IJMS
Vol 46, No 6, November 2021

Brief Report

Risk Factors for the Mortality in Hospitalized Patients with COVID-19: A Brief Report

Ramin Sami[1], MD; Mohammad-Reza Hajian[1], MD; Babak Amra[2], MD; Forogh Soltaninejad[1], MD; Marjan Mansourian[3], PhD; Sam Mirfendereski[4], MD; Raheleh Sadegh[5], MD; Nilufar Khademi[1], MD; Soheila Jalali[6], MSc; Nafiseh Shokri-Mashhadi[7], PhD

[1]Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran;
[2]Bamdad Respiratory and Sleep Research Center, Department of Internal Medicine, Pulmonary and Sleep Ward, Isfahan University of Medical Sciences, Isfahan, Iran;
[3]Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran;
[4]Department of Radiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran;
[5]Department of Community and Prevention Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran;
[6]Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran;
[7]Department of Clinical Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence:
Nafiseh Shokri-Mashhadi, PhD;
School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Hezarjareeb St., Postal code: 81746-73461, Isfahan, Iran
Tel: +91 9133311886
Fax: +98 31 36681378
Email: nafiseh.shokri@yahoo.com
Received: 01 November 2020
Revised: 10 March 2021
Accepted: 13 March 2021

What's Known

- The increasing growth of COVID-19-related mortality has highlighted the need to recognize the risk factors associated with severe COVID-19 infection.
- Recent epidemiological studies have investigated the relationship between various risk factors and the fatal risk of COVID-19.
- There is a lack of well-documented data regarding the association between impaired laboratory parameters and mortality risks related to COVID-19 infection.

What's New

- We identified certain clinical risk factors, including a history of chronic obstructive pulmonary disease COPD, hypoxia during hospitalization, and initial computed tomography scan (CT) scores, which independently increase the odds of COVID-19-related mortality.
- We provided an independent COVID-19-related mortality prediction model based on the initial recorded laboratory tests on the data of multi-center hospitals.

Abstract

The cumulative rate of death of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has necessitated better recognizing the risk factors of the disease and the COVID-19-induced mortality. This cross-sectional study aimed to determine the potential risk factors that predict COVID-19-related mortality concentrating on the initial recorded laboratory tests. We extracted admission's medical records of a total of 136 deaths related to COVID-19 and 272 discharged adult inpatients (≥18 years old) related to four referral centers from February 24th to April 12th, 2020, in Isfahan, Iran, to figure out the relationship between the laboratory findings and mortality beyond demographic and clinical findings. We applied the independent sample *t* test and a chichi square test with SPSS software to compare the differences between the survivor and non-survivor patients. A P value of less than 0.05 was considered significant. Our results showed that greater length of hospitalization (P≤0.001), pre-existing chronic obstructive pulmonary disease (P≤0.001), high pulse rate, hypoxia (P≤0.001), and high computed tomography scan score (P<0.001), in addition to high values of some laboratory parameters, increase the risk of mortality. Moreover, high neutrophil/lymphocyte ratio (OR, 1.890; 95% CI, 1.074-3.325, P=0.027), increased creatinine levels (OR, 15.488; 95% CI, 0.801-299.479, P=0.07), and elevated potassium levels (OR, 13.400; 95% CI, 1.084-165.618, P=0.043) independently predicted in-hospital death related to COVID-19 infection. These results emphasized the potential role of impaired laboratory parameters for the prognosis of fatal outcomes in adult inpatients.

Please cite this article as: Sami R, Hajian MR, Amra B, Soltaninejad F, Mansourian M, Mirfendereski S, Sadegh R, Khademi N, Jalali S, Shokri-Mashhadi N. Risk Factors for the Mortality in Hospitalized Patients with COVID-19: A Brief Report. Iran J Med Sci. 2021;46(6):487-492. doi: 10.30476/IJMS.2021.47835.

Keywords ● COVID-19 ● Risk factors ● Mortality ● Medical laboratory science

Introduction

The outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a threat to global public health.[1] In general, due to the rapid spread of COVID-19 through human-to-human communication, the prevalence is currently on an increasing trend. In this regard, the WHO's latest global data recorded, as of 14 March 2021, just about 141.5 million confirmed cases of COVID-19.[2] Additionally, recent statistics determined that in the Middle East, a high death rate of COVID-19 cases was observed in Iran (58.61%) and Turkey (30.86%).[3] Furthermore, The COVID-19 epidemic model predicted mortality of 11.7% of in-hospital mortality in patients with COVID-19 using a case-control study in Isfahan.[4, 5] These outcomes highlighted the need

to better recognize the risk factors associated with severe COVID-19 infection.[6]

Recently, studies have specified that the average COVID-19-related deaths have been found in the older population and male gender.[7] Additionally, released epidemiological data by the Centers of Disease Control and Prevention (CDC) has revealed that several pre-existing comorbidities, including cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers, are related to increased fatality risk.[8] In addition to the clinical and epidemiological characteristics, fluctuations in laboratory parameters are recently reported in COVID-19 to affect patients and have worse outcomes.[9] However, limited data are focusing on laboratory parameters beyond the epidemiology and clinical features of patients in the prognosis of COVID-19-related mortality. This short report aimed to determine the potential risk factors that predict COVID-19-related mortality concentrating on the initial recorded laboratory tests based on the data of multi-center population-based cohort study.

Methods

This cross-sectional study was conducted to determine the potential risk factors that predict COVID-19-related mortality. Therefore, we obtained the medical recorded information of 136 death cases caused by COVID-19 (≥18 years old) related to four referral centers from February 24th to April 12th, 2020, in Isfahan, Iran. To determine the relationship between the demographic, clinical, and laboratory findings and mortality, we analyzed the medical information of 272 discharged inpatients and compared it

Table 1: Baseline demographic and clinical characteristics of survivor and non-survivor hospitalized COVID-19 patients

	Patients characteristics		Total (n=408) N (%)	Survived (n=272) N (%)	Dead (n=136)	P value
Demographics	Age	<35	39 (9.6)	36 (13.2)	3 (2.2)	<0.001
		35-55	111 (27.2)	104 (38.2)	7 (5.1)	
		56-70	137 (33.6)	93 (34.2)	44 (32.4)	
		>70	121 (29.7)	39 (14.3)	82 (60.3)	
	Sex	Female	210 (51.5)	163 (59.9)	47 (34.6)	<0.001
		Male	198 (48.53)	109 (40.07)	89 (65.44)	
	Hospital length of stay (days)		9.65 (5.17)	9.01 (5.22)	10.39 (5.04)	<0.001
	Duration of symptom's onset to hospital admission (days)		6.99 (4.78)	7.47 (4.72)	5.99 (4.77)	0.004
Comorbidities	Hypertension		158 (38.8)	82 (30.1)	76 (56.3)	<0.001
	Heart failure		13 (3.2)	4 (1.5)	9 (6.6)	0.013
	Chronic obstructive pulmonary disease		43 (10.5)	12 (4.4)	31 (22.8)	<0.001
	Diabetes		130 (31.9)	68 (25.0)	62 (45.9)	<0.001
	Cancer		12 (2.9)	5 (1.8)	7 (5.2)	0.069
	Chronic kidney disease		25 (6.1)	10 (3.7)	15 (11.1)	0.007
	Hyperlipoproteinemia		58 (14.3)	31 (11.4)	27 (20.0)	0.024
Vital Symptoms	Chest Pain		74 (20.7)	64 (29.0)	10 (7.4)	<0.001
	Sore Throat		77 (21.0)	56 (24.2)	21 (15.4)	0.047
	Cough		324 (79.8)	218 (80.7)	106 (77.9)	0.515
	Shortness of Breath		299 (74.8)	179 (67.8)	120 (88.2)	<0.001
	Nausea		122 (32.2)	98 (40.3)	24 (17.6)	<0.001
	Vomiting		85 (22.3)	61 (24.9)	24 (17.6)	0.123
	Diarrhea		69 (18.4)	61 (25.6)	8 (5.9)	<0.001
	Headache		126 (34.4)	103 (44.8)	23 (16.9)	<0.001
	Chills		246 (62.3)	194 (74.9)	52 (38.2)	<0.001
	Weakness Fatigue		188 (52.1)	150 (66.7)	38 (27.9)	<0.001
	Fever Degree (°C)		37.66 (0.99)	37.61 (0.99)	37.76 (1.01)	0.153
	Fever Degree >38.5 °C		66 (16.5)	42 (15.8)	24 (17.9)	0.669
Vital Signs (on triage)	Systolic blood pressure)mm Hg(		128.67(20.01)	129.72 (17.75)	126.44 (24.04)	0.173
	Diastolic blood pressure)mm Hg(		79.18 (34.69)	81.87 (40.73)	73.48 (13.84)	0.024
	Peripheral capillary oxygen saturation (SpO2)		87.48 (9.37)	90.70 (5.37)	80.98 (11.99)	<0.001
	Pulse Rate >100		119 (29.3)	78 (28.9)	41 (30.1)	0.818
Global CT Score (mean±SD)			10.76 (5.44)	9.64 (4.84)	13.64 (5.87)	<0.001

Data are presented as number (%), mean±SD. Independent sample *t* test was used for continuous variables and Chi square test was used for categorical variables. Level of statistical significance=0.05. N: Number; CT: Computed tomography; SpO2: Peripheral capillary oxygen saturation

to the information of those, who experienced death in the hospital. Similar to previous studies, the diagnosis of COVID-19 relied on positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR).[9, 10] Investigators extracted demographic characteristics, medical history, pre-existing comorbidities, laboratory findings, and clinical outcomes on admission. Written informed consent was obtained from all the patients. This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.680).

Statistical Analysis

We utilized an independent sample *t* test for continuous data and a Chi square test for categorical data to compare the differences between the survivor and non-survivor patients considering a P value<0.05 as statistically significant using SPSS (IBM SPSS Statistics 20.0). Continuous and categorical variables were presented as mean±SD and number (%), respectively. Univariable and multivariable logistic regression models were employed to explore the potential risk factors associated with mortality. To analyze the association between the laboratory findings with mortality in patients affected by COVID-19, we categorized these according to previous studies.

Results

Table 1 represents the details of baseline characteristics of survivor (n=272) and non-survivor patients (n=136). A total of 408 cases (210 women and 198 men) were included in this study. Compared with the survived patients, those who experienced death were 55-70 years (P<0.001) and men (P<0.001). They also tended to have a higher mean length of patients' hospital stay (P<0.001) and a long duration of symptoms onset, the average duration of hospital admission until

Table 2: Top variables of clinical, epidemiological, and laboratory findings in predicting in-hospital death of COVID-19 patients

Patients characteristics			Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P value	OR (95% CI)	P value
Demographics	Age	55-70	5.67 (1.658,19.447)	0.006	-	-
	Sex	Female	0.35 (0.23, 0.54)	<0.001	-	-
		Male (Reference)				
	Hospital length of stay (days)		1.13 (1.08, 1.18)	<0.001	1.12 (1.07, 1.18)	<0.001
	Duration of symptom's onset to hospital admission (days)		0.92 (0.88, 0.97)	0.005	0.91 (0.86, 0.97)	0.004
Comorbidities	Hypertension		2.98 (1.94, 4.57)	<0.001	-	-
	Heart failure		4.74 (1.43, 15.71)	0.011	-	-
	Chronic obstructive pulmonary disease		6.07 (3.01, 12.26)	<0.001	5.36 (2.33, 12.30)	<0.001
	Diabetes		2.54 (1.64, 3.94)	<0.001	-	-
	Chronic kidney disease		3.27 (1.43, 7.502)	0.005	-	-
	Diastolic blood pressure (mm Hg)		0.96 (0.943, 0.979)	<0.001	0.98 (0.96, 1.00)	0.078
	SpO2		0.84 (0.812, 0.883)	<0.001	0.88 (0.84, 0.91)	<0.001
	SpO2 >90 (N, %)		217 (53.7%)	<0.001	114 (85.1%)	<0.001
	Pulse Rate >100		1.06 (0.67, 1.66)	0.793	2.05 (1.13, 3.71)	0.017
Laboratory Findings	White blood cell <4×10^9 (n/L)		2.70 (1.50, 4.85)	0.001	2.92 (1.42, 6.02)	0.004
	Neutrophil/ Lymphocyte ratio		1.20 (1.13, 1.26)	<0.001	1.18 (1.11, 1.26)	<0.001
	Hemoglobin <12 (g/dL)		2.72 (1.71, 4.34)	<0.001	1.63 (0.95, 2.81)	0.074
	Platelet count		0.99 (0.99, 1.00)	0.066	0.99 (0.99, 1.00)	0.044
	BUN >18 (mg/dL)		9.61 (5.82, 15.86)	<0.001	5.49 (3.06, 9.86)	<0.001
	Creatinine >1.4 (mg/dL)		13.73 (7.72, 24.40)	0.011	6.39 (3.41, 11.96)	<0.001
	Na (mmol/L)		1.15 (1.09, 1.22)	<0.001	1.18 (1.10, 1.27)	<0.001
	Potassium (mmol/L)		3.03 (1.80, 5.10)	<0.001	2.17 (1.18, 3.98)	<0.012
	ALT (U/L)		1.01 (1.00, 1.01)	0.003	1.01 (1.00, 1.02)	0.001
	AST (U/L)		1.01 (1.00, 1.02)	<0.001	1.02 (1.01, 1.03)	<0.001
	ALT /AST ratio		1.58 (1.22, 2.04)	<0.001	-	-
	ALP (U/L)		1.00 (1.00, 1.01)	<0.001	1.00 (1.00, 1.01)	<0.001
	Lactate dehydrogenase >800 (IU/L)		5.09 (1.79, 14.45)	0.011	4.77 (1.39, 16.33)	0.013
	Calcium (mg/dL)		0.67 (0.49, 0.91)	0.012	0.69 (0.493, 0.98)	0.042
	Phosphorus (mg/dL)		2.17 (1.67, 2.82)	<0.001	1.97 (1.47, 2.63)	<0.001
Global CT Score			1.15 (1.09, 1.22)	<0.001	1.19 (1.11, 1.27)	<0.001

Univariate and multivariate logistic regression models, *Adjusted by Sex and Age. Level of statistical significance=0.05. AST: Aspartate aminotransferase; ALT: Alanine transaminase; BUN: Blood urea nitrogen; ALP: Alkaline phosphatase; SpO2: Peripheral capillary oxygen saturation; CT: Computed Tomography

Table 3: Univariable and multivariable laboratory findings models of mortality of hospitalized COVID-19 patients

Clinical risk factors	Univariable laboratory findings model*		Multivariable laboratory findings model*	
	OR (95% CI)	P value	OR (95% CI)	P value
Neutrophil/Lymphocyte ratio	1.17 (1.10, 1.25)	<0.001	1.89 (1.07, 3.32)	0.027
Hemoglobin <12 (g/dL)	1.80 (1.01, 3.20)	0.044	-	-
White blood cell <4×10^9 (n/L)	2.56 (1.25, 5.25)	0.010	-	-
Creatinine >1.4 (mg/dL)	6.72 (3.46, 13.04)	<0.001	15.48 (0.80, 299.47)	0.070
LDH >800 (IU/ml)	5.18 (1.37,19.52)	0.015	-	-

Univariate and multivariate logistic regression models, *Adjusted by Sex and Age, COPD, and Diastolic blood pressure. Level of statistical significance=0.05. BUN: Blood urea nitrogen; LDH: lactate dehydrogenase

the onset of symptoms, (P=0.005). Moreover, univariate analysis identified that comorbidities, including hypertension (P<0.001), diabetes (P<0.001), COPD (P<0.001), chronic kidney disease (P=0.007), heart failure (P=0.013), and hyperlipoproteinemia (P=0.024) were significantly different between the two groups. These results are in accordance with those derived from a previous study, which might be on account of the higher prevalence of medical problems in the mentioned disease.[6] Having dyspnea (P<0.001), diarrhea (P<0.001), and chills (P<0.001) were the main clinical death-related symptoms. Furthermore, some laboratory findings and global CT scores remained significantly different between the two groups. As presented in table 2, the logistic model indicated that a history of COPD, hypoxia, and CT scores increased the odds of COVID-19 mortality. In the multivariate analysis, we also observed that pre-existing pulmonary disease was associated with the risk of mortality.

Regarding laboratory data, we found the influential role of neutrophil/ lymphocyte ratio, serum blood urea nitrogen (BUN) creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sodium, potassium, calcium, and phosphorus levels on the risk of mortality (table 3), in addition to other clinical characteristics. Furthermore, our investigation showed a significant relationship between low hemoglobin concentrations and mortality. The multivariate predictive model also indicated that high neutrophil/ lymphocyte ratio (OR, 1.890; 95% CI, 1.074-3.325, P=0.027), increased creatinine levels (OR, 15.488; 95% CI, 0.801-299.479, P=0.07), and elevated potassium levels (OR, 13.400; 95% CI, 1.084-165.618, P=0·043) are independent risk factors of the fatality of COVID-19 (table 3).

Discussion

The present study initially identified that a history of COPD, hypoxia, and CT scores increase the odds of COVID-19 mortality related to COVID-19 infection. However, unlike previous reports,[11-13] our multivariate analysis showed that only pre-existing pulmonary disease was associated with the risk of mortality. This result may be attributed to further adjustment for potential confounders.[14] We also indicated the risk of mortality accompanied by other clinical characteristics, similar to the previous papers.[15-17] As suggested by Chan and colleagues, patients with high creatinine, BUN, and potassium levels had a higher odds ratio (OR) of COVID-19 mortality.[18] Additionally, our investigation revealed the significant relationship between low hemoglobin concentrations and mortality for the first time. We assumed that this result might be owing to the critical role of hemoglobin in carrying oxygen.[19] Further analysis in our study indicated the raised neutrophil/ lymph ratio, creatinine, and elevated potassium levels as independent risk factors of the fatality of COVID-19 (table 2), due to neutrophils' role in the innate immune response and the dose-dependent relationship between acute kidney injury (AKI) stages and death.[16, 20]

Despite numerous strengths of our study, certain limitations should be noted; our comparison relied on inpatients' data. There were possibly some cases that were not hospitalized, and the information in our study was related to only those who required medically attended care. Therefore, the community-based study of patients infected with COVID-19 is needed to confirm our results.

Conclusion

This report indicated that a high neutrophil/ lymphocyte ratio, increased creatinine levels, and elevated potassium levels could independently predict mortality induced by COVID-19. These results emphasized the potential role of impaired laboratory parameters for the prognosis of fatal outcomes and their practical benefits regarding their ability to be used for the prognosis of fatal outcomes in adults with COVID-19. Our findings could also assist clinicians to recognize patients with a poor prognosis.

Acknowledgments

We thank the Vice-Chancellor in the research affairs of Isfahan University of Medical Sciences for the financial support (grant number: 199003).

Conflict of Interest: None declared.

References

1 Organization WH [Internet]. WHO Director-General's opening remarks at the media briefing on COVID-19. [cited 11 March 2020]. https://www.who.int/dg/speeches/detail/ who-director-general-s-opening-remarks-atthe-media-briefing-on-covid-19—11-march-2020
2 Organization WH. COVID-19 weekly epidemiological update, 16 March 2021. Geneva, World Health Organization.
3 Mohammed R. The prevalence study of coronavirus disease (Covid-19) cases in Asia, Europe and Middle East. IJARESM. 2012;9.
4 Abdollahpour I, Aguilar-Palacio I, Gonzalez-Garcia J, Vaseghi G, Otroj Z, Manteghinejad A, et al. Model Prediction for In-Hospital Mortality in Patients with COVID-19: A Case-Control Study in Isfahan, Iran. Am J Trop Med Hyg. 2021. doi: 10.4269/ajtmh.20-1039. PubMed PMID: 33591938; PubMed Central PMCID: PMCPMC8045635.
5 Moein S, Nickaeen N, Roointan A, Borhani N, Heidari Z, Javanmard SH, et al. Forecasting Covid-19 epidemic in Isfahan using a dynamic modeling approach. 2020. doi: 10.21203/rs.3.rs-33175/v1.
6 Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430-6. doi: 10.1038/s41586-020-2521-4. PubMed PMID: 32640463; PubMed Central PMCID: PMCPMC7611074.
7 Janani M, Beheshti-Nia F, Ahmadi H, Khazeni A, Yadegarafar G. Epidemiological features and hotspot of COVID-19 in Isfahan province of Iran: Results of a cohort study. 2020. doi: 10.21203/rs.3.rs-38143/v1.
8 Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. Crit Care. 2020;24:179. doi: 10.1186/s13054-020-02902-w. PubMed PMID: 32345311; PubMed Central PMCID: PMCPMC7187660.
9 Sabri A, Davarpanah AH, Mahdavi A, Abrishami A, Khazaei M, Heydari S, et al. Novel coronavirus disease 2019: predicting prognosis with a computed tomography-based disease severity score and clinical laboratory data. Pol Arch Intern Med. 2020;130:629-34. doi: 10.20452/pamw.15422. PubMed PMID: 32500700.
10 Sule WF, Oluwayelu DO. Real-time RT-PCR for COVID-19 diagnosis: challenges and prospects. Pan Afr Med J. 2020;35:121. doi: 10.11604/pamj.supp.2020.35.24258. PubMed PMID: 33282076; PubMed Central PMCID: PMCPMC7687508.
11 Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One. 2020;15:e0238215. doi: 10.1371/journal.pone.0238215. PubMed PMID: 32845926; PubMed Central PMCID: PMCPMC7449476.
12 Rabbani G, Shariful Islam SM, Rahman MA, Amin N, Marzan B, Robin RC, et al. Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis. Expert Rev Respir Med. 2021;15:705-16. doi: 10.1080/17476348.2021.1866547. PubMed PMID: 33334189.
13 Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. The lancet Respiratory medicine. 2021. doi: 10.1016/S2213-2600(21)00095-3.
14 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167:268-74. doi: 10.7326/M16-2607. PubMed PMID: 28693043.
15 Sarin SK, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int. 2020;14:690-700. doi: 10.1007/s12072-020-10072-8. PubMed PMID: 32623632; PubMed Central PMCID: PMCPMC7334898.
16 Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol. 2020;92:2573-81. doi: 10.1002/jmv.26061. PubMed PMID: 32458459; PubMed Central PMCID: PMCPMC7283791.
17 Shokri-Mashhadi N, Kazemi M, Saadat S, Moradi S. Effects of select dietary

supplements on the prevention and treatment of viral respiratory tract infections: a systematic review of randomized controlled trials. Expert Rev Respir Med. 2021;15:805-21. doi: 10.1080/17476348.2021.1918546. PubMed PMID: 33858268.

18 Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Baweja M, et al. Acute Kidney Injury in Hospitalized Patients with COVID-19. medRxiv. 2020. doi: 10.1101/2020.05.04.20090944. PubMed PMID: 32511564; PubMed Central PMCID: PMCPMC7274245.

19 Lee G, Choi S, Kim K, Yun JM, Son JS, Jeong SM, et al. Association of Hemoglobin Concentration and Its Change With Cardiovascular and All-Cause Mortality. J Am Heart Assoc. 2018;7. doi: 10.1161/JAHA.117.007723. PubMed PMID: 29378732; PubMed Central PMCID: PMCPMC5850255.

20 Leliefeld PH, Wessels CM, Leenen LP, Koenderman L, Pillay J. The role of neutrophils in immune dysfunction during severe inflammation. Crit Care. 2016;20:73. doi: 10.1186/s13054-016-1250-4. PubMed PMID: 27005275; PubMed Central PMCID: PMCPMC4804478.