Association between absolute eosinopenia and mortality in SARS-COV-2 infection on the 70+, a discussed observation

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Research Article

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Abstract

Background: This study aimed to seek for an association between absolute eosinopenia (eosinophils count < 10 /mm3) and mortality in an older adults suffering from COVID-19 hospitalized in a specific geriatric ward.

Methods: This observational retrospective study was conducted in a French geriatric ward from March 17 to April 18, 2020. All 118 patients hospitalized for COVID-19 over 70 yo in acute stay care were enrolled. Patients with a treatment or a pathology which could interfere with eosinophil count were excluded.

Results: No statistical difference was found between surviving or deceased patient regarding age (mean age (SD): 87 years (7)) and sex (34% of males). Differences for the most frequent acute events were statically different: Quick Sepsis-related Organ Failure Assessment (qSOFA) score was ≥ 2 at admission for 23% in the survivor group vs. 23 (72%) in the deceased ($p < .001$); acute kidney injury concerned 17% of the survivors vs. 69% of the decease ($p< .001$). Eosinopenia < 10/mm3 was significantly associated with mortality (OR (CI95%)) = 3.5 (1.2-11.4) after adjustment on age, gender, and activity of daily living.

Conclusion: Absolute eosinopenia was associated with in hospital mortality in older adults. This result, if confirmed in other study, may help to predict the outcome of a SARS-COV-2 infection on geriatric patients and calls for immunologist to explore more globally the impact of inflammaging on the SARS-CoV-2 infection.

Introduction

SARS-COV-2 outbreak, stated in winter 2020 as a public health emergency of international concerned by the World Health Organization (WHO) (1) disrupted societies, health systems and scientific paradigms: everything needed to be learned. Indeed, due to its large spreading and lethality, the understanding of its physiopathology as much as finding prognostic factors are needed for health system to be re-organized and clinician to make decisions. It has so far affected 200 countries, resulting in more than 25 million identified cases with 843 000 confirmed deaths since December 2019 (2). In this context, our elders (a world growing population) seem more vulnerable: since the first of March, 73% of the deceased were 75 years old or more in France (3).

Age has indeed been described to be a major independent prognostic factor, as hypertension, diabetes and obesity (4–8). Of note, our deceased in a geriatric COVID-19 ward this fall were highly dependent: activity of daily living (ADL) - scored over 6 which marks no disability (9) – (ref: ADL > 3), OR 1.84 (1.25–2.70) on the multivariate analysis on mortality (10). However, the age adjusted Charlson comorbidity index (11) did not seem to be a significant prognostic variable on mortality status: median (IQR) were 7 (6–9) and 7 (6–8) p=0.28.

Biological COVID-19 abnormalities include lymphopenia, increased levels of blood inflammatory markers (such as C-reactive protein (CRP), ferritin, ...) and a high lactate dehydrogenase (LDH) blood level (12).

Regarding physiological aspect, immune responses are usually classified in three types against pathogens: type 1 against intra-cellular pathogen including viruses, type 2 against extra-cellular pathogen like helminthes and type 3 against extra-cellular pathogen like bacteria and fungus (13). Eosinophils were for a long time included in the type 2 and explored for their implication in allergic or pulmonary diseases (14). Their role appears to be wider as they have been linked to immune response conferring host protection against fungi, bacteria, and viruses. Indeed, they appear to be able to play a part in recognition of virus and to have the capacity to perform direct action against viruses (14).

However, literature between eosinophils and infectious diseases – helminthes apart – appears to be scarce. Nonetheless, it seems to be an interesting marker, as high white cell count (over 10 000/mm3) with polynuclear eosinophil cell count under 40/mm3 was associated with bacterial infectious diseases (15,16); eosinophils < 10/mm3 alone or in association with high white blood cells count or high CRP blood level was strongly associated with sepsis (specificity 94-98 %) in an emergency department (17), eosinophils < 40/mm3 was a strong mortality (all cause) predictor (Hazard Ratio 1.85 (CI95% 1.01-3.42), p = 0.046) in intensive care unit (ICU) (18). Along with these observations, studies on SARS-COV-2 found that low count eosinophil seemed to be correlated with the prognosis (19–22). Interestingly, eosinophil levels improved in patients prior discharge, suggesting that following their rate might help to monitor betterment (23). In this way, eosinopenia could be a prognosis marker for mortality (18,24,25); however, none of these reports included geriatric patients.

Thus, this study aimed to seek for an association between absolute eosinopenia (eosinophil count < 10 /mm3) and mortality in older adults suffering from COVID-19 hospitalized in a specific geriatric ward.

Materials And Methods

Study Design, Setting, and Participants

This monocentric retrospective cohort is an ancillary study of the Zerah and al cohort which took place from March 13 to April 15 2020 (10). Informed consent was obtained for all participants and this study was approved by the University Hospital of Paris research committee on April 17, 2020 and by the institutional ethics board of Sorbonne University on May 11th, 2020 (2020-CER-2020-43). This report follows the STROBE recommendations.

Inclusion criteria were: age 70 years old and older, hospitalized for COVID-19 in a COVID-19 unit. Non-inclusion criteria were the patients without health insurance or who refused use of their medical data, other diseases or medications that might modify eosinophil blood cell count: immunosuppression (HIV with CD4 < 200/ mm3), chronic corticosteroid use, asthma, chemotherapy or immunosuppressive agents, documented lymphoproliferative or myeloproliferative disorders and documented parasitic diseases.

The diagnosis of COVID-19-19 was confirmed by a nasopharyngeal polymerase chain reaction (RT-PCR) for SARS-CoV-2, according to the WHO.

Data Collection Methods and Data Management

Patients' medical records were reviewed and analyzed by trained physicians. We included baseline characteristics before COVID-19-19: age, gender, home or nursing home residence, previous medical history, and chronic medications. Comorbidity severity was assessed with the Charlson's index (11) and functional status was assessed by the Activities of Daily Living (ADL) scale (6 basic human functions: bathing, dressing, toileting, transfer, continence, and feeding; 1 point for each function (9)). ADL was categorized in a binary variable: ADL < 3. Due to the very low eosinophils count on this cohort, cut-off for eosinopenia was < 10/mm3 because it has been associated with poor outcome during sepsis and defined absolute eosinopenia (17).

Acute events were recorded: acute atrial fibrillation, acute heart failure, acute pulmonary edema, altered consciousness defined by Glasgow score < 14, thromboembolic or hemorrhagic event, acute kidney failure identified according to the Kidney Disease Improving Global Outcomes (KDIGO) definition (26), fecal impaction, urinary retention, pressure ulcer, quick Sepsis-related Organ Failure Assessment ≥ 2 (qSOFA), defined by a range 0-3, with 1 point each for systolic hypotension ($\leq$ 100 mmHg), tachypnea ($\geq$ 22/min) or altered consciousness (Glasgow coma score < 14) (27). Biological data during infection were also collected: white blood cell count, neutrophil count, eosinophil count, lymphocytes count, platelets count, hemoglobin level, presence of a liver injury (aspartate aminotransferase or alanine aminotransferase $\geq$ 2 times normal level) and cholestasis with alkaline phosphatase or gamma-glutamyltransferase $\geq$ 2 times normal level. Prescription of antibiotic was recorded. Data at discharge were also reported: vital status (alive or dead), length of stay and discharge location (home; nursing home; long term stay unit rehabilitation center or other).

Statistical analysis

As we included all patients from the center, no power calculation was done *a priori*. Normality was assessed by a graphical representation of the distribution. Data are presented with mean and standard deviation (SD) for continuous variables and count (percentage) for categorical variables. A t-test was used for continuous variables and chi-squared test or Fisher's exact test for categorical variables. Patient characteristics are described overall and according to mortality status during the stay in the acute geriatric stay.

We assessed for missing values and their distributions in the two groups (deceased or survivor). They represented overall less than 8% of all of the data and 4% for the variable used in the multivariate analysis. Thus, no imputation of the missing data was performed.

We performed a logistic regression with adjustment on three variables as such: deceased = Intercept + x * Age + y * Sex + z * ADL. No stepwise was done due to the limited power and the number of missing data. ADL was chosen because it was a significant factor in the main study.

Analyses were performed with R V4.0.0.

Results

One hundred and eighteen patients were included during the study period. Demographic and clinical data of the population are presented **in table 1**. No statistical difference was found between surviving or deceased patient regarding age and sex (mean age (SD) was 87 years (7); p = 0.542)) and 40 (34%) were male (p=0.07). The age adjusted Charlson comorbidity index was high in the 2 groups with a trend for a higher score for the deceased (mean (SD) = 4.7 (2.7) vs 5.7 (2.9), p = 0.097), as well as a more frequent ADL score < 3 (47 (55%) for survivors vs. 23 (72%), p=0.06).

Differences for the two most frequent acute events were statically different:

- qSOFA score ≥ 2 at admission for 44 patients (37%) in total; 20 (23%) in the survivor group vs. 23(72%) in the deceased group (p < .001);
- Acute kidney injury concerned 37 patients (31%); 15 (17%) of the survivors vs. 22 (69%) of the deceased (p< .001).

Biological data are described in **table 2.** Regarding blood cells count, absolute eosinopenia (eosinophil count < 10/mm3), which concerned 53 patients (45%), was statistically different between our 2 groups: 36 patients (42%) vs. 17 subject (53%); p =0.008) respectively in survivors and deceased groups, as well as all biological variables except for the minimum count of lymphocytes which mean (SD) was 894 (512) /mm3.

The mean (SD) length of stay was 12 (7) days with a statistical difference between survivors (14 (7) days) and deceased (9 (8) days). 32 (27%) patients have died during their stay in our acute COVID-19 ward. As for the survivors, 42 (36%) patients were transferred to a rehabilitation ward, 33 (28%) patients returned home and 5 (4%) were transferred to another ward such as palliative care.

The multivariate analysis shows that low eosinophil count was associated with an OR of 3.54 (1.2-11.4) after adjustment on age, sex and ADL (**figure 1**).

Discussion

This study showed that an absolute eosinopenia (eosinophils count< 10/mm3) was associated with mortality: OR (CI95%) 3.5 (1.2-11.4) after adjustment on age, gender, and disability (i.e., ADL) in elders suffering from COVID-19. At first glance, these results seem to be in line with literature (28–32) where low eosinophil count is associated with poorer prognostic and conversely, a better prognosis when subjects present eosinophilia due to asthma (33,34).

However, this result does not seem consistent with Lucas and al (13). In this longitudinal analysis of immunological events in moderate and severe COVID-19 on 135 patients, compared to 108 healthy volunteers, they found that severe cases were associated with a higher eosinophil rate compare to moderate and control cases (1 to 7 longitudinal time points): p = 0.016 for severe cases vs moderate

cases and $p < 0.01$ for severe cases vs. controls. In order to discuss this difference between our results and this immunology mapping, some points need to be clarified.

First, in the Lucas and al. cohort, participants were much younger (mean age (SD) = 63 (17)) than our participants (mean age of 87 years old (6)). One might hypothesis that immunosenescence and inflammaging might be involved in the differences observed. Indeed, inflammaging is a chronic inflammatory state observed in the elderly where there is an elevation of pro-inflammatory mediators such as including interleukin-1, beta interleukin-6 and tumor necrosis factor alpha (35). This chronic pathological state may be worsened during the “cytokine storm” in which it has been found a significant elevation of the same factors on younger subjects and results in an immunodeficiency (36).

Secondly, as exposed in introduction, eosinophils are likely to be involved during immune responses against viruses. However, it has been described that during an acute inflammation state caused by bacterial infection, there is a drop of circulating eosinophils due accumulation of eosinophils at the periphery of the inflammatory site, and an inhibition of egress of eosinophils from the bone marrow which leads to inhibition of eosinopoiesis (37). Furthermore geriatric patients may be more vulnerable to bacterial secondary infection such as aspiration pneumonia due to swallowing disorder, are highly prevalent in geriatric population (44% in geriatric acute care) (38); the observed eosinopenia in this study might be in part explained by bacterial secondary infections as it can be a marker of bacterial sepsis. Moreover, even though recruitment in lungs tissue does not seem to appear during a COVID-19 infection (39), it has been suggested by Lindsley and al (40) that these eosinopenia could be the result of a similar mechanism than the one described during bacterial infection. Thus, eosinopenia might be a sign of host exhaustion imputable to the elimination of COVID-19 virus (41).

To conclude, on could make the assumption that a poor prognostic of a SARS-CoV-2 infection can, among other factors, be the result of a lack of the antiviral activity and immunomodulation provided by the eosinophils. Hence, it might be a marker to start specific therapy such as antiviral or immunomodulator.

We acknowledge that the non-inclusion of neutrophils in the multivariate analysis can be a major limit. However, due the conception of the main study, the contemporaneous rate of neutrophils was not accounted for and the minimum or maximum neutrophils count was not useable in the same model as the lowest eosinophil count.

The retrospective nature of this study precludes any causal inference of the results. Its lack of power is also a limit as it allowed us a limited multivariate analysis.

Conclusions and Implications

Although this study suffers some limits, this result if confirmed in other study, gives an additional element for clinician to predict the outcome of a SARS-COV-2 infection on geriatric patients, and calls for immunologist to explore more globally the impact of inflammaging on SARS-CoV-2 infection.

Declarations

Ethics approval and consent to participate: This study approved by the research committee of the University Hospital of Paris on April 17, 2020 and by the institutional ethics board of Sorbonne University on May 11th, 2020 (2020-CER-2020-43). Informed consent was obtained for all participants. This study is in line with article L1121-1 of French Public Health and French data protection authority.

Consent for publication: Not applicable.

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- Study concept and design: Duron Emmanuelle, Baudouin Edouard
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Tables

Table 1: Baseline characteristics and acute events

haracteristics	Total	Survivor	Deceased	*p*
	n = 118	n = 86 (73%)	n = 32 (27%)	
ocio-demographic data				
ge, mean (SD)*	87 (7)	86.7 (6.2)	87.6 (6.7)	0.542
ale, n (%)	40 (34)	25 (29)	15 (47)	0.07
omorbidities, mean (SD)				
djusted Charlson comorbidity Index	5 (3)	4.7 (2.7)	5.7 (2.9)	0.097
Missing values, n (%)	16 (14)	14 (16)	2 (6)	
umber of treatments	7.3 (3.5)	7.3 (3.6)	7.3 (3.2)	0.975
Missing values, n (%)	2 (2)	2 (2)	0 (0)	
utonomy				
ving in nursing home, n (%)	73 (62)	50 (58)	23 (72)	0.246
Missing values, n (%)	3 (3)	3 (3)	0 (0)	
DL<3, n (%)	70 (59)	47 (55)	23 (72)	0.06
Missing values, n (%)	10 (8)	7 (8)	3 (9)	
MI, mean (SD)	23.1 (4.9)	22.9 (4.7)	23.8 (5.8)	0.524
Missing values, n (%)	32 (27)	19 (22)	13 (41)	
cute events, n (%)				
cute atrial fibrillation	4 (3)	2 (2)	0 (0)	0.571
Missing values, n (%)	2 (2)	0 (0)	2 (1)	
cute heart failure	6 (5)	3 (3)	3 (9)	0.189
Missing values, n (%)	1 (1)	0 (0)	1 (3)	
cute coronary event	1 (1)	1 (1)	0 (0)	0.99
Missing values, n (%)	2 (2)	1 (1)	2 (6)	
lasgow score < 15	39 (33)	12 (14)	27 (84)	< .001
Missing values, n (%)	2 (2)	1 (1)	1 (3)	
hromboembolic event	1 (1)	1 (1)	0 (0)	0.99
Missing values, n (%)	4 (3)	2 (2)	2 (6)	

haracteristics	Total	Survivor	Deceased	*p*
	n = 118	n = 86 (73%)	n = 32 (27%)	
emorrhagic event	5 (4)	4 (5)	1 (3)	0.99
Missing values, n (%)	2 (2)	2 (2)	1 (3)	
cute kidney injury	37 (31)	15 (17)	22 (69)	< .001
Missing values, n (%)	5 (4)	3 (3)	2 (6)	
SOFA ≥ 2	44 (37)	20 (23)	23 (72)	< .001
Missing values, n (%)	13 (11)	8 (9)	5 (16)	
xygen n (%)				
None	54 (46)	48 (56)	6 (19)	
< 9 l/min	52 (44)	37 (43)	15 (47)	
9-15 l/min	12 (10)	1 (1)	11 (34)	
pecific treatments				
ntibiotics introduction, n (%)	75 (64)	52 (60)	23 (72)	0.252

*SD : Standard deviation
Abbreviations: ADL: Activities of Daily Living ; BMI: Body Mass Index; qSOFA: quick Sequential Organ Failure Assessment, Acute kidney injury: identified according to the Kidney Disease Improving Global Outcomes (KDIGO) definition.

Table 2: Laboratory findings

iological characteristics	Total	Survivor	Deceased	*p*
	n = 118	n = 86 (73%)	n = 32 (27%)	
ax Hemoglobin (g/dL)	13.2 (1.8)	13.2 (1.8)	13.4 (2)	0.674
Missing values, n (%)	9 (8)	1 (1)	8 (25)	
in Hemoglobin (g/dL)	11.4 (1.7)	11.3 (1.7)	11.6 (1.7)	0.532
Missing values, n (%)	9 (8)	1 (1)	8 (25)	
ax leukocyte count nm3)	7943 (2979)	7410 (2699)	9830 (3209)	0.002
Missing values, n (%)	9 (8)	1 (1)	8 (25)	
in leukocyte count mm3)	4704 (1925)	4320 (1172)	6063 (3147)	0.013
Missing values, n (%)	9 (8)	1 (1)	8 (25)	
ax neutrophil count mm3)	5629 (2688)	5025 (2249)	7934 (3019)	< .001
Missing values, n (%)	12 (10)	2 (2)	10 (31)	
in neutrophil count mm3)	3043 (1790)	2646 (1066)	4495 (2887)	0.006
Missing values, n (%)	11 (9)	2 (2)	9 (28)	
ax eosinophil count mm3)	150 (152)	169 (160)	79 (86)	< .001
Missing values, n (%)	12 (10)	2(2)	10 (31)	
in eosinophil count mm3)	31(58)	36(62)	13(36)	0.028
Missing values, n (%)	11 (9)	2(2)	9 (28)	
ax lymphocyte (/mm3)	1496 (689)	1521 (655)	1400 (816)	0.53
Missing values, n (%)	12 (10)	2 (2)	10 (31)	
in lymphocyte count mm3)	894 (512)	920 (494)	803 (570)	0.37
Missing values, n (%)	10 (8)	2 (2)	8 (25)	
ax platelet count (/mm3)	313 898 (108 902)	327 529 (108 814)	263 522 (95 400)	0.009
Missing values, n (%)	10 (8)	1 (1)	9 (28)	
in platelet count (/mm3)	194 000 (62 931)	198 518 (58 771)	178 000 (75 095)	0.23
Missing values, n (%)	9 (8)	1 (1)	9 (25)	

ax CRP (/mm3)	110.8 (87)	205.1 (85.5)	84.2 (66.5)	<.001
Missing values, n (%)	9 (8)	1 (1)	8 (25)	
iver Cytolysis, n (%)	9 (8)	4 (5)	5 (16)	0.035
Missing values, n (%)	62 (53)	44 (51)	18 (56)	
holestasis, n (%)	11 (9)	5 (6)	6 (19)	0.018
Missing values, n (%)	61 (52)	43 (50)	18 (56)	

Figures

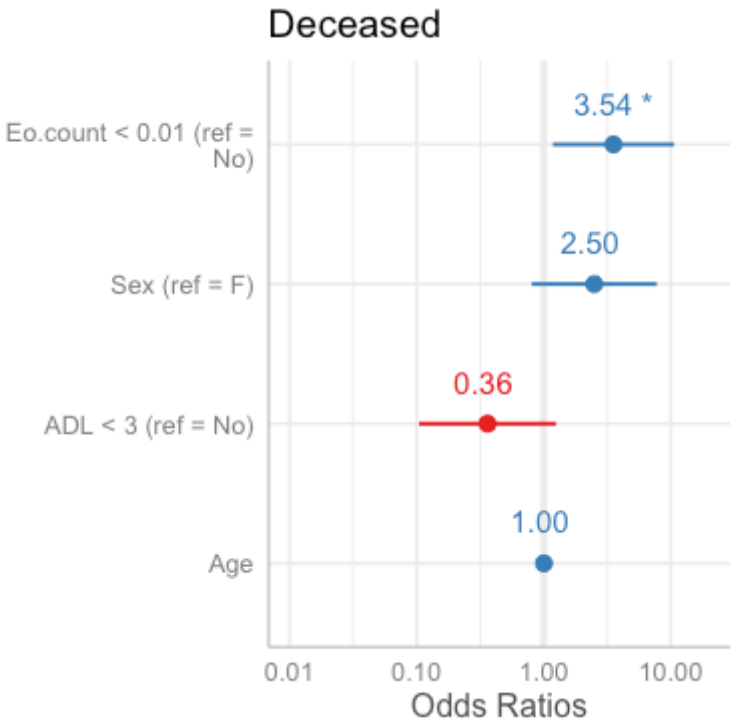

Figure 1

Multivariate analysis (deceased status adjusted on age, sex, eosinophil count and functional status), Forest Plot OR (IC 95%): Age: 1.0 (0.9-1.1, Sex (ref = F): 2.5 (0.8-7.9), Eosinophil count: 3.6 (1.2-11.4), ADL < 3 (ref = No): 0.4 (0.1-1.2)