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Whole-blood neutrophil gelatinase-associated lipocalin to predict adverse events in acute kidney injury: A prospective observational cohort study☆,☆☆

Oleksa Rewa, MD [a,*], Ron Wald, MDCM, MPH [b,c], Neill K.J. Adhikari, MDCM, MSc [a,d], Michelle Hladunewich, MD, MSc [a,e], Stephen Lapinsky, MD, MSc [a,f], John Muscedere, MD [g,h], Sean M. Bagshaw, MD, MSc [i,j], Orla M. Smith, RN, MN [c], Gerald Lebovic, PhD [c,k], Rottem Kuint, MD [l], David J. Klein, MD, MBA [a,c,k]

[a] Interdepartmental Division of Critical Care Medicine, University of Toronto, 2075 Bayview Ave, Room D1.08, Toronto, ON, Canada M4N 3M5
[b] Division of Nephrology, St. Michael's Hospital and University of Toronto, 30 Bond St, Toronto, ON, Canada M5B 1W8
[c] Keenan Research Institute, Li Ka Shing Knowledge Institute of St. Michael's Hospital, 30 Bond St, Toronto, ON, Canada M5B 1W8
[d] Department of Critical Care Medicine, 2075 Bayview Ave, Room D1.08, Toronto, ON, Canada M4N 3M5
[e] Division of Nephrology, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Suite A206a, Toronto, ON, Canada M4N 3M5
[f] Mount Sinai Hospital, 600 University Ave Suite 18 214, Toronto, ON, Canada M5G 1X5
[g] Queen's University, 99 University Ave, Kingston, ON, Canada K7L 3N6
[h] Kingston General Hospital, 76 Stuart St, Room 5-411, Angada 4, Kingston, ON, Canada K7L 2V7
[i] University of Alberta, 116 St and 85a Ave, Edmonton, AB, Canada T6G 2R3
[j] Division of Critical Care Medicine, University of Alberta, 8440 112 St NW, Critical Care Medicine 2-124E Clinical Sciences Bldg, Edmonton, AB, Canada T6G 2B7
[k] Applied Health Research Centre, Li Ka Shing Knowledge Institute, 193 Yong St, Toronto, ON, Canada M5B 1M8
[l] Department of Medicine, Hadassah-Hebrew University Medical Center, Kiryat Hadassah, POB 12000, Jerusalem, 91120, Israel

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ABSTRACT

Purpose: Acute kidney injury is common in intensive care units and is associated with increased morbidity and mortality. We evaluated the ability of whole-blood neutrophil gelatinase-associated lipocalin (wbNGAL) to predict mortality and need for renal replacement therapy (RRT) in critically ill patients with kidney dysfunction.
Methods: We prospectively enrolled adult patients in 5 Canadian intensive care units. We measured wbNGAL at the time of enrollment to determine whether NGAL concentration could predict the primary composite outcome of death or need for RRT by day 30 in addition to other secondary outcomes.
Results: We recruited 234 patients; 227 were included in the analysis. In a multivariable model, wbNGAL did not predict 30-day mortality or need for RRT (odds ratio, 1.05; 95% confidence interval, 0.99-1.12). Neutrophil gelatinase-associated lipocalin was similar in patients who died (654 [303-1180] ng/mL) vs those who survived (541.5 [255.5-1080] ng/mL, $P = .26$) by 90 days. Whole-blood NGAL poorly predicted the primary outcome (area under receiver operator curve, 0.65; 95% confidence interval, 0.58-0.73).
Conclusions: In a cohort of critically ill patients with abnormal kidney function, wbNGAL was not effective in the prediction of death or RRT within 30 days. These data do not support the use of this biomarker for the detection of clinical outcomes in this population.

1. Introduction

Acute kidney injury (AKI) complicates the clinical course of up to two thirds of patients with critical illness [1,2] and is associated with higher resource use, nonrecovery of kidney function, and mortality [3]. Consensus definitions and staging systems for AKI have been developed, such as Acute Kidney Injury Network criteria and Kidney Disease: Improving Global Outcomes (KDIGO) classifications [4–6]. However, all criteria, including KDIGO, rely on increments in serum creatinine (sCr) and decrements in urine output to diagnose and classify AKI. Unfortunately, both parameters have important limitations. Serum creatinine is a marker of glomerular filtration, whereas most cases of severe kidney

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* Corresponding author at: 9020 Jasper Avenue NW, Suite 1804, Edmonton, Alberta, Canada T5H 3S8. Tel.: +1 780 231 3280; fax: +1 780 492 1500.
E-mail addresses: oleksa.rewa@utoronto.ca, rewa@ualberta.ca (O. Rewa), waldR@smh.ca (R. Wald), neill.adhikari@sunnybrook.ca (N.K.J. Adhikari), Michelle.Hladunewich@sunnybrook.ca (M. Hladunewich), slapinsky@mtsinai.on.ca (S. Lapinsky), muscedej@KGH.KARI.NET (J. Muscedere), bagshaw@ualberta.ca (S.M. Bagshaw), Smitho@smh.ca (O.M. Smith), LebovicG@smh.ca (G. Lebovic), rottemk@yahoo.com (R. Kuint), KleinD@smh.ca (D.J. Klein).

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injury involve tubular damage. As a result, escalations in sCr may occur well after the time of injury and only after a decline in glomerular filtration has already occurred. During hospitalization, patients may develop significant muscle wasting; and using sCr may serve as an overestimating of kidney function. Serum creatinine is hence problematic, and many patients with apparently normal sCr can already have already developed significant AKI. Similarly, urine output may be influenced by factors independent of kidney parenchymal injury, including the use of diuretics, intravascular volume status, and the presence of kidney obstruction [7].

The shortcomings of sCr and urine output have spurred the discovery and characterization of novel biomarkers to enhance the diagnosis of AKI, inform decision making on initiation of renal replacement therapy (RRT), and provide prognostic information on outcomes once AKI is established. One promising biomarker is neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin family of proteins. Neutrophil gelatinase-associated lipocalin is a 25-kd protein bound to gelatinase and is one of the most rapidly upregulated transcripts in kidney tubular cells following acute injury [8,9]. Both urine NGAL and blood NGAL have been shown to be sensitive and specific for the diagnosis of AKI in a variety of cohorts [10–16]. However, the clinical utility of NGAL measurements remains undefined. In particular, the ability of NGAL to predict adverse clinical events in patients with established AKI or with undifferentiated kidney dysfunction of unknown acuity has not been adequately studied.

Accordingly, we conducted a prospective observational study of critically ill patients with kidney dysfunction to determine the ability of whole-blood NGAL (wbNGAL) to predict the composite outcome of the need for RRT or death within 30 days.

2. Materials and methods

2.1. Study design, setting, and population

This prospective, multicenter, observational study was conducted at 5 adult general medical/surgical Canadian intensive care units (ICUs) (St. Michael's Hospital, Toronto; Mount Sinai Hospital, Toronto; Sunnybrook Health Sciences Centre, Toronto; Kingston General Hospital, Kingston; University of Alberta Hospital, Edmonton) between December 2011 and January 2013.

All adults (>18 years) admitted to the study ICUs were continuously screened for evidence of abnormal kidney function as indicated by one of or more of (*a*) elevated sCr at the time of screening (sCr ≥ 133 μmol/L for men or ≥ 100 μmol/L for women), (*b*) 50% rise in sCr or an absolute rise of 27 μmol/L from baseline, or (*c*) urine output 0.5 mL/(kg h) or less for at least 6 hours [17]. *Baseline sCr* was defined as the most recent outpatient sCr before and within 180 days of hospital admission. If an outpatient sCr was not available, the lowest sCr during the current hospitalization before study inclusion was used as the baseline. Hence, a modified KDIGO criterion was used for defining AKI. Patients were excluded if they had undergone kidney transplantation within the last year; received RRT within the previous 2 months; required RRT for a drug overdose; or had or were suspected to have obstructive uropathy, vasculitis, or rapidly progressive glomerulonephritis, or if there was no commitment to ongoing life support. The Research Ethics Board at each hospital approved the study. Written informed consent was obtained from participants or their designated surrogates. A deferred consent process was approved for situations in which eligible patients were not capable of providing consent and surrogate decision makers were unavailable to provide consent. Consent was then sought from the surrogate decision maker if one became available. When initial consent was obtained via a surrogate decision maker or through a deferred consent process, we subsequently attempted to obtain consent from the patient when he/she became capable [18].

2.2. Definitions, data sources, and management

Using standard case report forms, data on the following clinical variables were collected at ICU admission and on the day of wbNGAL testing: age, sex, preexisting conditions (chronic kidney disease [CKD], hypertension, diabetes mellitus, coronary artery disease, or cerebrovascular disease), admission type (medical or surgical), mechanical ventilation, inotrope and vasopressor use, *presence of sepsis or suspected sepsis* (defined as antibiotic prescription and positive or pending blood cultures), modified KDIGO stage [5], sCr, and wbNGAL. Illness severity was assessed by the modified sequential organ failure assessment (SOFA) score using clinical data within 24 hours of study enrollment [19]. Assessments of sCr and urine output and use of RRT were recorded daily for up to 30 days from study enrollment until ICU discharge or death. Maximum modified KDIGO stage was calculated for each patient during his or her ICU stay.

Data were entered in to a secure online database, Research Electronic Data Capture [20], and then analyzed at the Applied Health Research Center of St. Michael's Hospital.

2.3. Outcomes

The primary outcome of this study was the composite of death or RRT initiation within 30 days of enrollment. Secondary outcomes included the components of the primary composite end point, 90-day mortality, and maximum modified KDIGO stage in the ICU in the 30 days that followed enrollment. After discharge from the ICU, all patients were followed to 90 days for assessment of vital status.

2.4. Sampling and quantification of wbNGAL

Within 48 hours after enrollment, we obtained 250 μL of EDTA anticoagulated blood from a central venous catheter, arterial catheter, or during routine peripheral vein sampling. We measured wbNGAL using commercially available fluorescence immunoassay test kits (Alere Triage NGAL; Alere, San Diego, CA) on a point-of-care testing platform (Triage MeterPro; Alere Inc., Ottawa, Ontario) with a measurable range of 15 to 1300 ng/mL. All research staff obtained formal training in the measurement of wbNGAL and calibration of the Triage MeterPro. Patients with a wbNGAL concentration that exceeded the upper limit of detectability for the assay (>1300 ng/mL) were assigned a wbNGAL value of 1300 ng/mL for the purpose of conducting the analyses as done in previous studies [16]. Investigators and caring physicians were not blinded to the measured wbNGAL values; however, the results were not readily made available to them and traditionally would not be included in decision making on initiation of RRT in our centers.

2.5. Statistical analysis

Continuous variables were summarized as means (standard deviation [SD]) or medians (interquartile range [IQR]) and compared using the *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were summarized as numbers (percentage) and compared between patients who met the primary outcome and those who did not using χ^2 or Fisher exact tests.

We examined predictors of the primary outcome, initially using univariable logistic regression models. A priori, we considered wbNGAL (per 100 ng/mL), age (per 5 years), sex, SOFA score, CKD (based on patient- and chart-reported history), sepsis or suspected sepsis, and sCr at time of wbNGAL sampling. We then constructed a multivariable logistic regression model to examine the association between wbNGAL and the primary outcome, adjusting for all the aforementioned covariates. Interaction terms were not examined. We avoided statistical selection procedures and therefore minimized the risk of model overfitting [21]. Continuous variables were nontransformed and modeled using a

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