Frailty phenotypes, gene expression and association with perioperative/interventional complications in elderly cardiac patients

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Background

Phenotypes of physical frailty are associated with worse prognosis. The specific pathophysiological pathways are not yet clearly understood. Transcriptomic analysis on skeletal muscle of frail patients can provide information on the pathophysiological process underscoring common phenotypes of frailty.

Purpose:

Determination of gene expression levels in frailty phenotypes associated with perioperative/interventional complications in older cardiac patients undergoing surgery (e.g. coronary artery bypass graft) or transcatheter aortic valve implantation (TAVI).

Methods

Patients included: ≥ 70 year of age referred for elective cardiac surgery or TAVI (from 06/'21 to 07/'22)

Phenotypes of frailty (assessed once at hospital admission):

Physical frailty: Timed Up-and-Go (TUG), 5-meters Walk Test (5-mWT), handgrip strength (dynamometer)

Nutritional frailty: Mini Nutritional Assessment-short from (MNA-sf)

Cognitive frailty: Mini Mental State Examination (MMSE)

Muscle sample: M. quadriceps femoris (during surgery/intervention)

Outcomes: perioperative complications (mortality and major morbidity e.g. need of transfusion, delirium)

Statistical analysis: regression analyses (Logistic: association of frailty phenotypes and complications; Linear: correlation of gene expression levels and frailty phenotypes) both adjusted (age, sex, num. of comorbidities, estimated glomerular filtration rate). Gene expression analysis was performed by DESeq2 (adjusted: age, sex, num. of comorbidities, estimated glomerular filtration rate).

Results

In total n= 63 patients (mean 77.6 ± 4.3 years); 74.6% male) were included. Of these, n= 37 patients (59%) experienced ≥ 1 complication: surgery n= 28 (82.4%) and TAVI n= 9 (31.0%); one patient died.

Physical frailty (Tab. 1) was associated with perioperative complications (TUG: odds ratio (OR) 1.33 per 1 sec, 95% confidence interval (CI) 1.02-1.75), particularly in TAVI patients. Nutritional (MNA-sf: OR per -1 pt. 0.91, 95% CI 0.63-1.31) or cognitive frailty (MMSE: OR per -1 pt. 0.95, 95% CI 0.63-1.44) were not associated.

Physically frail patients are characterized by overlapping parameters of frailty (Fig. 1), which are associated with altered gene expression patterns (Fig. 2). Notably, the expression of genes associated with muscular physiological functions correlates with impaired mobility (Fig. 3).

Tab. 1 Characteristic of frailty phenotypes

Frailty phenotypes and assessments	Surgery n= 34 (54%)		TAVI n= 29 (46%)	
Physical frailty	Mean	SD	Mean	SD
TUG (sec) n= 61	10.82	3.37	14.89	5.19
Moderate impaired mobility [≥ 10 sec; n (%)]	18 (54.5)		20 (71.4)	
Severe impaired mobility [≥ 20 sec; n (%)]	None		5 (17.9)	
5-mWT (sec) n= 62	5.32	1.65	6.40	2.85
Low gait speed [≥ 6 sec; n (%)]	8 (24.2)		11 (37.9)	
Handgrip (kg) n= 63	30.45	9.40	26.73	8.17
Low handgrip [≤ 27 kg ♂; ≤ 16 kg ♀; n (%)]	7 (20.6)		12 (41.4)	
Nutritional frailty				
MNA-sf (score 0-14) n= 63	12.9	1.7	12.3	2.8
Risk of malnutrition [≤ 12 pts; n (%)]	8 (23.5)		9 (31.0)	
Cognitive frailty				
MMSE (score 0-30) n= 62	26.5	2.9	26.5	2.5
Moderate-severe dementia [≤ 27 pts; n (%)]	17 (51.5)		16 (55.2)	

TAVI: transchateter aortic valve implantation; 5-mWT: 5 meter Walk Test; TUG: Timed Up-and-Go test; MNA-sf: Mini Nutritional Assessment-short form; MMSE: Mini Mental State Examination; SD: standard deviation
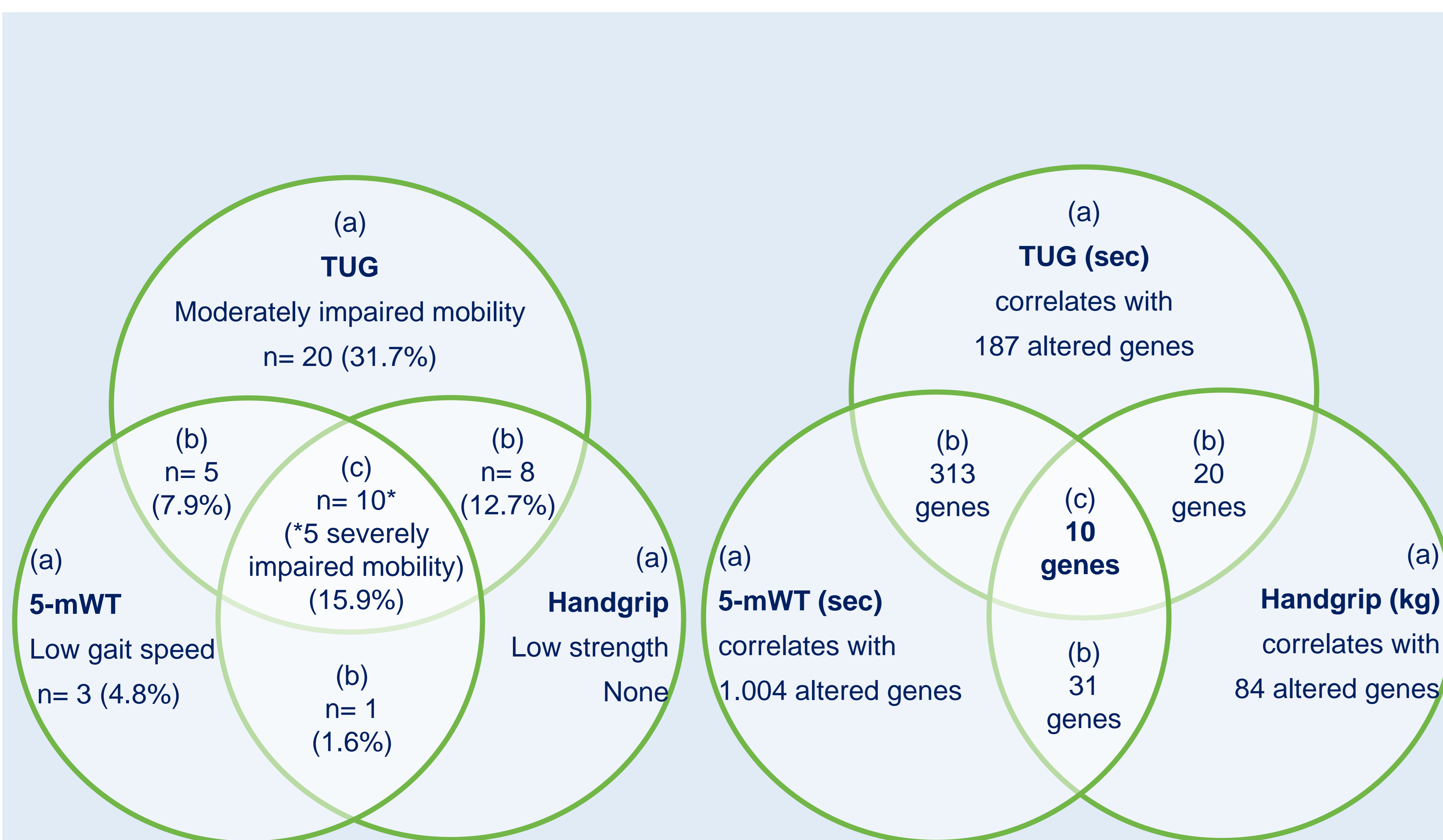

Fig. 1 The circles (a) outline surgery and TAVI patients (n) characterized by only one parameter of physical frailty. The intersections (b) represent patients with 2 overlapping frailty parameters while the central intersection (c) shows patients with 3.

Fig. 2 Number of genes with altered expression levels (upregulation or downregulation) that correlate significantly with the absolute values of the physical frailty parameters (circles, a) in surgical and TAVI patients. Intersections (b) show genes altered in 2 parameters and the central intersection (c) shows the number of genes simultaneously altered in the 3 frailty parameters.
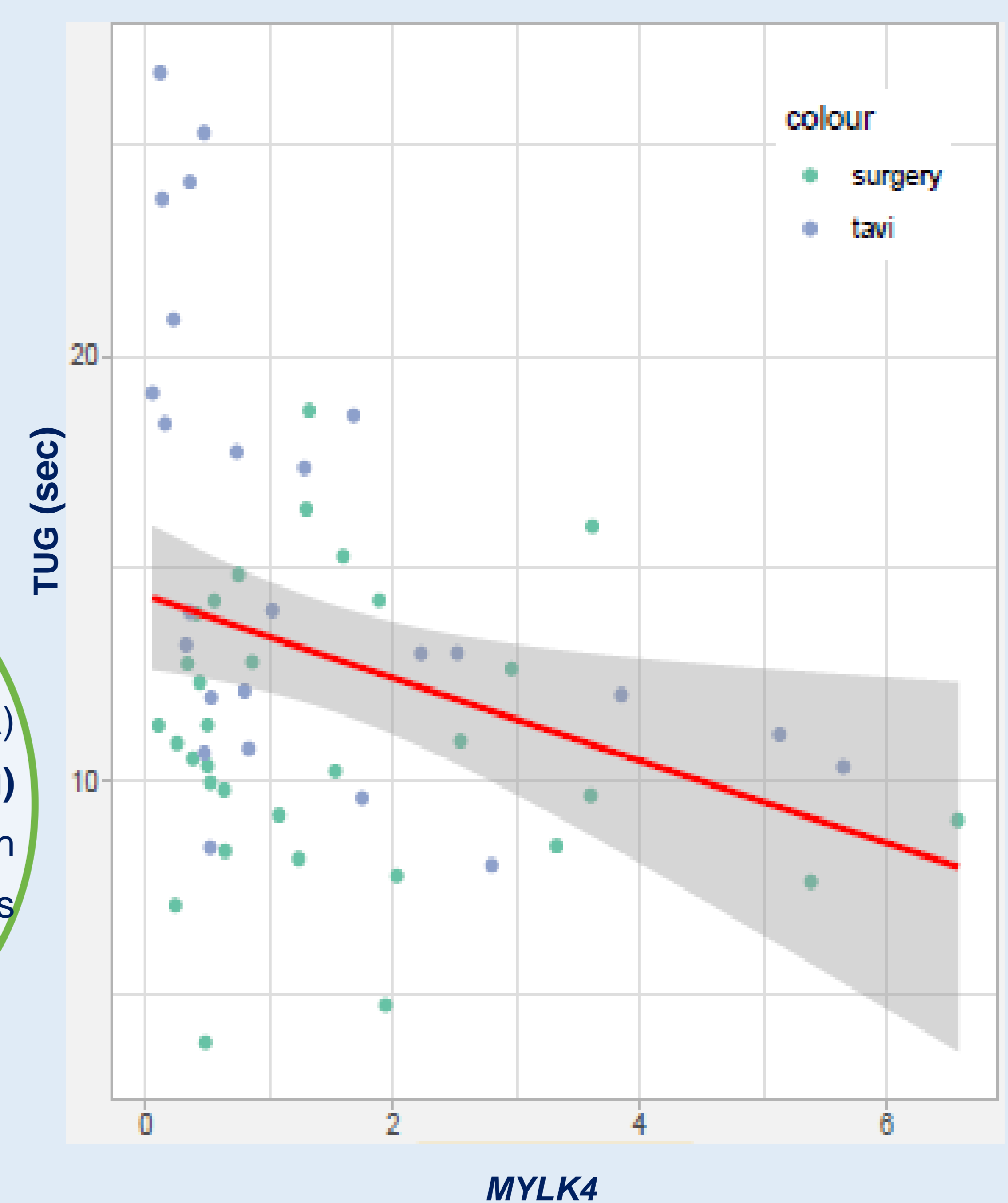
Fig. 3 The expression of the gene MYLK4 (associated with neuromuscular function and up-regulated by exercise) is inversely correlated with moderate or severe mobility impairment (R^2 0.327; R^2_{adj} 0.246; p= 0.037) in surgery and TAVI patients.

Conclusions

Dysregulation of genetic determinants underscores physical frailty, while moderate to severe limited mobility in particular is associated with perioperative/interventional complications in elderly TAVI patients.

Implications for future research

The detection of corresponding biomarkers (e.g. in plasma) could improve the accuracy of detection of physical frailty phenotypes associated with complications in elderly patients.