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Development and validation of a biological frailty score based on CRP, haemoglobin, albumin and vitamin D within an electronic health record database in France: a cross-sectional study

Aurélie Mailliez ,[1,2] Maxime Leroy,[3] Michael Génin,[3,4] Elodie Drumez,[3] François Puisieux,[1,4] Jean-Baptiste Beuscart,[1,4] Ivan Bautmans,[5,6] Pierre Balayé,[4,7] Eric Boulanger[1,2,8]

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AM and ML are joint first authors.

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For numbered affiliations see end of article.

Correspondence to
Prof. Eric Boulanger;
eric.boulanger@univ-lille.fr

ABSTRACT

Objectives To easily detect frailty in a timely fashion, enabling targeted interventions and appropriate monitoring, will be a major worldwide public health and economic challenge as the proportion of older people increases in the population. Based on a review and meta-analysis showing that C-reactive protein (CRP), haemoglobin, albumin and vitamin D are associated with frailty, we aimed to develop and validate a biological score using these biomarkers for the detection of frailty.

Design We conducted a retrospective, cross-sectional, monocentric study using the electronic healthcare database of Lille University Hospital, France.

Participants Inclusion criteria were patients aged 50 and over, being hospitalised at Lille University Hospital between 1 January 2008 and 31 December 2021. We identified patients whose CRP, haemoglobin, albumin and vitamin D levels were measured. We selected patients whose assays fell within normal thresholds, outside acute clinical situations.

Main outcome measures To assess frailty, we used a scale adapted to electronic healthcare database, called the Hospital Frailty Risk Score. To develop and validate the predictive frailty score, the whole population was divided into a development and a validation cohort.

Results 26 554 patients were included, of which 17 702 were in the development cohort and 8852 in the validation cohort. Based on the results of the multivariate analysis, we developed an equation combining CRP, haemoglobin, albumin and vitamin D with age and sex to obtain a score referred to as the bFRAil (biological FRAilty) score. Within the validation cohort, the area under the curve for this score is 0.78 (0.77–0.80) and the negative predictive value is 83.7%.

Conclusions This study has made it possible, for the first time, to develop and validate in a hospital setting a biological score called bFRAil score based on simple, easily measurable biomarkers for identifying frail patients in daily medical practice. Further studies are needed to validate its use.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several frailty scales have been proposed in the literature over the past 20 years, but none is really used in daily medical practice. The time needed to perform them, the lack of equipment sometimes required, and, above all, the absence of a gold standard are all limits to the use of frailty identification scales previously published in the literature. The earliest possible detection of frailty, while it is still a reversible condition, is a major public health and socioeconomic challenge in the face of the world's ageing population. The identification of biomarkers strongly associated with frailty would facilitate its use in medical practice and its appropriation by all healthcare professionals. We have previously reported in a review and meta-analysis that C-reactive protein, haemoglobin, albumin and vitamin D were associated with frailty.

WHAT THIS STUDY ADDS

⇒ We developed and validated in hospital a biological frailty score referred to as the bFRAil score (biological FRAilty score) which combines levels of these easily measurable biomarkers with age and sex for identifying frailty in daily medical practice. This biological score has a good negative predictive value.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The bFRAil score can be used as a simple means for healthcare professionals to target patients who require specialised evaluation. Thanks to this score, patients' risk of frailty can now be easily and quickly assessed, enabling patients who need it to be rapidly referred for interventions designed to promote healthy ageing.

INTRODUCTION

Ageing is very heterogeneous among individuals. If people age while retaining their functional independence they can be defined as 'robust', and this category may include those with well-managed, chronic illnesses or conditions. At the other end of the scale are 'dependent' people, for whom one or more pathologies, acute or chronic in nature, have led to an irreversible loss of functional independence. Between these two states exists a category of people defined as 'frail'. Frailty is common among older people and has been characterised as a loss of homeostasis among multiple physiological domains.[1] It is a dynamic, potentially reversible state in which declining physiological reserves across multiple systems lead to reduced resistance to stressors. The result is an increased risk of adverse outcomes such as unscheduled hospitalisation, falls, inability to perform normal, daily-life activities and an increased risk of institutionalisation and death.[2 3]

Early detection of frailty, while the possibility for its reversal remains, enables timely and targeted interventions aimed at returning the patient to a robust status or at the very least to delay the onset of dependency. It is also important in personalising a patient's care plan in cases of any chronic pathology. With the proportion of older people increasing worldwide, frailty will become a major public health and socioeconomic issue and one which general practitioners and specialist physicians will increasingly encounter. Nearly 80 frailty detection scales have already been identified in a literature review.[4] Among the best-known worldwide are the Physical Frailty Phenotype by L Fried, the Frailty Index by K Rockwood and the Clinical Frailty Scale (CFS) which use face-to-face patient assessments. The CFS classifies patients according to their level of robustness or frailty, from category 1 (very fit) to category 9 (terminally ill). The Frailty Index is defined as the proportion of deficits present in an individual in relation to the total number of age-related health variables considered. Fried's frailty scale offers a definition based on five physical criteria, enabling the patient to be categorised as robust (no criteria present), pre-frail (one to two criteria present) or frail (three to five criteria present). The more recent Hospital Frailty Risk Score (HFRS) uses digitalised patient records and diagnostic codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).[2 5 6] However, there is no international consensus yet for a gold standard complicating the implementation of frailty assessment in daily clinical practice.

Alongside these clinical scales, many potential biomarkers have also been suggested in the literature as useful for frailty assessment. Some are easy to measure such as inflammatory, hormonal or nutritional parameters, while others require special equipment such as candidate genes.[7] Notwithstanding numerous scientific publications on the subject, however, no validated biomarker (or suite of biomarkers) has been widely adopted for diagnosing frailty. For this reason, we previously performed a literature review and meta-analysis on biomarkers associated with frailty and proposed a list of five simply and routinely measured biomarkers: C-reactive protein (CRP), haemoglobin, albumin, vitamin D and free testosterone.[8] Here, we aimed to develop and validate a predictive score for risk of frailty derived from those biomarkers. We further compared our findings with results from the HFRS, which was also used to examine the Lille University Hospital patient database.

METHODS

Study design and patients

A single-centre, retrospective study was conducted at the Lille University Hospital, France (University Hospital Center (CHU) Lille). Inclusion criteria were patients aged 50 and over, who visited CHU Lille between 1 January 2008 and 31 December 2021. Hospital stays in long-term care units and nursing homes were excluded.

Data collection

We searched for patients whose CRP, haemoglobin, albumin and vitamin D levels were measured. We selected patients whose biological assays fell within the following ranges: between 10 and 16 g/dL for haemoglobin, 30 and 50 g/L for albumin, 0 and 20 mg/L for CRP and between 0 and 60 ng/mL for vitamin D. The CRP and vitamin D values were further stratified into three classes for our analyses. We assumed that outside of these ranges, the context was not suitable for detecting frailty. Patients who did not stay in hospital and whose sex or age was not provided were excluded.

When patients were admitted several times during the study period, we only examined data relating to their last stay. When they had several blood assays of the biomarkers of interest during the stay, we only retained the last measurement before discharge, the assumption being that they would be as close as possible to their baseline state at this time. To assess frailty in this electronic health database, we used the HFRS developed and validated by Gilbert *et al* and derived from the ICD-10 diagnostic codes.[6] The patients within the intermediate-risk and high-risk categories were classified as frail, while those within the low-risk category were classified as robust, as suggested by Gilbert *et al*. For each patient the following clinical and biological data were collected: age, sex, HFRS, CRP, haemoglobin, albumin and vitamin D levels.

Statistical analysis

Categorical variables were expressed as the frequency (percentage). Quantitative variables were expressed as the mean±SD or the median (IQR) in cases of non-normal distribution. Normal data distributions were checked graphically and by applying the Shapiro-Wilk test.

After extraction of data from the CHU Lille electronic database (called 'INCLUDE'), the number of included patients was 26 554. The dataset was divided into a

development data set (two-thirds of patients, n=17 702) and a validation data set (n=8852). We described candidate predictors and frailty status in both development and validation cohorts and calculated standardised differences between the two data sets with their 95% CIs; an absolute standardised difference >10% was interpreted as being a meaningful difference.

Candidate predictors were first analysed using bivariate logistic regression models; ORs were reported as effect size with their 95% CIs. For each quantitative predictor, the log-linearity assumption was assessed using restricted cubic spline functions. Since we found no evidence of non-log-linear relationships, all quantitative predictors were introduced as linear terms in analyses. To develop the prognostic model, candidate predictors significantly associated with a patient's frailty in bivariate logistic regression models were considered for entry into the multivariable logistic regression model. Despite gender not being significantly associated with frailty in the bivariate analysis, we retained it for the multivariate model since it is a well-known risk factor for frailty.[9]

The performance of the multivariate model was examined by assessing discrimination and calibration in the development cohort. Discrimination was evaluated using the c-statistic, which indicates to what extent the model distinguishes between patients with and without frailty. We performed exploratory analyses to assess the discriminatory power of biomarkers (CRP, haemoglobin, albumin, vitamin D), age and gender through various combinations. Calibration is the agreement between the predicted and observed frailty risk and was reported by the corresponding calibration plot.[10] Prognosis models derived from multivariable regression analysis are known to overestimate regression coefficients, which results in overestimated predictions when applied in future patients.[11] Therefore, we performed an internal validation by using bootstrap resampling with 200 repetitions to estimate the shrinkage factor and the c-statistic corrected for over-optimism.

We also performed a second, internal validation by assessing the model's discrimination and calibration performances in the validation data set. Predicted risks were calculated in the validation data set using the coefficient estimates (after applying the shrinkage factor) obtained from the derivation data set (see the scoring system). Youden Index was used to establish an optimal threshold of frailty score.

All tests were two-tailed, and the threshold for statistical significance was set to p<0.05. All analyses were performed using SAS software (V.9.4, SAS Institute, Cary, North Carolina, USA).

RESULTS

724 996 patients visited Lille University Hospital between 1 January 2008 and 31 December 2021, who had a biological assessment during their visit with at least one of the four biomarkers of interest. Finally, 26 554 patients were included of which 17 702 comprised the development cohort and 8852 the validation cohort (figure 1). Mean age was 71.8±12.6 years in the development cohort and 71.8±12.5 in the validation cohort, and 57% were women in the development cohort and 55% in the validation cohort. Mean HFRS score was 5.4±6.2 in the development cohort and 5.3±6.3 in the validation cohort (table 1). According to HFRS, 6610 patients in the development cohort (37.3%) and 3310 patients in the validation cohort (37.4%) were classified as Frail. Hence, as the absolute difference was less than 0.1% between the cohorts, they were deemed to be balanced. Online supplemental table 1 lists the ICD-10 codes and assigned points used to calculate the HFRS.

The multivariate analyses in the development cohort showed that CRP levels between six and strictly below 10 mg/dL compared with CRP<6 mg/dL increase the risk of frailty (OR=1.33 (1.21–1.47); p<0.001). Albumin higher than or equal to 35 g/L and haemoglobin higher than or equal to 12 g/dL were both associated with a lower

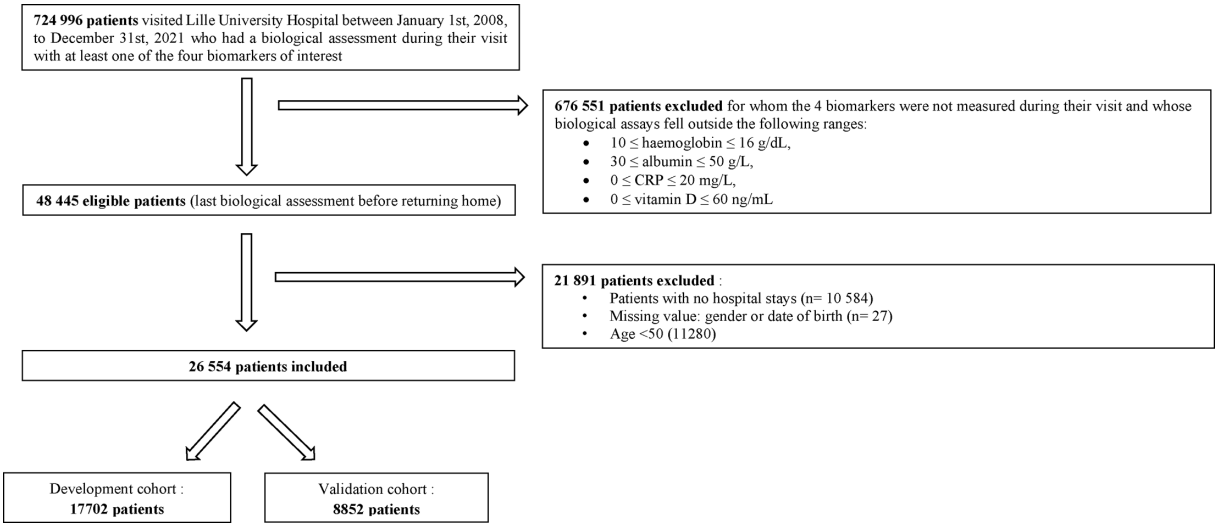

Figure 1 Flow chart. CRP, C-reactive protein.

Table 1 Characteristics in the whole population

	Development cohort (n=17 702)	Validation cohort (n=8852)	Standardised difference (95% CI)
Sex			
Female	10 046 (56.8)	4899 (55.3)	0.00 (–0.03–0.03)
Male	7656 (43.2)	3953 (44.7)	
Age (years)	71.8±12.6	71.8±12.5	0.00 (–0.03–0.03)
HFRS	5.4±6.2	5.3±6.3	0.00 (–0.03–0.03)
Biomarkers			
Hb (g/dL)	12.3±1.6	12.3±1.5	0.02 (–0.01–0.05)
Albumin (g/L)	37.3±4.8	37.3±4.8	0.00 (–0.04–0.03)
CRP (mg/L)			0.03 (0.00–0.06)
<6	9050 (51.1)	4478 (50.6)	
(6; 10)	3430 (19.4)	1736 (19.6)	
≥10	5222 (29.5)	2638 (29.8)	
25OHD (ng/mL)			0.02 (–0.01–0.05)
<20	7777 (43.9)	3969 (44.8)	
(20; 30)	5011 (28.3)	2441 (27.6)	
≥30	4914 (27.8)	2442 (27.6)	

Values are expressed as number (%) or mean±SD.
CRP, C-reactive protein; Hb, haemoglobin; HFRS, Hospital Frailty Risk Score; 25OHD, 25-hydroxy vitamin D.

risk of frailty (respectively OR=0.87, 95% CI (0.86–0.89) and OR=0.86, 95% CI (0.84–0.89); p<0.001). Vitamin D levels <20 ng/mL increased the risk of frailty compared with ≥30 ng/mL (OR=1.28, 95% CI (1.17–1.41), p<0.001) (table 2). Age was associated with a greater risk of frailty (p<0.001). Female gender was not significantly associated with frailty in multivariate analysis (p=0.30).

Based on the results of the multivariate analysis, we developed an equation (see below) combining these four biomarkers with age and sex to obtain a biological score predictive of frailty.

$$X = (16\,668 + (0.0578 \times \text{age}) + (0.0389 \times (1 \text{ if sex male or } 0 \text{ if sex female}) - 0.1481 \times \text{haemoglobin (g/dL)} - 0.1345 \times \text{albumin (g/L)} + 0.2872 \times 1 \text{ (if } (6 \leq \text{CRP (mg/L)}$$

Table 2 Univariate and multivariate analysis of risk factors of frailty

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.08 (1.07–1.08)	<0.001	1.06 (1.05–1.07)	<0.001
Sex (male vs female)	0.84 (0.78–0.89)	<0.001	1.04 (0.96–1.12)	0.30
Biomarkers				
Hb (g/dL)	0.68 (0.66–0.70)	<0.001	0.86 (0.84–0.89)	<0.001
Albumin (g/L)	0.82 (0.71–0.83)	<0.001	0.87 (0.86–0.89)	<0.001
CRP (mg/L)				
Reference: <6				
(6; 10)	1.98 (1.82–2.15)	<0.001	1.33 (1.21–1.47)	<0.001
≥10	2.59 (2.40–2.78)	<0.001	1.28 (1.17–1.39)	0.012
25OHD (ng/mL)				
Reference: ≥30				
(20; 30)	1.11 (1.02–1.21)	0.010	1.21 (1.09–1.33)	<0.001
<20	1.31 (1.21–1.41)	<0.001	1.28 (1.17–1.41)	<0.001

CRP, C-reactive protein; Hb, haemoglobin; 25OHD, 25-hydroxy vitamin D.

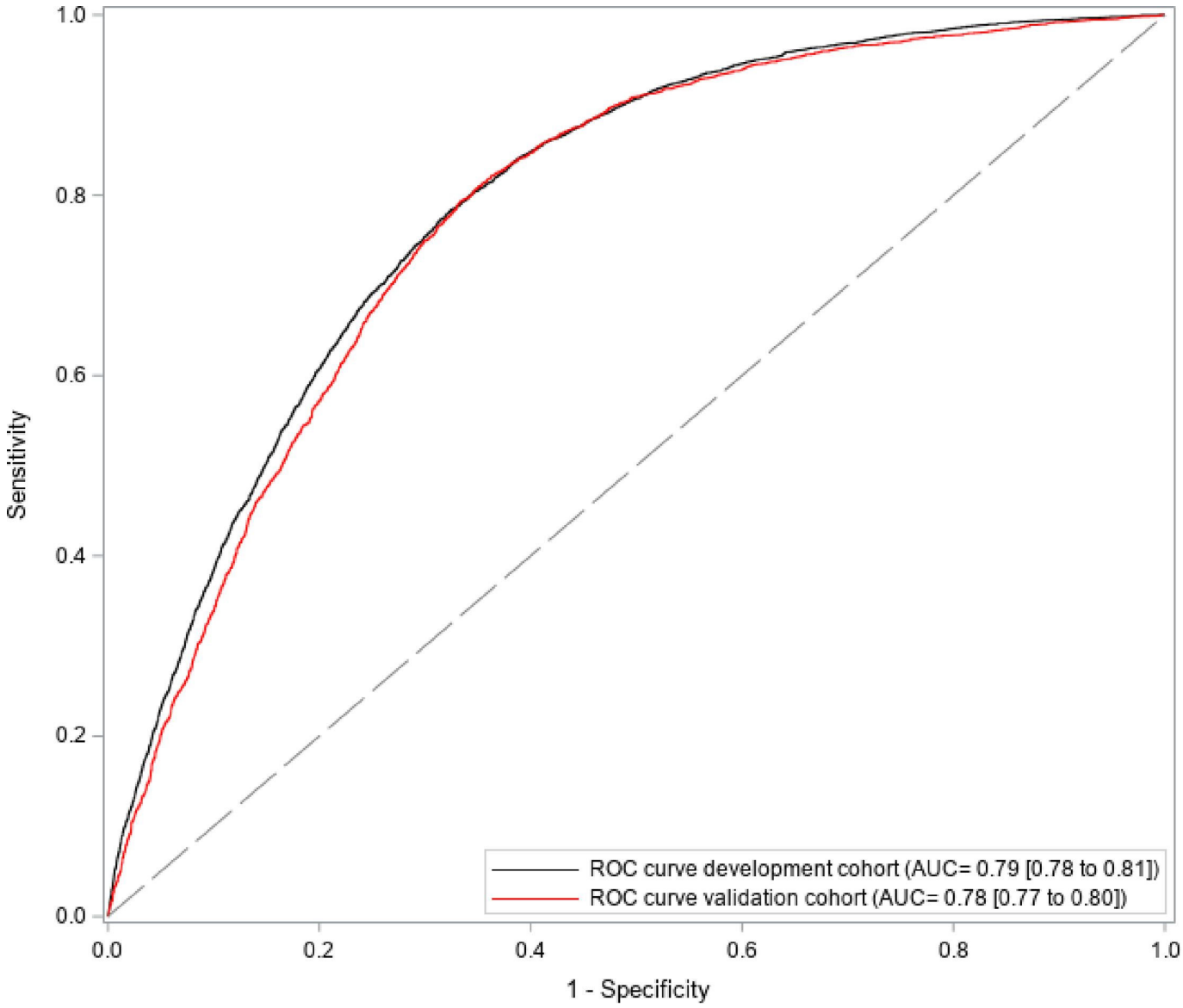

Figure 2 ROC curve in the development cohort and in the validation cohort. AUC, area under the curve; ROC, receiver operating characteristic.

<10)) + 0.2440 × 1 (if CRP (mg/L) ≥10) + 0.2503 × 1 (if vitamin D (ng/mL) <20) + 0.1876 × 1 (if (20≤vitamin D (ng/mL) <30)) × 0.9989466

Normalised biological frailty score (bFRAil score) = (exp(X) / (1 + exp(X))).

If result ≥0.3568: individual is defined as frail. If result <0.3568: individual is defined as non-frail.

Then, we evaluated this biological score in the validation cohort. As shown in figure 2, within the development cohort, the area under the curve (AUC) for this score was 0.79 (0.78–0.81). Within the validation cohort, the AUC was 0.78 (0.77–0.80). We also assessed the discriminatory power of different models combining age, sex, or biomarkers (figure 3). For comparison, AUC for the model with only age and sex was 0.74 (0.72–0.75) and AUC for the model with the four biomarkers alone was 0.75 (0.74–0.76). We performed a calibration of the biological score model in both the development cohort and the validation cohort, which confirmed the significant agreement between the predicted risk of frailty with our biological predictive score and observed risk of frailty with the HFRS (online supplemental figures 1 and 2).

We defined a threshold of frailty for our biological score derived from the multivariate model. Above the threshold the patient is defined as frail, below it as non-frail. We used the cut-off value of 0.3568 based on the Youden Index which maximised sensitivity and specificity. We found a good negative predictive value of 83.7%. We have also provided the positive and negative likelihood ratios (online supplemental tables 2 and 3 and online supplemental figure 3). The resulting score is referring to the bFRAil score. An Excel file for healthcare professionals to directly enter the biological and clinical parameters of interest for their patients will be available on a dedicated website after publication.

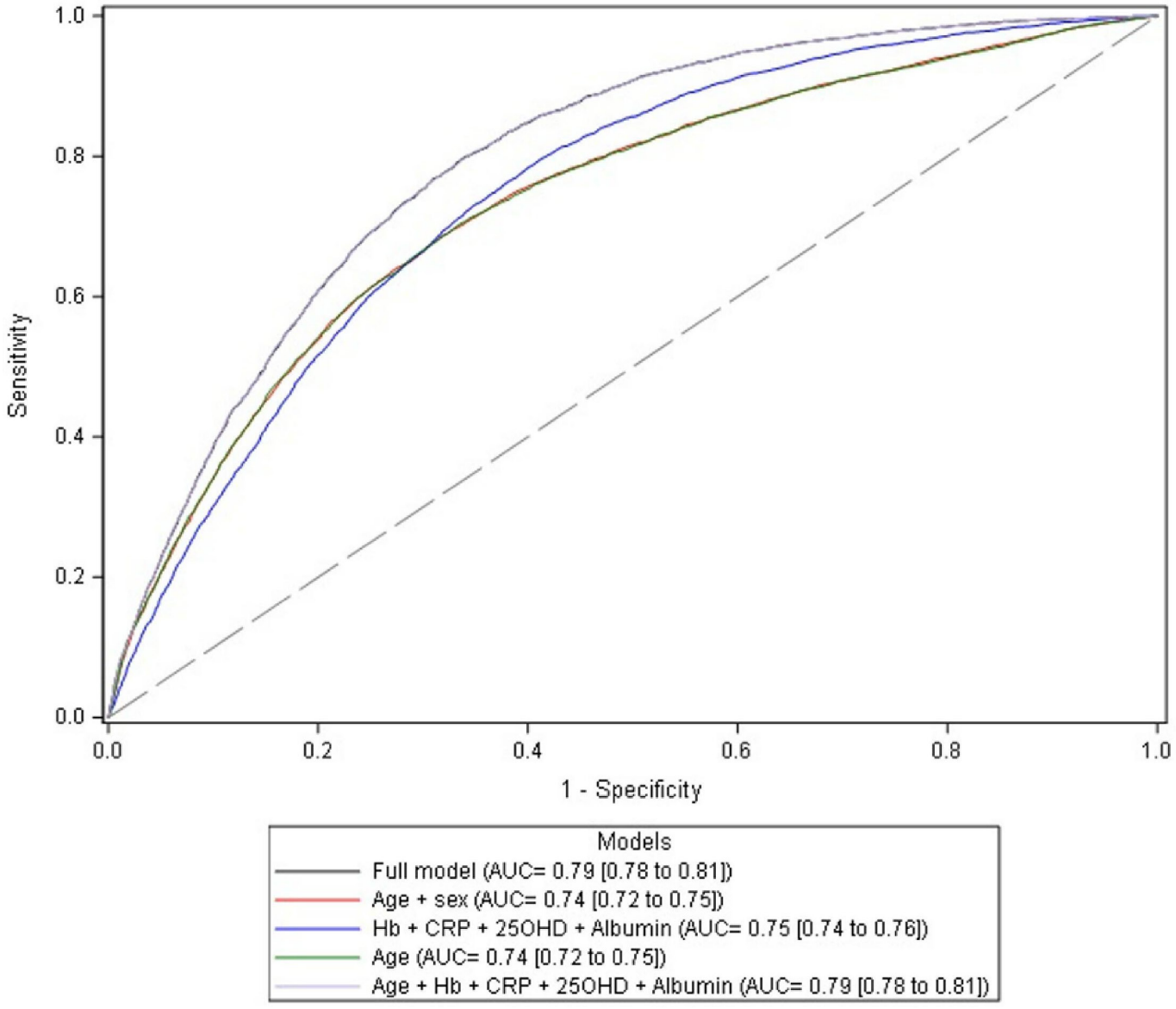

Figure 3 Evaluation of the discriminatory power of the models in the development cohort. AUC, area under the curve; CRP, c-reactive protein; Hb, haemoglobin; ROC, receiver operating characteristic; 25OHD, 25-hydroxy vitamin D.

DISCUSSION

We here describe a biological predictive risk score for frailty, the biological bFRAil score, which combines easily and routinely measurable biomarkers with the two basic clinical parameters of age and sex. This study confirms findings from our previous meta-analysis that levels of CRP, haemoglobin, albumin and vitamin D are associated with frailty, and translates these literature-based results into a highly usable, predictive clinical tool. We have shown that the bFRAil score has a good agreement with the HFRS with an AUC of 0.78 (0.77–0.80), which is a good predictive capacity.[12] We used the Youden Index, which maximises sensitivity and specificity, to select the positivity threshold for our score.[13]

All the biomarkers here have a significant body of evidence supporting their inclusion. Several authors have also suggested the association of those four biomarkers with frailty. Low 25-hydroxy vitamin D levels have been previously shown to be associated with low muscle strength and mass and higher risk of frailty.[14 15] As for several other peripheral inflammatory markers, CRP is a key marker of 'inflammaging', which is thought to be an underlying cause of frailty and of chronic, low-grade inflammation.[16–18] As in our study, Puts *et al* also showed in cross-sectional and prospective analyses that moderately elevated CRP (between 3 and 10 µg/mL) resulted in higher risk of frailty compared with levels of CRP greater than 10 µg/mL.[14] While moderately elevated CRP may indirectly reflect an underlying frailty phenotype, higher values are probably related to an acute event or infection. Other authors have reported that low levels of albumin and vitamin D are significantly associated with frailty.[19–22] In a review and meta-analysis, Picca *et al* confirmed that haemoglobin and albumin were negatively correlated with both frailty and sarcopenia.[23 24]

Several scores and indices have been published to assess frailty, and their accuracy to predict disability, mortality and institutionalisation has already been compared.[25] AUC of Groningen Frailty Indicator, Fried Physical Frailty Phenotype and Vulnerable Elders Survey were, respectively, 0.61; 0.69; 0.67 for mortality and 0.67; 0.63; 0.71 for institutionalisation. Some studies have also assessed the predictive ability of the HFRS in various clinical contexts. Schnieder *et al* showed that patients with a higher HFRS are at greater risk of mortality and adverse outcomes following large vessel occlusion stroke.[26] The sensitivity and specificity of the HFRS versus CFS to detect frailty have been compared among hospitalised patients with chronic obstructive pulmonary disease. They concluded the HFRS had a poor capacity for detection of frailty among these patients compared with a clinical scale such as the CFS.[27] In a study conducted in an emergency department, other authors reported that both HFRS and CFS predicted 30-day mortality, length of stay and 30-day readmission, but found a weak Pearson's correlation coefficient of 0.36 (0.34–0.38) between these two scales.[28] In the same manner, in an intensive care unit, other authors found that both HFRS and CFS predicted 1-year mortality, but there was only a very weak correlation between these scales with a Pearson's coefficient of 0.13.[29] In the literature, most authors have used the CFS as a comparative frailty scale to assess the value of the HFRS. It would be interesting to also use other well-known scales, such as the Fried scale or the frailty index, which would shed additional light on the multidimensional aspect of frailty.

As Gilbert and colleagues have already pointed out, the level of agreement between the HFRS and the Fried Physical Frailty Phenotype and the Rockwood Index has been, respectively, reported to have Cohen's kappa coefficients of 0.22 (0.15–0.30) and 0.30 (0.22– 0.38).[30] This clearly shows that all these scales have different criteria and angles of approach to the broad entity that is frailty. Among the various existing scales, some focus on specific areas of frailty, such as physical frailty, while others are multidimensional. This also underlines the major interest in having a single tool like the bFRAil score to standardise the identification of frailty. The diverse specialties that have tested the applicability of the HFRS in their clinical context since its publication underline the extent to which identifying frailty is necessary and desirable in many medical areas. The added value of the bFRAil score is that it provides a predictive risk score for frailty based on four easily and routinely measured biomarkers. Our work also highlights the importance of age in the onset of frailty, for which it is a well-known risk factor, as shown by the AUCs in figure 3. Sex was also retained in the multivariate model. Indeed, frailty is usually more common in women. In addition, for some of the biomarkers considered here, such as haemoglobin, the reference thresholds differ according to gender. This is why this parameter has been retained as a score variable.

The strengths of our study are the large electronic database used for the development and validation of the score, the wide age range of patients included, the fact that this is the first study to our knowledge which proposes a tool based on simple, easily measurable biomarkers for identifying frailty and the ease with which the bFRAil score can be integrated into daily medical practice.

Some limitations can be pointed out. These are retrospective and monocentric data. We have applied biological thresholds for the biomarkers in our population selection criteria from the large electronic health database which are open to debate. However, we feel that these thresholds are relevant to a broad range of clinical situations in which it would be particularly important to assess the risk of frailty. The equation could have been developed in a different way by not pre-supposing the interest of these four biomarkers and by testing all the biological parameters available in the health data warehouse. However, we would probably have obtained another equation combining more complex parameters that are not routinely dosed in any laboratory, which is not the case for our final equation. In addition, one of the biomarkers, vitamin D, is not routinely measured during hospitalisation, which may have limited the size of the final population included. But its measurement is specifically carried out in particular situations like after a fall or a fracture which can be negative health events associated with frailty, suggesting that the selected population may correspond to our target population.

This biological score has a good negative predictive value. It could be used regularly in patients, especially those who do not complain. When negative, it could be used to reassure healthcare professionals that there is no risk of frailty in most cases. Conversely, when positive, further investigations should be carried out to verify whether pre-frailty or frailty is underway. Indeed, as for each frailty scale, when the result is in favour of a risk of frailty, it is then necessary to carry out a comprehensive, in-depth assessment to identify which areas of intrinsic ability are impaired, which geriatric syndromes are in place and thus propose appropriate care and regular monitoring. The bFRAil score could so be used as a simple means to target patients who require specialised evaluation to assess any possible alterations in physiological domains that may have occurred. Future studies validating this score are needed.

CONCLUSION

This study has made it possible, for the first time, to develop and validate in a hospital setting a biological predictive frailty score referred to as the bFRAil score combining four easily measurable biomarkers (CRP, haemoglobin, albumin and vitamin D) with age and sex for identifying frailty in daily medical practice. The aim of using this score is to quickly and easily target patients requiring further standardised geriatric assessment to confirm the potentially altered physiological domains that may have led to the occurrence of frailty. Further studies are needed to validate its use.

Author affiliations
[1]Department of Geriatrics, CHU Lille, Lille, France
[2]Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1167-RID-AGE-Facteurs de Risque et Déterminants Moléculaires des Maladies Liées au Vieillissement, Lille, France
[3]Statistics, Economic Evaluation, Data-Management (SEED), CHU Lille, Lille Cedex, France
[4]University of Lille, CHU Lille, ULR 2694-METRICS: Evaluation des technologies de santé et des pratiques médicales, Lille, France
[5]Gerontology Department, Vrije Universiteit Brussel, Brussels, Belgium
[6]Frailty & Resilience in Ageing Research Unit, Vitality Research Group, Vrije Universiteit Brussel, Brussels, Belgium
[7]INCLUDE - INtegration Center of the Lille University hospital for Data Exploration, CHU Lille, Lille, France
[8]Special Interest Group on Aging Biology of European Geriatric Medicine Society

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Contributors AM, ML, ED, PB and EB designed the study. AM, ML, ED, PB and MG acquired and analysed the data. AM, ML, ED, FP, J-BB, IB, PB, MG and EB interpreted the data, wrote and revised the manuscript. AM and EB are responsible for the overall content as guarantor. AM and EB accept full responsibility for the finished work and the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of CHU Lille (CNIL agreement n°2202081).

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Data availability statement Data are available upon reasonable request. The data that support the findings of our study are available from the corresponding author upon reasonable request.

ORCID iD
Aurélie Mailliez http://orcid.org/0000-0002-6731-5352

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