213 (84.0)
Neant	589 (15.4)

	Overall
Delai_post_greffe (median [IQR])	3.00 [1.00, 6.87]
cmax (median [IQR])	15.77 [11.98, 20.80]
c0 (median [IQR])	6.74 [5.41, 8.14]
AUC (median [IQR])	134.00 [105.00, 175.50]
poso_reco_bas (median [IQR])	3.00 [2.00, 4.50]
poso_reco_haut (median [IQR])	3.50 [2.50, 5.50]
Type_demande (%)	
TACRO (ADVAGRAF)	858 (22.4)
TACRO (ENVARSUS)	45 (1.2)
TACRO (PROGRAF)	2924 (76.4)
Diabete (%)	
NON	1733 (45.3)
OUI	128 (3.3)
NA	1966 (51.4)
AUC_0_24 (median [IQR])	236.00 [192.00, 288.00]
age (median [IQR])	50.83 [34.01, 61.71]
Dose_j (median [IQR])	5.00 [3.00, 7.00]
C0_obs (median [IQR])	6.80 [5.40, 8.20]
AUC_dose (median [IQR])	49.20 [34.24, 71.33]
c0_dose (median [IQR])	1.43 [0.91, 2.17]
AUC_c0 (median [IQR])	34.50 [30.83, 39.64]
AUC_prec (median [IQR])	256.00 [206.00, 320.00]
cmax_prec (median [IQR])	17.44 [12.96, 23.95]
AUC_dose_prec (median [IQR])	48.67 [33.65, 71.33]
AUC_c0_prec (median [IQR])	35.08 [31.16, 40.41]
c0_prec (median [IQR])	7.20 [5.75, 8.90]
c0_dose_prec (median [IQR])	1.40 [0.88, 2.14]
delai_prec (median [IQR])	1.99 [0.31, 5.65]
poso_reco_bas_prec (median [IQR])	3.00 [2.00, 4.50]
poso_reco_haut_prec (median [IQR])	3.50 [2.50, 5.50]
delai_entre_visite (median [IQR])	0.88 [0.31, 1.01]
variation_rel_AUC (median [IQR])	-0.07 [-0.27, 0.15]
variation_rel_AUC_dose (median [IQR])	0.02 [-0.18, 0.24]
variation_rel_c0 (median [IQR])	-0.07 [-0.26, 0.19]
variation_rel_c0_dose (median [IQR])	0.03 [-0.19, 0.28]
variation_rel_AUC_c0 (median [IQR])	-0.01 [-0.13, 0.12]
rank_visite (median [IQR])	2.00 [1.00, 4.00]

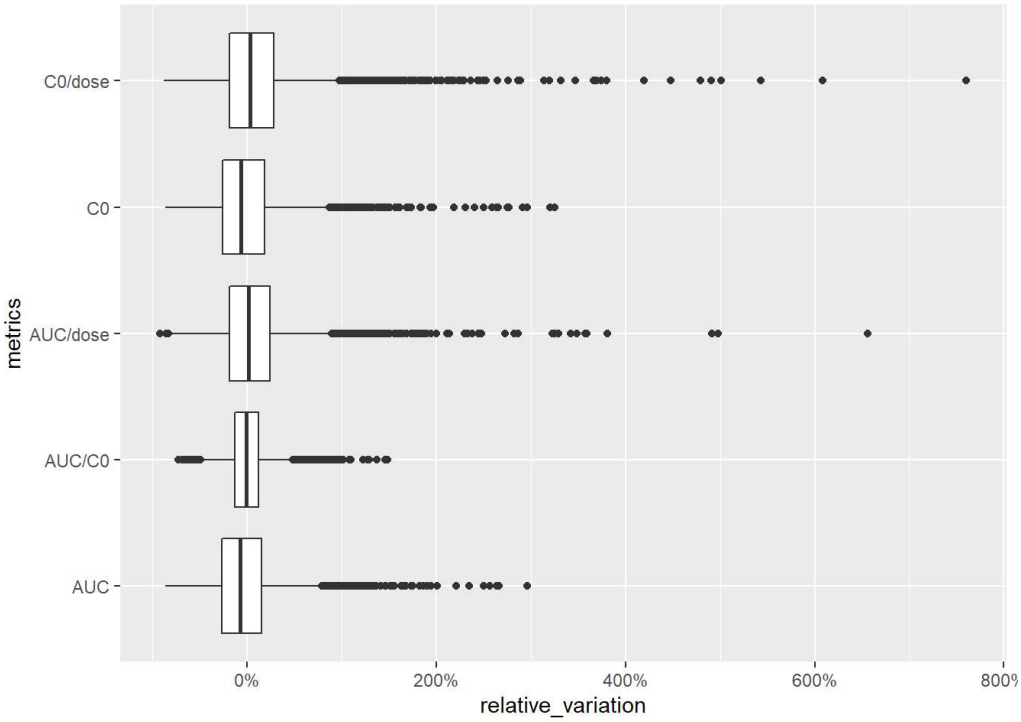
Exploratory data analysis

Study of relative variations between instance n and n-1 for the metrics

```
tac_boxplot_variation <- tac_multi %>% dplyr::select (Type_demande, variation_rel_AUC, variation_rel_AUC_dose, variation_rel
_c0_dose, variation_rel_AUC_c0, variation_rel_c0, delai_entre_visite, Delai_post_greffe) %>% filter(variation_rel_c0<20,vari
ation_rel_AUC<20 ) %>% rename("AUC" = variation_rel_AUC, "AUC/dose" = variation_rel_AUC_dose, "C0/dose" = variation_rel_c0_d
ose,"AUC/C0" = variation_rel_AUC_c0,"C0" = variation_rel_c0 ) %>% pivot_longer(cols = AUC:C0 ,names_to = "metrics", values_t
o = "relative_variation",values_drop_na = TRUE) %>% filter(!is.na(relative_variation)) %>% mutate (relative_variation = repl
ace(relative_variation,0,0.00001))

tac_boxplot_variation %>% group_by(metrics) %>% summarise (mean = mean(relative_variation)*100, sd = sd(relative_variation)*
100, cv = sd/mean )
```

```
## # A tibble: 5 x 4
##   metrics     mean    sd      cv
##   <chr>      <dbl> <dbl>   <dbl>
## 1 AUC      -2.37    38.0  -16.0
## 2 AUC/C0    0.637   22.3   34.9
## 3 AUC/dose  8.04    45.9    5.71
## 4 C0       -0.0477  41.3 -866.
## 5 C0/dose  11.7     53.7    4.61
```

```
#Log10 trans
ggplot(data = tac_boxplot_variation, mapping = aes(x =metrics , y = relative_variation))+ geom_boxplot() + coord_flip()+ sca
le_y_continuous(labels = scales::percent)
```



Extraction of extreme patient with relative variation > 200%

```
extreme_auc <- tac_boxplot_variation %>% filter(metrics=="AUC", relative_variation>2)
extreme_auc
```

```
## # A tibble: 8 x 6
## # Groups:   ID [8]
##   ID        Type_demande delai_entre_vis~ Delai_post_gref~ metrics relative_variat~
##   <fct>     <fct>                   <dbl>            <dbl> <chr>              <dbl>
## 1 17_ARE_AN TACRO (PROG~             1.47            11.5   AUC                 2.56
## 2 17_BOU_SE TACRO (ADVA~             3.57             4.13  AUC                 2.64
## 3 17_HOU_VE TACRO (PROG~             2.93             3.97  AUC                 2.21
## 4 17_LAM_PA TACRO (PROG~             3.36             4.76  AUC                 2.66
## 5 32_DEL_AL TACRO (PROG~             0.671           11.2   AUC                 2.5
## 6 34_BOR_VI TACRO (ADVA~             0.214            0.556 AUC                 2.01
## 7 34_GER_AS TACRO (PROG~             0.104            0.126 AUC                 2.96
## 8 4_GUI_MI  TACRO (ADVA~             0.761            1.02  AUC                 2.35
```

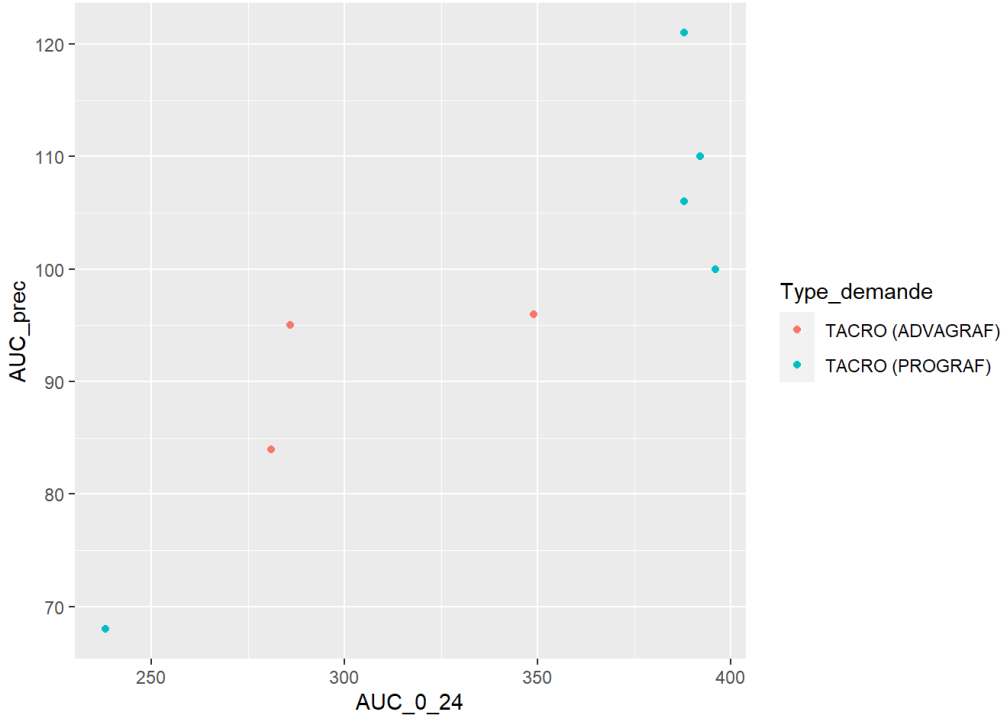
```
tac_multi %>% filter(ID %in% extreme_auc$ID)
```

```
## # A tibble: 32 x 39
## # Groups:   ID [8]
##    ID         Nodemande date_validation Tt_associe Date_greffe Date_dosage
##    <fct>          <dbl> <date>          <fct>      <date>      <date>
##  1 17_ARE_AN      37847 2011-03-01      MMF        2001-02-02  2011-02-28
##  2 17_ARE_AN      51888 2012-08-20      MMF        2008-02-02  2012-08-17
##  3 17_ARE_AN      66212 2014-02-13      MMF        2001-02-02  2014-02-11
##  4 17_BOU_SE      86404 2016-04-22      MMF        2016-03-19  2016-04-21
##  5 17_BOU_SE      88260 2016-07-04      Neant      2016-03-19  2016-07-01
##  6 17_HOU_VE      54491 2012-11-23      MMF        2008-12-03  2012-11-22
##  7 17_HOU_VE      64529 2013-12-17      MMF        2008-12-03  2013-12-16
##  8 17_LAM_PA      39263 2011-04-21      MMF        2011-01-20  2011-04-20
##  9 17_LAM_PA      41710 2011-07-22      MMF        2011-01-21  2011-07-20
## 10 17_LAM_PA      46283 2012-01-19      MMF        2011-01-20  2012-01-18
## # ... with 22 more rows, and 33 more variables: Delai_post_greffe <dbl>,
## #   cmax <dbl>, c0 <dbl>, AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>,
## #   Type_demande <fct>, Diabete <fct>, AUC_0_24 <dbl>, age <dbl>, Dose_j <dbl>,
## #   C0_obs <dbl>, AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>,
## #   date_greffe_mediane <date>, lag_id <fct>, AUC_prec <dbl>, cmax_prec <dbl>,
## #   AUC_dose_prec <dbl>, AUC_c0_prec <dbl>, c0_prec <dbl>, c0_dose_prec <dbl>,
## #   delai_prec <dbl>, poso_reco_bas_prec <dbl>, poso_reco_haut_prec <dbl>, ...
```

```
tac %>% filter(ID %in% extreme_auc$ID) %>% arrange(ID, date_validation)
```

```
## # A tibble: 44 x 21
##    Nodemande date_validation Tt_associe Date_greffe Date_dosage Delai_post_gref~
##        <dbl> <date>          <fct>      <date>      <date>                  <dbl>
##  1     28928 2010-03-20      MMF        2001-02-02  2010-03-18             9.12
##  2     37847 2011-03-01      MMF        2001-02-02  2011-02-28            10.1
##  3     51888 2012-08-20      MMF        2008-02-02  2012-08-17             4.54
##  4     66212 2014-02-13      MMF        2001-02-02  2014-02-11            13.0
##  5     41449 2011-07-12      Neant      2008-02-22  2011-07-11             3.38
##  6     53000 2012-09-27      Neant      2008-02-22  2012-09-26             4.59
##  7     86404 2016-04-22      MMF        2016-03-19  2016-04-21             0.0903
##  8     88260 2016-07-04      Neant      2016-03-19  2016-07-01             0.285
##  9     26589 2009-12-17      MMF        2008-12-04  2009-12-16             1.03
## 10     54491 2012-11-23      MMF        2008-12-03  2012-11-22             3.97
## # ... with 34 more rows, and 15 more variables: cmax <dbl>, c0 <dbl>,
## #   AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>, Type_demande <fct>,
## #   Diabete <fct>, AUC_0_24 <dbl>, ID <fct>, age <dbl>, Dose_j <dbl>,
## #   C0_obs <dbl>, AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>
```

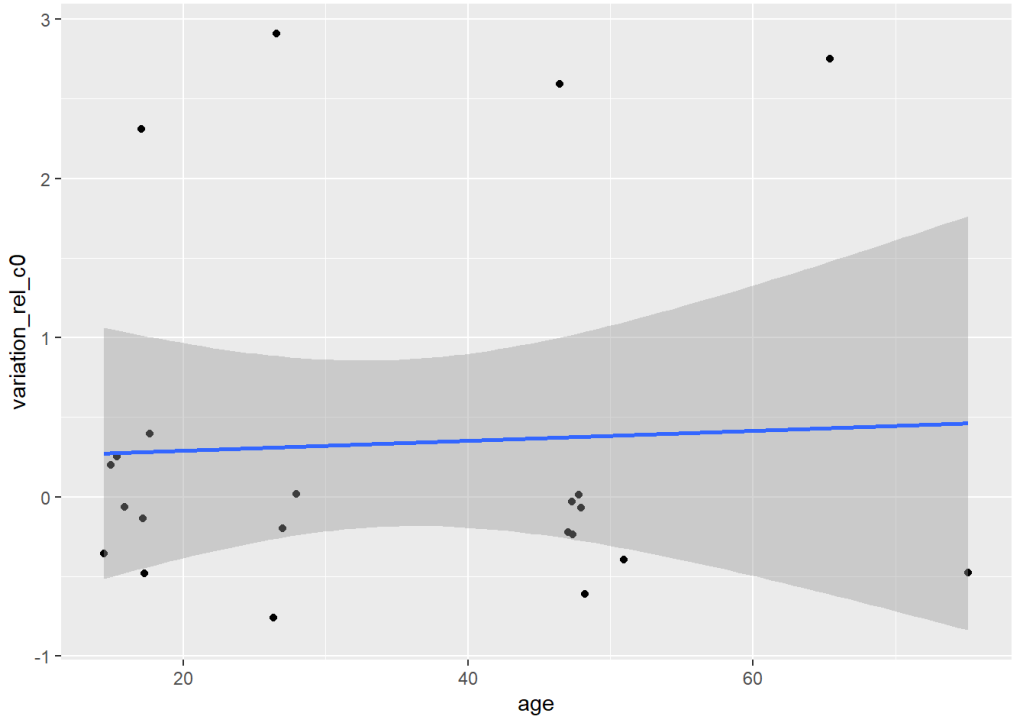
```
tac_multi %>% filter(ID %in% extreme_auc$ID, variation_rel_AUC>2) %>% ggplot(aes(x=AUC_0_24, y=AUC_prec, color=Type_demand
e)) + geom_point()
```



```
extreme_rel_var_200 <- tac_boxplot_variation %>% filter( relative_variation>2, metrics %in% c("AUC", "c0"))
extreme_rel_var_200 %>% group_by(metrics) %>% summarise(n = n())
```

```
## # A tibble: 1 x 2
##   metrics     n
##   <chr>   <int>
## 1 AUC         8
```

```
tac_multi %>% filter(ID %in% extreme_rel_var_200$ID ) %>% filter(delai_entre_visite<1) %>% ggplot(aes(x=age, y = variation_rel_c0 )) + geom_point() + geom_smooth(method ="lm")
```




```
tac_multi %>% filter(ID %in% "17_ADI_AL" )
```

```
## # A tibble: 1 x 39
## # Groups:   ID [1]
##   ID        Nodemande date_validation Tt_associe Date_greffe Date_dosage
##   <fct>         <dbl> <date>          <fct>      <date>      <date>
## 1 17_ADI_AL     92711 2016-12-26      MMF        2001-05-29  2016-12-23
## # ... with 33 more variables: Delai_post_greffe <dbl>, cmax <dbl>, c0 <dbl>,
## #   AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>, Type_demande <fct>,
## #   Diabete <fct>, AUC_0_24 <dbl>, age <dbl>, Dose_j <dbl>, C0_obs <dbl>,
## #   AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>, date_greffe_mediane <date>,
## #   lag_id <fct>, AUC_prec <dbl>, cmax_prec <dbl>, AUC_dose_prec <dbl>,
## #   AUC_c0_prec <dbl>, c0_prec <dbl>, c0_dose_prec <dbl>, delai_prec <dbl>,
## #   poso_reco_bas_prec <dbl>, poso_reco_haut_prec <dbl>, ...
```

ANOVA and post test Tuckey for metrics

```
res.aov1 <- aov(relative_variation ~ metrics,  data = tac_boxplot_variation)
summary(res.aov1)
```

```
##                Df Sum Sq Mean Sq F value Pr(>F)
## metrics         4     54  13.611   78.85 <2e-16 ***
## Residuals   19125   3301   0.173
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov1, which = "metrics")
```

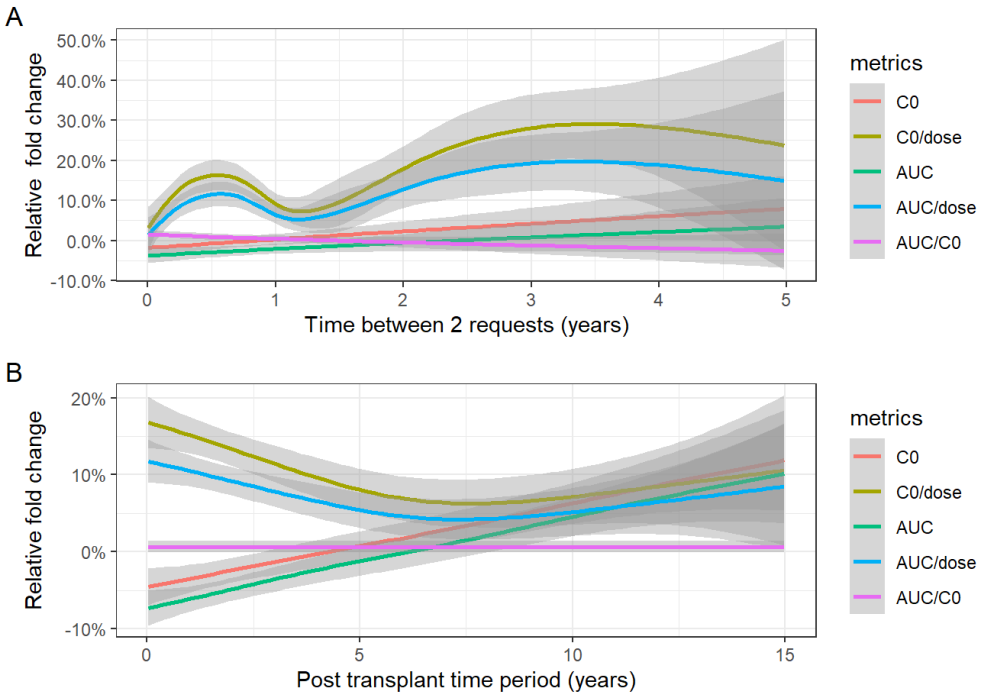
```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = relative_variation ~ metrics, data = tac_boxplot_variation)
##
## $metrics
##                          diff          lwr         upr     p adj
## AUC/C0-AUC         0.030098061  0.004183644  0.05601248 0.0133187
## AUC/dose-AUC       0.104103339  0.078188922  0.13001776 0.0000000
## C0-AUC             0.023246716 -0.002667701  0.04916113 0.1030584
## C0/dose-AUC        0.140255945  0.114341528  0.16617036 0.0000000
## AUC/dose-AUC/C0    0.074005278  0.048090861  0.09991969 0.0000000
## C0-AUC/C0         -0.006851345 -0.032765762  0.01906307 0.9516796
## C0/dose-AUC/C0     0.110157883  0.084243466  0.13607230 0.0000000
## C0-AUC/dose       -0.080856623 -0.106771040 -0.05494221 0.0000000
## C0/dose-AUC/dose   0.036152606  0.010238189  0.06206702 0.0013358
## C0/dose-C0         0.117009228  0.091094811  0.14292365 0.0000000
```

Scatter plot relative variations for each metrics as function of time post transplantation and time between 2 requests = Figure 2

```
plot_time_2_requests <-tac_boxplot_variation %>% filter(delai_entre_visite<5) %>% mutate(metrics = fct_relevel(metrics,
            "C0", "C0/dose", "AUC",
            "AUC/dose", "AUC/C0")) %>% ggplot() +
  geom_smooth(mapping = aes(x = delai_entre_visite, y = relative_variation, color = metrics), se =T) +
   # geom_point(mapping = aes(x = delai_entre_visite, y = relative_variation, color = metrics), alpha=0.2) +
  labs(
     # title = "Fold change as function of time between 2 requests censured at 5 years",
      y = "Relative  fold change",
      x = "Time between 2 requests (years)") + scale_y_continuous(labels=percent) + theme_bw()
# + scale_colour_discrete(name="Metrics",
                          # breaks=c("variation_rel_AUC", "variation_rel_AUC_c0", "variation_rel_AUC_dose","variation_rel_c
0","variation_rel_c0_dose"),
                          # labels=c("AUC", "AUC/c0", "AUC/dose","c0","c0/dose"))


tac_boxplot_variation %>% group_by(metrics) %>% filter(delai_entre_visite<5) %>% summarise (mean = mean(relative_variation),
sd = sd(relative_variation), cv = sd/mean )
```

```
## # A tibble: 5 x 4
##   metrics       mean    sd      cv
##   <chr>        <dbl> <dbl>   <dbl>
## 1 AUC      -0.0237   0.380  -16.0
## 2 AUC/C0    0.00637  0.223   34.9
## 3 AUC/dose  0.0804   0.459    5.71
## 4 C0       -0.000477 0.413 -866.
## 5 C0/dose   0.117    0.537    4.61
```

```
plot_time_post_transplant <- tac_boxplot_variation %>% filter(Delai_post_greffe<15) %>% mutate(metrics = fct_relevel(metric
s,
            "C0", "C0/dose", "AUC",
            "AUC/dose", "AUC/C0")) %>% ggplot() +
  geom_smooth(mapping = aes(x = Delai_post_greffe, y = relative_variation, color = metrics), se =T) +
  labs(
    # title = "Fold change as function of time post transplantation censured at 15 years",
     y = "Relative fold change",
      x = "Post transplant time period (years)") + scale_y_continuous(labels=percent) + theme_bw()

plot_time_2_requests / plot_time_post_transplant + plot_annotation(tag_levels = 'A')
```




```
ggsave("Figure2.pdf")
```

Boxplot relative variations between instance n and n+2

ANOVA and post test Tuckey

```
res.aov2 <- aov(variation_relative_lag2 ~ metrics,  data = tac_boxplot_variation2)
summary(res.aov2)
```

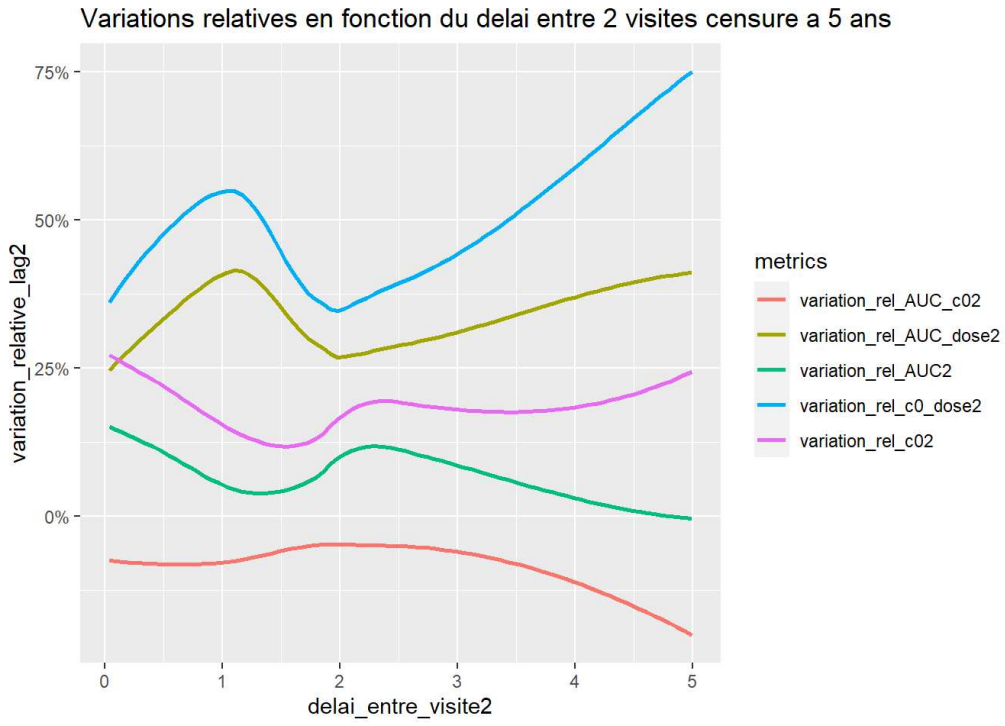
```
##               Df Sum Sq Mean Sq F value Pr(>F)
## metrics        4  134.6   33.65   210.6 <2e-16 ***
## Residuals   4675  747.1    0.16
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov2, which = "metrics")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative_lag2 ~ metrics, data = tac_boxplot_variation2)
##
## $metrics
##                                                 diff         lwr
## variation_rel_AUC_dose2-variation_rel_AUC_c02   0.3759962  0.32557023
## variation_rel_AUC2-variation_rel_AUC_c02        0.1486984  0.09827246
## variation_rel_c0_dose2-variation_rel_AUC_c02    0.4843954  0.43396942
## variation_rel_c02-variation_rel_AUC_c02         0.2347144  0.18428847
## variation_rel_AUC2-variation_rel_AUC_dose2     -0.2272978 -0.27772373
## variation_rel_c0_dose2-variation_rel_AUC_dose2  0.1083992  0.05797322
## variation_rel_c02-variation_rel_AUC_dose2      -0.1412818 -0.19170772
## variation_rel_c0_dose2-variation_rel_AUC2       0.3356970  0.28527100
## variation_rel_c02-variation_rel_AUC2            0.0860160  0.03559005
## variation_rel_c02-variation_rel_c0_dose2       -0.2496809 -0.30010690
##                                                       upr    p adj
## variation_rel_AUC_dose2-variation_rel_AUC_c02   0.42642215 0.00e+00
## variation_rel_AUC2-variation_rel_AUC_c02        0.19912438 0.00e+00
## variation_rel_c0_dose2-variation_rel_AUC_c02    0.53482133 0.00e+00
## variation_rel_c02-variation_rel_AUC_c02         0.28514038 0.00e+00
## variation_rel_AUC2-variation_rel_AUC_dose2     -0.17687181 0.00e+00
## variation_rel_c0_dose2-variation_rel_AUC_dose2  0.15882514 1.00e-07
## variation_rel_c02-variation_rel_AUC_dose2      -0.09085581 0.00e+00
## variation_rel_c0_dose2-variation_rel_AUC2       0.38612291 0.00e+00
## variation_rel_c02-variation_rel_AUC2            0.13644196 3.28e-05
## variation_rel_c02-variation_rel_c0_dose2       -0.19925499 0.00e+00
```

Scatter plots relative variations for each metrics vs time between 2 requests with lag **2** requests

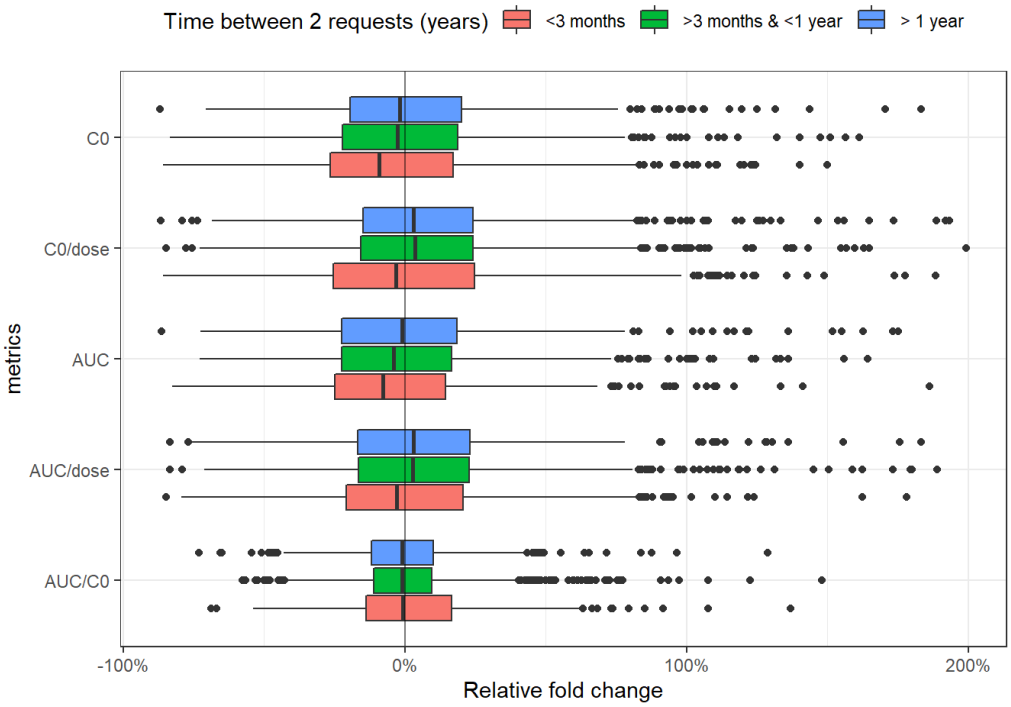
```
tac_boxplot_variation2 %>% filter(delai_entre_visite2<5) %>% ggplot() +
  geom_smooth(mapping = aes(x = delai_entre_visite2, y = variation_relative_lag2, color = metrics), se =F)+  labs(title = "V
ariations relatives en fonction du delai entre 2 visites censure a 5 ans")+ scale_y_continuous(labels = scales::percent)
```



Relative variations between 2 requests:

We created groups for <3 months and > 12 months and boxplots for different metrics (Figure 1)

```
tac_boxplot_variation_3visite <- tac_multi %>% group_by(ID) %>% filter(n()>3) %>% dplyr::select (Type_demande, variation_rel
_AUC, variation_rel_AUC_dose, variation_rel_c0_dose, variation_rel_AUC_c0, variation_rel_c0, delai_entre_visite, Delai_post_
greffe) %>%  mutate(group_delai_entre_visite = case_when(
    delai_entre_visite<0.25 ~ "inf_3mois",
    delai_entre_visite>1 ~ "sup_1an",
    TRUE~"3mois-1an"
    )) %>% filter(variation_rel_c0<20,variation_rel_AUC<20) %>% pivot_longer(cols = starts_with("variation_rel_") ,names_to
 = "metrics", values_to = "variation_relative",values_drop_na = TRUE) %>% filter(!is.na(variation_relative))

tac_boxplot_variation_3visite$group_delai_entre_visite <- factor(tac_boxplot_variation_3visite$group_delai_entre_visite,
    levels = c("inf_3mois","3mois-1an","sup_1an"),ordered = TRUE)

#boxplots
boxplot_delai_2_visites <- tac_boxplot_variation_3visite %>%
  filter(between(variation_relative,-2.0,2.0)) %>%
  mutate(metrics = fct_relevel(metrics,
             "variation_rel_AUC_c0","variation_rel_AUC_dose", "variation_rel_AUC", "variation_rel_c0_dose","variation_rel_c
0")) %>%
ggplot(mapping = aes(y = variation_relative, x = metrics, fill = group_delai_entre_visite )) +
  geom_boxplot() + coord_flip()+
   scale_fill_manual(values=c("red", "blue", "green")) +
  scale_fill_discrete(name="Time between 2 requests (years)",
                      breaks=c("inf_3mois", "3mois-1an", "sup_1an"),
                      labels=c("<3 months", ">3 months & <1 year", "> 1 year")) + scale_x_discrete(breaks=c("variation_re
l_c0","variation_rel_c0_dose",  "variation_rel_AUC","variation_rel_AUC_dose","variation_rel_AUC_c0"),labels=c("C0","C0/dose"
, "AUC","AUC/dose","AUC/C0")) +
  labs(y="Relative fold change") + theme_bw()+ scale_y_continuous(labels = scales::percent)+ theme(legend.position = "top")+
geom_hline(yintercept = 0, alpha = 0.5)  #+
boxplot_delai_2_visites
```




```
tac_boxplot_variation_3visite %>% group_by(metrics,group_delai_entre_visite ) %>% filter(delai_entre_visite<5) %>% summarise
(mean = mean(variation_relative), sd = sd(variation_relative))
```

```
## # A tibble: 15 x 4
## # Groups:   metrics [5]
##    metrics                group_delai_entre_visite     mean    sd
##    <chr>                  <ord>                       <dbl> <dbl>
##  1 variation_rel_AUC      inf_3mois                -0.0118  0.399
##  2 variation_rel_AUC      3mois-1an                -0.00320 0.331
##  3 variation_rel_AUC      sup_1an                   0.0151  0.357
##  4 variation_rel_AUC_c0   inf_3mois                 0.0264  0.261
##  5 variation_rel_AUC_c0   3mois-1an                 0.00714 0.210
##  6 variation_rel_AUC_c0   sup_1an                   0.00183 0.200
##  7 variation_rel_AUC_dose inf_3mois                 0.0516  0.495
##  8 variation_rel_AUC_dose 3mois-1an                 0.0895  0.444
##  9 variation_rel_AUC_dose sup_1an                   0.0665  0.396
## 10 variation_rel_c0       inf_3mois                 0.00825 0.448
## 11 variation_rel_c0       3mois-1an                 0.0133  0.355
## 12 variation_rel_c0       sup_1an                   0.0361  0.381
## 13 variation_rel_c0_dose  inf_3mois                 0.0861  0.598
## 14 variation_rel_c0_dose  3mois-1an                 0.119   0.530
## 15 variation_rel_c0_dose  sup_1an                   0.0908  0.405
```

```
res.aov3 <- aov(variation_relative ~ metrics + group_delai_entre_visite,  data = tac_boxplot_variation_3visite)
summary(res.aov3)
```

```
##                              Df Sum Sq Mean Sq F value Pr(>F)
## metrics                       4   18.0   4.507  29.043 <2e-16 ***
## group_delai_entre_visite      2    0.3   0.141   0.907  0.404
## Residuals                 11233 1743.1   0.155
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

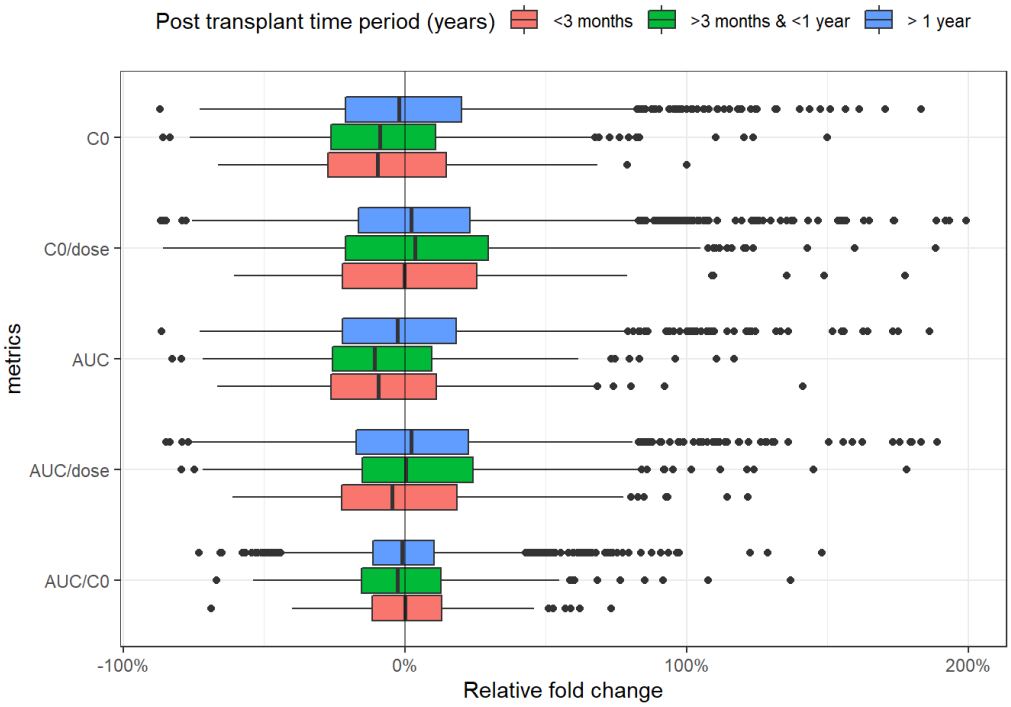
```
TukeyHSD(res.aov3, which = "metrics")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite, data = tac_boxplot_variation_3visite)
##
## $metrics
##                                                    diff          lwr
## variation_rel_AUC_c0-variation_rel_AUC        0.008653146 -0.023403008
## variation_rel_AUC_dose-variation_rel_AUC      0.073308130  0.041251976
## variation_rel_c0-variation_rel_AUC            0.018692578 -0.013363577
## variation_rel_c0_dose-variation_rel_AUC       0.102248454  0.070192300
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.064654984  0.032598830
## variation_rel_c0-variation_rel_AUC_c0         0.010039431 -0.022016723
## variation_rel_c0_dose-variation_rel_AUC_c0    0.093595308  0.061539154
## variation_rel_c0-variation_rel_AUC_dose      -0.054615553 -0.086671707
## variation_rel_c0_dose-variation_rel_AUC_dose  0.028940324 -0.003115831
## variation_rel_c0_dose-variation_rel_c0        0.083555877  0.051499722
##                                                    upr     p adj
## variation_rel_AUC_c0-variation_rel_AUC        0.04070930 0.9479931
## variation_rel_AUC_dose-variation_rel_AUC      0.10536428 0.0000000
## variation_rel_c0-variation_rel_AUC            0.05074873 0.5032504
## variation_rel_c0_dose-variation_rel_AUC       0.13430461 0.0000000
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.09671114 0.0000004
## variation_rel_c0-variation_rel_AUC_c0         0.04209559 0.9133187
## variation_rel_c0_dose-variation_rel_AUC_c0    0.12565146 0.0000000
## variation_rel_c0-variation_rel_AUC_dose      -0.02255940 0.0000333
## variation_rel_c0_dose-variation_rel_AUC_dose  0.06099648 0.0992261
## variation_rel_c0_dose-variation_rel_c0        0.11561203 0.0000000
```

Variations relative time post transplantation :

We created groups for <3 months and > 12 months and boxplots for different metrics (Figure 1)

```
tac_boxplot_variation_3visite_pg <- tac_multi %>% group_by(ID) %>% filter(n()>3) %>% dplyr::select (Type_demande, variation_
rel_AUC, variation_rel_AUC_dose, variation_rel_c0_dose, variation_rel_AUC_c0, variation_rel_c0, delai_entre_visite, Delai_po
st_greffe) %>%  mutate(group_delai_post_greffe = case_when(
    Delai_post_greffe<0.25 ~ "inf_3mois",
    Delai_post_greffe>1 ~ "sup_1an",
    TRUE~"3mois-1an"
    )) %>% filter(variation_rel_c0<20,variation_rel_AUC<20) %>% pivot_longer(cols = starts_with("variation_rel_") ,names_to
 = "metrics", values_to = "variation_relative",values_drop_na = TRUE) %>% filter(!is.na(variation_relative)) #%>% mutate (va
riation_relative = replace(variation_relative,0,0.00001))

tac_boxplot_variation_3visite_pg$group_delai_post_greffe <- factor(tac_boxplot_variation_3visite_pg$group_delai_post_greffe,
    levels = c("inf_3mois","3mois-1an","sup_1an"),ordered = TRUE)

#boxplots
boxplot_delai_post_greffe <- tac_boxplot_variation_3visite_pg %>%
   filter(between(variation_relative,-2.0,2.0)) %>%
   mutate(metrics = fct_relevel(metrics,
              "variation_rel_AUC_c0","variation_rel_AUC_dose", "variation_rel_AUC", "variation_rel_c0_dose","variation_rel_c
0")) %>%
ggplot(mapping = aes(y = variation_relative, x = metrics, fill = group_delai_post_greffe )) +
  geom_boxplot() + coord_flip()+
  # scale_fill_manual(values=c("red", "blue", "green")) +
scale_fill_discrete(name="Post transplant time period (years)",
                         breaks=c("inf_3mois", "3mois-1an", "sup_1an"),
                         labels=c("<3 months", ">3 months & <1 year", "> 1 year")) + scale_x_discrete(breaks=c("variation_re
l_c0","variation_rel_c0_dose",  "variation_rel_AUC","variation_rel_AUC_dose","variation_rel_AUC_c0"),labels=c("C0","C0/dose"
, "AUC","AUC/dose","AUC/C0")) + labs( y ="Relative fold change")  + theme_bw()+ scale_y_continuous(labels = scales::percent)
+ theme(legend.position = "top")+ geom_hline(yintercept = 0, alpha = 0.5)   #+ theme(legend.position = "none")

boxplot_delai_post_greffe
```




```
tac_boxplot_variation_3visite_pg %>% group_by(metrics,group_delai_post_greffe ) %>% filter(delai_entre_visite<5) %>% summari
se (mean = mean(variation_relative), sd = sd(variation_relative))
```

```
## # A tibble: 15 x 4
## # Groups:   metrics [5]
##    metrics               group_delai_post_greffe     mean    sd
##    <chr>                 <ord>                      <dbl> <dbl>
##  1 variation_rel_AUC     inf_3mois               -0.0268  0.443
##  2 variation_rel_AUC     3mois-1an               -0.0591  0.326
##  3 variation_rel_AUC     sup_1an                  0.0120  0.352
##  4 variation_rel_AUC_c0  inf_3mois                0.0233  0.251
##  5 variation_rel_AUC_c0  3mois-1an                0.0124  0.264
##  6 variation_rel_AUC_c0  sup_1an                  0.00813 0.209
##  7 variation_rel_AUC_dose inf_3mois               0.0485  0.406
##  8 variation_rel_AUC_dose 3mois-1an               0.113   0.517
##  9 variation_rel_AUC_dose sup_1an                 0.0697  0.430
## 10 variation_rel_c0      inf_3mois               -0.0246  0.410
## 11 variation_rel_c0      3mois-1an               -0.0238  0.410
## 12 variation_rel_c0      sup_1an                  0.0292  0.378
## 13 variation_rel_c0_dose  inf_3mois               0.0662  0.428
## 14 variation_rel_c0_dose  3mois-1an               0.175   0.663
## 15 variation_rel_c0_dose  sup_1an                 0.0942  0.486
```

```
res.aov4 <- aov(variation_relative ~ metrics + group_delai_post_greffe,  data = tac_boxplot_variation_3visite_pg)
summary(res.aov4)
```

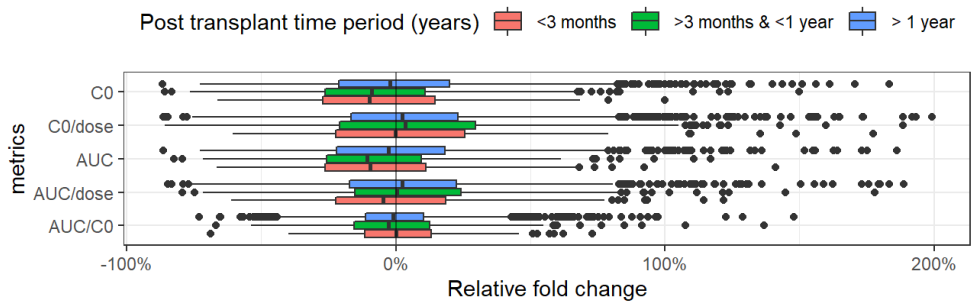
```
##                            Df Sum Sq Mean Sq F value Pr(>F)
## metrics                     4   18.0   4.507  29.044 <2e-16 ***
## group_delai_post_greffe     2    0.4   0.183   1.179  0.308
## Residuals               11233 1743.0   0.155
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov4, which = "group_delai_post_greffe")
```

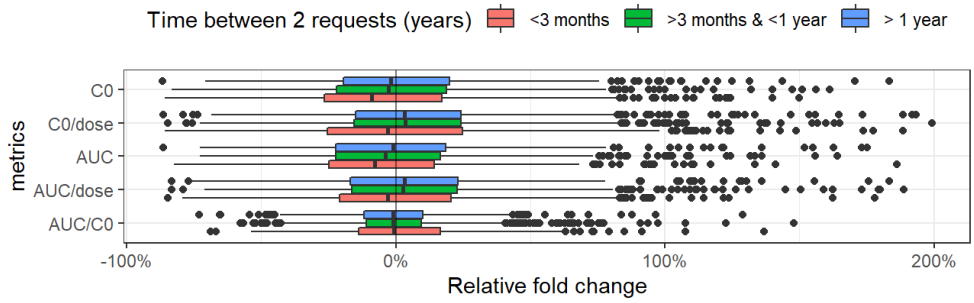
```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_post_greffe, data = tac_boxplot_variation_3visite_pg)
##
## $group_delai_post_greffe
##                              diff         lwr        upr     p adj
## 3mois-1an-inf_3mois  0.0261900968 -0.01878660 0.07116679 0.3594798
## sup_1an-inf_3mois    0.0253300513 -0.01372837 0.06438847 0.2814423
## sup_1an-3mois-1an   -0.0008600455 -0.02698827 0.02526818 0.9967233
```

```
boxplot_delai_post_greffe / boxplot_delai_2_visites + plot_annotation(tag_levels = 'A')
```

A



B




```
ggsave("Figure1.pdf", scale=2)
```

Two way anova and post hoc test

```
# Two-way ANOVA with interaction effect
# These two calls are equivalent
res.aov3 <- aov(variation_relative ~ metrics + group_delai_entre_visite, data = tac_boxplot_variation_3visite)
res.aov3 <- aov(variation_relative ~ metrics + group_delai_entre_visite + metrics:group_delai_entre_visite, data = tac_boxpl
ot_variation_3visite)
summary(res.aov3)
```

```
##                                  Df Sum Sq Mean Sq F value Pr(>F)
## metrics                           4   18.0   4.507  29.047 <2e-16 ***
## group_delai_entre_visite          2    0.3   0.141   0.907  0.404
## metrics:group_delai_entre_visite  8    1.5   0.186   1.197  0.296
## Residuals                     11225 1741.6   0.155
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov3, which = "group_delai_entre_visite")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite + metrics:group_delai_entre_visite, data = tac
_boxplot_variation_3visite)
##
## $group_delai_entre_visite
##                             diff          lwr        upr     p adj
## 3mois-1an-inf_3mois  0.013070326 -0.009765258 0.03590591 0.3720951
## sup_1an-inf_3mois    0.009961306 -0.014462124 0.03438474 0.6047613
## sup_1an-3mois-1an   -0.003109020 -0.023073140 0.01685510 0.9291888
```

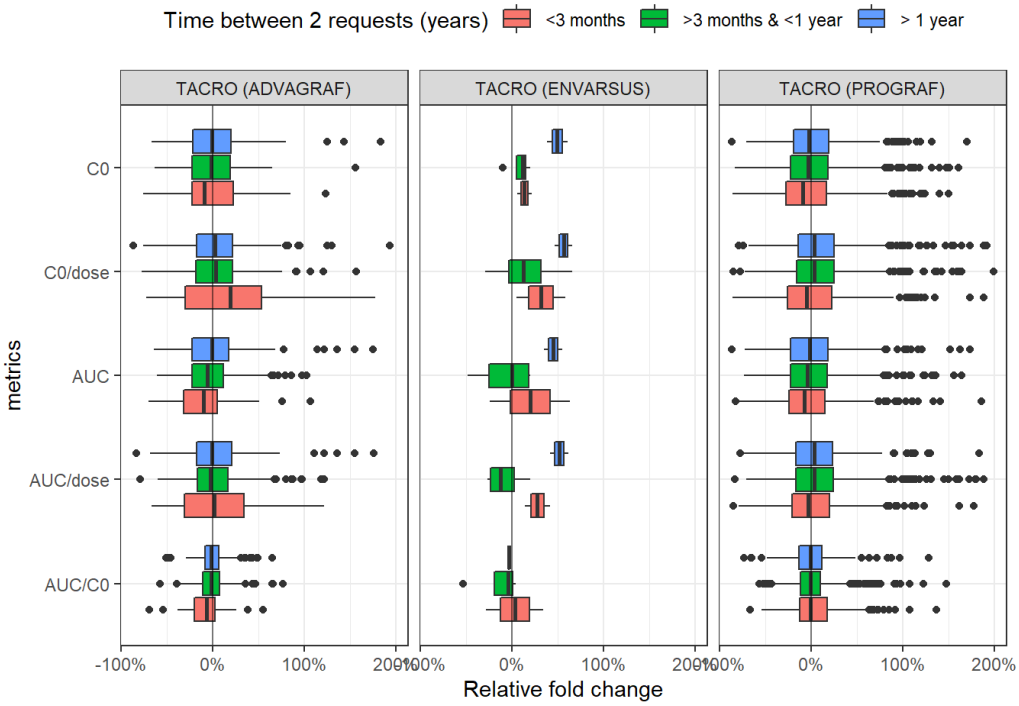
```
TukeyHSD(res.aov3, which = "metrics")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite + metrics:group_delai_entre_visite, data = tac
_boxplot_variation_3visite)
##
## $metrics
##                                                    diff          lwr
## variation_rel_AUC_c0-variation_rel_AUC        0.008653146 -0.023400761
## variation_rel_AUC_dose-variation_rel_AUC      0.073308130  0.041254223
## variation_rel_c0-variation_rel_AUC            0.018692578 -0.013361330
## variation_rel_c0_dose-variation_rel_AUC       0.102248454  0.070194547
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.064654984  0.032601077
## variation_rel_c0-variation_rel_AUC_c0         0.010039431 -0.022014476
## variation_rel_c0_dose-variation_rel_AUC_c0    0.093595308  0.061541400
## variation_rel_c0-variation_rel_AUC_dose      -0.054615553 -0.086669460
## variation_rel_c0_dose-variation_rel_AUC_dose  0.028940324 -0.003113584
## variation_rel_c0_dose-variation_rel_c0        0.083555877  0.051501969
##                                                    upr     p adj
## variation_rel_AUC_c0-variation_rel_AUC        0.04070705 0.9479803
## variation_rel_AUC_dose-variation_rel_AUC      0.10536204 0.0000000
## variation_rel_c0-variation_rel_AUC            0.05074649 0.5031782
## variation_rel_c0_dose-variation_rel_AUC       0.13430236 0.0000000
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.09670889 0.0000004
## variation_rel_c0-variation_rel_AUC_c0         0.04209334 0.9132983
## variation_rel_c0_dose-variation_rel_AUC_c0    0.12564922 0.0000000
## variation_rel_c0-variation_rel_AUC_dose      -0.02256165 0.0000333
## variation_rel_c0_dose-variation_rel_AUC_dose  0.06099423 0.0991846
## variation_rel_c0_dose-variation_rel_c0        0.11560978 0.0000000
```

Relative variations between 2 requests per formulation:

We create groups for <3 months and > 12 months and boxplots for different metrics/per formulation

```
#boxplots
boxplot_delai_2_visites_formulation <- tac_boxplot_variation_3visite %>%
  filter(between(variation_relative,-2.0,2.0)) %>%
  mutate(metrics = fct_relevel(metrics,
             "variation_rel_AUC_c0","variation_rel_AUC_dose", "variation_rel_AUC", "variation_rel_c0_dose","variation_rel_c
0")) %>%
ggplot(mapping = aes(y = variation_relative, x = metrics, fill = group_delai_entre_visite )) +
  geom_boxplot() + coord_flip()+
   scale_fill_manual(values=c("red", "blue", "green")) +
  scale_fill_discrete(name="Time between 2 requests (years)",
                        breaks=c("inf_3mois", "3mois-1an", "sup_1an"),
                        labels=c("<3 months", ">3 months & <1 year", "> 1 year")) + scale_x_discrete(breaks=c("variation_re
l_c0","variation_rel_c0_dose",  "variation_rel_AUC","variation_rel_AUC_dose","variation_rel_AUC_c0"),labels=c("C0","C0/dose"
, "AUC","AUC/dose","AUC/C0")) +
  labs(y="Relative fold change") + theme_bw()+ scale_y_continuous(labels = scales::percent)+ theme(legend.position = "top")+
geom_hline(yintercept = 0, alpha = 0.5) + facet_wrap(~Type_demande)
boxplot_delai_2_visites_formulation
```



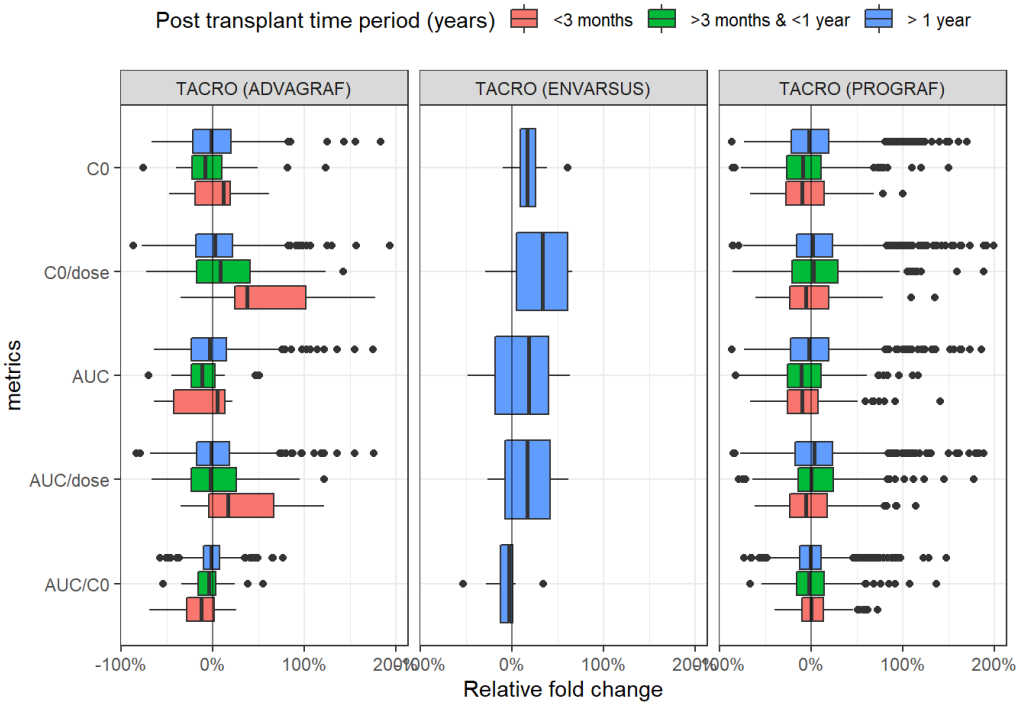

```
# descritpvie stat per metrics, time post trnapslantaiton and formulaiton
tac_boxplot_variation_3visite %>% group_by(metrics,group_delai_entre_visite, Type_demande ) %>% filter(delai_entre_visite<5)
%>% summarise (mean = mean(variation_relative), sd = sd(variation_relative))
```

```
## # A tibble: 45 x 5
## # Groups:   metrics, group_delai_entre_visite [15]
##    metrics              group_delai_entre_visite Type_demande         mean    sd
##    <chr>                <ord>                    <fct>               <dbl> <dbl>
##  1 variation_rel_AUC    inf_3mois                TACRO (ADVAGRAF) -0.0175  0.470
##  2 variation_rel_AUC    inf_3mois                TACRO (ENVARSUS)  0.199   0.616
##  3 variation_rel_AUC    inf_3mois                TACRO (PROGRAF)  -0.0122  0.391
##  4 variation_rel_AUC    3mois-1an                TACRO (ADVAGRAF) -0.0289  0.291
##  5 variation_rel_AUC    3mois-1an                TACRO (ENVARSUS) -0.0678  0.322
##  6 variation_rel_AUC    3mois-1an                TACRO (PROGRAF)   0.00315 0.340
##  7 variation_rel_AUC    sup_1an                  TACRO (ADVAGRAF)  0.0133  0.363
##  8 variation_rel_AUC    sup_1an                  TACRO (ENVARSUS)  0.452   0.147
##  9 variation_rel_AUC    sup_1an                  TACRO (PROGRAF)   0.0141  0.355
## 10 variation_rel_AUC_c0 inf_3mois                TACRO (ADVAGRAF) -0.0743  0.224
## # ... with 35 more rows
```

Variations relative time post transplantation :

We created groups for <3 months and > 12 months and boxplots for different metrics

```
#boxplots
boxplot_delai_post_greffe_formulation <- tac_boxplot_variation_3visite_pg %>%
   filter(between(variation_relative,-2.0,2.0)) %>%
   mutate(metrics = fct_relevel(metrics,
            "variation_rel_AUC_c0","variation_rel_AUC_dose", "variation_rel_AUC", "variation_rel_c0_dose","variation_rel_c
0")) %>%
ggplot(mapping = aes(y = variation_relative, x = metrics, fill = group_delai_post_greffe )) +
  geom_boxplot() + coord_flip()+
  # scale_fill_manual(values=c("red", "blue", "green")) +
scale_fill_discrete(name="Post transplant time period (years)",
                        breaks=c("inf_3mois", "3mois-1an", "sup_1an"),
                        labels=c("<3 months", ">3 months & <1 year", "> 1 year")) + scale_x_discrete(breaks=c("variation_re
l_c0","variation_rel_c0_dose",  "variation_rel_AUC","variation_rel_AUC_dose","variation_rel_AUC_c0"),labels=c("C0","C0/dose"
, "AUC","AUC/dose","AUC/C0")) + labs( y ="Relative fold change")  + theme_bw()+ scale_y_continuous(labels = scales::percent)
+ theme(legend.position = "top")+ geom_hline(yintercept = 0, alpha = 0.5) + facet_wrap(~Type_demande)   #+ theme(legend.posi
tion = "none")


boxplot_delai_post_greffe_formulation
```



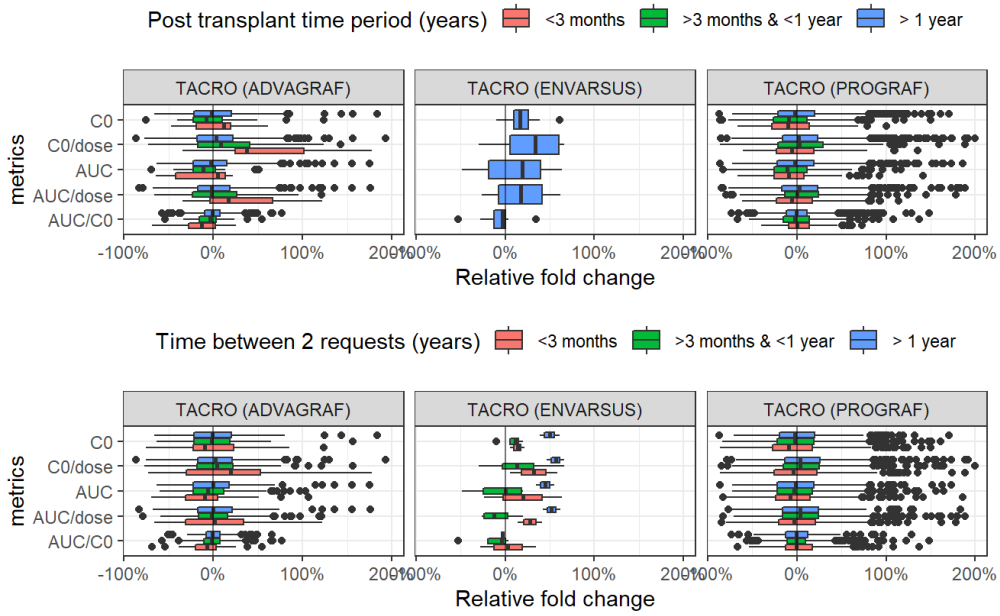

```
# descritpvie stat per metrics, time post trnapslantaiton and formulaiton
tac_boxplot_variation_3visite_pg %>% group_by(metrics,group_delai_post_greffe, Type_demande ) %>% filter(delai_entre_visite<
5) %>% summarise (mean = mean(variation_relative), sd = sd(variation_relative))
```

```
## # A tibble: 35 x 5
## # Groups:   metrics, group_delai_post_greffe [15]
##    metrics              group_delai_post_greffe Type_demande         mean    sd
##    <chr>                <ord>                   <fct>               <dbl> <dbl>
##  1 variation_rel_AUC    inf_3mois               TACRO (ADVAGRAF) -0.121   0.337
##  2 variation_rel_AUC    inf_3mois               TACRO (PROGRAF)  -0.0182  0.452
##  3 variation_rel_AUC    3mois-1an               TACRO (ADVAGRAF) -0.0271  0.463
##  4 variation_rel_AUC    3mois-1an               TACRO (PROGRAF)  -0.0630  0.306
##  5 variation_rel_AUC    sup_1an                 TACRO (ADVAGRAF) -0.00510 0.335
##  6 variation_rel_AUC    sup_1an                 TACRO (ENVARSUS)  0.129   0.394
##  7 variation_rel_AUC    sup_1an                 TACRO (PROGRAF)   0.0161  0.356
##  8 variation_rel_AUC_c0 inf_3mois               TACRO (ADVAGRAF) -0.147   0.265
##  9 variation_rel_AUC_c0 inf_3mois               TACRO (PROGRAF)   0.0389  0.246
## 10 variation_rel_AUC_c0 3mois-1an               TACRO (ADVAGRAF) -0.0434  0.205
## # ... with 25 more rows
```

```
# Supplemental figure
boxplot_delai_post_greffe_formulation / boxplot_delai_2_visites_formulation  +  plot_annotation(
  title = 'Supplemental Figure 1',
  subtitle = 'Boxplots of relative intra-individual variations of the metrics of interest censored beyond -100% and +200%, d
epending on the post-transplant period (A) and the time elapsed between 2 \ninstances (B) (categorized) per formulation typ
e. ', theme = theme(plot.title = element_text(size = 10),plot.subtitle = element_text(size = 6))
 )
```

Supplemental Figure 1

Boxplots of relative intra-individual variations of the metrics of interest censored beyond -100% and +200%, depending on the post-transplant period (A) and the time elapsed between 2 instances (B) (categorized) per formulation type.




```
ggsave("Figure_supplemental1_fold_change_formulation.pdf", scale=2)
```

Comparison of different metrics as function of formulation type ANOVA and post test

```
# auc_dose
tac_multi %>% kruskal.test(variation_rel_AUC_dose~Type_demande)
```

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 139084, df = 38, p-value < 2.2e-16
```

```
res.aov_AUC_dose <- aov(variation_rel_AUC_dose ~ Type_demande, data = tac_multi)
summary(res.aov_AUC_dose)
```

```
##                Df Sum Sq Mean Sq F value   Pr(>F)
## Type_demande    2    6.7   3.368   16.13 1.05e-07 ***
## Residuals    3824  798.3   0.209
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov_AUC_dose, which = "Type_demande")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_AUC_dose ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                        diff         lwr         upr     p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF)  0.36430076  0.20046928  0.52813225 0.0000006
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.05738467  0.01579056  0.09897878 0.0035165
## TACRO (PROGRAF)-TACRO (ENVARSUS)  -0.30691609 -0.46783740 -0.14599479 0.0000238
```

```
# c0_dose
tac_multi %>% kruskal.test(variation_rel_c0_dose~Type_demande)
```

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 139084, df = 38, p-value < 2.2e-16
```

```
res.aov_c0_dose <- aov(variation_rel_c0_dose ~ Type_demande, data = tac_multi)
summary(res.aov_c0_dose)
```

```
##                Df Sum Sq Mean Sq F value   Pr(>F)
## Type_demande    2    9.5   4.765   9.647 6.62e-05 ***
## Residuals    3824 1888.6   0.494
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
TukeyHSD(res.aov_c0_dose, which = "Type_demande")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_c0_dose ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                         diff         lwr        upr     p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF)  0.4604677  0.20848313  0.7124523 0.0000558
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.0488575 -0.01511722  0.1128322 0.1728429
## TACRO (PROGRAF)-TACRO (ENVARSUS)  -0.4116102 -0.65911872 -0.1641017 0.0002893
```

```
# auc_c0
tac_multi %>% kruskal.test(variation_rel_AUC_c0~Type_demande)
```

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 139084, df = 38, p-value < 2.2e-16
```

```
res.aov_AUC_c0 <- aov(variation_rel_AUC_c0 ~ Type_demande, data = tac_multi)
summary(res.aov_AUC_c0)
```

```
##                Df Sum Sq Mean Sq F value Pr(>F)
## Type_demande    2   0.19 0.09413    1.89  0.151
## Residuals    3824 190.40 0.04979
```

```
TukeyHSD(res.aov_AUC_c0, which = "Type_demande")
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_AUC_c0 ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                           diff          lwr        upr     p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF) -0.02666910 -0.106679158 0.05334095 0.7144310
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.01379682 -0.006516413 0.03411005 0.2489775
## TACRO (PROGRAF)-TACRO (ENVARSUS)   0.04046592 -0.038122895 0.11905474 0.4489026
```

```
# counts
tac_multi %>% group_by(Type_demande, Tt_associe) %>% count()
```

```
## # A tibble: 7 x 3
## # Groups:   Type_demande, Tt_associe [7]
##   Type_demande     Tt_associe      n
##   <fct>            <fct>       <int>
## 1 TACRO (ADVAGRAF) Corticoides    25
## 2 TACRO (ADVAGRAF) MMF           715
## 3 TACRO (ADVAGRAF) Neant         118
## 4 TACRO (ENVARSUS) MMF            34
## 5 TACRO (ENVARSUS) Neant          11
## 6 TACRO (PROGRAF)  MMF          2464
## 7 TACRO (PROGRAF)  Neant         460
```

```
tac_multi %>% group_by(Type_demande) %>% count()
```

```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande         n
##   <fct>            <int>
## 1 TACRO (ADVAGRAF)   858
## 2 TACRO (ENVARSUS)    45
## 3 TACRO (PROGRAF)   2924
```

Correlation AUC/c0

```
sample.data <- tac_multi %>%
  mutate(
    TAD = if_else(Type_demande == "TACRO (PROGRAF)", "TAD", "OAD"),
    age_group = if_else(age>18, "adults","children"),
    group_delai_post_greffe = case_when(
    Delai_post_greffe<0.25 ~ "< 3 months",
    Delai_post_greffe>1 ~ "> 1 year",
    TRUE~"between 3 months and 1 year"),
    group_delai_post_greffe = factor(group_delai_post_greffe, levels=c("< 3 months","between 3 months and 1 year","> 1 year"
)),
    c0_inf = c0*0.7,
    c0_sup = c0*1.3)

# adult_inf3mois
adult_inf3mois <-
  sample.data %>% filter(group_delai_post_greffe=="< 3 months" & age_group == "adults")
reg_adult_inf3mois <- lm(AUC_0_24 ~ c0 , data = adult_inf3mois)
intercept_a3 = reg_adult_inf3mois$coefficients[[1]]
slope = reg_adult_inf3mois$coefficients[[2]]
reg_adult_inf3mois_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_inf3mois)
intercept_inf_a3 = reg_adult_inf3mois_inf$coefficients[[1]]
slope_inf_a3 = reg_adult_inf3mois_inf$coefficients[[2]]
reg_adult_inf3mois_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_inf3mois)
intercept_sup_a3 = reg_adult_inf3mois_sup$coefficients[[1]]
slope_sup_a3 = reg_adult_inf3mois_sup$coefficients[[2]]

#plot
adult_inf3mois_plot <- adult_inf3mois %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a3+slope_inf_a3*c0, ymax =intercept_a3+slope_sup_a3*c0), fill = "grey70", alpha = 0.6) +
    geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
   # geom_abline(intercept = intercept, slope = slope, size=1,colour="grey")+
  theme_bw() +
    labs(
     title = "Adults & <3months",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
adult_inf3mois %>%
  mutate(ymax = intercept_a3+slope_inf_a3*c0,
         ymin =intercept_a3+slope_sup_a3*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.305   141
```

```
# adult_3mois_1y
adult_3mois_1y <-
  sample.data %>% filter(group_delai_post_greffe=="between 3 months and 1 year" & age_group == "adults")
reg_adult_3mois_1y <- lm(AUC_0_24 ~ c0 , data = adult_3mois_1y)
intercept_a31 = reg_adult_3mois_1y$coefficients[[1]]
slope = reg_adult_3mois_1y$coefficients[[2]]
reg_adult_3mois_1y_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_3mois_1y)
intercept_inf_a31 = reg_adult_3mois_1y_inf$coefficients[[1]]
slope_inf_a31 = reg_adult_3mois_1y_inf$coefficients[[2]]
reg_adult_3mois_1y_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_3mois_1y)
intercept_sup_a31 = reg_adult_3mois_1y_sup$coefficients[[1]]
slope_sup_a31 = reg_adult_3mois_1y_sup$coefficients[[2]]

#plot
adult_3mois_1y_plot <- adult_3mois_1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a31+slope_inf_a31*c0, ymax =intercept_a31+slope_sup_a31*c0), fill = "grey70", alpha = 0.
6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Adults & between 3 months \nand 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
adult_3mois_1y %>%
  mutate(ymax = intercept_a31+slope_inf_a31*c0,
         ymin =intercept_a31+slope_sup_a31*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1          0.3   610
```

```
# adult_sup1y
adult_sup1y <-
  sample.data %>% filter(group_delai_post_greffe=="> 1 year" & age_group == "adults")
reg_adult_sup1y <- lm(AUC_0_24 ~ c0 , data = adult_sup1y)
intercept_a1 = reg_adult_sup1y$coefficients[[1]]
slope = reg_adult_sup1y$coefficients[[2]]
reg_adult_sup1y_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_sup1y)
slope_inf_a1 = reg_adult_sup1y_inf$coefficients[[2]]
reg_adult_sup1y_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_sup1y)
slope_sup_a1 = reg_adult_sup1y_sup$coefficients[[2]]

#plot
adult_sup1y_plot <- adult_sup1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a1+slope_inf_a1*c0, ymax =intercept_a1+slope_sup_a1*c0), fill = "grey70", alpha = 0.6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Adults & > 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
adult_sup1y %>%
  mutate(ymax = intercept_a1+slope_inf_a1*c0,
         ymin =intercept_a1+slope_sup_a1*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.150  2614
```

```
# children_inf3mois
children_inf3mois <-
  sample.data %>% filter(group_delai_post_greffe=="< 3 months" & age_group == "children")
reg_children_inf3mois <- lm(AUC_0_24 ~ c0 , data = children_inf3mois)
intercept_c3 = reg_children_inf3mois$coefficients[[1]]
slope = reg_children_inf3mois$coefficients[[2]]
reg_children_inf3mois_inf <- lm(AUC_0_24 ~ c0_inf , data = children_inf3mois)
slope_inf_c3 = reg_children_inf3mois_inf$coefficients[[2]]
reg_children_inf3mois_sup<- lm(AUC_0_24 ~ c0_sup , data = children_inf3mois)
slope_sup_c3 = reg_children_inf3mois_sup$coefficients[[2]]

#plot
children_inf3mois_plot <- children_inf3mois %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c3+slope_inf_c3*c0, ymax =intercept_c3+slope_sup_c3*c0), fill = "grey70", alpha = 0.6) +
    geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & <3months",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_inf3mois %>%
  mutate(ymax = intercept_c3+slope_inf_c3*c0,
         ymin =intercept_c3+slope_sup_c3*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.293    82
```

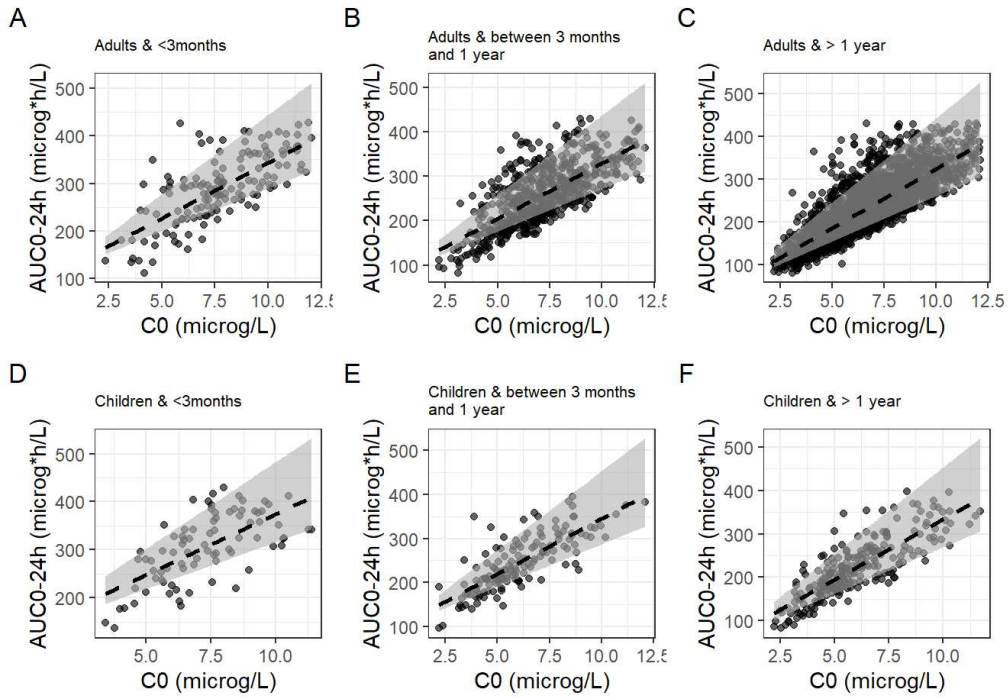
```
# children_3mois_1y
children_3mois_1y <-
  sample.data %>% filter(group_delai_post_greffe=="between 3 months and 1 year" & age_group == "children")
reg_children_3mois_1y <- lm(AUC_0_24 ~ c0 , data = children_3mois_1y)
intercept_c31 = reg_children_3mois_1y$coefficients[[1]]
slope = reg_children_3mois_1y$coefficients[[2]]
reg_children_3mois_1y_inf <- lm(AUC_0_24 ~ c0_inf , data = children_3mois_1y)
slope_inf_c31 = reg_children_3mois_1y_inf$coefficients[[2]]
reg_children_3mois_1y_sup<- lm(AUC_0_24 ~ c0_sup , data = children_3mois_1y)
slope_sup_c31 = reg_children_3mois_1y_sup$coefficients[[2]]

#plot
children_3mois_1y_plot <- children_3mois_1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c31+slope_inf_c31*c0, ymax =intercept_c31+slope_sup_c31*c0), fill = "grey70", alpha = 0.
6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & between 3 months \nand 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_3mois_1y %>%
  mutate(ymax = intercept_c31+slope_inf_c31*c0,
         ymin =intercept_c31+slope_sup_c31*c0,
         AUC_out = if_else(AUC_0_24 <ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.255   145
```

```
# children_sup1y
children_sup1y <-
  sample.data %>% filter(group_delai_post_greffe=="> 1 year" & age_group == "children")
reg_children_sup1y <- lm(AUC_0_24 ~ c0 , data = children_sup1y)
intercept_c1 = reg_children_sup1y$coefficients[[1]]
slope = reg_children_sup1y$coefficients[[2]]
reg_children_sup1y_inf <- lm(AUC_0_24 ~ c0_inf , data = children_sup1y)
slope_inf_c1 = reg_children_sup1y_inf$coefficients[[2]]
reg_children_sup1y_sup<- lm(AUC_0_24 ~ c0_sup , data = children_sup1y)
slope_sup_c1 = reg_children_sup1y_sup$coefficients[[2]]

#plot
children_sup1y_plot <- children_sup1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c1+slope_inf_c1*c0, ymax =intercept_c1+slope_sup_c1*c0), fill = "grey70", alpha = 0.6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & > 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_sup1y %>%
  mutate(ymax = intercept_c1+slope_inf_c1*c0,
         ymin =intercept_c1+slope_sup_c1*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_30_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.234   235
```

```
# graph

adult_inf3mois_plot + adult_3mois_1y_plot + adult_sup1y_plot + children_inf3mois_plot + children_3mois_1y_plot + children_su
p1y_plot + plot_annotation(tag_levels = 'A')
```



```
ggsave("new_figure3_220422.pdf")
```

Correlation for AUC, c0 and AUC/c0 between instances #1 and #2

Overall

```
tac_multi_rank2 <- ungroup(tac_multi) %>% filter(rank_visite==2, AUC_c0<150)

multi_auc_c0 <- tac_multi_rank2 %>% ggplot(aes(x = AUC_c0, y = AUC_c0_prec)) + geom_point(alpha = 0.5) + geom_smooth(method
 = lm) + labs(x = "AUC/C0 visit n", y = "AUC/C0 visit n-1" ) + theme_bw() + ggplot2::annotate("text",
                    x = 70,y = 90,
                    label="r = 0.37",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank2 %>% summarise(cor_AUC_c0 = cor(AUC_c0, AUC_c0_prec))
```

```
## # A tibble: 1 x 1
##   cor_AUC_c0
##        <dbl>
## 1      0.368
```

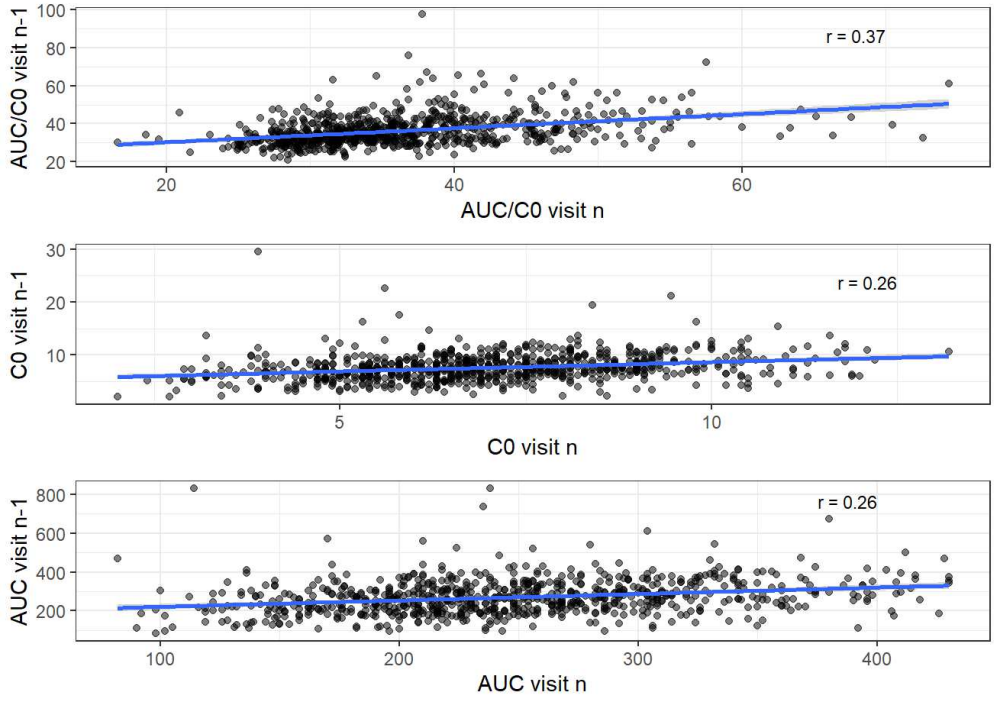
```
multi_c0 <- tac_multi_rank2 %>% ggplot(aes(x = C0_obs, y = c0_prec)) + geom_point(alpha = 0.5) + geom_smooth(method = lm)  +
labs(x = "C0 visit n", y = "C0 visit n-1" ) + theme_bw()+ ggplot2::annotate("text",
                    x = 12.5,y = 25,
                    label="r = 0.26",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank2 %>% summarise(cor_c0 = cor(C0_obs, c0_prec))
```

```
## # A tibble: 1 x 1
##   cor_c0
##    <dbl>
## 1  0.263
```

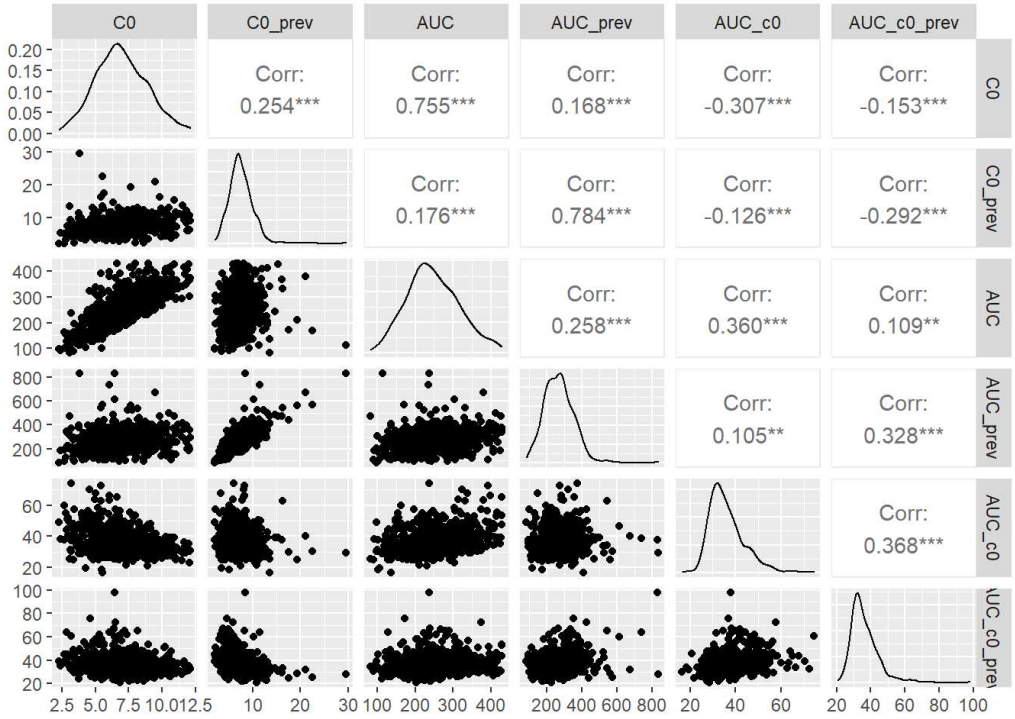
```
multi_auc <- tac_multi_rank2 %>% ggplot(aes(x = AUC_0_24, y = AUC_prec)) + geom_point(alpha = 0.5) + geom_smooth(method = l
m)  + labs(x = "AUC visit n", y = "AUC visit n-1" ) + theme_bw()+ ggplot2::annotate("text",
                    x = 400,y = 800,
                    label="r = 0.26",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank2 %>% summarise(cor_AUC = cor(AUC_0_24, AUC_prec))
```

```
## # A tibble: 1 x 1
##   cor_AUC
##     <dbl>
## 1   0.258
```

```
#patchwork plots
multi_auc_c0/multi_c0/ multi_auc
```




```
# ggsave("Figure5.pdf")

library(GGally)
#global
rank1_2 <- tac_multi_rank2 %>%
  dplyr::select(c0,c0_prec, AUC_0_24,AUC_prec,AUC_c0, AUC_c0_prec, -ID) %>% filter(AUC_c0<150) %>% rename(
C0_prev = c0_prec,
                                      AUC_prev = AUC_prec,
                                      AUC_c0_prev = AUC_c0_prec,
                                      C0 = c0,
                                      AUC = AUC_0_24) %>%

    ggpairs()
rank1_2
```




```
tac_multi_rank2 %>% group_by(Type_demande) %>% count()
```

```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande          n
##   <fct>             <int>
## 1 TACRO (ADVAGRAF)    163
## 2 TACRO (ENVARSUS)      4
## 3 TACRO (PROGRAF)     592
```

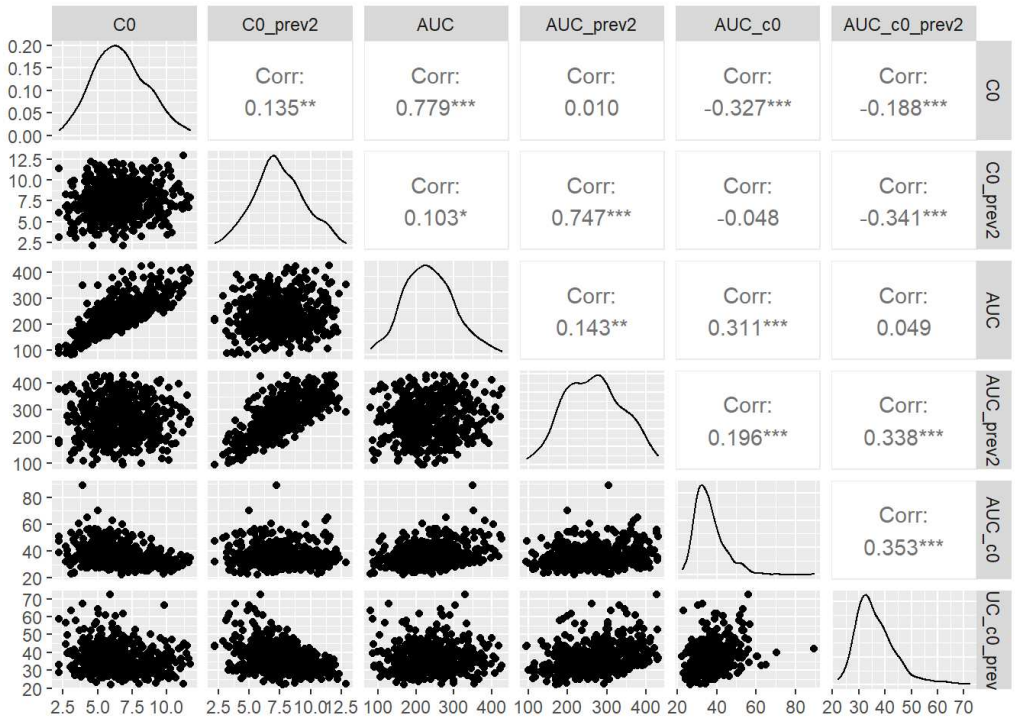
per formulation

```
tac_multi_rank2 %>%
  dplyr::select(Type_demande,Delai_post_greffe, c0,c0_prec, AUC_0_24,AUC_prec,AUC_c0, AUC_c0_prec, -ID) %>% filter(AUC_c0<15
0) %>%
           ggpairs(mapping = aes(color = Type_demande))
```

Correlation for AUC, c0 and AUC/c0 between instances #1 and #3

Overall

```
tac_multi_rank3 <- ungroup(tac_multi_lag2) %>% filter(rank_visite==3, AUC_c0<150)

#global
rank1_3 <- tac_multi_rank3 %>%
  dplyr::select(c0,c0_prec2, AUC_0_24,AUC_prec2,AUC_c0, AUC_c0_prec2) %>% filter(AUC_c0<150) %>% rename(
    C0 = c0,
    C0_prev2 = c0_prec2,
    AUC_prev2 = AUC_prec2,
    AUC_c0_prev2 = AUC_c0_prec2,
     AUC = AUC_0_24) %>%
    ggpairs(axisLabels = c("show", "internal", "none"))
rank1_3
```




```
tac_multi_rank3 %>% group_by(Type_demande) %>% count()
```

```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande         n
##   <fct>            <int>
## 1 TACRO (ADVAGRAF)   115
## 2 TACRO (ENVARSUS)     4
## 3 TACRO (PROGRAF)    402
```

```
multi_auc_c02 <- tac_multi_rank3 %>% ggplot(aes(x = AUC_c0, y = AUC_c0_prec)) + geom_point(alpha = 0.5) + geom_smooth(method
= lm) + labs(x = "AUC/C0 visit n", y = "AUC/C0 visit n-2" ) + theme_bw() + ggplot2::annotate("text",
                    x = 90,y = 80,
                    label="r = 0.36",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank3 %>% summarise(cor_AUC_c0 = cor(AUC_c0, AUC_c0_prec))
```

```
## # A tibble: 1 x 1
##   cor_AUC_c0
##        <dbl>
## 1      0.362
```

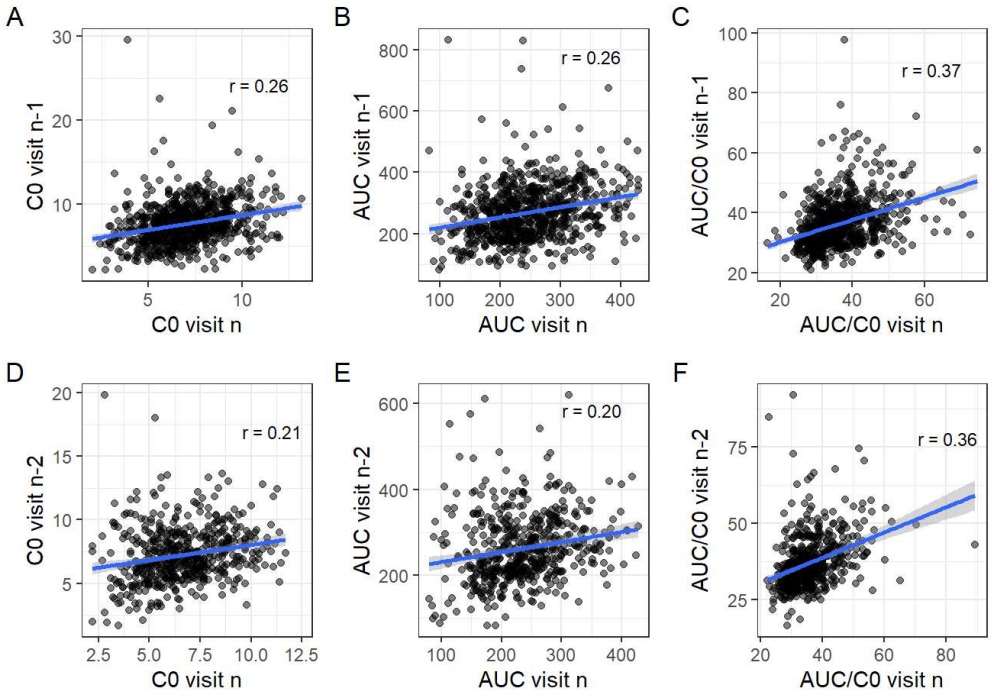
```
multi_c02 <- tac_multi_rank3 %>% ggplot(aes(x = C0_obs, y = c0_prec)) + geom_point(alpha = 0.5) + geom_smooth(method = lm)
 + labs(x = "C0 visit n", y = "C0 visit n-2" ) + theme_bw() + ggplot2::annotate("text",
                    x = 12.5,y = 17.5,
                    label="r = 0.21",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank3 %>% summarise(cor_c0 = cor(C0_obs, c0_prec))
```

```
## # A tibble: 1 x 1
##   cor_c0
##    <dbl>
## 1  0.211
```

```
multi_auc2 <- tac_multi_rank3 %>% ggplot(aes(x = AUC_0_24, y = AUC_prec)) + geom_point(alpha = 0.5) + geom_smooth(method = l
m)  + labs(x = "AUC visit n", y = "AUC visit n-2" ) + theme_bw() + ggplot2::annotate("text",
                    x = 400,y = 600,
                    label="r = 0.20",
                    # color = "red",
                    hjust = 1, vjust = 1, size = 3)

tac_multi_rank3 %>% summarise(cor_AUC = cor(AUC_0_24, AUC_prec))
```

```
## # A tibble: 1 x 1
##   cor_AUC
##     <dbl>
## 1   0.197
```

```
#patchwork plot and figure 5
(multi_c0 + multi_auc + multi_auc_c0+ multi_c02 + multi_auc2+ multi_auc_c02 ) + plot_annotation(tag_levels = 'A')
```




```
ggsave("Figure4.pdf")
```

per formulation

```
tac_multi_rank3 %>%
  dplyr::select(Type_demande,Delai_post_greffe, c0,c0_prec2, AUC_0_24,AUC_prec2,AUC_c0, AUC_c0_prec2) %>% filter(AUC_c0<150)
%>% ggpairs(mapping = aes(color = Type_demande))
```

AUC/C0 analysis vs CYP3A5 status in the subpopulation epigren/ephegren

```
epi_cyp3a5 <- read.csv2("cyp3a5_epigren_ephegren_150721.csv") %>%
mutate(AUC_0_24 = if_else(Type.AUC == "0-24h",AUC, AUC*2), AUC_c0 = AUC_0_24/C0, date_greffe = dmy(DATE.GREFFE), date_visite
= dmy(DATE.VISITE.ou.AUC), delai_post_greffe = as.numeric(date_visite - date_greffe)/365)  %>%
  select(id = CODE_PATIENT, CYP3A5, CYP3A4, SEXE, C0, AUC_0_24,Cmax,AUC_c0,delai_post_greffe ) %>%
  mutate(
    lag_id = lag(id),
    AUC_prec = ifelse(id==lag_id,lag(AUC_0_24),0),
    cmax_prec =  ifelse(id==lag_id,lag(Cmax),0),
# AUC_dose_prec =  ifelse(ID==lag_id,lag(AUC_dose),0),
AUC_c0_prec =  ifelse(id==lag_id,lag(AUC_c0),0),
  c0_prec =  ifelse(id==lag_id,lag(C0),0),
# c0_dose_prec =  ifelse(ID==lag_id,lag(c0_dose),0),
delai_prec =  ifelse(id==lag_id,lag(delai_post_greffe),0),
delai_entre_visite = delai_post_greffe - delai_prec,
variation_rel_AUC = ((AUC_0_24 - AUC_prec) / AUC_prec),
# variation_rel_AUC_dose = ((AUC_dose - AUC_dose_prec) / AUC_dose_prec),
variation_rel_c0 = ((C0 - c0_prec) / c0_prec),
# variation_rel_c0_dose = ((c0_dose - c0_dose_prec) / c0_dose_prec),
variation_rel_AUC_c0 = ((AUC_c0 - AUC_c0_prec) / AUC_c0_prec),
CYP3A5 = if_else(CYP3A5 == "GG", "non expressor", "expressor")
) %>% filter(delai_entre_visite>0, AUC_prec>0)
skim(ungroup(epi_cyp3a5))
```

Data summary

Name	ungroup(epi_cyp3a5)
Number of rows	220

Number of columns	19
_____	
Column type frequency:	
character	5
numeric	14
_____	
Group variables	None

Variable type: character

skim_variable	n_missing	complete_rate	min	max	empty	n_unique	whitespace
id	0	1	11	11	0	52	0
CYP3A5	0	1	9	13	0	2	0
CYP3A4	0	1	2	2	0	1	0
SEXE	0	1	7	8	0	2	0
lag_id	0	1	11	11	0	52	0

Variable type: numeric

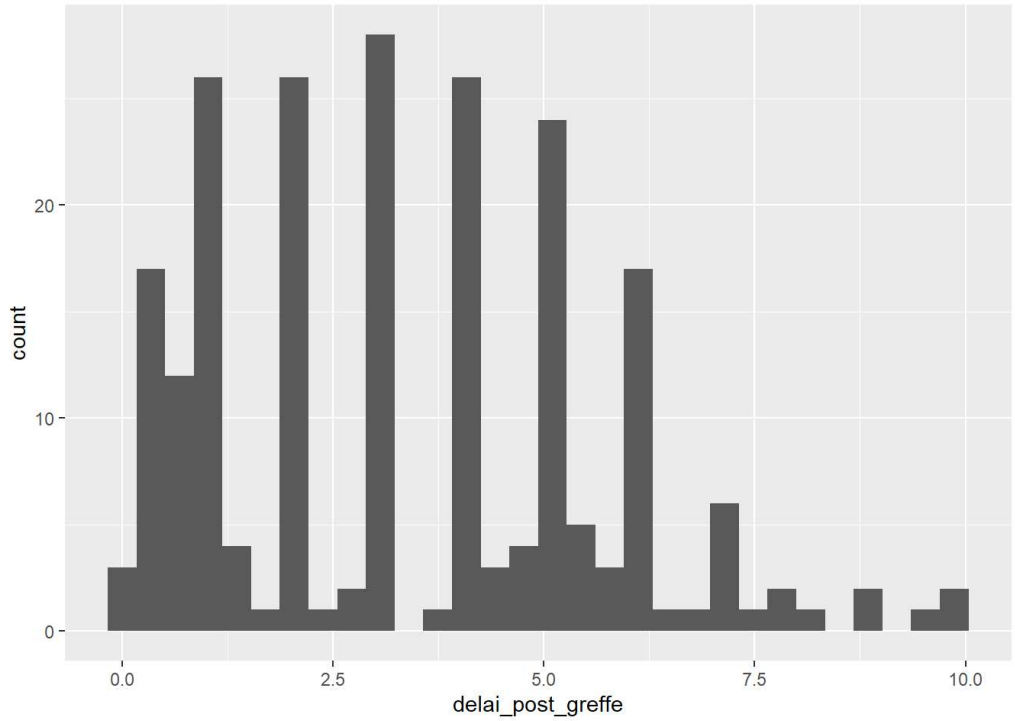
skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
C0	0	1	8.11	2.83	1.00	6.30	7.70	9.12	21.10	
AUC_0_24	0	1	285.94	97.52	38.00	224.00	270.00	324.50	728.00	
Cmax	0	1	20.31	9.17	2.51	14.01	18.20	24.56	54.96	
AUC_c0	0	1	36.08	7.71	22.25	30.69	35.09	39.66	82.00	
delai_post_greffe	0	1	3.35	2.26	0.09	1.07	3.03	5.01	9.96	
AUC_prec	0	1	309.01	107.63	90.00	233.50	282.00	368.50	728.00	
cmax_prec	0	1	22.26	10.30	6.27	15.21	19.50	26.49	65.47	
AUC_c0_prec	0	1	36.45	7.20	22.25	31.42	35.39	40.29	70.37	
c0_prec	0	1	8.65	3.13	2.00	6.60	8.00	9.93	23.00	
delai_prec	0	1	2.45	2.03	-0.03	0.67	2.00	4.02	8.95	
delai_entre_visite	0	1	0.90	0.54	0.02	0.63	0.99	1.01	3.88	
variation_rel_AUC	0	1	-0.01	0.35	-0.94	-0.24	-0.03	0.16	1.17	
variation_rel_c0	0	1	0.02	0.42	-0.96	-0.25	-0.03	0.19	2.30	
variation_rel_AUC_c0	0	1	0.02	0.25	-0.52	-0.14	-0.01	0.13	1.29	

```
epi_cyp3a5 %>% distinct(id, .keep_all = TRUE) %>% group_by(CYP3A5) %>% tally()
```

```
## # A tibble: 2 x 2
##   CYP3A5            n
##   <chr>         <int>
## 1 expressor         8
## 2 non expressor    44
```

Filtering out time post transplantation and histogram

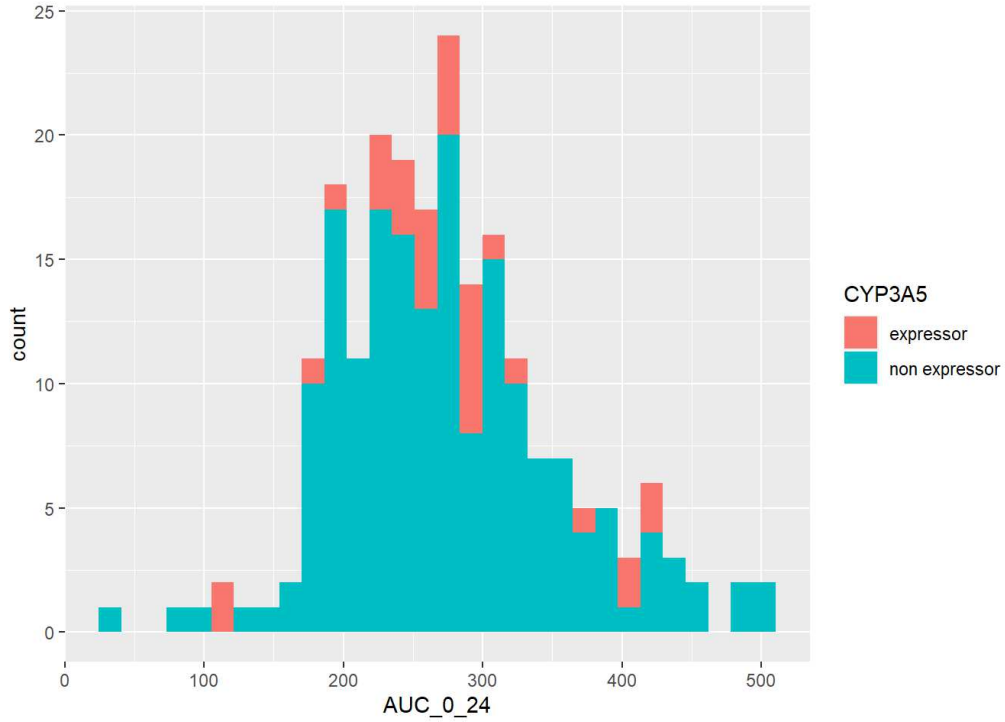
```
ggplot(epi_cyp3a5, mapping = aes(x = delai_post_greffe)) +
   geom_histogram()
```



Filtering out AUC and histogram

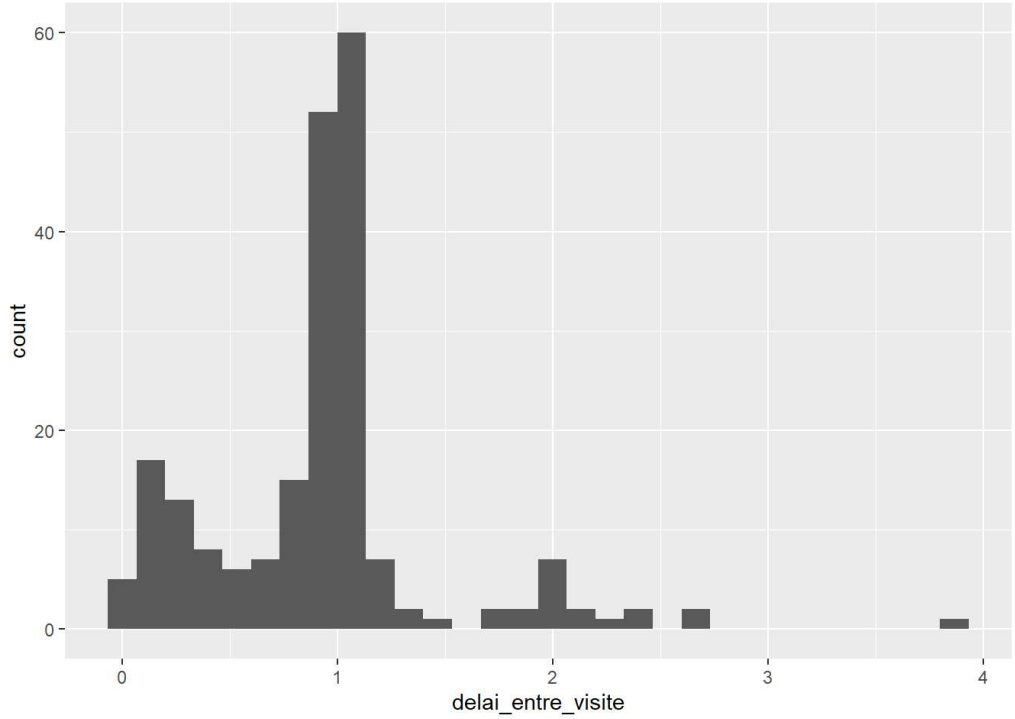
Removal of AUC > mean+/- 1.96 SD = [80-430]

```
# tac_multi <- tac_multi %>% filter(AUC_0_24 < 517)
epi_cyp3a5 <- epi_cyp3a5 %>% filter(between(AUC_0_24,0,517))
ggplot(epi_cyp3a5, mapping = aes(x = AUC_0_24, fill = CYP3A5)) +
   geom_histogram()
```



Filtering out time between requests and histogram

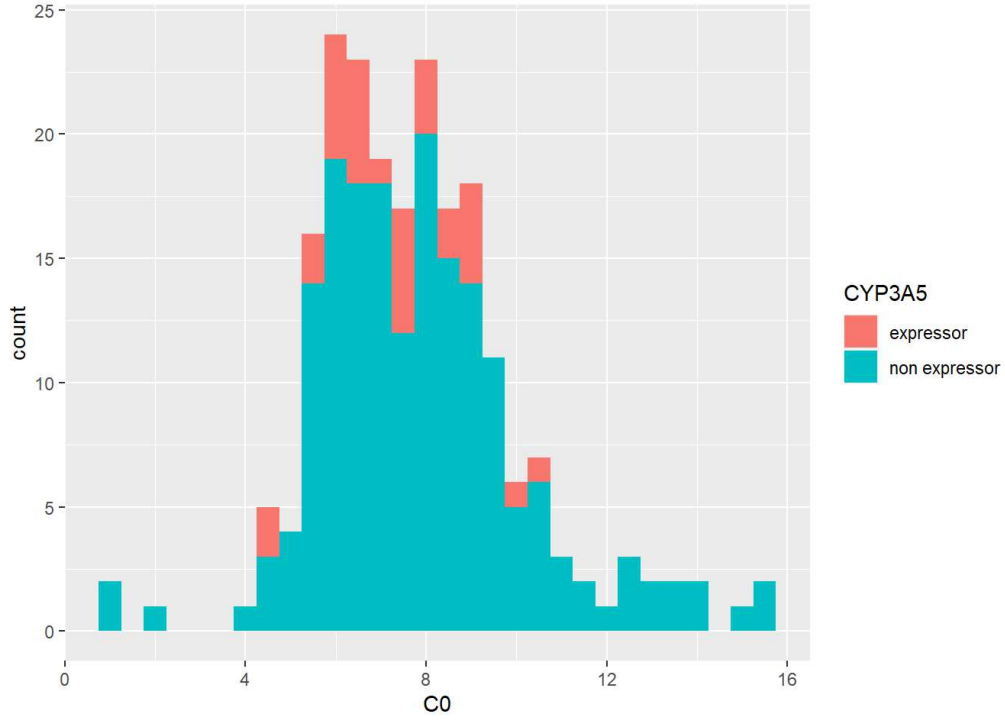
```
ggplot(data = epi_cyp3a5, mapping = aes(x = delai_entre_visite)) +
  geom_histogram()
```



Filtering out c0 and histogram

Removal of C0 > 1.96*SD [2.18-12.14]

```
ggplot(epi_cyp3a5, mapping = aes(x = C0, fill = CYP3A5)) +
   geom_histogram()
```



Rank of visit

```
epi_cyp3a5 <- epi_cyp3a5 %>% arrange(id,delai_post_greffe) %>% group_by(id) %>% mutate(rank_visite = row_number()) %>% ungro
up()
```

Summary of data after filtering out values

```
skim(ungroup(epi_cyp3a5))
```

Data summary

Name	ungroup(epi_cyp3a5)
Number of rows	212
Number of columns	20
_____	
Column type frequency:	
character	5
numeric	15
_____	
Group variables	None

Variable type: character

skim_variable	n_missing	complete_rate	min	max	empty	n_unique	whitespace
id	0	1	11	11	0	52	0
CYP3A5	0	1	9	13	0	2	0
CYP3A4	0	1	2	2	0	1	0
SEXE	0	1	7	8	0	2	0
lag_id	0	1	11	11	0	52	0

Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
C0	0	1	7.80	2.29	1.00	6.27	7.55	9.00	15.50	
AUC_0_24	0	1	274.84	79.36	38.00	224.00	268.00	316.50	508.00	
Cmax	0	1	19.50	8.15	2.51	13.84	17.84	23.20	54.96	
AUC_c0	0	1	36.00	7.57	22.25	30.70	35.04	39.55	82.00	
delai_post_greffe	0	1	3.39	2.25	0.09	1.13	3.05	5.02	9.96	
AUC_prec	0	1	305.12	106.25	90.00	231.50	277.59	358.50	728.00	
cmax_prec	0	1	21.95	10.05	6.27	15.04	19.33	26.35	65.47	
AUC_c0_prec	0	1	36.53	7.24	22.25	31.42	35.58	40.40	70.37	
c0_prec	0	1	8.52	3.07	2.00	6.50	7.95	9.55	23.00	
delai_prec	0	1	2.48	2.04	-0.03	0.72	2.00	4.02	8.95	
delai_entre_visite	0	1	0.91	0.54	0.02	0.68	1.00	1.01	3.88	
variation_rel_AUC	0	1	-0.03	0.33	-0.94	-0.26	-0.04	0.14	0.93	
variation_rel_c0	0	1	0.00	0.40	-0.96	-0.26	-0.05	0.17	2.30	
variation_rel_AUC_c0	0	1	0.01	0.25	-0.52	-0.14	-0.01	0.13	1.29	
rank_visite	0	1	3.02	1.79	1.00	2.00	3.00	4.00	9.00	

	Overall
n	212
CYP3A5 = non expressor (%)	181 (85.4)
CYP3A4 = CC (%)	212 (100.0)
SEXE = MASCULIN (%)	147 (69.3)
C0 (median [range])	7.55 [1.00, 15.50]
AUC_0_24 (median [range])	268.00 [38.00, 508.00]
Cmax (median [range])	17.84 [2.51, 54.96]
AUC_c0 (median [range])	35.04 [22.25, 82.00]

	Overall
delai_post_greffe (median [range])	3.05 [0.09, 9.96]
AUC_prec (median [range])	277.59 [90.00, 728.00]
cmax_prec (median [range])	19.33 [6.27, 65.47]
AUC_c0_prec (median [range])	35.58 [22.25, 70.37]
c0_prec (median [range])	7.95 [2.00, 23.00]
delai_prec (median [range])	2.00 [-0.03, 8.95]
delai_entre_visite (median [range])	1.00 [0.02, 3.88]
variation_rel_AUC (median [range])	-0.04 [-0.94, 0.93]
variation_rel_c0 (median [range])	-0.05 [-0.96, 2.30]
variation_rel_AUC_c0 (median [range])	-0.01 [-0.52, 1.29]
rank_visite (median [range])	3.00 [1.00, 9.00]

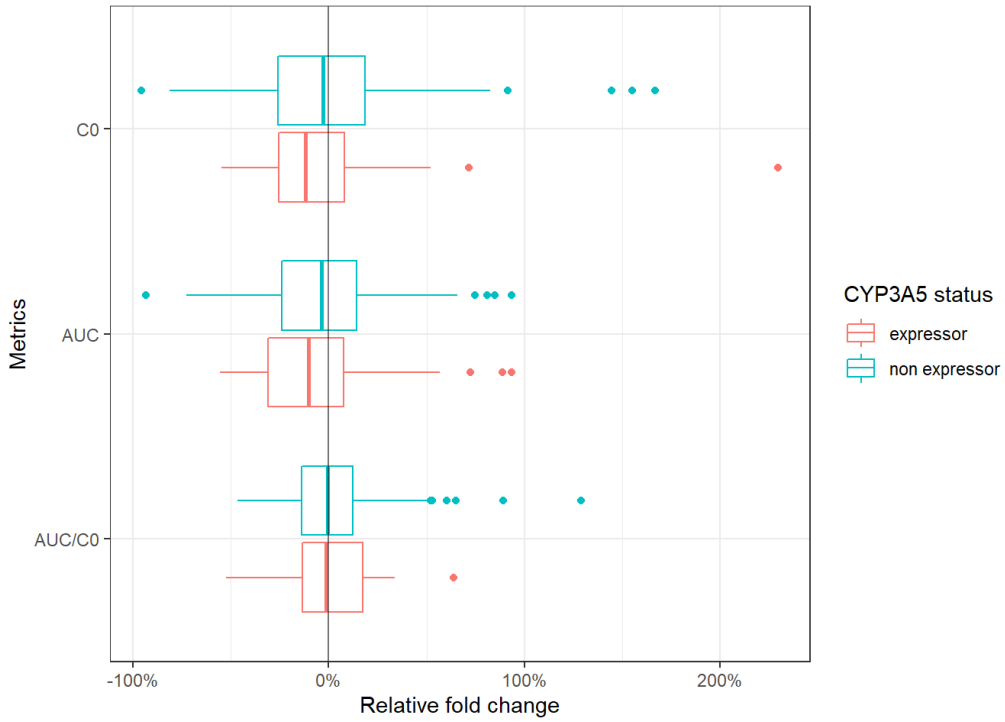
	Overall
n	212
CYP3A5 = non expressor (%)	181 (85.4)
CYP3A4 = CC (%)	212 (100.0)
SEXE = MASCULIN (%)	147 (69.3)
C0 (median [IQR])	7.55 [6.27, 9.00]
AUC_0_24 (median [IQR])	268.00 [224.00, 316.50]
Cmax (median [IQR])	17.84 [13.84, 23.20]
AUC_c0 (median [IQR])	35.04 [30.70, 39.55]
delai_post_greffe (median [IQR])	3.05 [1.13, 5.02]
AUC_prec (median [IQR])	277.59 [231.50, 358.50]
cmax_prec (median [IQR])	19.33 [15.04, 26.35]
AUC_c0_prec (median [IQR])	35.58 [31.42, 40.40]
c0_prec (median [IQR])	7.95 [6.50, 9.55]
delai_prec (median [IQR])	2.00 [0.72, 4.02]
delai_entre_visite (median [IQR])	1.00 [0.68, 1.01]
variation_rel_AUC (median [IQR])	-0.04 [-0.26, 0.14]
variation_rel_c0 (median [IQR])	-0.05 [-0.26, 0.17]
variation_rel_AUC_c0 (median [IQR])	-0.01 [-0.14, 0.13]
rank_visite (median [IQR])	3.00 [2.00, 4.00]

Relative variations between visit n and n-1 for metrics vs CYP3A5 status

```
tac_boxplot_variation <- epi_cyp3a5 %>% dplyr::select (CYP3A5, variation_rel_AUC,   variation_rel_AUC_c0, variation_rel_c0, delai_entre_visite, delai_post_greffe) %>% filter(variation_rel_c0<20,variation_rel_AUC<20) %>% rename("AUC" = variation_rel_AUC, "AUC/C0" = variation_rel_AUC_c0,"C0" = variation_rel_c0 ) %>% pivot_longer(cols = AUC:C0 ,names_to = "metrics", values_to = "relative_variation",values_drop_na = TRUE) %>% filter(!is.na(relative_variation)) %>% mutate (relative_variation = replace(relative_variation,0,0.00001)) %>% mutate(metrics = factor(metrics, levels = c("AUC/C0", "AUC", "C0" ), ordered = TRUE ))


tac_boxplot_variation %>% group_by(metrics) %>% summarise (mean = mean(relative_variation)*100, sd = sd(relative_variation)*100, cv = sd/mean )
```

```
## # A tibble: 3 x 4
##   metrics    mean    sd     cv
##   <ord>     <dbl> <dbl>  <dbl>
## 1 AUC/C0   1.23    24.7   20.0
## 2 AUC     -2.79    33.3  -11.9
## 3 C0       0.0366  40.4 1103.
```

```
#log10 trans
ggplot(data = tac_boxplot_variation, mapping = aes(x =metrics , y = relative_variation, color = CYP3A5))+ geom_boxplot() + c
oord_flip() + scale_y_continuous(labels = scales::percent) + theme_bw()+ geom_hline(yintercept = 0, alpha = 0.5) + labs(y="R
elative fold change",x = "Metrics", color = "CYP3A5 status")
```




```
ggsave("Figure5.pdf")
```

percentage of patients out of the 20% C0 interval around the regression line

We evaluated the % out of the 20% interval for adults >1 year to answer the reviewer 1 comment

20%

```
sample.data <- tac_multi %>%
  mutate(
    TAD = if_else(Type_demande == "TACRO (PROGRAF)", "TAD", "OAD"),
    age_group = if_else(age>18, "adults","children"),
    group_delai_post_greffe = case_when(
    Delai_post_greffe<0.25 ~ "< 3 months",
    Delai_post_greffe>1 ~ "> 1 year",
    TRUE~"between 3 months and 1 year"),
    group_delai_post_greffe = factor(group_delai_post_greffe, levels=c("< 3 months","between 3 months and 1 year","> 1 year"
)),
    c0_inf = c0*0.8,
    c0_sup = c0*1.2)

# adult_inf3mois
adult_inf3mois <-
  sample.data %>% filter(group_delai_post_greffe=="< 3 months" & age_group == "adults")
reg_adult_inf3mois <- lm(AUC_0_24 ~ c0 , data = adult_inf3mois)
intercept_a3 = reg_adult_inf3mois$coefficients[[1]]
slope = reg_adult_inf3mois$coefficients[[2]]
reg_adult_inf3mois_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_inf3mois)
intercept_inf_a3 = reg_adult_inf3mois_inf$coefficients[[1]]
slope_inf_a3 = reg_adult_inf3mois_inf$coefficients[[2]]
reg_adult_inf3mois_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_inf3mois)
intercept_sup_a3 = reg_adult_inf3mois_sup$coefficients[[1]]
slope_sup_a3 = reg_adult_inf3mois_sup$coefficients[[2]]

#plot
adult_inf3mois_plot <- adult_inf3mois %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a3+slope_inf_a3*c0, ymax =intercept_a3+slope_sup_a3*c0), fill = "grey70", alpha = 0.6) +
    geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
   # geom_abline(intercept = intercept, slope = slope, size=1,colour="grey")+
  theme_bw() +
    labs(
     title = "Adults & <3months",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 20% area
adult_inf3mois %>%
  mutate(ymax = intercept_a3+slope_inf_a3*c0,
         ymin =intercept_a3+slope_sup_a3*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.489   141
```

```
# adult_3mois_1y
adult_3mois_1y <-
  sample.data %>% filter(group_delai_post_greffe=="between 3 months and 1 year" & age_group == "adults")
reg_adult_3mois_1y <- lm(AUC_0_24 ~ c0 , data = adult_3mois_1y)
intercept_a31 = reg_adult_3mois_1y$coefficients[[1]]
slope = reg_adult_3mois_1y$coefficients[[2]]
reg_adult_3mois_1y_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_3mois_1y)
intercept_inf_a31 = reg_adult_3mois_1y_inf$coefficients[[1]]
slope_inf_a31 = reg_adult_3mois_1y_inf$coefficients[[2]]
reg_adult_3mois_1y_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_3mois_1y)
intercept_sup_a31 = reg_adult_3mois_1y_sup$coefficients[[1]]
slope_sup_a31 = reg_adult_3mois_1y_sup$coefficients[[2]]

#plot
adult_3mois_1y_plot <- adult_3mois_1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a31+slope_inf_a31*c0, ymax =intercept_a31+slope_sup_a31*c0), fill = "grey70", alpha = 0.
6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Adults & between 3 months \nand 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
adult_3mois_1y %>%
  mutate(ymax = intercept_a31+slope_inf_a31*c0,
         ymin =intercept_a31+slope_sup_a31*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.490   610
```

```
# adult_sup1y
adult_sup1y <-
  sample.data %>% filter(group_delai_post_greffe=="> 1 year" & age_group == "adults")
reg_adult_sup1y <- lm(AUC_0_24 ~ c0 , data = adult_sup1y)
intercept_a1 = reg_adult_sup1y$coefficients[[1]]
slope = reg_adult_sup1y$coefficients[[2]]
reg_adult_sup1y_inf <- lm(AUC_0_24 ~ c0_inf , data = adult_sup1y)
slope_inf_a1 = reg_adult_sup1y_inf$coefficients[[2]]
reg_adult_sup1y_sup<- lm(AUC_0_24 ~ c0_sup , data = adult_sup1y)
slope_sup_a1 = reg_adult_sup1y_sup$coefficients[[2]]

#plot
adult_sup1y_plot <- adult_sup1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_a1+slope_inf_a1*c0, ymax =intercept_a1+slope_sup_a1*c0), fill = "grey70", alpha = 0.6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Adults & > 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
adult_sup1y %>%
  mutate(ymax = intercept_a1+slope_inf_a1*c0,
         ymin =intercept_a1+slope_sup_a1*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.345  2614
```

```
# children_inf3mois
children_inf3mois <-
  sample.data %>% filter(group_delai_post_greffe=="< 3 months" & age_group == "children")
reg_children_inf3mois <- lm(AUC_0_24 ~ c0 , data = children_inf3mois)
intercept_c3 = reg_children_inf3mois$coefficients[[1]]
slope = reg_children_inf3mois$coefficients[[2]]
reg_children_inf3mois_inf <- lm(AUC_0_24 ~ c0_inf , data = children_inf3mois)
slope_inf_c3 = reg_children_inf3mois_inf$coefficients[[2]]
reg_children_inf3mois_sup<- lm(AUC_0_24 ~ c0_sup , data = children_inf3mois)
slope_sup_c3 = reg_children_inf3mois_sup$coefficients[[2]]

#plot
children_inf3mois_plot <- children_inf3mois %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c3+slope_inf_c3*c0, ymax =intercept_c3+slope_sup_c3*c0), fill = "grey70", alpha = 0.6) +
    geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & <3months",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_inf3mois %>%
  mutate(ymax = intercept_c3+slope_inf_c3*c0,
         ymin =intercept_c3+slope_sup_c3*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.524    82
```

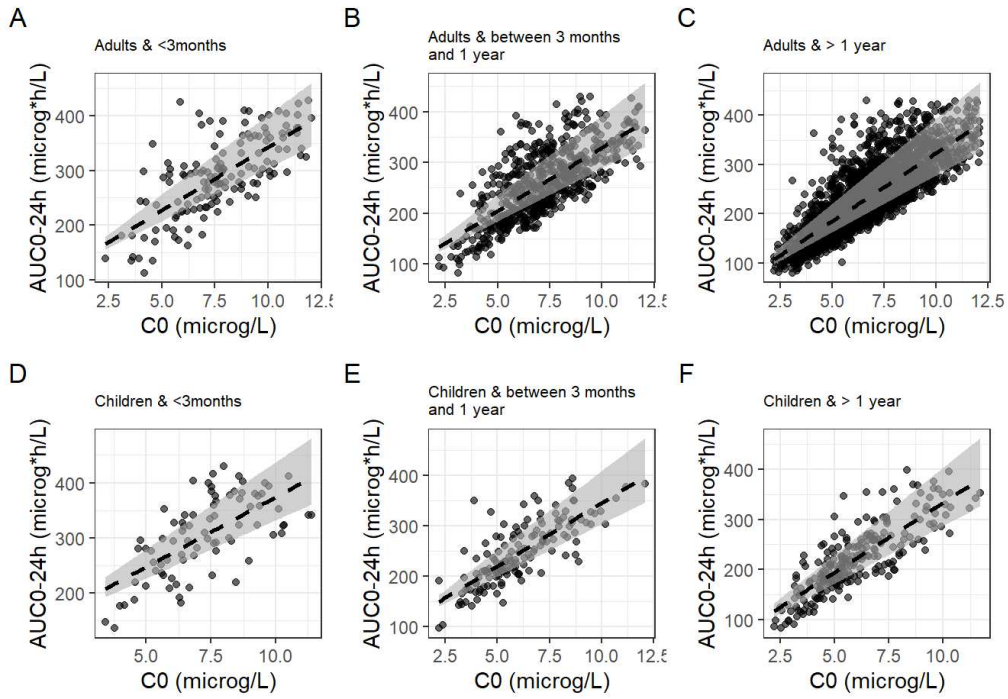
```
# children_3mois_1y
children_3mois_1y <-
  sample.data %>% filter(group_delai_post_greffe=="between 3 months and 1 year" & age_group == "children")
reg_children_3mois_1y <- lm(AUC_0_24 ~ c0 , data = children_3mois_1y)
intercept_c31 = reg_children_3mois_1y$coefficients[[1]]
slope = reg_children_3mois_1y$coefficients[[2]]
reg_children_3mois_1y_inf <- lm(AUC_0_24 ~ c0_inf , data = children_3mois_1y)
slope_inf_c31 = reg_children_3mois_1y_inf$coefficients[[2]]
reg_children_3mois_1y_sup<- lm(AUC_0_24 ~ c0_sup , data = children_3mois_1y)
slope_sup_c31 = reg_children_3mois_1y_sup$coefficients[[2]]

#plot
children_3mois_1y_plot <- children_3mois_1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c31+slope_inf_c31*c0, ymax =intercept_c31+slope_sup_c31*c0), fill = "grey70", alpha = 0.
6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & between 3 months \nand 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_3mois_1y %>%
  mutate(ymax = intercept_c31+slope_inf_c31*c0,
         ymin =intercept_c31+slope_sup_c31*c0,
         AUC_out = if_else(AUC_0_24 <ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.393   145
```

```
# children_sup1y
children_sup1y <-
  sample.data %>% filter(group_delai_post_greffe=="> 1 year" & age_group == "children")
reg_children_sup1y <- lm(AUC_0_24 ~ c0 , data = children_sup1y)
intercept_c1 = reg_children_sup1y$coefficients[[1]]
slope = reg_children_sup1y$coefficients[[2]]
reg_children_sup1y_inf <- lm(AUC_0_24 ~ c0_inf , data = children_sup1y)
slope_inf_c1 = reg_children_sup1y_inf$coefficients[[2]]
reg_children_sup1y_sup<- lm(AUC_0_24 ~ c0_sup , data = children_sup1y)
slope_sup_c1 = reg_children_sup1y_sup$coefficients[[2]]

#plot
children_sup1y_plot <- children_sup1y %>%
  ggplot(aes( c0,AUC_0_24)) +
    geom_point(alpha = 0.6) +
   geom_ribbon(aes(ymin = intercept_c1+slope_inf_c1*c0, ymax =intercept_c1+slope_sup_c1*c0), fill = "grey70", alpha = 0.6) +
   geom_smooth(
    # aes(color = age_group),
    method=lm, size=1,fullrange=TRUE, se=FALSE, colour="black",linetype="dashed") +
  theme_bw() +
    labs(
     title = "Children & > 1 year",
     y = "AUC0-24h (microg*h/L)",
      x = "C0 (microg/L)") + theme(legend.position="top", plot.title = element_text(size=8))

# evaluation of number outside the 30% area
children_sup1y %>%
  mutate(ymax = intercept_c1+slope_inf_c1*c0,
         ymin =intercept_c1+slope_sup_c1*c0,
         AUC_out = if_else(AUC_0_24<ymin | AUC_0_24>ymax,1,0)) %>%
  select(ID, ymin, ymax, AUC_0_24, AUC_out) %>%
  ungroup() %>%
  summarise(prop_20_prct = mean(AUC_out==1), n = n())
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.391   235
```

```
# graph

adult_inf3mois_plot + adult_3mois_1y_plot + adult_sup1y_plot + children_inf3mois_plot + children_3mois_1y_plot + children_su
p1y_plot + plot_annotation(tag_levels = 'A')
```



Can the Area Under the Curve/trough level ratio be used to optimize tacrolimus individual dose adjustment?

jbw

2022-08-16 15:21:37

Sensitivity analysis without filtering out the AUC and C0 outliers

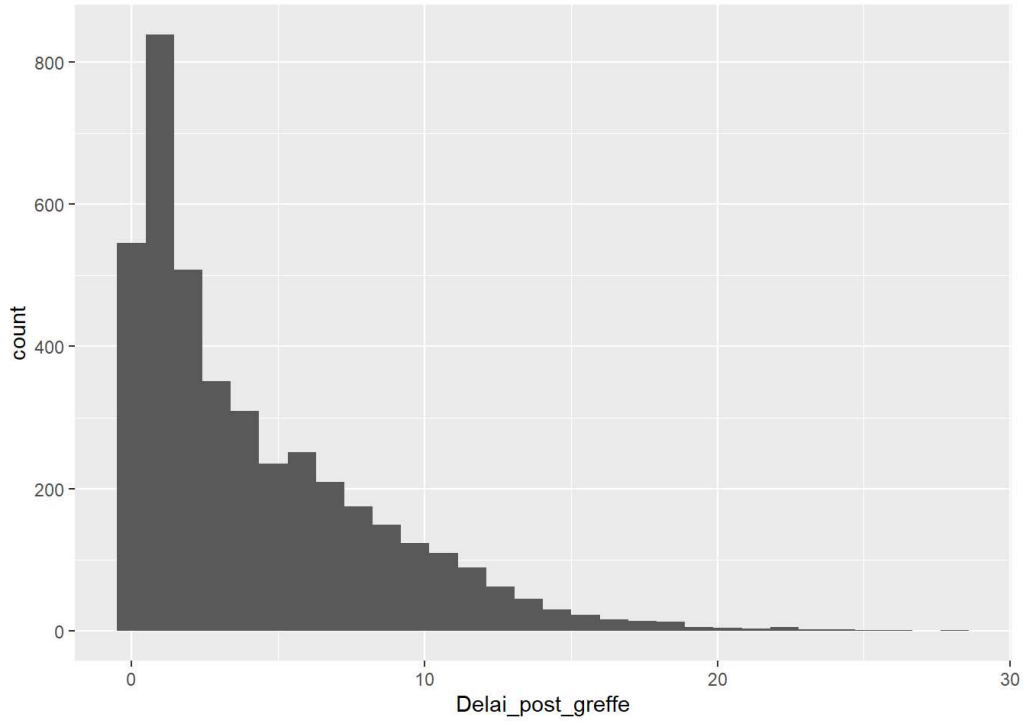
Loading of packages

Modification done on the csv to transform . in , for c1, T1, c2, t2 etc…

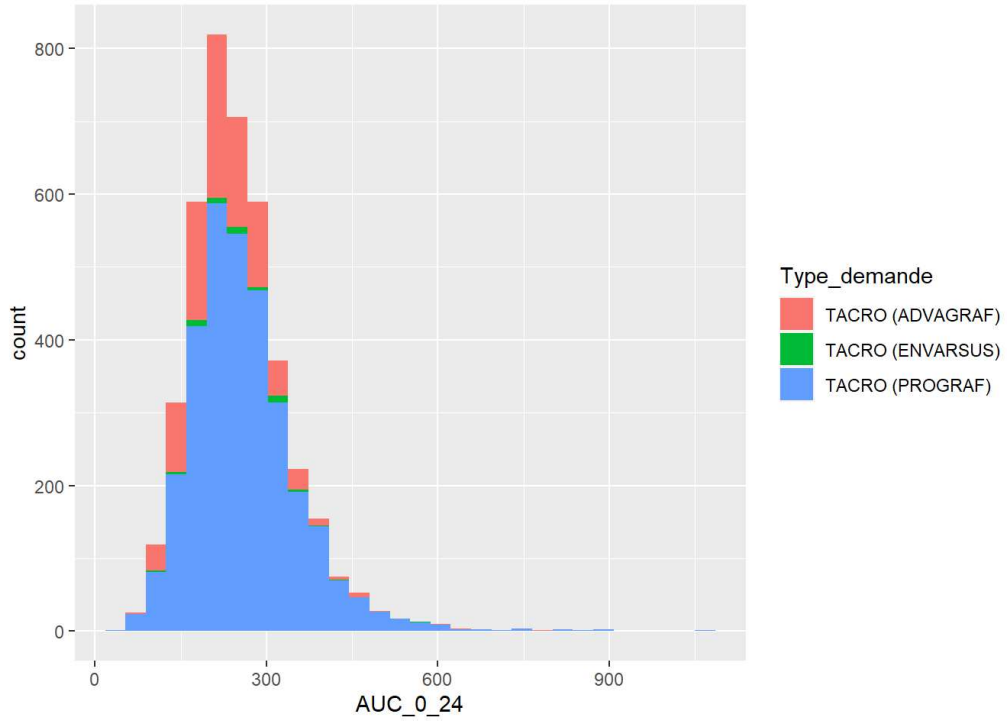
Every prograf AUC has been transformed to AUC0-24 by multiplying by 2 the prograf AUC0-12h. Daily dose corresponds to the sum of morning and evening dose for prograf

Filtering out aberrant values for Time post transplantation and histogram

Removal of time post transplantation > 33 years

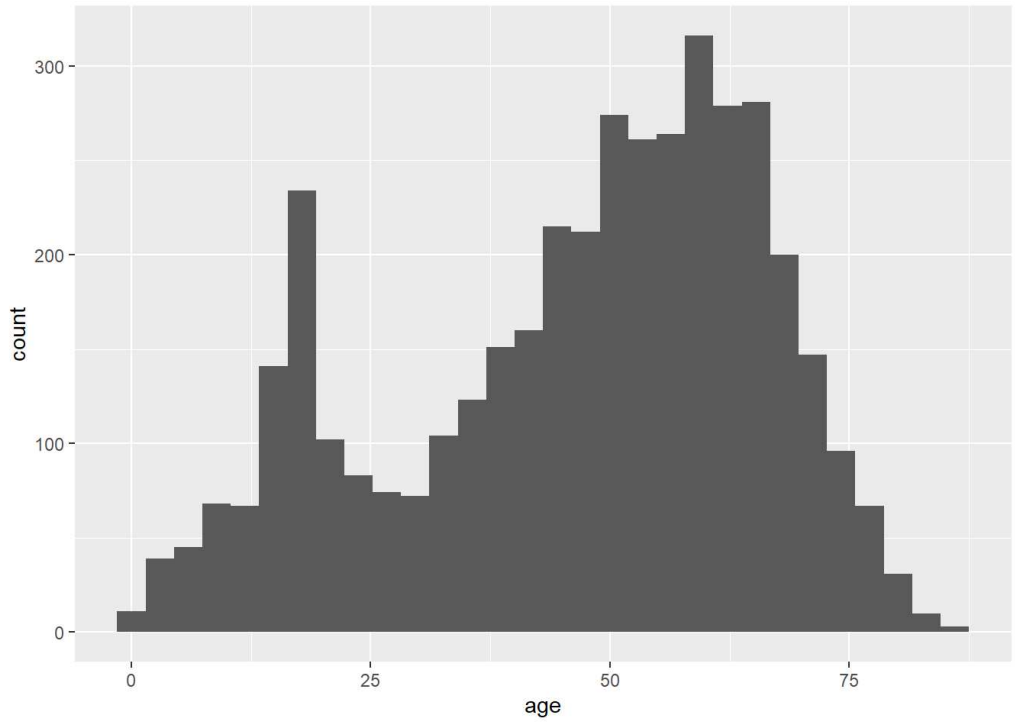


Filtering out aberrant values for AUC and histogram: removed for the sensitivity analysis



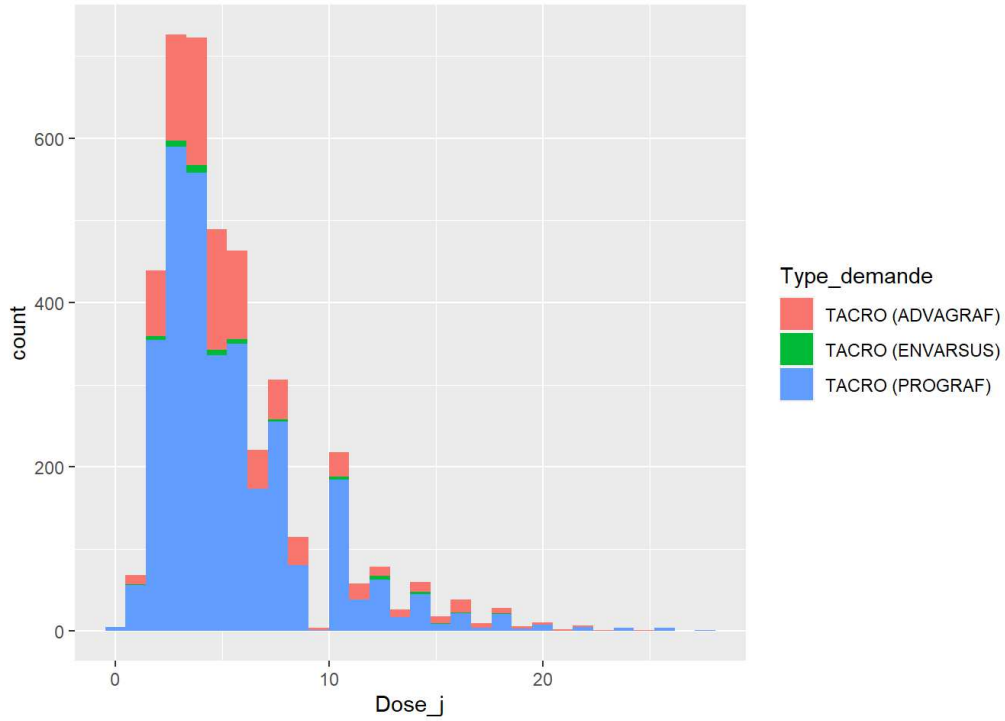
Filtering out aberrant values for age and histogram

Removal of age > 100 years



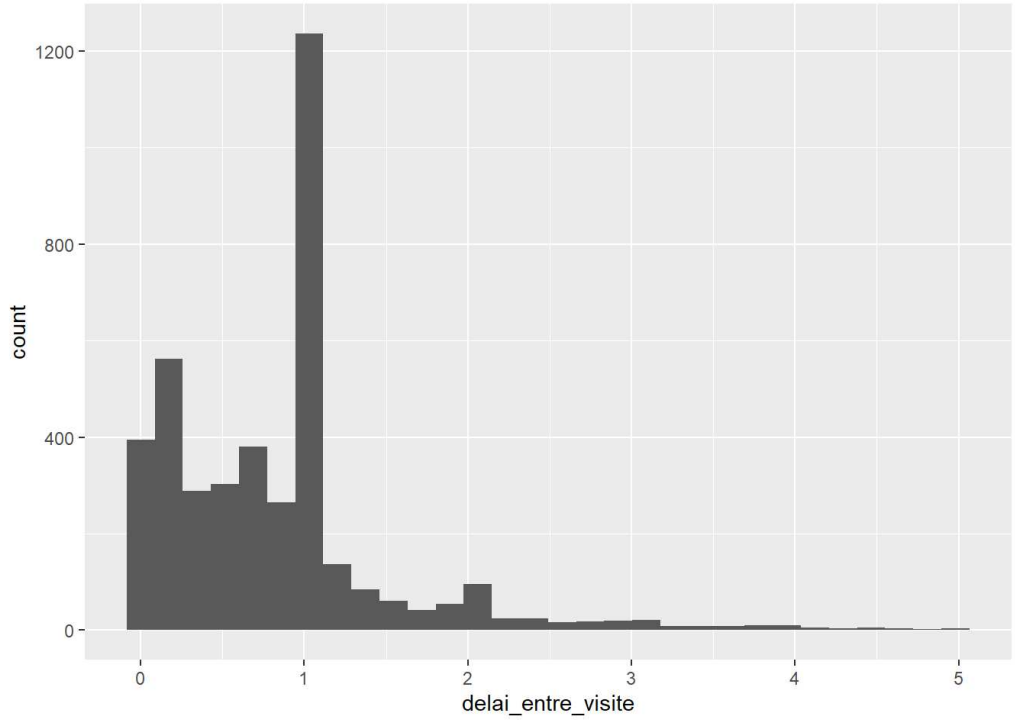
Filtering out aberrant values for daily dose and histogram

Removal of daily dose > 40 mg



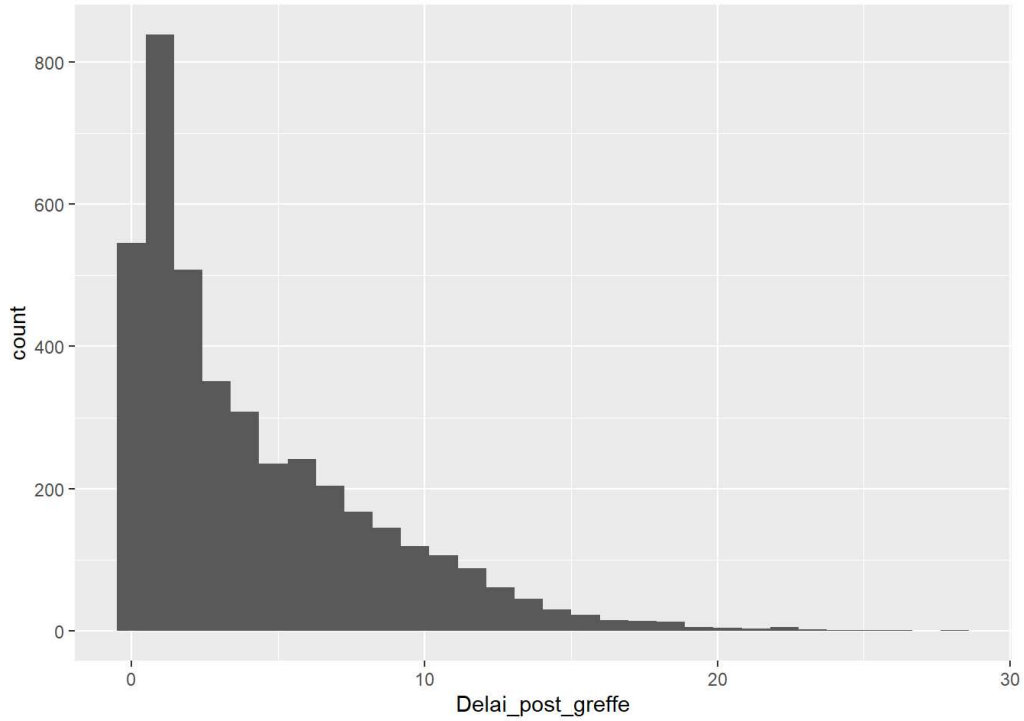
Filtering out aberrant values for time between two consecutive requests and histogram

Removal of time between 2 consecutive requests > 5 years

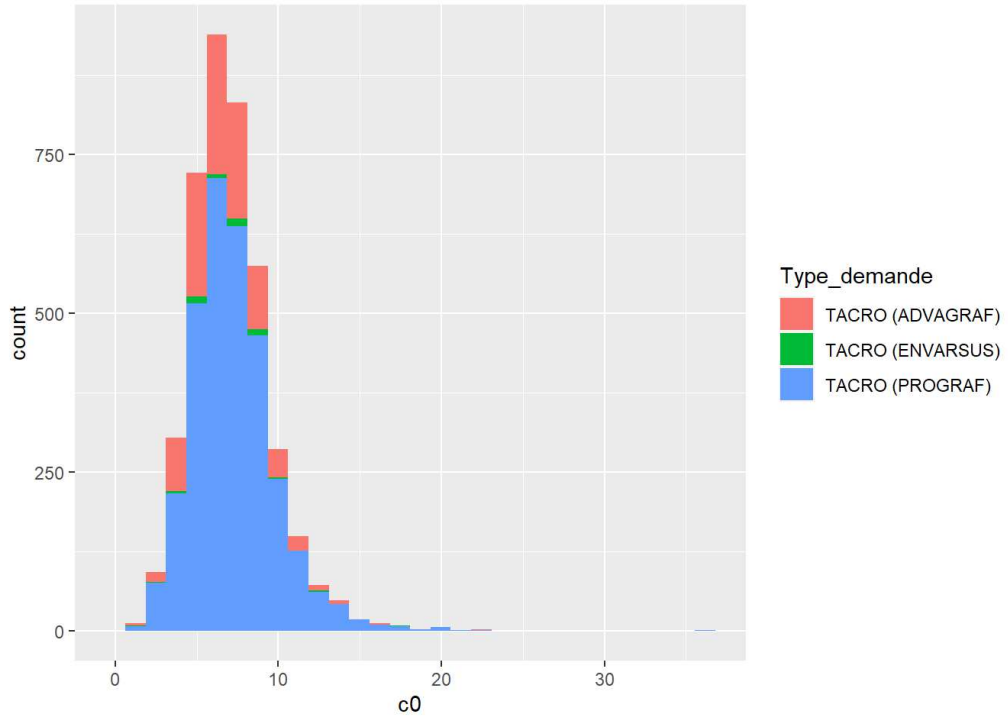


Histogram Time post transplantation

No value removed

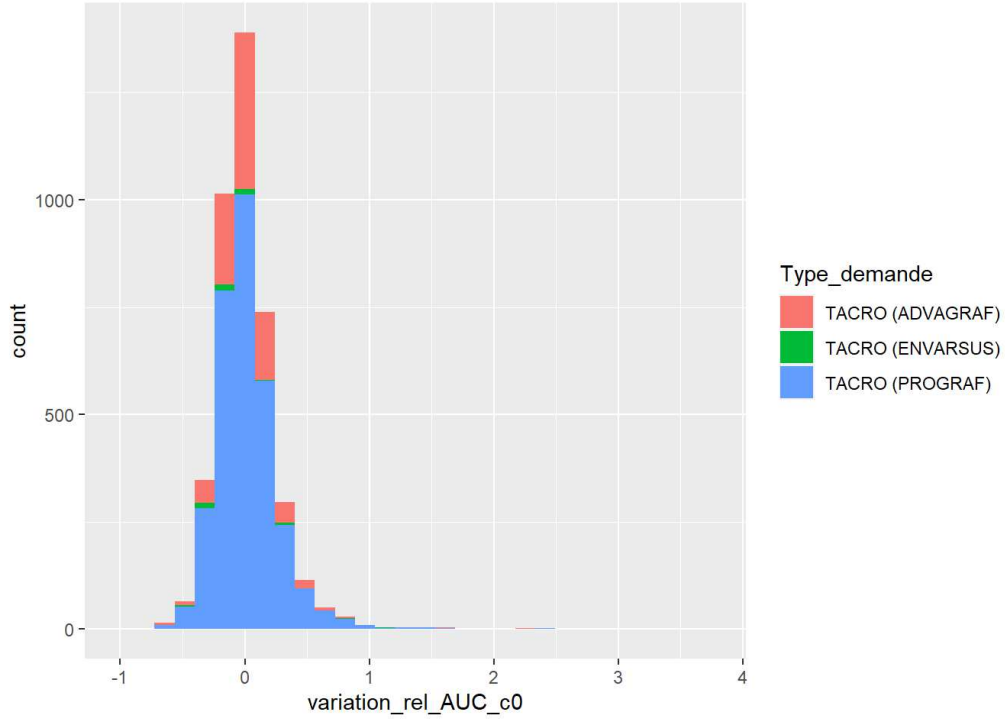


Filtering out aberrant values for c0: filtering removed for sensitivity analysis



Ranking of visits

Histogram relative variations AUC



Summary of data after filtering

Data summary

Name	ungroup(tac_multi)
Number of rows	4090
Number of columns	39
_____	
Column type frequency:	
Date	4
factor	5
numeric	30
_____	
Group variables	None

Variable type: Date

skim_variable	n_missing	complete_rate	min	max	median	n_unique
date_validation	0	1	2009-08-14	2019-10-31	2016-01-12	1877
Date_greffe	0	1	1986-11-22	2019-08-03	2011-10-21	1459
Date_dosage	0	1	2009-08-14	2019-10-31	2016-01-08	1929
date_greffe_mediane	0	1	1986-11-22	2019-08-03	2011-08-23	1208

Variable type: factor

skim_variable	n_missing	complete_rate	ordered	n_unique	top_counts
ID	0	1.00	FALSE	1357	32_: 50, 32_: 30, 32_: 26, 32_: 21
Tt_associe	0	1.00	FALSE	3	MMF: 3435, Nea: 630, Cor: 25, Cic: 0
Type_demande	0	1.00	FALSE	3	TAC: 3159, TAC: 881, TAC: 50, TAC: 0
Diabete	2123	0.48	FALSE	2	NON: 1834, OUI: 133
lag_id	0	1.00	FALSE	1357	32_: 50, 32_: 30, 32_: 26, 32_: 21

Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
Nodemande	0	1	80395.49	24263.88	23226.00	61600.25	83609.50	100455.00	119406.00	
Delai_post_greffe	0	1	4.32	4.22	0.02	1.00	3.00	6.66	28.13	
cmax	0	1	17.91	8.30	2.40	12.13	16.10	21.82	75.06	
c0	0	1	7.15	2.68	0.50	5.46	6.83	8.44	36.67	
AUC	0	1	153.15	68.08	22.00	106.00	138.00	185.75	787.00	
poso_reco_bas	6	1	3.58	2.88	0.25	2.00	2.75	4.50	30.50	
poso_reco_haut	8	1	4.53	3.74	0.50	2.00	3.50	5.50	43.50	
AUC_0_24	0	1	254.22	91.52	44.00	194.00	240.00	298.00	1076.00	
age	0	1	46.73	19.24	0.91	33.70	50.75	61.68	86.93	
Dose_j	0	1	5.67	3.65	0.40	3.00	5.00	7.00	28.00	
C0_obs	0	1	7.19	2.70	0.50	5.50	6.90	8.50	39.95	
AUC_dose	0	1	60.19	46.48	4.93	34.67	50.00	74.00	1084.00	
c0_dose	0	1	1.78	1.43	0.09	0.92	1.45	2.23	22.00	
AUC_c0	0	1	36.40	9.23	11.52	30.75	34.52	40.00	196.15	
AUC_prec	0	1	272.86	99.01	56.00	206.00	258.00	324.00	1076.00	
cmax_prec	0	1	19.65	9.22	3.35	12.99	17.55	24.27	75.06	
AUC_dose_prec	0	1	58.16	44.26	7.83	33.60	48.50	71.33	1084.00	
AUC_c0_prec	0	1	37.01	12.04	11.52	31.19	35.10	40.62	560.00	
c0_prec	0	1	7.59	2.80	0.10	5.80	7.20	8.95	34.10	
c0_dose_prec	0	1	1.69	1.30	0.10	0.88	1.39	2.13	22.00	
delai_prec	0	1	3.48	4.03	0.01	0.29	1.98	5.48	25.91	
poso_reco_bas_prec	5	1	3.63	3.04	0.50	2.00	3.00	4.50	38.50	
poso_reco_haut_prec	5	1	4.67	4.11	0.50	2.50	3.50	5.50	55.00	
delai_entre_visite	0	1	0.84	0.70	0.00	0.29	0.86	1.01	4.98	
variation_rel_AUC	0	1	0.02	0.45	-0.88	-0.26	-0.05	0.19	5.98	
variation_rel_AUC_dose	0	1	0.12	0.57	-0.92	-0.18	0.03	0.29	13.56	
variation_rel_c0	0	1	0.05	0.90	-0.89	-0.26	-0.05	0.21	43.00	
variation_rel_c0_dose	0	1	0.17	0.80	-0.91	-0.18	0.04	0.31	28.33	
variation_rel_AUC_c0	0	1	0.01	0.26	-0.94	-0.13	-0.01	0.12	3.73	
rank_visite	0	1	3.62	4.28	1.00	1.00	2.00	4.00	50.00	

Table 1 for the article

	Overall
n	4090
Tt_associe (%)	
Corticoides	25 (0.6)
MMF	3435 (84.0)
Neant	630 (15.4)
Delai_post_greffe (median [range])	3.00 [0.02, 28.13]
cmax (median [range])	16.10 [2.40, 75.06]
c0 (median [range])	6.83 [0.50, 36.67]
AUC (median [range])	138.00 [22.00, 787.00]
poso_reco_bas (median [range])	2.75 [0.25, 30.50]

	Overall
poso_reco_haut (median [range])	3.50 [0.50, 43.50]
Type_demande (%)	
TACRO (ADVAGRAF)	881 (21.5)
TACRO (ENVARSUS)	50 (1.2)
TACRO (PROGRAF)	3159 (77.2)
Diabete (%)	
NON	1834 (44.8)
OUI	133 (3.3)
NA	2123 (51.9)
AUC_0_24 (median [range])	240.00 [44.00, 1076.00]
age (median [range])	50.75 [0.91, 86.93]
Dose_j (median [range])	5.00 [0.40, 28.00]
C0_obs (median [range])	6.90 [0.50, 39.95]
AUC_dose (median [range])	50.00 [4.93, 1084.00]
c0_dose (median [range])	1.45 [0.09, 22.00]
AUC_c0 (median [range])	34.52 [11.52, 196.15]
AUC_prec (median [range])	258.00 [56.00, 1076.00]
cmax_prec (median [range])	17.55 [3.35, 75.06]
AUC_dose_prec (median [range])	48.50 [7.83, 1084.00]
AUC_c0_prec (median [range])	35.10 [11.52, 560.00]
c0_prec (median [range])	7.20 [0.10, 34.10]
c0_dose_prec (median [range])	1.39 [0.10, 22.00]
delai_prec (median [range])	1.98 [0.01, 25.91]
poso_reco_bas_prec (median [range])	3.00 [0.50, 38.50]
poso_reco_haut_prec (median [range])	3.50 [0.50, 55.00]
delai_entre_visite (median [range])	0.86 [0.00, 4.98]
variation_rel_AUC (median [range])	-0.05 [-0.88, 5.98]
variation_rel_AUC_dose (median [range])	0.03 [-0.92, 13.56]
variation_rel_c0 (median [range])	-0.05 [-0.89, 43.00]
variation_rel_c0_dose (median [range])	0.04 [-0.91, 28.33]
variation_rel_AUC_c0 (median [range])	-0.01 [-0.94, 3.73]
rank_visite (median [range])	2.00 [1.00, 50.00]

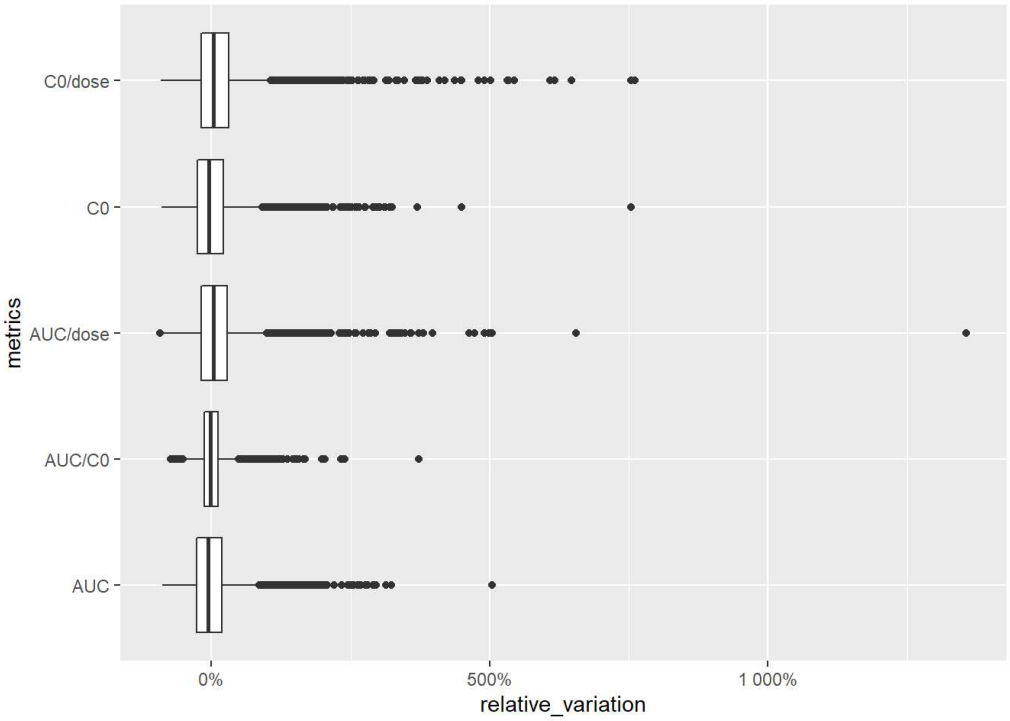
	Overall
n	4090
Tt_associe (%)	
Corticoides	25 (0.6)
MMF	3435 (84.0)
Neant	630 (15.4)
Delai_post_greffe (median [IQR])	3.00 [1.00, 6.66]
cmax (median [IQR])	16.10 [12.13, 21.82]
c0 (median [IQR])	6.83 [5.46, 8.44]
AUC (median [IQR])	138.00 [106.00, 185.75]

	Overall
poso_reco_bas (median [IQR])	2.75 [2.00, 4.50]
poso_reco_haut (median [IQR])	3.50 [2.00, 5.50]
Type_demande (%)	
TACRO (ADVAGRAF)	881 (21.5)
TACRO (ENVARSUS)	50 (1.2)
TACRO (PROGRAF)	3159 (77.2)
Diabete (%)	
NON	1834 (44.8)
OUI	133 (3.3)
NA	2123 (51.9)
AUC_0_24 (median [IQR])	240.00 [194.00, 298.00]
age (median [IQR])	50.75 [33.70, 61.68]
Dose_j (median [IQR])	5.00 [3.00, 7.00]
C0_obs (median [IQR])	6.90 [5.50, 8.50]
AUC_dose (median [IQR])	50.00 [34.67, 74.00]
c0_dose (median [IQR])	1.45 [0.92, 2.23]
AUC_c0 (median [IQR])	34.52 [30.75, 40.00]
AUC_prec (median [IQR])	258.00 [206.00, 324.00]
cmax_prec (median [IQR])	17.55 [12.99, 24.27]
AUC_dose_prec (median [IQR])	48.50 [33.60, 71.33]
AUC_c0_prec (median [IQR])	35.10 [31.19, 40.62]
c0_prec (median [IQR])	7.20 [5.80, 8.95]
c0_dose_prec (median [IQR])	1.39 [0.88, 2.13]
delai_prec (median [IQR])	1.98 [0.29, 5.48]
poso_reco_bas_prec (median [IQR])	3.00 [2.00, 4.50]
poso_reco_haut_prec (median [IQR])	3.50 [2.50, 5.50]
delai_entre_visite (median [IQR])	0.86 [0.29, 1.01]
variation_rel_AUC (median [IQR])	-0.05 [-0.26, 0.19]
variation_rel_AUC_dose (median [IQR])	0.03 [-0.18, 0.29]
variation_rel_c0 (median [IQR])	-0.05 [-0.26, 0.21]
variation_rel_c0_dose (median [IQR])	0.04 [-0.18, 0.31]
variation_rel_AUC_c0 (median [IQR])	-0.01 [-0.13, 0.12]
rank_visite (median [IQR])	2.00 [1.00, 4.00]

Exploratory data analysis

Study of relative variations between instance n and n-1 for the metrics

```
## # A tibble: 5 x 4
##   metrics   mean    sd    cv
##   <chr>    <dbl> <dbl> <dbl>
## 1 AUC       1.33  44.4 33.3
## 2 AUC/C0    1.44  25.9 18.0
## 3 AUC/dose 12.1   56.3  4.63
## 4 C0        3.55  48.6 13.7
## 5 C0/dose  15.6   62.0  3.97
```

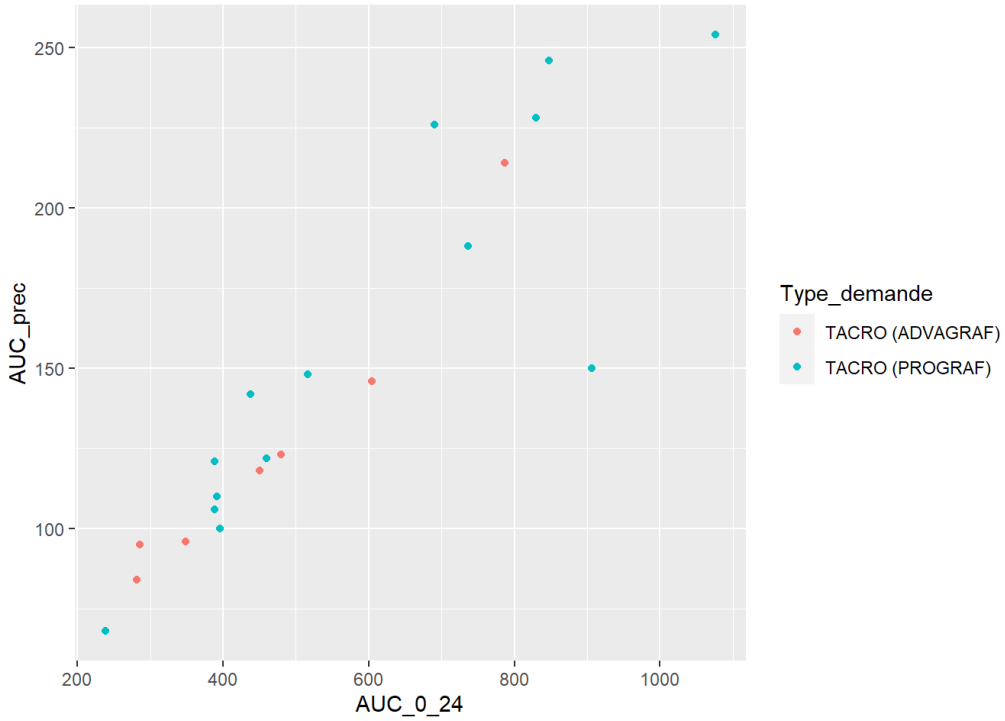


Extraction of extreme patient with relative variation > 200%

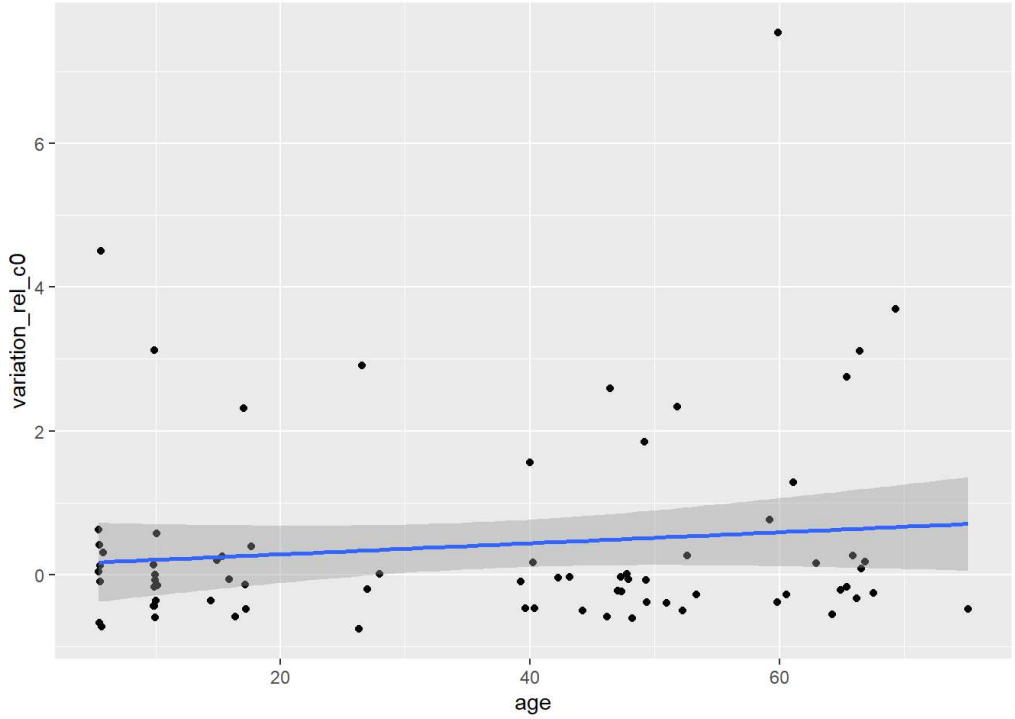
```
## # A tibble: 21 x 6
## # Groups:   ID [21]
##    ID        Type_demande delai_entre_vis~ Delai_post_gref~ metrics relative_variat~
##    <fct>     <fct>                   <dbl>            <dbl> <chr>              <dbl>
##  1 17_ARE_AN TACRO (PROG~           1.47             11.5   AUC                 2.56
##  2 17_BOU_SE TACRO (ADVA~           3.57              4.13  AUC                 2.64
##  3 17_DER_CH TACRO (ADVA~           2.72             18.7   AUC                 2.81
##  4 17_GOB_MA TACRO (PROG~           1.65              4.57  AUC                 2.08
##  5 17_HOU_VE TACRO (PROG~           2.93              3.97  AUC                 2.21
##  6 17_LAM_PA TACRO (PROG~           3.36              4.76  AUC                 2.66
##  7 17_LAT_SO TACRO (PROG~           0.0712            0.983 AUC                 5.04
##  8 17_LEB_ST TACRO (ADVA~           1.20              7.02  AUC                 2.90
##  9 17_SOU_DA TACRO (PROG~           0.375             2.05  AUC                 2.64
## 10 17_THO_BE TACRO (ADVA~           0.548             1.20  AUC                 2.68
## # ... with 11 more rows
```

```
## # A tibble: 95 x 39
## # Groups:   ID [21]
##    ID        Nodemande date_validation Tt_associe Date_greffe Date_dosage
##    <fct>         <dbl> <date>          <fct>      <date>      <date>
##  1 17_ARE_AN     37847 2011-03-01      MMF        2001-02-02  2011-02-28
##  2 17_ARE_AN     51888 2012-08-20      MMF        2008-02-02  2012-08-17
##  3 17_ARE_AN     66212 2014-02-13      MMF        2001-02-02  2014-02-11
##  4 17_BOU_SE     86404 2016-04-22      MMF        2016-03-19  2016-04-21
##  5 17_BOU_SE     88260 2016-07-04      Neant      2016-03-19  2016-07-01
##  6 17_DER_CH     60296 2013-07-03      MMF        2000-10-12  2013-07-02
##  7 17_DER_CH     84812 2016-02-24      Neant      2000-10-17  2016-02-23
##  8 17_DER_CH     87314 2016-05-27      MMF        2000-10-17  2016-05-27
##  9 17_DER_CH     90722 2016-10-12      Neant      2000-10-12  2016-10-11
## 10 17_DER_CH    116145 2019-07-02      MMF        2000-02-17  2019-07-01
## # ... with 85 more rows, and 33 more variables: Delai_post_greffe <dbl>,
## #   cmax <dbl>, c0 <dbl>, AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>,
## #   Type_demande <fct>, Diabete <fct>, AUC_0_24 <dbl>, age <dbl>, Dose_j <dbl>,
## #   C0_obs <dbl>, AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>,
## #   date_greffe_mediane <date>, lag_id <fct>, AUC_prec <dbl>, cmax_prec <dbl>,
## #   AUC_dose_prec <dbl>, AUC_c0_prec <dbl>, c0_prec <dbl>, c0_dose_prec <dbl>,
## #   delai_prec <dbl>, poso_reco_bas_prec <dbl>, poso_reco_haut_prec <dbl>, ...
```

```
## # A tibble: 118 x 21
##    Nodemande date_validation Tt_associe Date_greffe Date_dosage Delai_post_gref~
##        <dbl> <date>          <fct>      <date>      <date>                  <dbl>
##  1     28928 2010-03-20      MMF        2001-02-02  2010-03-18             9.12
##  2     37847 2011-03-01      MMF        2001-02-02  2011-02-28            10.1
##  3     51888 2012-08-20      MMF        2008-02-02  2012-08-17             4.54
##  4     66212 2014-02-13      MMF        2001-02-02  2014-02-11            13.0
##  5     41449 2011-07-12      Neant      2008-02-22  2011-07-11             3.38
##  6     53000 2012-09-27      Neant      2008-02-22  2012-09-26             4.59
##  7     86404 2016-04-22      MMF        2016-03-19  2016-04-21             0.0903
##  8     88260 2016-07-04      Neant      2016-03-19  2016-07-01             0.285
##  9     54811 2012-12-06      Neant      2000-10-16  2012-12-05            12.1
## 10     60296 2013-07-03      MMF        2000-10-12  2013-07-02            12.7
## # ... with 108 more rows, and 15 more variables: cmax <dbl>, c0 <dbl>,
## #   AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>, Type_demande <fct>,
## #   Diabete <fct>, AUC_0_24 <dbl>, ID <fct>, age <dbl>, Dose_j <dbl>,
## #   C0_obs <dbl>, AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>
```




```
## # A tibble: 1 x 2
##   metrics     n
##   <chr>   <int>
## 1 AUC        21
```




```
## # A tibble: 1 x 39
## # Groups:   ID [1]
##   ID        Nodemande date_validation Tt_associe Date_greffe Date_dosage
##   <fct>         <dbl> <date>          <fct>      <date>      <date>
## 1 17_ADI_AL     92711 2016-12-26      MMF        2001-05-29  2016-12-23
## # ... with 33 more variables: Delai_post_greffe <dbl>, cmax <dbl>, c0 <dbl>,
## #   AUC <dbl>, poso_reco_bas <dbl>, poso_reco_haut <dbl>, Type_demande <fct>,
## #   Diabete <fct>, AUC_0_24 <dbl>, age <dbl>, Dose_j <dbl>, C0_obs <dbl>,
## #   AUC_dose <dbl>, c0_dose <dbl>, AUC_c0 <dbl>, date_greffe_mediane <date>,
## #   lag_id <fct>, AUC_prec <dbl>, cmax_prec <dbl>, AUC_dose_prec <dbl>,
## #   AUC_c0_prec <dbl>, c0_prec <dbl>, c0_dose_prec <dbl>, delai_prec <dbl>,
## #   poso_reco_bas_prec <dbl>, poso_reco_haut_prec <dbl>, ...
```

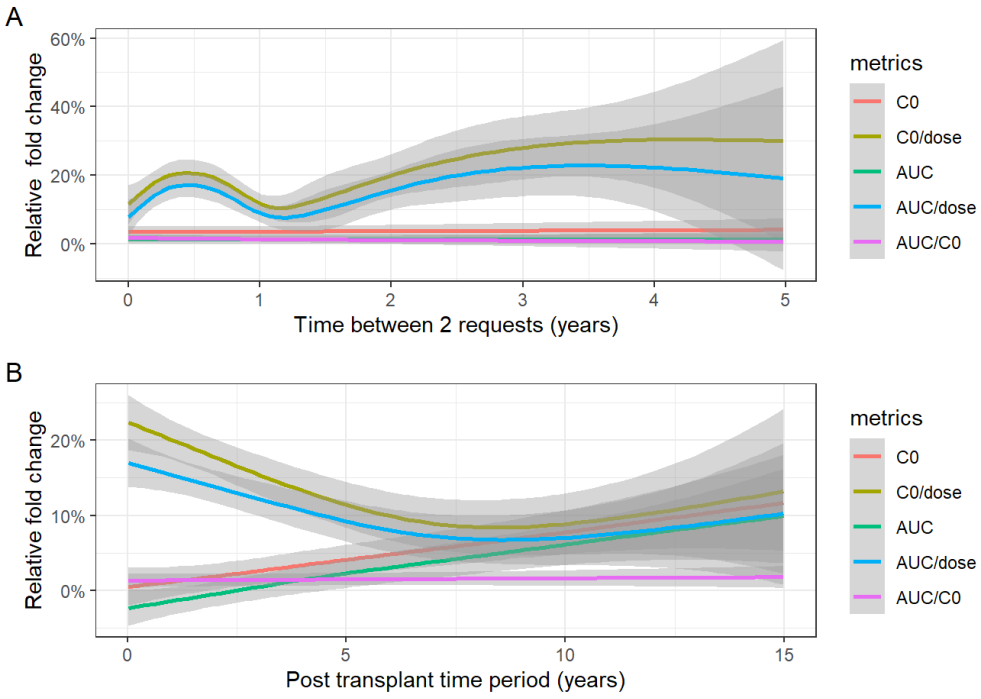
ANOVA and post test Tuckey for metrics

```
##                Df Sum Sq Mean Sq F value Pr(>F)
## metrics         4     72   17.93   74.61 <2e-16 ***
## Residuals   20435   4911    0.24
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = relative_variation ~ metrics, data = tac_boxplot_variation)
##
## $metrics
##                           diff          lwr         upr     p adj
## AUC/C0-AUC         0.001031421 -0.028547739  0.03061058 0.9999815
## AUC/dose-AUC       0.108173582  0.078594422  0.13775274 0.0000000
## C0-AUC             0.022167937 -0.007411223  0.05174710 0.2448029
## C0/dose-AUC        0.142754748  0.113175588  0.17233391 0.0000000
## AUC/dose-AUC/C0    0.107142162  0.077563002  0.13672132 0.0000000
## C0-AUC/C0          0.021136516 -0.008442644  0.05071568 0.2912631
## C0/dose-AUC/C0     0.141723328  0.112144168  0.17130249 0.0000000
## C0-AUC/dose       -0.086005646 -0.115584806 -0.05642649 0.0000000
## C0/dose-AUC/dose   0.034581166  0.005002006  0.06416033 0.0124384
## C0/dose-C0         0.120586812  0.091007652  0.15016597 0.0000000
```

Scatter plot relative variations for each metrics as function of time post transplantation and time between 2 requests = Figure 2

```
## # A tibble: 5 x 4
##   metrics    mean    sd    cv
##   <chr>     <dbl> <dbl> <dbl>
## 1 AUC      0.0133 0.444 33.3
## 2 AUC/C0   0.0144 0.259 18.0
## 3 AUC/dose 0.121  0.563  4.63
## 4 C0       0.0355 0.486 13.7
## 5 C0/dose  0.156  0.620  3.97
```



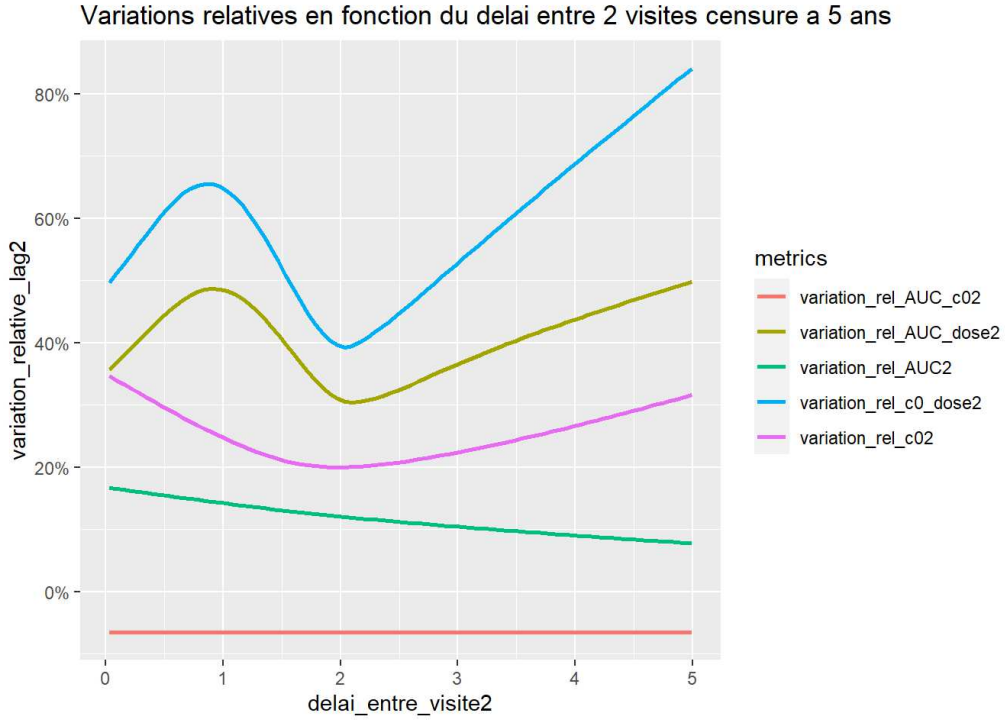
Boxplot relative variations between instance n and n+2

ANOVA and post test Tuckey

```
##               Df Sum Sq Mean Sq F value Pr(>F)
## metrics        4  186.8   46.69   182.7 <2e-16 ***
## Residuals   5165 1319.8    0.26
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

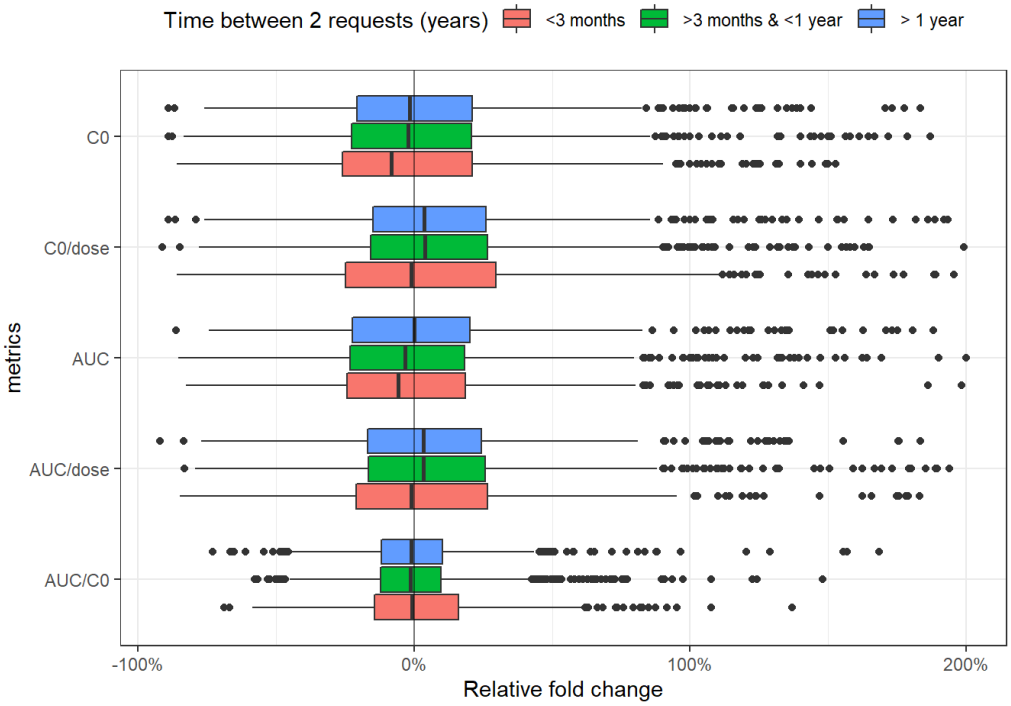
```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative_lag2 ~ metrics, data = tac_boxplot_variation2)
##
## $metrics
##                                                 diff         lwr
## variation_rel_AUC_dose2-variation_rel_AUC_c02   0.4283004  0.36763546
## variation_rel_AUC2-variation_rel_AUC_c02        0.1949556  0.13429065
## variation_rel_c0_dose2-variation_rel_AUC_c02    0.5514859  0.49082089
## variation_rel_c02-variation_rel_AUC_c02         0.3001262  0.23946120
## variation_rel_AUC2-variation_rel_AUC_dose2     -0.2333448 -0.29400978
## variation_rel_c0_dose2-variation_rel_AUC_dose2  0.1231854  0.06252045
## variation_rel_c02-variation_rel_AUC_dose2      -0.1281743 -0.18883923
## variation_rel_c0_dose2-variation_rel_AUC2       0.3565302  0.29586527
## variation_rel_c02-variation_rel_AUC2            0.1051705  0.04450558
## variation_rel_c02-variation_rel_c0_dose2       -0.2513597 -0.31202466
##                                                       upr    p adj
## variation_rel_AUC_dose2-variation_rel_AUC_c02   0.4889654 0.00e+00
## variation_rel_AUC2-variation_rel_AUC_c02        0.2556206 0.00e+00
## variation_rel_c0_dose2-variation_rel_AUC_c02    0.6121508 0.00e+00
## variation_rel_c02-variation_rel_AUC_c02         0.3607911 0.00e+00
## variation_rel_AUC2-variation_rel_AUC_dose2     -0.1726798 0.00e+00
## variation_rel_c0_dose2-variation_rel_AUC_dose2  0.1838504 3.00e-07
## variation_rel_c02-variation_rel_AUC_dose2      -0.0675093 1.00e-07
## variation_rel_c0_dose2-variation_rel_AUC2       0.4171952 0.00e+00
## variation_rel_c02-variation_rel_AUC2            0.1658355 2.27e-05
## variation_rel_c02-variation_rel_c0_dose2       -0.1906947 0.00e+00
```

Scatter plots relative variations for each metrics vs time between 2 requests with lag **2** requests



Relative variations between 2 requests:

We created groups for <3 months and > 12 months and boxplots for different metrics (Figure 1)



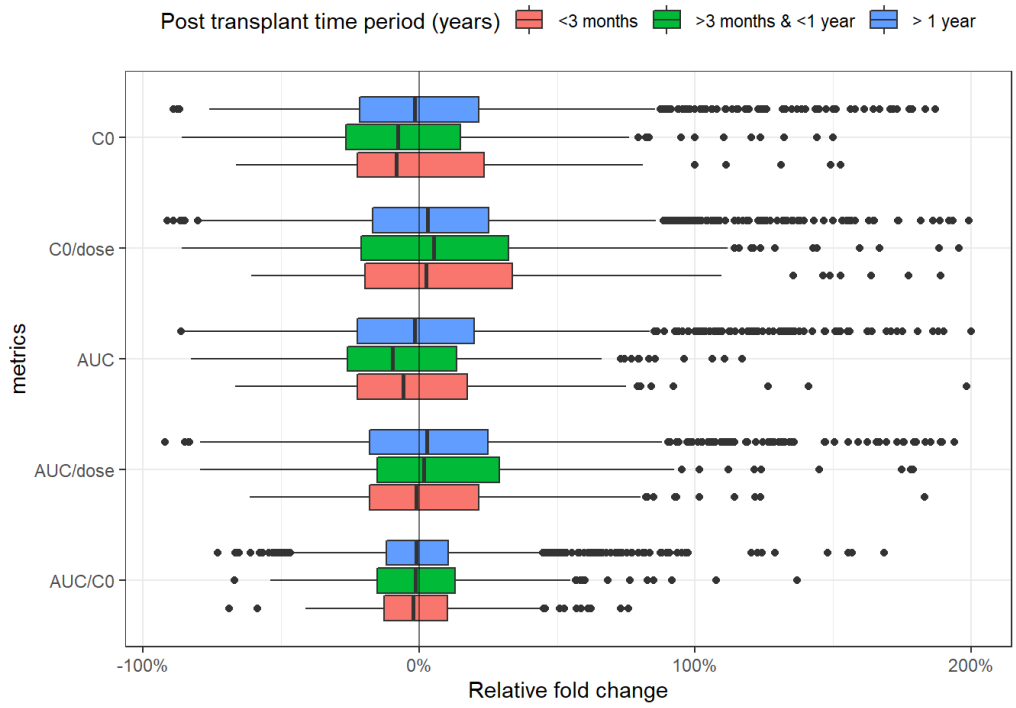

```
## # A tibble: 15 x 4
## # Groups:   metrics [5]
##    metrics               group_delai_entre_visite   mean    sd
##    <chr>                 <ord>                     <dbl> <dbl>
##  1 variation_rel_AUC     inf_3mois                0.0331 0.477
##  2 variation_rel_AUC     3mois-1an                0.0173 0.381
##  3 variation_rel_AUC     sup_1an                  0.0516 0.439
##  4 variation_rel_AUC_c0  inf_3mois                0.0337 0.287
##  5 variation_rel_AUC_c0  3mois-1an                0.0112 0.244
##  6 variation_rel_AUC_c0  sup_1an                  0.0139 0.246
##  7 variation_rel_AUC_dose inf_3mois               0.0963 0.556
##  8 variation_rel_AUC_dose 3mois-1an               0.114  0.486
##  9 variation_rel_AUC_dose sup_1an                 0.0982 0.472
## 10 variation_rel_c0      inf_3mois                0.0526 0.542
## 11 variation_rel_c0      3mois-1an                0.0346 0.408
## 12 variation_rel_c0      sup_1an                  0.0680 0.463
## 13 variation_rel_c0_dose inf_3mois                0.132  0.694
## 14 variation_rel_c0_dose 3mois-1an                0.146  0.592
## 15 variation_rel_c0_dose sup_1an                  0.118  0.499
```

```
##                            Df Sum Sq Mean Sq F value Pr(>F)
## metrics                     4   25.8   6.442  30.660 <2e-16 ***
## group_delai_entre_visite    2    0.1   0.043   0.202  0.817
## Residuals               12788 2686.7   0.210
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite, data = tac_boxplot_variation_3visite)
##
## $metrics
##                                                diff          lwr
## variation_rel_AUC_c0-variation_rel_AUC       -0.01442438 -0.049383483
## variation_rel_AUC_dose-variation_rel_AUC      0.07345923  0.038500120
## variation_rel_c0-variation_rel_AUC            0.01753555 -0.017423554
## variation_rel_c0_dose-variation_rel_AUC       0.10297831  0.068019200
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.08788360  0.052924496
## variation_rel_c0-variation_rel_AUC_c0         0.03195993 -0.002999177
## variation_rel_c0_dose-variation_rel_AUC_c0    0.11740268  0.082443576
## variation_rel_c0-variation_rel_AUC_dose      -0.05592367 -0.090882780
## variation_rel_c0_dose-variation_rel_AUC_dose  0.02951908 -0.005440026
## variation_rel_c0_dose-variation_rel_c0        0.08544275  0.050483648
##                                                     upr     p adj
## variation_rel_AUC_c0-variation_rel_AUC        0.02053473 0.7930151
## variation_rel_AUC_dose-variation_rel_AUC      0.10841833 0.0000001
## variation_rel_c0-variation_rel_AUC            0.05249466 0.6479834
## variation_rel_c0_dose-variation_rel_AUC       0.13793741 0.0000000
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.12284271 0.0000000
## variation_rel_c0-variation_rel_AUC_c0         0.06691904 0.0919675
## variation_rel_c0_dose-variation_rel_AUC_c0    0.15236179 0.0000000
## variation_rel_c0-variation_rel_AUC_dose      -0.02096457 0.0001254
## variation_rel_c0_dose-variation_rel_AUC_dose  0.06447819 0.1436807
## variation_rel_c0_dose-variation_rel_c0        0.12040186 0.0000000
```

Variations relative time post transplantation :

We created groups for <3 months and > 12 months and boxplots for different metrics (Figure 1)

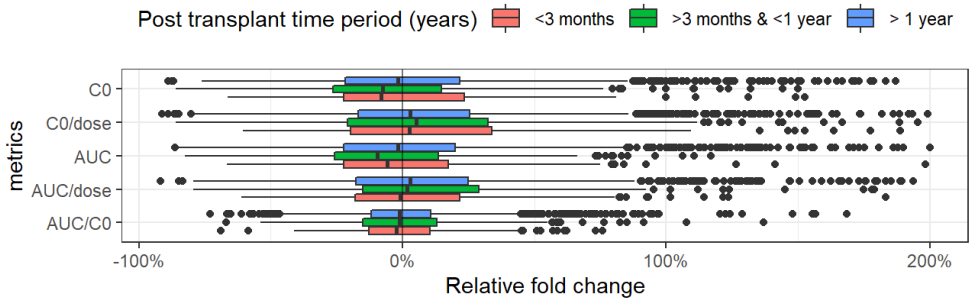


```
## # A tibble: 15 x 4
## # Groups:   metrics [5]
##    metrics               group_delai_post_greffe     mean    sd
##    <chr>                 <ord>                      <dbl> <dbl>
##  1 variation_rel_AUC     inf_3mois                 0.0254  0.473
##  2 variation_rel_AUC     3mois-1an                -0.0320  0.370
##  3 variation_rel_AUC     sup_1an                   0.0428  0.427
##  4 variation_rel_AUC_c0  inf_3mois                 0.0113  0.255
##  5 variation_rel_AUC_c0  3mois-1an                 0.0177  0.262
##  6 variation_rel_AUC_c0  sup_1an                   0.0174  0.254
##  7 variation_rel_AUC_dose inf_3mois                0.114   0.534
##  8 variation_rel_AUC_dose 3mois-1an                0.133   0.512
##  9 variation_rel_AUC_dose sup_1an                  0.0996  0.493
## 10 variation_rel_c0      inf_3mois                 0.0506  0.495
## 11 variation_rel_c0      3mois-1an                -0.00206 0.453
## 12 variation_rel_c0      sup_1an                   0.0577  0.456
## 13 variation_rel_c0_dose inf_3mois                 0.167   0.708
## 14 variation_rel_c0_dose 3mois-1an                 0.189   0.656
## 15 variation_rel_c0_dose sup_1an                   0.123   0.568
```

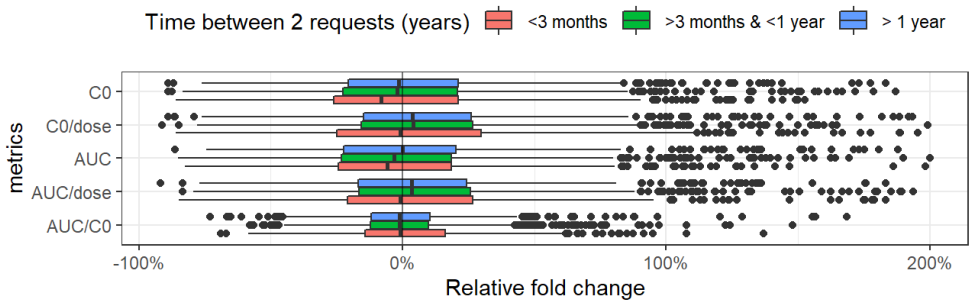
```
##                            Df Sum Sq Mean Sq F value Pr(>F)
## metrics                     4   25.8   6.442  30.660 <2e-16 ***
## group_delai_post_greffe     2    0.1   0.050   0.238  0.788
## Residuals               12788 2686.7   0.210
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_post_greffe, data = tac_boxplot_variation_3visite_pg)
##
## $group_delai_post_greffe
##                              diff         lwr        upr     p adj
## 3mois-1an-inf_3mois -0.012325177 -0.05930538 0.03465503 0.8119514
## sup_1an-inf_3mois   -0.005460055 -0.04622199 0.03530188 0.9471114
## sup_1an-3mois-1an    0.006865122 -0.02088107 0.03461132 0.8308490
```

A



B



Two way anova and post hoc test

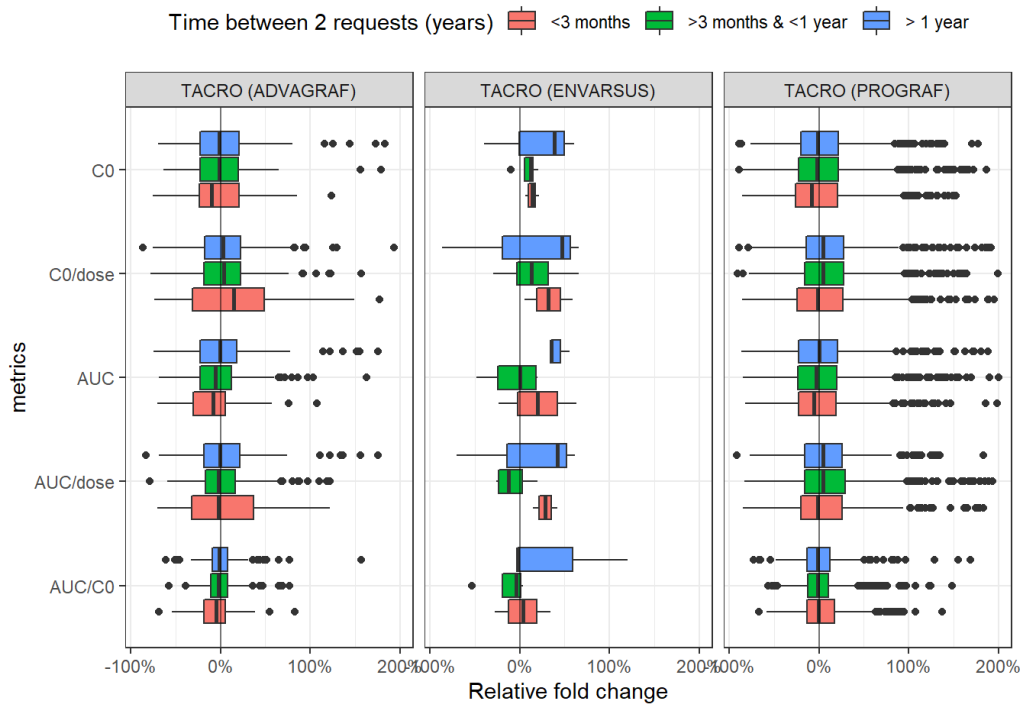
```
##                                   Df Sum Sq Mean Sq F value Pr(>F)
## metrics                            4   25.8   6.442  30.661 <2e-16 ***
## group_delai_entre_visite           2    0.1   0.043   0.202  0.817
## metrics:group_delai_entre_visite   8    1.8   0.223   1.061  0.387
## Residuals                      12780 2684.9   0.210
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite + metrics:group_delai_entre_visite, data = tac
_boxplot_variation_3visite)
##
## $group_delai_entre_visite
##                               diff         lwr        upr     p adj
## 3mois-1an-inf_3mois -0.0049873630 -0.02939656 0.01942184 0.8812648
## sup_1an-inf_3mois    0.0003055051 -0.02599098 0.02660199 0.9995912
## sup_1an-3mois-1an    0.0052928681 -0.01671488 0.02730061 0.8393850
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_relative ~ metrics + group_delai_entre_visite + metrics:group_delai_entre_visite, data = tac
_boxplot_variation_3visite)
##
## $metrics
##                                                 diff          lwr
## variation_rel_AUC_c0-variation_rel_AUC       -0.01442438 -0.049382815
## variation_rel_AUC_dose-variation_rel_AUC      0.07345923  0.038500788
## variation_rel_c0-variation_rel_AUC            0.01753555 -0.017422886
## variation_rel_c0_dose-variation_rel_AUC       0.10297831  0.068019868
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.08788360  0.052925165
## variation_rel_c0-variation_rel_AUC_c0         0.03195993 -0.002998509
## variation_rel_c0_dose-variation_rel_AUC_c0    0.11740268  0.082444245
## variation_rel_c0-variation_rel_AUC_dose      -0.05592367 -0.090882111
## variation_rel_c0_dose-variation_rel_AUC_dose  0.02951908 -0.005439358
## variation_rel_c0_dose-variation_rel_c0        0.08544275  0.050484316
##                                                    upr     p adj
## variation_rel_AUC_c0-variation_rel_AUC        0.02053406 0.7930035
## variation_rel_AUC_dose-variation_rel_AUC      0.10841766 0.0000001
## variation_rel_c0-variation_rel_AUC            0.05249399 0.6479666
## variation_rel_c0_dose-variation_rel_AUC       0.13793674 0.0000000
## variation_rel_AUC_dose-variation_rel_AUC_c0   0.12284204 0.0000000
## variation_rel_c0-variation_rel_AUC_c0         0.06691837 0.0919567
## variation_rel_c0_dose-variation_rel_AUC_c0    0.15236112 0.0000000
## variation_rel_c0-variation_rel_AUC_dose      -0.02096524 0.0001253
## variation_rel_c0_dose-variation_rel_AUC_dose  0.06447752 0.1436666
## variation_rel_c0_dose-variation_rel_c0        0.12040119 0.0000000
```

Relative variations between 2 requests per formulation:

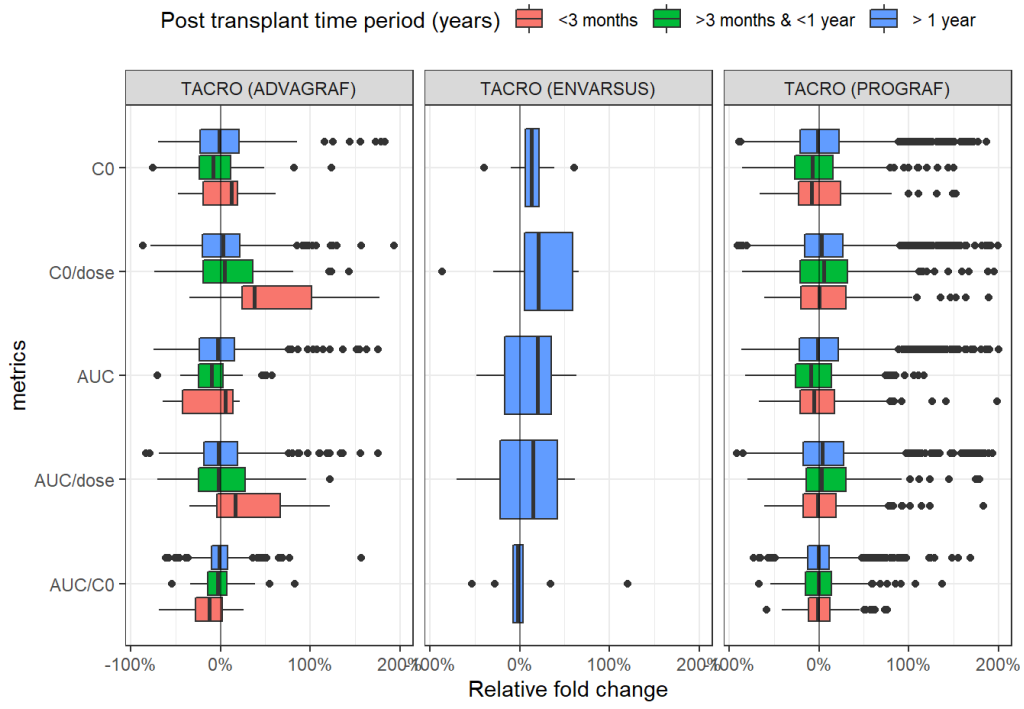
We created groups for <3 months and > 12 months and boxplots for different metrics/formulation




```
## # A tibble: 45 x 5
## # Groups:   metrics, group_delai_entre_visite [15]
##    metrics              group_delai_entre_visite Type_demande        mean    sd
##    <chr>                <ord>                    <fct>              <dbl> <dbl>
##  1 variation_rel_AUC    inf_3mois                TACRO (ADVAGRAF)  0.0435 0.639
##  2 variation_rel_AUC    inf_3mois                TACRO (ENVARSUS)  0.199  0.616
##  3 variation_rel_AUC    inf_3mois                TACRO (PROGRAF)   0.0315 0.459
##  4 variation_rel_AUC    3mois-1an                TACRO (ADVAGRAF) -0.0274 0.314
##  5 variation_rel_AUC    3mois-1an                TACRO (ENVARSUS) -0.0678 0.322
##  6 variation_rel_AUC    3mois-1an                TACRO (PROGRAF)   0.0273 0.394
##  7 variation_rel_AUC    sup_1an                  TACRO (ADVAGRAF)  0.0464 0.474
##  8 variation_rel_AUC    sup_1an                  TACRO (ENVARSUS)  0.413  0.124
##  9 variation_rel_AUC    sup_1an                  TACRO (PROGRAF)   0.0515 0.428
## 10 variation_rel_AUC_c0 inf_3mois                TACRO (ADVAGRAF) -0.0478 0.248
## # ... with 35 more rows
```

Variations relative time post transplantation :

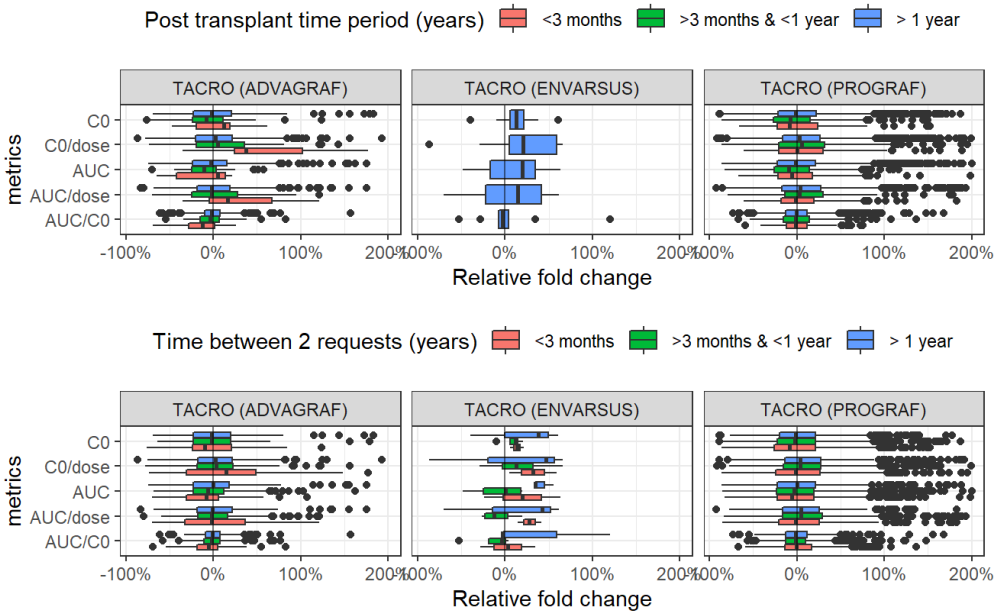
We created groups for <3 months and > 12 months and boxplots for different metrics



```
## # A tibble: 35 x 5
## # Groups:   metrics, group_delai_post_greffe [15]
##    metrics              group_delai_post_greffe Type_demande        mean    sd
##    <chr>                <ord>                   <fct>              <dbl> <dbl>
##  1 variation_rel_AUC    inf_3mois               TACRO (ADVAGRAF) -0.121  0.337
##  2 variation_rel_AUC    inf_3mois               TACRO (PROGRAF)   0.0359 0.480
##  3 variation_rel_AUC    3mois-1an               TACRO (ADVAGRAF) -0.0253 0.453
##  4 variation_rel_AUC    3mois-1an               TACRO (PROGRAF)  -0.0328 0.360
##  5 variation_rel_AUC    sup_1an                 TACRO (ADVAGRAF)  0.0190 0.434
##  6 variation_rel_AUC    sup_1an                 TACRO (ENVARSUS)  0.152  0.375
##  7 variation_rel_AUC    sup_1an                 TACRO (PROGRAF)   0.0482 0.425
##  8 variation_rel_AUC_c0 inf_3mois               TACRO (ADVAGRAF) -0.147  0.265
##  9 variation_rel_AUC_c0 inf_3mois               TACRO (PROGRAF)   0.0227 0.251
## 10 variation_rel_AUC_c0 3mois-1an               TACRO (ADVAGRAF) -0.0180 0.240
## # ... with 25 more rows
```

Supplemental Figure 1

Boxplots of relative intra-individual variations of the metrics of interest censored beyond -100% and +200%, depending on the post-transplant period (A) and the time elapsed between 2 instances (B) (categorized) per formulation type.



Comparison of different metrics as function of formulation type ANOVA and post test

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 148290, df = 38, p-value < 2.2e-16
```

```
##                Df Sum Sq Mean Sq F value  Pr(>F)
## Type_demande    2    7.2   3.602   11.29 1.3e-05 ***
## Residuals    4087 1304.3   0.319
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_AUC_dose ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                       diff         lwr         upr     p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF)  0.30097156  0.10841754  0.49352558 0.0007333
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.07985775  0.02939411  0.13032140 0.0006145
## TACRO (PROGRAF)-TACRO (ENVARSUS)  -0.22111380 -0.40990240 -0.03232521 0.0166811
```

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 148290, df = 38, p-value < 2.2e-16
```

```
##                Df Sum Sq Mean Sq F value   Pr(>F)
## Type_demande    2   10.5   5.232   8.211 0.000276 ***
## Residuals    4087 2604.1   0.637
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_c0_dose ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                          diff          lwr         upr
## TACRO (ENVARSUS)-TACRO (ADVAGRAF)  0.41292999  0.140857282  0.68500270
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.07990276  0.008599238  0.15120629
## TACRO (PROGRAF)-TACRO (ENVARSUS)  -0.33302723 -0.599779504 -0.06627495
##                                       p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF) 0.0010988
## TACRO (PROGRAF)-TACRO (ADVAGRAF)  0.0234772
## TACRO (PROGRAF)-TACRO (ENVARSUS)  0.0096346
```

```
##
##  Kruskal-Wallis rank sum test
##
## data:  .
## Kruskal-Wallis chi-squared = 148290, df = 38, p-value < 2.2e-16
```

```
##                Df Sum Sq Mean Sq F value Pr(>F)
## Type_demande    2   0.15 0.07543   1.121  0.326
## Residuals    4087 275.01 0.06729
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = variation_rel_AUC_c0 ~ Type_demande, data = tac_multi)
##
## $Type_demande
##                                           diff          lwr        upr
## TACRO (ENVARSUS)-TACRO (ADVAGRAF)  0.017033767 -0.071382804 0.10545034
## TACRO (PROGRAF)-TACRO (ADVAGRAF)   0.014723952 -0.008447844 0.03789575
## TACRO (PROGRAF)-TACRO (ENVARSUS)  -0.002309814 -0.088997384 0.08437776
##                                       p adj
## TACRO (ENVARSUS)-TACRO (ADVAGRAF) 0.8936587
## TACRO (PROGRAF)-TACRO (ADVAGRAF)  0.2959038
## TACRO (PROGRAF)-TACRO (ENVARSUS)  0.9978507
```

```
## # A tibble: 7 x 3
## # Groups:   Type_demande, Tt_associe [7]
##   Type_demande     Tt_associe      n
##   <fct>            <fct>       <int>
## 1 TACRO (ADVAGRAF) Corticoides    25
## 2 TACRO (ADVAGRAF) MMF           738
## 3 TACRO (ADVAGRAF) Neant         118
## 4 TACRO (ENVARSUS) MMF            38
## 5 TACRO (ENVARSUS) Neant          12
## 6 TACRO (PROGRAF)  MMF          2659
## 7 TACRO (PROGRAF)  Neant         500
```

```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande         n
##   <fct>            <int>
## 1 TACRO (ADVAGRAF)   881
## 2 TACRO (ENVARSUS)    50
## 3 TACRO (PROGRAF)   3159
```

Correlation AUC/c0

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.288   160
```

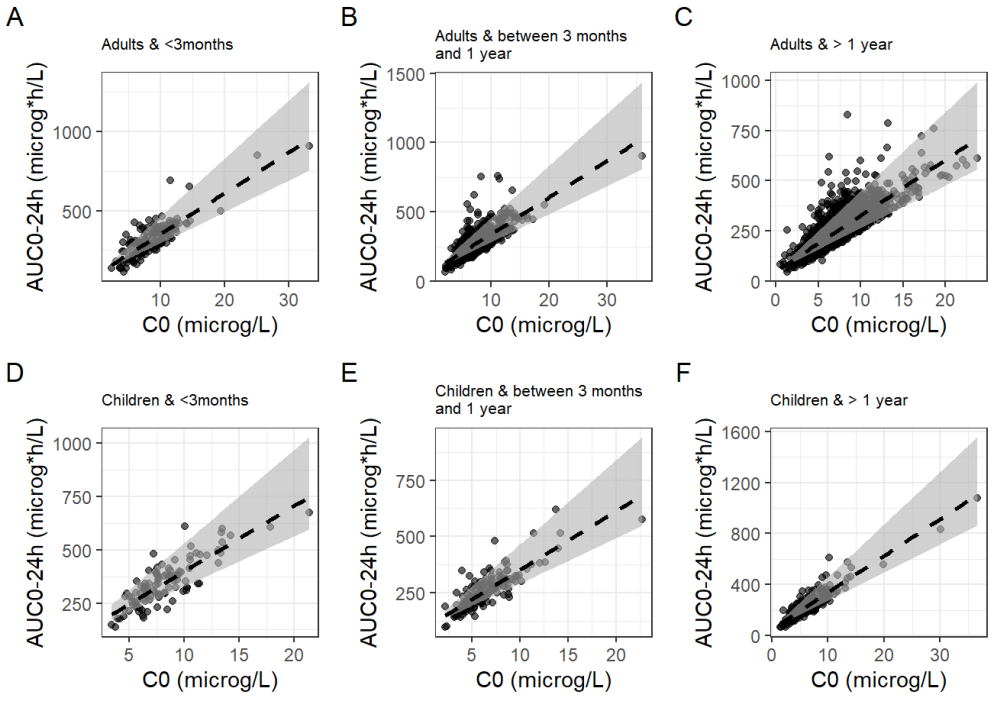
```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.307   667
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.174  2754
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1         0.24   100
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1         0.25   152
```

```
## # A tibble: 1 x 2
##   prop_30_prct     n
##          <dbl> <int>
## 1        0.268   257
```



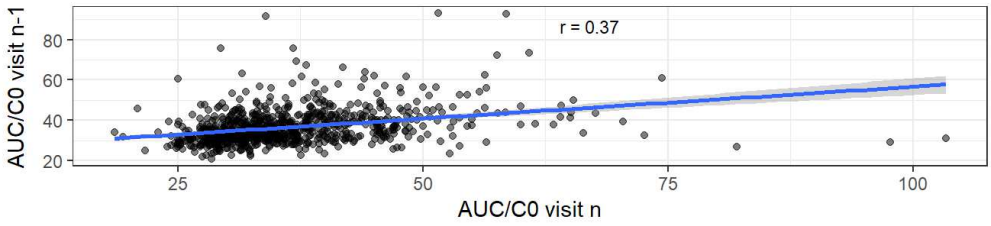
Correlation for AUC, c0 and AUC/c0 between instances #1 and #2

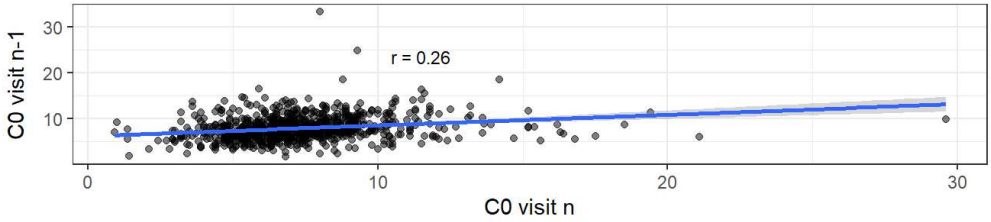
Overall

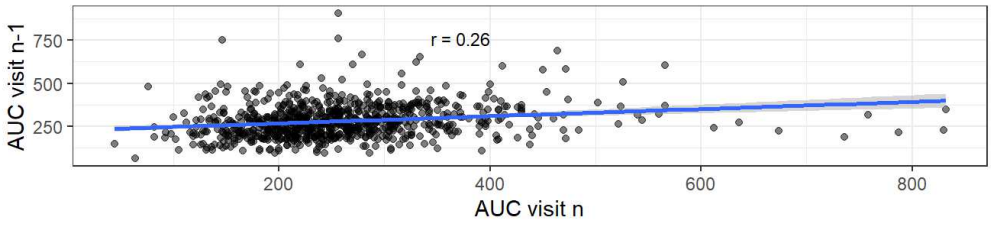
```
## # A tibble: 1 x 1
##   cor_AUC_c0
##        <dbl>
## 1      0.322
```

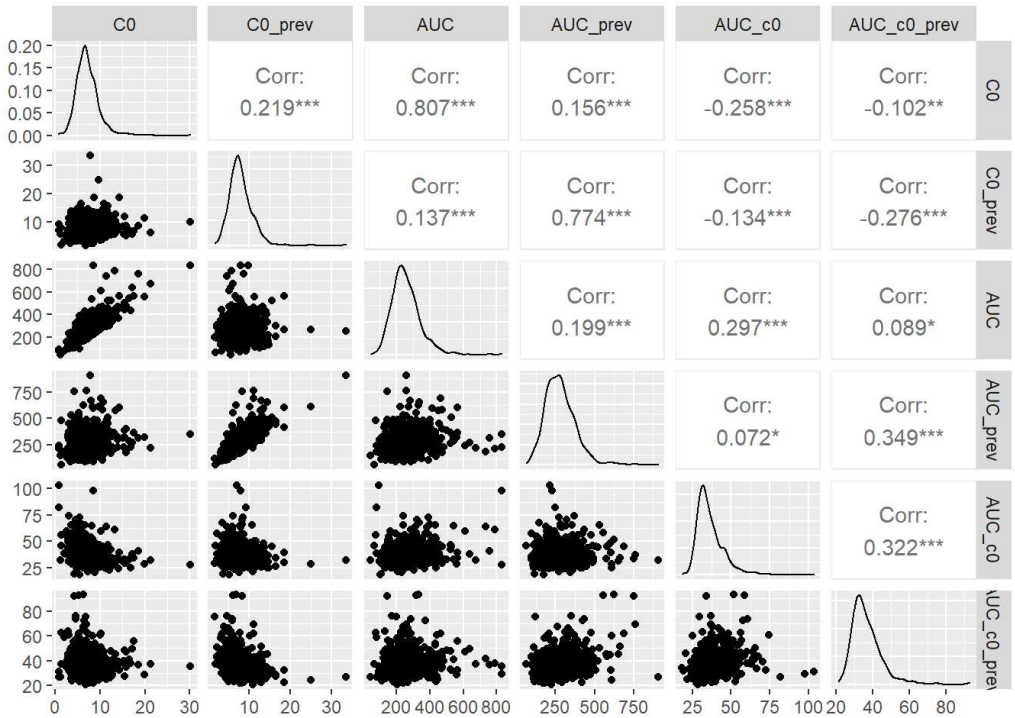
```
## # A tibble: 1 x 1
##   cor_c0
##    <dbl>
## 1  0.222
```

```
## # A tibble: 1 x 1
##   cor_AUC
##     <dbl>
## 1   0.199
```







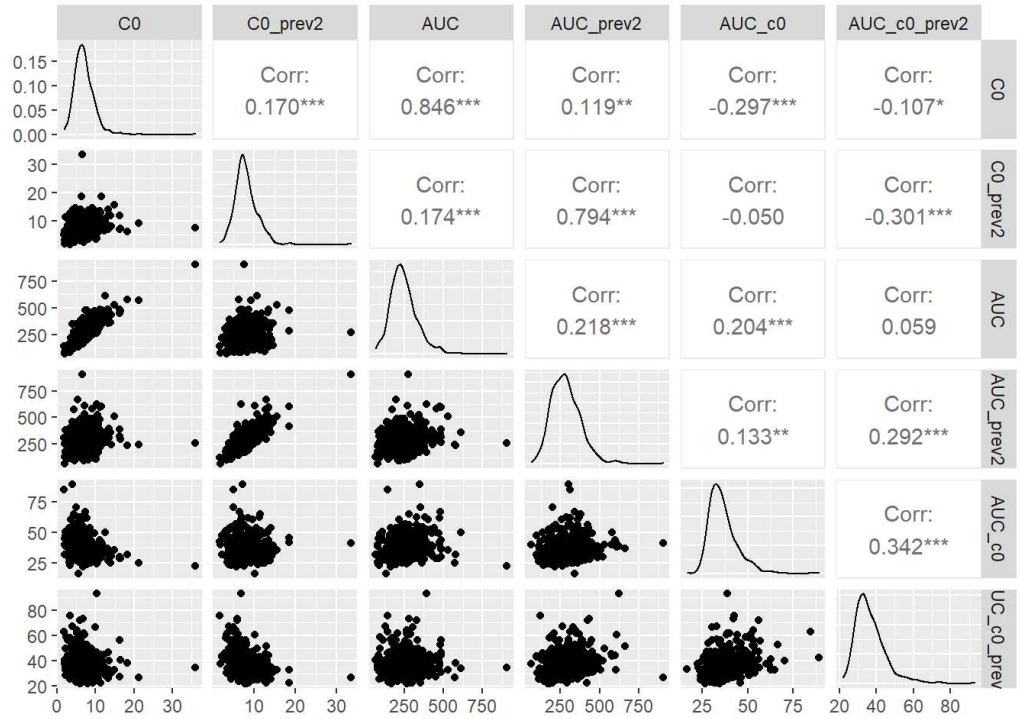


```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande          n
##   <fct>             <int>
## 1 TACRO (ADVAGRAF)    166
## 2 TACRO (ENVARSUS)      7
## 3 TACRO (PROGRAF)     621
```

per formulation

Correlation for AUC, c0 and AUC/c0 between instances #1 and #3

Overall

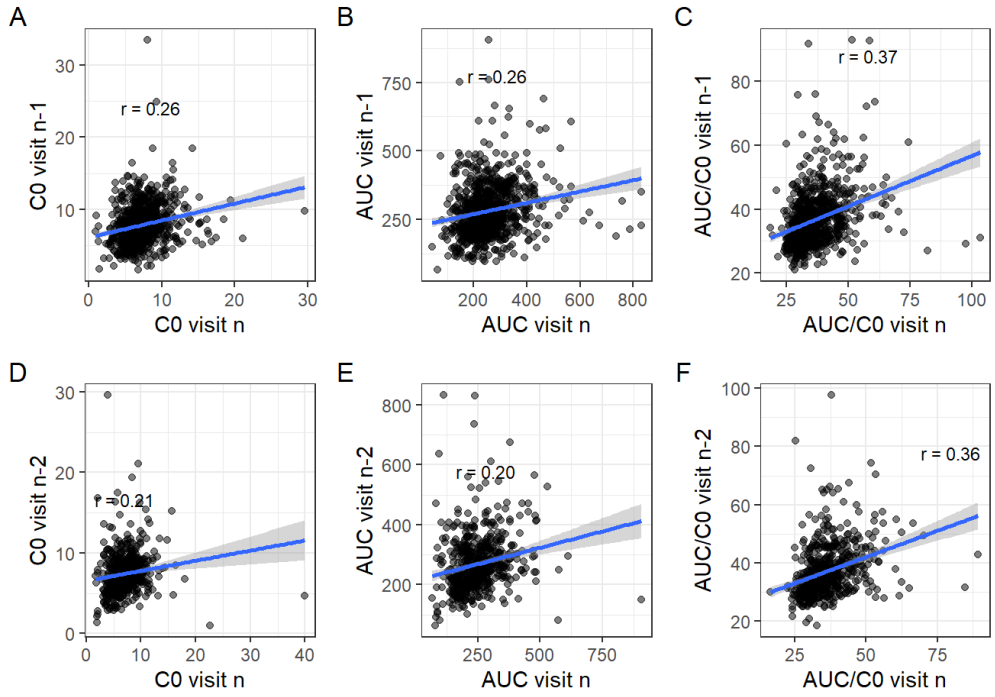



```
## # A tibble: 3 x 2
## # Groups:   Type_demande [3]
##   Type_demande         n
##   <fct>            <int>
## 1 TACRO (ADVAGRAF)   122
## 2 TACRO (ENVARSUS)     4
## 3 TACRO (PROGRAF)    423
```

```
## # A tibble: 1 x 1
##   cor_AUC_c0
##        <dbl>
## 1      0.329
```

```
## # A tibble: 1 x 1
##   cor_c0
##    <dbl>
## 1  0.139
```

```
## # A tibble: 1 x 1
##   cor_AUC
##     <dbl>
## 1   0.206
```



per formulation

AUC/C0 analysis vs CYP3A5 status in the subpopulation epigren/ephegren

Data summary

Name	ungroup(epi_cyp3a5)
Number of rows	220
Number of columns	19
_____	
Column type frequency:	
character	5
numeric	14
_____	
Group variables	None

Variable type: character

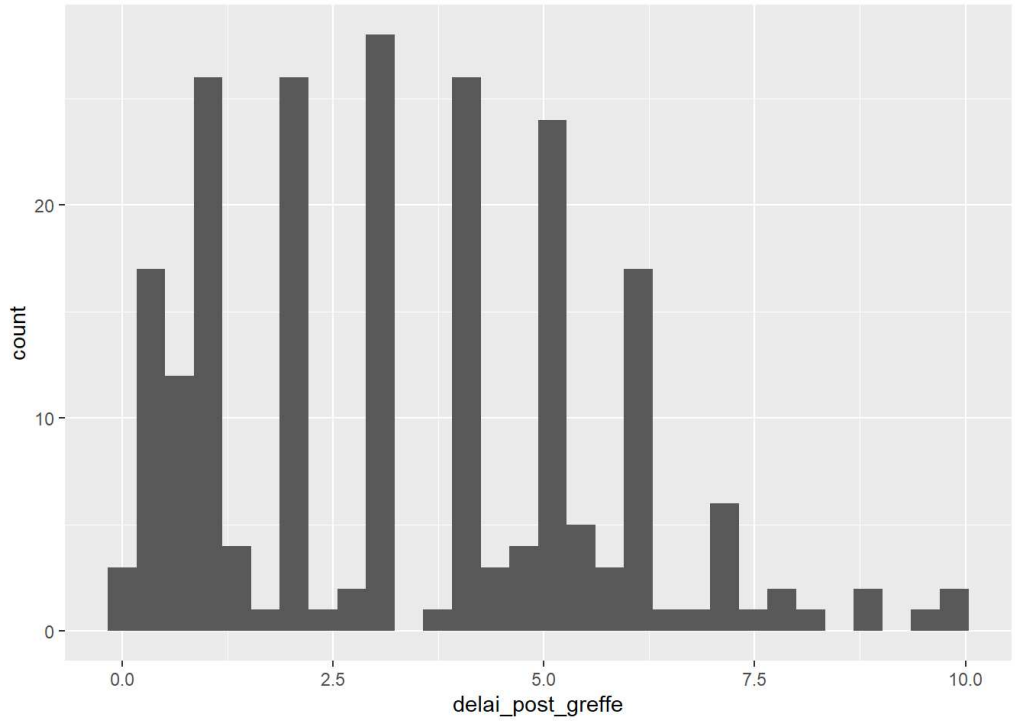
skim_variable	n_missing	complete_rate	min	max	empty	n_unique	whitespace
id	0	1	11	11	0	52	0
CYP3A5	0	1	9	13	0	2	0
CYP3A4	0	1	2	2	0	1	0
SEXE	0	1	7	8	0	2	0
lag_id	0	1	11	11	0	52	0

Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
C0	0	1	8.11	2.83	1.00	6.30	7.70	9.12	21.10	▆▃▁
AUC_0_24	0	1	285.94	97.52	38.00	224.00	270.00	324.50	728.00	▆▃▁
Cmax	0	1	20.31	9.17	2.51	14.01	18.20	24.56	54.96	▃▇▂▁
AUC_c0	0	1	36.08	7.71	22.25	30.69	35.09	39.66	82.00	▇▇▂▁
delai_post_greffe	0	1	3.35	2.26	0.09	1.07	3.03	5.01	9.96	▇▇▇▂▁
AUC_prec	0	1	309.01	107.63	90.00	233.50	282.00	368.50	728.00	▃▇▂▁
cmax_prec	0	1	22.26	10.30	6.27	15.21	19.50	26.49	65.47	▇▇▂▁
AUC_c0_prec	0	1	36.45	7.20	22.25	31.42	35.39	40.29	70.37	▃▇▂▁
c0_prec	0	1	8.65	3.13	2.00	6.60	8.00	9.93	23.00	▃▇▂▁
delai_prec	0	1	2.45	2.03	-0.03	0.67	2.00	4.02	8.95	▇▇▇▂
delai_entre_visite	0	1	0.90	0.54	0.02	0.63	0.99	1.01	3.88	▃▇▁
variation_rel_AUC	0	1	-0.01	0.35	-0.94	-0.24	-0.03	0.16	1.17	▁▇▃▁
variation_rel_c0	0	1	0.02	0.42	-0.96	-0.25	-0.03	0.19	2.30	▂▇▂▁
variation_rel_AUC_c0	0	1	0.02	0.25	-0.52	-0.14	-0.01	0.13	1.29	▂▇▂▁

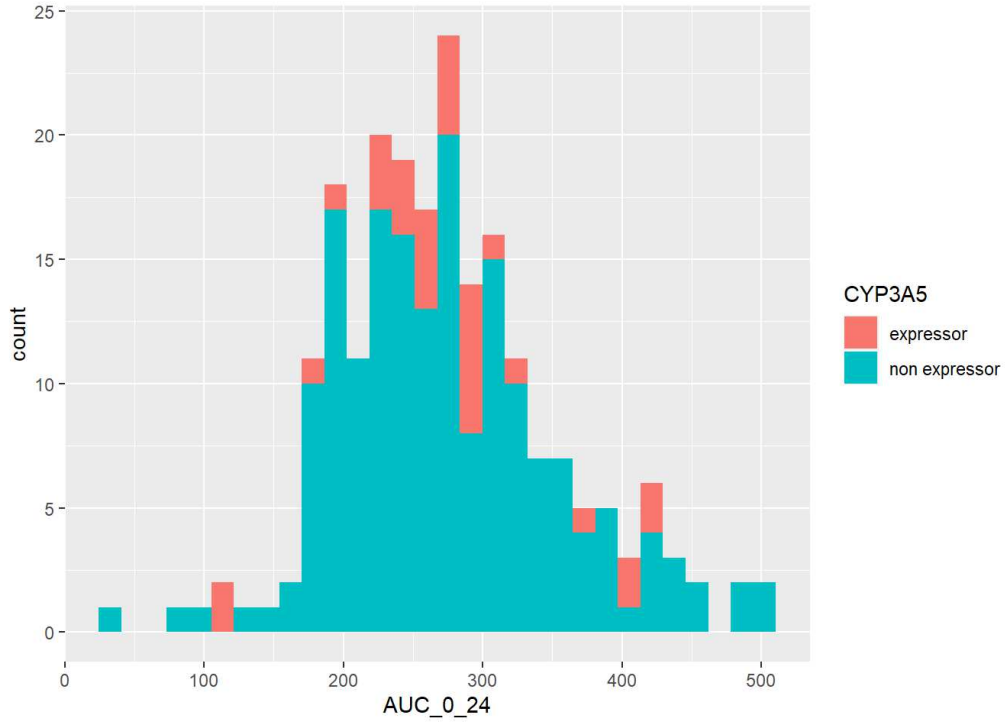
```
## # A tibble: 2 x 2
##   CYP3A5            n
##   <chr>         <int>
## 1 expressor         8
## 2 non expressor    44
```

Filtering out time post transplantation and histogram

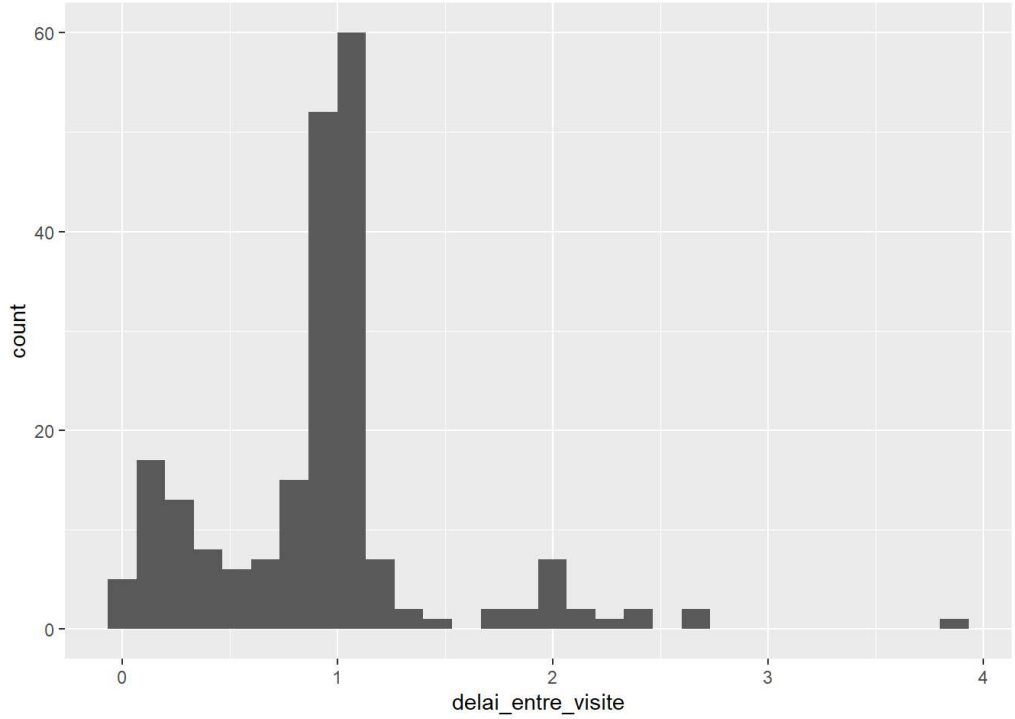


Filtering out AUC and histogram

Removal of AUC > mean+/- 1.96 SD = [80-430]

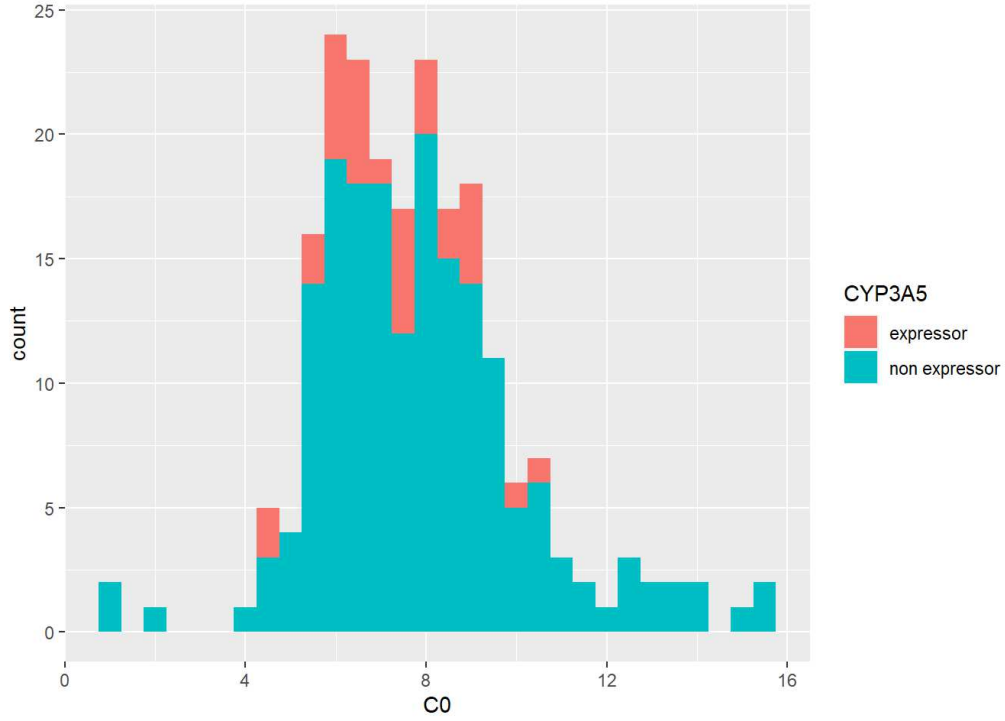


Filtering out time between requests and histogram



Filtering out c0 and histogram

Removal of C0 > 1.96*SD [2.18-12.14]



Rank of visit

Summary of data after filtering out values

Data summary

Name	ungroup(epi_cyp3a5)
Number of rows	212
Number of columns	20
_____	
Column type frequency:	
character	5
numeric	15

Group variables	None

Variable type: character

skim_variable	n_missing	complete_rate	min	max	empty	n_unique	whitespace
id	0	1	11	11	0	52	0
CYP3A5	0	1	9	13	0	2	0
CYP3A4	0	1	2	2	0	1	0
SEXE	0	1	7	8	0	2	0
lag_id	0	1	11	11	0	52	0

Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
C0	0	1	7.80	2.29	1.00	6.27	7.55	9.00	15.50	
AUC_0_24	0	1	274.84	79.36	38.00	224.00	268.00	316.50	508.00	
Cmax	0	1	19.50	8.15	2.51	13.84	17.84	23.20	54.96	
AUC_c0	0	1	36.00	7.57	22.25	30.70	35.04	39.55	82.00	
delai_post_greffe	0	1	3.39	2.25	0.09	1.13	3.05	5.02	9.96	
AUC_prec	0	1	305.12	106.25	90.00	231.50	277.59	358.50	728.00	
cmax_prec	0	1	21.95	10.05	6.27	15.04	19.33	26.35	65.47	
AUC_c0_prec	0	1	36.53	7.24	22.25	31.42	35.58	40.40	70.37	
c0_prec	0	1	8.52	3.07	2.00	6.50	7.95	9.55	23.00	
delai_prec	0	1	2.48	2.04	-0.03	0.72	2.00	4.02	8.95	
delai_entre_visite	0	1	0.91	0.54	0.02	0.68	1.00	1.01	3.88	
variation_rel_AUC	0	1	-0.03	0.33	-0.94	-0.26	-0.04	0.14	0.93	
variation_rel_c0	0	1	0.00	0.40	-0.96	-0.26	-0.05	0.17	2.30	
variation_rel_AUC_c0	0	1	0.01	0.25	-0.52	-0.14	-0.01	0.13	1.29	
rank_visite	0	1	3.02	1.79	1.00	2.00	3.00	4.00	9.00	

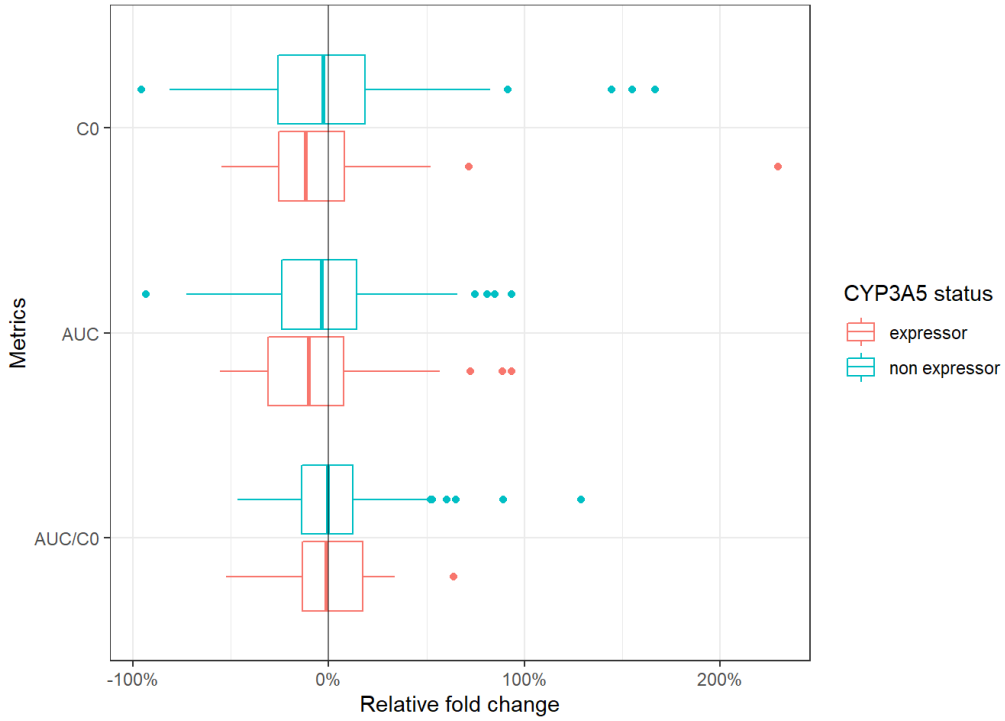
	Overall
n	212
CYP3A5 = non expressor (%)	181 (85.4)
CYP3A4 = CC (%)	212 (100.0)
SEXE = MASCULIN (%)	147 (69.3)
C0 (median [range])	7.55 [1.00, 15.50]
AUC_0_24 (median [range])	268.00 [38.00, 508.00]
Cmax (median [range])	17.84 [2.51, 54.96]
AUC_c0 (median [range])	35.04 [22.25, 82.00]
delai_post_greffe (median [range])	3.05 [0.09, 9.96]
AUC_prec (median [range])	277.59 [90.00, 728.00]
cmax_prec (median [range])	19.33 [6.27, 65.47]
AUC_c0_prec (median [range])	35.58 [22.25, 70.37]
c0_prec (median [range])	7.95 [2.00, 23.00]
delai_prec (median [range])	2.00 [-0.03, 8.95]
delai_entre_visite (median [range])	1.00 [0.02, 3.88]

	Overall
variation_rel_AUC (median [range])	-0.04 [-0.94, 0.93]
variation_rel_c0 (median [range])	-0.05 [-0.96, 2.30]
variation_rel_AUC_c0 (median [range])	-0.01 [-0.52, 1.29]
rank_visite (median [range])	3.00 [1.00, 9.00]

	Overall
n	212
CYP3A5 = non expressor (%)	181 (85.4)
CYP3A4 = CC (%)	212 (100.0)
SEXE = MASCULIN (%)	147 (69.3)
C0 (median [IQR])	7.55 [6.27, 9.00]
AUC_0_24 (median [IQR])	268.00 [224.00, 316.50]
Cmax (median [IQR])	17.84 [13.84, 23.20]
AUC_c0 (median [IQR])	35.04 [30.70, 39.55]
delai_post_greffe (median [IQR])	3.05 [1.13, 5.02]
AUC_prec (median [IQR])	277.59 [231.50, 358.50]
cmax_prec (median [IQR])	19.33 [15.04, 26.35]
AUC_c0_prec (median [IQR])	35.58 [31.42, 40.40]
c0_prec (median [IQR])	7.95 [6.50, 9.55]
delai_prec (median [IQR])	2.00 [0.72, 4.02]
delai_entre_visite (median [IQR])	1.00 [0.68, 1.01]
variation_rel_AUC (median [IQR])	-0.04 [-0.26, 0.14]
variation_rel_c0 (median [IQR])	-0.05 [-0.26, 0.17]
variation_rel_AUC_c0 (median [IQR])	-0.01 [-0.14, 0.13]
rank_visite (median [IQR])	3.00 [2.00, 4.00]

Relative variations between visit n and n-1 for metrics vs CYP3A5 status

```
## # A tibble: 3 x 4
##   metrics    mean    sd     cv
##   <ord>     <dbl> <dbl>  <dbl>
## 1 AUC/C0   1.23    24.7   20.0
## 2 AUC     -2.79    33.3  -11.9
## 3 C0       0.0366  40.4 1103.
```



percentage of patients out of the 20% C0 interval around the regression line

We evaluated the % out of the 20% interval for adults >1 year to answer the reviewer 1 comment

20%

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.475   160
```

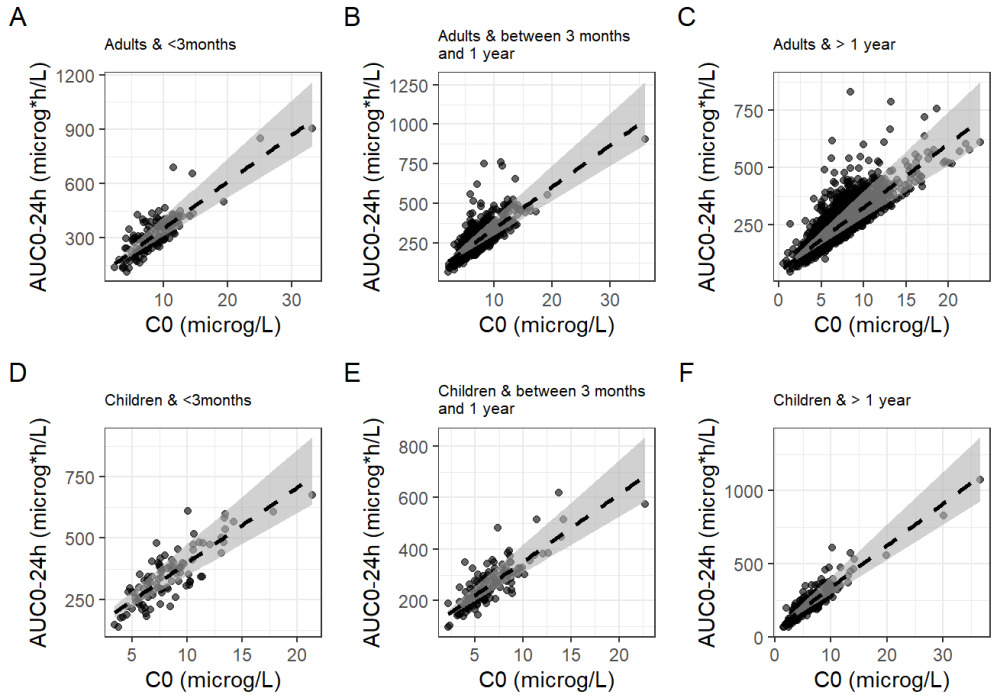
```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.514   667
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.370  2754
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1         0.41   100
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.408   152
```

```
## # A tibble: 1 x 2
##   prop_20_prct     n
##          <dbl> <int>
## 1        0.416   257
```


A
Adults & <3months
AUC0-24h (microg*h/L)
C0 (microg/L)
B
Adults & between 3 months and 1 year
AUC0-24h (microg*h/L)
C0 (microg/L)
C
Adults & > 1 year
AUC0-24h (microg*h/L)
C0 (microg/L)
D
Children & <3months
AUC0-24h (microg*h/L)
C0 (microg/L)
E
Children & between 3 months and 1 year
AUC0-24h (microg*h/L)
C0 (microg/L)
F
Children & > 1 year
AUC0-24h (microg*h/L)
C0 (microg/L)