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Ferritin as prognostic marker in COVID-19: the FerVid study

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ABSTRACT

Background: In COVID-19 patients the progressive clinical deterioration seems secondary to the activation of a cytokine storm. Ferritin is considered a direct mediator of the immune system and some evidences suggested a shared physio-pathogenic basis between COVID-19 and 'Hyperferritinemic Syndromes.' The aim of our study was to evaluate the prognostic role of ferritin in COVID-19 patients.
Methods: We retrospectively studied consecutive COVID-19 patients admitted to four Italian Internal Medicine Units. Role of potential prognostic markers was evaluated with binary logistic regression analysis and results were expressed as odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). Poor outcome was defined as death or need to transfer in the intensive care unit.
Results: Two hundred patients were included (mean age 68.75 ± 13.22 years). Ferritin value was highly elevated (>3000 ng/mL) in 8% of our population; 13% of patients were transferred to intensive care units and 12% of patients died. At multivariate analysis, highly elevated ferritin levels (OR 16.67 C.I. 4.89–57.57 $p < 0.001$) and hemoglobin < 10 g/dL (OR 8.88 C.I. 2.02–39.09 $p = 0.004$) were independently associated with a bad outcome.

Patients with ferritin values > 3000 ng/ml appeared to have an inflammatory activation with elevated values of CRP and D-dimer and low values of lymphocyte count.
Conclusion: Our results confirm the prognostic role of ferritin in hospitalized COVID-19 patients. Patients with high ferritin levels should be considered critically ill and treated in an adequate setting. Furthermore, COVID-19 seems to share some characteristics with hyperferritinemic syndromes with potential therapeutic implications.

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Ferritin; COVID-19; hyperferritinemic syndromes

Introduction

COVID-19, caused by SARS-CoV-2, is rapidly expanding worldwide and, despite most of the cases have good prognosis, it can turn into acute respiratory distress syndrome (ARDS) and death. Thus, it is of interest for clinicians to identify simple and accurate prognostic markers to promptly treat critically ill patients. Several studies have pinpointed some markers in serum of COVID-19 patients with a critical role of inflammation in the progression of disease.

In the last few years, literature has identified ferritin as a signaling molecule and a direct mediator of the immune system. Hyperferritinemia is associated with several clinical conditions and with worse prognosis in critically-ill patients [1].

Macrophage activation syndrome (MAS), adult onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (cAPS), and septic shock are four uncommon clinical conditions characterized by high levels of ferritin. These four conditions share similar clinical and laboratory features and also respond to similar treatments, suggesting that there is an underlying common pathogenic mechanism. The clinical evolution of some medical cases associated with COVID-19 and the findings from autoptic studies suggested a plausible shared physio-pathogenic basis between COVID-19 and 'Hyperferritinemic Syndrome' [2]. Recent studies suggest that high levels of ferritin could be associated both with a higher probability of developing ARDS and with increase mortality. Therefore, we may hypothesize that, as for the hyperferritinemic syndromes, ferritin could play a crucial physio pathogenic role in COVID-19 [3].

The aim of our study was to evaluate ferritin prognostic value in patients with COVID-19.

Material and methods

In this retrospective multicenter study, consecutive patients with SARS-CoV-2 infection who were admitted to the Internal Medicine COVID-19 Units of four Italian centers (Florence, Legnano, Viareggio, Varese) were included. Diagnosis of COVID-19 was confirmed by PCR-RNA detection of SARS-CoV -2 on nasopharyngeal swabs or bronchoalveolar lavage. For each patient we collected epidemiologic data (age, sex); comorbidities (smoking habit, hypertension, obesity, chronic renal impairment, diabetes mellitus, cardiovascular diseases

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including ischemic heart disease, heart failure and atrial fibrillation, history of stroke, solid or hematologic neoplasia); key symptoms of COVID-19 infection (fever, dyspnea, cough, tachypnea, diarrhea, myalgia or fatigue, ageusia, and/or anosmia), markers of respiratory function (Partial pressure of oxygen/Fraction of inspired oxygen, P/F ratio), and results of laboratory test on admission including: full white blood cells count (WBC), hemoglobin (Hb), platelet count (PLT), lymphocyte count, international normalized ratio (INR), D-dimer, creatinine, creatine phospho-kinase (CPK), lactate dehydrogenase (LDH), serum ferritin and C reactive protein (CRP).

Case report forms were prepared by the coordinating center (Florence) and were sent to all participating centers. Local investigators were asked to fill out the form and to send it back to the coordinating center. All data were cross-checked and centrally validated.

The primary endpoint of our study was to evaluate ferritin prognostic value in patients with COVID-19. In-hospital mortality or need for intensive care treatment were considered adverse outcomes for the study purpose. The independent prognostic role of ferritin was evaluated by means of multivariate analysis considering other potential risk factors.

According to recent literature we choose 3000 ng/ml as ferritin value for hyperferritinemic syndrome diagnosis [1].

Statistical analysis

Continuous variables were presented as mean ± standard deviation if normally distributed (evaluated with Shapiro-Wilk test) or with median and interquartile range if not, while dichotomous variables are expressed as number and percentage of patients for each category.

Factors associated with adverse outcome (in-hospital mortality or need for intensive care treatment) were identified through univariate analysis. In general, statistical comparisons were performed using Student's t test for the comparison of continuous normally distributed variables and Mann–Whitney U test for continuous not normally distributed variables. The Chi-square test or Fisher's exact test were used for the comparison of categorical variables.

We then performed logistic regression multivariate analysis (using a stepwise regression model, with an entry probability for each variable set at 0.05) to assess the independent contribution of the variables in predicting the chosen outcome. Variables with more than 10% of missing data were not included in the multivariate model to avoid odd results.

The receiver-operating characteristic (ROC) analysis was used to obtain the area under the curve (AUC) to summarize the overall diagnostic accuracy of the ferritin levels; the Youden's index was used to obtain the optimum ROC's cutoff. The results were considered statistically significant for values of $p < 0.05$ and they were expressed as odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). Statistical analysis was conducted with SPSS statistical software version 17.0 (SPSS Chicago, Illinois).

Due to the exploratory nature of our study a sample of convenience of 200 patients was chosen.

However, since we hypothesized that an adverse outcome occurred in at least 25% of our population we should be able to set up a multivariate model with up to five covariates to evaluate the independent role of potential prognostic factors (according to the commonly used rule of thumb).

The study was carried out and reported according to the STROBE guidelines for observational studies [4].

Institutional Review Board of each participating center approved the study waiving the need for written informed consent due to the retrospective nature of the study.

Results

We analyzed data of 200 patients admitted to four Italian centers (Florence, Varese, Viareggio, Legnano). Mean age was 68.75 ± 13.22 years, with a prevalence of men (65% of our population). The main comorbidity was hypertension (60%) followed by obesity (23%) and diabetes mellitus (19%). In our population 52% of patients had two or more comorbidities at the same time; 88.5% of patients had never smoked, 7.5% were former smokers and 4% were active smokers at time of admission. On admission, most patients had fever (81.5%), with a mean body temperature of 37.81 ± 0.73°C; cough (54%) and tachypnea (24.5%) were quite common; diarrhea affected 11.5% of patients, whereas symptoms like ageusia, anosmia and conjunctivitis were uncommon. P/F ratio was 213.12 ± 108.18.

Time between symptoms onset and hospitalization was on average 8.98 ± 4.90 days, Table 1. On admission mean ferritin

Table 1. Epidemiological and clinical findings.

	Patients (n. %)
Characteristics	**n 200**
Age (years)	68.75 ± 13.22
Sex	
Male	130 (65%)
Female	70 (35%)
Current smoking	8 (4%)
Days from onset of symptoms to hospitalization (days)	8.98 ± 4.90
Hospitalization length (days)	8.01 ± 6.02
Discharged	150 (75%)
Transferred in ICU	26 (13%)
Deaths	24 (12%)
Comorbidities	
Hypertension	120 (60%)
Obesity (BMI > 30)	46 (23%)
Diabetes	38 (19%)
Stroke	24 (12%)
Chronic kidney disease	21 (10.5%)
Malignancy	28 (14%)
Chronic obstructive pulmonary disease	17 (8.5%)
Rheumatic syndrome	4 (2%)
Cardiovascular diseases	53 (26.5%)
2 or more comorbidities	104 (52%)
3 or more comorbidities	57 (28.5%)
Signs and symptoms	
Fever	163 (81.5%)
Dyspnea	131 (65.5%)
Cough	108 (54%)
Tachypnea	49 (24.5%)
Diarrhea	23 (11.5%)
Myalgia or fatigue	20 (10%)
Ageusia and/or anosmia	10 (5%)
P/F ratio	213.12 ± 108.18

BMI: body max index; ICU: Intensive care unit; P/F: Partial pressure of oxygen/Fraction of inspired oxygen.

Table 2. Blood laboratory test results.

	Mean ± standard deviation
Blood laboratory tests	
White blood cell count (x 10^9/L)	7.52 ± 4.30
Hemoglobin (g/L)	13.04 ± 1.91
Platelet count (x 10^9/L)	207.58 ± 79.44
Lymphocyte count (x 10^9/L)	0.95 ± 0.51
INR	1.2 ± 0.4
D-dimer (ng/mL)	1255.02 ± 1339.5
Alanine aminotransferase (U/L)	37.81 ± 28.38
Creatinine kinase (U/L)	294.61 ± 997.09
Lactate dehydrogenase (U/L)	344.93 ± 164.06
Ferritin (ng/mL)	1650.93 ± 2396.39
CRP (mg/L)	119.48 ± 86.4
IL-6 (pg/ml)	33.20 ± 46.91

INR: international normalized ratio; CRP: C reactive protein.

levels were 1650.93 ± 2396.39 ng/mL. Values of the inflammatory markers were summarized in Table 2.

The average length of hospital stay in the internal medicine ward was 8.01 ± 6.02 days; 13% of patients were transferred to intensive care units, whereas 12% of patients died.

Continuous positive air pressure (CPAP) and/or Non invasive ventilation (NIV) was used in 36.5% of the patients.

At univariate analysis, cancer, hypertension, and the presence of three or more comorbidities were significantly more frequent in patients with adverse outcome, Table 3. Among the laboratory tests, platelet count, hemoglobin level, and lymphocyte count were significantly lower in patients with adverse outcome whereas D-dimer, LDH, and ferritin were significantly higher in this latter group, Table 4.

Table 3. Comparative analysis evaluating the association among potential risk factors and adverse outcome.

	Favorable outcome	Adverse outcome	p
Characteristics	**n 150**	**n 50**	
Age (years)	67.85 ± 13.65	71.44 ± 11.54	0.097
Male sex	94 (62.7%)	36 (72%)	0.304
Days from onset of symptoms to hospitalization (days)	9.50 ± 64.69	6.97 ± 5.23	0.073
Comorbidities			
Hypertension	84 (56%)	36 (72%)	0.048
Obesity (BMI > 30)	39 (26%)	7 (14%)	0.119
Diabetes	27 (18%)	11 (22%)	0.537
Stroke	18 (12%)	6 (12%)	1.000
Chronic kidney disease	13 (8.7%)	8 (16%)	0.181
Malignancy	14 (9.3%)	14 (28%)	0.002
Chronic obstructive pulmonary disease	12 (8%)	5 (10%)	0.770
Rheumatic syndrome	2 (1.3%)	1 (2%)	1.000
Cardiovascular diseases	38 (25.3%)	15 (30%)	0.580
2 or more comorbidities	72 (48%)	32 (64%)	0.052
3 or more comorbidities	37 (24.7%)	20 (40%)	0.047
Signs and symptoms			
Fever	122 (81.9%)	41 (82%)	1.000
Dyspnea	97 (64.7%)	34 (68%)	0.733
Cough	88 (58.7%)	20 (40%)	0.033
Tachypnea	33 (22%)	17 (34%)	0.088
Diarrhea	21 (14%)	2 (4%)	0.072
Myalgia or fatigue	7 (4.7%)	2 (4%)	1.000
Ageusia and/or anosmia	7 (4.7%)	3 (6%)	1.000
P/F ratio	206.73 ± 100.83	232.95 ± 124.58	0.183

P/F: Partial pressure of oxygen/Fraction of inspired oxygen; BMI: body max index.

To exclude collinearity and redundancy, cancer and hypertension were not included in the multivariate model since they were potentially included in the '3 or more comorbidities' covariate.

Furthermore, LDH and d-dimer were missing in more than 10% of patients and they were not included in the multivariate model.

At the multivariate analysis high ferritin levels (>3000 ng/mL (OR 16.67 C.I. 4.89–57.57 $p < 0.001$) and Hb < 10 g/dL (OR 8.88 C.I. 2.02–39.09 $p = 0.004$) resulted significantly associated with the adverse outcome whereas presence of three or more comorbidities, lymphocyte, and platelet count did not.

Patients with ferritin values > 3000 ng/ml appeared to have an inflammatory activation with elevated values of CRP and D-dimer and low values of lymphocyte count, Table 5,6.

The AUC of ferritin levels in predicting adverse outcome was 0.617 (95% CI, 0.49–0.74).

Ferritin level > 3000 ng/mL had a sensitivity of 34% (95% CI, 10.50–34.14) and a specificity of 96% (95% CI, 91.11–98.36) in predicting adverse outcome. The Youden's index identified 3250 ng/dL as optimum cutoff of ferritin's value associated to a poor outcome.

Discussion

Due to the variability in the short-term outcome of COVID-19 patients, identification of prognostic markers in this setting appears of clinical relevance for physicians. In several previous studies, a number of potential clinical and laboratory features were evaluated to better assess the prognosis of these patients [5–7].

In our population including 200 consecutive hospitalized COVID-19 patients from four Italian centers, low hemoglobin levels (OR 8.88 C.I. 2.02–39.09) and in particular high ferritin levels (OR 16.67 C.I. 4.89–57.57) resulted significantly associated with an adverse outcome at multivariate analysis.

High ferritin levels (> 500 ng/mL) were present in more than 50% of our population and 8% of patients had ferritin values highly suggestive for 'Hyperferritinemic syndromes' (> 3000 ng/mL).

Ferritin values > 3000 ng/mL have limited sensitivity (34%) (95% CI, 10.50–34.14) in identifying patients with adverse outcomes, while specificity seems satisfactory (96%) (95% CI, 91.11–98.36). Furthermore, in this subgroup of patients, other inflammatory markers including CRP and D-dimer were altered.

Our results were in agreement with a retrospective study by Ruan et al. [8] in which hospitalized COVID-19 patients with high ferritin levels had a significantly higher risk of death. Furthermore, in a recent systematic review and meta-analysis of the literature [9], patients suffering from COVID-19 with a poor outcome had a higher serum ferritin levels than patients with a good outcome.

Hyperferritinemia is the main hallmark of the 'Hyperferritinemic syndromes' and the remarkably high levels of ferritin seen in these conditions seem to be not just the product of the inflammation, but can also actively contribute to the development of the cytokine storm [10].

The umbrella term 'Hyperferritinemic syndromes' encompasses four potentially life-threatening clinical conditions

Table 4. Univariate analysis evaluating the association among potential laboratory tests and adverse outcome.

	Favorable outcome	Adverse outcome	p
Blood laboratory tests			
White blood cell count (x 10^9/L)	7.59 ± 4.55	7.30 ± 3.42	0.658
White blood cell count < 4000 (x 10^9/L)	12 (8.8%)	6 (12%)	0.382
Hemoglobin (g/L)	13.23 ± 1.84	12.32 ± 2.03	0.022
Hemoglobin < 10 g/L	5 (3.3%)	6 (12%)	0.011
Platelet count (x 10^9/L)	216.19 ± 80.69	181.74 ± 70.21	0.007
Platelet count < 100 (x 10^9/L)	6 (4%)	6 (12%)	0.076
Lymphocyte count (x 10^9/L)	1.08 ± 0.55	0.77 ± 0.38	0.003
INR	1.25 ± 0.42	1.38 ± 0.36	0.453
D-dimer (ng/mL)	857.72 ± 471.35	1905.14 ± 1945.89	0.003
Alanine aminotransferase (U/L)	40.46 ± 28.59	33.79 ± 28	0.296
Creatine kinase (U/L)	354.27 ± 1256.58	196.76 ± 211.92	0.437
Lactate dehydrogenase (U/L)	310.41 ± 109.99	393.2 ± 210.97	0.022
Lactate dehydrogenase > 300 U/L*	24 (18,4%)	20 (54%)	<0.001
Ferritin (ng/mL)	1309.39 ± 1618.34	2993.55 ± 4026.43	0.001
Ferritin > 500 ng/mL	88 (58.6%)	23 (46%)	0.809
Ferritin >1000 ng/mL	56 (37.3%)	17 (24%)	0.241
Ferritin >3000 ng/mL	6 (4%)	10 (20%)	<0.001
CRP (mg/L)	119.41 ± 86.83	119.7 ± 86.03	0.985

INR: international normalized ratio; CRP: C reactive protein.
* data evaluated on a total of 167 patients.

Table 5. Univariate and multivariate analyses evaluating the association among potential risk factors and adverse outcome.

	Univariate analysis	Multivariate analysis		
Variables	O.R.	O.R.	C.I.	p
Ferritin >3000 ng/mL	3.30	16.67	4.89–57.57	< 0.001
Hemoglobin level <10 g/dL	5.40	8.88	2.02–39.09	0.020
Platelets <100 x10^9/L	3.30	NS	NA	1.000
3 or more comorbidities	2.06	NS	NA	0.390
Lymphocyte count (x 10^9/L)	-	NS	NA	0.079

Table 6. Blood laboratory tests in 16 patients with ferritin values > 3000 ng/dl.

Blood laboratory tests	
White blood cell count (x 10^9/L)	8.54 ± 2.18
Hemoglobin (g/L)	13.13 ± 1.77
Platelet count (x 10^9/L)	173.75 ± 78.9
Lymphocyte count (x 10^9/L)	0.71 ± 0.54
INR	1.36 ± 0.28
D-dimer (ng/mL)	2328 ± 1965.05
Creatinine (mg/dL)	2.67 ± 2.16
Alanine aminotransferase (U/L)	40.5 ± 44.68
Creatinine kinase (U/L)	207.83 ± 113.88
Lactate dehydrogenase (U/L)	387.29 ± 128.71
Ferritin (ng/mL)	6759 ± 4340.34
CRP (mg/L)	183.29 ± 91.89

INR: international normalized ratio; CRP: C reactive protein.

namely MAS, AOSD, CAPS, and septic shock. These conditions shared a number of other clinical and laboratory features [1].

In the SARS-CoV-2 infection a massive cytokine storm activation may be present: as MAS and other conditions leading to the clinical phenotype of the cytokine storm syndrome, severe COVID-19 is characterized by elevated levels of IL-6, lower levels of lymphocytes in peripheral blood and high inflammatory parameters associated to hypercoagulability [1,11]. Moreover, the majority of infiltrated immune cells in lung lesions are monocytes and macrophages, but minimal lymphocytes infiltration is present [12,13]. Last, in recent studies the median time between illness onset and a clinical improvement or worsening is about 10–14 days a time frame consistent with cytokines activation Thus, some authors hypothesized that, like in hyperferritinemic syndromes, macrophage activation could actively contribute to ferritin production [14]. In our study patients with higher ferritin levels also had an inflammatory profile characterized by low values of hemoglobin and concurrent activation of the coagulation cascade with low values of platelets as well as in MAS.

Nevertheless, COVID-19 disease has some distinctive characteristics when compared to the four established hyperferritinemic syndromes: splenomegaly and hepatomegaly have never been described; hypertriglyceridemia and antiphospholipid antibodies have not been consistently associated with this syndrome; coagulation abnormalities of COVID-19 are characterized by increased levels of D-dimer and fibrinogen, mild thrombocytopenia and slight or no change in PT [15].

Especially COVID-19-associated coagulopathy seems to be different from bacterial sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC), where the increase of PT and the decrease of platelets count and fibrinogen iare predominant with normal or low D-dimer levels due fibrinolysis suppression [16].

These concepts may guide and support therapeutic choices, as all these entities respond to a similar approach including anti-inflammatory and immunomodulatory agents such as glucocorticoids, IVIg, cyclosporin, IL-1 and IL-6 inhibition.

The results of our study may have important implications for clinical practice. Assessment of ferritin level may help in early identification of patients at high risk of poor outcome who should be treated in a more protected setting. Furthermore evaluation of ferritin can help in making decisions related to treatment in order to prevent complications and/or death.

In a recent randomized controlled trial (RCT) in patients hospitalized for Covid-19, the use of dexamethasone, introduced at least 7 days after symptoms onset, resulted in lower 28-day mortality among patients with hypoxemic respiratory failure [17].

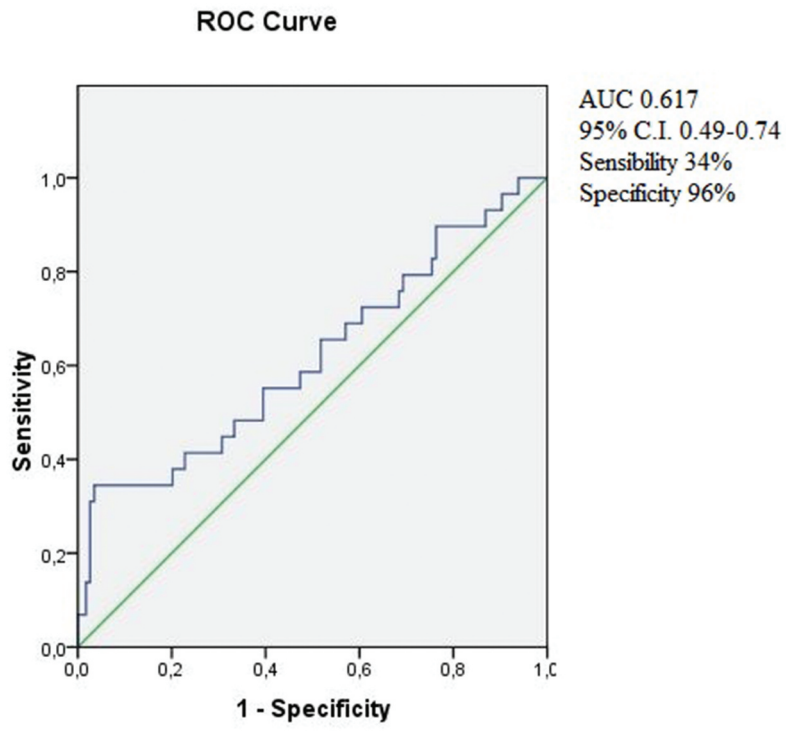

Image 1. ROC evaluating the accuracy of ferritin value > 3000 ng/ml in predicting the adverse outcome.

Evidence on the role of Tocilizumab, an interleukin 6 receptor antagonist, is less compelling. In critically-ill COVID-19 patients several retrospective or prospective cohort studies suggest a potential efficacy of this humanized monoclonal antibody in reducing cytokines response [18,19] although data from RCTs are still lacking.

Conversely to other studies, the relationship between diabetes and poor outcome was not significant in our population; this was probably due to lack of data related to severity and duration of chronic disease.

Our study has some limitations. First, the design of the study is retrospective. However, to overcome at least some of the limitations that are intrinsic to retrospective studies to avoid misleading results we paid meticulous attention in the ascertainment of the reported data. Furthermore, due to the retrospective study design, not all laboratory tests were done in every patient, including d-dimer, LDH and IL-6 (only available in 20% of patients). Thus, their role might be underestimated in predicting in-hospital death. Furthermore, in our study laboratory parameters were evaluated at the time of hospital admission only. Therefore, the potential prognostic role of their variation during hospital stay could not be evaluated. Last, due to the limited sample of our study population the likelihood of a false negative or positive results is not negligible. However, the strength of association between high ferritin values and adverse outcome makes this eventuality extremely unlikely.

Conclusions

Results of our study confirm the prognostic role of ferritin factor in patients hospitalized with COVID-19. Patients with high ferritin levels should be considered critically-ill and treated in an adequate setting. Furthermore, our findings suggest that COVID-19 could share some characteristics with hyperferritinemic syndromes with crucial therapeutic implications. However, other large prospective studies are needed to confirm our preliminary findings and to evaluate potential specific treatments.

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Author contributions

OP conceived of the presented idea. OP and LC developed the theory and performed the computations. FD verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

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