Computational Subphenotype Discovery and Validation of ICU Stratum Traumatic Brain Injury Patients

Han Kim MSE1,2, Robert D Stevens MD1,2
1 Department of Anesthesiology and Critical Care Medicine, 2 Laboratory of Computational Intensive Care Medicine
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction

Traumatic Brain Injury (TBI) is a significant health hazard worldwide that not only displays high incidences of mortality (approximately 20% of TBI cases lead to death) but also ultimately results in long-lasting deficits and impairments in many patients. Despite the progress in clinical advancements to detect the severity of TBI through CT/MRI imaging and notable identification of biochemical derangements such as perturbations of homeostasis, increased free radical generation, inflammation, apoptosis, and diffuse axonal injury, to date, there has yet to be any promising clinical trials to further advance TBI treatments. The leading consensus is that there is significant pathophysiological heterogeneity within the TBI patients and that each phenotype of TBI exhibits varying responses to treatment. Therefore, heterogeneity within TBI populations is recognized as a major barrier in efforts to find effective treatments and improve outcomes.

Objectives/Aims

The overarching premise for this work is that existing paradigms do not capture the complexity of TBI which encompasses a broad array of clinical and biological features. We hypothesize that combinations of features extracted from clinical electronic health records (EHR) and from physiological time series (PTS) monitoring data can be segregated using unsupervised machine learning, enabling discovery of latent, data-driven subphenotypes that have distinct hallmarks of clinical outcomes. To this end, a study has been conducted to potentially significantly enhance the ability to differentiate TBI patients based on quantifiable pathophysiological information, leading to better treatment selection and increased efficacy of developed treatments catering to a specific phenotype.

Methods

The eICU registry is a multi-center, comprehensive database of ICU patients with TBI. The cohort included 7,925 patients and 147 features. We identified four TBI clusters (a, b, c, d) each with a distinct outcome probability distribution and each associated with a unique, clinically relevant pattern of PTS and laboratory features. Subphenotype (a) captures TBI patients whose physiological features are associated with the highest likelihood of survival and favorable neurological outcome, while subphenotype (c) captured patients whose physiological features are associated with the highest likelihood of death and unfavorable neurological outcome, while subphenotypes (b) and (d) had intermediate outcome probabilities. Both the physiologic and outcome differences between clusters were reproducible in the MIMIC III cohort when eICU clusters were assigned using a multi-class classification model and mortality and neurological outcome differences proportion per subphenotype for the eICU cohort and assigned MIMIC III cohort can be seen in Figure 3.

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Results

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Conclusions & Future Work

Using unsupervised machine learning applied to EHR and PTS derived features of TBI patients admitted to the ICU, we identified four distinct and clinically meaningful TBI clusters. Patients assigned to specific clusters had distinct outcome probabilities and unique data-driven physiologic signatures which suggest that they are plausible candidate subphenotypes. Results indicate a novel approach to categorizing ICU stratum TBI patients based on objective, numerical patient physiological and metabolic data. Moreover, the four eICU TBI subphenotypes were successfully validated in the MIMIC III TBI cohort. Ongoing research will explore other characteristics of these TBI subphenotypes and in particular their differential response to specific treatments and interventions as well as extend the analyses to MIMIC IV, Amsterdam Medical Center (AUMC), and Johns Hopkins TBI cohorts.

References