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Predictors of mortality of hospitalized COVID-19 pneumonia patients in university hospital

Safa M. Wafy[1], Marina O. Saman[1] and Mostafa K. Ahmed[1*]

Abstract

Introduction COVID-19 pneumonia is a leading cause for worse outcome of infected patients. Factors associated with mortality in COVID-19 pneumonia vary among studies; identification of most possible factors related to worse outcome might add for management.

Patients and methods Consecutive COVID-19 pneumonia patients referred to the Assiut University Hospital, Egypt, from June 2020 to August 2022 were included in our study. All the included patients were followed up from admission until discharge to identify the factors that worsen the outcome. Our cohort study includes two groups: survivors and non-survivors. Clinical, laboratory, and management data of both groups were recorded.

Results Two-hundred and fifty-one confirmed COVID-19 pneumonia patients were included in the study; 147 (58.6%) patients were improved (survivors' group), and 104 (41.4%) patients were deteriorated and died (non-survivors' group). Non-survivors' group had significantly higher MMRC dyspnea scale, pneumonia severity index, CURB-65 score, and baseline respiratory rate. Non-survivors group had significantly lower mean lymphocytes (0.81 ± 0.61 vs. 1.25 ± 0.75; $p < 0.001$), higher ferritin (1272.45 ± 143.76 vs. 615.84 ± 75.47; $p < 0.001$), and higher d-dimer (6.65 ± 2.67 vs. 2.78 ± 0.38; $p < 0.001$), with interestingly significantly higher mean platelet volume (MPV) (10.34 ± 1.64 vs. 10.07 ± 1.93 (fl); $p < 0.001$). Non-survivors group was frequently admitted to ICU (88 (84.6%) vs. 38 (25.9%); $p < 0.001$) and had longer duration in ICU than survivors group (9.71 ± 3.36 vs. 5.90 ± 2.34 (days); $p < 0.001$). The predictors for mortality among patients with COVID-19 pneumonia were old age, high MPV, high CT score, and admission to ICU.

Conclusion Old age, severe lung infiltrate with HRCT, high mean platelet volume, and ICU admission are the main clinical determinants of worse outcome of COVID-19 pneumonia.

Keywords Mortality, Pneumonia, Predictors, Coronavirus disease 2019

Introduction

Coronavirus disease 2019 (COVID-19) was initiated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, spreading rapidly worldwide. Most patients may have mild or no illness, but some cases may develop severe pneumonia requiring intensive respiratory support [1].

Early in the starting of the pandemic, mortality from COVID-19 pneumonia was alarming sign to be considered with patient's management [2]; mortality was still high with going time especially patients had severe pneumonia [3]. Although the COVID-19 pandemic is run out, still some COVID-19 pneumonia cases and mortality are recorded [4]. These mortality burden necessitates aggressive investigation of its factors [5]. The findings from previous studies suggested many factors were correlated with COVID-19 pneumonia disease burden or death [2,

*Correspondence:
Mostafa K. Ahmed
Mostafak198173@aun.edu.eg; mostafak198173@yahoo.com
[1] Chest Diseases Department, Assiut University, Asyut, Egypt

3, 5]. These factors of worse COVID-19 pneumonia vary among studies; in the present study, these factors are displayed and confirmed.

Patients and methods

A prospective study was conducted in the Assiut University Hospital during the period of June 2020 to August 2022.

Selection criteria

Consecutive patients were diagnosed to have COVID-19 pneumonia and were eligible for the study after their consent.

Methods

All the enrolled patients in the study were subjected to history taking, and clinical evaluation included age, sex, comorbidities, and clinical presentations. In addition of laboratory data included, arterial blood gases, complete blood count, liver function, coagulation profile, serum electrolytes, and erythrocyte sedimentation rate were recorded. High-resolution chest computed tomography (HRCT) is recorded using COVID-19 Reporting and Data System (CO-RADS) [6].

Severity assessment

Admission CURB-65 score: It is five items score; each item scored 1 point, including confusion, urea more than 7 mmol/L, respiratory rate is 30 cycle per minute or above, systolic blood pressure is lower than 90 mmHg and/or diastolic blood pressure is 60 mmHg or less, and age is 65 years or more [7]. Admission pneumonia severity index (PSI scale) is recorded; PSI is 19 variables scale that is calculated based on age, the presence of comorbidity, abnormal clinical variables as respiratory rate of 30 cycle per minute or more, a temperature of 40 °C or more and abnormal laboratory findings as pH less than 7.35, a blood urea nitrogen 30 mg/dl or more, and a serum sodium level less than 130 mmol per liter [8, 9].

Statistical analysis

It was performed using SPSS version 20 (USA). Patient's variable analyses were done using standard descriptive methods: frequency (percentage) for qualitative variables and mean (SD) quantitative variables. Nominal data were compared by chi-square test, while continuous data were compared by Student *t*-test. With using logistic regression analysis, mortality predictors of patients with COVID-19 pneumonia were determined. All measured *p*-values were two sided with values less than 0.05 which were considered statistically significant.

Table 1 Baseline data of enrolled patients based on the outcome

	Survivors group (*n* = 147)	Non-survivor group (*n* = 104)	*p*-value
Age (years)	55.48 ± 17.32	65.22 ± 12.47	**< 0.001**
Sex			0.27
Male	79 (53.7%)	53 (51%)	
Female	68 (46.3%)	51 (49%)	
Residence			0.16
Rural	84 (57.1%)	52 (50%)	
Urban	63 (42.9%)	52 (50%)	
History of contact	84 (57.1%)	52 (50%)	0.16
Diabetes mellitus	58 (39.5%)	43 (41.3%)	0.43
Hypertension	63 (42.9%)	48 (46.2%)	0.34
Ischemic heart disease	15 (10.2%)	16 (15.4%)	0.15
Cerebrovascular stroke	5 (3.4%)	7 (6.7%)	0.17
Chronic kidney disease	7 (4.7%)	7 (6.7%)	0.50
Pregnant women	1 (0.7%)	0	0.58

Data expressed as mean (SD), frequency (percentage). *p*-value was significant if < 0.05

Results

Two-hundred and fifty-one patients were included in the study with confirmed COVID-19 pneumonia. Out of those patients, 147 (58.6%) patients were improved and discharged (survivor group), and 104 (41.4%) patients were deteriorated and died (non-survivor group).

Table 2 Symptomatology and clinical evaluation in patients based on the outcome

	Survivors group (*n* = 147)	Non-survivor group (*n* = 104)	*p*-value
Duration of symptoms	8.06 ± 5.37	7.34 ± 3.96	0.24
Anosmia	40 (27.2%)	23 (22.1%)	0.22
Diarrhea	24 (16.3%)	10 (9.6%)	0.08
Fever	125 (85%)	92 (88.5%)	0.27
Dyspnea	121 (82.3%)	99 (95.2%)	**< 0.001**
Cough	128 (87.1%)	90 (86.5%)	0.52
Dyspnea scale	3.45 ± 0.77	3.94 ± 0.29	**< 0.001**
CURB-65	1.37 ± 1.02	2.45 ± 1.07	**< 0.001**
PSI	82.96 ± 32.68	111.27 ± 26.70	**< 0.001**
Temperature (°C)	37.53 ± 0.79	37.67 ± 0.64	0.15
Heart rate (b/m)	93.65 ± 15.35	100.53 ± 20.57	**< 0.001**
SBP (mmHg)	123.87 ± 21.21	115.48 ± 25.46	**< 0.001**
DBP (mmHg)	77.89 ± 12.34	71.44 ± 16.97	**< 0.001**
RR (cycle/m)	28.93 ± 6.58	34.17 ± 7.75	**< 0.001**
Pulse oximetry saturation	82.83 ± 13.50	73.63 ± 15.71	**< 0.001**

Data expressed as mean (SD), frequency (percentage). *p*-value was significant if < 0.05

PSI pneumonia severity index, *RR* respiratory rate, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Baseline characteristics of included patients based on the outcome (Table 1)

Non-survivor group had significantly higher mean age in comparison to survivor group (65.22 ± 12.47 vs. 55.48 ± 17.32 (years); $p < 0.001$). All other baseline variables did not show significant differences between both groups ($p > 0.05$).

Symptomatology and clinical evaluation based on the outcome (Table 2)

Frequency of dyspnea was significantly higher among non-survivor group (121 (82.3%) vs. 99 (95.2%); $p < 0.001$). Also, non-survivor group had significantly higher dyspnea scale, pneumonia severity index, CURB-65, and baseline

Table 3 Laboratory and radiological data in patients based on the outcome

	Survivors group ($n = 147$)	Non-survivor group ($n = 104$)	*p*-value
Laboratory data			
Leucocytes (10^3/μl)	9.48 ± 5.31	12.01 ± 6.45	**< 0.001**
Neutrophils (10^3/μl)	7.56 ± 5.14	10.26 ± 5.82	**< 0.001**
Lymphocyte (10^3/μl)	1.25 ± 0.75	0.81 ± 0.61	**< 0.001**
Monocytes (10^3/μl)	0.52 ± 0.36	0.53 ± 0.43	0.93
Eosinophils (10^3/μl)	0.08 ± 0.05	0.02 ± 0.01	**< 0.001**
Hemoglobin (g/dl)	12.69 ± 2.22	12.15 ± 2.65	0.07
Platelets (10^3/μl)	256.79 ± 113.26	254.14 ± 118.91	0.27
Mean platelets volume (fl)	10.07 ± 1.93	10.34 ± 1.64	**< 0.001**
INR	1.10 ± 0.21	1.27 ± 0.73	**< 0.001**
D-dimer (mg/l)	2.78 ± 0.38	6.65 ± 2.67	**< 0.001**
LDH (μ/L)	345.74 ± 43.45	567.28 ± 88.87	**< 0.001**
CRP (mg/dl)	69.41 ± 73.33	110.35 ± 85.24	**< 0.001**
Ferritin (ng/ml)	615.84 ± 75.47	1272.45 ± 143.7	**< 0.001**
Urea (mmol/l)	9.94 ± 7.48	16.94 ± 9.65	**< 0.001**
Creatinine (mmol/l)	121.94 ± 24.80	178.25 ± 88.87	**< 0.001**
Sodium (mmol/l)	136.68 ± 5.17	138.23 ± 5.65	0.74
Potassium (mmol/l)	4.14 ± 0.74	4.26 ± 0.76	0.20
Calcium (mg/dl)	8.37 ± 0.84	8.26 ± 0.93	0.33
Magnesium (mg/dl)	2.02 ± 0.44	2.11 ± 0.46	0.18
Albumin (mg/dl)	35.10 ± 5.73	32.97 ± 5.33	**< 0.001**
Bilirubin (μmol/l)	9.20 ± 3.45	9.82 ± 2.83	0.56
Direct bilirubin (μmol/l)	3.79 ± 1.22	4.98 ± 1.09	0.08
AST (μ/L)	45.96 ± 9.45	80.23 ± 32.23	**< 0.001**
ALT (μ/L)	44.09 ± 11.34	54.83 ± 8.98	0.20
ALP (μ/L)	101.77 ± 63.44	114.45 ± 83.87	0.81
Troponin (ng/ml)	0.22 ± 0.09	0.97 ± 0.18	0.13
Arterial blood gases			
pH	7.46 ± 0.07	7.43 ± 0.11	**0.03**
PCO_2 (mmHg)	35.03 ± 12.30	33.21 ± 15.99	0.38
PO_2 (mmHg)	47.65 ± 13.81	40.97 ± 12.45	**< 0.001**
Lactate (mmol/l)	1.85 ± 1.23	2.98 ± 2.55	**< 0.001**
HCO_3 (mmol/l)	24.64 ± 6.86	21.72 ± 7.82	**< 0.001**
TCO_2 (mmol/l)	25.83 ± 6.99	22.73 ± 8.27	**< 0.001**
Base deficit (mmol/l)	2.96 ± 0.87	2.17 ± 1.19	0.25
Oxygen saturation (%)	81.42 ± 13.81	72.58 ± 17.41	**< 0.001**
Radiological data			
Computed tomography score	3.96 ± 1.34	5 ± 1.06	**< 0.001**
Pulmonary embolism	4 (2.7%)	1 (1%)	0.58

Data expressed as mean (SD). *p*-value was significant if < 0.05

INR international randomized ratio, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase

respiratory rate, while survivor group had significantly higher systolic and diastolic blood pressure ($p<0.001$).

Laboratory and radiological data based on the outcome(Table 3)

Non-survivor group had significantly lower mean lymphocytes (0.81 ± 0.61 vs. 1.25 ± 0.75 (103/µl); $p<0.001$) with significantly higher MPV (10.34 ± 1.64 vs. 10.07 ± 1.93 (fl); $p<0.001$), ferritin (1272.45 ± 143.76 vs. 615.84 ± 75.47 (ng/ml); $p<0.001$) and d-dimer (6.65 ± 2.67 vs. 2.78 ± 0.38 (mg/l); $p<0.001$). Also, arterial blood gases where all parameters were significantly impaired in non-survivor group.

CT score was significantly higher among dead patients (5 ± 1.06 vs. 3.96 ± 1.34; $p<0.001$). Four patients of survivors group and another patient from non-survivor group had pulmonary embolism.

Therapeutic regimens and length of stay based on the outcome (Table 4)

Hospital stay was significantly longer among non-survivor group in comparison to survivor group (19.71 ± 5.46 vs. 12.07 ± 4.64 (days); $p<0.001$). Non-survivor group was frequently admitted to ICU (88 (84.6%) vs. 38 (25.9%); $p<0.001$) with longer duration in ICU than survivor group (9.71 ± 3.36 vs. 5.90 ± 2.34 (days); $p<0.001$).

Table 4 Therapeutic regimens and length of stay based on the outcome

	Survivors group ($n=147$)	Non-survivor group ($n=104$)	*p*-value
Hospital stay (days)	12.07 ± 4.64	19.71 ± 5.46	**< 0.001**
Admission to ICU	38 (25.9%)	88 (84.6%)	**< 0.001**
NIV	29 (19.7%)	73 (70.2%)	**< 0.001**
MV	2 (1.4%)	57 (54.8%)	**< 0.001**
Vapotherm	17 (11.6%)	27 (26%)	**< 0.001**
Enoxaparin sodium use	127 (86.4%)	96 (92.3%)	0.07
NOAC	3 (2%)	3 (2.9%)	0.48
Warfarin	4 (2.7%)	6 (5.8%)	0.18
Oseltamivir	32 (21.8%)	10 (9.6%)	**0.01**
Remdesivir	28 (19%)	34 (32.7%)	**0.01**
Steroid therapy	124 (84.4%)	98 (94.2%)	**0.01**
Steroid dose (mg)	148.17 ± 98.76	300.82 ± 142.87	**< 0.001**
Steroid duration (days)	9.01 ± 2.34	11.87 ± 3.31	**0.02**
Tocilizumab	17 (11.6%)	18 (17.3%)	0.14
Hydroquine	29 (19.7%)	6 (5.8%)	**< 0.001**
ICU duration (days)	5.90 ± 2.34	9.71 ± 3.36	**< 0.001**

Data expressed as mean (SD), frequency (percentage). *p*-value was significant if < 0.05

ICU intensive care unit, *MV* mechanical ventilation, *NIV* noninvasive ventilation, *NOAC* new oral anticoagulants

Mortality predictors among patients with COVID-19 pneumonia (Table 5)

Based on the present study, mortality predictors among patients with COVID-19 pneumonia were old age, high MPV, high CT score, and admission to ICU.

Discussion

The present study discloses important factors affecting patient's outcome in large COVID-19 pneumonia hospitalized patients. A total of 251 patients were enrolled; 58.6% patients were improved and discharge from hospital, while 41.4% were deteriorated and died. This reflects the burden of hospitalized COVID-19 pneumonia to the patients, necessitating urgent and cautious deal to improve the outcome.

The non-survivors group had significantly higher mean age; with increasing age, there are significant changes in the immune system and the response of the inflammatory cells to infection including viral one especially if it is not previously identified and novel antigen to the immune cells [10]. These changes in the immune system with aging involve hematopoietic stem cells and its lymphoid progenitors cells responsible for defense against viral infection [11]. This also observed with others as Palaiodimos L. et al. who noted that old age was correlated with high mortality [12].

Gender effect on the mortality of COVID-19 pneumonia varies among studies; with interest in improving women outcome in most of them, this was proposed related to genetic, hormonal, and or behavioral factors that modulate the immune system differently in both genders [13, 14], this was not noted in the present study as no significant differences in gender were found, and

Table 5 Predictors of mortality among patients with COVID-19 infection

	Odd's ratio	95% confidence interval	*p*-value
Age	**2.34**	**1.23–5.01**	**0.01**
CURB-65	1.01	0.45–2.22	0.29
PSI	0.87	0.21–1.56	0.49
Lymphopenia	1.11	0.90–2.20	0.07
Ferritin	1.90	0.56–2.98	0.13
D-dimer	1.84	1.01–3.45	0.76
CRP	1.54	0.90–3.01	0.58
MPV	**2.22**	**1.11–4.44**	**< 0.001**
CT score	**3.45**	**2.34–7.89**	**< 0.001**
Steroid use	1.97	1.01–2.29	0.45
ICU admission	**2.20**	**1.98–4.56**	**0.01**

p-value was significant if < 0.05

CRP C-reactive protein, *PSI* pneumonia severity index, *MPV* mean platelets volume, *CT* computed tomography, *ICU* intensive care unit

our finding might be powered by the bias effect that commonly referred in the previous studies to explain the differences [13]. However. Jin et al. stated those male with COVID-19 pneumonia tended to be more serious than female, and men were more prone to dying respectively [15].

Breathlessness is an important clinical symptom that guides the patients to seek medical care; its severity could make physician decision for patient hospitalization and meticulous medical dealing and important prognostic factor for worse pneumonia outcome [16]; frequency of dyspnea was significantly higher among non-survivor group in the present study. This observation runs the study of Padmaprakash et al. which found out that dyspnea was positively correlated with the progression of COVID-19 pneumonia [17].

The present study shows admission PSI and CURB-65 score were significantly high in non-survivor group ($p < 0.001$) and also with using ROC analysis (Fig. 1) showing significant prognostic value (*AUC*: 0.743 and 0.752, respectively, p 0.0001). Chen J. et al. found that PSI and CURB-65 were significant in predicting mortality with PSI had higher sensitivity than CURB-65 [18]. Also, Arturo Artero et al. noted the important significant value of admission PSI and CURB-65 as a prognostic tool in hospitalized COVID-19 pneumonia patients that enforce the present finding [19].

Mean platelet volume increases significantly in non-survivors' group, and this goes with the study of Comer S. et al. [20]; COVID-19 is associated with thrombocytopenia which stimulates pulmonary megakaryocyte to produce more platelets. The new platelets were younger, immature, and larger which explains the increase of volume of platelet [21]. Although these finding was observed with others, however, there are some concern to consider these finding with interest as mean platelet volume may be not highly accurate calculated with the routine lab devices and the way of blood collection may be not ideal for calculation of MPV; however, as there are more than one study observing these finding, it should be considered and investigated in future studies to confirm its value [22, 23].

Many laboratory markers differ significantly between survivors and non-survivor as increase of absolute number of neutrophils and decrease of absolute number of lymphocytes and eosinophil's in non-survivor group; these hematological effect may be explained by the bidirectional effect of the virus and the immune system through stimulation with subsequent releasing or inhibiting inflammatory mediators as procoagulant, coagulant, autoimmune antibodies, and immune complex mediator [24]. These biomarkers have direct and indirect effect on hematopoietic stem cell and the lung immune system [25, 26]. Ferritin, CRP, D-dimer, and LDH were significantly higher in non-survivor group; these related

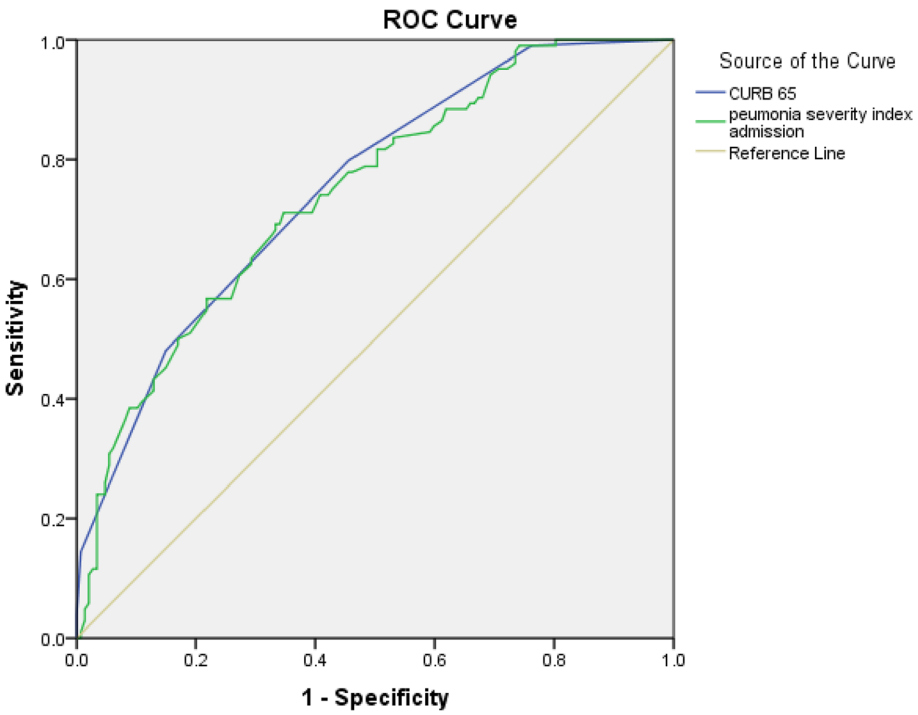

Fig. 1 ROC curve analysis showing the prediction of hospitalized COVID-19 pneumonia mortality using admission CURB-65 score (*AUC*: 0.752) and pneumonia severity index (*AUC*: 0.743)

to the cytokine releases from immune stimulate cells in response to excessive virus load [27], and previous studies were consistent with such data [28–30]. As predicted the need for intensive care and increase severity of the case; with worse outcome; as present analysis found; ICU admission was associated with higher mortality rate as also noted by the study of Yang et al. [31].

Conclusion

Old age, high MPV, high CT score, and admission to ICU can be used as predictors for mortality among patients with COVID-19 pneumonia. Future studies with longer duration of follow are warranted.

Abbreviations

COVID-19	Coronavirus disease 2019
HRCT	High-resolution chest computed tomography
ICU	Intensive care unit
LDH	Lactate dehydrogenase
MMRC	Modified Medical Research Council
MPV	Mean platelets volume
PSI	Pneumonia severity index
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPSS	Statistical Package for the Social Sciences

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Authors' contributions

SMW was shared in the study design, collection of data, analysis of data, result interpretations, manuscript writing and revision, and manuscript approval; MOS was shared in the study design, collection of data, analysis of data, result interpretations, manuscript writing and revision, and manuscript approval; and MKA was shared in the study design, collection of data, analysis of data, result interpretations, manuscript writing and revision, and manuscript approval.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

This study was approved by clinical trial number: NCT04481360 and the Assiut University Faculty of Medicine medical ethical committee number: 17101187.

Consent for publication

All the authors agree for submission and publication of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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