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The prognostic value of estimated glomerular filtration rate on admission for death within 30 days among COVID-19 inpatients using fractional polynomial and spline smoothing

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Abstract

Background The common regression models included estimated glomerular filtration rate (eGFR) in the continuous and categorical form for predicting the mortality in COVID-19 inpatients. However, the relationship may be non-linear, and categorizing implies a loss of information. This study aimed to assess the effect of eGFR on admission on death within 30 days among COVID-19 inpatients using flexible and smooth transformations of eGFR and compare the results against the common models.

Methods A retrospective study was conducted on hospitalized COVID-19 patients between April 2019 and July 2019 in Hamadan, Western Iran. The effect of eGFR on the death within 30 days was evaluated using different modeling: categorization, linear, unrestricted cubic spline (USC) with 4 knots, and fractional polynomial (FP). The results adjusted for older age and intensive care unit (ICU) admission. Discrimination power and model performance of the best-fitting model was evaluated using the area under the ROC (AUROC) and Brier score.

Results In total, 2945 patients (median age 61 years; interquartile range 48–73 years) were included, of whom the mortality rate was 9.23%. The relationship between the eGFR and death within 30 days is non-linear, so the degree-2 FP with powers $(-2, -1)$ is the best-fitting model. Using the FP model, the risk increased exponentially in eGFR < 45 and then increased linearly and slowly. The AUROC of the FP model involving eGFR, older age, and ICU admission was 0.92 (95% CI 0.90–0.93) with a Brier score of 0.09.

Conclusion There is a non-linear and asymmetric relationship between eGFR and death within 30 days among COVID-19 inpatients. Kidney function can be measured in COCID-19 patients on admission to know better understanding about prognosis of the patients.

Keywords Estimated glomerular filtration rate · Mortality · Nonlinear relationship · Fractional polynomial · Regression spline · COVID-19

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Introduction

COVID-19 cases have exceeded 650 million and resulted in more than 6.6 million deaths worldwide until 12 December 2022 [1]. Initially, COVID-19 was described as an exclusively respiratory system infection, but studies suggest the effect of COVID-19 on other organs like the kidney [2, 3]. Some pathophysiology and molecular mechanisms involving direct invasion of the kidneys and systemic effects of the virus, such as cytokine storm, thrombus development, and hypovolemia, are potential mechanisms of kidney damage [4, 5]. Coronavirus-induced renal dysfunction can manifest as mild proteinuria and hematuria. In severe cases, it can lead to acute kidney injury (AKI) [6]. AKI has occurred in 26% of patients with COVID-19, and mortality among such patients is higher than the overall COVID-19 mortality rate of patients without AKI [7].

The key indicator of kidney function is the glomerular filtration rate (GFR). GFR cannot be assessed directly but can be estimated from serum creatinine level, age, sex, and race as known eGFR [8]. Previous studies have suggested that eGFR has good predictive performance for mortality in patients with chronic conditions [9, 10]. Several studies also showed the prognostic value of eGFR for adverse outcomes, such as mortality and ICU admission, in COVID-19 patients [11, 12]. In previous studies, eGFR was included in prediction models in continuous and categorical forms, and a linear relationship is assumed between eGFR and mortality [13, 14]. However, in some scenarios, the relationship between a continuous covariate e.g., eGFR and mortality may be non-linear, such as *J*-shaped or *U*-shaped. Therefore, the results of models that consider the GFR as a continuous variable or categorized forms of the GFR variable may be biased. The use of flexible models, such as fractional polynomials and cubic splines, can provide the true relationship between continuous variables and a given outcome in the presence of nonlinearity. Considering the above issues, the present study aimed to explore the linear and non-linear association between eGFR on admission and death within 30 days in patients with COVID-19 using binary logistic regression, fractional polynomial, and cubic splines models.

Methods

The present retrospective study was conducted on COVID-19 patients who were hospitalized between April 2019 and July 2019 in Shahid Beheshti and Sina hospitals, two referral hospitals of Hamadan University of Medical Sciences, Hamadan, Iran. The inclusion criteria included patients with confirmed COVID-19 through PCR method. In other words, the reason for hospitalization was COVID-19 infection. Patients with registered medical history of chronic kidney disease (CKD) and hemodialysis in Shahid Beheshti hospital as tertiary referral center for these patients were excluded from the study.

The information was extracted by two trained nurses from the patient's medical records and, if necessary, through interviews or telephone calls with the patients, and entered into the researcher-made checklist. The information included the following parts: (1) Demographic variables: gender, age, BMI, and smoking (2) Comorbidities: hypertension, diabetes, heart disease, malignancy, and chronic pulmonary diseases (3) Vital signs at admission: heart rate, systolic blood pressure, diastolic blood pressure, and temperature, (4) Lab values at admission: eGFR, serum creatinine (Cr), blood urea nitrogen (BUN), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), Alanine transaminase (ALT), aspartate transaminase (AST), potassium (K), sodium (Na), platelet count (PLT), lactate dehydrogenase (LDH), prothrombin time (PT), partial thromboplastin time (PTT), lymphocytes, monocytes, and neutrophils, and (5) Hospitalization information of patients: duration of hospitalization, intensive care unit (ICU) admission, need for a ventilator, and death within 30 days.eGFR was calculated based on the CKD Epidemiology Collaboration (CKD-EPI) equation in milliliters per minute per 1.73 m^2 (ml/min/1.73 m^2) based on gender, age, and serum creatinine through the below formula [8]:

$$\begin{aligned}\text{eGFR} &= 141 \times \min(\text{CR}/0.9, 1)^{-0.411} \times \max(\text{CR}/0.9, 1)^{-1.209} \\ &\quad \times \left(0.993^{\text{Age}}\right) \quad \text{if Sex} == \text{male} \\ \text{eGFR} &= 141 \times \min(\text{CR}/0.7, 1)^{-0.329} \times \max(\text{CR}/0.7, 1)^{-1.209} \\ &\quad \times \left(0.993^{\text{Age}}\right) \times 1.018 \quad \text{if Sex} == \text{female}\end{aligned}$$

In the above formula, serum creatinine was in mg/dl. Based on the calculated scores, there is the following classification for the degree of kidney failure. Normal or high function if eGFR ≥ 90 ml/min/1.73 m^2 (G1), mildly decreased if eGFR between 60 and 89 ml/min/1.73 m^2 (G2), mildly to moderately decreased if eGFR between 45 and 59 ml/min/1.73 m^2 (G3a), moderately to sever decreased if eGFR between 30 and 44 ml/min/1.73 m^2 (G3b), severely decreased if eGFR between 15 and 29 ml/min/1.73 m^2 (G4), and kidney failure if eGFR < 15 ml/min/1.73 m^2 (G5).

Statistical analyses

Normality assumption of the variables was checked through the Shapiro–Wilk test. In case of violation of normality, the variables were expressed median (interquartile range). The chi-square test and Kruskal–Wallis test were used to assess

the relationship between the variables according to eGFR categories. The association between eGFR in categorized and continuous forms as independent variables and death within 30 days as dependent variables was evaluated using binary logistic regression. The linearity assumption was checked using the Wald-type test. The non-linear relationship between GFR and death within 30 days was assessed using the unrestricted cubic spline (UCS) model fractional polynomial (FP) model [15]. In the logistic regression model with UCSs, the non-linear effect of GFR, X, on 30 days of mortality is evaluated using the quadratic and cubic terms with four knots, k, at fixed and equally spaced percentiles 20%, 40%, 60%, and 80%.

$$y = b_0 + b_1X + b_2X^2 + b_3X^3 + \sum_{i=1}^{n} b_{3+i} \max\left(X - k_i, 0\right)^3$$

In FP model

$$y = b_0 + b_1X^{p1} + b_2X^{p2} + \cdots$$

where pi is fractional power. It suggested that powers are selected from among $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ [16]. In a FP model with powers set $\{1, 0, -2\}$, the equation is as follow—

$$y = b_0 + b_1X + b_2 \ln(X) + b_3 \frac{1}{x}^2$$

All developed models were adjusted for age and ICU admission which are well-known predictors of mortality among COVID-19 patients and surrogates of confounders in association between eGFR and in-hospital mortality relation [17–19]. It was according to the principle of parsimony in model building in which models should have as few parameters as possible. The effect measures were expressed as odds ratios (95% CI) and corresponding CIs.

The performance of the developed models was evaluated using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Smaller values for AIC and BIC indicate better fitness of the model on the data. Predicted probabilities of death within 30 days were estimated from the model with better performance. The power of the selected model to predict the incidence of death was determined by the area under the receiver operating characteristic (ROC) curves. The curve is a plot of sensitivity on the y-axis against false positive rate and area under curve (AUC) values closer to 1 representing stronger prediction. The calibration of the selected models was evaluated using a calibration plot and the Brier score. In the calibration plot, the predictions are plotted against the actual outcome, and agreement between them was assessed in different deciles. The line of 45 degrees in the calibration plot indicates perfect calibration, and 100% agreement between predicted and observed probabilities. The Brier score is calculated using dividing the squared difference between predictions and actual outcomes by the number of observations. The score ranged from 0 to 1 and a lower score may imply higher calibration. All statistical analyses were conducted using Stata version 14.

Results

In total, 2945 COVID-19 inpatients were included, and the number (%) of 30 days of in-hospital mortality was 566 (19.23%). Mean ± SD of eGFR on admission was 71.09 ± 24.78 ml/min/1.73 m^2. According to the CKD-EPI creatinine equation, 23% of patients were within the normal range of GFR (90), 44% of patients with stage G2, 26.6% with stage 3 combined, and about 6% had GFR of lower than 30. The distribution of demographics, comorbidities, vital signs, and lab value at admission as well as hospital course events according to GFR categories are presented in Table 1. In the eGFR categories, numbers and percentages of male aged over 50 years were higher than the comparison group (p-value < 0.001). There was no difference in the distribution of BMI and smoking according to eGFR categories. Numbers and percentages of comorbidities including hypertension, heart diseases, malignancy, and chronic pulmonary diseases were significantly different across eGFR categories. From GFR category G1–G5, the median heart rate significantly decreases by 2 units. All laboratory values were significantly different across eGFR categories, except for Na and PTT. The highest percentages of stay at the hospital (> 5 days), ICU admission, use of mechanical ventilation, and 30-day mortality were observed in eGFR categories of G4 and G5 (p-value < 0.001).

The result of Wald—the type test with 2 degrees of freedom indicates strong evidence against linearity (p-value < 0.001). Table 2 provides the results of three prediction models for the effect of eGFR on 30 days of mortality. In a model with eGFR as continuous form, the OR (95% CI) of 30 days of mortality was 0.98 (0.973, 0.985) after adjusting for age and ICU admission (AIC = 1609.36 and BIC = 1633.14) (Not shown in Table 2). Using AIC and BIC criteria, we found that the Degree-2 FP with powers $(-2, -1)$ have a better fit (smaller AIC and BIC) compared with other models. According to FP model, a non-linear association between eGFR and risk of death within 30 days was found, with a progressively higher risk association with eGFR of lower than 30 ml/min/1.73 m^2. The relationship between eGFR and death within 30 days in patients aged less than 50 years was linear FP with power (1) and it was non-linear in patients aged over 50 years with Degree-2 FP with powers $(-2, -0.5)$. According to fractional polynomials model, the OR of eGFR categories

Table 1 Characteristics of COVID-19 patients according to eGFR on admission

	G1 (*N* = 671)	G2 (*N* = 1293)	G3a (*N* = 525)	G3b (*N* = 278)	G4 (*N* = 133)	G5 (*N* = 45)	*p*-value
Demographics							
Sex							
Male	410 (59.77)	680 (52.31)	277 (52.96)	132 (50.38)	53 (39.55)	23 (57.50)	< 0.001
Female	276 (40.23)	620 (47.69)	246 (47.04)	130 (49.62)	81 (60.45)	17 (42.50)	
Age (years)	45 (57–36)	59 (70–48)	71 (80–62)	75 (82–68)	78.5 (84–70)	74 (83–64.5)	< 0.001
< 50	417 (60.79)	391 (30.08)	40 (7.65)	7 (2.67)	6 (4.48)	5 (12.50)	< 0.001
≥ 50	269 (39.21)	909 (69.92)	483 (92.35)	255 (97.33)	128 (95.52)	35 (87.50)	
BMI (kg/m^2)	26.12 (28.78–23.83)	26.24 (29.29–24.02)	25.95 (29.32–23.66)	25.39 (29.29–22.62)	25.55 (29.38–23.97)	25.29 (26.79–23.23)	0.32
< 20	16 (5.97)	26 (4.39)	15 (6.17)	9 (7.76)	2 (3.85)	0	
20–25	88 (32.84)	192 (32.43)	89 (36.63)	44 (37.93)	21 (40.38)	10 (50)	
25–30	119 (44.40)	255 (43.07)	90 (37.04)	41 (35.34)	19 (36.54)	7 (35)	0.63
> 30	45 (16.79)	119 (20.10)	49 (20.16)	22 (18.97)	10 (19.23)	3 (15)	
Smoking							
No	620 (90.64)	1215 (93.75)	474 (91.15)	244 (93.13)	120 (90.23)	35 (89.74)	
Yes	64 (9.36)	81 (6.25)	46 (8.85)	18 (6.87)	13 (9.77)	4 (10.26)	0.11
Comorbidities							
Hypertension							
No	580 (84.55)	906 (69.69)	269 (51.43)	120 (45.80)	55 (41.04)	22 (55)	
Yes	106 (15.45)	394 (30.31)	254 (48.57)	142 (54.20)	79 (58.96)	18 (45)	< 0.001
Diabetes							
No	594 (86.59)	1079 (83)	400 (76.48)	193 (73.66)	97 (72.39)	29 (72.50)	< 0.001
Yes	92 (13.41)	221 (17)	123 (23.52)	69 (26.34)	37 (27.61)	11 (27.50)	
Heart diseases							
No	637 (92.86)	1131 (87)	395 (75.53)	177 (67.56)	87 (64.93)	32 (80)	< 0.001
Yes	49 (7.14)	169 (13)	128 (24.47)	85 (32.44)	47 (35.07)	8 (20)	
Malignancy							
No	675 (98.40)	1275 (98.08)	516 (98.66)	251 (95.80)	129 (96.27)	38 (95)	0.04
Yes	11 (1.60)	25 (1.92)	7 (1.34)	11 (4.20)	5 (3.73)	2 (5)	
Chronic pulmonary diseases							
No	623 (90.82)	1175 (90.38)	445 (85.09)	225 (85.88)	111 (82.84)	35 (87.50)	0.001
Yes	63 (9.18)	125 (9.62)	78 (14.91)	37 (14.12)	23 (17.16)	5 (12.50)	
*Vital signs at admission**							
Heart rate (beats per minute)	94 (96–91)	93 (95–91)	93 (95–90)	92 (94–90)	92 (94–90)	92 (94–77)	< 0.001
Systolic blood pressure (mmHg)	120 (130–110)	120 (130–110)	120 (135–110)	120 (130–110)	110 (130–100)	117.5 (135–100)	< 0.001
Diastolic blood pressure (mmHg)	80 (80–70)	80 (80–70)	80 (80–70)	70 (80–70)	70 (80–60)	70 (82.5–60)	< 0.001
Temperature (°C)	37.1 (37.79–37)	37.1 (37.7–36.79)	37.1 (37.7–36.79)	37 (37.7–36.9)	37 (37.5–36.5)	37 (37.5–36.7)	0.14
*Lab values at admission**							
eGFR (ml/min/1.73 m^2)	101 (109–95)	76 (82–69)	54 (57–50)	39 (43–35)	23 (28–20)	12 (13–6)	< 0.001
Creatinine (mg/dl)	0.8 (0.9–0.7)	0.98 (1.1–0.86)	1.2 (1.38–1.1)	1.54 (1.78–1.32)	2.27 (2.62–2)	4.54 (7.85–3.85)	< 0.001
Blood urea nitrogen (mg/dl)	13 (16–10)	15 (19–12)	20 (25–16)	27 (36–21)	39.5 (55–28)	71 (95–41.74)	< 0.001
Erythrocyte sedimentation rate (mm/h)	36 (57–20)	37 (58–21)	40 (59–21)	43 (66–20)	46 (69–25)	61 (90–17)	0.009
Hemoglobin (g/dl)	14.2 (15.4–12.9)	14 (15.2–12.7)	13.9 (15.2–12.7)	13.3 (14.7–11.8)	13.3 (14.6–11.7)	13.8 (15.7–12)	< 0.001
Alanine aminotransferase (IU/l)	27 (43–17)	27 (42–17)	25 (39–16)	25 (45–15)	25 (43–14)	45.5 (99–22)	0.006
Aspartate aminotransferase (IU/l)	30 (44–21)	32 (47–23)	33 (49–22)	37 (58–25)	37 (69–26)	57.5 (143–32)	< 0.001

Table 1 (continued)

	G1 (*N* = 671)	G2 (*N* = 1293)	G3a (*N* = 525)	G3b (*N* = 278)	G4 (*N* = 133)	G5 (*N* = 45)	*p*-value
Potassium (mmol/l)	4 (4.3–3.7)	4.1 (4.4–3.8)	4.2 (4.5–3.9)	4.3 (4.6–4)	4.5 (4.9–4.1)	4.8 (5.5–4.3)	< 0.001
Sodium (mmol/l)	138 (140–136)	137.5 (140–135)	137 (139–135)	138 (140–135)	137 (141–133.5)	137.5 (140–135)	0.21
Platelet count ($\times 10^3$/mm^3)	191 (235–151)	184 (235–147)	182.5 (222–142)	170 (229–138)	180 (225–133)	174 (195–136.5)	0.02
Lactate dehydrogenase (U/l)	470 (598–376)	537 (684.5–413)	540.5 (697–411)	570.5 (802–435.5)	576 (802–430.5)	688 (1017–524)	< 0.001
Prothrombin time (s)	13 (14–13)	13 (14–12.5)	13 (14–12.5)	13 (14–12.5)	13.5 (15–13)	13.9 (15–13)	< 0.001
Partial thromboplastin time (seconds)	33 (39–29)	32 (39–28)	33 (39–28)	32 (38–27)	34.8 (42–29)	34 (38.5–27)	0.10
Lymphocytes ($\times 10^3$/mm^3)	21 (31.5–15)	20 (30–13)	19 (28–10)	16 (26–10)	15 (21–9)	11 (17–9)	< 0.001
Monocytes ($\times 10^3$/mm^3)	3 (4–2)	3 (4–2)	3 (4–2)	2 (4–2)	2 (3–2)	2 (3–2)	< 0.001
Neutrophils ($\times 10^3$/mm^3)	73 (80–64)	75 (83–66)	76 (84–67)	80 (86–70)	80 (88–74)	82 (88–80)	< 0.001
Hospital course events							
Stay at hospital (days)							
< 5	390 (56.85)	611 (47)	211 (40.34)	100 (38.17)	56 (41.79)	20 (50)	
5–10	222 (32.36)	438 (33.69)	184 (35.18)	94 (35.88)	42 (31.34)	10 (25)	< 0.001
10–20	64 (9.33)	221 (17)	111 (21.22)	59 (22.52)	26 (19.40)	8 (20)	
20–30	10 (1.46)	30 (2.31)	17 (3.25)	9 (3.44)	10 (7.46)	2 (5)	
ICU admission							
No	533 (82.64)	954 (76.20)	323 (63.21)	139 (55.16)	57 (42.54)	17 (42.50)	< 0.001
Yes	112 (17.36)	298 (23.80)	188 (36.79)	113 (44.84)	77 (57.46)	23 (57.50)	
Mechanical ventilation							
No	600 (93.02)	1064 (84.98)	371 (72.60)	156 (61.90)	55 (41.04)	16 (40)	< 0.001
Yes	45 (6.98)	188 (15.02)	140 (27.40)	96 (38.10)	79 (58.96)	24 (60)	
Outcome at 30 days							
Discharge	645 (94.57)	1110 (85.58)	378 (72.41)	169 (64.50)	55 (41.04)	15 (38.46)	< 0.001
Death	37 (5.43)	187 (14.42)	144 (27.59)	93 (35.50)	79 (58.96)	24 (61.54)	

* The significant level was *P*-value <0.05

Vital signs and lab values are expressed by Median (interquartile range)

G2–G5 versus G1 as reference were 1.19, 1.57, 2.21, 4.68, and 15.14, respectively. It means the odds of death within 30 days among patients with eGFR on admission of lower than 15 ml/min/1.73 m^2 are about 15 times of patients with eGFR ≥ 90 ml/min/1.73 m^2. Corresponding figures from the UCS model were 1.93, 2.49, 2.70, 8.70, and 16.05, respectively (Table 2).

Figure 1 shows smoothed graph of adjusted odds for the association between eGFR and the occurrence of death within 30 days. As shown in Fig. 1, the observed odds of death decrease more rapidly on eGFR 20 to 30 ml/min/1.73 m^2, and then the odds are declined gradually. The probabilities values of 30 days of mortality from FP models including eGFR, age, and ICU admission were estimated for judging discrimination (AUC) and calibration of the model. The sensitivity, specificity, and AUC (95% CI) were 67%, 93%, and 92 (0.90, 0.93), respectively. The Brier score value was 0.09 indicating acceptable agreement between observed and expected outcomes (Fig. 2). On stratification on age and ICU admission to determine the prediction power of eGFR alone, the results showed that the prediction power of the eGFR has better performance (AUC = 0.79) and well-calibrated (Brier score = 0.05) among patients aged 50 and over and not admitted to ICU compared with other subgroups (Fig. 3). The difference between AUCs from model D and model C (*p*-value < 0.001) and model D and model A (*p*-value = 0.005) was only statistically significant.

Discussion

This study aimed to apply flexible statistical methods to model the relationship between eGFR and COVID-19-related in-hospital mortality. We found that the eGFR death within 30-day relation was non-linear, and the FP model had better fitness on the dataset. Using the FP model, the risk of mortality increases exponentially in eGFR < 45, increases linearly in eGFR 45 to 60 and after that tends to plateau.

Table 2 Adjusted OR with 95% CI for the association of eGFR (ml/min/1.73 m^2) and 30 days of mortality from categorical, unrestricted cubic splines, and fractional polynomial

eGFR categories	Median eGFR	Categorical crude model	Categorical adjusted model	Unrestricted cubic splines model[a]	Fractional polynomial model[b]
G1	101	Reference	Reference	Reference	Reference
G2	76	2.83 (1.96, 4.08)	1.68 (1.08, 2.61)	1.93 (1.15, 3.23)	1.19 (1.13, 1.26)
G3a	54	6.39 (4.35, 9.37)	2.16 (1.32, 3.53)	2.49 (1.52, 4.09)	1.57 (1.37, 1.80)
G3b	39	8.69 (5.74, 13.16)	2.45 (1.41, 4.24)	2.70 (1.55, 4.71)	2.21 (1.75, 2.79)
G4	23	24.14 (14.96, 38.96)	7.22 (3.80, 13.71)	8.70 (4.60, 16.44)	4.68 (3.04, 7.21)
G5	12	29.79 (14.82, 59.88)	11.55 (4.32, 30.86)	16.05 (6.87, 37.48)	15.14 (7.45, 30.78)
AIC, BIC		2563.02, 2598.93	1606.69, 1654.26	1601.51, 1660.98	1594.11, 1623.84

All models adjusted for age and ICU admission

[a]Four knots at 31, 48, 60, and 77 eGFR

[b]Degree-2 fractional polynomials with powers (−2, −1)

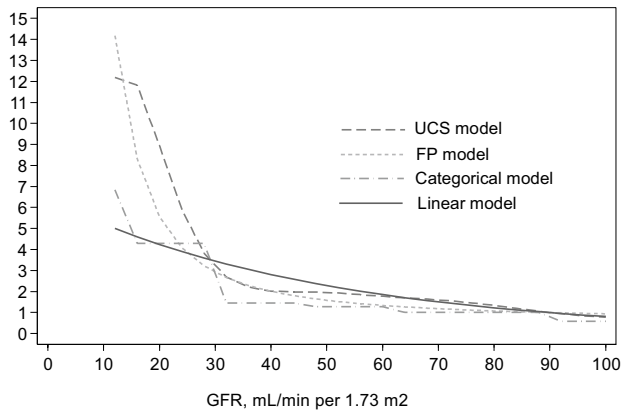

Fig. 1 Smooth curves from linear, categorical, degree-2 fractional polynomial with powers [−2, −1], unrestricted cubic spline with four knots at percentiles 20%, 40%, 60%, and 80% for association between eGFR (ml/min/1.73 m^2) and 30 days of mortality

The prediction power of eGFR in combination with ICU admission and older age (> 50 years) for in-hospital mortality was 92%. The eGFR alone had the strongest prediction power among patients who were not admitted to ICU and aged higher than 50 years.

A common approach used in previous studies for modeling eGFR in-hospital mortality non-linear relation is considering the categorical form of eGFR in regression models [11, 12, 20]. The main limitations of such a method are loss of information and misunderstanding of the nature of eGFR in-hospital mortality relation. For example, the main assumption is that the mortality risk is homogeneous across an eGFR category. It is known as a bad idea to incorporate categorization of the covariate or add a quadratic term in regression models [21]. We addressed this limitation by incorporating flexible and smooth transformations of the eGFR, such as fractional polynomials and regression splines in the prediction model. Our analysis suggested that these transformations are more robust alternatives to employing the categorical approach. Since 5.4% of patients in G1 had death outcomes while the corresponding figure for patients in the G5 category was 61.5%, it seems the *J*-shaped relation between eGFR and mortality is more compatible with the observed data. The non-linear relationship e.g., *J*-shaped and *U*-shaped patterns and critical cut-off of 60 ml/min/1.73 m^2 has been shown for the relationship between eGFR and cardiovascular disease death in the healthy population [22]. Moreover, the non-linear relationship is not limited to eGFR and COVID-19-related mortality. Other studies have also used flexible transformations to examine the power of other continuous determinants e.g., BMI for predicting mortality in COVID-19 patients [23, 24].

Since lower baseline eGFR is associated with development of AKI [25] and the COVID-19-related AKI is one of important risk factors of in-hospital mortality [26], then AKI is an important intermediate determinant in the association between baseline eGFR and in-hospital mortality. However, it argued the relationship between AKI during admission or peak creatinine and mortality in COVID-19 patients is prone to look-ahead bias [27]. Regardless of the previous important issues, our study found lower baseline eGFR independently and non-linearly is associated with death within 30 days in hospital. In previous studies [20, 28, 29], the eGFR of 60 ml/min/1.73 m^2 on admission has been used as a cut-off that affects considerably the mortality of COVID-19 patients. The percentage of eGFR < 60 ml/min/1.73 m^2 in our studies (33%) was similar to aforementioned previous studies [20, 28, 29]. It has been shown that Growth Differentiation Factor 15 (GDF-15) activity is only significant predictive cytokine for poor outcomes in COVID-19 patients, and the effect of GDF-15 tends to be stronger in the presence of eGFR < 45 ml/min/1.73 m^2 [30]. The results from a machine learning model indicate eGFR < 60 ml/min/1.73 m^2, along

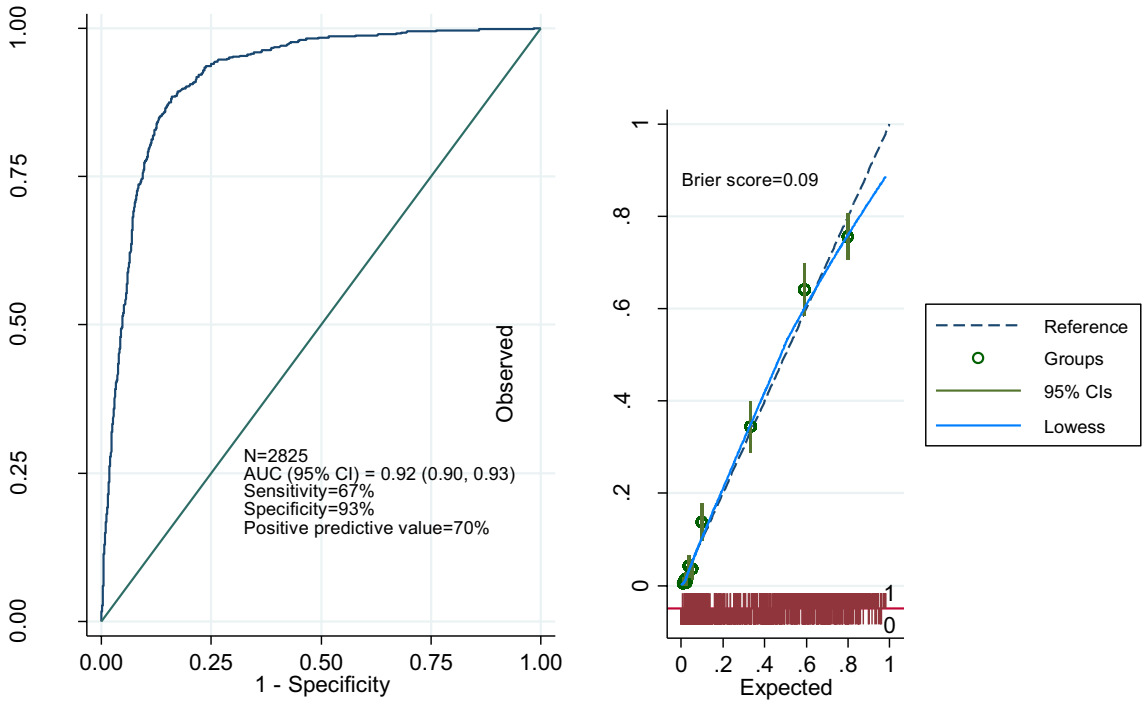

Fig. 2 Area under the curve (AUC) for prediction of 30 days of mortality from degree-2 fractional polynomial with powers [−2, −1] with including eGFR, age, and ICU admission (left graph) and calibration plot (right graph)

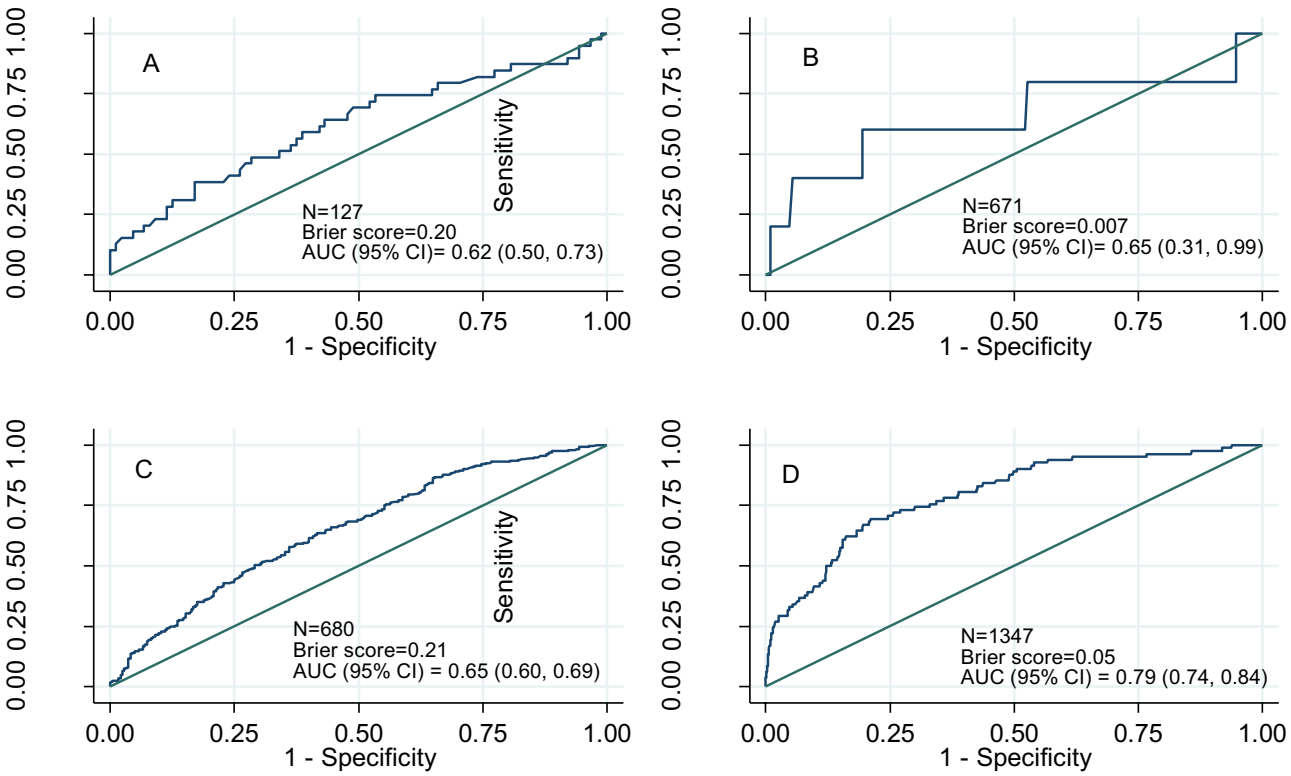

Fig. 3 Area under the curve (AUC) for assessing power of eGFR to predict 30 days of mortality in four subgroups of patients; **A** not admitted to ICU and aged lower than 50 years, **B** admitted to ICU and aged lower than 50 years, **C** admitted to ICU and aged higher than 50 years and **D** not admitted to ICU and aged higher than 50 years

with neutrophil and lymphocyte percentages were the leading predictors of mortality among COVID-19 patients [31].

In a study in England [14], compared with eGFR of 90, the relative risks for G2–G5 categories were 1.17, 2.07, 2.46, 3.71, and 8.35, respectively among people with type 1 diabetes with COVID-19 and 1.02, 1.39, 1.76, 2.31, and 4.91, respectively among people with type 2 diabetes with COVID-19. In another study that included patients aged 65 years or older [13], compared with eGFR of 60, the ORs of mortality for eGFR of 1–29, 30–44, and 45–69 were 1.42, 1.41, and 1.26, respectively. The effect measures in our study were in line with the two former studies [13, 14] in direction but different in magnitude. The OR for patients in the G5 category in our study was 15.14 based on the FP model. This inconsistency could be explained by differences in the comorbidities, type of model prediction building, and eGFR definition. The OR of 15.14 may indicate that there is an interaction between eGFR and older age on mortality among COVID-19 patients because the effect of baseline eGFR < 30 on the in-hospital mortality in other population than COVID-19 patients is much smaller than the OR of 15 [32, 33].

In our study, the prediction power of a combination of eGFR, age, and ICU admission was 92%. Stratification on age and ICU admission, eGFR alone had the prediction power of 79% among patients > 50 years and who were not admitted to the ICU. In one study, low admission eGFR and older age were the only significant and independent determinants of mortality among COVID-19 patients [29]. Older-aged COVID-19 patients are more at risk for AKI during admission and following COVID-19-related deaths [34–36]. In another study [12], eGFR on admission alone in older patients had a prediction power of 70% for mortality risk during hospitalization. The former study [12] also showed change in serum creatinine (s-Cr) levels during hospitalization further enhances the mortality prognosis. One meta-analysis showed pooled AKI events of 29.2% among patients admitted to the ICU [37]. Since a low level of eGFR is independent predictor of ICU admission [38], it can be assumed that ICU admission may be an intermediate variable in pathways between the eGFR and death among COVID-19 patients.

This study has some limitations. First, in this study, we evaluated baseline kidney function and risk of in-hospital mortality among COVID-19 patients. Several issues may influence the interpretation when examining association between eGFR on admission and in-hospital mortality. Acute decrease of GFR alone may not be enough to make judgments about AKI. AKI encompasses both injury (structural damage) and impairment (loss of function). Therefore, the effect of baseline eGFR on in-hospital mortality is better to be studied in generalized patients with hospital-acquired acute kidney injury. eGFR is time-dependent and AKI during admission may be occurred. In other words, using AKI categories based on creatinine change would be appropriate to evaluate the outcomes of AKI in hospitalized patients with COVID-19. Second, since the follow-up duration was limited to 30 days, then in this study, we only show the eGFR on admission is an independent predictor of short-term mortality in COVID-19 patients, after adjusting with well-known determinants of mortality; however, 90 days and 180 days of mortality are other important endpoints that should be considered. Third, there were only 45 cases in combination of G5 and in hospital mortality levels. Thus, the yielded OR (15.14) was relatively large and corresponding CI tends be wide (7.45, 30.78). This sparse data bias should be considered when interpreting the results.

Conclusion

The UCS and FP models are better in model fit compared to linear and categorical models to estimate the eGFR–mortality relationship. Odds of death within 30 days increased exponentially in eGFR < 45 and after that decreased linearly and slowly after adjusting for older age and ICU admission. A combination of eGFR, older age, and ICU admission could predict the mortality risk by 90%. This prediction power of eGFR among geriatric patients and those who not admitted to ICU is 70%. On admission, eGFR as a kidney function in geriatric patients hospitalized with COVID-19 may be important for prediction of in-hospital mortality; therefore, it can be measured in all COVID-19 patients on admission. Understanding the nature of the relation between eGFR and in-hospital mortality is important from clinical decision-making perspective and helpful for providing medical care for at-risk patients.

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Author contributions Conceptualization: EA, and SK; study design: EA and SK; methodology: MA, and FTA, data acquisition: MFS, and SKHO; data analysis and interpretation: EA and SK; supervision: FTA; writing: the first draft of the manuscript was written by EA. All authors revised the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets are available in the Stata format from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Consent to participate Not applicable.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the Hamadan University of Medical Sciences (Ethical Code: IR.UMSHA.REC.1401.1030).

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