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Linking lactate dehydrogenase to the severity of COVID-19 cannot ignore the employed methodology

Dear Editor,

We read with interest the paper by Henry et al. [1], who, through a pooled analysis of available studies, supports the evidence that lactate dehydrogenase (LDH) measurements in serum can be a significant predictor of severity and mortality in COVID-19 patients [2]. The link between LDH levels and COVID-19 severity may reflect both the direct lung injury and more widespread tissue damage [3,4]. This association was analyzed in 9 published studies. Although the information provided by these studies is potentially relevant for guiding patient care and permitting early identification of subjects at high risk of death or of developing severe disease, its practical implication and transferability among different health care locations is compromised by the fact that no studies discussed how their assays used to determine LDH comply with the available internationally agreed reference measurement system and therefore if they provided results standardized enough to allow the universal application of suggested decision thresholds [2,5]. This issue was briefly pointed out also by Henry et al. as a limitation of their work [1].

It has previously been stressed how the issue of laboratory measurement standardization represents an absolute priority for optimizing health care, even in COVID-19 pandemic [2,6]. Particularly, for LDH measurements it becomes extremely relevant since two different method principles, which use two different substrates (lactate and pyruvate), are commercially available and therefore there is a real possibility of obtaining significantly different results in different laboratories [7]. This lack of comparability can lead to significant differences in obtained results, thus making potentially ambiguous the interpretation of study conclusions.

In collaboration with the Clinical Pathology Unit of the 'Luigi Sacco' academic hospital, one of the two Italian reference centers for infectious diseases, the Research Centre for Metrological Traceability in Laboratory Medicine (CIRME) recently supervised studies on hospitalized COVID-19 patients performed to evaluate the role of laboratory tests as clinical predictors of disease severity, by selecting the worst results for each evaluated biomarker of the whole hospitalization period. Optimum biomarker cut-offs were specifically selected to have a high rule-in ability in detecting patients at risk of in-hospital death and a high rule-out ability in identifying patients at very low risk of intensive care unit (ICU) admission [8]. At the multivariate analysis, LDH concentrations were significantly associated with both higher odds of death [odds ratio (OR), 161.5 (95% confidence interval (CI): 2.28–11,422.8; $p = 0.019$], and lower odds of ICU admission [OR, 0.06 (95% CI: 0.01–0.54); $p = 0.011$]. The best LDH cut-off for death prediction was >731 U/L, while an LDH activity <425 U/L was associated with a negative likelihood ratio of 0.10 for intensive treatment [8]. One of the major strengths of the these results was represented by the use of an LDH measuring system of which the optimal analytical standardization had been previously verified and validated [9], enabling the universal application of obtained results and permitting their unambiguous interpretation, providing that institutions implementing them also use standardized LDH assays.

Similar concerns about the lack of result harmonization was recently reported for D-dimer [6,10], another marker which has been proven to be a predictor of COVID-19 severity [11]. However, while for D-dimer measurements the harmonization of results cannot be fully achieved at the moment since no universally accepted reference measurement system has yet been identified, for LDH a reference procedure has been established in 2002 by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [12], which is now widely accepted by the scientific community as the highest reference standard available to which assay manufacturers should align their measuring systems. Here, we want to remark that only the promotion and the adoption of assays that guarantee the equivalence of results obtained in different laboratories worldwide permits the universal application of results from studies performed in different settings (e.g., China vs. Europe).

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Declaration of Competing Interest

None.

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