

Original Article

ASSESSMENT OF BIOCHEMICAL CHANGES AMONG COVID-19 CASES IN A TERTIARY HOSPITAL OF BANGLADESH DURING EARLY PANDEMIC

Mithun S^{1*}, Abullah SAHM², Irfan SMN³

ABSTRACT

Background: Corona virus disease 2019 (COVID-19) involves various organs of the body causing several biochemical changes which plays an essential role in estimating the patients' condition and prognosis, directing treatment, and even evaluating the curative effects. The present study aimed to assess the biochemical changes among the COVID-19 patients during early pandemic.

Methods: This cross sectional study was conducted at Combined Military Hospital (CMH) Dhaka among purposively selected 237 confirm COVID-19 cases. Data were collected through face to face interview and review of medical records using a pre-tested semi-structured questionnaire. The study was conducted in the Combined Military Hospital Dhaka from 15 April 2020 to 31 May 2020

Results: Highest number of the respondents were in the age group of 31-40 years (37.1%) with male predominance (83.1%). About 95.6% were Muslim and 58.6% were educated up to secondary level. About 87.8% had contact with a confirmed case and having 47.7%, 37.2%, 15.1% cardiovascular, endocrine and respiratory comorbidities respectively. Fever (34.6%) was the most common presenting symptoms followed by cough (22.9%), sore throat (10.6%). Neutrophilia observed in 26.16%, lymphopenia in 20.7%, thrombocytopenia in 14.3% cases, 30.0% with positive D-dimer test, 22.4% either sepsis or systemic infection in procalcitonin estimation, 28.3% with increased ferritin, 28.7% with positive C reactive protein, 21.1% with increased LDH. Chi-square analysis revealed a statistically significant association between cardiovascular and endocrine diseases with several biochemical changes (p<0.05).

Conclusion: Early identification of various biochemical changes would help the physician for appropriate assessment and management.

JOPSOM 2021; 40(1):34-42
<https://doi.org/10.3329/jopsom.v40i1.56689>

Keywords: COVID-19, Biochemical changes, Hospital admitted patients

1. * Lt Col (Dr.) Sangita Mithun, MBBS, MPhil (Physiology), Instructor Physiology, Armed Forces Medical College, Dhaka
2. Dr. Syed Abul Hassan Md Abdullah, Consultant, Public Health Management, US CDC, Bangladesh Office.
3. Lt Col (Dr.) S. M. Nurul Irfan, MBBS, MPH (HM), Student Officer, MPhil (PSM), Armed Forces Medical Institute, Dhaka.

Correspondence: *Lt Col Sangita Mithun, E mail: sangitamithun@yahoo.com

INTRODUCTION

At the end of 2019, a cluster of pneumonia cases caused by a novel coronavirus (2019-nCoV) were detected in Wuhan, China. Its rapid spread and progression and lack of specific therapeutic strategy resulted in an epidemic. Soon after, this novel virus became a global concern; on January 30, 2020, the World Health Organization (WHO) declared that the epidemic of 2019-nCoV was a public health

emergency of international concern (PHEIC), and on February 11, 2020, the WHO designated the disease coronavirus disease 2019 (COVID-19)¹. As on August 2020, more than 22.5 million cases of COVID-19 have been reported in more than 216 countries and territories, resulting in almost 78549 deaths; approximately 15.08 million people have recovered. The virus was confirmed to have spread to Bangladesh in March 2020. The first three known cases were reported on 8 March 2020 by the country's

epidemiology institute, IEDCR². Since then, the pandemic has spread day by day over the whole nation and the number of affected people has been increasing exponentially and till now Bangladesh has reported 279144 confirmed cases among which 160591 has recovered and 3694 died³. As a part of the total community, members of Bangladesh armed forces also suffers from this disease. On 6 April 2020, army revealed its first case of COVID-19 and about 7000 affected individual treated in Combined Military Hospital (CMH) Dhaka⁴. It is well established that about one-fourth of the cases are asymptomatic and about 95% patient cured without any complications⁵. The diseases usually presented with respiratory tract infection characterized by a broad spectrum of clinical manifestations with different degree of severity and an incubation period vary from 1 to 14 days. The disease severity ranges from asymptomatic to pneumonia evolving into acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), leading to death. It is well established that elderly (>65 years) and individuals with associated comorbidities, such as diabetes, hypertension, and chronic obstructive pulmonary disease, are more susceptible to severe disease⁶.

For detection of the virus as well as to the follow-up of patients and for epidemiological surveillance via determination of serological markers, clinical laboratories play an essential role. With the help of various validated test for SARS-CoV-2, it is easy for the physicians for the timely management of COVID-19 cases because they support the clinical decision-making process for controlling infections and detecting asymptomatic cases which expedites the speedy isolation, adequate treatment and consequently reduces contagion rates. Many laboratory parameters such as absolute neutrophilia, thrombocytopenia, hypoalbuminemia, the elevation of liver enzymes, creatinine and nonspecific inflammatory markers such as C-reactive protein (CRP) and Interleukin 6 (IL-6) make it possible to assess the severity of the disease and predict the risk of it evolving toward more serious afflictions such as acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and multiple organ failure (MOF). In addition, lymphopenia, elevated D-dimer, ferritin as well as LDH, CPK and troponin markers are the main predictors for the progression of the disease⁷.

Several studies have reported the clinical manifestations and blood biochemical features of patients with COVID-19. As blood biochemical changes play an essential role in estimating the patients' condition and prognosis, directing treatment,

and even evaluating the curative effects, we aim to assess the biochemical changes among 237 COVID-19 cases reported to Combined Military Hospital Dhaka during early pandemic.

METHODS

Combined Military Hospital Dhaka is a tertiary level iconic military hospital which started to receive Covid-19 patients from 08 April 2020 and dedicated to render treatment for the entitled personnel of armed forces. This cross sectional study was conducted at Combined Military Hospital Dhaka from 15 April 2020 to 31 May 2020 among purposively selected 237 confirm COVID-19 cases with an objective to assess the biochemical changes. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase polymerase chain reaction (rt-PCR) assay using a nasopharyngeal and throat swab specimen. Data were collected from the patient through face to face interview by semi structured questionnaire and review of medical records. Informed written consent was taken from all the respondents and neither any intervention or any invasive procedure was undertaken. Prior to the commencement of the study ethical clearance was taken from the competent ethical committee of Combined Military Hospital Dhaka. The questionnaire includes sociodemographic information, contact history, comorbidities, clinical features and relevant hematological and biochemical investigations such as Blood for complete picture (CBC), serum ferritin, D-dimer, C-reactive protein, Serum procalcitonin, Serum ALT, serum AST and Lactate dehydrogenase which obtained from medical record review. According to the objective of the study data processing and analysis were done by SPSS version 23. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Highest number (37.1%) of the respondents were in the age group of 31-40 years which was followed by <30 years (30.0%). Average age of the respondents was 37 (± 10.84) years with age range of 20 to 67 years. Male (83.1%) and Muslim (95.6%) respondents are clearly higher. In regards to the educational qualification, 58.6% were educated up to secondary level. About 84% were married and 84.4% were serving respondents. Majority (57%) of the respondents stayed at hostel/mess and equal (45.1%) numbers were smoker and non-smokers with 9.7% were occasional smoker [Table-I].

Table – I: Sociodemographic Characteristics of the COVID-19 Positive Patients (n=237)

Characteristics	Frequency (%)	Characteristics	Frequency (%)
Age of the Respondents (Years)		Marital Status	
<30	71 (30.0)	Married	199 (84.0)
31-40	88 (37.1)	Single	38 (16.0)
>41	78 (32.9)	Profession	
Mean (±SD)	37.60 (±10.841)	Business	22 (9.3)
Range	20-67	Service	200 (84.4)
Sex		Others	13 (5.5)
Female	40 (16.9)	Living Status	
Male	197 (83.1)	Single	7 (3.0)
Religion		Family	95 (40.1)
Muslim	227 (95.8)	Hostel/Mess	135 (57.0)
Hindu	10 (4.2)	Smoking History	
Educational Qualification		Regular Smoker	107 (45.1)
Up to Primary	22 (9.3)	Occasional Smoker	23 (9.7)
Up to Secondary (HSC)	139 (58.6)	Non-smoker	107 (45.1)
Graduation and above	76 (32.1)		

In regards to the contact history, 87.8% had contact with a confirmed case of a Covid-19 positive case and 44.7% respondents had a history of visiting a crowded place in previous 14 days. Very few respondents gave

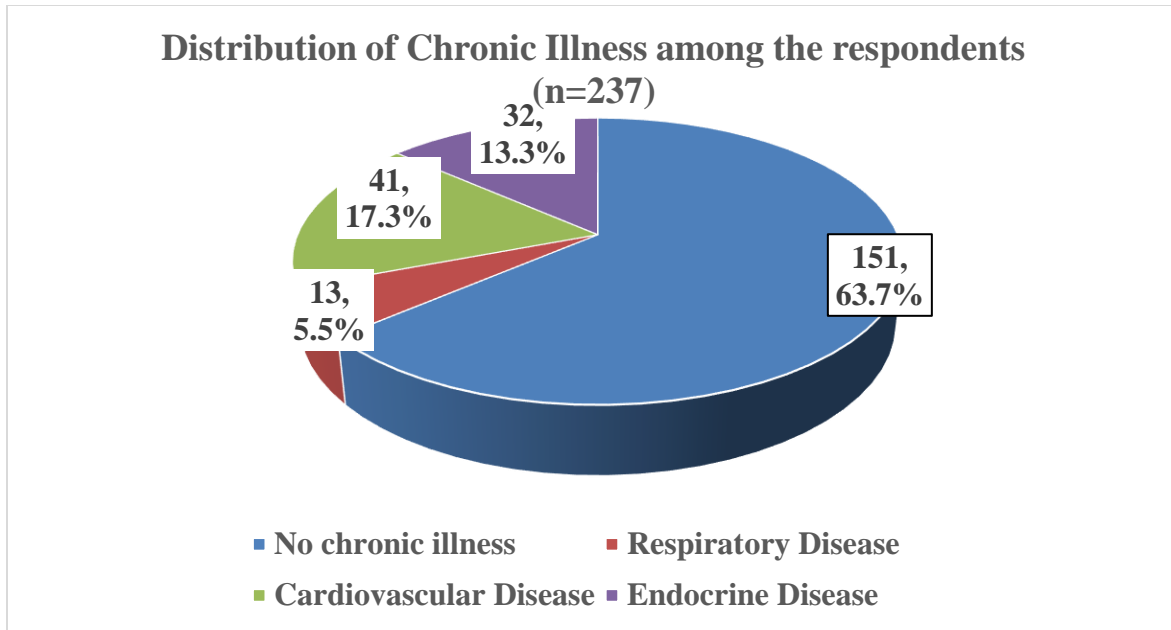
history of contact with a suspected case, contact with a person coming from abroad and recent fever [Table-II].

Table – II: Various Contact History of the COVID-19 Positive Patients (n=237)

	Frequency	Percentage
Contact with a Confirmed Cases		
Yes	208	87.8
No	29	12.2
Contact with a Suspected Cases		
Yes	9	3.8
No	228	96.2
Contact with a person coming from abroad		
Yes	3	1.3
No	234	98.7
Contact with a person having recent Fever		
Yes	2	0.8
No	235	99.2
Visited a Crowded Place		
Yes	106	44.7
No	131	55.3

In regards to the chronic diseases among the respondents, 17.3% suffering from cardiovascular diseases which was followed by endocrine disease like

Diabetes Mellitus (13.5%) and 5.5% was suffering from respiratory disease [Table-III].



Among the respondents, majority were presented with fever (34.6%), cough (22.9%), sore throat (10.6%), generalized weakness (9.2%). Others symptom

presentations were headache (8.4%), myalgia (7.8%), alteration of taste (2.0%) etc. About 1.1% respondents presented with no symptoms. (Table - IV)

Table – IV: Distribution of presenting symptoms among the respondents (n=237)

	n	Percent of Cases	Percent as only symptom
Asymptomatic	7	3.0%	1.1%
Fever	222	93.7%	34.6%
Cough	147	62.0%	22.9%
Sore Throat	68	28.7%	10.6%
Generalized Weakness	59	24.9%	9.2%
Headache	54	22.8%	8.4%
Myalgia	50	21.1%	7.8%
Other symptoms	35	14.7	5.5%

Majority of the respondents showed normal biochemical findings. But about 17.7% showed increased peripheral blood count like neutrophilia and 15.6% showed decreased count, 23.2% showed increased ESR, 30.0% showed positive D-dimer test, 22.4% showed either sepsis or systemic infection in

procalcitonin estimation, 28.3% with increased ferritin, 28.7% showed positive C reactive protein, 12.7% and 12.2% of the respondents showed increased ALS and AST respectively, 21.1% with increased LDH estimation (Table-VIII).

Table – VIII: Distribution of biochemical findings of the respondents (n=237)

	Frequency (%)
Neutrophil Count	
Within normal limit	165 (69.6)
Increased	72 (30.4)
Lymphocyte Count	
Within normal limit	188 (79.3)

	Frequency (%)
C reactive protein	
Normal	169 (71.3)
Positive	68 (28.7)
Serum ferritin	
Within Normal Limit	170 (71.7)

Decreased	49 (20.7)
Thrombocyte Count	
Within normal limit	203 (85.7)
Decreased	34 (14.3)
D-Dimer	
Normal	166 (70.0)
Positive	71 (30.0)
Procalcitonin	
Healthy Individual	184 (77.6)
Systemic Infection	13 (5.5)
Sepsis	40 (16.9)

Increased	67 (28.3)
ALT	
Normal	207 (87.3)
Increased	30 (12.7)
AST	
Normal	208 (87.8)
Increased	29 (12.2)
LDH	
Normal	187 (78.9)
Increased	50 (21.1)

To find out the factors associated with abnormal biochemical findings in relation to the chronic diseases like cardiovascular, respiratory and diabetes mellitus of the respondents, chi-square test was done which revealed that all the biochemical abnormalities were significantly associated with cardiovascular and

diabetes mellitus except lymphocyte and thrombocyte count ($p < 0.05$) but not with the respiratory diseases ($p > 0.05$). Association of D-dimer with respiratory disease revealed statistically significant ($p < 0.05$) (Table IV).

Table IV: Association between various chronic disease and biochemical abnormalities of the respondents (n=237)

Attributes	Cardiovascular Disease		p value	Respiratory Disease		p value	Endocrine Disease		p value
	Yes	No		Yes	No		Yes	No	
Neutrophil count									
Within normal limit	23 (9.7%)	142 (59.9%)	$p < 0.05$	7 (3.0%)	158 (66.7%)	$p > 0.05$	17 (7.2%)	148 (62.4%)	$p < 0.05$
Increased	18 (7.6%)	30 (12.7%)		6 (2.5%)	66 (27.8%)		15 (6.3%)	57 (24.1%)	
Lymphocyte count									
Within Normal Limit	30 (12.7%)	158 (66.7%)	$p > 0.05$	10 (4.2%)	178 (75.7%)	$p > 0.05$	23 (9.7%)	165 (69.6%)	$p > 0.05$
Decreased	11 (4.6%)	28 (10.0%)		3 (1.3%)	46 (19.4%)		9 (3.8%)	40 (16.9%)	
Thrombocyte count									
Within Normal Limit	37 (15.6%)	166 (70.0%)	$p > 0.05$	13 (5.5%)	190 (80.2%)	$p > 0.05$	28 (11.8%)	175 (73.8%)	$p > 0.05$
Decreased	4 (1.7%)	30 (12.7%)		0 (0.0%)	34 (14.3%)		4 (1.7%)	30 (12.7%)	
D-dimer									
Negative	19 (8.0%)	147 (62.0%)	$p < 0.05$	6 (2.5%)	160 (67.5%)	$P < 0.05$	11 (4.6%)	155 (65.4%)	$p < 0.05$
Positive	22 (9.3%)	49 (20.7%)		7 (3.0%)	64 (27.0%)		21 (8.9%)	50 (21.1%)	
C-reactive protein									
Normal	19 (8.0%)	150 (63.3%)	$p < 0.05$	7 (3.0%)	162 (68.4%)	$p > 0.05$	11 (4.6%)	158 (66.7%)	$p < 0.05$
Positive	22 (9.3%)	46 (19.4%)		6 (2.5%)	62 (26.2%)		21 (8.9%)	47 (19.8%)	
Procalcitonin									

Healthy Individual	27 (11.4%)	157 (66.2%)	p<0.05	8 (3.4%)	176 (74.3%)	p>0.05	20 (8.4%)	164 (69.2%)	p<0.05
Systemic infection	7 (3.0%)	6 (2.5%)		2 (0.8%)	11 (4.6%)		6 (2.5%)	7 (3.0%)	
Sepsis	7 (3.0%)	33 (13.9%)		3 (1.3%)	37 (15.6%)		6 (2.5%)	34 (14.3%)	
S. Ferritin									
Within Normal Limit	21 (8.9%)	149 (62.9%)	p<0.05	7 (3.0%)	163 (68.8%)	p>0.05	13 (5.5%)	157 (66.2%)	p<0.05
Increased	20 (8.4%)	47 (19.8%)		6 (2.5%)	61 (25.7%)		19 (8.0%)	48 (20.3%)	
ALT									
Normal	30 (12.7%)	177 (74.7%)	p<0.05	11 (4.6%)	196 (82.7%)	p>0.05	22 (9.3%)	185 (78.1%)	p<0.05
Increased	11 (4.6%)	19 (8.0%)		2 (0.8%)	28 (11.8%)		10 (4.2%)	20 (8.4%)	
AST									
Normal	31 (13.1%)	177 (74.7%)	p<0.05	11 (4.6%)	197 (83.1%)	p>0.05	23 (9.7%)	185 (78.1%)	p<0.05
Increased	10 (4.2%)	19 (8.0%)		2 (0.8%)	27 (11.4%)		9 (3.8%)	20 (8.4%)	
LDH									
Normal	22 (9.3%)	165 (69.6%)	p<0.05	8 (3.4%)	179 (75.5%)	p>0.05	18 (7.6%)	169 (71.3%)	p<0.05
Increased	19 (8.0%)	31 (13.1%)		5 (2.1%)	45 (19.0%)		14 (5.9%)	36 (15.2%)	

DISCUSSION

We conducted this cross sectional study on 237 RT-PCR positives cases admitted in combined Military Hospital Dhaka from 15 April 2020 to 31 May 2020 with an objective to assess the biochemical changes of COVID 19 patients. In our study the mean age of the respondents was 37 years with standard deviation (SD) of ± 10.84 years which is may be due the selection of study respondents (armed forces personnel). Similar finding revealed from the study conducted in Bangladesh by Morshed MS et al, Mawla SGM et al and Chowdhury AT et al where the majority of the respondents were from these age group⁸⁻¹⁰. We found that 83.1% of the respondents were male and rest are female which is similar to a study conducted by Morshed MS *et al.*, Mawla SGM *et al.*, Chowdhury AT *et al.*, Guan WJ *et al.*, Gupta N *et al.* and Huang C *et al.* where the majority of the respondents were male⁸⁻¹³. In regards to the educational qualification, it was revealed that 58.6% of the patients were educated up to secondary level which may be due to the service requirement for the armed forces where the minimum requirement for enrollment in armed forces is secondary school certificate qualification.

In regards to the contact history, we revealed that about 87.8% had contact with a confirmed case of a

COVID-19 positive case and 44.7% respondents had a history of visiting a crowded place in previous 14 days. Mawla SGM *et al.* revealed in their study that 60% of patients had positive contact history that highlights the importance of preventive and containment processes of pandemic including distancing, hand washing and proper usage of mask, etc.⁹. This finding also consistent with the study conducted by Nanshan Chen *et al.* who revealed that almost all the positive COVID-19 patients had a history of exposure to the Hunan seafood market¹⁵. Similar findings also revealed from the study conducted by Guan WJ *et al.* Chang D *et al.* also revealed the same findings where almost all the patients had some exposure either directly to the Wuhan sea food market or residents of Wuhan or having a history of visiting the city of Wuhan^{11,16}. Very few respondents gave history of contact with a suspected case, contact with a person coming from abroad and recent fever.

In our study we revealed that about 47.7% suffering from cardiovascular diseases like hypertension, Ischemic Heart Diseases which was followed by endocrine disease like Diabetes Mellitus (37.2%) and 15.1% was suffering from respiratory disease. This finding matched with the study findings done by Morshed MS *et al.*⁸. In their study conducted by Gao

M *et al.* revealed that 25.7% of the respondents present with a history of cardiovascular disease and 22.9% with digestive diseases¹⁷. Similar findings also revealed in their study conducted by Richardson *et al.* and Wang D *et al.*^{14,18}. Another study conducted by Guan WJ *et al.* revealed that hypertension (21%) and diabetes (16%) was the most common comorbidities which is also found in our patients like the world¹¹.

Among the respondents, majority were presented with fever (34.6%), cough (22.9%), sore throat (10.6%), generalized weakness (9.2%). Others symptom presentations were headache (8.4%), myalgia (7.8%), alteration of taste (2.0%) etc. About 1.1% respondents presented with no symptoms. These findings matched with the study conducted by Morshed MS *et al.*, Mawla SGM *et al.*, Chowdhury AT *et al.*, Guan WJ *et al.*, Gupta N *et al.* and Huang C *et al.* All the studies revealed that fever was the most common presenting symptoms which was followed by cough, weakness, head ache, sore throat, loss of appetite, difficulty in breathing, altered sensation of taste or smell and body ache etc.^{8,9,10,11,12,13}. Similarly, in a meta-analysis from China, most prevalent symptoms they found were fever (80.4%), cough (63.1%) and fatigue (46%)^{19,20}. In contrast, one study from Europe on mild to moderate patients reported that headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%) were the most common symptoms; fever was reported by only 45.4% of patients. We found that about 5.5% patient presented with loss of smell and about 4.5% with loss of taste sensation, which is not consistent with the findings of a study conducted by Lechien JR *et al.* where they found that 39% of mild cases, 40% of moderate cases and 12.5% of severe cases reported the altered sensation of taste or smell in this study. While olfactory and gustatory dysfunctions were prevalent symptoms in European patients, they were only rarely reported in Chinese patients^{21, 22}.

Majority of the respondents showed normal biochemical findings. But about 33.3% showed alteration of peripheral blood picture either increased or decreased in count, 23.2% showed increased ESR, 30.0% showed positive D-dimer test, 22.4% showed either sepsis or systemic infection in procalcitonin estimation, 28.3% with increased ferritin, 28.7% showed positive C reactive protein, 21.1% with increased LDH estimation. In a review conducted by Marcello Ciaccio and Luisa Agnello described about detail events of hematological, inflammatory and coagulation dysfunctions associated with COVID-19 disease especially blood for CBC, ESR, d-dimer, C-reactive protein, procalcitonin, ferritin, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase which was consistent with our findings²³. It was also consistent with the study

conducted by Chowdhury AT *et al.* and Chen J *et al.* where they revealed an increased level of ESR, CRP, SGPT, S. Ferritin, Prothrombin time, and D-Dimer, leukopenia and lymphopenia in 28.9% and 47.4% of the patients, respectively. Chen J *et al.* also revealed less common elevated levels of alanine aminotransferase, aspartate aminotransferase^{10,24}.

To see the association between chronic illness and biochemical abnormalities, we conducted chi-square test which revealed that all the biochemical abnormalities were significantly associated with cardiac and endocrine diseases ($p < 0.05$). Several studies and review conducted at China, Italy, Iran, Morocco, India, Iraq, UAE, USA revealed that various biochemical abnormalities are more prevalent among the COVID-19 patients with pre-existing comorbidities like hypertension, ischemic heart disease, diabetes which is similar to our study as well^{23,25-27,28-31}.

CONCLUSION

We conducted the study at the early days of the pandemic in CMH Dhaka where majority of the respondents showed normal hematological and biochemical abnormalities. Even though our findings revealed several abnormalities which helped the physicians in early recognition to the assessment of the disease severity. We also revealed that patient with pre-existing chronic diseases had several statistically significant biochemical abnormalities which helped in monitoring of such COVID-19 patients with disease progression, reduce mortality and there by useful in improving the recovery rate as well as monitoring of therapeutic intervention.

ACKNOWLEDGEMENT

The author thanks Major (Dr.) Md Faruk Ahmed and Major (Dr.) Zinnatun Nabi for their kind support during data collection. We also thank the Matron, ward master and all the in charges who support and help during data collection. Finally, we thank all the respondents who kindly contributed to this study.

REFERENCES

1. Deng X, Liu B, Li J, Zhang J, Zhao Y, Xu K. Blood biochemical characteristics of patients with coronavirus disease 2019 (COVID-19): a systemic review and meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020 Jun 17;1(ahead-of-print).
2. <https://iedcr.gov.bd/covid-19/covid-19-situation-updates>. Accessed on 15 March 2020

3. <https://www.worldometers.info/coronavirus/>. Accessed on 31 August 2020.
4. <https://www.dhakatribune.com/health/coronaviruses/2020/08/15/ispr-8-636-armed-forces-members-families-infected-with-covid-19-128-dead>. Accessed on 31 August 2020.
5. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, Ma K. A systematic review of asymptomatic infections with COVID-19. *Journal of Microbiology, Immunology and Infection*. 2020 May 15.
6. Ciaccio M, Agnello L. Biochemical biomarkers alterations in Coronavirus Disease 2019 (COVID-19). *Diagnosis*. 2020 Jun 24;1(ahead-of-print).
7. Letelier P, Encina N, Morales P, Riffo A, Silva H, Riquelme I, Guzmán N. Role of biochemical markers in the monitoring of COVID-19 patients. *Journal of Medical Biochemistry*. 2021 Mar 12;40(2):115.
8. Morshed MS, Al Mosabbir A, Chowdhury P, Ashadullah SM, Hossain MS. Clinical manifestations of patients with Coronavirus Disease 2019 (COVID-19) attending at hospitals in Bangladesh. *medRxiv*. ko2020 Jan 1
9. Mowla SG, Azad KA, Kabir A, Biswas S, Islam MR, Banik GC, Khan MM, Rohan KI, Alam MA. Clinical Profile of 100 Confirmed COVID-19 Patients Admitted in Dhaka Medical College Hospital, Dhaka, Bangladesh. *Journal of Bangladesh College of Physicians and Surgeons*. 2020 Jun 9:29-36.
10. Chowdhury AT, Karim MR, Mehedi HH, Shahbaz M, Chowdhury MW, Dan G, He S. Analysis of the primary presenting symptoms and hematological findings of COVID-19 patients in Bangladesh.
11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020 Apr 30;382(18):1708-20. DOI: 10.1056/NEJMoa2002032.
12. Gupta N, Agrawal S, Ish P, Mishra S, Gaiind R, Usha G, Singh B, Sen MK, Safdarjung Hospital COVID 2019 working group. Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India. *Monaldi Archives for Chest Disease*. 2020 Apr 10;90(1).
13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020 Feb 15;395(10223):497-506.
14. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *Jama*. 2020 Apr 22.
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia JA. Características epidemiológicas y clínicas de 99 casos de neumonía por el nuevo coronavirus de 2019 en Wuhan, China: un estudio descriptivo. *Lancet*. 2020;395(10223):507-13.
16. Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CS, Sharma L. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *Jama*. 2020 Mar 17;323(11):1092-3.
17. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, Ma K. A systematic review of asymptomatic infections with COVID-19. *Journal of Microbiology, Immunology and Infection*. 2020 May 15.
18. Wang D; Hu B; Hu C; Zhu F et al; Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China; *JAMA*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
19. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3,062 COVID-19 patients: a meta-analysis. *Journal of Medical Virology*. 2020 Apr 15.
20. Kakodkar P, Kaka N, Baig M (April 06, 2020) A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus* 12(4): e7560. DOI 10.7759/cureus.7560.
21. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, Huet K, Plzak10 J, Horoi M, Hans S, Barillari MR. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus.
22. Lechien JR, Chiesa-Estomba CM, De Siaty DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y. Olfactory and gustatory dysfunctions

- as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-Rhino-Laryngology*. 2020 Apr 6:1-1.
23. Ciaccio M, Agnello L. Biochemical biomarkers alterations in Coronavirus Disease 2019 (COVID-19). *Diagnosis*. 2020 Jun 24;1(ahead-of-print).
 24. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, Li F, Xu Q, Zhang Y, Xu S, Song Z. Clinical progression of patients with COVID-19 in Shanghai, China. *Journal of Infection*. 2020 Mar 19.
 25. Wang D, Li R, Wang J, Jiang Q, Gao C, Yang J, Ge L, Hu Q. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. *BMC infectious diseases*. 2020 Dec;20(1):1-9.
 26. Carobene A, Ferrari D, Campagner A, Cabitza F, Sabetta E, Ceriotti D, Di Resta C, Locatelli M. Evidence of significant difference in key COVID-19 biomarkers during the Italian lockdown strategy. A retrospective study on patients admitted to a hospital emergency department in Northern Italy. *Acta Bio Medica: Atenei Parmensis*. 2020;91(4).
 27. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2020 Nov;510:475.
 28. Kantri A, Ziati J, Khalis M, Haoudar A, El Aidaoui K, Daoudi Y, Chikhaoui I, El Yamani K, Mouhaoui M, El Bakkouri J, Dini N. Hematological and biochemical abnormalities associated with severe forms of COVID-19: A retrospective single-center study from Morocco. *Plos one*. 2021 Feb 4;16(2):e0246295.
 29. Kumar S, Triloki RK, Goyal S. A review on biochemical changes in COVID-19 patients: *International Journal of Scientific Research*. Volume-10, Issue-04, April 2021.
 30. Alyammahi SK, Abdin SM, Alhamad DW, Elgendy SM, Altell AT, Omar HA. The dynamic association between COVID-19 and chronic disorders: An updated insight into prevalence mechanism and therapeutic modalities. *Infection, Genetics and Evolution*. 2020 Nov 29:104647. Italy: 24
 31. Medhat L, Muhsin SS, Mohammed NS. Changes occurrence in biochemical aspect in patients with Corona virus (Covid-19). *Age*;20:39.