

The Nutritional Risk Index as a Predictor of 90-Day Dialysis Dependence After Acute Renal Failure: A Pilot Study

Dennis Emuron, MBChB,^{*} Kaleb Thomas, MD,[†] and Ryan Mullane, DO[‡]

Objective: Return of sufficient renal function to discontinue dialysis following acute renal failure is an important clinical and patient-oriented outcome. Our study sought to develop a model using the Nutritional Risk Index (NRI) to predict 90-day dialysis dependence.

Methods: We retrospectively analyzed 77 patients with acute renal failure admitted to a single university medical center's intensive care units between January 2015 and January 2019 with the need for continuous renal replacement therapy. We assessed the predictive ability of the NRI for 90-day dialysis dependence using age, serum total protein, number of vasopressor days, baseline predialysis estimated glomerular filtration rate (eGFR), and Sequential Organ Failure Assessment (SOFA) score as covariates.

Results: Of the analytic group, 20 (25.9%) had severe nutritional risk, and 16 (20.8%) recovered from acute renal failure at 90 days. The mean age was 57.1 years. The clinical model comprising the NRI, age, serum total protein, number of vasopressor days, SOFA score, and baseline predialysis eGFR had an area under the curve (AUC) of 0.89 (95% confidence interval [CI], 0.81-0.97), sensitivity 56.3%, and specificity 95%. Exclusion of baseline predialysis eGFR and SOFA score did not significantly decrease model discrimination, AUC 0.87 (95% CI, 0.78-0.97). The AUC was least when serum total protein was dropped from the final model, 0.79 (95% CI, 0.66-0.92).

Conclusions: The NRI when used together with other clinical parameters, including serum total protein, may improve the accuracy of predicting renal recovery and independence from dialysis at 90 days.

Keywords: Acute renal failure; dialysis dependence; nutrition; kidney recovery; prediction

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Introduction

PREDICTION OF RENAL recovery following acute renal failure (ARF) requiring dialysis is a common dilemma faced by clinicians. Plasma neutrophil gelatinase-associated lipocalin, B-type natriuretic peptide,¹ and urine biomarkers have been modeled as variables within clinical predictors including the Charlson Comorbidity Index and Acute Physiology and Chronic Health Evaluation II score in recent attempts at predicting renal recovery.² Small sample size and selection bias have limited generalizability

with modest model discrimination among the obstacles limiting their clinical utility.

Malnutrition is common in patients with ARF and is associated with increased morbidity and mortality.³ Metabolic implications of ARF include increased production of counterregulatory hormones, cytokines, and immune mediators that incite hypercatabolism and a negative nitrogen balance. ARF leads to reduced renal water excretion, increased total body fluid overload, extracellular volume expansion, and interstitial edema. While continuous renal replacement therapy (CRRT) may facilitate urea clearance and improvements in fluid balance, it is marked by significant micronutrient and amino acid losses in the dialysate effluent.⁴⁻⁷ Protein-energy malnutrition that develops with ARF may degrade the soluble endothelial glycocalyx, reduce colloid oncotic pressure, and further increase renal edema.⁸

In this pilot study, we sought to investigate the association between the Nutritional Risk Index (NRI) and 90-day dialysis dependence in patients with ARF requiring CRRT while assessing its accuracy in predicting renal recovery.

Methods

Study Design

We conducted a retrospective investigation of all patients with ARF admitted to a single academic medical center's medical, cardiovascular, cancer, and surgical intensive care units (ICUs) between January 1, 2015, and January 1,

^{*}Fellow, Division of Nephrology, University of Nebraska Medical Center, Omaha, Nebraska.

[†]Resident, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska.

[‡]Assistant Professor, Division of Nephrology, University of Nebraska Medical Center, Omaha, Nebraska.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Support: This study was funded through departmental funds from the University of Nebraska Medical Center.

Address correspondence to Ryan Mullane, DO, Division of Nephrology, Department of Internal Medicine, 983040 Nebraska Medical Center, Omaha, NE, 681983040. E-mail: ryan.mullane@unmc.edu

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1051-2276

<https://doi.org/10.1053/j.jrn.2022.03.009>

2019. Data were extracted from the electronic medical record by chart review. Inclusion criteria were patients with ARF requiring CRRT, adult (≥ 18 years), and baseline predialysis estimated glomerular filtration rate (eGFR) ≥ 30 mL/min per 1.73 m². Patients with a baseline predialysis eGFR < 30 mL/min per 1.73 m², end-stage renal disease (ESRD) on dialysis, ARF managed with intermittent hemodialysis, unknown baseline eGFR or serum creatinine level in the preceding 3 months, and those patients who died or were lost to follow-up within 90 days from the initiation of dialysis were excluded. Laboratory and demographic data including age, gender, ethnicity, body mass index, severity of illness scores (including Sequential Organ Failure Assessment [SOFA] and Simplified Acute Physiology II), and vasopressor requirements were abstracted from the day of initiation of dialysis.

Definitions

ARF was defined by Kidney Disease Improving Global Outcomes 2012 guidelines using serum creatinine and urine output criteria. All patients in our analytic cohort had Kidney Disease Improving Global Outcomes stage III ARF owing to the fact that they required renal replacement therapy.⁹ Chronic kidney disease was classified by eGFR as measured by the Modification of Diet in Renal Disease equation. The NRI,^{10,11} an objective nutritional assessment tool, was as calculated by

$$= (1.519 \times \text{Serum Albumin (g/dL)}) + \left(41.7 \times \frac{\text{Present weight}}{\text{Usual weight}} \right)$$

The serum albumin utilized for calculation was the most recent measure prior to the initiation of CRRT. Usual weight was defined as the average weight in the preceding 6 months, in absence of which ideal body weight was used. Severe nutritional risk (SNR) was defined as a NRI value < 83.5 and low-normal nutritional risk ≥ 83.5 .¹² The primary outcome was renal recovery defined as independence from hemodialysis at 90 days, the conventional cutoff for classification as ESRD.¹³

Statistics

Our primary analytic aim was to develop a model using NRI to predict 90-day dialysis dependence as a binary outcome. We used multiple logistic regression to measure the association between NRI and 90-day dialysis dependence adjusted for age, serum total protein, baseline predialysis eGFR, vasopressor requirements, and SOFA score. These covariates were selected a priori, considered biologically relevant, and modeled as continuous variables. Baseline characteristics were compared across nutritional risk groups using Fisher's exact test for categorical variables and analysis of variance for continuous variables. Predictive models were tested sequentially dropping potentially confounding covariates while comparing c-statistics. Model calibration was checked using the Hosmer-Lemeshow χ^2 goodness-of-fit test. In secondary analysis, we used body mass index and baseline predialysis eGFR in logistic regression models to predict 90-day dialysis dependence. Analysis was conducted using STATA (version 15.1; StataCorp LLC, College Station, TX).

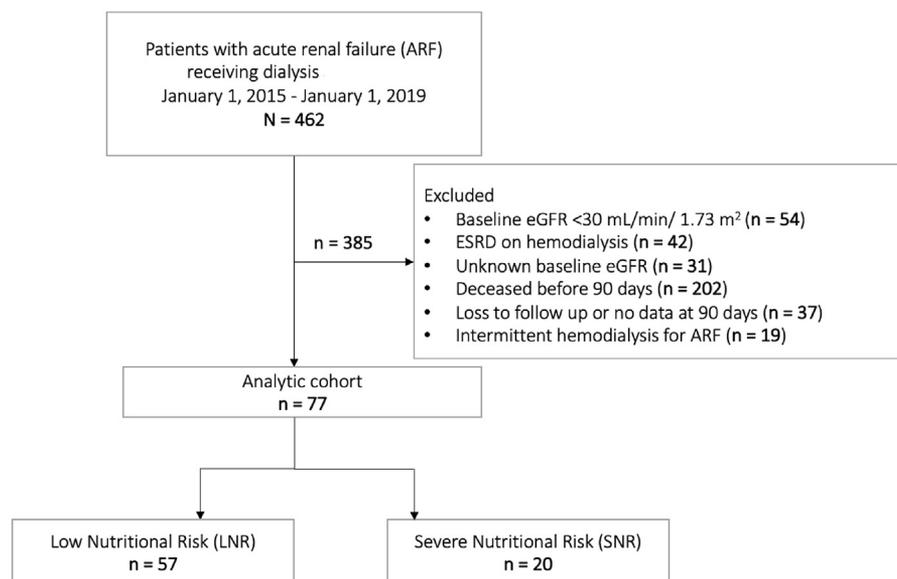


Figure 1. Cohort assembly for adult patients with acute renal failure (ARF) requiring continuous renal replacement therapy.

Table 1. Baseline Characteristics by Nutritional Risk Index

Variable*	Severe nutritional risk (N = 20)	Low nutritional risk (N = 57)	P†
Women, % (n)	40 (8)	36.8 (21)	.80
Age, yr	55 (16.8)	58 (13.1)	.26
Race, % (n)			
White	75 (15)	89.5 (51)	.02
Black	20 (4)	3.5 (2)	
Hispanic	0 (0)	7.0 (4)	
Asian	5.0 (1)	0 (0)	
BMI, kg/m ² , % (n)			
Normal (18.5-24.9)	25 (5)	10.5 (6)	.02
Overweight (25-29.9)	35 (7)	15.8 (9)	
Obese (30.0 and above)	40 (8)	73.7 (42)	
Service, % (n)			
Medicine	70 (14)	49.1 (28)	.13
Surgery	30 (6)	50.9 (29)	
Primary diagnosis, % (n)			
Septic shock	20 (4)	14 (8)	.16
Cardiogenic shock	5.0 (1)	17.4 (10)	
ARDS	15 (3)	1.8 (1)	
CABG	10 (2)	3.5 (2)	
Heart transplant	0 (0)	14.1 (8)	
Liver transplant	5.0 (1)	7.0 (4)	
Other	45 (9)	42.2 (24)	
Baseline eGFR, % (n)			
≥60	80 (16)	57.9 (33)	.19
45-59	10 (2)	29.8 (17)	
30-44	10 (2)	12.3 (7)	
Total protein	5.1 (0.9)	5.7 (0.8)	.004
Dialysis indication, % (n)			
Hyperkalemia	15 (3)	26.3 (15)	.49
Volume overload	35 (7)	40.4 (23)	
Uremia	15 (3)	7.0 (4)	
Acidosis	35 (7)	26.3 (15)	
Number of vasopressor days	1.4 (2.1)	7.3 (9.1)	.002
SOFA score	7.8 (2.9)	8.9 (2.5)	.04
SAPS score	42.7 (1.8)	44.6 (1.2)	.19

*Mean (standard deviation) unless otherwise specified.

†Probability range: 0.0-1.0.

Results

Cohort Characteristics

Data extraction from the electronic medical record yielded 462 patients with ARF who required renal replacement therapy; 77 met the eligibility criteria and were included in the analysis (Figure 1). Of the cohort, 29 (37.7%) were women and 20 patients (25.9%) were classified as SNR. The mean age was 57.1 years (14.0 standard deviations), and the mean duration of vasopressor use was 5.8 days (8.3 standard deviations). Common primary admission diagnoses within the cohort included septic shock, 12 (15.6%), cardiogenic shock, 11 (14.3%), congestive heart failure exacerbation, 2 (2.6%), and surgical interventions including coronary artery bypass graft, 4 (5.1%), heart transplant, 8 (10.4%), and liver transplant, 5 (6.5%) (Table 1) with aortic dissection, small bowel obstruction, and acute pancreatitis among others. Baseline predialysis

eGFR, serum total protein, and indications for initiation of dialysis did not differ between the groups.

Dialysis Dependence Outcomes

Across categories of nutritional risk, 16 (20.8%) patients were dialysis dependent at 90 days. In multiple variable analyses, SNR was associated with a 7-fold increase in the odds of dialysis dependence at 90 days (adjusted odds ratio [OR], 7.08; 95% confidence interval [CI], 1.19-41.3). A unit increase in serum total protein decreased the odds of 90-day dialysis dependence by 84% (adjusted OR, 0.16; 95% CI, 0.04-0.61).

A 1-day increase in pressor requirements and each 10-year increase in age were associated with a 16% (adjusted OR, 1.16; 95% CI, 1.05-1.28) and 1% (adjusted OR, 1.01; 95% CI, 0.99-1.01) increase in the odds of 90-day dialysis dependence, respectively. Baseline predialysis eGFR and SOFA score were not independently associated with the primary outcome in multivariable models (Table 2). In sensitivity analysis, we stratified age by <60 versus ≥60 years and baseline eGFR by ≥60 and <60 mL/min/1.73 m². As predicted by the nutritional risk, the OR for 90-day dialysis dependence was homogeneous across age strata but statistically significant across strata of baseline eGFR (Table 3).

In secondary analyses, we used univariate models to explore the effect of baseline predialysis eGFR on 90-day dialysis dependence. Baseline predialysis eGFR ≥60 was associated with 71% reduced odds (crude OR, 0.29; 95% CI, 0.14-0.57), baseline eGFR 45-59 with 36% reduced odds (crude OR, 0.64; CI, 0.15-2.63), and baseline eGFR 30-44 with 1.3% reduced odds (crude OR, 0.98; 95% CI, 0.18-5.45) of 90-day dialysis dependence. Adjusted logistic regression revealed the probability of 90-day dialysis dependence is near zero in patients with SNR and serum total protein 8 g/dL exponentially rising to above 50% with serum total protein below 5 g/dL (Figure 2).

Our final model that includes the NRI, age, serum total protein, number of vasopressor days, SOFA score, and baseline predialysis eGFR predicts 90-day dialysis dependence with 56.3% sensitivity and 95% specificity with both good calibration (Hosmer-Lemeshow χ^2 goodness-of-fit test; $P = 0.12$) and discrimination (area under the curve [AUC], 88.9%; 95% CI, 0.81-0.97). In sensitivity analyses, the model that excluded SOFA score and baseline predialysis eGFR from the final model had a C statistic of 87.3% (95% CI, 0.78-0.97), while the model that only included the NRI, age, number of vasopressor days, and baseline predialysis eGFR without serum total protein had a C statistic of 79.1% (95% CI, 0.66-0.92) (Figure 3).

Discussion

Our analysis retrospectively reviewed patients with ARF receiving CRRT in ICUs at a single institution. We

Table 2. Crude and Adjusted Logistic Regression Models for 90-Day Dialysis Dependence, Coefficients Reported as ORs

Variable	Univariable analysis: OR; 95% CI	P value	Multivariable analysis*: OR; 95% CI	P value
SNR	2.87; 0.89-9.18	.07	7.08; 1.19-41.8	.03
Total protein†	0.28; 0.12-0.67	.00	0.16; 0.04-0.61	.01
Pressors‡	1.07; 1.01-1.13	.03	1.16; 1.05-1.28	.01
Age§	1.00; 0.99-1.01	.43	1.01; 0.99-1.01	.05
Baseline eGFR	1.05; 0.98-1.12	.15	1.08; 0.97-1.19	.12
SOFA	1.12; 0.90-1.38	.30	1.09; 0.76-1.56	.62

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SNR, severe nutritional risk; SOFA, Sequential Organ Failure Assessment.

*Adjusted for age, total protein, pressor days, baseline eGFR, and SOFA score.

†Every 1-unit increase in total protein.

‡Every 1-day increase in pressor dependence.

§Each 10-year increase in age.

||Each 1-unit increase in predialysis baseline eGFR.

explored causal associations and developed a predictive model for 90-day dialysis dependence using NRI, age, serum total protein, number of vasopressor days, SOFA score, and baseline predialysis eGFR using variables we consider routinely available in clinical practice. These clinical parameters predicted dialysis dependence with an AUC 88.9%; the AUC did not significantly decrease when SOFA score and baseline predialysis eGFR were excluded from the clinical model but significantly decreased by 9.8% when serum total protein was excluded. The secondary findings that younger age and a higher baseline predialysis eGFR are strong predictors for renal recovery are consistent with prior studies.¹⁴⁻¹⁶

The multinational Beginning and Ending Supportive Therapy Kidney study showed dialysis dependence at hospital discharge was 13.8%,¹⁷ while the VA/NIH Acute Renal Failure Trial Network study showed only 16% were independent from dialysis at 60 days.¹⁸ Patients who fail to recover from ARF have a reduced quality of life and increased risk for chronic disease.¹⁹ This highlights the need to identify novel tools to improve renal recovery and reduce the incidence of negative outcomes in patients with ARF. In this study, we focused on the effects of the nutritional state and how they may affect renal recovery. The NRI is used to identify nutritional risk and is not a universally adopted tool for determining nutritional status. Its key features are integrating percentage weight loss during the past 6 months and serum albumin, both of which are typically readily available and commonly used measures to assess nutritional status. Severe malnutrition is prevalent in patients with acute kidney injury and is associated with increased in-hospital length of stay and all-cause mortality.^{3,20,21} Albumin has antioxidant and immunomodulatory properties, stabilizes the endothelium,²² and contributes to vascular integrity, thus modulating transcapillary fluid exchange.²³ Conversely, the metabolic implications of ARF are associated with increased production of stress mediators including counterregulatory hormones, cytokines, and immune mediators that enhance proteolysis, glycogenolysis,

gluconeogenesis, and lipolysis leading to increased urea production and a negative nitrogen balance.^{24,25} Under these conditions, the accepted optimal protein intake is 1 g/kg/day with greater amounts if tolerated and depending on the coexisting risk factors, such as severe protein-calorie malnutrition, liver disease, magnitude of hypermetabolic state, and whether dialysis has been initiated.²⁶⁻²⁸ As the process of dialysis can remove amino acids and intact proteins, patients receiving a more intense dialysis regimen may have even higher daily protein requirements. Patients at SNR may therefore be targeted for goal-directed supplementation while recognizing overall impairment in protein utilization, metabolic stress, and the risk of uremic complications.

Furthermore, the pharmacokinetic behavior in critically ill patients is unlike that in normal subjects for several reasons not limited to renal and hepatic dysfunction. In this context, drug metabolism or excretion is often significantly impaired. Hypoalbuminemia, common in critical illness, decreases protein binding and increases free-drug concentration. Because free drug is the only moiety available to tissue receptors, decreased protein binding increases the pharmacologic effect for a given plasma concentration potentially leading to toxicity to an already injured renal tubular system, as well as systemic adverse effects. This

Table 3. Models for Modification of the Effect of Nutritional Risk Index Across age, and baseline eGFR Strata, Coefficients Reported as Odds Ratios

Variable	\exp^{β_1} (95% CI); $\exp^{\beta_1+\beta_3}$ (95% CI)	P for heterogeneity
Age*	2.31 (0.44-12.1); 3.50 (0.67-18.3)	.73
Baseline eGFR†	1.59 (0.41-6.22); 7.75 (1.24-48.3)	.03

CI, confidence interval.

*Stratified by <60 and \geq 60 years.

†Stratified by estimated glomerular filtration rate (eGFR) \geq 60 and <60 mL/min/1.73 m².

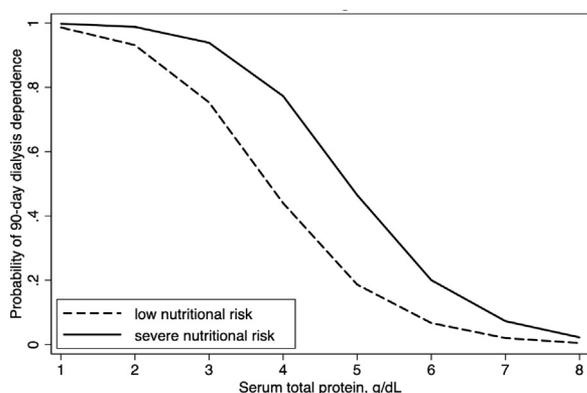


Figure 2. Graph of predicted probability of 90-day dialysis dependence by Nutritional Risk Index (NRI) plotted against serum total protein adjusted for age, Sequential Organ Failure Assessment (SOFA) score, and baseline predialysis estimated glomerular filtration rate (eGFR).

concept may be used to individualize medications for a particular patient. From a patient and family perspective, the ability of their nephrologist to predict dialysis dependence would guide decision-making regarding goals of care. Additionally, a multidisciplinary team could be better equipped to tailor care-related recommendations accordingly. At a population level, approximately 1 in every 24 patients registered as having ESRD in the US Renal Data System recovered to discontinue dialysis and had been misclassified as having permanent kidney failure.¹⁵ This has financial implications as reimbursement policies for dialysis services differ depending on if a patient is designated as having ESRD or ARF requiring dialysis. The Centers for Medicare and Medicaid Services only started payments for skilled nursing facility residents in the latter category in 2018.²⁹ Despite these initiatives, optimal management of patients with ARF requiring dialysis differs from those with ESRD,³⁰ questions arise if, when, or how they should be included in ESRD quality incentive programs. Whether predictive modeling may have a role to play in this arena remains to be seen.

The primary strength of our study is the heterogeneous group of critically ill patients with a wide range of medical and surgical primary diagnoses, allowing for our findings to be applied to other populations typical of US ICUs. Various factors may explain the low sensitivity of our predictive model. First, albumin is not a very sensitive indicator of nutritional status among ICU patients, as its synthesis is influenced by numerous factors including hepatic function and inflammation. Furthermore, the total body weight in many critically ill patients is often an insensitive parameter because of progressive total body salt and water retention. Second, due to data access constraints, we were confined to model accuracy and were unable to model predictive accuracy. Our model stands to be cross validated with a new data set. Third, attempts to minimize threats to validity of

causal inference may have been hampered by unmeasured confounding, small sample size, and selection bias due to our inclusion and exclusion criteria. However, a priori variable selection enhanced our predictive modeling. Additionally, our study design excluded patients with ARF managed with intermittent hemodialysis as they may have been different from those managed with CRRT. We selected against patients with baseline predialysis eGFR <30 mL/min/1.73 m²; Hsu et al in their study found 63% of patients with a baseline eGFR 15–29 mL/min/1.73 m² developed ESRD following hospitalization for ARF.¹⁶ Nonetheless, model discrimination remained good without significant change even when baseline predialysis eGFR was excluded.

Practical Application

The NRI can be used as a predictor of 90-day dialysis dependence in critically ill patients with ARF requiring CRRT. Despite good model calibration and discrimination, our model's low sensitivity highlights the intricacy in the various attributes affecting renal recovery. The addition of biomarkers to the NRI and clinical parameters, including serum total protein, may enhance predictive accuracy and further improve our understanding of ARF and renal recovery.

CRedit Authorship Contribution Statement

Dennis Emuron: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Kaleb Thomas:** Investigation, Data

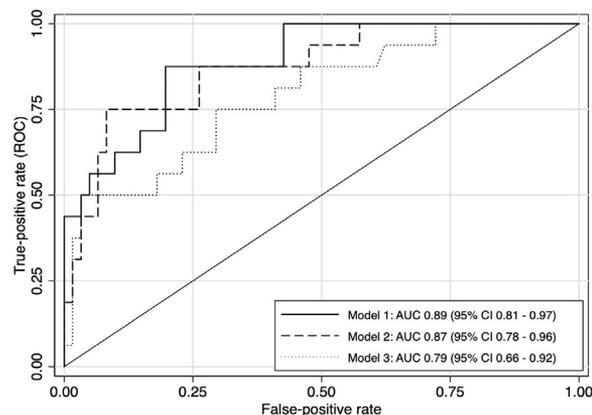


Figure 3. Receiver-operating characteristic curves for three models predicting 90-day dialysis dependence. Model 1: Covariates include Nutritional Risk Index (NRI), age, serum total protein, pressor days, Sequential Organ Failure Assessment (SOFA) score, and baseline predialysis estimated glomerular filtration rate (eGFR). Model 2: Excludes SOFA score and baseline predialysis eGFR from Model 1. Model 3: Includes all covariates in model 1 except serum total protein.

curation, Writing – review & editing. **Ryan Mullane:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Acknowledgments

The authors wish to thank Elizabeth Lyden, MS, for her review of the statistical analysis.

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