```r
# call library ----------------------------------------------------------

set.seed(1234)
pacman::p_load(rio,      #file import
      vroom,      #file import for
      here,    #file location
      tidyverse,  #data management, ggplot
      lubridate,  #data management on date
      visdat,     #vidualization for missing data
      naniar,     #summrize and vidualize for missing data
      tableone,   #create table
      GGally,     #plot overall
      coefplot,   #forestplot
      esquisse,   #vidualization using GUI
      ggsci,      #color on graphic
      ggridges,   #densityplot
      mice,       #MI
      ggrain,     #cloudplot
      gtsummary,
      broom,
      lme4)
par(family="HiraKakuProN-W3")



# import data ------------------------------------------------------------
here()

rawdb <- import(here("dataset", "rawfix_sarcopenicdysphagiaDB.xlsx"))
rawdb_drug <- import(here("dataset", "rawdata_drug.xlsx"))
iyacode <- import(here("yjcode", "y.xlsx"))
#診療報酬情報提供サービス HP から、医薬品マスターを使用した。
#https://shinryohoshu.mhlw.go.jp/shinryohoshu/kaitei/doKaiteiR02
iyacode <- iyacode %>%
  select(iyacode, yjcode, name)
```

```r
export(iyacode, "iyacode.xlsx")


dput(names(rawdb))
Db_drug <- rawdb %>%
  select(PID,NumberDrugusage,drug1:drug20)


# check database ---------------------------------------------------------



#check rawdata
#missing number-of-drug and detailed-drug-information


miss_var_summary(Db_drug, order = F)
#There is 10 missing value on the variable of number-of-drug
#> miss_var_summary(Db_drug, order = F)
# A tibble: 22 × 3
#variable        n_miss pct_miss
#<chr>           <int>   <dbl>
#1 PID               0     0
#2 NumberDrugusage   10    2.14
Db_drug_checkmissing <- Db_drug %>%
  arrange(NumberDrugusage)


Db_drug %>%
  group_by(NumberDrugusage) %>%
  summarise(
    n=n()
  )
#0 on NumberDrug(n=18)
#PID; 18,50,74,144,207,243,258,283,353,355,366,429,430,448,451,458,463,467


#missing on NumberDrug(n=10)
#PID; 35,186,244,245,246,247,248,259,250,301
# A tibble: 20 × 2
#NumberDrugusage    n
#<dbl> <int>
```

```
#1          0   18
#2          1   16
#3          2   20
#4          3   42
#5          4   45
#6          5   49
#7          6   59
#8          7   63
#9          8   39
#10         9   35
#11         10  29
#12         11  13
#13         12  8
#14         13  6
#15         14  7
#16         15  2
#17         17  3
#18         19  2
#19         20  1
#20         NA  10
```

```r
zero <- c(18,50,74,144,207,243,258,283,353,355,366,429,430,448,451,458,463,467)
miss <- c(35,186,244,245,246,247,248,259,250,301)
zerodrug <- rawdb %>%
  filter(PID %in% zero) %>% export("zerodrug.xlsx")
missdrug <- rawdb %>%
  filter(PID %in% miss) %>% export("missdrug.xlsx")
zerodrug <- zerodrug %>%
 mutate(Numdrug = 0)
missdrug <- missdrug %>%
  mutate(Numdrug = "missing")
check_drug <- rbind(zerodrug, missdrug)

library(tableone)
##データの特徴・列の名前確認
check_drug1 <- check_drug %>%
```

```r
  select(PID, ClassAffiliation, Age, FILS_atBL, Sex, DiseaseMain, BMI, LongTermCare:CCIscore,
Numdrug)

glimpse(check_drug1)
dput(names(check_drug1))
vars = c("ClassAffiliation", "Age", "FILS_atBL", "Sex", "DiseaseMain",
        "BMI", "LongTermCare", "CVA", "CHF", "COPD", "CKD", "HF", "Dementia",
        "TypeDementia", "Bonejointdisease", "DM", "Cancer", "Nervedisease",
        "CCIscore", "Numdrug")
factorVars =c("ClassAffiliation", "FILS_atBL", "Sex", "DiseaseMain",
          "LongTermCare", "CVA", "CHF", "COPD", "CKD", "HF", "Dementia",
          "TypeDementia", "Bonejointdisease", "DM", "Cancer", "Nervedisease",
          "CCIscore", "Numdrug")
##Table1 作成、strate で群分け
##vars は連続、factorVars はカテゴリ
tableOne <- CreateTableOne(vars = vars,
                  factorVars =factorVars,
                strata = c("Numdrug"),
                data = check_drug1,
                smd = F,
                addOverall = T,
                includeNA = T)


##CSV へ出力
write.csv(print(tableOne, nonmormal=T, noSpaces = T,showAllLevels = T), "Table1.csv", fileEncoding
= "CP932")



# drug_create relational data ――――――――――――――――――――――――
Db_drug <- rawdb %>%
  select(PID,NumberDrugusage,drug1:drug20)
Db_drug1 <- Db_drug %>%
  select(-NumberDrugusage)
Db_drug1 <- Db_drug1 %>%
  gather(2:21, key = numdrug, value = druginformation)
```

```
Db_drug1 <- Db_drug1 %>%
  drop_na(druginformation) %>%
  arrange(PID)
export(Db_drug1, "drug_information.xlsx")
a <- Db_drug1 %>%
  group_by(PID) %>%
  summarise(countDrug=n())
rdb_drug <- import("drug_information.xlsx")
rdb_drug <- rdb_drug %>%
  select(-druginformation_search, -numdrug) %>%
  mutate(Yjcode7 = substr(rdb_drug$druginformation, 1,7),
         Yjcode4 = substr(rdb_drug$druginformation, 1,4)) %>%
  arrange(PID)
table(rdb_drug$Yjcode4)
miss_var_summary(rdb_drug)
# A tibble: 5 × 3
#variable        n_miss pct_miss
#<chr>            <int>    <dbl>
#1 PID               0        0
#2 numdrug           0        0
#3 druginformation   0        0
#4 Yjcode7           0        0
#5 Yjcode4           0        0


kakuninn <- rdb_drug %>%
  filter(Yjcode7 == "1141005")


# Create maindataset -------------------------------------------------
dput(names(rawdb))
dataset <- rawdb %>%
  select(PID, ClassAffiliation,Sex, Age, BMI,FILS_atBL, DiseaseMain, ICD10Main,
         CVA, CHF, COPD, CKD, Dementia, TypeDementia, DM, Cancer,
         CCIscore, NumberDrugusage,
         DateAd,  DateEvaluatoinofDisphagia, GaitSpeed, Handgrip, CalfCircumference,
         Sit_to_stand5, SMI, LowPhysicalFunction, LowMuscleStrength, LowMuscleMass,
         GeneralSarcopenia, ClassSarcopanicDysphagia,
```

```r
                CauseofSD,  GLIMAssess,BI_score,DateFU, Fucondition,FILSatFU, Biscore_atFU,
TenkiduringAd, Death)


##Date
df_y <- dataset %>%
  mutate(ADdate = ymd(DateAd),
        BLdate = ymd(DateEvaluatoinofDisphagia),
        FUdate = ymd(DateFU),
        Deathdate = ymd(Death))
df_y %>% select(ADdate, BLdate, DateAd,FUdate, Deathdate)


##Date, CCI, Polypharmacy
df_y <- df_y %>%
  mutate(Duration_AD_BL = as.integer(BLdate-ADdate)+1,
        Duration_BL_FU = as.integer(FUdate-BLdate)+1,
        Duration_BL_Death = as.integer(Deathdate-BLdate)+1,
        Death1 = ifelse(Death>0, 1,0),
        CCI_category = case_when(CCIscore == 0 ~ "0",
                        CCIscore == 1 ~ "1",
                        CCIscore == 2 ~ "2",
                        CCIscore == 3 ~ "3",
                        CCIscore == 4 ~ "4",
                        CCIscore == 5 ~ "5",
                        CCIscore >= 6 ~ "≧6"))
df_y <- df_y %>%
  mutate(Polypharmacy = case_when(NumberDrugusage>=5 ~ "With polypharmacy",
                        NumberDrugusage<5 ~ "Without polypharmacy",
                        is.na(NumberDrugusage) ~ "Missing"),
      Polypharmacy6 = case_when(NumberDrugusage>=6 ~ "≥6",
                         NumberDrugusage<6 ~"0-5",
                         is.na(NumberDrugusage) ~ "Missing"))
df_y$Death1[is.na(df_y$Death1)] <- 0
table(df_y$Death1)
df_y$CCI_category <- factor(df_y$CCI_category, levels = c("0",  "1",  "2",  "3" , "4",  "5","≧6"))
table(df_y$CCI_category)
table(df_y$Polypharmacy6)
```

```r
table(df_y$NumberDrugusage)

table(df_y$Polypharmacy)

remove(df_y1)

df_y$Polypharmacy <- factor(df_y$Polypharmacy, levels = c("With polypharmacy","Without
polypharmacy","Missing"))

##Age, Gender, hospital_type

df_y <- df_y %>%
  mutate(Age_category = case_when(Age < 65 ~ "<65",
                      Age >= 65 & Age < 75 ~ "65-74",
                      Age >= 75 & Age < 85 ~ "75-84",
                      Age >= 85 ~ "≧85"),
        Gender = case_when(Sex == 0 ~ "Male",
                  Sex == 1 ~ "Female"),
        Hospital_type = case_when(ClassAffiliation==1 ~ "Acute hospital",
                    ClassAffiliation==2 ~ "Rehabilitation hospital",
                    ClassAffiliation==3 ~ "Long-term care hospital",
                    ClassAffiliation==4 ~ "Others"))

df_y$Age_category <- factor(df_y$Age_category, levels = c( "<65","65-74","75-84", "≧85"))

df_y$Hospital_type <- factor(df_y$Hospital_type, levels = c("Acute hospital","Rehabilitation
hospital","Long-term care hospital","Others"))

table(df_y$Gender)

table(df_y$Age_category)

table(df_y$Hospital_type)


##BMI & ADLcategoery

#Reference to WakabayashiJNHA2019

#The Barthel Index score at discharge and hospital death. Results: The number of patients with a
body mass index of <18.5 kg/m2 (underweight), 18.5-22.9 kg/m2 (low-normal weight), 23.0-24.9
kg/m2 (high-normal weight), 25.0-29.9 kg/m2 (overweight), and ≥30.0 kg/m2 (obesity)

#https://pubmed.ncbi.nlm.nih.gov/30697624/

df_y <- df_y %>%
  mutate(BMI_category = case_when(BMI < 18.5 ~ "<18.5",
                      BMI >= 18.5 & BMI < 23 ~ "18.5-22.9",
                      BMI >= 23 & BMI < 25 ~ "23.0-24.9",
                      BMI >=25 & BMI < 30 ~ "25.0-29.9",
                      BMI >= 30 ~ "≧30.0"),
```

```r
        Barthel_index_c = case_when(BI_score == 100 ~ "Independent(100)",
                             BI_score >= 21 & BI_score <100 ~ "Partial_assistance(21-99)",
                             BI_score <= 20 ~ "Total_assistance(0-20)"),
        Barthel_index_c1 = case_when(BI_score >= 60 ~ "60-100",
                              BI_score >= 40 & BI_score <60 ~ "40-59",
                              BI_score < 40 ~ "0-39"))
df_y$BMI_category <- factor(df_y$BMI_category, levels = c("<18.5", "18.5-22.9","23.0-24.9", "25.0-
29.9","≧30.0"))
df_y$Barthel_index_c <- factor(df_y$Barthel_index_c, levels =
c("Independent(100)","Partial_assistance(21-99)","Total_assistance(0-20)"))
df_y$Barthel_index_c1 <- factor(df_y$Barthel_index_c1, levels = c("60-100","40-59","0-39"))
table(df_y$BMI_category)
summary(df_y$BMI)


##Comorbity
df_y <- df_y %>%
  mutate(ICD10_a = substr(ICD10Main, 1,1),
         ICD10_2 = substr(ICD10Main, 2,3))
df_y <- df_y %>%
  mutate(Primary_diagnosis = case_when(ICD10_a == "A" ~ "Infection disease",
                          ICD10_a == "C" | ICD10_a=="D"~"Cancer",
                          ICD10_a == "E" ~ "Endrine, nutritional and metabolic disease",
                          ICD10_a == "G" ~ "Diseases of the nervous system",
                          ICD10_a == "I" & ICD10_2 >= 60 & ICD10_2 <= 69 ~ "Cerebralvascular
disease",
                          ICD10_a == "I" ~ "Diseases of the circulatory system",
                          ICD10_a == "J" ~ "Diseases of the respiratory system",
                          ICD10_a == "K" ~ "Diseases of the digestive system",
                          ICD10_a == "L" ~ "Diseases of the skin and subcutaneous tissue",
                          ICD10_a == "M" ~ "Diseases of the musculoskeletal system and
connective tissue",
                          ICD10_a == "N" ~ "Diseases of the genitourinary system",
                          ICD10_a == "S" ~ "Injury, poisoning and certain other consequences of
external causes",
                          ICD10_a == "T" ~ "Injury, poisoning and certain other consequences of
external causes"))
```

```
df_y <- df_y %>%
  mutate(Primary_diagnosis1 = case_when(ICD10_a == "A" ~ "Other diseases",
                        ICD10_a == "C" | ICD10_a=="D"~"Cancer",
                        ICD10_a == "E" ~ "Other diseases",
                        ICD10_a == "G" ~ "Other diseases",
                        ICD10_a == "I" & ICD10_2 >= 60 & ICD10_2 <= 69 ~ "Cerebralvascular
disease",
                        ICD10_a == "I" ~ "Other diseases",
                        ICD10_a == "J" ~ "Diseases of the respiratory system",
                        ICD10_a == "K" ~ "Other diseases",
                        ICD10_a == "L" ~ "Other diseases",
                        ICD10_a == "M" ~ "Other diseases",
                        ICD10_a == "N" ~ "Other diseases",
                        ICD10_a == "S" ~ "Injury, poisoning and certain other consequences of
external causes",
                        ICD10_a == "T" ~ "Injury, poisoning and certain other consequences of
external causes"))
table(df_y$Primary_diagnosis1)
df_y$Primary_diagnosis1 <- factor(df_y$Primary_diagnosis1, levels = c("Injury, poisoning and certain
other consequences of external causes","Cerebralvascular disease","Diseases of the respiratory
system","Cancer","Other diseases"))


table(df_y$CVA)
table(df_y$CHF)
table(df_y$CKD)
table(df_y$COPD)
table(df_y$DM)
table(df_y$Cancer)
table(df_y$GeneralSarcopenia)
table(df_y$GLIMAssess)
table(df_y$Fucondition)
table(df_y$Death1)
table(df_y$TenkiduringAd, df_y$Tenki)
```

```r
df_y <- df_y %>%
  rename(Cerebrovascular_disease = CVA,
         Heart_failure = CHF,
         Diabetes_mellitus = DM,
         Chronic_kidney_disease = CKD,
         Type_cognitiveimpairement = TypeCI,
         Barthel_index_score = BI_score,
         Charlson_comorbity_index_score = CCIscore,
         Body_mass_index = BMI,
         Functional_Intake_LEVEL_ScaleatBL = FILS_atBL)
```

Check Study flow --

```r
##Study flow
#missing on outcome data(FILS, ADL, Discharge)
#FILSatFU 5.57%
#BI_scoreatFU 5.37%
#Death 94.43%
#based on rechecked row-data, there was missing data on FILS and ADL at FU when there was
death condition.
df_outcome416 <- df_participants_drug1 %>%
  mutate(TimingAtFU = case_when(Fucondition==1~"AtDischarge",
                                Fucondition==2~"3months",
                                Fucondition==3~"Death"))
##1, n=40,aged20-64
##2, n=2, outpatients
##3, n=9, missing on number of drugs used
table(df_y$Age_category, df_y$Hospital_type)

#1, aged20-64
table(df_y$Age_category)
#<65 65-74 75-84  ≧85
#40    65   160   202
df_y_eligible1 <- df_y %>%
  filter(Age_category != "<65")
```

```r
df_y_64 <- df_y %>%
  filter(Age_category == "<65")
table(df_y_64$Gender)
#Female   Male
#  12     28


#2, outpatients
table(df_y_eligible1$Hospital_type)
#Acute hospital Rehabilitation hospital Long-term care hospital Others
#180                    196                     49         2
df_y_eligible2 <- df_y_eligible1 %>%
  filter(Hospital_type != "Others")
df_y_outpatients <- df_y_eligible1 %>%
  filter(Hospital_type == "Others")
table(df_y_outpatients$Gender)
#Female   Male
#  1      1


#3, missing on number of drug usage
df_y_eligible3 <- df_y_eligible2 %>%
  filter(!is.na(NumberDrugusage))
df_y_missingNumberDrugs <- df_y_eligible2 %>%
  filter(is.na(NumberDrugusage))
table(df_y_missingNumberDrugs$Gender)

df_participants <- df_y_eligible2
#n=425, included missing of number of drugs used


table(df_participants$Polypharmacy, df_participants$Gender)
table(df_participants$Polypharmacy, df_participants$Fucondition)



# data-proccesing for drug information --------------------------------
##PIMs based BEERS 2019 and 2022
df_drug <- rdb_drug %>%
  mutate(Yjcode8 = substr(rdb_drug$druginformation, 1,8))
```

```r
df_drug <- df_drug %>%
  select(-druginformation)
df_drug <- df_drug %>%
  mutate(First_generation_antihistamines = case_when(Yjcode4 %in% c(1331,4419, 4411,4413
  ) & Yjcode7 != 4419008 ~ 1,
  Yjcode7 %in% c(1179005)~1),
  Antiparkinsonian_agents = case_when(Yjcode7 %in% c(1169001, 1169002)~1),
  Antispasmodics = case_when(Yjcode7 %in% c(1242008, 1124028, 1249351, 1242002, 1242006)~1),
  Antithrombotics =case_when(Yjcode7 %in% c(2171010)~1),
  Peripheral_alpha1_blockers = case_when(Yjcode7 %in% c(2149026, 2149002, 2149023)~1),
  Central_alpha_agonists = case_when(Yjcode7 %in% c(2149001,1179057,2145001)~1),
  Digoxin = case_when(Yjcode7 %in% c(2113003, 2113004, 2113005)~1),
  Nifedipine_immediate = case_when(Yjcode8 %in% c("2171014C", "2171014F", "2171014M") ~ 1),
  Amiodarone = case_when(Yjcode7 %in% c(2129010)~1),
  Antidepressants = case_when(Yjcode7 %in%
c(1179002,1179001,1174002,1174006,1179004,1179041)~1),
  Antipsychotics1stand2nd = case_when(Yjcode7 %in%
c(1179011,1179030,1171005,1171001,1179015,1179032,1179024,1190004,1179026,1179036,1179020,1
179006, 1172009,1172010,1172005,1179028,1172006,1172007,1172004,1172013,1179035,1172014,
1179056,1179045, 1179044, 1179042, 1179049, 1179053,1179048,1179043,1179038)~1),
  Barbiturates = case_when(Yjcode7 %in% c(1125700, 1125003, 1125004, 1139100, 1139103, 1139104,
1139105, 1239101)~1),
  Benzodiazepines = case_when(Yjcode7 %in%
c(1124023,1124001,1124022,1124007,1124028,1139003,1124015,1124017, 1124019)~1),
  Nonbenzodiazepine = case_when(Yjcode7 %in% c(1129010, 1129009)~1),
  Isoxsuprine = case_when(Yjcode7 %in% c(2172002)~1),
  Estrogens = case_when(Yjcode7 %in% c(2479004)~1),
  Sulfonylureas = case_when(Yjcode7 %in% c(3961008,3961003)~1),
  Metoclopramide = case_when(Yjcode7 %in% c(2399004)~1),
  Proton_pump_inhibitors = case_when(Yjcode7 %in%
c(2329022,2329023,2329028,2329029,2329030,3399103)~1),
  NSAIDs = case_when(Yjcode7 %in% c(3399007, 1147002, 1149032,
1149001,1149035,1149027,1149007,1149026,1149017,1149015)~1),
  Indomethacin = case_when(Yjcode7 %in% c(1145005)~1),
  Skeletal_muscle_relaxants = case_when(Yjcode7 %in% c(1225003,2419700)~1))
df_drug[is.na(df_drug)]<-0
```

```r
vis_miss(df_drug)
class(df_drug$First_generation_antihistamines)


#PID
df_patient <- df_y %>%
  select(PID)


#Drug information
First_antihistamines <- df_drug %>%
  select(PID, First_generation_antihistamines) %>%
  filter(First_generation_antihistamines==1) %>%
  distinct(PID, .keep_all=TRUE)
df_patient  <- left_join(df_patient, First_antihistamines, by="PID")


Antiparkinsonian_agents <- df_drug %>%
  filter(Antiparkinsonian_agents==1) %>%
  select(PID, Antiparkinsonian_agents) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Antiparkinsonian_agents, by="PID")


Antispasmodics <- df_drug %>%
  filter(Antispasmodics==1) %>%
  select(PID, Antispasmodics) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Antispasmodics, by="PID")


Antithrombotics <- df_drug %>%
  filter(Antithrombotics==1) %>%
  select(PID, Antithrombotics) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Antithrombotics, by="PID")


Peripheral_alpha1_blockers <- df_drug %>%
  filter(Peripheral_alpha1_blockers==1) %>%
  select(PID, Peripheral_alpha1_blockers) %>%
  distinct(PID, .keep_all=TRUE)
```

```r
df_patient <- left_join(df_patient, Peripheral_alpha1_blockers, by="PID")

Central_alpha_agonists <- df_drug %>%
  filter(Central_alpha_agonists==1) %>%
  select(PID, Central_alpha_agonists) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Central_alpha_agonists, by="PID")

Digoxin <- df_drug %>%
  filter(Digoxin==1) %>%
  select(PID, Digoxin) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Digoxin, by="PID")

Nifedipine <- df_drug %>%
  filter(Nifedipine_immediate==1) %>%
  select(PID, Nifedipine_immediate) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Nifedipine, by="PID")

Amiodarone <- df_drug %>%
  filter(Amiodarone==1) %>%
  select(PID, Amiodarone) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Amiodarone, by="PID")

Antidepressants <- df_drug %>%
  filter(Antidepressants==1) %>%
  select(PID, Antidepressants) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Antidepressants, by="PID")

Antipsychotics1stand2nd <- df_drug %>%
  filter(Antipsychotics1stand2nd==1) %>%
  select(PID, Antipsychotics1stand2nd) %>%
```

```r
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Antipsychotics1stand2nd, by="PID")


Barbiturates <- df_drug %>%
  filter(Barbiturates==1) %>%
  select(PID, Barbiturates) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Barbiturates, by="PID")v


Benzodiazepines <- df_drug %>%
  filter(Benzodiazepines==1) %>%
  select(PID, Benzodiazepines) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Benzodiazepines, by="PID")


Nonbenzodiazepine <- df_drug %>%
  filter(Nonbenzodiazepine==1) %>%
  select(PID, Nonbenzodiazepine) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Nonbenzodiazepine, by="PID")


Isoxsuprine <- df_drug %>%
  filter(Isoxsuprine==1) %>%
  select(PID, Isoxsuprine) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Isoxsuprine, by="PID")


Estrogens <- df_drug %>%
  filter(Estrogens==1) %>%
  select(PID, Estrogens) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Estrogens, by="PID")


Growth_hormone <- df_drug %>%
  filter(Growth_hormone==1) %>%
  select(PID, Growth_hormone) %>%
```

```r
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Growth_hormone, by="PID")


Sulfonylureas <- df_drug %>%
  filter(Sulfonylureas==1) %>%
  select(PID, Sulfonylureas) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Sulfonylureas, by="PID")


Metoclopramide <- df_drug %>%
  filter(Metoclopramide==1) %>%
  select(PID, Metoclopramide) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Metoclopramide, by="PID")


Proton_pump_inhibitors <- df_drug %>%
  filter(Proton_pump_inhibitors==1) %>%
  select(PID, Proton_pump_inhibitors) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Proton_pump_inhibitors, by="PID")


NSAIDs <- df_drug %>%
  filter(NSAIDs==1) %>%
  select(PID, NSAIDs) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, NSAIDs, by="PID")


Skeletal_muscle_relaxants <- df_drug %>%
  filter(Skeletal_muscle_relaxants==1) %>%
  select(PID, Skeletal_muscle_relaxants) %>%
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Skeletal_muscle_relaxants, by="PID")


Indomethacin <- df_drug %>%
  filter(Indomethacin==1) %>%
  select(PID, Indomethacin) %>%
```

```r
  distinct(PID, .keep_all=TRUE)
df_patient <- left_join(df_patient, Indomethacin, by="PID")


df_patient[is.na(df_patient)]<-0
class(df_patient$First_generation_antihistamines)
df_patient <- df_patient %>%
  rowwise() %>%
  mutate(NumberPIMs = sum(c_across(2:24)))
table(df_patient$NumberPIMs)
#  0   1   2   3   4
#203 157  93  13   1
summary(df_patient$NumberPIMs, digits = 2)
#Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
#0.00    0.00    1.00    0.83    1.00    4.00
length(df_patient$NumberPIMs)
df_patient %>%
  ggplot(aes(x=NumberPIMs))+
  geom_histogram(color="white", binwidth = 1)+
  scale_y_continuous(breaks = seq(0,200, by=20))+
  theme_bw()
hist(df_patient$NumberPIMs)
df_patient <- df_patient %>%
  select(-NumberDrugusage)


df_participants_drug <- left_join(df_participants, df_patient, by="PID")
df_participants_drug <- df_participants_drug %>%
  mutate(Primary_diagnosis1 = case_when(ICD10_a == "A" ~ "Other diseases",
                          ICD10_a == "C" | ICD10_a=="D"~"Cancer",
                          ICD10_a == "E" ~ "Other diseases",
                          ICD10_a == "G" ~ "Other diseases",
                          ICD10_a == "I" & ICD10_2 >= 60 & ICD10_2 <= 69 ~ "Cerebralvascular
disease",
                          ICD10_a == "I" ~ "Other diseases",
                          ICD10_a == "J" ~ "Diseases of the respiratory system",
                          ICD10_a == "K" ~ "Other diseases",
                          ICD10_a == "L" ~ "Other diseases",
```

```
                    ICD10_a == "M" ~ "Other diseases",

                    ICD10_a == "N" ~ "Other diseases",

                    ICD10_a == "S" ~ "Injury, poisoning and certain other consequences of

external causes",

                    ICD10_a == "T" ~ "Injury, poisoning and certain other consequences of

external causes"))

table(df_participants_drug$Primary_diagnosis1)

df_participants_drug$Primary_diagnosis1 <- factor(df_participants_drug$Primary_diagnosis1, levels =

c("Injury, poisoning and certain other consequences of external causes","Cerebralvascular

disease","Diseases of the respiratory system","Cancer","Other diseases"))




# Create table1 ---------------------------------------------------------

df_participants_drug <- df_participants_drug %>%

  filter(Fucondition!=3)

df_participants_drugviss <- df_participants_drug %>%

  select("Gender", "Age","Age_category", "Body_mass_index",

        "Charlson_comorbity_index_score",

        "CognitiveFunction", "Primary_diagnosis1",

        "GeneralSarcopenia",

        "Barthel_index_score","Barthel_index_c1",

        "NumberPIMs", NumberDrugusage,"Hospital_type")

vis_miss(df_participants_drugviss, cluster = F)

?vis_miss

glimpse(df_participants_drug)

dput(names(df_participants))

vars = c("Gender", "Age","Age_category", "Body_mass_index",

        "Charlson_comorbity_index_score",

        "CognitiveFunction", "Primary_diagnosis1",

        "GeneralSarcopenia",

        "Barthel_index_score","Barthel_index_c1",

         "NumberPIMs","Hospital_type")

factorVars =c("Gender", "Age_category",

          "CognitiveFunction", "Primary_diagnosis1",

          "GeneralSarcopenia",

          "Barthel_index_c1","NumberPIMs","Hospital_type")
```

```
table(df_participants_drug$Polypharmacy)
##Table1 作成、strate で群分け
##vars は連続、factorVars はカテゴリ
tableOne <- CreateTableOne(vars = vars,
                  factorVars =factorVars,
                  strata = c("Polypharmacy"),
                  data = df_participants_drug,
                  smd = F,
                  addOverall = T,
                  includeNA = T)
write.csv(print(tableOne, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits = 1,catDigits =
1, format = "f"), "Table1f.csv",fileEncoding = "CP932")
write.csv(print(tableOne, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits = 1,catDigits =
1, format = "p"), "Table1p.csv",fileEncoding = "CP932")
write.csv(print(tableOne, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits = 1,catDigits =
1), "Table1bi.csv",fileEncoding = "CP932")



# Describe histogram of number of drug ------------------------------------
hist(df_participants_drug1$NumberDrugusage)
table(df_participants_drug1$NumberDrugusage)
#0  1  2  3  4  5  6  7  8  9 10 11 12 13 14 15 17 19 20
#12 14 19 36 39 39 51 51 34 30 27 10  8  6  7  1  3  2  1
length(df_participants_drug1$NumberDrugusage)
summary(df_participants_drug1$NumberDrugusage, digits = 2)
#> summary(df_participants_drug1$NumberDrugusage, digits = 2)
#Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
#0.0    4.0    6.0    6.4    8.0   20.0
df_participants_drug1 %>% ggplot(aes(x=NumberDrugusage))+
  geom_histogram(binwidth = 1, color="white",alpha=1)+
  scale_x_continuous(breaks = seq(0,20,by=1))+
  scale_y_continuous(breaks = seq(0,70, by=5))+
  theme_bw()
df_participants_drug1 %>% ggplot(aes(x=NumberDrugusage))+
  geom_histogram(binwidth = 1, color="white",alpha=1)+
  scale_x_continuous(breaks = seq(0,20,by=1))+
```

```
  scale_y_continuous(breaks = seq(0,70, by=5))+
  theme_bw()


df_participants_drug1 %>% ggplot(aes(x=NumberDrugusage))+
  geom_histogram(binwidth = 1, color="white",alpha=1)+
  scale_x_continuous(breaks = seq(0,20,by=1))+
  scale_y_continuous(breaks = seq(0,70, by=5))+
  theme_bw() +
  facet_grid(Hospital_type~.)
df_participants_drug %>%
  ggplot(aes(x=NumberPIMs))+
  geom_histogram(color="white", binwidth = 1)+
  scale_y_continuous(breaks = seq(0,200, by=25))+
  theme_bw()+
  facet_grid(Hospital_type~.)
df_participants_drug1 %>%
  group_by(Hospital_type) %>%
  summarise(n=n(),
        median= median(NumberDrugusage),
        q25 = quantile(NumberDrugusage, 0.25),
        q75 = quantile(NumberDrugusage, 0.75),
        min = min(NumberDrugusage),
        max = max(NumberDrugusage))
df_participants_drug1 %>%
  group_by(Hospital_type) %>%
  summarise(n=n(),
        median= median(NumberPIMs),
        q25 = quantile(NumberPIMs, 0.25),
        q75 = quantile(NumberPIMs, 0.75),
        min = min(NumberPIMs),
        max = max(NumberPIMs))
glimpse(df_participants_drug1)
##PIMs
summary(df_df_participants_drug1$NumberPIMs, digits = 2)
#Min. 1st Qu.  Median   Mean 3rd Qu.   Max.
#0.00   0.00   1.00   0.82   1.00   3.00
```

```r
length(df_participants_drug$NumberPIMs)
#n=425
df_participants_drug %>%
  ggplot(aes(x=NumberPIMs))+
  geom_histogram(color="white", binwidth = 1)+
  scale_y_continuous(breaks = seq(0,200, by=25))+
  theme_bw()
hist(df_participants_drug$NumberPIMs)


summary(df_participants_drug$NumberPIMs, digits = 1)


# Table3 Description of drug categories of PIMs ------------------------------------------
-----------


##Describe PIMs
df_participants_drug1 <- df_participants_drug %>%
  filter(Polypharmacy!="Missing")
df_participants_drug1$Polypharmacy <- fct_drop(df_participants_drug1$Polypharmacy)
table(df_participants_drug1$Polypharmacy)
dput(names(df_participants_drug1))
vars_PIMS = c("First_generation_antihistamines",
              "Antiparkinsonian_agents", "Antispasmodics", "Antithrombotics",
              "Peripheral_alpha1_blockers", "Central_alpha_agonists",
              "Digoxin", "Amiodarone", "Antidepressants", "Antipsychotics1stand2nd",
"Nifedipine_immediate",
              "Benzodiazepines", "Nonbenzodiazepine", "Isoxsuprine", "Estrogens",
              "Growth_hormone", "Sulfonylureas", "Metoclopramide", "Proton_pump_inhibitors",
              "NSAIDs", "Skeletal_muscle_relaxants", "Indomethacin")
factorvars_PIMS = c("First_generation_antihistamines",
              "Antiparkinsonian_agents", "Antispasmodics", "Antithrombotics",
              "Peripheral_alpha1_blockers", "Central_alpha_agonists",
              "Digoxin", "Amiodarone", "Antidepressants", "Antipsychotics1stand2nd",
"Nifedipine_immediate",
              "Benzodiazepines", "Nonbenzodiazepine", "Isoxsuprine", "Estrogens",
              "Growth_hormone", "Sulfonylureas", "Metoclopramide", "Proton_pump_inhibitors",
              "NSAIDs", "Skeletal_muscle_relaxants", "Indomethacin")
```

21

```
tableOnePIMs <- CreateTableOne(vars = vars_PIMS,
                              factorVars =factorvars_PIMS,
                              strata = c("Polypharmacy"),
                              data = df_participants_drug1,
                              smd = F,
                              addOverall = T,
                              includeNA = T)
write.csv(print(tableOnePIMs, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "f"), "Table2f.csv",fileEncoding = "CP932")
write.csv(print(tableOnePIMs, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "p"), "Table2p.csv",fileEncoding = "CP932")
write.csv(print(tableOnePIMs, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1), "Table2bi.csv",fileEncoding = "CP932")



# Table3 describe outcome data ------------------------------------------
dput(names(df_participants_drug))


#check outcome data
table(df_participants$FILSatFU, df_participants$Hospital_type)
vis_miss(df_participants, cluster = T)


##FILS FU
class(df_participants_drug$Functional_Intake_LEVEL_ScaleatBL)
class(df_participants_drug$FILSatFU)
table(df_participants_drug$Functional_Intake_LEVEL_ScaleatBL,df_participants_drug$FILSatFU)
df_participants_drug <- df_participants_drug %>%
  mutate(Change_in_FILS = case_when(FILSatFU > Functional_Intake_LEVEL_ScaleatBL ~
"Improvement",
                    FILSatFU == Functional_Intake_LEVEL_ScaleatBL ~ "No improvement",
                    FILSatFU < Functional_Intake_LEVEL_ScaleatBL ~"Decline"),
      delta_FILS = FILSatFU - Functional_Intake_LEVEL_ScaleatBL)
table(df_participants_drug$Change_in_FILS)
summary(df_participants_drug$delta_FILS)
hist(df_participants_drug$delta_FILS)
```

```r
df_participants_drug$Change_in_FILS <- factor(df_participants_drug$Change_in_FILS, levels =
c("Improvement","No improvement","Decline"))


##Barthel index FU
df_participants_drug <- df_participants_drug %>%
  mutate(Change_in_BI = case_when(Biscore_atFU > Barthel_index_score ~"Improvement",
                      Biscore_atFU == Barthel_index_score ~"No improvement",
                      Biscore_atFU < Barthel_index_score ~"Decline"),
      delta_BI = Biscore_atFU - Barthel_index_score)
table(df_participants_drug$Change_in_BI)
summary(df_participants_drug$delta_BI)
df_participants_drug$Change_in_BI <- factor(df_participants_drug$Change_in_BI, levels =
c("Improvement","No improvement","Decline"))
table(df_participants_drug$Barthel_index_score, df_participants_drug$Biscore_atFU)
hist(df_participants_drug$delta_BI)
df_participants_drug %>%
  ggplot(aes(x=delta_FILS))+
  geom_histogram()+
  facet_wrap(~Polypharmacy, ncol = 1)+
  scale_x_continuous(breaks = seq(-10,10,by=1))+
  theme_bw()


df_participants_drug %>%
  ggplot(aes(x=delta_BI))+
  geom_histogram()+
  facet_wrap(~Polypharmacy, ncol = 1)+
  scale_x_continuous(breaks = seq(-100,100,by=10))+
  theme_bw()
##Discharge distination
#death data "death1"
table(df_participants_drug$Death1)


#date death "deathdate"
table(df_participants_drug$Deathdate)


#duration death-BL
```

```
table(df_participants_drug$Duration_BL_Death)

#Discharge distination
table(df_participants_drug$Tenki)

df_outcome416 <- df_participants_drug %>%
  filter(Polypharmacy!="Missing")
df_outcome416$Polypharmacy <- fct_drop(df_outcome416$Polypharmacy)
table(df_outcome416$Polypharmacy)

df_death <- df_participants_drug %>%
  filter(!is.na(Duration_BL_Death))
df_death%>%
  group_by(Polypharmacy) %>%
  summarise(median=median(Duration_BL_Death),
         min = min(Duration_BL_Death),
         Q25 = quantile(Duration_BL_Death, 0.25),
         Q75 = quantile(Duration_BL_Death, 0.75),
         max = max(Duration_BL_Death))
##death
#With polypharmacy    20
#Without polypharmacy  6

#duration death and baseline
#Polypharmacy         median   min   Q25   Q75   max
#1 With polypharmacy     39     5   19   45.8   131
#2 Without polypharmacy  45.5    24  29.5 54.8   72

table(df_outcome416$Hospital_type, df_outcome416$Death1)
#                     0 death
#Acute hospital        164  15
#Rehabilitation hospital 186   2
#Long-term care hospital  40   9
#Others                0   0

df_acute <- df_outcome416 %>%
```

```
    filter(Hospital_type=="Acute hospital")
#n=179
table(is.na(df_acute$Tenki), df_acute$Polypharmacy)

df_reha <- df_outcome416 %>%
  filter(Hospital_type=="Rehabilitation hospital")
#n=188
df_longterm <- df_outcome416 %>%
  filter(Hospital_type=="Long-term care hospital")
#n=49
table(df_longterm$Tenki)

dput(names(df_outcome416))
vars = c("Functional_Intake_LEVEL_ScaleatBL", "FILSatFU","Change_in_FILS",
"Barthel_index_score","Biscore_atFU","Change_in_BI", "Tenki","Duration_BL_FU" )
factorVars =c("Change_in_FILS","Change_in_BI", "Tenki")
##Table1 作成、strate で群分け
##vars は連続、factorVars はカテゴリ
##
#acute
tableOneOutcome <- CreateTableOne(vars = vars,
                    factorVars =factorVars,
                  strata = c("Polypharmacy"),
                  data = df_acute,
                  smd = T,
                  addOverall = T,
                  includeNA = T)

##CSV へ出力
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "f"), "Table2f_acute.csv",fileEncoding = "CP932")
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "p"), "Table2p_acute.csv",fileEncoding = "CP932")

#Reha
```

```r
tableOneOutcome <- CreateTableOne(vars = vars,
                        factorVars =factorVars,
                        strata = c("Polypharmacy"),
                        data = df_reha,
                        smd = T,
                        addOverall = T,
                        includeNA = T)
```

##CSV へ出力
```r
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "f"), "Table2f_reha.csv",fileEncoding = "CP932")
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "p"), "Table2p_reha.csv",fileEncoding = "CP932")
```

#Longterm
```r
df_long <- rawdb %>%
  select(PID, TenkiatFacilityotHome)
df_longterm <- left_join(df_longterm, df_long, by="PID")

vars = c("Functional_Intake_LEVEL_ScaleatBL", "FILSatFU","delta_FILS",
"Barthel_index_score","Biscore_atFU","delta_BI", "TenkiatFacilityotHome","Duration_BL_FU" )
factorVars =c("Change_in_FILS","Change_in_BI", "TenkiatFacilityotHome")
tableOneOutcome <- CreateTableOne(vars = vars,
                        factorVars =factorVars,
                        strata = c("Polypharmacy"),
                        data = df_longterm,
                        smd = T,
                        addOverall = T,
                        includeNA = T)
```

##CSV へ出力
```r
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "f"), "Table2f_longterm.csv",fileEncoding = "CP932")
write.csv(print(tableOneOutcome, nonnormal = T, showAllLevels = T, noSpaces = T, contDigits =
1,catDigits = 1, format = "p"), "Table2p_longterm.csv",fileEncoding = "CP932")
```

```
### Plot outcome
wilcox.test(df_outcome416$Barthel_index_score, df_outcome416$Biscore_atFU, paired = T)
df_outcome416_1 <- df_outcome416 %>%
  select(PID,Hospital_type,Polypharmacy, FILSatFU, Functional_Intake_LEVEL_ScaleatBL)
a <- df_outcome416_1 %>%
  gather(key = Times, value = FILS, Functional_Intake_LEVEL_ScaleatBL, FILSatFU)


adata <- a %>%
  group_by(Times, Polypharmacy) %>%
  summarize(score_mean=mean(FILS, na.rm=T),
          sd=sd(FILS, na.rm=T),
          length=length(FILS),
          se=sd/sqrt(length))
length(a$FILS)
a$Times <-  factor(a$Times, levels = c("Functional_Intake_LEVEL_ScaleatBL", "FILSatFU"))
a %>% ggplot(aes(x =Times, y = FILS, fill =Polypharmacy)) +
  geom_flat_violin(aes(fill =Polypharmacy),position = position_nudge(x = .1, y = 0), adjust = 1.5, trim =
FALSE, alpha = .5, colour = NA)+
  geom_point(aes(x = as.numeric(Times)-.1, y = FILS, colour =Polypharmacy),position =
position_jitter(width = .04), size = .25, shape = 20)+
  geom_boxplot(aes(x = Times, y = FILS, fill = Polypharmacy),outlier.shape = NA, alpha = .5, width = .1,
colour = "black")+
  geom_line(data = adata, aes(x = as.numeric(Times)+.1, y = score_mean, group = Polypharmacy, colour
= Polypharmacy), linetype = 3)+
  geom_point(data = adata, aes(x = as.numeric(Times)+.1, y = score_mean, group = Polypharmacy,
colour = Polypharmacy), shape = 18) +
  geom_errorbar(data = adata, aes(x = as.numeric(Times)+.1, y = score_mean,group = Polypharmacy,
colour = Polypharmacy, ymin = score_mean-se, ymax = score_mean+se), width = .05)+
  scale_color_nejm()+
  scale_fill_nejm()+
  scale_y_continuous(breaks = seq(0,10, by=1), limits = c(0,10))+
  theme_bw()


df_outcome416_2 <- df_outcome416 %>%
  select(PID,Hospital_type,Polypharmacy, Biscore_atFU, Barthel_index_score)
```

```
b <- df_outcome416_2 %>%
  gather(key = Times, value = BI, Biscore_atFU, Barthel_index_score)
bdata <- b %>%
  group_by(Times, Polypharmacy) %>%
  summarize(score_mean=mean(BI, na.rm=T),
        sd=sd(BI, na.rm=T),
        length=length(BI),
        se=sd/sqrt(length))
length(b$BI)
b$Times <-  factor(b$Times, levels = c("Barthel_index_score", "Biscore_atFU"))
b %>% ggplot(aes(x =Times, y = BI, fill =Polypharmacy)) +
  geom_flat_violin(aes(fill =Polypharmacy),position = position_nudge(x = .1, y = 0), adjust = 1.5, trim =
FALSE, alpha = .5, colour = NA)+
  geom_point(aes(x = as.numeric(Times)-.1, y = BI, colour =Polypharmacy),position =
position_jitter(width = .04), size = .25, shape = 20)+
  geom_boxplot(aes(x = Times, y = BI, fill = Polypharmacy),outlier.shape = NA, alpha = .5, width = .1,
colour = "black")+
  geom_line(data = bdata, aes(x = as.numeric(Times)+.1, y = score_mean, group = Polypharmacy, colour
= Polypharmacy), linetype = 3)+
  geom_point(data = bdata, aes(x = as.numeric(Times)+.1, y = score_mean, group = Polypharmacy,
colour = Polypharmacy), shape = 18) +
  geom_errorbar(data = bdata, aes(x = as.numeric(Times)+.1, y = score_mean,group = Polypharmacy,
colour = Polypharmacy, ymin = score_mean-se, ymax = score_mean+se), width = .05)+
  scale_color_nejm()+
  scale_fill_nejm()+
  scale_y_continuous(breaks = seq(0,100, by=10), limits = c(0,100))+
  theme_bw()


##ANOVA

#Overall
df_outcome416_1 <- df_outcome416 %>%
  select(PID,Hospital_type,Polypharmacy, FILSatFU, Functional_Intake_LEVEL_ScaleatBL)
a <- df_outcome416_1 %>%
  gather(key = Times, value = FILS, Functional_Intake_LEVEL_ScaleatBL, FILSatFU)
df_outcome416_2 <- df_outcome416 %>%
```

```
  select(PID,Hospital_type,Polypharmacy, Biscore_atFU, Barthel_index_score)
b <- df_outcome416_2 %>%
  gather(key = Times, value = BI, Biscore_atFU, Barthel_index_score)


Anova(lm(FILS ~ Polypharmacy*Times, data=a))
Anova(lm(BI ~ Polypharmacy*Times, data=b))


#Acute
table(df_outcome416$Death1)
df_outcome416_1 <- df_outcome416 %>%
  filter(Hospital_type=="Acute hospital" & Death1!=1) %>%
  select(PID,Hospital_type,Polypharmacy, FILSatFU, Functional_Intake_LEVEL_ScaleatBL)
a <- df_outcome416_1 %>%
  gather(key = Times, value = FILS, Functional_Intake_LEVEL_ScaleatBL, FILSatFU)
df_outcome416_2 <- df_outcome416 %>%
  filter(Hospital_type=="Acute hospital") %>%
  select(PID,Hospital_type,Polypharmacy, Biscore_atFU, Barthel_index_score)
b <- df_outcome416_2 %>%
  gather(key = Times, value = BI, Biscore_atFU, Barthel_index_score)


Anova(lm(FILS ~ Polypharmacy*Times, data=a))
Anova(lm(BI ~ Polypharmacy*Times, data=b))


#Reha
df_outcome416_1 <- df_outcome416 %>%
  filter(Hospital_type=="Rehabilitation hospital") %>%
  select(PID,Hospital_type,Polypharmacy, FILSatFU, Functional_Intake_LEVEL_ScaleatBL)
a <- df_outcome416_1 %>%
  gather(key = Times, value = FILS, Functional_Intake_LEVEL_ScaleatBL, FILSatFU)
df_outcome416_2 <- df_outcome416 %>%
  filter(Hospital_type=="Rehabilitation hospital") %>%
  select(PID,Hospital_type,Polypharmacy, Biscore_atFU, Barthel_index_score)
b <- df_outcome416_2 %>%
  gather(key = Times, value = BI, Biscore_atFU, Barthel_index_score)


Anova(lm(FILS ~ Polypharmacy*Times, data=a))
```

```
Anova(lm(BI ~ Polypharmacy*Times, data=b))


#Longterm
df_outcome416_1 <- df_outcome416 %>%
  filter(Hospital_type=="Long-term care hospital") %>%
  select(PID,Hospital_type,Polypharmacy, FILSatFU, Functional_Intake_LEVEL_ScaleatBL)
a <- df_outcome416_1 %>%
  gather(key = Times, value = FILS, Functional_Intake_LEVEL_ScaleatBL, FILSatFU)
df_outcome416_2 <- df_outcome416 %>%
  filter(Hospital_type=="Long-term care hospital") %>%
  select(PID,Hospital_type,Polypharmacy, Biscore_atFU, Barthel_index_score)
b <- df_outcome416_2 %>%
  gather(key = Times, value = BI, Biscore_atFU, Barthel_index_score)


Anova(lm(FILS ~ Polypharmacy*Times, data=a))
Anova(lm(BI ~ Polypharmacy*Times, data=b))




# Regression on FILS by PIMs ------------------------------------------
?glm
table_regbyPIMS <- df_participants_drug %>%
  select(FILSatFU,  Polypharmacy, Proton_pump_inhibitors, NSAIDs, Antipsychotics1stand2nd,
        Nonbenzodiazepine, Benzodiazepines) %>%
  tbl_uvregression(
    method = glm,
    y = FILSatFU,
    exponentiate = T,
    method.args = list(family=poisson("log")),
    pvalue_fun = ~style_pvalue(.x, digits = 2))
table_regbyPIMS %>%
  as_flex_table()%>%
  flextable::save_as_docx(path = "20230412univariatebyPIMs.docx")

"First_generation_antihistamines",

"Antiparkinsonian_agents", "Antispasmodics", "Antithrombotics",
```

```
"Peripheral_alpha1_blockers", "Central_alpha_agonists", "Disopyramide",
"Digoxin", "Amiodarone", "Antidepressants", "Antipsychotics1stand2nd", "Nifedipine_immediate",
"Benzodiazepines", "Nonbenzodiazepine", "Isoxsuprine", "Estrogens",
"Growth_hormone", "Sulfonylureas", "Metoclopramide", "Proton_pump_inhibitors",
"NSAIDs", "Skeletal_muscle_relaxants", "Indomethacin"
univariate <- glm(FILSatFU~NSAIDs,data=df_participants_drug, family = poisson(link = "log"))
summary(univariate)
confint(univariate)
model <- glm(trd1 ~disease+sex+agec1+comorbid_quan, df_analysis_dm1, family = binomial)
model <- model %>% tbl_regression(exponentiate = T,
                        label=list(sex ~"Sex",
                                agec1 ~ "Age category",
                                comorbid_quan ~ "CCI score category")) %>%
  add_nevent(location = "level") %>%
  add_n(location = "level")



model %>%
  as_flex_table() %>%
  flextable::save_as_docx(path = "ICUmodel.docx")



# Table4 main analysis------------------------------------------
#GLMM with robust estimation using complete case analysis on base case analysis
#polypharmacy==5
df_participants_drug1$Polypharmacy <- relevel(df_participants_drug1$Polypharmacy, ref = "Without
polypharmacy")
df_participants_drug1$GeneralSarcopenia <-
relevel(as.factor(df_participants_drug1$GeneralSarcopenia), ref = "0")
table(df_participants_drug1$GeneralSarcopenia)
df_participants_drug2 <- df_participants_drug1 %>%

select(PID,FILSatFU,Polypharmacy,Age,Gender,GeneralSarcopenia,Primary_diagnosis1,Charlson_comor
bity_index_score,Functional_Intake_LEVEL_ScaleatBL,Hospital_type)
```

31

```
model1_CCA_poly5 <- robustbase::glmrob(formula = FILSatFU ~

Polypharmacy+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL +

Hospital_type,

                        data = na.omit(df_participants_drug2),

                        family = poisson,

                        method = "Mqle")

summary(model1_CCA_poly5)

export(model1_CCA_poly5, "20230519model1poly5GLMM.xlsx")

model2_CCA_poly5 <- robustbase::glmrob(formula = FILSatFU ~

Polypharmacy+Age+Gender+Charlson_comorbity_index_score+GeneralSarcopenia+Functional_Intake_L

EVEL_ScaleatBL + Hospital_type,

                        data = na.omit(df_participants_drug2),

                        family = poisson,

                        method = "Mqle")

summary(model2_CCA_poly5)

export(model2_CCA_poly5, "20230519model2poly5GLMM.xlsx")

model3_CCA_poly5 <- robustbase::glmrob(formula = FILSatFU ~

Polypharmacy+Age+Gender+Primary_diagnosis1+Charlson_comorbity_index_score+GeneralSarcopenia+

Functional_Intake_LEVEL_ScaleatBL + Hospital_type,

                        data = na.omit(df_participants_drug2),

                        family = poisson,

                        method = "Mqle")

summary(model3_CCA_poly5)

export(model3_CCA_poly5, "20230519model3poly5GLMM.xlsx")


#polypharmacy==6

df_participants_drug6 <- df_participants_drug1 %>%


select(PID,FILSatFU,Polypharmacy6,Age,Gender,GeneralSarcopenia,Primary_diagnosis1,Charlson_como

rbity_index_score,Functional_Intake_LEVEL_ScaleatBL,Hospital_type)

table(df_participants_drug6$Polypharmacy6)

df_participants_drug6$Polypharmacy6 <- factor(df_participants_drug6$Polypharmacy6, levels =c("0-

5","≥6") )
```

```r
model1_CCA_poly6 <- robustbase::glmrob(formula = FILSatFU ~
Polypharmacy6+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL +
Hospital_type,
                          data = na.omit(df_participants_drug6),
                          family = poisson,
                          method = "Mqle")
summary(model1_CCA_poly6)
export(model1_CCA_poly6, "20230519model1poly6GLMM.xlsx")


model2_CCA_poly6 <- robustbase::glmrob(formula = FILSatFU ~
Polypharmacy6+Age+Gender+Charlson_comorbity_index_score+GeneralSarcopenia+Functional_Intake_L
EVEL_ScaleatBL + Hospital_type,
                          data = na.omit(df_participants_drug6),
                          family = poisson,
                          method = "Mqle")
summary(model2_CCA_poly6)
export(model2_CCA_poly6, "20230519model2poly6GLMM.xlsx")


model3_CCA_poly6 <- robustbase::glmrob(formula = FILSatFU ~
Polypharmacy6+Age+Gender+Primary_diagnosis1+Charlson_comorbity_index_score+GeneralSarcopenia
+Functional_Intake_LEVEL_ScaleatBL + Hospital_type,
                          data = na.omit(df_participants_drug6),
                          family = poisson,
                          method = "Mqle")
summary(model3_CCA_poly6)
export(model3_CCA_poly6, "20230519model3poly6GLMM.xlsx")


##Sensitive analysis
#Proton_pump_inhibitors
df_participants_PPI <- df_participants_drug1 %>%

select(Proton_pump_inhibitors,Age,Gender,Primary_diagnosis1,Charlson_comorbity_index_score,General
Sarcopenia, Functional_Intake_LEVEL_ScaleatBL,Hospital_type, FILSatFU)
df_participants_PPI$Proton_pump_inhibitors <- as.factor(df_participants_PPI$Proton_pump_inhibitors)
table(df_participants_PPI$Proton_pump_inhibitors)
class(df_participants_PPI$Proton_pump_inhibitors)
```

```r
model1_CCA_PPI <- robustbase::glmrob(formula = FILSatFU ~
Proton_pump_inhibitors+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_Scale
atBL + Hospital_type,
                                data = na.omit(df_participants_PPI),
                                family = poisson,
                                method = "Mqle")
export(model1_CCA_PPI, "20230519model1PPIGLMM.xlsx")



model2_CCA_PPI <- robustbase::glmrob(formula = FILSatFU ~
Proton_pump_inhibitors+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_I
ntake_LEVEL_ScaleatBL + Hospital_type,
                                data = na.omit(df_participants_PPI),
                                family = poisson,
                                method = "Mqle")
export(model2_CCA_PPI, "20230519model2PPIGLMM.xlsx")


model3_CCA_PPI <- robustbase::glmrob(formula = FILSatFU ~
Proton_pump_inhibitors+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_inde
x_score+Functional_Intake_LEVEL_ScaleatBL + Hospital_type,
                                data = na.omit(df_participants_PPI),
                                family = poisson,
                                method = "Mqle")
export(model3_CCA_PPI, "20230519model3PPIGLMM.xlsx")

#NSAIDs
df_participants_PIMs <- df_participants_drug1 %>%
  select(NSAIDs,Age,Gender,Primary_diagnosis1,Charlson_comorbity_index_score,GeneralSarcopenia,
Functional_Intake_LEVEL_ScaleatBL,Hospital_type, FILSatFU)
df_participants_PIMs$NSAIDs <- as.factor(df_participants_PIMs$NSAIDs)
table(df_participants_PIMs$NSAIDs)
model1_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
NSAIDs+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL +
Hospital_type,
                                data = na.omit(df_participants_PIMs),
                                family = poisson,
```

```
                                  method = "Mqle")
summary(model1_CCA_PIMs)
export(model1_CCA_PIMs, "20230519model1NSAIDsGLMM.xlsx")




model2_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
NSAIDs+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_Intake_LEVEL_
ScaleatBL + Hospital_type,
                            data = na.omit(df_participants_PIMs),
                            family = poisson,
                            method = "Mqle")
summary(model2_CCA_PIMs)
export(model2_CCA_PIMs, "20230519model2NSAIDsGLMM.xlsx")


model3_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
NSAIDs+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_index_score+Functi
onal_Intake_LEVEL_ScaleatBL + Hospital_type,
                            data = na.omit(df_participants_PIMs),
                            family = poisson,
                            method = "Mqle")
summary(model3_CCA_PIMs)
export(model3_CCA_PIMs, "20230519model3NSAIDsGLMM.xlsx")


#Antipsychotics1stand2nd
df_participants_PIMs <- df_participants_drug1 %>%

select(Antipsychotics1stand2nd,Age,Gender,Primary_diagnosis1,Charlson_comorbity_index_score,Gener
alSarcopenia, Functional_Intake_LEVEL_ScaleatBL,Hospital_type, FILSatFU)
df_participants_PIMs$Antipsychotics1stand2nd <-
as.factor(df_participants_PIMs$Antipsychotics1stand2nd)
table(df_participants_PIMs$Antipsychotics1stand2nd)
model1_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Antipsychotics1stand2nd+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_Sca
leatBL + Hospital_type,
                            data = na.omit(df_participants_PIMs),
                            family = poisson,
```

```
                                   method = "Mqle")
summary(model1_CCA_PIMs)
export(model1_CCA_PIMs, "20230519model1Antipsychotics1stand2ndGLMM.xlsx")



model2_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Antipsychotics1stand2nd+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Function
al_Intake_LEVEL_ScaleatBL + Hospital_type,
                        data = na.omit(df_participants_PIMs),
                        family = poisson,
                        method = "Mqle")
export(model2_CCA_PIMs, "20230519model2Antipsychotics1stand2ndGLMM.xlsx")


model3_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Antipsychotics1stand2nd+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_in
dex_score+Functional_Intake_LEVEL_ScaleatBL + Hospital_type,
                        data = na.omit(df_participants_PIMs),
                        family = poisson,
                        method = "Mqle")
summary(model3_CCA_PIMs)
export(model3_CCA_PIMs, "20230519model3Antipsychotics1stand2ndGLMM.xlsx")


#Benzodiazepines
df_participants_PIMs <- df_participants_drug1 %>%

select(Benzodiazepines,Age,Gender,Primary_diagnosis1,Charlson_comorbity_index_score,GeneralSarcop
enia, Functional_Intake_LEVEL_ScaleatBL,Hospital_type, FILSatFU)
df_participants_PIMs$Benzodiazepines <- as.factor(df_participants_PIMs$Benzodiazepines)
table(df_participants_PIMs$Benzodiazepines)
model1_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Benzodiazepines+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL +
Hospital_type,
                        data = na.omit(df_participants_PIMs),
                        family = poisson,
                        method = "Mqle")
summary(model1_CCA_PIMs)
```

```
export(model1_CCA_PIMs, "20230519model1BenzodiazepinesGLMM.xlsx")


model2_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Benzodiazepines+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_Intake_
LEVEL_ScaleatBL + Hospital_type,
                              data = na.omit(df_participants_PIMs),
                              family = poisson,
                              method = "Mqle")
export(model2_CCA_PIMs, "20230519model2BenzodiazepinesGLMM.xlsx")


model3_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Benzodiazepines+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_index_scor
e+Functional_Intake_LEVEL_ScaleatBL + Hospital_type,
                              data = na.omit(df_participants_PIMs),
                              family = poisson,
                              method = "Mqle")
export(model3_CCA_PIMs, "20230519model3BenzodiazepinesGLMM.xlsx")


#Non-Benzodiazepines
df_participants_PIMs <- df_participants_drug1 %>%

select(Nonbenzodiazepine,Age,Gender,Primary_diagnosis1,Charlson_comorbity_index_score,GeneralSar
copenia, Functional_Intake_LEVEL_ScaleatBL,Hospital_type, FILSatFU)
df_participants_PIMs$Nonbenzodiazepine <- as.factor(df_participants_PIMs$Nonbenzodiazepine)
table(df_participants_PIMs$Nonbenzodiazepine)
model1_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Nonbenzodiazepine+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatB
L + Hospital_type,
                              data = na.omit(df_participants_PIMs),
                              family = poisson,
                              method = "Mqle")
summary(model1_CCA_PIMs)
export(model1_CCA_PIMs, "20230519model1NonbenzodiazepineGLMM.xlsx")
```

```
model2_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Nonbenzodiazepine+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_Inta
ke_LEVEL_ScaleatBL + Hospital_type,
                              data = na.omit(df_participants_PIMs),
                              family = poisson,
                              method = "Mqle")
summary(model2_CCA_PIMs)
export(model2_CCA_PIMs, "20230519model2NonbenzodiazepineGLMM.xlsx")


model3_CCA_PIMs <- robustbase::glmrob(formula = FILSatFU ~
Nonbenzodiazepine+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_index_s
core+Functional_Intake_LEVEL_ScaleatBL + Hospital_type,
                              data = na.omit(df_participants_PIMs),
                              family = poisson,
                              method = "Mqle")
export(model3_CCA_PIMs, "20230519model3NonbenzodiazepineGLMM.xlsx")



#Missing value on number of drug
#Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls
#Model_1; age、gender、CCI、FILS on admission
#Model_2; model1 + sarcopanie
#Model_3; model2 + primary diagnosis at hospitalization
dput(names(df_y_miss))

df_y_miss <- df_participants_drug %>%
  select(PID, Gender, Hospital_type,Age, NumberDrugusage, Functional_Intake_LEVEL_ScaleatBL,
Charlson_comorbity_index_score, GeneralSarcopenia,Primary_diagnosis1,
FILSatFU,Proton_pump_inhibitors, NSAIDs, Antipsychotics1stand2nd,
        Nonbenzodiazepine, Benzodiazepines)
vis_miss(df_y_miss)

df_y_miss <- df_y_miss %>%
  mutate(Polypharmacy = case_when(NumberDrugusage>=5 ~ "1",
                          NumberDrugusage<5 ~ "0"))
df_y_miss <- df_y_miss %>%
```

```r
  select(-NumberDrugusage)
df_y_miss$GeneralSarcopenia <- as.character(df_y_miss$GeneralSarcopenia)
table(df_y_miss$Polypharmacy)
##0   1
#120 270
vis_miss(df_y_miss, cluster = T)
df_miced <- mice(df_y_miss,
          m = 20,
          maxit = 50,
          method = "pmm",
          seed = 1234,
          print = T)
table(df_y_miss$Polypharmacy)
##0   1
#120 270
vis_miss(df_y_miss, cluster = T)
df_miced <- mice(df_y_miss,
          m = 20,
          maxit = 50,
          method = "pmm",
          seed = 1234,
          print = T)
###exposure
#polypharmacy==5
mice::complete(df_miced, "all") %>%
  purrr::map(robustbase::glmrob,
          formula = FILSatFU ~
Polypharmacy+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL
+Hospital_type,
          family = poisson("log"),
          method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model1_MICE_GLMM_poly5.xlsx")


mice::complete(df_miced, "all") %>%
```

```r
  purrr::map(robustbase::glmrob,
          formula = FILSatFU ~
Polypharmacy+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_Intake_L
EVEL_ScaleatBL +Hospital_type,
          family = poisson("log"),
          method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model2_MICE_GLMM_poly5.xlsx")



mice::complete(df_miced, "all") %>%
  purrr::map(robustbase::glmrob,
          formula = FILSatFU ~
Polypharmacy+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_index_score+
Functional_Intake_LEVEL_ScaleatBL +Hospital_type,
          family = poisson("log"),
          method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model3_MICE_GLMM_poly5.xlsx")

##Sensitive analysis
#polypharmacy==6
df_y_miss6 <- df_participants_drug %>%
  select(PID, Gender, Hospital_type,Age, NumberDrugusage, Functional_Intake_LEVEL_ScaleatBL,
Charlson_comorbity_index_score, GeneralSarcopenia,Primary_diagnosis1,
FILSatFU,Proton_pump_inhibitors, NSAIDs, Antipsychotics1stand2nd,
        Nonbenzodiazepine, Benzodiazepines)
vis_miss(df_y_miss6)

df_y_miss6 <- df_y_miss6 %>%
  mutate(Polypharmacy6 = case_when(NumberDrugusage>=6 ~ "1",
                              NumberDrugusage<6 ~ "0"))
df_y_miss6 <- df_y_miss6 %>%
  select(-NumberDrugusage)
```

```r
df_y_miss6$GeneralSarcopenia <- as.character(df_y_miss6$GeneralSarcopenia)
mean(df_y_miss6$Polypharmacy6, na.rm = T)
##0   1
#159 231
vis_miss(df_y_miss6, cluster = T)
df_miced6 <- mice(df_y_miss6,
            m = 20,
            maxit = 50,
            method = "pmm",
            seed = 1234,
            print = T)
###exposure
mice::complete(df_miced6, "all") %>%
  purrr::map(robustbase::glmrob,
        formula = FILSatFU ~
Polypharmacy6+Age+Gender+Charlson_comorbity_index_score+Functional_Intake_LEVEL_ScaleatBL
+Hospital_type,
        family = poisson("log"),
        method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model1_MICE_GLMM_poly6.xlsx")
vignette("mice")
?pool
mice::complete(df_miced6, "all") %>%
  purrr::map(robustbase::glmrob,
        formula = FILSatFU ~
Polypharmacy6+Age+Gender+GeneralSarcopenia+Charlson_comorbity_index_score+Functional_Intake_L
EVEL_ScaleatBL +Hospital_type,
        family = poisson("log"),
        method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model2_MICE_GLMM_poly6.xlsx")
```

```
mice::complete(df_miced6, "all") %>%
  purrr::map(robustbase::glmrob,
          formula = FILSatFU ~
Polypharmacy6+Age+Gender+Primary_diagnosis1+GeneralSarcopenia+Charlson_comorbity_index_score
+Functional_Intake_LEVEL_ScaleatBL +Hospital_type,
          family = poisson("log"),
          method = "Mqle") %>%
  pool() %>%
  summary() %>%
  export("Model3_MICE_GLMM_poly6.xlsx")
```