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ORIGINAL ARTICLE

Using the newer Kidney Disease: Improving Global Outcomes criteria, beta-2-microglobulin levels associate with severity of acute kidney injury

Kevin T. Barton[1], Aadil Kakajiwala[1], Dennis J. Dietzen[2], Charles W. Goss[3], Hongjie Gu[3] and Vikas R. Dharnidharka[1]*

[1]Division of Pediatric Nephrology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA, [2]Department of Pathology, Division of Laboratory and Genomic Medicine, Washington University in St. Louis School of Medicine, St. Louis, MO, USA and [3]Department of Biostatistics, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

Correspondence and offprint requests to: Kevin T. Barton; E-mail: Barton_k@wustl.edu

ABSTRACT

Beta-2-microglobulin (B2M) is a marker of proximal tubular injury and glomerular filtration. Analyses using older/non-standardized definitions have shown low efficacy of B2M to predict acute kidney injury (AKI). We assessed if elevated levels of B2M would associate with either the diagnosis of AKI [under current Kidney Disease: Improving Global Outcomes (KDIGO) criteria] or recovery from AKI. We performed a retrospective study, including children who had urine B2M (uB2M) and/or serum B2M (sB2M) measured by immunoturbidimetry in our clinical laboratory between January 2011 and December 2015. We defined AKI based on KDIGO criteria [increase of serum creatinine (sCr) 0.3 mg/dL over 48 h or >50% baseline over 7 days] or urine output <0.5 mL/kg/h for 24 h. Recovery from AKI was defined as a return to baseline sCr within 6 months. We calculated receiver operating characteristics (ROC) area under the curve (AUC). Of 529 patients, 245 developed AKI. Serum and uB2M associated with AKI development (AUCs 0.84 and 0.73, respectively). Patients had a graded higher median sB2M and uB2M with each higher AKI stage. sB2M differentiated Stage I from Stage III AKI ($P < 0.001$) and Stage II from Stage III AKI ($P = 0.004$). However, neither uB2M nor sB2M levels associated with recovery from AKI. Only older age {hazard ratio [HR] 0.97, [95% confidence interval (CI) 0.94–0.99]} and need for dialysis [HR 0.39 (95% CI 0.23–0.61)] predicted incomplete recovery after AKI. Using KDIGO criteria, sB2M and uB2M associate with the severity of AKI. Given its relative ease and lower cost, we suggest more widespread use of B2M for AKI detection.

Keywords: acute kidney injury, beta-2-microglobulin, biomarkers, pediatrics, renal recovery

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BACKGROUND

Acute kidney injury (AKI) often occurs in hospitalized patients and is associated with increased morbidity and mortality [1]. The incidence of AKI varied considerably in the past, partly due to the use of many different definitions using variations of either serum creatinine (sCr), urine output or need for dialysis [2, 3]. Standardized definitions and staging such as Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) and the AKI Network (AKIN) were recently merged into the current consensus Kidney Disease: Improving Global Outcomes (KDIGO) definitions and staging [2, 4]. The Acute Kidney Injury–Epidemiologic Prospective Investigation study was a multination cross-sectional study that recently described the epidemiology of AKI in hospitalized adults in 97 intensive care units (ICUs) from 33 different countries. Using the KDIGO criteria, the overall incidence of AKI was 57% with >30% developing KDIGO Stage III AKI [1]. Furthermore, AKI conferred a clearly increased risk of chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) at hospital discharge of 57 with AKI versus 95 without AKI; $P < 0.001$) and mortality (27% with AKI versus 7% without AKI; $P < 0.001$) [1]. The incidence of AKI in critically ill pediatric patients was recently reported as 23.6% by the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) trial using the current KDIGO standard definition [5]. They reported 11% mortality for those with severe AKI (KDIGO Stage II or III) and found that severe AKI increased the risk of death [odds ratio (OR) 1.77] [5]. Most importantly, sCr alone failed to identify AKI in 18% of patients with low urine output [3, 5, 6].

sCr, the historical surrogate for kidney function, used in the RIFLE, AKIN and KDIGO classifications, does not increase until significant kidney injury has already occurred. In pediatrics, moreover, sCr levels change with age. Creatinine is falsely low in children with chronic illness whose muscle mass is well below normal, further complicating a creatinine-based AKI definition. Due to the imprecision of creatinine, multiple serum and urine biomarkers have been investigated over the past decade [7, 8].

Beta-2-microglobulin (B2M, molecular weight 12 000 Da) is a component of the major histocompatibility antigen. By coupling with the neonatal Fc receptor, it helps regulate serum levels of immunoglobulin G, albumin and hepcidin [9]. It is hence implicated in a multitude of disease processes, including glomerulonephritis, AKI and iron overload diseases. B2M is filtered at the glomerulus and 99.9% is reabsorbed by the proximal tubule. B2M allows for functional assessment of both the glomerulus and the renal tubules. In the 1980s, multiple studies analyzed the ability of B2M to assess kidney function and found it in most cases superior to sCr [10–12]. For the diagnosis of AKI, using older, nonstandardized definitions, Herget-Rosenthal *et al.* [13] found that urine B2M (uB2M) performed poorly at predicting the need for renal replacement therapy [area under the curve (AUC) 0.51]. Under modified pediatric RIFLE (pRIFLE) criteria, Du *et al.* [14] studied B2M and reported a low receiver operating characteristics (ROC) curve AUC of 0.59 [14].

To date, B2M has not been studied using KDIGO criteria or evaluated as a marker for kidney recovery or progression to CKD after AKI. At our center we have routinely used B2M as a marker for the diagnosis of AKI and monitoring kidney function in children with CKD. We have used B2M both in outpatient clinics to monitor patients recovering from AKI and to assess for AKI in hospitalized patients. For outpatients, uB2M is used more frequently to assess tubular function while using creatinine only for glomerular function. For inpatients, both uB2M and serum B2M (sB2M) are used when possible, but this is limited in patients with anuric AKI. The aims of this study were to compare B2M levels (serum and urine) between patients with and without AKI (as defined by KDIGO) and determine the ability of elevated B2M levels to discriminate between AKI stages and to assess the relationship between B2M elevation and recovery or progression to CKD after AKI.

MATERIALS AND METHODS

We performed a single-center retrospective cohort study to assess if elevated levels of B2M, defined as serum levels >1.8 mg/L or urine levels >0.2 mg/L (based on historical controls), would diagnose AKI or predict recovery from or progression to CKD after AKI. We included all patients >1 year of age with a uB2M and/or sB2M value determined in the St. Louis Children's Hospital clinical laboratory between January 2011 and December 2015. We included patients in the outpatient clinic and all inpatient units. B2M values in serum and urine were assessed by immunoturbidimetry using a Cobas 6000 system (Roche Diagnostics, Indianapolis, IN, USA). Our biomedical informatics division then gathered pertinent clinical laboratory data from our electronic medical record, which was then reviewed and verified by one study team member (Kevin T. Barton). We gathered data on baseline sCr (lowest value 3 months prior to B2M lab draw when available), sCr at the time of B2M lab draw, maximum sCr during admission, sB2M, uB2M, urine protein, urine creatinine, urine output and percent fluid overload over 24–48 h prior to B2M lab draw. We also identified any past history of CKD, diagnosis on admission, lengths of hospital stay, ICU admission and length of stay and recovery from AKI. This study was approved by the institutional review board.

Using the KDIGO creatinine definition of AKI, we identified patients who met the KDIGO sCr definition of AKI and its stages. We used modified urine criteria of urine output <0.5 mL/kg/h over 24 h, as charting in smaller time periods was incomplete. Patients <1 year of age were excluded due to a lack of normative values for B2M in this population at the time of the study.

Recovery was defined as a return to baseline sCr within 6 months of AKI. Time to recovery and degree of recovery were recorded—complete or incomplete. If there was incomplete recovery, the stage of CKD was defined per standard criteria [15].

For comparisons between the AKI and no AKI groups, age was analyzed using a Wilcoxon rank sum test and categorical variables were analyzed using a chi-square test or Fisher's exact test, as appropriate. The sB2M and uB2M measures were analyzed using nonparametric approaches (Kruskal–Wallis and Wilcoxon rank sum) to test for differences among AKI groups and stages. The ability of sB2M and uB2M to predict AKI diagnosis was assessed using an ROC curve and the AUC statistic. Univariable association of covariates with time to recovery from AKI was analyzed using Cox regression analysis. Patients that did not recover were censored at the most recent follow-up date available in the database (date of lab draw up to 6 months after hospital discharge or date of death). P-values <0.05 were considered significant.

RESULTS

Demographic characteristics

A total of 637 charts had available sB2M or uB2M results available in the study time period; 529 patients were >1 year of age (Figure 1). Of these 529 244 total patients met the KDIGO

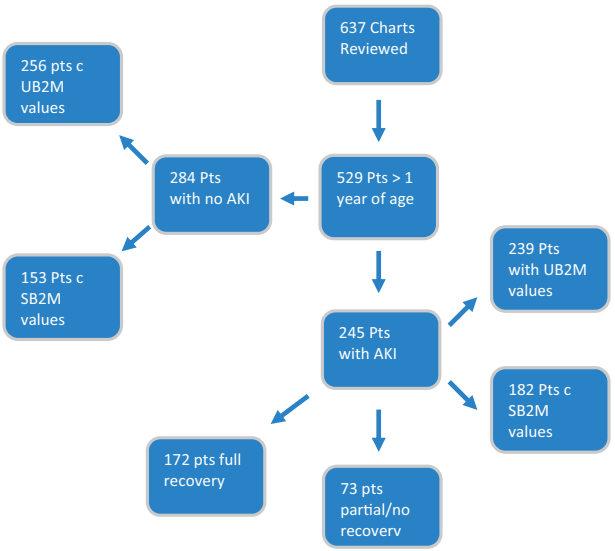


FIGURE 1: Consort style flow diagram.

definition of AKI and 285 patients had sB2M and/or uB2M testing but did not meet the KDIGO definition of AKI.

There was a significant difference in age between the AKI and no AKI groups (median 14.29 versus 9.89 years; $P < 0.001$; Table 1). There was no difference between groups based on race, gender or those with preexisting CKD. The most common diagnosis was medication toxicity ($n = 56$) followed by primary renal disease and dehydration (Table 1). There was a significant difference between groups in percentages of heart transplant recipients ($P < 0.03$ and $P < 0.001$), solid organ transplants overall ($P < 0.001$), bone marrow transplant recipients ($P = 0.004$), viral illness ($P = 0.002$) and sepsis ($P < 0.001$). There was no significant association between AKI and time from transplant, suggesting a more diverse range of causes than chronic medication/calcineurin toxicity. In patients who received a solid organ transplant, the most common causes for AKI were medication toxicity, dehydration and cardiac dysfunction. However, there was not a significant difference between those with and without AKI (Table 2).

Prediction of AKI

Serum and urine B2M were both strongly associated with AKI development, with an AUC of 0.84 and 0.73, respectively (Figure 2). The median values for sB2M and uB2M were significantly higher in the AKI group versus the no AKI group (Table 3). We analyzed patients who had both uB2M and sB2M values and the results were nearly identical to when we included patients who had only uB2M or sB2M. We only included analyses for patients who had both uB2M and sB2M values. By the Kruskal–Wallis test, patients also had a graded higher and significantly different median sB2M and uB2M with each higher AKI stage (Tables 3 and 4). Pairwise comparisons among stages revealed that sB2M and uB2M differentiated between no AKI and Stage II or III AKI ($P < 0.001$; Tables 4 and 5). sB2M also differentiated between no AKI and Stage I AKI ($P < 0.001$), Stages I and II AKI ($P < 0.001$) and Stages II and III AKI ($P = 0.004$; Table 4). Although there is literature supporting uB2M as a specific marker for drug-induced AKI, we found no statistically significant difference in our population (Table 6).

Table 1. Demographic characteristics of study cohort

Variable	AKI (n = 244)	No AKI (n = 285)	P-value
Age (years), mean (IQR)	14.29 (9.36–17.18)	9.89 (3.92–15.93)	<0.001
Male, *n* (%)	120 (49.2)	145 (50.9)	0.73
Race, *n* (%)			
Caucasian	169 (69.6)	204 (71.6)	0.49
African American	56 (23.1)	67 (23.5)	
Other	18 (7.4)	14 (4.9)	
Diagnosis, *n* (%)			
Medication toxicity	56 (23.0)	20 (7.0)	<0.001
Primary renal disease	47 (19.3)	86 (30.2)	0.004
Dehydration	50 (20.5)	19 (6.7)	<0.001
Solid organ transplant	41 (16.8)	22 (7.7)	0.001
Sepsis	37 (15.2)	9 (3.2)	<0.001
Bone marrow transplant	21 (8.6)	8 (2.8)	0.004
Cardiac dysfunction	33 (13.5)	15 (5.3)	0.001
UTI	11 (4.5)	11 (3.9)	0.71
Viral illness	26 (10.7)	11 (3.9)	0.002
Prematurity	3 (1.2)	5 (1.8)	0.73
Other	111 (45.5)	162 (56.8)	0.009
Lung transplant	21 (8.6)	13 (4.6)	0.06
Liver transplant	6 (2.5)	5 (1.8)	0.57
Heart transplant	16 (6.6)	3 (1.1)	<0.001
Kidney transplant	3 (1.2)	2 (0.7)	0.67

Table 2. Association between diagnosis and AKI in solid organ transplant patients

Variable	AKI (*n* = 41)	No AKI (*n* = 22)	P-value
Medication toxicity, *n* (%)	12 (29.3)	2 (9.1)	0.11
Dehydration, *n* (%)	12 (29.3)	1 (4.6)	0.024
Cardiac dysfunction, *n* (%)	9 (22.0)	2 (9.1)	0.30

Need for renal replacement therapy

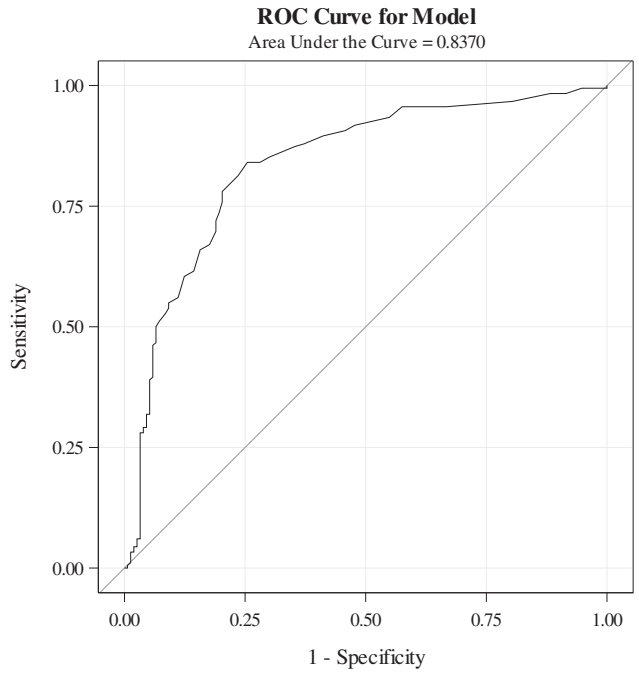
Both uB2M and sB2M were associated with a need for renal replacement therapy. For this analysis we used all patients, not just those with both uB2M and sB2M values, to account for anuric patients (Table 7).

Recovery from AKI

Of those 245 patients with AKI, our results showed 172 patients had complete recovery, with 73 patients developing CKD or death (66 CKD, 4 chronic dialysis, 12 died, not mutually exclusive). Cox regression analysis indicated that older age and need for dialysis were the only variables that were significantly associated with a greater risk of not recovering after AKI {hazard ratio [HR] 0.967 [confidence interval (CI) 0.941–0.993] and 0.388 (CI 0.233–0.610), respectively; Table 8}. Neither uB2M nor sB2M was associated with the time-to-recovery outcome.

DISCUSSION

Our study highlights the ability of sB2M to identify patients with AKI to a high degree of accuracy, using the newer and current standardized and consensus KDIGO definition. Serum B2M also showed a graded increase with increasing severity of AKI.



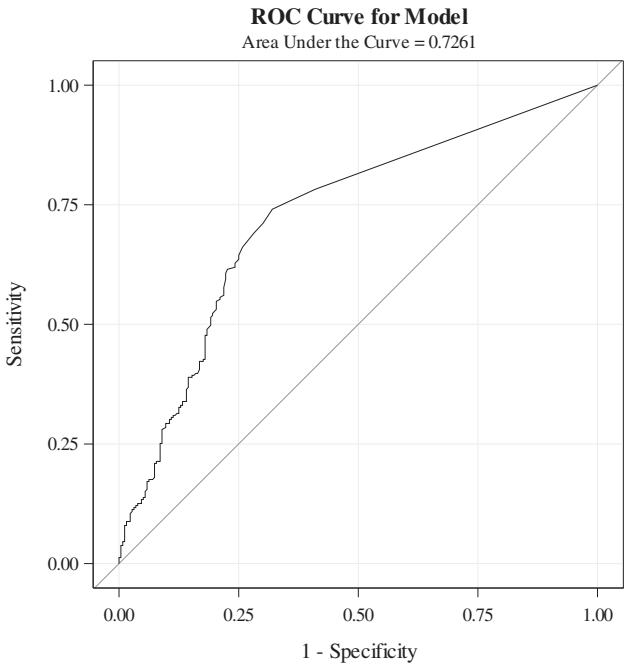


FIGURE 2: ROC curves for sB2M and uB2M versus AKI.

Table 3. sB2M and uB2M versus AKI

Variable	AKI, median (IQR)	No AKI, median (IQR)	P-value
sB2M (mg/L)	4.4 (2.8–9.4)	1.9 (1.4–2.6)	<0.001
uB2M (mg/L)	3.9 (0.4–17.3)	0.2 (0.2–2.9)	<0.001

Table 4. Nonparametric analyses of sB2M and AKI stages

Group comparison	Group 1, median (IQR)	Group 2, median (IQR)	P-value
No versus Stage I	1.9 (1.4–2.6)	3.1 (2.2–5)	<0.001
No versus Stage II	1.9 (1.4–2.6)	3.8 (2.6–7.4)	<0.001
No versus Stage III	1.9 (1.4–2.6)	5.7 (3.7–10.1)	<0.001
Stage I versus Stage II	3.1 (2.2–5)	3.8 (2.6–7.4)	0.14
Stage I versus Stage III	3.1 (2.2–5)	5.7 (3.7–10.1)	<0.001
Stage II versus Stage III	3.8 (2.6–7.4)	5.7 (3.7–10.1)	0.004

Table 5. Nonparametric analyses of uB2M and AKI stages

Group comparison	Group 1, median (IQR)	Group 2, median (IQR)	P-value
No versus Stage I	0.2 (0.2–2.9)	1.5 (0.2–13.6)	0.028
No versus Stage II	0.2 (0.2–2.9)	8 (0.4–22.7)	<0.001
No versus Stage III	0.2 (0.2–2.9)	3.7 (0.6–16.8)	<0.001
Stage I versus Stage II	1.5 (0.2–13.6)	8 (0.4–22.7)	0.06
Stage I versus Stage III	1.5 (0.2–13.6)	3.7 (0.6–16.8)	0.10
Stage II versus Stage III	8 (0.4–22.7)	3.7 (0.6–16.8)	0.44

Urine B2M was also able to identify patients with AKI, but with slightly less accuracy than sB2M. Neither uB2M nor sB2M were significantly associated with recovery from AKI. Our study showed that recovery was less likely in children who were older or requiring renal replacement therapy during their AKI. These results most likely reflect accumulation of nephrotoxicity from chronic diseases such as congenital heart disease or refractory malignancy in addition to their treatment regimes.

Table 6. uB2M versus drug-induced AKI

Variable	Drug-induced AKI, median (IQR)	AKI (other causes), median (IQR)	P-value
uB2M (mg/L)	3.5 (0.3–18.0)	3.1 (0.4–16.0)	0.92

Table 7. sB2M and uB2M versus dialysis (within AKI)

Variable	Dialysis, median (IQR)	No dialysis, median (IQR)	P-value
uB2M (mg/L)	9.5 (0.7–29.9)	2.6 (0.3–15.2)	0.043
sB2M (mg/L)	8.5 (5.5–14.2)	3.9 (2.7–8.3)	<0.001

The ideal renal biomarker should have a regular production rate and be eliminated only via glomerular filtration, without tubular secretion or reabsorption. Creatinine has multiple limitations as a biomarker, including tubular secretion and its dependence on the patient's muscle mass, age or gender. Most importantly, it is a late and nonspecific marker of injury [16].

Our results show that B2M is strongly associated with AKI in the pediatric population. Using KDIGO criteria versus pRIFLE criteria, the AUC improved dramatically from the previously reported 0.59 to our value of 0.84 for sB2M and 0.73 for uB2M. Serum B2M was statistically significantly different between almost all stages of AKI, making it a potentially useful tool for estimating the functional severity of AKI. The uB2M values peaked at Stage II AKI and decreased at Stage III, likely due to decreased urine output in that group, limiting its utility at severe stages of AKI. The higher AUC for sB2M compared with

Table 8. Univariable time to event associations of covariates for likelihood of complete recovery from AKI

Variable	HR (95% CI)	P-value
Age (per year increment)	0.967 (0.941–0.993)	0.01
Urine protein (mg/dL)	0.999 (0.998–1.001)	0.39
Urine protein:creatinine ratio	0.991 (0.939–1.035)	0.72
Urine B2M (mg/L)	1.003 (0.998–1.008)	0.23
Serum B2M (mg/L)	0.984 (0.945–1.021)	0.41
Fractional excretion of B2M	1.11 (0.439–1.966)	0.79
Male	1.158 (0.857–1.567)	0.34
Race, Caucasian[a]	0.755 (0.533–1.088)	0.30
Race, other[†]	0.907 (0.468–1.64)	
CKD	0.616 (0.33–1.052)	0.08
ICU	0.832 (0.613–1.125)	0.23
Solid organ transplant	0.761 (0.481–1.15)	0.20
Diagnosis, BMT	0.62 (0.306–1.115)	0.12
Dialysis	0.388 (0.233–0.61)	<0.001
Lung transplant	0.698 (0.356–1.229)	0.23
Liver transplant	2.515 (0.886–5.579)	0.08
Heart transplant	0.833 (0.435–1.444)	0.54
Kidney transplant	0.94 (0.053–4.228)	0.95

[a]Reference group for race was African American.

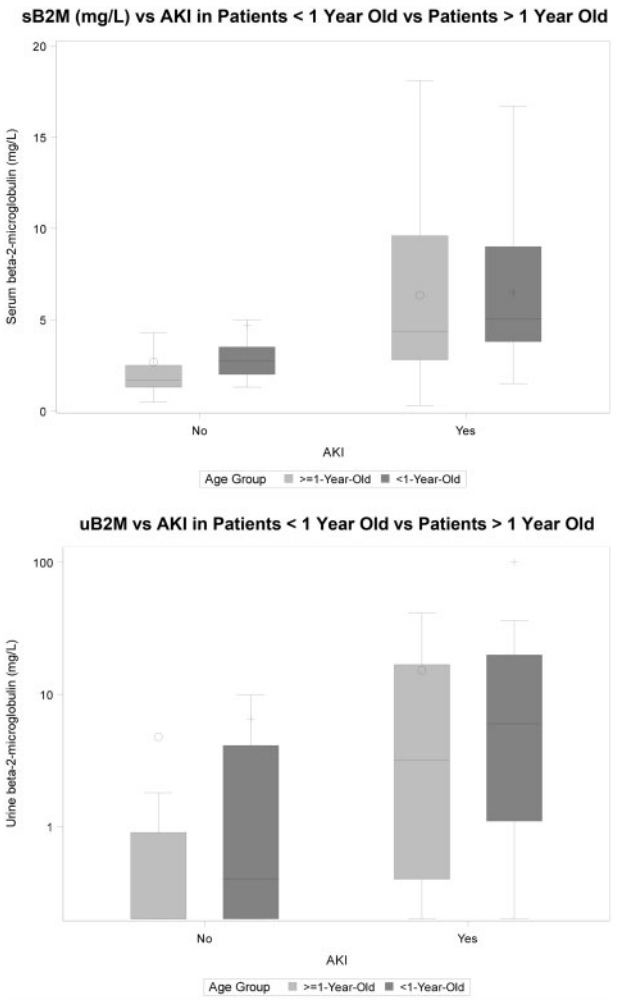


FIGURE 3: Box plots of sB2M and uB2M versus AKI.

uB2M is likely due to some prerenal AKI cases being classified as Stage I KDIGO AKI, as would be expected.

To our knowledge, this is the first study to analyze B2M as a marker for AKI under a standardized KDIGO definition. Previous studies have analyzed multiple biomarkers using nonstandardized or older definitions or specific populations. Du *et al.* [14], for example, studied patients presenting to an emergency department using pRIFLE criteria, with an AUC of 0.59 for uB2M. They also examined neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 and kidney injury molecule 1 (KIM-1), which all had AUC values ranging from 0.44 to 0.66, comparable with B2M. Compared with other newer biomarkers being developed, the AUC of sB2M in mixed-etiology AKI populations compares favorably with the AUCs of the newer biomarkers in similar mixed-etiology populations, which range from 0.61–0.96 for NGAL to 0.69–0.85 for KIM-1 and 0.70–0.75 for L-type fatty acid binding protein (L-FABP) [8]. In the Translational Research Investigating Biomarker Endpoints in AKI study, investigators found urine NGAL, L-FABP and KIM-1 to be highly accurate markers of Stages II and III AKI in pediatric cardiac surgery patients (AUC 0.75, 0.77 and 0.70, respectively), where the exact time of injury is known and the type of injury is predominantly ischemic, thus biomarkers tend to be more accurate [17]. Furthermore, sB2M can be used for all hospitalized patients and not just those who are critically ill. However, we have not tested B2M versus the other biomarkers head to head using common KDIGO criteria.

Although we found a significant association between uB2M and sB2M with the need for renal replacement therapy, there was significant overlap in B2M values between those who did and did not need renal replacement therapy. The utility of B2M as a predictor of renal replacement therapy is therefore limited, but warrants further study.

Neither sB2M nor uB2M were significantly associated with recovery from AKI, which may be due to the retrospective nature of this study. Although there are consensus definitions for recovery in adults, there is currently no corresponding definition of renal recovery after AKI in the pediatric population [18]. Most longitudinal follow-up studies are limited to dialysis requirement or transplant, largely ignoring the early stage of CKD. One report describes 34% of patients with residual CKD or dialysis dependence after AKI [19]. More importantly, at the 3- to 5-year follow-up, 60% of those patients who did completely recover went on to develop signs of CKD, including proteinuria, hypertension or decreased GFR [19]. This study highlights the importance of longitudinal follow-up in patients with AKI, even with apparent full recovery. Some of the newer biomarkers such as NGAL, KIM-1 and L-FABP have moderately high AUCs of 0.67–0.82 for prediction of a composite outcome of AKI progression, dialysis or death in either cardiac bypass or mixed-etiology critically ill populations [8]. To our knowledge, AUC data for the isolated outcome of less than complete recovery from AKI in mixed-etiology critically ill patients is not available for these newer biomarkers.

There were multiple limitations to this study. Due to the multifactorial nature of the causes of AKI, it is difficult to study direct causality. As a retrospective chart analysis, there is always the possibility of missing or inaccurate data. Inherent in our study also is a selection bias for patients who are likely to have significant kidney injury and/or kidney disease and therefore had B2M tested. AKI in the neonatal population has new criteria that were standardized after the completion of data collection. We analyzed B2M versus AKI in this population and subjectively it showed no difference between those with and

without AKI and a wider range of values in those without AKI (Figure 3). This may be due to the maturation of tubular function in this population. A future study could analyze this population controlling more specifically for age and prematurity.

In addition, the timing of B2M draws was mostly at the time of initial recognized elevated creatinine, but the exact timing was inconsistent. We also only analyzed single measurements of B2M per patient. In the future, serial measurements could help clarify the role of B2M as a predictor of AKI and recovery from AKI. Our lab does not adjust the pH of urine samples, which may have affected our uB2M results. Furthermore, we had to modify KDIGO urine output criteria, which may have misidentified some early AKI as no AKI. However, using a longer time period of decreased urine output would decrease the number of Stage I AKI patients detected, increasing the overall severity of the cohort. For recovery data, some patients were lost to follow-up and were assumed to have not recovered, which may not have been true.

B2M, while a better biomarker than creatinine, still has limitations. It is increased in hematologic malignancies and multiple autoimmune diseases such as Crohn's disease and Sjögren's syndrome and, importantly, lupus erythematosus. Despite these limitations, B2M still showed high AUC values for the prediction of AKI.

Multiple biomarkers have been identified and continue to be studied in an attempt to identify AKI earlier and more accurately to improve treatment and outcomes. We have shown that B2M is a good predictor of AKI, but not necessarily specific to the severity of AKI. Most importantly, with a unified definition through KDIGO criteria, we have shown B2M to be better at predicting AKI development than has been previously reported. With its relatively low cost ($2.45/test at our center) and potentially wider clinical availability, we suggest B2M be implemented more widely as a functional biomarker for AKI.

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CONFLICT OF INTEREST STATEMENT

Part of this work was presented as an oral abstract at the annual meeting of the American Society of Nephrology in November 2017.

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