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Editorial

Next-Generation Approaches to Predicting the Need for Heart Failure Hospitalization

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See article by Singh et al., pages 471–479 of this issue.

Heart failure (HF) is a leading cause for hospitalization in Canada and globally. Readmission rates following HF hospitalization remain upward of 20% within 30 days and 50% within 6 months.[1,2] Although predicting the need for HF hospitalization (including readmission) is recognized as a health care priority, developing accurate predictive tools to identify at-risk patients has remained an elusive challenge. Such analytics, if sufficiently reliable, could identify patients at risk and allow the deployment of preventive interventions to avert the need for hospitalization.

Approaches to Predicting the Need for HF Hospitalization

Hospitalization for HF is typically preceded by a gradual rise in ventricular filling pressures.[2] As these hemodynamic changes often precede the onset of overt clinical manifestations by days to weeks,[3] detecting rising filling pressures has been the focus of many predictive approaches to date. Such approaches include implantable hemodynamic monitoring devices[4-7] and blood-based biomarkers of congestion (NT-proBNP, troponin, and soluble ST2).[8-11] Clinical variables may be predictive. For example, hospital length of stay may be predictive, given that shorter lengths of stay are associated with increased rates of readmission for HF (perhaps reflecting inadequate decongestion prior to discharge).[12] Electrocardiographic (ECG) changes suggesting myocardial ischemia are also associated with an increase in short-term adverse events in patients with HF.[13] Although offering promise, many of these approaches have potential challenges, and the search for a clinically reliable predictive approach remains ongoing.

Challenges and Potential Solutions Toward Improved Prediction

A potential limitation of such approaches may be that increases in ventricular filling pressures, although preceding the onset of clinical symptoms, are nonetheless consequences and not causes of underlying progression and destabilization of HF. It may be that in patients in whom ventricular pressures have already started to rise, preventive interventions may act too late. What is missing from current approaches is a mechanistic insight into why some patients remain stable over time, whereas others decompensate. Moving further upstream in the trajectory of destabilization to identify causes (and not consequences) of disease destabilization may offer greater potential to identify predictors— and perhaps mediators—of HF stability in an individual patient. With parallel revolutions in high-dimensional molecular and clinical diagnostics; detailed remote patient monitoring; and advanced predictive analytics, the promise of more individualized, cause-oriented approaches to risk prediction that identify more "upstream" markers and mediators of HF stability may be closer at hand.

High-dimensional biomarker approaches using peripheral blood samples may support such efforts and can involve profiling the complement of genes (genomics), messenger RNA (transcriptomics), proteins (proteomics), and metabolites (metabolomics) in concert.[14] The dimensionality of such data can grow rapidly. For example, beyond quantifying a particular protein in circulation, different states of protein activity and localization can be determined by quantifying

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numerous post-translational modifications, allowing a deeper understanding of biology and potentially more personalized prediction of risk.[15,16] This high dimensionality may require more advanced predictive statistical or other analytical approaches to handle its complexity.

An Initial Step Toward "Next-Generation" Clinical-Molecular Risk Prediction

In this issue of the *Canadian Journal of Cardiology*, Singh and colleagues[17] attempt to improve on current approaches to predicting the need for HF hospitalization by integrating high-dimensional clinical and molecular data using advanced analytic approaches to build an accurate predictive algorithm. They performed transcriptomic and proteomic profiling in peripheral blood in 58 patients with HF and followed for the need for hospitalization by 3 months. They also examined continuous ECG data from 48-hour Holter monitors as well as routine clinical data and biomarkers. In comparison to patients with clinical stability, those patients requiring hospitalization had lower ambulatory blood pressures, higher brain natriuretic peptide, higher creatinine, and a longer duration of HF diagnosis. In this pilot study, a predictive model based on clinical variables had an area under the receiver operating characteristic curve of 0.76. When markers from the proteogenomic and sensory (Holter) data were introduced, the predictive accuracy of the model increased to 0.88. Although the small sample size of this pilot study requires expansion and eventual replication in much larger and external patient cohorts, these promising results offer optimism for next-generation predictive analytics to be developed in patients with HF.

Of note, patients who required hospitalization had transcriptional upregulation of several inflammatory pathways including the interleukin-1 signalling pathway. Although inflammation plays important roles in HF pathogenesis, its effective therapeutic targeting in HF has been challenging.[18] It may be that between-patient variability in the degree of chronic inflammatory activation contributed to previous challenges in translation. This observation by Singh and colleagues highlights both the potential for individualized, "precision medicine" prognostication—and eventually treatment—in patients with HF as well as, more broadly, the ability of predictive approaches to provide insight into underlying disease biology. Such potentially causal pathways may lie upstream of increases in ventricular filling pressure and may hence represent important markers of progression and destabilization of underlying disease, identifying risk, and potential targets for therapy.

Next Steps Forward Toward Individualized, Cause-Oriented Risk Prediction

Advanced bioanalytic approaches will be required to support the emergence of increasingly large and complex integrated clinical and molecular data. Employing modelling approaches that are more nimble than traditional regression models could enable the creation of more accurate predictive models. For example, in the study by Singh and colleagues, the authors employed advanced statistical tools to fine-tune their models and optimize variable selection. This included applying elastic net and least absolute shrinkage and selection operator (LASSO) penalties, which incorporate a zeroing/regularization step (involving parameter shrinkage and variable selection). Such methods drive low and correlated model β-coefficients to zero and hence create more parsimonious prediction models that better account for high degrees of correlation inherent in these types of data. Such approaches to statistical variable selection can complement systems biology-based approaches—such as network analysis, pathway enrichment, and other tools—to build accurate prediction models as well as to identify potential key disease mediators.

The application of machine learning (ML) methods may offer further opportunities to build accurate, integrative, high-dimensional clinical-molecular risk prediction tools. ML approaches seem well suited to handle increasingly large and complex patient-level datasets generated from molecular and clinical data, as they offer flexible tuning parameters, often handle correlation better than penalized regression models, and expand the scope of predictors beyond what is input into the model by creating "hidden layers" of data interactions.[19] Deep learning extends this by using stacked layers of increasingly higher order representations of objects. These layers could represent clinical measurements such as continuous vital signs, Holter monitor-based ECG data, and high-dimensional biomarker data for risk stratification and prediction.

There is growing evidence that applying ML methods to high-dimensional, patient-level data may improve upon traditional predictive analytics. For example, applying an ML approach, called neural networks, to cardiopulmonary exercise test data from patients with HF allowed a complete breath-by-breath analysis, which was of greater discriminative value than the information provided by summary results alone.[20] ML may one day provide the potential for combining data from multiple sources, including remote "early warning" systems such as telemonitoring,[21] along with various clinical risk-prediction tools such as the EHMRG30-ST risk score,[22,23] with high-dimensional biomarker data, to predict adverse events, including the need for hospitalization, in patients with HF.[24]

Conclusions

Predicting the need for HF hospitalization remains a high public health priority. Current approaches have important limitations, including a focus on consequences rather than causes of disease progression and destabilization, low-dimensional clinical and biomarker data, and reliance on limited statistical modelling approaches. Next-generation risk-prediction models that incorporate high-dimensional clinical and molecular data—perhaps with the support of ML approaches—may one day offer opportunities for personalized, cause-oriented, systems biology-based risk prediction in patients with HF.

Disclosures

The authors have no conflicts of interest to disclose.

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