The clinical frailty scale predicts 1-year mortality in emergency department patients aged 65 years and older

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INTRODUCTION

Frailty is a state of increased vulnerability for poor resolution of homeostasis after a stressor event, so that frail individuals are at risk for adverse health outcomes and prolonged convalescence. In the emergency department (ED), triage acuity predicts the outcomes of ED length of stay, hospitalization, intensive care unit (ICU) admission, and mortality within 30 days, but may be ill-suited for prediction of adverse outcomes beyond this time frame. In a large Danish study, for example, abnormal vital signs were strong risk factors for mortality within the first 2 days, but hereafter, the association declined with time from arrival most rapidly until day 7. Longer term prognostication is likely more dependent on physiological reserve such as the degree of frailty rather than how ill or...
seriously injured the patient was at ED presentation.4 Such prognostication is relevant as accurate predictions empower more informed shared decision-making,5,6 and should ideally encompass the period of acute illness or injury. Second, predictions about mortality guided by frailty measures enable physicians not usually invested in geriatrics to consider concepts essential to appropriate geriatric care.7,8 Third, advancing an understanding of geriatric core concepts to the doorstep is essential because decisions in the ED sets the direction of many downstream actions,9,10 and, for patients, an ED visit represents a “unique teachable moment” to consider goals of care.11 Hence, this could contribute to a shift towards an integrated, patient-centric approach that aligns with the vision of personalized medicine and geriatricized emergency care.12-15

Frailty, as measured by the Clinical Frailty Scale (CFS)16 has been validated for use in several ED settings,17-19 and in other medical specialties,20-23 and is one of the most commonly used frailty measures. The popularity of the CFS in acute settings is likely due to its practical applicability in routine clinical care.24-26 It takes less than a minute to complete.27 is simple and multidimensional, and is therefore feasible to be used at triage.25,26

Frailty and triage acuity seem to be complementary measures, and if combined, a better understanding about complexity and vulnerability is provided.15,28,29 We have previously shown that the CFS was superior to triage acuity (as measured by the Emergency Severity Index [ESI]) for prediction of 30-day mortality, ICU admission, and hospitalization when corrected for age, sex, and presenting condition.30,31 Furthermore, the CFS has been shown to be predictive for 1-year mortality in a community dwelling population.16 Other constructs that capture frailty in the hospital setting, Winograd’s, Rockwood’s, Donini’s, and Schoevaerdts’ index are well associated with 1-year mortality,31 but have inappropriately low diagnostic accuracy.32 In these studies, measurements were obtained as part of a Comprehensive Geriatric Assessment on admitted patients up to 1 week after admission. Hence, prediction of 1-year mortality with a construct that measure frailty has not yet been investigated prospectively in the ED setting using consecutive sampling.

OBJECTIVE

The primary objective of this study was to validate the CFS for predicting 1-year all-cause mortality in the ED setting and to compare its prognostic performance to that of the ESI when adjusted for chronological age, sex and presenting condition.

METHODS

Study design and setting

This was a prospective observational study with consecutive sampling conducted from March 18 to May 20, 2019, in the ED of the University Hospital Basel (UHBS), a tertiary care center which evaluates over 52,000 ED visits per year. Approximately two-thirds of our ED population was raised in Northern or Central Europe. Most of the remaining population was raised in Mediterranean countries, Turkey, and Southeast Europe.33

Participants

All patients aged 65 years and older were screened consecutively for inclusion. Patients who were unable to provide informed verbal consent due to treatment in the resuscitation bay or immediate transfer to the ICU were not screened for inclusion. In accordance with previous recommendations, we did not exclude patients with mild cognitive impairment.34 Patients denying informed consent and patients unable to provide oral consent were not included. Ophthalmologic, pediatric and obstetric patients are treated at separate locations and were not screened for inclusion. A sample size estimation was performed for the validation study. As this study used the same population, we expected high mortality rates in this older population over the course of 1 year, ensuring that a sufficient number of events would be observed during the follow-up period.

Outcome

The primary endpoint was 1-year all-cause mortality. Data on all-cause mortality at the 1-year follow-up were collected using a combination of electronic health records, official registries, insurance data, contact with patients, primary care physicians or patients’ proxies as previously demonstrated.4 Sufficient power for our analysis was targeted at an inclusion of 2100 patients, including 5% for missing data.35,36

Predictors

All study team members took a 30-min teaching session on the fundamental concept of frailty, visualized by a short explanatory video, and its assessment with the CFS as previously described.30 A German version of the CFS was used for this purpose.16,30 The CFS was assessed by a member of the study team, as soon as patients entered a treatment bay, immediately after evaluation by a triage nurse who assigned the ESI level. The study team consisted of 4th to 6th year (of 6 years) medical students. We have previously demonstrated a weighted Cohen’s kappa of 0.74 (95% CI 0.64–0.85) between the study team and two experts, an Advanced Nurse Practitioner and an emergency physician, using a small, predefined subsample of the study population.30 In a different study, interrater reliability of CFS assignments between ED nurses and an ED physician with expertise in geriatric emergency medicine was excellent.18

Patient characteristics including demographics, ESI acuity level as assigned by triage nurses,2 and presenting condition (medical vs. surgical) were retrieved from electronic health records. Medical patients
are patients in whom conservative management is anticipated (e.g., dyspnea, localized weakness, chest pain); surgical patients are patients with injuries or disease who are anticipated to potentially require surgery (e.g., acute abdomen, femur fracture). The label "medical" versus "surgical" is assigned to patients upon ED arrival by the triage nurse; this serves to split these patients to dedicated teams. The ED is staffed with three teams of ED physicians (who see all patients), internal medicine residents on ED rotation (who see medical patients), and surgical residents on rotation (who see surgical patients). All patients are evaluated under the supervision of attending emergency physicians. Importantly, the CFS levels assigned at ED presentation were not reassessed during the observation period of 365 days.

Data analysis

Categorical data are presented as counts with relative frequencies and continuous data as means and standard deviations (SDs). Patients who presented several times to the ED during the study period only had their first ED visit included in the analysis to avoid confounding. Observations with missing values were omitted in data analyses. All analyses were based on complete data only. The CFS independence from age, sex, and condition regarding prediction of mortality was assessed, using a Cox proportional hazards regression model adjusted for age (continuous), gender (binary), and presenting condition (binary: medical vs. surgical).

Patients of the groups "very fit" (CFS 1), "well" (CFS 2), "managing well" (CFS 3), "vulnerable" (CFS 4), "mildly frail" (CFS 5), "moderately frail" (CFS 6), "severely frail" (CFS 7), and "very severely frail" (CFS 8) were monitored for a time interval of 365 days. Multivariable logistic regression models including age, sex, presenting condition, and either CFS or ESI, all categorical variables, were created. We collapsed CFS levels 1 and 2 to one group, as there were no events in the CFS level 1 group, making it unsuitable as reference level for statistical models. Patients with a CFS level 9 ("terminally ill") were excluded as done previously. Otherwise, the terminal illness, a prerequisite of level 9, will confound the observed relationship between CFS and 1-year mortality. Hazard ratios with 95% confidence intervals (CIs) were calculated for each predictor. The full-factor CFS model was assessed regarding effect with a likelihood ratio test. The proportional hazards assumption for the covariates was tested using Schoenfeld’s Test. Discriminative performance of each model was evaluated by calculating receiver operating characteristic (ROC) curves and the areas under the curve (AUROCs) with 95% CIs. We tested differences in AUROCs with the DeLong test. To assess calibration performance, calibration slope and intercept were extracted. Additionally, we calculated Brier scores to compare models. The predictive performance estimates were internally validated by bootstrapping as implemented in the package “rms” in R with 200 repetitions.38

Restricted mean survival time (RMST) was calculated for all CFS levels over 365 days.39 Survival curves were plotted for CFS levels 1 to level 8 to visualize 1-year all-cause mortality.

A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using R, version 4.0.2 (https://www.r-project.org/). This study is presented in adherence with Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting standards.40

RESULTS

Patient characteristics

After screening of 7859 patients for inclusion, 550 patients aged 18 years and older denied verbal consent, resulting in a total number of 7309 included patients. Among these, 4850 patients were aged 64 years or younger, leaving 2459 consecutive patients aged 65 years and older for further analysis of whom 268 were re-presentations. Thirty-eight (1.7%) patients had missing data on CFS level, and 15 (0.7%) patients were lost to 1-year follow up. The final study population included 2191 patients (Figure 1). Mean age (SD) was 78.9 years (8.4), 1124 (51.3%) were female, and 1281 (58.5%) received a medical diagnosis. 1040 (47.5%) patients were assigned a medium urgency triage level of ESI 3 (Table 1). The five presenting chief complaints dyspnea, abdominal pain, chest pain, dizziness, and back pain, based on a list of 36 predefined presenting chief complaints,26 were the most commonly reported. Regarding patient characteristics (age, sex, triage level, and presenting condition), there does not appear to be a difference between the population of patients lost to follow-up or between the population of patients with missing data on CFS level compared with patients analyzed (Of note, Table 1 depicts the overall population of 2191 patients aged 65 and older, for baseline demographics of the final study population, see Supporting Information Table S1).

Main results

All-cause mortality was 17% (372 deaths) within 365 days. Table 1 demonstrates the mortality rate stratified by CFS level.

The effect of the factor “CFS group” was estimated in a Cox regression model and tested using a likelihood ratio test \(X^2 = 175.43; \ p \leq 0.001\). Survival curves for all CFS levels, except level 9, are shown in Figure 2. Higher frailty levels were associated with higher hazard ratios (see Table 2). Results of the Schoenfeld test were only significant for the independent variable “CFS group,” indicating that proportionality for the hazard ratios of the CFS groups cannot be assumed \(X^2 = 38.48; \ p \leq 0.001\). The RMST is 365 days for the CFS level 1, while declining or remaining constant for every upgrade in CFS level down to 219 days in CFS level 8 (Table 2).

The ROC curves of the multivariable logistic models with CFS group and ESI level (Figure 3) visualize models’ discriminative performance for 1-year all-cause mortality. The CFS model yielded an AUROC of 0.767 (95% CI 0.741–0.793), while the ESI model (both models adjusted for age, sex, and presenting condition) yielded an AUROC of 0.703 (95% CI 0.673–0.732), with a significant DeLong’s test comparing the AUCs \(z = 5.69; \ p\text{-value} <0.001\). Bootstrapped
estimates of calibration slope and intercept yielded 0.960 and 
−0.047, respectively, for the CFS model, while calibration slope 
and intercept were 0.973 and −0.029 for the ESI model respectively. 
Additionally, the Hosmer-Lemeshow test was non-significant for 
both models, confirming acceptable fit. A lower Brier score of 0.126 
for the CFS model compared to 0.134 for the ESI model in the same 
population indicates overall better predictive performance of the 
CFS model (Supporting Information Table S2).

Odds ratios (ORs) for the different predictors in the CFS model 
are shown in Table 2.

**DISCUSSION**

We performed a prospective validation of the CFS in a sample of 
consecutive ED patients aged 65 and older for predicting 1-year 
all-cause mortality. We found the CFS to be an independent predic -
tor for 1-year all-cause mortality after correcting for age, sex, and 
medical condition and that each increase in CFS level is associated 
with decreased survival times. In addition, the CFS displays superior 
discriminatory performance compared to the ESI when adjusted for 
age, sex, and presenting condition.

We found the CFS to be superior to the ESI in accurately dis- 
criminating between those who would experience the outcome and 
those who would not over 1 year. This is in line with our previous 
findings for 30 day-follow-up. Previous studies investigating prog-
nostic performance of the CFS produced survival curves that largely 
confirm the separation observed in this study at 1 year in both the 
acute care setting and the primary care setting. However, the 
CFS in these studies was collapsed into different subgroups render- 
ing it difficult to compare results directly. For clinical purposes, we 
believe that the use of RMST in this study could potentially facilitate 
a better comprehension of prognosis in conversations with patients, 
an aspect that is of particular importance in the emergency setting.

Very few observations were lost to follow-up during this study, 
allowing for a complete case analysis and omitting imputation proce-
dures often necessary in prognostic research. This also enables us to 
correct a high number of events per predictor variable, increasing 
the validity of our findings.

Measures of illness acuity should guide immediate actions by 
predicting high urgency outcomes (e.g., ICU-admission within a short 
timespan). Frailty describes the ability to recover after acute illness. 
Measures of frailty should demonstrate the ability to provide graded 
risk estimates to more meaningful patient-centered modulation 
of treatment plans for low urgency outcomes in the long term. We 
show that the CFS does indeed perform well in a 1-year time-horizon, 
stratifying the population in distinguishable subsets with worsening 
outcomes for each CFS level increase and may, thus, be a valuable 
addition to the ESI for emergency clinicians. Imagine two 80-year-old 
patients (A and B) with suspected pneumonia both assigned an ESI 
level of 3. The needs of patient A living with mild frailty might be very 
different from the very severely frail patient B who spends most of 
her time in bed and might be in her last year of life.

The CFS has been reported to be predictive in a variety of clinical 
scenarios, such as cardiopulmonary resuscitation and trauma. In 
some scenarios, however, the CFS may be of limited use compared to 
estimates of illness acuity, but this is controversial. For example, CFS 
did not predict mortality well in patients admitted with COVID-19 in one 
study, and illness acuity as measured using Early Warning Score outper-
formed CFS in a similar study. Both studies suggest the presence of a 
protective interaction term between CFS and the presence of coronavi-
rus disease 2019 (COVID-19) that may be attributed to immune senes-
cence in older more frail adults. However, these findings are likely biased 
by selection as they are restricted to patients who were ultimately ad-
mitted after their initial evaluation in the ED and at least 65 years old. 
Other studies did find that frailty was associated with adverse outcomes 
in COVID-19 that worsened with increasing frailty.

To our surprise, we found separation on the survival plot for 
CFS level 8 compared to lower levels. A CFS of 7 or above has

**FIGURE 1** The chart displays recruitment and follow-up 
procedure of consecutive ED patients aged 65 and older
been considered a range that indicated futility of resuscitation attempts previously, and subjects with CFS levels 6 to 9 have been grouped when examining outcomes after cardiopulmonary resuscitation. Given the considerable separation we observe in Figure 2 between CFS levels 5 to 7 and level 8, despite excluding patients treated in the resuscitation bay, grouping levels 6 to 9 seems inappropriate because of the significant differences in survival-rates. Hence, outcome-incidences should be presented without grouping in future studies of the CFS. Furthermore, surviving cardiac resuscitation is often also related to other adverse clinical outcomes and more knowledge is needed on the ability to recover after cardiopulmonary resuscitation depending on the degree of frailty.

**Limitations**

This was a single-center study, which might limit generalizability, and the sample may not be representative of the general ED population. The sampled population came from the Northwestern part of Switzerland, which has a well-established primary care infrastructure and we expect 7% to be nursing home residents based on previous studies from this site on a similar population. Many older patients are referred to the ED after initial evaluation by their primary care physician, which may lead to the inclusion of a relatively high percentage of frail and possibly acutely ill patients. However, we found the observed 1-year mortality in this study to be lower than what is being reported on the general population.
in the acute care setting elsewhere. This may imply that the observed ability to accurately predict individual risk will be impacted in other settings and suggests an underestimation of 1-year mortality compared to the general population. However, this limitation likely applies to most areas of prospective research where procuring verbal consent is essential, by which those who are most ill are filtered out. Furthermore, the older population will often experience temporary cognitive impairment due to the acute illness itself, which may put measures of acute illness at further disadvantage to frailty models for study designs that require consent. We included patients with minor cognitive impairment, which we expect will have reduced the observed differences in overall mortality to the general ED population. Studies used for service evaluation may be better suited despite severe limitations of this design. To comprehend the possible impact on prognostic performance, studies are needed that compare the case-mix using these two different types of sampling in one population. Using assessments of frailty at arrival to predict adverse outcomes has been likened with "predicting speed at traffic lights" in that frailty may be progressing at different paces and patient preferences and social networks may affect the estimate of prognosis more than expected. Also, frailty likely varies over time getting both better and worse, although improvements in degree of frailty may not be associated with improvements in prognosis. Hence, our observations may be confounded by variability in frailty and patient preferences that we cannot account for. However, comprehension of 1-year-mortality risk may promote addressing long-term problems often neglected or presumed to be handled in the primary sector.

**TABLE 2** Odds ratios and RMST for 1-yr mortality

<table>
<thead>
<tr>
<th>CFS level</th>
<th>1-Yr mortality</th>
<th>OR</th>
<th>CI</th>
<th>RMST</th>
<th>SE (RMST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (reference)</td>
<td>Age, (yr)</td>
<td>1.04</td>
<td>1.03–1.06</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2 (reference)</td>
<td>Female gender</td>
<td>0.66</td>
<td>0.54–0.82</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Medical condition</td>
<td>1.28</td>
<td>1.03–1.58</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>CFS level</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1 (reference)</td>
<td>—</td>
<td>—</td>
<td>365</td>
<td>0.00</td>
</tr>
<tr>
<td>6</td>
<td>2 (reference)</td>
<td>—</td>
<td>—</td>
<td>359</td>
<td>1.80</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>3.22</td>
<td>1.59–6.52</td>
<td>342</td>
<td>3.05</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>4.72</td>
<td>2.33–9.56</td>
<td>336</td>
<td>4.33</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>7.18</td>
<td>3.53–14.59</td>
<td>311</td>
<td>7.37</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>8.90</td>
<td>4.37–18.11</td>
<td>305</td>
<td>8.62</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>10.76</td>
<td>5.28–21.94</td>
<td>298</td>
<td>10.24</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>22.93</td>
<td>11.30–46.54</td>
<td>219</td>
<td>16.84</td>
</tr>
</tbody>
</table>

Note: The CFS group “fit/well” (CFS level 1 and 2) was defined as reference category for the ORs. The RMSTs were calculated for each CFS group of the cox proportional hazards model. Medians and corresponding CIs for each RMST could statistically not be estimated, as too few events occurred in each CFS group. Abbreviation: SE, standard error.
the "price" of additional predictors, such as a detailed history to de-
tiated patients. At this time point, few predictors are available, and
of outcome prediction in this study is at arrival and on undifferen-
effect magnitude likely require updating. 53 Importantly, the timing
selection of comorbidities as well as the weights representing the
We do not have information on comorbidities, like the Charlson-
was only available at ED presentation. (medical versus surgical) for our regression models because
of the CFS model’s superiority remains stable nevertheless.
We included only the covariables age, sex, and condition
(medical versus surgical) for our regression models because
parameters were routinely available at ED presentation.
We do not have information on comorbidities, like the Charlson-
-Comorbidity Index (CCI). 53 While the CFS is a tool for the measure-
ment of "frailty," the CCI is a tool to measure "comorbidity." There
may be some overlap between these parameters; however, they
should be considered as different. 52 Furthermore, the CCI score
was not available for our study patients at ED arrival. The CCI may
not be properly used in the emergency setting, since diagnoses in
inpatients’ discharge reports are more carefully maintained than
those of outpatients’ discharge reports. ED diagnoses lists may be
incomplete due to the short average ED length of stay of approxi-
mately 5 h, possibly leading to a distortion of data concerning co-
 morbidity. In addition, the CCI was derived in 1987. 51 Therefore, the
selection of comorbidities as well as the weights representing the
effect magnitude likely require updating. 53 Importantly, the timing
of outcome prediction in this study is at arrival and on undifferen-
tiated patients. At this time point, few predictors are available, and
the "price" of additional predictors, such as a detailed history to de-
termining specific phenotypes, is high in terms of time consumption
and resources that may be better spent after differentiation. This
is also indicated in a recent retrospective study from the United
Kingdom, where CCI was only available on those who were eventu-
ally admitted. Of note, that study found that the CFS was a strong
independent predictor after adjusting for CCI, illness severity, age,
and sex. 25 In addition, we did not include health literacy, nutritional
status, depression, or dementia because we did not seek to upgrade
the CFS or the ESI models, but rather compare these given covari-
ates that are readily available in the acute care setting on arrival.
Furthermore, mortality might not be the ideal outcome as it is not
the only health care outcome important to patients, 54 especially
if they have exceeded their life expectancy. However, as an approx-
imation, a 79-year-old Swiss has an average life expectancy of over
10 years. Demographically (and emotionally), most of our patients
were not close to death, even 95 year-old Swiss having an average
life expectancy of years ("survivors effect"). As our study was not
designed to correct for individual theoretical life expectancies, we
are not able to present such numbers. However, great care should
be taken when assuming the utilitarian perspective that time added
to life at old age is worth less than when added at a younger age.
We do not have complete data on the number of hospitalizations
and the number of ICU admissions over 1 year, which are other rele-
vant outcomes. Hospitalization and ICU admission rates would have
to be collected from several hospitals in the Basel area, for which we
lack ethical approval. Second, profound interactions among these
co-variates (CFS level, number of hospitalizations, number of ICU
admission, number of institutionalizations) are to be expected when
included in one single model. This would likely reduce transportabil-
ity and clinical utility of the model considerably. The purpose of this
work was not to develop yet another model for prediction, which is
unlikely to be validated, 5 but rather compare acuity to frailty at ar-
ival with an intentional focus on validation of existing models.

The CFS requires raters assess the baseline state, a feat that may
be difficult in the acute care setting. 8 Even though we did not ad-
minister a "criterion-standard" frailty test in this study, 55 we previ-
ously found good agreement with an expert panel for the CFS ratings
performed on this cohort, despite raters being senior medical stu-
dents. 30 Additionally, the CFS displayed excellent reliability, regard-
less of clinical experience even after brief online training in a similar
setting. 23 Hence, we expect limited bias for the CFS measurements
compared to routinely collected ESI. However, we acknowledge that,
ideally, to better assess real-world clinical relevance, ratings would
have been performed by both research assistants and clinicians.
It is well established that it is both stressful and difficult to make
predictions in the clinical context, 56 and that illness acuity cannot
stand alone when assessing prognosis. 57 Whereas life expectancy can
be accurately calculated for a population, it is more difficult to deter-
mine for individuals. This study shows that it is possible to make sur-
prisingly accurate estimates of the risk of death for up to 1 year based
on knowledge available at arrival to the ED. In patients living with ma-
lignant conditions, 1-year or even extended survival is likely to be dis-
cussed, whereas in patients living with frailty and carrying comparably
serious outcomes, prognosis is less often considered or recognized
by care givers. Awareness of and acceptance around a likely 1-year
prognosis may create a paradigm shift for emergency physicians to use

![FIGURE 3](https://example.com/image.png)  
Comparison of the three adjusted logistic regression models for prediction of 1-year mortality, featuring CFS groups or ESI levels, and Null model. The AUROC of the CFS model was 0.767 (95% CI 0.741–0.793) and of the ESI model was 0.703 (95% CI 0.673–0.732). The calibration slope measured 0.959 in the CFS model and 0.973 in the ESI model.
a disease-oriented approach to solve the immediate problem and to engage an integrated, individually tailored model of care.\textsuperscript{12,13,14,56} Our study provides a foundation to justify intervention studies evaluating impact and unintended consequences of accelerating or altering ED processes resulting from CFS +/- ESI screening.

**CONCLUSIONS**

The CFS predicts 1-year all-cause mortality for older ED patients and predicts survival time in a graded manner for each CFS level. As a predictor of 1-year mortality, the CFS is superior to the ESI when adjusted for age, sex, and presenting condition.

**ACKNOWLEDGMENTS**

We thank Gilles Dutlih, PhD, Clinical Trial Unit for statistical advice. We thank John Kellett MD for helpful discussions on prognostication.

**CONFLICT OF INTEREST**

M.R. reports no conflict of interest. S.K.N. reports no conflict of interest. We thank John Kellett MD for helpful discussions on prognostication.

**ETHICS APPROVAL**

The study was approved by a local ethics committee (www.eknz.ch, 236/13) and registered on Clinical Trials Registry (NCT03892551).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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