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Interaction between geriatric syndromes in predicting three months mortality risk

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ABSTRACT

Objectives: Capturing frailty using a quick tool has proven to be challenging. We hypothesise that this is due to the complex interactions between frailty domains. We aimed to identify these interactions and assess whether adding interactions between domains improves mortality predictability.

Methods: In this retrospective cohort study, we selected all patients aged 70 or older who were admitted to one Dutch hospital between April 2015 and April 2016. Patient characteristics, frailty screening (using VMS (Safety Management System), a screening tool used in Dutch hospital care), length of stay, and mortality within three months were retrospectively collected from electronic medical records. To identify predictive interactions between the frailty domains, we constructed a classification tree with mortality as the outcome using five variables: the four VMS-domains (delirium risk, fall risk, malnutrition, physical impairment) and their sum. To determine if any domain interactions were predictive for three-month mortality, we performed a multivariable logistic regression analysis.

Results: We included 4,478 patients. (median age: 79 years; maximum age: 101 years; 44.8% male) The highest risk for three-month mortality included patients that were physically impaired and malnourished (23% (95%-CI 19.0–27.4%)). Subgroups had comparable three-month mortality risks based on different domains: malnutrition without physical impairment (15.2% (96%-CI 12.4–18.6%)) and physical impairment and delirium risk without malnutrition (16.3% (95%-CI 13.7–19.2%)).

Discussion: We showed that taking interactions between domains into account improves the predictability of three-month mortality risk. Therefore, when screening for frailty, simply adding up domains with a cut-off score results in loss of valuable information.

1. Introduction

Frailty is a medical condition of increased vulnerability and poor resolution of homeostasis after a stressor event. This is a consequence of cumulative decline in many physiological systems during a lifetime (Clegg et al., 2013). Around 40% of older hospitalised patients are frail, which is associated with functional decline, readmission, institutionalisation, and mortality (Joosten et al., 2014; Vu et al., 2017; Apostolo et al., 2017; De Vries et al., 2011; Dent et al., 2016). Identifying frail patients is important to prevent frailty progression, to lower the risk of poor health outcomes and to aid in decision-making.

For many years, there has been a growing demand for quick and easy frailty screening tools to deal with the increasing number of older hospital patients despite limited availability of geriatric expertise and hospital resources. However, capturing frailty using a quick tool has proven to be challenging, and consensus on a gold standard for frailty screening has yet to be reached (van Dam et al., 2018; Winters et al., 2018; Calf et al., 2020; van Loon et al., 2017; Van Munster et al., 2016; Heim et al., 2015; Warnier et al., 2020; Apostolo et al., 2017; Hoogendijk et al., 2019). What makes frailty difficult to measure is its complexity; it is associated with many variables such as age, illness severity, nutrition, exercise, social factors and mental health (Clegg

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et al., 2013; Fried et al., 2001; Rockwood et al., 1994; Pijpers et al., 2012).

Dutch hospitals are required to screen every patient aged ≥70 years with the VMS frailty instrument (Safety Management System screening 'frail older patients' Heim et al. (2015), Rooij et al. (2009), Oud et al. (2019), Winters et al. (2018), Calf et al. (2020), Heim et al. (2015), Warnier et al. (2020), Oud et al. (2015), Folbert et al. (2017), Souwer et al. (2019), Hermans et al. (2019), Schuijt et al. (2020), Snijders et al. (2020)). This screening tool was originally developed to identify and reduce avoidable damage due to hospitalisation by identifying the presence of an increased risk of geriatric syndromes and to take adequate preventive measures accordingly. The tool includes four geriatric syndromes associated with frailty and adverse outcomes: risk for delirium, recurrent falls, the presence or absence of malnutrition, and functional impairment.

Lately, there are an increasing number of studies using the VMS frailty instrument to identify frailty, rather than assessing the individual domains to prevent or reduce functional decline in older patients. There are, however, some pitfalls. Because the VMS frailty instrument was not originally designed as an integrated frailty instrument, a cut-off for frailty was not established before its introduction. As a consequence, in clinical practice and in research, many different scores are used. The different VMS scores are based on the four individual domains and are either used as a continuous score or a sum score with various cut-offs (van Loon et al., 2017; Heim et al., 2015; Warnier et al., 2020; Souwer et al., 2019; Snijders et al., 2020; Van der Ven et al., 2015). The different scores all have high sensitivity, but moderate specificity for discriminating between frail and non-frail patients (Calf et al., 2020; Van Munster et al., 2016; Heim et al., 2015; Warnier et al., 2020). These cut-off scores for frailty do not likely reflect the heterogeneity of the frail older population (Looman et al., 2018). We hypothesise that simply adding up the number of domains and dichotomising will result in a loss of information due to the complex interactions between the frailty domains with differing effects on mortality risk.

We aimed to identify these interactions and assess whether adding interactions between domains improves mortality predictability.

2. Method

This was a retrospective cohort study. We selected all consecutive patients aged 70 years and older who had been admitted to a non-ICU ward of a teaching hospital in the Netherlands for at least 48 h, between April 2015 and April 2016.

Data collected for the study came from hospital files and was manually checked with municipality data. These data included patient characteristics, scores on the domains of the VMS screening at admission, length of stay and mortality within three months after discharge (including in-hospital mortality). If a patient had been admitted to hospital multiple times during the study period, we used data from the first admission.

The VMS frailty questions were scored within 24 h of admission. The complete VMS screening tool consists of 13 questions (Rooij et al., 2009). Delirium risk was assessed with three items: memory problems, history of an acute episode of confusion or delirium and help in activities of daily living (ADL). Delirium risk was scored as present if a patient scored ≥ 1 item (out of 3) positive. Fall risk was scored as present if the patient had sustained a fall incident in the past 6 months. Malnutrition was scored as present if a patient scored ≥ 2 points on the Short Nutritional Questionnaire (Kruizenga et al., 2005 Feb) Physical impairment was defined as a Katz-ADL 6 score ≥ 2 points (Katz et al., 1963).

According to the Medical Ethical Committee the study did not need to be formally evaluated on medical ethics, as it was based on anonymous retrospective Electronic Medical Record data (reference number UMCG M1 7.207322/ 2016/680). The study was performed according to the principles of the Declaration of Helsinki.

2.1. Data analysis

Differences in groups were tested with the Chi Square test for nominal data and the Mann-Whitney test for ordinal and non-normally-distributed continuous variables.

In order to get insight into the various combinations of domains, we constructed an UpSet plot of the four domains showing the different frequencies of unique combinations. An UpSet plot is a modified bar chart in which each bar shows the frequency of a specific combination of variables (here: domains).

We used Recursive Partitioning Analysis (RPA) to analyse potentially predictive domain interactions. RPA is an alternative to model-based regression techniques for multivariable analyses. Compared to, for example, logistic regression (and resultant regression formulas), RPA trees readily identify patient characteristics and variable interactions, are easy to interpret clinically, and require no mathematical calculations (James et al., 2005). An RPA classification tree is obtained by recursively finding a split – a variable and its value (or cut-point value) that 'best' partitions the whole group of patients into two subgroups. The term 'best' refers to a partition resulting in the highest purity (i.e., homogeneity of a set) with respect to an event, in this case mortality, in the resulting subgroups.

In our application, RPA generated a classification tree for five variables: the individual score of the four domains and their sum score. This tree can be interpreted as a collection of variable interactions in the form of 'if-then rules', each with a condition part ('if') and a conclusion part ('then'). An example tree path: if a patient has physical impairment and is malnurished, then the risk for three-month mortality was 22.9%. We trained the classification tree with RPA on the fully imputed dataset (imputation method described below) and corrected for optimism of the predictive performance of the classification tree by means of bootstrapping (Freedman, 1981). Imputation and bootstrapping are described below. The optimal size of the tree was determined by cross validation.

To determine if the found domain interactions, in the form of the tree paths, were predictive for mortality, we performed a logistic regression (LogR) analysis that included the individual domain scores and the paths of the tree as interaction terms. We assessed the predictive performance of the LogR model in terms of (Clegg et al., 2013) discrimination with the area under the ROC curve (ROCAUC); (Joosten et al., 2014) positive predictive value (PPV) at the optimal decision threshold, which was determined with the Youden (1950, Vu et al. (2017) accuracy of the predicted probabilities by means of the Brier score (Brier, 1950; Apostolo et al., 2017) the calibration curve, which shows the correspondence between the predicted probabilities and the actual proportions of mortality.

We evaluated the complete modeling strategy (which included tuning the tree size with cross validation, learning the tree and building the LogR prediction model) by means of bootstrapping (200 iterations) in three ways: (Clegg et al., 2013) to test model performance, we obtained performance assessment of the logistic regression (LogR) model that uses the tree-based interaction terms; (Joosten et al., 2014) to assess predictor-based performance of the interaction terms, we selected the tree path predictors in a backward stepwise regression model using the Akaike Information Criterion (AIC) (Akaike, 1974; Vu et al., 2017) to assess model-based performance of the interaction terms, we used Chi Square ANOVA likelihood-ratio tests of the LogR model without tree paths and the logR model with tree paths (where we performed separate tests for both the full LogR models and the AIC models).

Based on the patterns of missing data as observed in visualizations of the missing data (using heatmap and UpSet plots), and because there were no differences in baseline characteristics between complete cases and all cases, we assumed the missing values were Missing At Random (MAR).

Data was imputed by a single imputation with five iterations using the Multiple Imputation by Chained Equations (MICE) approach (van

Buuren & Groothuis-Oudshoorn, 2011). The imputed dataset was used for generating the descriptive statistics and the analysis. Statistics on the missing values are also provided.

To analyse the data we used the statistical environment R version 3.6.1. We used the UpSetR package to generate the upset plot, the MICE package for imputation, the MASS package for stepwise model selection, and the Rpart package for recursive partitioning. The R packages are available for download from https://cran.r-project.org/web/packages/.

3. Results

Table 1 shows the patient characteristics. We included 4,478 patients. Median age was 79 years (maximum age: 101 years) and 44.8% were male. In 1,680 (38%) patients we found no positive score on any of the domains, 1,163 (26%) scored positive on one domain, 884 (19.7%) scored positive on two domains, 576 (12.9%) scored positive on three domains and 175 (3.9%) scored positive on all four domains. Delirium risk was the most frequent positive domain (Table 1, Fig. 1).

Fig. 1 shows frequencies and overlapping relationships of domains. The first bar from the left shows that there were 421 patients who had a fall risk but none of the other risks. The most common combination of three domains was physical impairment plus fall risk and delirium risk ($n = 335$). The most common combination of two domains was physical impairment plus delirium risk ($n = 365$).

Missing data on the 4 VMS domains ranged from 3.6% to 16.6% per question. In 74 (1.7%) patients there was no VMS screening data available. (Supplement S1).

Within the three-month period after discharge, 407 (9.1%) patients had died (Table 1). Table 2 shows that all VMS domains scores were predictive for mortality with ORs ranging from 1.5 to 3.2. We also checked the sum score of the VMS domains, which showed higher ORs for higher scores.

Fig. 2 shows the classification tree. Every patient fit the criteria of just one of the mutually exclusive subgroups defined by the path from the top (root) to a leaf. The likelihood of death within three months is given in the corresponding box. For example, patients without physical impairment but with malnutrition had a risk of death within three months after discharge of 15.2%. At highest risk for mortality were patients with physical impairment and malnutrition (23.0%). Different patient groups had comparable mortality risks but this was based on various combinations of domain scores (e.g., with malnutrition but without physical impairment the risk was 15.2%; with physical impairment and delirium risk, but without malnutrition this risk was 16.3%).

The tree only includes variables and interactions that contributed to the prediction of the outcome. For example, fall risk does not appear at all in the tree because it did not provide added predictive value. For patients with physical impairment and malnutrition (the rightmost tree path), delirium risk had no added predictive value to trigger further stratification.

Predictive performance of the classification tree for discrimination was fair as it achieved an optimism-corrected ROC-AUC of 0.711 (optimism = 0.0096) based on 200 bootstrap samples. The PPV was 0.18 (bootstrapped CI: 0.14–0.19). For accuracy, an optimism-corrected Brier score of 0.078 (optimism = -0.0008) was obtained. The calibration curve is included in Supplement Fig. 2 and shows (in the range [0.03–0.23] of predicted probabilities) that the curve closely follows the ideal line, where predicted probability of three-month mortality equalled the actual, observed, proportion of death.

Regarding the evaluation of the modelling strategy, we observed in all 200 bootstrap samples: the stepwise regression model selection always resulted in selecting at least one tree path as predictor; ANOVA likelihood tests showed significant difference ($p < 0.05$) between the logistic regression models with and without the tree path predictors; and a significant difference was found between the stepwise selection models with and without the tree path predictors (in 199/200 bootstraps, $p < 0.05$).

Table 1
Patient characteristics.

Variable	Total n = 4478	Alive n = 4071	Deceased n = 407	*P* value
Age, years (median, range)	79 (70-101)	79(70-101)	82 (70-97)	<0.001
Sex, male, n (%)	2007 (44.8)	1813 (44.5)	194 (47.7)	0.25
Delirium risk, n (%)	1811 (40.4)	1541 (37.9)	270 (66.3)	<0.001
Fall risk, n (%)	1378 (30.8)	1221 (30.0)	157 (38.6)	<0.001
Malnutrition, n (%)	898 (20.1)	732 (18.0)	166 (40.8)	<0.001
Physical impairment, n (%)	1272 (28.4)	1058 (26.0)	214 (52.6)	<0.001
Number of domains positive (n, %)				<0.001
0	1680 (37.5)	1629 (40.0)	51 (12.5)	
1	1163 (26.0)	1076 (26.4)	87 (21.4)	
2	884 (19.7)	756 (18.6)	128 (31.4)	
3	576 (12.9)	476 (11.7)	100 (24.6)	
4	175 (3.9)	134 (3.3)	41 (10.1)	
Acute admission, n (%)	2881 (64.3)	2557 (62.8)	324 (79.6)	<0.001
Length of stay, days (median, range)	5 (2-134)	6 (2-134)	8 (2-64)	<0.001
Medical admission, n (%)	2765 (61.7)	2450 (60.2)	315 (77.4)	<0.001

4. Discussion

Our study shows that in older patients a wide range of different VMS frailty domains (delirium risk, fall risk, malnutrition, physical impairment) and combinations of domains were present. Three-month mortality risk varied with different combinations of domains. At highest risk for three-month mortality were patients with a combination of the two domains physical impairment and malnutrition. We also showed that adding the combinations of domains as interaction terms to a logistic regression model improved the performance of the model. In other words, taking the interaction between the various domains into account instead of looking at the total score of positive domains or only the individual risk domain, increased predictive performance.

As expected, we found that the VMS was predictive for mortality (Winters et al., 2018; Heim et al., 2015; Oud et al., 2015; Folbert et al., 2017; Souwer et al., 2019; Schuijt et al., 2020; Van der Ven et al., 2015). There are strong indications that the paths of the classification tree that we constructed represent meaningful interactions for mortality risk. The calibration curve of the tree closely follows the ideal line where predicted probability equals the actual, observed probability. Also, we found a significant difference between the logistic regression models with and without the tree path predictors and a significant difference between the stepwise selection models with and without them. This implies that there are relevant interactions between frailty domains, and that taking these interactions into account improves prediction. For example, at highest risk for mortality were patients with a combination of physical impairment and malnutrition, and this suggests that the combination of these domains leads to a synergistic negative effect on mortality risk. The explanation might be that these are patients with sarcopenia, a strong risk factor for mortality in older patients (Cruz-Jentoft et al., 2010).

Another illustration of interaction between frailty domains is that, unexpectedly, increased fall risk did not have additive predictive value for mortality, and hence did not appear in the tree. This is in contrast to previous research (Oud et al., 2015). One possible explanation: a fall is a multifactorial geriatric syndrome, associated with many aspects of the

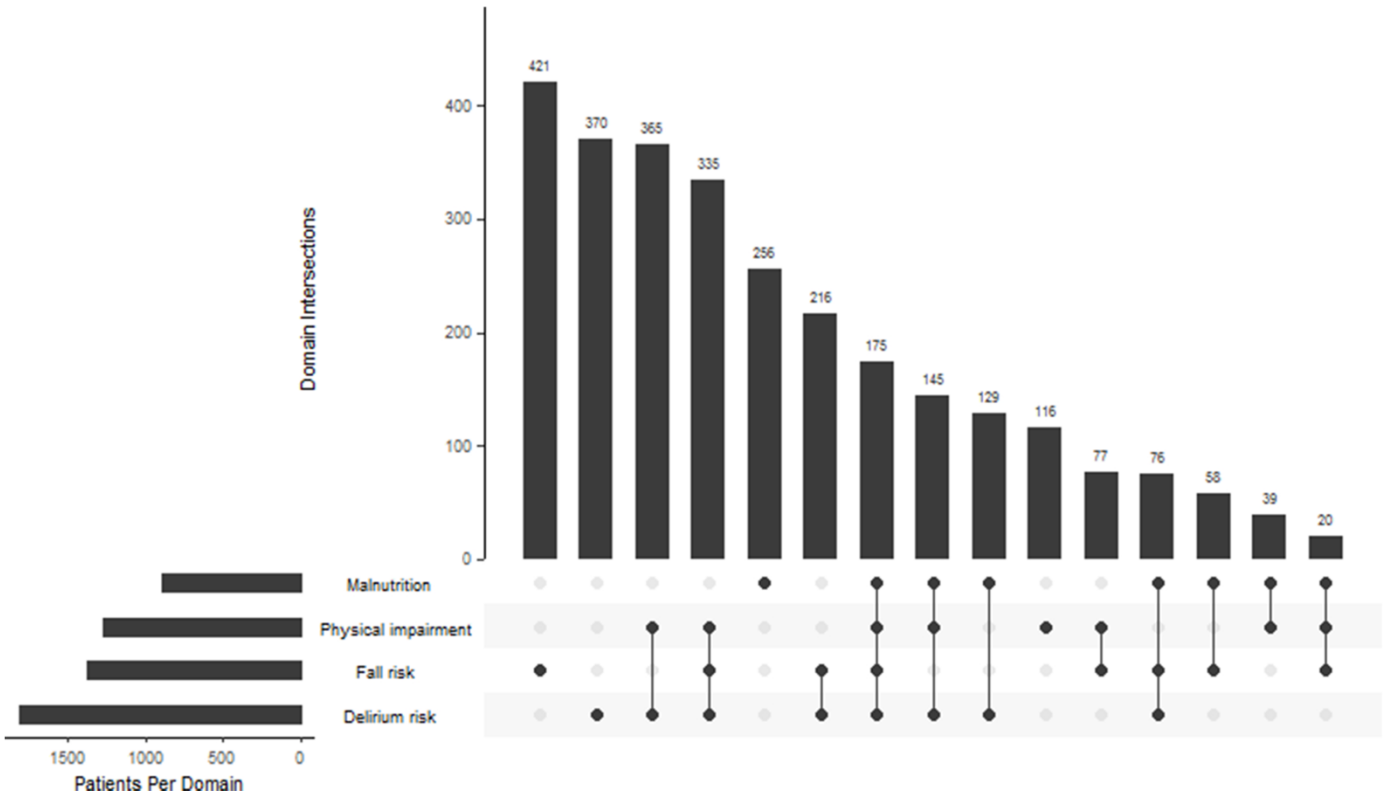

Fig. 1. UpSet plot showing frequencies of unique and combinations of frailty domain scores. Example: the first bar on the left shows that 421 patients had fall risk but none of the other risks.

Table 2
Individual domain scores and cumulative VMS frailty scores and three month mortality risk.

Variabele	Univariate OR (95%-CI)	P
Delirium risk	3.2 (2.6-4.0)	<0.001
Fall risk	1.5 (1.2-1.8)	<0.001
Malnutrition	3.1 (2.5-3.9)	<0.001
Physical impairment	3.2 (2.6-3.9)	<0.001
Number of domains		
0	*Ref.*	
1	2.6 (1.8-3.7)	<0.001
2	5.4 (3.9-7.6)	<0.001
3	6.7 (4.7-9.5)	<0.001
4	9.8 (6.2-15.3)	<0.001

other frailty domains, such as cognitive impairment, malnutrition and physical impairment. If we take into account the interaction between variables such as malnutrition and physical impairment, which are associated with both falls and mortality, then fall risk does not add to a higher mortality risk than the patient already had based on the other risk domains.

It is important to account for interactions between frailty domains when screening for frailty in older patients. Simply adding up domains with a cut-off score results in a loss of valuable information. This loss of information, in addition to the heterogeneity of frailty, makes the frailty concept very difficult to capture in simple (screening) tools. Agreement between screening tools and sensitivity and specificity of screening tools varies. How to screen for frailty is therefore an ongoing topic of debate (van Dam et al., 2018; Winters et al., 2018; Calf et al., 2020; van Loon et al., 2017; Van Munster et al., 2016; Heim et al., 2015; Warnier et al., 2020; Apostolo et al., 2017; Hoogendijk et al., 2019).

Rather than using a frailty instrument with a dichotomous cut-off score or a cumulative score, it seems to be more relevant to note which frailty domain(s) have positive scores and how they interact. Depending on the domains at risk, each frail older patient has different needs. For example, a patient with malnutrition needs dietary intervention and a patient with high risk of delirium benefits from help with orientation. The interventions aimed at preventing or reducing frailty progression and avoidance of negative health outcomes should therefore not be ''one size fits all''. The interventions should be, as with the VMS frailty program, domain-specific and tailored to the patient's needs. In addition, if a patient has a high risk interaction, we recommend a comprehensive assessment by a health care professional with expertise in geriatric medicine to explore the complex interactions and make a tailor-made treatment plan. For example, patients with malnutrition and functional impairment might have sarcopenia and be in need of a specific intervention, both nutritional (high protein) and physical (exercise, e.g., resistance based training) (Dent et al., 2016). Another example is that malnutrition and high delirium risk could both be related to cognitive impairment. In patients with this high risk interaction, it is important to rule out the diagnosis of underlying dementia in addition to interventions aimed at reducing malnutrition and prevention of delirium.

5. Strengths and limitations

We are the first to explore the distribution of frailty domains, the interaction between the different domains and the impact of this interaction on mortality risk. Moreover, our analytic approach is comprehensive in terms of validation strategy and the performance measures considered. We have shown a need to include interaction terms in future prediction models with frailty screeners.

A limitation of our study is that we collected the data retrospectively in a hospital where the VMS is being used in standard care. The outcome may have been influenced by preventive actions for high risk patients, such as the consultation by a geriatrician, dietician or physical therapist.

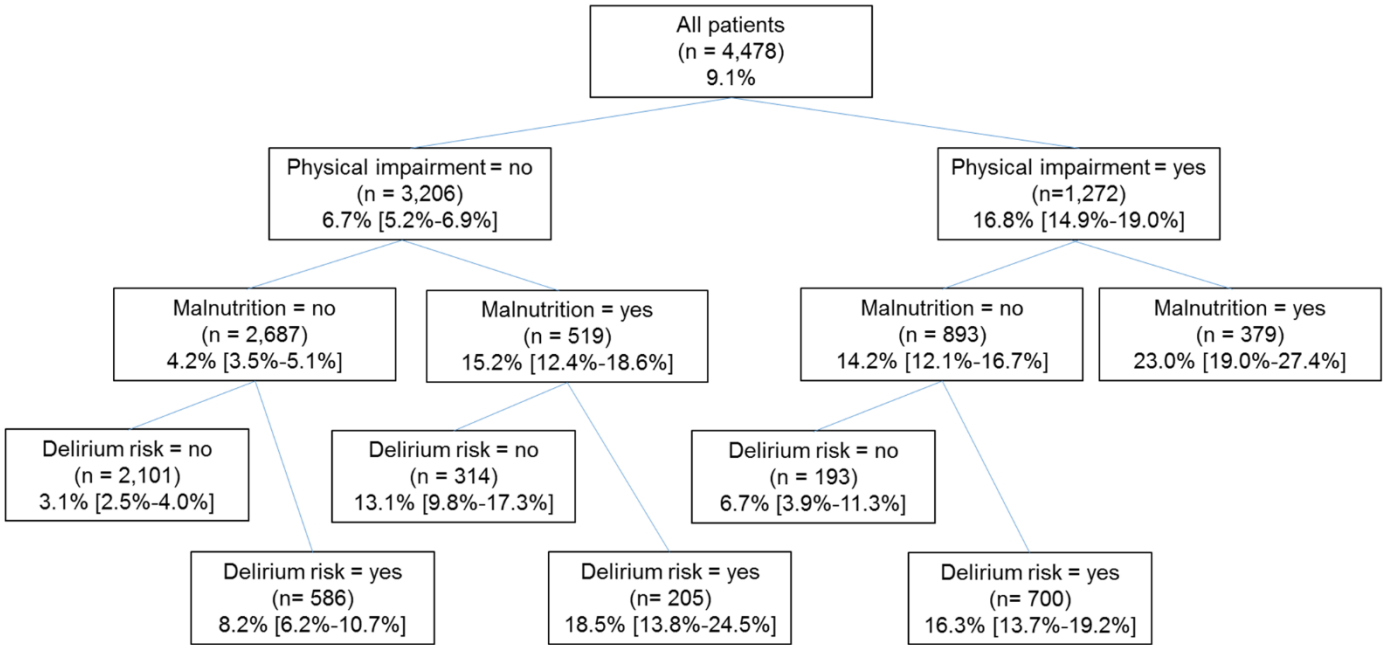

Fig. 2. Classification tree of VMS frailty domain scores Percentages represent the likelihood [95% confidence intervals] of three-month mortality for patients in each subgroup.

The VMS might be a stronger predictor without this intervention bias and interactions might also be stronger predictors. Our methodological approach can be nonetheless applied to populations in which the VMS was not used to inform clinical decisions.

Our outcome measure is limited to mortality. Other outcomes such as functional decline would also be interesting, since older patients often value independent living more than a longer life expectancy.

6. Conclusion and implications

We have shown that there are many meaningful interactions between frailty domains. Taking interactions between domains into account improves the prediction of three-month mortality risk. Therefore, when screening for frailty in older patients, simply adding up domains with a cut-off score results in loss of valuable information.

Author contributions

Study concept and design: FMM Oud, MC Schut, PE Spies, SEJA de Rooij, HJ van der Zaag, A. Abu-Hanna, BC van Munster; Acquisition of data: FMM Oud; Analysis and interpretation of data: FMM Oud, MC Schut, HJ van der Zaag; Drafting of the manuscript: FMM Oud, MC Schut; Critical revision of the manuscript for important intellectual content: FMM Oud, MC Schut, PE Spies, HJ van der Zaag, SEJA de Rooij A. Abu-Hanna, BC van Munster

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Declaration of Competing Interest

The authors have no personal or financial conflicts of interest.

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Supplementary materials

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