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Original Article

Normoblastemia in COVID-19 patients is associated with more severe disease and adverse outcome

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Abstract: Objectives: The clinical, pathological, and laboratory correlates of normoblastemia in COVID-19 patients have not been adequately explored. We sought to assess the frequency of normoblastemia in COVID-19, its association with other markers of disease, as well as other clinical outcomes. Methods: All COVID-19 patients seen at our institution with at least one automated complete blood count (aCBC) evaluation from March to May 2020 were included in this retrospective cohort analysis. Results of aCBC and tests for markers of the acute phase response performed within 5 days before the first COVID-19 positive test and 14 days after the last positive test were reviewed. We also evaluated histologic features of the reticuloendothelial system of COVID-19 decedents. Results: Among a total of 2501 COVID-19 patients, 715 (28.6%) were found to have normoblastemia. Patients with this abnormality had significantly higher (median, (1st quartile, 3rd quartile) WBC (15.7 (11.2, 23.1) u/L vs. 8.3 (6.2, 11.5) u/L), absolute neutrophil count (7.0 (5.1, 10.1) u/L vs. 5.1 (3.7, 7.3) u/L), immature granulocyte percentage (0.8 (0.5, 1.3)% vs. 0.5 (0.3, 0.8)%), ESR (76.0 (60.5, 100.0) mm/hr vs. 66.0 (45.0, 87.0) mm/hr), ferritin (1404.5 (645.0, 2871.0) ng/mL vs. 672.7 (313.4, 1348.0) ng/mL), INR (1.4 (1.2, 1.7) vs. 1.2 (1.1, 1.3)), D-dimer (8.2 (2.8, 20.0) ug/mL FEU vs. 1.5 (0.8, 3.7) µg/mL FEU), and IL-6 (216.6 (77.7, 315.0) pg/mL vs. 54.3 (23.2, 127.8) pg/mL) levels, and lower hemoglobin (12.5 (10.7, 14.2) g/dL vs. 13.2 (11.8, 14.6) g/dL) and absolute lymphocyte count (1.0 (0.7, 1.3) u/L vs. 1.1 (0.8, 1.5) u/L). The incidence of intubation and ventilation support (61.3% (65/106) vs. 10.5% (31/263)) and mortality rates (37.9%, 271/715 vs. 11.8%, 210/1786), were higher in normoblastemic patients. Multivariable logistic regression revealed normoblastemia to be an independent predictive biomarker of short-term mortality in COVID-19. Conclusion: Normoblastemia in COVID-19 is associated with markers of severe disease, extramedullary erythropoiesis, and adverse clinical outcome.

Keywords: COVID-19, normoblastemia, leukoerythroblastosis, extramedullary erythropoiesis, acute phase response

Introduction

The clinical course of Coronavirus Disease 2019 (COVID-19) is highly variable. In a minority of patients, severe disease ensues, resulting in significant morbidity and mortality. Ever since the beginning of the pandemic, multiple studies have described abnormalities in several laboratory parameters in COVID-19, with some having been proposed to be predictive or indicative of disease progression and severity [1, 2]. Lymphopenia, neutrophilia, thrombocytopenia, elevated AST and ALT, hypoalbuminemia, and high LDH have all been associated with severe disease, higher likelihood of disease progression, mechanical ventilation, and mortality [1, 3-6]. However, there still exists an unmet clinical need to identify predictors and correlates of severe disease to allow for prompt and effective intervention.

Normoblastemia, the presence of nucleated red blood cells (nRBC) in the peripheral blood (PB), is observed in various conditions including solid and hematologic malignancies, infections, and hemolysis [7]. A handful of case reports and small case series have described normoblastemia in COVID19 patients [8-11]. However, the presence and frequency of this abnormality in COVID-19 patients, and its association

with alterations of other laboratory parameters and correlation with disease severity have not been well studied. Hence, we investigated the prevalence of normoblastemia in a large cohort of COVID-19 patients by analyzing automated complete blood count (aCBC) results and determined its correlations with other laboratory abnormalities and clinical outcomes. Additionally, we evaluated post-mortem bone marrow (BM), spleen, and liver samples from a subset of COVID-19 patients in order to gain insights into the possible source of normoblastemia.

Materials and methods

Case selection

The study was a retrospective cohort analysis. All COVID-19 patients seen at our institution with at least one aCBC evaluation from March to May 2020 were included in this study. We studied two overlapping cohorts (A and B) described below. The study was approved by the Institutional Review Board of the New York Presbyterian Hospital/Columbia University Irving Medical Center.

Cohort A: We retrospectively searched the laboratory information system (LIS) of the Department of Pathology and Cell Biology at the Columbia University Irving Medical Center, for all COVID-19 positive patients with aCBC performed during the study period. Clinical and laboratory data for these patients were collected from the electronic medical records. Clinical data included demographics (age, sex, ethnicity), requirement for intubation and ventilation support, and mortality. Laboratory data included arterial blood gases (pCO_2, pO_2, pH, HCO_3), aCBC and differential cell counts, and acute phase inflammatory biomarkers (D-dimer, fibrinogen, haptoglobin, ferritin, ESR, INR, aPTT, IL-6), all performed within a 5-day period before the first COVID-19 positive test and 14 days after the last positive test was documented. COVID-19 testing was performed by reverse transcriptase PCR of nasopharyngeal swabs. Normoblastemia was defined as an automated nRBC count > 0.1/100 WBC.

Cohort B: All deceased COVID-19 patients with postmortem examination performed during the study period were included. These patients were a small subset of cohort A. Histopathologic features of H&E-stained sections of formalin-fixed, paraffin embedded tissue samples derived from the reticuloendothelial system including BM (from a thoracic rib squeeze), spleen and liver were evaluated. The presence of normoblastemia in antemortem aCBC was assessed for these patients. BM hematopoietic activity was assessed as usual. The presence of extramedullary erythropoiesis (EMH) in the liver and spleen was graded as rare to absent, mild to moderate, or markedly increased. The latter two groups were combined together because of low sample numbers.

Data analysis

For cohort A, aCBC parameters, available inflammatory biomarkers and clinical outcomes when applicable, were compared between patients with normoblastemia and those without. In cohort B, we compared BM findings and presence of EMH in the liver and spleen of decedents with ante-mortem normoblastemia. Since patients typically have a range of results on multiple testing for same parameters over time, for each laboratory value, two separate statistical analysis was performed, first comparing the highest recorded values and then the lowest values for each patient. Laboratory indices were considered different between normoblastemic and non-normoblastemic patients if the difference between their means were significant (adjusted p-value < 0.05) and consistent for both analyses comparing the lowest and highest values. Quantitative results are reported as medians and interquartile ranges. Categorical data were reported as counts and percentages. Statistical analyses of categorical variables were performed using Pearson Chi-squared tests, and continuous variables were compared using linear ANOVA and Kruskal-Wallis rank sum tests. Correction for multiple testing was performed separately in the lowest and highest test value sets using the Benjamini-Hochberg false discovery rate method [12]. Univariable logistic regression analysis was performed using the glm function of the stats R package, to predict COVID-19 Short Term Mortality. Multivariable logistic regression was then performed using the same glm function, and non-significant terms were removed from the model using a stepwise approach to minimize the Akaike Information Criterium (AIK) as calculated by the package MASS. A detailed description of the regression analysis is pre-

sented in the supplementary material (Supplementary B). All statistical analyses were performed using the R environment for statistical computing.

Results

Cohort A

Patient characteristics: A total of 2501 COVID-19 patients had at least one aCBC within the study period (M:F = 1098:1403, age 0.0-101.1). None of the patients were vaccinated, as the study period preceded the availability of any Covid vaccines. All other relevant demographic data are summarized in **Table 1**. Seven-hundred and fifteen patients (28.6%) were found to have normoblastemia (**Figure 1A**). The automated nRBC count for the normoblastemic group ranged from 0.2-139.5/100 WBC. The median age of normoblastemic patients was 66.7 yrs (55.6-77.0) and that of non-normoblastemic patients was 62.5 yrs (47.2-74.4).

Hematological markers: We found significant differences (adjusted p value < 0.05) between normoblastemic and non-normoblastemic patients among different laboratory and clinical indices (**Table 1**). Among hematological markers, normoblastemic patients had higher total white blood cell count (15.7 (11.2, 23.1) u/L vs. 8.3 (6.2, 11.5) u/L), absolute neutrophil count (7.0 (5.1, 10.1) u/L vs. 5.1 (3.7, 7.3) u/L), and immature granulocyte percentage (0.8 (0.5, 1.3)% vs. 0.5 (0.3, 0.8)%) than non-normoblastemic patients, and a lower absolute lymphocyte count (1.0 (0.7, 1.3) u/L vs. 1.1 (0.8, 1.5) u/L) and hemoglobin level (12.5 (10.7, 14.2) g/dL vs. 13.2 (11.8, 14.6) g/dL).

Markers of the acute phase response: Normoblastemic patients had significantly higher acute phase response marker levels such as ESR (76.0 (60.5, 100.0) mm/hr vs. 66.0 (45.0, 87.0) mm/hr), INR (1.4 (1.2, 1.7) vs. 1.2 (1.1, 1.3)), D-dimer (8.2 (2.8, 20.0) µg/mL FEU vs. 1.5 (0.8, 3.7) µg/mL FEU), ferritin (1404.5 (645.0, 2871.0) ng/mL vs. 672.7 (313.4, 1348.0) ng/mL), and IL-6 (216.6 (77.7, 315.0) pg/mL vs. 54.3 (23.2, 127.8) pg/mL). Other laboratory markers did not show significant and/or consistent differences between normoblastemic and non-normoblastemic patients (**Table 1** and Supplementary Table A).

Clinical outcome: A significantly higher proportion of normoblastemic patients were intubated compared to non-normoblastemic patients (61.3% (65/106) vs. 10.5% (31/263), p value < 0.001) and the mortality of normoblastemic patients (37.9%, 271/715) was significantly higher than for non-normoblastemic patients (11.8%, 210/1786).

Univariable and multivariable logistic regression analysis: Univariable logistic regression using deceased status as the response variable revealed normoblastemia to be among the features associated with increased risk of short-term mortality (OR = 4.01 (2.69-5.99) P < 0.001) (**Table 2**). Normoblastemia was also an independent predictor of short-term mortality on multivariable logistic regression (OR = 3.45 (2.61-4.) P < 0.001) (**Table 3**). Other laboratory markers significantly associated with deceased status in the multivariable analysis included absolute neutrophil count and WBC, which were associated with higher and lower risk of short-term mortality respectively (**Table 3**).

Cohort B

Evaluation of the reticuloendothelial system of 30 COVID-19 decedents (19 (63.3%) with antemortem record of normoblastemia, 11 (36.7%) without normoblastemia) showed variable findings in the BM, including left shifted myeloid maturation and reduced erythropoiesis. There was no increase in BM erythroid precursors in either group. In patients without antemortem normoblastemia, the liver and spleen had only rare to absent nRBC (11/11, 100% livers and 10/10, 100% spleens). Mild to markedly increased extramedullary erythropoiesis was seen only in the livers (11/19, 57.9%, **Figure 1B**) and spleens (17/19, 89.5%, **Figure 1C**) of decedents with a history of antemortem normoblastemia (P = 0.002 and P < 0.001 compared with livers and spleens of non-normoblastemic decedents, respectively).

Discussion

In this study we investigated the frequency of normoblastemia in COVID-19 and its association with other hematologic and biochemical markers, and clinical outcomes. We also investigated the possible source of circulating nRBC by analyzing reticuloendothelial tissue samples

Table 1. Comparison of demographics, encounter types, and laboratory markers between normoblastemic and non-normoblastemic patients. Comparison of the highest laboratory value for each patient is shown; comparison of the lowest values for displayed markers showed similar significant differences

Feature	Non-normoblastemic	Normoblastemic	Total	*P* value*
Sex				0.497[1]
Female	792 (44.3%)	306 (42.8%)	1098 (43.9%)	
Male	994 (55.7%)	409 (57.2%)	1403 (56.1%)	
	N = 1786	N = 715	N = 2501	
Age (yrs)				< 0.001[2]
Mean (SD)	59.6 (20.5)	64.3 (18.5)	60.9 (20.0)	
Median (Q1, Q3)	62.5 (47.2, 74.4)	66.7 (55.6, 77.0)	64.1 (50.1, 75.3)	
	N = 1786	N = 715	N = 2501	
Encounter type				< 0.001[1]
Emergency	59 (3.3%)	81 (11.3%)	140 (5.6%)	
In-patient	1596 (89.4%)	603 (84.3%)	2199 (87.9%)	
Out-patient	131 (7.3%)	31 (4.3%)	162 (6.5%)	
	N = 1786	N = 715	N = 2501	
NRBC auto (per 100 WBC)				< 0.001[2]
Mean (SD)	0.0 (0.0)	2.4 (9.1)	0.7 (5.0)	
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.6 (0.3, 1.6)	0.0 (0.0, 0.2)	
WBC ($\times 10^3/\mu L$)				< 0.001[2]
Mean (SD)	9.7 (7.2)	18.4 (11.5)	12.2 (9.5)	
Median (Q1, Q3)	8.3 (6.2, 11.5)	15.7 (11.2, 23.1)	9.6 (6.8, 14.8)	
	N = 1786	N = 715	N = 2501	
ANC ($\times 10^3/\mu L$)				< 0.001[2]
Mean (SD)	5.9 (3.3)	7.8 (3.9)	6.3 (3.5)	
Median (Q1, Q3)	5.1 (3.7, 7.3)	7.0 (5.1, 10.1)	5.5 (3.9, 7.8)	
	N = 663	N = 188	N = 851	
IG%				< 0.001[2]
Mean (SD)	0.7 (0.6)	1.0 (0.7)	0.7 (0.6)	
Median (Q1, Q3)	0.5 (0.3, 0.8)	0.8 (0.5, 1.3)	0.6 (0.4, 0.9)	
	N = 663	N = 187	N = 850	
Hgb (g/dL)				< 0.001[2]
Mean (SD)	13.1 (2.0)	12.4 (2.5)	12.9 (2.2)	
Median (Q1, Q3)	13.2 (11.8, 14.6)	12.5 (10.7, 14.2)	13.1 (11.5, 14.5)	
	N = 1786	N = 714	N = 2500	
ALC ($\times 10^3/uL$)				0.042
Mean (SD)	1.2 (0.6)	1.1 (0.6)	1.1 (0.6)	
Median (Q1, Q3)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	1.1 (0.8, 1.5)	
	N = 663	N = 188	N = 851	
ESR (mm/hr)				< 0.001[2]
Mean (SD)	67.4 (30.1)	78.6 (30.9)	70.4 (30.7)	
Median (Q1, Q3)	66.0 (45.0, 87.0)	76.0 (60.5, 100.0)	69.0 (48.0, 92.0)	
	N = 493	N = 179	N = 672	
D-dimer (μg/mL FEU)				< 0.001[2]
Mean (SD)	4.0 (5.6)	10.3 (7.8)	6.1 (7.1)	
Median (Q1, Q3)	1.5 (0.8, 3.7)	8.2 (2.8, 20.0)	2.5 (1.0, 9.5)	
	N = 1212	N = 627	N = 1839	

Ferritin (ng/mL)				< 0.001[2]
Mean (SD)	1220.4 (3135.5)	3642.5 (9588.0)	2000.6 (6125.9)	
Median (Q1, Q3)	672.7 (313.4, 1348.0)	1404.5 (645.0, 2871.0)	847.4 (373.4, 1815.2)	
	N = 1410	N = 670	N = 2080	
Haptoglobin (mg/dL)				0.054[2]
Mean (SD)	330.5 (159.6)	285.3 (158.0)	297.7 (159.4)	
Median (Q1, Q3)	335.0 (210.5, 439.0)	278.0 (167.0, 386.5)	305.0 (183.0, 407.0)	
	N = 71	N = 187	N = 258	
IL-6 (pg/mL)				< 0.001[2]
Mean (SD)	95.5 (99.6)	196.1 (117.8)	136.8 (118.2)	
Median (Q1, Q3)	54.3 (23.2, 127.8)	216.6 (77.7, 315.0)	91.0 (34.4, 278.7)	
	N = 771	N = 536	N = 1307	
INR				< 0.001[2]
Mean (SD)	1.3 (0.9)	1.8 (1.9)	1.5 (1.3)	
Median (Q1, Q3)	1.2 (1.1, 1.3)	1.4 (1.2, 1.7)	1.2 (1.1, 1.4)	
	N = 1437	N = 676	N = 2113	
pCO_2 arterial (mm/Hg)				0.165[2]
Mean (SD)	38.5 (12.5)	40.3 (12.1)	39.6 (12.3)	
Median (Q1, Q3)	37.0 (32.0, 42.2)	37.0 (34.0, 46.0)	37.0 (33.0, 44.0)	
	N = 156	N = 267	N = 423	
pH arterial				0.398[2]
Mean (SD)	7.4 (0.1)	7.4 (0.1)	7.4 (0.1)	
Median (Q1, Q3)	7.4 (7.4, 7.5)	7.4 (7.4, 7.5)	7.4 (7.4, 7.5)	
	N = 156	N = 267	N = 423	
pO_2 arterial (mm/Hg)				0.164[2]
Mean (SD)	156.0 (78.3)	166.2 (62.1)	162.4 (68.6)	
Median (Q1, Q3)	161.5 (86.8, 203.2)	171.0 (124.5, 209.0)	169.0 (110.0, 207.5)	
	N = 156	N = 267	N = 423	
Intubation				< 0.001[1]
	31 (10.5%)	65 (61.3%)	96 (26.0%)	
	N = 263	N = 106	N = 369	
Death				< 0.001[1]
	210 (11.8%)	271 (37.9%)	481 (19.2%)	
	N = 1786	N = 715	N = 2501	

*Benjamini-Hochgberg adjusted *p*-value (false discovery rate). 1. Pearson's Chi-square test (adjusted for multiple comparisons of all highest test values; not all comparisons are shown). 2. Linear Model ANOVA (adjusted for multiple comparisons of all highest test values; not all comparisons are shown). Abbreviations: ALC: absolute lymphocyte count, ANC: absolute neutrophil count, Auto: automated, ESR: erythrocyte sedimentation rate, FEU: fibrinogen equivalent units, Hgb: hemoglobin, IG%: immature granulocyte percent, IL-6: interleukin 6, Q1: first quartile, Q3: third quartile, SD: standard deviation, WBC: white blood cell count.

of COVID-19 decedents. Normoblastemia was identified in approximately 29% of COVID-19 patients on aCBC suggesting it is not an uncommon finding in COVID-19.

Severe disease and mortality in COVID-19 have both been shown to be associated with an excessive immune response to the virus (so called "cytokine storm") [13]. An array of cytokines and pro-inflammatory markers have been implicated including IL-6, ferritin, ESR, and D-dimer [14]. In our study, normoblastemia was associated with higher levels of these cytokines and markers compared to non-normoblastemic patients. In addition, severe COVID-19 has been associated with elevations of the WBC and neutrophil counts, decrease in lymphocyte and platelet counts, and anemia [15, 16]. We found that normoblastemic patients compared to non-normoblastemic patients,

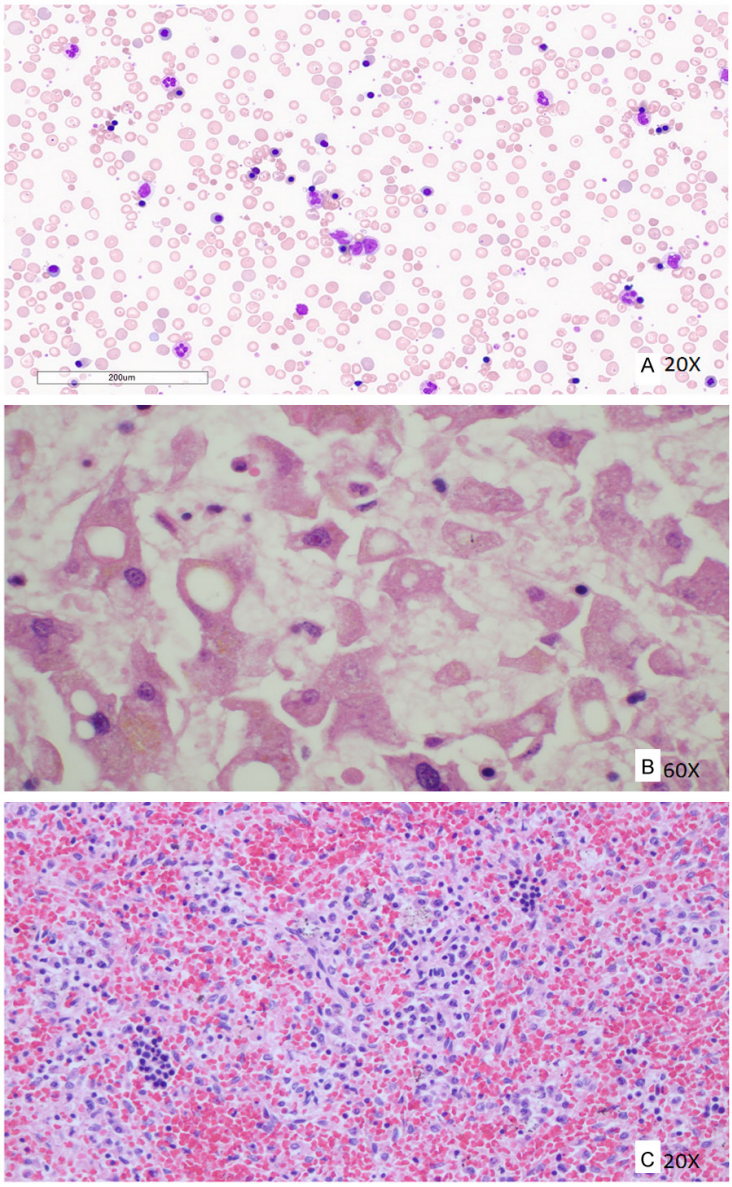

Figure 1. (A) Peripheral blood smear showing many nucleated red blood cells and scattered immature granulocytes; H&E sections of (B) liver and (C) splenic red pulp showing extramedullary erythropoiesis in COVID-19 infected patients with antemortem normoblastemia.

had higher WBC and neutrophil counts, and lower lymphocyte counts and hemoglobin levels. The pattern of differences in these biomarkers and hematologic values is consistent with an association of normoblastemia with severe disease. This association is further validated not only by the higher incidence of intubation and increased mortality of normoblastemic patients but also by demonstration of normoblastemia as an independent predictor of short-term mortality on multivariable regression analysis.

The proposed mechanisms for normoblastemia have included: compensatory BM erythropoiesis secondary to anemia or hypoxia, EMH, disruption of the blood BM barrier, or a combination of these mechanisms [17]. We examined postmortem tissues from the reticuloendothelial system of COVID19 patients and found decreased BM erythroid progenitors and a significantly higher degree of EMH in the livers and spleens of normoblastemic patients, arguing for a role of extramedullary erythropoiesis rather than increased BM erythropoiesis and premature release as the source of normoblastemia, although the possibility exists that terminal events might include BM exhaustion and therefore a lack of observed compensatory erythropoiesis. The trigger for extramedullary erythropoiesis is unclear, but the presence in normoblastemic patients of significantly lower hemoglobin levels and higher inflammatory markers point towards anemia and cytokine mediated effects as culprits. IL-6, which we found to be elevated in normoblastemic patients, has pleiotropic effects and could contribute to the observed findings such as lymphocytopenia, myeloid expansion, reduced efficiency of BM erythropoiesis, and consequently, extramedullary erythropoiesis [18, 19].

As our study was a retrospective analysis, it was limited in its ability to be selective about the choice of controls. Additionally, the study is limited by its short duration, covering only three months, with absence of long term follow-up data. Thus we could not assess the distribution of long term sequalae of COVID-19 infection between normoblastemic and non-normoblastemic patients. Also, becuase COVID-19 vaccines were not available during the period of the study, and as such, none of the patients in our study had been vaccinated, we could not

Table 2. Univariable logistic regression to predict short term mortality

	OR	CI lower	CI upper	*p* value	Concordance	Missed
Intubation	6.23	3.91	9.92	< 0.001	0.69	2067
NRBC > 0.1%	4.01	2.69	5.99	< 0.001	0.58	1526
Immature granulocyte %	1.64	1.31	2.06	< 0.001	0.64	1704
NRBC %	1.44	1.12	1.85	0.004	0.59	1526
RDW CV	1.24	1.15	1.33	< 0.001	0.66	1524
Absolute neutrophil count	1.16	1.11	1.21	< 0.001	0.66	1702
INR	1.13	1.01	1.28	0.041	0.65	1788
WBC	1.10	1.06	1.13	< 0.001	0.63	1524
Interleukin 6	1.01	1.01	1.02	< 0.001	0.80	2311
ESR	1.01	1.00	1.01	0.013	0.57	1881
Hgb	0.92	0.86	0.98	0.011	0.55	1524
Monocyte count	0.89	0.85	0.94	< 0.001	0.64	1702
MCHC	0.81	0.74	0.89	< 0.001	0.58	1524
Absolute lymphocyte count	0.36	0.25	0.51	< 0.001	0.65	1702
Eosinophil count	0.35	0.22	0.57	< 0.001	0.62	1702
Basophil count	0.14	0.05	0.43	< 0.001	0.58	1702

Only significant variables are shown. OR = Odds ratio; CI = 95% confidence limits for the OR.

Table 3. Stepwise multivariable logistic regression to predict deceased status, performed with all significant variables by univariable regression except interleukin-6 and including NRBC > 0.1%, after stepwise iterations to minimizing AIC (N = 849, AIC = 812)

	OR	CI low	CI Hi	z value	*p* value
(Intercept)	0.26	0.20	0.33	-5.42	5.9E-08
NRBC > 0.1	3.45	2.61	4.55	4.47	8.0E-06
Absolute Neutrophil Count	2.32	2.03	2.65	6.25	4.2E-10
WBC	0.51	0.45	0.58	-5.33	9.9E-08

assess the effect of vaccination on the association of normoblastemia with markers of disease severity and clinical outcome.

We have shown that normoblastemia is not uncommon in COVID-19 patients, and have demonstrated its association with other hematologic values and biomarkers of severe disease and worse clinical outcomes such as higher incidence of intubation and increased mortality. Our study also implicates increased hepatic and splenic EMH as the source of nRBC in the PB. These findings are in keeping with studies in other disease settings linking normoblastemia with worse clinical course and higher mortality [20]. Considering that aCBC is an inexpensive test, widely available and routinely performed in the hospital setting, it can be quite helpful in monitoring normoblastemia and predicting adverse outcomes and guiding appropriate management of COVID-19 patients.

Disclosure of conflict of interest

None.

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Supplementary Table A. Laboratory markers that did not show a consistent difference between normoblastemic and non-normoblastemic patients; e.g., decreased in a group when comparing lowest values recorded for marker among patients in the group but increased in the group when comparing highest values recorded for patients in the group

Feature	Non-normoblastemic	Normoblastemic	Total	*P* value*
APTT (s)^{H}				< 0.001[2]
Mean (SD)	42.8 (29.6)	71.8 (51.2)	52.1 (40.2)	
Median (Q1, Q3)	34.5 (31.1, 39.9)	44.6 (35.9, 96.0)	36.5 (31.9, 45.8)	
	N = 1420	N = 671	N = 2091	
APTT (s)^{L}				< 0.001[2]
Mean (SD)	32.0 (5.7)	31.3 (7.5)	31.8 (6.3)	
Median (Q1, Q3)	31.2 (28.6, 34.3)	29.9 (26.9, 33.9)	30.9 (28.0, 34.2)	
	N = 1420	N = 671	N = 2091	
Fibrinogen^{H} (mg/dL)				0.005[2]
Mean (SD)	609.3 (200.5)	659.0 (241.6)	633.6 (222.8)	
Median (Q1, Q3)	598.5 (464.8, 729.2)	651.0 (486.2, 807.0)	620.0 (475.5, 763.0)	
	N = 352	N = 336	N = 688	
Fibrinogen^{L} (mg/dL)				< 0.001[2]
Mean (SD)	572.9 (196.5)	480.6 (229.2)	527.8 (217.9)	
Median (Q1, Q3)	577.0 (444.0, 706.2)	467.5 (306.0, 638.2)	534.0 (377.5, 678.0)	
	N = 352	N = 336	N = 688	
Arterial HCO_3^{H} (mmol/L)				0.016[2]
Mean (SD)	25.9 (5.9)	27.5 (6.3)	26.9 (6.2)	
Median (Q1, Q3)	26.0 (23.0, 29.0)	27.0 (23.0, 31.0)	26.0 (23.0, 30.0)	
	N = 156	N = 267	N = 423	
Arterial HCO_3^{L} (mmol/L)				0.028[2]
Mean (SD)	23.1 (5.0)	22.0 (4.6)	22.4 (4.8)	
Median (Q1, Q3)	23.5 (20.0, 26.0)	22.0 (19.0, 25.0)	23.0 (19.0, 26.0)	
	N = 156	N = 267	N = 423	
Platelets^{H} (u/L)				< 0.001[2]
Mean (SD)	288.9 (133.2)	361.6 (176.8)	309.5 (150.4)	
Median (Q1, Q3)	259.0 (193.0, 363.0)	351.0 (240.0, 451.0)	281.5 (202.0, 394.0)	
	N = 1761	N = 693	N = 2454	
Platelets^{L} (u/L)				< 0.001[2]
Mean (SD)	209.2 (87.8)	177.3 (105.2)	200.2 (94.2)	
Median (Q1, Q3)	196.0 (148.0, 252.0)	166.0 (108.0, 227.0)	187.5 (140.0, 245.8)	
	N = 1761	N = 693	N = 2454	

*Benjamini-Hochgberg adjusted *p*-value (false discovery rate). 1. Pearson's Chi-squared test (adjusted for multiple comparisons of all highest test values; not all comparisons are shown). 2. Linear Model ANOVA (adjusted for multiple comparisons of all highest test values; not all comparisons are shown). H: Comparison of highest recorded values for feature; L: Comparison of lowest recorded values for feature.

Supplementary B. Logistic regression to predict COVID-19 short term mortality

Univariable logistic regression analysis was performed using the *glm* function of the *stats* R package, to predict COVID-19 Short Term Mortality (patient status during the study period = deceased vs. alive). **Table B1** shows which independent variables were significantly associated with the patient deceased status.

Table B1. Univariable logistic regression to predict short term mortality

	OR	CI lower	CI upper	*p* value	Concordance	Missed
Intubation	6.23	3.91	9.92	< 0.001	0.69	2067
NRBC > 0.1%	4.01	2.69	5.99	< 0.001	0.58	1526
Immature Granulocyte %	1.64	1.31	2.06	< 0.001	0.64	1704
NRBC %	1.44	1.12	1.85	0.004	0.59	1526
RDW CV	1.24	1.15	1.33	< 0.001	0.66	1524
Absolute neutrophil count	1.16	1.11	1.21	< 0.001	0.66	1702
INR	1.13	1.01	1.28	0.041	0.65	1788
WBC	1.10	1.06	1.13	< 0.001	0.63	1524
Interleukin 6	1.01	1.01	1.02	< 0.001	0.80	2311
ESR	1.01	1.00	1.01	0.013	0.57	1881
Hgb	0.92	0.86	0.98	0.011	0.55	1524
Monocyte count	0.89	0.85	0.94	< 0.001	0.64	1702
MCHC	0.81	0.74	0.89	< 0.001	0.58	1524
Absolute lymphocyte count	0.36	0.25	0.51	< 0.001	0.65	1702
Eosinophil count	0.35	0.22	0.57	< 0.001	0.62	1702
Basophil count	0.14	0.05	0.43	< 0.001	0.58	1702

Only significant variables are shown. OR = Odds ratio; CI = 95% confidence limits for the OR.

Multivariable linear regression was then performed using the same *glm* function, and non-significant terms were removed from the model using a stepwise approach to minimize the Akaike Information Criterium (AIK) in the package *MASS*. The following model was selected, showing that IL6 had a very minimal (OR = 1.02) but significant (P = 0.0005) effect on short term mortality (**Table B2**). However, note that this model used only 86 complete measurements.

Table B2. Multivariable logistic regression model after stepwise iterations to maximize AIK

	OR	CI low	CI Hi	z value	*p* value
(Intercept)	0.01	0.01	0.04	-3.89	0.0001
NRBC > 0.1	0.10	0.02	0.54	-1.372	0.17
INR	2.81	1.43	5.52	1.533	0.13
Interleukin 6	1.02	1.01	1.02	3.45	0.0005

Thereafter, we repeated the stepwise multivariable logistic regression analysis without the IL6 variable resulting in the following model, shown on **Table B3**.

Table B3. Stepwise multivariable logistic regression after omitting IL6 variable

	OR	CI low	CI Hi	z value	*p* value
(Intercept)	0.05	0.02	0.13	-2.86	0.004
NRBC > 0.1	1.90	1.26	2.87	1.55	0.121
RDW CV	1.17	1.09	1.25	2.20	0.028
Absolute neutrophil count	1.14	1.10	1.18	3.77	1.6E-04
Absolute lymphocyte count	0.31	0.23	0.42	-3.86	1.1E-04

This model showed no significant interactions among the predictors. Since NRBC > 0.1 had the strongest association (OR = 1.9) but did not reach statistical significance in this model, we repeated the analysis with NRBC and all other significant co-variables (**Table B4**).

Table B4. Stepwise multivariable logistic regression including NRBC > 0.1 as a variable and after stepwise iterations to minimizing AIC (N = 849, AIC = 812)

	OR	CI low	CI Hi	z value	*p* value
(Intercept)	0.26	0.20	0.33	-5.42	5.9E-08
NRBC > 0.1	3.45	2.61	4.55	4.47	8.0E-06
Absolute neutrophil count	2.32	2.03	2.65	6.25	4.2E-10
WBC	0.51	0.45	0.58	-5.33	9.9E-08

The effect of the predictors on short term mortality is illustrated in **Figure B1**.

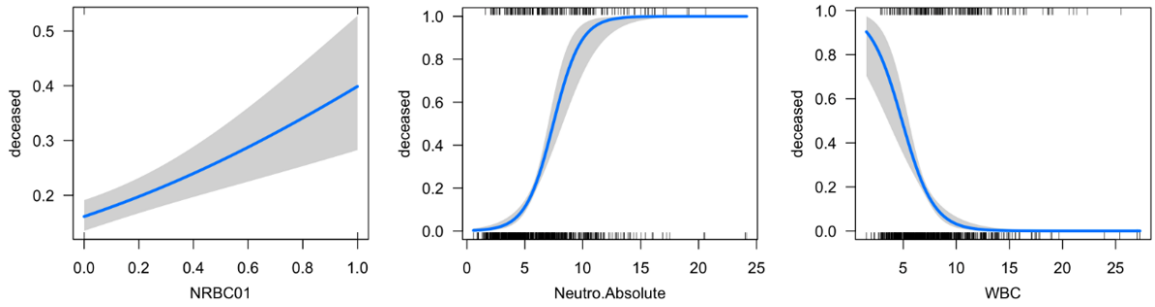

Figure B1. Plot of the deceased status response to variables NRBCs > 0.1%, ANC, and WBCs.

Interaction analysis using the Johnson-Neyman interval method and the R package *interactions* showed a significant interaction between WBCs and NRBCs > 0.1. Increased WBCs resulted in decreased association of NRBCs > 0.1 with mortality, expecially when WBCs > 6.0 (**Figure B2**).

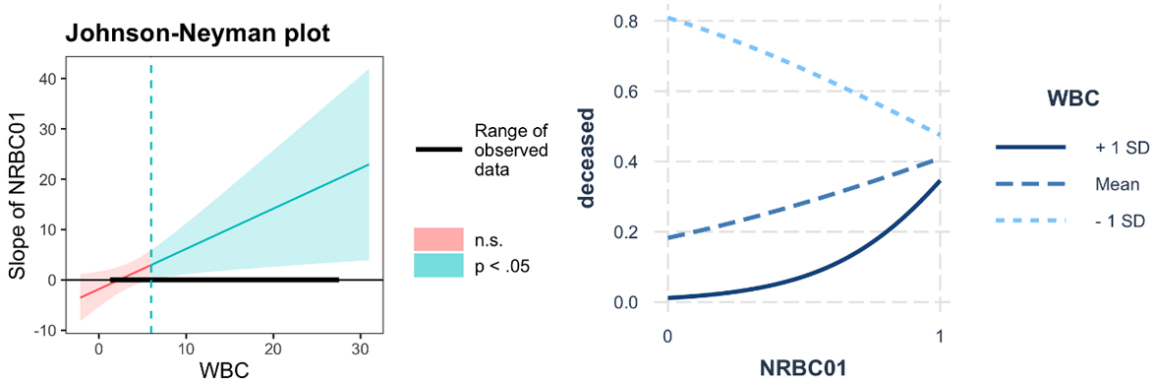

Figure B2. Effect of WBCs on the association of NRBC with mortality.