EBioMedicine 34 (2018) 12–13

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

How to Eliminate Uncertainty in Clinical Medicine – Clues from Creation of Mathematical Models Followed by Scientific Data Mining

Yoshihiro Asano

Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Medicine and science have evolved through processes of robust information accumulation, appropriate analyses, and proper evaluation. The ability to predict individual risk of disease progression, judge therapeutic effects, and predict accurate prognosis is a core principle of precision medicine [1]. Given that we can now comprehensively search clinical indicators and biomarkers and collect such information, it is time to use these abilities in practice. But how?

Clinical researchers investigate disease phenotypes and actively collected clinical information in order to provide early diagnosis, predict prognosis, and achieve better clinical outcomes. Biomedical researchers carefully observe changes in levels of DNA, RNA, protein, or metabolites and identify novel biomarkers [2]. To translate basic science to clinical intervention, we have conducted large-scale clinical trials to validate hypotheses and practice the bench-to-bedside process [3]. This process has been a popular strategy for recent clinical epidemiological research.

When the target molecular mechanisms are clear and a moderately sized affected population is available, it is critically useful to find relationships between individual survival times and factors of interest. Infectious diseases, immune diseases, and cancer are among the best examples of such conditions. As the characteristics of a disease are manifested, the evidentiary value of biomarkers is further strengthened. Such diseases are characterized based on average values of the biomarkers, and the characteristics of each individual case can be explained by average values of the disease population, i.e., "average medicine".

However, in multifactorial diseases (e.g., cardiovascular diseases, diabetes, and kidney diseases), searching for biomarkers using the "average medicine" approach may not necessarily be effective. Multifactorial diseases have multiple regulators or prognostic parameters that are independent, diverse, and intertwined with a wide variety of genetic and environmental factors. Disease progression can be unpredictable because conventional approaches have failed to consider multiple marker interactions [4]. In other words, it is undesirable for an affected population with a certain disease to be represented by one averaged parameter, because the important information and the diversity of other parameters can be lost. Many past studies focused on specific disease populations, divided them into two or more groups using specific biomarkers, and asked whether the average values of indicators exhibited epidemiologically significant differences among groups. However, this is undesirable when an exponential increase in the number of candidate markers requires a large multiple-testing correction factor, which can conceal significance. For example, hypertension does not necessarily result in myocardial infarction, and myocardial infarction can be caused by syndromes other than hypertension. Therefore, for these diseases, we must pursue "individual medicine" rather than "average medicine". Specifically, we must avoid losing clinical information about multiple parameters of individuals, find new methods for making use of patient data in medical care, and achieve precision medicine.

In addition, when dealing with multiple biomarkers, careful attention must be paid to eliminating arbitrariness in the selection process. To eliminate uncertainty, we need a method for discovering specific rules from large amounts of data using mathematical calculations (without going through researchers' hands) and applying these rules to clinical practice. Such efforts would represent effective solutions in the era of computational resources [5]. Kitakaze et al. tried to find clinically useful rules by eliminating data arbitrariness using a data mining method from more than 10 years earlier [6] [7] [8] [9]. In the study for which that method was developed (Fukuda et al. [10]), the authors targeted heart failure, which is an aggregate of complex pathological conditions. Using comprehensive clinical information, they applied mathematical science to data mining, and thus identified a factor related to disease prognosis. Such data science applications are in demand not only in cardiology but also in other medical fields. In fact, recent trends in science and technology have changed how we use 'big data', which are now analyzed by data mining, artificial intelligence, or machine learning. For example, weather forecasts predict the atmospheric pressure, occurrence of thunder, and movement of rain clouds by observing temperature, previous atmospheric pressure, and humidity on a given lattice point of the earth and solving hydrodynamic equations.

Fukuda et al. [10] also followed a similar approach in their research strategy. They obtained big data from patients of heart failure and solved a mathematical equation to predict cardiovascular events. In general, many factors influence the risk of cardiovascular outcomes. At the same time, clinicians are seeking very clear markers that can be seen at a glance, like BNP, to improve our understanding of pathophysiology of heart failure patients. Together, these two issues are points that research must overcome. In fact, Fukuda et al.'s study provides a potential solution: they narrowed down the number of important factors in the network and proposed two clinical factors that predict the cardiovascular outcomes: the use of inotropic agents and diuretics with normal heart rate by LAMP methods. Given the contributions of this technology to other areas of research, the results obtained from their study are not surprising.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.06.001.
E-mail address: asano@cardiology.med.osaka-u.ac.jp.

https://doi.org/10.1016/j.ebiom.2018.07.001

These new lines of evidence may open a new era for clinical medicine. To achieve this goal, we need to obtain big data in each clinical field, and then develop mathematical models with which to analyze them.

Disclosure

The author declared no conflicts of interest.

References

[1] Precision Medicine Initiative. http://www.nih.gov/precisionmedicine/; 2015.
[2] Abu-Asab MS, Chaouchi M, Alesci S, et al. Biomarkers in the age of omics: time for a systems biology approach. OMICS 2011;15:105–12.
[3] MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. Lancet 2001;357:455–62.
[4] Relator RT, Terada A, Sese J. Identifying statistically significant combinatorial markers for survival analysis. BMC Med Genomics 2018;11:31.
[5] Boudreau RL. The next best thing in cardiovascular research: highlights from the basic cardiovascular sciences scientific sessions. J Am Heart Assoc 2017;6.
[6] Kitakaze M. Trends in characteristics of CVD in Asia and Japan: the importance of epidemiological studies and beyond. J Am Coll Cardiol 2015;66:196–8.
[7] Kitakaze M, Asakura M, Kim J, et al. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet 2007;370:1483–93.
[8] Kitakaze M, Asakura M, Nakano A, Takashima S, Washio T. Data mining as a powerful tool for creating novel drugs in cardiovascular medicine: the importance of a "back-and-forth loop" between clinical data and basic research. Cardiovasc Drugs Ther 2015;29:309–15.
[9] Kim J, Washio T, Yamagishi M, et al. A novel data mining approach to the identification of effective drugs or combinations for targeted endpoints–application to chronic heart failure as a new form of evidence-based medicine. Cardiovasc Drugs Ther 2004;18:483–9.
[10] Fukuda H, Shindo K, Sakamoto M, Ide T, Kinugawa S, Fukushima A, et al. Elucidation of the Strongest Predictors of Cardiovascular Events in Patients with Heart Failure. EBioMedicine 2018;33:185–95.