



Original Article

Early laboratory hematological parameters associated with COVID-19 mortality in an Amazonian population of Peru

Parámetros hematológicos y laboratoriales tempranos asociados con la mortalidad por COVID-19 en una población amazónica del Perú

Sebastián Iglesias-Osores^{1,a}, Arturo Rafael-Heredia^{2,b}, Eric R Rojas-Tello^{3,c}, Washington A Ortiz-Uribe^{2,b}, Walter R Leveau-Bartra^{2,b}, Orison A Leveau-Bartra^{2,b}, Lizbeth M Córdova-Rojas^{4,b}, Wagner Colmenares-Mayanga^{4,b}, Virgilio E. Failoc-Rojas^{5,c}

DOI

<https://doi.org/10.35434/rcmhnaaa.2022.154.1529>

ABSTRACT

Background: COVID-19 has a significant impact on the hematopoietic system and hemostasis. Leukocytosis, lymphopenia, and thrombocytopenia are associated with increased severity and even death in COVID-19 cases.

Objective: The aim is to examine the laboratory results of COVID-19 patients from a hospital in the Peruvian Amazon and their clinical prognosis.

Material and Methods: An analytical cross-sectional study was carried out whose purpose was to identify the laboratory tests of patients with COVID-19 and mortality in a hospital in Ucayali, Peru during the period from March 13 to May 9, 2020, selecting a total of 127 with Covid-19. Mean and the standard deviation was described for age, leukocytes, neutrophils, platelets, RDW-SD; median and interquartile range for the variables lymphocyte, RN / L, fibrinogen, CRP, D-dimer, DHL, hematocrit, monocytes, eosinophils. **Results:** No differences were observed in this population regarding death and sex (OR: 1.31; 95% CI 0.92 to 1.87), however, it was observed that, for each one-year increase, the probability of death increased by 4% (PR: 1.04, 95% CI 1.03 to 1.05). The IRR (Incidence Risk Ratio) analysis for the numerical variables showed results strongly associated with hematological values such as Leukocytes (scaled by 2500 units) (IRR: 1.08, 95% CI 1.03 to 1.13), neutrophils (scaled by 2500 units) (IRR: 1.08; 95% CI 1.03 to 1.13), on the contrary, it is observed that the increase of 1000 units in lymphocytes, the probability of dying decreased by 48% (IRR: 0.52; 95% CI 0.38 to 0.71). **Conclusions:** Parameters such as leukocytes, neutrophils and D-dimer were statistically much higher in patients who died.

Keywords: Coronavirus-2019; 2019-nCoV; COVID-19; Novel Coronavirus (SARS-CoV-2/HCoV-19); SARS-CoV-2; Laboratory findings; Prognosis; Diagnosis (Source: DeCS-BIREME).

RESUMEN

Introducción: COVID-19 tiene un impacto significativo en el sistema hematopoyético y la hemostasia. La leucocitosis, la linfopenia y la trombocitopenia se asocian con una mayor gravedad e incluso la muerte en los casos de COVID-19. **Objetivo:** examinar los resultados de laboratorio de pacientes con COVID-19 de un hospital de la Amazonía peruana y su pronóstico clínico. **Material y métodos:** Se realizó un estudio transversal analítico cuyo propósito fue identificar las pruebas de laboratorio de pacientes con COVID-19 y mortalidad en un hospital de Ucayali, Perú durante el periodo del 13 de marzo al 9 de mayo del 2020, seleccionando un total de 127 con COVID-19. Se describió la media y la desviación estándar para edad, leucocitos, neutrófilos, plaquetas, RDW-SD; mediana y rango intercuartílico para las variables linfocito, RN/L, fibrinógeno, PCR, dímero D, DHL, hematocrito, monocitos, eosinófilos. **Resultados:** No se observaron diferencias en esta población en cuanto a

FILIATION

1. Facultad de Ciencias Biológicas, Universidad Nacional Pedro Ruiz Gallo, Lambayeque, Peru.
2. Facultad de Medicina Humana, Universidad Nacional de Ucayali, Ucayali, Peru.
3. Hospital II Essalud Pucallpa, Ucayali, Peru.
4. Universidad Nacional de Jaén, Cajamarca, Peru.
5. Universidad San Ignacio de Loyola, Lima, Peru.
 - a. Biólogo.
 - b. Estudiante de medicina.
 - c. Médico Cirujano.

ORCID

1. Sebastian Iglesias-Osores / [0000-0002-4984-4656](https://orcid.org/0000-0002-4984-4656)
2. Arturo Rafael-Heredia / [0000-0001-7461-0176](https://orcid.org/0000-0001-7461-0176)
3. Eric R Rojas-Tello / [0000-0001-9351-4497](https://orcid.org/0000-0001-9351-4497)
4. Washington A Ortiz-Uribe / [0000-0002-0371-6325](https://orcid.org/0000-0002-0371-6325)
5. Walter R Leveau-Bartra / [0000-0003-3485-1340](https://orcid.org/0000-0003-3485-1340)
6. Orison A Leveau-Bartra / [0000-0002-6582-900X](https://orcid.org/0000-0002-6582-900X)
7. Lizbeth M Córdova-Rojas / [0000-0002-9998-5019](https://orcid.org/0000-0002-9998-5019)
8. Charles Ruiz Torres / [0000-0001-6052-543X](https://orcid.org/0000-0001-6052-543X)
9. Virgilio E Failoc-Rojas / [0000-0003-2992-9342](https://orcid.org/0000-0003-2992-9342)

CORRESPONDENCE

Virgilio E Failoc-Rojas³, MD. Av La Fontana 505, La Molina, Lima 5051, Peru.
Teléfono: 948845837

EMAIL

virgiliofr@gmail.com

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

FINANCING

Self-financing.

PEER REVIEW

Received: 29/05/2022
Accepted: 22/10/2022

HOW TO CITE

Iglesias-Osores S, Rafael-Heredia A, Rojas-Tello ER, Ortiz-Uribe WA, Leveau-Bartra WR, Leveau-Bartra OA, Córdova-Rojas LM, Colmenares-Mayanga W, Failoc-Rojas VE. Parámetros hematológicos y laboratoriales tempranos asociados con la mortalidad por COVID-19 en una población amazónica del Perú. Rev. Cuerpo Med. HNAAA [Internet]. 6 de febrero de 2023 [citado 9 de abril de 2023];15(4). DOI: [10.35434/rcmhnaaa.2022.154.1529](https://doi.org/10.35434/rcmhnaaa.2022.154.1529)



This work is under a Licencia Creative Commons Atribución 4.0 Internacional.

Printer Version: ISSN: 2225-5109
Electronic Version: ISSN: 2227-4731
Cross Ref. DOI: 10.35434/rcmhnaaa
OJS: <https://cmhnaaa.org.pe/ojs>

muerte y sexo (OR: 1,31; IC 95% 0,92 a 1,87), sin embargo, se observó que, por cada aumento de un año, la probabilidad de muerte aumentaba un 4% (RP: 1,04). , IC del 95%: 1,03 a 1,05). El análisis de RIR (Razón de incidencia de riesgos) para las variables numéricas mostró resultados fuertemente asociados con valores hematológicos como Leucocitos (escala de 2500 unidades) (RRI: 1.08, 95% CI 1.03 a 1.13), neutrófilos (escala de 2500 unidades) (RRI: 1.08; IC 95% 1.03 a 1.13), por el contrario, se observa que al aumento de 1000 unidades en linfocitos, la probabilidad de morir disminuyó en un 48% (TIR: 0.52; IC 95% 0.38 a 071). **Conclusiones:** Parámetros tales como los leucocitos, los neutrófilos y el dímero D fueron estadísticamente mucho más altos en los pacientes que fallecieron.

Palabras Clave: Coronavirus-2019; 2019-nCoV; COVID-19; Novel Coronavirus (SARS-CoV-2/HCoV-19); SARS-CoV-2; Hallazgos de laboratorio; Pronóstico; Diagnóstico. (Fuente: DeCS-BIREME).

INTRODUCTION

The SARS-Cov-2 health emergency and the high death rate have caused enormous inequalities in health, leading to the oversaturation of hospital services during epidemic waves⁽¹⁾. Peru has produced more than 3 million cases with more than 212,000 deaths with a fatality rate of 5.98%⁽²⁾; SARS-CoV-2 infection has affected more in Amazonian areas than coastal areas of Peru, with seroprevalences of 70%(3) and 29%⁽⁴⁾, respectively.

The clinical characteristics of COVID-19 are very diverse but can be arranged into four categories: systemic, respiratory, gastrointestinal, and cardiovascular⁽⁵⁾. There are a wide number of symptoms in patients with COVID-19, only six symptoms occurred in 50% of people such as cough, sore throat, fever, myalgia or arthralgia, fatigue, and headache^(6,7). Of these, fever, myalgia or arthralgia, fatigue, and headache could be considered red flags⁽⁵⁾. Loss of smell taste is a highly specific symptom of COVID-19⁽⁸⁾. Knowing the specific symptoms of COVID-19 does not help to have a quick diagnosis, better follow-up, and prognosis of infected patients.

The main cause of death is respiratory failure due to acute respiratory distress syndrome⁽⁹⁾. The overall combined mortality rate from respiratory failure in COVID-19 patients is discharged; however, this varies significantly between countries⁽¹⁰⁾. People younger than 65 have a very small risk of death even in the epicenters of a pandemic, and deaths in people younger than 65 without any underlying conditions are rare.⁽¹¹⁾ The prognosis of patients with COVID-19 can be affected by comorbidities such as diabetes,⁽¹²⁾ hypertension, stroke, cancer, kidney disease, and high cholesterol⁽¹³⁾. Risk factors should be considered to avoid rapid progression and poor prognosis of COVID-19 disease. More attention should be paid to these patients, in case of rapid deterioration.

Laboratory medicine is of great help for the early detection of SARS-CoV-2 and allows us to discriminate between patients with severe and non-severe COVID-19⁽¹⁴⁾. Findings in COVID-19 patients will help better understand key disease traits and could be used for future disease research, control, and prevention⁽¹⁵⁾. COVID-19 has a significant impact on the hematopoietic system and hemostasis⁽¹⁶⁾. Leukocytosis, lymphopenia, and thrombocytopenia are associated with

increased severity and even death in COVID-19 cases⁽¹⁷⁾. Lymphopenia can be considered a key laboratory finding, with prognostic potential⁽¹⁶⁾. A significant decrease in peripheral CD4 + and CD8 + T lymphocytes was observed⁽¹⁸⁾. These findings are important to knowing the prognosis of patients with COVID-19.

There are still questions to be resolved about COVID-19, it is with us a short time, which is a short time to give accurate details about it, that is why it is necessary to increase research in all fields of science, to help us fight the pandemic and get back to the new normal. This study examined the laboratory results of COVID-19 patients from a hospital in the Peruvian Amazon and their clinical prognosis.

MATERIALS AND METHODS

Study design

A retrospective longitudinal study was carried out, the purpose of which was to identify the laboratory tests of patients with COVID-19 and mortality in a hospital in Ucayali (located in the Central Jungle, in eastern Peru). Ucayali has a population of approximately 500,000 inhabitants.

Population and sample

The population consisted of hospitalized patients with a confirmed diagnosis of COVID-19 in a hospital in Ucayali, Peru during the period from March 13 to May 9, 2020, selected a total of 127 people consecutively. Only patients with a history of hematological disorders were excluded (leukemias, thrombocytopenias, anemias, etc.).

Procedures

The diagnosis of COVID-19 was made based on the provisional guidelines of the World Health Organization (WHO)⁽¹⁹⁾. A confirmed case of Covid-19 was defined as a positive result in the polymerase chain reaction-transcriptase (RT-PCR) assay of nasopharyngeal swab samples and rapid immunochromatographic test. The only laboratory-confirmed cases were included in the analysis. Follow-up was carried out until discharge or death.

The laboratory tests were performed within the hospital headquarters at the time of admission, these were corroborated by a pathologist. All the laboratory tests were carried out following the clinical care needs of the patient

following the technical standard of the Ministry of Health of Peru. Laboratory evaluations consisted of leukocytes, neutrophils, platelets, red cell distribution width-standard deviation (RDW-SD), Relation neutrophils/lymphocyte (RN/L), fibrinogen, c-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), hematocrit, monocytes, eosinophils.

Statistical analysis

Statistical analysis was performed in the STATA v.16.1 software (StataCorp LP, College Station, TX, USA). Mean and the standard deviation was described for age, leukocytes, neutrophils, platelets, RDW-SD; median and interquartile range for the variables lymphocyte, RN / L, fibrinogen, CRP, D-dimer, DHL, hematocrit, monocytes, eosinophils; the variables sex, ICU, and death were reported as frequencies and percentages.

In the bivariate analysis of categorical variables, the chi-square test was used to explore the association between laboratory factors and COVID-19 mortality, after evaluating the assumption of expected frequencies. For the numerical variables, the student's t-test was used for independent samples, or the Mann Whitney U test according to the normality distribution. In the simple regression analysis, prevalence ratios(PR) and 95% confidence intervals(IC 95%) were estimated, using the Poisson distribution family, log link function, and robust variance. For the multiple models, a parsimonious model was built by performing a nesting process between the variables that were found to contribute significantly to the model, using the Likelihood-ratio test.

The area under the curve (AUC) values with their 95% confidence intervals of the hematological variables were calculated for the prediction of mortality.

Ethical aspects

The present research was approved by the ethics committee of the “Universidad Nacional de Ucayali” (IE005-FMH-UNU) and the informed consent obtained from the participants who participated was requested.

Codes were used to maintain the confidentiality of data for COVID-19 patients eligible for this study. The ethical principles of the Declaration of Helsinki were respected.

RESULTS

Information was collected from 127 people from Hospital II Essalud Pucallpa. It is a population with an average age of 59.6 years, where the female sex predominated (67.72%). Of this population, it was found that 21 (83.46 %) patients were in the ICU, also the entire population had a mortality of 75 people (59.06 %).

Regarding the laboratory tests, it is observed that, on average, the general population had high levels of biochemical and hematological values. However, when stratifying according to mortality, the parameters such as leukocytes and neutrophils were statistically much higher in patients who died (p <0.001 in both cases), also, those who died had lymphocytopenia compared to normal values in

survivors (720 vs 1360 respectively, p <0.001), something similar happened with monocytes and eosinophils.

It can be seen that in other parameters such as RN / L, and fibrinogen among others, they were higher in the population that died compared to the one that survived. Platelet, RDW-SD, and D-dimer values were statistically similar in both groups. See Table 1.

Table 1. Clinical, laboratory, and hematological characteristics of the population hospitalized with COVID-19, Ucayali.

	Total		Died		Survived		p-value
	Mean	SD	Mean	SD	Mean	DS	
Numeric variables *							
Age	59.6	14.21	66.1	10.8	50.2	13.3	<0.001
Leukocytes	13 778.12	6 973.44	15 503.9	7 438	11 289.1	5 400	<0.001
Neutrophils	12 037.04	7 183.8	14 034.5	7 413	9 099.6	5 735	<0.001
Platelets	286 119	130 685	290 202	14 156	280 307	19 890	0.677
RDW-SD	45.42	3.9	45.3	3.6	45.6	4.5	0.642
Numeric variables ±							
Lymphocyte	900	690	720	520	1360	1770	<0.001
Fibrinogen	672	490	774.3	264	373.5	182	<0.001
PCR	2.45	13.5	1.8	2.8	3.85	15.4	0.012
D-dimer	1.48	2.7	4.7	6.2	1.35	1.6	0.091
DHL	715	390	817	261	495.5	298	<0.001
Hematocrit	39.5	8.2	42.2	6.4	37.65	7.4	<0.001
Monocytes	390	300	300	300	480	390	<0.001
Eosinophils	20	80	10	45	125	290	<0.001
Categorical variablesY							
Sex	N	%	N	%	N	%	p-value
Female	86	32.28	20	48.78	31	36.05	0.104
Male	41	67.72	55	63.95	31	36.05	
RN/L Categorized							
RN/L>= 30	101	80.16	71	70.3	30	29.7	<0.001
RNL/L <30	25	19.84	4	16	21	84	
Condition							
UCI	21	83.46	5	23.8	16	76.2	<0.001
No-UCI	106	16.54	70	66.1	36	33.9	

SD: Standard deviation. IQR: Interquartile range. * Values are presented in mean and SD, p-value calculated with the t-student test. ± Median and IQR values are presented, p-value calculated with the Mann-Whitney test. Y Absolute and relative frequencies are presented, p-value calculated with the chi-square test. RNL: Relation neutrophils/lymphocyte. CRP: c-reactive protein. LDH: lactate dehydrogenase. RDW-SD: Red cell distribution width-standard deviation.

No differences were observed in this population regarding death and sex (OR: 1.31; 95% CI 0.92 to 1.87), however, it was observed that, for each one-year increase, the probability of death increased by 4% (PR: 1.04, 95% CI 1.03 to 1.05). The IRR (Incidence Risk Ratio) analysis for the numerical variables showed results strongly associated with hematological values such as Leukocytes (scaled by 2500 units) (IRR: 1.08, 95% CI 1.03 to 1.13), neutrophils (scaled by 2500 units) (IRR: 1.08; 95% CI 1.03 to 1.13), on the contrary, it is observed that the increase of 1000 units in lymphocytes, the probability of dying decreased by 48% (IRR: 0.52; 95% CI 0.38 to 0.71). It is worth mentioning that the one with the greatest strength of association was the D-dimer since for each 1 mg / L increase in D-dimer, the risk of dying increased by 25% (IRR: 1.25, 95% CI 1.10 to 1.43). The other results are shown in Table 2.

Table 2. Comparison of hematological and clinical values in the hospitalized population with COVID-19, Ucayali.

	Crude Analysis			Parsimonious model		
	RPc	CI 95%	p*	RPa	CI 95%	p±
Sex						
Male	Ref			-		
Female	1.31	0.92 - 1.87	0.133			
	IRRc	IC 95%	valor-p	IRRa	IC 95%	valor-p
Age	1.04	1.03 - 1.05	<0.001	-		
Neutrophils (Staggered 2500)	1.09	1.05 - 1.14	<0.001	1.08	0.99 - 1.17	0.089
Lymphocyte (Staggered 1000)	0.52	0.38 - 0.71	<0.001	0.22	0.08 - 0.57	0.002
D-dimer	1.25	1.10 - 1.43	0.001	1.14	1.01 - 1.29	0.039
Hematocrit	1.04	1.01 - 1.07	0.008	-		
RDW-SD	0.99	0.95 - 1.03	0.652	-		
Platelets (Staggered 1000000)	1.27	0.41 - 3.97	0.682	-		
Leukocytes (Step 2500)	1.08	1.04 - 1.13	<0.001	-		
RN/L Categorized						
RN/L < 30	Ref			-		
RN/L >=30	4.39	1.77 - 10.92	0.001	-		
Fibrinogen (Tier 100)	1.03	1.01 - 1.06	0.013	-		
PCR	0.98	0.085 - 1.01	0.085	-		
DHL	1	1.00 - 1.00	0.34	-		
Monocytes	0.99	0.99 - 1.00	0.226	-		
Eosinophils	0.99	0.99 - 1.00	0.053	-		

*P-value obtained from the generalized linear model, using the Poisson family and the robust Log and variance link function. ± p-value obtained from the generalized linear model for a parsimonious model with backward elimination, Poisson family, and robust Log link function and variance were used. 95% CI: 95% confidence interval. RP: Prevalence ratio. IRR: Incidence Risk Ratio. c: Crude. a: Adjusted. RNL: Relation neutrophils/lymphocyte. Ref: Reference. RNL: Relation neutrophils/lymphocyte. CRP: c-reactive protein. LDH: lactate dehydrogenase. RDW-SD: Red cell distribution width-standard deviation.

In the explanatory variables model, it was observed that D-dimer and lymphocytes (scaled by 1000 units) had a strong association with mortality (IRR: 1.18 and 0.22 respectively), neutrophils (scaled by 2500 units) had a marginal association (IRR: 1.08, 95% CI: 0.99 to 1.17). See Table 2.

These results were complemented with the search for the area under the curve (AUC), where it was found that fibrinogen had the best AUC (AUC: 82.5%, 95% CI 72.17 to 92.83), followed by RN / L with AUC: 79.01 %. These and other variables can be seen in table 3 and figure 1.

Table 3. Areas under the curve (AUC) of hematological variables and mortality prediction in patients with COVID-19 in Ucayali.

hematological variables	AUC (%)	CI 95%
Leukocytes	67.35	57.94 to 76.76
Neutrophils	70.78	61.61 to 79.97
Platelets	53.47	43.03 to 63.91
RDW-SD	50.51	39.73 to 61.30
Lymphocyte	75.46	66.44 to 84.49
RN / L	79.01	70.87 to 87.15
Fibrinogen	82.5	72.17 to 92.83
CRP	64.39	53.65 to 75.14
D-dimer	65.14	44.44 to 85.83
LDH	73.42	61.33 to 85.51
Hematocrit	71.36	61.99 to 80.72
Monocytes	66.17	56.56 to 75.78
Eosinophils	76.59	64.86 to 88.33

RNL: Neutrophil Lymphocyte Ratio. * AUC: Area under the curve. RNL: Relation neutrophils/lymphocyte. CRP: c-reactive protein. LDH: lactate dehydrogenase. RDW-SD: Red cell distribution width-standard deviation.

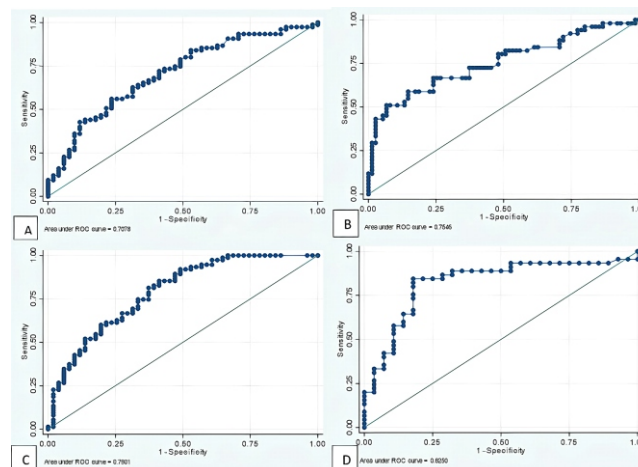


Figure 1
ROC curves of main hematological tests for predicting mortality in patients with COVID-19. A: Neutrophil. B: Lymphocytes. C: Neutrophil / lymphocyte ratio. D: Fibrinogen.

DISCUSSION

We look at the clinical symptoms of 127 COVID-19 patients, here, we mainly analyze and summarize the laboratory tests of COVID-19 patients, especially the biochemical and hematological parameters. In our study, the laboratory tests of the general population studied that was infected by SARS-CoV-2 had high levels of biochemical and hematological values, these findings have also been found in other systematic reviews of patients with COVID-19 and SARS^(17,20,21). These findings can be explained why the blood presents a state of hypercoagulation, which becomes more acute in critically ill patients.⁽²²⁾ Our results show important biochemical and hematological changes in patients with COVID-19.

It was found that the parameters such as leukocytes and neutrophils were statistically much higher in patients who died (p <0.001 in both cases), these risk factors related to immunity can predict the mortality of patients with COVID-19⁽²³⁾. Patients who died presented lymphocytopenia compared to normal values in survivors (720 vs 1360 respectively, p <0.001), something similar happened with monocytes and eosinophils. Lymphocytopenia is an independent risk factor for hospital mortality for COVID-19 patients, especially men⁽²⁴⁾. Risk factors related to the mortality of patients with COVID-19 were found such as increased leukocytes and neutrophils along with lymphocytopenia, the evaluation of these parameters can help to identify people at high risk with COVID-19.

It can be seen that in other parameters such as the neutrophil-lymphocyte ratio (RN / L), and fibrinogen among others, they were higher in the population that died compared to the one that survived. Elevated fibrinogen level has been considered an epiphenomenon of pulmonary edema rather than activation of coagulation in affected patients⁽²⁵⁾. Platelet values, red cell distribution width with standard deviation (RDW-SD), and D-dimer were statistically similar in both groups. There are findings in which an increase in D-

dimer levels is found and this increases according to the severity in patients with COVID-19^(25,26). RDW-SD was a predictor in the group of severe patients in which its values were significantly higher than those of the group of patients with moderate COVID-19⁽²⁷⁾.

In this study, it was observed that, for each one-year increase, the probability of dying increased by 4%, these results have been reported in other studies⁽²⁸⁾. It is worth mentioning that the one who presented the greatest strength of association was D-dimer, since for every 1 mg / L increase in D-dimer, the risk of dying increased by 25%, these high values are associated with those with severe disease⁽²⁹⁾.

Laboratory parameters in patients with COVID-19 such as leukocytes, neutrophils and D-dimer were statistically higher and adequate association in patients who died.

REFERENCIAS BIBLIOGRÁFICAS

- Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med*. 2020;382(21):2049-55. doi: 10.1056/NEJMs2005114
- Peru COVID - Coronavirus Statistics - Worldometer [Internet]. [cited 2022 Apr 25]. Available from: <https://www.worldometers.info/coronavirus/country/peru>
- Álvarez-Antonio C, Meza-Sánchez G, Calampa C, Casanova W, Carey C, Alava F, et al. Seroprevalence of anti-SARS-CoV-2 antibodies in Iquitos, Peru in July and August, 2020: a population-based study. *Lancet Glob Heal*. 2021;9(7):e925-31. doi: [https://doi.org/10.1016/S2214-109X\(21\)00173-X](https://doi.org/10.1016/S2214-109X(21)00173-X)
- Díaz-Vélez C, Failoc-Rojas VE, Valladares-Garrido MJ, Colchado J, Carrera-Acosta L, Becerra M, et al. SARS-CoV-2 seroprevalence study in Lambayeque, Peru. June-July 2020. *PeerJ*. 2021;9:e11210. doi: 10.7717/peerj.11210
- Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev*. 2020;2020(7). doi: 10.1002/14651858.CD013665.
- Halboub E, Al-Maweri SA, Alanazi RH, Qaid NM, Abdulrab S. Orofacial manifestations of COVID-19: a brief review of the published literature. *Braz Oral Res*. 2020;34. doi: 10.1590/1807-3107bor-2020.vol34.0124
- Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. *Am J Gastroenterol*. 2020;115(5):766-73. doi: 10.14309/ajg.0000000000000620.
- Makaronidis J, Mok J, Balogun N, Magee CG, Omar RZ, Carnemolla A, et al. Seroprevalence of SARS-CoV-2 antibodies in people with an acute loss in their sense of smell and/or taste in a community-based population in London, UK: An observational cohort study. *PLoS Med*. 2020;17(10):e1003358. doi: 10.1371/journal.pmed.1003358
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China [published correction appears in *Intensive Care Med*. 2020 Apr 6]. *Intensive Care Med*. 2020;46(5):846-848. doi: 10.1007/s00134-020-05991-x.
- Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environ Res*. 2020;188:109890. doi: 10.1016/j.envres.2020.109890.
- Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant H a., et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. *Expert Rev Respir Med*. 2020;14(11):1149-63. doi: 10.1080/17476348.2020.1804365.
- Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;36(7). doi: 10.1002/dmrr.3319.
- Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. *Diabetes Metab Syndr Clin Res Rev*. 2020;14(5):1133-42. doi: 10.1016/j.dsx.2020.07.005.
- Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. *Clin Chim Acta*. 2020;510:475-482. doi:10.1016/j.cca.2020.08.019.
- Xie Y, Wang Z, Liao H, Marley G, Wu D, Tang W. Epidemiologic, Clinical, and Laboratory Findings of the COVID-19 in the current pandemic. *Res Sq [Preprint]*. 2020 May 28:rs.3.rs-28367. doi: 10.21203/rs.3.rs-28367/v1. Update in: *BMC Infect Dis*. 2020;20(1):640. doi: 10.21203/rs.3.rs-28367/v1.
- Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-47. doi: 10.1002/ajh.25829.
- Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-8. doi: 10.1515/cclm-2020-0369.
- Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. *Ann Hematol*. 2020;99(7):1421-1428. doi:10.1007/s00277-020-04103-5.
- Organization WH. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization; 2020 [cited 2022 Apr 25]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf?sequence=1&isAllowed=y>.
- Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. Afrin F, editor. *PLoS One*. 2020;15(8 August):e0238160. doi: 10.1371/journal.pone.0238160.
- Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol*. 2007;170(4):1136-47. doi: 10.2353/ajpath.2007.061088.
- Yuan X, Huang W, Ye B, Chen C, Huang R, Wu F, et al. Changes of hematological and immunological parameters in COVID-19 patients. *Int J Hematol [Internet]*. 2020;112(4):553-9. doi: 10.1007/s12185-020-02930-w.
- Zhao Y, Nie HX, Hu K, Wu XJ, Zhang YT, Wang MM, et al. Abnormal immunity of non-survivors with COVID-19: Predictors for mortality. *Infect Dis Poverty*. 2020;9(1):108. doi: 10.1186/s40249-020-00723-1
- Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect*. 2020;81(1):e6-12. doi: 10.1016/j.jinf.2020.04.002.
- Hayiroglu MI, Cinar T, Tekkesin AI. Fibrinogen and D-dimer variances and anticoagulation recommendations in Covid-19: Current literature review. *Rev Assoc Med Bras*. 2020;66(6):842-8. doi: 10.1590/1806-9282.66.6.842.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-7. doi: 10.1111/jth.14768.
- Wang C, Deng R, Gou L, Fu Z, Zhang X, Shao F, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. *Ann Transl Med*. 2020;8(9):593-593. doi: 10.21037/atm-20-3391.
- Mallapaty S. The coronavirus is most deadly if you are older and male-new data reveal the risks. *Nature*. 2020;16-7. doi: 10.1038/d41586-020-02483-2.
- Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. *Thromb Haemost*. 2020;120(5):876-7. doi: 10.1055/s-0040-1709650. .