A More Important Role of Diabetes Mellitus in Mortality in Elderly Critical COVID-19 Patients: a Single-center Retrospective Study

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Abstract

Background

COVID-19 has been circulating worldwide since December 2019. However, its independent risk factors of mortality need further insights in elderly critical COVID-19 patients.

Methods

Totally 48 elderly and critically ill COVID-19 patients with clear end point were enrolled when the data were collected, with 16 discharged and 32 died. Kaplan-Meier analysis and Cox regression were performed to identify the risk factors of mortality in elderly critical COVID-19 patients. Survival curve was conducted to present the impact of Diabetes Mellitus on mortality. Mann-Whitney U and t tests were used to 39 clinical variates between the survivor and non-survivor groups.

Results

As Kaplan-Meier analysis confirmed, only three variates Diabetes Mellitus, chronic obstructive pulmonary disease and family aggregation showed significant difference between the survivor and non-survivor groups. However, only variate Diabetes Mellitus presented significance in Cox regression. Higher C-reaction protein, interleukin-2 (IL-2), IL-8 and creatinine were detected in survivor group than non-survivor group, which was reverse to estimated glomerular filtration rate. The other laboratory finding showed no significant difference between survivor and non-survivor groups.

Conclusions

Diabetes Mellitus, chronic obstructive pulmonary disease and family aggregation can contribute to mortality by COVID-19 while Diabetes Mellitus also reduces the survival time of elderly and critically ill COVID-19 patients, highlighting the more important role of Diabetes Mellitus. Laboratory findings could not serve as good predictors of death for elderly and critically ill COVID-19 patients.

Introduction

SARS-CoV-2, the agent of COVID-19 (1, 2), was first isolated on Jan 7, 2020 (3). COVID-19, first outbreak in Wuhan city in December, 2019 (4), has since been circulating worldwide, with more than 270 million confirmed cases and more than 5,310,000 deaths worldwide as of December 12, 2021, presenting a mortality rate nearing 2.0%. However, at the beginning of COVID-19, the case fatality rate (CFR) was far higher than 2.0%. In Wuhan, China, 50,333 people were infected and 3,869 died (4), showing a rate of 7.7%. In Italy, 7.5% was observed for CFR (5).

Early case studies have comprehensively described the population characteristics, clinical manifestations, laboratory tests and imaging features of COVID-19 patients. The clinical manifestations of COVID-19 varied: about 20% of patients had no symptoms, and 10% to 20% developed respiratory
failure (6). Early detection and early treatment of critically ill patients may contribute to a reduction in mortality. In a retrospective study, authors analyzed the clinical characteristics of the death group and the survival group in the early endemic stage in Wuhan, and found that old age, higher Sequential Organ Failure Assessment score (SOFA) and high D-dimer level were the risk factors for death upon admission (7). Knowledge of patients with need for admission to the intensive care units (ICU) and hospital mortality is not so clear. The ICU admission rate varied in different regions (5). Past reports showed male sex, hypertension, cardiovascular disorders, and type 2 diabetes are common comorbidities, which were associated with the eventual mortality rate (8-15). Patients with COVID-19 and admission to ICU showed a mortality rate ranging from 16% to 78% (7, 11-14, 16-18). Significant negative correlation was found between the CFR and ICU admission rate (5), verifying the important role of ICU against COVID-19.

This study report ICU outcomes of 48 patients critically ill with COVID-19 and admitted to Optical Valley Hospital in Wuhan in 2020. The baseline traits of the patients, characteristics of laboratory findings and their associations with death are discussed.

Methods

Experimental design and patient enrollment

The COVID-19 patients admitted to the intensive care unit of Optical Valley Hospital of Wuhan Union Medical College Hospital from 10th February to 15th March 2020 were screened retrospectively. All the patients were critically ill. All patients were diagnosed COVID-19 by positive nucleic acid testing for SARS-CoV-2. During case collection, a total of 86 patients were admitted to the ward, 43 of which died, with a CFR of 50.0%. 48 patients with clear end point were enrolled when the data were collected. Among the enrolled patients, 16 were discharged and 32 died. Data were collected as of April 20, 2020. Patients met the discharge criteria if they had no fever for at least three days, significantly improved respiratory function, and had negative SARS-CoV-2 laboratory test results twice in succession. This study was approved by the Ethics Committee of Zhuhai People's Hospital.

Clinical data collection

Epidemiological, demographic, clinical, laboratory, and outcome data were extracted from electronic medical records using a standardized data collection form. All data were checked by two physicians (YL and HZ) and a third researcher (DH) adjudicated any difference in interpretation between the two primary reviewers.

RNA extraction and real-time RT-PCR assay

Nasopharyngeal swabs were collected from all the 48 patients and then extracted for total RNAs using the respiratory sample RNA isolation kit. Two target genes, including open reading frame1ab (ORF1ab) and nucleocapsid protein (N), were amplified for SARS-CoV-2 analysis. Target 1 (ORF1ab): forward primer CCCTGTGGGTTTTACACTTAA; reverse primer ACGATTGTGCATCAGCTGA. Target 2 (N): forward primer
GGGAACCTTCTCC TGCTAGAAT; reverse primer CAGACATTTTGCTCTCAAGCTG. The following conditions were set for Real-time RT-PCR assay: incubation at 50°C for 15 minutes and 95°C for two minutes, followed by 40 cycles of denaturation at 95°C for three seconds, then annealing, extending and collecting fluorescence signal at 55°C for 30 seconds. The diagnostic criteria were in line with the recommendation by the National Institute for Viral Disease Control and Prevention (China).

**Blood routine, cytokines, cardiac function, liver function, kidney function tests**

Interleukin-6 (IL-6), IL-10, and TNF-α were analyzed by ELISA methods. Myoglobin, Creatine Kinase Isoenzyme-MB (CKMB), hypersensitive Troponin I (hsTNI) and pro-brain natriuretic peptide (pro-BNP) were analyzed by chemiluminescence methods, C-reaction protein, pre-albumin and D-dimer by immunoturbidimetric assays. Leukocytes, lymphocytes, hemoglobin and platelets were determined by cytometry. Prothrombin time and activated partial thromboplastin time were determined by magnetic bead method. Creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase were analyzed by chemical methods. All such analyses were done on the day all the 48 patients entered ICU from general wards.

**Statistical analysis**

The data were analyzed by SPSS25.0 statistical software (SPSS, Chicago, IL, USA) and GraphPad Prism 8 (GraphPad Software Inc., USA). The normality analysis was performed using Kolmogorov-Smirnov test, homogeneity of variance analysis between two groups by Levene's test and survival analysis by Kaplan-Meier analysis (Log Rank). \( P > 0.10 \) in the normality and \( P < 0.05 \) in mean comparison and survival analysis were considered statistically significant. Variates with \( P < 0.10 \) in Kaplan-Meier analysis were further analyzed using Cox regression (Wald).

**Results**

**Kaplan-Meier analysis of variates**

As shown in Table 1, Log Rank method was used for Kaplan-Meier survival analysis of 42 variates. Variates Diabetes Mellitus, chronic obstructive pulmonary disease and family aggregation showed \( P \) values < 0.05, indicating important roles in mortality, while the others showed no significance.

**Survival curve of variate Diabetes Mellitus**

As shown in Figure 1, survival curve of variate DM declined drastically, suggesting its vital role inducing death.

**Cox regression of three variates**

As shown in Table 2, the three variates with \( P \) values < 0.05 in Table 1 were taken to analyze Cox regression. However, only variate Diabetes Mellitus yielded a \( P \) value < 0.05, suggesting its pivotal role in
reducing survival time of COVID-19 patients admitted to ICU.

**Comparisons of laboratory findings between the survivor group and non-survivor group**

All the aforementioned 26 laboratory variates (Table 1) were also compared using $t$ test or Mann-Whitney U test between the survivor and non-survivor groups. Table 3 showed all the variates with $P < 0.05$. Higher C-reaction protein, IL-2, IL-8 and Creatinine were detected in the survivor group than the non-survivor group, which was reverse for eGFR.

**Discussion**

Forty-eight COVID-19 patients with complete medical records were included in the retrospective study, and all patients were in critical illness. According to the prognosis, the patients were classified into the non-survivor group and the survivor group, and the clinical characteristics of the two groups were statistically analyzed. There were 32 cases in the non-survivor group and 16 cases in the survivor group, all of which in the survivor group had been discharged at the end of the study data collection.

COVID-19 showed multiple risk factors confirmed in past documents (19-21). However, such factors may play different roles in certain stratifications of COVID-19 patients. Kaplan-Meier analysis was performed to identify differences between the survivor and non-survivor groups. As shown in Table 1, Log Rank method was used for Kaplan-Meier survival analysis of 42 variates. Variates Diabetes Mellitus, chronic obstructive pulmonary disease and family aggregation showed $P$ values < 0.05, indicating their pivotal roles in mortality, while the others showed no significance. Furthermore, Table 2 confirmed significance of only Diabetes Mellitus, suggesting a more important role than those of the other two. Among the basic diseases of the two groups, the proportion of diabetes in the non-survivor group was significantly higher than that in the survivor group ($P = 0.039$). Intriguingly, the survivor group showed a higher rate of coronary heart disease than the non-survivor group. Apart from the two diseases, there was no statistical difference in other underlying diseases. Survival curve of variate DM, as shown in Fig. 1, suggested the mortality risk of diabetic patients was significantly higher than that of non-diabetic patients.

A retrospective study by Cao of early COVID-19 inpatients in Wuhan, China, found that elderly age, high D-dimer (greater than one ug/mL), and high SOFA score were high risk factors for patient mortality (7). The average age of the patients in the study was 67.5 years, including 71.5 years in the non-survivor group and 65.4 years in the survivor group. The patients included in our study were those in the late stage of the epidemic in Wuhan. The vast majority of patients included were old, which may be the reason for no statistical difference between the two groups. The CFR in this study was higher than that in the reference (22) (32/48 vs 836/1715, $\chi^2 = 5.999$, $P = 0.014$), which may be attributable to elderly age. The ranging CFR in different investigations may be explained by different patient traits, different organization, availability of ICU beds, and different lengths of follow-up (13, 16, 17, 22). In Cao's study (7), the proportion of diabetes in the non-survivor group was 31%, and the survivor group was 14%. In univariable
analysis, odds of in-hospital death were higher in patients with diabetes. The results were same as our study, suggesting that COVID-19 patients with diabetes should be fully paid attention to.

In our study, there was no significant difference in GCS, RASS and CAM-ICU scores between the two groups at the time of admission, and no statistical difference in blood test indicators such as leukocyte, hemoglobin, platelet, C-reaction protein and IL-6. Another retrospective study found that high troponin, high myoglobin, high C-reaction protein, and high IL-6 levels were likely predictors of death in COVID-19 patients (23). But the study did not detail the severity of the patients in survivor group. In our study, all patients enrolled were critically ill and ICU patients. C-reaction protein, IL-6, troponin, myoglobin, etc., were mostly at high levels in the survivor group and the non-survivor group, but only C-reaction protein, IL-2, IL-8, Creatinine and eGFR presented significant differences between the two groups. These results suggested these hematological indicators may not be sensitive enough to predict the risk of death in critically ill COVID-19 patients.

In conclusion, this study conducted a retrospective analysis of the clinical treatment of elderly and critically ill COVID-19 patients admitted to the single-center ICU, and found that diabetes was a more crucial factor for death, suggesting that full attention should be paid to the patients with diabetes in elderly critical COVID-19 patients. Although lower C-reaction protein, IL-2, IL-8, creatinine and higher eGFR were found in the non-survivor group than the survivor group, regular laboratory items could not serve as good predictors of death for elderly and critically ill COVID-19 patients admitted to ICU.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Zhuhai People's Hospital.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets analysed during the current study are available online permanently (https://pan.baidu.com/s/1EZj4-vo3j8PSIhBzJiTvhQ; Key1234).

**Competing interests**

The authors declare that they have no competing interests.

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Authors' Contributions

YL and DH conceived the study. YL and XL collected the data. YL, XL, YZ, YY and YY analysed the data. YL, XL and YZ prepared the manuscript, which was revised by HZ and DH. All authors read and approved the final manuscript.

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Tables

**Table 1** Demographic, clinical, laboratory findings of patients on admission to ICU
| Variates                        | Survivor\(n = 16\) | Non-survivor\(n = 32\) | Kaplan-Meier (Log Rank) |
|--------------------------------|---------------------|-------------------------|-------------------------|
|                                | Mean ± SD; P50      | Mean ± SD; P50          | Chi-square              |
|                                | (P25, P75)          | (P25, P75)              |                         |
| Sex (M/F)                      | 11/5                | 18/14                   | 0.205                   |
| Age (year)                     | 74.0 (63.8, 80.8)   | 70.0 (58.5, 76.8)       | 0.004                   |
| GCS\(^a\)                     | 15.0 (8.3, 15.0)    | 15.0 (15.0, 15.0)       | 0.876                   |
| RASS\(^b\)                    | 1.0 (-1.8, 1.0)     | 0.0 (0.0, 0.5)          | 1.823                   |
| CAM-ICU\(^c\)                 | 0 : 14              | 0 : 26                  |                         |
| Smoking                        | 3                   | 5                       | 0.003                   |
| Temperature (°C)               | 37.3 (36.5, 38.1)   | 36.5 (36.2, 38.5)       | 0.506                   |
| Respiratory rate (beats/min)   | 26 (20, 32)         | 22 (20, 28)             | 1.632                   |
| Heart rate (times/min)         | 99 (83, 115)        | 91 (82, 99)             | 3.093                   |
| Systolic blood pressure (mmHg) | 137 (111, 149)      | 132 (119, 140)          | 0.021                   |
| Hypertension                   | 10                  | 20                      | 1.184                   |
| Diabetes Mellitus              | 0                   | 8                       | 8.476                   |
| COPD\(^d\) (Y/N)              | 0                   | 6                       | 4.364                   |
| Coronary heart diseases        | 7                   | 4                       | 0.012                   |
| Liver diseases                 | 0                   | 0                       | 0.396                   |
| Chronic kidney diseases        | 2                   | 1                       | 0.073                   |
| Malignancy                     | 0                   | 1                       | 0.124                   |
| Family aggregation             | 2                   | 2                       | 4.860                   |
| Hemoglobin (g/l)               | 131.9 ± 17.3        | 129.0 ± 20.4            | 0.265                   |
| Leukocyte (10^9/l)             | 10.91 (6.46, 16.25) | 8.12 (6.37, 9.47)       | 1.157                   |
| Lymphocyte (10^9/l)            | 0.56 (0.43, 0.84)   | 0.86 (0.48, 1.21)       | 1.602                   |
| Platelet (10^9/l)              | 137 (101, 214)      | 146 (112, 254)          | 0.047                   |
| C-reaction protein (mg/l)      | 152.4 ± 78.3        | 93.9 ± 59.0             | 0.530                   |
| IL-1β (pg/ml)                  | 4.9(4.9, 4.9)       | 4.9(4.9, 5.7)           | 0.001                   |
| IL-2 (pg/ml)                   | 1447(1258, 1681)    | 964(772, 1263)          | 0.010                   |
| Parameter                              | Mean 1 (95% CI)       | Mean 2 (95% CI)       | p-value 1        | p-value 2        |
|----------------------------------------|-----------------------|-----------------------|-----------------|-----------------|
| IL-6 (pg/ml)                           | 30.79 (24.26, 180.60) | 25.43 (11.26, 83.90)  | 0.025           | 0.874           |
| IL-8 (pg/ml)                           | 52.30 (26.10, 93.20)  | 17.80 (11.80, 38.00)  | 0.391           | 0.532           |
| IL-10 (pg/ml)                          | 6.2 (4.9, 12.5)       | 5.4 (4.9, 8.9)        | 0.597           | 0.440           |
| Tumor necrosis factor-α (pg/ml)        | 13.3 (11.5, 20.7)     | 10.4 (7.9, 17.0)      | 0.997           | 0.318           |
| Prothrombin time (s)                   | 16.0 (15.3, 18.8)     | 14.8 (13.3, 16.2)     | 0.631           | 0.427           |
| International normalized ratio         | 1.29 (1.22, 1.58)     | 1.19 (1.04, 1.32)     | 1.043           | 0.307           |
| Activated partial thromboplastin time (s)| 39.2 (35.4, 42.6)     | 37.8 (36.0, 43.3)     | 0.219           | 0.640           |
| D-dimer (mg/l)                         | 21.10 (3.21, 21.10)   | 6.83 (1.65, 21.10)    | 1.632           | 0.201           |
| hsTNI (pg/ml)                          | 35.3 (6.7, 299.8)     | 23.1 (8.9, 121.0)     | 0.335           | 0.563           |
| Myoglobin (pg/ml)                      | 243.8 (96.6, 762.6)   | 126.3 (67.6, 290.2)   | 2.042           | 0.153           |
| CKMB (pg/ml)                           | 2.4 (1.6, 6.2)        | 2.4 (1.1, 3.5)        | 2.415           | 0.120           |
| pro-BNP (pg/ml)                        | 1108 (386, 3608)      | 780 (408, 2653)       | 1.744           | 0.187           |
| Creatinine (mmol/l)                    | 101 (80, 146)         | 73 (56, 103)          | 1.152           | 0.283           |
| eGFR\textsuperscript{e} (ml/min)       | 60.9 ± 23.9           | 84.0 ± 33.8           | 0.008           | 0.930           |
| Total bilirubin (μmol/l)               | 13.8 (10.9, 26.7)     | 12.3 (9.1, 19.2)      | 0.394           | 0.530           |
| Alanine aminotransferase (IU/l)        | 24 (18, 39)           | 32 (17, 50)           | 1.903           | 0.168           |
| Aspartate aminotransferase (IU/l)      | 45 (31, 60)           | 33 (21, 68)           | 1.028           | 0.311           |
| Lactate dehydrogenase (IU/l)           | 574 (408, 1038)       | 491 (345, 748)        | 0.004           | 0.951           |
| Oxygenation index (mmHg)               | 67.9 (61.7, 74.1)     | 106.2 (61.7, 149.0)   | 2.072           | 0.150           |

*a*: Glasgow Coma Scale; *b*: Richmond Agitation and Sedation Scale; *c*: Confusion Assessment Method for the ICU; *d*: Chronic obstructive pulmonary disease; *e*: Estimated glomerular filtration rate.

**Table 2** Cox Regression analysis of three variates
| variates         | B*     | SE†   | Wald | RR‡ (95% CI)         | P     |
|------------------|--------|-------|------|----------------------|-------|
| Diabete Mellitus | -0.931 | 0.446 | 4.352| 0.394 (0.164, 0.945) | 0.037 |
| Family aggregation | 0.996 | 1.083 | 0.845| 2.707(0.324, 22.619) | 0.358 |
| COPD             | 0.813  | 0.655 | 1.541| 2.254(0.625, 8.136)  | 0.214 |

*: partial regression coefficient; †: standard error; ‡: relative risk.

**Table 3** Comparisons of 26 laboratory items between the survivor group and non-survivor group on admission to ICU

| Variates               | Survivorn = 16 | Non-survivorn = 32 | t     | P     | Mann-Whitney U | P (exact) |
|------------------------|----------------|--------------------|-------|-------|----------------|-----------|
|                        | Mean ± SD; P50 (P25, P75) | Mean ± SD; P50 (P25, P75) |       |       |                |           |
| C-reactive protein (mg/l) | 152.4 ± 78.3     | 93.9 ± 59.0         | 2.700 | 0.010 |                |           |
| IL-2 (pg/ml)           | 1447 (1258, 1681) | 964 (772, 1263)     | 94    | 0.028 |                |           |
| IL-8 (pg/ml)           | 52.30 (26.10, 93.20) | 17.80 (11.80, 38.00) | 75    | 0.005 |                |           |
| Creatinine (mmol/l)    | 101 (80, 146), 14 | 73 (56, 103), 31    | 133   | 0.039 |                |           |
| eGFR                   | 60.9 ± 23.9, 14  | 84.0 ± 33.8, 31    | 2.212 | 0.032 |                |           |

**Figures**
Figure 1

Survival curves of patients with and without Diabetes Mellitus

DM: Diabetes Mellitus.