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The three facets of the SARS-CoV-2 pandemic during the first two waves in the northern, central, and southern Italy

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ABSTRACT

Background: There is a scarcity of information in literature regarding the clinical differences and co-morbidities of patients affected by Coronavirus disease 2019 (COVID-19), which could clarify the different prevalence of the outcomes (composite and only death) between several Italian regions.
Objective: This study aimed to assess the heterogeneity of clinical features of patients with COVID-19 upon hospital admission and disease outcomes in the northern, central, and southern Italian regions.
Methods: An observational cohort multicenter retrospective study including 1210 patients who were admitted for COVID-19 in Infectious diseases, Pulmonology, Endocrinology, Geriatrics and Internal Medicine Units in Italian cities stratified between north (263 patients); center (320 patients); and south (627 patients), during the first and second pandemic waves of SARS-CoV-2 (from February 1, 2020 to January 31, 2021). The data, obtained from clinical charts and collected in a single database, comprehended demographic characteristics, co-morbidities, hospital and home pharmacological therapies, oxygen therapy, laboratory values, discharge, death and Intensive care Unit (ICU) transfer. Death or ICU transfer were defined as composite outcomes.
Results: Male patients were more frequent in the northern Italian region than in the central and southern regions. Diabetes mellitus, arterial hypertension, chronic pulmonary and chronic kidney diseases were the

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comorbidities more frequent in the southern region; cancer, heart failure, stroke and atrial fibrillation were more frequent in the central region. The prevalence of the composite outcome was recorded more frequently in the southern region. Multivariable analysis showed a direct association between the combined event and age, ischemic cardiac disease, and chronic kidney disease, in addition to the geographical area.
Conclusions: Statistically significant heterogeneity was observed in patients with COVID-19 characteristics at admission and outcomes from northern to southern Italy. The higher frequency of ICU transfer and death in the southern region may depend on the wider hospital admission of frail patients for the availability of more beds since the burden of COVID-19 on the healthcare system was less intense in southern region. In any case, predictive analysis of clinical outcomes should consider that the geographical differences that may reflect clinical differences in patient characteristics, are also related to access to health-care facilities and care modalities. Overall, the present results caution against generalizability of prognostic scores in COVID-19 patients derived from hospital cohorts in different settings.

Introduction

According to data from the World Health Organization (WHO), Italy was particularly affected by the Coronavirus disease 2019 (COVID-19) pandemic. Since February 2020, COVID-19 has spread progressively throughout Italy's entire national territory, from the northern to the southern region, with approximately 23,000,000 cases of SARS-CoV-2 infections recorded by the Italian Surveillance System and 173,000 patients dying from severe disease [1]. Several studies showed that pre-existing comorbidities (diabetes mellitus and hyperglycemia, obesity, arterial hypertension, kidney disease, cancer, and liver disease) and elderly age were the main risk factors for severe disease evolution and death [2–5]. However, infection and death rates were not homogeneous. Available national data at the beginning of pandemic showed that infection cases and death rates were approximately 7–12 times higher in the northern region than in the southern region [6]. More recent data show a narrowing of this gap, as death rates were approximately 1.2–2 times more frequent in the north of Italy compared to central-southern Italy and the islands [7].

In Italy, incidence and case fatality rate (CFR) of COVID-19 during the first waves of pandemic showed a significant geographic heterogeneity [8]. Moreover, when comparing the first with the second wave, the latter was characterized by longer duration and greater burden of cases. This could also be attributed to differences concerning tracing and testing activities, as many cases during the first wave went undetected due to lack of knowledge, resources, and available tests; these underdiagnoses may be a confounding factor that could bias mortality and epidemiological analyses [9]. Likewise, a higher number of COVID-19 related deaths in Italy was recorded during the second wave [10]. However, when analyzing data across the Lombardy region, studies conducted in patients admitted to emergency room during the first and the second waves showed that severity and mortality associated with COVID-19 were lower during the second wave of pandemic despite the greater number of hospitalized subjects during the second wave compared to the first wave. It is plausible that the limited number of intensive care unit beds in the Northern Regions of Italy during the first wave contributed to worsening mortality rates associated with COVID-19 [11,12].

Indeed, besides age distribution, prevalence of comorbidities and severity of COVID-19, a larger availability of hospital beds in certain regions could also be a factor associated with a lower CFR in those regions [13–16]. Moreover, it has been suggested that the increased burden on health care systems caused by the sudden increase in number of cases may have contributed to a CFR increase by reducing the standard of care of affected individuals in need of hospital treatment. In fact, the rapid surge of cases and the limited capacity of intensive care beds posed a serious threat to the Italian national health system that was close to the breaking point [17]. Furthermore, a decentralized healthcare system and a highly bureaucratic political system with low coordination and conflicts between government, regions, and local authorities [18] contributed both to ineffective economic investments, and the inability to restructure the Italian healthcare system at territorial and hospital levels [19].

In light of this complexity of factors, it is important to assess heterogenicity of patient characteristics and outcomes among different regions; however, to the best of our knowledge, data are still very sparce and inconclusive. In fact, it is unclear how SARS-CoV-2 infection varies throughout the Italian territory and whether there are significant differences in clinical features, comorbidities, and outcomes in several national areas.

Material and methods

This observational cohort multicenter retrospective study included patients admitted for COVID-19 to Infectious diseases, Pulmonology, Endocrinology, Internal Medicine, Nutrition, Geriatrics Units in several Italian cities during the first two pandemic waves between February 1, 2020 and January 31, 2021. In particular, the first wave is defined from February 2020 to May 2020 and the second one from October 2020 to January 2021 [9,20,40,41]. Patients were stratified according to the area of origin as follows: northern area (endocrinology, clinical nutrition, and cardiovascular prevention service units, San Donato Polyclinic in Milan; center for studies and research on obesity, University of Milan; and endocrinology unit, University of Pisa); central area (internal medicine unit-obesity center, Tor Vergata Polyclinic, Rome and diabetes unit, Santa Maria Goretti Hospital, Latina); and southern area (clinical nutrition, COVID-19 internal medicine, infectious and tropical diseases, and COVID-19 pneumology units, Polyclinic University Hospital, Palermo; pneumology unit, ARNAS Civic Hospital, Palermo and Madonna dell'Alto Petralia Sottana Hospital, Palermo; geriatrics unit of ARNAS Garibaldi of Catania; infectious and tropical diseases unit, *"Mater Domini"* Teaching Hospital, Catanzaro). A map showing the distribution of the collaborating centers across Italy is shown in Fig. 1. The following information were obtained by examining clinical charts and collected in a single shared database and were included in the analysis: demographic data, comorbidities, hospital and home pharmacological therapies, oxygen therapy, laboratory values, discharge, death and intensive care unit (ICU) transfer. Inclusion criteria were as follows: 1) age ≥ 18 years; 2) positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swabs; 3) need for hospitalization for COVID-19; and 4) admission during first or second pandemic waves in the temporal range between February 1, 2020 and January 31, 2021 [21,22]. Death and/or ICU transfer were defined as composite outcome.

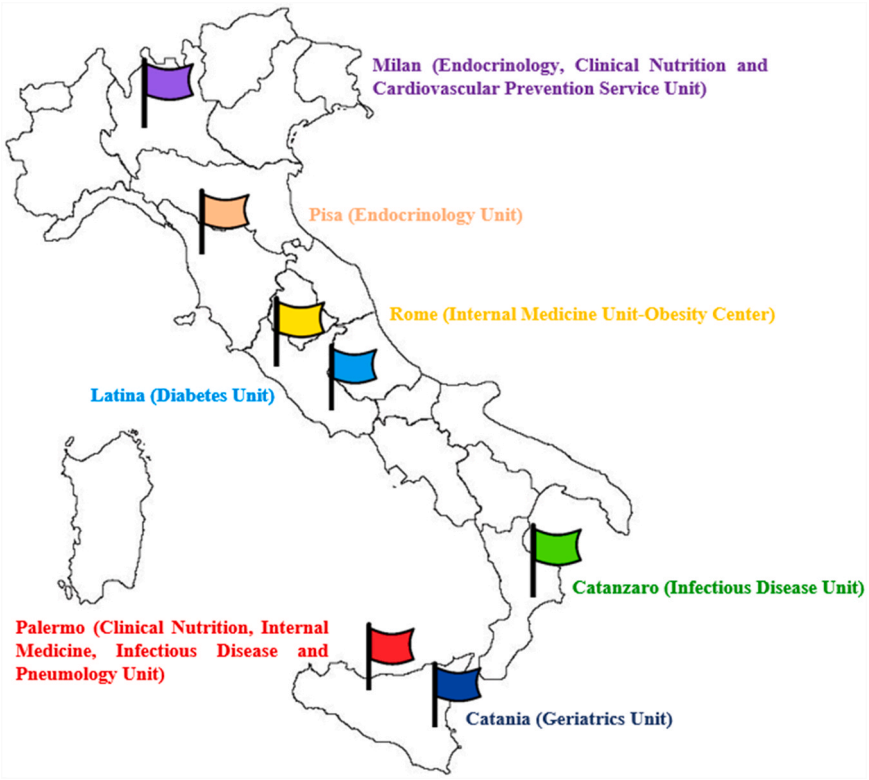

Fig. 1. Distribution of the centers participating to the study in the Italian regions.

The study was approved by the Ethics Committee "Palermo I" of the A.O.U. Policlinico "Paolo Giaccone", Palermo, Italy (N. 11/2020, December 18th, 2020). The need for written informed consent was waived owing to the observational and retrospective nature of the study.

Statistical analysis

Descriptive statistics (absolute and percent frequency) have been calculated for qualitative variables. Quantitative variables have been described by mean, standard deviation, min-max, median, first and third quartile. Comparisons among the three Italian areas has been carried out by the chi-squared test in the case of qualitative variables and by means of one-way analysis of variance (ANOVA) followed by pairwise contrasts with Bonferroni's correction. Multivariable logistic regression has been used for multivariate analysis on the primary and secondary outcome. The first model included all the variables with a statistically significant result at the univariate analysis with a backward elimination of the variables not statistically significant until the final model. Goodness of fitting has been assessed by the Hosmer-Lemeshow test. The statistical significance has been obtained for $P < 0.05$. The statistical analysis has been carried out by SAS 9.4.

Results

Of the 1596 patients that were registered, 386 patients were excluded from the evaluation due to missing data. So, from the 1210 patients included in the analysis 263 (21.7 %), 320 (26.4 %), and 627 (51.8 %) patients were from northern, central, and southern region hospitals, respectively.

Table 1 shows the main clinical features of the patients with COVID-19. In the total sample, approximately half of the patients (51.5 %) were male, with a higher percentage in the northern region

Table 1
Comparison between patients with COVID-19 main features in the three Italian regions.

Variables	All patients (N = 1210)	North (N = 263)	Center (N = 320)	South (N = 627)	*P*-value
Demographic features					
Male sex (N, %)	708 (51.5 %)	181 (68.8 %)	172 (53.8 %)	355 (56.6 %)	*0.0004*
Age (years, mean ± SD)	67.8 ± 14.8	65.2 ± 14.1	65.7 ± 15.1	69.9 ± 14.7	*< 0.0001*
Comorbidities (N, %)					
Diabetes mellitus	259 (21.7 %)	41 (15.6 %)	47 (14.8 %)	171 (27.8 %)	*< 0.0001*
Arterial Hypertension	655 (54.8 %)	114 (43.4 %)	155 (48.9 %)	386 (62.7%)	*< 0.0001*
Ischemic Heart Disease	114 (11.5 %)	23 (8.8 %)	11 (9.2 %)	80 (13.1 %)	0.12
Chronic Heart Failure	86 (8.7 %)	10 (3.8 %)	16 (13.3 %)	60 (9.8 %)	*0.002*
Atrial Fibrillation	102 (10.3 %)	13 (5.0 %)	15 (12.5 %)	74 (12.2 %)	*0.004*
Cancer	116 (11.7 %)	12 (4.6 %)	31 (25.8%)	73 (12.0 %)	*< 0.0001*
Chronic Pulmonary Disease	103 (10.4 %)	16 (6.1 %)	13 (10.8 %)	74 (12.1 %)	*0.03*
Bronchial Asthma	29 (2.9 %)	5 (1.9 %)	3 (2.5 %)	21 (3.5 %)	0.45
Chronic Kidney Disease	120 (12.1 %)	10 (3.8%)	14 (11.7%)	96 (15.7%)	*< 0.0001*
Stroke	60 (6.1 %)	9 (3.4 %)	12 (10.0 %)	39 (6.4 %)	*0.04*
Pulmonary Embolism	20 (2.0 %)	4 (1.5 %)	3 (2.5 %)	13 (2.1 %)	0.77

Table 2
Comparison between patients with COVID-19 outcomes in the three Italian regions.

Variables	All patients (N = 1210)	North (N = 263)	Center (N = 320)	South (N = 627)	*P*-value
Outcomes (N, %)					
Discharge	1011 (83.6 %)	244 (92.8 %)	290 (90.6 %)	477 (76.2 %)	*< 0.0001*
Exitus	166 (13.7 %)	6 (2.3 %)	26 (8.1 %)	134 (21.4 %)	*< 0.0001*
Exitus and Intensive Care Unit transfer	221 (18.3 %)	28 (10.7 %)	29 (9.1 %)	164 (26.2 %)	*< 0.0001*

than in the central and southern regions (68.8 %, 53.8 % and 56.6 %; $p = 0.0004$). Mean age increased in ascending order from northern to central and southern region of Italy (65.2 years, 65.7 years and 69.9 years; $p < 0.0001$).

The most prevalent comorbidity throughout the Italian territory was arterial hypertension (54.8 %), followed by diabetes mellitus (21.7 %), chronic kidney disease (12.1 %), cancer (11.7 %), ischemic heart disease (11.5 %), chronic pulmonary disease (10.4 %), atrial fibrillation (10.3%), chronic heart failure (8.7 %), previous cerebrovascular events (6.1 %), bronchial asthma (2.9 %), and pulmonary embolism (2.0 %). Additionally, diabetes mellitus, arterial hypertension, chronic pulmonary disease, and chronic kidney disease (27.8 %, 62.7 %, 12.1 % and 15.7 %) were more frequent comorbidities in the southern Italian region, while cancer, chronic heart failure, atrial fibrillation, and cerebrovascular events (25.8 %, 13.3 %, 12.5 % and 10.0 %) were more frequent in the central region.

Table 2 shows outcomes of the patients with COVID-19. Generally, the discharge proportion of the patients included was 83.6%. Specifically, in northern region, patients were discharged more frequently than in the central or southern region (92.8 %, 90.6 % and 76.2 %; $p < 0.0001$). The composite outcome and deaths occurred at frequencies of 18.3 % and 13.7 %, respectively. The death rate was higher in the southern region compared to the central and northern regions (21.4 %, 8.1 % and 2.3 %; $p < 0.0001$). Lastly, 26.4 %, 10.7 %, and 9.1% of patients experienced composite outcomes in the southern, northern, and central region, respectively ($p < 0.0001$).

Variables statistically associated with composite event at the univariate level, as shown in Table 1**,** were inserted into the multivariable logistic model. Notably, only the following variables were confirmed in the final model of the logistic regression analysis to be independently associated with the combined event: age (odds ratio [OR] = 1.05 for each year, 95 % confidence interval [CI] 1.04–1.07; $p < 0.0001$), ischemic heart disease (OR = 1.89, 95 % CI 1.21–2.94; $p = 0.0052$), and chronic kidney disease (OR = 2.06, 95 % CI 1.33–3.20, $p = 0.0012$). In addition, the place of residence had a significant impact on the rate of the composite outcome. Indeed, it was 1.4 and 2.1 times more frequent in central and south Italy, respectively, than in the northern region reaching statistical significance ($p = 0.0025$) (Table 3).

Discussion

The present study assessed the heterogeneity of demographics and clinical features of patients with COVID-19 upon hospital admission and disease outcomes in the northern, central, and southern Italian region. Its contribution to the existing literature is reflected by the very few studies focusing on the clinical differences and outcomes of COVID-19 patients admitted to hospitals across Italy. In fact, the ISS COVID-19 Report published in January 2021 analyzed data concerning the whole population infected by SARS-CoV-2 throughout the national territory, regardless of need to hospital admission [20]. Other Authors [7,23–25] explored COVID-19 inpatients characteristics in specific settings. This study allows a broader epidemiological perspective by providing data on COVID-19 hospitalized patients not only in different Italian regions, but also in very diverse settings, as it was conducted in the main kinds of medical departments involved in facing SARS-CoV-2 pandemic (Infectious Diseases, Pulmonology, Internal Medicine, Endocrinology, Geriatrics).

Table 3
Logistic regression analysis of variables independently associated with composite event. *odds ratio for each increment of unit age.

Variables	Odds ratio	95 %CI	*p*-value
Center vs North	1.359	0.720–2.563	*0.0025*
South vs North	2.124	1.351–3.339	
Age*	1.050	1.035–1.065	*< 0.0001*
Ischemic Heart Disease: Yes vs No	1.887	1.209–2.943	*0.0052*
Chronic Kidney Disease: Yes vs No	2.061	1.329–3.197	*0.0012*

The study analysis highlighted a heterogeneity of patient characteristics throughout the Italian regions and during different periods of the pandemic in terms of age and gender, comorbidities, and outcomes.

The present data related to the first and second waves of the pandemic showed that median age defined on all patients admitted for COVID-19 was progressively higher from northern, to central, and southern regions. It is difficult to explain this finding, but it can be hypothesized that more severe clinical conditions of elderly patients and greater availability of hospital beds for admitting these patients in the south are responsible for their over-representation, as will be discussed more in depth in the following part of the discussion. It is now widely recognized that the COVID-19 clinical manifestations differ with age and that the probability of severe disease is higher among people aged ≥ 60 years, especially those with comorbidities and those living in nursing homes or long-term care facilities [26]. However, age remains the main risk factor for mortality, which was shown to be higher in patients older than 70 years, regardless of the presence of chronic medical conditions [27,28]. This consideration should be taken in account as a possible explanation for a gradient towards a worse clinical outcome in the southern region, another main finding of our study. Indeed, our analysis highlighted that the composite outcome (death and ICU transfer) was higher in the southern region compared to the northern region. The death frequency in the southern region was 4.2 times higher than in the central and northern regions and the composite event was 2.9 times higher in the southern region. Along the same line, we found that comorbidities were overall less frequent in the northern region when compared to the rest of Italy. Clearly, since comorbidities increase the risk of death and severe COVID-19 [3,29], comorbidities are likely another explanation for worse clinical outcomes in the south compared to the north of Italy. Moreover, the main comorbidities that constitute risk factors for severe COVID-19 are diabetes, cardiovascular diseases and chronic lung diseases, cancer, chronic kidney diseases, liver diseases, obesity, sickle cell disease, dementia and other neurological conditions, disabilities, mental health conditions, physical inactivity, and immunocompromising conditions [30–35].

The present analysis showed a different distribution pattern of comorbidities in the Italian territory (diabetes mellitus, arterial hypertension, chronic pulmonary disease and chronic kidney disease were more frequent in the southern Italian region, while cancer, atrial fibrillation and ischemic stroke had a higher prevalence in the central region). Therefore, it has to be seen whether qualitative differences in comorbidities are responsible for the increased risk of

death and severe COVID-19. Unfortunately, our analysis was not powered enough to answer to this question, but several studies investigating the comorbidities that greatly impact on COVID-19 prognosis may give a deeper insight on this matter. Studies show, for example, that particular conditions such as hypertension and underlying cardiovascular diseases are strongly associated with more severe symptoms and death in COVID-19 inpatients, along with diabetes and kidney disease [3,29,36–38]. Polverino et al., in their Italian nationwide observational multicenter study involving 61 hospitals, found differences in the number of comorbidities across hospitals and regional areas and showed that the geographic/hospital variation did not influence the associations between comorbidities and mortality [29].

The multivariate logistic regression analysis demonstrated that in addition to the geographical area, a negative prediction for the combined event exists when age, ischemic cardiac disease and chronic kidney diseases are considered risk factors. These results therefore suggest that the impact of age and selected co-morbidities is predominant, notwithstanding differences across Italy and heterogeneous hospital settings. However, at the same time, we underline the important regional differences in patient characteristics and related outcomes across heterogeneous hospital settings.

Overall, these considerations are important and should lead for example to reconsider the applicability and generalizability of prognostic scores obtained in diverse limited settings in COVID-19 patients [39]. It may be that geographic area captures differences in patient characteristics or in the disease management which may act as unmeasured confounders in the prognostic risk scores.

Of relevance is the consideration that the study patients were selected from hospital wards, therefore they do not represent the "universe" of patients with the disease. Notwithstanding this consideration, the present data should be interpreted in the broader context of the evolution of the epidemics, as reported by the National Institute of Health (*Istituto Superiore di Sanità*, ISS) on the full population of patients diagnosed with COVID-19 [20]. The report showed that distribution of deaths due to COVID-19 over time was heterogeneous among the Italian regions; while mortality was significantly higher in the northern region during the first wave of the pandemic, the central and southern regions showed a death curve with higher peaks in correspondence with the second wave [20]. This may be explained by the fact that the central and southern regions, which were partially spared by the first wave, were hardest hit during the second wave [40–42]. In particular, the delayed peak of infection spread in the southern region could have led it to equal and even exceed (according to our data) the northern and central regions in terms of unfavorable outcome (ICU transfers and death). It is possible to speculate that the higher prevalence of comorbidities evidenced in the southern region compared to the northern region, together with a higher mean age, may be the fundamental reasons of this unfavorable trend. Another consideration is that the very high burden of disease experienced in the northern region (especially during the first phase of pandemic) and the subsequent limited availability of hospital beds may have led to a reduced hospital admission of fragile and elderly patients in the north, a phenomenon that did not occur at a similar extent in the southern region, leading to a negative selection of the most fragile patients even from national statistics on the entire population of patients diagnosed with COVID-19. Our considerations are supported by the work of Timelli et al. [13], who explored the possible association between the CFR and measures of disease burden in the Italian regions and found that the CFR was significantly associated with the cumulative incidence of COVID-19 cases, median patient age but also ICU load (defined as ratio between the maximum number of COVID-19 patients in the ICU and number of ICU beds available before the pandemic). The decentralized national healthcare service that generated different regional responses to the COVID-19 emergency, in terms of hospital capacity and strategy and access to cure, should also be taken into account when comparing outcomes throughout Italy [42].

The present study is affected by several limitations. First, it provides updated information on hospitalized COVID-19 patients throughout Italy, but data are limited to a small sample of patients, providing only a partial insight on the Italian situation. Second, this study is retrospective in nature, some missing data from the observed sample were present and data collection period was short. Third, only hospitalized patients were included, while the progression and outcome of COVID-19 patients managed by peripheral territorial points of care was not taken into account. Fourth, we could not provide precise information on the bed capacity of each Center involved in our study throughout the whole period of observation because hospital capacity and bed availability varied very rapidly from moment to moment; therefore, we were not able to estimate the relationship between bed availability in COVID-19 dedicated units and the number of patients in need of hospitalization for the three regions. This could be a further confounding variable, which could have influenced the study outcomes.

Conclusions

Significant differences in clinical features at admission and outcomes of COVID-19 patients have been found among North, Center and South of Italy. The higher COVID-19 mortality and higher frequency of ICU transfer in the southern region could be explained by the higher frequency of comorbidities and the greater fragility of patients who came for hospital observation in the southern region, unlike what happened in the central and northern regions, probably for the reduced availability of hospital admission compared to the high prevalence of the disease. Therefore, predictive analysis of clinical outcomes should consider that the geographical differences that may reflect epidemiological and clinical differences in patients are also related to access to health facilities and care modalities.

Elderly and immunocompromised patients, as well as multi-comorbid subjects, hospitalized inpatients and residents in care homes have a higher risk of infection and mortality, so greater efforts should be made in order to reduce transmission in these categories [43]. With this objective in mind, the provision of adequate healthcare to patients is fundamental to keep mortality low and accurate testing allows identification of people who might benefit from treatment and of subjects who should be isolated to prevent spreading of the infection [44].

Addressing and inquiring about not only clinical, but also epidemiological, economic, sociocultural and healthcare systems differences in Italy could help to improve our understanding of the effectiveness of measures applied in facing COVID-19 pandemic and, consequently, provide useful tools for planning and improving public health strategies to tackle and alleviate the consequences of this infection [45].

Conflict of interest

Authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.02.002.

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