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Original research

The sex-related discrepancy in laboratory parameters of severe COVID-19 patients with diabetes: A retrospective cohort study

Maha O. Hammad[a,*], Mahmoud M. Alseoudy[b]

[a] Department of Medical Biochemistry, Faculty of Medicine, Mansoura University, Mansoura, Egypt
[b] Department of Anaesthesia and Surgical Intensive Care, Faculty of Medicine, Mansoura University, Mansoura, Egypt

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ABSTRACT

Aim: This study aimed at providing evidence to consider sex differences in interpretations of laboratory parameters of severe COVID-19 patients with diabetes.
Methods: For 118 diabetic patients, laboratory measurements and clinical outcomes were compared between males and females. This study also compared inflammatory ratios obtained from combinations of six inflammatory markers between the two groups. The risk factors for mortality were identified through logistic regression.
Results: Males were 54 (45.8%) and females were 64 (54.2%). Males showed a significant increase in ALT (P = 0.003), CRP (P = 0.03), mean platelet volume (MPV)-to-lymphocyte ratio (P = 0.001), and C-reactive protein-to-albumin ratio (P = 0.044), whereas females had a significant increase in lymphocytes (P < 0.005) and MPV (P = 0.01). In all participants, multivariate analysis illustrated that older age, male sex, increased serum total bilirubin, and decreased PO_2 were significant independent predictors of mortality (P < 0.05).
Conclusion: In severe COVID-19 patients with diabetes, there were significant sex differences in many laboratory characteristics with a higher risk of mortality among males.

1. Introduction

Since December 2019, novel coronavirus-infected pneumonia (COVID-19) has rapidly spread throughout China and around the world [1,2]. Increasing evidence suggests that comorbid conditions have a vital role in the course and progression of COVID-19 [3].

Diabetes mellitus (DM) is identified as an independent risk factor for developing respiratory tract infections [4]. It was found that confirmed COVID-19 patients with diabetes are at higher risk of mortality than their non-diabetic counterparts [5,6].

Many studies have proven that there are considerable sex-specific differences in the laboratory parameters, as well as in the progression of COVID-19 patients as a whole [7,8], but these sex-associated differences were not efficiently investigated among severe COVID-19 patients with diabetes in particular, even though the role of sex differences in the risk and complications of diabetes is of fundamental importance [9,10].

This knowledge is essential to promote the development of relevant sex-based therapeutic methods and preventive strategies for severe COVID-19 patients with diabetes in an attempt to reduce the risk of fatality in this patient population and to allow for more awareness in terms of sex-specific risk factors.

Thus, this research aimed at exploring the possible roles of sex-specific differences in laboratory characteristics and the clinical outcome of diabetic patients with severe COVID-19 pneumonia. This study also focused on the potential feasibility of sex-related discrepancies in inflammatory ratios obtained from combinations of six inflammatory markers. The secondary endpoint will be to find other predictors of fatality among the study population.

Abbreviations: ABG, arterial blood gases; ALT, alanine transaminase; AST, aspartate transaminase; CAR, CRP/albumin ratio; CBC, complete blood count; CI, confidence interval; CLR, CRP/lymphocyte ratio; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DM, diabetes mellitus; FiO_2, fraction of inspired O_2; INR, international normalized ratio; IQR, interquartile range; LAR, LDH/albumin ratio; LDH, lactate dehydrogenase; MPV, mean platelet volume; MPVLR, mean platelet volume/lymphocyte ratio; OR, odds ratio; $PaCO_2$, arterial carbon dioxide partial pressure; PaO_2, arterial O_2 partial pressure; PAR, platelet/albumin ratio; PLR, platelet/lymphocyte ratio; SaO_2, arterial O_2 saturation; STROBE, The Strengthening the Reporting of Observational Studies in Epidemiology.

* Corresponding author at: Department of Medical Biochemistry, Faculty of Medicine, Mansoura University, Abdelsalam Aref St., Mansoura, El-Dakahliya Governorate, Egypt.
E-mail address: maha_osman@mans.edu.eg (M.O. Hammad).

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2. Methods

2.1. Study design

This is a retrospective, cohort observational analysis performed on severe COVID-19 patients with diabetes who were admitted to Mansoura University Hospital between July and November 2020. This study was approved by the Institutional Research Board (IRB) of the Faculty of Medicine, Mansoura University (approval number: R.20.12.1133). Informed consent was waived as the study involved no potential risk and no breach of privacy to patients. This manuscript adheres to the applicable STROBE guidelines.

2.2. Patients

This study included 118 patients previously diagnosed with diabetes (type 2) with hypoglycaemic agent prescriptions and random blood glucose >11.1 mmol/L. All patients of the study had a confirmed positive result for real-time polymerase chain reaction assay for COVID-19 nucleic acid from pharyngeal swab samples. All patients had been diagnosed with severe COVID-19 previously by a respiratory physician according to these criteria: arterial oxygen saturation (SaO_2) ≤92%, PaO_2 (arterial oxygen partial pressure)/FiO_2 (fraction of inspired oxygen) <300, respiratory rate >30 breaths/min, or lung infiltrates detected by CT were more than 50%. Patients were divided into two groups based on sex into male and female groups.

We excluded non-severe COVID-19 patients with diabetes, patients who had no history of diabetes, newly diagnosed patients with diabetes at isolation hospital, patients aged ≤18 years, pregnant females with COVID-19 infection and diabetes, severe COVID-19 patients with type 1 diabetes, and severe COVID-19 patients with missing data.

2.3. Data collection

Information on age, sex, and comorbidities was recorded upon hospital admission. The clinical outcome (either dead or improved) was obtained at the final date of follow-up (the end of November 2020). The following initial routine laboratory findings were assessed upon hospital admission: complete blood count (CBC), arterial blood gases (ABG), coagulation profile (D-dimer, INR, prothrombin time), liver function tests [(serum albumin, alanine transaminase (ALT), aspartate transaminase (AST)], total bilirubin, serum creatinine, lactate dehydrogenase (LDH), and C-reactive protein (CRP).

Six inflammation-related ratios were obtained by dividing the four upregulated inflammatory markers [mean platelet volume (MPV), platelets, LDH, and CRP] by two downregulated inflammatory markers (lymphocytes and albumin). The six combinations of inflammatory markers examined were: MPVLR = mean platelet volume (fL)/lymphocyte count (10^9/L) ratio; PLR = platelet count (10^9/L)/lymphocyte count (10^9/L) ratio; CLR = CRP (mg/L)/lymphocyte count (10^9/L) ratio; CAR = CRP (mg/L)/serum albumin level (g/L) ratio; LAR = LDH (U/L)/serum albumin level (g/L) ratio; PAR = platelet count (10^9/L)/serum albumin level (g/L) ratio.

2.4. Statistical analysis

Data were entered and analyzed using SPSS software (version 25.0). Differences between the two groups were analyzed using the chi-square test for categorical variables. Continuous variables were initially tested for normality using Kolmogorov-Smirnov test with data being normally distributed if P-value >0.05. Normally distributed continuous variables were compared via independent samples t-test, whereas the nonparametric Mann–Whitney U-test was used if the data were non-normally distributed. Univariate logistic regression was used to predict the likelihood of mortality using only one predictor. The multivariate logistic regression model was then applied to variables significant at the univariate analysis to create a prediction model for detecting significant "independent" predictors with their OR (95% CI). For any used tests, results were considered statistically significant if P-value <0.050.

3. Results

3.1. Patients' clinic-demographic characteristics

The patients' clinic-demographic data are demonstrated in Table 1. Of the entire patient cohort, the mean age was 63 (±9.7) years with 45 patients (38.2%) died at the final follow-up of this study. Besides, diabetes coexisted together with hypertension in 80 patients (67.8%). There were 64 females (54.2%) and 54 males (45.8%). Male patients with diabetes had a significantly higher mortality rate than female patients with diabetes (48.1% vs. 29.7%, P = 0.04).

3.2. Comparison of laboratory characteristics between sexes

All patients with diabetes had abnormalities of D-dimer, LDH, and CRP at admission. Male patients with diabetes had a significant increase in RBC parameters, including RBC count, haematocrit, and haemoglobin than female patients with diabetes (P < 0.05). Moreover, there was a significant decrease in lymphocyte count (P < 0.005) and MPV (P = 0.01) in male patients compared to females. There were other sex differences reported in which males had a significant increase in ALT (P = 0.003) and CRP (P = 0.03) than females. Meanwhile, other laboratory parameters were not different in both sexes (P > 0.05) (Table 2).

3.3. Sex-related differences in the inflammation-related ratios

The inflammatory ratios were similar in both male and female groups except for MPVLR and CAR in which male patients with diabetes had higher MPVLR (median of 8 vs. 6.3, P = 0.001) and CAR (median of 1.4 vs. 2, P = 0.044) than females (Table 3).

3.4. Predictors of mortality among severe COVID-19 patients with diabetes

Univariate logistic regression analysis revealed that older age (P < 0.005), male sex (P = 0.04), increased serum bilirubin levels (P = 0.04), and increased ALT (P = 0.01) were demonstrated to be significant positive predictors of mortality among severe COVID-19 patients with diabetes, whereas PO_2 (P = 0.001) and serum albumin levels (P = 0.04) were demonstrated to be negative predictors of mortality (Table 4).

The multivariable logistic regression model was statistically significant, χ^2 (df) = 39.484(6), $P < 0.0005$. The model correctly classified 81.9% of cases. Specificity was 86.04%, and NPV was 84.09%, whereas sensitivity was 75.9%, and PPV was 78.6%. Age, sex, PO_2, and total bilirubin remained significantly associated with mortality among severe COVID-19 patients with diabetes. Older age, male sex, increased serum total bilirubin levels were significant positive independent predictors of mortality. The odds ratio of mortality increased 1.11-fold for older age, 4.788-fold for the male sex, and 6.359-fold for increased serum total bilirubin, whereas PO_2 was a significant negative independent predictor of mortality; PO_2 had 0.949 times lower odds to exhibit mortality (Table 5).

Table 1
Patients' clinic-demographic data.

Parameter	All patients (n = 118)	Male patients (n = 54)	Female patients (n = 64)	Statistic	P
Age (years)	63.1 ± 9.7	63.7 ± 9.9	62.8 ± 9.6	t = 0.511	*0.611
Age categories					
≤59 years	38 (32.2%)	18 a (33.3%)	20 a (31.3%)	χ^2 (df) = 138 (2)	**0.933
60–70 years	52 (44%)	24 a (44.4%)	28 a (43.8%)		
≥70 years	28 (23.8%)	12 a (22.2%)	16 a (25%)		
Outcome					
Dead	45 (38.2%)	26 (48.1%)	19 (29.7%)	χ^2 (df) = 4.231 (1)	**0.04
Improved	73 (61.8%)	28 (51.9%)	45 (70.3%)		
Comorbidity					
DM only	38 (32.2%)	22 (40.7%)	16 (25%)	χ^2 (df) = 3.324 (1)	**0.07
DM with hypertension	80 (67.8%)	32 (59.3%)	48 (75%)		

P-value by *Independent samples t-test (data are presented as mean ± SD). P value by **Chi-square test (data are presented as count and percentage. Z-test for column proportions (with adjusted P value by Bonferroni method) is presented by letters; similar letter = insignificant difference.

Table 2
Laboratory characteristics of male and female patients with diabetes and severe COVID-19.

Parameter	*Reference range*	All patients (n = 118)	Male patients (n = 54)	Female patients (n = 64)	P
Haematology					
RBC (m/uL)	Female: 3.8–5.5 Male: 4.5–6.5	4.59 (4.31–4.98)	4.8 (4.3–5.2)	4.5 (4.3–4.8)	0.03
Haematocrit (%)	Female: 38–48 Male: 45–52	38.5 (35.1–41.3)	40.2 (37.3–43.9)	36.5 (34.9–40.1)	<0.005
Haemoglobin (g/dL)	Female: 11–16 Male: 13–18	12.7 (11.2–13.3)	13.2 (11.9–14.6)	12 (10.9–12.9)	0.001
WBC ($\times 10^9$/L)	4–11	9.7 (6.6–13)	10 (6.6–12.2)	9.6 (6.6–14.1)	0.66
Lymphocyte count ($\times 10^9$/L)	0.6–4.1	1.3 (1–1.8)	1.2 (0.9–1.5)	1.6 (1.1–2.3)	<0.005
Lymphocyte %	10–58.5	14.1 (10.5–20)	12 (10.2–16.7)	15 (10.7–26.9)	0.03
Platelet ($\times 10^9$/L)	140–450	202 (156–270)	195 (125–245)	215 (156–286)	0.3
Mean platelet volume (fL)	7.2–11.8	9 (8.5–9.6)	8.9 (8.5–9.2)	9.2 (8.6–10.1)	0.01
Arterial blood gases					
PH	7.35–7.45	7.39 (7.34–7.43)	7.39 (7.35–7.44)	7.39 (7.34–7.43)	0.634
$PaCO_2$, mmHg	32–48	38.3 (33–47.6)	40.5 (33–47.6)	38.8 (33–47.7)	0.5
PaO_2, mmHg	83–108	59.6 (46–76.6)	56.6 (41.4–	62.4 (47.2–79.3)	0.32
SaO_2 (%)	95–100	87 (71–91.9)	87 (65.9–91.9)	89 (77–93)	0.4
Na^+ (mmol/L)	136–145	139 (135–146)	138 (135–143)	139 (133–148)	0.27
K^+ (mmol/L)	3.5–5.1	3.8(3.5–4.3)	4.1 (3.5–4.3)	3.8 (3.5–4.4)	0.7
Biochemistry					
Albumin (g/L)	35–55	34 (31–37)	34 (31–37)	33 (31–35)	0.2
AST (U/L)	5–40	37.5 (26–52)	38.5 (24–52)	34.5 (26–53)	0.52
ALT (U/L)	7–56	31 (21–50)	38.5 (30–59)	26 (20–47)	0.003
Total bilirubin (mg/dL)	0.2–1.2	0.7 (0.6–0.8)	0.8 (0.6–0.9)	0.7 (0.6–0.8)	0.16
Creatinine (mg/dL)	Female:0.6–1.1 Male: 0.8–1.3	1.2 (0.9–1.3)	1.1 (0.9–1.2)	1.2 (1–1.5)	0.75
Lactate dehydrogenase (U/L)	240–480	647 (466–928)	647 (549–845)	654 (466–928)	0.860
C-reactive protein (mg/L)	<10	53.5 (23.5–96)	65 (40–96)	45.3 (12–73)	0.03
Coagulation profile					
Prothrombin time (s)	12–13 s	14.5 (13–15.2)	14.6 (13–14.9)	14.3 (13–15.9)	0.46
INR	0.8–1.2	1.1 (1–1.2)	1.13 (1.1–1.2)	1.05 (1–1.3)	0.9
D-dimer (ng/mL)	≤250	420 (250–1350)	480 (330–1100)	368 (215–1880)	0.55

P-value by Mann–Whitney U test [(data are presented as median and interquartile range (IQR)]. Abbreviations: RBC: red blood cells; WBC: white blood cells; $PaCO_2$: arterial carbon dioxide partial pressure; PaO_2: arterial oxygen partial pressure; SaO_2: arterial oxygen saturation; AST: aspartate transaminase; ALT: alanine transaminase; INR: international normalized ratio.

Table 3
Comparison between male and female patients with severe COVID-19 pneumonia and diabetes regarding the inflammatory ratios.

Ratio	All patients (n = 118)	Male patients (n = 54)	Female patients (n = 64)	P
MPVLR	7 (5.1–8.6)	8 (6.5–10.3)	6.3 (4.3–7.5)	0.001
PLR	156 (97.5–224)	164 (120–224)	150.5 (83.3–230)	0.12
CLR	38.8 (17.3–68.3)	28.2 (13.6–68.6)	39.9 (18.7–73.6)	0.421
CAR	1.7 (0.66–2.6)	2 (1.01–2.8)	1.4 (0.39–2)	0.044
LAR	19.4 (12.8–24.9)	19.4 (16.1–24.7)	19.3 (12.5–27.8)	0.78
PAR	5.9 (4.4–8)	5.9 (4.5–7.1)	5.9 (4.4–9.1)	0.3

P-value by Mann–Whitney U test [(data are presented as median and interquartile range (IQR)]. Abbreviations: MPVLR: mean platelet volume/lymphocyte ratio; PLR: platelet/lymphocyte ratio; CLR: CRP/lymphocyte ratio; CAR: CRP/albumin ratio; LAR: LDH/albumin ratio; PAR: platelet/albumin ratio.

4. Discussion

There is increasing evidence that sex disparity is important in epidemiology, pathophysiology, treatment, and outcomes in many diseases. Males and females exhibit a different response to viral infections in which females mount a stronger immune response because estrogen and progesterone can help increase the innate and adaptive immune responses, and many immune genes are

Table 4
Univariate logistic regression analysis for predicting the likelihood of mortality among severe COVID-19 patients with diabetes.

	Crude OR	CI	P
Age	1.099	1.047–1.153	<0.005
Sex	2.199	1.032–4.687	0.04
PO_2	0.965	0.944–0.986	0.001
Albumin	0.413	0.177–0.962	0.04
Bilirubin	11.348	1.766–72.431	0.01
ALT	1.025	1.005–1.045	0.01

P-value by univariate logistic regression analysis. Abbreviations: Crude OR, crude odds ratio; 95% CI, 95% confidence interval.

encoded on X-chromosome [11]. Despite this, sex is profoundly ignored in research related to infectious diseases, especially COVID-19 infection.

In this study, sex differences were reported in some laboratory parameters, as well as the clinical outcome of COVID-19 pneumonia among patients with diabetes. Besides, independent predictors of mortality among the study population were advanced age, male sex, increased serum total bilirubin, and decreased PO_2.

In total, 45 (38.2%) of the 118 severe COVID-19 patients with diabetes died, which confirms the results of other studies that diabetes is one of the conditions that increase mortality among COVID-19 patients [6,12]. Furthermore, males are more likely to die than females (48.1% vs. 29.7%, P = 0.04). This result was in line with another study by Meng et al. [13] on a cohort of 168 severe COVID-19 patients, as they found deaths occurred in 12.8% of men compared to 7.3% of women, but the higher percentage in our study is due to the presence of another factor, which is diabetes.

When comparing the routine haematologic parameters performed upon hospital admission between males and females, males had a trend to have higher RBC parameters (P > 0.05), the same trend was reported in previous studies [13,14]. It might be due to the effect of testosterone which activates erythropoiesis by stimulating erythropoietin production [15].

Our data showed that lymphocytes of males were significantly lower than those of females (P < 0.005), in agreement with the results of Meng et al. [13], this finding is attributed to that of the healthy females in general exhibit higher cytotoxic T-cell activity along with an upregulation of CD8+ genes [16], many of which have estrogen response elements in their promoters. Estrogen hormone could also promote activation, maturation, differentiation of B cells [17].

This study showed that females had significantly higher MPV levels than males (median of 8.9 vs. 9.2 fL, P = 0.01). This finding was inconsistent with other studies that demonstrated that females tend to have higher MPV than males [18,19]. MPV is a predictive parameter reflecting the platelet activity, and was shown to be associated with the severity of inflammation. Previous researches have revealed that the increase in MPV is relevant to the adverse prognosis of COVID-19 patient with severe pneumonia [20,21], however, the MPV level in females of this study is still within normal range, and has not risen to affect the prognosis of the disease.

Concerning the biochemical parameters, the present study demonstrated that males had higher ALT values than females, suggesting that diabetic males are more likely to have more severe liver damage due to COVID-19 than females. Moreover, a high ALT was associated with a decline in hepatic insulin sensitivity [22]. Liver injury noted among COVID-19 patients could be explained by multiple hypotheses, such as direct viral cytotoxicity through angiotensin-converting enzyme-2, hepatotoxic medications, immune-mediated injury, and passive congestion [23].

This study demonstrated a higher CRP level for all 118 patients with diabetes (median of 53.5 mg/L). Elevated CRP level was associated with an increased risk of cardiovascular sequel and mortality in patients with type-2 diabetes [24]. Moreover, Liu et al. had demonstrated that COVID-19 patients with CRP > 41.8 mg/L were more likely to develop severe disease and worse outcomes [25]. Further, our data illustrated that males had a higher CRP level than females (median of 65 vs. 45.3 mg/L, P = 0.03). This finding was in agreement with the finding of another study [13], suggesting an enhanced inflammatory process and poor prognosis in males

Inflammation-related ratios were of great clinical significance and became a research hotspot as they may serve as simple, convenient, and cost-effective biomarkers to monitor the disease course. To date, a number of inflammation-related ratios such as the PLR [26] and CAR [27] have been proposed as prognostic markers in COVID-19 pneumonia. To our knowledge, no study has investigated the sex differences in inflammation-related ratios in severe COVID-19 pneumonia. In that context, our current study investigated sex discrepancies in inflammatory ratios in severe COVID-19 patients with diabetes.

The MPVLR was considered a simple biomarker of inflammation and was initially proposed by Hudzik et al. [28] in 2016. Our results illustrated that males tend to have more MPVLR than females (P = 0.001), indicating a higher risk of inflammation and thrombosis in males. MPVLR, which was calculated using MPV instead of the platelet count, was claimed to be more representative of platelet activity than PLR [29]. Many studies have suggested that MPVLR may be a predictor of worse outcomes linking inflammation and thrombosis in diabetic patients with myocardial infarction [30] and diabetic nephropathy [31].

CRP is a positive acute-phase reactant significantly increasing during infection and inflammation, and it is upregulated by pro-inflammatory cytokines, especially IL-6 [32]. Albumin, on the other hand, is a negative acute-phase reactant decreasing during infection and/or inflammation. The CAR, first introduced by Fairclough et al., is believed to The CAR, first introduced by Fairclough et al. [33], is believed to be an inflammation-based prognostic score. Previous studies had suggested that a combination of albumin and CRP into a single ratio might have clinical implications in many inflammatory diseases than CRP or albumin alone [34,35]. Moreover, CAR had the potential to detect high-risk patients for a high

Table 5
Predictors of the likelihood of mortality among severe COVID-19 patients with diabetes.

Parameter	B	S.E.	Wald	P	OR	95% CI	
						Lower	Upper
Age (years)	0.106	0.039	7.497	0.006	1.112	1.031	1.199
Sex							
Female							
Male	1.566	0.769	4.150	0.042	4.788	1.061	21.605
PO_2	−0.052	0.019	7.631	0.006	0.949	0.914	0.985
Albumin	0.239	0.714	0.112	0.738	1.270	0.314	5.142
Bilirubin	1.850	0.941	3.867	0.049	6.359	1.006	40.188
ALT	0.04	0.024	2.743	0.098	1.041	0.993	1.091

P-value by binomial (multivariate) logistic regression analysis. Abbreviations: SE, standard error; OR, odds ratio.

intracoronary thrombus burden [36]. It is now well appreciated that the innate immune response and elevated acute phase reactants, such as CRP may contribute to COVID-associated hypercoagulability [37].

Compared to females, males had higher CAR (P = 0.044), reflecting that males tend to experience higher inflammatory burden, which increases the possibility of sex effect in the association between inflammation and COVID-19, especially among diabetics, as studies had reported the fundamental role of sex-differences in complication, as well as manifestation, and management of diabetes [10,38].

The coexistence of diabetes with severe COVID-19 pneumonia has been reported to increase disease severity and mortality risk [39,40]. Therefore, early risk prediction of death among this vulnerable population has become a serious health challenge.

In our cohort, older age was an important independent predictor of mortality. Many studies had confirmed that increased age was associated with death in patients with COVID-19 as a whole [41] or among diabetics [6,42].

Moreover, our data illustrated that diabetic males with severe COVID-19 were associated with an increased risk of death with 4.788 times higher odds for mortality. This finding was in parallel to those of Agarwal et al. [43]; they included 1126 hospitalized patients with diabetes and COVID-19 and founded that in all age categories, mortality was higher with increasing body mass index in males compared with females. However, this result was in disagreement with another study by Acharya et al. [6], on a Korean cohort of 55 COVID-19 patients with diabetes as they found male sex could not predict mortality. This discrepancy may be due to two factors. First: ethnic differences. Second, the study was performed on a relatively small number of 55 COVID-19 patients with diabetes.

Additionally, we also found that increased serum total bilirubin level was a high-risk factor for mortality in severe COVID-19 patients with diabetes with 6.359 times higher odds for mortality. This finding was in accordance with other studies [44,45]. Further, low PO_2 was an effective predictor of mortality in our study. This result was in harmony with a study done by Xie et al. [46], which revealed that hypoxaemia was an independent predictor of mortality in COVID-19 patients.

In view of that study, the presence of advanced age, male sex, increased serum total bilirubin, and decreased PO_2 could be used to alert clinicians to better monitor for signs of worsening and to provide more care in an attempt to reduce the growing mortality rate.

5. Conclusion

This study highlights the importance of sex variables in the measured laboratory test results, thus revealing the veil of the central role of the sex differences in the pathophysiology of the disease, which helps clinicians tailor treatments more effectively and improve patient care. This study also found that older age, male sex, higher serum total bilirubin level, and lower PO_2 were independently predictive of mortality, which helps guide risk stratification for patients with diabetes and COVID-19.

Conflict of interest

None.

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Authors' contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission

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