Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China

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Brief summary

Nearly 50% patients of novel coronavirus (SARS-CoV-2)-infected pneumonia (COVID-19) could not reach obvious clinical and radiological remission within 10 days after hospitalization. These refractory COVID-19 patients showed an obvious difference with the general patients in clinical characteristics.

Abstract

Background: Since December 2019, novel coronavirus (SARS-CoV-2)-infected pneumonia (COVID-19) occurred in Wuhan, and rapidly spread throughout China. This study aimed to clarify the characteristics of patients with refractory COVID-19.

Methods: In this retrospective single-center study, we included 155 consecutive patients with confirmed COVID-19 in Zhongnan Hospital of Wuhan University from January 1st to February 5th. The cases were divided into general and refractory COVID-19 groups according to the clinical efficacy after hospitalization, and the difference between groups were compared.

Results: Compared with general COVID-19 patients (45.2%), refractory patients had an older age, male sex, more underlying comorbidities, lower incidence of fever, higher levels of maximum temperature among fever cases, higher incidence of breath shortness and anorexia, severer disease assessment on admission, high levels of neutrophil, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and C-reactive protein, lower levels of platelets and albumin, and higher incidence of bilateral pneumonia and pleural effusion (P<0.05). Refractory COVID-19 patients were more likely to receive oxygen, mechanical ventilation, expectorant, and adjunctive treatment including corticosteroid, antiviral drugs and immune enhancer (P<0.05). After adjustment, those with refractory COVID-19 were also more likely to have a male sex and manifestations of anorexia and fever on admission, and receive oxygen, expectorant and adjunctive agents (P<0.05) when considering the factors of disease severity on admission, mechanical ventilation, and ICU transfer.

Conclusion: Nearly 50% COVID-19 patients could not reach obvious clinical and radiological remission within 10 days after hospitalization. The patients with male sex, anorexia and no fever on admission predicted poor efficacy.

Key words: COVID-19; SARS-CoV-2; clinical efficacy; predictors

Introduction

Since December 2019, an outbreak of pneumonia of unknown cause occurred in Wuhan, and rapidly spread throughout China [1-3]. The pathogen was confirmed to be a distinct clade from the β-coronaviruses associated with the Middle East syndrome (MERS) and severe acute respiratory syndrome (SARS) [4, 5]. The novel virus was officially named SARS-CoV-2, with the disease termed COVID-19 [6]. Epidemiological data demonstrated person-to-person transmission in hospital and family settings [7, 8] The high infectivity of COVID-19 resulted in a rapid increase of new cases and a worldwide outbreak [9, 10].

Up to now, there found no antiviral drug with definite effects, and the main therapeutic strategy focused on symptomatic support. Partial patients showed poor treatment efficacy after hospitalization, and developed severe pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS) or multiple organ failure. At present, information regarding the clinical characteristics of refractory COVID-19 was scarce. In this study, we aimed to clarify the characteristics of patients with refractory COVID-19.

METHODS

Study design and participants

This retrospective study was approved by the ethics committee of Zhongnan Hospital of Wuhan University (No. 2020011). All consecutive patients with confirmed COVID-19 admitted to Zhongnan Hospital of Wuhan University from January 1st to February 5th were enrolled. Written or oral informed consent was obtained from patients.

Definitions

COVID-19 was confirmed by detecting SARS-CoV-2 RNA in throat swab samples using a virus nucleic acid detection kit according to the manufacturer's protocol (Shanghai BioGerm Medical Biotechnology Co.,Ltd). For hospitalized patients, general COVID-19 was defined according to following criteria: (i) obvious alleviation of respiratory symptoms (*eg.* cough, chest distress and breath shortness) after treatment; (ii) maintenance of normal body temperature for ≥3 days without the use of corticosteroid or antipyretics; (iii) improvement in radiological abnormalities on chest CT or X-ray after treatment; (iv) a hospital stay of ≤10 days. Otherwise, it was classified as refractory COVID-19. **Figure 1** showed the chest-imaging dynamics of a refractory COVID-19 patient.

In severity assessment on admission, serious illness was defined if satisfying at least one of the following items: (i) breathing rate ≥30/min; (ii) pulse oximeter oxygen saturation (SpO_2) ≤93% at rest; (iii) ration of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ≤300mmHg (1mmHg=0.133kPa). Critical illness was defined if satisfying at least one of the following items: (i) respiratory failure occurred and received mechanical ventilation; (ii) shock; (iii)

combined with failure of other organs and received care in the intensive care unit (ICU).

Data collection

A COVID-19 case report form was designed to document primary data regarding demographic, clinical, laboratory, radiological and therapeutic characteristics from electronic medical records. The following information was extracted from each patient: age, gender, medical history, COVID-19-related exposure history, symptoms, signs, severity assessment on admission, laboratory findings, chest CT or X-ray findings, and treatment like antivirus, corticosteroid and respiratory support.

Statistical analysis

Categorical data were described as percentages, and continuous data as median with interquartile range (IQR). Nonparametric comparative test for continuous data and χ^2 test for categorical data were used to compare variables between groups. $P<0.05$ was considered statistically significant. The variables identified by univariate analysis ($P<0.05$) were put into the multivariate analysis, in which these variables were adjusted by three main factors (disease severity on admission, mechanical ventilation, and ICU transfer). All statistical analyses were performed using SPSS Statistics version 21.0 software.

RESULTS

Baseline characteristics

155 patients with COVID-19 pneumonia were included in this study (**Table 1**). The median age was 54 years (IQR: 42~66), and 86 patients (55.5%) were male. 6 patients (3.9%) were current smokers, and 37 (23.9%) had a history of exposure to source transmission (Huanan seafood market or infected individuals). 71 patients (45.8%) had at least one comorbidity, including hypertension (23.9%), diabetes (9.7%) and cardiovascular diseases (9.7%). Fever (81.3%), fatigue (73.2%), cough (62.6%), and myalgia/arthralgia (61.0%) were the most common symptoms, while digestive symptoms were scare. On admission, 55 (35.5%) and 37 (23.9%) patients were categorized into serious and critical illness respectively.

After hospitalization, 70 patients (45.2%) reached obvious clinical and radiological remission within 10 days. Compared with these general COVID-19 patients, refractory patients were significantly older (P<0.001) and male dominated (P=0.011). Meanwhile, refractory patients have more underlying comorbidities (P<0.001) including diabetes (P=0.039), cardiovascular diseases (P=0.002) and cerebrovascular diseases (P=0.039), lower incidence of fever (P=0.012), higher levels of maximum temperature among fever cases (P=0.005), and higher incidence of breath shortness (P=0.009) and anorexia (P=0.005), and severer disease assessment on admission (P<0.001).

Laboratory and radiological findings

On admission, the majority of patients had lymphopenia and abnormalities of neutrophils, platelets, aspartate aminotransferase (AST), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and inflammatory biomarkers as described in

Table 2. According to CT or X-ray findings, 143 patients (92.3%) showed bilateral pneumonia, and pleural effusion occurred in 16 patients (10.3%).

Compared with general patients, refractory patients had a higher level of neutrophils (P=0.017), AST (P=0.004), LDH (P=0.017) and C-reactive protein (CRP, P=0.001), and lower level of platelets (P=0.049) and albumin (P=0.001). Moreover, refractory patients had a higher incidence of bilateral pneumonia (P=0.031) and pleural effusion (P=0.006).

Treatment

Of the 155 patients, 102 patients (65.8%) received oxygen, and 36 (23.2%) with mechanical ventilation (**Table 3**). 87 patients (56.1%) received expectorant, and 79 (51%) received intravenous corticosteroid. 45 patients (29%) received special antiviral treatment (arbidol, 20.0%; lopinavir and ritonavir, 17.4%; interferon inhalation, 19.4%). 14 patients (9%) received immune enhancing treatment (thymalfasin, 7.1%; immunoglobulin, 5.8%). The frequency of combined administration of adjunctive agents was 18.7% for corticosteroid plus antiviral drugs, 8.4% for corticosteroid plus immune enhancer, 6.5% for antiviral drugs plus immune enhancer, and 5.8% for the all.

Compared with general patients, refractory patients were more likely to receive oxygen (P<0.001), mechanical ventilation (P<0.001), expectorant (P<0.001), corticosteroid (P<0.001), lopinavir and ritonavir (P=0.008), and immune enhancer (P=0.015) especially thymalfasin (P=0.005).

Multivariate analysis of factors associated with COVID-19 refractoriness

24 significant factors in univariate analysis were put into the multivariate analysis to identify reliable predictive factor for COVID-19 refractoriness (**Table 4**). The results indicated male sex (*P*=0.047; OR: 2.206, 95% CI: 1.012-4.809) and anorexia on admission (*P*=0.030; OR: 3.921, 95% CI: 1.144-13.443) as the risk factors for disease refractoriness, and fever on admission as the protective factor (*P*=0.039; OR: 0.331, 95% CI: 0.116-0.945). Moreover, refractory patients were more likely to receive oxygen (*P*=0.020; OR: 3.065, 95% CI: 1.189-7.897), expectorant (*P*=0.016; OR: 2.688, 95% CI: 1.204-6.003), corticosteroid (*P*=0.042; OR: 2.232, 95% CI: 1.030-4.838), lopinavir and ritonavir (*P*<0.001; OR: 13.975, 95% CI: 3.274-59.655), and immune enhancer (*P*=0.009; OR: 8.959, 95% CI: 1.724-46.564).

DISCUSSION

Since the outbreak of COVID-19, the number of patients had increased dramatically, and some patients had died from the disease. It had been reported that the median hospital stay of patients with COVID-19 pneumonia was 10 days [11]. In our study, the median hospital stay for dead cases (n=22) was 10.5 days (IQR: 8~16), and 10 days (IQR: 7~15) for the recovered cases. After 10 days or longer treatment, some patients had an exacerbation in clinical symptoms or radiological findings. Therefore, clinicians should identify refractory and critical illness timely and provide early interventions, which was conducive to shorten the course of disease, prevent disease progression and reduce mortality. Up to now, large-scale analyses of clinical characteristics of refractory COVID-19 had been scarce. In this study, 155 COVID-19 patients were divided into general and refractory groups. We compared the clinical features, imaging manifestations, serological examination and the treatment between two groups.

We found that despite of a similar proportion of male and female patients in COVID-19, male patients had a higher incidence of disease refractoriness. The mean age of refractory patients was significantly older than that of general patients. In addition, 49% of patients with COVID-19 had other chronic diseases, which was consistent with recent reports [11, 12]. Thus, it could be seen that the elderly male patients with certain chronic diseases were more difficult to treat, resulting in a long hospital stay and slow recovery.

COVID-19 was similar to SARS and MERS in some clinical manifestations. In COVID-19 patients, fever, cough and myalgia were the most common symptoms, followed by chest distress and shortness of breath. However, upper respiratory tract symptoms (*eg.* nasal congestion, nasal discharge and sore throat) and gastrointestinal symptoms (*eg.* abdominal pain and diarrhea) were relatively rare. Fever occurred in 98~100% of SARS or MERS patients, compared to 81.3% COVID-19 patients in this study [13, 14]. 18.7% of patients presented no fever on admission, suggesting that the absence of fever could not rule out the possibility of COVID-19. If fever was used to trigger screening/testing for COVID-19, a substantial number of patients without fever might be missed. It was worth noting that only 74.1% of refractory patients presented fever, and it was significantly lower than general patients. These findings suggested that patients with a slow or meager response to the virus were more likely to have a severe disease.

In radiological findings, all patients in this study had abnormal chest CT results. The lung lesions were mainly manifested as ground glass-like shadows and patchy shadows on CT. Refractory patients had a higher incidence of pleural effusion than general patients, suggesting a more obviously inflammatory response in the lung. These findings also indicated that SARS-CoV-2 mainly targeted the cells in the lower respiratory tract.

In laboratory findings, 73.5% COVID-19 patients had lymphopenia, but no significant difference was detected between the groups. In refractory patients, blood LDH and CRP levels increased significantly. LDH was an inflammatory predictor in many pulmonary diseases, such as obstructive disease, microbial pulmonary disease, and interstitial pulmonary disease [15, 16]. CRP was a widely used biochemical indicator for inflammation, reflecting the acute severe systemic inflammatory response caused by viral infection. In a recent study, COVID-19 patients treated in the ICU had a higher level of LDH and CRP than those not treated in the ICU [11]. These indicated that SARS-CoV-2 might mainly act on lymphocytes, and involve in the cell-mediated immunity and cytokine storms. The immunological mechanism needed further study.

Currently, there are no data from any of the published experience that any of the antiviral agents used in this outbreak have had a significant impact on the outcome. Most patients recovered despite receiving antiviral and anti-inflammatory treatments, but it was more due to the supportive care with oxygen, fluid management, mechanical ventilation as needed, pressor support, and intensive care management. In this study, refractory patient were more likely to receive oxygen therapy, ventilator support and a variety of adjunctive agents, indicating the treatment insensitivity for these patients and resulting in a delay of the clinical course.

There were some limitations in this study. First, selection bias might occur for this retrospective study, and further prospective studies were needed. Second, this study was based on a single center, and a large-scale nationwide study was needed

In conclusion, nearly 50% COVID-19 patients could not reach obvious clinical and radiological remission within 10 days after hospitalization. The patients with anorexia and no fever on admission predicted poor efficacy.

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Conflict of Interest: None.

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Figure legends:

Figure 1. Chest computed tomographic images of a 42-year-old patient with refractory COVID-19 pneumonia. Chest computed tomographic images obtained on January 19th (D0), January 24th (D5), January 29th (D10) and February 3rd (D15). The patient reached remission at day 15.

Table legends:

Table 1. Baseline characteristics of patients with refractory COVID-19 pneumonia.

Table 2. Laboratory and radiological findings of patients with refractory COVID-19 pneumonia .

Table 3. Treatment of patients with refractory COVID-19 pneumonia .

Table 4. Multivariate analysis of factors associated with refractory COVID-19 pneumonia .

Table 1. Baseline characteristics of patients with refractory COVID-19 pneumonia.

	No. (%)			*P* value
	Total (n=155)	**General (n=70)**	**Refractory (n=85)**	
Age, median (IQR), years	54 (42-66)	46 (35-56)	61 (51-70)	<0.001
Male	86 (55.5)	31 (44.3)	55 (64.7)	0.011
Current smoking	6 (3.9)	2 (2.9)	4 (4.7)	0.861
Exposure to source transmission	37 (23.9)	16 (22.9)	21 (24.7)	0.788
Comorbidities, median (IQR), No.	0 (0-1)	0 (0-1)	1 (0-1)	<0.001
Hypertension	37 (23.9)	15 (21.4)	22 (25.9)	0.517
Diabetes	15 (9.7)	3 (4.3)	12 (14.1)	0.039
Cardiovascular diseases	15 (9.7)	0 (0)	14 (16.5)	0.002
Cerebrovascular diseases	7 (4.5)	0 (0)	7 (8.2)	0.039
Malignancy	7 (4.5)	2 (2.9)	5 (5.9)	0.607
Chronic liver diseases	7 (4.5)	2 (2.9)	5 (5.9)	0.607
Chronic renal diseases	6 (3.9)	2 (2.9)	4 (4.7)	0.861
COPD	5 (3.2)	0 (0)	4 (4.7)	0.489
Tuberculosis	3 (1.9)	0 (0)	3 (3.5)	0.317
HIV	2 (1.3)	0 (0)	2 (2.4)	0.564
Symptoms and signs	3 (2-4)	3 (2-4)	3 (2-4)	0.823
Fever	126 (81.3)	63 (90.0)	63 (74.1)	0.012
Maximum temperature, ℃	38.5 (38.0-39.0)	38.3 (38.0-39.0)	38.8 (38.1-39.2)	0.005
Cough	97 (62.6)	43 (61.4)	54 (63.5)	0.788

Chest distress	61 (39.4)	22 (31.4)	39 (45.9)	0.067
Fatigue	60 (73.2)	33 (75.0)	27 (71.1)	0.687
Breath shortness	50 (32.3)	15 (21.4)	35 (41.2)	0.009
Myalgia or arthralgia	50 (61.0)	28 (63.6)	22 (57.9)	0.595
Anorexia	26 (31.7)	8 (18.2)	18 (47.4)	0.005
Headache	8 (9.8)	3 (6.8)	5 (13.2)	0.554
Diarrhea	7 (4.5)	2 (2.9)	5 (5.9)	0.607
Abdominal pain	3 (1.9)	0 (0)	2 (2.4)	>0.999
Nausea	3 (3.7)	2 (4.5)	0 (0)	>0.999
Vomiting	3 (3.7)	0 (0)	2 (5.3)	0.897
Chest pain	3 (3.7)	2 (4.5)	0 (0)	>0.999
Dizziness	2 (2.4)	0 (0)	1 (2.6)	>0.999
Dyspnea	2 (2.4)	0 (0)	2 (5.3)	0.411
Severity assessment on admission				
Stable	63 (40.6)	43 (61.4)	20 (23.5)	
Serious	55 (35.5)	24 (34.3)	31 (36.5)	<0.001
Critical	37 (23.9)	3 (4.3)	34 (40.0)	

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; COVID-19, coronavirus disease 2019; No., number.

Table 2. Laboratory and radiological findings of patients with refractory COVID-19 pneumonia.

	Normal range	Median (IQR)			*P* value
		Total (n=155)	General (n=70)	Refractory (n=85)	
Blood routine					
White blood cell count, $\times10^9$/L	3.5-9.5	4.36 (3.30-6.03)	4.16 (3.33-5.18)	4.65 (3.14-6.84)	0.059
Neutrophil count, $\times10^9$/L	1.8-6.3	2.89 (1.97-4.41)	2.72 (1.88-3.53)	3.28 (1.99-5.08)	0.017
Lymphocyte count, $\times10^9$/L	1.1-3.2	0.90 (0.66-1.11)	0.97 (0.79-1.28)	0.80 (0.56-1.04)	0.105
Platelet count, $\times10^9$/L	125-350	170 (127-208)	179 (146-219)	159 (119-202)	0.049
Blood biochemistry					
Alanine aminotransferase, U/L	9-50	23 (16-38)	20 (15-33)	28 (17-42)	0.545
Aspartate aminotransferase, U/L	15-40	32 (24-48)	32 (23-38)	37 (25-65)	0.004
Albumin, g/L	40-55	38 (34-41)	39 (36-42)	36 (32-40)	0.001
Globulin, g/L	20-30	28 (26-31)	29 (26-32)	28 (26-31)	0.766
Creatinine, μmol/L	64-104	71 (60-87)	65 (58-78)	79 (65-96)	0.158
Lactate dehydrogenase, U/L	125-243	277 (195-404)	241 (198-338)	293 (193-434)	0.017
Creatine kinase, U/L	<171	93 (60-139)	100 (60-146)	89 (60-140)	0.560
Coagulation function					
D-dimer, ng/mL	0-500	191 (123-358)	178 (100-289)	213 (126-447)	0.288

Infection-related biomarkers					
ESR, mm/h	0-15	25 (14-47)	23 (13-41)	28 (16-51)	0.087
C-reactive protein, mg/L	0-10	33 (16-74)	23 (10-47)	46 (22-106)	0.001
Interleukin-6, pg/mL	0-7	45 (17-96)	23 (9-57)	64 (31-165)	0.260
Procalcitonin, ng/mL	<0.05	0.05 (0.05-0.09)	0.05 (0.05-0.05)	0.05 (0.05-0.19)	0.304
Co-infected respiratory pathogens	na.	12 (7.7)	3 (4.3)	9 (10.6)	0.144
Parainfluenza virus, No. (%)	na.	3 (1.9)	0 (0)	2 (2.4)	>0.999
Syncytial virus, No. (%)	na.	3 (1.9)	0 (0)	2 (2.4)	>0.999
Adenovirus, No. (%)	na.	3 (1.9)	0 (0)	3 (3.5)	0.317
Mycoplasma, No. (%)	na.	2 (1.3)	1 (1.4)	1 (1.2)	>0.999
Influenza virus A, No. (%)	na.	2 (1.3)	0 (0)	2 (2.4)	0.564
Influenza virus B, No. (%)	na.	2 (1.3)	0 (0)	2 (2.4)	0.564
Chest CT or X-ray findings					
Bilateral distribution, No. (%)	na.	143 (92.3)	61 (87.1)	82 (96.5)	0.031
Pleural effusion, No. (%)	na.	16 (10.3)	2 (2.9)	14 (16.5)	0.006

IQR, interquartile range; COVID-19, coronavirus disease 2019; ESR, erythrocyte sedimentation rate; na., not available; No., number.

Table 3. Treatment of patients with refractory COVID-19 pneumonia.

	No. (%)			*P* value
	Total (n=155)	**General (n=70)**	**Refractory (n=85)**	
Oxygen	102 (65.8)	30 (42.9)	72 (84.7)	<0.001
Mechanical ventilation	36 (23.2)	0 (0)	35 (41.2)	<0.001
Expectorant	87 (56.1)	24 (34.3)	63 (74.1)	<0.001
Corticosteroid	79 (51.0)	24 (34.3)	55 (64.7)	<0.001
Antiviral treatment	45 (29.0)	18 (25.7)	27 (31.8)	0.409
Arbidol	31 (20.0)	14 (20.0)	17 (20.0)	>0.999
Lopinavir and ritonavir	27 (17.4)	6 (8.6)	21 (24.7)	0.008
Interferon inhalation	30 (19.4)	9 (12.9)	21 (24.7)	0.063
Immune enhancer	14 (9.0)	2 (2.9)	12 (14.1)	0.015
Thymalfasin	11 (7.1)	0 (0)	11 (12.9)	0.005
Immunoglobulin	9 (5.8)	2 (2.9)	7 (8.2)	0.28

COVID-19, coronavirus disease 2019; No., number.

Table 4. Multivariate analysis of factors associated with refractory COVID-19 pneumonia.

	B	SE	Wals	*P* value	OR (95% CI)
Age	0.02	0.01	2.73	0.098	1.023 (0.996-1.052)
Male	0.79	0.40	3.96	0.047	2.206 (1.012-4.809)
Comorbidities	0.41	0.26	2.41	0.121	1.501 (0.899-2.505)
Diabetes	0.76	0.76	1.00	0.317	2.138 (0.483-9.471)
Cardiovascular diseases	2.13	1.10	3.74	0.053	8.377 (0.973-72.15)
Cerebrovascular diseases	20.21	13501.26	0.00	0.999	na.
Fever	-1.10	0.53	4.26	0.039	0.331 (0.116-0.945)
Maximum temperature	0.33	0.27	1.49	0.222	1.393 (0.818-2.371)
Breath shortness	-0.42	0.52	0.66	0.418	0.655 (0.236-1.822)
Anorexia	1.37	0.63	4.72	0.030	3.921 (1.144-13.443)
Blood test					
Neutrophils	0.05	0.09	0.28	0.595	1.051 (0.876-1.261)
Platelets	0.00	0.00	1.15	0.283	0.997 (0.992-1.002)
Aspartate aminotransferase	0.00	0.01	0.00	0.972	1.000 (0.984-1.0150)
Albumin	-0.02	0.04	0.33	0.565	0.980 (0.914-1.050)
Lactate dehydrogenase	0.00	0.00	0.95	0.331	0.998 (0.994-1.002)
C-reactive protein	0.01	0.01	2.05	0.152	1.009 (0.997-1.021)
Chest CT or X-ray					
Bilateral distribution	0.07	0.77	0.01	0.925	1.074 (0.240-4.817)
Pleural effusion	1.17	0.85	1.89	0.169	3.217 (0.607-17.036)
Treatment					
Oxygen	1.12	0.48	5.38	0.020	3.065 (1.189-7.897)

Expectorant	0.99	0.41	5.82	0.016	2.688 (1.204-6.003)
Corticosteroid	0.80	0.39	4.14	0.042	2.232 (1.030-4.838)
Lopinavir and ritonavir	2.64	0.74	12.68	<0.001	13.975 (3.274-59.655)
Immune enhancer	2.19	0.84	6.80	0.009	8.959 (1.724-46.564)
Thymalfasin	21.27	10401.18	0.00	0.998	na.

COVID-19, coronavirus disease 2019; na., not available; OR, odds ratio; CI, confidence interval.

Figure 1