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Review Article

COVID-19 Patients: A Systematic Review and Meta-Analysis of Laboratory Findings, Comorbidities, and Clinical Outcomes Comparing Medical Staff versus the General Population

Mina Ebrahimi [a, b], Amal Saki Malehi [c], Fakher Rahim [a, d,*]

[a] *Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[b] *Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[c] *Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[d] *Clinical Research Development Unit, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

This review compared coronavirus disease 2019 (COVID-19) laboratory findings, comorbidities, and clinical outcomes in patients from the general population versus medical staff to aid diagnosis of COVID-19 in a more timely, efficient, and accurate way. Electronic databases were searched up to 23rd March, 2020. The initial search yielded 6,527 studies. Following screening, 24 studies were included [18 studies (11,564 cases) of confirmed COVID-19 cases in the general public, and 6 studies (394 cases) in medical staff] in this review. Significant differences were observed in white blood cell counts ($p < 0.001$), lymphocyte counts ($p < 0.001$), platelet counts ($p = 0.04$), procalcitonin levels ($p < 0.001$), lactate dehydrogenase levels ($p < 0.001$), and creatinine levels ($p = 0.03$) when comparing infected medical staff with the general public. The mortality rate was higher in the general population than in medical staff (8% versus 2%). This review showed that during the early stages of COVID-19, laboratory findings alone may not be significant predictors of infection and may just accompany increasing C-reactive protein levels, erythrocyte sedimentation rates, and lactate dehydrogenase levels. In the symptomatic stage, the lymphocyte and platelet counts tended to decrease. Elevated D-dimer fibrin degradation product was associated with poor prognosis.

Introduction

Coronavirus disease 2019 (COVID-19) was first detected in Wuhan, China, before rapidly affecting 199 countries and territories around the world. According to the World Health Organization, as of the 24th March, 2020, the total number of patients with COVID-19 was 537,881 with 24,293 deaths [1]. USA, China, Italy, Spain, Germany, and Iran have the most reported laboratory-confirmed COVID-19 cases and deaths [2]. Genetic studies revealed that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus has an 88% similarity with severe acute respiratory syndrome (SARS), and 50% similarity with Middle East respiratory syndrome (MERS) [3]. Compared with SARS, MERS, and pneumonia, SARS-CoV-2 has a longer incubation time, greater pathogenicity and rapid transmission [4]. Currently there is no vaccine or specific treatment for COVID-19. SARS-CoV-2 infects people of all ages and may cause the respiratory system to rapidly develop acute respiratory distress syndrome (ARDS), cardiovascular complications, and acute kidney injury [5-7]. A fever, cough,

*Corresponding author: Fakher Rahim
Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
E-mail: bioinfo2003@gmail.com
ORCID: Mina Ebrahimi https://orcid.org/0000-0001-8595-5639, Amal Saki Malehi https://orcid.org/0000-0002-0952-5861, Fakher Rahim https://orcid.org/0000-0002-2857-4562

dyspnea, fatigue, normal or decreased white blood cells (WBC), and radiographic abnormality in the lungs, are considered as the most frequent clinical manifestation of COVID-19 diagnosis [8]. However, in a study that was conducted by Hu et al [9] only 20.8% of COVID-19 diagnosed patients had typical symptoms, but radiological abnormalities in the lungs was observed in 50% of COVID-19 patients.

Currently, reverse real-time PCR is considered an accurate technique for the diagnosis of COVID-19 however, false-negative results may occur especially in the early stages of the disease. Studies have reported different laboratory findings [10,11]. Nevertheless, a specific laboratory diagnosis, along with other clinical characteristics and their association with the severity of the disease, are necessary. This current review of studies aimed to collect and analyze laboratory findings, comorbidities, and clinical outcomes of infected patients to identify patterns to accurately diagnose COVID-19 more timely and efficiently in infected medical staff compared with the general public.

Materials and Methods

1. Search strategy

Electronic databases including Scopus, Medline/PubMed, EMBASE, Web of Sciences (WOS), and Cochrane library were systematically searched until April 8th, 2020 using MeSH keywords/terms, such as "COVID-19," "2019 novel coronavirus," "2019 nCoV," "COVID-19," "SARS-CoV-2," "laboratory findings," "clinical characteristics," "medical staff," "hospital staff," "medical cares," and all possible combinations. There was no date and language restriction applied. The present review was performed base on Preferred Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) statement [12]. The search was updated on the 12th April, 2020.

2. Study selection

Two reviewers independently performed title-abstract screening on all selected studies, then the full-text of the selected articles were reviewed. In cases of duplicate information from the same patient, the data were checked and combined, but only considered as a single case.

3. Inclusion criteria

Studies reporting hematological, coagulation, biochemistry, and serological laboratory tests, as well as COVID-19 related comorbidities and clinical outcomes were selected.

4. Exclusion criteria

Studies which were just molecular reports, studies that reported laboratory results as percentages, case reports, and commentaries were excluded.

5. Data extraction

Two reviewers separately extracted the data from included studies, considering key characteristics including author, publication year, country, type of study, sample size, laboratory findings, comorbidities, and final clinical outcomes.

6. The assessment of methodological quality and risk of bias

Quality appraisal checklist and the critical appraisal methodological index for non-randomized studies were used as tools for bias risk assessment [13]. The funnel-plot and Egger's regression test were used to assess publication bias [14].

7. Statistical analysis

Cochran, Chi-square test, and I^2 were used to assess heterogeneity amongst studies. A fixed-effects model was used when $I^2 < 50\%$, and when $I^2 > 50\%$, a random-effects model was selected. The fixed-model assumed that the population effect sizes were the same for all studies [15]. In contrast the random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies were random samples from a larger population [16]. If there was statistical heterogeneity amongst the results, a further sensitivity analysis was conducted to determine the source of heterogeneity. After significant clinical heterogeneity was excluded, the randomized effects model was used for meta-analysis. When $p < 0.05$ the result was considered statistically significant (2-sided). All data were analyzed using the STAT 15 software (IBM, NY, USA).

Results

The initial search yielded 6,527 studies, with duplicate studies removed resulting in 1,759 studies remaining. Following the inclusion exclusion criteria 24 studies were selected. This included 11,950 confirmed cases of COVID-19 and comprised of 18 studies (11,556 cases) of patients from the general population, and 6 studies (394 cases) where medical staff were the patients (Figure 1).

1. Study characteristics and methodological quality assessment

The 24 selected studies obtained from the systematic review are presented in Table 1. Of these, 41.7% [17] were case-control
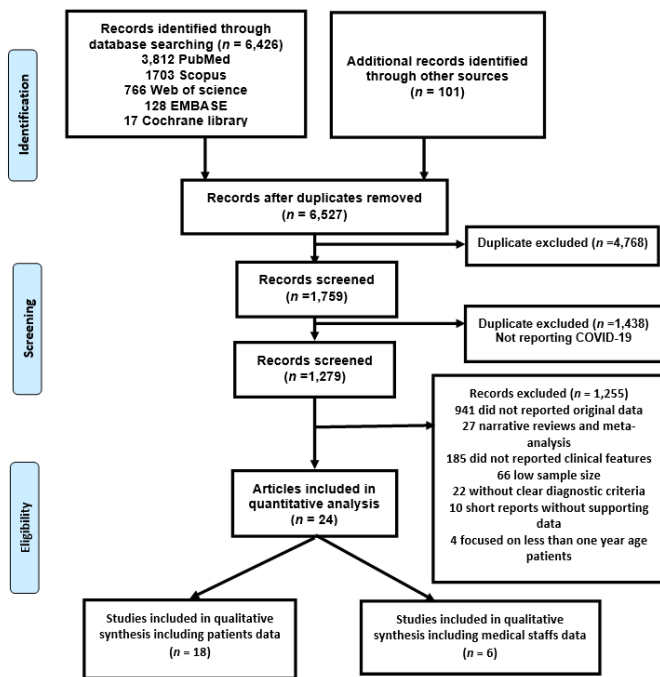
Figure 1. Flow diagram of the inclusion criteria of studies eligible for meta-analysis.

studies [6,8,9,18-23], and 58.3% [20] were cross-sectional design studies [5,18,24-28]. There was 1 study that investigated the association between coagulation abnormalities and prognosis in COVID-19 patients [20]. Just 2 studies had a sample size greater than 1,000 [25,29] (Table 1).

All eligible studies that evaluated medical staff who had contracted COVID-19 were selected. Of these 6 studies there were 394 infected medical staff [19,24,26] (Table 1). Other details of the data are available in Table S1.

2. Laboratory findings analysis

The result of laboratory finding analysis in the general public showed, lymphocytopenia (0.93×10^9/L; 95% CI: 0.84-1.02), hypoalbuminemia (34.05 g/L; 95% CI: 32.07-36.04) significantly lower, C-reactive protein (CRP) (14.92 mg/L; 95% CI: 4.68-25.16) significantly higher compared with the effects of COVID-19 in medical staff (Table 2).

Further statistical tests revealed that the laboratory variables in infected medical staff were significantly different to the general public who were infected. A lower WBC ($p < 0.001$), a higher lymphocyte count ($p < 0.001$), platelet count ($p = 0.04$), and PCT ($p < 0.001$), a lower LDH ($p < 0.001$), and creatinine ($p = 0.03$) were observed in infected medical staff (Table 2). The

detailed data are available in Table S2 and S3.

3. Clinical characteristics, comorbid conditions, and clinical outcome analysis

The most reported clinical findings for all cases in this review were a fever 77% (95% CI: 63-89%), a cough 60% (95% CI: 53-68%), and fatigue 38% (95% CI: 28-48%). Further analysis revealed the frequency of clinical manifestations in infected medical staff were similar to patients in the general public (Table 3). Egger test results revealed there was no publication bias in the studies (Table 3).

After investigating comorbidities, it was revealed that patients with hypertension 17% (95% CI: 12-23%), cardiovascular disease (CVD) 0.8% (95% CI: 0.4-12%), or diabetes 10% (95% CI: 0.7-13%) were more susceptible to COVID-19 (Table 4). As shown in Table 5, these frequencies were lower amongst infected medical staff. The clinical outcome showed that the mortality rate was higher in patients from the general population [8% (95% CI: 4-13%)] than patients who were medical staff [2% (95% CI: 0-10%)]. There were 51% (95% CI: 27-75%) of patients from the general population who required hospitalization. Medical staffs had shorter number of days in hospital than patients with relative frequency of 73% (95% CI: 38-97%) (Table S4).

Discussion

The absence of specific laboratory findings and clinical manifestations during the early stages of COVID-19 in patients complicated early diagnosis of the disease. Additional to the rapid progression in late-stage COVID-19, development of ARDS was more severe than ARDS observed with other virus infections which occur routinely [30]. There are several systematic and meta-analysis studies of COVID-19 which mainly discussed comorbidities, clinical manifestations, and treatments [31-35]. In this current review, laboratory abnormality interpretations in early and late stage disease were considered. In this regard, 24 studies, including 11,556 general patients and 394 infected medical staff were evaluated.

Like other viral infections, a fever, a cough, and fatigue were the most commonly observed clinical findings in COVID-19 patients, but the absence of these clinical characteristics cannot rule out infection. In this regard, Hu et al [9] reported just 20.8% of infected patients developed these symptoms during hospitalization. Despite the typical symptom of SARS and MERS infections being diarrhea, it has a low prevalence in COVID-19 [36]. It has been reported in a case without typical COVID-19 clinical characteristics and laboratory results, that the virus was detected in the stool sample suggesting that
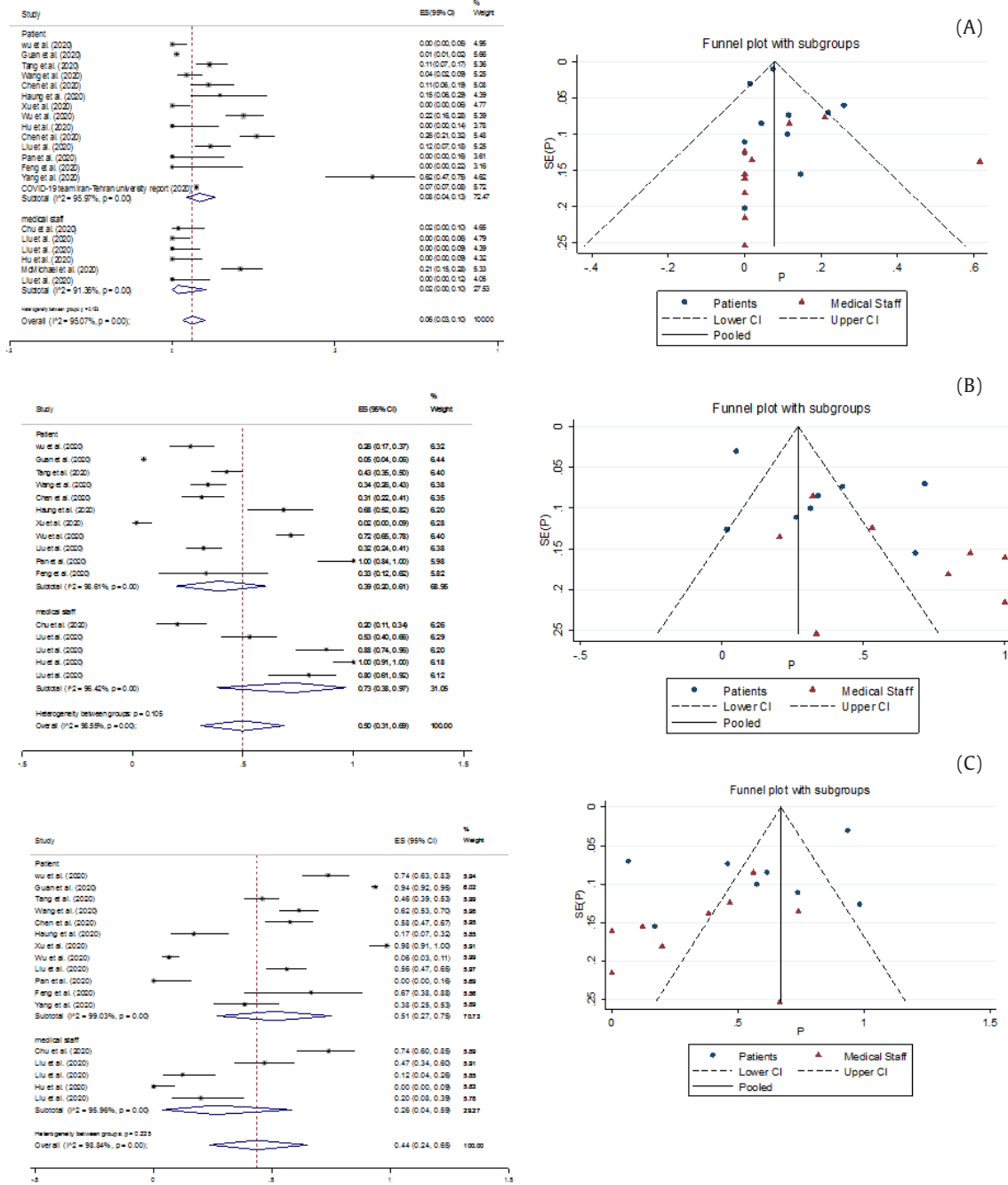
Figure 2. Plots of the proportions of deaths (A), discharge rates (B), and those remaining in hospital due to COVID-19 (C) in the general population and in medical staff.

suspected cases of COVID-19 where diarrhea was present but no laboratory abnormalities are observed should be considered for follow up COVID-19 testing [37]. Additionally, this review supports other data to show that COVID-19 in patients with underlying disease, mainly hypertension, diabetes, and CVD, results in these patients being hospitalized Wang et al [8] showed that patients admitted to the intensive care unit (ICU)

had more comorbidities compared with patients not treated in the ICU.

The main mechanism for inflammation and organ damage associated with COVID-19 appears to be attributable to cytokines, especially in pulmonary vascular endothelial cells. SARS-CoV-2 enters the alveolar epithelial cells through angiotensin-converting enzyme 2 receptors [38,39].

Table 1. Characteristics of the included studies on COVID-19 confirmed cases, 2020.

Study [ref.]	Year	Country	No. patients	Median age (y)	Sex (Female; %)	Discharge rate (%)	Fatality rate (%)	Quality score
Available papers on patients with COVID-19								
Wu et al [21]	2020	China	80	46.1	51.25	23.75	0	13
Guan et al [25]	2020	China	1,099	47	41.9	5	1.4	10
Tang et al [20]	2020	China	183	54.1	46.5	42.6	11.5	13
Zhang et al [22]	2020	China	140	57	49.3	N/R	N/R	10
Wang et al [8]	2020	China	138	56	45.7	34.1	4.3	13
Chen et al [17]	2020	China	99	55	32	31	11	12
Hung et al [6]	2020	China	41	49	27	68	15	13
Xu et al [27]	2020	China	62	35	44	2	0	13
Wu et al [41]	2020	China	201	51	36.3	N/R	N/R	12
Zhu et al [28]	2020	China	116	40	53	N/R	N/R	10
Zhao et al [23]	2020	China	34	48	42.11	N/R	N/R	13
Hu et al [9]	2020	China	24	32.5	0	N/R	0	13
Chen et al [18]	2020	China	274	68	37.5	39	63	13
Liu et al [11]	2020	China	137	57	55.5	32.1	11.7	13
Pan et al [46]	2020	China	21	40	74	100	0	13
Feng et al [47]	2020	China	15	7	66.66	33.33	0	10
Yang et al [48]	2020	China	52	59.7	33	38.4	61.5	13
Iranian COVID-19 research group report [29]	2020	Iran	8,840	51.2	43.9	N/R	N/R	11
Available papers on medical staff with COVID-19								
Chu et al [24]	2020	China	54	47	33.3	N/R	N/R	13
Liu et al [26]	2020	China	64	35	64	53	0	13
Liu et al [19]	2020	China	41	39.1	58.5	87.9	0	13
Hu et al [44]	2020	China	38	36	60.5	100	0	12
McMichael et al [45]	2020	China	167	72	67	N/R	21	12
Liu et al [49]	2020	USA	30	35	33.33	80	0	13

Hung et al [16] showed increasing inflammatory cytokines (IL-1β, IL-6, IL-12, IL-10, IFN-γ, and MCP-1) were higher in patients admitted to ICU [6]. Due to the elevated levels of inflammatory cytokines, there was an increasing neutrophil count and infiltration into lung cells, promoting development of ARDS. This indicated that an elevated neutrophil count should be considered protective for lung injury. The elevated levels of CRP and eosinophils (ESR) are the result of these inflammatory cytokines. Hung et al [37] showed that an increase in inhibitory cytokines like IL-4 and IL-10 were associated with COVID-19, which lead to erythropoiesis inhibition and lymphocytopenia. Additionally, there are reports that SARS-CoV-2 infection of immune cells and damage to T lymphocytes leads to lymphocytopenia [5,40,41]. This review of 24 studies is in line with this observation and indicated lymphocytopenia, increasing CRP, and ESR to consider in the diagnosis of COVID-19. It is worth noting that eosinophil count decreases in COVID-19, and the correlation between eosinopenia and lymphocytopenia was observed which could be a useful diagnostic marker for COVID-19 [22].

Table 2. The result of analysis of laboratory findings in COVID-19 patients in the general public and in medical staff.

Laboratory variables	Population	N	ES (95% CI)	p (between subgroups)	I²	Chi-square	Egger test
WBC	General public	12	5.43 (4.80 - 6.04)		98.5	749 (p < 0.001)	5.92 (p < 0.001)
	Medical staff	2	4.73 (4.71 - 4.74)	< 0.001	0	0.44 (p = 0.51)	0.68 (p = 0.86)
Lymphocyte	General public	12	0.93 (0.84 - 1.02)		96	293.5 (p < 0.001)	2.33 (p = 0.38)
	Medical staff	2	1.32 (1.17 - 1.46)	< 0.001	74	3.85 (p = 0.05)	2.06 (p = 0.51)
Neutrophil	General public	9	4.17 (3.52 - 4.83)		98	667 (p < 0.001)	12.28 (p < 0.001)
	Medical staff	2	4.53 (2.05 - 7.0)	0.79	99	97.8 (p < 0.001)	12.52 (p < 0.001)
Hemoglobin	General public	8	12.76 (11.84 - 13.68)		99	261 (p < 0.001)	0.02 (p = 0.86)
	Medical staff	2	13.0 (12.98 - 13.02)	0.60	0	< 0.001 (p = 0.98)	2.54 (p = 0.48)
Platelet	General public	9	175.04 (163.03 - 187.06)		98	329.2 (p < 0.001)	0.93 (p = 0.67)
	Medical staff	2	183.69 (183.32- 184.07)	0.04	0	0.81 (p =0.37)	3.07 (p = 0.42)
PT	General public	7	12.24 (11.17- 13.30)		99	5,609 (p < 0.001)	1.44 (p = 0.2)
	Medical staff	1	10.9 (10.74 - 11.06)	0.02	----	-----	----
PTT	General public	7	30.53 (25.75 - 35.31)	0.02	99	5,066 (p < 0.001)	1.21 (p = 0.27)
	Medical staff	1	25.7 (24.82 - 26.58)		----	-----	----
D-dimer	General public	9	0.67 (0.40 - 0.94)		99	678 (p < 0.001)	6.1 (p < 0.001)
	Medical staff	0	----	----	-----	------	------
ESR	General public	6	0.68 (-2.38 - 3.73)		0	0.03 (p = 0.99)	2.18 (p = 0.09)
	Medical staff	1	0.21 (-0.05 - 0.47)	0.76	-----	------	------
CRP	General public	6	14.92 (4.68 - 25.16)		96	246 (p < 0.001)	1.3 (p = 0.36)
	Medical staff	0	-----	-----	-----	------	------
PCT	General public	6	0.37 (0.16 - 0.55)		99	635.8 (p < 0.001)	1.95 (p = 0.11)
	Medical staff	1	0.05 (0.04 - 0.06)	< 0.001	-----	------	------

Table 2. (Continued).

Laboratory variables	Population	N	ES (95% CI)	p (between subgroups)	I^2	Chi-square	Egger test
LDH	General public	9	283.7 (244.5 - 322.95)	< 0.001	99	1,088 (p < 0.001)	1.36 (p = 0.36)
	Medical staff	2	182.8 (167.6- 198.1)		80	5.01 (p = 0.03)	2.28 (p = 0.09)
Creatinine	General public	5	72.75(70.5 - 75.0)	0.03	87	37 (p < 0.001)	0.48 (p = 0.91)
	Medical staff	2	65.3 (58.9 - 71.8)		86	7.5 (p = 0.006)	1.82 (p = 0.26)
CK-MB	General public	3	16.8 (13.6 - 20.02)	-----		349 (p < 0.001)	1.39 (p = 0.39)
	Medical staff	0	-----		-----	------	------
CK	General public	8	103.3 (89.9 - 116.7)	-----	98	353 (p < 0.001)	1.87 (p = 0.11)
	Medical staff	0	-----		-----	------	------
AST	General public	9	22.39 (19.64 - 25.13)	< 0.001	97	295 (p < 0.001)	1.79 (p = 0.72)
	Medical staff	2	32.24 (29.73 - 34.75)		57	2.34 (p =0.13)	1.0 (p = 0.37)
ALT	General public	9	29.56 (26.12 - 33.01)	0.02	97	349 (p < 0.001)	1.69 (p = 0.31)
	Medical staff	2	20.24 (12.96 - 27.52)		86	7.3 (p = 0. 01)	1.0 (p = 0.37)
Alb	General public	5	34.05 (32.07 - 36.04)	< 0.001	99	599.9 (p < 0.001)	0.95 (p = 0.39)
	Medical staff	1	38.4 (36.9 - 39.9)		-----	------	------
BUN	General public	4	5.81 (4.94 - 6.69)	-----	98	216 (p < 0.001)	1.69 (p = 0. 23)
	Medical staff	0	-----		-----	------	------
Bilirubin	General public	6	10.96 (9.47 - 12.44)	0.29	99	758 (p < 0.001)	1.53 (p = 0.52)
	Medical staff	2	9.89 (8.57 - 11.21)		72	3.63 (p = 0.06)	0.36 (p = 0. 67)
Glucose	General public	2	6.75 (5.87 - 7.63)	------	98	76.27 (p < 0.001)	1.0 (p = 0.37)
	Medical staff	0	-----		-----	-----	------

Alb = albumin; ALT = alanine transaminase; BUN = blood urea nitrogen; CC = case-control; CK-MB = creatine kinase myocardial band; CRP = C-reactive protein; Eos = eosinophils; ES = effect size; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; PCT = procalcitonin; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.

Table 3. The result of symptom analysis in COVID-19 patients in the general public and in medical staff.

Symptoms	Population	N	ES (95% CI)	p (between subgroups)	I²	Chi-square	Egger test
Fever	General public	16	77 (63% - 89%)		98	751.23 (p < 0.001)	3.52 (p = 0.11)
	Medical staff	4	74 (65% - 87%)	0.74	48	5.82 (p = 0.12)	2.52 (p = 0.07)
Cough	General public	16	60 (53% - 68%)		90	161 (p < 0.001)	1.11 (p = 0.12)
	Medical staff	4	56 (49% - 63%)	0.04*	84	19.5 (p < 0.001)	2.65 (p = 0.66)
Fatigue	General public	12	38 (28% - 48%)		94	188.4 (p < 0.001)	0.09 (p = 0.93)
	Medical staff	4	40 (32% - 50%)	0.47	94	53.6 (p < 0.001)	9.45 (p = 0.26)
Shortness of breath	General public	1	19 (16% - 21%)		----	------	------
	Medical staff	1	47 (28% - 66%)	< 0.001†	----	------	------
Muscle ache	General public	2	16 (11% - 22%)		0	------	0.39 (p = 0.76)
	Medical staff	1	0.6 (0.1% - 15%)	0.04*	----	------	------
Headache & mental disorder	General public	11	10 (0.7% - 14%)		79	47.6 (p < 0.001)	0.3 (p = 0.51)
	Medical staff	4	11 (0.7% - 15%)	0.63	91	36.2 (p < 0.001)	6.33 (p = 0.28)
Sore throat	General public	3	11 (0.6% - 17%)	0.75	----	------	0.61 (p = 0.53)
	Medical staff	2	11 (0.5% - 18%)		----	------	------
Rhinorrhea	General public	2	0.5 (0.2% - 0.9%)		----	------	------
	Medical staff	2	0.5 (0.1% - 10%)	0.9	----	------	------
Chest pain	General public	3	0.3 (0.1% - 0.5%)		0	2.63 (p = 0.45)	2.41 (p = 0.09)
	Medical staff	1	0.3 (0% -11%)	0.9	----	------	------
Diarrhea	General public	11	0.6 (0.2% - 11%)		93	139.7 (p < 0.001)	0.13 (p = 0.87)
	Medical staff	3	0.9 (0.2% - 18%)	0.56	91	39.8 (p < 0.001)	4.90 (p = 0.21)
Nausea & vomiting	General public	7	0.7 (0.3% - 12%)		89.4	56.5 (p < 0.001)	0.31 (p = 0.67)
	Medical staff	2	0.9 (0.3% - 16%)	0.51	----	------	------

* Staistically significant; † Highly significant.
ES = effect size.

Table 4. The result of comorbidity analysis in COVID-19 patients in the general population and in medical staff.

Comorbidities	Population	N	ES (95% CI)	p (between subgroups)	I^2	Chi-square	Egger test
Hypertension	General public	11	17 (12% - 23%)	0.62	89	95.2 ($p < 0.001$)	5.47 ($p = 0.05$)
	Medical staff	4	11 (0% - 38%)		96	78.5 ($p < 0.001$)	0.06 ($p = 0.94$)
CVD	General public	11	0.8 (0.4% - 12%)	0.89	89	97.3 ($p < 0.001$)	4.88 ($p = 0.004$)
	Medical staff	3	0.9 (0% - 46%)		--	-----	0.98 ($p = 0.07$)
Diabetes	General public	11	10 (0.7% - 13%)	0.49	76	42.75 ($p < 0.001$)	2.78 ($p = 0.07$)
	Medical staff	4	0.5 (0% - 20%)		92	38.12 ($p < 0.001$)	0.35 ($p = 0.37$)
Malignancy	General public	11	0.5 (0.1% - 0.3%)	0.27	55	22.14 ($p = 0.01$)	0.81 ($p = 0.24$)
	Medical staff	3	0.4 (0% - 12%)		---	------	0.15 ($p = 0.32$)
CBD	General public	10	0.2 (0.1% - 0.4%)	------	62	23.5 ($p = 0.01$)	1.54 ($p = 0.6$)
	Medical staff	----	------		----	------	------
COPD	General public	12	0.1 (0.1% - 0.2%)	0.99	17	13.2 ($p = 0.28$)	4.11 ($p = 0.01$)
	Medical staff	2	0.1 (0% - 0.5%)		----	------	0.11 ($p = 0.23$)
Kidney	General public	9	0.1 (0% - 0.2%)	< 0.001	17	9.68 ($p = 0.29$)	0.18 ($p = 0.01$)
	Medical staff	2	18 (13% - 23%)		----	------	4.79 ($p = 0.01$)
Liver	General public	7	0.4 (0.2% - 0.6%)	0.84	32	8.77 ($p = 0.19$)	0.23 ($p = 0.65$)
	Medical staff	2	0.4 (0.1% - 0.7%)		----	------	0.16 ($p = 0.56$)
Gastrointestinal	General public	4	0.4 (0.1% - 10%)	0.64	83	17.34 ($p < 0.001$)	1.08 ($p = 0.36$)
	Medical staff	2	0.3 (0% - 0.7%)		----	------	1.31 ($p = 0.27$)
Endocrine	General public	4	0.5 (0.1% -0.11%)	0.33	85	18.89 ($p < 0.001$)	0.80 ($p = 0.48$)
	Medical staff	1	0.2 (0% - 0.8%)		----	------	------
HIV	General public	3	0 (0% - 0.1%)	-----	0	------	1.0 ($p = 0.32$)
	Medical staff	----	------		----	------	------

CBD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; ES = effect size; HIV = human immunodeficiency virus.

No significant abnormality was observed in liver function laboratory findings (e.g. AST, ALT, LDH, and bilirubin). SARS-CoV-2 has receptors on the surface of the bile duct, and abnormalities in liver tests can be a result of collateral damage to this organ [21,39,42]. This could be an explanation of normal laboratory findings related to the liver in the early stages of COVID-19. Hypoxia is another pathogenesis associated with COVID-19, which is one of the main causes of sudden death in patients, hence increasing creatine kinase may be due to hypoxia and must be causally interpreted [22].

A critical issue not discussed in earlier systematic and meta-analysis studies are coagulation parameters. Inflammatory cytokine activation of monocytes and endothelial cells, tissue factor expression, and secretion of Von Willebrand clotting factor protein causes the development of and dissemination of intravascular coagulation [21]. It was demonstrated that SARS infection is accompanied by dysregulation of the urokinase pathway, activation of fibrinolysis, increasing fibrin degradation products (FDP), and is associated with poor prognosis [20,43]. The findings of this review indicated that elevated D-dimer was associated with COVID-19. It was demonstrated that disease progression was accompanied by coagulation parameters increasing thus, increasing D-dimer and FDP were observed in patients admitted to ICU [8,20,22].

In the present study, SARS-CoV-2 infected medical staff were compared with SARS-CoV-2 infected patients from the general public and the mean laboratory results showed that medical staff had milder symptoms with slightly less disease severity than the patients from the general population. The clinical outcome analysis revealed 51% of patients from the general population required hospitalization, and the mortality rate was 8%. Whereas in patients who were medical staff, mortality and hospitalization rates were lower, and the discharge rate was higher. This could be due to a lower rate of comorbidities, as well as timely access to diagnostic tools and care [9,19,26]. Amongst the included 24 studies, only Hu et al [44] evaluated asymptomatic patients, hence in the other studies, the clinical outcome was reported among symptomatic and severely affected patients. In this regard, in the study of McMichael et al [45], mortality was reported as high thus, the possible reason could be that the mean age and comorbidities were higher than in the other studies.

Conclusion

The findings of this COVID-19 meta-analysis review revealed that the normal or abnormal outcome of a patient's laboratory results may shed light on the stage of the disease and its progression. In asymptomatic patients, in the early stages of COVID-19, misdiagnosis may occur due to lack of abnormal laboratory findings, or increasing CRP, ESR, and LDH. In the symptomatic stage, the lymphocyte and platelet counts tended to decrease. In later stages of the disease, inflammatory markers and liver enzymes increased, whereas reduced lymphocyte and platelet counts were associated with a poor prognosis in COVID-19. Though COVID-19 was associated with a reduced mortality rate in medical staff compared to the general public, the use of appropriate personal protective equipment and hand hygiene may help to reduce infection rates. Elevating D-dimer FDP were associated with a poor prognosis, and most of these patients were admitted to the ICU. However, there is a need for longer follow-up time points to evaluate which laboratory parameters return to the normal range.

There are several limitations of this study. Inaccessibility to the full text of articles, lack of reporting laboratory findings, and reporting of results as decreasing or increasing laboratory results by percentage limited this current study. Patients with different stages of COVID-19 were included, and this is one of the main reasons for heterogenicity. In several studies, due to the incomplete treatment periods, the clinical outcome was not reported. The lack of laboratory results in the medical staff studies was another limitation.

Supplementary Materials

Supplementary data is available at http://www.kcdcphrp.org.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

References

[1] World Health Organization. Coronavirus disease 2019. Geneva (Switzerland): World Health Organization; 2019. p. 2633.
[2] Khafaie MA, Rahim F. Cross-country comparison of case fatality rates of Covid-19/SARS-CoV-2. Osong Public Health Res Perspect 2020;11(2):74-80.
[3] Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China. N Engl J Med 2020;382(8):727-33.
[4] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019

infection. Clin Chem Lab Med 2020;58(7):1131-4.

[5] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395(10223): 507-13.

[6] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.

[7] Ebrahimi M, Saki A, Rahim F [Preprint]. Laboratory findings, signs and symptoms, clinical outcomes of Patients with COVID-19 Infection: An updated systematic review and meta-analysis. medRxiv: 2020.03.25.20043703. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.25.20043703v1.

[8] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061-9.

[9] Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 2020;63(5):706-11.

[10] Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: A retrospective study. Chin Med J (Engl) 2020;133(11):1261-7.

[11] Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020;133(9):1025-31.

[12] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.

[13] Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. ANZ J Surg 2003;73(9):712-6.

[14] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22(4):719-48.

[15] Cheung MWL, Ho RCM, Lim Y, et al. Conducting a meta-analysis: Basics and good practices. Int J Rheum Dis 2012;15(2):129-35.

[16] Lim RBC, Zhang MWB, Ho RCM, et al. Prevalence of all-cause mortality and suicide among bariatric surgery cohorts: A meta-analysis. Int J Environ Res Public Health 2018;15(7):1519.

[17] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet 2020;395(10229):1038.

[18] Chen H, Guo J, Wang C, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.

[19] Liu R, Ming X, Zhu H, et al [Preprint]. Association of Cardiovascular Manifestations with In-hospital Outcomes in Patients with COVID-19: A Hospital Staff Data. medRxiv: 2020.02.29.20029348. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.29.20029348v1.

[20] Tang N, Li D, Wang X, Sun Z. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(5):1233-4.

[21] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-42.

[22] Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730-41.

[23] Zhao D, Yao F, Wang L, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis 2020;71(15):756-61.

[24] Chu J, Yang N, Wei Y, et al. Clinical Characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China. J Med Virol 2020;92(7):807-13.

[25] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382(18):1708-20.

[26] Liu J, Ouyang L, Guo P, et al [Preprint]. Epidemiological, Clinical Characteristics and Outcome of Medical Staff Infected with COVID-19 in Wuhan, China: A Retrospective Case Series Analysis. medRxiv: 2020.03.09.20033118. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.09.20033118v1.

[27] Xu X-W, Wu X-X, Jiang X-G, 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 2020;368:m606.

[28] Zhu W, Xie K, Lu H, et al. Initial clinical features of suspected Coronavirus Disease 2019 in two emergency departments outside of Hubei, China. J Med Virol 2020 [Epub ahead of print]. Epub 2020 Mar 13.

[29] COVID-19 Epidemiology Committee TUoMS: Epidemiological report of covid patients 19 in Hospitals covered by Tehran University of Medical Sciences. In., vol. Report No.: 1 2020 .

[30] Kang H-Y, Wang Y-S, Tong Z-H. et al. Personal knowledge on novel coronavirus pneumonia. Chin Med J (Engl) 2020;133(9):1121-2.

[31] Li L-Q, Huang T, Wang Y-Q, et al. 2019 Novel Coronavirus Patients' Clinical Characteristics, Discharge Rate and Fatality Rate of Meta-Analysis. J Med Virol 2020;92(6):577-83.

[32] Pormohammad A, Ghorbani S, Baradaran B, et al. Clinical Characteristics, Laboratory Findings, Radiographic Signs and Outcomes of 52,251 Patients with Confirmed COVID-19 Infection: A Systematic Review and Meta-analysis. Rev Med Virol 2020;30(4):e2112.

[33] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.

[34] Wynants L, Calster B Van, Bonten MM, et al [Preprint]. Systematic review and critical appraisal of prediction models for diagnosis and prognosis of COVID-19 infection. medRxiv: 2020.03.24.20041020. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.24.20041020v1.

[35] Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.

[36] Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018; 23(2):130-137.

[37] Tang A, Tong Z-D, Wang H-L, et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerg Infect Dis 2020;26(6):1337-9.

[38] Jiang F, Deng L, Zhang L, et al. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med 2020;35(5):1545-9.

[39] Wan Y, Shang J, Graham R, et al. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020;94(7):e00127-20.

[40] Liu WJ, Zhao M, Liu K, et al. T-cell immunity of SARS-CoV: Implications for vaccine development against MERS-CoV. Antiviral Res 2017;137:82-92.

[41] Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):1-11.

[42] Chai X, Hu L, Zhang Y, et al [Preprint]. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv: 2020.02.03.931766. 2020. Available from: https://www.biorxiv.org/content/10.1101/2020.02.03.931766v1.

[43] Gralinski LE, Bankhead A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. mBio 2013;4(4):e00271-13.

[44] Hu J, Wang W [Preprint]. Clinical characteristics of survivors and non-survivors, medical and non-medical staff members with 2019- nCoV pneumonia in Wuhan, China : A descriptive study. doi: 10.21203/rs.3.rs-20714/v1. 2020. Available from: https://www.researchsquare.com/article/rs-20714/v1.

[45] McMichael TM, Clark S, Pogosjans S, et al. COVID-19 in a Long-Term Care Facility - King County, Washington. MMWR Morb Mortal Wkly Rep 2020;69(12):339-42.

[46] Pan F, Ye T, Sun P, et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. Radiology 2020;295(3):715-21.

[47] Feng K, Yun YX, Wang XF, et al. Analysis of CT features of 15 Children with 2019 novel coronavirus infection. Zhonghua Er Ke Za Zhi 2020;58(0):E007. [in Chinese].

[48] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475-81.

[49] Liu M, He P, Liu HG, et al. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(3):209-14. [in Chinese].