**The effects of vaccination on the disease severity and factors for viral clearance and hospitalization in Omicron-infected patients：A retrospective observational cohort study from recent regional outbreaks in China**

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**Supplementary Methods**

**Inclusion Criteria**

All cases with positive nucleic acid testing were enrolled from the recent local SARS-CoV-2 surges from Fujian, including 3,265 cases of Omicron variant (BA.2; the Omicron group) in Quanzhou from March 13th, 2022 to May 6th, 2022 and 226 cases of Delta variant (B.1.167.2; the Delta group) in Putian from September 10 to October 20, 2021.

**Statistical analysis main script**

#####Study on Influencing Factors of Nucleic Acid Negative Time#####

###missing value interpolation

w<-read.csv("C:\\Users\\jiyue\\Desktop\\qzxg\_data\\zhuanyin\_raw.csv",head=TRUE)

str(w)

attach(w)

#install.packages("missForest")

library(missForest)

library(randomForest)

iris.imp <- missForest(w,verbose = TRUE)

#iris.imp$ximp #data after interpolation

iris.imp$OOBerror #estimate error

write.csv(iris.imp$ximp,file="C:\\Users\\jiyue\\Desktop\\qzxg\_data\\zhuanyin\_inter.csv",row.names=F,quote=F)

###linear regression

##read the interpolated dataset

dat<-read.csv("C:\\Users\\jiyue\\Desktop\\qzxg\_data\\zhuanyin\_inter.csv",header = T,

row.names = NULL)

str(dat)

##factor variable transformation

for (i in names(dat)[c(2,4:9,11,18)]){dat[,i] <- as.factor(dat[,i])}

str(dat)

##unary linear regression

t1<- lm(time~sex,data=dat)

summary(t1)

t2<- lm(time~age,data=dat)

summary(t2)

t3<- lm(time~age\_level,data=dat)

summary(t3)

t4<- lm(time~fever,data=dat)

summary(t4)

t5<- lm(time~cough,data=dat)

summary(t5)

t6<- lm(time~Basic.diseases,data=dat)

summary(t6)

t7<- lm(time~vaccination,data=dat)

summary(t7)

t8<- lm(time~class,data=dat)

summary(t8)

t9<- lm(time~IL.6,data=dat)

summary(t9)

t10<- lm(time~CRP,data=dat)

summary(t10)

t11<- lm(time~PCT,data=dat)

summary(t11)

t12<- lm(time~WBC,data=dat)

summary(t12)

t13<- lm(time~LDH,data=dat)

summary(t13)

t14<- lm(time~L,data=dat)

summary(t14)

t15<- lm(time~DDi,data=dat)

summary(t15)

t16<- lm(time~APTT,data=dat)

summary(t16)

t17<- lm(time~Special.treatment,data=dat)

summary(t17)

t18<-lm(time~ORF1lab,data=dat)

summary(t18)

t19<-lm(time~N,data=dat)

summary(t19)

##multiple linear regression

attach(dat)

str(dat)

mod1<-lm(time~sex+age+fever+cough+Basic.diseases+vaccination+class+L+Special.treatment,data=dat)

summary(mod1)

#####Comparison of clinical symptoms between Omicron and Delta#####

#install.packages("forestmodel")

#install.packages("survival")

#install.packages("dplyr")

#install.packages("forplo")

library(forestmodel)

library(survival)

library(dplyr)

library(forplo)

dat<-read.csv("C:\\Users\\jiyue\\Desktop\\qzxg\_data\\qvsp.csv",header = T,row.names = NULL)

str(dat)

dat$place<-factor(dat$place,levels=c(0,1), labels=c("Delta","Omicron"))

dat$Fever<-factor(dat$Fever,levels=c(0,1), labels=c("NO","Yes"))

dat$Nasal.congestion<-factor(dat$Nasal.congestion,levels=c(0,1), labels=c("NO","Yes"))

dat$Sore.throat<-factor(dat$Sore.throat,levels=c(0,1), labels=c("NO","Yes"))

dat$Cough<-factor(dat$Cough,levels=c(0,1), labels=c("NO","Yes"))

dat$Expectoration<-factor(dat$Expectoration,levels=c(0,1), labels=c("NO","Yes"))

dat$Fatigue<-factor(dat$Fatigue,levels=c(0,1), labels=c("NO","Yes"))

dat$Dyspnea<-factor(dat$Dyspnea,levels=c(0,1), labels=c("NO","Yes"))

dat$Diarrhea<-factor(dat$Diarrhea,levels=c(0,1), labels=c("NO","Yes"))

dat$Inappetence<-factor(dat$Inappetence,levels=c(0,1), labels=c("NO","Yes"))

dat$Emesis<-factor(dat$Emesis,levels=c(0,1), labels=c("NO","Yes"))

dat$Headache.or.Sore.muscle<-factor(dat$Headache.or.Sore.muscle,levels=c(0,1), labels=c("NO","Yes"))

str(dat)

attach(dat)

###binary logistic regression

mod1<-glm(place~.,data=dat,family="binomial")

summary(mod1)

forest\_model(mod1)

###draw forest map

forplo(mod1,

 sort=TRUE, #order by OR value

 left.align=TRUE,

 add.arrow.left=TRUE,

 add.arrow.right=TRUE,

 shade.every=1,

 ci.edge=T,

 ci.lwd = 2,

 char=20,

 col = "darkorange",

 right.bar = T,

 row.labels=c('Fever',

 'Nasal.congestion',

 'Sore.throat',

 'Cough',

 'Expectoration',

 'Fatigue','Dyspnea','Diarrhea',

 'Inappetence','Emesis',

 'Headache.or.Sore.muscle'),

 title='Logistic regression, sorted by OR',

 save = TRUE,

 save.path = "C:\\Users\\jiyue\\Desktop\\qvsp",

 save.name = "froplo",

 save.type = "png",

 save.height = 5.5,

 save.width = 7)

#####Percentage plot of stacked columnar#####

#install.packages("ggplot2")

library(ggplot2)

data<-read.csv("C:\\Users\\jiyue\\Desktop\\qzxg\_data\\type\_class.csv",header=T,

row.names = NULL)

data

##factor sort, set to the order when the table is imported

sorder1 = factor(data$type1,levels=unique(data$type1),order=TRUE)

porder1 = factor(data$class1,levels=unique(data$class1),order=TRUE)

##set font

windowsFonts(A=windowsFont("Times New Roman"),

 B=windowsFont("Arial"))

##Taking strain type as abscissa, proportion as ordinate, typing and classification, drawing stacking map

P <- ggplot(data=data,aes(x=sorder1,y=num1,fill=porder1)) +

geom\_bar(stat="identity",position="stack") +

labs(x="Variants",y="Proportion",fill="Disease severity")

P+theme(axis.text.x=element\_text(angle=0,vjust=1,hjust=0.5,family="A",face="bold",size=15))

**Figure S1.** The flow chart of the study design

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**FigureS1 in appendix：The flow chart of study design**

**NAN:nucleic acid negativization**

**Reference1：**Li H, Lin H, Chen X, et al. Unvaccinated Children Are an Important Link in the Transmission of SARS-CoV-2 Delta Variant (B1.617.2): Comparative Clinical Evidence From a Recent Community Surge. *Frontiers in cellular and infection microbiology* 2022; **12**: 814782.

**Table S1.** Test kits and apparatus used for the Omicron infection in Quanzhou surge

|  |  |  |  |
| --- | --- | --- | --- |
| **Number** | **Test Item** | **Apparatus** | **Kit** |
| 1 | Blood routine test | SYSMEX, XN-10 or XN-20, Japan | Corollary Reagent |
| 2 | Biochemistry analysis | BECKMAN, AU5800, American | Corollary Reagent |
| 3 | CRP | PUMEN ,PA990, China | Corollary Reagent |
| 4 | Humoral immunity test | BECKMAN,IMMGE800, American | Corollary Reagent |
| 5 | IL-6 | Roch,cobas8000, Switzerland | Corollary Reagent |
| 6 | Urine test | Sysmex, UF-5000, Japan | Corollary Reagent |
| 7 | Blood coagulation function | WERFEN, ACL TOP700, American | Corollary Reagent |
| 8 | Lymphocyte and subsets count | BECKMANCOULTER, NAVIOS , American | BECKMANCOULTER Multitest IMK Kit  |
| 9 | Cytokines | BECKMANCOULTER, NAVIOS , American | BECKMANCOULTER Multitest IMK Kit |
| 10 | SARS-Cov-2 RT-PCR | Nucleic Acid Extraction System：BOJIE,SHANGHAIPCR Amplifier：ABI,Q5,American | Extraction kit： BioerNucleic acid amplification Kit: Shanghai BJ |
| 11 | Microbe testing | BD,PHOENIX100, American | Corollary Reagent |

**Table S2.** Normal value of blood test results

|  |  |  |
| --- | --- | --- |
| **Number** | **Test Item** | **Normal value** |
| 1 | WBC count(10^9/l) | 3.5-9.5 |
| 2 | Lymphocyte count(10^9/l) | 1.1-3.2 |
| 3 | CRP（mg/l） | ≤8 |
| 4 | PCT（ng/l） | <0.5 |
| 5 | IL-6(pg/ml) | 0-7 |
| 6 | LDH（U/L） | 120-250 |
| 7 | APTT（s） | 24.9-37.6 |
| 8 | Ddi（mg/l） | 0-0.55 |
| 9 | SARS-Cov-2 RT-PCR | >35 |

#

**Table S3. The effects of the 7 categories of different vaccination doses and intervals on the disease severity of the Omicron group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Coefficients** | **OR（95%CI）** | **p-value** |
| **Threshold** | Asymptomatic | 0.226 | 1.254  | 0.055 |
|  | Mild | 3.185 | 24.167  | 0 |
| **Location** | No vaccination | Reference |
|  | <21 days post dose one | -0.504 | 0.604(0.054-6.753) | 0.682 |
|  | ≥21 days post dose one，but no dose two | 0.069 | 1.071(0.696-1.649) | 0.755 |
|  | <21 days post dose two | -1.728 | 0.178(0.021-1.470) | 0.109 |
|  | ≥21 days post dose two，but no dose three | -0.252 | 0.777(0.601-1.006) | 0.056 |
|  | <21 days post dose three | -0.276 | 0.759(0.517-1.113) | 0.158 |
|  | ≥21 days post dose three  | -0.481 | 0.618(0.475-0.803) | <0.001 |

Note: The effects of 7 different vaccination doses and intervals on disease severity (with “asymptomatic”, “mild” and “moderate” indicating the increasing disease severity) in the Omicron group were analyzed by multivariate ordered logistic regression.

**Table S4. The effects of the 5 categories of different vaccination doses and intervals on the disease severity of the Omicron group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Coefficients** | **OR（95%CI）** | **p-value** |
| **Threshold** | Asymptomatic | 0.24 | 1.271（1.008-1.605） | 0.043 |
|  | Mild | 3.197 | 24.459（18.047-33.149） | <0.001 |
| **Location** | No vaccination |  |  |  |
|  | <21 days post dose one | -0.49 | 0.613（0.055-6.848） | 0.691 |
|  | ≥21 days post dose one to <21 days post dose two | -0.025 | 0.975（0.638-1.492） | 0.908 |
|  | ≥21 days post dose two to <21 days post dose three | -0.235 | 0.791（0.612-1.020） | 0.071 |
|  | ≥21 days post dose three | -0.467 | 0.627（0.482-0.815） | 0.001 |

Note: The effects of 5 different vaccination doses and intervals on disease severity (with “asymptomatic”, “mild” and “moderate” indicating the increasing disease severity) in the Omicron group were analyzed by multivariate ordered logistic regression.

**Table S5.** Analysis of hospitalization risk factors in Delta infection

|  |  |  |
| --- | --- | --- |
|  | **Total regression** | **After removing insignificant variants one by one** |
| **Coefficients** | **OR(95%CI）** | **p-value** |  | **OR(95%CI）** | **p-value** |
| （Intercept) | -0.605  |  | 0.150  | -0.388  | —— | 0.159  |
| Age | 0.046  | 1.04（1.01-1.07） | 0.005 \*\* | 0.041  | 1.04（1.02-1.07） | 0.003 \*\* |
| Sex | 0.119  | 1.13（0.6-2.09） | 0.714  |  |  |  |
| Fever | 0.082  | 1.17（0.62-2.21） | 0.808  |  |  |  |
| Nasal congestion | -19.021  | —— | 0.996  |  |  |  |
| Sore throat | -19.012  | —— | 0.996  |  |  |  |
| Cough | 0.298  | 1.84（0.83-4.22） | 0.497  | 0.914  | 2.49（1.32-4.87） | 0.006 \*\* |
| Expectoration | 0.764  | 1.70（0.59-5.09） | 0.190  |  |  |  |
| Fatigue | -0.200  | 0.89（0.44-1.80） | 0.596  |  |  |  |
| Dyspnea | 15.897  | —— | 0.995  |  |  |  |
| Diarrhea | 1.369  | 2.54（0.30-54.18） | 0.287  |  |  |  |
| Inappetence | 15.727  | —— | 0.990  |  |  |  |
| Emesis | -0.554  | 1.63（0.13-38.37） | 0.729  |  |  |  |
| Headache or Sore muscle | 17.007  | —— | 0.987  |  |  |  |
| Underlying conditions | 0.450  | 1.54（0.41-7.55） | 0.611  |  |  |  |
| Vaccination |  |  |  |  |  |  |
|  One-dose | 0.710  | 2.01（0.25-42.27） | 0.552  | 0.588  | 1.80（0.23-37.58） | 0.618  |
|  Two-dose | -1.122  | 0.36（0.12-1.01） | 0.049 \* | -1.066  | 0.34（0.12，0.92） | 0.038 \* |

Note: In the Delta group, except few asymptomatic and severe cases, mild level was set as 0 and moderate level (hospitalization risk population） as 1 and a disordered multi-category logistic regression model was constructed for analysis.