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Classification of ≥80-year-old individuals into healthy, moderately healthy, and frail based on different frailty scores affects the interpretation of laboratory results

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ABSTRACT

Background: Interpretation laboratory analyses are crucial when assessing the patient's condition. Reference intervals from apparently healthy and disease-free individuals may cause problems when outcomes from elderly patients with chronic diseases and on medications are being interpreted. Elderly individuals are a heterogeneous group ranging from individuals managing their daily life independently to individuals with diseases and impairment, in need of nursing care around the clock, that is, frail; a term widely used although there is no consensus on the definition. **Aims and Objectives:** The aim of the study was to study the effect of classification of elderly into healthy, moderately healthy, and frail, based on activities of daily living (ADL) and Mini-Mental State Examination (MMSE) or frailty index (FI), on the interpretation of outcomes regarding: Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and gamma-glutamyltransferase (γ-GT) levels. **Materials and Methods:** Individuals ≥80 years (n = 568) were classified either on ADL and MMSE or number of deficits, (FI). **Results:** Individuals classified as frail based on FI had lower mean levels for ALT, creatinine and γ-GT than individuals classified based on ADL and MMSE ($P < 0.05$). **Conclusion:** The model to define health status to some extent affected laboratory analyte levels in ≥80 years old, classified as healthy, moderately healthy, and frail based on ADL and MMSE versus FI.

Key words: Aging; Frail elderly; Analyte; Reference interval; Clinical interpretation

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INTRODUCTION

Evaluating laboratory analyte levels are a crucial part of assessing the patient's condition. This may be done by comparing with previously recorded levels from the same individual or against a set of appropriate group-based reference intervals.[1,2] Conventional reference intervals are often developed from apparently healthy, that is, disease-free individuals aged 18–65 years.[3-5] Only a few reference intervals for people aged ≥80 have been published. In one study on reference intervals in 80 years old, individuals with fasting glucose ≥7.0 mmol/L were excluded from

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the study.[6] In another study, the inclusion criterion for being considered healthy was not specified.[6,7] Other studies have included individuals ≤79 years, while excluding all persons ≥80 years.[7,8] The Nordic Reference Interval Project (NORIP) included healthy individuals above 17 years old, but among the 3000 participants, there were only 64 who were >79 years.[9]

If conventional criteria, such as being apparently healthy, are used for developing reference intervals in ≥80 years old, only a small proportion will meet the current criteria for inclusion. We have reported that only 7% of an elderly cohort of nursing home residents (NHRs) fulfilled the criterion free from disease and medication.[10] Providing reference intervals for children are also complicated, as consideration must be taken to the different phases of physiological development during childhood.[11] Furthermore, in elderly individuals, similar complexity applies due to the physiological decline. The aging process is influenced by a general decline in organ functions and loss of muscle mass, so called sarcopenia, as a result of malnutrition and meno/adenopause.[12] In addition, the risk of chronic disease increases with increasing age. In accordance with the aging process, we reported[10] that the levels of some commonly used analytes differed in ≥80-year-old NHRs in relation to the reference intervals provided by NORIP.[9]

Elderly individuals, 80 years and older, are a heterogeneous group ranging from individuals managing their daily life independently to individuals with diseases and impairment, in need of nursing care around the clock, often referred to as "frail." Thus, the health status should impact laboratory analyte levels. Accordingly, in 569 ≥80-year-old individuals, covering a health spectrum from NHRs to individuals without disease or medication, we noted intergroup differences in levels of some laboratory analytes, when classifying them into healthy, moderately healthy, and frail, based on diseases, physical and cognitive functions, including ADL and MMSE.[13] However, health is not a well-defined condition; rather, health and disease are part of the same continuum with no fixed points for either "health" or "disease," for example, in relation to aging.[14] In addition, although many elderly persons suffer from ill health, there are others who, despite increasing age stay in good health, often with diagnosed but well treated diseases. There is a lack of reference interval studies that include elderly individuals' health status, for example, in relation to frailty.

Frailty is described as a multidimensional syndrome in terms of loss of reserves that give rise to vulnerability.[15] However, frail individuals are not a homogeneous group, as this multidimensional syndrome presents in many different ways and there is a great diversity in combinations of different diseases.[16,17] Still, frailty is a term that is widely used even if there is no consensus on the definition.[18] One definition, often adopted regarding frailty as a clinical syndrome, is based on at least three of five criteria: Low grip strength, low energy, slow walking speed, impaired physical activity, and unintentional weight loss.[19] Another definition is based on assessment of the person's ability to perform activities of daily living (ADL) and cognitive function measured by the Mini-Mental State Examination (MMSE).[13,15,17,20] A third definition is based on summing deficits in health to define frailty, that is, the more deficits individuals have, the more likely they are to be frail.[21-23] These deficits, which form the basis for the frailty index (FI), can be symptoms, signs, diseases, disabilities, laboratory analyte levels, radiographic, or electrocardiographic abnormalities. The FI is expressed as a ratio of present deficits to the total number of deficits considered.

Using reference intervals developed from apparently healthy and disease-free individuals might not be valid or even misleading, when laboratory outcomes from frail elderly with chronic diseases and on medication are being interpreted. Furthermore, elderly individuals with well-treated diseases need to be assessed in a proper way when becoming ill.

Aims and objectives

The aim of the present study was to investigate the effect of classification elderly above 80 years into healthy, moderately healthy, and frail, based on ADL/MMSE or FI, on the interpretation of the laboratory analytes albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and gamma glutamyltransferase (γ-GT).

MATERIALS AND METHODS

Data originated from three different cohort studies, described elsewhere, for which blood samples were collected from altogether 568 individuals aged ≥80 years: NHRs,[16] the Elderly in Linkoping Screening Assessment (ELSA 85)[17] and the NORIP (NORIP raw origin 80).[9] Individuals in NHRs were all in need of care around the clock[16] and in ELSA 85, most of them lived in ordinary housing, some in sheltered accommodation, and a few more in nursing homes. Within ELSA 85, the whole range from disease free to frail was represented, together with many with a health condition in between, actually with well-treated diseases.[17] Briefly, individuals included in NORIP were disease free and met the inclusion criteria for conventional reference intervals.[9] For NHR, ELSA 85, and NORIP, non-fasting venous blood samples were collected in evacuated tubes and centrifuged. The plasma was frozen

to −80°C until analyzed, which varied between a few weeks and several years between the three different studies.

Because different anticoagulants were used; ethylenediaminetetraacetic acid (EDTA) for NHRs and lithium heparin for the ELSA 85 and NORIP, it was decided that all analytes for the present study had to be suitable not only for lithium heparin but also with EDTA. Therefore, included analytes were restricted to albumin, ALT, AST, creatinine, and γ-GT, analyzed using routine methods.

Study cohorts: Healthy, moderately healthy, and frail individuals

In our previous study of levels of analytes in the elderly,[13] the individuals were classified into three cohorts: Healthy, moderately healthy, and frail according to ADL/MMSE.[20] Healthy elderly people were classified as individuals with an ADL equivalent of ≤4 and an MMSE of 27–30 and, in accordance with the NORIP raw origin 80 study, without any chronic disease or medication. A frail NHR was defined as a person with an ADL of ≥5 points[24,25] and a MMSE of 0–26.[20,26] For ELSA 85, frailty was classified as all eight IAM items being assessed as "difficult" or "too difficult," and needing assistance to manage any of the following: bathing, dressing, toileting and feeding, and having a MMSE of 0–26. Individuals classified as moderately healthy had an ADL equivalent of ≥5 points, or a MMSE of 0–26 or some kind of chronic disease or diseases.

FI

The FI was constructed according to the procedure used by Searle et al.,[27] who developed a standard procedure for creating a FI by accumulation of deficits contributing to the individual's risk of death. The instrument includes variables that are available for the investigated individuals, on function, cognition, comorbidity, and physical performance. According to Searle et al., variables can be included if they satisfy five criteria: (1) Being a deficit associated with health status; (2) a deficit's prevalence must generally increase with age; (3) the chosen deficits must not saturate too early. For instance, age-related lens changes are nearly universal by age 55. (4) The deficits that make up a FI must cover a range of systems; and (5) if a single FI is to be used serially on the same person, the items that make up the FI need to be the same from one iteration to the next.[27] FI variables can accommodate ordinal and continuous variables as deficits, graded into a between 0 (where no deficit is present) and 1 (where the deficit is maximally expressed by the given variable). For calculating FI in the present study, we used variables that were documented by health-care personnel, concerning chronic diseases, medications, nutritional status (Mini Nutritional Assessment), ADL and MMSE, and living conditions and anthropometry (Table 1). In accordance with others,[28] in the present study, we used the classifications of FI ≤0.08 as healthy, FI ≥0.25 as frail, and the rest as moderately healthy.

Table 1: Variables and cutoff points for the frailty index (FI)

List of variables included in the frailty index	Cutoff points
Chronic heart disease	Yes=1, No=0
Stroke	Yes=1, No=0
Cancer	Yes=1, No=0
Diabetes mellitus	Yes=1, No=0
Chronic lung disease	Yes=1, No=0
Dementia	Yes=1, No=0
Thyroid disease	Yes=1, No=0
Antidepressants	Yes=1, No=0
Sleeping pills	Yes=1, No=0
Sedatives	Yes=1, No=0
Painkillers	Yes=1, No=0
Smoker	Yes=1, No=0
MNA[a]	Yes=1, Risk of=0.5, No=0
MMSE[b] score	*
Feel anxious	Most of the time=1, Sometimes=0.5, Rarely=0
Feel pain	Most of the time=1, Sometimes=0.5, Rarely=0
Help bathing	Yes=1, Some help=0.5, No=0
Help dressing	Yes=1, Some help=0.5, No=0
Help using toilet	Yes=1, Some help=0.5, No=0
Help eating	Yes=1, Some help=0.5, No=0
Help shopping	Yes=1, Some help=0.5, No=0
Help cleaning	Yes=1, Some help=0.5, No=0
Help with meal preparations	Yes=1, Some help=0.5, No=0
Help taking medication	Yes=1, Some help=0.5, No=0
Ability to walk inside	Yes=1, Some help=0.5, No=0
Ability to walk outside	Yes=1, Some help=0.5, No=0
Security alarm	Yes=1, No=0
Living alone	Yes=1, No=0
Marital	Yes=0, No=1
BMI[c]	**

[a]Mini Nutritional Assessment. [b]Mini-Mental State Examination. [c]Body mass index. *<10=1; ≥10 to ≤17=0.75; ≥18 to ≤20=0.5; >20 to <24=025; ≥24=0. **<18.5 or ≥30=1; 25 to <30=0.5; 18.5 to <25=0.

Coding of individual variables used as deficits in the FI

The binary variables were recoded "0" to indicate the absence and "1" to denote the presence of a deficit. For variables that included an intermediate answer, for example, "sometimes" or "maybe," an additional value of "0.5" was used. Regarding MMSE results, we recoded deficits according to the severity of the impairment.[29] We assigned 1 for scores <10, denoting severe dementia, 0.75 for scores ≥10 and ≤17 denoting moderate dementia, 0.5 for scores ≥18 and ≤20, denoting mild dementia, 0.25 for scores >20 and <24, denoting mild cognitive impairment (MCI), and 0 for scores ≥24, denoting no cognitive impairment.[1] A body mass index (BMI) <18.5 or ≥30 was considered a deficit "1," while 25 to <30 was regarded as a half deficit, "0.5," and 18.5 to <25 as the absence of deficit, "0."[27]

Statistical analysis

Descriptive statistics were used to present the distribution of healthy, moderately healthy, and frail individuals based on ADL/MMSE or FI. The 25th–75th percentiles are presented in box plots, illustrating the distribution of the analytes, with whiskers indicating minimum and maximum values. Reference intervals proposed for the Nordic countries, based on NORIP [9], are shown by vertical lines. Further, the 2.5th and 97.5th percentiles represent lower and upper limits for the analytes in the different groups.

For statistical comparisons of mean values of the analytes in relation to classification of health status, the individuals were randomly divided into two groups using PASW Statistics 25 (SPSS Inc., Chicago, IL.). Thereafter, the groups were classified as healthy, moderately healthy, or frail according to ADL/MMSE or FI. Student's t-test was used to compare the mean analyte values between the groups and $P<0.05$ was required for statistical significance.

RESULTS

Individuals in the NHR (n=167), ELSA 85 (n=338), and NORIP raw origin 80 (n=63) were classified into healthy, moderately healthy, and frail in two different classification models, that is, using ADL/MMSE or FI (Table 2).

The coherence of classification into healthy, moderately healthy, and frail, based on the two classification models, is presented in Table 3. All individuals classified as frail based on ADL/MMSE were also classified as frail using the FI. Nine individuals classified as healthy using ADL/MMSE were classified as frail using the FI. Altogether 8.8% of individuals (50/568) were classified as healthy based on ADL/MMSE, but as moderately healthy using the FI. Conversely, 3% (17/568) classified as moderately healthy based on their ADL/MMSE were considered healthy according to the FI. Individuals who fell under the same classification with both classification models, 378 out of 568 (67%), are given in bold numbers, as shown in Table 3.

As biological materials are often not normally distributed, the outcomes were also presented using percentiles or confidence intervals. In Table 4, the distribution of analyte levels, showing the 2.5 and 97.5 percentile, is shown for individuals divided according to the two classification models.

To illustrate medians, minimum and maximum values for the analytes, levels of albumin, ALT, AST, creatinine, and γ–GT are presented as box plots divided into healthy, moderately healthy, and frail based on the two classification models (ADL/MMSE vs. FI) (Figure 1a-e). The figure also provides the reference intervals proposed by the NORIP.[9]

Table 2: Distribution of 568 elderly persons classified into healthy, moderately healthy, or frail, using two different classification models

Classification based on ADL[a] and MMSE[b]	n (%)	Classification based on FI[c]	n (%)
Healthy	163 (28.7)	Healthy	121 (21.3)
Moderately healthy	254 (44.7)	Moderately healthy	173 (30.5)
Frail	151 (26.6)	Frail	274 (48.2)

[a]Activities of daily living. [b]Mini-Mental State Examination. [c]Frailty index

Table 3: Coherence in classification of individuals into healthy, moderately healthy, and frail based on two classification models. Bold numbers indicate same classification result with both classifications

Based on ADL[a] and MMSE[b]	Based on the FI[c]			Total
	Healthy	Moderately healthy	Frail	
Healthy	**104**	50	9	163
Moderately healthy	17	**123**	114	254
Frail			**151**	151
	121	173	274	568

[a]Activities of daily living. [b]Mini-Mental State Examination. [c]Frailty index

For 17 of the 568 included individuals, analytes were missing. After random division, the two groups were classified into healthy, moderately healthy, or frail, based on ADL/MMSE or FI (Table 4). No statistically significant differences were seen in mean levels for any of the analytes in individuals classified as healthy or moderately healthy. However, individuals classified as frail based on FI showed significantly ($P<0.05$) lower ALT, creatinine, and γ-GT levels compared with those classified as frail based on ADL/MMSE (Figure 1).

DISCUSSION

Elderly individuals are a heterogeneous group ranging from individuals managing their daily life independently to individuals with diseases and impairment, in need of nursing care around the clock. The present study investigated different ways of defining health status, that is, healthy, moderately healthy, and frail, in elderly individuals in relation to levels of laboratory analytes. No differences were found between the groups of healthy or moderately healthy individuals for any of the analytes, whereas individuals classified as frail based on FI had lower mean levels of ALT, creatinine, and γ-GT than individuals classified as frail based on ADL/MMSE.

Table 4: Distribution of analyte levels, showing the 2.5 and 97.5 percentile, in 568 elderly individuals divided into healthy, moderately healthy, and frail based on two classification model either according to ADLa and the MMSE[b], or based on the FI[c]

Analyte and classification model	Lower limit: 2.5 percentile	Upper limit: 97.5 percentile
Albumin (g/L)		
Healthy based on ADL and MMSE	34	44
Healthy based on FI	34	46
Moderately healthy based on ADL and MMSE	31	45
Moderately healthy based on FI	33	45
Frail based on ADL and MMSE	27	41
Frail based on FI	27	44
Alanine aminotransferase (ALT) (µkat/L)		
Healthy based on ADL and MMSE	0.14	0.55
Healthy based on FI	0.13	0.76
Moderately healthy based on ADL and MMSE	0.12	0.56
Moderately healthy based on FI	0.14	0.53
Frail based on ADL and MMSE	0.08	0.39
Frail based on FI	0.09	0.48
Aspartate aminotransferase (AST) (µkat/L)		
Healthy based on ADL and MMSE	0.22	0.61
Healthy based on FI	0.20	0.76
Moderately healthy based on ADL and MMSE	0.18	0.58
Moderately healthy based on FI	0.18	0.48
Frail based on ADL and MMSE	0.22	0.90
Frail based on FI	0.19	0.73
Creatinine (µmol/L)		
Healthy based on ADL and MMSE	56	130
Healthy based on FI	57	139
Moderately healthy based on ADL and MMSE	56	198
Moderately healthy based on FI	54	189
Frail based on ADL and MMSE	40	188
Frail based on FI	42	194
Gamma-glutamyltransferase (γ-GT) (µkat/L)		
Healthy based on ADL and MMSE	0.20	2.0
Healthy based on FI	0.20	2.1
Moderately healthy based on ADL and MMSE	0.17	1.9
Moderately healthy based on FI	0.19	2.2
Frail based on ADL and MMSE	0.15	5.6
Frail based on FI	0.15	4.3

[a]Activities of daily living. [b]Mini-Mental State Examination. [c]Frailty index

For albumin, special reference intervals developed by the NORIP apply to individuals >70 years old.[9] In frail individuals in the present investigation, independent of classification model, albumin levels were lower than in healthy and moderately healthy individuals, probably explained by sarcopenia.[12] Moreover, the albumin levels of frail individuals were lower and outside the NORIP's proposed interval[9] for about half of the individuals.

Results for ALT in the present study show that frail individuals classified based on their FI had lower ALT levels compared with frail individuals classified on the basis of their ADL/MMSE. This, in turn, means that if FI is used to assess health status, the low levels of ALT may be easier to detect compared to using ADL/MMSE. The lower limits for ALT, independent of classification model and health status, were higher for all the participants in the present study than reported by Helmersson-Karlqvist et al.,[6] although their upper limit was fairly similar to the upper limit for the healthy and moderately healthy elderly in the present study. The present results show that even if healthy and moderately healthy individuals had higher ALT levels than frail individuals independent of classification model, all levels in healthy and moderately healthy individuals were low, although still within the reference interval proposed by the NORIP.[9] This could lead to misinterpretation of the laboratory outcome as a high level of ALT in an investigated elderly person would still be within the reference interval and would, therefore, possibly be interpreted as a normal result, for example, in liver damage due to diseases.

The creatinine levels of the participants classified as frail in terms of ADL/MMSE were similar to the reference interval provided by the NORIP.[9] A commonly used measure of renal function is to use estimated glomerular filtration rate (eGFR), which in addition to the level of creatinine takes age and weight into consideration. In the present study, levels of creatinine have been used, as that is the analyte behind the estimation. The healthy and moderately healthy, independent of classification model, had slightly higher creatinine levels although still within the reference interval. In our previous study, 25% of increased creatinine levels in the elderly were associated with kidney disease, chronic obstructive pulmonary disease, male gender, and a high MMSE.[13] In the study by Helmersson-Karlqvist et al., only cardiovascular disease (CVD) was taken into consideration; the authors found higher levels of creatinine in males with CVD than in males without CVD.[6] In our previous study, almost 30% of the elderly were diagnosed with chronic heart disease, which was not, however, linked to the increase in creatinine levels.[13]

In the present study, both AST and γ-GT levels were at the lower end, but within the reference intervals proposed

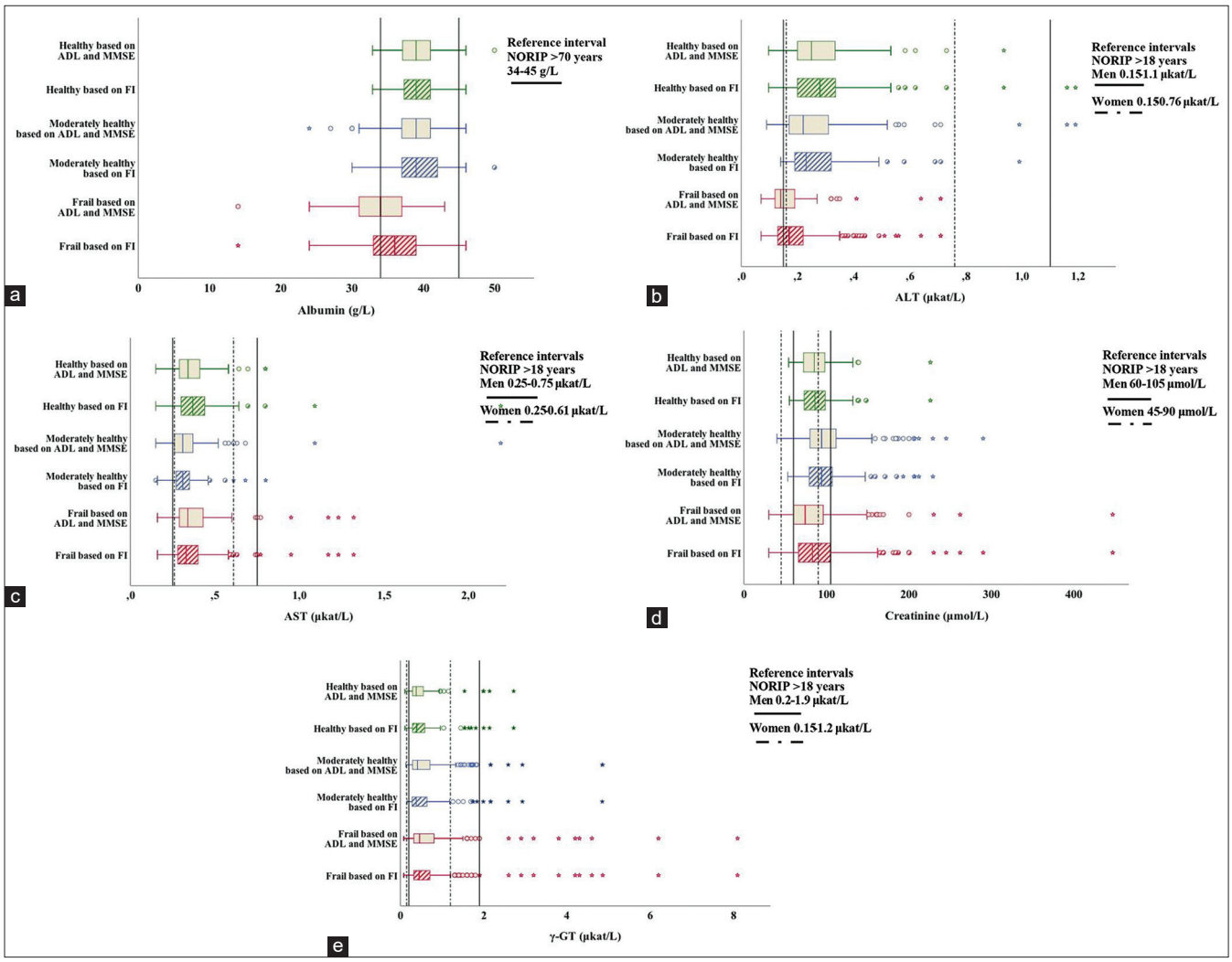

Figure 1: (a-e) Distribution of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and γ-glutamyl transferase (γ-GT) levels across the three subcohorts, of healthy, moderately healthy, and frail elderly individuals, classification based on activities of daily living (ADL) and Mini-Mental State Examination (MMSE) or FI. Medians and variation between 25th and 75th percentiles are presented in the box, and whiskers indicate minimum and maximum values. Circles represent values between 1.5 and 3 times the interquartile range, and asterisks (*) represent values that are more than 3 times the interquartile range. Two values for γ-GT in the frail, independent on classification form, are not displayed, 15.5 and 16.5 µkat/L. In vertical lines, the reference intervals proposed by NORIP

by the NORIP,[9] for all subgroups independently of classification model and health status. Therefore, clinically, it may be more important to be extra observant in elderly people with the high levels of AST and γ-GT, even if they are still within the reference intervals for these analytes. Interestingly, Helmersson-Karlqvist et al.,[6] found lower limit for AST to be higher than for all our subgroups of elderly individuals, while the upper limit for AST was similar to that in our present study. For γ-GT levels, the opposite was found in comparison of our findings, that is, the upper limit[6] was lower than for all of our subgroups.

Importantly, models for defining health status are not the only factor for interpreting laboratory values. The lower and upper limits of the reference intervals can be defined in several different ways. In the present study, we have used the 2.5 and 97.5 percentiles to determine the limits. This is in accordance with the proposed reference intervals both from NORIP[9] and according to Helmersson-Karlqvist et al.,[6] even if they used the computer program RefVal 4.0 (Department of Clinical Chemistry, Rikshospitalet, N-0027 Oslo, Norway).[30,31] RefVal implements the recommendations of the International Federation of Clinical Chemistry (IFCC) in the statistical treatment of reference values and handles outliers and data that are not normally distributed. When dividing the elderly into healthy, moderately healthy, and frail, as in the present study, the reference intervals provided by the NORIP and Helmersson-Karlqvist et al., seem to be appropriate for the healthy and moderately healthy, but not for the group of frail elderly individuals, independent of classification model. One probable reason is that the

NORIP only included healthy individuals and in the study by Helmersson-Karlqvist et al., only CVD was taken into consideration.[6,9] Although further studies are needed, our findings suggest that health status should be taken into consideration and not only that the individuals are above the age of 80, when developing reference intervals and for the interpretation of the outcome, for elderly people. Finally, there is a need for an international definition of frailty elderly individuals.

Limitations of the study

The scale of measuring frailty and the classification of participants into different levels of frailty can be done in different ways. Some studies have used a dichotomized classification, for example, frail/non-frail,[20] and Hoover has raised arguments for dividing the elderly population into four groups: Non-frail, pre-frail, more frail, and most frail, based on FI.[23] In the present study, we classified the participants in three different groups; healthy, moderately healthy, and frail, rather than non-frail and pre-frail as used by others.[22,23] Not every healthy individual will eventually become frail, and non-frail may be a precursor of frail. The rational for this was to differentiate moderately healthy elderly from both healthy elderly and frail elderly. If we had adopted, for example, Rockwood et al.,'s categorization[22] based on the FI (using one cutoff value at 0.25 to divide the elderly into non-frail and frail), the moderately healthy elderly had been classified as healthy. However, it is reasonable to assume that moderately healthy elderly, in contrast to such dichotomized classification, may use health services more than the healthy and the frail, since frail elderly are being taken care of in nursing homes.

In the present study, blood from the participating individuals was collected from different studies and the selection of anticoagulants differed. Thus, in NHR,[16] EDTA was used as anticoagulant, while in the ELSA 85[17] and NORIP[9] cohorts, tubes without anticoagulant or addition of lithium heparin were used. In the present study, the EDTA anticoagulant limited the choice and number of investigated analytes; hence, five of the common laboratory analytes could be studied. The majority of the NHRs suffered from heart disease. Unfortunately, as the studies were restricted to the use of EDTA plasma, they, therefore, excluded analysis of some analytes of interest in CVD. Using blood samples collected and frozen, pre-analysis can affect the activity of the investigated analytes, such as loss of enzyme activity for ALT after freezer storage.[32] Plasma from the study cohorts was analyzed at different laboratories using measurement methods of different manufacturers, which could be a disadvantage. Nevertheless, the accreditation system includes traceability for the calibrators of the analytes, to the same references.[33]

CONCLUSION

Although many elderly individuals suffer from ill health, there are others who, despite increasing age stay in good health, often with diagnosed but well treated diseases. Thus, the health status, defined as healthy, moderately healthy, and frail, may affect laboratory analytes with implication for reference values. The present study demonstrated that two models to define health status, by defining frail using either the ADL/MMSE or FI model, to some extent affected laboratory analytes levels in ≥80 years old, classified as healthy, moderately healthy, and frail. No differences were found between the groups of healthy or moderately healthy individuals for any of the analytes, whereas individuals classified as frail based on FI had lower mean levels of ALT, creatinine, and γ-GT than individuals classified as frail based on ADL/MMSE. The present study showed that the reference intervals provided by NORIP seem to be suitable for the analytes studied for the individuals classified as healthy or moderately healthy, but not for the individuals classified as frail. Defining reference intervals for laboratory analytes in the elderly, where also the person's health status and not only the age are taken into account, have potential but need to be further developed, as a complement to the reference intervals used today, which are mostly based on healthy and younger individuals.

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ETHICS APPROVAL AND INFORMED CONSENT

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Health Sciences, Linkoping University, Sweden (Dnr: M-8206 and 141-06). The health service directors of community care and the geriatric chief staff nurse gave their permission to conduct the study. The NORIP was approved by ethics committees in the five Nordic countries[34]. All participants, or their next of kin, gave written informed consent within the NHR, ELSA 85, and NORIP cohorts. It was made clear that participation was voluntary and could be withdrawn at any time.

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