Original Research Article

Effects of comorbidities on COVID-19 biomarkers: a retrospective study

Pradnya M. Bagalkote[1]*, Rekha S. Sharma[2]

[1]Department of Home Science, Dharampeth M. P. Deo Memorial Science College, Nagpur, Maharashtra, India
[2]UGC-Malviya Mission Teacher Training Centre, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India

*Correspondence:
Dr. Pradnya M. Bagalkote,
E-mail: shymalipink@gmail.com

ABSTRACT

Background: This retrospective investigation aimed to assess the effects of comorbidities on COVID-19 biomarkers at admission and during the post-discharge recovery period.

Methods: A total of 369 confirmed and hospitalized COVID-19 patients were included in this study. Biomarkers including D-dimer, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were recorded at three time points: hospital admission, 15 days post-discharge, and 30 days post-discharge. Data were retrieved from hospital records, and comorbidities were classified using the Charlson comorbidity index (CCI). Study design was retrospective cohort study

Results: About 44.87% of patients had diabetes as a pre-existing comorbidity, followed by hypertension (HTN) (27.07%) and cardiovascular disease (CVD) (25.78%). About 79.95% patients had diabetes mellitus (DM)+CVD+HTN. The age (p=0.108) and gender (p=0.481) showed an insignificant association with the comorbidity of COVID-19 patients. The patients with diabetes as a comorbidity showed the highest levels of D-dimer, Ferritin and LDH, while patients with CVD showed the highest levels of CRP. The mean D dimer, ferritin and CRP levels at admission and after 15- and 30-days post-discharge did not differ significantly (p>0.05) with respect to comorbidities. However, the mean LDH differ significantly (p=0.00) for patients with diabetes and other comorbidities at admission and 15 days post-discharge.

Conclusions: The mean levels of COVID-19 biomarkers-D-dimer, ferritin, and CRP-measured at admission and at 15- and 30-days post-discharge showed no significant differences across comorbidity groups. In contrast, LDH levels at two time points differed significantly with respect to comorbidity. This significant variation in LDH suggests that it may serve as a useful indicator for assessing disease severity in patients with comorbid conditions.

Keywords: COVID-19 biomarkers, D-dimer, Ferritin, C-reactive protein, Lactate dehydrogenase, Comorbidity

INTRODUCTION

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most dreaded pandemic of recent times. A significant proportion of the COVID-19 patients have been reported to suffer from other pathophysiological conditions as well. COVID-19, caused by SARS-CoV-2, represents the most devastating pandemic in recent history. A substantial number of patients suffer from various pathophysiological conditions alongside COVID-19 infection. Comorbidities often lead to adverse outcomes.[1] Numerous researchers have documented poor prognoses resulting from COVID-19-associated comorbidities, particularly acute and chronic conditions.[2-6] Consequently, this investigation was undertaken to address these concerns.

Objectives

Diabetes, CVD, renal and pulmonary diseases, are frequently observed comorbidities that increase the case fatality rate in acute respiratory diseases caused by SARS-CoV. The present investigation was aimed at assessing the effects of comorbidities on biomarkers of COVID-19.

METHODS

This retrospective cohort study analysed data from 369 COVID-19 patients admitted to Viveka Hospitals, Nagpur, Maharashtra, India, between April 1, 2020, and July 31, 2021. Biomarkers including D-dimer, ferritin, CRP, and LDH, along with comorbidities, were documented at admission, day 15, and day 30 post-discharge from hospital records. Multimorbidity classification was performed using the Charlson multimorbidity index (CCI).[7]

Study design

It was a retrospective cohort study.

Study size

The 369 COVID-19 patients selected for the study.

Inclusion criteria

The study included all adults (> 18 years old) hospitalized in non-ICU isolated patients with COVID-19 infection confirmed by "nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) positive for SARS-CoV2" of all disease severity.

Exclusion criteria

The study excluded all adults (>18 years old) hospitalized in ICU isolated patients with COVID-19 infection confirmed by "nasopharyngeal RT-PCR positive for SARS-CoV2 of all disease severity.

Statistical analysis

Data was analysed using chi-square test and ANOVA. The study was initiated after approval from the institutional ethics committee.

RESULTS

Comorbidity, multimorbidity and CCI-wise distribution of COVID-19 patients (n=368)

The study revealed diabetes as the most prevalent comorbidity (44.87%), followed by HTN (27.07%) and CVD (25.78%). A substantial majority (79.95%) presented with combined DM+CVD+HTN. The CCI distribution showed 39.02% patients with CCI score 2, while 26.28%

had a score of 3. Most patients exhibited multiple comorbidities, with isolated conditions being rare (DM: 1.90%, CVD: 0.54%) (Table 1).

Table 1: Comorbidity, multimorbidity and CCI-wise distribution of COVID-19 patients, (n=368).

CCI	N (%)
Comorbidities	
Diabetes	315 (44.87)
CVD	181 (25.78)
High blood pressure	19 (27.07)
Arthritis	4 (0.57)
Asthma	5 (0.71)
Bronchitis	7 (1.00)
Comorbidities/multimorbidity	
DM	7 (1.90)
DM+CVD+HTN	295 (79.95)
CVD	2 (0.54)
CVD+HTN	48 (13.01)
DM+CVD+arthritis/bronchitis/asthma	13 (3.52)
CVD+HTN/asthma/bronchitis	3 (0.81)
CCI	
1	33 (8.94)
2	144 (39.02)
3	97 (26.28)
4	37 (10.02)
5	48 (13.00)
6	9 (2.43)
7	1 (0.27)

Gender-wise comorbidity

Table 2 shows that males comprise 89.67% (n=330) and females 10.33% (n=38). The triple comorbidity DM+CVD+HTN was most prevalent, affecting 78.79% of males and 92.11% of females. CVD+HTN was present in 13.64% of males and 7.89% of females. Isolated DM occurred in 2.42% of males only, while isolated CVD was rare (0.61% in males). Additional comorbidities including arthritis, bronchitis, and asthma were found exclusively in males (4.55%). Statistical analysis revealed no significant gender-based association with comorbidity patterns (χ^2=4.494, p=0.481).

Age-wise comorbidity

The study showed that the predominant comorbidity pattern was DM+CVD+HTN, affecting 295 patients (80.16%), with highest prevalence in the 46-59 age group (83.55%). The 26-45 age group was largest (43.48%), followed by 46-59 years (41.30%). Isolated comorbidities were rare: DM in 2.17% and CVD in 0.54% of patients. CVD+HTN affected 13.04% overall, particularly in older patients (18.37% in >60 years). Additional comorbidities including arthritis, bronchitis, and asthma were present in 4.08% of patients. Statistical analysis (χ^2=21.993, p=0.108) revealed no significant association between age groups and comorbidity distribution pattern. The

biomarker analysis revealed distinct patterns across different comorbidity combinations.

D-dimer and comorbidity

D-dimer levels showed considerable variation, with isolated diabetes patients displaying the highest initial mean values (1177.88±855.17 ng/ml), while isolated CVD patients had the lowest (351±258.8 ng/ml).

However, these differences were not statistically significant at admission (F=0.63, p=0.67), 15 days post-discharge (F=0.76, p=0.58), or 30 days post-discharge (F=2.1, p=0.06). Notably, CVD+HTN patients exhibited elevated D-dimer levels at 30 days (644.88±1698.23 ng/ml).

Ferritin and comorbidity

Ferritin levels demonstrated similar non-significant patterns across comorbidity groups. Initial ferritin was highest in isolated diabetes patients (499.44±490.71 ng/ml) and lowest in isolated CVD patients (143.5±58.68 ng/ml), with p=0.88. At 15 days, CVD+HTN patients showed elevated levels (374.61±1146.95 ng/ml), though this remained statistically insignificant (p=0.53).

By 30 days, isolated CVD patients paradoxically showed increased ferritin (355±205.06 ng/ml), but overall differences remained non-significant (p=0.77).

CRP and comorbidity

CRP levels exhibited no significant associations with comorbidity patterns at any time point (initial: p=0.96; A15D: p=0.74; A30D: p=0.48).

Isolated CVD patients consistently showed elevated CRP initially and at 15 days (86.35±11.81 mg/l), while CVD+HTN patients demonstrated the highest values at 15 days (109.21±377.32 mg/l). However, these elevations lacked statistical significance.

LDH and comorbidity

In stark contrast, LDH levels showed highly significant associations with comorbidity status. Patients with isolated diabetes demonstrated markedly elevated LDH levels both initially (1726.6±4137.34 U/l) and at 15 days (1726.63±4137.34 U/l), significantly higher than all other comorbidity groups (F=8.99, p=0.000 and F=9.07, p=0.000, respectively).

The DM+CVD+HTN combination, CVD+HTN, and DM+CVD+arthritis/bronchitis/asthma groups showed relatively similar LDH values ranging from the 227-297 U/L.

Isolated CVD patients maintained intermediate levels (462.5±183.14 U/l), while CVD+HTN/asthma/bronchitis patients had the lowest values (123-151.67 U/l).

Table 2: Gender and comorbidity-wise distribution of COVID-19 patients.

Gender	DM, N (%)	DM+CVD+HTN, N (%)	CVD, N (%)	CVD+HTN, N (%)	DM+CVD+ arthritis/ bronchitis/ asthma, N (%)	CVD+HTN/asthma/ bronchitis, N (%)	Total, N (%)
Male	8 (2.42)	260 (78.79)	2 (0.61)	45 (13.64)	12 (3.64)	3 (0.91)	330 (89.67)
Female	0 (0.00)	35 (92.11)	0 (0.00)	3 (7.89)	0 (0.00)	0 (0.00)	38 (10.33)
Total	8 (2.17)	295 (80.16)	2 (0.54)	48 (13.04)	12 (3.26)	3 (0.82)	368 (100)
χ^2 value	4.494						
P value	0.481						

Table 3: Age and comorbidity-wise distribution of COVID-19 patients.

Age groups (in years)	Comorbidities/multimorbidity						
	DM, N (%)	DM+CVD+ HTN, N (%)	CVD, N (%)	CVD+ HTN, N (%)	DM+CVD+ arthritis/ bronchitis/ asthma, N (%)	CVD+HT/ asthma/ bronchitis, N (%)	Total, N (%)
18-25	0 (0)	7 (100)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1.90)
26-45	5 (3.13)	123 (76.88)	0 (0)	23 (14.38)	7 (4.38)	2 (1.25)	160 (43.48)
46-59	3 (1.97)	127 (83.55)	0 (0)	16 (10.53)	5 (3.29)	1 (0.66)	152 (41.30)
>60	0 (0)	38 (77.55)	2 (4.08)	9 (18.37)	0 (0)	0 (0)	49 (13.32)
Total	8 (2.17)	295 (80.16)	2 (0.54)	48 (13.04)	12 (3.26)	3 (0.82)	368 (100)
χ^2 value	21.993						
P value	0.108						

Table 4: Mean D-dimer, ferritin, CRP and LDH levels of COVID-19 patients with comorbidities.

Biomarkers		Comorbidities						Total	F	P value
		DM	DM+CVD+HTN	CVD	CVD+HTN	DM+CVD+arthritis/bronchitis/asthma	CVD+HTN/asthma/bronchitis			
		n=8	n=294	n=2	n=48	n=12	n=3	n=367		
D-dimer initial (ng/ml)	Mean	1177.88	776.14	351	885.88	543.5	499.67	787.06	0.63	0.67
	SD	855.17	967.41	258.8	1162.46	759.59	216.17	981.27		
D-dimer 15 days post discharge (ng/ml)	Mean	201.63	307.38	373	248.68	197.93	182.23	293.19	0.76	0.58
	SD	135.1	341.81	244.66	178.81	154.15	183.78	316.44		
D-dimer 30 days post discharge (ng/ml)	Mean	208.13	326.12	200	644.88	296.33	533.33	365.17	2.1	0.06
	SD	128.73	271.95	141.42	1698.23	265.11	230.94	666.24		
Ferritin-initial (ng/ml)	Mean	499.44	365.39	143.5	403.81	392.31	214.33	371.81	0.35	0.88
	SD	490.71	465.94	58.68	415.15	518.76	158.64	458.23		
Ferritin 15 days post discharge (ng/ml)	Mean	265.13	241.59	105	374.61	178.38	97.33	255.26	0.83	0.53
	SD	185.02	261.65	7.07	1146.95	122.78	15.53	475.81		
Ferritin 30 days post discharge (ng/ml)	Mean	184.63	220.16	355	216.09	166.07	97.33	216.68	0.51	0.77
	SD	124.75	232.87	205.06	183.81	132.86	15.53	221.26		
CRP initial (mg/l)	Mean	45.19	62.96	86.35	48.52	35.63	30.58	59.63	0.21	0.96
	SD	35.3	157.58	11.81	59.13	20.6	30.68	142.95		
CRP 15 days post discharge (mg/l)	Mean	37.36	62.11	86.35	109.21	54.24	31.2	67.38	0.55	0.74
	SD	29.69	157.17	11.81	377.32	43.81	30.58	195.94		
CRP 30 days post discharge (mg/l)	Mean	32.18	49.23	9.05	34.46	28.33	21.93	45.86	0.91	0.48
	SD	23.4	69.71	5.59	37.81	22.53	29.67	64.56		
LDH initial (U/l)	Mean	1726.6[abc]	277.97[a]	462.5	291.2[b]	244.54[c]	151.67	309.98	8.99	0.000
	SD	4137.34	198.44	183.14	195.75	93.98	141.62	639.08		
LDH 15 days post discharge (U/l)	Mean	1726.63[abcd]	275.07[a]	462.5	297.7[b]	227.18[c]	123[d]	307.58	9.07	0.000
	SD	4137.34	196.37	183.14	194.38	162.08	105.15	638.37		

*a-dsimilar superscripts differ significantly.

DISCUSSION

Comorbidity-wise distribution of COVID-19 patients

Multiple studies have documented that comorbidities such as CVD and HTN combined with DM represent the most common conditions in COVID-19 patients.[8-10] The current investigation revealed a higher prevalence of DM (44.87%), HTN (27.07%), and CVD (25.78%) among participants. Prior research demonstrated a comorbidity rate of 50.7%, with HTN (21.6%) and DM (15%) being the most frequent.[11] Another study identified HTN (16.9%) as the predominant comorbidity, followed by diabetes (8.2%).[12] Various studies have established chronic diseases and COVID-19 infection as associated with diverse risk factors, including DM, obesity, HTN, heart failure, COPD, chronic kidney disease, and CVD.[4,13-19]

The present study demonstrated that approximately 65.3% of patients had a CCI score of 2-3, with only 2.7% having scores of 6-7. A systematic review and meta-analysis of hospitalized patients revealed that CCI scores ≥3 correlated with increased mortality, with each point increase raising mortality risk by 16%.[20]

Gender-wise comorbidity

In India, males and elderly individuals demonstrated greater susceptibility to COVID 19.[21] This study revealed higher comorbidity prevalence in males. COVID-19 mortality rates for infected individuals were 2.8% in Chinese men compared to 1.7% in Chinese women.[22] Biological variations in immune systems between genders may influence COVID-19 resistance. Males exhibited increased vulnerability due to distinct lifestyle factors including smoking, drinking, working patterns, sex hormones, HTN, and additional comorbidities.[23] Women naturally generate higher levels of interferon, particularly type I interferon and T lymphocytes, which eliminate infected cells. The female hormone estradiol provides infection protection. Conversely, research suggests testosterone may suppress male immune responses, potentially explaining the observed gender disparity.[24,25]

Age-wise comorbidity

Comorbidities such as CVD+HTN+DM are highly prevalent in older adults and have been associated with worse outcomes in COVID-19.[26] The present investigation demonstrated that the predominant comorbidity pattern was DM+CVD+HTN, affecting 295 patients (80.16%), with the highest prevalence in the 46-59 age group (83.55%). According to a study, older adults with comorbidities were the most vulnerable for adverse outcomes, the risk of adverse outcomes among older adults without comorbidities was less than that of younger adults with comorbidities.[27] Another study reported that HTN (8.8%), DM (7.67%), and CVD such as CHF and hypothyroidism (p=0.0481), were higher in incidence among the age group 60-69 years and were statistically significant (p<0.0001). It was also seen that DM+HTN were notably more common in ages 70-79 years, 50-59 years, and 40-49 years.[28]

D-dimer and comorbidity

The current study demonstrated that isolated diabetes patients had the highest D-dimer levels, though insignificant. Multiple studies revealed a significant association between high D-dimer level and severity of COVID-19 among diabetic patients.[29-31] A study reported that diabetics were associated with higher levels of D-dimer compared to non-diabetics.[32] The present study also showed the lowest D-dimer for isolated CVD patients. In contrast, the high D-dimer concentrations have been reported to be associated with CVD and prognosis in COVID-19 patients.[33,28]

Ferritin and comorbidity

The present study demonstrated the highest mean ferritin levels in DM patients and the lowest in CVD. COVID-19 patients with one or more comorbidities, DM, thrombotic complications, and cancer had significantly higher levels of ferritin than those without (p<0.01).[34] Multiple studies revealed that patients with diabetes had higher ferritin levels than those without.[35] Multiple scientists have reported that the serum ferritin levels of patients with DM significantly increased with increasing HbA1c levels (p<0.01) in non-COVID-19 patients.[36] Perhaps the trend of increasing ferritin in diabetic patients has also been reflected in COVID-19 patients.[37]

The present study demonstrated higher levels of ferritin in patients with HTN as a comorbidity. The prevalence of HTN increased as ferritin levels increased in non-COVID individuals.[37] However, a study reported that COVID-19 patients with HTN had slightly lower levels of ferritin than those patients who were without WMD.[34]

CRP and comorbidity

CRP has been found as an important marker that changes significantly in severe patients with COVID-19.[38] In the present study, the highest CRP levels were observed in COVID-19 patients with CVD in the initial days of the illness. Scientists also reported a higher mean difference in CRP (78.2 mg/l) (p<0.001) for ≥3 comorbidities.[38] DM+HTN were significantly correlated with CRP level (p=0.05), whereas dyspepsia did not demonstrate a significant relationship with CRP level (p>0.05).

Patients with HTN had a 2.709-fold risk of having increased CRP levels compared with patients without HTN.[39] Studies demonstrated that serum CRP were significantly higher in COVID-19 diabetic patients. This occurs because of the inflammatory reaction and tissue damage that occurs, and the increase in CRP is closely related to the severity of the DM condition that accompanies COVID-19 patients.

LDH and comorbidity

The current investigation found that individuals with diabetes alone exhibited significantly increased LDH levels, a finding consistent with previous research demonstrating higher LDH in diabetic individuals.[35] The levels of LDH, CRP and glucose on admission can each individually able to predict 75% or more of COVID-19 severity.[40] LDH was a greater predictor of severity compared to glucose and CRP alone (p<0.001). LDH did not change even after the 15 days post-discharge.

Limitations

Study limited for Nagpur district (MH, India) only.

CONCLUSION

The biomarkers viz., D-dimer, ferritin and CRP and LDH recorded at admission, after 15th day and 30th day of discharge were retrieved from the hospital records. The presence of comorbidity was not substantially correlated with either gender (p=0.481) or age (p=0.108). CVD patients had the highest CRP levels, while diabetic patients had the highest d-dimer, ferritin, and LDH values. Initial assessments of d-Dimer, ferritin, and CRP, as well as follow-ups at 15 and 30 days, revealed no significant changes (p>0.05) between groups with diabetes and other comorbidities. In contrast, patients with diabetes had substantially different mean LDH levels (p=0.00) than those with other comorbidities. In terms of comorbidity, the COVID-19 biomarkers, such as d-dimer, ferritin, and CRP, did not differ substantially. When comorbidity is present, the mean LDH levels change dramatically. The mean levels of COVID-19 biomarkers-D-dimer, ferritin, and CRP-measured at admission and at 15- and 30-days post-discharge showed no significant differences across comorbidity groups. In contrast, LDH levels at two time points differed significantly with respect to comorbidity. This significant variation in LDH suggests that it may serve as a useful indicator for assessing disease severity in patients with comorbid conditions.

ACKNOWLEDGEMENTS

REFERENCES

1. Singh MK, Mobeen A, Chandra A, Joshi S, Ramachandran S. A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection? Comput Biol Med. 2021;130:104219.
2. Chen N, Zhou M, Dong X, Jieming Q, Fengyun G, Yang H, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
3. Guan WJ, Liang WH, Zhao Y, Heng-Rui L, Zi-Sheng C, Yi-Min L, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a-nationwide-analysis. Eur Respir J. 2020;55(5):2000547.
4. Yan H, Vijay A, Jiang F, Nanhong Z, Yaoren H, Honghua Y, et al. Serum glucose, lactate dehydrogenase and hypertension are mediators of the effect of body mass index on severity of COVID-19. Endocrinol Diabetes Metab. 2021;4(2):e00215.
5. Dolan ME, Hill DP, Mukherjee G. Investigation of COVID-19 comorbidities reveals genes and pathways coincident with the SARS-CoV-2 viral disease. Preprint. bioRxiv. 2020;09.21.306720.
6. Lau EH, Hsiung CA, Cowling BJ. A comparative epidemiologic analysis of SARS in Hong Kong, Beijing and Taiwan. BMC Infect Dis. 2010;10:50.
7. Charlson ME, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
8. Abi-Ayad B, Mohammed B, Mohammed B, Souad G, Ikram M, Amel M, Rachid M, et al. The effect of inflammatory biomarkers on COVID-19 patients with diabetes and comorbidities. Roman J Diabetes Nutrit Metabolic Dis. 2024;31(3):337-46.
9. Adab P, Haroon S, O'Hara ME, Jordan RE. Comorbidities and COVID-19. BMJ. 2022;377:O1431.
10. Sanyaolu A, Okorie C, Marinkovic A, Risha P, Kokab Y, Priyank D, et al. Comorbidity and Its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069-76.
11. Argun Barış S, Boyacı H, Akhan S, Mutlu B, Deniz M, Başyiğit İ, et al. Charlson Comorbidity Index in Predicting Poor Clinical Outcomes and Mortality in Patients with COVID19. Turk Thoracic J. 2022;23(2),145-53.
12. Guan WJ, Liang WH, Zhao Y, Heng-Rui L, Zi-Sheng C, Yi-Min L, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a-nationwide-analysis. Eur Respir J. 2020;55(5):2000547.
13. Grasselli G, Greco M, Zanella A, Giovanni A, Massimo A, Giacomo B, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345-55.
14. Atkins JL, Masoli JAH, Delgado J, Luke CP, Chia-Ling K, George AK, et al. Preexisting Comorbidities Predicting COVID-19 and Mortality in the UK

Biobank Community Cohort. J Gerontol A Biol Sci Med Sci. 2020;75(11):2224-30.

15. Reilev M, Kristensen KB, Pottegård A, Lars CL, Jesper H, Martin TE, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol. 2020;49(5):1468-81.

16. Richardson S, Hirsch JS, Narasimhan M, James MC, Thomas McG, Karina WD, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-9.

17. Iaccarino G, Grassi G, Borghi C, Claudio F, Massimo S, Massimo V, et al. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension. 2020;76(2):366-72.

18. Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, Poncel-Falcó A, Bliek-Bueno K, Cano-Del Pozo M, et al. Baseline Chronic Comorbidity and Mortality in Laboratory-Confirmed COVID-19 Cases: Results from the PRECOVID Study in Spain. Int J Environ Res Public Health. 2020;17(14):5171.

19. Tartof SY, Qian L, Hong V, Rong W, Ron FN, Heidi F, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results from an Integrated Health Care Organization. Ann Intern Med. 2020;173(10):773-81.

20. Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K, et al. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14(6):2103-9.

21. Swain CK, Rout HS. Gender and age group-wise inequality in health burden and value of premature death from COVID-19 in India. Aging Health Res. 2023;3(3):100151.

22. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Rosemary M, Sabra LK. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1):29.

23. Smith T. A supercomputer analyzed COVID-19-and an interesting new theory has emerged. 2020. Elemental. Available at: https://elemental.medium.com/a-supercomputer-analyzed-covid-19-and-an-interesting-new-theory-has-emerged-31cb8eba9d63. Accessed on 15 June 2025.

24. Peckham H, de Gruijter NM, Raine C, Anna R, Coziana C, Lucy RW, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commu. 2020;11(1):6317.

25. Traish AM, Morgentaler A. What's testosterone got to do with it? A critical assessment of the contribution of testosterone to gender disparities in COVID-19 infections and deaths. Androgens Clin Res Therapeut. 2021;2(1):1810.

26. Abid A, Umar A, Qamar S. Disease Outcomes of COVID-19 in Diabetic and Hypertensive Patients During the Hospital Stay. Cureus 2023;15(10):e46943.

27. Assiri RA, Bepari A, Patel W, Syed AH, Shaik KN, Asma Al, et al. Exploration of Sex and Age-Based Associations in Clinical Characteristics, Predictors of Severity, and Duration of Stay among COVID-19 Patients at the University Hospital of Saudi Arabia. Healthcare (Basel). 2023;11(5):751.

28. Endeshaw Y, Campbell K. Advanced age, comorbidity and the risk of mortality in COVID-19 infection. Natl Med Assoc. 2022;114(5):512-7.

29. Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. Hypertension Res. 2020;43(8):824-31.

30. Elemam NM, Hannawi H, Salmi IA, Naeem KB, Alokaily F, Hannawi S, et al. Diabetes mellitus as a comorbidity in COVID-19 infection in the United Arab Emirates. Saudi Med J. 2021;42(2):170-80.

31. Wang X, Tang N, Li D, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.

32. Hashim IEI, Kamal AMH, Adam EME, Seri I. Comparison between D-dimer levels in diabetic and non-diabetic positive COVID-19 adult patients: A hospital-based study. Endocrinol Diabetes-Meta. 2022;5(4):e349.

33. Simes J, Robledo KP, White HD, David E, Ralph AS, David RS, et al. D-Dimer Predicts Long-Term Cause-Specific Mortality, Cardiovascular Events, and Cancer in Patients with Stable Coronary Heart Disease: LIPID Study. Circulation. 2018;138(7):712-23.

34. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020;34(10):e23618.

35. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X, et al. Clinical characteristics and outcomes of cancer patients with COVID-19. J Med Virol. 2020;92(10):2067-73.

36. Sheu WH, Chen YT, Lee WJ, Chen-Wen W, Lih-Yuan L. A relationship between serum ferritin and the insulin resistance syndrome is present in non-diabetic women but not in non-diabetic men. Clin Endocrinol (Oxf). 2003;58(3):380-5.

37. Rajpathak SN, Wylie-Rosett J, Gunter MJ, Negassa A, Kabat GC, Rohan TE, et al. Biomarkers of body iron stores and risk of developing type 2 diabetes. Diabetes Obes Metab. 2009;11(5):472-9.

38. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol. 2005;117(2):104-11.

39. Fachri M, Hatta M, Widowati E, Risky A, Ressy D, Ahmad S, et al. Correlations between comorbidities, chest X-ray findings, and C-Reactive protein level in

patients with COVID-19. Ann Med Surg. 2022;77:103553.

40. Iskandar A, Mayashinta DK, Robert R, Samsu N, Endharti AT, Widjajanto E, et al. Correlation Between IL-8, C-Reactive Proteins (CRP) and Neutrophil to Lymphocyte Ratio (NLR) as Predictor of Mortality in COVID-19 Patients with Diabetes Mellitus Comorbidity. Int-J-Gen-Med. 2023;16:2349-54.