Archivos Venezolanos de Farmacología y Terapéutica
ISSN: 0798-0264
revista.avft@gmail.com
Sociedad Venezolana de Farmacología Clínica y Terapéutica
Venezuela

Aberration in monocyte count as anticipator of adverse terminal events in COVID-19: case-control study

Shaheed Mohammed, Haider; Hussein, Methaq A. M.
Aberration in monocyte count as anticipator of adverse terminal events in COVID-19: case-control study
Archivos Venezolanos de Farmacología y Terapéutica, vol. 40, núm. 2, 2021
Sociedad Venezolana de Farmacología Clínica y Terapéutica, Venezuela
Disponible en: https://www.redalyc.org/articulo.oa?id=55969713011
DOI: https://doi.org/10.5281/zenodo.4715950

Artículos

Aberration in monocyte count as anticipator of adverse terminal events in COVID-19: case-control study

Aberración en el recuento de monocitos como anticipador de eventos terminales adversos en COVID-19:

Haider Shaheed Mohammed
Lecturer, Department of internal medicine, college of medicine, University of Thi-qar, Iraq, Irak
Hayder.sh@utq.edu.iq

Methaq A. M. Hussein
College of Medicine, University of Thi-Qar, Iraq, Irak
methaq-abd@utq.edu.iq

DOI: https://doi.org/10.5281/zenodo.4715950
Redalyc: https://www.redalyc.org/articulo.oa?id=55969713011

Recepción: Diciembre , 28, 2020
Aprobación: Enero , 15, 2021
Publicación: Marzo , 10, 2021

Abstract:

Background: Aberrancy in monocytes account is customarily recognized in patients with COVID-19 strikingly in gravely affected patients, the exacting interrelation with detrimental consequences still in the gap. The study was carried out to found any significant monocyte level changes in COVID-19 and its relation to diagnostic usefulness and expectation of adverse outcomes. A sample of 100 patients was recruited into the analysis; all with diagnosis compatible with pneumonia underwent care inwards of Al-Hussein Hospital for isolation; 50 participators with COVID-19 as cases and 50 participators with influenza A elected control. The diagnosis was suggested by clinical and radiological attributes and verified by polymerase chain reaction. Monocytes total and laboratory analysis of inflammatory indices and organ vitality were achieved for all participants. The mean age was 64.4, including 56 males and 44 females. 66% of cases were monocytopenic, 34% were non-monocytopenic. 12% of control were monocytopenic while 88% were non-monocytopenic with significant difference (P value=0.001). Forty-five participants were critical while 55 were non-critical, 37 COVID-19, and eight controls were critical and admitted to the ICU. Forty-one participants died, 35 from the COVID-19 category and six from controls. 30 of COVID-19 who were critical in ICU were monocytopenic (all died), three were non-monocytic (only one died) and 4 had monocytosis (all died), 6 of control who were critical in ICU were monocytopenic (all died), 2 had normal count (all survived) and no one had monocytopenia (Odd ratio=1.200). Deviation in monocyte count from the norm is a valuable discriminator for the diagnosis of COVID-19 and a suitable anticipator across all spectrums for its adverse consequences.

Keywords: COVID-19, Monocytes, Influenza A, ICU.

Resumen:

Antecedentes: la aberrancia en los monocitos se reconoce habitualmente en pacientes con COVID-19 de manera sorprendente en pacientes gravemente afectados, la interrelación exigente con consecuencias perjudiciales aún está en la brecha. El estudio se llevó a cabo para encontrar cambios significativos en el nivel de monocitos en COVID-19 y su relación con la utilidad diagnóstica y la expectativa de resultados adversos. Se reclutó para el análisis una muestra de 100 pacientes, todos con diagnóstico compatible de neumonía atendidos en las salas del Hospital Al-Hussein para aislamiento; 50 participantes con COVID-19 como casos y 50 participantes con influenza A elegidos como control. El diagnóstico fue sugerido por atributos clínicos y radiológicos y verificado por reacción en cadena de la polimerasa. Se logró el análisis total de monocitos y de laboratorio de los índices inflamatorios junto con la vitalidad del órgano para la suma total de todos los participantes. La edad media fue de 64,4 años, incluidos 56 varones y 44 mujeres. El 66% de los casos fueron monocitopénicos, el 34% no monocitopénicos. El 12% de los controles eran monocitopénicos mientras que el 88% eran no monocitopénicos con una diferencia significativa (valor de p = 0,001). 45 participantes fueron críticos mientras que 55 no lo fueron, 37 COVID-19 y 8 controles fueron críticos y fueron admitidos en UCI. 41 de los participantes murieron, 35 de la categoría COVID-19 y 6 de los controles. 30 de los COVID-19 que fueron críticos en la UCI fueron monocitopénicos (todos murieron), 3 no monocitopénicos (solo 1 murió) y 4 tuvieron monocitosis (todos murieron), 6 de los controles que fueron críticos en la UCI fueron monocitopénicos (todos murieron), 2 tenían un recuento normal (todos sobrevivieron) y nadie tenía monocitopenia (Odd ratio = 1.200). La desviación en el recuento de monocitos de la norma es un

discriminador valioso para el diagnóstico de COVID-19 y un anticipador adecuado en todos los espectros por sus consecuencias adversas.

Palabras clave: COVID-19, Monocitos, Influenza A, UCI.

Introduction:

COVID-19 pandemic is the biggest terrible fulmination to humankind in the new century that retrogresses life's standardness. COVID-19 caused by SARS-CoV-2 spread intercontinentally impulse world health organization (WHO) to certify it as pandemic [1] . COVID-19 sustains a significant health, social, and economic strain with measurable morbidness and lethality [2,3] . It is fundamentally acute unspecified pulmonary sickness but eventually incorporates a multitude of systems, its manifestations are intermingled with a diversity of respiratory disorders of varied causations endorsing a secure analysis for discrimination, particularly when the cases are overwhelmed [4] .

Despite the fact that the verificatory diagnostic investigation for COVID-19 is polymerase chain reaction, its employment is impeded by irrefutable shortcomings encompassing protracted overturn time with elevated false negative yields uniquely in poverty-stricken nations [5] . Instantaneous authentication of the diagnosis of COVID-19 with sooner discerning those who are in neediness for vigorous interventions is pivotal in COVID-19, so mandating conceptualization a parameter that is effortlessly approachable and promptly obtainable [6] . Monocytes and other innate immune cells execute an orchestrated duty in the pathogenesis of a multitude of viral infections, infiltrating regionally and spread out distantly with antagonistic viral defensive influences [7] . Monocytes are thought-about the front-line defender among other immune cells, and they are the cardinal originator of the inflammatory milieu in COVID-19; they serve bi-directionally as inflammatory instigators and tissue repairers thus contributing to the diversity of end results encompassing resolution [8] . There are several affirmations for monocyte dysregulation in predisposing to hyperinflammatory upset and thence instigating to build up the seriousness and fatality of COVID-19 [9] . Monocytes, among other defensive cells, carry out an influential participant in the advancement of varied complexities and grim residual jeopardy in COVID-19 substantially thrombotic perturbations, organ dysfunctions, and hyperinflammatory distress predisposing to the upraised incidence of deadly consequences of this potentially lethal infection [10] . Various hematological parameters submit to aberrancy in COVID-19 incorporating aberration in monocytes count and its interconnection with the aggressiveness of outcome that deserves methodical exploration [11] . Plenty of studies theorize utilization of hematological indicators that seems to be linked to heightened seriousness and lethality of COVID-19 [12] .

We hypothesized that the remarkable alterations of monocytes inspected recurrently in COVID-19 are noteworthy and plausibly have impactful diagnostic and prognostic implications. We intend to devise an inventive, easily memorized, affordable, reputable, and simply practicable test with diagnostic and expectation magnitude for unfavorable implications of COVID-19.

Materials and methods

Type of study: A case-control study had been preceded from the beginning of first week of February 2020 to the end of the last week of April 2020.

Study population: The participators constituted patients looking for medical facilities in isolation departments of AL-Hussein teaching hospital in Al-Nasiriya city, the diagnosis was assured by any feasible details in the case sheets of patients, whole numbers of patients accounted for in the analysis was 100 patients,

with 50 cases affirmed to be COVID-19 pneumonia and 50 candidate verified to be influenza A pneumonia elected as control.

Inclusion criteria: whatever patients who were exceedingly suspicious to harbor pneumonia from a radiological and clinical point of view and proved by positive polymerase chain reaction for COVID-19 or influenza A.

Exclusion criteria: 1-Whatever patient had receiving medications currently or remotely known to affect monocytes level; 2-Whatever patients are known to have blood dyscrasia or malignancy; 3-Whatever patient with a known background of autoimmune disorders.

Sampling size: Sampling size was acceptable, restrained by the approachability of patients and time scale of analysis, but sampling task for control, systematized strategy for random sampling was accomplished to construct the control.

Ethical concern: An ethical endorsement was derived from Al-Hussein teaching hospital authority; an enlightened acceptance was adopted from all participators.

Study tools:The questionnaire: Unique design of the questionnaire was fabricated for harvesting the information and was inspected and gauged by three official persons (of community medicine and physician) for checking the validness and prospering of the questionnaire. The questionnaire delineated by 2 subsections:

First subsection: Inclusive of questioning relevant to identity (age, gender, marital status, residency, and occupation).

Second subsection: Inclusive of questioning relevant to manifestations of present complaints, history of preexisting co-morbidities, duration of manifestations, existing and precedent medications consumption.

Third subdivision: Assigning complexities evolved for the time of accessing care in isolation division of the hospital that direct referral of patients to intensive care department inclusive of recovery and death.

Diagnostic procedures: Every patient was appraised by focus clinical examination inclusive of vital signs, oxygen saturation was determined for all participators to assign for grading of severity, the patients were rendered hypoxic when oxygen saturation is lower than 93% [13]. The radiological valuation was carried out for all participators by CT-scan of the chest that skillful radiologist interpreted to prescribe abnormalcy. Polymerase chain reaction handled on nasopharyngeal swab sample was practiced upon entrance to the medical ward. All candidates submitted to laboratory assessment by complete blood count to count on monocytes; the average count of monocytes in the laboratory of our hospital is 200-800 cell/microliter.The participators were partitioned into monocytopenic when monocytes lower than 200 cells/microliter and non-monocytopenic, non-monocytopenic is further partitioned into normomonocytic in those possessing average monocytes to count and those with monocytosis when monocytes count greater than 800 cells/microliter. Laboratory indicant of inflammatory reactants was explored in sort of ferritin, C-reactive protein titer (CRP), ESR, lactate dehydrogenase (LDH), d-dimer, creatinine phosphokinase (CPK), and interleukin-6. An estimation of organ vitality was implemented by blood urea, serum creatinine, liver function, coagulation profile, and arterial blood gas analysis. Cardiac function was gauged for all participants by troponin and electrocardiogram. The participators were categorized into critical and non-critical categories in agreement with the grading of severity. Non-critical-categories are of moderate and severe COVID-19 pneumonia stayed in the common isolation ward, cases of critical status transposed to ICU. Critical severe type, meet any of the following: (a) respiratory failure occurred and mechanical ventilation was required; (b) shock happened; (c) patients complicated with organ failure required ICU admission [14]. Any patient match WHO criteria for discharge was appointed to be recovered [15].

Statistical analysis: statistical package of social sciences (SPSS) version 25 was employed for data assay, descriptive statistics, frequencies, percentages, associations, the test of significance (Chi-square, Fischer exact test, T-test, and ANOVA test) was employed for interpretation for categorical variables, means, and standard

deviation were employed to present data of continuous variables. A p-value of less than (0.05) was specified as statistically significant.

Results

A sum of 100 participators engaged within the analysis, dispersed evenly in two categories (COVID-19) as cases and (influenza A) as control, mean age of the overall sample was 64.4, mean age of case group was 63.54 simultaneously for control was 65.26 with no significant statistical association (P-value: 0.599). Come on, bio-demographic attributes mostly they displayed no significant statistical association where P values greater than 0.05. Whilst gender was statistically significant amongst two categories (P-value: 0.001) as illustrated in Table 1. Pertaining to co-morbidities, hypertension and pulmonary disease display significant statistical difference among cases and control where P values: 0.0001 and 0.002 respectively, whilst no significant statistical difference between cases and control in respect to diabetes mellitus and heart disease where P values: 0.834 and 0.545 respectively as shown in table 2. 66%, 26% and 8% of COVID -19 category had monocytopenia, normal count, and monocytosis respectively whilst 12%,54%, and 34% of influenza A category had monocytopenia, normal count, and monocytosis respectively with a significant statistical difference where P value = 0.001 as displayed in Figure 1.

74% of COVID-19 were critical whilst 16% of control were critical, 26% of COVID-19 group were non-critical whilst 84% of the control group were non-critical with a significant difference where (p value=0.001), as illustrated in figure 2. There is the significant statistical difference amongst cases and controls in all outcomes (ICU admission, death, and recovery) where (P-value=0.001 for all) as displayed in table 3.

37 participators with COVID-19 were critically ill, 35 died and 2 recovered, 30 dead were monocytopenic, 1 was normomonocytic whilst 4 have had monocytosis, 2 who were recovered were normomonocytic with significant statistical significance where P value=0.0001 for both death and recovery in critical patients in relation to monocytes count as exhibited in table 5.

Of 33 COVID-19 participators, 30 people with COVID-19 who were monocytopenic died, 4 with monocytosis died whilst just 1 normomonocytic died, 12 with normomonocytic recovered, whilst no participator with monocytosis recovered, with significant statistical significance between recovery and death where (P value =0.001) for both as displayed in table 6.

TABLE 1
Socio-Demography of analyzed population.

		PCR		Total	Chi-square
		COVID -19	Influenza A		P value
Gender	Male	36	20	56	10.390
		64.3%	35.7%	100%	0.001
	Female	14	30	44	
		31.8%	68.2%	100%	
Occupation Total	Governmental	18	12	30	1.731
		60.0%	40.0%	100%	0.630
	Self-employer	5	6	11	
		45.5%	54.5%	100%	
	Housewife	8	9	17	
		47.1%	52.9%	100%	
	Retired	19	23	42	
		45.2%	54.8%	100%	
Marital status	Single	1	0	1	1.010[a]
		100%	0.0%	100%	0.315
	Married	49	50	99	
		49.5%	50.5%	100%	
Residence	Nasiriya.	15	14	29	0.471[a]
		51.7%	48.3%	100%	0.631
	Suq - Alsyookh	14	13	27	
		51.9%	48.1%	100%	
	Shatra	7	9	16	
		43.8%	56.3%	100%	
	Chibayesh	8	9	17	
		47.1%	52.9%	100%	
	Rifaee	6	5	11	
		54.5%	45.5%	100%	
Total		50	50	100	
		50.0%	50.0%	100%	

TABLE 2
Distribution according to comorbid diseases

		PCR		Total	Chi-square
		COVID	Influenza A		P value
hypertension	**No**	8	29	37	18.919[a] .0001
		21.6%	78.4%	100%	
	Yes	42	21	63	
		66.7%	33.3%	100%	
Heart disease	**No**	30	27	57	.367[a] .545
		52.6%	47.4%	100%	
	Yes	20	23	43	
		46.5%	53.5%	100%	
Diabetes mellitus	**No**	17	18	35	.044[a] .834
		48.6%	51.4%	100%	
	Yes	33	32	65	
		50.8%	49.2%	100%	
Pulmonary diseases	**No**	42	17	59	25.837[a] 0.002
		71.2%	28.8%	100%	
	Yes	8	33	41	
		19.5%	80.5%	100%	
Total		50	50	100	
		50.0%	50.0%	100%	

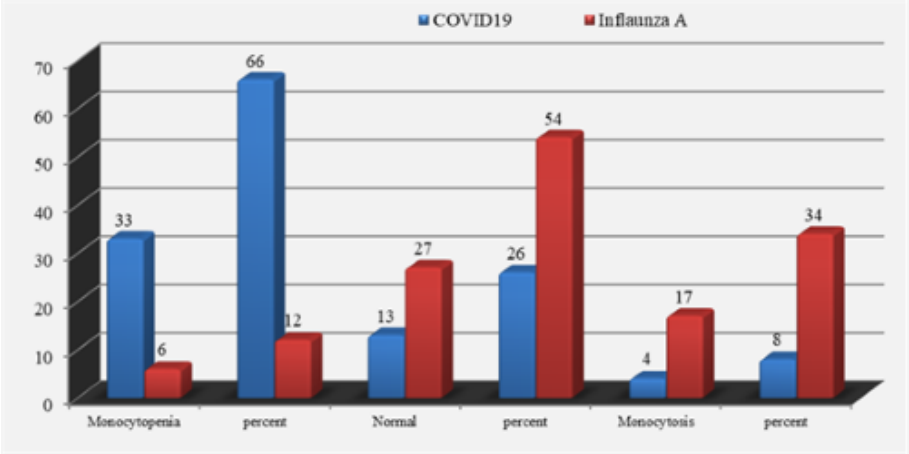

FIGURE 1
Distribution of cases and control according to monocyte count. Chi-square=31.640, P value=0.001.

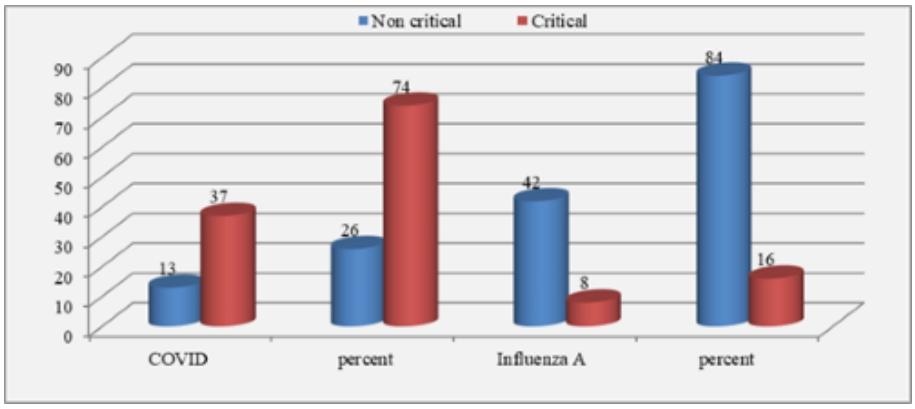

FIGURE 2:
Distribution of cases and control according to severity. Chi-square=33.812, Pvalue: 0.001.

TABLE 3
Difference in distribution of main point outcomes of COVID-19 and influenza

		Total			
		COVID-19	Influenza A	Total	X^2, P value
Admission	**Isolation ward**	13	42	55	33.980[a], 0.001
		23.6%	76.4%	100%	
	ICU	37	8	45	
		82.2%	17.8%	100%	
Recovery	**No**	35	6	41	34.766[a], 0.001
		85.4%	14.6%	100%	
	Yes	15	44	59	
		25.4%	74.6%	100%	
Death	**No**	15	44	59	34.766[a], 0.001
		25.4%	74.6%	100%	
	Yes	35	6	41	
		85.4%	14.6%	100%	
Total		50	50	100	
		50.0%	50.0%	100%	

TABLE 4
Difference in distribution of monocytes of COVID-19 and influenza A according to their main points of outcomes

Outcome		Monocytopenia				Normal monocyte				Monocytosis			
		COVID- 19	Influenza A	Total	X^2, P, odd's ratio	COVID- 19	Influenza A	Total	X^2, P, odd's ratio	COVID- 19	Influenza A	Total	X^2P, odd's ratio
Severity	Non critical	3	0	3	591[d] 0.442	10	25	35	1.970[e] 0.160	0	17	17	21.000 0.001
		100.%	0.0%	100%		28.6%	71.4%	100%		0.0%	100%	100%	
	Critical	30	6	36	1.200	3	2	5	.267	4	0	4	0.067
		83.3%	16.7%	100%		60.0%	40.0%	100%		100%	0.0%	100%	
Admission	Isolation word	3	0	3	591[d] .442	10	25	35	1.970[e] .160	0	17	17	21.000[f] 0.001 a
		100%	0.0%	100%		28.6%	71.4%	100%		0.0%	100%	100%	
	ICU	30	6	36	1.200	3	2	5	.267	4	0	4	
		83.3%	16.7%	100%		60.0%	40.0%	100%		100%	0.0%	100%	
Recovery	Absent	30	6	36	591[d] .442	1	0	1	2.130[e] .144	4	0	4	21.000 0.001a
		83.3%	16.7%	100%		100%	0.0%	100%		100%	0.0%	100%	
	Present	3	0	3	833	12	27	39	3.250	0	17	17	
		100%	0.0%	100%		30.8%	69.2%	100%		0.0%	100%	100%	
Death	Absent	3	0	3	591[d] .442	12	27	39	2.130[e] .591[d]	0	17	17	21.000[f] 0.001
		100%	0.0%	100%		30.8%	69.2%	100%		0.0%	100%	100%	
	Present	30	6	36	1.200	1	0	1	.308	4	0	4	.058
		83.3%	16.7%	100%		100%	0.0%	100%		100%	0.0%	100%	
Total		33	6	39		13	27	40		4	17	21	
		84.6%	15.4%	100%		32.5%	67.5%	100%		19.0%	81.0%	100%	

TABLE 5
Comparison of monocyte between critical recovered patients and critical died COVID-19 patients

Critical- Severity			Recovery		Total	FE, p value
			No	Yes		
Recovery	Monocytopenia	Count	30	0	30	23.962 0.0001
		%	100.0%	0.0%	100.0%	
	Normal	Count	1	2	3	
		%	33.3%	66.7%	100.0%	
	Monocytosis	Count	4	0	4	
		%	100.0%	0.0%	100.0%	
	Total	Count	35	2	37	
		%	94.6%	5.4%	100.0%	
			No	**Yes**		
Death	Monocytopenia	Count	0	30	30	23.962 0.0001
		%	0.0%	100.0%	100.0%	
	Normal	Count	2	1	3	
		%	66.7%	33.3%	100.0%	
	Monocytosis	Count	0	4	4	
		%	0.0%	100.0%	100.0%	
Total		Count	2	35	37	
		%	5.4%	94.6%	100.0%	

TABLE 6
Comparison of monocyte between recovered patients and died among COVID-19

			Death	Recovery	Total	Chi-square, p value
Monocyte	Monocytopenia	Count	30	3	33	32.617 0.001
		%	90.9%	9.1%	100.0%	
	Normal	Count	1	12	13	
		%	7.7%	92.3%	100.0%	
	Monocytosis	Count	4	0	4	
		%	100.0%	0.0%	100.0%	
Total		Count	35	15	50	
		%	70.0%	30.0%	100.0%	

Discussion

In our analysis, we are approaching substantive perceptions: two-thirds of COVID-19 presented with reduced monocytes count, and the bulk of influenza A participators have had more elevated monocytes than counterpart COVID-19 with significant statistical difference implying that monocyte is a vigorous diagnostic indicant that is useful for discrimination, we are nearly in line with Chen et al. [16]. Monocytes were much lower in passed away COVID-19 participators than those who remained alive with significant difference between fatality and recovery patients according to monocytes (P value: 0.001), and monocytes were anticipant for death in COVID-19 by 20 folds (Odd ratio=1.200). Our study determinations are concordant with Pakos et al. [17] that perceive dead persons had lower monocytes and had an inverse relation with fatality. Our study 30 monocytopenic who were critically ill with COVID-19 died (P value=0.0001), concluding that monocytopenia is intimately interrelated with lethality in critically COVID-19. A study done by Blomme et al. [18] extrapolating that passed away patients with COVID-19 had lower monocytes than alive patients. Our analysis's Pivotal determination is that monocytes are lower in critical than non-critical grouping and it anticipating severity by 17 folds (Odd ratio=1.200) and anticipates admittance to ICU (odd ratio=1.200), a recent meta-analysis by Bao et al. [19] surmised that monocytes is much reduced in severely affected clients. In contrast to our study, Bastug et al. [20] did not set up dissimilarity between critical and non-critical patients in regard to monocytes in COVID-19, this is owing to the fact that there might be a difference in study population or design of the study. But Anurag et al. [21] declare comparable findings to our discernment in that monocytes discordantly reciprocating with severity. Peculiarly bulk of recovered patients 12 out of 13 with COVID-19 had normal monocytes count. Two out of three of critical normomonocytic clients were saved, substantiate impactful evidence that normalizing monocytes at any grade of severity might harbinger the onset of recovery. Fathi et al. [22] ascertained that COVID-19 patients had appreciably higher monocytes sooner in recovered patients with COVID-19. Strikingly all critically ill patients in the COVID-19 grouping who undergone admittance to ICU with monocytosis died with high statistical significance disclosing that monocytosis is an expectant for lethality and most facets of dreadful terminal events of COVID-19. Mei et al. [23] revealed the hospitalized patients with COVID-19 exhibiting monocytosis in the midst of other laboratory variables go through all spans of unfavorable terminal events with exposing the worse prognostication properties. Looking at a bio-demographic trait of our analysis, cases, and control were in a nearly exact fitting situation to elude from selection bias, so most traits displayed no significant statistical relation. Come to comorbidities in our study; COVID-19 grouping demonstrates a sizable number of underlying pre-existing conditions, hypertension was the dominating then diabetes mellitus, heart disease and the slightest is pulmonary illnesses, our discerning in agreement with Guan et al. [24]

. There is significant statistical interrelation joining cases and control regarding hypertension and pulmonary disorders where P values=0.001 and 0.002 respectively in accordance with Shen et al. [25,] but there was no significant interrelation regarding diabetes and cardiac diseases where P values=0.834, 0.545, respectively, this is nearly compatible with what was attained by virtue of Zayet et al. [26]

Conclusion

Deviation in monocytes count from the norm is a valuable discriminator for diagnosis of COVID-19 and suitable anticipator overall spectrum of adverse consequences.

References

1. Martinez FO, Combes TW, Orsenigo F, Gordon S. Monocyte activation in systemic Covid-19 infection: Assay and rationale. E Bio Medicine. 2020 Sep 1; 59:102964. DOI: https://doi.org/10.1016/j.ebiom.2020.102964
2. Abousenna MS. Alignment of SARS-CoV-2 in comparison with other coronaviruses. J. Life Sci. Biomed., 2020; 10(2):17-20. DOI: https://dx.doi.org/10.36380/scil.2020.jlsb3
3. Gómez-Rial J, Currás-Tuala MJ, Rivero-Calle I, Gómez-Carballa A, Cebey-López M, Rodríguez-Tenreiro C, Dacosta-Urbieta A, Rivero-Velasco C, Rodríguez-Núñez N, Trastoy-Pena R, Rodríguez-García J. Increased Serum Levels of sCD14 and sCD163 Indicate a Preponderant Role for Monocytes in COVID-19 Immunopathology. Frontiers in Immunology. 2020 Sep 23; 11:2436. https://doi.org/10.3389/fimmu.2020.560381
4. Le Joncour A, Biard L, Vautier M, Bugaut H, Mekinian A, Maalouf G, Vieira M, Marcelin AG, Rosenzwajg M, Klatzmann D, Corvol JC. Neutrophil–Platelet and Monocyte–Platelet Aggregates in COVID-19 Patients. Thrombosis and Haemostasis. 2020 Oct 29. DOI: 10.1055/s-0040-1718732
5. Afzal A. Molecular diagnostic technologies for COVID-19: Limitations and challenges. Journal of advanced research. 2020 Aug 6. https://doi.org/10.1016/j.jare.2020.08.002
6. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. Jama. 2020 Aug 11;324(6):603-5. doi:10.1001/jama.2020
7. Zhao Y, Cui C, Zhang K, et al. A systemic Approach to Early Identification and Healthcare Worker Protection. Front. Public Health 2020; 8:205. doi:10.3389/fpubh.2020.002
8. Jafarzadeh A, Chauhan P, Saha B, Jafarzadeh S, Nemati M. Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: lessons from SARS and MERS, and potential therapeutic interventions. Life sciences. 2020 Jul 18, 257:118102. doi: 10.1016/j.lfs.2020.118102
9. McNeely CL, Schintler LA, Stabile B. Social Determinants and COVID - 19 Disparities: Differential Pandemic Effects and Dynamics. World Medical & Health Policy. 2020 Sep; 12(3): 206-17. https://doi.org/10.1002/wmh3.370
10. Asghar MS, Khan NA, Haider Kazmi SJ, Ahmed A, Hassan M, Jawed R, Akram M, Rasheed U, Memon GM, Ahmed MU, Tahniyat U. Hematological parameters predicting severity and mortality in COVID-19 patients of Pakistan: a retrospective comparative analysis. Journal of Community Hospital Internal Medicine Perspectives. 2020 Nov 1;10(6):514-20.https://doi.org/10.1080/20009666.2020.1816276
11. Rizo-Téllez SA, Méndez-García LA, Flores-Rebollo C, Alba-Flores F, Alcántara-Suárez R, Manjarrez-Reyna AN, Baltazar-López N, Hernández-Guzmán VA, León-Pedroza JI, Zapata-Arenas R, González-Chávez A. The Neutrophil-to-Monocyte Ratio and Lymphocyte-to-Neutrophil Ratio at Admission Predict In-Hospital Mortality in Mexican Patients with Severe SARS-CoV-2 Infection (Covid-19). Microorganisms. 2020 Oct;8(10):1560. doi:10.3390/microorganisms8101560.
12. Ding X, Yu Y, Lu B, Huo J, Chen M, Kang Y, Lou J, Liu Z. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. Clinical Chemistry and

Laboratory Medicine (CCLM). 2020 May 22;1(ahead-of-print).DOI: https://doi.org/10.1515/cclm-2020-0411.

13. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Frontiers in immunology. 2020 Jul 10; 11:1708. doi:10.3389/fimmu.2020.01708. PMCID: PMC7365923. PMID: 32754163.

14. Rosenthal PJ. The importance of diagnostic testing during a viral pandemic: early lessons from novel coronavirus disease (CoVID-19). The American journal of tropical medicine and hygiene. 2020 May;102(5):915. doi:10.4269/ajtmh.20-0216. PMCID: PMC7204570

15. Temgoua MN, Endomba FT, Nkeck JR, Kenfack GU, Tochie JN, Essouma M. Coronavirus disease (COVID-19) as a multi-systemic disease and its impact in low-and middle-income countries (LMICs). SN Comprehensive Clinical Medicine.

16. Chen J, Pan Y, Li G, Xu W, Zhang L, Yuan S, Xia Y, Lu P, Zhang J. Distinguishing between COVID - 19 and influenza during the early stages by measurement of peripheral blood parameters. Journal of Medical Virology. 2021 Feb;93(2):1029-37.https://doi.org/10.1002/jmv.26384.

17. Pakos IS, Lo KB, Salacup G, Pelayo J, Bhargav R, Peterson E, Gul F, DeJoy III R, Albano J, Patarroyo - Aponte G, Rangaswami J. Characteristics of peripheral blood differential counts in hospitalized patients with COVID - 19. European journal of haematology. 2020 Dec;105(6):773-8. https://doi.org/10.1111/ejh.13509

18. Blomme S, Smets L, Van Ranst M, Boeckx N, Van Laer C. The influence of COVID-19 on routine hematological parameters of hospitalized patients. Acta Clinica Belgica. 2020 Sep 6:1-6. DOI:10.1080/17843286.2020.1814649

19. Bao J, Li C, Zhang K, et al. Comparative analysis of laboratory indexes of Severe and non- severe patients infected With COVID-19. Clinica Chemica Acta, 509(2020): 180-194. https://doi.org/10.1016/j.cca.2020.06.009. PMID: 32511971; PMCID: PMC7274996.

20. Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, Ozbay BO, Gok G, Turan IO, Yilmaz G, Gonen CC. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. International immunopharmacology. 2020 Nov 1;88:106950.https://doi.org/10.1016/j.intimp.2020.106950

21. Anurag A, Jha PK, Kumar A. Differential white blood cell count in the COVID-19: A cross-sectional study of 148 patients. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Nov 1;14(6):2099-102.https://doi.org/10.1016/j.dsx.2020.10.029

22. Fathi F, Sami R, Mozafarpoor S, Hafezi H, Motedayyen H, Arefnezhad R, Eskandari N. Immune system changes during COVID-19 recovery play key role in determining disease severity. International journal of immunopathology and pharmacology. 2020 Oct; 34: 2058738420966497. doi:10.1177/2058738420966492020 Jul 20:1-1. doi:10.1007/s42399-020-00417-7. PMCID: PMC7371790. 2019

23. Mei Y, Weinberg SE, Zhao L, Frink A, Qi C, Behdad A, Ji P. Risk stratification of hospitalized COVID-19 patients through comparative studies of laboratory results with influenza. EClinicalMedicine. 2020 Sep 1;26:100475.; https://doi.org/10.1016/j.eclinm.2020.100475.

24. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European Respiratory Journal. 2020 May; 55(5):2000547. doi:10.1183/13993003.00547-2020.PMCID:PMC7098485

25. Shen C, Tan M, Song X, Zhang G, Liang J, Yu H, Wang C. Comparative Analysis of Early-Stage Clinical Features Between COVID-19 and Influenza A H1N1 Virus Pneumonia. Frontiers in Public Health. 2020 May 15;8:206. doi:10.3389/fpubh.2020.00206. PMCID: PMC7243732. PMID:32574297

26. Zayet S, Lepiller Q, Zahra H, Royer PY, Toko L, Gendrin V, Klopfenstein T. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes and infection. 2020 Oct 1;22(9):481-8. doi: 10.1016/j.micinf.2020.05.016 PMCID: PMC7297177, PMID:32561409