“Integration of Biomarkers and Artificial Intelligence in Cardiac Disease”

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Disclosures

• Co-founder and President of Brainstorm Medical
The right time - healthcare AI revolution
Byte marks

The digital universe
Zettabytes

Companies mentioning
AI in earnings calls

Sources: IDC; Bloomberg

Economist.com
Definitions

• Raise your hand if you’ve been caught in the confusion of differentiating artificial intelligence (AI) vs machine learning (ML) vs deep learning (DL)...
What is artificial intelligence?

• loosely interpreted to mean incorporating human intelligence to machines.

• Whenever a machine completes tasks based on a set of stipulated rules that solve problems (algorithms), such an “intelligent” behavior is what is called artificial intelligence.

• For example, such machines can move and manipulate objects, recognize whether someone has raised the hands, or solve other problems.
What is machine learning?

• Machine learning is a method of data analysis that learns from experience, enabling computers to find hidden insights without being explicitly programmed to do so.

• Machine learning analyzes data and learns from it to make decisions and predictions, and includes supervised (manual entry of data and solutions) and unsupervised learning.
AI should incorporate Biomarkers since they bring pathophysiological data that cannot otherwise be ascertained clinically.
My neural networks (machine learning) knows how to combine features of history, physical exam and biomarkers so that appropriate weight can be given to each variable.
Lets say your dyspneic patient has a BNP of 1000 pg/ml- must be heart failure- right?

• Hx of previous heart failure and a fever pneumonia
• Large pulmonary embolism and right heart failure
• Sepsis and AKI
BNP is 90 in a dyspnic patient- it can’t be heart failure can it?

• obesity

• Acute hypertensive pulmonary edema
Not more than normal statistics?

To focus on hidden data structure algorithmically and make predictions or classifications vs To conduct inference about sample or population parameters
Using approximately 250 variables representing demographics, socioeconomic status, medical history, clinical symptoms, vital signs, laboratory values, and discharge interventions, machine learning algorithms were unable to predict 30-day readmission better than logistic regression.

The findings are potentially limited by a lack of many strong predictors of heart failure readmission.
Analysis of Machine Learning Techniques for Heart Failure Readmissions

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Background—The current ability to predict readmissions in patients with heart failure is modest at best. It is unclear whether machine learning techniques that address higher dimensional, nonlinear relationships among variables would enhance prediction. We sought to compare the effectiveness of several machine learning algorithms for predicting readmissions.

Methods and Results—Using data from the Telemonitoring to Improve Heart Failure Outcomes trial, we compared the effectiveness of random forests, boosting, random forests combined hierarchically with support vector machines or logistic regression (LR), and Poisson regression against traditional LR to predict 30- and 180-day all-cause readmissions and readmissions because of heart failure. We randomly selected 50% of patients for a derivation set, and a validation set comprised the remaining patients, validated using 100 bootstrapped iterations. We compared C statistics for discrimination and distributions of observed outcomes in risk deciles for predictive range. In 30-day all-cause readmission prediction, the best performing machine learning model, random forests, provided a 17.8% improvement over LR (mean C statistics, 0.628 and 0.533, respectively). For readmissions because of heart failure, boosting improved the C statistic by 24.9% over LR (mean C statistic 0.678 and 0.543, respectively). For 30-day all-cause readmission, the observed readmission rates in the lowest and highest deciles of predicted risk with random forests (7.8% and 26.2%, respectively) showed a much wider separation than LR (14.2% and 16.4%, respectively).

Conclusions—Machine learning methods improved the prediction of readmission after hospitalization for heart failure compared with LR and provided the greatest predictive range in observed readmission rates. ([Circ Cardiovasc Qual Outcomes](https://doi.org/10.1161/CIRCOUTCOMES.116.003303))
Ngal in Predicting Primary Endpoint of AKINESIS in Patients with eGFR < 60 on admission
(an increase in creatinine of 0.5 mg/dl or ≥50% or renal-replacement therapy)

Original AKINESIS Study

AI Model

Top 3 variables:
Delta uNGAL/creatinine, Peak uNGAL/creatinine and Gal3
1. Type 1 vs. 2 MI
2. Women MI
3. Syncope
4. Pulmonary embolism
5. Shortness of breath
6. Atrial Fibrillation
7. Cardio-oncology
8. Cardiac Amyloidosis
9. Acute heart failure
10. Chronic heart failure
Chest pain
Heart failure
Arrhythmias/devices
Potential applications in chest pain

- Myocardial infarction and injury
  - Troponin positive patients
    - Type 1 vs type 2 MI vs Myocardial injury
  - Timing of blood draws
  - Predicting readmissions after PCI
    - MACE including type 4 MI
    - Bleeding
  - Differentiating Type 2 MI from Myocardial injury
- What to do with type 2 MI
  - Find cause
  - Treat and possibly send home
- What to do with Myocardial Injury
Type 1 vs. 2 MI

- Up to 40% of type 2’s sent to cath lab
- $677M = annual cost of complications of cardiac cath
- Type 2’s = 10% of all readmitted patients, or $57M in penalties

Cath complications:
1. Bleeding
2. Stroke
3. Kidney failure
4. Recurrent MI
5. Emergency coronary bypass surgery
6. Pericardial tamponade
7. Heart failure
8. Death
Excellent clinical performance!

94.5% separation power!

<table>
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<th>Scorer</th>
<th>Final ensemble external validation scores +/- standard deviation</th>
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<td>GINI</td>
<td>0.8916 +/- 0.068757</td>
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<tr>
<td>MCC</td>
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<td>F05</td>
<td>0.95039 +/- 0.021658</td>
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<td>F1</td>
<td>0.9533 +/- 0.023513</td>
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<td>F2</td>
<td>0.9777 +/- 0.011838</td>
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<td>ACCURACY</td>
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<tr>
<td>AUCPR</td>
<td>0.98104 +/- 0.012288</td>
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<tr>
<td>AUC</td>
<td>0.9458 +/- 0.034378</td>
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30 AI features affect type 1/2 outcome

AI features ranked by impact (diagnostic prediction)

No need for any extra diagnostic tests

ALL VARIABLES CAN BE OBTAINED BY HISTORY AND EMR BY THE TIME FIRST TROPOININ RESULT IS READY ( OR SECOND)
Here is how docs can learn- (example) –patient admitted for heaviness in chest after forgetting to take diuretic

Print out after second troponin

• Probability:
  • Type One 12%
  • Type Two 88%

• Key features for type two:
  Elevated BNP
  History of heart failure
  Dyspnea on minimal exertion
  Dynamic troponin change < 20%
Three applications for women with chest pain

1. Chest pain at home. Opens site on AHA, etc fills out symptoms- told to go to ED or not

2. Chest pain in the ED Type 1 vs type 2 MI vs Myocardial Injury

Special circumstances for women
Coronary Dissection
Takatsubo syndrome

6000 Takatsubo patients – largest in world
4000 SCAD – largest in world
3000 patients STEMI versus Takatsubo- only study in the world
Who needs CT scan?

- Pulmonary Embolism is the most preventable cause of death in hospitalized patients in the United States. (anticoagulation, thrombolytic therapy, surgery)

- Tools to predict who needs CT scan are required.
Who should be sent to CT?
Incidence of PE was 12.1% in the "unlikely" group vs. 37.1% in the "likely" group.

Chest pain

Shortness of breath/Heart failure

Arrhythmias/devices
Too many causes

Pneumonia

Yes

Acute

Fever?

No

Chest pain?

No

Wheeze?

No

Losspiratory muscle weakness

Asthma
Anaphylaxis
Aspiration
COPD exacerbation

No

Yes

Chronic obstructive pulmonary disease

Asthma
Chronic obstructive pulmonary disease

No

Yes

Interstitial lung disease
Malignancy
Chronic pneumonia
Pleural effusion

No

Yes

Pulmonary hypertension
Cardiomyopathy
Deconditioning
Anemia
Neuromuscular

Myocardial ischemia
Pericardial

Spontaneous pneumothorax
Pulmonary
Biomarker panel and AI for SOB: diagnosis, medications, admit versus discharge,

- Acute MI
- AHF
- PE
- Aortic dissection
- Acute bacterial pneumonia

Potentially:
- Myocarditis
- Amyloid
Applications for heart failure/shortness of breath including biomarkers: **Acute heart failure**

- In the ED
- In the hospital
- At discharge and beyond
- Cardiogenic shock
- Starting Sacubitril/Valsarten and other drugs
- Cardio-renal issues.
Applications for heart failure/shortness of breath: **Acute heart failure**

- 1. Patients with high troponin-type one or two?; do they need admission?
- 2. Can patients in the ED go home after treatment?
- 4. Who will develop cardiogenic shock?
  - Suggestion of devices:
    - ECMO, Impella, balloon pump
- 5. Who can start Sacubitril/Valsartan safely during Acute HF?
Acute Heart Failure in Hospital

• Ruling out underlying causes:
  o Amyloid
  o Myocarditis
  o Suspicion of prior a-fib

• Who can start Sacubitril/Valsartan safely during Acute HF?

• Predicting 30 day readmission

• Predicting AKI during hospitalization.

• Can a patient with AKI leave before the 3-4 days required from creatinine to drop

• Titrating iv to po diuretics: when? How?
Who will develop cardiogenic shock?

• Prediction so that devices can be offered:
  o Angiogram
  o IABP
  o ECMO
  o Impella
  o Tandem Heart
  o LVAD
Combined Measurement of Soluble ST2 and Amino-Terminal Pro-B-Type Natriuretic Peptide Provides Early Assessment of Severity in Cardiogenic Shock Complicating Acute Coronary Syndrome

Heli Tolppanen, MD\textsuperscript{1,3}; Mercedes Rivas-Lasarte, MD\textsuperscript{1,4}; Johan Lassus, MD, PhD\textsuperscript{3}; Malha Sadoune, MSc\textsuperscript{1}; Etienne Gayat, MD, PhD\textsuperscript{1,5}; Kari Pulkki, PhD\textsuperscript{6}; Mattia Arrigo, MD\textsuperscript{1,5,7,8}; Evguenia Krastinova, MD, PhD\textsuperscript{1,9}; Alessandro Sionis, MD\textsuperscript{4}; John Parissis, MD, PhD\textsuperscript{10}; Jindrich Spinar, MD, PhD\textsuperscript{11,12}; James Januzzi, MD, PhD\textsuperscript{13}; Veli-Pekka Harjola, MD, PhD\textsuperscript{14}; Alexandre Mebazaa, MD, PhD\textsuperscript{1,5,15}; for the CardShock Study Investigators and the GREAT Network
Figure 1. Kinetics of soluble ST2 (sST2) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). Levels of sST2 (A) and NT-proBNP (B) in 30-d survivors (white boxes) and nonsurvivors (gray boxes) in time course. Central line represents median, box represents interquartile range, and whiskers represent fifth and 95th percentile.
A

sST2 and NT-proBNP at 12 hours

Survival

Days

Both below cut-off, n=30, 3 deaths
Either above cut-off, n=55, 17 deaths
Both above cut-off, n=34, 27 deaths

p = 0.038
p < 0.001

B

30-day mortality

Time from detection of shock

0h 12h 24h 36h 48h 72h 96h 5-10 days

both below cut-off either above cut-off both above cut-off

p<0.10 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01 p<0.01
HFpEF- Mechanisms

- Increased Wall Stress
- Epicardial CAD
- Oxidative Stress
- Neurohormonal Activation
- Altered Calcium Handling
- Inflammatory Cytokines
HFpEF- co morbidities

- Atrial fib
- Diabetes
- Copd/osa
- Hyptertension
- obesity
- Renal Failure
HFpEF Biomarkers

- N.peptides
- sST2
- Genomic
- creatinine
- Hs Troponin
AI and Cardio-Oncology

• Many potential opportunities in this new medical subspecialty

• Initial strategies
  • Baseline risk production pre cancer treatment
  • Follow up surveillance in Hodgkin Lymphoma survivors
  • Checkpoint inhibitors and CV complications including myocarditis
  • AF risk and bleeding risk prediction in CLL patients receiving Bruton Kinase Inhibitors

Dr. Alexander Lyon (London) and Professor Simon Matskepishvili (Moscow)
Chest pain
Heart failure
Arrhythmias/devices
• Atrial fibrillation
  • Finding patients for earlier ablation
  • Sending acute a-fib home from the ED
  • Acute a-fib with high troponin - what to do
  • Who deserves a sleep apnea work up

• Syncope - 6000 patients
  • High vs low risk
  • Admission vs no admission
  • Who should get a loop recorder
• **TAVI for aortic stenosis**
  • Who is best to get TAVI
  • Who is best for AVR
  • Earlier TAVI
  • TAVI in younger patients

• **Mitral regurgitation**
  • Surgery vs medical care vs. device
  • Optimal timing for procedure
AI = Big Eater

• AI/machine learning takes an enormous amount of data to train a deep learning model because of the vast number of parameters that must be estimated.
Garbage In Garbage Out

- Even a perfect model is limited by the quality and magnitude of signal in the dataset from which it is trained.
- Algorithm does not get better than the data.
Who is responsible?

- Although AI-based driverless cars are generally safer than human drivers, a pedestrian death due to a driverless car error caused great alarm.
- Who is responsible for the failure of healthcare management made by AI?
• Identification of novel genotypes or phenotypes of heterogeneous syndromes such as HF.

• Exploration of novel factors in score systems or add hidden risk factors to existing models.

• AI will drive improved patient care because physicians will be able to interpret big data in greater depth than ever before.

• We need to use AI sufficiently to generate hypotheses, perform big data analytics, and optimize AI applications in clinical practice to bring on the era of precision CV medicine.