Tabari Biomedical Student Research Journal

OPEN ACCESS

REVIEW: Clinical and Paraclinical Characteristics of COVID-19 patients: A Systematic Review and Meta-Analysis

Keyvan Heydari — Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
Parisa Lotfi — Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
Nima Shadmehri — Science Department, University of Tehran, Tehran, Iran.
Mohammad Yousefi — Department of Medicine, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.
Maedeh Raei — School of Medicine, Sari Branch, Islamic Azad University, Sari, Iran.
Pouya Houshmand — School of Veterinary Medicine, University of Tehran, Tehran, Iran.
Mohammad Zahedi — Department of Medical Laboratory Sciences, School of Allied Medical Science, Mazandaran University of Medical Sciences, Sari, Iran. Department of Medical Biotechnology, Student Research Committee, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran.
Reza Alizadeh-Navaei — Gastrointestinal Cancer Research Center, Non-communicable diseases institute, Mazandaran University of Medical Sciences, Sari, Iran.
Sahar Bathaeian — Influenza Research Lab, Department of Virology, Pasteur Institute of Iran, Tehran, Iran.
Sahar Rismantab — Ramsar Campus, Mazandaran University of Medical Sciences, Ramsar, Iran.

ARTICLE INFO

Submitted: 29 Sep 2021
Accepted: 05 Dec 2021
Published: 01 Mar 2022

Keywords:
Clinical Manifestation;
Coronaviridae;
COVID-19;
SARS-CoV-2

Correspondence:
Sahar Rismantab, Ramsar Campus, Mazandaran University of Medical Sciences, Ramsar, Iran.
Email: rismantab.gastroenterologist@gmail.com
ORCID: 0000-0002-0618-5347
Reza Alizadeh-Navaei, Gastrointestinal Cancer Research Center, Non-communicable diseases institute, Mazandaran University of Medical Sciences, Sari, Iran.
Email: reza_nava@yahoo.com
ORCID: 0000-0003-0580-000X

Heydari K, Lotfi P, Shadmehri N, Yousefi M, Raei M, Houshmand P, Zahedi M, Alizadeh-Navaei R, Bathaeian S, Rismantab S. Clinical and Paraclinical Characteristics of COVID-19 patients: A Systematic Review and Meta-Analysis. Tabari Biomed Stu Res J. 2022;4(1):30-47.

10.18502/tbsrj.v4i1.8772

ABSTRACT

Introduction: Recently, a new strain of coronaviruses, which originated from Wuhan City, Hubei Province, China has been identified. According to the high prevalence of new coronavirus, further investigation on the clinical and paraclinical features of this disease seems essential. Hence, we carried out this systematic review and meta-analysis to figure out the unknown features.

Material and Methods: This study was performed using databases of Web of Science, Scopus and PubMed. We considered English cross-sectional and case-series papers which reported clinical, radiological, and laboratory characteristics of patients with COVID-19. We used STATA v.11 and random effect model for data analysis.

Results: In the present meta-analysis, 32 papers including 49504 COVID-19 patients were studied. The most common clinical symptoms were fever (84%), cough (65%) and fatigue (42%), respectively. The most common radiological and paraclinical features were bilateral pneumonia (61%), ground-glass opacity (50%), thrombocytopenia (36%) and lymphocytopenia (34%). The study also showed that the frequency of comorbidities and early symptoms was higher in critically severe patients. Moreover, we found the overall mortality rate of three percent.

Conclusion: According to that there are many cases without Computed Tomography Scan findings or clear clinical symptoms, it is recommended to use other confirming methods such RNA sequencing in order to identification of suspicious undiagnosed patients. Moreover, while there is no access to clinical and paraclinical facilities in in public places such as airports and border crossings, it is recommended to consider factors such as fever, cough, sputum and fatigue.

[DOI: 10.18502/tbsrj.v4i1.8772]

Introduction

Coronavirus is a type of enveloped RNA virus with size of 60 to 140 nanometers in diameter. They have spike-like projections with a crown-like appearance under the electron microscope (1). This family of viruses, which can be divided into four type of alpha, beta, delta, and gamma, can infect multiple types of different species. For instance, they have been isolated from humans (alpha and beta), bats, Canidae, and Felidae (2, 3). Although the coronavirus family is mainly responsible for human mild respiratory diseases such as common cold, in some cases, they can cause serious illnesses (3). Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) are among epidemic diseases caused by coronaviruses in recent decades (4).

Recently, a novel strain of coronaviruses, which originated from Wuhan City, Hubei Province, China, has been identified (1). This strain (SARS-CoV-2) has been discovered in 2019 and characterized as a pandemic disease in March 2020 (5). According to World Health Organization (WHO), up to 17 March 2020, over 188,000 confirmed cases of COVID-19 had been reported throughout the world with the mortality rate of 3.4 % (6).

In a study, Sun et al. assessed the incidence of fever, cough, myalgia, fatigue and ARDS in patients with CoVID-19 (7). Given the increasing prevalence of the disease, further investigation of the clinical and paraclinical features of this disease seems necessary. In this regard, we conducted this systematic and meta-analysis review. In this study, we investigated the risk of incidence of different type of clinical finding and comorbidities in severe and non-severe patients.

Methods

Source information

This systematic review and meta-analysis has been carried out on cross-sectional and case-series studies. We searched databases of Web of Science, Scopus, and PubMed without any time limitation for publications up to March 13, 2020. As manual search, the list of imported references, list of related reviews, and the results of Google Scholar have been investigated.

Search strategy

All processes of searching, screening and reporting were done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We used following keywords in our systematic search in order to find English papers: “2019 novel coronavirus infection”, COVID19, “coronavirus disease 2019”, “coronavirus disease-19”, “2019-nCoV disease”, “2019 novel coronavirus disease”, and “2019-nCoV infection.”; all in title/abstract field.

Eligibility Criteria

We considered following criteria for study selection:

- The study should have an observatory approach investigated COVID-19 patients.
- Studies on a particular group of people (e.g. pregnant women) has been excluded.
- Studies included with desired variables such as symptoms, comorbidity, laboratory findings, etc.
- Studies should be in English. English abstracts of other language studies were investigated for eligible data.
- All the case report and animal studies were excluded.

Study Selection

Duplicated papers were deleted using EndNote software. Two researchers screened the remaining papers according to the criteria, separately. In case of disagreement between the two investigators, a third person was making the final decision.

Quality assessment

For the quality assessment, a modified version of Newcastle-Ottawa Quality Assessment (NOS) have been used. The investigated papers categorized into two

[DOI: 10.18502/tbsrj.v4i1.8772]

categories. The studies with a score of 1 or 2 as poor quality, and studies with a score of 3 to 5 as high quality.

Data Extraction

Data such as authors' information, publication year, sample size, average/median age, death rate, hospitalization status, early symptoms, laboratory findings, radiological findings and underlying diseases of patients have been extracted and recorded.

Statistical Analysis

Statistical analysis was performed using STATA v.11 software. The heterogeneity of studies has been investigated using I-square (I^2) test. Based on the results, for I^2 more than 50%, we used a random-effects model to pool the results. Moreover, to study the heterogeneity of the added study, subgroup analysis in severe and non-severe patients have been done.

Ethical approval

The proposal of this systematic review and meta-analysis has been registered in research committee of Mazandaran University of Medical Sciences (code number: 7319).

Results

Study Selection Process

The search in databases yields 351 results. After excluding duplicated papers, 364 results were admitted to the screening step. Then, 65 papers have been selected for full-text analysis. Finally, 19 studies were entered into the meta-analysis. Additionally, 13 studies obtained from manual search were included in the meta-analysis. The PRISMA flow diagram for the study selection process presented in ***Figure 1***.

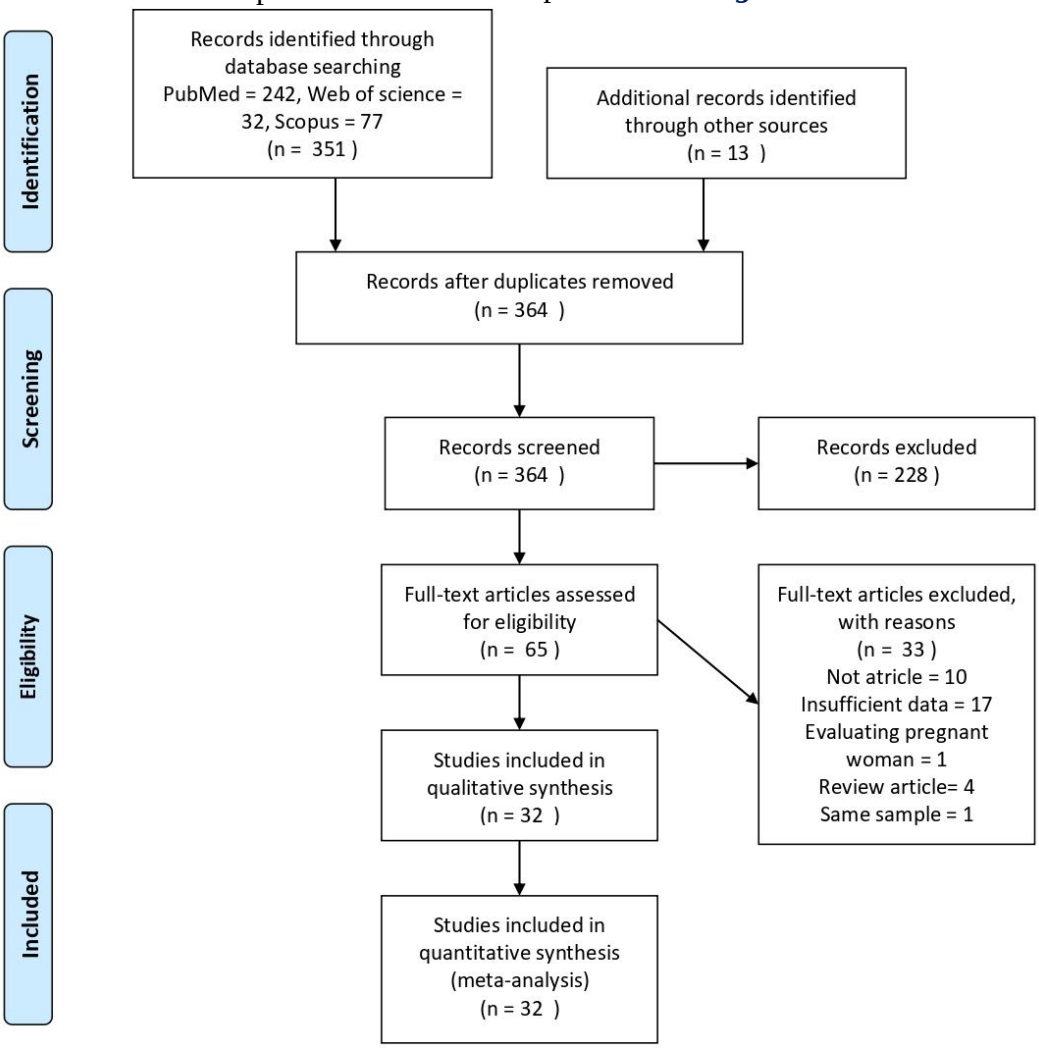

Figure 1. PRISMA flowchart for study selection process

[DOI: 10.18502/tbsrj.v4i1.8772]

Table 1. Characteristics of studies entered into the meta-analysis

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Ai (8)	China	R	1014 (467/547)	51 (15)	-	-	-	-	-	-	3
Jiehao (9)	China	CS	10 (4/6)	-	Fever, Cough, Sneezing, Nasal congestion, Rhinorrhea, Sore throat	-	-	-	-	-	3
Chen (A) (10)	China	R	99 (67/32)	55.5 (13.1)	Fever, Myalgia, Cough, Rhinorrhea, Sore throat, Shortness of breath, Confusion, Headache, Chest pain, Diarrhea, N/V	-	-	-	-	CVD, DD, ESD, MD, CNSD, RSD	4
Chen (B) (11)	China	R	29	-	Fever	-	-	-	-	-	3
Hu (12)	China	CS	24	-	-	-	-	-	-	-	3
Huang (13)	China	R	41 (30/11)	49	Fever, Myalgia, Cough, Sputum production, Dyspnea, Headache, Diarrhea	6.2 (4.1-10.5)	5 (33-8.9)	0.8 (0.6-1.1)	-	CVD, DM, HTN, DD, MD, RSD	5
Ki (14)	Korea/ China	CS	28 (15/13)	-	Fever, Myalgia, Sneezing, Sputum production, Chills, Sore throat, Headache	-	-	-	-	-	4

Table 1. Continued

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Liu (A) (15)	China	CS	12 (8/4)	-	Fever, Myalgia, Cough, Chills, Diarrhea, N/V	-	-	-	-	CVD, DM, HTN, RSD, CKD	4
Liu (B) (16)	China	CS	61 (31/30)	40*	Fever, Cough, Sputum production, Chills, Sore throat, Shortness of breath, Dyspnea, Headache, Fatigue, Chest pain, Diarrhea, Anorexia, N/V	4.3 (3.5-5.1)	2.5 (2.1-3.5)	-	164 (135.0-219.5)	CVD, DM, HTN, RSD	4
Qin (17)	China	CS	452 (235/217)	58*	Abdominal pain, Pharyngalgia, Hemoptysis, Expectoration, Fever, Myalgia, Sneezing, Dizziness, Rhinorrhea, Shortness of breath, Confusion, Headache, Fatigue, Diarrhea, Anorexia, N/V	5.3(3.9-7.5)	3.9 (2.6-5.8)	0.9 (0.6-1.2)	-	CVD, DM, CD, HTN, CLD, MD, RSD, CKD	4
Wu (A) (18)	China	R	80 (39/41)	46.1 (15.42)	Fever, Myalgia, Cough, Rhinorrhea, Sore throat, Shortness of breath, Headache, Diarrhea, N/V	4.1 (3.2-5.7)	4.3 (2.3-5.9)	0.6 (0.4-1.0)	155 (116-188)	CVD, DD, CLD, ESD, MD, CNSD,RSD, CKD	5

Table 1. Continued

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Wu (B) (19)	China	R	201 (128/73)	51*	Fever, Cough, Dyspnea, Fatigue	5.94 (3.80-9.08)	4.47 (2.32-7.70)	0.91 (0.60-1.29)	-	CVD, DM, HTN, CLD, MD, RSD, ESD	3
Zhu (20)	China	R	32 (15/16)	46*	Expectoration, Fever, Cough, Headache, Fatigue, Diarrhea	-	-	-	157.2 (83 - 284)	CVD, DM, HTN, CLD, MD, ESD, CD	4
Xie (21)	China	-	9 (4/5)	-	Fever, Cough, Fatigue, Diarrhea	-	-	-	-	-	4
Xu (22)	China	CS	62 (36/27)	-	Hemoptysis, Expectoration, Myalgia, Cough, Headache, Chest pain, Diarrhea	4.7 (3.5-5.8)	2.0 (2.0-3.7)	1.0 (0.8-1.5)	176 (135.8-215.5)	CVD, DM, HTN, CLD, RSD	5
Yu (23)	China	-	887	-	-	-	-	-	-	-	3
Guan (24)	China	R	1099 (640/459)	47*	Hemoptysis, Fever, Myalgia, Cough, Sputum production, Chills, Nasal congestion, Sore throat, Shortness of breath, Headache, Fatigue, Diarrhea, N/V	4.7 (3.5-6)	-	-	168 (132-207)	CVD, DM, CD, HTN, MD, RSD, ID, CKD	5
Bernheim (25)	China	CS	121 (61/60)	45 (15.6)	Fever, Cough, Sputum production	-	-	-	-	-	3

Table 1. Continued

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Chung (26)	China	CS	21(13/8)	51 (14.5)	Fever, Cough, Myalgia, Headache, Fatigue, N/V	-	-	1.0 (0.7-1.3)	-	-	5
Chang (27)	China	CS	13 (10/3)	34	Myalgia, Cough, Nasal congestion, Rhinorrhea, Headache, Diarrhea	5.83	3.67	-	-	-	4
Cheng (28)	China	CS	11 (8/3)	50..36 (15.5)	Fever, Cough, Myalgia, Sputum production, Sore throat, Shortness of breath, Diarrhea	4.38 (3.2–5.01)	3.13 (2.02–3.67)	1.10 (1.03–1.33)	-	-	4
Pan (A) (29)	China	R	21 (6/15)	40*	Expectoration, Fever, Myalgia, Cough, Chills, Fatigue, Chest pain, Anorexia	4.9 (3.1-6.9)	3.1 (2.1(4.6)	1.4 (0.7-2.5)	-	-	4
Pan (B) (30)	China	CS	63 (33/30)	44.9 (15.2)	-	-	-	-	-	-	4
Yang (31)	China	R	52 (35/17)	59.7 (13.3)	Fever, Myalgia, Cough, Rhinorrhea, Headache, Chest pain, N/V	-	-	-	-	DM, CD, MD, CNSD, RSD, CKD	3
China CDC (32)	China	CS	44672(22981/21691)	-	-	-	-	-	-	-	5

Table 1. Continued

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Zhang (33)	China	CS	9 (5/4)	36*	Pharyngalgia, Myalgia, Fever, Cough, , Nasal congestion, Rhinorrhea, Fatigue	-	-	-	-	-	4
Han (34)	China	CS	108 (38/70)	45*	Pharyngalgia, Fever, Myalgia, Cough, Headache, Chest pain, Fatigue, Diarrhea	-	-	-	-	-	3
Feng (35)	China	CS	15 (5/10)	-	-	-	-	-	-	-	3
Wang (A) (36)	China	CS	138 (75/63)	56*	Abdominal pain, Pharyngalgia, Expectoration, Fever, Myalgia, Cough, Dizziness, Dyspnea, Headache, Fatigue, Diarrhea, Anorexia, N/V	4.5 (3.3-6.2)	3.0 (2.0-4.9)	0.8 (0.6-1.1)	163 (123-191)	CVD, DM, CD, HTN, CLD,MD, RSD, ID, CKD	5
Wang (B) (37)	China	R	34 (14/20)	-	Pharyngalgia, Fever, Cough	3.82(2.98-5.57)	2.35(1.62-367)	1.15 (0.82 – 1.46)	171 (142 – 211)	-	4

Table 1. Continued

Author	Country	Type of study	No. of Patients	Mean Age (SD)	Clinical findings	WBC count (10^9/L)	Neutrophil count (10^9/L)	Lymphocyte count (10^9/L)	Platelet count (10^9/L)	Comorbidities	Q/A score
Wang (C) (38)	China	R	69 (32/37)	-	Pharyngalgia, Myalgia, Cough, Dizziness, Sputum production, Dyspnea, Headache, Fatigue, Diarrhea, Anorexia, N/V, Chest pain	3.82(2.98-5.57)	2.35(1.62-367)	1.15(0.82-1.46)	171 (142 - 211)	CVD, DM, HTN, CLD, MD, RSD	4
Li (39)	China	CS	17 (9/8)	45.1 (12.8)	Fever, Myalgia, Cough, Sputum production, Dizziness, Rhinorrhea, Fatigue, Diarrhea	-	-	-	-	HTN, CLD, RSD	4

*: Median

R; retrospective, CS: Case series, N/V: Nausea/vomiting, CVD: cardiovascular disease, DM: Diabetes, CD: cerebrovascular disease, HTN: hypertension, DD: digestive disease, CLD: chronic liver disease, ESD: endocrine system disease, MD: malignant disease, CNSD: Central neurons system disorder, RSD: respiratory system disease, ID: immunodeficiency, CKD: chronic kidney disease

Table 2. Summarized pooled values of considered findings

Variable	All Patients			Severe			Non-severe		
	N. of study	I-squared	ES% (95%CI)	N. of study	I-squared	ES% (95%CI)	N. of study	I-squared	ES% (95%CI)
Clinical outcomes									
Discharge	5	96.58	26 (11–41)	-	-	-	-	-	-
Death	6	77.22	3 (2–4)	-	-	-	-	-	-
Hospitalization	5	98.24	69 (49–88)	-	-	-	-	-	-
Clinical findings									
Fever	22	90.82	84 (79–88)	6	53.10	94 (90–97)	6	92.97	90 (84–96)
Cough	20	81.36	65 (59–71)	6	48.60	75 (69–82)	5	78.66	68 (60–76)
Sore throat	7	73.04	14 (8–19)	2	-	14 (9–19)	2	-	14 (12–16)
Headache	14	74.25	13 (10–16)	5	39.32	12 (8–16)	5	86.22	14 (8–20)
Myalgia	17	82.18	24 (19–29)	6	67.23	21 (14–28)	5	88.09	27 (17–36)
Diarrhea	16	90.03	9 (5–12)	4	14.77	8 (3–12)	5	73.49	9 (4–14)
Fatigue	13	88.72	42 (34–49)	6	88.70	53 (40–66)	6	86.66	44 (35–53)
Anorexia	5	89.13	24 (13–34)	4	91.54	30 (9–51)	4	78.88	17 (9–26)
Chills	5	61.50	19 (11–27)	2	-	16 (11–21)	2	-	11 (9–13)
Shortness of breath	6	97..16	27 (12–42)	3	-	39 (20–59)	3	-	19 (7–32)
Dyspnea	5	95.41	31 (14–48)	6	87.78	59 (41–76)	4	2.45	24 (19–29)
Chest pain	7	68.44	6 (2–9)	2	-	2 (-1–6)	2	-	4 (0-7)
Confusion	2	-	1 (0–2)	-	-	-	-	-	-
Nausea/ Vomiting	9	81.88	6 (3–8)	6	55.44	9 (5–13)	4	42.88	6 (4–9)
Sneezing	3	-	26 (14–39)		-	-	-	-	-
Nasal congestion	4	85.68	24 (1–48)	-	-	-	-	-	-
Rhinorrhea	7	27.70	4 (1–6)	2	-	2 (1–4)	-	-	-
Hemoptysis	3	-	2 (0–3)	3	-	3 (1–5)	3	0	1 (0–1)
Expectoration	4	85.52	39 (27–51)	2	-	39 (34–45)	2	0	36 (30–41)
Abdominal pain	2	-	4 (2–5)	2	0	7 (4–10)	2	-	6 (3–8)
Pharyngalgia	5	83.00	12 (5–19)	3	-	14 (-2–29)	3	-	8 (5–12)
Dizziness	4	00.00	8 (6–10)	3	-	12 (5–18)	3	-	5 (3–8)
Sputum production	8	78.20	27 (20–35)	4	53.39	41 (27–54)	4	0	33 (30–36)
Laboratory findings									
Leukocytosis	10	82.05	8 (4–12)						
Leukocytopenia	13	95.29	26 (17–35)	-	-	-	-	-	-
Lymphocytopenia	5	96.87	34 (12–57)	-	-	-	-	-	-
Neutrophilia	4	82.16	25 (11–39)	-	-	-	-	-	-
Thrombocytopenia	3	-	36 (30–42)	-	-	-	-	-	-
Thrombocytosis	2	-	4 (1–8)	-	-	-	-	-	-
Increase in C-Reactive Protein	8	99.34	56 (21–92)	-	-	-	-	-	-
Increase in Procalcitonin	6	58.22	5 (1–8)	-	-	-	-	-	-
Increase in D-dimer	4	92.14	14 (0–28)	-	-	-	-	-	-
Increase in ESR	5	96.60	54 (28–79)	-	-	-	-	-	-
Increase in IL-6	2	-	42 (34–50)						
Radiologic findings	5	74.69	84 (79–88)	-	-	-	-	-	-
Ground-glass opacity	11	99.52	50 (29–70)	-	-	-	-	-	-
Consolidation	7	97.29	27 (10–44)	-	-	-	-	-	-
Unilateral pneumonia	5	98.58	24 (3–44)	-	-	-	-	-	-
Bilateral pneumonia	9	99.77	61 (30–91)	-	-	-	-	-	-

[DOI: 10.18502/tbsrj.v4i1.8772]

Table 2. Continued

Variable	All Patients			Severe			Non-severe		
	N. of study	I-squared	ES% (95%CI)	N. of study	I-squared	ES% (95%CI)	N. of study	I-squared	ES% (95%CI)
Comorbidities									
Cardiovascular disease	12	92.35	10 (7–114)	5	70.43	15 (5–26)	5	66.11	4 (1–6)
Cerebrovascular disease	4	44.55	2 (1–3)	3	-	10 (0–20)	3	-	1 (1–2)
Diabetes	11	79.17	10 (7–14)	7	4.03	17 (14–21)	7	67.85	6 (4–9)
Hypertension	11	84.54	18 (13–23)	5	76.93	31 (19–44)	6	46.20	14 (11–18)
Chronic kidney disease	7	30.24	1 (1–2)	3	-	24 (-3–51)	3	-	1 (0–2)
Digestive system disease	3	-	5 (1–10)	-	-	-	-	-	-
Chronic liver disease	8	33.07	2 (1–4)	-	-	-	3	-	2 (1-4)
Endocrine system disease	3	-	6 (-1–13)	-	-	-	-	-	-
Malignancy	9	60.45	2 (1–3)	3	-	2 (0-4)	3	-	2 (0-3)
CNS disorder	4	5.30	2 (1–4)	-	-	-	-	-	-
Respiratory system disease	13	41.45	2 (1–3)	5	21.15	6 (2–10)	5	0	1 (0-1)
Immunodeficiency	2	-	0	-	-	-	-	-	-
Complications									
Acute kidney injury	3	-	2 (-1–5)	-	-	-	-	-	-
Acute respiratory distress syndrome	4	91.70	21 (6–35)	-	-	-	-	-	-

Study Characteristics

Out of selected papers, a total of 49504 patients infected with CoVID-19 with age ranged between 40 to 58 years old were included in our investigation. All of the papers were conducted in China and only one study was a collaboration between China and South Korea. Characteristics of studies entered into meta-analysis are presented in ***Table 1***.

Quality Assessment

According to quality assessment using NOS tool, all of the studies categorized as high quality. The quality assessment graph is presented in ***Figure 2*** and ***Supplementary Figure 1***.

Characteristics of Patients

Regarding hospitalization, our findings showed that 69% of the patients need to be hospitalized. About 26% of patients were discharged after receiving outpatient treatment and only 3% of patients have been expired (***Figure 3***).

Clinical Findings

Patients with COVID-19 referred to the hospital with variety symptoms. Fever, cough, and sour throat are among the most common symptoms of the patients, which were reported respectively in 22, 20, and 7 studies. Meta-analysis findings are as follows respectively: 84% (95% CI, 79-88), 65% (95% CI, 59-71), and 14% (95% CI 8-19) (***Figure 4*** and ***5***).

Headache, myalgia, diarrhea, and fatigue were reported in 14, 17, 16, and 13 studies with the risk of 13% (95% CI, 8-19), 24% (95% CI 19-29), 9% (95% CI, 5-12), and 42% (95% CI, 34-49) (***Figure 6*** and ***Supplementary File***). Anorexia, Chills, Shortness of breath, dyspnea, chest pain, confusion, and nausea/vomiting were reported in respectively 5, 5, 6, 5, 7, 2, and 9 studies. Overall prevalence of these symptoms was 24% (95% CI, 13-34), 19% (95% CI, 11-27), 27% (95% CI, 12-42), 31% (95% CI, 14-48), 6% (95% CI, 2-9), 1% (95% CI, 0-2) and 6% (95% CI, 3-8) (***Supplementary File and Table 2***).

[DOI: 10.18502/tbsrj.v4i1.8772]

In addition, sneezing, nasal congestion, rhinorrhea, hemoptysis, and expectoration were reported in 3, 4, 7, 3, and 4 studies, respectively. Pooling results were 26% (95% CI, 14-39), 24% (95% CI, 1-48), 4% (95% CI 1-6), 2% (95% CI, 0-3), and 39% (95% CI, 27-51) (***Supplementary File and Table 2***).
Abdominal pain, pharyngula, dizziness, and sputum production have been reported in 2, 5, 4, 8 studies, respectively. Meta-analysis findings were 4% (95% CI 2 – 5), 12% (95% CI 5 – 19), 8% (95% CI 6 – 10), and 27% (95% CI 20 – 35) (***Supplementary File and Table 2***).

Laboratory Findings

Many studies have investigated the laboratory findings of the patients. Most common observing in these patients were leukocytopenia (26%, 95% CI 17 – 35), neutrophilia (25%, 95% CI 11 – 39), thrombocytopenia (36%, 95% CI 30- 42) and lymphocytopenia (34%, 95% CI 12 – 57) by following thrombocytosis (4%, 95% CI 1 – 8), increased C-reactive protein (CRP) (56%, 95% CI 21 – 92), procalcitonin (5%, 95% CI 1 – 8), IL-6 (42%, 95% CI 34 – 50), D-dimer (14%, 95% CI 0 – 28), and Erythrocyte sedimentation rate (ESR) (54%, 95%CI 28 – 79) (***Figure 7*** and ***8***).

Radiological Findings

Regarding radiological findings, 84% (95% CI 79 – 88) of patients who underwent a Computed tomography (CT) scan were positive for pneumonia. The most common radiological findings in these patients were Ground-glass opacity (50%, 95% CI 29 – 70), consolidation (27%, 95% CI 10 – 44), unilateral pneumonia (24%, 95% CI 3 – 44), and bilateral pneumonia (61%, 95% CI 30 – 91) (***Supplementary File*** and ***Table 2***).

Comorbidities

Different studies investigated the underlying diseases in patients with COVID-19. The cardiovascular disease, diabetes, and cerebrovascular disease were reported in 12, 11, and 4 original studies, respectively. In this regard, pooling of the results was 10% (95% CI 7 – 114), 10% (95% CI 7 – 14), and 2% (95% CI 1 – 3), respectively. Also, other underlying diseases like hypertension and chronic kidney disease were investigated in 11 and 7 studies. The general outbreak of these disorders was 18% (95% CI 13 – 23) and 1% (95% CI 1 – 2) respectively (***Supplementary File*** and ***Table 2***).
Other disorders prevalence was as follows: digestive tract (5%, 95% CI 1 – 10), chronic liver disease (2%, 95% CI 1 – 4), endocrine disease (6%, 95% CI -1 – 13), malignancies (2%, 95% CI 1 – 3), central nervous system (2%, 95% CI 1 – 4), respiratory system (2%, 95% 1 – 3) and immunodeficiency (0%) (***Supplementary File*** and ***Table 2***).
The acute respiratory distress syndrome and acute kidney injury after infecting with COVID-19 have been investigated in 4 and 3 studies, respectively. Meta-analysis showed the prevalence of 21% (95% CI 6 – 35) and 2% (95% CI -1-5) respectively (***Supplementary File Table 2***).

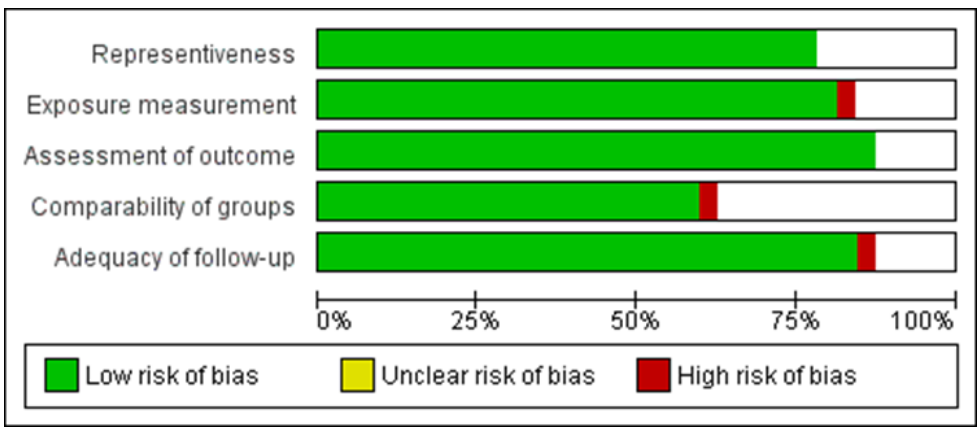

Figure 2. Risk of bias summary (A)

[DOI: 10.18502/tbsrj.v4i1.8772]

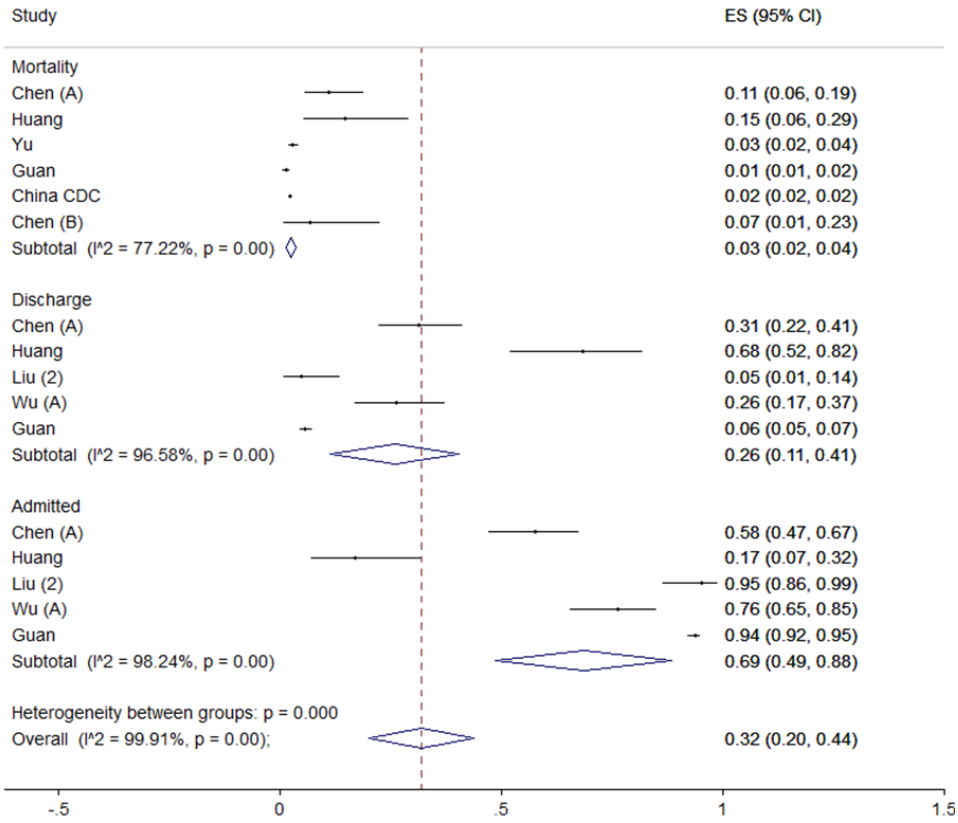

Figure 3. Meta-analysis of incidence of clinical outcome of patients

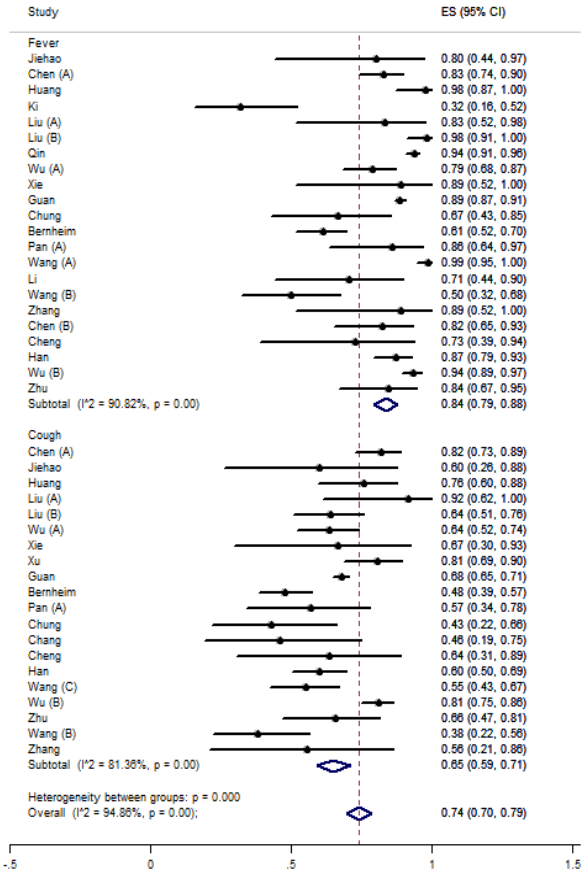

Figure 4. Meta-analysis of incidence of clinical findings of patients (A)

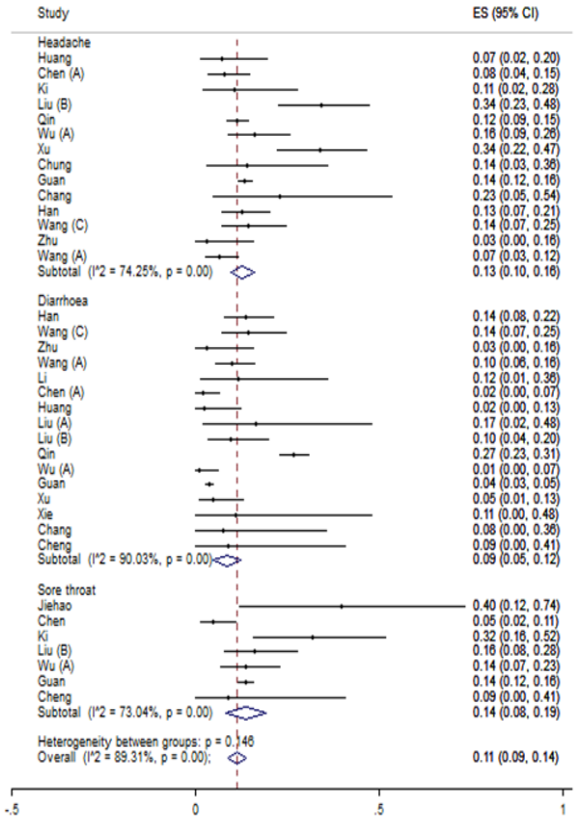

Figure 5. Meta-analysis of incidence of clinical findings of patients (B)

[DOI: 10.18502/tbsrj.v4i1.8772]

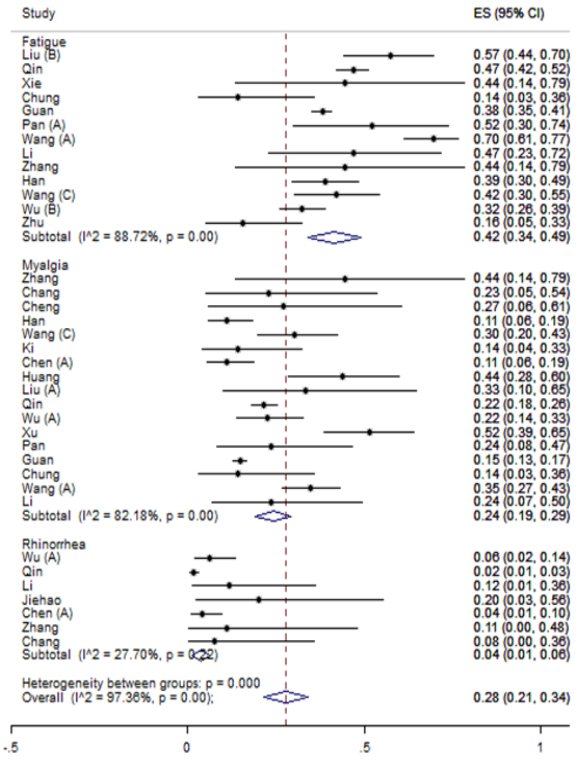

Figure 6. Meta-analysis of incidence of clinical findings of patients (C)

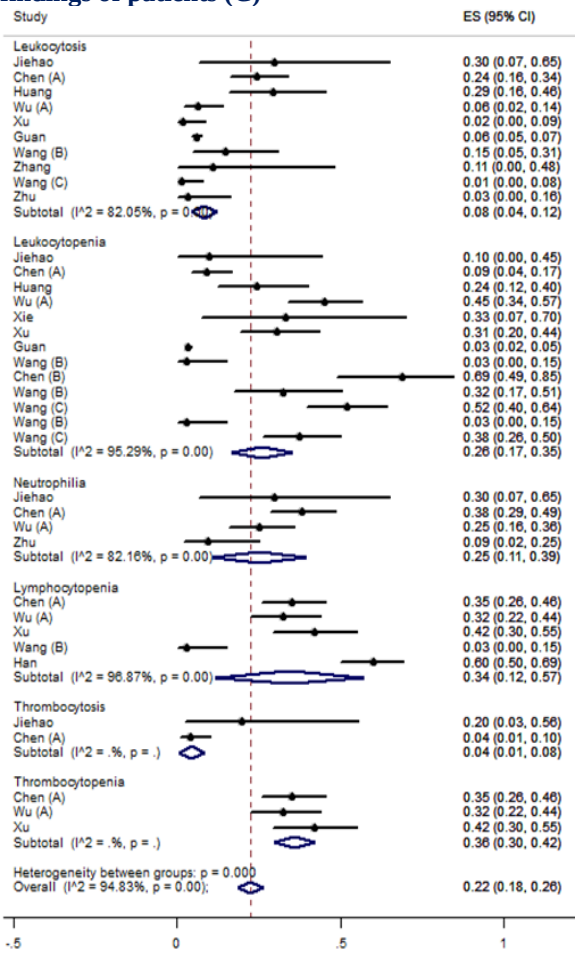

Figure 7. Meta-analysis of incidence of laboratory findings of patients (A)

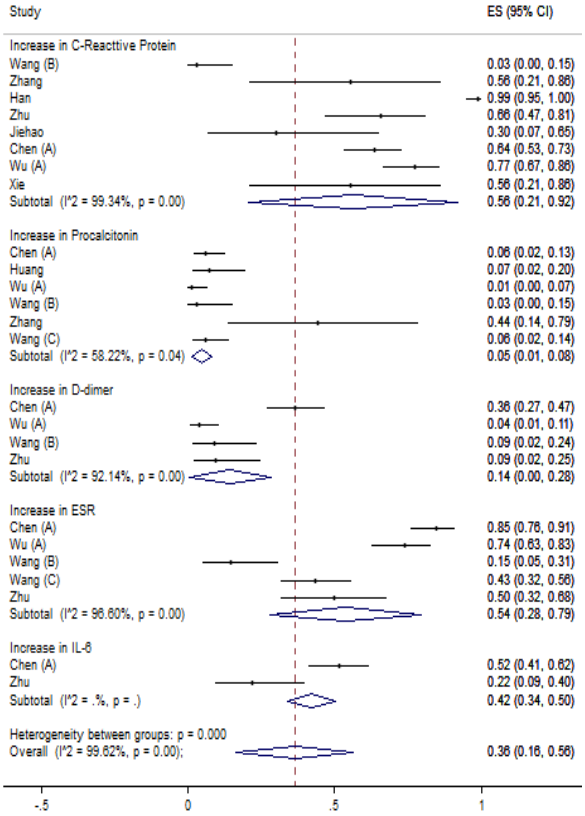

Figure 8. Meta-analysis of incidence of laboratory findings of patients (B)

Comorbidities and clinical findings based on severity of disease

In this systematic review for detecting the source of heterogeneity, we analyzed the subgroups based on the severity of the disease. The results are as follows:

The prevalence of the symptoms such as sore throat, sputum production, headache, and fatigue in stable patients did not need to be admitted into intensive care unit (ICU) were 14%, 33%, 14%, 44%, respectively. However, these statistics for patients with severe symptoms were 14%, 41%, 12%, 53%. Other symptoms like diarrhea, anorexia, nausea/vomiting, and dyspnea in mild patients showed the prevalence of 9%, 17%, 6%, and 24%, which were 8%, 30%, 9%, and 59%, respectively in severe cases (***Supplementary File*** and ***Table 2***).

The prevalence of symptoms like abdominal pain, pharyngalgia, hemoptysis, expectoration, and fever in mild cases were 6%, 8%, 1%, 36%, 90%. The same symptoms for the severe cases were 7%, 14%, 3%, 39%, 94% respectively. Furthermore, the prevalence of

[DOI: 10.18502/tbsrj.v4i1.8772]

the symptoms of myalgia, cough, dizziness, chills, and shortness of breath were 27%, 68%, 5%, 11%, and 19% whereas in severe cases were 21%, 75%, 12%, 16%, and 39%, respectively (***Supplementary File*** and ***Table 2***).

The meta-analysis showed that the prevalence of the underlying diseases like cardiovascular disease, diabetes, cerebrovascular disease and hypertension in COVID-19 patients were 4%, 6%, 1%, 14%, respectively. However, in critically severe patients were 15%, 17%, 10%, and 31%. The prevalence of other underlying diseases like chronic liver disease and respiratory diseases were 2% and 1% whereas in severe cases, respiratory diseases prevalence is 6% (***Supplementary File*** and ***Table 2***).

The prevalence of malignancies (2%) and chronic kidney disease (1%) mostly reported in mild patients whereas in severe cases, were 2% and 24%, respectively (***Supplementary File*** and ***Table 2***).

Discussion

Due to the novelty of Coronavirus 2019, there is no clear picture of the clinical and para-clinical features of the disease. Moreover, the reported frequencies of these features are variable. Therefore, this systematic review and meta-analysis study was performed to evaluate the clinical and paraclinical features of the disease. In this systematic review, 20 studies including 48967 cases of COVID-19 have been studied. All the studies were conducted in China, with one exception which studies some case in South Korea along with Chinese cases.

It was difficult to diagnose this disease at the time of onset, as the general symptoms of the disease can also be seen in other respiratory diseases. A wide range of clinical, laboratory, and imaging findings have been observed in relation to this disease. Symptoms such as fever, cough, fatigue, and sputum were common clinical symptoms in this study, but cases such as diarrhea, chest pain and nausea were less common. As mentioned, gastro-intestinal symptoms such as diarrhea and nausea are less common and symptoms such as fever and cough are more common in viral infections such as seasonal influenza, SARS and MERS. (40, 41). Many patients with coronavirus may be unrecognized and present in the community because, according to the results of this study, none of the clinical symptoms were definitively present in all patients. Therefore, definitive diagnosis of patients is difficult and one should expect hidden and vector-borne patients in the community. In the meta-analysis of Sun et al. which conducted on the symptoms of COVID-19 patients, the results have shown that fever, cough, and fatigue are among the most common symptoms (7).

The rate of death and the outcome of patients after hospitalization have been investigated in this meta-analysis. The results have shown more than two-thirds of the patients (69%) who referred to the hospitals get hospitalized, and about 26% will be released after outpatient treatment. Around 3% of the patients, however, will expire. It should be noted that the real mortality rate would be higher than this statistics. In the study of Baud et al. It has been shown that the mortality of this disease is higher than that typically obtained by dividing the death rate by the total number of patients. Because at the time of infection the number of persons is much lower than the number entered into the denominator (42). Based on the present meta-analysis findings in 84% of suspected cases, CT-Scan findings were positive, indicating that a high proportion of patients can be identified by relying on CT-Scan.

On the other hand, 84% of suspected cases had high fever and cough was seen in many patients. Changes in laboratory findings are less common than radiological and clinical findings and appear to be less reliable. According to the study in the group of patients with severe conditions and outpatients, it was found that the symptoms associated with the disease are more common in critically ill patients at the time of diagnosis and treatment. Also, underlying diseases were more common in these patients.

The limitations of this study include:

[DOI: 10.18502/tbsrj.v4i1.8772]

1. All of the studies have been conducted in China
2. High methodological heterogeneity in the included studies
3. Due to the lack of information by sex and age, it was not possible to calculate the mortality and morbidity of patients in these subgroups.

Conclusion

Given the high proportion that may occur without CT-Scan findings or clinical symptoms, it is advisable to use several combination methods to better diagnose the disease, to minimize undiagnosed patients. Moreover, while there is no access to clinical and paraclinical facilities in in public places such as airports and border crossings, it is recommended to consider factors such as fever, cough, sputum and fatigue. Since the prevalence of underlying diseases is higher in patients with more severe conditions, the risk of serious illness in those with underlying diseases should be considered.

Acknowledgments

The authors would like to thank the Student Research Committee of Mazandaran University of Medical Sciences for supporting this project (Project No. 7319).

Conflicts of Interest

The authors have no conflicts of interest to declare.

Financial Disclosure

None.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://tbsrj.mazums.ac.ir/article-1-3757-en.html

References

1. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). The Indian Journal of Pediatrics. 2020:1-6.
2. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virology journal. 2019;16(1):69.
3. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. Jama. 2020;323(8):707-8.
4. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nature Reviews Microbiology. 2016;14(8): 523.
5. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020: World Health Organization; 11 March 2020 [Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
6. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 57: World Health Organization; 17 March 2020 [Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200317-sitrep-57-covid-19.pdf?sfvrsn=a26922f2_2.
7. Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. Journal of Medical Virology. 2020.
8. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020:200642.
9. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
10. Chen NS, Zhou M, Dong X, Qu JM, Gong FY, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019

[DOI: 10.18502/tbsrj.v4i1.8772]

novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395 (10223):507-13.
11. Chen L, Liu H, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases. 2020;43:E005.
12. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Science China Life sciences. 2020.
13. Huang CL, Wang YM, Li XW, Ren LL, Zhao JP, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223): 497-506.
14. Ki M, nCo VT. Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Republic of Korea. Epidemiology and health. 2020:e2020007.
15. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Science China Life sciences. 2020; 63(3):364-74.
16. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. MedRxiv. 2020.
17. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
18. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020.
19. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine. 2020.
20. Zhu W, Xie K, Lu H, Xu L, Zhou S, Fang S. Initial clinical features of suspected Coronavirus Disease 2019 in two emergency departments outside of Hubei, China. J Med Virol. 2020.
21. Xie C, Jiang L, Huang G, Pu H, Gong B, Lin H, et al. Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020.
22. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ (Clinical research ed). 2020;368:m606.
23. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes and infection. 2020.
24. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020.
25. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020:200463.
26. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020:200230.
27. Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CSD, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. Jama. 2020.
28. Cheng Z, Lu Y, Cao Q, Qin L, Pan Z, Yan F, et al. Clinical Features and Chest CT Manifestations of Coronavirus Disease 2019 (COVID-19) in a Single-Center Study in

[DOI: 10.18502/tbsrj.v4i1.8772]

Shanghai, China. AJR American journal of roentgenology. 2020:1-6.
29. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370.
30. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. European radiology. 2020:1-4.
31. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020.
32. Novel CPERE. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi. 2020;41(2): 145.
33. Zhang M, Wang X, Chen Y, Zhao K, Cai Y, An C, et al. Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing. Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases. 2020;43(3):215.
34. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia. AJR American journal of roentgenology. 2020:1-6.
35. Feng K, Yun Y, Wang X, Yang G, Zheng Y, Lin C, et al. Analysis of CT features of 15 Children with 2019 novel coronavirus infection. Zhonghua er ke za zhi= Chinese journal of pediatrics. 2020;58:E007.
36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020.
37. Wang X, Yuan J, Zheng Y, Chen J, Bao Y, Wang Y, et al. Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen. Zhonghua er ke za zhi= Chinese journal of pediatrics. 2020;58:E008.
38. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
39. Li J, Li S, Cai Y, Liu Q, Li X, Zeng Z, et al. Epidemiological and Clinical Characteristics of 17 Hospitalized Patients with 2019 Novel Coronavirus Infections Outside Wuhan, China. medRxiv. 2020.
40. Leung WK, To K-f, Chan PK, Chan HL, Wu AK, Lee N, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology. 2003;125(4):1011-7.
41. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. New England Journal of Medicine. 2013;369(5):407-16.
42. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. The Lancet Infectious Diseases. 2020.

[DOI: 10.18502/tbsrj.v4i1.8772]