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Mortality Prediction For COVID-19 Patients Based on Demographic, Typical Laboratory Results, and Clinical Data

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ABSTRACT

Background*:Timely identification of patients with a high risk of mortality from COVID-19 can make a big improvement in triage, bed placement, time saving, and even outcome .* ***Objectives****: construct and evaluate individual mortality risk estimates based on anonymised demographic, clinical, and laboratory data at admission, as well as to find out the probability of death* ***Materials and methods****: Data included 681 patients, obtained from two Muhammadiyah Hospitals in Kebumen, Central Java, Indonesia. Data was collected between January 2020 to December 2022. The medical records were examined to identify the demographic data, vital signs, clinical data and typical laboratory test. In bivariate analysis, the Chi-square test was used..* ***Results****: Patients were 48.02% males, and mortality was 18.05%. The five top predictors were Respiratory Failure(OR 7.420, 95% CI (1.169-47.103) , Myocardial Infarction (OR 1.639, 95% CI (0.881-3.050), D-dimer (OR 1.493, 95% CI (1.112-2.004), Chronic Kidney Disease (OR 1.493, 95% CI (1.112-2.004), Lymphocyte (OR 1.397, 95% CI (1.232-1.584).* ***Conclusions****: Comorbidities including chronic kidney disease, myocardial Infarction and DM 1 type; laboratory test results including D-dimer, lymphocyte, neutrophil, creatinine, leukocytes, glucose, hemoglobin; age, SPO2 and respiratory failure were associated with and can predict mortality in COVID-19 patients.*

INTRODUCTION

The pandemic caused by the coronavirus disease 2019 (COVID-19) is still having an effect on people all over the world. As of 24 2023, the World Health Organization (WHO) has received reports of more than 763 million total confirmed cases and 6.9 million deaths worldwide((COVID-19), 2023). The three provinces in Indonesia with the highest number of confirmed cases were DKI Jakarta, West Java, and Central Java.(Sri Hartutik, 2023) As of the 24th of April 2023, more than 13.3 billion doses of the COVID-19 vaccination had been administered all over the world((COVID-19), 2023). However, around 28,000 additional COVID-19 mortality have been identified in last 28 days(Dong, Du and Gardner, 2023). Despite continuing efforts to develop vaccines and antivirals that are effective against new SARS-CoV-2 strains, there are additional challenges to be resolved(Herscu *et al.*, 2022)

The evidence indicates that severe outcomes of COVID-19 are usually correlated with getting older, men gender , and clinical conditions such as hypertension, diabetes, obesity, heart illness, chronic renal disease, and liver disease (Petrilli *et al.*, 2020)(Lewnard *et al.*, 2020)(Richardson *et al.*, 2020)(F. Zhou *et al.*, 2020)(Oliveira *et al.*, 2021).

Another factors regarding mortality in COVID-19 patients were laboratory findings. A systematic review by Setiati *et al.*, (2020) demonstrates that laboratory test including lymphopenia, D-dimer and creatinine were risk factor for mortality of COVID-19 patients.

Neutrophil dysfunction and abnormal thrombosis may have an impact in the pathogenesis of severe COVID-19 and increase the risk of mortality(Narang *et al.*, 2023). Both the leucocyte count and the neutrophil count were important predictors of mortality in both non-elderly and older people patients(Ghobadi *et al.*, 2022). INR, D-Dimer and ferritin were biomarkers that accurately predicted the mortality of COVID-19(Huyut and Huyut, 2023). There was an increase in the risk of death associated with Hb values that were either extremely low or extremely high(Patiño-Aldana *et al.*, 2022). Hemoglobin, albumin, lymphocytes, and platelets can accurately predict in-hospital mortality for COVID-19 patients (Kılıç, Ak and Alışkan, 2023)

Nevertheless, despite the amount of evidence indicating a correlation between clinical data and laboratory findings and poorer results of COVID-19, there is a lack of evidence originating from Indonesia, particularly central Java. The relevant studies about mortality in COVID-19 patients in Indonesia were carried out in Padang (Usman and Katar, 2023), Jakarta (Febrianti *et al.*, 2023) and Surabaya (Awwaliyah, Hotimah and Shimabukuro, 2022).

Therefore, the The objective of this study was to investigate the role of age, gender, laboratory test results and comorbidities on the outcome of hospitalized COVID-19 patients in PKU Muhammadiyah Hospital in Kebumen, Central Java.

METHODS AND MATERIALS

Study design and research sample

This retrospective study conducted at two PKU Muhammadiyah hospitals in Kebumen, central Java.. The study included 681 who were hospitalized between January 2020 and December 2022. Slovin's formula was used to calculated the sample size based on a

population size (N) about 4099, where n = required sample size

$$n = \frac{N}{1 + Ne^2}$$

With a 95% CI and a 5% margin error. Therefore, we required a sample size of at least 364.

Inclusion and exclusion criteria

The inclusion criteria were: 1) positive results of an RT PCR/Molecular Rapid Test (TCM)SARS-CoV-2 collected from a nasal/nasopharyngeal swab; 2) individuals who had been hospitalized; 3) Age > 18 years; Excluded from the analysis were patients who died during hospitalization, pregnancy and those who didn't have baseline data.

Operational definition

The variables in this study were separated into several independent variables: age, gender, hypertension, diabetes mellitus, chronic renal disease, history of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and laboratory findings. A dependent variable, which is the outcome of COVID-19 patients who have been confirmed to be clinically critical (survival or non survival).

Research ethics approval

The study has obtained ethical approval from the PKU Muhammadiyah Gamping Hospital Ethical Research Committee 003.6/II.3.AU/F/KEPK/I/2023.

Data analysis

The results of the univariate analyze are presented as percentages and frequencies. In bivariate analysis, the Chi-square test was performed and the risks ratio was calculated. If $p < 0.05$, it is considered to be significant. SPSS version 25.0 was used to analyze the data

RESULTS AND DISCUSSION

To avoid biases, patients under 18 years was not included in this study. Treatment and therapies for COVID-19 patients were different between adult and children(Panda *et al.*, 2021)

Table 1 shows gender and comorbid Pneumonia, Hypertension, DM 2 type, asthma, anemia, Cerebral Infarction, Congestive Heart Failure had no association with mortality in COVID-19 patients. But, there was an association between comorbid Chronic Kidney Disease, diabetes mellitus type 1 and Myocardial Infarction. ($p< 0.05$). Almost all laboratory test result including Lymphocyte , Leukocytes, Neutrophil, D-dimer, Glucose , Creatinine and Hemoglobin were have association with

mortality in COVID-19 patients (p<0.05). Significantly, the four top odds ratios were Respiratory Failure (7.42), Myocardial Infarction(1.639), D-dimer (1.559),Chronic Kidney Disease (1.493), Lymphocyte (1.397). Myocardial Infarction and D-dimer were the top predictor among comorbidities and laboratory test results (figure 1).

Table 1. Bivariat analysis of Demographic, comorbidity, laboratory findings

Parameter	Survived		Non survived		OR (95%CI)	P value
	555	(81.49)	126	(18.5)		
Comorbidity						
Pneumonia	28	(4.5)	6	(0.9)	0.989 (0.843-1.161)	0.895
Hypertension	97	(15.6)	27	(4.3)	1.051 (0.951-1.162)	0.300
Chronic Kidney Disease	20	(3.2)	16	(2.5)	1.493 (1.112-2.004)	0.000*
DM 2 type	54	(8.7)	12	(1.9)	0.996 (0.883-1.122)	0.944
DM 1 type	113	(18.2)	50	(8.0)	1.231 (1.105-1.371)	0.000*
Asthma	8	(1.2)	0	(0.0)	0.813 (0.784-0.843)	0.193
Anemia	5	(0.8)	0	(0.0)	0.814 (0.785-0.844)	0.358
Respiratory Failure	1	(0.1)	8	(1.2)	7.420 (1.169-47.103)	0.000*
CHF	91	(14.7)	27	(4.3)	1.069 (0.962-1.188)	0.178
Myocardial Infarction	5	(0.8)	5	(0.8)	1.639 (0.881-3.050)	0.023*
Vital sign and Laboratory Result						
High Blood Pressure	103	(16.6)	33	(5.3)	1.095 (0.988-1.213)	0.053
SPO_2 <95%	200	(32.3)	75	(12.1)	1.202 (1.108-1.304)	0.000*
Lymphocyte <22 or >40 mg/dL	98	(15.8)	59	(9.5)	1.397 (1.232-1.584)	0,000*
Leukocytes <3.800 or >10.500 mg/dL	132	(21.3)	62	(10.0)	1.277 (1.152-1.414)	0.000*
Thrombocytes <150.000 or >450.000 mg/dL	29	(4.6)	6	(0.9)	0.983 (0.841-1.148)	0.832
Neutrophil <50 or >70	235	(38.0)	102	(16.5)	1.334 (1.236-1.439)	0.000*
D-dimer >0.5 mg/dL	23	(3.7)	20	(3.2)	1.559 (1.177-2.064)	0.000*
Glucose <70 or >120 mg/dL	201	(32.5)	73	(11.8)	1.186 (1.094-1.285)	0.000*
Creatinine <0.6 or >1.4 mg/dL	36	(5.8)	20	(3.2)	1.292 (1.059-1.575)	0.001*
Hemoglobin <12 mg/dL	148	(23.9)	51	(8.2)	1.135 (1.038-1.242)	0.002
Demographics						
Gender (male)	267	(43.2)	60	(9.7)	0.996 (0.928-1.070)	0.921
Age >65	132	(21.3)	54	(8.7)	1.204 (1.091-1.329)	0.000*

*p<0.05 considered significant; based on Chi-square test. DM2 type: Diabetes Mellitus type 2, DM 1 type : Diabetes Mellitus type 1, SPO_2: Peripheral oxygen saturation, CHF: Congestive Heart Failure, OR: Odd Ratio, CI : Confidence Interval

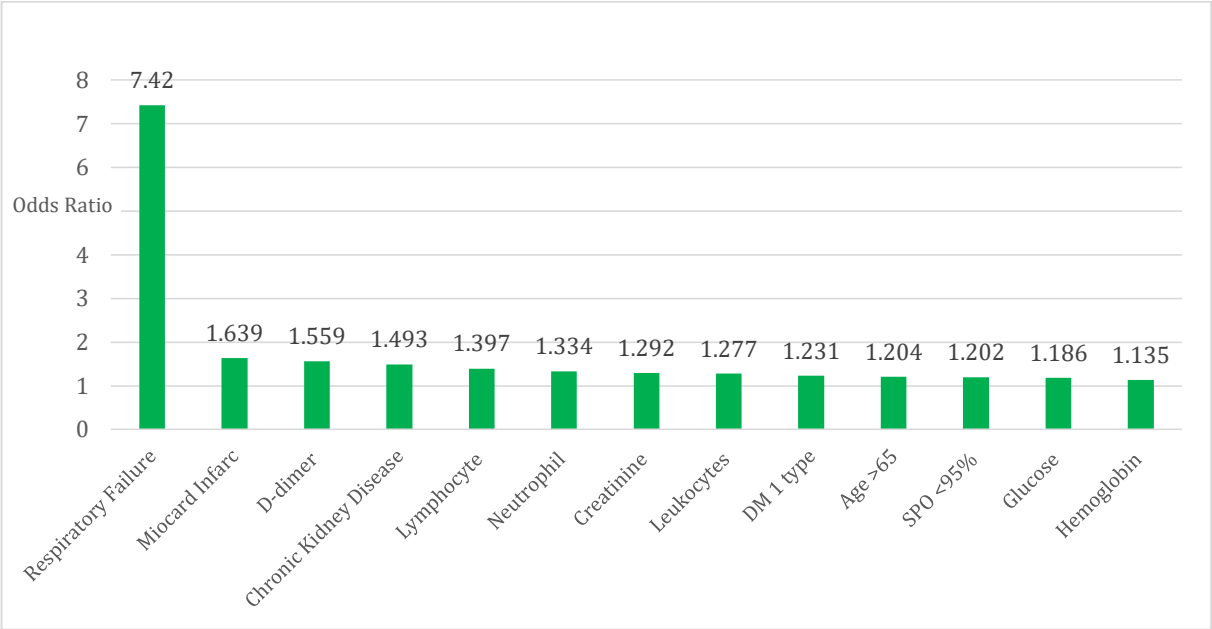

Figure 1. Odds ratio top 13 predictor based on bivariate analysis (p <0.05)

In this study, Respiratory Failure was the variable with the highest odds ratio, (OR 7.420 , CI(1.169-47.103). There is a correlation between respiratory symptoms, such as respiratory failure and low oxygen levels (SPO_2 <90%), and a higher risk of mortality. Additionally, this area of study has been investigated in United States 1461 populations; low oxygen saturation and elevated respiratory rate on admission, are risk factors for in-hospital mortality (Bahl *et al.*, 2020).

According to the meta-analysis and systematic review carried out by Mesas *et al.*, in 2020, higher creatinine is correlated with raised mortality in COVID-19 patients. Patients who were identified as having severe illness had significantly greater levels of serum creatinine and urea than patients who were identified as having mild or moderate illness. (Cheng *et al.*, 2020)Creatinine and urea levels that are higher than normal in patients with COVID-19 may be an indication of abnormal renal function, but they may also be an indication of poor glomerular filtration related to heart failure(Geri *et al.*, 2021).

In this research, the presence of comorbidities including Chronic Kidney Disease, Diabetes Mellitus type 1 and

Myocardial Infarction had only a minor impact on the prediction of the mortality risk (table 1). These findings consistent with the result from different research (Tezza *et al.*, 2021), but only partially consistent with those of international research, which shows that comorbidities also have a major impact in mortality risk prediction (Kim, Jin and Eom, 2021)(Kar *et al.*, 2021)(Usman and Katar, 2023).

Our findings shows that type 1 diabetes had an increased risk than type 2 diabetes. This could have several causes. Type 1 and type 2 diabetes different in COVID-19- associated mortality due to the various causes and Pathophysiology, variations of complications or iatrogenic harms (including hypoglycemia), therapies, frequency, and time period of glycemic, and the effects of comorbidities that were either ot taken into account or weren't taken into account appropriately(Barron *et al.*, 2020). People with diabetes have a condition of chronic low-grade inflammation, which established the foundation for subsequent increases of inflammatory cytokines in the COVID-19 population. In addition, immunological dysregulation in diabetes mellitus reduces the host's capacity to fight off the disease, which results these population in poorer infection outcomes(Feldman *et al.*, 2020)(Berbudi *et al.*, 2020).

In this research, among comorbidity, myocardial infarction has the higher Odds Ratio. (Figure 1). Elevated level of neutrophil will increased platelet activity, deficient fibrinolysis and larger reduced anticoagulant function of the endothelium(B. Zhou *et al.*, 2020)(Alnima *et al.*, 2022).

A Systematic Review and Meta-analysis including 348 studies by Chung *et al.*, (2021) indicate that individual who have Chronic Kidney Disease (CKD) but do not require kidney substitution treatment or people who have received a kidney or pancreas/kidney transplant may have a fewer possibility of contracting COVID-19 than those who are getting continuous dialysis. People who have CKD and also have COVID-19 may have a greater mortality rate than people who have CKD but do not have COVID-19.

There is evidence that patients with CKD have microcirculatory dysfunction, which may make these patients more susceptible to COVID-19. Patients who have CKD have a increased risk of serious consequences associated with lung infections in general, which may be another reason why CKD may be correlated with COVID-19-related complications in some

cases(Sörling *et al.*, 2023). It is reasonable that the activating of the renin-angiotensin system that occurs in CKD is the aspect that determines the risk to COVID-19. Patients who have CKD are therefore more likely to experience a more severe manifestation of the disease(Nangaku and Fujita, 2008)

In our study, leukocyte, neutrophil, creatinine, and d-dimer increases upon admission were significant mortality risk factors. (Table 1)

International study conducted in China suggest that higher neutrophil have been correlated with a higher risk of death in patients with COVID-19 (Xu *et al.*, 2020). Neutrophils are cells that are a part of the immune system and play an essential function in the body's defense against microbial and fungal illnesses(Veras *et al.*, 2020). However, the role that they play in the immune system's defense against the virus is not completely known. Neutrophil infiltration into the lungs has been described in human investigations with COVID-19, regardless of the reality that the relevance of neutrophils in animal research has not been detected (Tomar *et al.*, 2020).

When compared to patients who only had a mild case of COVID-19 infection, those who had severe COVID-19 infection had significantly higher leukocyte and neutrophil counts, and these counts continued to rise during the course of the infection(Yamada *et al.*, 2020)(Lin Zhang *et al.*, 2020).

In COVID-19, elevated total leucocyte counts have been correlated with an elevated risk of mortality as reported by zhu *et al* (Zhu *et al.*, 2021). The primary reason for the rise in white blood cell count was an increase in the number of neutrophils (Thungthienthong and Vattanavanit, 2023). It is possible to explain this activation process by referring to the hyper inflammatory state and the cytokine storm(Palladino, 2021).

In the case of thrombotic event assessment, the D-dimer is a recognized and commonly utilized laboratory measure(Lippi and Plebani, 2020). It has been found that between 36 and 43% of COVID-19 patients had an elevated level of the D-dimer(Simes *et al.*, 2018). A systemic review and meta analysis by Baris *et al* (2020) suggest that Elevated blood amounts of D-dimer on admission are substantially associated with the level of severity of COVID-19 and may be predictive of mortality in hospitalized patients.

Several research have revealed a relationships between greater D-dimer amounts and an increased risk of mortality in the COVID-19 patient population (Yu *et al.*, 2020)(Litao Zhang *et al.*, 2020)(Weitz *et*

al, 2017). It has been found that between 36% and 43% of COVID-19 had an increased level of the D-dimer(Simes *et al.*, 2018). In the case of thrombotic event assessment, the D-dimer is a recognized and commonly utilized laboratory measure(Lippi and Plebani, 2020). It is now commonly understood that COVID-19 individuals have a hyper coagulable state, and that increases in D-dimer levels are an adaptation to the pro thrombotic phenomenon that is occurring in these patients' cardiovascular systems (Hayıroğlu, Çınar and Tekkeşin, 2020)

Patients who were identified as having severe illness had significantly greater levels of serum creatinine and urea than patients who were identified as having mild or moderate illness. Creatinine and urea levels that are higher than normal in patients with COVID-19 may be an indication of abnormal renal function, but they may also be an indication of poor glomerular filtration related to heart failure(Geri *et al.*, 2021).

CONCLUSIONS AND SUGGESTIONS

Comorbidities including chronic kidney disease, myocardial Infarction and DM 1 type; laboratory test results including D-dimer, lymphocyte, neutrophil, creatinine, leukocytes, glucose, hemoglobin; age, SPO2 and respiratory failure were associated with and may decide predict mortality in confirmed COVID-19 patients .

In future research, we suggest constructing a specific multi-item scoring system to predict mortality in COVID-19 patients.

In future times, if there is another COVID-19 pandemic or another infectious disease pandemic, medical institutions be capable of figure out patients who are more susceptible to get sicker or even die based on data from comorbidities, laboratory test results and age that are closely linked to whether or not COVID-19 patients die in the hospital. After analyzing the probabilities of death and serious illness in COVID-19 patients who are admitted to the hospital, medical institutions can better use their limited medical resources.

Furthermore, governments should help medical facilities develop shared databases of people' physiological indicator data whereas protecting their privacy.

LIMITATION

First, There was no information about radiology results in the data used in this study, Because the treatments that patients receive can have substantial effects on their prognosis,

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which could have been useful as a predictor (Yuan *et al.*, 2020) (Feng *et al.*, 2020). Second,

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we presumed that all of these patients were receiving standard therapy.

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REFERENCES

Journal

(COVID-19), W.C.D. (2023) 'Dashboard., World Health Organization.', *[Accessed 24 April 2023]*. [Preprint].

Alnima, T. *et al.* (2022) 'COVID-19 Coagulopathy: From Pathogenesis to Treatment.', *Acta haematologica*, 145(3), pp. 282–296. Available at: https://doi.org/10.1159/000522498.

Awwaliyah, E., Hotimah and Shimabukuro, M. (2022) 'Clinical characteristics and mortality associated with COVID-19 in islamic hospital of Jemursari, Surabaya, Indonesia: A hospital-based retrospective cohort study', *Bali Medical Journal*, 11(3), pp. 1202–1206. Available at: https://doi.org/10.15562/bmj.v11i3.3541.

Bahl, A. *et al.* (2020) 'Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort.', *Internal and emergency medicine*, 15(8), pp. 1485–1499. Available at: https://doi.org/10.1007/s11739-020-02509-7.

Baris Gungor, M.D. a, Adem Atici, M.D. b, Omer Faruk Baycan, M.D. b, Gokhan Alici, M.D. c, Fatih Ozturk, M.D. d, Sevil Tugrul, M.D. e, Ramazan Asoglu, M.D. f, Erdem Cevik, M.D. g, Irfan Sahin, M.D. e, Hasan Ali Barman, M.D. (2020) 'Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis', (January).

Barron, E. *et al.* (2020) 'Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study', *The Lancet Diabetes and Endocrinology*, 8(10), pp. 813–822. Available at: https://doi.org/10.1016/S2213-8587(20)30272-2.

Berbudi, A. *et al.* (2020) 'Type 2 Diabetes and its Impact on the Immune System.', *Current diabetes reviews*, 16(5), pp. 442–449. Available at: https://doi.org/10.2174/1573399815666191024085838.

Cheng, Y. *et al.* (2020) 'Kidney disease is associated with in-hospital death of patients with COVID-19.', *Kidney international*, 97(5), pp. 829–838. Available at: https://doi.org/10.1016/j.kint.2020.03.005.

Chung, E.Y.M. *et al.* (2021) 'Incidence and Outcomes of COVID-19 in People With CKD: A Systematic Review and Meta-analysis.', *American journal of kidney diseases : the official journal of the National Kidney Foundation*, 78(6), pp. 804–815. Available at: https://doi.org/10.1053/j.ajkd.2021.07.003.

Dong, E., Du, H. and Gardner, L. (2023) 'An interactive web-based dashboard to track COVID-19 in real time.', *The Lancet. Infectious diseases*. United States, pp. 533–534. Available at: https://doi.org/10.1016/S1473-3099(20)30120-1.

Febrianti, T. *et al.* (2023) 'Determinant Factors of Mortality in Pre-elderly and Elderly Patients With COVID-19 in Jakarta, Indonesia.', *Journal of preventive medicine and public health = Yebang Uihakhoe chi*, 56(3), pp. 231–237. Available at: https://doi.org/10.3961/jpmph.23.008.

Feldman, E.L. *et al.* (2020) 'COVID-19 and Diabetes: A Collision and Collusion of Two Diseases.', *Diabetes*, 69(12), pp. 2549–2565. Available at: https://doi.org/10.2337/dbi20-0032.

Feng, Z. *et al.* (2020) 'Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics', *Nature Communications*, 11(1), pp. 1–9. Available at: https://doi.org/10.1038/s41467-020-18786-x.

Geri, G. *et al.* (2021) 'Acute kidney injury in SARS-CoV2-related pneumonia ICU patients: a retrospective multicenter study.', *Annals of intensive care*, 11(1), p. 86. Available at: https://doi.org/10.1186/s13613-021-00875-9.

Ghobadi, H. *et al.* (2022) 'Role of leukocytes and systemic inflammation indexes (NLR, PLR, MLP, dNLR, NLPR, AISI, SIR-I, and SII) on admission predicts in-hospital mortality in non-elderly and elderly COVID-19 patients', *Frontiers in Medicine*, 9.

Available at: https://doi.org/10.3389/fmed.2022.916453.

Hayıroğlu, M.İ., Çınar, T. and Tekkeşin, A.İ. (2020) 'Fibrinogen and D-dimer variances and anticoagulation recommendations in Covid-19: current literature review.', *Revista da Associacao Medica Brasileira (1992)*, 66(6), pp. 842–848. Available at: https://doi.org/10.1590/1806-9282.66.6.842.

Herscu, P. *et al.* (2022) 'Safety and Evaluation of the Immune Response of Coronavirus Nosode (BiosimCovex) in Healthy Volunteers: A Preliminary Study Extending the Homeopathic Pathogenetic Trial.', *Medicines (Basel, Switzerland)*, 10(1). Available at: https://doi.org/10.3390/medicines10010008.

Huyut, M.T. and Huyut, Z. (2023) 'Effect of ferritin, INR, and D-dimer immunological parameters levels as predictors of COVID-19 mortality: A strong prediction with the decision trees.', *Heliyon*, 9(3), p. e14015. Available at: https://doi.org/10.1016/j.heliyon.2023.e14015.

Kar, S. *et al.* (2021) 'Multivariable mortality risk prediction using machine learning for COVID-19 patients at admission (AICOVID)', *Scientific Reports*, 11(1), pp. 1–11. Available at: https://doi.org/10.1038/s41598-021-92146-7.

Kim, H.R., Jin, H.S. and Eom, Y. Bin (2021) 'Association between manba gene variants and chronic kidney disease in a korean population', *Journal of Clinical Medicine*, 10(11). Available at: https://doi.org/10.3390/jcm10112255.

Kılıç, M., Ak, R. and Alışkan, H. (2023) 'The utility of hemoglobin, albumin, lymphocyte and platelet (HALP) score in predicting mortality among COVID-19 patients: a preliminary study', *Signa Vitae*, 19(1), pp. 143–147. Available at: https://doi.org/10.22514/sv.2022.080.

Lewnard, J.A. *et al.* (2020) 'Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study.', *BMJ (Clinical research ed.)*, 369, p. m1923. Available at: https://doi.org/10.1136/bmj.m1923.

Lippi, G. and Plebani, M. (2020) 'Laboratory abnormalities in patients with COVID-2019 infection.', *Clinical chemistry and laboratory medicine*. Germany, pp.

1131–1134. Available at: https://doi.org/10.1515/cclm-2020-0198.

Mesas, A.E. *et al.* (2020) 'Predictors of in-hospital COVID-19 mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions', *PLoS ONE*, 15(11 November), pp. 1–23. Available at: https://doi.org/10.1371/journal.pone.0241742.

Nangaku, M. and Fujita, T. (2008) 'Activation of the renin-angiotensin system and chronic hypoxia of the kidney.', *Hypertension research : official journal of the Japanese Society of Hypertension*, 31(2), pp. 175–184. Available at: https://doi.org/10.1291/hypres.31.175.

Narang, J. *et al.* (2023) 'Abnormal thrombosis and neutrophil activation increase hospital-acquired sacral pressure injuries and morbidity in COVID-19 patients.', *Frontiers in immunology*, 14, p. 1031336. Available at: https://doi.org/10.3389/fimmu.2023.1031336.

Oliveira, E.A. *et al.* (2021) 'Clinical characteristics and risk factors for death among hospitalised children and adolescents with COVID-19 in Brazil: an analysis of a nationwide database.', *The Lancet. Child & adolescent health*, 5(8), pp. 559–568. Available at: https://doi.org/10.1016/S2352-4642(21)00134-6.

Palladino, M. (2021) 'Complete blood count alterations in COVID-19 patients: A narrative review.', *Biochemia medica*, 31(3), p. 30501. Available at: https://doi.org/10.11613/BM.2021.030501.

Panda, P.K. *et al.* (2021) 'COVID-19 treatment in children: A systematic review and meta-analysis.', *Journal of family medicine and primary care*, 10(9), pp. 3292–3302. Available at: https://doi.org/10.4103/jfmpc.jfmpc_2583_20.

Patiño-Aldana, A.F. *et al.* (2022) 'Interaction Effect Between Hemoglobin and Hypoxemia on COVID-19 Mortality: an observational study from Bogotá, Colombia.', *International journal of general medicine*, 15, pp. 6965–6976. Available at: https://doi.org/10.2147/IJGM.S371067.

Petrilli, C.M. *et al.* (2020) 'Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study.', *BMJ (Clinical research ed.)*, 369, p. m1966.

Available at: https://doi.org/10.1136/bmj.m1966.

Richardson, S. *et al.* (2020) 'Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area', *JAMA - Journal of the American Medical Association*, 323(20), pp. 2052–2059. Available at: https://doi.org/10.1001/jama.2020.6775.

Setiati, S. *et al.* (2020) 'Risk Factors and Laboratory Test Results Associated with Severe Illness and Mortality in COVID-19 Patients: A systematic review', *Acta Medica Indonesiana*, 52(3), pp. 227–245.

Simes, J. *et al.* (2018) 'D-Dimer Predicts Long-Term Cause-Specific Mortality, Cardiovascular Events, and Cancer in Patients With Stable Coronary Heart Disease: LIPID Study.', *Circulation*, 138(7), pp. 712–723. Available at: https://doi.org/10.1161/CIRCULATIONAHA.117.029901.

Sörling, A. *et al.* (2023) 'Association Between CKD, Obesity, Cardiometabolic Risk Factors, and Severe COVID-19 Outcomes.', *Kidney international reports*, 8(4), pp. 775–784. Available at: https://doi.org/10.1016/j.ekir.2023.01.010.

Sri Hartutik1, E.H.L. (2023) 'VACCINATION IN THE WORK AREA OF THE HEALTH DEPARTMENT OF', *GASTER JURNAL KESEHATAN*, 21(11).

Tezza, F. *et al.* (2021) 'Predicting in-hospital mortality of patients with covid-19 using machine learning techniques', *Journal of Personalized Medicine*, 11(5). Available at: https://doi.org/10.3390/jpm11050343.

Thungthienthong, M. and Vattanavanit, V. (2023) 'Platelet-to-White Blood Cell Ratio as a Predictor of Mortality in Patients with Severe COVID-19 Pneumonia: A Retrospective Cohort Study', *Infection and Drug Resistance*, 16(January), pp. 445–455. Available at: https://doi.org/10.2147/IDR.S398731.

Tomar, B. *et al.* (2020) 'Neutrophils and Neutrophil Extracellular Traps Drive Necroinflammation in COVID-19.', *Cells*, 9(6). Available at: https://doi.org/10.3390/cells9061383.

Usman, E. and Katar, Y. (2023) 'the Role of Age and Comorbidities on the Outcome of Confirmed Clinically Critical Covid-19 Patients Treated With Remdesivir At Indonesia'S National Referral Hospital', *African*

Journal of Infectious Diseases, 17(1), pp. 55–59. Available at: https://doi.org/10.21010/Ajidv17i1.5.

Veras, F.P. *et al.* (2020) 'SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology.', *The Journal of experimental medicine*, 217(12). Available at: https://doi.org/10.1084/jem.20201129.

Weitz, J.I., Fredenburgh, J.C. and Eikelboom, J.W. (2017) 'A Test in Context: D-Dimer.', *Journal of the American College of Cardiology*, 70(19), pp. 2411–2420. Available at: https://doi.org/10.1016/j.jacc.2017.09.024.

Xu, J. bo *et al.* (2020) 'Associations of procalcitonin, C-reaction protein and neutrophil-to-lymphocyte ratio with mortality in hospitalized COVID-19 patients in China', *Scientific Reports*, 10(1), pp. 1–10. Available at: https://doi.org/10.1038/s41598-020-72164-7.

Yamada, T. *et al.* (2020) 'Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis.', *Clinica chimica acta; international journal of clinical chemistry*, 509, pp. 235–243. Available at: https://doi.org/10.1016/j.cca.2020.06.008.

Yu, B. *et al.* (2020) 'Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis.', *Journal of thrombosis and thrombolysis*, 50(3), pp. 548–557. Available at: https://doi.org/10.1007/s11239-020-02171-y.

Yuan, M. *et al.* (2020) 'Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China', *PLoS ONE*, 15(3), pp. 1–10. Available at: https://doi.org/10.1371/journal.pone.0230548.

Zhang, Litao *et al.* (2020) 'D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19.', *Journal of thrombosis and haemostasis : JTH*, 18(6), pp. 1324–1329. Available at: https://doi.org/10.1111/jth.14859.

Zhang, Lin *et al.* (2020) 'Retrospective analysis of clinical features in 134 coronavirus disease 2019 cases.', *Epidemiology and infection*, 148, p. e199. Available at: https://doi.org/10.1017/S0950268820002010.

Zhou, B. *et al.* (2020) 'Duration of Viral

Shedding of Discharged Patients With Severe COVID-19.', *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 71(16), pp. 2240–2242. Available at: https://doi.org/10.1093/cid/ciaa451.

Zhou, F. *et al.* (2020) 'Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.', *Lancet (London, England)*, 395(10229), pp. 1054–1062. Available at: https://doi.org/10.1016/S0140-6736(20)30566-3.

Zhu, B. *et al.* (2021) 'Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study.', *BMC infectious diseases*, 21(1), p. 574. Available at: https://doi.org/10.1186/s12879-021-06277-3.

Information from Internet:

(COVID-19), W. C. D. (2023) 'Dashboard., World Health Organization.', https://covid19.who.int/ *[Accessed 24 April 2023]*.