Quantification of Myocardial Inflammation in Salmon Hearts Using a Machine Learning Model

TriNation, Belfast | April 2026

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Myocardial inflammation model

Background

- Heart and skeletal muscle inflammation (HSMI) and cardiomyopathy syndrome (CMS) are among the most important disease problems in the Norwegian salmon industry
  - Causing significant welfare problems and economic losses.
  - Myocardial inflammation is a prominent feature and is regarded as the primary cause of the morbidity and mortality frequently observed.
- Semiquantitative scoring of the myocarditis severity is commonly done as part of experimental research focusing on CMS and HSMI.
- Several published scoring protocols with well-defined grading criteria exist for both diseases.

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HSMI Myocarditis Scoring Protocol

Score	Description
0	No significant lesions, normal
1	Up to 2 small foci of inflammation, up to 2 necrotic fibers, or 2 small foci of reactive changes in either compactum or spongiosa
2	Focal to multifocal inflammatory foci/fiber necrosis (3-10 foci or up to 15% affected) in the compact layer and/or spongious part (2-10 foci). Inflammation typically extends along small vessels and perivascular infiltration
3	Multifocal or diffuse inflammation/fiber necrosis in the compact layer, often concentrated along small blood vessels; multifocal to diffuse changes in the spongious layer; >10 foci and up to 80% affected
4	Widespread to diffuse infiltration of inflammatory/necrotic cells in compact and spongy layers; >80% of ventricle affected; atrium also affected
Comment	*Changes in heart ventricle (spongy and compact layers) are scored as above*

Non-Specific Myocarditis Scoring Protocol

Score	Description
0	Normal (one focus with less than 10 cells is accepted)
1	Minimal (>10 cells and <5% of tissue affected)
2	Mild (5%–20% of tissue affected)
3	Moderate (20%–50% of tissue affected)
4	Severe (>50% of tissue affected)
Comment	*Inflammation dominated by lymphocytes (independent of cause) is scored in heart as above. Ventricle and atrium are scored separately.*

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Myocardial inflammation model

Training of model for using annotated selection of tiles (jpegs)

Image dataset:

- A total of approximately 300 000 annotated jpeg images were obtained from whole slide images (WSI) of:
  - inflamed salmon myocardium — 50%
  - non-inflamed salmon myocardium
  - other salmon tissues — 50%
- Splitting of the dataset before training:
  - 70% of the images for training
  - 20% for validation during the training process
  - 10% for validation/testing after completed training (“Hold-out”)

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Myocardial inflammation model

Training of model for using annotated selection of tiles (jpegs)

Environment:

- Model development and training were conducted using **Jupyter Notebooks** hosted on the **Microsoft Azure** cloud platform.

Framework and Tools:

- Use of open-source tools only
- Deep learning model implemented with **Keras** (TensorFlow backend).

Computing Resources:

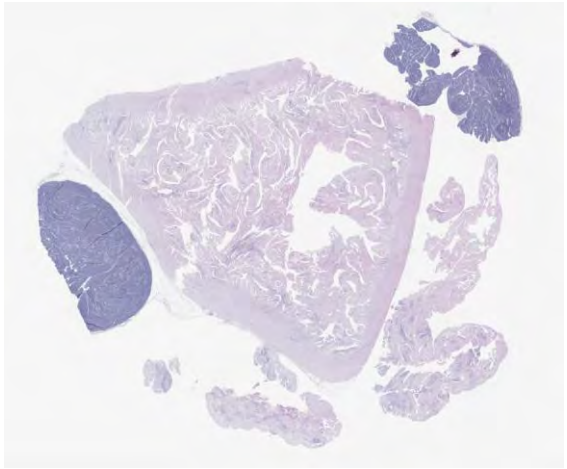
- Scalable compute resources to optimize performance.

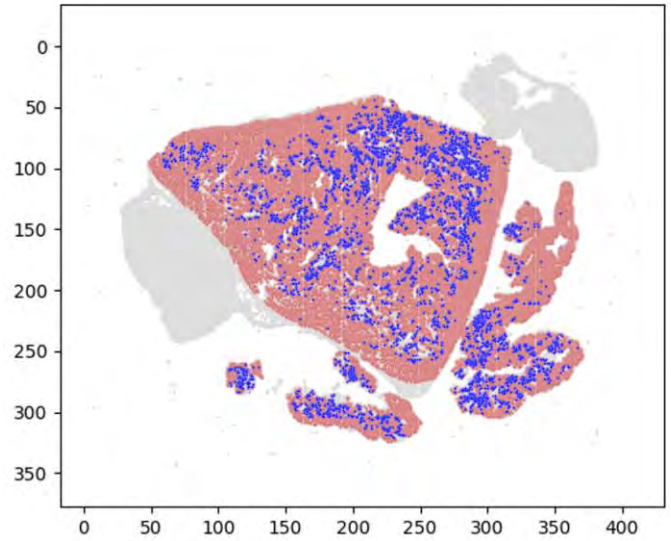
Myocardial inflammation model

Estimating extent of myocardial inflammation in whole slide images (WSI)

- Each WSI is divided into multiple sectors
- For each sector in the slide prediction (classification) is done using two different ML models:
  - Myocarditis detection model (sensitivity and specificity 0.97)
  - Myocardium detection model (performance details not presented)

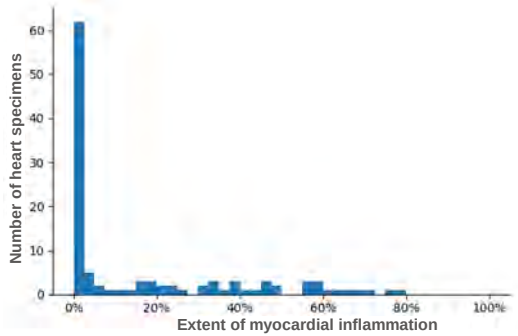
$$\text{Extent of myocardial inflammation} = \frac{\text{Area of inflamed myocardium}}{\text{Area of myocardium}}$$





Myocardial inflammation model

Sample ID	Label	Positive sectors
1	F1	0,25 %
2	F2	0,24 %
3	F3	0,19 %
4	F4	0,74 %
5	F5	0,27 %
6	F6	0,62 %
7	F7	0,17 %
8	F8	0,32 %
9	F9	0,08 %
10	F10	0,05 %
11	F11	0,54 %
12	F12	0,26 %
13	F13	0,12 %
60	F60	16,43 %
61	F61	21,38 %
62	F62	15,24 %
63	F63	79,51 %
64	F64	17,37 %
65	F65	75,17 %
66	F66	4,45 %
67	F67	31,63 %
68	F68	48,30 %
69	F69	0,09 %
70	F70	7,68 %
71	F71	58,24 %



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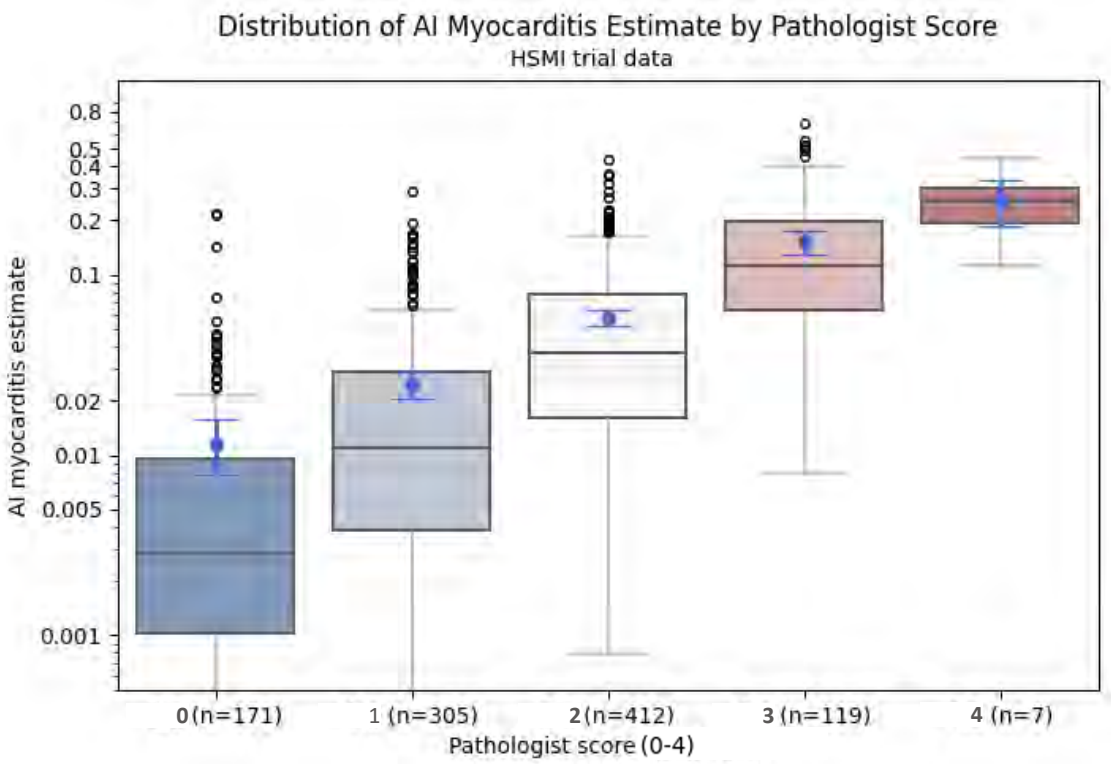
Myocardial inflammation model

Validation of model for quantification of myocardial inflammation (HSMI)



Correlation between AI myocarditis estimate and pathologist myocarditis score (ventricle) : Spearman correlation: ***0.64***, p << 0.0001

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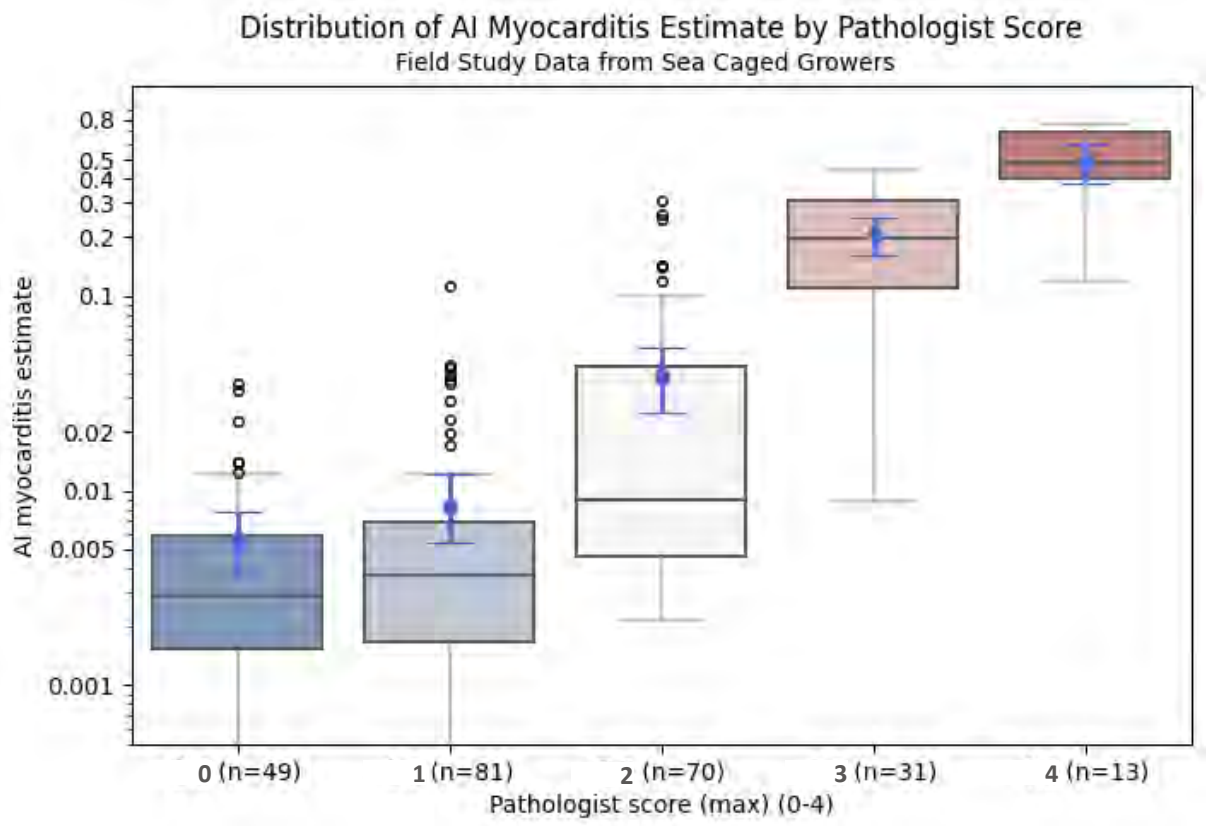
Myocardial inflammation model

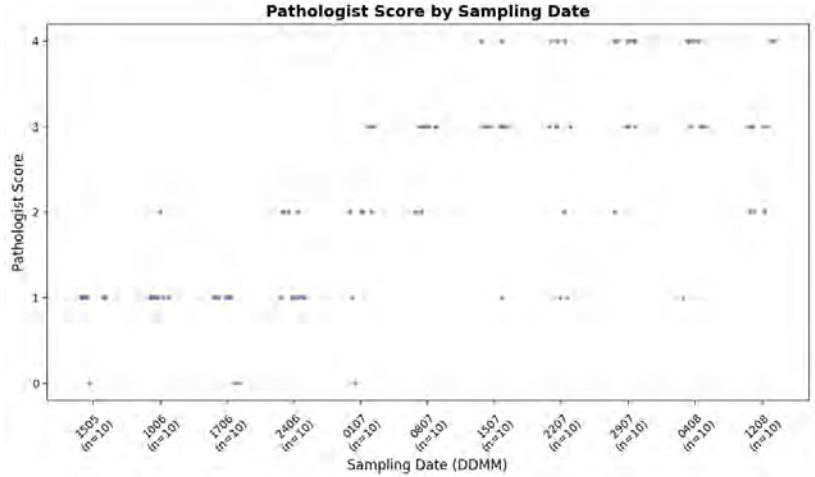
- Validation of model for quantification of myocardial inflammation (any)

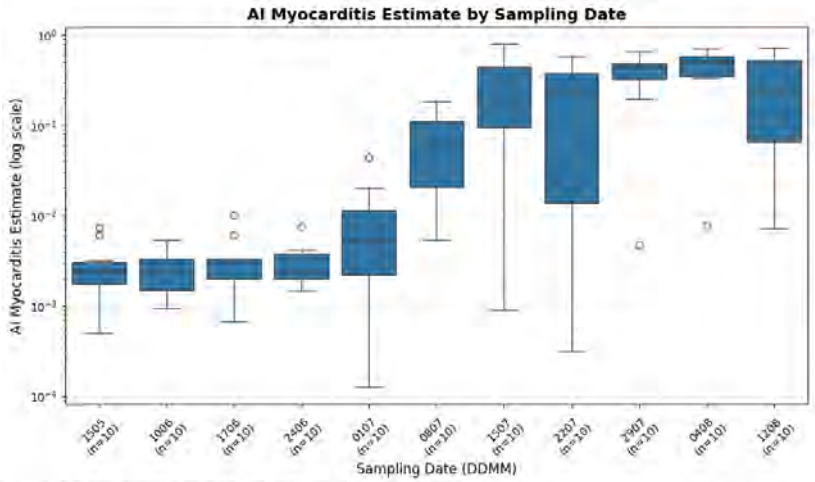


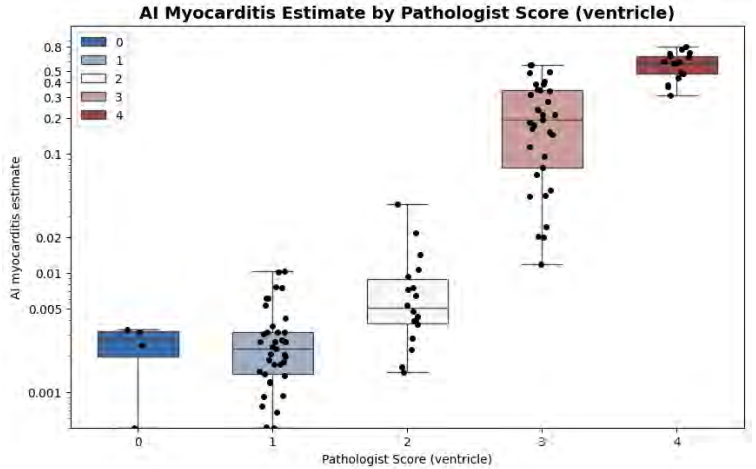
Correlation between AI myocarditis estimate and myocarditis score (max): Spearman correlation: ***0.68***, P-value: << 0.0001

Myocardial inflammation model

Material from client performing a HSMI challenge trial







Correlation between AI-myocarditis estimate and pathologist myocarditis score (ventricle): Spearman's rho: **0,89**, p << 0,0001.

Myocardial inflammation model

Conclusions

- Detects inflammation caused by **HSMI** and **CMS**
- Image (sector/tile) level:
  - **Excellent performance** of ML myocarditis detection with sensitivity and specificity values in the range of 0.95 to 0.99
- Slide (WSI) level:
  - **Strong positive correlation** between the **ML estimated** myocarditis severity and **pathologist score** suggests the ML method **reliably reflects** the pathologist's assessments in terms of relative severity or scoring.

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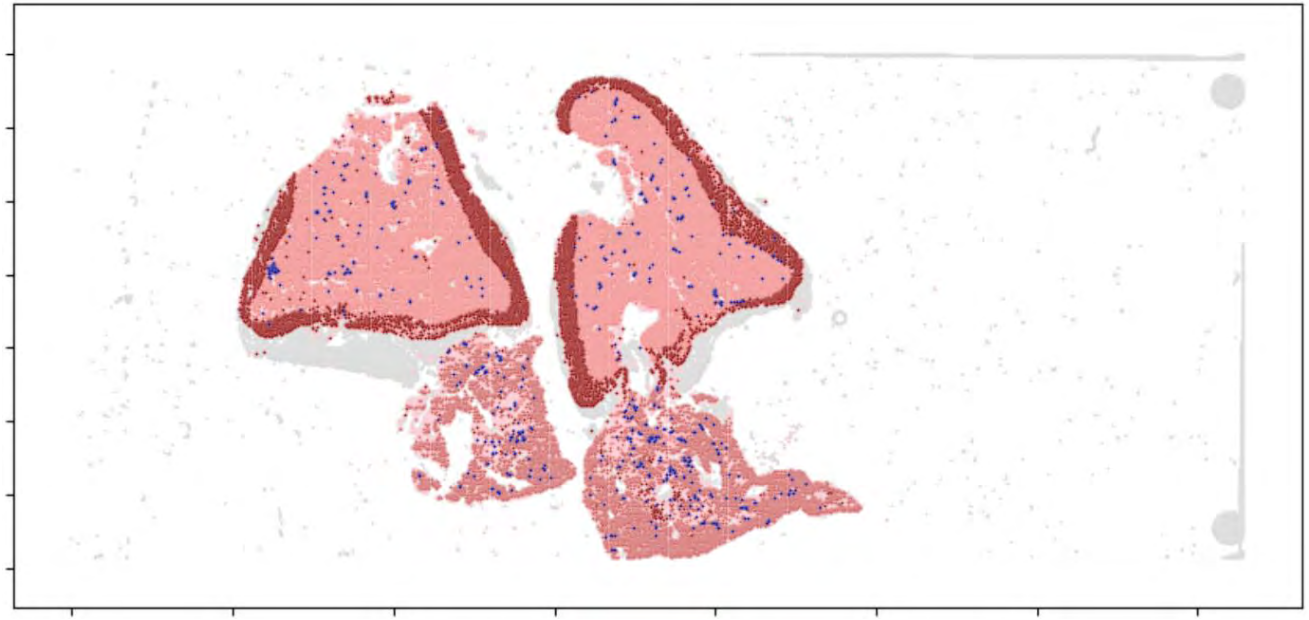
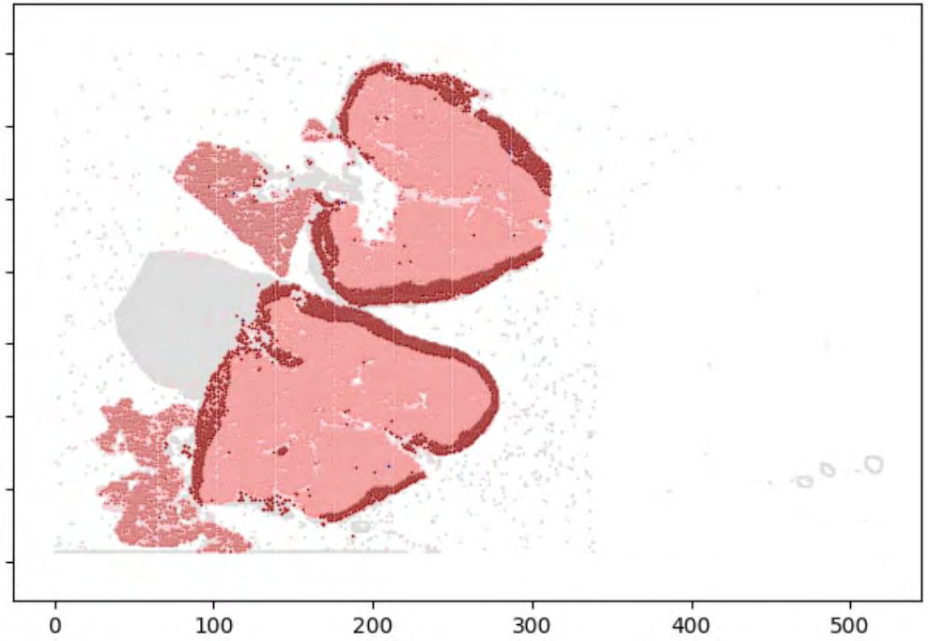
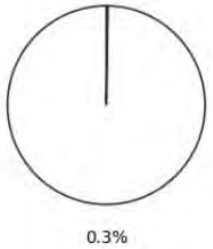
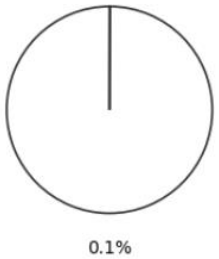
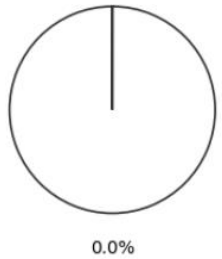
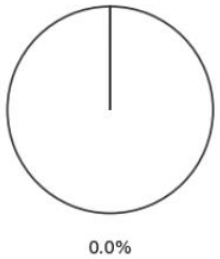
Myocardial inflammation model

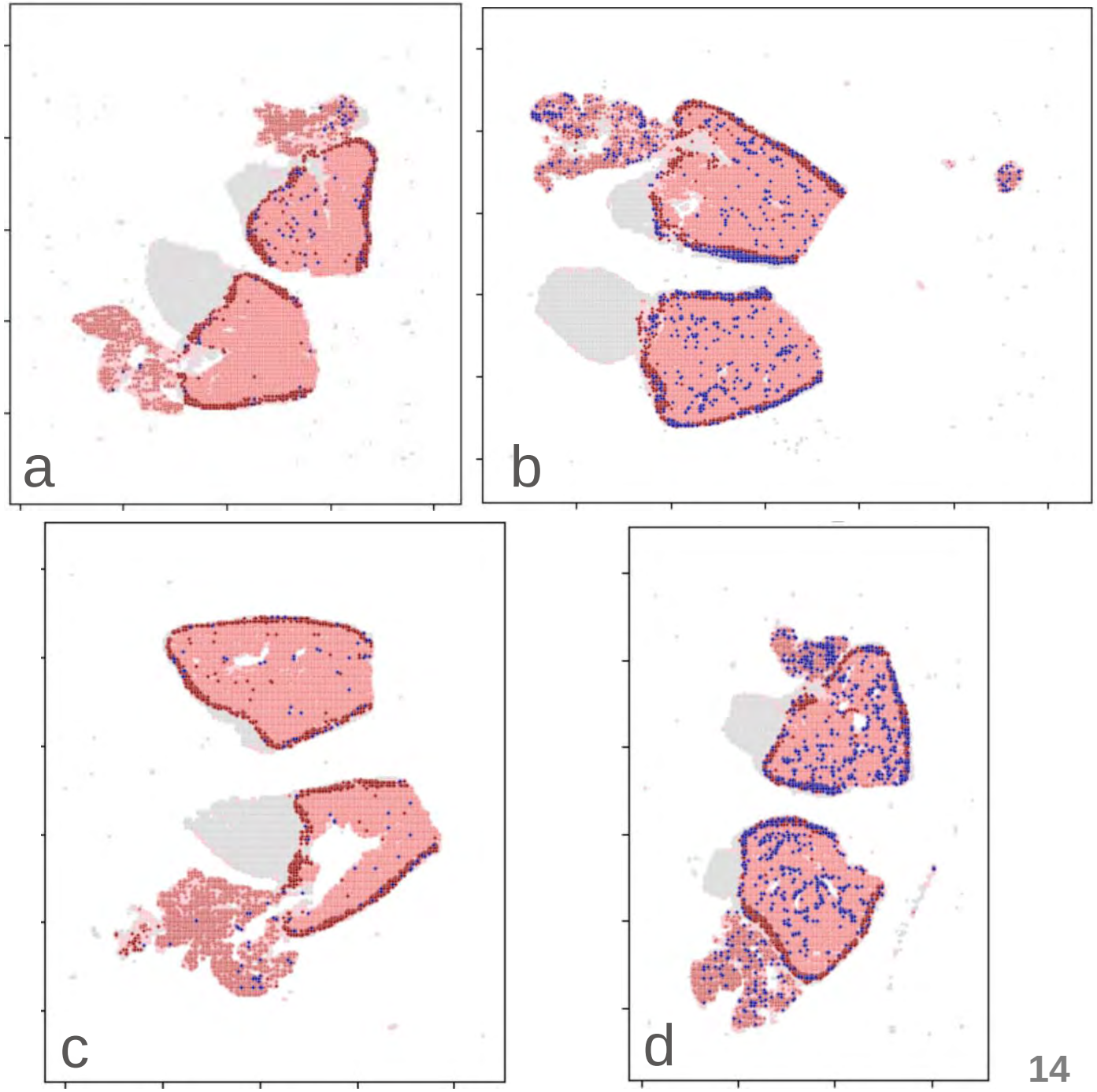
Why use ML based quantification of myocardial inflammation?

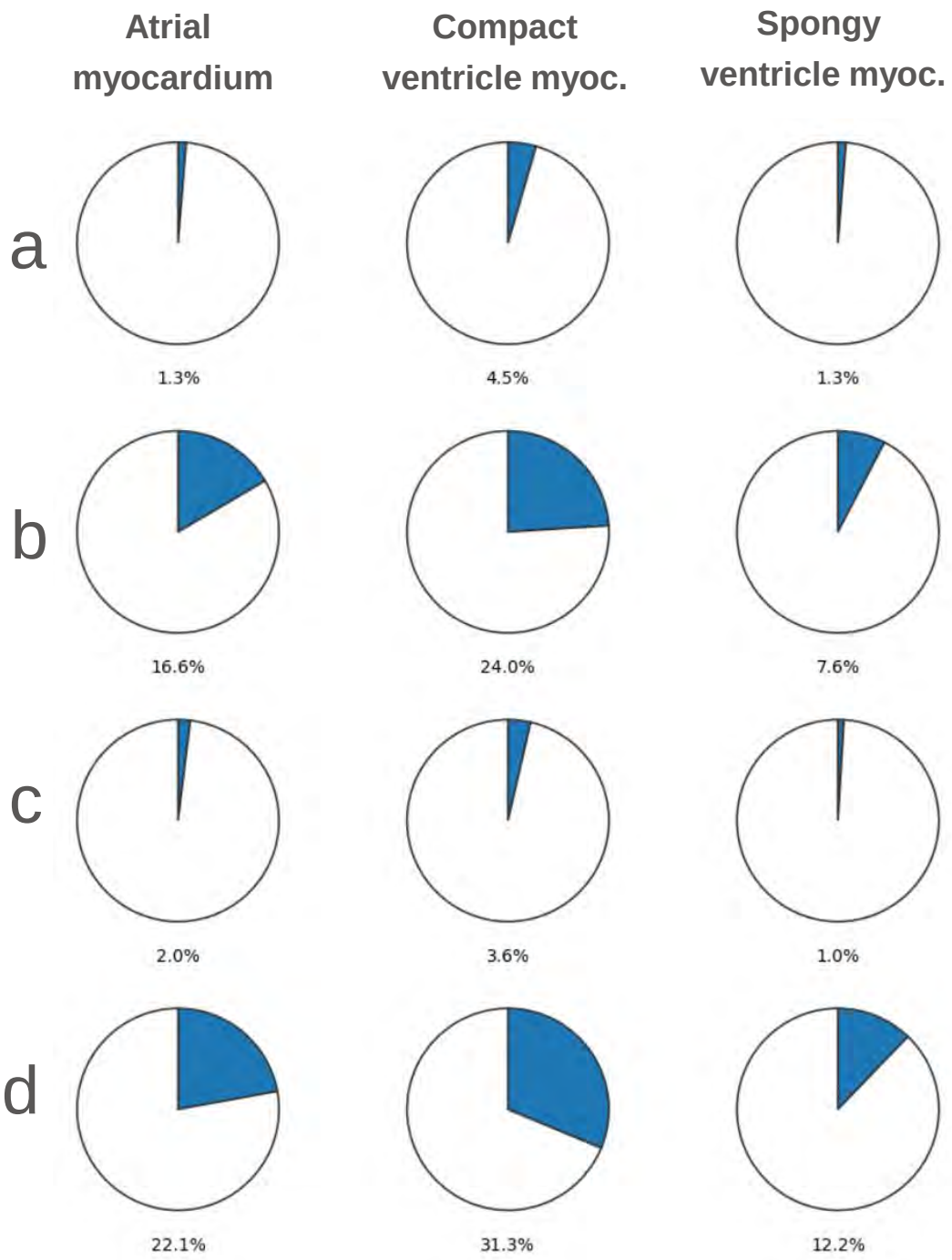
- Extent of inflammation as continous numerical variables
  - Advantages of continuous variables over ordinal scores:
    - More information granularity.
    - Wider range of statistical methods
    - Better modeling capabilities
- Highly reproducible analysis
  - No interobserver variability
  - No intraobserver variability / diagnostic drift
- Faster turnaround times for larger projects
  - Working 24/7
  - Scalable compute resources





Atrial myocardium	Compact ventricle myoc.	Spongy ventricle myoc.
		
2.9%	0.3%	1.5%
Pathologist score: 2		Pathologist score: 2
		
0.1%	0.0%	0.0%
Pathologist score: 1		Pathologist score: 0


a
b
c
d


Atrial myocardium
Compact ventricle myoc.
Spongy ventricle myoc.
a
1.3%
4.5%
1.3%
b
16.6%
24.0%
7.6%
c
2.0%
3.6%
1.0%
d
22.1%
31.3%
12.2%

Thank you!

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