Cutting the Gordian knot of heterogeneity: Can integrated systems biology modelling rescue critical care syndromes?

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Critical care is perhaps the principal custodian of sepsis and the acute respiratory distress syndrome (ARDS). Both syndromes are beset by multifactorial heterogeneity owing to their respective broad and non-specific clinical diagnostic criteria. Coupled with the heterogeneity of host responses (genetic and acquired) and timing and severity of the insult, it is perhaps unsurprising that critical care has been fertile grounds for negative clinical trials. Even in COVID-19, where aetiology is uniform and sample sizes unwantedly generous, findings of clinical trials for immunomodulatory drugs and antivirals have been uncertain, again alluding to underlying heterogeneity.[1] A precision medicine approach to treatment, based on biologically plausible subtypes, has been proposed as a more viable alternative to "one size fits all."[2] However, identifying which patients benefit from which therapy – and when – remains a critical question in the field. It seems intuitive that algorithms that incorporate complex systems biology to model disease heterogeneity are likely to aide in optimising interventions.

In this issue of *EBioMedicine*, Subudhi and colleagues present the results of a mathematical model in COVID-19 that seeks to simulate the effects of immunomodulatory therapies on distinct patient subtypes derived from their baseline characteristics.[3] Utilizing a previously validated systems biology model of COVID-19,[4] the authors first defined six patient types based on known COVID-19 risk factors: young/healthy, diabetic, obese, hypertensive, older, and hyperinflammed. The effect of three therapies (corticosteroids, anti-IL6, and anti-IL6R) and timing of their administration (from viral exposure on day 1 to day 14) were then simulated using the model. The effect of each therapy was quantified based on the closeness of return to baseline on day 1 (i.e., full treatment effect) versus day 20 in an untreated patient (i.e., no treatment effect).

Based on model results, immunomodulatory therapy has limited efficacy in young/healthy, diabetic, and obese patients, even with early initiation. By contrast, hypertensive patients respond to most therapies, irrespective of timing. Older and hyperinflammed patients only benefit from anti-IL6 therapy when given early (e.g., days 1–4 after viral exposure) and from corticosteroids when given later in disease course (e.g., days 7–10). The latter finding has been observed in clinical trials of corticosteroids in COVID-19 and suggests that identification of the phase of host inflammatory response is important to tailor treatment.[5] Notably, according to their modelling, hyperinflammed patients responded to anti-IL6 but not anti-IL6R therapy.

Next, the authors used a feature extraction technique called non-negative matrix factorization to describe "biological programs" that speculates on potential mechanisms for the observed findings. For example, their analysis identified heightened activity of extra-pulmonary cytokine production, systemic microthrombosis, and pulmonary neutrophil recruitment in older patients with untreated COVID-19. Timely administration of immunomodulator therapy reduced activity of this program to baseline levels. Finally, they applied regression models derived from their algorithm to show the relevance of some the proposed biomarkers (e.g., IL-6, neutrophils, and D-dimer) and their predictive performance for COVID-19 severity in each subtype using clinical data. The biomarkers were informative in accordance with the findings of their modelling. Although, it should be acknowledged that in other studies, these biomarkers have been shown to predict disease severity in all-comers with COVID-19, irrespective of patient subtype.[6,7]

Subudhi and colleagues present a novel study with notable strengths. The systems biology approach allows interrogation of potential mechanistic insights that are not readily apparent from routine observation of clinical outcomes in either retrospective or prospective clinical trials. By describing potential biological pathways

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underpinning clinical heterogeneity, the mathematical model suggests specific prognostic variables or therapeutic targets that can be further evaluated in selected populations. Moreover, this type of in silico "virtual clinical trial" design can allow for accelerated timeline of discovery that is not feasible in real-world clinical trials. The observed prognostic utility of biomarkers identified in the modelling in a real-world cohort adds face-validity to their modelling and is a major strength of the paper.

There are, however, important limitations. The analysis does not model an exhaustive feature set of known modulators of severe COVID-19, most notably excluding race and gender.[8] Moreover, to represent various subgroups, model parameters are altered deterministically according to mechanistic plausibility, which probably oversimplifies biological variability. Finally, while this study evaluates each risk factor independently, real-world patients do not neatly fall into a singular patient type and the interaction between multiple competing risk factors remains unknown. The constraints of linear interactions of the presented modelling, as a consequence of the authors' use of single sets of parameter values for the subgroups, raises the question of whether the algorithms presented here are sufficiently complex to capture the biological heterogeneity we observe in our patients, which is a myriad of non-linear and deeply networked responses. It may be that the more complex mathematical modelling is needed to fully realise the potential of such analyses.

Nevertheless, as a proof of concept, this study is a novel and disruptive contribution to a growing body of literature seeking to identify homogeneous patient subtypes within heterogenous clinical syndromes by leveraging modern data science techniques.[9,10] The promise of such precision medicine approaches is two-fold: (1) to advance biological understanding of disease and, more importantly, (2) provide prognostic and therapeutic information to directly impact patient care. Confirming the utility of biological subtypes through prospective trials will be a key step in translating hypothetical frameworks into valuable clinical tools. Mathematical modelling has the potential to accelerate our knowledge gathering of underlying heterogeneity and potential treatment implication to enable more efficient hypothesis generation to test in patient populations.

Declaration of interests

The authors do not have any conflicts of interest to disclose.

Contributors

PS and MM both reviewed the literature and prepared this commentary.

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