# Short communication: Elevated neutrophil/ lymphocyte ratio, creatinine, and potassium levels are the most important independent predictor of mortality in-hospital patients in Isfahan, Iran

# Abstract

Iran is the third country with the highest reported COVID-19 cases, and the first in the Middle East region regarding the cumulative number of deaths. In this study, admission's medical records concerning the total of 136 death induced by COVID-19 of four referral centers and 272 discharged adult inpatients was extracted to determine the potential risk factors and the predictive laboratory model of mortality. The multivariable model indicated that high CT scores, history of COPD, and hypoxia increase odds of COVID-19 mortality. Moreover, according multivariable laboratory model, increased neutrophil/ lymphocyte ratio, creatinine and potassium levels are significant predictors of in-hospital death.

# ****Keywords:****COVID-19, Predictive model, Mortality

**Introduction**

The outbreak of novel human coronavirus (COVID-19) has become a threat to global public health (Ghebreyesus 2020). In general, due to the rapid spread of COVID-19 through human-to-human communication, the prevalence currently continues to increase. The WHO's latest global data shows that there are 25,884,895 COVID-19 approved cases, including 859,130 deaths (Organization 2020). In this regard, the WHO Southeast Asia region recorded the highest growth in new cases in the past week, with over 500,000 new cases, in the middle east countries (Arab-Mazar et al. 2020; Organization 2020). Additionally, recent statistics determined that Iran is the third country with the highest reported COVID-19 cases after China and Italy, and the first in the Middle East region regarding the cumulative number of deaths. Furthermore, up to 13 June, the incidence of COVID-19 in Isfahan was 27.5%, with over 4% hospitalized and mortality cases (Moein et al. 2020). These outcomes highlight the need to recognize some epidemiological characteristics and the risk factors of COVID-19-related severe results (Williamson et al. 2020). Recently, studies specified that of the total confirmed deaths in Iran, the average COVID-19-related deaths have been in the elderly population, and most cases were male (Janani et al. 2020). Moreover, released epidemiological data by the CCDC revealed that several pre-existing comorbidities, including cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers, have also been related to increased fatality risk (Deng et al. 2020). Besides the clinical characteristics, fluctuations in laboratory parameters, as well as computed tomography high scores, were previously reported in COVID-19 affected patients with worse outcomes (Sabri et al. 2020). This study aimed to determine the potential risk factors as well as a COVID-19-induced mortality predictive model concentrating on the initial recorded laboratory tests apart from clinical characteristics and CT scan results based on data of multi-center hospitals.

**Materials and methods**

**Data**

We obtained medical recorded information about 136 deaths induced by COVID-19 (≥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 demographic, clinical, and laboratory findings and mortality, we also analyzed medical information from 272 discharged inpatients to compare with those who experience death in the hospital. Similar to the previous studies, the diagnosis of COVID-19 relied on positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) or chest computed tomography imaging features (Sabri et al. 2020). Investigators extracted demographic characteristics, medical history, pre-existing comorbidities, laboratory findings, and clinical outcomes on admission.

**Methods**

We applied the independent sample t-test for continuous data and a chi-square test for categorical data to compare differences between the survivor and non-survivor patients considering a P-value <0.05 as statistically significant. Continuous and categorical variables were presented as mean (±SD) and number (%), respectively. Univariable and multivariable logistic regression models were performed to explore the potential risk factors associated with mortality. To analysis the association of laboratory findings with mortality in patients affected by COVID-19, we categorized those according with previous studies.

**Results and discussion**

Baseline characteristics of survivor (n=272) and non-survivor patients (n=136) are detailed in Table 1. A total of 408 cases (210 female and 198 male) were included in this study. Compared with survived patients, those who experienced death were more likely to be male, older than 35 years, and tended to have a higher mean length of patients’ hospital stay, long duration of symptoms onset (The average duration of hospital admission until the onset of symptoms), more outstanding global CT scores, and pre-exciting comorbidities, including hypertension, diabetes, ischemic heart disease (IHD), and hyperlipoproteinemia (all p<0.05). Having shortness of breath, diarrhea and chills were the main clinical signs related to death (all p<0.05).

As presented in Table 2, in accordance with previous studies, the logistic model indicated that high CT scores, history of COPD, and hypoxia increase odds of COVID-19 mortality (Bonetti et al. 2020). Surprisingly, inverse to previous reports (Ssentongo et al. 2020), we observed that only pre-existing pulmonary disease was associated with the risk of mortality may be due to further adjustment for potential confounders.

Regarding laboratory data, we revealed the influential role of neutrophil/ lymphocyte ratio, serum AST, AST, ALP, LDH, creatinine, BUN, sodium, calcium, phosphorus, and potassium levels on the risk of mortality accompanied by other clinical characteristics, similar to the previous description (Sarin et al. 2020; Yu et al. 2020). As suggested by Chan et al., patients with high creatinine, BUN and potassium levels had higher ORs of COVID-19 mortality (Chan et al. 2020). Besides, our investigation showed 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.

The multivariate predictive model also indicated the raised neutrophil/ lymph ratio, creatinine, and elevated potassium levels as independent risk factors for the fatality of COVID-19, owing to neutrophils' role in the innate immune response and dose-dependent relationship between AKI stages and death (Yan et al. 2020). Recently, the variances between severe and non-severe COVID-19 patients' laboratory results were stated. However, this report suggests that, in addition to clinical models in predicting mortality induced by COVID-19, our novel laboratory model may have practical benefits in the ability to use for the prognosis of fatal outcomes in adults with COVID-19. And may assist clinicians recognizing patients with a poor prognosis at an early stage.

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**Ethical approval and consent to participate**

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**Availability of data and materials**

 All data and materials used in this work are publicly available.

**Consent for publication**

Not applicable.

**Conflict of interest**

Not applicable.

**Disclaimer**

The funding recourses had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, and approval of the manuscript, or in the decision to submit the manuscript for publication.

**References**

Arab-Mazar Z, Sah R, Rabaan AA, Dhama K, Rodriguez-Morales AJ. 2020. Mapping the incidence of the covid-19 hotspot in iran–implications for travellers. Travel Medicine and Infectious Disease.

Bonetti G, Manelli F, Patroni A, Bettinardi A, Borrelli G, Fiordalisi G, Marino A, Menolfi A, Saggini S, Volpi R et al. 2020. Laboratory predictors of death from coronavirus disease 2019 (covid-19) in the area of valcamonica, italy. Clinical chemistry and laboratory medicine. 58(7):1100-1105.

Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Baweja M, Campbell K, Chun N, Chung M, Deshpande P et al. 2020. Acute kidney injury in hospitalized patients with covid-19. medRxiv : the preprint server for health sciences.

Deng G, Yin M, Chen X, Zeng F. 2020. Clinical determinants for fatality of 44,672 patients with covid-19. Critical Care. 24(1):1-3.

Ghebreyesus TA. 2020. Who director-general’s opening remarks at the media briefing on covid-19-11 march 2020. World Health Organization. 11.

Janani M, Beheshti-Nia F, Ahmadi H, Khazeni A, Yadegarafar G. 2020. Epidemiological features and hotspot of covid-19 in isfahan province of iran: Results of a cohort study.

Moein S, Nickaeen N, Roointan A, Borhani N, Heidari Z, Javanmard SH, Ghaisari J, Gheisari Y. 2020. Forecasting covid-19 epidemic in isfahan using a dynamic modeling approach.

Organization WH. 2020. Coronavirus disease (‎ covid-19)‎: Weekly epidemiological, update 1.

Sabri A, Davarpanah AH, Mahdavi A, Abrishami A, Khazaei M, Heydari S, Asgari R, Nekooghadam SM, Dobranowski J, Taheri MS. 2020. Novel coronavirus disease 2019: Predicting prognosis with a computed tomography-based disease severity score and clinical laboratory data. Polish archives of internal medicine. 130(7-8):629-634.

Sarin SK, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, Hwang J, Qi X, Cua IH, Suh JI et al. 2020. 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). Hepatology international.1-11.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P. 2020. Factors associated with covid-19-related death using opensafely. Nature. 584(7821):430-436.

Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, Deng Y, Wang H, Chen R, Yu Z. 2020. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross‐sectional study. Journal of Medical Virology.

Yu C, Lei Q, Li W, Wang X, Liu W, Fan X, Li W. 2020. Clinical characteristics, associated factors, and predicting covid-19 mortality risk: A retrospective study in wuhan, china. Am J Prev Med. 59(2):168-175.

**Table 1. Baseline demographic, and clinical characteristics of survivor and non-survivor inpatients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patients characteristics** | Total (n =408) | Survived (n=272) | Dead (n=136) | P-value |
| Age (%)<3535-5555-70>70 | 39(9.6)111(27.2)137(33.6)121(29.7) | 36(13.2)104(38.2)93(34.2)39(14.3) | 3(2.2)7(5.1)44(32.4)82(60.3) | <0.001 |
| Sex, female (%) | 210(51.5) | 163(59.9) | 47(34.6) | <0.001 |
| 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, yes (%)** |  |  |  |  |
| 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](https://www.allacronyms.com/hyperlipoproteinemia/abbreviated) | 58(14.3) | 31(11.4) | 27(20.0) | 0.024 |
| **symptoms (on triage),** yes **(%)** |  |  |  |  |
| Chills | 246(62.3) | 194(74.9) | 52(38.2) | <0.001 |
| 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 |
| Sore Throat | 77(21.0) | 56(24.2) | 21(15.4) | 0.047 |
| Chest Pain | 74(20.7) | 64(29.0) | 10(7.4) | <0.001 |
| Weakness Fatigue | 188(52.1) | 150(66.7) | 38(27.9) | <0.001 |
| **Vital Signs,** yes **(%)** |  |  |  |  |
| 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 |
| **Laboratory Findings**, n (%) |  |  |  |  |
| Platelet count, 109/L | 182.55(70.16) | 187.18(70.41) | 173.53(69.02) | 0.065 |
| Neutrophil/ Lymphocyte ratio | 6.06(6.61) | 4.47(3.64) | 9.14(9.43) | <0.001 |
| Hemoglobin less than 12 g/dL  | 101(25.2%) | 49(18.5%) | 52(38.2%) | <0.001 |
| White blood cell, less than 4× 109 /L | 65(17.2) | 57(22.7) | 8(6.2) | <0.001 |
| Na, mEq/L | 135.17(4.38) | 134.35(3.33) | 136.82(5.61) | <0.001 |
| Creatinine, more than 1.4 mg/dL | 89(22.2%) | 19(7.2%) | 70(51.5%) | <0.001 |
| C-reactive protein, mg/L | 43.63(42.70) | 39.28(22.42) | 49.54(59.87) | 0.111 |
| Erythrocyte sedimentation rate, mm/h | 45.95(31.14) | 42.97(25.74) | 53.58(41.13) | 0.020 |
| potassium, mmol/L | 3.84(0.54) | 3.70(0.38) | 4.11(0.69) | <0.001 |
| Lactate dehydrogenase, more than 800 IU/L | 45(38.5%) | 5(15.2%) | 40(47.6%) | 0.001 |
| AST, IU/L | 56.15(76.96) | 43.84(27.74) | 83.27(127.67) | 0.002 |
| ALT, IU/L | 36.59(37.95) | 32.02(26.72) | 46.46(53.73) | 0.008 |
| ALT /AST ratio |  1.84(1.35) | 1.66 (0.76) | 2.23(2.08) | <0.001 |
| Calcium, mg/dL | 8.33(0.78) | 8.40(0.70) | 8.16(0.93) | 0.023 |
| Phosphorus, mg/dL | 3.22(1.37) | 2.87(0.69) | 4.08(2.11) | <0.001 |
| BUN, more than 18 mg/dL | 191(47.6%) | 81(30.6%) | 110(80.9%) | <0.001 |
| **Global** **CT Score, , mean (SD)** | 10.76(5.44) | 9.64(4.84) | 13.64(5.87) | <0.001 |

Data are presented as n (%), mean ± SD

# **Table 2. Top variables predicting**in-hospital mortality in Isfahan, Iran

|  |  |  |
| --- | --- | --- |
| **Multivariate analysis\*** | **Univariate analysis** |  |
| P-value | OR (95% CI) | P-value | OR (95% CI) | **characteristics** |
| - | - | -0.006- | Ref.-5.677(1.658,19.447)- | Age<3535-5555-70>70 |
| - | - | <0.001 | 0.353(0.230,0.542) | Sex (female) (%) |
| <0.001 | 1.124(1.070,1.180) | <0.001 | 1.130(1.081,1.182) | Hospital length of stay, days |
| 0.004 | 0.916(0.863,0.973) | 0.005 | 0.929(0.882,0.978) | Duration of symptom's onset to hospital admission, days |
|  |  |  |  | **Comorbidities**, yes (%) |
| - | - | <0.001 | 2.985(1.947,4.577) | Hypertension  |
| - |  - | 0.011 | 4.748(1.435,15.710) | Heart failure |
| <0.001 | 5.360(2.336,12.300) | <0.001 | 6.079(3.012,12.267) | Chronic obstructive pulmonary disease |
| - | - | <0.001 | 2.548(1.648,3.940) | Diabetes |
| - | - | 0.005 | 3.275(1.430,7.502) | Chronic kidney disease |
|  |  |  |  | **Vital Symptoms** |
| 0.078 | 0.981(0.961,1.002) | <0.001 | 0.961(0.943,0.979) | Diastolic blood pressure, mm Hg |
| <0.001 | 0.881(0.845,0.918) | <0.001 | 0.847(0.812,0.883) | SpO2, (%) |
| <0.001 | 114(85.1%) | 103(38.1%) | 217(53.7%) | SpO2, less than 90%  |
|  |  |  |  | **Laboratory Findings** |
| 0.044 | 0.996(0.993,1.000) | 0.066 | 0.997(0.994,1.000) | Platelet count |
| <0.001 | 1.186(1.114,1.263) | <0.001 | 1.201(1.136,1.269) | Neutrophil/ Lymphocyte ratio |
| 0.074 | 1.639(0.954,2.816) | <0.001 | 2.729(1.715,4.342) | Hemoglobin, less than 12 g/dL |
| 0.004 | 2.923(1.420,6.020) | 0.001 | 2.700(1.501,4.857) | White blood cell, less than 4× 109 /L |
| <0.001 | 1.185(1.106,1.270) | <0.001 | 1.153(1.090,1.220) | Na, mEq/L |
| <0.001 | 6.396(3.419,11.965) | 0.011 | 13.732(7.725,24.409) | Creatinine, more than 1.4 mg/dL |
| 0.012 | 2.171(1.183,3.985) | <0.001 | 3.032(1.800,5.109) | Potassium, more than 3.5 mmol/L |
| 0.013 | 4.772(1.394,16.331) | 0.011 | 5.091(1.793,14.453) | lactate dehydrogenase, more than 800 IU/L |
| 0.001 | 1.016(1.007,1.025) | 0.003 | 1.010(1.003,1.016) | ALT, U/L |
| <0.001 | 1.021(1.010,1.031) | <0.001 | 1.016(1.008,1.024) | AST, U/L |
| - | - | <0.001 | 1.583(1.226,2.045) | ALT /AST ratio |
| <0.001 | 1.008(1.005,1.012) | <0.001 | 1.008(1.005,1.011) | ALP, U/L |
| 0.042 | 0.697(0.493,0.987) | 0.012 | 0.674(0.495,0.918) | calcium, mg/dL |
| <0.001 | 1.973(1.477,2.636) | <0.001 | 2.175(1.672,2.829) | phosphorus, mg/dL |
| <0.001 | 5.494(3.060,9.865) | <0.001 | 9.611(5.823,15.861) | BUN, more than 18 mg/dL |
| <0.001 | 1.192(1.112,1.278) | <0.001 | 1.157(1.098,1.220) | **Global CT Score** |

\*Adjusted Model by Sex and Age

**Table 3. Univariable and Multivariable laboratory findings models in-hospital mortality**

|  |  |  |
| --- | --- | --- |
| **Multivariable laboratory findings model\***  | **Univariable laboratory findings model\***  |  |
| P-value | OR (95% CI) | P-value | OR (95% CI) | **characteristics** |
| 0.027 | 1.890(1.074, 3.325) | <0.001 | 1.173(1.101,1.251) | Neutrophil/ Lymphocyte ratio |
| - | - | 0.044 | 1.804(1.015,3.208) | Hemoglobin, less than 12 g/dL |
| - | - | 0.010 | 2.566(1.253,5.253) | White blood cell, less than 4×109 /L |
| 0.070 | 15.488(0.801, 299.479) | <0.001 | 6.723(3.464,13.048) | Creatinine, more than 1.4 mg/dL |
| - | - | 0.015 | 5.181(1.375,19.522) | LDH, more than 800 IU/ml |
| 0.043 | 13.400(1.084, 165.618) | 0.014 | 2.265(1.183,4.338) | Potassium, more than 3.5 mg/dL |
| - | - | <0.001 | 6.479(3.394,12.370) | BUN, more than 18 mg/dL |

\*Adjusted model for Age, Sex, COPD, and Diastolic blood pressure