

Open letter to Mandeep R. Mehra, Sapan S. Desai, SreyRam Kuy, Timothy D. Henry, and Amit N. Patel, authors of “**Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19**”. **NEJM**. **2020 May 1 DOI: 10.1056/NEJMoa2007621**

and to Eric J Rubin (Editor-in-Chief of the New England Journal of Medicine and NEJM Group).

Expression of concern regarding data integrity and results

A recent publication in The Lancet [1], using data owned and analysed by *Surgisphere* (obtained via the international registry “The Surgical Outcomes Collaborative”), has had a major global adverse impact on ongoing randomized controlled trials evaluating chloroquine or hydroxychloroquine in the prevention or treatment of COVID-19. Serious, and as yet unanswered, concerns have been raised about the statistical methods, the integrity and provenance of the data, and the lack of ethical oversight [2].

Results from an earlier *Surgisphere* data set were reported by some of the same authors (Mehra, Desai and Patel) in the New England Journal of Medicine (NEJM). This study analyzed cardiovascular disease and mortality in hospitalized patients with COVID-19 [3]. The dataset included 8910 patients with PCR confirmed COVID-19 infections from 169 hospitals in Asia, Europe and North America, admitted up until the 15th March 2020. We observe similar issues with those noted for the recent Lancet paper. In each of the countries, a relatively small number of hospitals are reported to have provided electronic patient record data to *Surgisphere*, yet these reports describe a remarkably high proportion of all PCR-confirmed cases in the respective countries hospitalized by March 15.

It is difficult to reconcile the UK data from *Surgisphere* with publicly available government data. Mehra et al [3] report electronic patient data from 706 patients hospitalized with PCR confirmed COVID-19 in just 7 of the UK’s 1,257 NHS hospitals. A high proportion of patients hospitalized in the UK on March 15th were in London [4], and yet no London borough, let alone hospital, had more than 100 PCR positive confirmed cases by this date [4].

The numbers from Turkey also appear incorrect. Countrywide, the first COVID-19 case was diagnosed at Istanbul Faculty of Medicine on the 9th of March. The second COVID-19 patient in that hospital was not seen until the 16th of March. The Turkish Ministry of Health reported a total of only 191 PCR positive cases by the 18th of March (this accounts for a delay of up to 72 hours for PCR results, <https://covid19.saglik.gov.tr>), which is compatible with frontline observations across multiple institutions. Yet, *Surgisphere* report electronic patient data from 346 patients with PCR confirmed COVID-19 from three Turkish hospitals, admitted up until the 15th of March.

The reliability of the *Surgisphere* database is further questioned by comparing the estimated age-dependent mortality with other published estimates. The odds ratios for death shown in Figure S1 in [3] do not show a log-linear increase for ages over 60 years, which would be expected as others consistently report an exponential relationship between age and death, e.g.

[5,6]. For example, the odds ratio for death estimated for 81+ years relative to <10 years is 5.076 (95% confidence interval, 1.185 to 21.735), whereas from Table S2 in [5] the odds ratio for death for 81+ relative to <20 years is 76.5 (95% CI, 34.0 to 159.3); this 15-fold difference cannot be explained by the difference in comparator groups alone.

The integrity of the *Surgisphere* database is critical to the validity of both studies [1,3]. Major concerns have been raised. In the interests of transparency and public health, we believe it is imperative that:

1. *Surgisphere* provides details on data provenance. At the very minimum, this means sharing the aggregated patient data at the hospital level (for all covariates and outcomes). We note that NEJM signed the [Wellcome statement](#) on data sharing for COVID-19 studies.
2. The NEJM commissions or facilitates an independent validation of the data and the analysis to be performed by an external group(s).
3. An assurance that in each jurisdiction, any mined data was legally and ethically collected and patient privacy aspects respected.

This open letter is signed by clinicians, medical researchers, statisticians, and ethicists from across the world. The full list of signatories and affiliations can be found below.

References

- [1] Mehra, Mandeep R., et al. "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis." *The Lancet* (2020).
- [2] James Watson on behalf of 201 signatories. (2020, May 28). An open letter to Mehra et al and The Lancet (Version 4). *Zenodo*. <http://doi.org/10.5281/zenodo.3871094>
- [3] Mehra, Mandeep R., et al. "Cardiovascular disease, drug therapy, and mortality in Covid-19." *New England Journal of Medicine* (2020).
- [4] <https://data.london.gov.uk/dataset/coronavirus--covid-19--cases>
- [5] Salje, Henrik, et al. "Estimating the burden of SARS-CoV-2 in France." *Science* (2020)
- [6] Docherty, Annemarie B., et al. "Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study." *BMJ* (2020).

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