Can't Beat the Clock: Evaluation of Ten Epigenetic Clocks for the Prediction of Mortality and Length of Stay in Critically Ill ICU Patients

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Objective

To assess the utility of epigenetic clocks, based on DNA methylation marks, in predicting ICU outcomes.

Introduction

Epigenetic clocks use DNA methylation markers to measure biological or "epigenetic" age. Some are designed to predict chronological age while others are designed to predict clinically significant outcomes, such as health status or long-term mortality. Studies have demonstrated associations between epigenetic age and ICU survivorship, disease-specific outcomes (Binnie et al., 2020; Sharma-Oates et al., 2024), and unplanned readmissions (Ho et al., 2023). We evaluated ten epigenetic clocks and their predictive value for ICU mortality and ICU free days to 28 (length of stay).

Methods

- We analyzed data from **144 critically ill patients** admitted to four Canadian ICUs participating in the DYNAMICS trial (`NCT01355042`).
  - The population was oversampled for non-survivors with lower MODS scores, which we account for in Figure 2.
  - In addition, we computed clinical scores (APACHE II) against the randomly sampled cohort ($n = 757$) as a control (Table 1).
- Using the `dnaMethyAge` R-package (Wang et al., 2023), we calculated **epigenetic age according to 10 epigenetic clocks**, based on whole blood DNA methylation profiles from the day of ICU admission.
  - Clocks chosen were designed to predict a range of outcomes, such as chronological age, health status, and mortality (see Table 1).
- We calculated **"age acceleration"** as the difference between predicted epigenetic age and the individual's chronological age.
- **Our primary outcome was ICU mortality** (in hospital).
- Our secondary outcome was days alive and out of the ICU at day 28 (**ICU Free Days to 28**). Non-survivors were assigned a score of −1.
  - This provides a continous outcome where higher score = better outcome.
- We assessed correlation between epigenetic age and outcomes, and compared means between survivors/non-survivors using Cohen's d.
- To assess the predictive value of epigenetic clocks, we performed k-fold cross-validated logistic regression and calculated the area under the curve (AUC) for each clock.

Scan for references and more information.

In-Text References (Scan QR for Full Reference List)

Binnie, A., Tsang, J. L. Y., Hu, P., Carrasqueiro, G., Castelo-Branco, P., & Dos Santos, C. C. (2020). Epigenetics of Sepsis. *Critical Care Medicine, 48*(5), 745–756. https://doi.org/10.1097/CCM.0000000000004247

Ho, K. M., Morgan, D. J., Johnstone, M., & Ediburn, C. (2023). Biological Age Is Superior to Chronological Age in Predicting Hospital Mortality of the Critically Ill. *Internal and Emergency Medicine, 18*(7), 2019–2028. https://doi.org/10.1007/s11739-023-03397-3

Sharma-Oates, A., Sullivan, J., Pestana, D., Dos Santos, C. C., Binnie, A., & Lord, J. M. (2024). Association of Epigenetic Age and Outcome in Critically Ill Patients. *Critical Care Explorations, 6*(2), e1044. https://doi.org/10.1097/CCE.0000000000001044

Wang, Y., Grant, O. A., Zhai, X., Mcdonald-Maier, K. D., & Schalkwyk, L. C. (2023). Insights into Ageing Rates Comparisons across Tissues from Recalibrating Cerebellum DNA Methylation Clock. *Geroscience, 46*(1), 39–56. https://doi.org/10.1007/s11357-023-00871-w

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Primary Outcome: Mortality

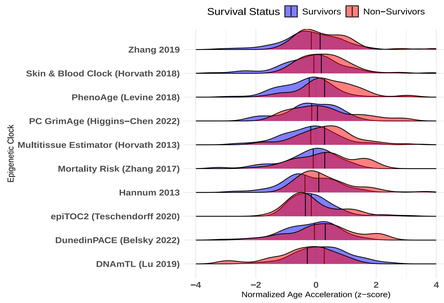

Figure 1: Distribution of estimated age acceleration for survivors and non-survivors, normalized by z-score.

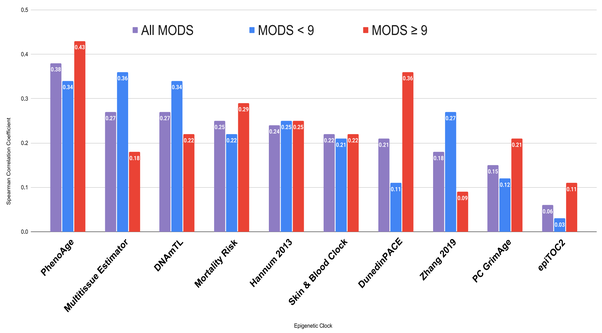

Figure 2: Spearman Correlation of Age Acceleration with Mortality, binned by MODS Score.

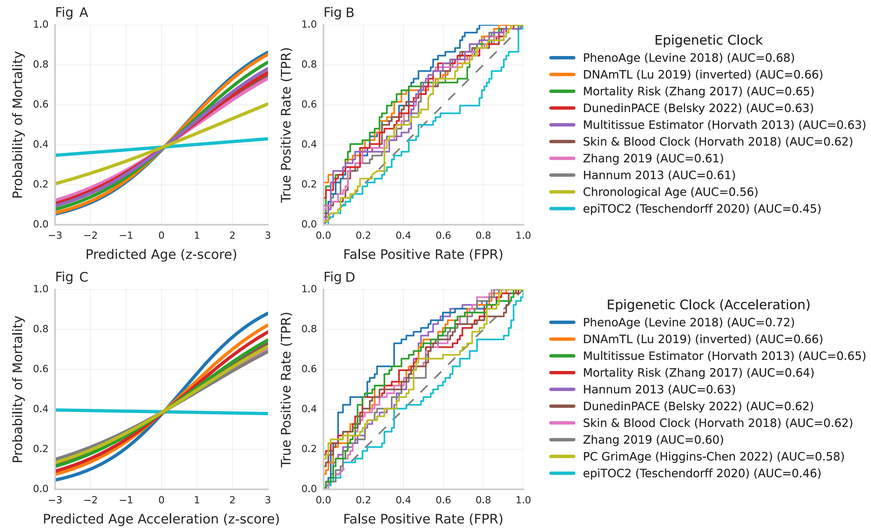

Figure 3: Logistic regression curves of predicted epigenetic age (A) and age acceleration (C) in predicting mortality, and the corresponding receiver operator characteristic (ROC) curves of epigenetic age (B) and age acceleration (D).

		Age / Epigenetic Age					Epigenetic Age Acceleration				
Clock	**Training Variable**	**Correlation**	**p**	**95% CI**	**Cohen's d**	**p**	**Correlation**	**p**	**95% CI**	**Cohen's d**	**p**
PhenoAge (Levine 2018)	Mortality Risk	**0.308**	< 0.001	0.15, 0.45	**0.736**	< 0.001	**0.384**	< 0.001	0.23, 0.52	**0.791**	< 0.001
Multitissue Estimator (Horvath 2013)	Chronological Age	**0.222**	0.010	0.05, 0.38	**0.560**	0.002	**0.273**	0.001	0.11, 0.42	**0.516**	0.004
DNAmTL (Lu 2019)	Leukocyte Telomere Length	**-0.286**	0.001	-0.43, -0.12	**0.723**	0.000	**-0.270**	0.002	-0.42, -0.11	**0.664**	0.000
Mortality Risk (Zhang 2017)	Mortality Risk	**0.274**	0.001	0.11, 0.42	**0.616**	0.001	**0.246**	0.004	0.08, 0.40	**0.572**	0.002
Hannum 2013	Chronological Age	**0.207**	0.017	0.04, 0.36	**0.523**	0.003	**0.238**	0.006	0.07, 0.39	**0.488**	0.006
Skin & Blood Clock (Horvath 2018)	Chronological Age	**0.223**	0.010	0.06, 0.38	**0.497**	0.004	**0.216**	0.012	0.05, 0.37	**0.436**	0.009
DunedinPACE (Belsky 2022)	Pace of Aging	**0.229**	0.008	0.06, 0.38	**0.537**	0.003	**0.210**	0.015	0.04, 0.37	**0.481**	0.011
Zhang 2019	Chronological Age	**0.204**	0.018	0.04, 0.36	**0.481**	0.006	**0.181**	0.036	0.01, 0.34	**0.419**	0.017
PC GrimAge (Higgins-Chen 2022)	GrimAge Lifespan	**NA**	NA	NA	**NA**	NA	**0.151**	0.082	-0.02, 0.31	**0.470**	0.014
APACHE II (DYNAMICS Cohort)	Severity of Disease (Clinical)	**0.176**	< 0.001	0.44, 0.24	**NA**	NA	**NA**	NA	NA	**NA**	NA
APACHE II (EPSIS Cohort)	Severity of Disease (Clinical)	**0.131**	0.132	-0.04, 0.30	**0.306**	0.086	**NA**	NA	NA	**0.306**	0.086
Chronological Age	Age (Non-epigenetic)	**0.131**	0.133	-0.04, 0.29	**0.296**	0.086	**NA**	NA	NA	**0.296**	0.086
epiTOC2 (Teschendorff 2020)	Mitotic Divisions	**-0.032**	0.716	-0.20, 0.14	**0.060**	0.750	**-0.059**	0.501	-0.23, 0.11	**0.013**	0.945

Table 1: Summary Clock Statistics: Spearman Correlation and Cohen's d (effect size) for Mortality.

Secondary Outcome: Length of Stay

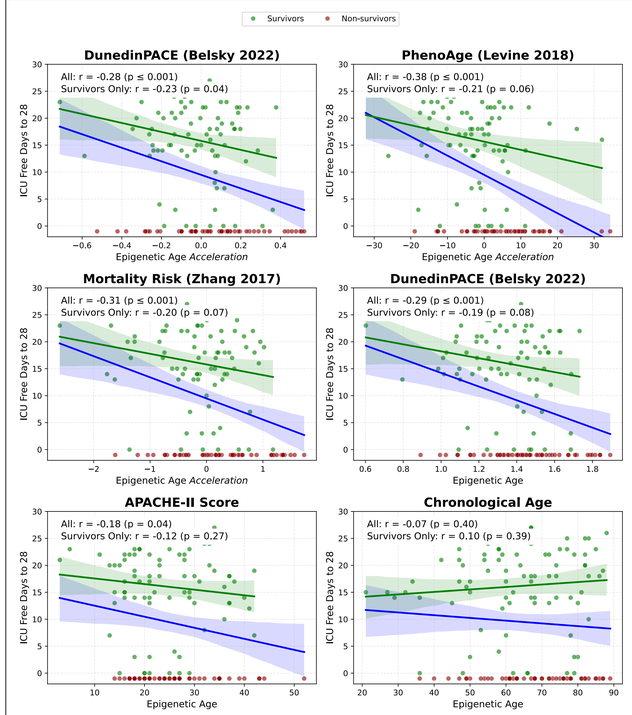

Figure 4: Correlation between selected (top 4) epigenetic clocks and ICU-free-days to 28.

Conclusion

- **Epigenetic clocks consistently outperformed chronological age and APACHE-II score in predicting mortality and length of stay amongst critically-ill patients admitted to ICU.**
- Epigenetic age acceleration is more strongly associated with ICU outcomes of stay than epigenetic age.
- PhenoAge was the most strongly assosciated with mortality. Mean *PhenoAge* acceleration was **11.5 years older** in non-survivors than survivors.
- Epigenetic clocks have predictive value for mortality, with PhenoAge showing an **area-under-curve of 0.72, with good PPV (0.73), NPV (0.71), and specificity (0.90).**
- Epigenetic clcocks, as well as chronological age and APACHE II, demonstrated poor correlation with ICU Free Days after adjusting for mortality prediction. DunedinPACE performed the best, with $r = -0.23$.
- Preliminary multivariate models were promising, demonstrating AUC up to 0.8.