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Cohort Study

Factors associated with increased mortality in hospitalized COVID-19 patients

Chirag Shah, Donna J. Grando, Rebecca A. Rainess, Lydia Ayad, Emad Gobran, Payam Benson, Meika T. Neblett, Vinod Nookala *

Community Medical Center, 99NJ-37, Toms River, NJ, 08755, USA

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ABSTRACT

Background: The rapid spread of the coronavirus disease 2019 (COVID-19) epidemic has significantly impacted global health. So far, the evidence regarding the risk factors that predict the outcomes of COVID-19 patients is limited. In this study, we identified several risk factors that are associated with increased mortality in COVID-19 patients.

Methods: We performed a retrospective review of electronic medical records of the patients admitted with an initial diagnosis of COVID-19. We extracted several patient variables (including demographics, lab results, and pre-existing conditions) and examined for their association with increased mortality.

Results: Of the 487 people included in the study, 340 survived and 147 expired. Significant differences existed in demographics and underlying comorbidities between the two groups. A higher proportion of patients were age 65 and older (87.76% vs 53.24%, $p < 0.001$), and were predominantly male (63.27% vs 52.94%, $p = 0.0351$). Multivariate analysis showed five variables to be the predictors for mortality: age ≥65 [OR = 3.87, 95% CI (2.01, 7.46), $p < 0.001$], initial presentation with dyspnea [OR = 1.71, 95% CI (1.03, 2.82), $p = 0.037$], history of cardiomyopathy [OR = 3.33, 95% CI (1.07, 10.41), $p < 0.038$], positive initial chest imaging findings [OR = 2.24, CI (1.26, 3.97), $p = 0.006$], and acute kidney injury (AKI) [OR = 3.33 CI (2.10, 5.28), $P < 0.001$].

Conclusion: Identifying COVID-19 patients with these characteristics may help guide the management and improve mortality.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic initially began as an outbreak of acute respiratory illness in China's Hubei Province and has rapidly evolved into a global health emergency [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes severe illness in a significant proportion of infected individuals, most notably in older patients and those with underlying comorbidities, including hypertension, diabetes, coronary heart disease, and malignancy [2–4]. The disease presentation varies widely. According to a study of ~44,500 confirmed COVID-19 patients, a major proportion (80%) of patients presented with mild respiratory symptoms, but a significant percentage of patients (19%) presented with either severe disease including hypoxia or critical illness including respiratory failure [5]. Some have developed fatal complications including multiple organ failure, septic shock, pulmonary edema, severe pneumonia, acute respiratory distress syndrome (ARDS), and death [6–8].

SARS-CoV-2 is believed to cause cytokine storm, which triggers an exaggerated inflammatory response in the body, and results in acute respiratory distress syndrome, shock, and multi-organ failure [9,10]. The disease severity correlates with various pro-inflammatory cytokines, although it is not yet clear what is triggering the cytokine storm [11]. The pathophysiology, clinical presentation, and the management of COVID-19 still need to be more clearly defined. A significant proportion of patients deteriorate rapidly after initially presenting with milder symptoms [12–14]. This poses a challenge for frontline healthcare professionals and reinforces the need for early risk stratification.

Government and public health care agencies have taken several measures to mitigate the effect. Still, numerous health care systems have faced a shortage of the resources necessary to manage these patients.

* Corresponding author.
E-mail addresses: chiragmshah715@gmail.com (C. Shah), Donna.Grando@rwjbh.org (D.J. Grando), rebeccarainess2@gmail.com (R.A. Rainess), ayad_lydia@hotmail.com (L. Ayad), dr_emad282@yahoo.com (E. Gobran), Payam.Benson@EnvisionHealth.com (P. Benson), Meika.Neblett@rwjbh.org (M.T. Neblett), vinod.nookala@rwjbh.org, vinfai@gmail.com (V. Nookala).

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Identifying independent high-risk factors for increased mortality of COVID-19 patients is crucial. Early identification of critically ill patients who require early medical intervention may reduce overall morbidity and mortality. Additionally, it helps effectively channel resources, especially in already challenged ICU environments.

2. Methods

2.1. Study population

We obtained the study population from the patients admitted to Community Medical Center with COVID-19 from January 1 through May 31, 2020. We included initial admission of adult patients with a confirmed laboratory diagnosis of SARS-CoV-2 infection. Patients <18 years old and those who refused medical treatment were excluded from the study. This study (IRB # 20-014) was approved by the Community Medical Center Institutional Review Board (HHS IRB Registration #: 00000942), New Jersey. This work has been reported in line with the strengthening the reporting of cohort studies in surgery (STROCSS) criteria [45].

2.2. Methods of data collection

We utilized a retrospective review of electronic medical records of the patients admitted to Community Medical Center with a confirmed diagnosis of SARS-CoV-2 infection. Demographics, clinical characteristics, laboratory results, and imaging findings were extracted from the patients' charts, and evaluated for the association with mortality in COVID-19 patients. A total of 487 people were included in the study.

2.3. Research methods

We analyzed and compared the outcomes in COVID-19 patients, and their association with the extracted variables. The extracted variables among survivors and expired were examined.

2.4. Statistical analysis

Continuous variables were reported as means with standard deviation (SD) or medians, and categorical variables as proportions. We used Student's t-test or the Wilcoxon rank-sum test to analyze between-group differences, as appropriate for the continuous variables. Fisher's exact test or Chi-square test was used for the categorical variables. Additional analyses were performed with the use of the multivariable logistic regression adjusted for the significant covariates. Odds ratios with 95% confidence intervals were reported for all the predictors. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC). A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

3. Results

In total, we included 487 people in the study. Of these, 147 expired and 340 survived. Baseline demographics are described in Table 1. Compared to survivors, expired patients were older, with more patients age 65 years and older (87.76% vs 53.24%, p = 0.001). Males were predominant in the expired group than the survivor group (63.27% vs 52.94%, p = 0.035). The proportion of patients admitted from the ICU was higher in the expired group than the survivor group (23.3% vs 6.18%, p < 0.001). The expired group had more underlying comorbidities than the survivor group (Table 2): hypertension (77.55% vs 56.76, p < 0.001), hyperlipidemia (39.46% vs 25.88%, p = 0.002), cardiomyopathy [identified by physician's diagnosis or inclusion in past medical history] (6.80% vs 1.76%, p = 0.009), atrial fibrillation (20.41% vs 12.94%, p = 0.035), COPD (27.89% vs 16.18%, p = 0.002), cerebrovascular accidents (12.93% vs 6.76%, p = 0.026), diabetes mellitus (36.05% vs 26.76%, p = 0.039), dementia (25.85% vs 15.00%, p = 0.004), active cancer (17.01% vs 10.29%, p = 0.038), acute kidney injury [defined as increase in serum creatinine of 0.3 mg/dL in 48 h, serum creatinine increase of 1.5 mg/dL from baseline in 7 days or urine output of <0.5 mL/kg/hour in 6 h] (63.27% vs 28.53%, p < 0.001). Certain clinical features and laboratory findings were more prevalent in the expired group: dyspnea (72.11% vs 55.59%, p < 0.001), positive initial chest imaging findings (82.31% vs 65.59%, p < 0.001) [infiltrates, opacities, ground glass opacities, etc.], increased WBC count (mean-14.0 vs 8.4, p = 0.001), low albumin (mean-27 vs 30, p < 0.001), higher ferritin (mean-1247.9 vs 916, p = 0.001), higher procalcitonin (mean-3.9 vs 3.4, p < 0.001), higher IL-6 levels (mean 1200.9 vs 162.6,

Table 1
Patient demographics.

Total number of patients (N = 487)	Expired (N = 147)		Survived (N = 340)		p-Value
Age in years- mean (SD), range	78.4 (11.5)	28–94	64.1 (18.5)	19–101	<0.001
Age 65 and older – no. %	129	87.76%	181	53.24%	<0.001
Gender (Male) – no. %	93	63.27%	180	52.94%	0.035
BMI - mean (SD), range	28.6 (6.7)	13.6–50.1	29.5 (6.9)	15.8–61.7	0.158
Admission Unit (ICU) – no. %	34	23.13%	21	6.18%	<0.001
Admission Source (Home) – no. %	80	54.42%	234	68.82%	0.002

SD - standard deviation, BMI - body mass index in kg/m^2, ICU - intensive care unit.

Table 2
Variables related to the past medical history.

Total number of patients (N = 487)	Expired (N = 147)		Survived (N = 340)		p-Value
Hypertension – no. %	114	77.55%	193	56.76%	<0.001
HLD– no. %	58	39.46%	88	25.88%	0.002
Hypercholesterolemia– no. %	14	9.52%	25	7.35%	0.417
CAD– no. %	37	25.17%	66	19.41%	0.153
CHF– no. %	22	14.97%	38	11.18%	0.242
Cardiomyopathy – no. %	10	6.80%	6	1.76%	0.009
A.fib– no. %	30	20.41%	44	12.94%	0.035
Asthma– no. %	6	4.08%	25	7.35%	0.174
COPD– no. %	41	27.89%	55	16.18%	0.002
O2 dependent at home– no. %	7	4.76%	8	2.35%	0.163
CKD– no. %	11	7.48%	23	6.76%	0.775
ESRD– no. %	3	2.04%	16	4.71%	0.163
Dialysis– no. %	3	2.04%	18	5.29%	0.104
CVA– no. %	19	12.93%	23	6.76%	0.026
TIA– no. %	5	3.40%	7	2.06%	0.359
PVD– no. %	3	2.04%	7	2.06%	1.000
PAD– no. %	5	3.40%	5	1.47%	0.177
DM– no. %	53	36.05%	91	26.76%	0.039
Hypothyroidism– no. %	24	16.33%	44	12.94%	0.322
Seizures– no. %	9	6.12%	15	4.41%	0.423
Dementia– no. %	38	25.85%	51	15.00%	0.004
Anemia– no. %	16	10.88%	26	7.65%	0.242
Active cancer– no. %	25	17.01%	35	10.29%	0.038
AKI – no. %	93	63.27%	97	28.53%	<0.001
Anticoagulation (treatment) – no. %	45	30.61%	82	24.12%	0.134
Smoking status					
Non-smoker	94	63.95%	230	67.85%	0.401
Former smoker – no. %	45	30.61%	85	25.07%	
Active smoker – no. %	8	5.44%	24	7.08%	

HLD – hyperlipidemia, CAD - coronary artery disease, CHF - congestive heart failure, A.fib - atrial fibrillation, COPD - chronic obstructive pulmonary disease, CKD - Chronic kidney disease, ESRD - end stage renal disease, CVA - cerebrovascular accident, TIA - transient ischemic attack, PVD - peripheral vascular disease, DM - diabetes mellitus, AKI - acute kidney injury.

p < 0.001), higher C-reactive protein (mean 140.3 vs 81.2, p < 0.001), higher lactic acid levels (mean-3.1 vs 2.0, p < 0.001), higher LDH levels (mean-630.3 vs 360.3, p < 0.001) were predominant in the expired group vs the survivor group. Lymphopenia was more common in the expired group than the survivor group (mean-0.9 vs 1.2, p < 0.001). A greater number of patients in the expired group were on dialysis and needed more oxygen support.

We identified several patient factors that predict mortality in multivariate analysis: age 65 and older [OR = 3.87, 95% CI (2.01, 7.46), p < 0.001], initial presentation with dyspnea [OR = 1.71, 95% CI (1.03, 2.82), p = 0.037], past medical history of cardiomyopathy [OR = 3.33, 95% CI (1.07, 10.41), p < 0.038], positive initial chest imaging findings (infiltrates, opacities, ground glass opacities, etc.) [OR = 2.24, CI (1.26, 3.97), p = 0.006] and acute kidney injury (AKI) (defined as increase in serum creatinine of 0.3 mg/dL in 48 h, serum creatinine increase of 1.5 mg/dL of baseline in 7 days or urine output of <0.5 mL/kg/hour in 6 h) [OR = 3.33 CI (2.10, 5.28), p < 0.001]. Table 3 describes the initial presenting symptoms in the emergency department and initial lab reports of the patients.

4. Discussion

Identifying the risk factors that predict the outcomes in COVID-19 patients would help clinicians to stratify the patients based on the severity of the disease and prognosis. Earlier identification of the patients with poor clinical outcomes aids in the management of the patients efficiently and proper allocation of resources. The available data suggests that advanced age, underlying co-morbidities, various laboratory findings such as lymphopenia, thrombocytopenia, elevated inflammatory markers, and certain chest imaging findings are associated with poor clinical outcomes [15–20]. In this study, we examined for several factors that are associated with increased mortality in hospitalized COVID-19 patients.

The demographics of the study population are listed in Table 1. The proportion of the patients admitted from the ICU was significantly higher in the expired group than the survivor group (23.13% vs 6.18%). Patients were much older in the expired group than the survivor group (mean age 78.4 Years vs 64.1 Years). The proportion of male patients was also higher in the expired group than the survivor group (63.27% vs 52.94%). Furthermore, the patients with age 65 years and older were higher in the expired group compared to the survivor group [OR = 3.87, 95% CI (2.01, 7.46), p < 0.001] (Table 5). Older age and male sex are poor prognostic factors, and these findings are consistent with previous studies [5,19,21–24].

Table 3
Initial presenting symptoms in the emergency department and initial lab reports.

Total Number of Patients (N = 487)	Expired (N = 147)		Survived (N = 340)		p-Value
Symptoms in ED:					
Cough - no. %	76	51.70%	164	48.24%	0.482
Fever - no. %	82	55.78%	190	55.88%	0.983
Dyspnea - no. %	106	72.11%	189	55.59%	<0.001
Initial positive CXR/CT findings - no. %	121	82.31%	223	65.59%	<0.001
Initial lab values during presentation – (mean, median):					
WBC - 10^9/L	14.0	8.7	8.4	7.3	0.001
Albumin - g/L	27	27	30	30	<0.001
Ferritin - μg/L	1247.9	1017.0	916.5	626.0	0.001
Procalcitonin - μg/L	3.9	0.7	3.4	0.2	<0.001
IL-6 - pg/mL	1200.9	245.6	162.6	56.4	<0.001
CRP - mg/L	140.3	133.0	81.2	67.4	<0.001
Absolute lymphocytes - 10^9/L	0.9	0.7	1.2	0.9	<0.001
Highest absolute lymphocytes level - 10^9/L	1.0	0.9	1.6	1.3	<0.001
Lactic acid – mmol/L	3.1	2.3	2.0	1.5	<0.001
Highest lactic acid level – mmol/L	3.8	2.6	2.2	1.6	<0.001
LDH – U/L	630.3	449.5	360.3	317.0	<0.001
Highest LDH Level – U/L	645.5	464.0	373.0	322.5	<0.001

ED - emergency department, CXR - chest x-ray, CT - computed tomography, IL-6 - interleukin-6, CRP - C-reactive protein, LDH - lactate dehydrogenase.

Our study showed the patients with respiratory symptoms during an initial presentation were more common in the expired group than the survivor group (dyspnea - 72.11% vs 55.59%, cough −51.70% vs 48.24%) (Table 3). The percentage of the patients presenting with positive chest imaging findings at initial presentation was higher in the expired group than the survivor group (82.31% vs 65.59%). Patients initially presenting with dyspnea [OR = 1.71, CI (1.03, 2.82), p = 0.037] and positive chest imaging findings on presentation [OR = 2.24, CI (1.26, 3.27), p = 0.006] have higher odds of mortality. Increased WBC count (mean – 14.0 vs 8.4), lymphopenia (mean-0.9 vs 1.2), and low albumin (mean-27 vs 30) were observed in the expired group when compared with the survivor group (Table 3). Several inflammatory markers such as ferritin, procalcitonin, IL-6 levels, and C-reactive protein were elevated in the expired group (Table 3). Lactic acid levels (mean-3.1 vs 2.0) and LDH levels (mean-630.3 vs 360.3) were elevated in the expired group than the survivor group (Table 3). Active cancer diagnosis was higher in the deceased group, but did not predict mortality in multivariate analysis. This may be due to a smaller sample size [25]. Various patient factors including clinical features, laboratory, and positive imaging findings have been identified as predictors of clinical outcomes in other studies [26]. The novel coronavirus is known to induce a cytokine storm that results in various clinical manifestations in patients [10,27]. This is likely the cause of several elevated inflammatory markers in critically ill patients. Lymphopenia, high serum lactate, D-dimer levels, interleukin-6, and cardiac troponins have been associated with poor outcomes [12,13,28–31]. COVID-19 patients in the intensive care unit have been found to have higher levels of various proinflammatory cytokines [32].

This study showed the odds of mortality in patients with a history of cardiomyopathy were higher [OR = 3.33, 95% CI (1.07, 10.41), p < 0.038]. Previous studies have demonstrated the association of poor patient outcomes with various cardiovascular conditions such as hypertension, coronary artery disease, heart failure, and cardiac arrhythmia, but there is limited evidence showing the association with cardiomyopathy [33–35]. A recent study demonstrated that the novel coronavirus might cause cardiac injury and the patients with elevated cardiac troponins and LDH had poor clinical outcomes [36]. Thus, it was hypothesized that severe inflammatory response in COVID-19 patients with preexisting cardiovascular conditions may precipitate cardiac injury [37].

This study also showed that the odds of mortality were higher in patients with acute kidney injury [OR = 3.33 CI (2.10, 5.28), p < 0.001]. A recent prospective cohort study by Cheng et al. showed that COVID-19 patients with underlying renal disorders and the development of AKI during hospitalization were associated with higher in-hospital mortality [38]. Several other studies have also showed the association between AKI and increased mortality [39]. Although the exact mechanism of renal injury in COVID-19 is not yet clear, several studies have shown the association between SARS-CoV-2 and renal involvement [40–44]. More studies are needed to evaluate risk factors and long-term outcomes, especially for patients who developed AKI, proteinuria, and microscopic hematuria associated with COVID-19.

4.1. Limitations

Several limitations must be considered while interpreting this study. First, as it is a single center study with a largely geriatric population, it is vulnerable to certain tendencies, such as selection bias. Second, since this is a retrospective study using electronic medical records, we cannot make inferences regarding causality. Third, we cannot generalize the findings to the outpatient setting, as this was an inpatient hospital study. Additional limitations include variations in treatment protocol based on

patient setting; for example: proning of patients by a dedicated team in the ICU, vs. encouragement of self-proning for patients on medical units (Table 4). We identified history of cardiomyopathy (Table 2) by chart review (physician diagnosis or inclusion in past medical history); ejection fraction information was not available for all patients. Similar studies at multiple centers with larger sample sizes are needed to substantiate these results.

5. Conclusion

Overall, our study supports the findings of the previous studies. We identified several predictors for increased mortality in hospitalized COVID-19 patients. These are: age 65 and older, an initial presentation with dyspnea, positive chest imaging findings during initial presentation, past medical history of cardiomyopathy, and AKI. Out of these variables, the current evidence regarding the association between cardiomyopathy and mortality in COVID-19 patients is very limited. Particular consideration should be given to these variables, as they help to identify patients requiring early intervention and improve the chances of survival. In addition, mortality was higher for those with several underlying conditions, and although this was not significant in multivariate analysis, it warrants further study. Larger multiple center studies are needed to establish a stronger evidence.

Availability of the data and materials

The datasets and the other information related to this study are available with the corresponding author.

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This study did not receive any grant from any funding agency.

Author contribution

Chirag Shah - methodology, formal analysis and writing original draft.

Donna J. Grando – methodology and writing original draft.

Rebecca A. Rainess – methodology and writing original draft.

Lydia Ayad – methodology and writing original draft.

Emad Gobran – methodology and writing original draft.

Payam Benson – methodology and writing original draft.

Meika T. Neblett - writing original draft, review & editing and supervision.

Vinod Nookala - has complete access to all the information pertaining to the study and contributed to conceptualization, methodology, validation, analysis, manuscript writing, review and supervision.

Trial registry number

1. Name of the registry: Research Registry.

2. Unique Identifying number or registration ID: researchregistry6156.

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-theregistry#home/registrationdetails/5f94fe8051b3ea00155ae960/.

Guarantor

Vinod Nookala.

Consent

The identity of the patient population is protected. Stringent measures have been taken in order to make the study population's identifying information confidential throughout the research process. Written consent is waived due to the retrospectivenature of this study.

Table 4
Patient outcomes.

Total Number of Patients (N = 487)	Expired (N = 147)		Survived (N = 340)		p-Value
Total length of stay in days - mean (SD), range	6.67 (4.7)	0–25	6.36 (3.8)	0–22	0.478
ICU stay – no. %	67	45.58%	34	10.00%	<0.001
ICU LOS - mean (SD), range	4.48 (3.2)	1–15	3.76 (3.0)	1–13	0.285
Proning – no. %	23	15.65%	9	2.65%	<0.001
Number of proning days - mean (SD), range	2.78 (2.7)	1–10	3.25 (3.1)	1–10	0.696
Required dialysis inpatient - no. %	14	9.52%	20	5.88%	0.147
Vented – no. %	57	38.78%	12	3.53%	<0.001
Vented LOS - mean (SD), range	4.09 (3.1)	0–15	5.17 (3.4)	1–11	0.288
O2 [defined as high flow, CPAP, vent mask, NRB]) – no. %	136	92.52%	231	67.94%	<0.001
Stroke – no. %	0	0.00%	2	0.59%	1.000
Readmission within 7 days – no. %	0	0.00%	23	6.76%	0.001
Readmission within 30 days – no. %	1	0.68%	30	8.82%	<0.001

SD - standard deviation, LOS- length of stay (in days), CPAP- continuous positive airway pressure, NRB- non-rebreather mask.

Table 5
Risk factors and symptoms: predictors for mortality.

Effect	Odds Ratio	95% Wald Confidence Limits		p-Value
Age 65 and older	3.87	2.01	7.46	<0.001
Gender (Male)	1.24	0.78	1.97	0.359
Patient admitted from home	1.18	0.69	2.03	0.552
PMH hypertension	1.04	0.59	1.83	0.883
PMH hyperlipidemia	1.36	0.83	2.21	0.221
PMH Cardiomyopathy	3.33	1.07	10.41	0.038
PMH A. fib	0.91	0.50	1.65	0.760
PMH COPD	1.21	0.70	2.09	0.505
PMH CVA	1.54	0.73	3.26	0.258
PMH DM	1.09	0.67	1.78	0.723
PMH Dementia	1.38	0.76	2.50	0.294
PMH Active cancer	1.44	0.77	2.71	0.253
AKI (Defined as increase in serum creatinine of 0.3 mg/dL in 48 h, serum creatinine increase of 1.5 mg/dL from baseline in 7 days or urine output of <0.5 mL/kg/hour in 6 h)	3.33	2.10	5.28	<0.001
Dyspnea in ED noted as positive	1.71	1.03	2.82	0.037
Initial CXR/CT findings	2.24	1.26	3.97	0.006

PMH - past medical history, CHF - congestive heart failure, A. fib - atrial fibrillation, COPD - chronic obstructive pulmonary disease, CVA - cerebrovascular accident, CKD - chronic kidney disease, DM - diabetes mellitus, AKI - acute kidney injury, CXR - chest x-ray, CT - computed tomography.

Ethical approval

This study was approved by the Community Medical Center Institutional Review Board, New Jersey.

IRB # 20-014.

HHS IRB Registration #: 00000942.

Declaration of competing interest

No conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2020.10.071.

Provenance and peer review

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References

[1] C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis, R. Agha, World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19), Int. J. Surg. 76 (2020) 71–76, https://doi.org/10.1016/j.ijsu.2020.02.034.

[2] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.

[3] A. Sanyaolu, C. Okorie, A. Marinkovic, R. Patidar, K. Younis, P. Desai, Z. Hosein, I. Padda, J. Mangat, M. Altaf, Comorbidity and its impact on patients with COVID-19, SN Compr. Clin. Med. 2 (2020) 1069–1076, https://doi.org/10.1007/s42399-020-00363-4.

[4] Y. Zhou, Q. Yang, J. Chi, B. Dong, W. Lv, L. Shen, Y. Wang, Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis, Int. J. Infect. Dis. 99 (2020) 47–56, https://doi.org/10.1016/j.ijid.2020.07.029.

[5] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China, J. Am. Med. Assoc. 323 (2020) 1239, https://doi.org/10.1001/jama.2020.2648.

[6] S. Colafrancesco, C. Alessandri, F. Conti, R. Priori, COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? Autoimmun. Rev. 19 (2020) 102573, https://doi.org/10.1016/j.autrev.2020.102573.

[7] Y. Du, L. Tu, P. Zhu, M. Mu, R. Wang, P. Yang, X. Wang, C. Hu, R. Ping, P. Hu, T. Li, F. Cao, C. Chang, Q. Hu, Y. Jin, G. Xu, Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study, Am. J. Respir. Crit. Care Med. 201 (2020) 1372–1379, https://doi.org/10.1164/rccm.202003-0543OC.

[8] S.A. Hassan, F.N. Sheikh, S. Jamal, J.K. Ezeh, A. Akhtar, Coronavirus (COVID-19): a review of clinical features, diagnosis, and treatment, Cureus 12 (2020), e7355, https://doi.org/10.7759/cureus.7355.

[9] K.-S. Yuen, Z.-W. Ye, S.-Y. Fung, C.-P. Chan, D.-Y. Jin, SARS-CoV-2 and COVID-19: the most important research questions, Cell Biosci. 10 (2020) 40, https://doi.org/10.1186/s13578-020-00404-4.

[10] F. Coperchini, L. Chiovato, L. Croce, F. Magri, M. Rotondi, The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system, Cytokine Growth Factor Rev. 53 (2020) 25–32, https://doi.org/10.1016/j.cytogfr.2020.05.003.

[11] R. Castelli, A. Gidaro, Abnormal hemostatic parameters and risk of thromboembolism among patients with COVID-19 infection, J. Hematol. 9 (2020) 1–4, https://doi.org/10.14740/jh636.

[12] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, J. Am. Med. Assoc. 323 (2020) 1061, https://doi.org/10.1001/jama.2020.1585.

[13] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[14] K.J. Goh, S. Kalimuddin, K.S. Chan, Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from coronavirus disease 2019 (COVID-19) infection, Ann. Acad. Med. Singapore 49 (2020) 108–118.

[15] J. Xu, X. Yang, L. Yang, X. Zou, Y. Wang, Y. Wu, T. Zhou, Y. Yuan, H. Qi, S. Fu, H. Liu, J. Xia, Z. Xu, Y. Yu, R. Li, Y. Ouyang, R. Wang, L. Ren, Y. Hu, D. Xu, X. Zhao, S. Yuan, D. Zhang, Y. Shang, Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China, Crit. Care 24 (2020) 394, https://doi.org/10.1186/s13054-020-03098-9.

[16] L. Zhang, X. Yan, Q. Fan, H. Liu, X. Liu, Z. Liu, Z. Zhang, D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19, J. Thromb. Haemostasis 18 (2020) 1324–1329, https://doi.org/10.1111/jth.14859.

[17] L. Tan, Q. Wang, D. Zhang, J. Ding, Q. Huang, Y.-Q. Tang, Q. Wang, H. Miao, Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study, Signal Transduct. Target. Ther. 5 (2020) 33, https://doi.org/10.1038/s41392-020-0148-4.

[18] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med. 46 (2020) 846–848, https://doi.org/10.1007/s00134-020-05991-x.

[19] R.-H. Du, L.-R. Liang, C.-Q. Yang, W. Wang, T.-Z. Cao, M. Li, G.-Y. Guo, J. Du, C.-L. Zheng, Q. Zhu, M. Hu, X.-Y. Li, P. Peng, H.-Z. Shi, Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study, Eur. Respir. J. 55 (2020) 2000524, https://doi.org/10.1183/13993003.00524-2020.

[20] D. Colombi, F.C. Bodini, M. Petrini, G. Maffi, N. Morelli, G. Milanese, M. Silva, N. Sverzellati, E. Michieletti, Well-aerated lung on admitting chest ct to predict adverse outcome in COVID-19 pneumonia, Radiology 296 (2020) E86–E96, https://doi.org/10.1148/radiol.2020201433.

[21] L. Palaiodimos, D.G. Kokkinidis, W. Li, D. Karamanis, J. Ognibene, S. Arora, W. N. Southern, C.S. Mantzoros, Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York, Metabolism 108 (2020) 154262, https://doi.org/10.1016/j.metabol.2020.154262.

[22] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, D.P. Barnaby, L.B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J. N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area, J. Am. Med. Assoc. 323 (2020) 2052–2059, https://doi.org/10.1001/jama.2020.6775.

[23] L. Fu, J. Fei, H.-X. Xiang, Y. Xiang, Z.-X. Tan, M.-D. Li, F.-F. Liu, H.-Y. Liu, L. Zheng, Y. Li, H. Zhao, D.-X. Xu, Analysis of death risk factors among 200 COVID-19 patients in Wuhan, China: a hospital-based case-cohort study, SSRN Electron. J. 200 (2020), https://doi.org/10.2139/ssrn.3551430.

[24] J.-M. Jin, P. Bai, W. He, F. Wu, X.-F. Liu, D.-M. Han, S. Liu, J.-K. Yang, Gender differences in patients with COVID-19: focus on severity and mortality, Front. Public Health 8 (2020) 152, https://doi.org/10.3389/fpubh.2020.00152.

[25] M. Dai, D. Liu, M. Liu, F. Zhou, G. Li, Z. Chen, Z. Zhang, H. You, M. Wu, Q. Zheng, Y. Xiong, H. Xiong, C. Wang, C. Chen, F. Xiong, Y. Zhang, Y. Peng, S. Ge, B. Zhen, T. Yu, L. Wang, H. Wang, Y. Liu, Y. Chen, J. Mei, X. Gao, Z. Li, L. Gan, C. He, Z. Li, Y. Shi, Y. Qi, J. Yang, D.G. Tenen, L. Chai, L.A. Mucci, M. Santillana, H. Cai, Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak, Canc. Discov. 10 (2020), https://doi.org/10.1158/2159-8290.CD-20-0422. CD-20-0422.

[26] D. Ji, D. Zhang, J. Xu, Z. Chen, T. Yang, P. Zhao, G. Chen, G. Cheng, Y. Wang, J. Bi, L. Tan, G. Lau, E. Qin, Prediction for progression risk in patients with COVID-19 pneumonia: the call score, Clin. Infect. Dis. 71 (2020) 1393–1399, https://doi.org/10.1093/cid/ciaa414.

[27] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (2020) 1033–1034, https://doi.org/10.1016/S0140-6736(20)30628-0.

[28] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.

[29] J. Wu, J. Liu, X. Zhao, C. Liu, W. Wang, D. Wang, W. Xu, C. Zhang, J. Yu, B. Jiang, H. Cao, L. Li, Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu province: a multicenter descriptive study, Clin. Infect. Dis. 71 (2020) 706–712, https://doi.org/10.1093/cid/ciaa199.

[30] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan, Y. Shang, Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. 8 (2020) 475–481, https://doi.org/10.1016/S2213-2600(20)30079-5.

[31] M. Kermali, R.K. Khalsa, K. Pillai, Z. Ismail, A. Harky, The role of biomarkers in diagnosis of COVID-19 – a systematic review, Life Sci. 254 (2020) 117788, https://doi.org/10.1016/j.lfs.2020.117788.

[32] T.P. Velavan, C.G. Meyer, Mild versus severe COVID-19: laboratory markers, Int. J. Infect. Dis. 95 (2020) 304–307, https://doi.org/10.1016/j.ijid.2020.04.061.

[33] P. Ssentongo, A.E. Ssentongo, E.S. Heilbrunn, D.M. Ba, V.M. Chinchilli, Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis, PloS One 15 (2020), e0238215, https://doi.org/10.1371/journal.pone.0238215.

[34] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 811–818, https://doi.org/10.1001/jamacardio.2020.1017.

[35] A. Santoso, R. Pranata, A. Wibowo, M.J. Al-Farabi, I. Huang, B. Antariksa, Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: a meta-analysis, Am. J. Emerg. Med. (2020), https://doi.org/10.1016/j.ajem.2020.04.052.

[36] C. Wu, X. Hu, J. Song, C. Du, J. Xu, D. Yang, D. Chen, M. Zhong, J. Jiang, W. Xiong, et al., Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19), MedRxiv (2020), https://doi.org/10.1101/2020.02.26.20028589.

[37] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, W. Gong, X. Liu, J. Liang, Q. Zhao, H. Huang, B. Yang, C. Huang, Association of cardiac injury with mortality in

hospitalized patients with COVID-19 in Wuhan, China, JAMA Cardiol. 5 (2020) 802–810, https://doi.org/10.1001/jamacardio.2020.0950.

[38] Y. Cheng, R. Luo, K. Wang, M. Zhang, Z. Wang, L. Dong, J. Li, Y. Yao, S. Ge, G. Xu, Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (2020) 829–838, https://doi.org/10.1016/j.kint.2020.03.005.

[39] Q. Yan, P. Zuo, L. Cheng, Y. Li, K. Song, Y. Chen, Y. Dai, Y. Yang, L. Zhou, W. Yu, Y. Li, M. Xie, C. Zhang, H. Gao, Acute kidney injury is associated with in-hospital mortality in older patients with COVID-19, Journals Gerontol. Ser. A, 2020, https://doi.org/10.1093/gerona/glaa181.

[40] W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, J. Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Y. Hu, P. Peng, J. Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, N. Zhong, Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720, https://doi.org/10.1056/NEJMoa2002032.

[41] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X.-G. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273, https://doi.org/10.1038/s41586-020-2012-7.

[42] L. Wang, X. Li, H. Chen, S. Yan, D. Li, Y. Li, Z. Gong, Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China, Am. J. Nephrol. 51 (2020) 343–348, https://doi.org/10.1159/000507471.

[43] B. Diao, Z. Feng, C. Wang, H. Wang, L. Liu, C. Wang, R. Wang, Y. Liu, Y. Liu, G. Wang, et al., Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, MedRxiv (2020), https://doi.org/10.1101/2020.03.04.20031120.

[44] H. Su, M. Yang, C. Wan, L.-X. Yi, F. Tang, H.-Y. Zhu, F. Yi, H.-C. Yang, A.B. Fogo, X. Nie, C. Zhang, Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, Kidney, Bar Int. 98 (2020) 219–227, https://doi.org/10.1016/j.kint.2020.04.003.

[45] R. Agha, A. Abdall-Razak, E. Crossley, N. Dowlut, C. Iosifidis, G. Mathew, STROCSS 2019 guideline: strengthening the reporting of cohort studies in surgery, Int. J. Surg. (2019), https://doi.org/10.1016/j.ijsu.2019.11.002.