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THE PHYSIOLOGICAL IMPACT OF IMMUNIOHEMATOLOGICAL AND LIFESTYLE FACTORS ON COVID-19 SEVERITY: A CASE–CONTROL INVESTIGATION

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ABSTRACT

Background: Coronavirus disease (COVID-19) has triggered stern medical crises universally and it is branded by severe respiratory suffering that can tempts inflammatory reaction and shows a broad range of clinical representations from minor to stern disease. Numerous biochemical and hematological, immunological, and lifestyle-inclined factors may add to the disease severity and clinical results.

Objectives: This study attempted to assess the connection between blood groups, smoking and some chosen laboratory biomarkers, which include to ferritin, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), pro-inflammatory cytokines (IL-6, D-dimer, TNF-α, and C-reactive protein [CRP]), with COVID-19 severity.

Methods: A total of 150 male participants were enrolled and classified into control (n = 50), mild COVID-19 (n = 50), and severe COVID-19 (n = 50) groups. The age of all participants ranged between 40 and 55 years. Blood group distribution, smoking status, and serum levels of LDH, CK-MB, ferritin, D-dimer, IL-6, TNF-α, and CRP were analyzed. Data were expressed as mean values, and statistical significance was considered at $p < 0.05$.

Results: Smoking prevalence differed significantly across the studied groups (χ^2 test, $p < 0.001$), with smokers being more frequent among patients with severe COVID-19 (70%) compared with mild cases (50%) and controls (20%), whereas non-smokers predominated in the control group (80%) relative to mild (50%) and severe cases (30%). The distribution of ABO blood groups and Rh factor differed significantly among control, mild, and severe COVID-19 groups ($\chi^2 = 38.36$, df = 16, $p = 0.0013$), with blood group A being the most prevalent among COVID-19 patients, particularly in mild and severe cases. Mean serum LDH levels were significantly higher in mild (360.94 ± 78.64) and severe cases (503.28 ± 105.66) compared with controls (156.68 ± 30.82) ($p < 0.001$). CK-MB levels were elevated in mild (5.71 ± 12.12) and severe patients (4.64 ± 13.76) relative to controls (1.60 ± 2.64) ($p < 0.001$). Ferritin concentrations were higher in mild (429.28 ± 63.84) and severe cases (526.68 ± 106.74) than in controls (262.48 ± 69.57) ($p < 0.001$). Pro-inflammatory markers IL-6, TNF-α, and CRP were markedly elevated in severe cases (9.91 ± 18.66, 29.25 ± 9.72, and 6.06 ± 15.88, respectively) compared with mild and control groups ($p < 0.001$–0.00001). Additionally, D-dimer levels were significantly increased in severe cases (473.24 ± 143.45) compared with mild (260.88 ± 155.36) and control groups (163.32 ± 62.82) ($p < 0.00001$).

Conclusion: Blood group type, smoking, and elevated inflammatory, coagulation, and tissue damage biomarkers are strongly associated with COVID-19 severity, highlighting their potential role as predictors of disease progression.

KEYWORDS: Interleukins, Corona virus, LDH, Blood group, CRP, D-dimer, Ferritin, CK-MB

1. INTRODUCTION

Coronavirus disease of 2019 popularly known as (COVID-19) has triggered stern medical problems worldwide and is branded by severe has caused severe respiratory anguish, endures to exert essential effects on global health owing to stern respiratory failure and multi-organ malfunction. This inconsistency underlines the essence of finding host biological and lifestyle aspects that can influence disease susceptibility and advancement. Among these factors, the ABO blood group system has been implicated in COVID-19 severity and clinical outcomes [1, 17]. Lifestyle factors such as smoking have also been associated with COVID-19 outcomes, potentially due to smoking-induced modulation of immune function and up regulation of angiotensin-converting enzyme 2 (ACE2), the key receptor for SARS-CoV-2 reception into host cells. Immune deregulation, mainly extreme manufacture of pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and severe stage reactants like C-reactive protein (CRP), is a hallmark of severe COVID-19 [17, 26, 28]. Research suggested that smoking may increase symptom severity and disease risk, although findings vary across populations and study designs COVID-19 induces severe

inflammatory processes in many organs due to the recruitment of inflammatory cells at the site of inflammation and increased secretion of proinflammatory cytokines. These cascade events in many organs lead to disorders and failure of physiological function, ultimately leading to increased mortality and morbidity. Several studies have demonstrated that the serum levels of the proinflammatory cytokines IL-8, IL-1, TNF-α, and IL-6 are increased in patients with coronavirus disease [1, 27]. Elevated inflammatory markers, along with increased levels of ferritin, D-dimer, lactate dehydrogenase (LDH), and cardiac enzymes such as creatine kinase-MB (CK-MB), have consistently been associated with disease severity, indicating systemic inflammation, coagulation abnormalities, and tissue damage. Moreover, many studies have revealed a significant increase in the serum LDH and creatine kinase-MB (CK-MB) levels in patients with severe coronavirus infection these reflects the degree of damage to the lung tissue and the severity of the inflammatory process [1,4, 28] .Given the limited local data addressing the combined impact of blood groups, smoking, inflammatory cytokines, and biochemical markers on COVID-19 severity, this study seeks to assess their connection with less and stern COVID-19 cases in comparison with healthy controls. Perception of these connections may add to early risk stratification and Improved clinical management of COVID-19 patient.

2.1 MATERIALS AND METHODS

2.2 Patient Groups and Ethical Considerations

2.2.1 Patient Groups

A total of 150 male participants were enrolled in this case–control study, including 100 patients diagnosed with Coronavirus Disease 2019 (COVID-19) and 50 apparently healthy control subjects. Female participants were excluded to eliminate potential confounding effects related to sex-associated hormonal and immunological differences, thereby enhancing the internal validity of the study. COVID-19 patients were recruited from Baghdad Teaching Hospital between October 2020 and March 2022. According to the World Health Organization (WHO) clinical classification criteria, patients were stratified into two groups: mild COVID-19 (n = 50) and severe COVID-19 (n = 50). Severe COVID-19 cases were defined by the presence of at least one of the following criteria: oxygen saturation (SpO_2) < 93% at rest, respiratory rate > 30 breaths per minute, PaO_2/FiO_2 ratio < 300 mmHg, and radiological evidence of pneumonia on chest X-ray or computed tomography (CT) scan. Mild COVID-19 cases included patients who did not meet the criteria for severe disease. The control group consisted of healthy male individuals with no clinical symptoms or laboratory evidence of COVID-19 infection. The age of all participants ranged between 40 and 55 years. COVID-19 diagnosis was confirmed using standard hematological, immunological and RT-PCR investigations. Individuals with chronic inflammatory diseases, autoimmune disorders, or malignancies were excluded to minimize potential confounding factors.

2-3 Ethical Considerations

This study was carried out based on the ethical tenets explained in the Declaration of Helsinki. The study procedure was reviewed and authorized by the Scientific and Ethical Committee of the College of Science, University of AL-Karkh, in partnership with Baghdad Teaching Hospital. Written well-versed accord was acquired from all respondents preceding to acceptance. All personal and clinical data were treated with strict confidentiality and used solely for scientific research purposes

2.4 Collection of blood samples

Five milliliters of blood were collected from both the patient and control groups, adhering to rigorous aseptic protocols. The serum was obtained by centrifuging the blood at 3000 rpm for 10 minutes, after which the collected serum was promptly frozen at -20°C until needed, with only one frozen sample thawed at a time for testing.

2.5 Determination of LDH and CKMB .

LDH and CKMB activity was quantified using a colorimetric approach as outlined in the protocol accompanying the Randox U.K. Kit.

2.6 Determination of Immunoinflammatory Elements

Venous blood samples were obtained under stringent aseptic conditions, and the serum was isolated and assessed for IL-6 and TNF-α levels using the Enzyme Amplified Sensitivity Immunoassay (EASIA).

2.7 Determination of CRP, Ferritin and D.dimer

The serum levels of these markers detected by immunofluorescent assay (IFA).

2.8 Statistics

Data were collected and processed by the means of SPSS, all the data are presented as Group contrasts were carried out with the use of independent samples *t*-tests with Bonferroni correction for manifold comparisons. Data are offered as number (percentage) and The Chi-square test was measured numerically essential A P value of $p<0.05$.

3.1 RESULTS

Table 1: Distribution of ABO and Rh blood groups among control, mild and sever covid-19 groups.

Blood Groups	Control(n=50) N (%)	Mild covid -19 N=50 (%)	Sever covid-19 N=50 (%)

A+	(22.0 %) 11	(40.0 %) 20	(38.0 %) 19
A-	(10.0 %) 5	(6.0 %) 3	(10.0 %) 5
B+	(4.0 %) 2	(28.0 %) 14	(24.0 %) 12
B-	(6.0 %) 3	(0.0 %) 0	(2.0 %) 1
AB+	(18.0 %) 9	(12.0 %) 6	(14.0 %) 7
AB-	(2.0 %) 1	(6.0 %) 3	(6.0 %) 3
O+	(24.0 %)12	(8.0 %) 4	(10 .0 %) 5
O-	(14.0%) 7	(0.0 %) 0	(4.0 %) 2
Total	(100 %) 50	(100 %) 50	(100 %) 50

The distribution of blood group and Rh differed significantly among control ,mild and sever covid-19 group (χ^2 =38.36, df = 16, p =0.0013). Blood group A was the most prevalent among covid-19 patients, particularly in mild and sever cases,compared to the control group.

Table 2. Association between smoking status and COVID-19 severity

Variable Smoking Status	Control (%) n	Mild Covid-19 n (%)	Severe Covid-19 n (%)	n Total (%)	P-value
Smokers	10 (20.0)	25 (50.0)	35(70.0)	70 (46.7)	< 0.001
Non – Smokers	40 (80.0)	25 (50.0)	15(30.0)	80 (53.3)	
Total	50 (100)	50 (100)	50 (100)	50 (100)	

The association between smoking status and COVID-19 severity was evaluated among the study groups (Control, Mild COVID-19, and Severe COVID-19). The results shows a statistically significant difference in smoking prevalence across the studied groups (Chi-square test, P < 0.001). The proportion of smokers was markedly higher among patients with severe COVID-19 (70%) compared to those with mild COVID-19 (50%) and the control group (20%). In contrast, non-smokers were predominantly observed in the control group (80%) compared to mild (50%) and severe cases (30%). These findings indicate a significant association between smoking and increased severity of COVID-19 infection.

Table 3: Comparison between control group and serum concentrate levels of LDH(U/L) during mild and sever infected covid-19 .

Group	NO.	Mean ± SD. LDH (U/L)	P-Value
Control	50	156.68 ± 30.82	
Mild Covid-19	50	360.94 ± 78.64	0.001
Sever Covid-19	50	503.28 ± 105.66	0.001

Comparisons between each experimentation group and the controlled group were conducted with the use of independent samples *t*-tests with Bonferroni correction for manifold comparisons. Data are offered as mean ± standard deviation (SD). The Mild covid -19 group showed a significantly higher mean value of LDH (360.94 ± 78.64) compared to the Control group (156.68 ± 30.82 (t = 17.10, p < 0.001, Bonferroni-adjusted). Similarly, the Severe covid-19 group demonstrated a highly significant increase in the mean of LDH (503.28 ± 105.66)
Compared to the Control group (156.68 ± 30.82 (t = 22.27, p < 0.001, Bonferroni-adjusted).

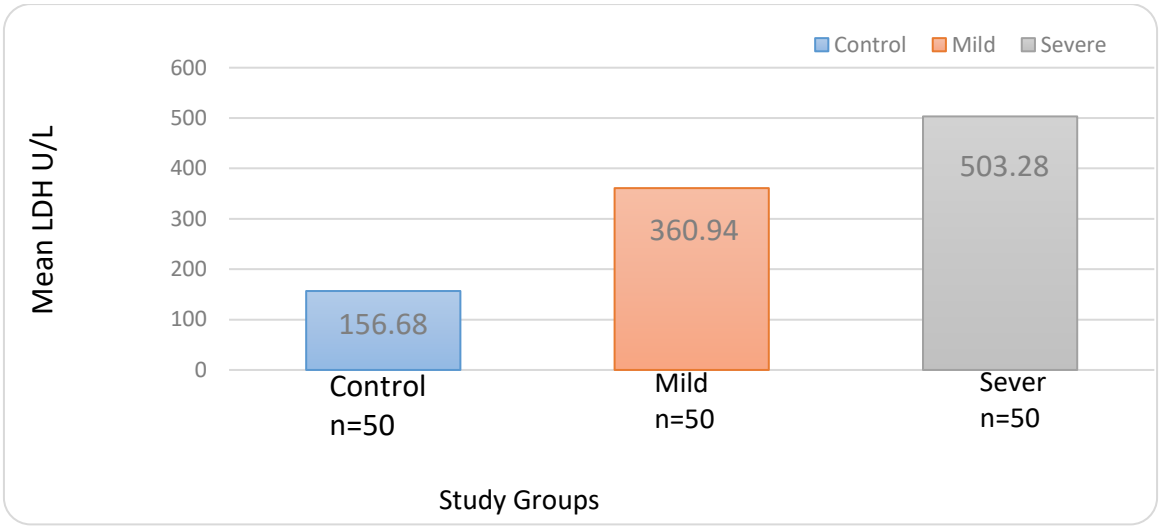

Figure 1 : LDH levels a highly significant variation (p < 0.001) of sever and mild covid-19 viral infection compared to control group

Table 4: Comparison the Concentrate levels of serum CKMB (ng/ml) during (Mild and Sever Covid-19) with the control group

Group	NO.	Mean ± SD. CKMB (ng/ml)	p-value
Control	50	1.60± 2.64	
Mild Covid-19	50	5.71± 12.12	0.001
Sever Covid-19	50	4.64±13.76	0.001

The Comparisons between each experimental group and the control group were conducted through independent samples *t*-tests with Bonferroni improvement for manifold comparisons , shows an increase in the mean concentration levels of CKMB in mild and severe covid -19 (5.71± 12.12 , 4.64±13.76) respectively compared with control group (1.60± 2.64) p < 0.001.

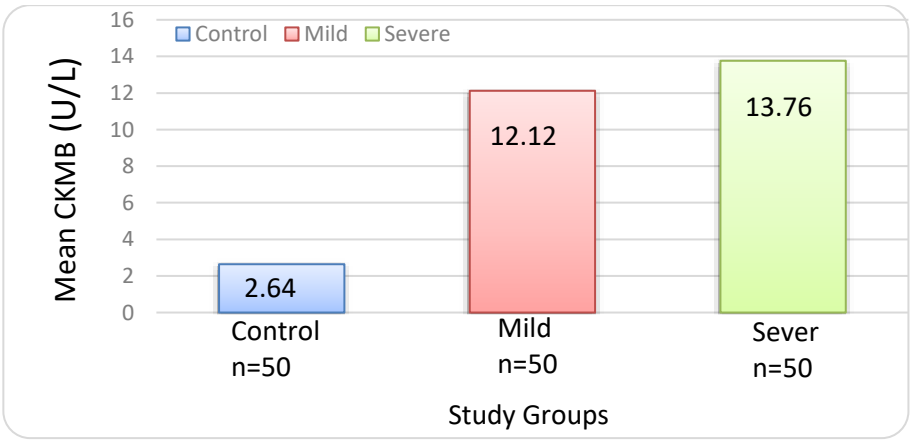

Figure 2 : CKMB levels a highly significant variation (p < 0.001) of sever and mild covid-19 viral infection compared to control group

Table 5: Comparison the Concentrate levels of serum Ferittin (ng/ml) during (Mild and Sever Covid-19) with the control group

Group	(N=50	Mean ± SD. Ferritin (ng/ml)	p-value
Control	50	262.48± 69.57	
Mild Covid-19	50	429.28± 63.84	0.001
Sever Covid-19	50	526.68± 106.74	0.001

Result shows an increase in the mean Ferritin level in patient with mild and sever covid -19 (429.28± 63.84, 526.68± 106.74, $p < 0.001$) respectively compared with that in the control group (262.48± 69.57). The statistical comparison of the patient groups (mild and sever) and control group, which was conducted via a t-test, revealed highly significant differences ($p<0.001$).

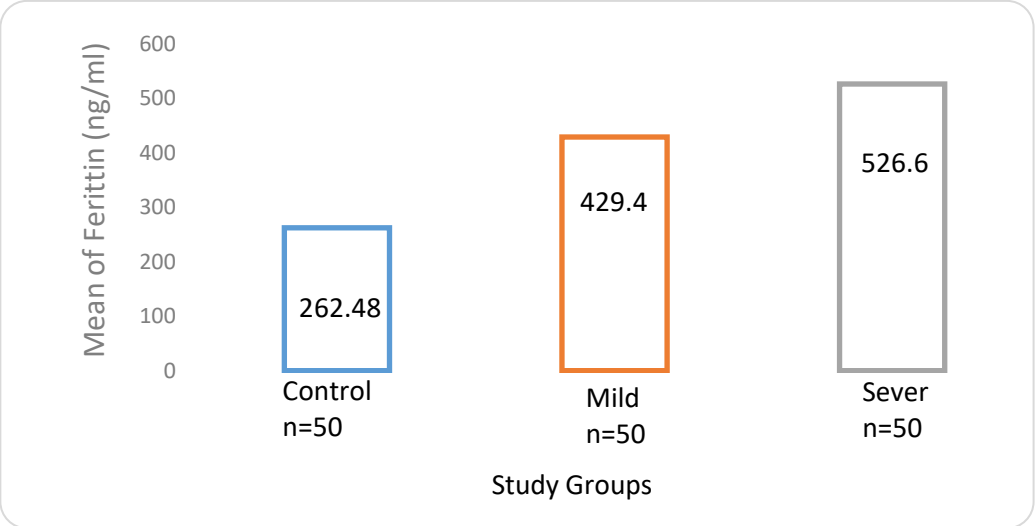

Figure 3: Serum ferritin levels highly significant differences ($p<0.001$) of sever and mild covid-19 viral infection compared to control group.

Table 6 : Comparison the Concentrate levels of serum D- dimer (ng/L) during (Mild and Sever Covid-19) with the control group

Group	NO	Mean ± SD D- dimer ng/L	P-value
Control	50	163.32 ± 62.82	
Mild covid-19	50	260.88 ± 155.36	0.0001
Sever covid-19	50	473.24± 143.45	0.00001

The statistical analysis show a significant increase in the serum concentration level of D-dimer across covid-19 patient groups compared to the control group. The mean ±standard deviation for the control group was 163.32 ± 62.82 (n = 50). In comparison , patient with mild covid -19 showed a significantly higher mean value of 260.88 ± 155.36 (n=50) , with a stisticaly significan difference when compared to control ($p < 0.0001$). Furthermore, the sever covid-19 group demonstrated a markedly elevated mean value of D-dimer 473.24± 143.45 (n=50) , which was highly significant compared to the control group ($p< 0.00001$) .

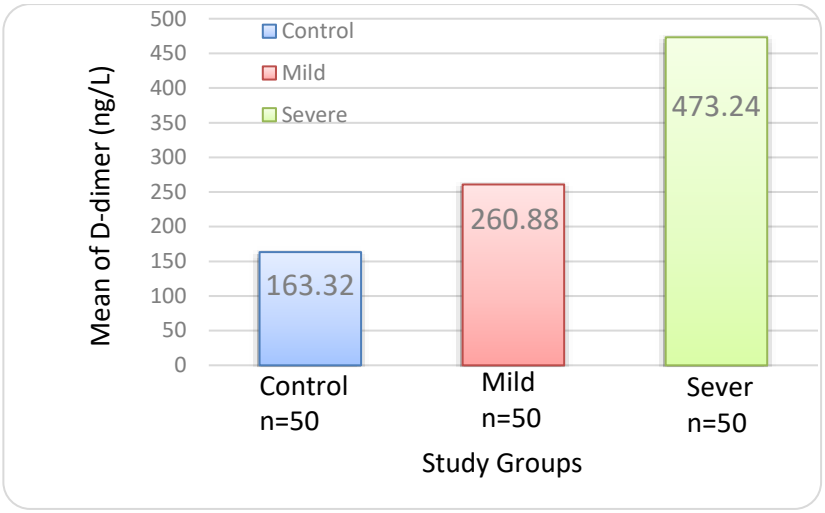

Figure 4: D-dimer levels a highly significant variation (p< 0.00001) of sever and mild covid-19 viral infection compared to control group

Table 7: Comparison the Concentrate levels of serum CRP (mg/L) during (Mild and Sever Covid-19) with the control group

Groups	NO	Mean ± SD CRP mg/L	P-value
Control	50	1.04 ± 1.67	
Mild covid-19	50	4.80 ± 9.82	0.0001
Sever covid-19	50	6.06± 15.88	0.00001

Data was expressed as mean ± standard devition . Independent samples t.- test was used to compare mean value of CRP in patient gropes with the control group. The results showed a highly significant increase in Mild covid-19 patient (4.80 ± 9.82) compared to control (1.04 ± 1.67)), p < 0.0001.Similary, the sever covid-19 patients showed markedly a higher mean value of CRP (6.06± 15.88) compared to controls, with a highly significant difference (p < 0.00001).

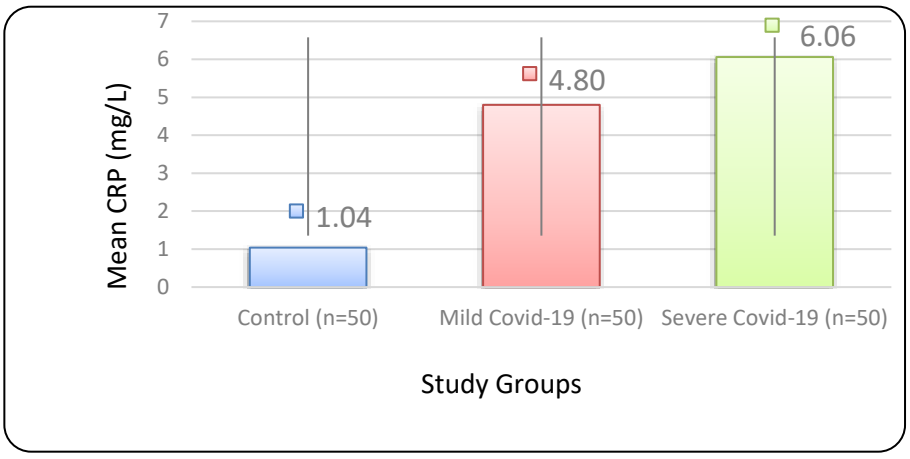

Figure 5: Serum CRP levels highly significant differences (p < 0.00001) of sever and mild covid-19 viral infection compared to control group.

Table 8: Comparison the Concentrate levels of serum IL-6 (ng/ml) during (Mild and Sever Covid-19) with the control group

Group	(N=50	Mean ± SD. IL-6 (ng/ml)	p-value
Control	50	1.35±2.33	
Mild Covid-19	50	3.86±8.26	0.001

Sever Covid-19	50	9.91± 18.66	0.001

The results was expressed as mean± standard deviation. Statistical analysis was performed using an independent samples t – test to compared the concentration levels of IL-6 (ng/ml) in each covid-19 groups with the control group. Statistically significant increase was observed in the mild covid-19 group (3.86±8.26) compared with control (1.35±2.33, $p < 0.001$) . Furthermore, the sever covid -19 group showed a highly significant elevated in mean concentration of IL-6 (mg/ml) (9.91± 18.66) compared with the control group (1.35±2.33) ($p < 0.001$).A p-value < 0.05 was considered statistically significant.

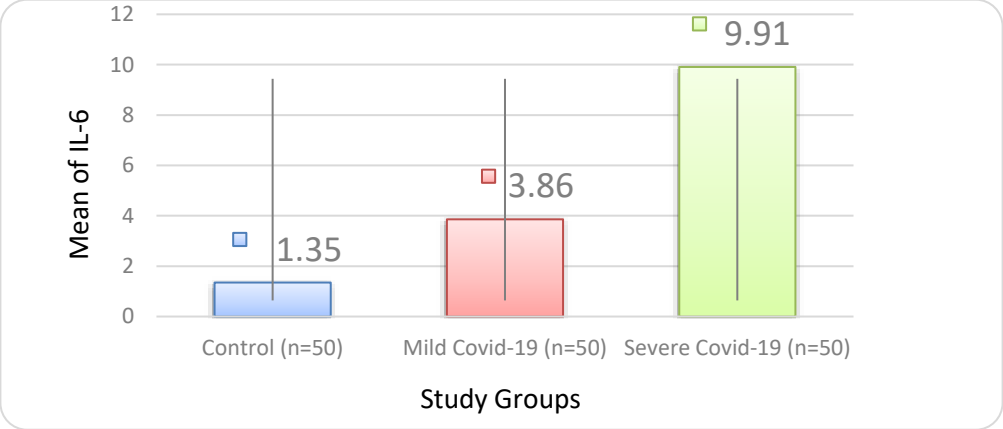

Figure 6: Serum IL-6 levels highly significant differences ($p < 0.001$) of sever and mild covid-19 viral infection compared to control group.

Table 9: Comparison the Concentrate levels of serum TNF-α (pg/ml) during (Mild and Sever Covid-19) with the control group

Groups	NO.	Mean ± SD TNF-α (pg/ml)	p.-value
Control	50	14.18 ± 4.83	
Mild covid-19	50	25.54 ± 11.03	0.0001
Sever covid-19	50	29.25 ± 9.72	0.0001

Data was expressed as mean ± standard devition . Independent samples t.- test was used to compare the serum concentration of TNF-α in patient groups with the control group. The results showed a significant increase in Mild covid-19 patient (25.54 ± 11.03) compared to controls (14.18 ± 4.83), $p < 0.0001$.Similary, sever covid-19 patients showed a highly significant elevation of mean concentration of TNF-α (29.25 ± 9.72) compared to controls ($p < 0.0001$)

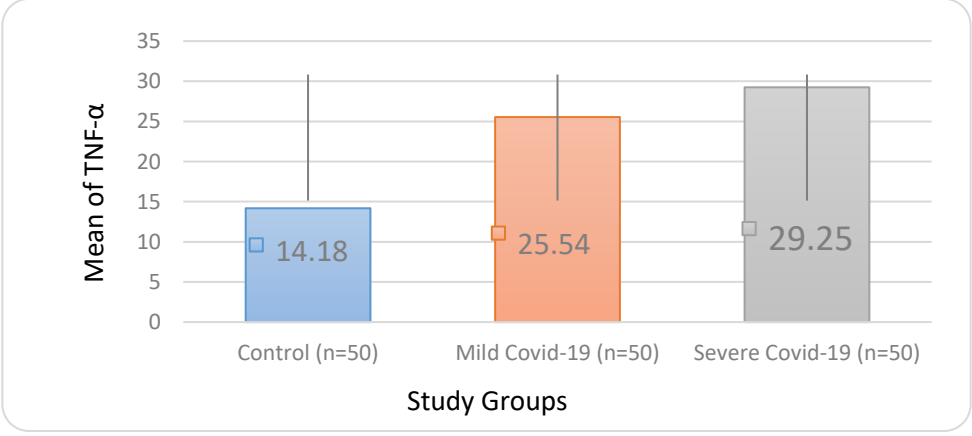

Figure 7: Serum TNF-α levels highly significant differences ($p < 0.001$) of sever and mild covid-19 viral infection compared to control group.

4. DISCUSSION

The current study provides compelling evidence that biological and lifestyle factors—including smoking status, blood group distribution, pro-inflammatory cytokines, and key biochemical markers are significantly associated with COVID-19 severity. These findings are in consonance with literature on clinical and biomarkers findings. These results show maximum frequencies of blood groups A and B among the severity-inclined people with O and AB, showing potential variations in disease severity and clinical findings. This aligns with epidemiological explanations which recommends that the dedicative blood group O may converse relative defense against stern COVID-19, while blood group A is habitually overrepresented among stern cases. These findings aligns with past studies on blood groups and the Rh aspect and the sternness of coronavirus infections [14, 15]. Comparable findings designated that individuals with COVID-19 who contain blood group A and negative Rh practiced a condensed evolution of the infection and a lower inevitability for intubation. Conversely, Ray et al. identified a significant correlation between the Rh– blood group and a reduced risk of severe COVID-19 infection. These discrepancies may reflect population-specific genetic backgrounds and differences in study design. Our findings partially agree with previous reports but do not allow definitive conclusions regarding Rh status. Our results showed a significant association between smoking and disease severity ($p < 0.001$) in this study is consistent with reports linking smoking to enhanced viral entry mechanisms and immune dysregulation. Smoking has been shown to enhance ACE2 receptor expression in airway epithelial cells, which may partly explain the elevated risk for severe outcomes. Although some studies report contrasting results due to cohort differences, the trend toward greater severity in smokers remains a recurrent finding in observational research. [27, 28] . However, the present study revealed that the smokers were overrepresented among severe cases compared with nonsmokers (53% vs. 47%), as shown in Table (2). These results are in agreement with other studies showing an association between cigarette smoking and the severity of COVID-19 [16, 17]. A study published by Rohin K Reddy presented a significant analysis of the relationship between coronavirus progression and a history of heavy smoking [18]. Some authors have reported that the severity of COVID-19 and worse in-hospital outcomes are related to a history of smoking [17, 18]. Our results revealed, patients with severe COVID-19 show significantly increase in serum concentration levels of IL-6, TNF-α, CRP, CKMB and LDH compared with mild cases and control subjects as illustrated in Tables (3,4,5,6,7,8,9) , these reflecting an amplified systemic inflammatory response. These results are in accordance with recent meta-analyses and large-scale cohort studies reporting that elevated IL-6, TNF-α, CRP, CKMB and LDH levels are indicative of cytokine-driven immune dysregulation, whereas increased LDH concentrations reflect cellular injury and hypoxic damage, particularly within pulmonary tissue. The simultaneous elevation of these biomarkers accentuates the interrelated inflammatory and cytotoxic paths included in stern COVID-19 and metabolic stress. Together, IL-6, TNF-α, CRP, and LDH emerge to act as combined indicators of disease in acute stratification and prognostic evaluation. This result aligns with prior research to indicate IL-6 and CRP increases in stern cases are in line with recent results of cohort data indicating raised IL-6, CRP, ferritin, LDH, and D-dimer absorptions with growing clinical severity, authorizing that these markers associate with universal inflammation and poor prognosis in COVID-19 patients[30 , 31] . A methodical review and meta-analysis described that CRP, D-dimer, ferritin, IL-6, and LDH were essentially raised in stern and critical COVID-19 cases and were connected with ICU admission and mortality risk, emphasizing their worth as prognostic pointers. [30]. Furthermore, our study discovered that the headway of pulmonary CT was connected with a significant increase in CRP, D-dimer, ferritin, IL-6, and LDH levels at admission [19, 20, 21]. Additionally proinflammatory cytokines, the important increase in serum concentration stages of D-dimer and ferritin observed in stern COVID-19 patients highlights a tricky interface between hyperactive inflammation and coagulation dysregulation. Elevated D-dimer levels refer improved fibrin development and degradation, to suggest a hypercoagulable state that underwrites to micro vascular thrombosis and lessened pulmonary perfusion. Concomitantly, raised serum levels ferritin concentrations characterize not only an acute-stage reactant but also an indicator of immune-mediated hyper inflammation, every so often associated with macrophage activation and cytokine amplification. The concurrent upsurge in D-dimer and ferritin supports the concept that stark COVID-19 is categorized by an immunothrombotic procedure, wherein excessive inflammatory responses promote endothelial injury, coagulation activation, and multi-organ dysfunction. These findings reinforce the prognostic value of D-dimer and ferritin as integrative biomarkers reflecting both inflammatory burden and thrombotic risk in severe disease. Recent observational studies have reinforced that elevated inflammatory markers such as IL-6, TNF-α - CRP, D-dimer, and ferritin are associated with increased severity and adverse outcomes across diverse populations, including unvaccinated cohorts. For example, elevated IL-6 and ferritin were found to correlate significantly with severe disease and end-organ damage in hospitalized patients, supporting the current findings on the utility of these markers for severity stratification [29, 30, 31]. Additionally, other clinical research has identified similar patterns of significant associations between elevated inflammatory and coagulation biomarkers with severity metrics, such as oxygen requirement and need for intensive care, confirming that these parameters are robust indicators of disease progression [30, 31] .The restriction of the study population to male participants was intentionally applied to reduce the potential confounding effects of sex- related hormone and immunological differences this approach enhanced the internal validity of the study and allowed for more precise assessment of the

association between inflammatory biomarkers and covid -19 severity. However, this restricts the generalizability of the findings to female populations.

5- CONCLUSION

This study demonstrates that smoking, certain blood group types (A and B), and elevated mean concentration levels of pro-inflammatory cytokines (IL-6, TNF-α, CRP) and biochemical markers (ferritin, D-dimer, LDH, CK-MB) are strongly related with COVID-19 severity. These parameters show significant differences between mild and severe cases and correlate with established risk profiles reported in recent scientific literature. As such, they can serve as valuable prognostic biomarkers for early risk stratification and clinical decision-making in COVID-19 management. Future research should consider longitudinal designs with larger multicenter cohorts to validate these findings, explore underlying biological mechanisms, and evaluate interventions targeting inflammatory pathways. This study included only male subjects, therefore, our results cannot be generalized to female patients, and further studies should include both sexes to detect the potential gender-specific differences in covid-19 severity and immunity response.

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Declaration of Competing Interest: This research did not obtain funding from public, commercial, or not-for-profit agencies. This work is personal, and the declaration of interests is solely my own. Support has been subjective throughout the research conducted over the past three years.

Ethical approve: The ethical approval necessary approval was obtained by the institute according Helsinki declaration

REFERENCES

1. Bah ram, N.;Sabah, H.; and et al. ; (2023) "Elevated interleukin (IL)-6 as a predictor of disease severity among Covid-19 patients: a prospective cohort study"BMC Infectious Diseases volume 23, Article number: 311.
2. Hind, E.; Antoine El Kik, Omar, M., et al (2022) “Evaluation of lactic dehydrogenation (LDH) in predicting the severity of lung involvement and pneumomediasstinum in hospitalized covid -19 " Medicina clinic practice, Vol.5. issue 4
3. Tong Mu, Xingguang Wang, Zhiming Lu. and Ja Tong (2023) “Implications of LDH in patients with coronavirus disease 2019 pneumonia " About journal, Volume 13
4- Han Y, Yang H. The transmission and diagnosis of 2019 novel Coronavirus infection disease (COVID?19): A Chinese perspective. J Med Virol, 2020; 92: 639-644.
5- Mitra R, Mishra N, Rath GP. Blood group systems. Indian J Anaesth. (2014) 58:524–8. 10.4103/0019-5049.144645.
6- Hui DS, Chan MC, Wu AK, Ng PC. Severe acute respiratory syndrome (SARS): epidemiology and clinical features. Postgrad Med J. 2004 Jul 1; 80(945): 373-81.
7- Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, et al. (2021) "The impact of ABO blood group on COVID-19 infection risk and mortality: a systematic review and meta-analysis". Blood Rev. 48:100785.
8- Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. (2021) “Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility." Clin Infect Dis. 73:328–31.
9- Rohin K Reddy , Walton N Charles , Alexandros Sklavounos, et al. (2020). " The effect of smoking on COVID-19 severity: A systematic review and meta-analysis J Med Virol .13;93(2):1045–1056.
10- Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med. 2020; 75:107-108.
11- Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis [published online ahead of print April 15, 2020]. J Med Virol. 10.1002
12- Ji D, Zhang D, Xu J, et al. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score [published online ahead of print April 9, 2020]. Clin Infect Dis. 10.1093.
13- Sorlie, D. (1995)."Medical biostatistics & Epidemiology". 1st ed., Norwalk, Connecticut, Appleton & Lange: 47-88.

14- Hoiland RL, Fergusson NA, Mitra AR, Griesdale DE, Devine DV, Stukas S, et al. The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. Blood Adv. (2020) 4:4981–9.
15- Jelinek HF, Mousa M, Alkaabi N, Alefishat E, Daw Elbait G, Kannout H, et al. Allelic variants within the ABO blood group phenotype confer protection against critical COVID-19 hospital presentation. Front Med (Lausanne). (2021) 8:759648. 10.3389
16- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1054-1062.
17- Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis. 2020; 18:20.
18- Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis [published online ahead of print April 15, 2020]. J Med Virol. 10.1002
19- M. Zhou, C. Dong, C. Li, Y. Wang, H. Liao, H. Shi, et al. Longitudinal changes in COVID-19 clinical measures and correlation with the extent of CT lung abnormalities. Int J Med Sci., 18 (2021), pp. 1277-1284
20 - H. Huang, S. Cai, Y. Li, Y. Li, Y. Fan, L. Li, et al. Prognostic factors for COVID-19 pneumonia progression to severe symptoms based on earlier clinical features: a retrospective analysis Front Med (Lausanne)., 7 (2020)
21- Ding, J., Karp, J. E., Emadi, A. (2017). Elevated lactate dehydrogenase (ldh) can be a marker of immune suppression in cancer: interplay between hematologic and solid neoplastic clones and their microenvironments. Cancer biomark. 19, 353–363.
22- Gu Y, et al. Role of the innate cytokine storm induced by the influenza a virus. Viral Immunol. 2019;32(6):244–51.
23 - Liu B, et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine syndrome (CRS). J Autoimmun. 2020; 111:102452.
42- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19. The Lancet. 2020;395(10229):1054–1062.

25- Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. Nature Communications. 2020;11:5761.
26- Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and smoking. Nicotine & Tobacco Research. 2020;22(9):1650–1652.
27-- Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. Journal of Clinical Investigation. 2020;130(5):2620–2629.
28- Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019. Clinical Chemistry and Laboratory Medicine. 2020;58(7):1021–1028.
29 - Henry BM, Lippi G. Inflammatory biomarkers and COVID-19 severity. Clinical Chemistry and Laboratory Medicine. 2021.
30 - Hiwa O. Abdullah, *etal*. "Role of Inflammatory Markers in Severity, ICU Admission, and Mortality in COVID-19: A Systematic Review and Meta-analysis of 79,934 Patients". Medical journal, Volume 2, Issue 3, 2024
31- Mahetab R. *etal.* "Evaluation of clinically relevant serum proteins as biomarkers for monitoring COVID-19 severity, and end-organ damage among hospitalized unvaccinated patients". BMC journals, vol.24, No.231, 2024.