Importance of glucovigilance during these times

***Background*[1,2,3]**

- Recent times has witnessed rise of various infectious disease and millions of people have been affected by the virus since the beginning of 2020.
- The virus responsible for causing the disease triggers pneumonia and acute, even lethal, lung failure.
- Elderly patients and patients with comorbidities such as hypertension, cancer, cardiovascular disease, acute kidney injury and diabetes mellitus have emerged as a group susceptible to developing the disease as well as suffering a high risk of mortality.

Diabetes: A risk factor

- Diabetes mellitus is one of the most prevalent disease, not only in India but also worldwide, and can lead to morbidity and mortality in affected patients.[1]
- Studies have demonstrated a higher susceptibility to infectious disease in people with diabetes; might be owing to dysregulated immune system.[1]
- Several studies and hypotheses have been published to establish the link between diabetes and the virus infection.[2]
- Diabetes has been identified as a primary risk factor for the development of pneumonia and a septic course due to virus infection and occur in approximately 20% of patients.[3,4]
- Reports from Centers for Disease Control and Prevention, other national centers, hospital and other epidemiological observation in heavily affected regions demonstrate that **risk of fatal outcome in diabetic patients affected with the virus are up to 50% compared to non-diabetics.**[5]

To understand diabetes as a risk factor for progression and prognosis for the infectious disease, Guo W, et al. from China conducted a **retrospective study on 174 infected patients** affected by the virus who were admitted in the Wuhan Union hospital.[1]

Patients were separated into two groups: with diabetes and without diabetes. Demographic data, medical history, sign and symptoms, laboratory findings, chest computed (CT) tomography as well as treatment measures were collected and analyzed. Patients with other comorbidities were excluded.[1]

- **Retrospective study from Wuhan, China**
- **n=174**
- **Two groups: Diabetes (n=24) and non-diabetes (n=26)**
- **Biochemical, CT and Treatment measures collected and analyzed**

Table 1 compares the laboratory parameters between diabetic and non-diabetic patients without other comorbidities.[1]

		Median (IQR)			
	Normal Range	Total (n=50)	Non-diabetes (n=26)	Diabetes (n=24)	P value
HBDH (U/L)	72-182	150 (136.75-185)	141.5 (124.75-150.5)	181 (170-204.5)	<0.01
ALT (U/L)	5-35	20.5 (16-30.5)	18.5 (13-24)	26.5 (20-43)	0.02
LDH (U/L)	109-245	195.4 (177-247.5)	186.5 (177-204.5)	250.5 (189.6-292.5)	0.01
GGT (U/L)	11-50	15 (13-22.5)	13 (11-15.25)	20 (15.75-33)	<0.01
Total protein (mg/L)	64-83	63.1 (59.83-67.25)	67.7 (63.4-69)	60 (54.8-62.8)	<0.01
Prealbumin (mg/L)	0.17-0.42	0.18 (0.14-0.22)	0.21 (0.18-0.23)	0.14 (0.12-0.18)	0.02
Albumin (mg/L)	35-55	39.2 (35.75-42.1)	41.45 (39.28-43.43)	35.4 (29.75-38.7)	<0.01
ALB/GLB	1.5-2.5	1.6 (1.3-1.7)	1.6 (1.48-1.7)	1.4 (1.05-1.6)	0.04
Lymphocytes (*10^9/L)	1.1-3.2	1.04 (0.64-1.36)	1.33 (.17-1.63)	0.59 (0.41-0.89)	<0.01
Neutrophils (*10^9/L)	1.8-6.3	2.91 (2.09-4.13)	2.54 (2.05-3.22)	4 (2.3-6.52)	0.02

RBCs (*10^{12}/L)	3.8-5.1	4.16 (3.88-4.47)	4.36 (4.14-4.64)	3.88 (3.63-4.16)	<0.01
Hemoglobin (g/dL)	115-150	124 (116-135)	133 (120-137.75)	118 (107.5-126)	<0.01
C-ractive protein (mg/L)	<8	11.8 (3.14-37.8)	7.43 (3.14-13.45)	76.4 (12.4-93)	<0.01
Serum ferritin (ng/ml)	21.8-275	193.15 (85.73-802.2)	128.9 (57.25-193.15)	764.8 (164-1496)	<0.01
ESR (mm/h)	<15	26.5 (7-62.25)	8 (7-26)	76 (59-85)	<0.01
IL-6 (pg/ml)	0.1-2.9	7.99 (3.52-15.86)	4.13 (3.14-10.61)	13.73 (7.28-28.31)	<0.01
D-dimer(μg/L)	<0.5	0.42 (0.24-1.15)	0.25 (0.22-0.31)	1.16 (0.74-1.89)	<0.01
FIB (g/L)	2.0-4.0	4.52 (3.28-5.27)	3.75(3.04-4.75)	5.01 (4.48-6.25)	<0.01

IQR: interquartile range; HBDH: α-Hydroxybutyrate Dehydrogenase, ALT: Alanine aminotransferase, LDH: Lactic dehydrogenase, GGT: γ-glutamyltransferase; ALB: albumin, GLB: Globlulin, ESR: erythrocyte sedimentation rate, FIB: Fibrinogen. P values indicate difference between diabetes and non-diabetes patients. P<0.05 was considered statistically significant.

Significant difference in the various biochemical parameters suggests that diabetes may contribute to a poorer prognosis of the disease. Along with biochemical parameters, higher quantifiable CT imaging score was found in diabetes patients compared to non-diabetes group, which implies that pneumonia in diabetes is more severe than non-diabetic patients.[1]

Researchers also evaluated the effect of the virus on the pathology of diabetes in patients managing their blood glucose with diabetes on insulin or oral medicine before admission.[1]

- Among them, **29.2% of the patient took insulin before and increased the dose after admission.**[1]
- **37.5% of the patients were on oral medicine before admission and started insulin therapy after admission.** [1]

These observations suggest that patients had poor glycemic control during hospitalization.

It was concluded that, diabetes could be considered as a risk factor for the outcome of pneumonia caused by the virus, and attention should be paid to such patients, in case of rapid deterioration. [1]

Blood glucose control and outcomes

The glycemic management and benefit/risk of overall treatment during these time is a key challenge. Thus, to address this researchers from Hubei Province, China conducted multi-centered, retrospective cohort study (n=7337). Out of all patients 952 had pre-existing T2D.[6]

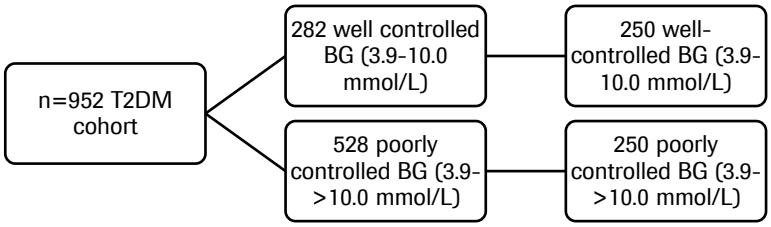

Figure 1: Participant enrollment in the cohort study. 250 from each were used for propensity score-matched analysis

Patients affected by the virus and pre-existing T2DM required more intensive integrated treatment to manage their symptoms of the disease compared to non-diabetic subjects.

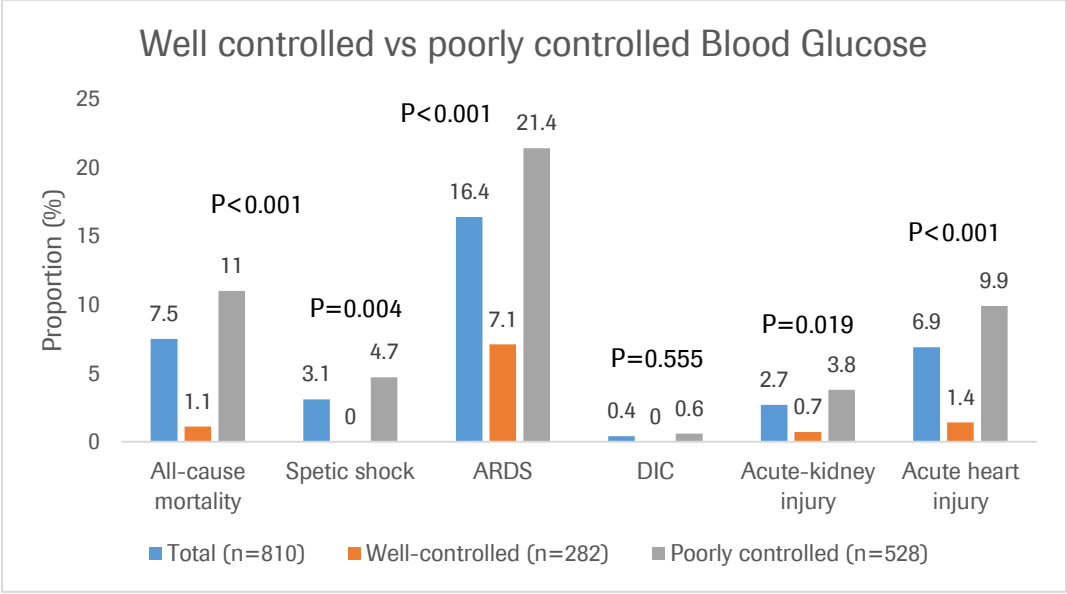

Figure 2: Incidence of primary and secondary outcomes of patients in well-controlled or poorly controlled blood glucose group. ARDS: Acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; p value calculated by Fisher's exact test or x^2 test.

In-hospital death rate was significantly lower (1.1% vs 1.0%) in the well-controlled group relative to the poorly controlled group (Figure 2). [6]

Glycemic variability (GV) has been a critical indicator and possible risk predictor for death and other complications in individuals with type 2 diabetes. This study demonstrated that there was significant reduction in medical interventions, major organ injuries and all cause of mortality associated with the patients having GV 3.9 and 10.0 mmol/L. Authors concluded that, **improved glycemic control correlates with better outcome in the patients affected by the infection and pre-existing diabetes**.[6]

Another observational study conducted by researcher from the United States of America (USA) delineates **more than 4 times in-hospital mortality rate and increased length of stay for people with diabetes and hyperglycemia.**[7]

- **Retrospective observational study**
- **n=1122 patients in 88 USA hospitals**
- **Key results**
  - ~ 29% mortality rate in patient groups with diabetes/HbA1c>6.5% experiencing hyperglycemia during hospital stay
  - ~ 42% mortality rate in patients with no prior history of diabetes but who developed hyperglycemia in the hospital.

Patients with diabetes and/or controlled hyperglycemia had longer length of hospital stay and markedly higher mortality compared to patient without diabetes and/or uncontrolled hyperglycemia [7]

Consensus recommendations on plasma glucose level during these times[1]

Out-patient care

Prevention of infection in diabetes

- Sensitisation of patients with diabetes for the importance of optimal metabolic control
- Optimisation of current therapy if appropriate
- Caution with premature discontinuation of established therapy
- Utilisation of Telemedicine and connected health models

In-patient or intensive care unit

Monitor for new onset of diabetes in infected patients (in-patient) care.

Management of infected patients with diabetes (intensive care unit)

- Plasma glucose monitoring, electrolyte, pH, blood ketones or β-hydroxybutyrate
- Liberal indication for early i.v insulin therapy in severe courses (ARDS, hyperinflmmation) for exact titration, avoiding variable s.c resorption and management of commonly seen very high insulin consumption

Therapeutic aims

- Plasma glucose concentration: 72-144 mg/dL*
- HbA1c: <7%
- CG/FGM targets
    - Time in Range (3.9-10 mmol/L): >70% (>50% and older people)
    - Hypoglycemia (<3.9 mmol/L): <4% (<1% in frail and older people)

Plasma glucose concentration: 72-180 mg/dL

Figure 3: Consensus recommendations for diabetes during these times. *Target concentration of lower plasma glucose can be adjusted to 90 mg/dl in frail patients

All patients affected with the virus and diabetes require continuous and reliable glycemic control as recommended by the physicians

Disclaimer: This article is rewritten by Medical and Scientific Affairs team, Roche Diabetes Care India and reviewed by Dr. Shishir Kumar, Chief diabetologist, Bombay hospital, Mumbai, India.

References:

1. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020 Mar 31:e3319. doi: 10.1002/dmrr.3319. [Epub ahead of print].
2. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020 Apr 23. pii: S2213-8587(20)30152-2. doi: 10.1016/S2213-8587(20)30152-2. [Epub ahead of print].
3. Hespanhol VP, Barbara C. Pneumonia mortality, comorbidities matter? Pulmonology 2019; published online Nov 28; DOI:10.1016/ j.pulmoe.2019.10.003.
4. Zou Q, Zheng S, Wang X, Liu S, Bao J, Yu F. et al. Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments. Int J Infect Dis. 2020 Mar;92:208-213.
5. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225–28.
6. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020 May 1. pii: S1550-4131(20)30238-2. doi: 10.1016/j.cmet.2020.04.021. [Epub ahead of print].
7. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. J Diabetes Sci Technol. 2020 May 9:1932296820924469. doi: 10.1177/1932296820924469. [Epub ahead of print].