

RESEARCH ARTICLE

Colchicine, COVID-19 and hematological parameters: A meta-analysis

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Abstract

Introduction: Colchicine has the potential in reducing patient morbidity and mortality in COVID-19 infection owing to its anti-inflammatory properties. This study aims to determine the efficacy of colchicine in optimizing inflammatory hematological biomarker levels among COVID-19 patients.

Methods: In accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines, a systematic search was conducted using the following keywords: Colchicine, covid*, SARS-CoV-2, anti-inflammatory, trials, clinical, hematological, laboratory. Databases were searched from December 2019 until August 26, 2021: MEDLINE/PubMed, Web of Science, Cochrane, Scopus, and EMBASE. Other sources were located through ClinicalTrials.gov, manually searching SAGE, Science Direct, Elsevier, and Google Scholar. The meta-analysis was conducted using Review Manager 5.4.

Results: In total, six studies were included, of which four reported c-reactive protein (CRP) standardized mean reductions in the colchicine group (N = 165) as opposed to the control (N = 252; SMD = -0.49, $p < 0.001$). On noting lactate dehydrogenase (LDH) values post treatment, the colchicine group (N = 204) showed significant reductions at the end of treatment compared to control (N = 290; SMD = -0.85, $p < 0.001$). Finally, the D-dimer values in colchicine groups (N = 129) compared to control (N = 216) also documented a negative effect size (SMD = -0.9, $p < 0.001$).

Conclusion: Colchicine has efficacy in reducing inflammatory biomarkers observed in moderate-to-severe COVID-19 patients. It may be worthwhile to consider monitoring the clinical and laboratory parameters of patients in further trials to consider colchicine as a strong candidate for an adjunct to COVID-19 treatment.

KEYWORDS

colchicine, COVID-19, CRP, D-dimer, LDH

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1 | INTRODUCTION

There is evidence of the underlying inflammatory processes contributing to COVID-19 infection severity.¹ The association between inflammation, thrombosis, and COVID-19 has been established.² Patients admitted to the intensive care unit (ICU) have markedly elevated c-reactive protein (CRP) levels, lactate dehydrogenase (LDH) levels, and d-dimer levels among other markers.^{3,4} Underlying profound inflammatory states that accompany elevated biomarker levels are associated with lung and vascular inflammation during infection.⁵ The severity of COVID-19 infection is characterized by extra-pulmonary and extravascular manifestations.⁵ The cytokine storm identified in COVID-19 infection is indicative of multisystem organ injuries.⁶ Treatments targeting the underlying inflammatory responses have been considered including the steroid dexamethasone which reduces mortality risk in select patients who require supplemental oxygen or mechanical ventilation.⁷ The inhaled budesonide has also shown efficacy in the open label STOID trial in reducing the need for urgent medical care in patients with early COVID-19 infection.⁸ However, certain intrinsic immunosuppressive actions of dexamethasone pose a challenge to its application in COVID-19 patients.⁹ Colchicine is FDA-approved and is one of the oldest anti-inflammatory therapies available with no potential immunosuppressive actions.¹⁰ So far, it is being used for the treatment of acute gout, familial Mediterranean fever, and off-label use for other inflammatory conditions.¹⁰ Mechanistically, colchicine inhibits neutrophil activity, an important aspect of innate immunity.⁹ Further, colchicine is observed to prevent cytokine production, through a reduction in IL-1 β , IL-6, and TNF as well as further recruitment of macrophages and neutrophils.⁹ Finally, colchicine also acts to prevent the release of α -defensin by neutrophils, which inhibits the inflammation/thrombosis interface without directly impacting platelet function.⁹ With its safe profile, tolerability, and low cost, colchicine may be a useful agent for COVID-19 patients and has the potential to reduce patient morbidity and mortality.

The meta-analysis aims to determine the efficacy of colchicine for patients with COVID-19 compared to control (placebo or standard care) by observing inflammatory hematological biomarker reduction.

2 | METHODS

By using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Statement 2020, clinical trials, and observational studies with a treatment group and a control group were included that reported the hematological parameters at baseline and endline. The specific outcomes were reported for the Colchicine treatment and Control groups. The meta-analytical findings are pertinent evidence for in-hospital COVID-19 care.

2.1 | Inclusion and exclusion criteria

The following types of studies were included: Randomized and/or controlled clinical trials, prospective or retrospective cohorts, case-controlled studies. Case series, case reports, and letters were omitted due to the high risk of associated biases and the lack of control groups. The studies comprised of adult participants, aged 18 or above, with any genders. No follow-up period was determined for inclusion due to the limitations of data. The target condition was COVID-19 and in-hospital studies were included, employing patients with any severity of disease (i.e., mild, moderate, or severe pneumonia as per the NIH guideline).

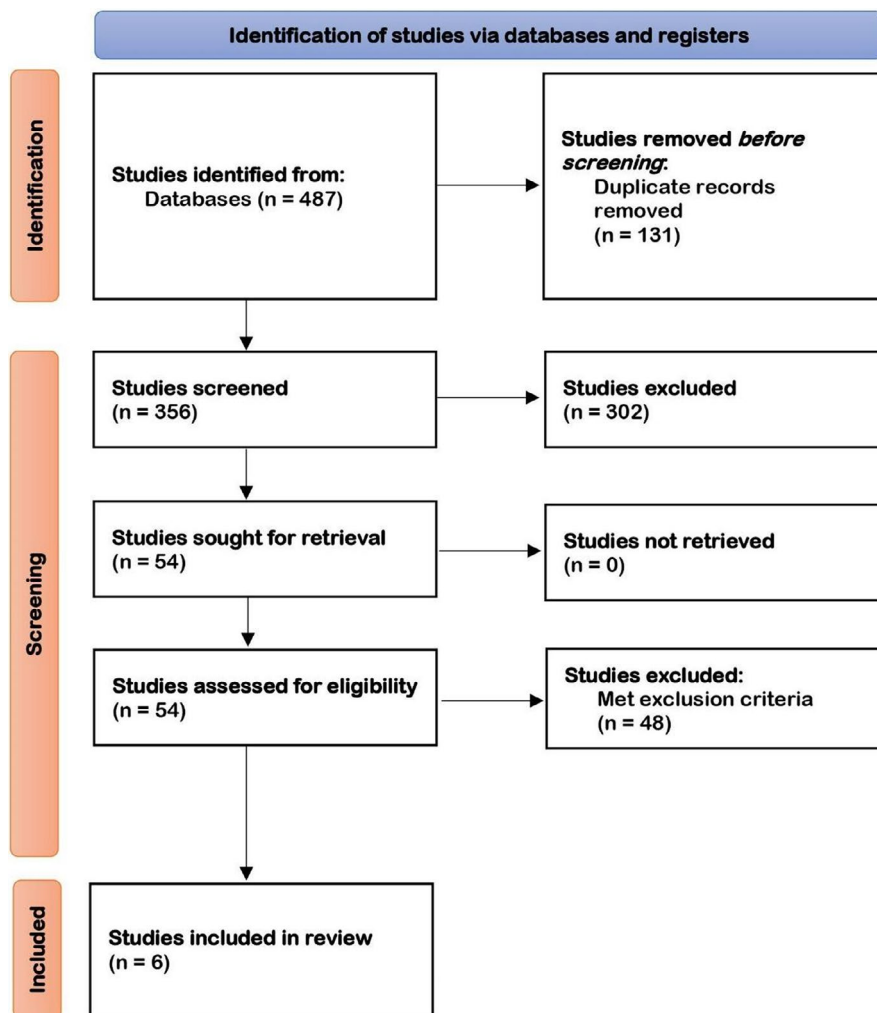
2.2 | Search strategy

A systematic search strategy was employed to search key electronic databases and clinical trial registers as per the PRISMA 2020 Statement.¹¹ The following databases were searched from December 2019 to August 26, 2021: MEDLINE/PubMed, Web of Science, Cochrane, Scopus, and EMBASE. Other sources were located through ClinicalTrials. Gov, manually searching SAGE, Science Direct, Elsevier, and Google Scholar. The search terms across all databases and additional sources were as followed: Colchicine, covid*, SARS-CoV-2, anti-inflammatory, trials, clinical, hematological, laboratory. There were no language restrictions. The titles and abstracts of shortlisted studies from the databases or online sources were screened independently by all reviewers; in case of any disagreements, the final reviewer was present. Cohen's Coefficient of Agreement was calculated to quantify the inter-reviewer agreements. Figure 1 presents the search process for the meta-analysis.

2.3 | Statistical analysis

All studies identified from the databases were stored into Endnote X9 (Clarivate Analytics). The duplicates were removed using the Endnote X9 deduplication tool. No duplicates were found using the online resources (i.e., ClinicalTrials. Gov and websites). The methodology was quantitative and analytical to ascertain the benefits or lack thereof on the use of Colchicine. The laboratory variables were continuous, and the difference in means along with standard deviation was computed.¹² On noting these values, as listed in Table 1, the standardized mean difference (SMD) was computed, reported as Cohen's d, along with a 95% confidence interval (CI). A fixed-effects model was applied as the sample size and included study count was limited. Forest plots were generated for every outcome documenting SMD, 95% CI, heterogeneity, and overall results through Figures 2-4. The minimum requirement to meta-analyze the findings was two or more studies reporting on the same outcome measure. While a funnel plot was not generated to test for publication bias due to the limited number of studies (<10), the heterogeneity

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart



between the included studies was tested using the χ^2 -based Q test and the I^2 index. The statistical analysis was conducted using Review Manager 5.4 (RevMan, Cochrane).

3 | RESULTS

The overall Kappa score computed for the inter-reviewer agreement was 0.86, suggesting good agreement. The features of the included studies with the statistical sheet are listed in Table 1. The studies were conducted in the USA, Brazil, Greece, Iran, and Russia. Colchicine was administered for 10–21 days for 0.5–1.5 mg daily.

All values of the SMD lesser than zero indicated the degree to which the hemodynamic lab values improved on treatment. Four of the six studies reported CRP values in the Colchicine (N = 165) versus Control (N = 252) group at baseline and endline. Negative effect size was found for CRP in the Colchicine treatment group (Cohen's $d = -0.49$, 95% CI = $-0.75, -0.23$, $p < 0.001$), meaning that the treatment reduced CRP values. Large heterogeneity was noted in the included studies, owing to the diversity across them ($I^2 = 99\%$).

Four of the six studies reported LDH values in the Colchicine (N = 204) and Control (N = 290) groups at baseline and endline. On assessing whether Colchicine treatment reduced LDH values, we found a negative effect size (Cohen's $d = -0.85$, 95% CI = $-1.08, -0.62$, $I^2 = 99\%$). In the sample set of 494 patients, Colchicine treatment led to a standardized reduction in LDH values, with statistical significance ($p < 0.001$).

Three of the six studies presented D-Dimer values in Colchicine (N = 129) groups versus Control (N = 216) groups. Across 345 patients, a negative effect size was computed for patients treated with Colchicine meaning that Colchicine led to reductions in the abnormally high level of fibrin degradation products (Cohen's $d = -0.9$, 95% CI = $-1.22, -0.57$, $I^2 = 99\%$). The results from this analysis were statistically significant ($p < 0.001$).

An additional objective-based summary of all Colchicine trials registered with ClinicalTrials. Gov is given in Table S1.

4 | DISCUSSION

We assessed the difference in hematological parameters of patients with moderate-to-severe COVID-19 infection who received

TABLE 1 Features of the included studies with the statistical sheet

No.	Author, year	Study type	Setting	Colchicine regimen	Sample size (Colchicine vs. Control)	CRP mg/L (mean difference [SD]) Colchicine vs. Control	LDH U/L (mean difference [SD]) Colchicine vs. Control	D-Dimer ng/ml (mean difference [SD]) Colchicine vs. Control
1	Lopes et al., 2020 ¹³	RCT, RBR-8jyhxx	Brazil	0.5 mg thrice daily for 5 days; then 0.5 mg twice daily for 5 days	36 vs. 36	-88.42 (46.3) vs. -73.65 (71.8)	-93.34 (41.15) vs. -68.85 (41.62)	NR
2	GRECO-19, 2020 ¹⁴	RCT, NCT04326790	Greece	1.5-mg loading dose followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily for as long as 3 weeks	55 vs. 50	-1.78 (19.74) vs. -3.77 (18.5)	-60.7 (43) vs. -36.15 (53.9)	-265.14 (258.8) vs. -446.4 (465.4)
3	Mostafaie et al., 2021 ¹⁵	RCT, NCT04392141	Iran	Colchicine plus a Herbal extraction containing a Phenolic Monoterpene Fractions	60 vs. 60	NR	-15.81 (54.3) vs. -1 (34.1)	NR
4	COLORIT, 2021 ¹⁶	Quasi-Randomized Trial	Russia	1 mg for 1-3 days followed by treatment at a dose of 0.5 mg/day for 14 days	21 vs. 22	-86.7 (46.35) vs. -52 (56.9)	NR	-185.3 (174.65) vs. 93.5 (151.86)
5	Brunetti et al., 2020 ¹⁷	Prospective Cohort	USA	Loading dose of 1.2 mg, with a maintenance dose of 0.6 mg twice daily	33 vs. 33	-70 (91) for colchicine group only	NR	NR
6	Sandhu et al., 2020 ¹⁸	Case-Control	USA	0.6 mg twice a day for 3 days and then 0.6 mg once a day for a total of 12 days	53 vs. 144	-33 (4.42) vs. 15 (0.75)	-118 (2.26) vs. -61 (5)	125 (17.1) vs. 721 (60.1)

low-dose long-term colchicine. Colchicine is one of the oldest anti-inflammatory drugs with multiple mechanistic targets. The anti-inflammatory drug, colchicine, is also highly effective in reducing crystal-induced inflammation on gout, in addition to being investigated as an anti-inflammatory drug in atherosclerotic vascular disease states.¹⁹ Concerning COVID-19, there are three distinct phases of infection progression including the early infection phase, pulmonary phase, and inflammatory cascade.⁹ The third inflammatory cascade is associated with the activation of cytokines and chemokines which are targeted by colchicine.⁹

In other disease states such as chronic rheumatic valvular disease, the importance of reductions in serum inflammatory markers such as CRP and IL-6 has been noted in a pilot study. The role of inflammatory markers as important prognostic and diagnostic tools have been corroborated in literature.²⁰ In patients with moderate-to-severe COVID-19 infection, elevated biomarkers of inflammation such as CRP predict the development of vascular events. Low-dose colchicine (0.5–1.5 mg daily for 10–21 days) was observed to decrease CRP levels in COVID-19 patients in our study with a moderate effect (Cohen's $d = -0.49$, 95% CI = $-0.75, -0.23$, $p < 0.001$). CRP is a protein that is produced by the liver and it is an early marker of infection and inflammation. Typically, normal levels of CRP are less than 10 mg/L. However, it may rise when there is ongoing inflammation or tissue damage within 6–8 h.²¹ Additional controlled studies are merited to confirm and assess whether the use of long-term low-dose colchicine may improve clinical outcomes associated with CRP levels reduction. Available studies have demonstrated that a significant increase in CRP levels amongst COVID-19 patients was prevalent in up to 86% of severe patients which was not seen in milder patients.^{22–24} CRP levels were found to be 10-fold higher among deceased patients compared to recovered patients (median 100 vs. 9.6 mg/L).²⁵ A strong correlation was found between CRP levels and aggravation of severity of COVID-19.^{26,27} Therefore, CRP has been considered a proxy marker for estimating the aggravation of severity in mild COVID-19 patients with a 5% risk increase for every unit increase of CRP levels.²⁸ The prognostic potential of CRP is associated with inflammatory cytokine production that occurs in severe COVID-19 patients. The cytokine storm occurs due to the hyper-activation of the immune system and leads to tissue destruction. The elevation of CRP levels is a predictor of higher morbidity and mortality among COVID-19 patients. Consequently, our findings shed light on the protective effect of colchicine by a reduction in CRP levels among COVID-19 patients.

Our analysis demonstrates an association between low-dose colchicine and a large reduction in LDH levels among moderate-to-severe COVID-19 patients. LDH is an intracellular enzyme that is found in almost all systems of the body and it has been observed traditionally as a marker of cardiac damage.²⁹ However, severe infections also result in cytokine-mediated tissue damage and the release of LDH. LDH elevation has been observed in COVID-19 as an individual predictor of worse outcomes in hospitalized patients.³⁰ A study demonstrated that a 6-fold increase in odds of severity and a 16-fold increase in mortality was seen with elevated LDH levels.³¹

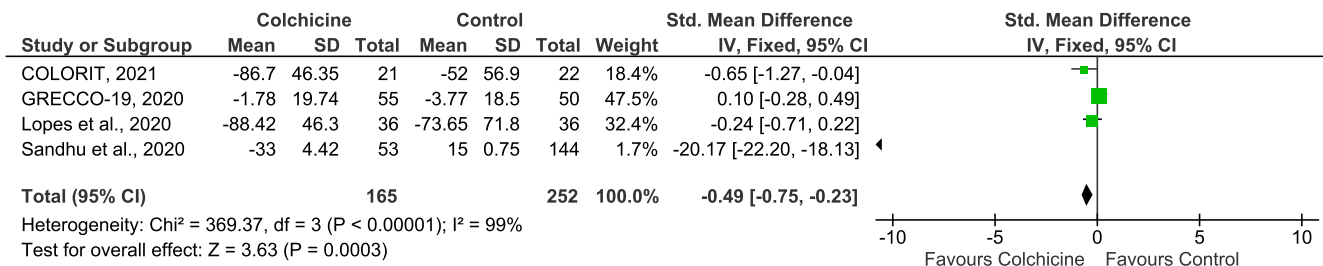


FIGURE 2 c-reactive protein (CRP) mg/L (mean difference [SD]) Colchicine versus Control. SMD = -0.49 (95% CI = $-0.75, -0.23$); Heterogeneity: $\chi^2 = 369.37$, $df = 3$ ($p < 0.00001$); $I^2 = 99\%$; Test for overall effect: $Z = 3.63$ ($p = 0.0003$)

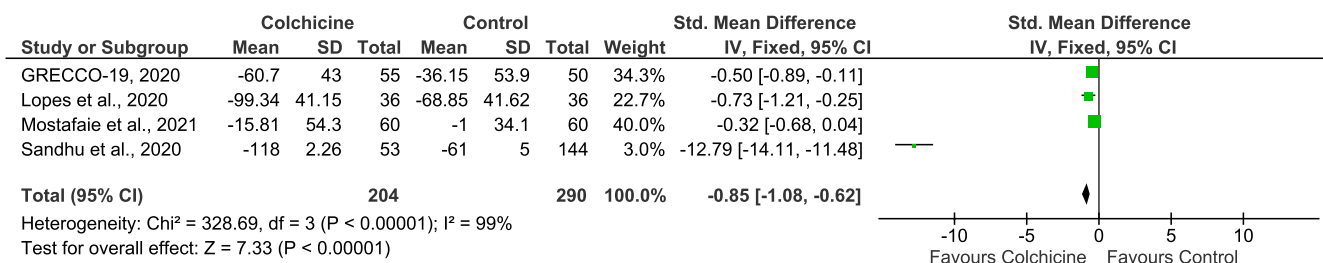


FIGURE 3 Lactate dehydrogenase (LDH) U/L (mean difference [SD]) Colchicine versus Control. SMD = -0.85 (95% CI = $-1.08, -0.62$); Heterogeneity: $\chi^2 = 328.69$, $df = 3$ ($p < 0.00001$); $I^2 = 99\%$; Test for overall effect: $Z = 7.33$ ($p < 0.00001$)

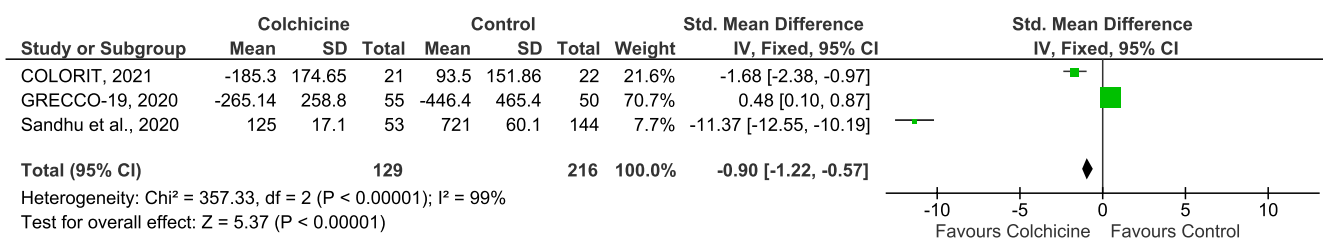


FIGURE 4 D-Dimer ng/ml (mean difference [SD]) Colchicine versus Control. SMD = -0.9 (95% CI = $-1.22, -0.57$); Heterogeneity: $\chi^2 = 357.33$, $df = 2$ ($p < 0.00001$); $I^2 = 99\%$; Test for overall effect: $Z = 5.37$ ($p < 0.00001$)

It is suspected that the rise in LDH levels is associated with multiple organ injury and failure, thereby representing an important marker for clinical outcomes in COVID-19 patients.³² Therefore, the beneficial effect of colchicine on large effect size reduction of LDH levels provides novel insight into its clinical efficacy among COVID-19 patients.

Another inflammatory marker, d-dimer, is also predictive of the risk of progression and severity in COVID-19 infection. Our study demonstrates a large reduction in d-dimer levels among patients who received colchicine compared to those who did not. D-dimers are a fragment of fibrin that is created after plasmin cleaves it to break down clots.³³ The d-dimer levels are indicative of fibrin production or breakdown.³³ D-dimer levels are also associated with in-hospital mortality, as noted by Zhou et al.³⁴ that a level of >1 $\mu\text{g/ml}$ is an independent risk factor for mortality. Specifically, in COVID-19 patients, elevated d-dimer levels are indicative of venous thromboembolism (VTE) and prediction of disseminated intravascular coagulation (DIC).³⁵ Evidence of elevated d-dimer levels is also noted with the severity of lung involvement in COVID-19 patients.³⁶ Consequently, a large reduction in mean d-dimer levels among moderate-to-severe

patients who received colchicine suggests the potential efficacy of colchicine in reducing worse outcomes in our study. Therefore, colchicine may work by reducing the d-dimer levels that predispose patients to in-hospital mortality, especially patients who present with elevated d-dimer levels on admission and may be suitable candidates for adjuvant colchicine treatment.³⁷

5 | STRENGTHS AND LIMITATIONS

Our study has certain strengths that may be pointed out. This is the first study that identifies a significant reduction in important inflammatory biomarkers for example, CRP, D-dimer, and LDH, in colchicine versus control groups. This study has a moderate sample size with a significant reduction in well-known prognostic biomarkers. While the individual studies had small sample sizes, our pooled analysis is sufficient to consider colchicine for clinical practice in COVID-19 infection. A limitation of this study was the lack of ability to characterize the severity of infection on a case-by-case basis. Overall, the included sample was of moderate-to-severe intensity.

However, due to the paucity of data, it is unclear if the significant reduction was primarily seen in moderately-ill patients or the effect was also due to the reduction of biomarker levels in severe patients. However, so far, colchicine is being considered in mild-to-moderate patients.⁸ We found that the effect of colchicine may be pronounced in patients with ongoing inflammatory processes, which may potentially be observed across the entire clinical spectrum of COVID-19 infection. Therefore, we recommend administering colchicine as an adjuvant to supportive treatment in patients with elevated biomarkers in an attempt to reduce morbidity and mortality following COVID-19 infection.

6 | CONCLUSION

Our findings support the use of colchicine in moderate-to-severe COVID-19 patients with a rise in inflammatory prognostic biomarkers. The most pronounced reduction was observed in d-dimer levels followed by LDH levels and CRP levels in our pooled analysis. It is worth noting that our study reported beneficial effects of colchicine administered low-dose and long-term in hospitalized patients. It is, therefore, of importance to consider colchicine in further clinical trials by focusing on laboratory markers as well as clinical indicators of severity. As colchicine is tolerable, safe, and cheap, our results are noteworthy with a demonstrable reduction in prognostic inflammatory biomarkers.

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None

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

All data used and acquired for this study is available online.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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