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Original Article

# Prognostic relevance of glomerular filtration rate estimation obtained through different equations in hospitalized elderly patients

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ABSTRACT

The estimated glomerular filtration rate (eGFR) is a predictor of important outcomes and its reduction has been associated with the risk of all-cause mortality in both general population and elderly patients. However while reduced renal function is common in older people, the best method for estimating GFR remains unclear, especially in an acute care setting. Most studies analyzing the accuracy of eGFR in the elderly were carried out in different heterogeneous settings. In this study, we compare the prognostic value of different formulas estimating GFR in predicting the risk of in-hospital morbidity and mortality within 3 months from discharge in elderly hospitalized patients. Data were extracted from "Registro Politerapia Società Italiana di Medicina Interna (REPOSI)". Patients with available creatinine values at hospital admission were selected and eGFR was calculated according to the different formulas: Cockcroft-Gault, Modification of Diet in Renal Disease equation, Chronic Kidney Disease Epidemiology Collaboration, Berlin Initiative Study and Full Age Spectrum. 4621 patients were included in the analysis. Among these, 4.2% and 14.2% died during hospitalization and within 3 months from discharge, respectively. eGFR $>$ 60 ml/min/1.73 $m^2$ at admission was associated with a very low risk of mortality during the hospital stay and within 90 days from discharge, while an eGFR $<$ 60 ml/min/1.73 $m^2$ was associated with unfavorable outcomes, although with a poor level of accuracy (AUC 0.60–0.66). No difference in predictive power between different equations was found. Physicians should be aware of the prognostic role of eGFR in a comprehensive assessment of elderly in-patients.

## 1. Introduction

Multimorbidity is a common problem in elderly populations as its prevalence rises with age [1]. As a result, an increasing number of patients with many chronic medical conditions are hospitalized in internal medicine and geriatric wards, with a subsequent increase of polypharmacy and its attendant risks. Among chronic diseases, chronic kidney diseases (CKD) affects more than one-third of people aged 70 years and often coexists with conditions that increase the risk of hospitalization and death [2–5]. Therefore, the evaluation of renal function, mainly for polypharmacy, represents an important topic.

Some studies have suggested that the age-related decline in estimated glomerular filtration rate (eGFR) is physiological and does not substantially increase the risk of death [6,7]. Conversely, it has been reported that reduced eGFR is independently associated with all-cause mortality in the overall population, including the elderly populations [8–13]. La Higuera et al. [14] recently demonstrated that severely reduced eGFR in elderly in-patients is a strong predictor of the risk of dying during hospitalization and that eGFR at discharge helps to predict early death. Several formulas have been developed to estimate eGFR [15–17], because serum creatinine alone is not an adequate marker as its value is affected by several factors. Older and malnourished patients in the acute care hospital are at special risk of having a depressed eGFR with normal creatinine [18–20]. Anyhow, while reduced renal function is common in older people, the best method for estimating the GFR remains unclear and a reliable assessment for this population is a challenge, especially in an acute setting. The Cockcroft-Gault (CG) equation [21] was the first published formula and it is still widely used, being recommended for drug dosing and contraindication checking in the package leaflets of several medications. In the last years, new GFR

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estimating equations (Modification of Diet in Renal Disease, MDRD; Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI; Berlin Initiative Study, BIS) have been validated but only the BIS in persons aged 70 and older [16,22–25]. Finally, FAS (Full Age Spectrum) equation has been developed and validated across the entire age spectrum [26].

All these formulas have merits and drawbacks. For example, CG does not take into account the variability of creatinine production and calculates its clearance overestimating systematically the eGFR in obese or edematous patients [21,27]. MDRD has not been validated in patients with normal renal function and the elderly [28,29]; CKD-EPI is based on creatinine and has been validated in a population including relatively few people older than 70 years of age; FAS equation is somewhat new. Additionally many drugs may interfere with creatinine filtration and secretion, particularly in critical settings, and these variables are difficult to take into account.

Therefore, even though reduced eGFR has been reported to be independently associated with all-cause mortality, its prognostic significance is not universally defined, as it might vary with the formula used to estimate it, the outcome (i.e. functional decline, short or long term mortality) and the setting (community dwelling subjects, nursing home residents or hospitalized patients). Moreover, studies on the accuracy of different formulas for GFR estimation in older patients were carried out in ambulatory or outpatient settings [9,10,16,22,23] and the prognostic implication of eGFR in acute settings was not an object of research [30]. Therefore, to our knowledge, the role of different formulas estimating GFR as a marker of short-term mortality in older people in acute care wards has not been investigated. With this background and gaps of knowledge, the present study aims to compare the prognostic significance (in terms of risk stratification and predictive power) of GFR estimated with five different formulas (CG, MDRD, CKD-EPI, BIS and FAS) regarding short-term mortality (in-hospital and three months mortality) in elderly patients admitted to acute medical and geriatric wards.

## 2. Patients and methods

We extracted data from a validated database employed by internal and geriatric medical wards participating in the “Registro Politerapia SIMI (REPOSI)”, which is a registry including hospitalized patients aged 65 years or more and organized by the Italian Society of Internal medicine (SIMI), and by the Istituto di Ricovero e Cura a Carattere Scientifico - IRCCS Istituto di Ricerche Farmacologiche “Mario Negri” and IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, both in Milan. The collection of data occurred every 2 years in 2008, 2010, 2012, 2014 and since 2015, data collection has become annual. The design is described in details elsewhere [31].

All patients admitted to the participating wards during the four selected week windows separated by three months were consecutively recruited. Three months after discharge, ward physicians performed a telephone interview. All the data were revised and rechecked by a central monitor at the IRCCS-Mario Negri Institute. The study was approved by the Ethical Committee of the IRCCS Cà Granda Maggiore, Policlinico Hospital Foundations in Milan, as well as by the local Ethical Committees of the participating centers. All patients with available serum creatinine values at hospital admission were selected and the eGFR was calculated according to the CG (ml/min/1.73 $m^2$), CKD-EPI, MDRD, BIS and FAS formulas.

From the full database of 4713 patients admitted to 107 Italian wards participating to the study in the 2010–2016 period, 35 patients were excluded because of unavailable data at hospital discharge and 57 for unavailable creatinine values. Of the remaining 4621 subjects analyzed, 1408 were lost at 3-month follow-up. The main study outcomes were in- hospital mortality and mortality three months after discharge. All the other clinical and demographic characteristics were retrieved.

The association between eGFR according to the different equations and in-hospital and 3-month mortality was estimated through log-binomial regression models and expressed as risk ratios (RRs) with 95% confidence intervals (95% CI). In order to find out the best model fit, eGFR was firstly modeled with a restricted cubic spline function and, as exposed afterward, the risk of short term mortality was expressed as RRs for eGFR greater or below 60 ml/min/1.73 $m^2$ and for every 10 units decrease of eGFR below this cut-off.

Nested multivariable models were used to study the effect of selected variables on the associations between eGFR equations and mortality. A first multivariable model was adjusted for demographical characteristics, such as age and sex. Then, since nutritional status and comorbidities may differently affect the eGFR estimates, and the related relationship between estimated eGFR and survival, a second multivariable model was fitted including also albumin levels, as a surrogate of nutritional status, and the Cumulative Illness Rating Scale Comorbidity Index, CIRS-CI, a comorbidity index.

Finally, the discriminatory performance of different eGFR equations were evaluated considering the under the receiver operating characteristic curve (AUC) of the above mentioned regression models for in-hospital and three months' mortality. Sensitivity, specificity and predictive values of eGFR $<$ 60 ml/min/1.73 $m^2$ were also computed. All analyses were performed using R 3.3.3 software for Mac (R Foundation).

## 3. Results

### 3.1. Main characteristics of the study population

The general characteristics of the study population, overall and according to survival status, are reported in Table 1. Out of 4621 patients, 193 (4.2%) died during hospitalization, while 457 (14.2% of the initial 4621 minus the 1408 patients lost at follow-up) had died at 3 months after discharge. As expected, age, creatinine levels and CIRS were significantly higher in patients who died. In addition, these patients were physically and cognitively more compromised, had a lower BMI and the eGFR was significantly lower independent from the equation used to compute it.

### 3.2. eGFR and mortality

The relation between eGFR and the risk of mortality is reported in Fig. 1. While showing a positive trend for eGFR values above 100 ml/min/1.73 $m^2$ and below 60 ml/min/1.73 $m^2$, the mortality risk does not significantly increase for patients with eGFR above 100 ml/min/1.73 $m^2$ compared to those having eGFR between 60 and 100 ml/min/1.73 $m^2$ (RRs not shown). Conversely, mortality risk linearly and sharply increases for decreasing eGFR values below 60 ml/min/1.73 $m^2$. Accordingly, any further reduction in eGFR below this cut-off was significantly associated with both in-hospital and three-month mortality, as shown by the means of all estimating equations in Table 2. Concerning the strength of this association, all formulas showed comparable RR with the established outcomes.

When eGFR was also tested for its discriminative properties, the AUCs were poor and each formula showed a similar prediction of in-hospital and 3 months mortality with AUC of, respectively, 0.61 (95%CI 0.56–0.66) and 0.62 (95%CI 0.58–0.65) for CKD-EPI, 0.66 (95%CI 0.61–0.71) and 0.64 (95%CI 0.61–0.68) for CG, 0.60 (95%CI 0.55–0.65) and 0.60 (95%CI 0.57–0.64) for MDRD, 0.64 (95%CI 0.59–0.68) and 0.62 (95%CI 0.59–0.65) for BIS, 0.65 (95%CI 0.61–0.70) and 0.62 (95%CI 0.59–0.66) for FAS. The cut-off of 60 ml/min/1.73 $m^2$ had poor sensitivity and specificity, but showed a good negative predictive value (0.97–0.98 for in hospital mortality; 0.92–0.94 for 3-month mortality; Table 3).

After correction for factors potentially affecting GFR estimations, as well as for those affecting the relationship between eGFR and survival,

**Table 1**
Main demographic, anthropometric and clinical characteristics of study population (overall and by survival status).

| | All | Alive at discharge | Dead at discharge | Alive at 3 months[a] | Dead at 3 months[a] |
|---|---|---|---|---|---|
| | 4621 | 4428 (95.8%) | 193 (4.2%) | 2756 (85.8%) | 457 (14.2%) |
| Age (years) | 79.4 (7.5) | 79.2 (7.5) | 82.5 (7.3) | 78.9 (7.5) | 82.1 (7.6) |
| Sex (male) | 48.8% | 48.6% | 54.4% | 47.4% | 58% |
| BMI (kg/m$^2$) | 25.9 (5) | 26 (5) | 24.1 (4.5) | 26.2 (5.1) | 24.2 (4.7) |
| Albuminemia (g/dL) | 3.4 (0.6) | 3.4 (0.6) | 2.9 (0.7) | 3.5 (0.6) | 3 (0.7) |
| Disability (Barthel Index ≤ 90) | 49% | 47.8% | 75.7% | 45.5% | 71.9% |
| Cognitive impairment[b] | 44% | 43% | 78% | 42.3% | 61.2% |
| Depressive symptoms[c] | 41.9% | 41.6% | 55% | 40.8% | 52.1% |
| CIRS Severity Index | 1.7 (0.3) | 1.7 (0.3) | 1.8 (0.4) | 1.7 (0.3) | 1.8 (0.4) |
| CIRS Comorbidity Index | 3.1 (1.9) | 3 (1.9) | 3.6 (2) | 3.1 (1.9) | 3.5 (2) |
| Creatinine (mg/dL) | 1.3 (0.9) | 1.2 (0.8) | 1.7 (1.6) | 1.2 (0.8) | 1.6 (1.3) |
| eGFR CKD-EPI ml/min/1.73 m$^2$ | 59.3 (24.2) | 59.8 (24) | 49.6 (27.1) | 59.8 (23.4) | 52.1 (26.8) |
| eGFR Cockcroft-Gault ml/min/1.73 m$^2$ | 55.4 (28.2) | 55.9 (28.2) | 43.3 (26.2) | 56.3 (27.1) | 45.1 (26.1) |
| eGFR MDRD ml/min/1.73 m$^2$ | 63.5 (31.7) | 63.8 (31.4) | 54.8 (35) | 63.3 (28.9) | 57.7 (35.7) |
| eGFR BIS ml/min/1.73 m$^2$ | 53.5 (21.5) | 53.8 (21.3) | 45.7 (23.5) | 53.7 (20) | 47.7 (23.6) |
| eGFR FAS ml/min/1.73 m$^2$ | 53.8 (24.6) | 54.1 (24.4) | 45.6 (26.8) | 53.9 (22.6) | 47.8 (27.0) |

eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; CG: Cockcroft-Gault; BIS: Berlin Initiative Study.

[a] 1408 subjects have been lost at follow-up.

[b] Diagnosis according to Short Blessed Test ≥ 10.

[c] Diagnosis according to Geriatric depression scale ≥ 2.

eGFR decline below 60 ml/min/1.73 m$^2$ remained independently associated with mortality (Table 2). Even in multivariable models including albumin levels and the CIRS-CI at admission, all formulas confirmed similar associations (Table 2) and discriminations for in-hospital and 3-month mortality with AUC of, respectively, 0.74 (95%CI 0.69–0.79) and 0.75 (95%CI 0.72–0.79) for CKD-EPI, 0.76 (95%CI 0.71–0.81) and 0.76 (95%CI 0.72–0.79) for CG, 0.74 (95%CI 0.69–0.79) and 0.75 (95%CI 0.72–0.79) for MDRD, 0.74 (95%CI 0.69–0.79) and 0.75 (95%CI 0.72–0.78) for BIS, 0.74 (95%CI 0.69–0.79) and 0.75 (95%CI 0.72–0.78) for FAS.

## 4. Discussion

Our study shows that in elderly patients admitted to acute care medical wards eGFR is associated with short-term mortality, even if its predictive capacity remains rather poor. Indeed, while normal eGFR undoubtedly identifies low risk patients, the reverse is not true for decreased eGFR. In addition, we demonstrated for the first time that the predictive power does not depend upon and does not vary with the different equations used to estimate GFR.

Clearly, from accruing evidence in the literature, eGFR is a predictor of important outcomes such as in-hospital mortality, hospital readmission and death within 3 months [11–13]. Most studies analyzing the accuracy of GFR estimation in the elderly, using the different formulas, were carried out in an ambulatory or outpatient setting [6–10]. In the study by La Higuera et al. [14], the only one to our knowledge that did assess the association between eGFR and in-hospital mortality in elderly patients, renal function was estimated only by means of the CKD-EPI

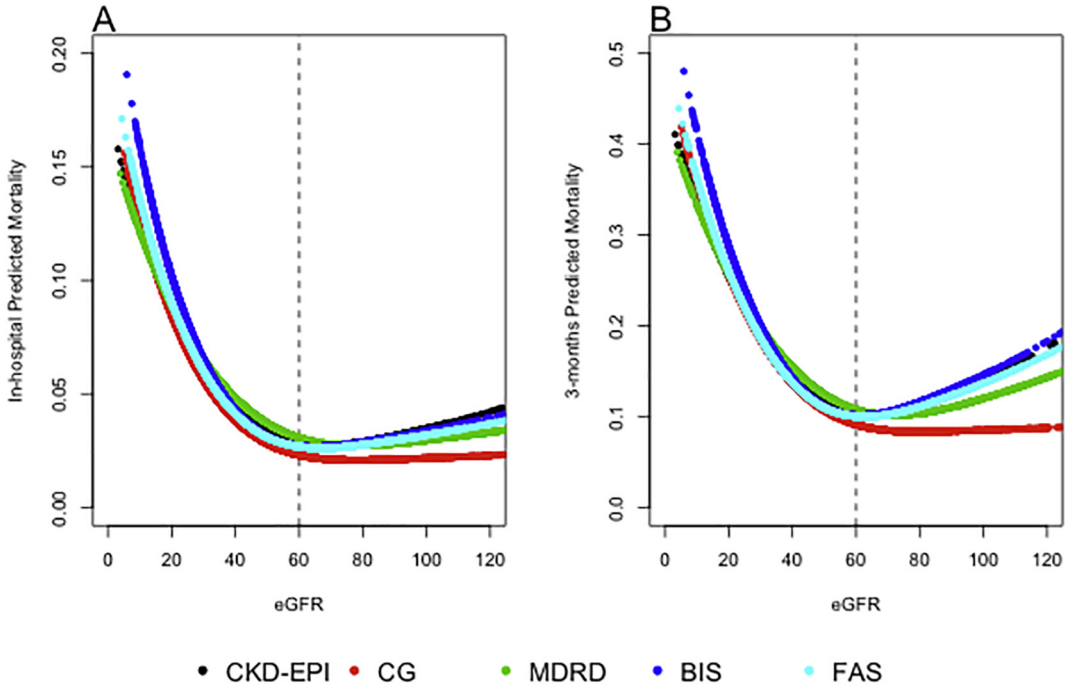


**Fig. 1.** Relation between GFR and in-hospital and 3-month mortality by different estimating equations.

**Table 2**
Uni- and multivariate analysis of different GFR estimating formula and mortality.

| | | In-hospital mortality | | | 3 months mortality | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted | Age-sex adjusted | Multiple adjusted | Unadjusted | Age-sex adjusted | Multiple adjusted |
| CKD-EPI | ≥ 60 ml/min/1.73 $m^2$ | 1 | 1 | 1 | 1 | 1 | 1 |
| | < 60 ml/min/1.73 $m^2$ | 1.9 (1.43–2.55) | 1.13 (0.75–1.7) | 1.14 (0.76–1.72) | 1.48 (1.24–1.76) | 1.09 (0.84–1.42) | 1.07 (0.82–1.39) |
| | 10 ml/m'fall below 60 ml/min/1.73 $m^2$ | 1.31 (1.16–1.46) | 1.39 (1.16–1.65) | 1.33 (1.11–1.59) | 1.27 (1.18–1.37) | 1.25 (1.12–1.41) | 1.2 (1.07–1.36) |
| CG | ≥ 60 ml/min/1.73 $m^2$ | 1 | 1 | 1 | 1 | 1 | 1 |
| | < 60 ml/min/1.73 $m^2$ | 1.9 (1.34–2.75) | 0.96 (0.56–1.67) | 1.04 (0.61–1.83) | 1.62 (1.32–2.02) | 0.91 (0.66–1.28) | 0.89 (0.64–1.25) |
| | 10 ml/m'fall below 60 ml/min/1.73 $m^2$ | 1.48 (1.31–1.67) | 1.4 (1.15–1.69) | 1.32 (1.09–1.6) | 1.37 (1.27–1.47) | 1.33 (1.18–1.51) | 1.27 (1.12–1.43) |
| MDRD | ≥ 60 ml/min/1.73 $m^2$ | 1 | 1 | 1 | 1 | 1 | 1 |
| | < 60 ml/min/1.73 $m^2$ | 1.88 (1.41–2.53) | 1.16 (0.78–1.75) | 1.16 (0.78–1.74) | 1.45 (1.22–1.73) | 1.1 (0.85–1.43) | 1.07 (0.83–1.39) |
| | 10 ml/m'fall below 60 ml/min/1.73 $m^2$ | 1.3 (1.15–1.46) | 1.38 (1.15–1.65) | 1.32 (1.09–1.59) | 1.26 (1.17–1.35) | 1.25 (1.11–1.4) | 1.2 (1.06–1.36) |
| BIS | ≥ 60 ml/min/1.73 $m^2$ | 1 | 1 | 1 | 1 | 1 | 1 |
| | < 60 ml/min/1.73 $m^2$ | 1.65 (1.21–2.3) | 1.07 (0.68–1.71) | 1.1 (0.71–1.75) | 1.39 (1.15–1.69) | 0.96 (0.72–1.3) | 0.98 (0.73–1.31) |
| | 10 ml/m'fall below 60 ml/min/1.73 $m^2$ | 1.45 (1.29–1.63) | 1.36 (1.14–1.62) | 1.31 (1.08–1.57) | 1.33 (1.23–1.43) | 1.26 (1.12–1.41) | 1.21 (1.07–1.37) |
| FAS | ≥ 60 ml/min/1.73 $m^2$ | 1 | 1 | 1 | 1 | 1 | 1 |
| | < 60 ml/min/1.73 $m^2$ | 1.58 (1.16–2.18) | 0.96 (0.62–1.51) | 0.98 (0.64–1.54) | 1.34 (1.11–1.62) | 0.95 (0.72–1.27) | 0.98 (0.74–1.31) |
| | 10 ml/m'fall below 60 ml/min/1.73 $m^2$ | 1.47 (1.31–1.65) | 1.4 (1.18–1.67) | 1.36 (1.14–1.63) | 1.35 (1.25–1.45) | 1.27 (1.13–1.42) | 1.21 (1.07–1.36) |

Data expressed as risk ratios (RRs) with 95% confidence intervals (95% CI). Multiple adjusted models corrected for age and sex + albumin and CIRS Comorbidity Index.

**Table 3**
Predictive performances of eGFR < 60 ml/min/1.73 $m^2$ as estimated by different formulas.

| | In-hospital mortality | | | | 3 months mortality | | | |
|---|---|---|---|---|---|---|---|---|
| | Sens | Spec | PPV | NPV | Sens | Spec | PPV | NPV |
| CKD-EPI < 60 ml/min/1.73 $m^2$ | 0.65 | 0.51 | 0.05 | 0.97 | 0.6 | 0.51 | 0.17 | 0.89 |
| CG < 60 ml/min/1.73 $m^2$ | 0.76 | 0.38 | 0.05 | 0.98 | 0.74 | 0.38 | 0.15 | 0.9 |
| MDRD < 60 ml/min/1.73 $m^2$ | 0.65 | 0.51 | 0.05 | 0.97 | 0.6 | 0.51 | 0.17 | 0.88 |
| BIS < 60 ml/min/1.73 $m^2$ | 0.75 | 0.36 | 0.05 | 0.97 | 0.72 | 0.36 | 0.16 | 0.89 |
| FAS < 60 ml/min/1.73 $m^2$ | 0.74 | 0.37 | 0.05 | 0.97 | 0.71 | 0.37 | 0.16 | 0.88 |

formula and severely reduced eGFR was a strong predictor of the risk of dying during hospitalization [22].

Other studies showing an association between decreased eGFR on admission and mortality were conducted in patients with cardiovascular diseases and were focused on long-term mortality [32–34]. Bario et al. described the role of eGFR in predicting short-term prognosis only in patients admitted with ST-elevation myocardial infarction in a coronary care unit [35]. On the other hand, also a lack of association between reduced eGFR and risk of death was reported, but these studies were conducted in non-hospitalized cohorts [6,7].

With this background and gaps of knowledge, we comparatively assessed the short-term prognostic value of five equations frequently used in clinical practice to estimate GFR in hospitalized patients over 65 years, and found that this risk increases for every 10 ml/min/1.73 $m^2$ step-fall in GFR values below 60 ml/min/1.73 $m^2$. At the same time, risk estimates for the different equations remained substantially similar even after correction for factors potentially affecting GFR estimations, such as albumin levels and burden of comorbidity (CIRS Comorbidity Index at admission). Therefore, the association between eGFR and mortality seems to exceed the intrinsic structure and meaning of a given formula, because all formulas show a similar predictive power independently from clinical confounders like changes in the intravascular volume due to conditions like heart failure and liver disease, other hemodynamic damage, loss of lean body and poor nutritional mass. At the same time, all of them maintain implicitly the prognostic influence of variables associated with each formulas. This suggests that eGFR is probably able to capture an additional dimension of frailty, representing per se a predictor of mortality in elderly in-patients. Finally, this finding is in keeping with the demonstration that the combination of eGFR and a comprehensive geriatric assessment may improve the predictive accuracy [36].

The observed U shaped association between eGFR and mortality (especially at 90-days) suggests that sarcopenic patients might partly clusterize in the higher eGFR groups. Indeed, in the context of severe sarcopenia and frailty and ensuing fall in serum creatinine due to muscle wasting, the computation of eGFR might yield inappropriately high values despite a normal or depressed renal function. In addition, other mechanisms involved in the pathogenesis of hyperfiltration may justify the association between elevated eGFR and mortality [37]. The observation that in our study the relationship between high eGFR and mortality weakens if eGFR was obtained through CG (Fig. 1) probably finds its explanation in the structural differences between the equations and in the CG intrinsic attitude to underestimate eGFR in older people [30].

The strength of our study is the multicenter design of REPOSI, which result in a representative sample of hospitalized population of the elderly in Italy. A limitation is that lack of information for 3-month follow-up except for the living status and the lack of the geriatric assessment and of the evaluation of muscle mass and strength. Moreover we included all patients with available creatinine level at hospital admission being not able to exactly discriminate the type and stage of renal injury. Furthermore confounding factors interfering with the eGFR predictive role should be taken into account. Obviously, as an observational study, no causative associations can be inferred.

In conclusion, our study confirms that an eGFR > 60 ml/min/1.73 $m^2$ at admission is associated with a lower risk of mortality during the hospital stay and within 90 days from discharge. On the other hand, eGFR < 60 ml/min/1.73 $m^2$ is associated with unfavorable outcomes, but with a poor level of accuracy. The new important message is the exclusion of any difference in predictive power between different GFR estimating equations. Further efforts should be made to define the role of eGFR as a prognostic tool in the context of comprehensive geriatric assessment as well as to verify whether eGFR fluctuations during the hospital stay add to the predictive power of the eGFR value on admission. Finally, assessing the body composition of the probands might help to understand to which extent eGFR prognostic ability depends upon the body composition and not merely the renal function.

## Authors' disclosures

The authors declare no conflict of interest and confirm no financial

interest in a business or commercial entity that relates to the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.04.001.

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