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RESEARCH ARTICLE

Analysis of different risk factors of hospitalized COVID-19 patients from North-Eastern Bangladesh

Mohammad Golam Rob Mahmud [1], *Md. Toasin Hossain Aunkor* [2*], *Fatima Rahman* [2], *Darimi Hasin* [2], *Jilwatun Noor* [3], *Md. Faruque Miah* [2]

[1] Department of Internal Medicine, Jalalabad Ragib Rabeya Medical College and Hospital, Sylhet, Bangladesh

[2] Department of Genetic Engineering and Biotechnology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

[3] Department of Microbiology, Sylhet Woman's Medical College, Sylhet, Bangladesh

ABSTRACT

Background: In Bangladesh, fighting with the delta sub variety of SARS-CoV-2 was most difficult than its previous and following waves. The aim of this study is to shed light upon different risk factors of COVID-19 and their influences across age-groups inpatients in North-Eastern Districts.

Methods: In this case control study, we included 75 positive and 24 negative patients admitted to Jalalabad Ragib Rabeya Medical College and Hospital, Sylhet, Bangladesh from 1st August to 30th September 2021. Different demographic, clinical and radiographic data were collected, analyzed, and compared between/among patients to assess diseases severity.

Results: On average patients with COVID-19 were more likely to display remarkably 4, 1.3, and 1.5 times higher serum D-dimer, C-reactive protein, and ferritin level compared to non-COVID-19 people. Higher number of elderly inpatients from the age of 40; specially 60 years and older accounted for the abnormal rise of the aforesaid biochemical risk factors. This age range was also concerning for intensive care unit admission and multiple biomarker elevation. Nevertheless, the percentage of hospitalized COVID-19 patients with hypertension and diabetes is calculated 45% and 30.3%. Alarmingly, 96% of our patients showed COVID-19 assisted lung abnormalities diagnosed by computerized tomography scan and hither the order for degree of damage was bilateral consolidation>ground-glass opacity>pulmonary lesion>chronic obstructive pulmonary disease>cardiomegaly.

Conclusions: Age is the principle demographic risk factor of COVID-19, and it has positive correlation with different hospital outcomes, biochemical risk factors, abnormal radiographic manifestations and comorbidities.

Keywords: COVID-19, outcomes, risk factors, biomarkers, comorbidities

Correspondence:
Md. Toasin Hossain Aunkor

Address: Department of Genetic Engineering and Biotechnology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

Email: toasin-geb@sust.edu

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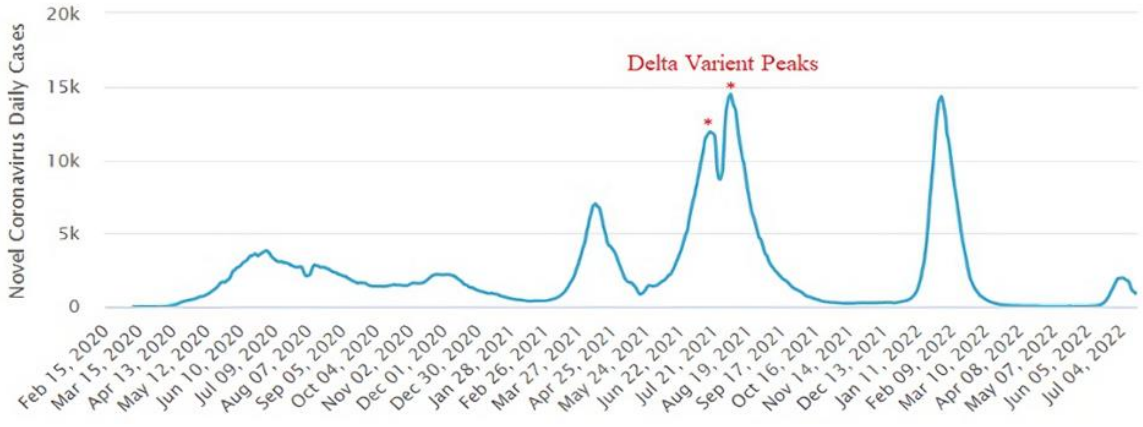
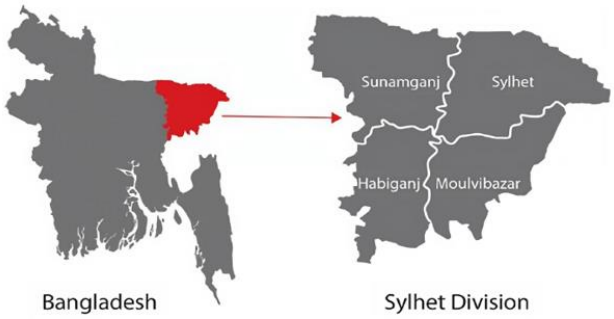
INTRODUCTION

As of January 2023, more than 6.5 million people have died as a result of COVID-19 since it was discovered in Wuhan, China, in December 2019 [1]. Over time genetic mutation generates novel variety of SARS-COV-2, which become significantly different from the original one. However, virus strain delta caused more global illnesses and fatalities than earlier variants due to its easier transmission. Primarily, COVID-19 is a multisystemic respiratory sickness generally confirmed by RT-PCR, but different inflammatory markers include serum D-dimer, C-reactive protein (CRP), and ferritin are the common biochemical risk factors to monitor progress of sepsis. Alongside with biochemical and clinical characteristics, computerized tomography (CT) scan of chest also plays a precious role in prediction, early recognition, prognosis, triage, and follow-up of COVID-19 [2]. Increased age itself a risk factor for COVID-19 patients and it has reportedly been connected to COVID-19 catastrophic consequences [3]. Also, age related comorbidities specially pre-existing hypertensive and diabetic patients are more vulnerable to grow serious complications of COVID-19 [4, 5]. Bangladesh is the eighth-most densely populated nation in the world with a substandard healthcare system; more than 165 million people living in an area of.



(a)



(b)

Figure 1. (a) Daily active cases of COVID-19 from February 2020-July 2022 (red star sings indicate period of this study [12]) & (b) Geographical location of Sylhet division in the country map with its districts (study area) [13]

148,460 square kilometers. Like other parts of the world, the residents of Bangladesh were also the worst sufferer of COVID-19 delta variant. Sylhet division located at North-Eastern corner of Bangladesh consisting of four districts namely Sylhet, Sunamganj, Habiganj, and Moulvibazar. Being a hot spot of native and international tourism and having 3,073 km open land border with two Indian States: Meghalaya and Assam, Sylhet was one of the high-risk COVID-19 zone throughout the pandemic specially during the time frame of Indian delta havoc. The management of this delta wave was a terrible threat for Bangladesh because of our population density, less public interest to follow social distancing, poverty, inadequate healthcare capacity and insufficient vaccine availability [6].

Different sorts of research were led by biological researchers from various regions of Bangladesh that analyzed data on the clinical characteristics, diagnosis, and treatment of COVID-19 along with the risk factors associated with it [7-11]. But there is no such study particularly for North-Eastern Region to translate clinical data into statistical analysis with a view to exploring the contribution of different COVID-19 risk factors in diseases progression during the delta wave. In this write-up, at first, we deemed age as a major demographic risk factor and accounted its role on two hospitalization outcomes. Secondly, we assessed elevation of three most common biochemical risk factors or biomarkers of COVID-19 monitoring: D-dimer, ferritin, and CRP with age of our hospitalized patients.

We also estimated the number of aforenamed elevated biomarkers with their distribution against age and gender. Remarkably, the interrelation of single to multiple elevation of the biomarkers with aging was discussed. However, many patients underwent lung CT scan at admission and the current study elucidated, which CT findings led the principal damage of lung tissue. Furthermore, a good number of our hospitalized patients had hypertension and diabetes; therefore, here we disclosed the correlation of these two common comorbidities with age. Moreover, we also mapped other necessary risk factors provided equal importance in patients care, although their detail analysis is beyond the objective of this study.

METHODS

A total number of 75 confirmed patients with common COVID-19 symptoms including fever, cough, diarrhea, muscle pain, dyspnea, loss of smell and test, shortness of breath, tiredness, sore throat and fatigue were recruited retrospectively from August 1st to September 30th, 2021 (part a in **Figure 1**), when Bangladesh went through a critical peak position of pandemic period for the most infectious and transmissible Indian delta variant (daily cases=12k to 15k).

At the same time, there were 24 patients admitted in the hospital with some of the aforementioned symptom together

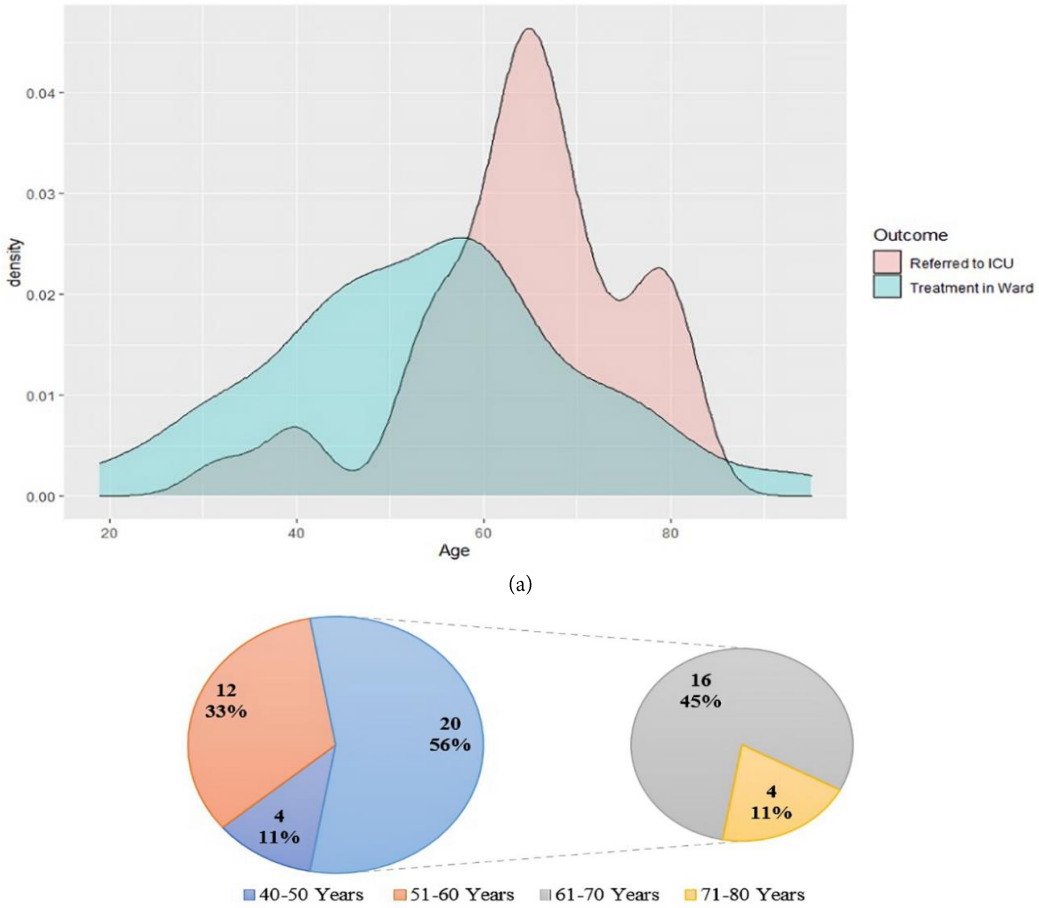


Figure 2. (a) Density plot of hospitalized patients age & outcome & (b) Percentage of ICU admitted patients according to age range (Source: Authors' own elaboration)

with other complication but tested negative in RT-PCR test. Patients were admitted to Jalalabad Ragib Rabeya Medical College, Sylhet, which is one of the largest comprehensive privet medical center in North-Eastern part of the country with special COVID-19 treatment unit and followed for the study until discharge. For being an affiliated institute of Shahjalal University of Science and Technology, Sylhet; we retroactively collected clinical data, demographic information, nasopharyngeal swab test results, laboratory serological and imaging data with other necessary medical records using standardized data collection chart from the admitted patients of four constituent districts of Sylhet division (part b in **Figure 1**). All of the categorical variables such as number and percentage and continuous variables such as mean and standard deviation (SD) or median and interquartile range (inter-quartile range [IQR], stated as 25th and 75th percentiles) were calculated using the available data. The density plots and missingness map were constructed by R statistical package.

RESULTS

The average age of the 99 patients was 57.82 years, ranging from 20 to 80 years. The mean time from symptom onset to admission was 3±2 days and the average length of hospital stay forward, and intensive care unit (ICU) was 10±4 and 22±8, respectively. RT-PCR test confirmed 75 patients positive, and 24 patients negative upon hospitalization.

Part a in **Figure 2** shows the graphics for age distribution of 99 hospitalized patients for both ICU and wards including positive and negative. Patients taking treatment in the ward is distributed from 20 to 80 years displaying a peak between 40 to 60 age range. In contrast, patients referred to ICU showed a right shifted curve with a sharp peak towards a greater age range, i.e., 60-70. Afterwards, there were 36 patients referred in the ICU and they were all older than 40.

However, part b in **Figure 2** exhibits the percentage of their age range and states that 78% of the people staying in ICU were between 50-70 years old.

The elevation of D-dimer (>500 ng/ml) was found 75.8% (75/99) of the patients, which were positive in RT-PCR, and this amount was increased up to 4500 ng/ml as their clinical status deteriorated (part a in **Figure 3**). The mean and interquartile range of COVID-19 negative patients were calculated 304.97 and 255.55 whereas these values for COVID-19 positive patients were increased to 1,177 and 673, respectively. Apart from that, patients were grouped into D-

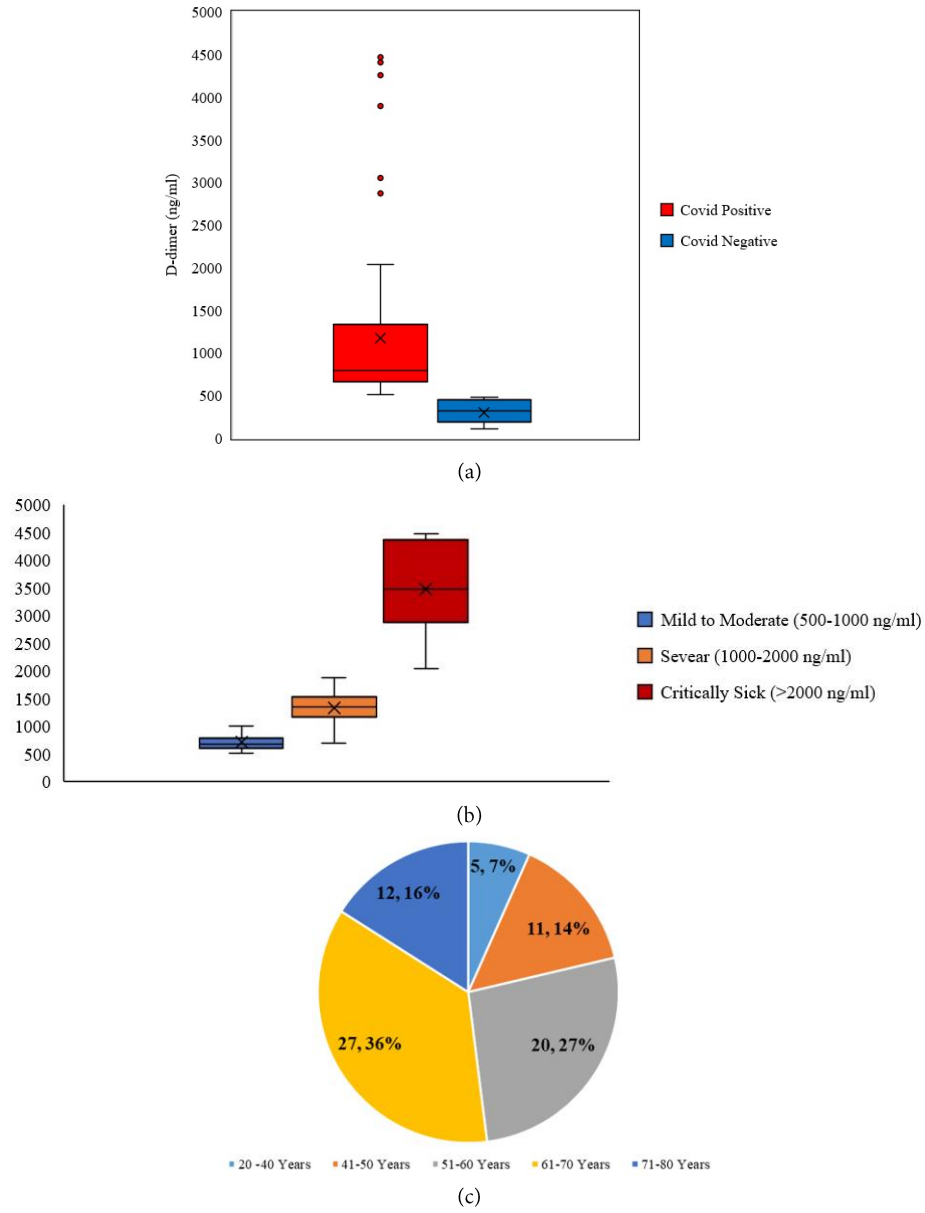


Figure 3. (a) D-dimer levels of patients with COVID-19 positive & negative; (b) Relationship of D-dimer with diseases severity; & (c) Percentage of elevated D-dimer level in different age groups of COVID-19 positive people (Source: Authors' own elaboration)

dimer levels of >500, >1,000, and >2,000 ng/ml to study the diseases severity (part b in **Figure 3**).

Herein, from mild-moderate to severe, the median D-dimer level increases by around two folds (680 vs. 1,340 ng/ml), and from severe to critically ill, it increases by 2.5 folds (1,340 vs. 3,475 ng/ml). In part c in **Figure 3**, the relationship of age with the elevated D-dimer for all of the COVID-19 positive individuals is depicted. It is seen that, only 7% of patients in the lowest age group, 20 to 40 years, showed increased D-dimer levels. Besides, 41% of patients showed an uplifted level of D-dimer within 41-60 years and this ratio was increased of 11% to 52% for 61-80 years. Amongst 75 positive patients, 49 people's serum CRP was diagnosed during hospitalization.

However, from part a in **Figure 4**, the mean and interquartile range of CRP for COVID-19 positive and negative patients are calculated 64.16 mg/L (IQR 20.7-92) and 48.96 mg/L (IQR 8-90). In the following pie chart in part b in **Figure 4**, the elevation of CRP level with the increment of age is displayed. Here, 42% (20 out of 49) and 23% (11 out of 49) patients were above 50 years old to show increased amount of CRP than other two age groups i.e., 41-50 (7 out of 49,14%) years and 20-40 years (10 out of 49, 21%). Besides, patients of elevated CRP level with RT-PCR positive result showed different characteristic radiographic findings in chest CT scan as shown in **Table 1**.

From 75 hospitalized COVID-19 patients, 96% (72 patients) had abnormal chest CT results ranging in age from 20 to 80, with a male to female ratio of 39:33. Here, the average age range for all of the abnormal imaging category was above 53 year commonly showed difficulties of breathing during hospital admission.

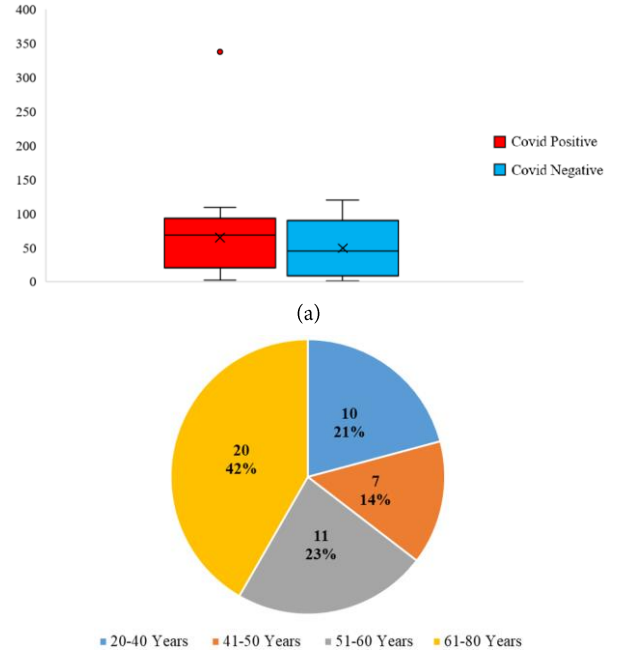


Figure 4. (a) Box plot of CRP levels from COVID-19 positive & negative patients & (b) Percentage of elevated CRP level in different age groups of COVID-19 positive people (Source: Authors' own elaboration)

Table 1. Comparison of chest CT scan abnormalities with age & gender

RF	Gender (M/F)	Mean±SD (AR)	NP
Bilateral consolidation	13/12	55.26±13.19 (28-80)	25
GGO	13/11	53.89±11.99 (29-78)	24
Pulmonary lesion	4/7	59.81±20.67 (20-80)	11
COPD	8/2	65.25±11.88 (48-80)	10
Cardiomegaly	1/1	75.00±7.07 (70-80)	2

Note. RF: Radiographic findings; M: Male; F: Female; AR: Age range; & NP: Number of patients

Consequently, a pareto chart is developed in **Figure 5** and according to the pareto principle, the bilateral consolidation, ground-glass opacities (GGO) and pulmonary lesions accounted for 80% of lung abnormalities, with COPD and cardiomegaly caused 20% of the damage.

Part a in **Figure 6** exhibits the status of serum ferritin test from 45 admitted patients (positive: negative=32:15) affirming that the mean and interquartile range for COVID-19 positive and negative patients are 369.5 ng/ml (IQR 458-203) and 241.3 ng/ml (IQR 200-52.4), respectively i.e., the level of ferritin in positive patients was multiplied almost 1.5 folds than the negative. Additionally, it's significant to note that 11 (or 35% of the 32 positive patients whose ferritin was identified) had normal ferritin, encompassing both males and females. Here, in comparison to individuals with lower ferritin levels (55%), 65% of those with higher ferritin levels were between the ages of 51 and 80 (part b in **Figure 6**).

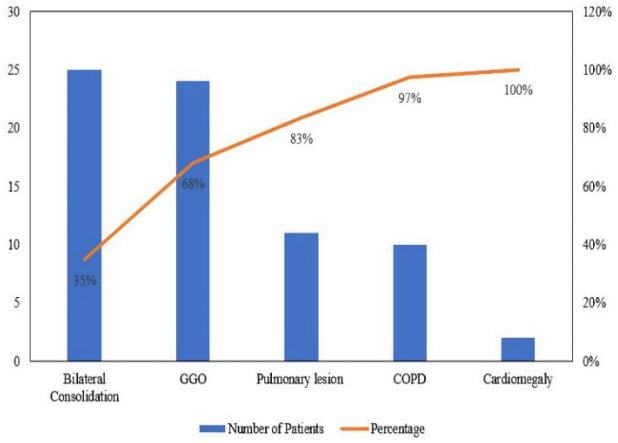


Figure 5. Pareto chart of chest CT manifestation from 72 COVID-19 positive patients (Source: Authors' own elaboration)

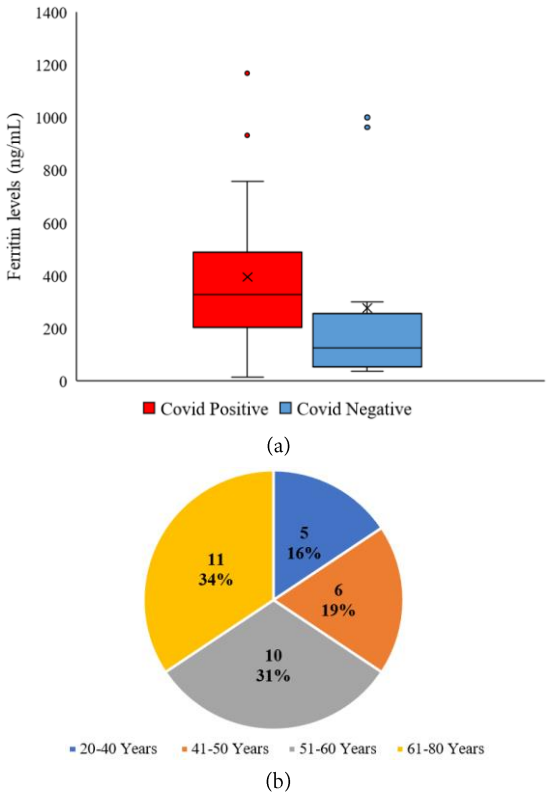


Figure 6. (a) Box diagram of blood ferritin level of COVID-19 positive and negative personnel & (b) percentage of elevated ferritin level in different age groups of COVID-19 positive people (Source: Authors' own elaboration)

Besides, the optimum amount of serum ferritin for male is 10-300 ng/ml and for female it is 10-150 ng/ml, which we consider as threshold. Here, IQR (part a in **Figure 7**) and mean±SD value (**Table 2**) for COVID-19 positive male are 408.09 and 428±316 whereas for female patients these are 345.2 and 276±223.14.

These results clearly indicate that the climbing of ferritin level was higher in male than their counterpart. Contrariwise, these statistical values showed opposite trend for D-dimer (female>male) i.e., the values of mean±SD and inter quartile range for male and female are calculated

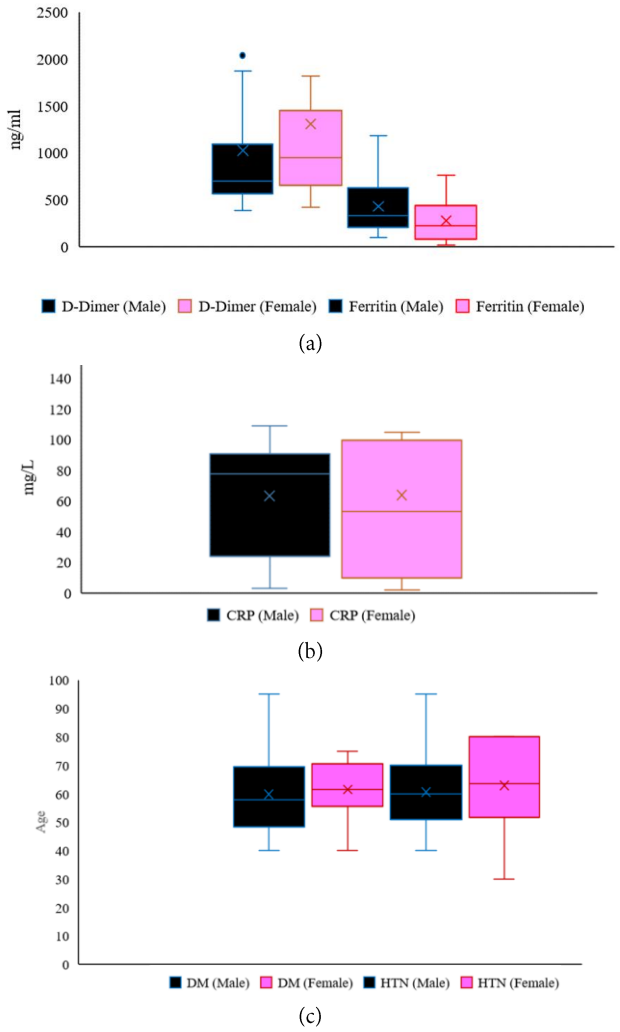


Figure 7. Plotting between (a) D-dimer & ferritin with gender & (b) CRP with gender of COVID-19 positive patients & (c) Gender possessed common comorbidities with age for COVID-19 positive patients (Source: Authors' own elaboration)

1,026±813.83 (IQR 580-1,030) and 1,306.44±1,045.42 (IQR 663-1,429), respectively (part a in **Figure 7**).

Nevertheless, we have pondered equal to or greater than 10 mg/L as elevated CRP ranging from 12 to 337.3 mg/L amongst 51 positive patients (68%) including male and female (part b in **Figure 7**). Here, IQR is calculated 12-99 for male and 24.75-90 for female. Asides from the analyses indicated above, this study also divulges the compatibility of COVID-19 patients having hypertension and diabetes with their age and gender.

According to **Table 2** and part c in **Figure 7**'s data, both male and female should be near about 40 years old to effectively combat hypertension and diabetes. Also, the age evolution after 40 is directly correlated with their emergence. Noticeably, in our 99 hospitalized patients, both male and female, 44 (45%) were witnessed to have hypertension, and 30 (30.3%) had diabetes.

Table 2. Calculation of different statistical parameters using patient's age & gender for biomarkers & comorbidities

Biomarkers & comorbidities[a]	Median	Mean	SD	Minimum	Maximum	IQR
D-dimer (Male)	700.00	1,026.10	813.80	380.00	4,410.00	450.00
D-dimer (Female)	949.10	1,306.40	1,045.40	420.00	4,473.00	765.60
CRP (Male)	63.30	77.50	35.02	3.00	109.00	65.25
CRP (Female)	63.30	53.00	69.70	1.70	337.30	87.00
Hypertension (Male)$_{Age}$	60.00	60.50	13.53	40.00	95.00	17.25
Hypertension (Female)$_{Age}$	63.50	62.90	16.08	30.00	80.00	24.25
Diabetes (Male)$_{Age}$	58.00	59.90	15.02	40.00	95.00	18.00
Diabetes (Female)$_{Age}$	61.50	61.50	10.16	40.00	75.00	11.75

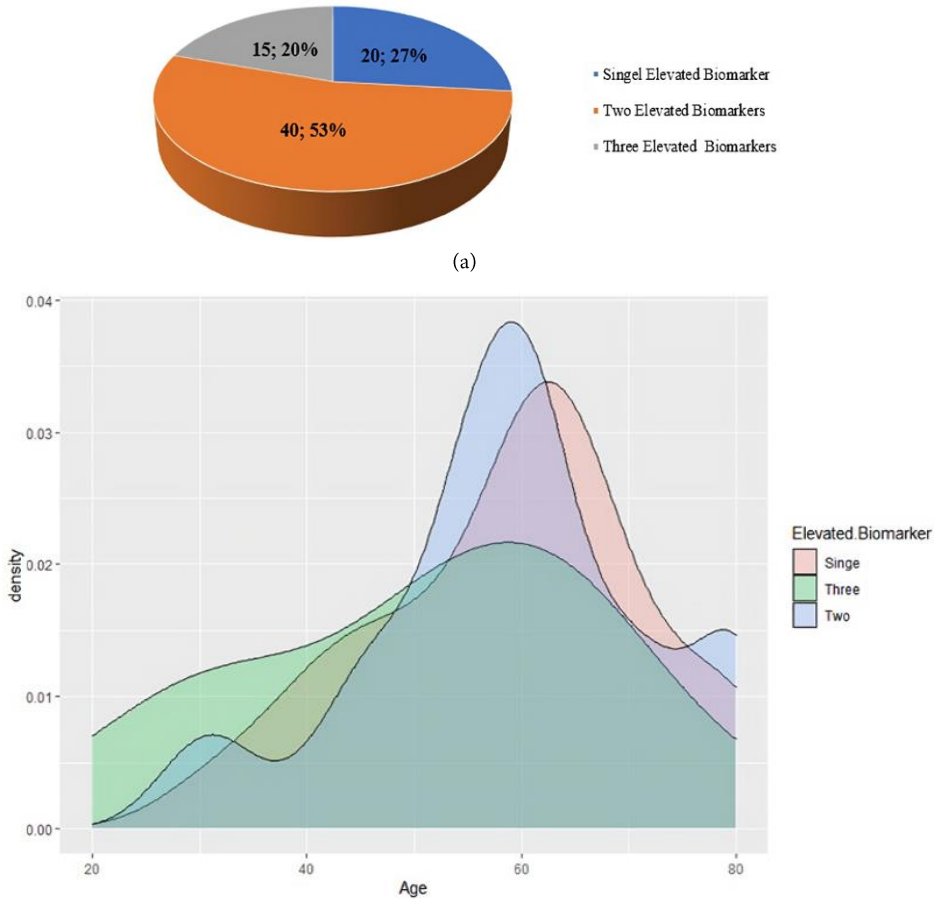


Figure 8. (a) Frequency of single to multiple elevated common biomarkers & (b) Density plot of age vs. single to multiple elevated biomarkers for COVID-19 positive patients (Source: Authors' own elaboration)

In part a in **Figure 8**, the appearance of single or multiple elevated COVID-19 biomarkers amongst D-dimer, CRP, and ferritin is displayed, which means that more than half of our patients had two or more elevated biomarkers; however, these proportions were 27% and 20% for patients with one and three rising biomarkers, separately. From the standpoint of age (part b in **Figure 8**), the exposition of single to multiple biomarkers showed right shifted curves towards greater age range.

At last, the missingness map drawn in **Figure 9** elicits the presence and absence of other diagnostic tests conducted during hospital administration. The value of hemoglobin (Hb), white blood cell (WBC) and platelets were counted by complete blood counting (CBC). Supportively, ESR test was available in most of the patients to trace the level of inflammation. The serum creatine was diagnosed for some COVID-19 patients with renal complications. Furthermore, the electrolyte and acid-base imbalance is quite severe in COVID-19 patients; therefore, the checking of serum sodium, potassium, chloride and bi-carbonate ion was also common in many patients.

DISCUSSION

Age is referred to as a vital demographic risk factor to deal COVID-19 since the rate of hospitalization, admission to ICU, mechanical ventilation, and death vary across ages [14]. In our study, the amount of patient's ICU referral is proportionally affected by age. However, D-dimer is a small serum protein fragment produced after a blood clot is degraded by plasmin during fibrinolysis. The elevation of D-dimer level in COVID-19 patients is given top priority to swiftly consider diseases prognosis. In this study, it is elucidated that the level of abnormal blood coagulation in response to D-dimer emersion was positively correlated with RT-PCR positive results [15]. In addition, from the point of clinical staging, higher number of severe and critically sick patients with extensively increased D-dimer were admitted to the hospital, which is another evidence of the relationship between D-dimer level increment and disease severity [16]. Hither, the number or percentage of populations showed anxiously high to very high D-dimer was from early middle age to late adulthood (40 to 60 and above). These persons had significant number of dissolved clots in their blood that could be life-threatening by arising thromboembolic complications as a direct consequence of the acute lung injury [17]. Secondly, CRP is a blood protein synthesized by

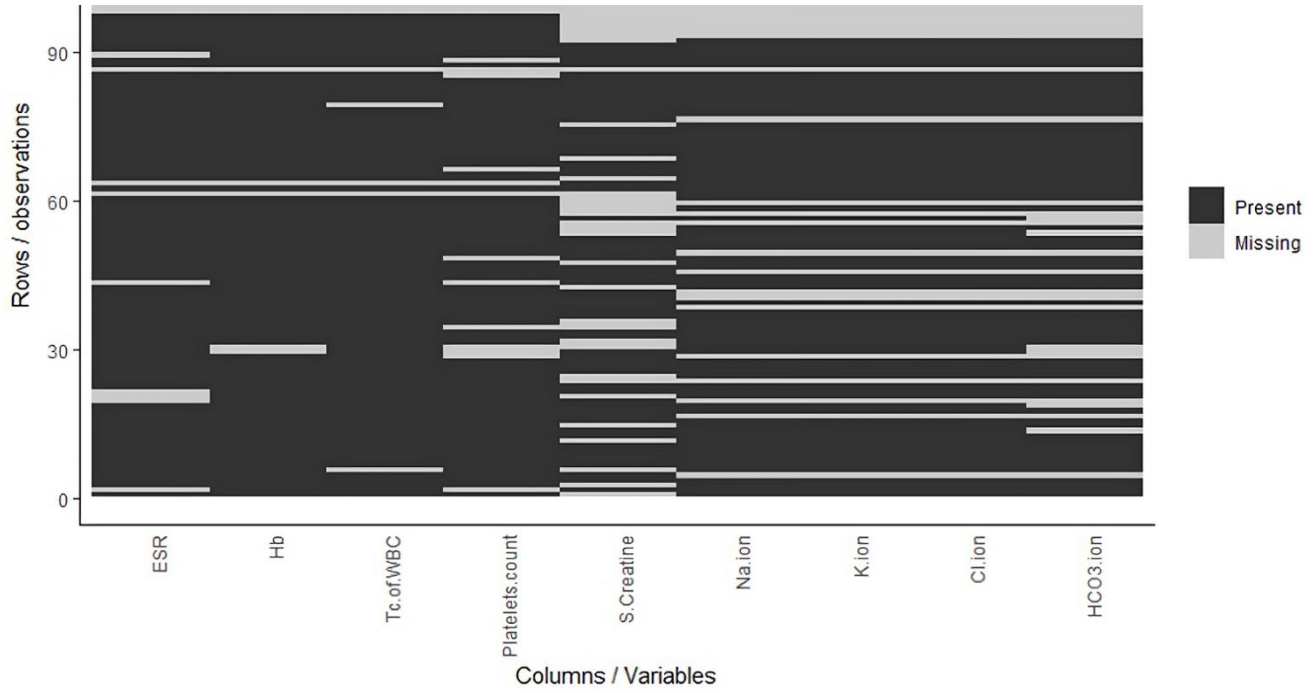


Figure 9. Missingness map of other blood compounds/risk factors tested during hospital admission (Source: Authors' own elaboration)

the liver in response to inflammation in the body. It ideally binds with phosphocholine that expressed highly on the outer membrane of damaged cell. This binding calls the classical complement cascades of the innate immune system to operate the phagocytic activity in order to neutralize pathogens and clear damaged cells or debris from the body [18]. However, the median CRP level of COVID-19 positive and negative patients in our study was six and four times higher than the optimal range (<10 mg/L), respectively. CRP levels appear to be boosted in people infected with SARS-CoV-2 with a view to over-producing inflammatory cytokines and interleukins generally termed as chemical messengers to fight the virus. But elevated CRP does not mean that someone must has COVID-19. Because it is sensible to see higher CRP level with acute bacterial, protozoal or other viral infection like H1N1 influenza as well as different autoimmune diseases [19-22]. Alike stress, smoking, vitamin deficiency, sleep deprivation and hormonal imbalance might have contributions to this context [23-27].

Furthermore, the likelihood of CRP increment has a good relation with age i.e., the possibility of CRP increment is proportional to age progression besides COVID-19 [28]. Nonetheless, the aforementioned chemical messengers synthesized upon the overreaction of immune system can create lesion in the lung tissue leading to show higher serum CRP in diagnosis report. Also, the chest CT scan of 72 patients with higher CRP was checked in this study because it is evidenced that the over expression of CRP causes lung damage [29]. Here, by applying the principle of 80-20 rule, the first three disorders: Bilateral consolidation, GGO and pulmonary lesion were the major causes of making patients lung perilous and taking care of these three problems would cure 80% of our hospitalized patients from further respiratory illnesses. On the other hand, 10 of our patients developed COPD required intensive follow up in post-COVID-19 period to prevent subsequent damage. Because COPD is uncurable and right disease management with medicines, oxygen therapy and pulmonary rehabilitation are the most widely used methods to slow down disease progression [30]. Incidentally, this study accounted for only two people to have cardiomegaly in CT image, which actually might not be the consequence of COVID-19. They might have pre-existing cardiovascular disease and were under serious risk of heart failure [31]. Correspondingly, another COVID-19 biomarker the blood ferritin is hollow globular protein consisting of two different subunits: the heavy (H) and light (L) subunit. Several studies have revealed that H subunit show both of the pro-inflammatory and immune-suppressive activities, which expression is induced by inflammatory stimuli [32, 33]. However, over production of ferritin i.e. the Hyperserotonemia was found in this study that confirms COVID-19 progression and severity. During viral infection macrophage not only produces active ferritin but also releases several inflammatory stimuli including cytokine also known as cytokine storm. This production of active ferritin consequently contributes to produce several anti-inflammatory (IL-10) and pro-inflammatory (IL-1ß) cytokines [31]. Moreover, IL-6 an important member of cytokine family can induce ferritin biosynthesis [34]. Therefore, in the blood sample of our COVID-19 patients the concentration of ferritin was obtained high specially amongst the age-old people that also interrelates diseases rapidity with age. Interestingly, a good number of positive

patients showed normal ferritin level despite of viral invasion. A probable reason for this reduction might be the administration of long-term iron chelation therapy with deferoxamine or other iron chelator for anemia or thalassemia treatment [35]. Moving to the next, like previous several studies we found pointedly higher D-dimer levels in aged women compared to men suggesting that our female was more susceptible to venous thromboembolism, coronary heart disease (CHD), and pulmonary embolisms (PE) [36-39]. On the contrary, in serological diagnostics, male found to have high ferritin levels. Besides COVID-19 inflammation, it is possibly due to the fact of higher availability of obesity, fatty liver, daily alcohol consumption and existence of mutate hemochromatosis gene (HFE) in male [40]. Thereafter, CRP test is most useful for people who have a chance of developing cardiovascular diseases in future or already have the problem [41, 42]. From our study, almost one third of the hospitalized COVID-19 positive patients (68%) considering both of the gender might be at this jeopardized condition need prominent cardiological treatment. But at the point of inter gender comparison, female was in more danger here. However, our study also discloses that around half and a third of COVID-19 patients from elderly stage were a menace to high blood pressure and diabetes, respectively, necessitating careful monitoring and appropriate medication after discharge. This study also designed to determine the number of patients whether a constellation of biomarkers would affect clinical outcomes, reflecting that 20% of our COVID-19 patients specially the aged population have three elevated biomarkers, which were at higher risk of critical illness compared to the patients with one and two elevated biomarkers [42]. However, the exhibition of single and multiple biomarkers is directly proportional to age progression. Interestingly, the age in the region of 60 is crucial for the existence of any elevated COVID-19 biomarker. Moreover, CBC test was carried out to detect the overall health condition to many individuals; remarkably the hospital seriously contemplated platelets counts of many admitted patients on account of dengue suspect. Because in Bangladesh dengue fever generally moves toward to its peak between July to October and the dengue ward of the hospital also had increased number of patients during our study period [43]. Next, fluid and electrolyte disturbances associated disorders like hyponatremia, hypernatremia, hypokalemia, hypocalcemia, hypochloremia, hypervolemia, and hypovolemia are more common in hospitalized and intensive care COVID-19 patients [42]. Sometimes lower levels of sodium and potassium during admission were linked to the application of mechanical ventilation [44]. The hospital diagnosed serum sodium, potassium, chloride and bi-carbonate level of many patients with related complains to pay special attention on their treatment and chose right intravenous infusion.

CONCLUSIONS

We have pointed out age as a major demographic risk factor crucially the range of 40 to 60 and older. We also figured out the proportional effects of three common biochemical risk factors and two hospital outcomes over age progression of patients with COVID-19 from North-East Bangladesh. Afterwards, for the first time we studied various radiographic findings to show the lung health of our many hospitalized individuals and found that Bilateral consolidation was the main culprit to wound lung. In addition to, the association of age with two most available pre-existing comorbidities e.g., hypertension and diabetes has been drawn here. Also, we have discussed the linkage of gender with our analyzed inflammatory markers and comorbidities showed asymmetric results between male and female. Miscellaneously, we summarized other biochemical risk factors parallelly considered by the hospital in patients care. This study may benefit researchers and policy makers to get a clear sketch about the health of our North-Eastern territory during the disaster of COVID-19 delta wave. Furthermore, it will promote subsequent awareness about this pandemic as it is not fully over yet. Above all, our findings also embolden health care providers and the society to put much attention about our elderly population.

Author contributions: THA: contributed to analyzing & writing of whole manuscript; **MGRM & JN:** treated patients during their hospital admission & collected data; **FR & DH:** arranged & compiled all data; & **FM:** planned & guided the study. All authors have agreed with the results and conclusions.

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Ethics statement: Authors stated that the institutional research ethics committee's ethical standards were followed during the study's execution. The Shahjalal University of Science and Technology's institutional Ethical Review Board (ERB) gave formal ethics approval for this study procedure (Reference Number: IEC-101(1)003). In addition to, we discussed the hospital governing body to conduct research using some admitted patients and the superior authority put no objection on that. We later spoke with our study participants and received their verbal consent to utilize their data for research purposes.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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