

# Gender differences in patients with COVID-19: Focus on severity and mortality

Jian-Min Jin<sup>1</sup>, Peng Bai<sup>2</sup>, Wei He<sup>2</sup>, Fei Wu<sup>3</sup>, Xiao-Fang Liu<sup>2</sup>, De-Min Han<sup>2</sup>, Shi Liu<sup>3</sup>, Jin-Kui Yang<sup>2\*</sup>

<sup>1</sup>Beijing Tongren Hospital, Capital Medical University, China, <sup>2</sup>Beijing Tongren Hospital, Capital Medical University, China, <sup>3</sup>Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

### *Author contribution statement*

JMJ, PB, FG, WH, SL, FW, DMH SL and JKY collected the epidemiological and clinical data and processed statistical data. JKY drafted the manuscript. MJM, SL and JKY revised the final manuscript. JKY is responsible for summarizing all epidemiological and clinical data.

### *Keywords*

SARS-CoV-2, COVID-19, SARS, Morbidity, Mortality, gender

### *Abstract*

Word count: 204

**Objective:** The recent outbreak of Novel Coronavirus Disease (COVID-19) is reminiscent of the SARS outbreak in 2003. We aim to compare the severity and mortality between male and female patients with COVID-19 or SARS.

**Study Design and Setting:** We extracted the data from (1) a case series of 43 hospitalized patients we treated, (2) a public data set of the first 37 cases died of COVID-19 and 1019 survived patients in China, and (3) data of 524 patients with SARS, including 139 deaths, from Beijing in early 2003.

**Results:** Older age and high number of comorbidities were associated with higher severity and mortality in patients with both COVID-19 and SARS. Age was comparable between men and women in all data sets. In the case series, however, men tend to be more serious than women ( $P=0.035$ ). In the public data set, the number of men is 2.4 times that of women in the deceased group (70.3% vs. 29.7%,  $P=0.016$ ). In SARS patients, the gender role in mortality was also observed. The percentage of male were higher in the deceased group than in the survived group ( $P=0.015$ ).

**Conclusion:** Male gender is a risk factor for worse outcomes independent of age and susceptibility in patients with COVID.

### *Contribution to the field*

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In review

## **Gender differences in patients with COVID-19: Focus on severity and mortality**

Jian-Min Jin, MD, PhD<sup>1,2</sup>, Peng Bai, MD<sup>1,2</sup>, Wei He, MD<sup>3,2</sup>, Fei Wu, MD<sup>2</sup>, Xiao-Fang Liu, MD, PhD<sup>1</sup>, De-Min Han MD, PhD<sup>4</sup>, Shi Liu, MD<sup>2</sup>✉ and Jin-Kui Yang MD, PhD<sup>5</sup>✉

<sup>1</sup>Department of Respiratory and Critical Care Medicine, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

<sup>2</sup>Department of Internal Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

<sup>3</sup>Department of Critical Care Medicine, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

<sup>4</sup>Department of otolaryngology and head surgery, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China. Electronic address: [1455019296@qq.com](mailto:1455019296@qq.com)

<sup>5</sup>Department of Medicine, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China. Electronic address: [jkyang@ccmu.edu.cn](mailto:jkyang@ccmu.edu.cn)

✉Address correspondence and reprint requests to

Professor Jin-Kui YANG, Department of Medicine, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China

Tel: +86-10-58268445

Fax: +86-10-65288736

Cell: +86-13911167636

E-mail: [jkyang@ccmu.edu.cn](mailto:jkyang@ccmu.edu.cn)

or

Professor Shi Liu, Department of Internal Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

Cell: +86-13871162084

E-mail: [1455019296@qq.com](mailto:1455019296@qq.com)

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## **What is new?**

- This is the first preliminary study investigating the gender role in morbidity and mortality in patients with Novel Coronavirus Disease (COVID-19).
- Male gender is a risk factor for worse outcomes and death independent of age in patients with COVID-19.
- While males and females have the same prevalence of COVID-19, male patients have a higher mortality.

In review

## **Abstract**

**Objective:** The recent outbreak of Novel Coronavirus Disease (COVID-19) is reminiscent of the SARS outbreak in 2003. We aim to compare the severity and mortality between male and female patients with COVID-19 or SARS.

**Study Design and Setting:** We extracted the data from (1) a case series of 43 hospitalized patients we treated, (2) a public data set of the first 37 cases died of COVID-19 and 1019 survived patients in China, and (3) data of 524 patients with SARS, including 139 deaths, from Beijing in early 2003.

**Results:** Older age and high number of comorbidities were associated with higher severity and mortality in patients with both COVID-19 and SARS. Age was comparable between men and women in all data sets. In the case series, however, men tend to be more serious than women ( $P=0.035$ ). In the public data set, the number of men is 2.4 times that of women in the deceased group (70.3% vs. 29.7%,  $P=0.016$ ). In SARS patients, the gender role in mortality was also observed. The percentage of male were higher in the deceased group than in the survived group ( $P=0.015$ ).

**Conclusion:** Male gender is a risk factor for worse outcomes independent of age and susceptibility in patients with COVID.

**Keywords:** SARS-CoV-2; COVID-19; SARS; morbidity; mortality

## 1. Introduction

In early December 2019, an outbreak of a novel coronavirus disease (COVID-19) in Wuhan city and the rapidly spread throughout China has put the world on alert. High-throughput sequencing has revealed a novel  $\beta$ -coronavirus that is currently named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], which resembled severe acute respiratory syndrome coronavirus (SARS-CoV)[2]. Most patients with COVID-19 were *Mild*. *Moderate* patients often experienced dyspnea after one week. *Severe* patients progressed rapidly to *Critical* conditions including acute respiratory distress syndrome (ARDS), acute respiratory failure, coagulopathy, septic shock, and metabolic acidosis.

Early identification of risk factors for *Critical* conditions is urgently warranted not only to identify the defining clinical and epidemiological characteristics with greater precision, but also facilitated appropriate supportive care and promptly access to the intensive care unit (ICU) if necessary.

The Chinese health authority has announced that the total number of confirmed cases on the Chinese mainland has reached 76,936, and 2,442 people have died of the disease as of Feb 23. Among the 2,442 deceased patients, most were old and two-thirds were males, though the detailed data has not been reported[3]. This raises a question: Are men more susceptible to getting and dying from COVID-19?

Here, we reported the clinical characteristics of a recent case series of 43 patients we treated, a public data set of the first 37 cases died and the 1019 survived patients with COVID-19. We aimed to compare the severity and mortality in male and female patients with COVID-19, to explore the most useful prognostic factor for individualized assessment. SARS-CoV-2 infection is reminiscent of the SARS-CoV outbreak in early 2003, because both viruses attack cells via the same ACE2 receptor[3]. In this study,

we also analyzed the data of 524 SARS patients, including 139 deaths, from Beijing in early 2003.

## **2. Materials and methods**

### **2.1 Patients and data sources**

**Cases series of COVID-19:** In the case series analysis, a recent case series of 43 patients with COVID-19 was treated at Wuhan Union Hospital by the medical team of Beijing Tongren Hospital from January 29, 2020 to February 15, 2020.

**Public data set of COVID-19:** the first 37 cases died and 1019-cases of COVID-19 survivors from the public data set from the Chinese Public Health Science Data Center.

**Cases series of SARS:** This study also included data of 524 SARS patients including 139 deaths from 29 hospitals, in early 2003. These patients were hospitalized in Beijing between 25 March and 22 May 2003.

Diagnosis and clinical classification criteria and treatment plan (trial version 5) of COVID-19 was launched by the National Health Committee of the People's Republic of China (<http://www.nhc.gov.cn/>). The clinical classification of severity is as follows: (1) *Mild*, only mild symptoms, imaging shows no pneumonia. (2) *Moderate*, with fever, respiratory tract symptoms, and imaging shows pneumonia. (3) *Severe*, meet any of the following signs: a) respiratory distress, respiratory rate  $\geq 30$  beats / min; b) in the resting state, finger oxygen saturation  $\leq 93\%$  arterial blood oxygen partial pressure ( $\text{PaO}_2/\text{oxygen concentration (FiO}_2) \leq 300\text{mmHg}$  (1mmHg = 0.133kPa). (4) *Critical*, one of the following conditions: a) respiratory failure occurs and requires mechanical ventilation; b) Shock occurs; c) ICU admission is required for combined organ failure.

The study protocol was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University.

### **2.2 Statistical analysis**



Data were expressed as mean  $\pm$  SD, median (interquartile range (IQR)) or percentage, as appropriate. Compared the differences between the two groups, mean values and percentages were compared between the two groups by the Student *t*-test, Mann-Whitney U test or chi-square ( $\chi^2$ ) test. Kaplan–Meier survival curves and the log-rank test was used for testing the survival between males and females. Statistical analyses were performed using the SAS software (version 9.4).  $P < 0.05$  (two-tailed) was considered to be statistically significant.

### **3. Results**

#### **3.1 Case series of COVID-19**

The demographic and clinical characteristics are shown in [Table 1](#). The median age was 62 years (IQR, 51 to 70). Fever (95.3%) and cough (65.1%) were the most common symptoms, while diarrhea (16.3) was not common. 37.2% of patients had at least one underlying disorder (i.e., hypertension, diabetes, cardiovascular diseases and chronic lung diseases). There is no significant difference in median age between male and female groups, but the maximum of the range of IQR is lower in male (66 years in men vs. 73 years in women). Symptoms and comorbidities were comparable between men and women. As expected, men had a higher level of hemoglobin. However, male patients also had elevated serum creatinine, white blood cells and neutrophils. Among the 43-case series, 13 (30.2%) were diagnosed with *Mild* or *Moderate* pneumonia, 14 (32.6%) and 16 (37.2%) were diagnosed with *Severe* and *Critical* pneumonia, respectively. Chi-square ( $\chi^2$ ) test for trend indicated that men tend to be more serious than women ( $P=0.035$ ) according to the clinical classification of severity ([Figure 1](#)).

#### **3.2 Public data set of COVID-19**

In the deceased patients, fever (86.5%) and cough (67.6%) were common, while diarrhea was uncommon (18.9%), 64.9% had at least one underlying disorder (i.e.,

hypertension, diabetes, cardiovascular disease, or chronic obstructive pulmonary disease). The median period from symptom onset to death was 13 days (ranging from 11 to 18 days). Of these deceased patients, (Table 2).

The deceased patients were significantly older (median (IQR), 70.3 (65-81) years) and had a higher percentage of  $\geq 65$  years (83.8%), in comparison to those who survived (47 (35-57) years old and 13.2%  $\geq 65$  years). COVID-19 was diagnosed throughout the whole spectrum of age. There were 30 (2.9%) pediatric patients ( $< 14$  years) in the survived group. None of the 37 deceased cases was pediatric patient (Table 2 and Figure 2A). Ages were comparable between men and women in both deceased and survived patients (Figure 2B). Of the 37 deceased patients, 70.3% were men, 29.7% were woman. the number of men is 2.4 times that of women in the deceased patients. While men and women had the same susceptibility, men were more prone to dying ( $\chi^2$  test,  $P=0.016$ ) (Figure 2C).

### **3.3 Cases series of SARS, in 2003**

Between March 25 and May 22, 2003, a total of 524 SARS patients including 139 deaths in Beijing area reported from 29 hospitals were enrolled in our analysis. Fever (98.4%) and cough (76.9%) were the most common symptoms, while diarrhea (6.7%) was not common. 57.0% of the patients had at least one of the concomitant diseases including hypertension, diabetes, cardiovascular diseases and chronic lung diseases. The mean duration from self-reported symptom to death was 15 (IQR: 10-19) days. Table 2 summarizes the clinical and biochemical characteristics of all SARS patients. The median age of the deceased patients was much higher than that of the survived patients (57 vs. 32,  $P<0.001$ ). The rate of the concomitant diseases in the deceased patients was also higher than that of the survived patients (57.0% vs. 17.9%,  $P<0.001$ ). While the deceased patients were significantly older than the survived patients (Figure

3A), ages were comparable between men and women in both deceased and survived patients with SARS (Figure 3B). The proportion of male gender was higher in the deceased group (53.2%) than in the survived group (42.3%) ( $\chi^2$  test, P=0.027) (Figure 3C). Survival analysis showed that men had a significantly higher mortality rate than women (31.2% vs. 22.6%) in this hospital-based cohort (hazard ratio [95% CI] 1.47 [1.05-2.06], P= 0.026) (Figure 3D).

#### 4. Discussion

Coronavirus is a large family of viruses that cause illness ranging from the common cold to severe pneumonia such as SARS[2] and Middle East Respiratory Syndrome (MERS)[4]. SARS-CoV-2 was first identified in Wuhan city, China by the Chinese Center for Disease Control and Prevention (CDC)[5]. Both epidemiological[6, 7] and clinical[8, 9] features of patients with COVID-19 have recently been reported. However, few data on prognostic factors of COVID-19 have been reported.

In *Case series of COVID-19*, consistent with previous reports[9-11], older patients ( $\geq 65$  years old), were more likely to have a *Severe* type of COVID-19. Men tend to be more serious than women according to the clinical classification of severity. In *Public data set of COVID-19*, we also found that the percentage of older age ( $\geq 65$  years) was much higher in the deceased patient than in the survived patients (83.8% in 37 deceased patients vs. 13.2% in 1019 survived patients).

The number of men is 2.4 times that of women in the deceased patients. While men and women had the same susceptibility, men were more prone to dying.

This is the first preliminary study investigating the gender role in morbidity and mortality of SARS-CoV-2 infection. One study in 425 patients with COVID-19 indicated that 56% were males [6]. Another study in 140 patients found that 50.7% were males [10]. In the present study, similar susceptible to SARS-CoV-2 between males and

females was observed in 1019 survived patients (50.0% males) collected from public data set and in a case series of 43 hospitalized patient (51.2% males). Although the deceased patients were significantly older than the survived patients with COVID-19, ages were comparable between males and females in both the deceased and the survived patients. Therefore, Gender is a risk factor for higher severity and mortality in patients with COVID-19 independent of age and susceptibility. This gender factor, as well as higher incidence in men for most of the diseases, could correlate with a general demographic fact of a shorter life expectancy in men compared to women in China and in general in the world. Although there is no significant difference in median age between male and female groups, the maximum of the range of IQR is lower in male in the case series.

In early 2003, we participated in the Beijing Municipal Medical Taskforce of SARS[12]. Here, we re-analyzed the data of a large population of 520 SARS patients including 135 deaths in Beijing, and summarized the experience and lessons for present use, because SARS-CoV-2 and SARS-CoV attack cells via the same receptor, ACE2[3]. We have previously reported that high protein expression of ACE2 receptor in specific organs correlated with specific organ failures indicated by corresponding clinical parameters in SARS patients[12, 13]. It has been shown that circulating ACE2 levels are higher in men than in women and in patients with diabetes or cardiovascular diseases[14].

This study has some limitations. First, for severity analysis only a case series of 43 patients with SARS-CoV-2 were included, because detailed patient information, particularly regarding clinical outcomes was unavailable in the public data set; Second, for mortality analysis only the first 37 cases died of SARS-CoV-2 were included. Due to the urgent circumstances we are living, there was no access with enough time for a

unique, homogeneous data for COVID. It could affect the analysis and any possible bias results. However, this is the first preliminary data investigating the gender role in morbidity and mortality in patients with SARS-CoV-2. More clinical and basic research regarding gender and other prognostic factors for individualized assessment and treatment is needed in the future.

In conclusion, this is the first preliminary study investigating the gender role in morbidity and mortality in patients with COVID-19. Male gender is a risk factor for worse outcomes and death independent of age and susceptibility.

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<https://www.medrxiv.org/content/10.1101/2020.02.23.20026864v2>. (Jin et al.)[15]

### **Author Contributions**

JMJ, PB, FG, WH, SL, FW, DMH SL and JKY collected the epidemiological and clinical data and processed statistical data. JKY drafted the manuscript. MJM, SL and JKY revised the final manuscript. JKY is responsible for summarizing all epidemiological and clinical data.

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**Table 1. Characteristics of a *Case series of COVID-19*.**

	Total (n=43)	Male (n=22)	Female (n=21)	<i>P</i> - value
Age, median (range) – year	62 (51-70)	59 (51-66)	63 (52-73)	0.734
Symptoms				
Fever – n (%)	41 (95.3)	21 (95.5)	20 (95.2)	0.490
Diarrhea –n (%)	7 (16.3)	3 (13.6)	4 (19.0)	0.946
Cough – n (%)	28 (65.1)	16 (72.7)	12 (57.1)	0.452
Comorbidities –n (%)				
Hypertension –n (%)	10 (23.3)	6 (27.3)	4 (19.0)	0.782
Diabetes history –n (%)	5 (11.6)	4 (18.2)	1 (0.5)	0.370
Cardiovascular diseases –n (%)	4 (9.3)	2 (9.1)	2 (10.0)	0.634
Chronic lung diseases –n (%)	1 (0.2)	1 (0.5)	0 (0)	0.981
From symptom to diagnosis, median (range) – day	12 (8-14)	12 (7-13)	12 (10-14)	0.250
Aspartate aminotransferase – IU/l	42.4±18.9	43.0±15.3	41.7±22.6	0.872
Alanine aminotransferase – IU/l	42.8±19.0	45.0±18.0	40.4±19.5	0.590
Alkaline phosphatase – IU/l	53.4±10.6	52.6±11.9	54.3±9.0	0.736
Lactate dehydrogenase – IU/l	369.4±132.7	414.8±136.2	321.8±112.9	0.064
Serum creatinine – µmol/l	<b>75.3±21.1</b>	<b>90.4±22.2</b>	<b>59.4±10.9</b>	<b>0.000</b>
Fasting Blood Glucose – mmol/l	7.3±1.8	7.7±2.0	6.7±1.5	0.325
High sensitive C-reactive protein – mg/l	52.3±27.8	58.9±29.2	45.6±25.3	0.323
White blood cells – ×10 <sup>9</sup> /l	<b>6.8±2.2</b>	<b>7.7±2.3</b>	<b>5.8±1.5</b>	<b>0.027</b>
Hemoglobin – g/l	128.8±13.6	139.0±11.2	117.6±8.6	0.000
Platelets – ×10 <sup>9</sup> /l	225.2±57.4	230.4±54.1	219.6±60.0	0.682
Neutrophils – ×10 <sup>9</sup> /l	<b>5.4±2.2</b>	<b>6.4±2.4</b>	<b>4.3±1.3</b>	<b>0.019</b>
Lymphocytes – ×10 <sup>9</sup> /l	1.0±0.4	0.9±0.3	1.1±0.4	0.284

Data are presented as mean ± SD, medians (interquartile ranges, IQR) and no. (%).

**Table 2. Characteristics of a *Public data set of COVID-19* and a *Cases series of SARS*,  
in 2003**

	COVID-19		SARS	
	Deceased (n=37)	Survived (n=1019)	Deceased (n=139)	Survived (n=385)
Age, median (range) – year	70 (65-81) **	47 (35-57)	57 (45-69) ††	32 (24-44)
Male – n (%)	26 (70.3)*	510 (50.0)	74 (53.2)†	163 (42.3)
Symptoms				
Fever – %	32 (86.5)		136 (97.8)	379 (98.4)
Diarrhea – %	7 (18.9)		30 (21.6)	26 (6.8)
Cough – %	25 (67.6)		107 (77.0)	185 (48.1)
Comorbidities – %	24 (64.9)		79 (56.8)††	69 (17.9)
Hypertension – %	18 (48.6)		64 (46.0)††	44 (11.4)
Diabetes history – %	11(29.7)		30 (21.6)††	15 (3.9)
Cardiovascular disease – %	8 (21.6)		40 (28.8)††	23 (6.0)
Chronic lung disease – %	3 (8.1)		5 (3.6)	6 (1.6)
From onset to death, median (range) – day	13 (11-18)		15 (10-19)	

Data are presented as medians (interquartile ranges, IQR) and n (%).

\* p<0.05, \*\* p<0.01, vs. COVID-19 survived patients.

† p<0.05, †† p<0.01, vs. SARS survived patients.



## Figure legend

### **Figure 1 Trend data of clinical classification of severity in a *Case series of COVID-19*.**

Numbers of cases of men or women in different clinical classes of severity. Chi-square ( $\chi^2$ ) test for trend indicated that males tend to be more serious than females according to the clinical classification of severity including *Mild+Moderate*, *Severe* and *Critical*.

### **Figure 2 Role of age and gender in morbidity and mortality in a *Public data set of COVID-19*.**

- (A) The whole spectrum of age in deceased and survived patients with COVID.
- (B) Comparison of age between males and females in both deceased and survived patients with COVID.
- (C) Gender distribution in both deceased and survived patients with COVID.

### **Figure 3 Role of age and gender in morbidity and mortality in a *Cases series of SARS, in 2003*.**

- (A) The whole spectrum of age in deceased and survived patients with SARS.
- (B) Comparison of age between males and females in both deceased and survived patients with SARS.
- (C) Gender distribution in both deceased and survived patients with SARS.
- (D) Survival analysis comparing mortality rates between male and female patients with SARS.

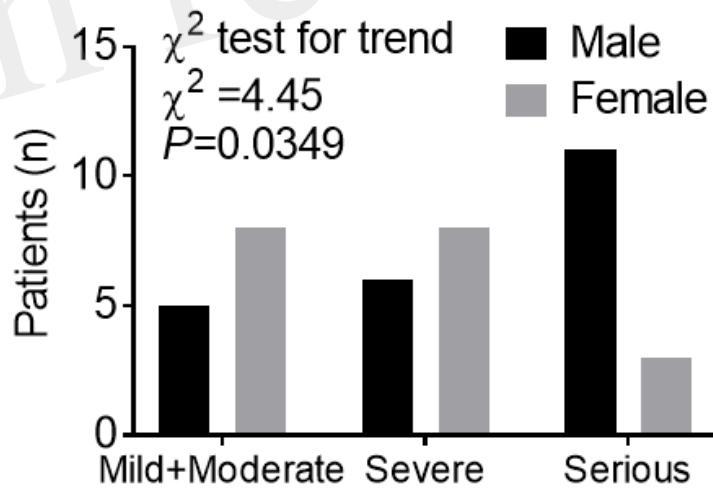


Figure 1

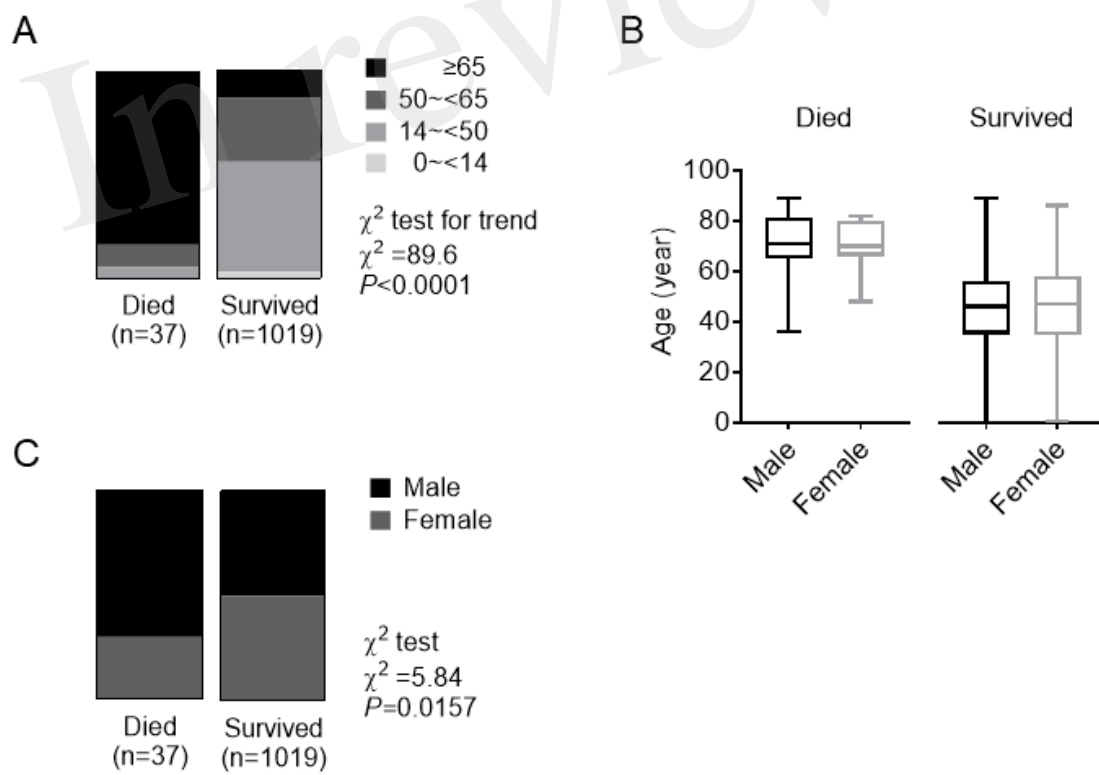


Figure 2

Figure 3

