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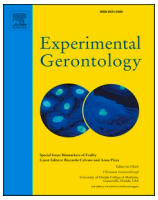

Higher blood biochemistry-based biological age developed by advanced deep learning techniques is associated with frailty in geriatric rehabilitation inpatients: RESORT

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ABSTRACT

Background: Accelerated biological ageing is a major underlying mechanism of frailty development. This study aimed to investigate if the biological age measured by a blood biochemistry-based ageing clock is associated with frailty in geriatric rehabilitation inpatients.
Methods: Within the REStORing health of acutely unwell adulTs (RESORT) cohort, patients' biological age was measured by an ageing clock based on completed data of 30 routine blood test variables measured at rehabilitation admission. The delta of biological age minus chronological age (years) was calculated. Ordinal logistic regression and multinomial logistic regression were performed to evaluate the association of the delta of ages with frailty assessed by the Clinical Frailty Scale. Effect modification of Cumulative Illness Rating Scale (CIRS) score was tested.
Results: A total of 1187 geriatric rehabilitation patients were included (median age: 83.4 years, IQR: 77.7–88.5; 57.4 % female). The biochemistry-based biological age was strongly correlated with chronological age (Spearman $r = 0.883$). After adjustment for age, sex and primary reasons for acute admission, higher biological age (per 1 year higher in delta of ages) was associated with more severe frailty at admission (OR: 1.053, 95 % CI:1.012–1.096) in patients who had a CIRS score of <12 not in patients with a CIRS score >12. The delta of ages was not associated with frailty change from admission to discharge. The specific frailty manifestations as cardiac, hematological, respiratory, renal, and endocrine conditions were associated with higher biological age.
Conclusion: Higher biological age was associated with severe frailty in geriatric rehabilitation inpatients with less comorbidity burden.

1. Introduction

Frailty is an ageing syndrome characterized by functional decline across multiple physiological systems and an increased vulnerability to adverse outcomes (Thillainadesan et al., 2020). Frailty has been associated with a lower quality of life, disability, falls, fractures, hospitalization, institutionalization and mortality (Hoogendijk et al., 2019). Biological age-related changes defined as an accumulation of cellular

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and molecular damage over the life course are an essential component of the frailty phenotype (Kane and Sinclair, 2019).

Biological age has been measured by various "ageing clocks" based on different underlying cellular processes including epigenetics (Hannum et al., 2013; Horvath, 2013), transcriptomics (Peters and others Peters et al., 2015), and metabolomics (Robinson et al., 2020). The use of these ageing clocks has demonstrated that an individual's chronological age and biological age are not necessarily correlated. Individuals who experience an accelerated biological ageing phenotype enter a frailty state earlier and have a higher risk of adverse outcomes compared to their peers (Clegg et al., 2013; Kirkwood, 2005). Recently, an ageing clock was developed to measure biological age using routine clinical blood exams and a sophisticated machine learning approach which included a feed-forward deep neural network technique (Putin et al., 2016). It has been hypothesized that this blood biochemistry-based ageing clock maybe more clinically useful compared to other ageing clocks as the utilization of readily available blood biochemistry data that accounts for the changes across various organ systems, allowing physicians to monitor organ systems that are at a higher risk of deteriorating (Zhavoronkov and Mamoshina, 2019). A higher biological age determined by this blood biochemistry-based ageing clock was observed in smokers compared to non-smokers (Mamoshina et al., 2019). The same ageing clock demonstrated that individuals with a biological age 5 years older than their chronological age had a higher mortality compared to individuals with similar biological age to their chronological age regardless of ethnicity (Mamoshina et al., 2018). However, whether the biological age measured by a blood biochemistry-based ageing clock is associated with frailty is unknown.

This study aims to investigate the association between biological age determined by the blood biochemistry-based ageing clock and frailty in geriatric rehabilitation inpatients.

2. Methods

2.1. Study design

REStORing health of acutely unwell adulTs (RESORT) is a longitudinal, observational, prospective cohort of patients admitted to the geriatric rehabilitation wards of the Royal Melbourne Hospital (Melbourne, Victoria, Australia). A Comprehensive Geriatric Assessment (CGA) which included medical, nutritional, physical, psychological, and social domain assessment was performed by a multidisciplinary team on all patients at admission (within 48 h) and discharge of the geriatric rehabilitation unit. Patients were excluded from this cohort if they were receiving palliative care at admission or were unable to provide consent (e.g. due to severe delirium or dementia) and had no nominated proxy to consent on their behalf. This cohort included 1890 patients admitted from 16th October 2017 and discharged until 18th March 2020. This study was approved by the Melbourne Health Human Research Ethics Committee (No.: HREC/16/MH/346) and conducted following the Declaration of Helsinki (Association, 2013) and the National Statement on Ethical Conduct in Human Research (Anderson, 2011).

2.2. Patient characteristics

Age, sex and ethnicity data was obtained from a questionnaire filled out by patients or with the assistance of their next of kin and/or a researcher. Length of stay in acute hospitalization and rehabilitation was extracted from the patients' medical records. Primary reasons for acute admission were obtained from patients' medical records and categorized into musculoskeletal, neurological, cardiovascular, infections and others. The comorbid condition was evaluated by Cumulative Illness Rating Scale (CIRS) which is a severity rating scale on 14 physiological systems with each assigned a score ranging from 0 (no problem) to 4 (extremely severe). A higher score indicates a greater comorbid burden (Hudon et al., 2007; Linn et al., 1968). Cognitive impairment was defined as the presence of dementia reported in the medical records or CCI, or a score under the cut-offs of standardized Mini-Mental State Examination (sMMSE) (24 points) (Folstein et al., 1975), or a Montreal Cognitive Assessment (MoCA) (26 points) (Nasreddine et al., 2005), or a Rowland Universal Dementia Assessment Scale (RUDAS) (23 points) (Storey et al., 2004). Medication count was extracted from the patients' hospital medication records. Malnutritional risk was defined as a Malnutrition Screening Tool (MST) score of >2 points (Ferguson et al., 1999). Physical performance was assessed by the Short Physical Performance Battery (SPPB) which encompasses standing balance, a four-meter walk test and a chair sit-to-stand test on a scale of 0 to 12 points (Guralnik et al., 1994). A higher score demonstrates better physical performance. Functional performance was determined by the Katz index of activities of daily living (ADLs) (0–6 points) (Katz et al., 1963) and the Lawton and Brody scale of instrumental activities of daily living (IADLs) (0–8 points) (Lawton and Brody, 1969), where a higher score represents a higher level of functional independence on both scales.

2.3. Frailty

The frailty phenotype was assessed at admission and discharge by using the Clinical Frailty Scale (CFS). The CFS is an ordinal scale where 1 is very fit and 9 is terminally frail (Rockwood et al., 2005). The severity of frailty at admission was categorized into CFS ≤ 5, CFS $= 6$, CFS ≥ 7 groups and treated as an ordinal variable from mild to severe frailty. The change of frailty severity from admission to discharge was defined as *stable* (CFS at admission = CFS at discharge), *improved* (CFS at admission $>$ CFS at discharge), *deteriorated* (CFS at admission $<$ CFS at discharge).

2.4. Blood biochemistry-based ageing clock

Pathology tests were generally ordered based on clinical indication. Blood tests of 30 frequently measured parameters undertaken close to rehabilitation admission as part of the routine practice were used to measure biological age using the ageing clock developed by the Feed-Forward Deep Neural Networks (Mamoshina et al., 2018; Putin et al., 2016). Supplementary Table 1 shows the frequency of 30 blood parameters measured in the entire cohort of 1890 geriatric rehabilitation inpatients. The biological age was output after age, sex and completed pathology data of 30 laboratory variables were input into the online system through the SenoClock platform (https://www.deeplongevity.com/senoclock). The delta of ages (years) was defined as the computed biological age minus chronological age.

2.5. Statistics

Normal distributed continuous variables are presented as mean $\pm$ standard deviation (SD). Skewed distributed continuous variables are presented as median and interquartile range (IQR). Categorized variables are presented as frequency and percentage. To indicate model accuracy, the correlation between biological and chronological age was determined by Spearman correlation analysis and plotted with a regression line; the average difference was expressed as a median or mean absolute error (MAE) calculated by the sum of the absolute difference between biological and chronological age divided by the total sample size. The ANOVA test was used to compare the delta of ages among frailty status if it was normally distributed, while the Kruskal-Wallis H test was used for non-normally distributed data. The delta of ages was treated as a continuous variable. Ordinal logistic regression was performed to analyse the association between the delta of ages and the severity of frailty at admission. Multinomial logistic regression was used to analyse the association of the delta of ages with the change of frailty severity from admission to discharge. The outcome group of '*stable*' frailty from admission to discharge was considered as a reference. All analyses included a crude model and a model adjusted for

chronological age, sex and primary reasons for acute admission. The severity of frailty at admission was additionally adjusted in the analyses of the association between the delta of ages and frailty change. The analyses were stratified by the median of CIRS score to see if CIRS score is an effect modifier. The Student's *t*-test was used to compare delta of ages between CIRS groups if it was normally distributed; if not, Mann-Whitney *U* test was used. Results were reported as odds ratio (OR) with a 95 % confidence interval (CI). A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 26.0 (IBM Corp, Armonk, NY, USA). Figures were created using Prism GraphPad 6.0 (GraphPad Software Incorporated, San Diego, CA, USA).

3. Results

3.1. Patient characteristics

The median chronological age of the cohort with complete biochemistry data ($n = 1187$) was 83.4 years (IQR: 77.7–88.5), 57.4 % of patients were female, and 88.0 % were Caucasian. The median length of stay in acute hospitalization was 6.6 days (IQR: 3.8–11.1) and 19.8 days (IQR: 13.6–31.0) in geriatric rehabilitation. The most common primary reasons for hospital admission were musculoskeletal conditions (46.8 %). The median CIRS score was 12 (IQR: 9–16). Patients had a median ADL score of 2 points (IQR: 1–2) and a median IADL score of 1 point (IQR: 0–2). The median CFS score was 6 (IQR: 5–7) at both admission and discharge. Among the total included patients, 33.1 %, 34.5 % and 32.4 % of patients had CFS $\leq$ 5, CFS = 6 and CFS $\geq$ 7 at admission, respectively; 43.8 %, 34.5 % and 21.7 % of patients had stable, improved, and deteriorated frailty from admission to discharge, respectively (Table 1).

Table 1
Characteristics of patients at geriatric rehabilitation admission.

	n	Total (N = 1187)
Age, years	1187	83.4 [77.7–88.5]
Female, n (%)	1187	681 (57.4)
European/Caucasian, n (%)	1154	1016 (88.0)
LOS in acute hospitalization	1156	6.6 [3.8–11.1]
LOS in geriatric rehabilitation hospitalization	1187	19.8 [13.6–31.0]
Morbidity		
Primary reasons for acute admission, n (%)	1187	
Musculoskeletal		556 (46.8)
Neurological		167 (14.1)
Cardiovascular		98 (8.3)
Infections		75 (6.3)
Other reasons		291 (24.5)
Cumulative illness rating scale, score	1187	12 [9–16]
Cognitive impairment, n (%)	1187	796 (67.1)
Medication count	1187	9 [6–12]
Nutrition and physical function		
Malnutrition risk (MST $\geq$ 2), n (%)	1168	508 (43.5)
Short physical performance battery, score	1133	1 [0–4]
Katz ADL, score	1177	2 [1–2]
Lawton and Brody Scale IADL, score	1177	1 [0–2]
Frailty		
CFS, score	1187	6 [5–7]
CFS at discharge, score	690	6 [5–7]
Categories of frailty at admission	1187	
CFS $\leq$ 5, n (%)		393 (33.1)
CFS = 6, n (%)		409 (34.5)
CFS $\geq$ 7, n (%)		385 (32.4)
Change of frailty from admission to discharge	690	
Stable, n (%)		302 (43.8)
Improved, n (%)		238 (34.5)
Deteriorated, n (%)		150 (21.7)

Data are presented as median [interquartile range] unless otherwise indicated. Abbreviations: LOS: Length of stay; MST: Malnutrition screening tool; ADL: Activities of daily living; IADL: Instrumental activities of daily living; CFS: Clinical frailty scale.

3.2. Biological age determined by the blood biochemistry-based ageing clock

The median biological age of the cohort was 83 years (IQR: 77–89). The biological age was strongly correlated with chronological age (Spearman correlation $r = 0.883$, $p < 0.001$; $R^2 = 0.792$) (Fig. 1A). The median delta between biological and chronological age was −0.61 years (IQR: −3.43–2.91). The MAE between ages was 3.22 years (Fig. 1B).

3.3. Association with the severity of frailty at admission

A higher delta of ages (per 1 year higher) was associated with more severe frailty independent of chronological age and sex (adjusted OR: 1.044, 95 % CI: 1.015–1.074, $p = 0.002$). This association was maintained significant in patients with a CIRS score of $\leq$12 (adjusted OR: 1.053, 95 % CI: 1.012–1.096, $p = 0.011$), but not in patients who had a CIRS score of >12 (adjusted OR: 1.012, 95 % CI: 0.971–1.053, $p = 0.575$) (Table 2). The delta of ages tended to be higher in patients with higher CFS scores at admission without statistical significance. The delta of ages was higher in patients with CIRS >12 compared to CIRS $\leq$12 and reached significance within CFS $\leq$ 5 and CFS = 6 groups (Fig. 2A).

3.4. Association with change in the severity of frailty

The delta of ages at admission was not significantly associated with improved or deteriorated change of frailty from admission to discharge regardless of CIRS scores (Table 2). The delta of ages was not significantly different among the stable, improved and deteriorated frailty groups from admission to discharge. The delta of ages was higher in patients with CIRS >12 compared to CIRS $\leq$12 and significant in patients with stable frailty (Fig. 2B).

3.5. Association of biological age with components of CIRS

The CIRS is a scale representing the overall comorbid condition of a patient based on an aggregation of the health of 14 particular physiological systems (Hudon et al., 2007; Linn et al., 1968). Among the 14 components of the CIRS, five had been identified as the systems in which higher severity score was associated with higher biological age: cardiac, hematological, respiratory, renal, and endocrine, metabolic, breast systems ($p < 0.05$) (Fig. 3).

4. Discussion

The blood biochemistry-based ageing clock was highly correlated with chronological age in geriatric rehabilitation inpatients. A higher biological age was associated with higher severity of frailty at rehabilitation admission in patients with a lower CIRS score. The difference between biological and chronological age at admission was not associated with the change of frailty from admission to discharge.

The biological age was unexpectedly predicted to be younger than the chronological age in the present geriatric rehabilitation inpatients who were old, frail, and suffering from multimorbidity. This is in line with previous findings, although the biological age of this cohort was measured to be older compared to the same age group from previous studies (Cohen et al., 2016; Mamoshina et al., 2018). The biological age of older individuals was underestimated probably because the ageing clock was trained on a healthy population with a wide age range and contained fewer older individuals (Putin et al., 2016). Survivor bias might also account for the younger biological age predicted (Banack et al., 2019). Nevertheless, the association of higher biological age with severe frailty at geriatric rehabilitation admission was observed in patients with milder comorbid conditions (CIRS $\leq$12). Consistently, older biological age or accelerated biological ageing determined by blood biomarkers was associated with age-related diseases such as stroke, cancer, diabetes and dementia, which might contribute to a higher risk

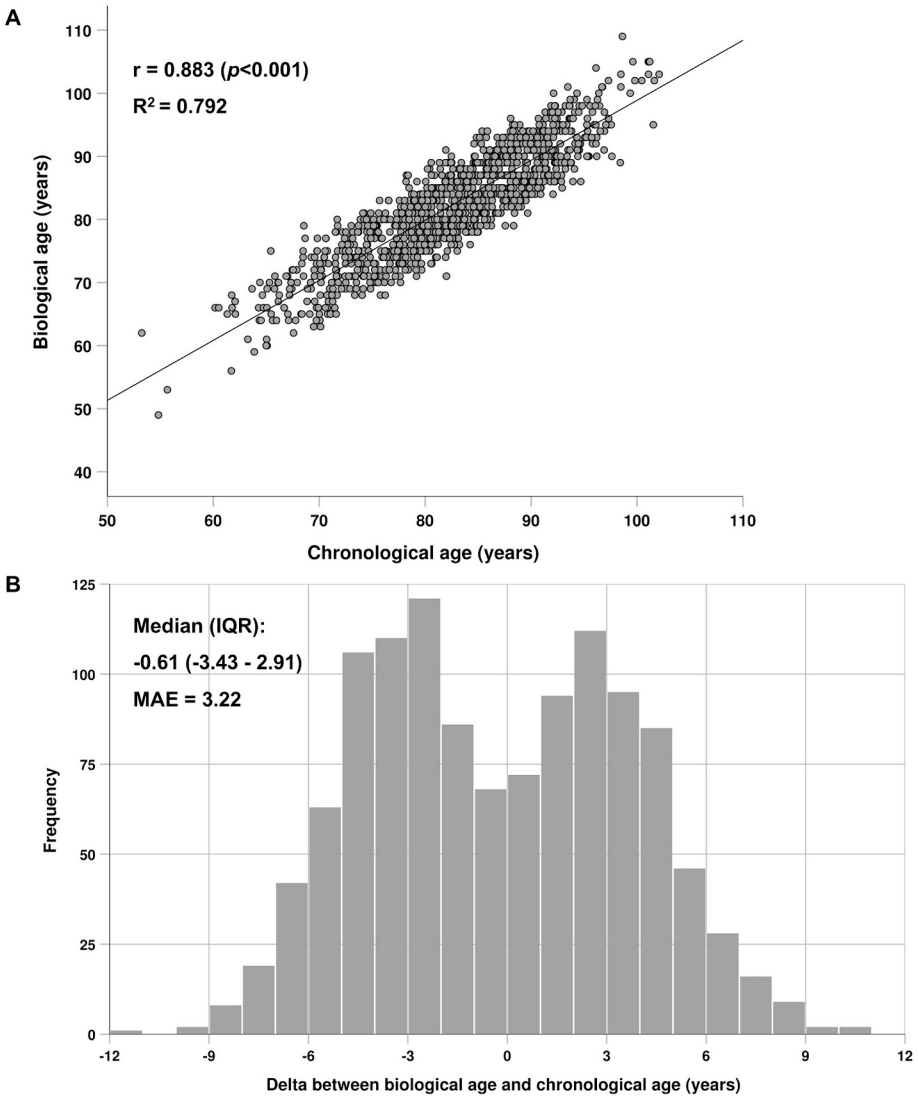

Fig. 1. Characteristics of the measured biological age (n = 1187). (A) Linear association between chronological age and biological age. (B) Histogram of the delta between biological and chronological age (delta = biological age - chronological age). r: Spearman correlation coefficient; R^2: Coefficient of determination; MAE: Median absolute error. IQR: Interquartile range.

of developing future frailty and mortality (Drewelies et al., 2022; Elliott et al., 2021; Waziry et al., 2019; Wu et al., 2021). The blood parameters included in the current algorithm account for various physiological systems and functions such as hematological, electrolytes, metabolic, hepatic and renal. Deficits in multiple systems are the main feature of frailty which has been measured by the accumulation of laboratory abnormalities (Guan et al., 2022; Howlett et al., 2014) or clinical health deficits (Mitnitski et al., 2001; Rockwood and Mitnitski, 2007). On the other hand, patients who had severe comorbid condition were already in a frail state and had received more intensive healthcare to manage their conditions, where biological age has less pronounced impact on frailty. No relationship was found between biological age at admission and change in frailty from admission to discharge regardless of the comorbid conditions. The impact of type of care such as physiotherapy, nutritional therapy and quality of care on change of frailty from admission to discharge maybe more robust than the impact of biological age measured at admission (Rezaei-Shahsavarloo et al., 2020).

Biological age measured at one time point might not adequately reflect the health status of the patients at the end of the rehabilitation process. A proper assessment of the connection between the ageing rate and the efficiency of a therapy would require taking a second biological age measurement at discharge. The study setting did not allow us to determine if ageing deceleration can be used as a proxy for the efficiency of a therapy. However, since biological age does not have a statistically significant effect on the outcome of the treatment, it may be concluded that both slow and fast agers may gain equally large health benefits from an appropriately chosen therapy. Previous studies on deep blood biochemistry-based ageing clock identified the association of this measure of biological age with COVID-19 mortality, smoking, and psychological well-being (Galkin et al., 2022; Galkin et al., 2021; Mamoshina et al., 2019). This study is the first one to apply this digital ageing model to geriatric rehabilitation inpatients and demonstrate the association between biological ageing and frailty. More specifically, using the decomposed CIRS, this study demonstrated that diseases affecting cardiac, hematological, respiratory, renal, and endocrine, metabolic, breast systems are more representative of the ageing-related blood profile changes. More severe conditions, namely, frailty manifestations in these systems contributed higher biological age.

Sophisticated machine learning techniques outperform conventional mathematic methods in complex and multidimensional data analysis (Zhavoronkov and Mamoshina, 2019). Nevertheless, some limitations are recognized. The blood biochemistry-based ageing clock was trained

Table 2
Associations of the difference between biological and chronological age with the severity of frailty at admission and change of frailty from admission to discharge.

		Frailty at admission			Change of frailty from admission to discharge			
		From mild to severe			Stable vs Improved		Stable vs Deteriorated	
	n	OR (95 % CI)	*p*	n	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Total								
Crude model								
Delta of ages	1187	**1.029 (1.002–1.057)**	**0.036**	690	1.019 (0.977–1.064)	0.377	1.008 (0.960–1.059)	0.754
Adjusted model								
Delta of ages	1187	**1.044 (1.015–1.074)**	**0.002**	690	0.993 (0.949–1.040)	0.780	1.021 (0.967–1.079)	0.449
CIRS score ≤ 12								
Crude model								
Delta of ages	632	1.036 (0.997–1.077)	0.072	357	1.038 (0.972–1.107)	0.266	1.019 (0.953–1.089)	0.589
Adjusted model								
Delta of ages	632	**1.053 (1.012–1.096)**	**0.011**	357	1.023 (0.952–1.099)	0.543	1.041 (0.966–1.122)	0.289
CIRS score > 12								
Crude model								
Delta of ages	555	0.994 (0.957–1.033)	0.777	333	0.989 (0.933–1.047)	0.696	1.004 (0.931–1.081)	0.925
Adjusted model								
Delta of ages	555	1.012 (0.971–1.053)	0.575	333	0.966 (0.908–1.028)	0.277	0.993 (0.909–1.086)	0.885

Delta of ages (per 1 year higher) = biological age - chronological age.
Adjusted model: adjusted for chronological age, sex and primary reasons for acute admission. Additionally adjusted for frailty at admission in the analyses of association between delta of ages and change of frailty from admission to discharge.
Abbreviations: CIRS: Cumulative illness rating scale; OR: Odds ratio; 95 % CI: 95 % Confidence interval.
Bold values indicate statistically significant results ($p < 0.05$).

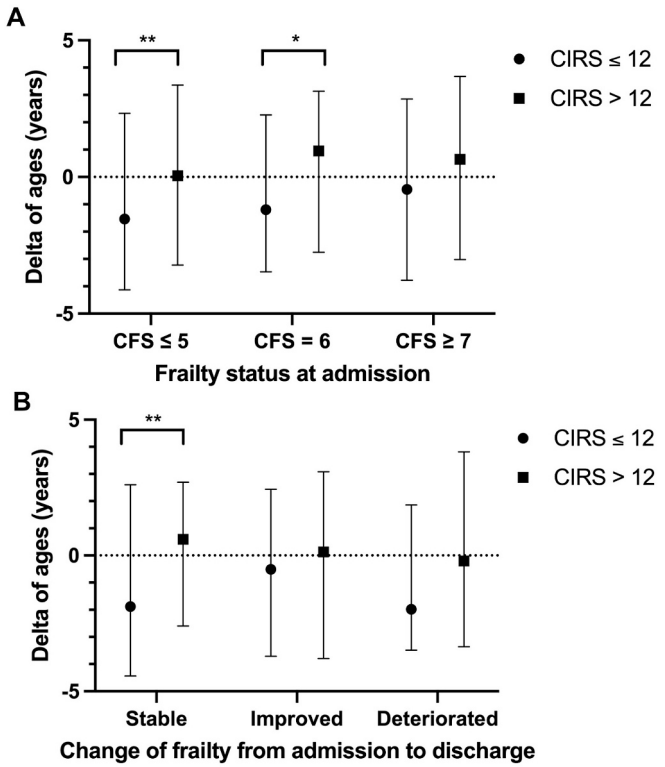

Fig. 2. Delta of ages (biological age - chronological age) in geriatric rehabilitation inpatients with different frailty status at admission ($n = 1187$) (A) and changed frailty status from admission to discharge ($n = 690$) (B), stratified by the median of CIRS socres. Data are presented as median with an interquartile range. The overall *p* values for delta of ages obtained from the Kruskal-Wallis H test were 0.193 in CIRS ≤12 and 0.977 in CIRS >12 acorss frailty status groups at admission (A); 0.547 in CIRS ≤12 and 0.936 in CIRS >12 across change of frailty groups (B). *: $p < 0.05$; **: $p < 0.01$. CIRS: Cumulative illness rating scale.

in a healthy community-dwelling population, which might not accurately account for the biological age in a population with multimorbidity, especially those with severe comorbid conditions. The findings are not generalizable to the older populations in acute hospitals or community settings. Generalizability may also be compromised by selecting those patients with complete biochemistry data. Other biological age measures such as DNA methylation age and skin age were not performed in the present study. The goodness of the blood biochemistry-based ageing clock on biological age prediction compared to other ageing clocks remains unknown.

5. Conclusions

Higher biological age, determined by the blood biochemistry-based ageing clock, was associated with severe frailty at admission but not with the change of frailty from admission to discharge in geriatric rehabilitation inpatients dependent on the severity of comorbid conditions. Future studies should train and apply the model to a larger sample size of geriatric rehabilitation inpatients and explore potential associations with more rehabilitation outcomes such as functional decline, institutionalization and mortality to validate the clinical application value in geriatric rehabilitation inpatients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2024.112421.

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CRediT authorship contribution statement

Lihuan Guan: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Camilla S.L. Tuttle:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Fedor Galkin:** Writing – review & editing, Visualization, Software, Methodology. **Alex Zhavoronkov:** Resources. **Andrea B. Maier:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

Alex Zhavoronkov and Fedor Galkin are employees at Deep

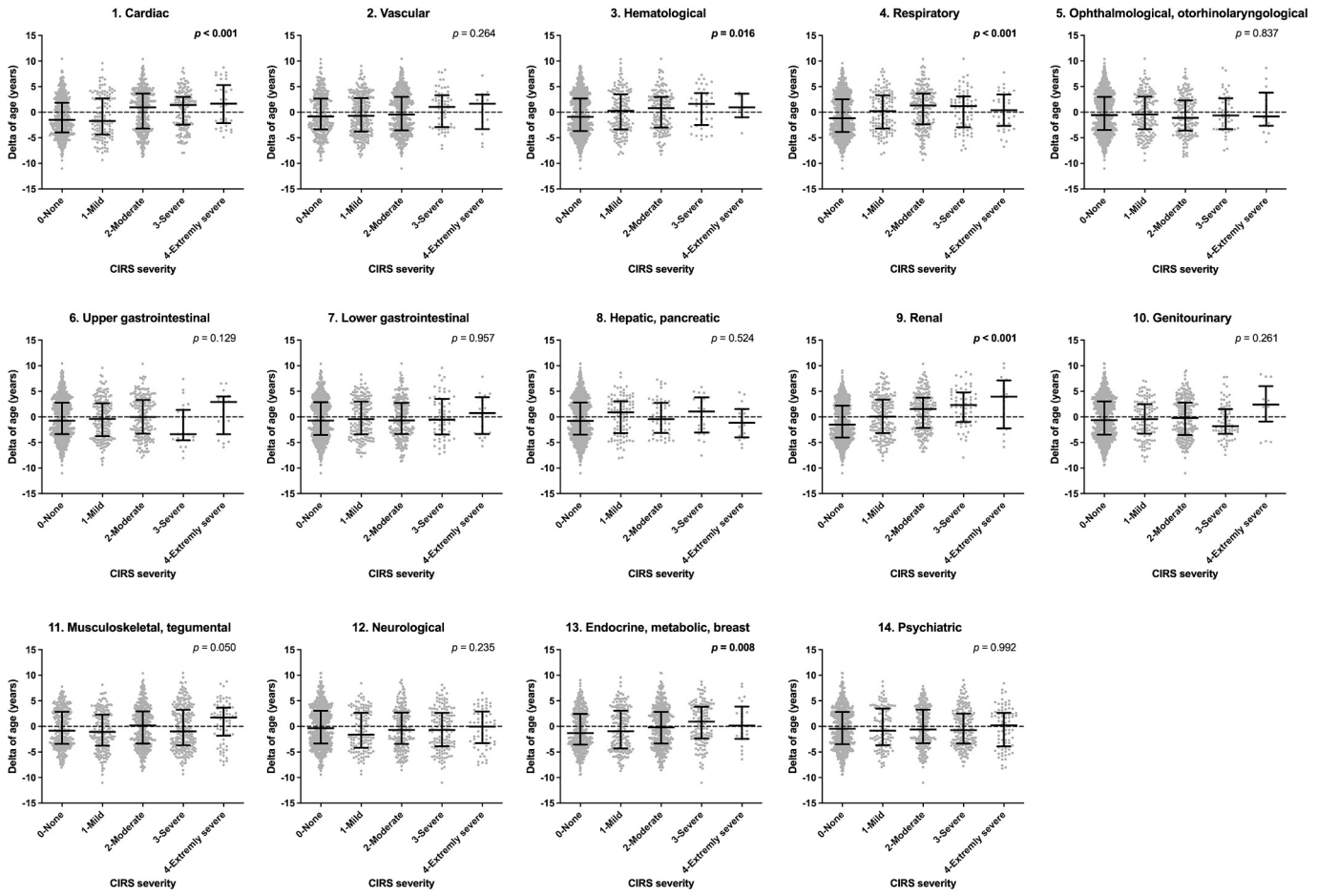

Fig. 3. Delta of ages (biological age - chronological age) in geriatric rehabilitation inpatients with none, mild, moderate, severe and extremely severe levels of severity in 14 physiological systems defined in Cumulative illness rating scale (CIRS). The *p* values were obtained from Kruskal-Wallis H test.

Longevity, a for-profit Hong Kong company, subsidiary of a public company Endurance RP (0575.HK). The blood ageing clock described in this article is available for commercial use via the Senoclock online platform. Lihuan Guan, Camilla S.L. Tuttle and Andrea B. Maier declare no conflicts of interest.

Data availability

Data will be made available on request.

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