RESEARCH ARTICLE

# Can blood glucose levels predict biochemical and haematological abnormalities in COVID -19 patients - Experience from a tertiary care hospital in Balochistan

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## Abstract

**Objective:** To find out the association between poor glycaemic levels and biochemical and haematological abnormalities in patients of corona virus disease-2019.

**Methods:** The prospective, observational, cohort study was conducted at the Combined Military Hospital, Quetta, Pakistan, from September 2020 to February 2021, and comprised all patients who tested positive for coronavirus disease-2019 on polymerase chain reaction test and were subsequently admitted. The patients were divided into two groups on the basis of random blood glucose level at the time of admission; ≥11.1mmol/l (206mg/dl) in group A and 4-11.1mmol (74-206mg/dl) in group B. Association between categorical variables was evaluated and hazard ratio was measured. Data was analysed using SPSS 21.

**Results:** Of the 349 patients, there were 56(16%) in group A; 40(71.4%) males and 16(28.6%) females with age range 39-61 years. There were 293(84%) subjects in group B; 239(81.5%) males and 54(18.5%) females with age range 27-53 years. Overall, 75(21.4%) patients were known type 2 diabetics. A significant association was found between poor glycaemic control and raised levels of C-reactive protein, lactate dehydrogenase, ferritin, erythrocyte sedimentation rate, troponin, creatine kinase, creatine kinase-MB, alanine aminotransferase, creatinine and D-dimers ($p$<0.05). Inter-group differences were significant for acute kidney injury, acute liver injury, Intensive care unit admission for coagulation abnormalities and for overall mortality ($p$<0.05).

**Conclusion:** Poor glycaemic control was found to be a risk factor for developing multisystem complications in patients of coronavirus disease-2019.

**Keywords:** Biochemical, COVID-19, Hyperglycaemia. (JPMA 72: 1369; 2022)

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## Introduction

Due to its rapid global progression, corona virus disease-2019 (COVID-19) was declared a pandemic by the World Health Organisation (WHO) on March 11, 2020.[1] Severe acute respiratory syndrome COVID-2 (SARS-Cov-2), an enveloped beta corona virus, generally spreads directly from human to human through droplets, fomite or aerosols.[2] It presents with diverse types of symptoms, ranging from no symptoms at all to mild symptoms, like flu, fever, loss of sense of taste and smell, etc. Some patients develop severe complications, like acute respiratory distress syndrome (ARDS), pneumonia, multi-organ failure, and even death.[3,4] Many international studies have shown that diabetic patients are more prone to develop COVID-19-related complications.[5] According to Amir et al.,[6] prevalence of diabetes in Pakistan is 16.98%. Together, COVID-19 and diabetes can cause disaster in the health systems of a developing country like Pakistan. During the influenza A (H1N1) pandemic in 2009, poor glycaemic level of patients was found to be an independent predictor of severe complications.[7] Although SARS-Cov-2 pathophysiology is not completely understood, there is evidence suggestive of its role in triggering inflammatory pathways, altered immune response, glucose variability and hypercoagulability.[8] Many pro-inflammatory markers, like C-reactive protein (CRP), ferritin and interleukin-6 (IL-6), are common in the pathophysiology of COVID-19 and diabetes. The common pathologies between the two conditions are the possible cause behind severe complications.

Several haematological and biochemical parameters have been studied to predict prognosis and outcome in COVID-19 patients. No local study could be found that may have used a simple investigation, like blood glucose level, with clear cut-off to predict the severity of COVID-19 in diabetics and non-diabetics. The current study was planned to find out the association between poor glycaemic levels and biochemical and haematological abnormalities in COVID-19 patients.

## Patients and Methods

The prospective, observational, cohort study was

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conducted at the Combined Military Hospital, Quetta, Pakistan, from September 2020 to February 2021. After approval from the institutional ethics review board, the sample size was calculated using OpenEpi calculator[9] with 95% confidence interval and exposure 23.7%.[10]

The sample was raised using non-probability consecutive sampling technique. Those included were patients aged >18 years who tested positive for COVID-19 on PCR test and were admitted to the hospital for >24 hours. Patients with chronic diseases, chronic liver disease (CLD), chronic kidney disease (CKD), autoimmune disorders and cancers, and those taking steroids were excluded.

Blood glucose levels of all admitted patients were measured. Patients having one blood glucose level of ≥ 206 mg/dl (11.1 mmol/l) were included in the poorly controlled hyperglycaemic group. While patients with Random Blood glucose between 74 – 206 mg/dl (4-11.1 mmol/l) were included in the Good control group. HbA1C of those non-diabetics falling into poorly controlled glycaemic groups was done to confirm their diabetic status. The patient's investigation details were collected from the institutional laboratory information management system (LIMS) after taking verbal consent from each subject.

Data was analysed using SPSS 21. Association between categorical variables was evaluated using Pearson's chi-square test. Cox regression analysis was done to measure the hazard ratio (HR). P<0.05 was considered statistically significant.

## Results

Of the 349 patients, there were 56(16%) in group A; 40(71.4%) males and 16(28.6%) females with age range 39-61 years. There were 293(84%) subjects in group B; 239(81.5%) males and 54(18.5%) females with age range 27-53 years. Overall, 75(21.4%) patients were known type 2 diabetics. The duration of hospital admission of patients in group A was significantly longer than group B ($p$<0.05). Group A had significantly higher levels of blood glucose, CRP, ferritin, erythrocyte sedimentation rate (ESR), urea, creatinine and cardiac enzymes (Table 1). Of the 75(21.4%) diabetics, 43(57.3%) were in group A, while, of the 274(78.5%) non-diabetics, 12(4.3%) were in group A.

A significant association was found between poor glycaemic control and raised levels of CRP, lactate dehydrogenase (LDH), ferritin, ESR, troponin-T (Trop-T), creatine kinase (CK), creatine kinase-MB (CKMB), alanine aminotransferase (ALT), creatinine and D-dimers ($p$<0.05) (Table 2).

Inter-group differences were significant for acute kidney injury (AKI), acute liver injury (ALI), intensive care unit (ICU) admission for coagulation abnormalities and for overall mortality ($p$<0.05).

**Table-1:** Demographic features of and laboratory findings of patients in the two study groups.

| Variables | Patients With poor glycaemic control (n=56) | Patients With good glycaemic control (n= 293) | *p*-value |
|---|---|---|---|
| **Age** in years (mean) | 50±11(39-61) | 40 (27- 53) | 0.03 |
| **Gender** | | | |
| Male | 40 (71.4 %) | 239( 81.5 %) | |
| Female | 16 (28.6 %) | 54 ( 18.5%) | |
| **Average hospital stay** in days 10 (3.48-16.52) | | 3.9 (1.0 – 7.1) | <0.001 |
| TLC × $10^9$/l | 9.01 ± 3.96 | 7.4 ± 3.02 | <0.001 |
| **Blood glucose** level (Random ) mg/dl | 268 (190.8 - 345.6) | 268 (190.8 - 345.6) | <0.001 |
| **CRP** (mg/l) | 156.5 (142.6-170.4) | 48.2 (30.8– 65.6) | <0.001 |
| **Ferritin** (ng/ml) | 865 (631-1113) | 640.5 (597.4-683.5) | <0.001 |
| **ESR** in first hour | 40.3 (28.8-52.5) | 15.1 (13.0-17.7) | <0.001 |
| **Creatine kinase**-MB (U/l) | 38.9 (31.2-47.7) | 24.4 (21.0-28.2) | <0.001 |
| **Creatine kinase**(U/l) | 297.8 (221-382.5) | 186 (150.9-232.0) | <0.001 |
| **Lymphocyte count** % | 17.6 (14.7 -20.8) | 23.2 (20.3 -26.1) | 0.003 |
| **Total Bilirubin** (umol/l) | 13.7(10.6 – 16.8) | 11.1(9.9 – 12.3)s | 0.067 |
| **ALT** (U/l) | 57.2 (43.7- 74.2) | 43.2 (36.2 – 50.4) | 0.3 |
| **ALP** (U/l) | 122.2 (97.3 – 147.1) | 103.1 (97.2 – 109) | 0.027 |
| **Urea** mg/dl (mmol/l) | 39.03(36-42) | 28.8 (27-30.6) | <0.001 |
| **S. Creatinine** mg/dl (umol/l) | 1.34 (1.16-1.54) | 1.02 (0.97-1.06) | <0.001 |
| **LDH** (U/l) | 335.9 (262-415.3) | 253.6 (221.7-286.5) | 0.07 |

TLC: Total leukocyte count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase LDH: Lactate dehydrogenase.

**Table-2:** Association of biochemical and haematological findings with poor and good glycaemic control.

| Variables | With poor glycaemic control (>11.1mmol/l) HbA1C > 6.5 % 206 mg/dl **High** | With good glycaemic control (4-11.1mmol/l) HbA1C < 6.5 %74-206 mg/dl **Normal** | Chi square | *p*-value |
|---|---|---|---|---|
| | n (%) | n (%) | | |
| **CRP** | 37(66.1) | 277(94.2) | 131 | <0.001 |
| **Ferritin** | 34(60.7) | 185(62.9) | 11 | <0.001 |
| **LDH** | 37 (66) | 232 | 4.3 | 0.03 |
| **ESR** | 39(79.6) | 169(62.1) | 29 | <0.001 |
| **Trop -T** | 4 | 290 | 7.0 | <0.001 |
| **Ck** | 35(62.5) | 156(53.1) | 4.5 | 0.03 |
| **CKMB** | 29(51.8) | 196(66.7) | 6.9 | <0.001 |
| **D-Dimers** | 45(80.4) | 168(57.1) | 27 | <0.001 |
| **ALT** | 34(60.7) | 190(66.4) | 14.6 | <0.001 |
| **Creatinine** | 20(35.7) | 277(94.5) | 46 | <0.001 |
| **Acidosis** | 27(48.2) | 227(77.2) | 16 | <0.001 |
| **Lymphocyte** | 37(61.1) | 153(52) | 6.1 | 0.13 |
| **ICU admission** | 47(83.90 | 262(89.1) | 143 | <0.001 |

Reference value: CRP < 100 mg/l, Ferritin male < 230ng/ml, Ferritin female < 230ng/ml, Lymphocyte <20%, Creatinine < 115 nmol/l, ALT <42 U/L, Acidosis pH <7.35, D-Dimers <200,ESR > 11, LD <460U/L, CK<190U/l, CKMB<25U/l ,ESR <11mm; CRP: C-reactive protein, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate, Trop-T: Troponin-T, CK: Creatine kinase, ALT: Alanine aminotransferase, ICU: Intensive care unit.

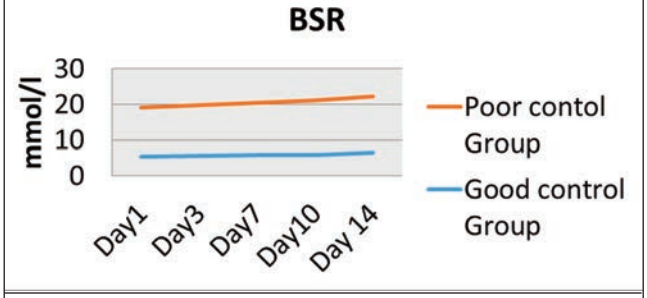


**Figure-1:** Dynamics of serum blood glucose level in Good and Poor control groups during 14 days of admission.

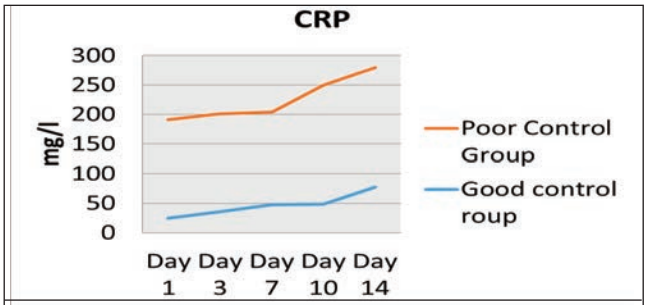


**Figure-2:** Dynamics of serum C-reactive protein (CRP) levels in Good and Poor control groups during 14 days of admission.

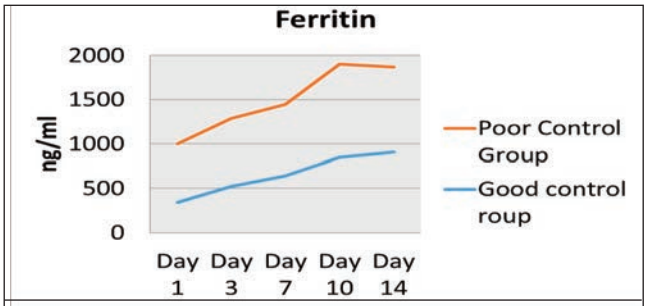


**Figure-3:** Dynamics of serum ferritin in Good and Poor control groups during 14 days of admission.

Before initiating the treatment, mean blood glucose levels were higher in group A ($p<0.05$). The rise in values of blood glucose (Figure 1) level, CRP (Figure 2) and ferritin (Figure 3) in group A compared to group B remained persistent over the period of the following 14 days.

## Discussion

Due to the short time since the COVID-19 pandemic set in, its pathophysiology is not completely understood. However, it is clear that like Middle East respiratory syndrome (MERS) and SARS-1, this virus gains entry into the cells by getting attached to angiotensin-converting enzyme (ACE) 2 receptors. Moreover, this virus also infects immune cells, causes lymphocyte apoptosis, and increases the production of inflammatory cytokines. COVID-19 causes adverse effects by superimposing pre-existing inflammation of diabetes.[11] Identification of risk factors associated with complications in SARS-Cov-2 patients is essential for timely clinical decisions to improve patient care. Data from around the world has demonstrated higher incidence of severe complications in patients suffering from comorbidities, like diabetes and hypertension. These findings have implications in the clinical management of patients.[12]

The current study demonstrated significant association of glycaemic control with hepatic, renal, cardiac and coagulation abnormalities. The kinetics of these abnormalities suggest multi-system involvement in hyperglycaemic COVID-19 patients. Studies have also shown similar results.[9,13]

Diabetic patients showed higher mean glucose levels than non-diabetics in the current study. Poorly-controlled hyperglycaemic levels were associated with higher levels of CRP, ferritin and ESR. Zhu et al. showed similar results.[14] Hyperglycaemia impairs endothelial functions, induces defective phagocytosis and chemotaxis. This underlying inflammatory state provides an environment for virus progression, promoting the vicious cycle of cytokine release along with hyperglycaemia, leading to injury in multiple organs. These features are more pronounced when blood glucose levels are >11mmol/l (206mg/dl).[15] Moreover, COVID-19 itself can induce hyperglycaemia in non-diabetics which increases the incidence of complications.[16] Raised ALT levels are suggestive of an enhanced toxic effect of the virus on hepatic cells in patients with poor glycaemic controls. One study demonstrated ALT as an independent predictor of poor 7-day mortality in COVID-19 patients.[17] In comparison to patients with good glycaemic control, a significantly greater number of patients in the poor control group showed raised levels of Trop-T. Akther et al. have shown similar results in Bangladesh.[18] Lymphocytopenia, which is an indicator of COVID-19 severity, was non-significantly associated with poor glycaemic levels in the current study, and similar results have been presented earlier.[18]

The proportion of patients with poor glycaemic controls requiring ICU support was twice those falling in the good control group. Zhang et al.[3] demonstrated fasting plasma glucose (FPG) level >7.54 mmol/l (140mg/dl) as an independent predictor of increased mortality. A meta-analysis of 8 studies showed patients with poor diabetic control having increased risk of ICU admission.[19]

Poorly-controlled glycaemic levels emerged as an important parameter and conferred higher morbidity in age-matched groups which was in line with studies conducted in the United Kingdom.[20,21]

The current findings may prove useful for developing future strategies for targeted intervention in special groups of patients to improve outcomes. Further multi-centre studies on larger sample sizes are required to assess the relationships in depth.

## Conclusion

COVID-19 patients with poor glycaemic control were found to be at a higher risk of developing multisystem complications. Elevated inflammatory markers, deranged coagulation, liver and renal functions, and cardiac enzymes contributed to a higher rate of morbidities.

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**Conflict of interest:** None

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