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In the Emergency Department, Are Serum Biomarkers useful to Screen Independent Frail Seniors Exposed to Future Functional Decline or Mobility Impairments after a Minor Injury?

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Abstract

Background: Frailty is a geriatric syndrome conferring a high risk of declining functional capacities. Some serum biomarkers are associated with frailty, but no study has specifically investigated the possible association between frailty and serum biomarkers in independent community-dwelling seniors who consulted the emergency department (ED) following a minor injury.

Objective: 1) To explore baseline associations between six serum biomarkers and the frailty status of independent community-dwelling seniors who were seen in the ED for minor injuries, 2) to determine if ED serum biomarker assay combined with frailty status improves the prediction of 3-month functional decline or mobility impairments in this population, beyond frailty status alone.

Methods: The study includes 190 participants (age ≥ 65 years, independent in daily activities and discharged home). Biomarkers were obtained at baseline from blood samples and values were identified as "normal" or "at risk". Seniors were classified as "robust" or "pre-frail/frail" according to the CHSA-CFS and SOF scales. The seniors were screened for frailty at baseline (ED visit) while their functional status (OARS scale) and mobility characteristics (less than 5 outings/week and fear of falling) were assessed at the ED visit and three months later.

Results: When compared to robust, a greater proportion of pre-frail/frail seniors had at-risk creatinine levels (p=0.02) at baseline. All the other biomarkers were not significant. In the prospective analysis, we found that having at least one at-risk biomarker slightly increased the prediction of 3-month mobility impairments in robust seniors (RR:0.44[0.10-1.91]). However, ED frailty status clearly remained the stronger predictor of future mobility impairments in pre-frail/frails having normal biomarkers (RR:3.11(0.98-9.84), p=0.007). Results were not significant for prospective functional decline.

Conclusion: ED biomarker assays are not useful in predicting 3-month functional decline or mobility impairments beyond what is predicted by frailty status alone in independent community-dwelling seniors who consulted for minor injuries.

Keywords: Frailty; Serum biomarkers; Emergency department; Minor injury; Functional decline; Mobility decline; Seniors

Introduction

Frailty is a multidimensional geriatric syndrome characterized by a state of increased vulnerability [1]. It is the result of cumulative deficits of multiple physiologic systems and is associated with reduced capacities to maintain homeostasis in older persons [2]. It was found that frail seniors have a lack of resilience to physical, physiological or psychological stressors, putting them at risk of decreased physical functions that can lead to mobility decline [3].

Frailty-induced mobility decline has recently been observed among seniors presenting to emergency departments (ED) with minor injuries [4,5]. Several studies have shown that nearly 15% of previously independent seniors consulting in EDs for a minor injury experience mobility decline six months after the event [6-8]. In this injured older population, frailty and its correlates were found to be important risk factors for post-injury mobility decline and functional impairment [3,8-11].

The physiology behind frailty is not well defined but is likely to include dysregulation in multiple physiological processes such as hormonal dysregulation or a pro-inflammatory state, which can be assessed with serum biomarkers. Consequently, considerable research

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efforts have been directed towards the development and validation of biomarkers for frail patients [12-14]. Some of the most investigated biomarkers in relation to frailty in seniors are interleukin-6 (IL-6) and C-reactive-protein (CRP) [15-17] (related to inflammatory response), albumin [15,18] (nutritional parameters and liver function], insulin-growth factor (IGF-1) [19] and Vitamin D 25-OH [20] (muscle regulation) as well as glucose [21].

We have previously reported that measuring frailty with simple clinical tools can help ED physicians identify independent seniors at risk of functional decline after minor injuries [11]. To our knowledge, no study has investigated the relationship between biomarkers and frailty status among community-dwelling seniors with minor injuries seen in the ED. Furthermore, identifying specific biomarkers in frail seniors who sustained minor injuries could help improve the clinical detection of those at risk of future functional decline or mobility impairments after the ED visit.

Therefore, the specific aims of this study were: 1) to explore the baseline association between six serum biomarkers' clinical threshold values and the frailty status of independent community-dwelling seniors with minor injuries seen in ED, 2) to determine if ED serum biomarker assay combined with frailty status improves the prediction of 3-month functional or mobility impairments in this population, beyond frailty status alone.

Methods

Design and participants

This is a planned sub-study of the Canadian Emergency Team Initiative (CETI) prospective cohort study [8], which includes data collected between October 2013 and February 2015 among 190 senior patients from four Canadian EDs: CHU de Québec (Québec City), Hôpital Sacré-Coeur de Montréal (Montréal), Hamilton General Hospital (Hamilton), and Sunnybrook Health Science Center (Toronto). The CETI Research Program on mobility and aging was a prospective multi-center cohort study (2010-2016) involving eight EDs from three Canadian provinces as previously described [8]. Inclusion criteria were: age ≥ 65 years, ED consultation within 2 weeks of a minor traumatic injury (significant soft tissue or osseous lesions such as lacerations, contusions, sprains, extremity fractures, minor thoracic injuries, concussions), being independent in basic daily activities (ADLs) 4 weeks prior to injury and, being discharged home from the ED. Hospitalized patients, those living in nursing homes/long-term care, and those unable to provide consent or to communicate in French or English were excluded [8].

Procedure

The study was approved by the Centre Hospitalier Affilié Universitaire de Québec-Research Ethics Board. Also, the research ethics board of each ED approved the study. During consultations, ED physicians (EPs) and research assistants (RAs) identified eligible participants. Clinical variables (injury types and mechanisms) were obtained from EPs, while all other variables were collected by RAs. Blood samples were collected at baseline (ED consultation) or until a maximum of 7 days post-visit. Patients were not in a fasting state. The patients were screened for frailty at baseline while their functional status and mobility characteristics were assessed at baseline and at the 3-month follow-up.

Measures

General characteristics

Clinical variables included types and mechanisms of injuries. Comorbidities were assessed with the Québec Health Surveys questionnaires [22]. Sociodemographic variables included age, gender and social status (living alone or with others).

Frailty measure

Two frailty measures were used in this study. EPs used the Canadian Study of Health and Aging-Clinical Frailty Scale (CSHA-CFS) by Rockwood et al. [23] to evaluate frailty status at baseline. The CSHA-CFS is based on clinicians' judgment and was validated in the Canadian Study of Health and Aging (CSHA) population-based cohorts of Canadian seniors [24]. This scale classifies seniors as: very fit (level 1), well (level 2), well with treated comorbidities (level 3), apparently vulnerable (level 4), mildly frail (level 5), moderately frail (level 6) or severely frail (level 7). In the current study, patients were either classified as "robust" (CHSA-CFS levels 1 and 2) or "pre-frail/frail" (CHSA-CFS levels ≥ 3). The Study of Osteoporotic Fracture (SOF) frailty index frailty index was also used to evaluate the patients' physical frailty at baseline [25]. This 3-item index includes: unintentional weight loss ≥ 10 pounds, leg strength and low energy. The patients were classified as "robust" (SOF: 0) or "prefrail/frail" (SOF ≥ 1).

Serum biomarkers

Blood samples were collected at baseline. All serum biomarkers were analysed at the coordinating centre of CHU Québec. Please see the biomarkers' analysis techniques as well as their coefficients of variation in Appendix 1. All biomarker levels were classified as "normal" or "at risk" according to threshold values presented in Appendix 2. The threshold values used for each biomarker are those used at the CHU-Québec and are generally recognized as clinically "normal", "low" or "high" values, reflecting a normal or impaired physiological state.

Functional status

(The patients' functional status was measured at baseline and at the 3-month follow-up with the Older American Adult Resources and Service (OARS) scale, which includes seven basic Activities of Day Living {ADLs (14 points)}, eating, grooming, dressing, transferring, walking, bathing and continence] and seven Instrumental Activities of Day Living {IADLs (14 points)}; meal preparation, homemaking, shopping, using transportation, using the phone, managing medication and money). Scores range from 0 (dependent) to 28 (independent) [26]. A loss of ≥ 2/28 OARS points from baseline to follow-up, which represents a decrease of 7%, was considered a clinically significant decline in functional status [8]. A loss of at least 1 point in basic ADLs score has also been found clinically significant [27].

Mobility characteristics

All mobility characteristics were measured at baseline and at the 3-month follow-up. The "Timed Up-and-Go" test (TUG) was used to assess the patients' basic mobility [28]. In the CETI cohort, a baseline TUG ≥ 15 seconds (slow walker) was associated with increased functional decline three months post-injury. Other mobility measures included: occasional use of a walking aid, which signals performance issues in lower extremities, and number of times/week the individual leaves home (≤ 5 indicates limited outings) [29]. The Short Falls Efficacy Scale (Short FES-1) was used to evaluate fear of falling [30]. A

score <9.8/10 indicates that patients are very concerned about falling during their ADLs.

Statistical analyses

Patients' characteristics, including their biomarkers values, functional status and mobility characteristics, were described with means and proportions and compared across frailty groups (robust vs prefrail/frail) with Student t-tests, Chi-square or Fisher exact tests when appropriate. To examine if abnormality in any of the six biomarkers (1/6, sensitive panel), in all six biomarkers (6/6, specific panel) or if a combination of biomarkers would correlate with frailty at baseline, the proportions (with 95% CIs) of patients with at risk blood marker values were compared across frailty levels using partial Pearson correlations and log-binomial regressions, both adjusting for comorbidities, age and for renal function in the specific case of creatinine. To examine the potential contribution of baseline biomarkers in addition to the frailty status in predicting 3-month post-injury functional decline or mobility impairments, four sub-groups were created: pre-frail/frail with at risk levels of circulating biomarkers, pre-frail/frail with normal levels, robust with at risk levels of circulating biomarkers, robust with normal levels. The risk exposure of the four groups was assessed as relative risks [31-33]. Simple generalized linear models with a binomial distribution and a log link function were used to explore the differences in functional and mobility outcomes at three months across sub-groups (p-value reflecting at least one of the groups is different from the "robust/normal biomarker levels" sub-group). Finally, sensitivity analyses regarding the impact of the timing of blood sample acquisition were performed. Two-sided P-values ≤ 0.05 were considered statistically significant. Analyses were performed with the Statistical Analysis System (SAS Institute, Cary, NC, version 9.4).

Results

Table 1 shows the baseline characteristics of all patients (n=190) according to their method of measuring frailty, i.e., CHSA-CFS (n=111) or SOF (n=82). The three subsamples (total, CSHA-CFS, SOF) were similar regarding sociodemographic variables, functional status, mobility characteristics and serum biomarkers except for blood sample time and TUG results. Patients were independent in basic ADLs prior to injury, and 13.8% used a cane on occasion (e.g., during a period of exacerbating pain or for safety on icy sidewalks). Overall, 76.8% of them were independent in IADLs before the ED visit (OARS-IADL score=14/14). Due to the inclusion criteria, there were no severely frail seniors in the sample. The CHSA-CFS was missing in 41.6% (n=79) because clinicians failed to report their evaluation in the ED. The SOF was missing in 57.4% (n=108) mostly because many patients were unable to perform the test due to lower limb injuries.

Overall, a greater proportion of patients had normal values of serum biomarkers, although the majority had at least one at risk biomarker (78.4%). At baseline, at risk biomarkers, analysed in isolation, grouped together or in any combination, were not significantly associated with frailty status in multivariate analyses. Of note, approximately 3/4 patients had blood samples collected during their ED visit (n=139), while others had theirs drawn two to seven days post-visit. Sensitivity

Characteristics	Total (n=190)	CSHA-CFS (n=111)	SOF (n=82)
	N*(%)	N*(%)	N*(%)
General characteristics Age (years)			
65-84	175 (92.1)	103 (92.8)	72 (89.8)
≥ 85	15 (7.9)	8 (7.2)	10 (12.2)
Gender (male)	101 (53.2)	58 (52.2)	46 (56.1)
Number of comorbidities (≥ 5)	62 (33.0)	33 (30.3)	29 (35.4)
Lives alone	63 (33.2)	33 (29.7)	22 (26.8)
Mechanism of minor injury			
Fall, own height	118 (65.2)	65 (60.2)	46 (59.7)
Fall, high height	17 (9.4)	12 (11.1)	9 (11.7)
Motor vehicle accident	9 (5.0)	6 (5.6)	3 (3.9)
Other	37 (20.4)	25 (23.1)	19 (24.7)
Frailty status			
Very fit	--------	20 (10.5)	--------
Well	--------	38 (20.0)	--------
Well, with treated comorbidities	--------	36 (19.0)	--------
Apparently vulnerable	--------	13 (6.8)	--------
Mildly/moderately frail	--------	4 (2.1)	--------
Missing	--------	79 (41.6)	--------
0/3	--------	--------	55 (29.0)
1/3	--------	--------	23 (12.1)
≥ 2/3	--------	--------	4 (2.1)
Not done due injury	--------	--------	33 (17.4)
Missing	--------	--------	75 (39.4)
Functional status and mobility characteristics			
OARS - IADL (< 14/14)	44 (23.2)	29 (26.1)	17 (20.7)
Slow walkers (Timed-Up-Go ≥ 15 seconds)	69 (51.5)	36 (47.4)	25 (32.1)
Occasional use of a walking aid	25 (13.8)	13 (12.1)	6 (7.4)
Less than 5 outings/week	43 (23.9)	23 (22.6)	15 (18.5)
Short FES-1 (VAS < 9.8/10)	74 (40.4)	37 (34.6)	33 (40.7)
Serum biomarkers[b]			
Albumin (g/L)			
Normal values	186 (97.9)	109 (98.2)	81 (98.8)
At risk values	4 (2.1)	2 (1.8)	1 (1.2)
Creatinine (µmol/L)			
Normal values	145 (76.3)	79 (71.2)	64 (78.1)
At risk values	45 (23.7)	32 (28.8)	18 (22.9)
CRP (mg/L)			
Normal values	149 (78.4)	91 (82.0)	70 (85.4)
At risk values	41 (21.6)	20 (18.0)	12 (14.6)
Vitamin D (nmol/L)			
Normal values	122 (64.6)	71 (64.0)	54 (66.7)
At risk values	67 (35.4)	40 (36.0)	27 (33.3)
Glucose (mmol/L)			
Normal values	99 (52.7)	54 (48.7)	45 (55.6)
At risk values	89 (47.3)	57 (51.3)	36 (44.4)
IGF-1 (µg/L)			
Normal values	173 (93.5)	105 (95.4)	76 (96.2)
At risk values	12 (6.5)	5 (4.6)	3 (3.8)
At least one biomarker at risk			
No	41 (21.6)	20 (18.0)	22 (26.8)
Yes	149 (78.4)	91 (82.0)	60 (73.2)

[a]Because of missing data, the number of patients does not always add up to the total
[b]Biomarkers: Appendix 3 for normal versus at risk clinical threshold values
CSHA-CFS: Canadian Study of Health and Aging-Clinical Frailty Scale
SOF: Study of Osteoporotic Fracture frailty index
CRP: C-reactive protein; IGF-1: insulin growth factor
OARS: Older American Adult resources and Service scale; IADL: Instrumental Activities of Day Living
Short FES-1: Short Falls Efficacy Scale

Table 1: Baseline characteristics of subsamples of independent seniors who consulted the Emergency Department for minor injury[a].

analyses on timing of blood sample acquisition did not impact the results (data not shown).

Baseline characteristics, serum biomarkers as well as 3-month functional status and mobility characteristics, all according to ED frailty status, are shown in Table 2. There were no statistical differences in the general characteristics of pre-frail/frail and robust patients, regardless of the frailty scale used. However, a greater proportion of pre-frail/frail patients had worse baseline functional statuses and mobility characteristics, compared to robust patients for both scales. Regarding serum biomarkers at baseline, only creatinine was significantly different across groups; a greater proportion of prefrail/frail patients had at risk creatinine levels compared to robust patients (39.6% vs 19.0%, p=0.02). After controlling for history of chronic kidney disease, this result remained significant.

Overall, the 3-month incidence of functional decline was 9.5% (loss ≥ 2 OARS points, mean scores 28 ± 1 vs 27 ± 2 at baseline and 3-month follow-up, respectively; p=0.02). Also, except for TUG performances, almost all mobility characteristics worsened (Appendix 3). As demonstrated in Table 2, at the 3-month post-injury follow-up, the proportion of pre-frail/frail seniors who showed a functional decline was twice that found among robust patients. However, this result did not reach statistical significance (5.7% vs 12.5% according to the CSHA-CFS, and 4.1% vs 8% according to the SOF). Moreover, baseline pre-frail/frail patients (according to SOF scale) were more fearful of falling during their ADLs at 3-month follow-up and went outside less often.

Overall, in the sub-group analyses for functional decline, adding baseline biomarkers did not significantly contribute to the identification of 3-month functional decline beyond what was identified by the ED frailty measures alone (OARS scale, data not shown). However, Table 3 shows the results pertaining to the most statistically significant analyses between biomarkers and frailty status in predicting mobility impairments at follow-up (less than 5 outings per week and fear of falling). Globally, these trends indicate that CRP increased the prediction of 3-month mobility impairments in robust seniors [RR: 3.33 (0.77-14.42)]. On the other hand, vitamin D [RR: 0.51 (0.07-3.94)], glucose [RR: 0.27 (0.03-2.16)] and creatinine [RR: 1.10 (0.40-2.97)] slightly increased this risk in pre-frail/frail patients. However, as with functional status, the ED-determined frailty status, regardless of the scale used, clearly remains the stronger predictor of mobility impairments after injury (RR ranging from 1.83 to 3.11 across biomarkers and mobility characteristics, p≤0.02) This trend is also depicted in robust seniors presenting at least one at-risk biomarkers (RR: 0.44 (0.10-1.91)) when compared to pre-frail/frails presenting normal biomarkers (RR: 3.11 (0.98-9.84), p=0.007).

Discussion

The aims of this prospective study were to explore the baseline association between six serum biomarkers' clinical threshold values and the frailty status of community-dwelling seniors with minor injuries screened in ED, and to determine if ED serum biomarker assay combined with frailty status improves the prediction of 3-month

Variables	Baseline CSHA-CFS			Baseline SOF		
	Robust	Pre-frail/ frail	p-value	Robust	Pre-frail/ frail	p-value
Patients, n (%)	58 (52.3)	53 (47.7)	-	55 (67.1)	27 (32.9)	-
Baseline cross-sectional results						
Baseline general characteristics, % (95% CI)						
Age, mean ± SD	74.0 ± 7.1	75.8 ± 6.5	NS	75.6 ± 6.9	76.8 ± 7.5	NS
Male	56.9 (45.5-71.2)	47.2 (35.5-62.7)	NS	61.8 (50.2-76.1)	44.4 (29.2-67.8)	NS
Number of comorbidities (≥ 5)	24.1 (15.3-38.1)	37.3 (26.1-53.2)	NS	30.9 (20.8-45.9)	44.4 (29.2-67.8)	NS
Lives alone	32.8 (22.7-47.4)	26.4 (16.9-41.4)	NS	21.8 (13.2-36.0)	37.0 (22.6-60.6)	NS
Baseline functional status and mobility characteristics, % (95% CI)						
OARS - IADL (<14/14)	13.8 (7.2-26.2)	39.6 (28.4-55.2)	0.004	21.8 (13.2-36.0)	18.5 (8.4-40.9)	NS
Slow walkers (Timed-Up-Go ≥ 15 seconds)	38.6 (26.6-56.6)	59.4 (44.6-79.1)	0.07	23.1 (14.0-37.9)	50.0 (34.0-73.4)	0.02
Occasional use of a walking aid	5.2 (1.7-15.6)	20.4 (11.7-35.5)	0.03	3.6 (0.9-14.2)	15.4 (6.2-37.9)	0.08
Less than 5 outings/week	15.8 (8.7-28.8)	31.1 (20.1-48.1)	0.07	9.1 (3.9-21.0)	38.5 (23.7-62.5)	0.004
Short FES-1 (VAS <9.8/10)	22.4 (13.9-36.2)	49.0 (36.8-65.2)	0.006	31.5 (21.2-46.7)	59.3 (43.3-81.0)	0.01
Baseline serum biomarkers[a] (At risk values, % (95% CI)						
Albumin	1.7 (0.2-11.2)	1.9 (0.3-12.2)	NS	Non convergent	-	-
Creatinine	19.0 (11.1-32.3)	39.6 (28.4-55.2)	0.02	16.4 (9.0-29.7)	33.3 (19.6-56.8)	0.08
CRP	19.0 (11.1-32.3)	17.0 (9.4-30.8)	NS	18.2 (10.4-31.9)	7.4 (2.0-28.1)	NS
Vitamin D	36.2 (25.7-51.0)	35.8 (25.0-51.4)	NS	36.4 (25.6-51.6)	26.9 (14.3-50.7)	NS
Glucose	46.6 (35.3-61.3)	56.6 (44.7-71.7)	NS	40.7 (29.5-56.2)	51.9 (36.1-74.6)	NS
IGF-1	Non-convergent	-	-	1.9 (0.3-12.4)	7.4 (1.9-25.2)	NS
At least one biomarker at risk	79.3 (69.5-90.5)	84.9 (75.8-95.1)	NS	72.7 (61.9-85.5)	74.1 (59.3-92.6)	NS
Prospective results						
Functional decline at 3 months, % (95% CI)						
↓ OARS ≥ 2	5.7 (1.9-17.4)	12.5 (5.9-26.4)	NS	4.1 (1.0-14.9)	8.0 (2.0-26.9)	NS
↓ OARS-ADL ≥ 1	11.3 (5.3-24.1)	20.8 (12.0-36.2)	NS	8.2 (3.2-20.9)	16.0 (6.5-39.3)	NS
Mobility characteristics at 3 months, % (95% CI)						
OARS - IADL (<14/14)	11.3 (5.3-24.1)	33.3 (22.3-49.7)	0.01	20.4 (11.7-35.5)	12.0 (4.2-34.7)	NS
Slow walkers (Timed-Up-Go ≥ 15 seconds)	Non-convergent	-	-	18.2 (7.5-44.1)	11.1 (1.8-70.5)	NS

Occasional use of a walking aid	12.0 (5.7-25.4)	22.0 (12.3-39.1)	NS	4.5 (1.2-17.6)	20.0 (9.1-43.8)	0.06
Less than 5 outings/week	25.0 (15.6-40.0)	39.0 (26.6-57.2)	NS	13.0 (6.2-27.5)	52.0 (35.7-75.8)	0.001
Short FES-1 (VAS <9.8/10)	45.1 (33.3-61.0)	51.2 (38.0-69.1)	NS	34.8 (23.4-51.7)	64.0 (47.7-85.9)	0.02

[a]Biomarkers: see Appendix 2 for normal versus abnormal clinical threshold values
CSHA-CFS: Canadian Study of Health and Aging-Clinical Frailty Scale
SOF: Study of Osteoporotic Fracture frailty index
CRP: C-reactive protein; IGF-1: insulin growth factor
OARS: Older American Adult resources and Service scale; IADL: Instrumental Activities of Day Living
Short FES-1: Short Falls Efficacy Scale (fear of falling)

Table 2: Baseline characteristics and serum biomarkers along with 3-month functional and mobility characteristics according to ED frailty status.

Variables	3-month post-injury mobility characteristics			
	Less than 5 outings/week		Short FES-1 (VAS <9.8/10)	
ED biomarker and frailty status	**RR**	**p-value**	**RR**	**p-value**
Creatinine				
Normal creatinine/Robust	-	-	ref.	0.05
At risk creatinine/Robust	Non-convergent	-	1.10 (0.40-2.97)	
Normal creatinine/Pre-frail/Frail	-	-	2.06 (1.21-3.53)	
At risk creatinine/Pre-frail/Frail	-	-	1.46 (0.64-3.32)	
CRP				
Normal CRP/Robust	ref.	0.01	Non-convergent	-
At risk CRP/Robust	3.33 (0.77-14.42)			
Normal CRP/Pre-frail/Frail	5.22 (1.90-14.31)			
At risk CRP/Pre-frail/Frail	5.00 (0.94-26.53)			
Vitamin D				
Normal Vitamin D/Robust	ref.	0.008	ref.	0.01
At risk Vitamin D/Robust	0.51 (0.07-3.94)		1.52 (.070-3.33)	
Normal Vitamin D/Pre-frail/Frail	2.93 (1.12-7.65)		1.83 (0.95-3.55)	
At risk Vitamin D/Pre-frail/Frail	4.40 (1.64-11.79)		2.75 (1.47-5.16)	
Glucose				
Normal glucose/Robust	ref.	0.02	ref.	0.06
At risk glucose /Robust	0.27 (0.03-2.16)		0.62 (0.26-1.49)	
Normal glucose /Pre-frail/Frail	2.36 (0.85-6.55)		1.29 (0.64-2.60)	
At risk glucose /Pre-frail/Frail	2.97 (1.20-7.37)		1.69 (0.97-2.95)	
At least one biomarker at risk				
Normal biomarkers/Robust	ref.	0.007	ref.	0.07
At risk biomarkers /Robust	0.44 (0.10-1.91)		1.31 (0.51-3.36)	
Normal biomarkers /Pre-frail/Frail	3.11 (0.98-9.84)		1.75 (0.55-5.54)	
At risk biomarkers /Pre-frail/Frail	2.21 (0.73-6.70)		2.39 (0.99-5.79)	

Frailty status according to SOF frailty index ("robust" SOF=0 versus "pre-frail/frail" SOF ≥ 1)
Short FES-1: Short Falls Efficacy Scale (fear of falling)
Biomarkers: see Appendix 2 for normal versus at risk clinical threshold values

Table 3: Mobility characteristics three months after minor injury according to ED biomarkers threshold values (normal versus at risk) and frailty (SOF) subgroups.

functional decline or mobility impairment in this population beyond frailty status alone. To the best of our knowledge, very few studies have examined the contribution of biomarkers in such a population and clinical setting.

Baseline measures at the ED showed that, when compared to robust patients, pre-frail/frail patients were less functional in their IADLs, were slower walkers, were more frequent users of walking aids, were more fearful of falling during their IADLs, went outside their home less often weekly and had impaired creatinine levels. Three months after the ED visits, we observed an overall 3-month functional decline in around 10% of patients as revealed by a 2-point decreased in OARS scores combined with worsened mobility characteristics. Finally, we observed that baseline CRP, vitamin D, glucose and creatinine modulate 3-month mobility characteristics associated with ED frailty status. However, results were inconsistent across biomarkers and the clinically determined ED frailty status clearly remained the stronger predictor of mobility impairments 3-month post-injury.

In this study, the proportion of patients with clinically at-risk creatinine levels was significantly higher in those who were classified as pre-frails/frail (40%) compared to those classified as robust (19%) and this result remained statistically significant after controlling for history of chronic kidney disease. It might be an indication that renal function, reflected by blood creatinine concentrations, could be an indication of adverse outcomes in frail seniors [34-36]. Vitamin D 25-OH and glycemia values tended to modulate the risk of 3-month mobility decline in frail seniors only. The relevance of Vitamin D in the pathogenesis of frailty and its impact on muscle function and strength have been largely documented [20,37]. Regarding glycaemia, Zaslavsky et al. suggested that higher glucose levels and diabetes may increase the risk of frailty in older patients [21]. These authors identified several potential mechanisms such as chronic inflammation, chronic hyperglycemia that increases microvascular damage, and skeletal muscle mitochondrial dysfunction, through which patients' frailty could be increased [21]. Inflammatory response is also modulated by CRP levels and has been associated with frailty [15-17].

As mentioned previously, even if some biomarkers modulated the relationship between 3-month mobility impairment and ED frailty status, our results indicate that frailty status clearly remains the stronger predictor of mobility impairments in this population. In this regard, these results concur with previous larger studies of the role that frailty measures can have on predicting 3-month post-injury functional or mobility impairments in previously independent injured seniors seen in ED [8,11]. Therefore, our results highlight that ED serum biomarker assays do not add significant predictive values to clinical frailty measures regarding 3-month functional decline or mobility impairments in this population.

Our results could be due to a lack of power, the type of population (ED versus community dwelling elders) or the chosen frailty scales (CHSA-CFS and SOF vs Fried phenotype gold standard [3]. In fact, the small sample size may have decreased the power to find group differences, but it did not prevent finding interesting prospective results. Also, frailty measures were missing in about 40% of patients since clinicians failed to report their evaluation in the ED (CHSA-CFS) or due to patient's lower limb injuries (SOF). There were no differences in sociodemographic, functional statuses or serum biomarkers according to whether CHSA-CFS was available or not. However, patients with missing SOF score were younger (65-74 y.o.: 61.1% vs 41.5%, p=0.01), slower walkers (TUG ≥ 15 sec.: 78.6% vs 32.1%, p<0.0001), used walking aids more frequently (19.0% vs 7.4%, p=0.02), had shorter blood collection time (89.6% vs 54.9%, p<0.0001), and had more at-risk CRP values (26.9% vs 14.6%, p=0.04). These characteristics of patients without SOF measures may have led to an overestimation of the risk of adverse outcomes in those with abnormal CRP values. Furthermore, some patients had their blood puncture after the initial ED visit, (2-7 days post-visit). Since some biomarkers are sensitive and change quickly over days, this may also have decreased some group differences. Finally, we lost about 12% of patients at follow-up.

Conclusion

In conclusion, except for creatinine, results of this prospective study argue that ED serum biomarkers are not useful in adequately screening for frailty among independent, community-dwelling seniors who consulted the ED for minor injuries. Moreover, ED biomarker assays are not useful in predicting 3-month functional decline or mobility impairments beyond what is predicted by frailty status alone in this population. Since emergency visits are reported as missed opportunities for interventions and since many seniors are discharged without receiving proper care [38,39] we believe that the use of quick and easy tools (such as the CSHA-CFS or SOF scales) seem more useful to help screen frail seniors who are at risk of functional or mobility impairment after an ED visit for a minor injury.

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The authors have no financial or personal conflicts of interest to declare. Dr Marie-Josée Sirois is the guarantor of this work, had full access to all the data, and takes full responsibility for the integrity of data and the accuracy of data analysis. Drs Mélissa Blouin and Marie-Josée Sirois wrote the manuscript, researched and analyzed data. Drs Mylène Aubertin-Leheudre, Lauren Griffith, Raoul Daoust, Jacques Lee and Dr Marcel Émond collaborated to the design of the study, contributed to the data collection and revised the manuscript. Dr Linda Nadeau ensured the coordination and integrity of pre-analytical, analytical and post-analytical biomarkers analyses. This study was supported by the Canadian Institutes of Health Research (CIHR).

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