Research Article

Disentangling the Impact of Chronic Kidney Disease, Anemia, and Mobility Limitation on Mortality in Older Patients Discharged From Hospital

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Abstract

Backgrounds. Chronic kidney disease (CKD), anemia, and mobility limitation are important predictors of mortality. We aimed at investigating the interactions between estimated glomerular filtration rate (eGFR), anemia, and physical performance on 1-year mortality in older patients discharged from acute care hospitals.

Methods. Four hundred and eighty seven patients enrolled in a multicenter, prospective observational study were included in the analysis. eGFR was estimated by the Berlin Initiative Study 1 equation. Anemia was defined on the basis of hemoglobin values. Mobility limitation was rated by the Short Physical Performance Battery (SPPB). Covariates included demographics, nutritional status, cognitive performance, and comorbidity. The outcome of the study was mortality over 1-year follow-up. Interactions among study variables were investigated by survival tree analysis.

Results. eGFR < 30 mL/min/1.73 m², anemia, and SPPB = 0–4 were significantly associated with mortality, as were hypoalbuminemia and cognitive impairment. Survival tree analysis showed that compared to patients with SPPB ≥ 4 and eGFR ≥ 46.7 mL/min/1.73 m² (ie, patients with the least mortality), patients with SPPB < 4 and hemoglobin < 12.2 g/dL had the highest risk of mortality [hazard ratio (HR) = 28.9, 95%CI 10.3–81.2]. Patients with SPPB ≥ 4 and eGFR < 46.7 mL/min/1.73 m² and those with SPPB > 4, hemoglobin ≥ 12.2 g/dL, and eGFR ≥ 58.6 mL/min/1.73 m² had intermediate risk (HR = 6.58, 95%CI = 2.15–20.2, and HR = 15.11, 95%CI=4.42–51.7, respectively). Having SPPB
Conclusions. Interactions among eGFR, anemia, and mobility limitation define different profiles of risk in older patients discharged from acute care hospitals, which deserve to be considered to identify patients needing special care and careful follow-up after discharge.

Key Words: Estimated glomerular filtration rate—Short physical performance battery—Anemia—Mobility limitation—Survival tree analysis—1-year mortality—Net reclassification improvement.

The severity of chronic kidney disease (CKD) significantly predicts mortality in both the general population and selected diseased populations (1,2). The risk of death in different adult populations dramatically increased for every 15 mL decrease in glomerular filtration rate (GFR) below 60 mL/min/m² (1). Though at a lower threshold compared to younger individuals, CKD severity constantly predicts mortality in older populations (3–5).

CKD is often complicated by anemia, mainly due to reduced secretion of renal erythropoietin (6). Furthermore, the prevalence of anemia increases with advancing age up to 20% in subjects aged 85 years and older (7). Anemia is also considered as a risk factor for increased mortality in older patients (8), but CKD itself is a major determinant of functional limitation in this age group (9). Reduced kidney function is associated with poorer physical performance measured by Short Physical Performance Battery (SPPB) (10), and lower SPPB score has been shown to predict mortality in several different older populations (11).

Evidence suggests that CKD, anemia, and physical performance could interactively affect survival of older persons. For example, CKD causes anemia and, anemia, in turn, may affect muscle strength and physical performance by impairing muscular oxygenation (12). Moreover, anemia may increase the risk of cognitive impairment and falls in older persons (13), which are both risk factors for death (14,15). On the other hand, CKD could per se affect physical performance by determining important metabolic dysfunctions (16). Nevertheless, only few studies have investigated these interactions in older populations. The combination of decreased kidney function and anemia was an independent and significant predictor of all-cause mortality in patients with left ventricular dysfunction (17). Interestingly, in a recent study conducted in patients with acute myocardial infarction, anemia was associated with a greater relative risk of mortality in the group with preserved estimated GFR (eGFR) than in that with impaired renal function (18), suggesting that anemia could not modulate the prognostic weight of depressed GFR.

Currently, there are no studies testing the prognostic role of the interaction among physical performance, kidney function, and anemia. Therefore, the aim of this study was to evaluate this interaction in predicting mortality over 1-year follow-up in a population of older patients discharged from acute care hospitals in Italy.

Methods

Study Design and Data Collection

This study uses data from a multicenter prospective study, the PharmacosurVeillance in the elderly Care (PVC), based in community and university hospitals throughout Italy aimed at surveying drug consumption, occurrence of adverse drug reactions, and quality of hospital care (19,20). The methods of the PVC study have been described previously (19,20). Briefly, all patients consecutively admitted to 11 acute care medical wards and 3 long-term care/rehabilitation units from April 1st to June 30th 2007 were invited to participate in the study. After obtaining a written informed consent from each patient, a physician with specific training completed a questionnaire at the time of hospital admission as well as on a daily basis. A training session was carried out at the coordinating center in order to collect a standardized battery of tests and has been described previously (19).

Data collection included demographics, pharmacological therapy information, comprehensive geriatric assessment, socioeconomic, and clinical information. Once discharged, patients underwent follow-up visits every 3 months for 1 year.

Overall, 762 patients were initially screened for the survey period and 72 (9.4%) refused to participate. We excluded 25 patients who died during the hospital stay, patients enrolled in long-term care/rehabilitation units (n = 159), and those with missing data on serum creatinine concentrations (n = 20), thus our final study population consisted of 487 patients. The study protocol was approved by the Ethical Committee of the Italian National Research Center on Aging (INRCA), Ancona, Italy (ID SC/07/169; Ref# 206/March 5th, 2007).

Outcome

The outcome was 1-year survival of patients discharged from participating acute care medical wards. At each follow-up visit, information was collected on vital status, functional status, changes in drugs prescriptions, and occurrence of adverse drug reactions. For patients who died during the follow-up period, information about date, place, and cause of death were collected from death certificates provided by relatives or caregivers. City or town registers were consulted to retrieve information about death when death certificates were not provided (N = 7).

Study Variables

Serum creatinine was measured in stable conditions (ie, at the time of discharge) by standardized Jaffé method in all laboratories of participating centers. Renal function was estimated using the Berlin Initiative Study 1 (BIS1) equation (21): eGFR=3736 × creatinine−0.87 × age−0.95 × 0.82 (if female).

The BIS1 equation has been shown to be more accurate than Modification of Diet in Renal Disease (MDRD) and CKD-EPI-derived measures in predicting measured GFR. Additionally, BIS1 equation is the only method specifically developed in a population older than 70 years (21). Participants were grouped into four categories according to their estimated eGFR (mL/min/1.73 m²) as follows: ≥60, 45–59.9, 30–44.9, and <30. Given that the relationship between creatinine-based eGFR and mortality is U-shaped among older and oldest old people, with mortality risk increasing for GFR lower than 45 mL/min/1.73 m² (3,22), eGFR = 45–59.9 mL/min/1.73 m² was considered as the reference group in our analysis.

Anemia was defined in accordance with the World Health Organization (WHO) criteria (hemoglobin levels<13 g/dL in men and <12 g/dL in women) (23).
Physical performance was measured by SPPB as reported previously (24). The trained physicians administered all performance-based measures the day before discharge. The SPPB includes gait speed (usual time to walk 6 m), five chair-stands test (time to rise from a chair and return to the seated position five times without using arms), and balance test (ability to stand with the feet together in the side-by-side, semitandem, and tandem positions). Time to walk 6 m was converted using the formula suggested by Studenski and coworkers (25). Each task was scored from 0 (unable to complete or bedridden patient) to 4. For time to walk 6 m and time to complete chair-stands test scores of 1–4 were assigned based on quartiles of performance measured in enrolled patients, as reported previously. For balance test, the side-by-side stand, semitandem stand, and full tandem stand were considered hierarchical in difficulty and assigned a score of 1–4 on the basis of the most complex task completed. Summing the three individual categorical scores, a summary performance score was created for each participant (range 0–12), with higher scores indicating better lower body function. The SPPB total score was categorized as 0–4, 5–8, and 9–12 (24).

Comprehensive geriatric assessment also was carried out the day before discharge. Cognitive status was rated by Mini Mental State Examination (MMSE) (26). Overall comorbidity was measured by Cumulative Illness Rating Scale (CIRS) (27).

Covariates

Age, gender, and variables known to affect prognosis in older patients were included in the analysis. Body mass index <20kg/m² and hypoalbuminemia (defined as serum albumin<3.5g/dL) were considered in the analysis as indices of poor nutritional status. Cognitive impairment (ie, age- and education-adjusted MMSE score <24) and overall comorbidity (ie, CIRS comorbidity score) were included in the analysis. CIRS partial scores were also considered in the analysis. Since CKD-related anemia appears at a higher threshold of eGFR among diabetic patients compared to the general population (28),

Table 1. General Characteristics of Patients Divided According to the Occurrence of Death During Follow-up.

<table>
<thead>
<tr>
<th></th>
<th>All Patients, N = 487</th>
<th>Survivors, N = 421</th>
<th>Dead, N = 66</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80.1 ± 6.0</td>
<td>79.6 ± 5.7</td>
<td>83.2 ± 6.6</td>
<td>.001</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>264 (54.2%)</td>
<td>226 (53.7%)</td>
<td>38 (57.6%)</td>
<td>.555</td>
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<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>172 (35.3%)</td>
<td>149 (35.4%)</td>
<td>23 (34.8%)</td>
<td>.961</td>
</tr>
<tr>
<td>Current smokers</td>
<td>26 (5.3%)</td>
<td>25 (5.9%)</td>
<td>1 (1.5%)</td>
<td>.312</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>249 (51.1%)</td>
<td>198 (47.0%)</td>
<td>51 (77.3%)</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>124 (25.5%)</td>
<td>105 (24.9%)</td>
<td>19 (28.8%)</td>
<td>.505</td>
</tr>
<tr>
<td>Hypertension</td>
<td>346 (71.0%)</td>
<td>303 (72.0%)</td>
<td>43 (65.2%)</td>
<td>.256</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>196 (40.2%)</td>
<td>148 (35.2%)</td>
<td>48 (72.7%)</td>
<td>.001</td>
</tr>
<tr>
<td>CIRS comorbidity score</td>
<td>3.7 ± 1.9</td>
<td>3.7 ± 1.8</td>
<td>4.1 ± 2.0</td>
<td>.097</td>
</tr>
<tr>
<td>CIRS partial scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>2.7 ± 1.2</td>
<td>2.7 ± 1.2</td>
<td>2.8 ± 1.1</td>
<td>.474</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.5 ± 1.1</td>
<td>2.6 ± 1.1</td>
<td>2.4 ± 1.0</td>
<td>.096</td>
</tr>
<tr>
<td>Vascular</td>
<td>2.2 ± 1.1</td>
<td>2.2 ± 1.1</td>
<td>2.0 ± 1.0</td>
<td>.112</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.3 ± 1.4</td>
<td>2.4 ± 1.5</td>
<td>2.1 ± 1.2</td>
<td>.161</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>1.3 ± 0.7</td>
<td>1.3 ± 0.7</td>
<td>1.2 ± 0.7</td>
<td>.565</td>
</tr>
<tr>
<td>Digestive upper tract</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.8</td>
<td>1.5 ± 0.9</td>
<td>.201</td>
</tr>
<tr>
<td>Digestive lower tract</td>
<td>1.4 ± 0.8</td>
<td>1.4 ± 0.8</td>
<td>1.6 ± 0.9</td>
<td>.153</td>
</tr>
<tr>
<td>Liver</td>
<td>1.3 ± 0.7</td>
<td>1.2 ± 0.7</td>
<td>1.4 ± 0.9</td>
<td>.048</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.5 ± 0.9</td>
<td>1.4 ± 0.9</td>
<td>1.9 ± 1.0</td>
<td>.001</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.7 ± 1.0</td>
<td>1.7 ± 1.0</td>
<td>2.1 ± 1.1</td>
<td>.003</td>
</tr>
<tr>
<td>Muscle/skeletal</td>
<td>1.9 ± 1.1</td>
<td>1.9 ± 1.1</td>
<td>2.2 ± 1.2</td>
<td>.014</td>
</tr>
<tr>
<td>Nervous</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>1.7 ± 1.1</td>
<td>.367</td>
</tr>
<tr>
<td>Endocrine/metabolism</td>
<td>1.7 ± 1.0</td>
<td>1.7 ± 1.0</td>
<td>1.8 ± 1.0</td>
<td>.616</td>
</tr>
<tr>
<td>Psychiatry/behavior</td>
<td>2.1 ± 1.2</td>
<td>2.1 ± 1.1</td>
<td>2.6 ± 1.3</td>
<td>.001</td>
</tr>
<tr>
<td>No. of drugs</td>
<td>7.0 ± 2.8</td>
<td>6.9 ± 2.9</td>
<td>7.1 ± 2.9</td>
<td>.507</td>
</tr>
<tr>
<td>BMI &lt; 20 kg/m²</td>
<td>40 (8.2%)</td>
<td>33 (7.8%)</td>
<td>7 (10.6%)</td>
<td>.446</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>218 (44.8%)</td>
<td>168 (39.9%)</td>
<td>50 (75.8%)</td>
<td>.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>50.4 ± 14.7</td>
<td>51.5 ± 13.8</td>
<td>43.1 ± 18.0</td>
<td>.001</td>
</tr>
<tr>
<td>&gt;60</td>
<td>117 (24%)</td>
<td>107 (25.4%)</td>
<td>10 (15.2%)</td>
<td>.001</td>
</tr>
<tr>
<td>45–59.9</td>
<td>207 (42.5%)</td>
<td>190 (45.1%)</td>
<td>17 (25.8%)</td>
<td></td>
</tr>
<tr>
<td>30–44.9</td>
<td>122 (25.1%)</td>
<td>98 (23.3%)</td>
<td>24 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>41 (8.4%)</td>
<td>26 (6.2%)</td>
<td>15 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.7 ± 2.4</td>
<td>12.9 ± 2.4</td>
<td>11.2 ± 2.0</td>
<td>.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>196 (40.2%)</td>
<td>148 (35.2%)</td>
<td>49 (72.7%)</td>
<td>.001</td>
</tr>
<tr>
<td>SPPB</td>
<td>5.1 ± 3.6</td>
<td>5.6 ± 3.5</td>
<td>2.4 ± 3.1</td>
<td>.001</td>
</tr>
<tr>
<td>9–12</td>
<td>202 (41.5%)</td>
<td>113 (26.8%)</td>
<td>4 (61.1%)</td>
<td></td>
</tr>
<tr>
<td>5–8</td>
<td>168 (34.5%)</td>
<td>155 (36.8%)</td>
<td>13 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>117 (24.0%)</td>
<td>153 (36.3%)</td>
<td>49 (74.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: p refers to differences between dead and survived patients. BMI = body mass index; CIRS = Cumulative Illness Rating Scale; eGFR = estimated glomerular filtration rate; SPPB = Short Physical Performance Battery.
diabetes was separately considered in the analysis. Hypertension and smoking habits were also separately considered in the analysis as risk factors for impaired kidney function. Finally, the cumulative number of risk factors (eGFR < 30 mL/min/1.73 m², SPPB = 0–4, and anemia) was also calculated and included in the analysis.

Analytic Approach

Firstly, we compared dead and survived patients with regard to study variables and covariates. We used one-way analysis of variance for continuous variables and chi-square for categorical ones. Therefore, the distribution of eGFR categories according to SPPB (column) and anemia status (raw) was graphically investigated by histograms.

Kaplan–Meier survival curves with the Mantel–Cox log-rank test were separately calculated to compare crude survival of patients in relation to eGFR, SPPB, and anemia. The analysis was also repeated to investigate survival in relation to the cumulative number of study risk factors (range 0–3). The time from hospital discharge through the day of death was used as the time to failure variable for the model. Survivors were censored on the day of the last follow-up visit. The relative risk of mortality related to eGFR, SPPB, anemia, or cumulative number of risk factors was investigated by Cox regression models. The proportional hazard assumption was tested graphically, plotting the log-minus-log survival function over time. The model was adjusted for all the variables that were associated with mortality in preliminary analysis.

Finally, in order to obtain an easy to use graphical predictive model, we fitted a survival tree model based on eGFR, SPPB score, and hemoglobin values. Survival trees are popular nonparametric alternatives to (semi) parametric models as they offer great flexibility and can automatically detect certain types of interactions without the need to specify them beforehand. In our analysis, the splitting criterion was based on a node deviance measure between a saturated model log-likelihood and a maximized log-likelihood as proposed by Leblanc and Crowley (29). In order to evaluate the performance of the fitted survival tree, the leaf node membership was put back as a categorical variable in a Cox regression model using the node showing the best survival as reference category. Bootstrap model validation (1,000 resampling) was performed to obtain unbiased estimates. C-statistic was used as measure of accuracy performance of the model. Differences among nodes in regards to covariates included in the analysis were also investigated. Finally, in order to compare the predictive performance of leaf nodes membership obtained from survival tree analysis with individual risk factors (eGFR < 30 mL/min/1.73 m², anemia, or SPPB < 5) or number of risk factors, the Net Reclassification Improvement (NRI) was calculated (30).

Analyses were performed using SPSS (version 10.0; SPSS, Chicago, IL), rpart (31), rms (32), and survIDINRI (30) packages of R.

Results

Baseline characteristics of patients divided according to survival status are summarized in Table 1. Eighty-two out of 487 patients scored 0 at SPPB evaluation. Patients who died during follow-up were older and had a greater prevalence of hypoalbuminemia, cognitive impairment and dependency in at least 1 basic activity of daily living at discharge. Higher CIRS partial scores related to liver, kidney, genitourinary, muscle skeletal, and psychiatric disorders characterized patients who died during follow-up. The prevalence of eGFR < 45 mL/min/1.73 m², anemia and SPPB < 5 was higher among patients who died compared to survivors.

The distribution of eGFR categories in relation to SPPB and anemia status is reported in Figure 1. The prevalence of impaired kidney function (ie, eGFR < 30 mL/min/1.73 m²) increased for decreasing physical performance, and such a trend was more evident among patients with anemia. Among patients with GFR < 30 mL/min/1.73 m², 24.4% had coexisting diabetes and hypertension, 7.3% had diabetes alone, and 53.7% had hypertension alone. In 6 out of the 41 patients with eGFR<30 we could not find diabetes or hypertension, but 4.9% of them were current smokers and 22.0% were former smokers.

Figure 1. eGFR distribution in relation to SPPB categories and anemia status.
smokers. Additionally, 67 out of 196 (34.2%) anemic patients had GFR < 30 mL/min/1.73 m² (or < 60 mL/min/1.73 m² and coexisting diabetes).

Kaplan–Meier curves show that reduced eGFR, anemia and SPPB < 5 were significantly associated with mortality. Additionally, the mortality rate dramatically increased for increasing number of study risk factors (Figure 2). After adjusting for potential confounders, patients with eGFR < 30 mL/min/1.73 m², anemia, and SPPB < 5 remained significantly associated with an increased mortality rate (Table 2). Hypoalbuminemia and cognitive impairment were also independent predictors of mortality. When patients with SPPB = 0 were excluded from that analysis, SPPB = 1–4 remained significantly associated with the mortality (HR = 3.11, 95% CI = 1.09–10.7). The analysis including the number of study risk factors instead of individual variables showed that the contemporary presence of all three risk factors was associated with a 10-fold increase in mortality.

Results obtained by survival tree analysis are reported in Figure 3. The cut-offs individuated by survival tree analysis to optimally split the dataset in terms of survival were similar to the accepted thresholds (46.7 and 58.6 mL/min/1.73 m² for eGFR, 4 for SPPB, and 12.2 in both genders for hemoglobin). Node 3 (SPPB ≥ 4 and eGFR ≥ 46.7 mL/min/1.73 m², N = 205) showed the least mortality and was considered as reference category in the Cox model. The highest risk of mortality was observed among patients pertaining to node 9 (SPPB < 4 and hemoglobin levels < 12.2, N = 84, HR = 28.9, 95% CI 10.3–81.2). Node 4 (SPPB ≥ 4 and eGFR < 46.7 mL/min/1.73 m², N = 105) and node 8 (SPPB < 4, hemoglobin ≥ 12.2, and eGFR ≥ 58.6 mL/min/1.73 m², N = 27) had an intermediate risk of 1-year mortality (HR = 6.58, 95% CI = 2.15–20.2, and HR = 15.11, 95% CI = 4.42–51.7, respectively). Node 7 (SPPB < 4, hemoglobin ≥ 12.2, and eGFR < 46.7 mL/min/1.73 m², N = 66) was not significantly associated with the outcome (HR = 2.95, 95% CI = 0.74–11.8). Patients pertaining to node 8 had the greater prevalence of body mass index < 20 kg/m² (22.2% compared to 5.4% in node 3, 5.7% in node 4, 10.6% in node 7, and 11.9% in node 9, p = .016). No other statistically significant difference was observed among nodes.

The leaf node membership showed a good accuracy in predicting survival (c-statistic = 0.80; 95% CI = 0.76–0.85). Finally, leaf node membership significantly improved the prognostic stratification

Figure 2. Kaplan–Meier survival curves of patients grouped according to eGFR (A), anemia (B), SPPB score (C), and number of study risk factors (D).
compared to both individual risk factors or number of risk factors (Table 3).

**Discussion**

Our study adds to current knowledge by demonstrating that patients carrying two or all three of the study risk factors, namely eGFR <30, anemia, and SPPB < 5 have an additive risk of 1-year mortality. More importantly, this is the first study demonstrating that relevant interactions exist among the three risk factors studied, which need to be taken into account in clinical practice.

The lack of significant interaction between eGFR and anemia apparently conflicts with former studies of patients with heart failure (17) or myocardial infarction (18), and suggest that eGFR and anemia may reduce survival through pathways not necessarily interacting. Indeed, anemia was found to predict mortality, cardiovascular hospitalizations, and end-stage renal disease independent of eGFR in a population of CKD patients (33). Additionally, about two thirds
of anemic patients had GFR greater or equal to 30 mL/min/1.73 m² (or 60 mL/min/1.73 m² with coexisting diabetes) in our study, which suggests that anemia was likely of nonrenal origin in the majority of patients in our study population.

On the contrary, physical performance interacted with both eGFR and anemia in our study. Patients with SPPB ≥ 4 and eGFR < 46.7 mL/min/1.73 m² had a 6.5-fold increased risk of death compared to reference category. These findings confirm that the eGFR threshold at which the risk increases may be lower among older patients compared to younger ones (3). Indeed, older people with eGFR < 60 mL/min/1.73 m² exhibit a slow progression of CKD (34). Our results showing that eGFR < 46.7 mL/min/1.73 m² is significantly associated with the outcome among older patients with relatively preserved physical performance is in keeping with the need to use lower threshold in order to avoid overdiagnosis. On the contrary, physical limitation, if present, outweighs depressed GFR as a risk factor. Indeed, patients with SPPB < 4, Hb ≥ 12.2 g/dL and eGFR ≥ 58.6 mL/min/1.73 m² had 15.1-fold increased risk of death, while patients with SPPB < 4, Hb ≥ 12.2 g/dL and eGFR < 58.6 mL/min/1.73 m² had only a tendency to increased risk. This latter counterintuitive finding might reflect the existence of a U-shaped relationship between creatinine-based eGFR and mortality (3,35,36). Indeed, high eGFR may partly reflect depressed serum creatinine secondary to sarcopenia. The high prevalence of sarcopenia in older adults (37), and its strong association with declining kidney function in adults supports this hypothesis (38). Additionally, both low serum creatinine and low 24-hour urine creatinine are associated with adverse outcomes (39), which could help to explain the observed interaction between eGFR ≥ 58.6 mL/min/1.73 m² and impaired physical performance.

Instead, the interaction between SPPB and anemia allows to identify a group of patients carrying an extremely increased risk of mortality. Such an interaction might find an explanation in pathogenetic mechanisms common to frailty and anemia, such as chronic inflammation. Indeed, the inflammatory pathway is known to impact prognosis by affecting muscle mass and strength, as well as other key biologic functions, including erythropoiesis (40). Unfortunately, the lack of information on the inflammatory status prevented us from testing this hypothesis.

These findings have at least three relevant clinical implications. First, combining eGFR and SPPB may improve prognostic stratification in older nonanemic patients discharged from hospital. Second, a measure of physical performance may help to identify those patients at high risk with apparently normal kidney function presenting with low circulating creatinine values due to sarcopenia. This kind of patients likely requires other measures of kidney function not biased by reduced muscle mass, such as cystatin C, β-trace protein or β2-microglobulin (41). Third, our study confirms the clinical utility of SPPB measurement in older hospitalized patients (42,43).

Limitations of our study deserve consideration. First, our study was not originally designed to test this topic. Accordingly, it did not include information on muscle mass and inflammatory markers, which limits our insight into the mechanisms underlying the observed associations and interactions. Second, our database lacked a direct measurement of GFR or other markers of renal function, such as cystatin C, which may yield different results. Third, the wide confidence intervals of selected associations indicate limited statistical power. Thus, our study may lack precision in estimates of the observed associations and interactions, which suggests the need to replicate these findings in other and larger population samples in order to verify the strength of the observed associations. Fourth, iron status, as well as vitamin B12 and folates levels were not available in our study, which limits significantly the understanding of causes of anemia in our study. Fifth, other comorbidities, as well as other non measured factors may likely explain our findings that CKD might play a minor prognostic role in this study population. However, even with this limitation the survival tree analysis approach allowed us to obtain a significant improvement of prognostic classification. Finally, our results apply to a population of older patients discharged from hospital in which anemia was not CKD related in the majority of patients. Thus, they are unlikely to apply to a pure CKD population.

Despite these limitations, our study demonstrates that eGFR, anemia, and physical performance variably interact in predicting survival of older patients discharged from acute care hospitals. If confirmed on larger series, such interaction might have important clinical and prognostic implications. Indeed, a better understanding of this interaction may lead to the identification of novel pathways to reduce mortality and to prevent the development of disability in older adults. The screening of elderly patients for CKD, anemia and mobility limitation might help to select those needing special care and careful follow-up after discharge. In this perspective, hospital physicians caring for older adults should consider SPPB measurement as an important component of routine assessment, especially for prognostic implication.

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Conflict of Interest
All Authors declare to have no conflict of interest with this manuscript.

References

Table 3. Net Reclassification Improvement (NRI) in Predicting 1-Year Mortality Obtained by Leaf Nodes Membership From Survival Tree Analysis Compared to Individual Risk Factors or Number of Risk Factors.

<table>
<thead>
<tr>
<th>Model</th>
<th>NRI</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>0.52</td>
<td>0.22–0.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SPPB</td>
<td>0.56</td>
<td>0.42–0.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.55</td>
<td>0.26–0.66</td>
<td>.004</td>
</tr>
<tr>
<td>Number of risk factors*</td>
<td>0.37</td>
<td>−0.01 to 0.60</td>
<td>.05</td>
</tr>
</tbody>
</table>

Notes: eGFR = estimated glomerular filtration rate; SPPB = Short Physical Performance Battery.

*eGFR<30 mL/min/1.73 m², anemia, and SPPB < 5.


