European Journal of Internal Medicine 112 (2023) 126–127

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Colchicine and mortality outcomes in patients with coronavirus disease (COVID-19)

Dear Editor-in-Chief,

One of the therapeutic hallmarks of the ongoing (COVID-19) pandemic has been the different iterations of successful and sometimes unsuccessful attempts at re-purposing of drugs with pre-existing market authorization for use in COVID-19 patients. We therefore read with interest Perricone et al's., recent report on the clinical outcomes of hospitalized COVID-19 patients exposed to colchicine [1]. This randomized controlled clinical trial (RCT) evaluating efficacy and safety of generic colchicine found no significant difference in the primary composite endpoints of intensive care admissions (ICU) and the need for mechanical ventilation between patients exposed to colchicine added to standard of care ($N = 77$) vs. controls ($N = 75$) stabilized on usual standard of care (mechanical ventilation 5.2% vs 4%, ICU 1.3% vs 5.3%, death 9.1% vs. 6.7%, overall 11 (14.3%) vs. 10 (13.3%) patients, P=not significant). Perricone et al's., report has "arrived" at critical time against a backdrop of ongoing uncertainty regarding the exact relationship between colchicine exposure and hard clinical endpoints in COVID-19 patients. Discordant studies from both observational as well as clinical trials have reported both mortality-reducing propensity of colchicine in these cohorts of patients, as well *null* effect by others [2]. In a welcome attempt to resolve this uncertainty, several subsequent meta-analytic syntheses of these studies have been commissioned and published [2–10], unfortunately with discordant outcomes. Whilst some of these such as those by Elshafei et al., have clearly shown a mortality reduction benefit of colchicine [3], others such as Sanghavi et al. et al., have not only reported a *null* effect of colchicine exposure but have raised potential safety concerns regarding it use [4]. Our meta-analysis examined 9 studies ($n = 5522$ patients) comprising of four observational and four RCTs [3]. We found exposure to colchicine in the setting of COVID-19 clinical syndrome was associated with significantly lower risks of mortality compared to controls stabilized on usual standard of care (Odds ratio [OR] 0.35, 95% confidence interval [CI] 0.25–0.48, I^2 0%). Obviously, the interesting backdrop to the pooled estimates of our review remains the unvaccinated characteristics of the constituent studies we included in our synthesis.

Several factors could account for the marked disparities in mortality outcomes between these studies. These includes differences in study design (observational vs. RCTs), as well as the socio-demographic "mix" of the various study populations. Earlier studies exploring the role of colchicine were carried out in the initial phase of the pandemic when COVID-19 immunization was not part of "usual standard of care" in these cohorts of patients. It has since been established that COVID-19 immunization in common with other factors (such as face masks and social distancing) represents the most significant interventions that not only reduced mortality in these patients, but also assisted in returning

Table 1
A Compendium of M eta-analytic synthesis of the role of colchicine on mortality outcomes vis-a-vis recent RCT in patients with COVID-19 clinical syndrome.

Author ID	Study design	Evaluated outcome	Outcome effect size (Hazard ratio, [95% confidence interval])	Outcome	COVID-19 Vaccination status
Chiu et al. [2]	Meta-analysis	mortality	0.25 (0.09, 0.66)	Reduced	Vaccinated population
Sanghavi et al. [4]	Systematic review	Mortality	NA	Equivocal	NA
Lien et al. [8]	Meta-analysis	Mortality	0.57 (0.38–0.87)	Reduced	NA
Elshafei et al. [3]	Meta-analysis	Mortality	0.35 (0.25- 0.48)	Reduced	NA
Zein et al. [8]	Meta-analysis	Mortality	0.66 (0.53, 0.83)	Reduced	NA
Yasmin et al. [9]	Meta-analysis	Mortality	0.98 (0.83, 1.16)	Not reduced	NA
		COVID-19 severity.	0.41 (0.22, 0.76)	Reduced	
Lan et al. [10]	Meta-analysis	Mortality	1.00 (0.91–1.09)	Not reduced	NA
Zhang et al. [7]	Network Meta-analysis	Mortality	0.48 (0.16–1.27)	Not	Not vaccinated.
		Mechanical ventilation	0.42 (0.20,0.83)	Reduced Reduced	
Perricone et al. [1]	Randomized Control Trial	Composite[a]	11 (14.3%) vs 10 (13.3%)[b]	*Null*	A proportion were vaccinated

NA; Not available.
[a] Composite of rate of critical disease in 30 days defined as need of mechanical ventilation, intensive care unit (ICU), or death [1].
[b] Number (Percentages).

Abbreviations: COVID-19, corona virus disease 2019; RCT, randomized controlled clinical trial.

https://doi.org/10.1016/j.ejim.2023.02.009
Received 19 January 2023; Received in revised form 8 February 2023; Accepted 10 February 2023
Available online 16 February 2023

human populations back to near-normal level of activities. It is therefore possible the mortality reduction or "trends" reported by studies in COVID-19 vaccinated patients exposed to colchicine may have had these benefits driven wholly or partially by immunization rather than the drug. A proportion of Perricone et al's., patient cohort received COVID-19 vaccination, although it remains uncertain how this may have contributed to the *null* composite outcome reported in the study.

Differences between meta-analytic syntheses on the other hand could be attributable to differences in the design of constituent studies as well as distinct characteristics of the study cohorts. Whilst most of the published meta-analyses explored the role of colchicine in hospitalized patients, others (such as those by Sanghavi et al. [4]) undertook a pooled synthesis of studies exploring efficacy and safety of colchicine in outpatient settings. Of the nine studies explored by our review for example, four were cohort studies (retrospective and prospective); three RCT's; a quasi-RCT; and a case-control study. Pooling of point estimates from these studies with disparate designs and effect sizes meant that uncertainty still pervades regarding their final pooled estimates.

Owing to these discordant outcomes from studies from both systematic and observational studies as well as meta-analytical syntheses (that were hitherto supposed to resolve residual uncertainty) in these patient cohorts, more studies involving large patient populations are needed to conclusively establish the exact role of colchicine in COVID-19 patients exposed to it. As recent events in China have shown, this pandemic in all its forms is by no means over. This therefore calls for more work in both therapeutics and prevention tracks of the disease, especially around ascertaining the exact efficacy and safety of repurposed agents (such as colchicine) Table 1.

Declaration of competing interest

None of the authors have any relevant conflict of interest to declare.

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