Editorial Commentary

Patient selection in sepsis: precision medicine using phenotypes and its implications for future clinical trial design

Daisuke Hasegawa, Osamu Nishida

Department of Anesthesiology and Critical Care Medicine, Fujita Health University School of Medicine, Aichi, Japan

Correspondence to: Osamu Nishida, MD, PhD. Department of Anesthesiology and Critical Care Medicine, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. Email: nishida@fujita-hu.ac.jp.

Provenance: This is an invited article commissioned by the Section Editor Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Seymour CW, Kennedy JN, Wang S, *et al.* Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 2019;321:2003-17.

Submitted Aug 22, 2019. Accepted for publication Sep 08, 2019.

doi: 10.21037/jtd.2019.09.31

View this article at: http://dx.doi.org/10.21037/jtd.2019.09.31

Recently, Seymour *et al.* reported in *The Journal of the American Medical Association* (1) that they had identified 4 clinical phenotypes (α, β, γ, and δ) in sepsis patients by applying machine learning methods to the data available at patients' hospital presentation. The authors found that these phenotypes were correlated with host reaction patterns to the treatment and with clinical outcomes.

The ultimate goal of their study was to investigate the heterogeneity in responses to treatment and the sensitivity of clinical trial results according to the frequency distributions of these phenotypes. The definition of sepsis (2) is broad and includes a vast, multidimensional array of clinical and biological features, and that has been a major barrier to progress in finding effective therapies (1). Their idea was that this newly established method of separation by phenotypes may identify different risks for poor outcomes and, more importantly, may predict different responses to specific treatments.

They found that, of the 4 derived phenotypes, the α phenotype was the most common (33%) and included patients with the lowest level of vasopressor administration; the β phenotype (27%) included patients who were older and had more chronic illnesses and renal dysfunctions; the γ phenotype (27%) included patients with more inflammation and pulmonary dysfunctions; and the δ phenotype (13%) included patients with more liver dysfunction, coagulopathy, and septic shock. In addition, they demonstrated that mortality rates were significantly higher among the δ phenotype than among the other 3 phenotypes. Moreover, in simulation models, they found that the proportion of randomised controlled trials (RCTs) reporting benefit, harm, or no effect changed by varying the phenotype frequencies.

It has recently been emphasised that selecting the right population and the right intervention at the right time are of paramount importance to create well-designed RCTs (3). We believe that the main result of Seymour *et al.*'s research is epoch-making and possibly has the potential to overturn the results of RCTs up to now by offering us 2 insights into the design of RCTs.

First, Seymour *et al.* tell us how to select the right patients. In critical care settings, the diseases most often encountered are syndromes with broad definitions, including sepsis (2), acute respiratory distress syndrome (ARDS) (4), and acute kidney injury (AKI) (5). Among these, sepsis is one of the most prevalent heterogeneous diseases in the intensive care unit (ICU) (6). Thus, in the absence of one specific treatment, it has been quite difficult to find effective treatment options effective in all patients with the same syndrome. Even if one treatment might be effective in some specific subgroups in the overall population, if the same treatment is not effective or even harmful in other subgroups in the same population, the conclusion of a clinical trial would probably be no effect (3).

For example, recent studies using machine learning methods demonstrated that there are 2 subphenotypes

within ARDS, with 1 subphenotype having more severe inflammatory reaction, shock, and metabolic acidosis and worse outcomes (7). Response to positive end-expiratory pressure treatment strategies differed based on the subphenotype. Therefore, selecting the specific subgroups with probable positive treatment responses prior to designing a clinical trial would make it more feasible to conduct RCTs with positive results.

Second, Seymour *et al.*'s research gives us insight into performing interventions at the right time. In critical care settings, the condition of the patient often changes dynamically over time, which implies that effective treatment in some specific subgroups does not work well if the interventions are delayed. By dividing sepsis patients based on early data, as in this research, it would be possible to conduct more precise RCTs by treating specific populations with prompt and early interventions.

Based on the findings of Seymour *et al.*, it may be feasible to predict organ dysfunction in a particular patient and therefore, deal with it more appropriately and quickly than at present. This may be done in the near future by dividing patients into the 4 clinical phenotypes using data obtained soon after presentation and applying machine learning methods to the data. Seymour *et al.*'s research also implies that clinical trials that had a conclusion of no effect might possibly show beneficial effects if conducted again only in specific phenotypes, especially those trials which have shown benefit in some specific subgroups.

Here, we mention 3 well-known therapeutic interventions for sepsis patients without overall significant effects, but for which subgroup analyses have demonstrated some benefit. We discuss albumin (8), antithrombin (9), and recombinant thrombomodulin (10) and their possible effects on specific phenotypes.

Albumin

Caironi *et al.* conducted an RCT to evaluate whether the use of albumin for severe sepsis is effective (8). A total of 1,818 patients with severe sepsis were randomly assigned to be administrated either 20% albumin and crystalloids or only crystalloids. In the albumin-administrated group, the target serum albumin concentration was no less than 30 g/L, and these patients' primary outcome was 28-day mortality. Their secondary outcome was 90-day mortality. At 28 days, 31.8% and 32.0% had died in the albumin-administrated and crystalloids-only group, respectively [relative risk (RR) in the albumin group, 1.00; P=0.94]. At 90 days, 41.1% in the albumin-administrated group had died, while 43.6% in the crystalloids-only group had died (RR in the albumin group, 0.94; P=0.29). The other secondary outcomes were not significantly different between these 2 groups. Thus, the authors concluded that, in patients with severe sepsis, albumin administration in addition to crystalloids, in comparison with crystalloids only, did not show 28- and 90-day mortality improvement. However, in a post hoc analysis, a significant difference was found in 90-day mortality in a septic shock subgroup (RR in the albumin group, 0.87; P=0.03). According to this analysis, patient selection was too broad, and different results might be expected if patients were selected based on prediction of developing septic shock. It could be that if only patients with δ phenotype, characterised by septic shock and high mortality rate, were selected, different results might be expected.

Antithrombin III (ATIII)

Warren *et al.* conducted an RCT to evaluate whether ATIII would induce better outcomes in survival in patients with severe sepsis and septic shock (9). They randomly assigned 2,314 adult patients with severe sepsis or septic shock to receive either intravenous (IV) ATIII or a placebo. Their primary endpoint was 28-day mortality. Overall 28-day mortality in the ATIII-administrated group was 38.9%, while 38.7% in the placebo group (P=0.94). The authors concluded that ATIII administration had not improved 28-day mortality in adult patients with severe sepsis and septic shock. However, post hoc analysis of this trial has shown that ATIII-treated patients who developed disseminated intravascular coagulation (DIC) had an absolute reduction in 28-day mortality of 14.6%, in comparison with the control group (P=0.02), while no effect on 28-day mortality was seen in patients who did not develop DIC (P=1.0) (11). According to this analysis, different results might be expected if patients were selected based on prediction of developing DIC. If only patients with δ phenotype, characterised by coagulopathy and high mortality rate, had been selected, this RCT could have shown different results.

Recombinant thrombomodulin

Vincent *et al.* conducted an RCT to evaluate whether recombinant thrombomodulin administration would be effective in patients who developed sepsis-associated DIC (10).

They randomised 750 adult septic patients who developed DIC, with the use of a modified International Society on Thrombosis and Haemostasis score. Included patients were randomly assigned to be administrated either IV recombinant thrombomodulin or placebo for 6 days. Their primary outcome was reduction in mortality. In this trial, 28-day mortality was 17.8% in the recombinant thrombomodulin-administrated group, while that was 21.6% in the control group (Cochran-Mantel-Haenszel two-sided P value of 0.273 in favour of recombinant thrombomodulin, which met the predefined statistical test for evidence suggestive of efficacy). The survival improvement was the most significant in patients who had respiratory or cardiac dysfunction and coagulopathy, characterised by prothrombin time-international normalised ratio more than 1.4 at baseline and a platelet level between 30 and 150×10^9/L. Among them, the mortality rate in the recombinant thrombomodulin group was 26.3%, while that in the control group was 38.2%. Thus, a phase 3 RCT was conducted involving only patients who met the above criteria based on the subgroup analysis of a phase 2 trial (12). However, ART-123 failed to show any differences in 28-day mortality compared to placebo. Based on this result, the population of the study might be adequate. However, it is possible that the administration of ART-123 was too late to work effectively, since only patients who had already developed coagulopathy were included. Based on all the findings, it could be that by involving only patients with δ phenotype, characterised by coagulopathy, and by giving treatment in an early phase before these coagulopathy candidates actually develop coagulopathy, this RCT might show positive results.

Recently, researchers have tended to increase the number of patients in clinical trials to obtain more reliable, generalisable, and definite conclusions. However, many trials, especially in critical care settings, reach a conclusion of no effect presumably because of the heterogeneity of response to treatments. In this current situation, Seymour *et al.*'s research created a stir in relation to the design of clinical trials. There were several limitations in their research. Some crucial factors such as causal pathogens and patients' ethnicity that could affect the results were not included in the analysis. Additionally, because multiple therapeutic interventions could have been conducted within the time window for data capture, which in this analysis is the first 6 hours of hospital presentation, the results may be influenced by the treatments the patients received within that time window. However, we believe that their research is a landmark study, and the direction that they suggested will lead to more appropriate trial designs with more definite results in the very near future. Future research is warranted to further divide these phenotypes by identifying and more carefully selecting variables that will allow the application of this in a real clinical setting.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

References

1. Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 2019;321:2003-17.
2. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801-10.
3. Vincent JL. Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? No. Intensive Care Med 2016;42:1778-80.
4. ARDS Definition Task Force., Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-33.
5. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. Kidney Int 2015;87:62-73.
6. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
7. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2:611-20.
8. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock.

N Engl J Med 2014;370:1412-21.
9. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869-78.
10. Vincent JL, Ramesh MK, Ernest D, et al. A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013;41:2069-79.
11. Kienast J, Juers M, Wiedermann CJ, et al. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost 2006;4:90-7.
12. Vincent JL, Francois B, Zabolotskikh I, et al. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. JAMA 2019;321:1993-2002.

Cite this article as: Hasegawa D, Nishida O. Patient selection in sepsis: precision medicine using phenotypes and its implications for future clinical trial design. J Thorac Dis 2019;11(9):3672-3675. doi: 10.21037/jtd.2019.09.31