Electrolyte imbalance in patients with COVID-19 pneumonia

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Introduction
Coronavirus disease 2019 (COVID-19) is an unrelenting emerged pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This pandemic led to millions of infections and deaths worldwide, affecting society, healthcare systems, and governmental policies (1-4). Patients with COVID-19 exhibit mild to severe presentations, among which approximately 15% of the patients experience severe pneumonia, and less than 5% of them develop acute respiratory distress syndrome and multiple organ failure (5).

The exact mechanism of COVID-19 infection is partially elucidated, but to date, it has been suggested that SARS-CoV-2 invades human cells through binding of its spikes to angiotensin I converting enzyme 2 (ACE2) on the cell membrane (6). This enzyme is generally expressed on the cell surface of different tissues, particularly in the lungs.

Implication for health policy/practice/research/medical education:
In the study on 323 patients with COVID 19 pneumonia, we found that electrolyte imbalances are common laboratory abnormalities during COVID-19. However, we found no associative role, since ions balance plays a crucial prognostic role for COVID-19.

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Physiologically, ACE2 has a crucial role in the renin-angiotensin system (RAS), controlling blood pressure and electrolyte balance. In patients with COVID-19, SARS-CoV-2 binds ACE2 and induces degradation of ACE2, which leads to reabsorption of sodium and water, the elevation of blood pressure, and potassium excretion. An emerging body of evidence represents other electrolyte imbalances in patients with COVID-19 (7,8).

Sodium, calcium, potassium, chloride, phosphate, and magnesium are the common electrolytes involved in many metabolic and homeostatic functions such as enzymatic and biochemical reactions, neurotransmission, and hormone function. Electrolytes have to be balanced for the management of many clinical conditions (9). Electrolyte imbalance is generally defined as an abnormality in fluids and electrolytes concentration. Various mechanisms such as impaired absorption and distribution, excessive or inadequate administration, hormonal changes, altered excretion via gastrointestinal and renal losses are responsible for electrolyte imbalance (10). Recent studies have presented that, patients with more severe COVID-19 exhibit a higher proportion of electrolyte imbalance, hypokalemia in particular (11). Besides, sodium metabolism imbalance was a prognostic factor in patients with COVID-19 pneumonia. In this regard, hypo and hypernatremia were found in 20.5% and 3.7% of COVID-19 patients, respectively (12).

**Objectives**
The current study aims to assess electrolyte imbalance in hospitalized patients due to COVID-19 in Isfahan, the center of Iran.

**Patients and Methods**

**Study design**
The present observational study was conducted on patients with COVID-19 admitted at Amin, and Al-Zahra hospitals, affiliated at Isfahan university of medical sciences, from May to June 2020.

The study protocol was explained to the patients or their legal guardians; they were reasured about the confidentiality of personal information and signed written consent.

All over 18 years old patients admitted to the mentioned centers with a documented diagnosis of COVID-19 pneumonia according to signs/symptoms, high resolution computed tomography of the chest, and positive polymerase chain reaction (PCR) were included in the study.

**Data collection**
The study checklist consisted of three sections was completed by an internal medicine specialist.

The first section assesses the demographic characteristics (age and gender) and on-admission presentations of the patients, including pulse rate (per minute), respiratory rate (per minute), oxygen saturation (O₂ sat), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (mm Hg), and sublingual body temperature (°C).

Blood samples were taken from the antecubital vein of the patients and sent to a reference laboratory to evaluate complete blood count and differentiation (CBC with diff), C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin, and electrolytes (sodium, potassium, magnesium and calcium).

The COVID-19 infection treatment and electrolyte imbalance correction were conducted according to the national and World Health Organization (WHO) guidelines. Based on the treating physician’s opinion, the electrolytes were rechecked during the hospitalization, if necessary.

Electrolyte imbalance was classified as, hyponatremia (Na < 135 mEq/L) / hypernatremia (Na > 145 mEq/L), hypokalemia (K < 3.5 mEq/L) / hyperkalemia (K > 5.5 mEq/L), hypomagnesemia (Mg < 1.7 mg/dL) / hypermagnesemia (Mg > 2.4 mg/dL) and hypocalcemia (Ca < 8.5 mg/dL) / hypercalcemia (Ca > 10.5 mg/dL). The serum level of sodium was corrected according to plasma glucose. In this term, by any 100 mg/dL serum glucose level above 400 mg/dL, the sodium level was 1.6 mEq reduced.

Besides, the calcium level was corrected based on albumin concentration according to the formula:

\[
\text{Corrected calcium (mg/dL)} = \text{Serum calcium (mg/dL)} + 0.8 \times (4 - \text{serum albumin (g/dL)})
\]

The third section of the study assessed the way of oxygenation (non-invasive ventilation or orotracheal intubation), intensive care unit (ICU) admission requirement duration of hospital stay, and in-hospital outcomes (discharge or death).

**Statistical analysis**
The mean and standard deviation of all statistical indicators were used to describe the quantitative frequency of data. The one-way analysis of variance (ANOVA) statistical test was administered to examine the significance of the quantitative variables in different residency fields. The χ² test was applied to examine the qualitative variables in different fields. Data were analyzed using SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). The P value of less than 0.05 was considered statistically significant.

**Results**

In the present study, 323 patients with COVID-19 pneumonia were enrolled for the analysis. The studied population was predominantly males (184 patients, 57%) and had the mean age of 60.02 ± 17.18. In terms of past medical history, 12 (3.8%) patients had chronic obstructive pulmonary disease, 21 (6.6%) end-stage renal disease, 15 (4.7%) malignancies, 20 (6.3%) cerebrovascular
accidents, 5 (1.6%) pulmonary thromboembolism, 71 (2.3%) diabetes mellitus and 61 (19.1%) ones had ischemic heart disease.

According to Table 1, hypo/hypernatremia, hypo/hyperkalemia, hypo/hypermagnesemia and hypo/hypercalcemia were presented in 14.5%/9.4%, 3.8%/10.3%, 7.9%/9.3%, and 19.9%/10.8%, respectively.

SBP ($P = 0.035$) and time to discharge ($P = 0.031$) were statistically different parameters in the patients with sodium ion balance disturbances. Other demographic, clinical, laboratory tests and in-hospital outcomes were not affected by serum sodium level differences (Table 2).

Based on the findings of Table 3, on-admission potassium level was not associated with any of the manifestations of the patients. Detailed information is shown in this table.

Magnesium imbalance was not associated with any of the demographic, clinical, laboratory, and in-hospital outcomes of the patients, except for oxygen saturation in which those with hypermagnesemia had better saturations than the other two groups ($P = 0.037$; Table 4).

The levels of CRP ($P = 0.25$) and ICU-admission ($P = 0.018$) were remarkably fewer in hypercalcemic patients. The other variables did not differ, as demonstrated in Table 5.

### Discussion

In the current investigation, the balance of the most significant body electrolytes, including sodium, potassium, magnesium, and calcium, were assessed to figure out the potential role of their imbalance on the outcomes of the patients with COVID-19 pneumonia. Our findings showed that approximately 25% of the patients had

| Table 1. The frequency of electrolytes imbalance in patients with COVID-19 |
|---------------------------------|
| No. | %  |
| Sodium |
| Hyponatremia | 46 | 14.5 |
| Normal | 242 | 76.1 |
| Hypernatremia | 30 | 9.4 |
| Potassium |
| Hypokalemia | 12 | 3.8 |
| Normal | 275 | 85.9 |
| Hyperkalemia | 33 | 10.3 |
| Magnesium |
| Hypomagnesemia | 23 | 7.9 |
| Normal | 240 | 82.8 |
| Hypermagnesemia | 27 | 9.3 |
| Calcium |
| Hypocalcemia | 57 | 19.9 |
| Normal | 198 | 69.2 |
| Hypercalcemia | 31 | 10.8 |

| Table 2. The characteristics of the COVID-19 pneumonia patients with sodium imbalance |
|---------------------------------|
| Demographic characteristics |
| Age (years) | 58.17 ± 20.17 | 60.47 ± 17.7 | 58.2 ± 19.85 | 0.64 |
| Gender (male) | 25 (54.3) | 140 (57.9) | 16 (53.3) | 0.832 |

| Clinical manifestations |
|-------------------------|
| Pulse rate (per minute) | 94.20 ± 19.13 | 92.46 ± 18.74 | 94.73 ± 21.81 | 0.881 |
| Systolic blood pressure (mm Hg) | 121.28 ± 17.78 | 123.90 ± 20.53 | 133.20 ± 23.27 | 0.035 |
| Diastolic blood pressure (mm Hg) | 74.39 ± 10.62 | 79.27 ± 42.74 | 80.97 ± 12.77 | 0.167 |
| Respiratory rate (per minute) | 23.07 ± 6.52 | 24.08 ± 6.60 | 22.70 ± 5.07 | 0.316 |
| <90% | 90 (43.5) | 157 (64.9) | 18 (60) |
| O₂ saturation, 90% ≤ O₂ sat < 93% | 14 (30.4) | 46 (19) | 6 (20) |
| ≥93% | 12 (26.1) | 39 (16.1) | 6 (20) |
| Temperature (°C) | 37.42 ± 1.04 | 37.32 ± 0.79 | 37.10 ± 0.68 | 0.470 |

| Laboratory tests |
|-------------------|
| C-reactive protein (mg/L) | 58.93 ± 45.06 | 72.88 ± 46.37 | 75.34 ± 37.23 | 0.135 |
| Lactate dehydrogenase (U/L) | 908.32 ± 526.03 | 1074.09 ± 982.50 | 965.37 ± 544.15 | 0.810 |
| Absolute lymphocyte count (10³ cells/µL) | 1081.06 ± 822.56 | 1283.72 ± 1023.63 | 1277.84 ± 726.35 | 0.362 |

| In-hospital outcomes |
|----------------------|
| ICU admission | 28 (60.9) | 126 (52.1) | 18 (60) |
| Otracheal intubation/non-invasive ventilation | 15 (32.6)/31 (67.4) | 51 (21.1)/191 (78.9) | 22 (73.3)/8 (26.7) |
| Death, n (%) | 12 (26.1) | 48 (19.8) | 7 (23.3) |
| Time to ICU admission (days) | 2 ± 2 | 4 ± 7 | 2 ± 4 |
| Time to discharge (days) | 13 ± 16 | 13 ± 9 | 18 ± 15 |
| Time to death (days) | 14 ± 8 | 14 ± 9 | 12 ± 16 |

Data are expressed as mean ± SD or No. (%).
Table 3. The characteristics of the COVID-19 pneumonia patients with potassium imbalance

|                       | Hyponatremia      | Normal            | Hypernatremia    | P value |
|-----------------------|-------------------|-------------------|------------------|---------|
| **Demographic characteristics** |                   |                   |                  |         |
| Age (years)           | 55.42 ± 16.10     | 60.34 ± 18.45     | 59.18 ± 17.54    | 0.63    |
| Gender (male)         | 5 (41.7)          | 156 (56.7)        | 21 (63.6)        | 0.417   |
| **Clinical manifestations** |                   |                   |                  |         |
| Pulse rate (per minute) | 94.17 ± 2.41      | 92.95 ± 18.51     | 92.12 ± 22.99    | 0.859   |
| Systolic blood pressure (mm Hg) | 124.00 ± 22.55    | 124.54 ± 20.25    | 124.73 ± 25.94   | 0.961   |
| Diastolic blood pressure (mm Hg) | 77.08 ± 14.13     | 78.82 ± 39.81     | 78.79 ± 22.07    | 0.962   |
| Respiratory rate (per minute) | 24.67 ± 8.47      | 23.77 ± 5.74      | 23.91 ± 10.39    | 0.491   |
| Hyponatremia (P value) |                   |                   |                  |         |
| <90%                  | 6 (50)            | 173 (62.9)        | 17 (51.5)        |         |
| O₂ saturation, ≥93%  | 2 (33.33)         | 58 (21.1)         | 6 (18.2)         | 0.198   |
| Temperature (°C)      | 37.60 ± 1.18      | 37.31 ± 0.82      | 37.25 ± 0.73     | 0.775   |
| **Laboratory tests**  |                   |                   |                  |         |
| C-reactive protein (mg/L) | 70.36 ± 43.09     | 72.58 ± 45.84     | 58.63 ± 44.77    | 0.308   |
| Lactate dehydrogenase (U/L) | 1483.70 ± 2372.19 | 960.25 ± 915.92   | 886.03 ± 641.36  | 0.329   |
| Absolute lymphocyte count (10³ cells/μL) | 1086.92 ± 536.20 | 1272.37 ± 994.28 | 1293.33 ± 1044.83 | 0.981   |
| **In-hospital outcomes** |                   |                   |                  |         |
| ICU admission         | 8 (66.7)          | 145 (52.7)        | 20 (60.6)        | 0.464   |
| Orotracheal intubation/non-invasive ventilation | 4 (33.33) / 8 (66.67) | 62 (22.5%) / 213 (77.5%) | 9 (27.3%) / 24 (72.7%) | 0.592   |
| Death, n (%)          | 2 (16.7)          | 60 (21.8)         | 6 (18.2)         | 0.823   |
| Time to ICU admission (days) | 5 ± 4             | 3 ± 5             | 6 ± 13           | 0.557   |
| Time to discharge (days) | 15 ± 9            | 13 ± 10           | 15 ± 4           | 0.138   |
| Time to death (days)  | 26 ± 12           | 13 ± 10           | 15 ± 4           | 0.557   |

Data are expressed as mean ± SD or No. (%).

Table 4. The characteristics of the COVID-19 pneumonia patients with magnesium imbalance

|                       | Hyponatremia      | Normal            | Hypernatremia    | P value |
|-----------------------|-------------------|-------------------|------------------|---------|
| **Demographic characteristics** |                   |                   |                  |         |
| Age (years)           | 62.96 ± 17.81     | 60.97 ± 17.85     | 50.67 ± 20.76    | 0.016   |
| Gender (male)         | 16 (69.6)         | 143 (59.6)        | 12 (44.4)        | 0.177   |
| **Clinical manifestations** |                   |                   |                  |         |
| Pulse rate (per minute) | 94.61 ± 22.05     | 93.36 ± 18.49     | 90.93 ± 23.48    | 0.393   |
| Systolic blood pressure (mm Hg) | 126.04 ± 15.03    | 124.58 ± 21.38    | 121.26 ± 18.16   | 0.593   |
| Diastolic blood pressure (mm Hg) | 75.74 ± 10.58     | 79.25 ± 49.63     | 77.30 ± 13.44    | 0.853   |
| Respiratory rate (per minute) | 23.61 ± 6.44      | 23.85 ± 6.51      | 23.11 ± 5.52     | 0.876   |
| Hyponatremia (P value) |                   |                   |                  |         |
| <90%                  | 14 (60.9)         | 154 (64.2)        | 10 (37)          |         |
| O₂ saturation, ≥93%  | 7 (30.4)          | 45 (18.8)         | 8 (29.6)         | 0.037   |
| Temperature (°C)      | 37.44 ± 0.99      | 37.36 ± 0.86      | 37.09 ± 0.55     | 0.484   |
| **Laboratory tests**  |                   |                   |                  |         |
| C-reactive protein (mg/L) | 57.86 ± 46.45     | 74.49 ± 46.26     | 64.71 ± 36.59    | 0.204   |
| Lactate dehydrogenase (U/L) | 979.25 ± 421.93   | 1072.80 ± 983.94  | 894.80 ± 600.90  | 0.396   |
| Absolute lymphocyte count (10³ cells/μL) | 1218.13 ± 1047.73 | 1252.26 ± 976.62  | 1483.04 ± 117.13 | 0.473   |
| **In-hospital outcomes** |                   |                   |                  |         |
| ICU admission         | 11 (47.8)         | 128 (53.3)        | 15 (55.6)        | 0.849   |
| Orotracheal intubation/non-invasive ventilation | 7 (30.4) / 16 (69.6) | 52 (21.7%) / 188 (78.3%) | 8 (29.6%) / 19 (70.4%) | 0.444   |
| Death, n (%)          | 5 (21.7)          | 47 (19.6)         | 8 (29.6)         | 0.470   |
| Time to ICU admission (days) | 3 ± 4             | 4 ± 7             | 2 ± 4            | 0.231   |
| Time to discharge (days) | 15 ± 9            | 13 ± 10           | 15 ± 4           | 0.138   |
| Time to death (days)  | 26 ± 12           | 13 ± 10           | 15 ± 4           | 0.557   |

Data are expressed as mean ± SD or No. (%).
Electrolyte imbalance in COVID-19

Systolic blood pressure was remarkably higher among the cases with hypernatremia. Similarly, Hu et al showed that hyponatremia is a common condition among hospitalized patients with COVID-19, in general. They also presented that hyponatremia was associated with older age, more severe symptoms, course of the disease, and lung involvement. The comparison of hypernatremic patients with normonatremic ones revealed more length of stay and mortality (13). Sterns et al and Reynolds et al separately presented that gastrointestinal source of fluid loss and renal insufficiency is the underlying conditions associated with sodium imbalance. Therefore, it seems that more severe COVID-19, which leads to multi-organ failure, is responsible for sodium imbalance (14,15).

However, we found no associative outcome between sodium imbalance and the clinical, laboratory, and in-hospital outcomes; it has been emphasized on the role of hypernatremia on clinical outcomes of the patients and its association with heart failure (16). In confirmation, the higher fatality of hypernatremic patients may be attributed to the high expression of ACE2 on myocytes. Therefore, more severe COVID-19 infections can concurrently affect sodium ion balance in the kidneys and myocardium ion-dependent channels (17).

Table 5. The characteristics of the COVID-19 pneumonia patients with calcium imbalance

|                     | Hyponatremia | Normal   | Hypernatremia | P value |
|---------------------|--------------|----------|---------------|---------|
| **Demographic characteristics** |              |          |               |         |
| Age (years)         | 61.93 ± 18.06| 59.67 ± 18.59| 55.71 ± 18.66| 0.32    |
| Gender (male)       | 30 (52.6)    | 121 (61.1)| 15 (48.4)     | 0.267   |
| **Clinical manifestations** |              |          |               |         |
| Pulse rate (per minute) | 90.32 ± 19.38| 93.07 ± 19.63| 97.29 ± 17.87| 0.641   |
| Systolic blood pressure (mm Hg) | 122.26 ± 19.26| 124.91 ± 20.35| 123.19 ± 20.68| 0.483   |
| Diastolic blood pressure (mm Hg) | 75.12 ± 11.61| 80.44 ± 46.12| 74.81 ± 9.94 | 0.258   |
| Respiratory rate (per minute) | 25.58 ± 7.80 | 23.30 ± 6.10 | 23.03 ± 5.72 | 0.108   |
| O₂ saturation, >90% | 39 (68.4)    | 123 (62.1)| 17 (54.8)     |         |
| O₂ saturation, 90% ≤ O₂ sat < 93% | 8 (14) | 42 (21.2) | 6 (19.4) | 0.551   |
| O₂ saturation, ≥93% | 10 (17.5)    | 33 (16.7)| 8 (25.8)      |         |
| Temperature (°C)    | 37.17 ± 0.87 | 37.36 ± 0.85| 37.23 ± 0.76 | 0.082   |
| **Laboratory tests** |              |          |               |         |
| C-reactive protein (mg/L) | 78.06 ± 48.08| 73.05 ± 44.93| 50.39 ± 40.70| 0.025   |
| Lactate dehydrogenase (U/L) | 871.74 ± 478.78| 961.82 ± 763.89| 2336.69 ± 1321.04| 0.821   |
| Absolute lymphocyte count (10³ cells/μL) | 1272.97 ± 944.06| 1261.59 ± 1044.80| 1278.87 ± 811.90| 0.777   |
| **In-hospital outcomes** |              |          |               |         |
| ICU admission       | 24 (42.1)    | 117 (59.1)| 12 (38.7)     | 0.017   |
| Orotracheal intubation/non-invasive ventilation | 11 (19.3) / 46 (80.7) | 52 (26.3) / 146 (73.3) | 4 (12.9) / 27 (87.1) | 0.188   |
| Death, n (%)        | 8 (14)       | 41 (20.7)| 9 (29)        | 0.239   |
| Time to ICU admission (days) | 4 ± 4 | 3 ± 7 | 4 ± 4 | 0.142   |
| Time to discharge (days) | 13 ± 12 | 14 ± 11 | 11 ± 7 | 0.676   |
| Time to death (days) | 18 ± 16      | 13 ± 8 | 10 ± 10      | 0.495   |

Data are expressed as mean ± SD or No. (%).
excitability and precipitates complete heart block and sinus arrest (22). Accordingly, multi-organ failure is the outcome of severe COVID-19, affecting kidney function and potassium imbalance, which deteriorates the condition. It is noteworthy that hyperkalemia represents acid-base balance disorders and can be considered a manifestation of more severe respiratory distress (23).

The other side of potassium imbalance is hypokalemia that has not been presented as perilous as hyperkalemia but is common, particularly in patients under diuretics. As most critically ill COVID-19 patients are in adulthood, hypokalemia should be considered; however, no association with ICU admission requirement or mortality was noted (24).

In addition, 7.9% of patients suffered from hypomagnesemia, and 9.3% had hypermagnesemia. Our finding also uncovered that O₂ saturation is significantly related to magnesium imbalances; however, we found no logic for that. Magnesium is an ion associated with immune function, and impressive numbers of studies tried to make an association between magnesium supplemental therapy and COVID-19 infection outcomes (25). Hypomagnesemia has been presented as a risk factor of increased mortality due to COVID-19, which may be attributed to the negative effect of hypomagnesemia on potassium balance on a hand elongation of QT-interval on ECG (26). The other study stated a surprising hypothesis that, hypomagnesemia was more common among the COVID-19 patients requiring hospital admission, but the critically ill ones mainly presented hypomagnesemia (27). Nevertheless, magnesium imbalance has not been well elucidated in COVID-19.

Moreover, the present study showed that 19.9% of patients were hypocalcemic, and 10.8% were hypercalcemia. Although this high rate of calcium ion imbalance seems surprising, numerous other studies have notified this finding. In this regard, recent studies have raised hypothesis regarding intestinal absorption, imbalance in regulatory mechanism involving parathyroid hormone and vitamin D, or a direct effect caused by SARS-CoV-2 (28,29). It should be noted that, viruses require calcium ion for their structure formation, entry, gene expression, virion maturation and release (30), nevertheless, the mechanism by which calcium ion imbalance occurs has not been well detected. This type of electrolyte imbalance was significantly related to ICU admission and CRP level. Surfing the literature has shown that hypocalcemia is a common electrolyte imbalance in viral infections (31). The exact mechanism of hypocalcemia during COVID-19 is not precise; however, some evidence showed that patients with COVID-19 commonly suffer from chronic malnutrition leading to vitamin D deficiency and low intestinal absorption of calcium. Besides, calcium is predominantly bound to albumin in the plasma and a decrease in serum albumin will cause hypocalcemia (32-34). To determine the prognostic value of calcium imbalance, Liu et al showed that serum calcium levels were negatively associated with leukocytes, CRP, procalcitonin, IL-6 and D-dimer, nevertheless positively correlated with lymphocytes and albumin. They also showed that patients with hypocalcemia presented poor outcomes more commonly (35).

**Conclusion**

The present study showed that electrolyte imbalances are common laboratory abnormalities during COVID-19. However, we found no associative role, but ions balance plays a crucial prognostic role for COVID-19.

**Limitations of the study**

Along with the strength, this study has some limitations. The study has been conducted on the patients with COVID-19 pneumonia, nevertheless not both in-patients and outpatients. However, logically electrolyte disturbances are more prominent among admitted ones. Moreover, the study of outpatients could provide a better vision for supplementation in the course of the disease. Furthermore, the authors could assess the patients in separated groups of ICU admitted and general wards to make a better vision of electrolytes imbalance. Further studies with larger sample populations can help better generalizability of the outcomes.

**Authors’ contribution**

SS, EK and EN contributed to the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ZN and SP contributed to the conception of the work, conducting the study, revising the draft.

**Ethical issues**

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.495). Accordingly, written informed consent was taken from all participants before any intervention. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

**Conflicts of interest**

The authors declare that they have no competing interests.

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