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Longitudinal associations of platelet activation phenotypes with frailty and physical performance in older adults living at high southern latitudes

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Abstract

Background: Aging is accompanied by chronic low-grade inflammation, altered platelet biology, and progressive vulnerability to adverse health outcomes. Platelet activation has been proposed as a potential biomarker of immunothrombotic aging, but longitudinal evidence linking platelet phenotypes with frailty and physical performance in older adults remains limited. This study examined the longitudinal associations of resting and activated platelet phenotypes with frailty and physical performance in community-dwelling older adults living at high southern latitudes. **Methods**: A total of 137 older adults from Punta Arenas, Chile, were assessed across three time points over one year. Platelet phenotypes were characterized by flow cytometry based on CD41 and CD62 expression, distinguishing resting $CD41^{+}/CD62^{-}$ and activated $CD41^{+}/CD62^{+}$ platelet populations. Frailty was assessed using the FRAIL scale, and physical performance was evaluated through handgrip strength (HGS), chair sit-to-stand (CSTS), arm curl, and timed up-and-go (TUG) tests. Bayesian multilevel models were used to estimate longitudinal associations while accounting for repeated measurements and adjusting for age, sex, and body mass index (BMI). **Results:** Frailty scores remained relatively stable over time, whereas platelet phenotype distributions showed clear temporal changes, particularly a decline in the $CD41^{+}/CD62^{-}$ platelet population. Higher BMI was consistently associated with greater frailty. Platelet phenotypes showed modest and uncertain associations with frailty, $CD41^{+}/CD62^{-}$ tending toward a protective association. In contrast, higher proportions of $CD41^{+}/CD62^{+}$ and $CD41^{+}/CD62^{-}$ platelets were associated with better physical performance, particularly in CSTS, arm curl, and TUG outcomes. **Conclusions:** Platelet activation phenotypes may provide useful biological information about functional aging trajectories in older adults. Although associations with frailty were modest, the

relationship between platelet phenotypes and physical performance suggests that platelet biology may reflect aspects of physiological reserve. These findings should be interpreted as exploratory and require replication in larger cohorts incorporating inflammatory, pharmacological, and environmental measures.

Keywords: platelet activation; CD62P; frailty; physical function; aging; high southern latitudes.

BACKGROUND

The older population worldwide is currently rapidly increasing. In Chile, according to the National Statistics Institute, 14% of the Chilean population corresponds to individuals over 65 years old, and it is projected that by 2050, this group will increase to 25%, due to the lower birth rates and increased longevity (1). In regard of that, it is relevant to take in account how environmental factors can affect a person's quality of life, as it is the case of people who live in extreme latitudes, such the population in the Magallanes y Antarctica Chilena region to acknowledge the physical and mental capacities of older individuals to prevent dependency and improve their quality of life (2,3). The decline in a person's physiological reserve, physical and mental capacities can lead to frailty (4,5), a state of increased mental and physical vulnerability characterised by a decrease in the recovery from acute stressors (6), commonly occurring during the later years in a person's life as a result of a decline of several physiological systems, increasing the susceptibility to adverse outcomes, a general decrease of their physical performance which include dependency, falls, weight loss, poor endurance and energy, and cognitive decline that includes delirium, diminishing of balance, disorientation and dementia (7–9).

A chronic pro-inflammatory state is a characteristic feature of aging, increasing the risk of age-related morbidities, including cardiovascular disease (CVD), rheumatoid arthritis (RA), Alzheimer's disease (AD), and frailty (10,11). It is now known that platelets have an important role in inflammation and immune response (12).

Platelets are anucleate cells present in circulating blood derived from megakaryocytes in the bone marrow (13). The most well-known function of platelets is in hemostasis and thrombosis, with a fast response after injury (14). Additionally, circulating platelets play a key role in inflammation and in the intravascular innate and acquired immune systems (15,16). Platelets are present in circulating blood in a resting state (17). Upon stimulation, platelets rapidly become activated by several stimuli, including open wounds in the vascular system, stress, or exercise. The activation implies a shape change, secretion of granular content, and further coagulation (18). P-selectin (CD62) is a glycoprotein that, after stimulation, translocates from platelet α-granules to the platelet surface, allowing platelet interaction with neutrophils and monocytes, supporting platelet-platelet interactions, and facilitating the binding of circulating procoagulant molecules (19,20). Therefore, CD62 is a widely used membrane marker to differentiate activated from inactive platelets associated with inflammatory responses (21).

In middle-aged individuals, platelet counts remain practically stable (20-60 years old), but in older individuals (>70 years old), they decrease by approximately 10% (22,23). However, platelet reactivity generally increases, which is associated with an increased risk of thrombotic diseases among older individuals (24). Additionally, Hernández and collaborators showed that platelet activation was significantly higher in the frail older adults compared to a robust group, indicating greater platelet activation during aging, particularly in the presence of frailty (9).

It has been reported that platelet-related markers correlate with inflammatory trajectories and are linked to frailty, however, literature regarding the association between platelet phenotypes and frailty is still emerging (25).

Despite growing evidence that platelet activation is altered in aging and frailty, evidenced by significant increases in platelet function and reactivity in frail older adults, and distinct alterations in mitochondrial dynamics and circulating oxidative stress biomarkers like GDF-15 (2), longitudinal studies examining platelet activation phenotypes in relation to functional aging remain scarce (9). Most available studies have focused on total platelet counts, platelet reactivity, or inflammatory markers in cross-sectional designs, limiting the understanding of how platelet subpopulations may relate to changes in frailty and physical performance over time (26). This gap is particularly relevant in older adults living in geographically and environmentally challenging regions, such as high southern latitudes, where seasonal variability, cold exposure, and social-environmental conditions may interact with biological aging processes. However, because environmental exposures were not directly quantified in the present study, the term 'high southern latitude' should be interpreted as the ecological context of the cohort rather than as a causal explanatory factor.

Therefore, this study aimed to evaluate the longitudinal associations of platelet phenotypes, defined by CD41 and CD62 expression, with frailty and physical function in community-dwelling older adults from the Magallanes region of Chile. We hypothesized that resting and activated platelet phenotypes would show differential associations with frailty and physical performance over time, reflecting distinct aspects of inflammatory aging and physiological reserve.

MATERIAL AND METHODS

Study design

This was a longitudinal observational study with repeated measurements conducted at three time points over one year (T0, T1= 6 months, T2= 12 months). Assessments were performed during late winter, late summer, and the following late winter, allowing the evaluation of within-participant changes in platelet phenotypes, frailty, and physical function.

Before data collection began, all participants were well informed about the study's objectives, procedures, and potential implications. Informed consent was obtained from every participant to ensure ethical integrity and respect for individual autonomy. The data collection procedures were approved by The Ethics Committee of the University of Magallanes (N°008/SH/2022)

Setting

Data collection occurred in the extreme south of Chile, a high southern latitude environment (located at high southern latitudes 48°36' to 56°30') with marked seasonality at the Centro Asistencial Docente e Investigación (CADI-UMAG), the University of Magallanes academic healthcare and research centre associated with the University of Magallanes, in Punta Arenas, Chile. Assessments were conducted from 9:00 to 11:00 a.m. to minimize potential circadian variations in physiological or cognitive outcomes, in a controlled environment with constant temperature (~20 °C), artificial lighting, and a quiet, private room.

Participants

Participants were recruited from the local community through advertisements and outreach through a non-probabilistic convenience sampling. The study included 137 participants, of whom 42 were male and 95 were female. The mean age of the sample was 70.4 ± 6.1 years, with no meaningful difference between sexes (70.9 ± 5.9 in males vs 70.2 ± 6.3 in females). Participants were included in the analysis if they: (i) permanently resided in the Magallanes region, (ii) were 60 years or older, and (iii) were functionally independent to respond to self-reported questionnaires.

However, participants were excluded if they: (i) had severe cognitive impairments or dementia that could hinder their ability to provide reliable self-reported data, (ii) had significant communication barriers that prevented them from completing the self-report questionnaires effectively, or (iii) were currently undergoing primary medical treatments or facing severe health conditions that could confound the study results.

Because platelet activation may be influenced by pharmacological and clinical factors, information on antiplatelet therapy, anticoagulant use, anti-inflammatory medication, dyslipidemia, and recent acute inflammatory or infectious conditions was recorded when available. These variables were considered during the interpretation of the findings. However, medication use was not fully incorporated into the primary models, which represents an important limitation of the study.

Procedures

Participants fasted for 12 h, and refrained from strenuous exercise and alcohol consumption. Upon arrival, participants provided informed consent and underwent a brief health screening to confirm eligibility per inclusion/exclusion criteria, including a blood pressure assessment (SBP < 140 mmHg and DBP < 90 mmHg). While 130/80 mmHg is the diagnostic threshold for hypertension, the more conservative 140/90 mmHg cut-off is widely used to balance safety with participant inclusion and was thus appropriate for our study design.

Following the initial registry, body composition measurements were performed using multi-frequency bioelectrical impedance analysis (BIA) according to standardized procedures. Participants were asked to empty their bladders immediately before this assessment.

A peripheral venous blood sample (4 mL) was collected in EDTA tubes by a trained nurse. Samples were gently homogenized and maintained at room temperature for subsequent immunophenotypic analysis and processed within 2 h of collection.

Assessments

Flow cytometry for platelet phenotype identification

Platelet phenotypes were assessed by flow cytometry using whole blood collected in EDTA tubes. Samples were processed within 2 hours of collection to minimize ex vivo platelet activation. Whole blood samples were gently homogenized and centrifuged at 1500 rpm for 10 minutes at room temperature to obtain platelet-rich plasma (PRP). From this fraction, 50 µL aliquots were collected and incubated under standardized conditions with fluorochrome-conjugated monoclonal antibodies: anti-CD41a APC (BD Biosciences, #559777), used for platelet identification, and anti-CD62P PE (BD Biosciences, #555524), used as a marker of platelet activation. Following incubation, samples were diluted in Isoflow buffer (Beckman Coulter) and acquired at low flow rate using a four-laser CytoFLEX S flow cytometer (Beckman Coulter). All samples were processed within 2 hours of collection to minimize ex vivo platelet activation.

The analysis strategy included doublet exclusion based on FSC-A versus FSC-H, followed by forward and side scatter gating (FSC vs SSC). Platelets were subsequently identified as $CD41a^+$ events. Platelet subpopulations were defined as $CD41a^+/CD62P^-$ (resting or non-activated platelets) and $CD41a^+/CD62P^+$ (activated platelets). Results were expressed as the percentage of events within the platelet gate.

Quality control measures included the use of compensation controls, fluorescence-minus-one (FMO) controls when available, exclusion of debris and aggregates, and the application of standardized instrument settings across all acquisition sessions.

Frailty questionnaire

The Spanish version of the FRAIL questionnaire was employed (27). It encompasses fatigue, resistance, ambulation, illness, and weight-loss criteria, as previously described in our group (28). One point is attributed to each domain, and the scale scores from 0 to 5 points (0 = best to 5 = worst). Individuals are categorized as non-frail (0 points), pre-frail (1 or 2 points), or frail (3 or more points).

Body composition

Body composition, including body mass index (BMI), body fat percentage, lean muscle mass, body water, and bone mass, was assessed using multi-frequency bioelectrical impedance analysis (BIA). Measurements were performed using the Tanita BC-558 Ironman Segmental Body Composition Monitor (Tanita Ironman, Arlington Heights, IL 60005 USA). Participants were instructed to fast for at least 4 h before the assessment and to avoid strenuous physical exercise and alcohol consumption for at least 12 h. They were also asked to empty their bladder before the measurement. Participants stood barefoot on the device's foot electrodes and held the hand electrodes while wearing light clothing.

Handgrip strength (HGS) assessment

Handgrip strength (HGS) was measured using an electronic hand dynamometer (CAMRY EH101, Sensun Weighing Apparatus Group Ltd, Guangdong, China), which has demonstrated high validity and reliability in the older population (29,30) and provides measurements with an accuracy of 0.1 kg. Participants were seated with the shoulder adducted and neutrally rotated, the elbow flexed at 90°, and the forearm and wrist in a neutral position (31). After the handle was adjusted to the participant's hand size, they were instructed to exert maximal isometric strength for at least 3 seconds. Three trials were performed for each hand with 1-minute rest intervals. The primary outcome was the mean of the maximum values from both hands (kg). The same chair, position, and instructions were given for each evaluation.

Chair-Sit-To-Stand (CSTS) Test

Lower body strength and power were assessed using the CSTS Test (32). Participants were seated in a standard chair, with their feet flat on the floor and their arms crossed over their chests. They were instructed to stand up completely and then sit back down as many times as possible within 30 seconds. The outcome measure was the total number of stands completed in 30s.

Timed Up-and- Go (TUG) Test

Functional mobility, including balance and gait speed, was assessed using the TUG test (33). Individuals were seated on a standard armchair. Upon the command "Go", they stood from the chair, walked 3 m, turned around, walked back to the chair, and sat down. A stopwatch was used to take the time that the individual takes to complete the task (seconds), starting from the command "Go" and stopping when the participant was fully seated back in the chair. The average time of the two-timed trials was used as the outcome measure.

Arm curl test

The arm curl test is a standardized measure of upper-body strength and endurance, commonly used in functional fitness assessments. The protocol was adapted from Rikli & Jones (1999). Briefly, participants were asked to perform as many elbow flexion repetitions as possible within 30 seconds while seated, using a fixed dumbbell weight (3 kg for female, 4 kg for male). The

movement was performed through a full range of motion (from 0° of extension to maximal possible flexion), without using momentum to move the weight. The total number of correctly executed repetitions was recorded as the final score.

Statistical analysis

We analyzed the data using Bayesian multilevel regression models. Time was treated as an ordered factor with three occasions (T0, T1, and T2), and the model used polynomial contrasts for this factor. Accordingly, the time effect was represented by two orthogonal components, a linear term and a quadratic term, rather than by pairwise comparisons against a single reference level. The main aim of the models was to evaluate whether the longitudinal association between platelet subtypes and the study outcomes changed over time, while adjusting for sex, age, and BMI. Participant-level heterogeneity was modelled through random intercepts. Because the same participants contributed repeated measurements, this random-intercept structure was used to account for within-person correlation across visits.

Let $i = 1, \ldots, N$ index participants and $t \in \{1,2,3\}$ index measurement occasions. Let

$$\mathbf{z}_{it} = \begin{pmatrix} P_{it}^{-} \\ P_{it}^{+} \\ \text{sex}_i \\ \text{age}_i \\ \text{BMI}_i \end{pmatrix},$$

where P_{it}^{-} denotes the standardised percentage of $CD41^{+}/CD62^{-}$ platelets and P_{it}^{+} denotes the standardized percentage of $CD41^{+}/CD62^{+}$ platelets. To represent the ordered time factor, let

$$\mathbf{c}_t = \begin{pmatrix} L_t \\ Q_t \end{pmatrix},$$

where L_t and Q_t are the linear and quadratic polynomial contrast scores for time, respectively. This notation keeps the model specification compact while preserving the structure of the fitted formulas. In all cases, time-by-covariate terms were included so that the association between platelet composition and the outcomes could vary across the longitudinal trajectory in its linear and quadratic components.

Frailty model

Frailty was analysed as a binomial outcome with four trials per observation, corresponding to the FRAIL questionnaire score ranging from 0 to 4. Let F_{it} denote the frailty score for participant i at time t. The model was specified as

$$F_{it} \sim \text{Binomial}(4, p_{it}),$$

with logit link

$$\text{logit}(p_{it}) = \eta_{it}^{(F)}.$$

The linear predictor was written as

$$\eta_{it}^{(F)} = \alpha_F + \mathbf{c}_t^{\top}\boldsymbol{\tau}_F + \mathbf{z}_{it}^{\top}\boldsymbol{\beta}_F + (\mathbf{c}_t \otimes \mathbf{z}_{it})^{\top}\boldsymbol{\Gamma}_F + u_i^{(F)},$$

where α_F is the intercept, $\boldsymbol{\tau}_F$ contains the linear and quadratic time effects, $\boldsymbol{\beta}_F$ contains the main effects of platelet percentages and covariates, and $\boldsymbol{\Gamma}_F$ contains the interactions between the time polynomial terms and the predictors. The term $u_i^{(F)} \sim \mathcal{N}(0, \sigma_F^2)$ is the participant-specific random intercept. This formulation implies that the association between each platelet subtype and frailty can differ not only over time in general, but specifically across the linear and quadratic

components of the ordered time factor. Because the platelet predictors were included through mi (), missing values were handled inside the model rather than by complete-case deletion, so uncertainty in those predictors was propagated into the frailty estimates.

Although the FRAIL questionnaire score has four ordered levels, it was modelled as a binomial count with four trials because the score is bounded between 0 and 4 and the brms formulation directly accommodates this structure. The resulting coefficients are interpreted on the log-odds scale. Exponentiating a coefficient gives an odds ratio associated with a one-unit increase in the predictor, holding the remaining covariates constant. The coefficients for the time contrasts represent the shape of change across the three measurement occasions: the linear term captures monotonic increase or decrease across time, and the quadratic term captures curvature. The interaction terms indicate whether that temporal pattern differs according to platelet subtype or covariate level.

Physical function model

Physical function was modelled in the same multivariate framework, but with four Gaussian outcomes. Let D_{it} denote standardised average HGS, S_{it} standardised CSTS performance, E_{it} standardised arm curl test performance, and T_{it} standardised TUG performance. The joint response was

$$\mathbf{Y}_{it}^{(F)} = \begin{pmatrix} D_{it} \\ S_{it} \\ E_{it} \\ T_{it} \end{pmatrix} \sim \mathcal{N}_4\left(\boldsymbol{\mu}_{it}^{(F)}, \boldsymbol{\Sigma}^{(F)}\right).$$

The corresponding linear predictor was

$$\boldsymbol{\mu}_{it}^{(F)} = \boldsymbol{\alpha}_F + \mathbf{B}_F\mathbf{z}_{it} + \mathbf{A}_F\mathbf{c}_t + \mathbf{G}_F(\mathbf{c}_t \otimes \mathbf{z}_{it}) + \mathbf{u}_i^{(F)}.$$

$\boldsymbol{\alpha}_F$ is a vector of intercepts, $\mathbf{B}_F$ contains the main effects, $\mathbf{A}_F$ contains the linear and quadratic effects of time, $\mathbf{G}_F$ contains the time-by-predictor interactions, and $\mathbf{u}_i^{(F)}$ denotes the participant-specific random intercepts. The covariance matrix $\boldsymbol{\Sigma}^{(F)}$ captures residual dependence among the four function outcomes after adjustment.

This multivariate specification is appropriate because the physical function tests are related but not identical aspects of performance. HGS, CSTS, arm curl test, and TUG may share common determinants, yet each outcome also retains outcome-specific variation. Joint modelling allows the estimated associations with platelet subtypes to be assessed simultaneously across all four outcomes, while preserving their correlation structure. In practice, this is preferable to running separate univariate models if the aim is to compare effect patterns across the functional domain and to obtain a coherent multivariate summary.

RESULTS

Sample characteristics

The study included 137 participants, of whom 42 (30.7%) were male, and 95 (69.3%) were female. The mean age of the sample was 70.4 ± 6.1 years, with no meaningful difference between sexes (70.9 ± 5.9 in males vs 70.2 ± 6.3 in females). Cardiometabolic conditions were common, with diabetes present in 32.8% of participants and hypertension and dyslipidemia each affecting 62.0% of the sample.

Anthropometric measures differed by sex. Males had lower BMI (29.1 ± 4.3 vs 31.9 ± 7.0 kg/m²). Body composition also showed marked differences, with males presenting lower total body fat

mass (24.6 ± 5.8% vs 40.3 ± 6.5%) and higher total muscle mass (56.2 ± 7.7 kg vs 41.3 ± 5.7 kg), appendicular muscle mass, skeletal muscle index, body water percentage, and bone mass.

Physical performance measures were consistently higher in males. HGS was 32.1 ± 5.3 kg in males and 21.2 ± 4.4 kg in females, and males also showed slightly higher repetitions in CSTS and arm curl tests. In contrast, females had longer TUG durations (6.4 ± 2.0 vs 5.2 ± 1.5 seconds), indicating lower mobility performance. Frailty distribution was skewed toward lower scores, with 53.7% of participants scoring 0 and fewer than 2% scoring 3, 4 or 5. Platelet subtype distributions were similar between sexes, with no clear differences in the relative proportions of $CD41^{+}/CD62^{-}$ and $CD41^{+}/CD62^{+}$ platelets. The complete sample characterization can be observed in **Table 1**.

Table 1. ***Sample description and sociodemographic characterization.*** *Data is presented as mean ± standard deviation for numerical variables, and absolute and relative frequency were used for discrete ones. The difference between males and females is based on a standardised mean difference with 95% confidence interval.*

Characteristic	**Overall** N = 137	**Male** N = 42	**Female** N = 95	**Difference**	**95% CI**
Age (years old)	70.4 ± 6.1	70.9 ± 5.9	70.2 ± 6.3	0.12	-0.25, 0.49
Diabetes (n)	45 (33%)	18 (43%)	27 (28%)		
Hypertension (n)	85 (62%)	29 (69%)	56 (59%)		
Dyslipidemia (n)	85 (62%)	29 (69%)	56 (59%)		
Systolic blood pressure (mmHg)	131.7 ± 16.8	134.9 ± 17.8	130.3 ± 16.3	0.27	-0.10, 0.64
Diastolic blood pressure (mmHg)	77.6 ± 10.7	81.0 ± 11.0	76.2 ± 10.4	0.45	0.07, 0.82
Mean arterial pressure (mmHg)	96.4 ± 11.4	99.2 ± 11.7	95.2 ± 11.1	0.35	-0.02, 0.72
Pulse pressure (mmHg)	54.0 ± 14.9	54.0 ± 15.2	54.1 ± 14.8	-0.01	-0.38, 0.36
Heart rate (bpm)	73.0 ± 12.9	72.5 ± 17.5	73.2 ± 10.4	-0.05	-0.42, 0.32
Weight (kg)	76.0 ± 15.5	79.6 ± 12.7	74.5 ± 16.4	0.35	-0.02, 0.73
Height (cm)	156.6 ± 9.2	165.3 ± 7.3	152.9 ± 7.2	1.7	1.3, 2.2
BMI (km/m²)	31.1 ± 6.4	29.1 ± 4.3	31.9 ± 7.0	-0.48	-0.85, -0.10
Total fat mass (%)	35.5 ± 9.5	24.6 ± 5.8	40.3 ± 6.5	-2.6	-3.0, -2.1
Total muscle mass (kg)	45.8 ± 9.3	56.2 ± 7.7	41.3 ± 5.7	2.2	1.8, 2.7
Appendicular muscle mass (kg)	20.6 ± 5.1	25.9 ± 4.1	18.3 ± 3.6	2.0	1.6, 2.5
Skeletal muscle index (km/m²)	8.3 ± 1.6	9.5 ± 1.2	7.8 ± 1.4	1.3	0.85, 1.7
Body water (%)	48.0 ± 6.9	56.0 ± 4.4	44.5 ± 4.4	2.6	2.2, 3.1
Bone mass (kg)	2.5 ± 0.5	3.0 ± 0.3	2.2 ± 0.3	2.4	1.9, 2.9
HGS - Average (kg)	24.5 ± 6.9	32.1 ± 5.3	21.2 ± 4.4	2.3	1.8, 2.8
HGS - Left hand (kg)	24.2 ± 7.2	32.0 ± 5.7	20.8 ± 4.6	2.2	1.7, 2.7
HGS - Right hand (kg)	24.8 ± 7.1	32.2 ± 5.8	21.5 ± 4.7	2.0	1.6, 2.5
Total FRAIL score				-0.24	-0.62, 0.13
0	72 (54%)	22 (55%)	50 (53%)		
1	39 (29%)	15 (38%)	24 (26%)		
2	21 (16%)	3 (7.5%)	18 (19%)		
3	1 (0.7%)	0 (0%)	1 (1.1%)		
4	1 (0.7%)	0 (0%)	1 (1.1%)		
5	0 (0%)	0 (0%)	0 (0%)		
Chair sit-to-stand (reps)	15.2 ± 4.9	16.5 ± 5.0	14.7 ± 4.8	0.36	-0.02, 0.74
Elbow flexion test (reps)	17.7 ± 4.5	18.7 ± 4.7	17.3 ± 4.3	0.33	-0.05, 0.71
Timed-up and Go (seconds)	6.0 ± 2.0	5.2 ± 1.5	6.4 ± 2.0	-0.70	-1.1, -0.31
$CD41^{-}CD62^{-}$ (%)	10.3 ± 12.3	13.1 ± 18.7	9.2 ± 8.6	0.28	-0.20, 0.75
$CD41^{-}CD62^{+}$ (%)	0.2 ± 0.3	0.3 ± 0.3	0.2 ± 0.3	0.15	-0.32, 0.63
$CD41^{+}CD62^{-}$ (%)	68.9 ± 17.8	64.9 ± 22.9	70.5 ± 15.4	-0.29	-0.77, 0.18
$CD41^{+}CD62^{+}$ (%)	20.6 ± 13.4	21.8 ± 16.9	20.2 ± 11.9	0.11	-0.36, 0.59

Frailty model

In the frailty model, the strongest and most consistent association was with BMI. The coefficient for standardized BMI was positive and clearly different from zero (β = 0.48, $CI_{95\%}$[0.25, 0.7], pd = 100%, ps = 99.9%), indicating higher frailty scores at higher BMI after adjustment for time,

sex, age, and platelet subtypes. Age showed a smaller positive association, compatible with a modest effect, although the interval approached the null (β = 0.24, $CI_{95\%}$[-0.01, 0.48], pd = 97.5%, ps = 87.1%). Sex was not clearly associated with frailty (β = 0.25, $CI_{95\%}$[-0.3, 0.81], pd = 81.2%, ps = 70.6%). The polynomial time terms did not provide strong evidence of a trend in frailty across visits (β = -0.36, $CI_{95\%}$[-1.17, 0.44], pd = 81.1%, ps = 74%). The interaction terms between time and sex, age, or BMI also indicated no clear effect modification, as all intervals spanned zero with low posterior probability.

For the platelet predictors, there was mild evidence that platelet subtype was associated with frailty at the reference time structure of the model. The main effect of the $CD41^{+}/CD62^{-}$ percentage was negative, suggesting that higher proportions of this platelet subtype were associated with lower frailty scores; however, these effects were uncertain (β = -0.19, $CI_{95\%}$[-0.65, 0.28], pd = 79.4%, ps = 64.9%). On the contrary, the corresponding effect from $CD41^{+}/CD62^{+}$ subtype on frailty scores was essentially null (β = 0.01, $CI_{95\%}$[-0.35, 0.36], pd = 51.9%, ps = 30.2%) **(Figure 1A)**. Likewise, the time-by-platelet interactions were imprecise for $CD41^{+}/CD62^{-}$ subtypes for linear interaction effects (β = 0.36, $CI_{95\%}$[-0.33, 1.04], pd = 85.5%, ps = 77.9%). Similar findings were observed for $CD41^{+}/CD62^{+}$ (β = 0.29, $CI_{95\%}$[-0.25, 0.84], pd = 84.8%, ps = 75.2%). Taken together, the estimates from this model suggest that the effect of platelet subtype on frailty scores was relatively constant over time (i.e., no time-by-platelet interaction). In contrast, the $CD41^{+}/CD62^{-}$ platelet subtype was deemed protective against frailty. However, these effects are based on uncertain estimates and should be regarded as suggestive trends rather than definitive evidence of a mechanistic link.

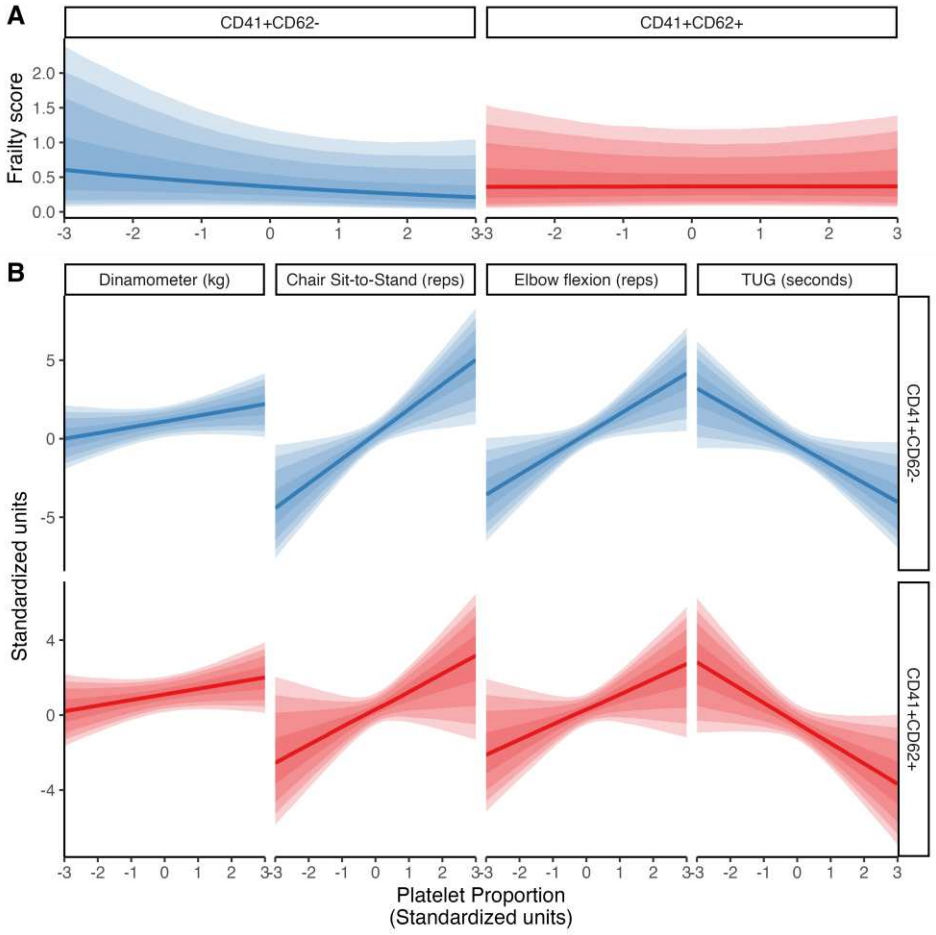


Figure 1. Model-derived estimates of the effect of platelet subtypes on frailty score and physical function measures. A. Blue (left) figure shows the negative association between the CD41+CD62- and frailty scores, while red (right) figure shows no association between CD41+CD62+ platelets **B.** Shows the associations between CD41+CD62- (blue) and

CD41+CD62+ (red) and each physical outcome. Model-based estimates are displayed as median and quantile-based credible intervals (95% for the outside envelope, 90%, 80%, and 50% for inner envelope) computed from the posterior distribution of model estimates. All effects are adjusted for confounding factors.

The platelet submodels, however, did show a clear temporal pattern. The percentage of $CD41^{+}/CD62^{-}$ platelets declined over time, with both the linear and quadratic terms strongly negative (linear effect, β = -0.96, $CI_{95\%}$[-1.13, -0.79], pd = 100%, ps = 100%; quadratic effect, β = -0.48, $CI_{95\%}$[-0.65, -0.3], pd = 100%, ps = 100%). The $CD41^{+}/CD62^{+}$ percentage also tended to decrease, though more modestly **(Figure 2)** (β = -0.24, $CI_{95\%}$[-0.45, -0.02], pd = 98.7%, ps = 91.1%). Thus, the main temporal signal in the frailty model was not a strong outcome change in frailty itself, but a downward trend in platelet composition over follow-up.

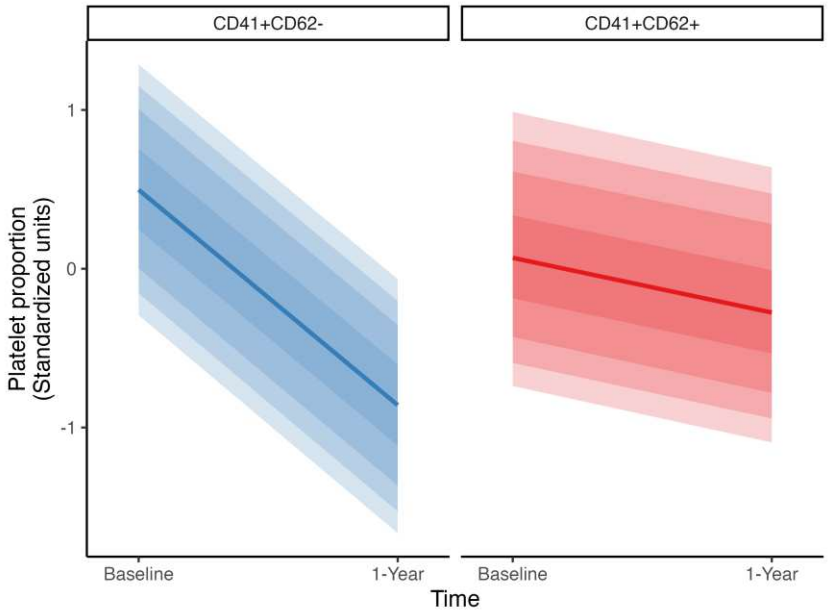


Figure 2. Temporal dynamics of platelet subtypes proportions over a 1-year evolution. Decline of CD41+CD62- (blue, left) and CD41+CD62+ (red, right) platelet subtypes is shown in standardized units. Model-based estimates are displayed as median and quantile-based credible intervals (95% for the outside envelope, 90%, 80%, and 50% for inner envelope) computed from the posterior distribution of model estimates. All effects are adjusted for confounding factors.

Physical function model

Main findings are shown in figure 1B. The physical-function model showed the clearest set of associations with platelet subtype, especially for the $CD41^{+}/CD62^{+}$ percentage. Females demonstrated lower HGS than male (β = -1.52, $CI_{95\%}$[-1.76, -1.27], pd = 100%, ps = 100%), and age was also associated with lower average HGS values (β = -0.12, $CI_{95\%}$[-0.23, -0.01], pd = 98.5%, ps = 66.7%). The time terms for HGS were not clearly different from zero (β = 0.28, $CI_{95\%}$[-0.33, 0.87], pd = 83.8%, ps = 74%). Importantly, a small effect was observed for platelets subtypes, suggesting that higher proportions in both phenotypes were linked with greater HGS levels ($CD41^{+}/CD62^{-}$, β = 0.37, $CI_{95\%}$[-0.28, 0.89], pd = 89.4%, ps = 82.5%; $CD41^{+}/CD62^{+}$, β = 0.3, $CI_{95\%}$[-0.24, 0.85], pd = 87.4%, ps = 78.2%). By contrast, CSTS performance and arm curl test showed positive associations with the $CD41^{+}/CD62^{+}$ subtype. For CSTS, higher $CD41^{+}/CD62^{-}$ was indicative of better performance (β = 1.57 $CI_{95\%}$[0.32, 2.69], pd = 98.9%, ps = 98.4%), and the interaction with the linear time contrast was also positive (β = 0.29, $CI_{95\%}$[0, 0.58], pd = 97.5%, ps = 90%), suggesting that as time goes by, the effect of $CD41^{+}/CD62^{-}$ on CSTS performance further increases. The $CD41^{+}/CD62^{+}$ subtype showed a similar effect association, although more uncertain, with the same outcome (β = 0.96, $CI_{95\%}$[-0.46, 2.08], pd =

91.6%, ps = 89.4%), although its linear interaction was also positive (β = 0.2, $CI_{95\%}$[0, 0.42], pd = 97.3%, ps = 82.6%). For elbow flexion, the $CD41^+/CD62^+$ term was again positive (β = 1.28, $CI_{95\%}$[0.19, 2.31], pd = 98.1%, ps = 97.5%), with a suggestive but less definitive linear interaction (β = 0.26, $CI_{95\%}$[-0.06, 0.59], pd = 93.4%, ps = 82.4%).

TUG showed the opposite direction. The main effects of the platelet subtype were negative ($CD41^+/CD62^+$, β = -1.21, $CI_{95\%}$[-2.2, -0.06], pd = 97.3%, ps = 96.4%; $CD41^+/CD62^-$, β = -1.08, $CI_{95\%}$[-2.18, 0.09], pd = 96.3%, ps = 94.9%). Because the TUG outcome is measured in seconds, lower values indicate better performance, so these estimates are consistent with better mobility at higher platelet percentages, particularly for the $CD41^+/CD62^+$ subtype. The time interaction terms for TUG were not clearly different from zero ($CD41^+/CD62^-$, β = -0.04, $CI_{95\%}$[-0.32, 0.25], pd = 61.5%, ps = 34.3%; $CD41^+/CD62^+$, β = -0.03, $CI_{95\%}$[-0.24, 0.17], pd = 61.7%, ps = 24.8%). The direct time effects for the function outcomes were also informative: CSTS and arm curl increased over time (CSTS, β = 1.76, $CI_{95\%}$[0.66, 2.83], pd = 99.8%, ps = 99.7%; arm curl test, β = 2.03, $CI_{95\%}$[1.05, 3.09], pd = 99.9%, ps = 99.9%), whereas TUG times declined (β = -1.14, $CI_{95\%}$[-2.14, -0.12], pd = 98.2%, ps = 97.5%). Finally, the residual correlations were substantial across the functional tests, especially between CSTS arm curl (β = 0.86, $CI_{95\%}$[0.62, 0.96], pd = 100%, ps = 99.9%), and strongly negative between TUG and the strength/endurance measures (HGS - TUG, r = -0.6, $CI_{95\%}$[-0.84, -0.23], pd = 99.4%, ps = 98.6%; CSTS-TUG, r = -0.82, $CI_{95\%}$[-0.95, -0.55], pd = 99.9%, ps = 99.9 arm curl - TUG, r = -0.77, $CI_{95\%}$[-0.93, -0.42], pd = 99.9%, ps = 99.7%). These residual associations support the multivariate specification and indicate that the function outcomes shared substantial unexplained variation.

DISCUSSION

This longitudinal study examined the association between platelet activation phenotypes, frailty, and physical function in older adults living at high southern latitudes. Three main findings emerged. First, platelet phenotype distributions changed over time, particularly through a marked decline in the CD41+/CD62− platelet population. Second, associations between platelet phenotypes and frailty were modest and uncertain, whereas frailty scores remained relatively stable or showed slight improvement across follow-up. Third, platelet phenotypes, especially CD41+/CD62+ and CD41+/CD62− populations, were more consistently associated with physical function outcomes, including strength, lower-limb performance, upper-limb endurance, and mobility.

These findings suggest that platelet phenotypes may provide relevant biological insights into functional aging. However, rather than indicating a direct causal role of platelet subtypes in frailty or physical function, the results should be interpreted as evidence that platelet activation profiles may reflect systemic biological conditions related to physiological reserve, inflammatory aging, vascular regulation, and functional capacity in older adults.

Platelet phenotypes and frailty

Previous studies have suggested that platelet hyperactivation may increase with age and may contribute to frailty-related biological processes (Hernández et al., 2019; Vismara et al., 2025). In this context, platelet activation has been proposed as part of the broader inflammatory and immunothrombotic changes associated with aging (Price et al., 2020; Sanada et al., 2018).In the present study, however, the associations between platelet phenotypes and frailty were modest. The CD41+/CD62− phenotype showed a tendency toward an inverse association with frailty, suggesting that a higher proportion of resting platelets may be compatible with a more preserved physiological profile. Nevertheless, this association was uncertain and should not be interpreted as definitive evidence of a protective effect.

One possible explanation is that the cohort was relatively old but not highly frail. Most participants showed low FRAIL scores, which may have restricted the variability needed to detect stronger associations between platelet activation and frailty burden. Therefore, the present findings may be more informative for understanding early or subtle biological changes in

functional aging than for explaining advanced frailty. Future studies should include participants with a broader frailty spectrum, including robust, pre-frail, and frail older adults, to determine whether the inverse association between CD41+/CD62− platelets and frailty is maintained across different stages of aging-related vulnerability.

Longitudinal changes in platelet phenotypes

A relevant finding of this study was the longitudinal decline in the CD41+/CD62− platelet population. This phenotype is commonly interpreted as representing resting or non-activated platelets, whereas CD41+/CD62+ platelets reflect an activated phenotype characterized by P-selectin surface expression. P-selectin, also known as CD62P, is translocated from platelet α-granules to the platelet surface after activation and supports platelet–platelet and platelet–leukocyte interactions (André, 2004; Merten & Thiagarajan, 2000). Therefore, the more pronounced decline in the resting platelet phenotype may indicate a progressive shift in platelet biology over time, potentially reflecting increased platelet activation, altered platelet turnover, or a change in the balance between platelet production and clearance.

This observation is consistent with previous evidence showing that platelet biology changes with aging. Although platelet count may remain relatively stable until midlife, it tends to decline in older age, while platelet reactivity may increase (Balduini & Noris, 2014; Johnson et al., 1975; Jones, 2016; Montenont et al., 2019). Aging is also associated with chronic low-grade inflammation, changes in megakaryocyte biology, mitochondrial dysfunction, and altered platelet lifespan (Davizon-Castillo et al., 2019; Esparza et al., 2020; Ramos-Costa et al., 2025). These processes may contribute to the production of more reactive platelets and to a reduction in the circulating pool of functionally competent resting platelets.

Mechanistically, age-related changes in the bone marrow may contribute to this pattern. With aging, the proportion of hematopoietic tissue declines, reducing the capacity for progenitor cell self-renewal, proliferation, and differentiation into mature blood cell lineages (Karnik et al., 2023; Prabhakar et al., 2009). At the same time, chronic inflammation may alter megakaryocyte function and promote the generation of platelets with a more inflammatory and reactive profile (Davizon-Castillo et al., 2019; Esparza et al., 2020). In addition, older platelets may show reduced expression of anti-apoptotic proteins, activation of pro-apoptotic pathways, and increased clearance, which may affect platelet quality independently of total platelet count (Anjum et al., 2025; Hamad et al., 2022; Reusswig et al., 2024).

Additionally, atherosclerotic processes may contribute to platelet activation in older adults. Interactions between circulating platelets and disrupted atherosclerotic lesions may increase P-selectin surface expression and generate a more reactive platelet phenotype (Reusswig et al., 2024). This could partly explain why the resting CD41+/CD62− phenotype declined more prominently than the activated CD41+/CD62+ phenotype over time. However, these mechanisms were not directly tested in the present study. Therefore, the observed decrease in CD41+/CD62− platelets should be interpreted as a longitudinal biological signal that requires further mechanistic validation using platelet function assays, inflammatory biomarkers, and molecular markers of platelet activation.

Platelet phenotypes and physical function

The most consistent findings of this study were observed for physical function. Higher proportions of platelet phenotypes were TUG. These results suggest that platelet phenotype composition may be more closely related to physical performance than to frailty burden in this relatively non-frail cohort.

The association between platelet phenotypes and physical performance may reflect several biological processes. Platelets are not only involved in hemostasis and thrombosis but also participate in inflammation, vascular regulation, immune signaling, and tissue repair (Eriksson et al., 2019; Franco et al., 2015; Maouia et al., 2020; Sonmez & Sonmez, 2017). Upon activation,

platelets release growth factors, cytokines, and other bioactive molecules stored in α-granules, which may influence endothelial function, muscle repair, and local regenerative processes (Scully et al., 2018). This biological role has contributed to growing interest in platelet-rich plasma and platelet-derived factors in musculoskeletal repair and regenerative medicine (Halpern et al., 2012; Zhou et al., 2025).

Nevertheless, the present findings should be interpreted with caution. The positive association between CD41+/CD62+ platelets and better physical function does not necessarily imply that platelet activation directly improves strength or mobility. Instead, activated platelet phenotypes may act as systemic biomarkers of biological activity related to repair, vascular responsiveness, or physiological reserve. In other words, platelet phenotypes may reflect the biological state of individuals who maintain better physical function, rather than being the direct cause of better performance. This interpretation is particularly relevant because platelet activation can have both adaptive and maladaptive implications. In some contexts, platelet activation may participate in tissue repair and immune regulation, whereas in others it may reflect inflammation, endothelial dysfunction, or increased thrombotic risk (De Simone et al., 2023; Price et al., 2020; Sonmez & Sonmez, 2017). Therefore, the clinical significance of CD41+/CD62+ platelets in aging should be interpreted within the broader physiological context, including comorbidities, medication use, inflammatory status, and functional reserve.

Potential biological interpretation

Taken together, the findings support a possible dual-profile interpretation of platelet phenotypes in aging. The CD41+/CD62− phenotype may reflect a more quiescent or preserved platelet state, potentially associated with a lower frailty burden or greater biological stability. In contrast, the CD41+/CD62+ phenotype may reflect platelet activation processes that are more closely associated with functional performance, possibly through mechanisms related to tissue repair, vascular function, or systemic physiological responsiveness. However, this dual-profile model should be considered exploratory. The present study did not include direct measurements of platelet aggregation, platelet signaling pathways, inflammatory cytokines, oxidative stress, endothelial function, or muscle biomarkers. Therefore, it is not possible to determine whether the observed platelet phenotypes represent beneficial physiological reserve, compensatory activation, or early immunothrombotic dysregulation.

Future studies should incorporate molecular and functional platelet assessments, including platelet aggregation assays in response to agonists such as ADP or thrombin, as well as response to antiplatelet agents such as aspirin. In addition, analysis of signaling proteins associated with platelet activation, including p-PKC and p-p38, could help determine whether platelet phenotype changes are linked to measurable intracellular signaling pathways. These approaches would strengthen the mechanistic interpretation of the observed associations among platelet activation, frailty, and physical function (Hernández et al., 2019).

High southern latitude context

An important feature of this study is that participants were older adults living in the extreme south of Chile, a region at high southern latitude characterized by marked seasonality, a cold climate, photoperiod variation, and geographic isolation. This context is relevant for aging research because environmental and seasonal conditions may influence physical activity, inflammatory status, vascular regulation, mood, sleep, and functional trajectories in older adults (Arauna et al., 2020; Mabe-Castro et al., 2024; Méndez Muñoz et al., 2026).

However, the present study did not directly measure environmental exposures such as ambient temperature, daylight duration, vitamin D status, physical activity patterns, sleep, or seasonal behavior. Therefore, the high-latitude setting should be interpreted as an ecologically distinctive context rather than as a demonstrated causal mechanism. Future studies should integrate platelet phenotyping with environmental, behavioral, and exposomic variables to determine whether high-latitude conditions modulate platelet activation, inflammatory aging, and functional decline. This

approach could be particularly valuable for understanding aging in geographically underrepresented populations and for identifying biomarkers sensitive to both biological aging and environmental context.

Strengths and limitations

Several limitations should also be acknowledged. First, the cohort was relatively non-frail, which may have reduced the ability to detect stronger associations between platelet phenotypes and frailty. Second, medication use, particularly antiplatelet therapy, anticoagulants, anti-inflammatory drugs, and statins, was not fully incorporated into the primary models. This is especially relevant because these medications may influence platelet activation and function, particularly in older adults with multimorbidity (Crickx et al., 2023). Third, even though comorbidities such as diabetes, hypertension, dyslipidemia, and cardiovascular disease may affect platelet biology and physical function were not included in the statistical models. Fourth, the study did not include platelet aggregation assays, inflammatory biomarkers, endothelial markers, or molecular signaling analyses, limiting mechanistic interpretation. Fifth, environmental exposures related to the high-latitude context were not directly measured. Finally, because this was an observational study, causal inferences cannot be established.

This study has several strengths. First, it used a longitudinal repeated-measures design, allowing within-participant changes in platelet phenotypes, frailty, and physical function to be examined over time. Second, it focused on older adults living at high southern latitudes, a population and context that remain underrepresented in aging and platelet biology research. Third, the study integrated platelet phenotyping with clinically interpretable outcomes, including frailty and standardized physical function tests. Fourth, the use of Bayesian multilevel models allowed the repeated-measures structure of the data to be considered while quantifying uncertainty in the estimated associations.

Future directions

Our findings shape new opportunities into individualized biomarker-based predictions. We argue that a potentially promising way to further interpret our results is by predicting individual functional and frailty trajectories based on platelet phenotyping. Since we observed a linear decreasing trend in frailty despite progressive decline in platelet subtypes over time, and that the decrease of $CD62^-$ phenotype over time results in a decline in physical performance, these findings suggest a potential protective role of the $CD62^-$ subtype. However, as these observations are restricted to the age window effectively measured in this study, we hypothesize that once protective effects of the $CD62^-$ are diminished by aging, the trajectory may shift, potentially leading to a change in the observed pattern by extrapolating the obtained data (**Figure 3)**.

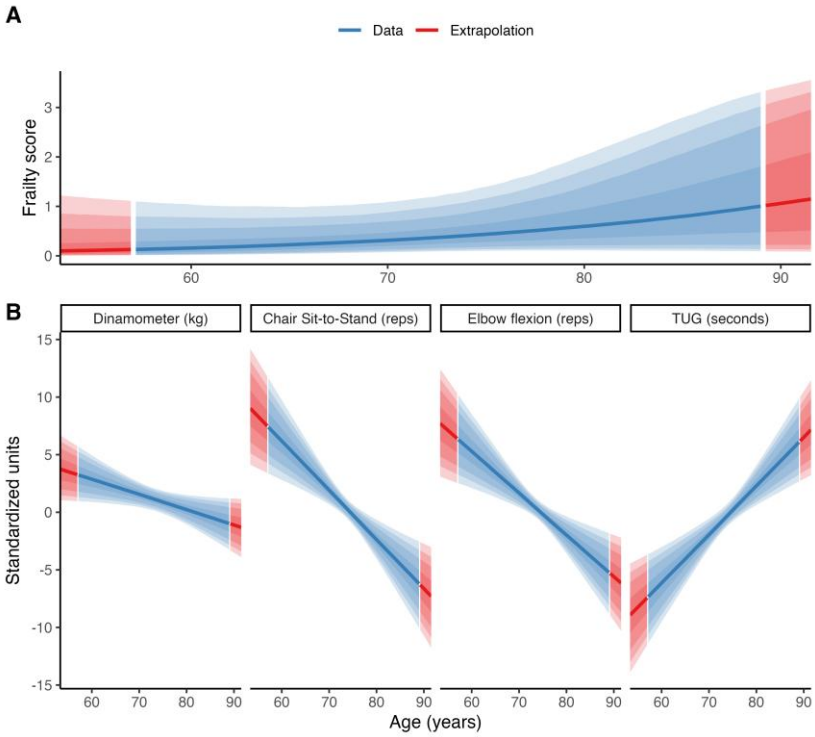


Figure 3. Model-derived estimates of frailty scores and physical function measures dependent on chronological age and platelet temporal dynamics. Predictions are computed for the age window supported by the data (blue) and predicted (red) estimates from the model for frailty scores (**A**) and physical function measures (**B**). Predicted dynamics are based on the assumption of a continuous temporal decline of platelet proportions as age increases. Model effects are displayed as median and quantile-based credible intervals (95% for the outside envelope, 90%, 80%, and 50% for inner envelope) computed from the posterior distribution of model estimates. All effects are adjusted for confounding factors.

Future studies should confirm these findings in larger, more frail cohorts and integrate medication data, platelet function assays, inflammatory biomarkers, and environmental exposure measures to clarify the mechanisms underlying these associations. The inclusion of adults over 75 or 80 years could help determine whether platelet phenotype associations become stronger in populations with greater frailty burden and multimorbidity. However, this approach will require careful control for comorbidities and medication use, particularly antiplatelet and anticoagulant therapies, which are highly prevalent in advanced age (Crickx et al., 2023). Future studies should also incorporate functional platelet assays, inflammatory biomarkers, oxidative stress markers, endothelial function measures, and molecular signaling pathways involved in platelet activation. In addition, integrating environmental and behavioral variables, such as seasonality, photoperiod, cold exposure, sleep, physical activity, and vitamin D status, would help clarify whether the high-latitude environment influences platelet activation and functional aging trajectories.

Conclusion

In conclusion, this longitudinal study suggests that platelet activation phenotypes are associated with functional aging profiles in older adults living at high southern latitudes. While associations with frailty were modest and uncertain, platelet phenotypes showed more consistent relationships with physical performance, particularly lower-limb function, upper-limb endurance, and mobility. These findings support the potential role of platelet phenotyping as a biomarker framework for studying physiological reserve and functional aging.

Rather than indicating that platelet subtypes directly cause changes in frailty or physical performance, the present results suggest that platelet activation profiles may reflect systemic

biological conditions related to inflammatory aging, vascular regulation, tissue repair, and functional capacity.

Declarations

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of the University of Magallanes (N°008/SH/2022)

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Competing interests

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

Author Contributions

Conceptualization: A.U-O., M.C-A., D.M-C., C.N-E; Data curation, A.U-O., M.C-A., D.M-C., C.N-E; Investigation, A.U-O., M.C-A., C.N-E.; Methodology, A.U-O., M.C-A., A.C.S., C.N-E; Supervision, A.U-O., M.C-A., C.N-E.; Formal analysis, A.U-O., M.C-A.; Visualization, A.U-O., C.N-E.; Writing–original draft, A.U-O., M.C-A., R.M.M., D.M-C., A.C.S., P.D-F., J. H-M., P.V-B., C.N-E.; Writing–review & editing, A.U-O., M.C-A., R.M.M., D.M-C., A.C.S., P.D-F., J. H-M., P.V-B., C.N-E. All authors have read and agreed to the published version of the manuscript.

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