

MATTERS ARISING

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Reply to “PROVENT-C19 repeated prone positioning analysis”: not everything that differs is inconsistent

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We thank Dr. Walter for the careful reading of our article [1] and for the thoughtful comments [2]. We appreciate the constructive spirit of the Matter Arising and welcome the opportunity to clarify the analytical framework of our study. At the same time, we respectfully submit that the concerns raised do not reveal internal inconsistencies or inappropriate overinterpretation, but rather reflect the inherent complexity of a registry-based observational analysis focused on repeated prone-positioning cycles [3].

First, regarding the alleged population inconsistency, we believe that the figures cited in the Matter Arising reflect different analytical denominators rather than inconsistencies. The 1523 patients reported in Tables 1 and 2 correspond to the cohort with complete data available for analysis. By contrast, the 1372 patients reported in the Results section represent the subset of those 1523 patients who underwent more than one prone-positioning cycle, namely the subgroup specifically relevant to analyses of consecutive cycles beyond the first. These figures therefore do not reflect competing definitions of the study population, but two distinct and complementary

analytical denominators. In registry-based studies, especially those involving progressive restriction of the sample according to analytical objectives, such differences in denominator are expected and methodologically legitimate [4, 5]. We therefore consider the manuscript internally coherent on this point.

Second, concerning the suggestion that we may have drawn causal conclusions from an associative framework, we agree on the general principle but respectfully disagree with the implication that our interpretation exceeded the limits of the data. Our study was explicitly designed as an observational registry analysis [3], and the Discussion states that the findings do not establish causation. We also explicitly noted that the concept of identifying possible “negative responders” to prone-positioning would require validation in studies specifically designed to assess causality.

The trajectory observed in non-survivors, namely the progressive rise in ventilatory ratio during and after prone-positioning, may indeed reflect worsening disease severity, progressive ventilatory inefficiency, or evolving dead-space impairment, rather than a harmful effect directly caused by prone-positioning itself [6–9]. We do not dispute this interpretation; rather, we consider it entirely compatible with our reading of the data. However, the fact that an observation is associative does not deprive it of clinical relevance. Our point was not that prone-positioning causes deterioration in patients with a rising ventilatory ratio, but that such a pattern may identify patients following a more unfavorable physiological course. In that context, the value of ventilatory ratio lies

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in monitoring and prognostic stratification, not in establishing a treatment-directing causal threshold [6, 7].

Accordingly, the statement that prone-positioning “should be reconsidered” in the context of an increasing ventilatory ratio should not be interpreted as prescriptive guidance to discontinue prone-positioning solely on that basis. It should instead be understood as a call for clinical caution and individualized reassessment within the broader context of the patient’s trajectory.

Third, regarding the late-supine timing, we agree that the timing of the late-supine assessment may differ between patients, particularly between those who subsequently underwent another prone-positioning cycle and those who did not. However, this is an inherent feature of real-world observational design. As stated in the Methods, the duration of prone cycles and the supine intervals between them were not standardized, and the registry recorded the actual start and end times of each cycle precisely to reconstruct exposure to prone and supine positioning as it occurred in clinical practice.

In this context, the definition of late supine necessarily reflects bedside reality: its timing is intrinsically linked to patient evolution and clinician judgment. That is not a defect of the analysis; it is the nature of multicenter registry data.

Moreover, this temporal heterogeneity was explicitly acknowledged in the manuscript, and cumulative pronation and supination times were separately reported across cycles. These exposure data provide the temporal framework within which the physiological measurements should be interpreted. Thus, while the exact distribution of late-supine timing may differ across groups, the manuscript already offers a transparent representation of the real-life timing structure underlying the analysis. More broadly, this comment identifies a general limitation of observational registry studies rather than a flaw specific to the present report. Because the decision whether and when to re-pronate is itself part of the observed care process, it cannot be fully disentangled from the physiological trajectories being described. This is precisely why our conclusions were framed as associative rather than causal, and why we view the study as hypothesis-generating rather than treatment-directing.

Fourth, with respect to the omission of first-cycle data from the cumulative prone-time analysis, we fully agree that the duration of the first prone-positioning cycle is an important variable. However, its exclusion from the present analysis was intentional and methodologically pre-specified. The duration and physiological significance of the first prone-positioning cycle in this same registry population had already been the focus of a previous dedicated publication, in which

we demonstrated that the length of the first cycle was inversely associated with ICU mortality and remained independently associated with outcome in multivariable analysis [10]. That earlier article also specifically addressed the relationship between first-cycle duration, oxygenation response, ventilatory ratio, and mortality.

The present study was therefore deliberately designed to address a different and previously unexplored question: the physiological and prognostic significance of cycles subsequent to the first. Reintroducing first-cycle duration into the present article would have substantially overlapped with findings already published from the same dataset, with the obvious risk of redundancy. The analytical separation between the first cycle, already studied in depth (also by several other authors [11–15]), and the subsequent cycles, which constitute the novel focus of the present work, was therefore deliberate and justified. For the same reason, Supplementary Fig. 5 was not intended to reconstruct each patient’s entire lifetime prone exposure from the first maneuver onward. Its purpose was to evaluate whether, after the first cycle, cumulative prone exposure during subsequent cycles retained an association with ICU mortality. In other words, the study was intentionally framed around the post-first-cycle phase, because that phase had not been specifically addressed in the literature, whereas the first cycle has already been extensively studied by us and by others. We therefore respectfully submit that this analytical choice reflects focus and avoidance of redundancy, rather than incompleteness.

In summary, we are grateful for these comments, which allow us to restate more clearly the logic of the study. The present work was an observational, registry-based, hypothesis-generating analysis aimed at characterizing the physiological and prognostic significance of repeated prone-positioning cycles beyond the first. Read within that framework, we believe the manuscript is methodologically coherent, internally consistent, and appropriately cautious in its conclusions. The Matter Arising usefully underscores the need for careful interpretation of analytical levels and timing heterogeneity, but in our view does not identify flaws that undermine the validity of the descriptive and prognostic signals reported. On the contrary, it reinforces the central message of our article: that the behavior of subsequent prone-positioning cycles deserves dedicated attention and should now be tested in prospective studies specifically designed to permit stronger causal inference. In conclusion, while different analytical levels may require careful reading, they should not be mistaken for contradiction: not everything that differs is inconsistent.

Clinical trial number

Not applicable.

Authors' contributions

All authors directly accessed and verified the underlying data reported in the manuscript, and accepted responsibility to submit for publication. All authors approved the final version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

No datasets were generated or analysed during the current study.

Declarations**Ethics approval and consent to participate**

The registry was designed following the Declaration of Helsinki and the study protocol was firstly approved by the Ethics Committee of the Saint Bortolo Hospital, Vicenza, Italy (Study ID Numbers: 22/21). Patient consent was obtained according to the national regulations of each participating institution. In cases the patient was incompetent because of critical illness or the use of sedative or anesthetic drugs, consent could be delayed, and a provision for delayed consent was applied: as soon as competent, each patient was fully informed on what had been done, and a written permission of using data collected was obtained. The patients or their legal surrogates were informed of their right to request that the study procedures be discontinued and their right to refuse the study-related use of their medical records.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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