Bangladesh J Microbiol, Volume 39, Number 1, June 2022, pp 1-6

Original Article

Hospitalized Coronavirus Disease 2019 (Covid-19) with Pre-existing Diabetes Mellitus: Comparison between Survived and Deceased Patients

Md. Shahed Morshed[1], Abdullah Al Mosabbir[2], Mohammad Sorowar Hossain[2]*

[1]*Emergency medical officer, Kurmitola general hospital, Dhaka, Bangladesh,* [2]*Department of Emerging and Neglected Diseases, Biomedical Research Foundation,Dhaka, Bangladesh.*

Patients with pre-existing diabetes mellitus (DM) are at high risk of severe outcomes from coronavirus disease 2019 (COVID-19). However, there is limited data on these patients from South Asia, especially Bangladesh. Besides, comparative studies between survived and deceased patients with DM and COVID-19 are rare in literature. This retrospective cross-sectional study was conducted among RT-PCR confirmed COVID-19 patients with pre-existing DM in a specialized COVID-19 hospital in Bangladesh. Data from hospital records were analyzed. Among 921 RT-PCR confirmed patients with COVID-19 admitted during the study period, 231 (~25%) patients had pre-existing DM. The overall mortality and intensive care unit (ICU) mortality rate among patients with DM was 11.3% (26/231) and 46.2% (12/26), respectively. The median age of the deceased patients was slightly higher (63.5 vs. 59 years, p 0.21). The most common comorbidity in both groups was hypertension. The clinical features were not significantly different between survived and deceased. However, deceased patients had significantly lower blood oxygen level (85% vs. 93%, p <0.001), and higher neutrophil-lymphocyte ratio (7.9 vs. 4.5, p 0.003) and serum ferritin levels (946.0 vs. 425.0 ng/mL, p 0.03). Glycemic status was poor in both groups. This study would help identify a subgroup of diabetic patients with COVID-19 who are at higher risk of in-hospital death requiring rigorous clinical management.

Keywords: COVID-19, Diabetes Mellitus, COVID-19 in Bangladesh, In-hospital mortality

Introduction

The ongoing pandemic of coronavirus disease 2019 (COVID-19) is one of the greatest disasters that the world has ever witnessed. While the clinical spectrum of COVID-19 is highly variable, the disease severity and mortality were reported to be significantly higher among patients with co-morbidities, particularly diabetes mellitus (DM)[1,2]. However, disproportionate clinical outcomes (particularly mortality) have been reported among South Asian immigrants in the UK and New York[3]. Based on a large study in the UK, 40% of hospitalized COVID-19 patients with South Asian background had diabetes and the mortality rate was nearly 20% higher among them as compared to white British[4]. India, Pakistan, and Bangladesh are among the top 10 countries globally by the number of affected people and undiagnosed cases. Moreover, Bangladesh had the second largest number of people with diabetes in the South-East Asia region, with an estimated prevalence of 8.1%[5]. South Asian countries are largely similar in terms of socio-demographic status, lifestyle and epidemiologic transition. Despite diabetes being a major public health concern, there are limited studies on diabetic patients with COVID-19 from these regions, especially Bangladesh. Moreover, studies comparing survived and diseased patients with DM and COVID-19 are rare in literature, which we believe is vital to identify cases requiring urgent clinical attention. This study aimed to address the clinical epidemiology and outcome of COVID-19 patients with DM in Bangladesh, along with a detailed comparison between survived and deceased.

Material and Methods

Study setting

This retrospective cross-sectional observational study was conducted among RT-PCR confirmed COVID-19 patients with pre-existing DM from 1 to 30 June 2020 admitted in a specialized COVID-19 hospital (Kurmitola General Hospital) located in Dhaka, the epicenter of the COVID-19 pandemic in Bangladesh.

Case definitions

Patients with known DM and taking antidiabetic agents were considered to have pre-existing DM. Patients having glycated hemoglobin (HbA1c) e"6.5% done within three months of admission were also included as having pre-existing DM. The severity of COVID-19 was described by WHO interim guidance[6].

Statistical analysis

Data were extracted from hospital records using a relevant questionnaire. All information was double-checked before analysis to ensure quality. The institutional review board of the Biomedical Research Foundation, Bangladesh, approved the study protocol (Ref. no: BRF/ERB/2020/003). Data were analyzed

Corresponding author
Mohammad Sorowar Hossain, PhD, Scientist and Executive Director, Biomedical Research Foundation, Dhaka, Bangladesh,
Email: sorowar.hossain@brfbd.org, Phone: +88 01963378441

by SPSS Statistics software version 22.0 (Armonk, NY: IBM Corp). We used Pearson's chi-square test/ Fisher's exact test and Mann-Whitney U test to compare different groups. A p-value <0.05 was set as statistically significant.

Results

A total of 921 RT-PCR confirmed COVID-19 patients were admitted to the hospital during the study period. The median age of all hospitalized patients was 54 years. Of them, 25.5% patients (n=235) had pre-existing DM. However, due to inadequate data, four patients were excluded from the analysis. Finally, 231 patients were included in this study.

While the death rate among all hospitalized patients (with and without DM) was only 2.8% (58/921), it was four times higher (11.3%, 26/231) among patients with DM. The median age of the deceased patients with DM was slightly higher compared to survived (63.5 vs 59 years, p 0.21). There was a clear male predominance in both groups. About three-fourths of patients with DM (75.3%) had at least one comorbidity. The most common comorbidity in both survived and deceased patients were hypertension (HTN) (59.5% and 73.1%, respectively). The most common clinical presentation in all patients with DM was fever (71%) followed by breathlessness (64.5%) and cough (57.1%). The clinical presentations were not significantly different between survived and deceased except for significantly lower blood oxygen levels among deceased (85% vs. 93%, p <0.001). Overall, the median hospital stay for patients with DM was 12 days (IQR 10.0-16.0). Interestingly, hospital days were significantly higher among survivors (13 vs. 5 days, p <0.001) (Table 1).

Table 1. *Baseline characteristics, clinical features and laboratory findings of patients with COVID-19 and DM*[a]

Variables	Total	Survived	Deceased	P value
Baseline Characteristics	231 (100)	205 (88.7)	26 (11.3)	
Age, years	60.0 (51.0-65.0)	59.0 (51.0-65.0)	63.5 (50.0-68.3)	0.21
Age groups				
<40	17 (7.4)	14 (6.8)	3 (11.5)	
40 – 59	96 (41.6)	91 (44.4)	5 (19.2)	0.05
≥60	118 (51.1)	100 (48.8)	18 (69.2)	
Sex				
Male	151 (65.4)	132 (64.4)	19 (73.1)	0.40
Female	80 (34.6)	73 (35.6)	7 (26.9)	
Co-morbidities[b]				
Any	174 (75.3)	150 (73.2)	24 (92.3)	0.05
Hypertension	141 (61.0)	122 (59.5)	19 (73.1)	0.21
Chronic Kidney Disease	41 (17.7)	34 (16.6)	7 (26.9)	0.27
Ischemic Heart Disease	36 (15.6)	28 (13.7)	8 (30.8)	0.04
Obstructive lung disease	22 (9.5)	18 (8.8)	4 (15.4)	0.29
Cerebrovascular disease	11 (4.8)	9 (4.4)	2 (7.7)	0.36
Clinical features[c]				
Predominant symptoms				
Fever	164 (71.0)	146 (71.2)	18 (69.2)	1.00
Breathlessness	149 (64.5)	129 (62.9)	20 (76.9)	0.20
Cough	132 (57.1)	122 (59.5)	10 (38.5)	0.06
Anorexia	20 (8.7)	19 (9.3)	1 (3.8)	0.71
Sore throat	15 (6.5)	15 (7.3)	0 (0.0)	0.23
Signs at presentation				
Temperature (^{O}C)	36.0 (35.6-36.4)	36.0 (35.6-36.4)	36.2 (35.8-36.7)	0.10
Oxygen saturation (%)	93.0 (86.0-96.0)	93.0 (88.0-96.0)	85.0 (79.0-91.0)	<0.001
Severity of disease at presentation				
Mild	78 (33.8)	75 (36.6)	3 (11.5)	<0.001
Moderate	68 (29.4)	63 (30.7)	5 (19.2)	
Severe	83 (35.9)	67 (32.7)	16 (61.5)	
Critical	2 (0.9)	0 (0.0)	2 (7.7)	
Hospital days	12.0 (10.0-16.0)	13.0 (10.5-17.0)	5.0 (2.0-8.3)	<0.001

[a]Number (%) or Median (IQR) was used where appropriate; Parentheses: (percentages over column total of each variable)
[b]Other co-morbidities: hypothyroidism (6), chronic liver disease (3), benign enlargement of prostate (2), malignancy (1), rheumatoid arthritis (1), gout (1), etc
[c]Other symptoms: fatigue (14), diarrhea (11), vomiting (10), chest pain/ tightness (7), headache (5), altered taste/ smell (5), dizziness (3), etc

Among hematological parameters, the absolute neutrophil count and neutrophil-lymphocyte ratio (NLR) of deceased patients with DM were significantly higher than survived. Besides, serum ferritin was more than two times higher among the deceased (946.0 vs. 425.0 ng/mL, p 0.03). The glycemic profile showed that most patients (both survived and deceased) had uncontrolled DM; median HbA1c was 8.3% and 8.6%, respectively. In addition, random blood sugar (RBS) at admission was significantly higher among deceased (16.9 vs. 14.0 mmol/L, p 0.002) (Table 2).

Among different medications (Table 3), intervention with ivermectin, an anti-parasite drug, was significantly higher among survived (66.3% vs. 42.3%, p <0.02). Convalescent plasma therapy (CPT) was given to a significantly higher proportion of deceased patients with DM (19.2% vs. 2.9%, p 0.004). Similarly, a significantly higher proportion of deceased patients with DM received tocilizumab, an anti–interleukin-6 receptor monoclonal antibody. Among antidiabetic agents used, a significantly higher proportion of deceased patients required insulin than survived.

While intensive care unit (ICU) support was indicated for 31.2% (72/231) patients with DM, only 12.5% (29/231) of them got ICU admission. Among deceased patients, 46% (12/29) were from ICU admitted patients and statistically similar with patients who cold not admit in ICU (Fig 1).

Table 2. *Laboratory findings of patients with COVID-19 and DM*[a, b]

Variables	Total	Survived	Deceased	P value
Hematological parameters				
Hemoglobin, gm/dL	11.8 (10.5-13.3) [185]	11.8 (10.7-13.3) [169]	10.8 (9.6-13.2) [16]	0.24
Total leukocytes, $\times10^3/\mu L$	8.6 (6.8-12.8) [185]	8.4 (6.6-11.3) [169]	14.8 (10.9-19.1) [16]	**<0.001**
Absolute neutrophils count, $\times10^3/\mu L$	6.61 (4.54-10.34) [185]	6.25 (4.49-9.34) [169]	13.11 (9.31, 15.83) [16]	**<0.001**
Absolute lymphocytes count, $\times10^3/\mu L$	1.55 (1.05-2.16) [185]	1.55 (1.05-2.15) [169]	1.55 (1.05-2.24) [16]	0.969
Neutrophils:Lymphocytes	4.6 (2.6-7.7) [185]	4.5 (2.4-7.1) [169]	7.9 (4.3-10.0) [16]	**0.003**
Platelet count, $\times10^3/\mu L$	261.0 (185.0-354.0) [185]	256.0 (181.0-350.5) [169]	289.5 (212.0-364.8) [16]	0.58
Biochemical parameters				
Alanine aminotransferase, U/L	54.5 (36.5-87.3) [154]	54.0 (35.0-86.0) [139]	62.0 (53.0-88.0) [15]	0.34
Serum creatinine, mg/dL	1.2 (1.0-1.5) [178]	1.1 (1.0-1.4) [159]	1.2 (1.0-1.9) [19]	0.440
eGFR, ml/min/1.73 m^2 body surface area	62.50 (43.25-78.25) [178]	63.0 (45.0-79.0) [159]	56.0 (34.0-70.0) [19]	0.435
Serum Sodium, mmol/L	139.0 (135.0-142.0) [163]	139.0 (136.0-142.0) [142]	137.0 (128.5-141.0) [21]	0.130
Serum Potassium, mmol/L	4.4 (4.0-4.8) [163]	4.4 (4.0-4.9) [142]	4.2 [3.9-4.8) [21]	0.40
Serum C-reactive protein, mg/L	24.0 (6.0-24.0) [156]	24.0 (6.0-24.0) [140]	24.0 [7.5-24.0) [21]	0.40
Serum ferritin. ng/mL	463.5 (226.0-987.3) [96]	425.0 (213.0-936.0) [83]	946.0 (399.5-1690.5) [13]	**0.03**
Serum D-dimer, mg/L	0.4 (0.2-1.1) [97]	0.4 (0.1-1.1) [88]	0.6 (0.3-6.4) [9]	0.13
Serum lactate dehydrogenase, U/L	507.5 (375.0-683.0) [44]	480.0 (373.0-640.0) [39]	750.0 (461.0-958.0) [5]	0.15
Glycemic profile				
Random blood glucose, mmol/L	14.9 (9.6-18.2) [231]	14.0 (9.1-18.2) [205]	16.9 (15.3-20.0) [26]	**0.002**
HbA1c (%)	8.3 (7.1-9.5) [50]	8.3 (7.3-9.5) [41]	8.6 (6.8-10.0) [9]	0.90

[a]Number (%) or Median (IQR) was used where appropriate; Parentheses: (percentages over column total of each variable); [available number]

[b]Data were not available for all patients as investigations were done on a need basis

Table 3. *Treatment of COVID-19 patients with DM (n=231)*[a]

Variables	Total	Survived	Deceased	P value
Antivirals[b]	51 (22.1)	42 (20.5)	9 (34.6)	0.13
Oral antibiotics[c]	182 (78.8)	165 (80.5)	17 (65.4)	0.12
Intravenous antibiotics	154 (66.7)	136 (66.3)	18 (69.2)	0.83
Ivermectin	147 (63.6)	136 (66.3)	11 (42.3)	0.02
Anticoagulants[d]	203 (87.9)	182 (88.8)	21 (80.8)	0.33
Steroids	129 (55.8)	113 (55.1)	16 (61.5)	0.68
Convalescent plasma therapy	11 (4.8)	6 (2.9)	5 (19.2)	0.004
Tocilizumab	9 (3.9)	5 (2.4)	4 (15.4)	0.01
ACEI/ ARB	122 (52.8)	107 (52.2)	15 (57.7)	0.68
Oral antidiabetic agents	94 (40.7)	89 (43.4)	5 (19.2)	0.02
Insulin	161 (69.7)	138 (67.3)	23 (88.5)	0.04

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers
[a]Within parentheses are percentages over column total of each variable; Number (%) was used
[b]Antivirals: favipiravir-27 (11.7%); remdesivir- 25 (10.8%)
[c]Oral antibiotics: doxicycline- 122 (52.8%); coamoxiclav- 61 (26.4%); azithromycin- 42 (18.2%), etc
[d]Anticoagulant: Low molecular weight heparin, all enoxaparin

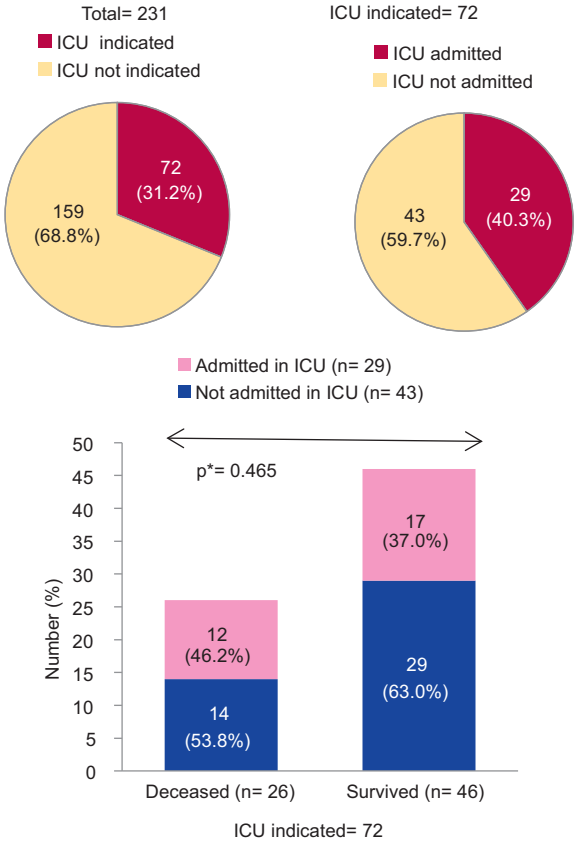

Fig. 1. *Outcome of patients with DM and COVID-19 who required ICU care. Patients referred to ICU with proper indication were considered as ICU indicated. *Chi-square test was done; within parentheses are percentages over column total.*

Discussion

Our study found that one in four hospitalized patients (235/921) with COVID-19 had pre-existing DM. One study from the southern region of Bangladesh reported a slightly lower prevalence (19.8%) of DM among hospitalized patients[7]. The prevalence showed wide variability in other countries ranging from 5.3% in China to 33% in Europe and nearly 50% in India[1,8]. This could be due to regional variation of healthcare policy and perception of diabetic patients towards COVID-19.

It is now well established that diabetes is a major contributor to mortality in patients with COVID-19. Dysregulation of the immune system and altered pulmonary function in diabetes patients were implicated[9]. In this study, the mortality rate among hospitalized patients with DM was more than 11%. However, the overall case fatality rate in Bangladesh is only 1.5%[10]. This trend largely agrees with other studies, although the death rate was comparatively higher in our study[1,8,11]. While we are not certain about the cause of this observation, we found that some parameters were significantly different between the two groups. While both deceased and survived patients with DM had poor glycemic control, deceased patients had significantly higher RBS. The association between poorly controlled blood glucose and higher mortality in patients with DM and COVID-19 has been reported in many studies[1,12]. Additionally, median NLR and serum ferritin levels were almost double among deceased compared to survived. Highly elevated NLR and serum ferritin essentially indicate excessive inflammation leading to cytokine storm and multiple organ damage in patients with COVID-19. Significantly higher

NLR and serum ferritin levels among non-survivors compared to survivors were reported in already published studies[13,14].

The survived patients took ivermectin at a higher frequency than the deceased due to easy administration and some initial promising results[15]. However, due to lack of evidence, it is not recommended in routine practice. Convalescent plasma therapy and tocilizumab were more frequently used in deceased patients as they presented with more severe and critical conditions. However their efficacy in COVID-19 is not clearly established[16,17]. Similarly, oral antidiabetic agents were more frequently taken by survived patients and insulin by deceased patients. Most of the antidiabetic agents are generally safe at least in mild to moderate COVID-19 and glycemic control is important for preventing disease progression[18].

Our study reports another intriguing observation. While ICU support was indicated in over 30% (72/231) of diabetic patients, more than half of them (43/72) could not be admitted into ICU due to the acute bed crisis (only a ten bedded ICU support in the study hospital). The unprecedented COVID-19 pandemic added huge pressure on ICUs world wide[19]. Likewise, being a resource-poor country, the pandemic overwhelmed the healthcare system of Bangladesh. Interestingly, however, the death rate between the ICU admitted vs. not admitted among diabetic patients who required ICU care was not statistically different (46.2% vs. 53.2%, respectively, n=26, p 0.465) (Figure 1). We could not find any literature to compare such observations as this kind of situation is unique for countries with limited resources like Bangladesh. We believe this is a unique finding for resource-poor settings and needs further research. Small sample size and overcautious referral to ICU of relatively less severe patients might be two important factors.

Our study has some limitations. The sample size was not large enough to evaluate the predictive performance of different parameters for death in diabetic patients. Besides, we could not collect data on the type of DM or new-onset DM.

Conclusions

Our study found deceased patients with DM and COVID-19 had significantly lower oxygen saturation and significantly higher NLR, RBS and serum ferritin levels compared to survived. We believe findings from this study will help clinicians to identify a subgroup of diabetic patients with COVID-19 who are at higher risk of in-hospital death; hence, requiring rigorous clinical management.

Acknowledgement

We are grateful to Brigadier General Jamil Ahmad, director, Kurmitola General Hospital (KGH) and all nurses of KGH for their generous support in data collection. We humbly acknowledge the contribution of our patients as well.

Conflicts of interest: none

Ethics approval and consent to participate and publish

The institutional review board of the Biomedical Research Foundation, Bangladesh, approved the study protocol (Ref. no: BRF/ERB/2020/003).

Authors' contributions

MSM: Conceptualization, Methodology, Formal analysis, Data Curation, Writing - Review & Editing; AAM: Methodology, Writing - Original Draft, Visualization; MSH: Writing - Review & Editing, Supervision

References

1. Caballero AE, Ceriello A, Misra A, Aschner P, McDonnell ME, Hassanein M, et al. COVID-19 in people living with diabetes: an international consensus. *J Diabetes Complications.* 2020;34(9): 107671. doi:https://doi.org/10.1016/j.jdiacomp.2020. 107671
2. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol.* 2020;8(10):813–822. doi:10.1016/S2213-8587(20) 30272-2
3. Gupta R, Hussain A, Misra A. Diabetes and COVID-19: evidence, current status and unanswered research questions. *Eur J Clin Nutr.* 2020; 74(6):864–870. http://dx.doi.org/10.1038/s41430-020-0652-1
4. Harrison EM, Docherty AB, Barr B, Buchan I, Carson G, Drake TM, et al. Ethnicity and outcomes from COVID-19: the ISARIC CCP-UK prospective observational cohort study of hospitalised patients. *Preprints with the Lancet (SSRN).* 2020;41. Available at: http://dx.doi.org/10.2139/ssrn.3618215
5. International Diabetes Federation. IDF Diabetes Atlas 9th edition 2019. Accessed February 9, 2021. https://www.diabetesatlas.org/en/
6. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. Accessed February 9, 2021. https://www.who.int/publications/i/item/clinical-management-of-covid-19
7. Akter F, Mannan A, Mehedi HMH, Rob MA, Ahmed S, Salauddin A, et al. Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with and without diabetes in Bangladesh. *Diabetes Metab Syndr Clin Res Rev.* 2020;14(6):2031-2038. doi:https://doi.org/10.1016/j.dsx.2020.10.016
8. Mithal A, Jevalikar G, Sharma R, Singh A, Farooqui KJ, Mahendru S, et al. High prevalence of diabetes and other comorbidities in hospitalized patients with COVID-19 in Delhi, India, and their association with outcomes. *Diabetes Metab Syndr Clin Res Rev.* 2021;15(1):169-175. doi:https://doi.org/10.1016/j.dsx.2020.12.029
9. Chee YJ, Tan SK, Yeoh E. Dissecting the interaction between COVID-19 and diabetes mellitus. *J Diabetes Investig.* 2020;11(5):1104–1114. doi: 10.1111/jdi.13326
10. Coronavirus Disease 2019 (COVID-19) Information Bangladesh. Accessed February 9, 2021. https://corona.gov.bd/graph
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72/ 314 cases from the Chinese center for disease control and prevention. *JAMA.* 2020;323(13):1239–1242. doi:10.1001/jama.2020.2648
12. 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;31(6):1068-1077.e3. doi:10.1016/j.cmet.2020.04.021

13. Zeng ZY, Feng SD, Chen GP, Wu JN. Predictive value of the neutrophil to lymphocyte ratio for disease deterioration and serious adverse outcomes in patients with COVID-19: a prospective cohort study. *BMC Infect Dis.* 2021;21(1):80. doi:10.1186/s12879-021-05796-3

14. 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. doi:https://doi.org/10.1002/jcla.23618

15. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in COVID nineteen study. *Chest.* 2021;159(1):85–92. Available from: https://doi.org/10.1016/j.chest.2020.10.009

16. Devarasetti PK, Rajasekhar L, Baisya R, Sreejitha KS, Vardhan YK. A review of COVID-19 convalescent plasma use in COVID-19 with focus on proof of efficacy. *Immunol Res.* 2021;69(1):18–25. doi: 10.1007/s12026-020-09169-x

17. Khan FA, Stewart I, Fabbri L, Moss S, Robinson K, Smyth AR, et al. Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. *Thorax.* 2021;76(9):1-13. http://dx.doi.org/10.1136/thoraxjnl-2020-215266

18. Sun B, Huang S, Zhou J. Perspectives of antidiabetic Drugs in diabetes with coronavirus infections. *Front Pharmacol.* 2021;11(January):1–8. doi: 10.3389/fphar.2020.592439

19. Vincent JL, Creteur J. Ethical aspects of the COVID-19 crisis: how to deal with an overwhelming shortage of acute beds. *Eur Hear Journal Acute Cardiovasc Care.* 2020;9(3):248–252. doi: 10.1177/2048872620922788