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10 Year Kidney Outcomes & Healthcare Utilization in a Cohort of Pediatric Patients with Severe AKI by Subphenotype

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Abstract

Background: The incidence of acute kidney injury (AKI) in critically ill children is high, and AKI is associated with worse in-hospital outcomes. However, reports of long-term outcomes are limited. Evidence suggests that the pathogenic mechanism (subphenotype) of AKI may impact outcomes for patients. This study aims to describe the 10-year outcomes for critically ill patients with severe AKI (stage II or greater), stratified by subphenotype.

Methods: Children and young adults admitted to a single, tertiary care PICU in 2013 were eligible, excluding those with advanced CKD. 10-year follow-up data was collected in October 2023. AKI was defined using the Kidney Disease Improving Global Outcomes serum creatinine criteria. Assigned clinical subphenotypes included sepsis-associated, nephrotoxic medication-associated, hemato-oncologic, cardiac, primary kidney, and other. We highlight differences in long-term kidney and healthcare utilization outcomes.

Results: Of 572 eligible patients, 57 met criteria for severe AKI. The in-hospital mortality was 16%. AKI was stage II in 28 and stage III in 29 patients. The most common AKI subphenotype was cardiac. At maximum follow-up, 23 patients with severe AKI had CKD.

Discussion: This study highlights differences in long-term kidney and healthcare utilization outcomes in patients with severe AKI. The observed differences emphasize the need for ongoing monitoring and targeted interventions. We provide a framework to consider the prognostic value of AKI subphenotypes. Further research will deepen our understanding of outcomes for patients with AKI and capture potential differences dictated by mechanisms of AKI.

Introduction

Acute kidney injury (AKI) in patients admitted to the pediatric intensive care unit (PICU) is common, with estimated rates between 18–82%.[1–5] AKI is an independent risk factor for morbidity and mortality during the hospital admission, and this risk extends beyond the initial hospitalization.[3–9] Emerging evidence supports an increased risk of long-term chronic kidney disease (CKD) following AKI events. A recent publication by Robinson et. al demonstrates 18% of children with AKI had a major adverse kidney event (death, kidney failure, or chronic kidney disease) within 10 years of their initial AKI event.[1,4,6,10–15] Given the concern that chronic kidney disease (CKD) may be going underrecognized, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend post-AKI evaluation within three months, with nephrology referral for high-risk pediatric patients.[16] Evidence suggests that the uptake of this recommendation is low (less than 50%).[2,14,16,17] As our understanding of the long-term risks of AKI evolve, the diverse nature of these AKI events and the underlying mechanisms that drive them has advanced as well. This evolving understanding supports the development of AKI subphenotype classifications, which may help guide follow-up recommendations.[18,19] The importance of considering

the impacts of various AKI subphenotype classification systems on the risk of morbidity and mortality has been discussed, but literature describing these differences is limited.[17]

The aim of this study was to describe long-term kidney related outcomes (kidney recovery, CKD, proteinuria or hypertension) and healthcare utilization (hospital length of stay, subsequent number of hospital admission days, and laboratory follow up) in a cohort of children during the 10 years following an admission during which they developed severe AKI (KDIGO stage II/III), stratified by clinical subphenotype of AKI.

Methods

Cohort

This analysis was determined exempt by the University of Iowa Institutional Review Board (IRB). All children and young adults who were admitted to the pediatric intensive care unit (PICU) of a single, tertiary care center in the calendar year 2013 were eligible for inclusion. Given the time of data collection (late 2023), 2013 was chosen to provide the possibility of ten years of follow up for the entire cohort. Data was collected from the electronic medical record (EMR). 648 unique patients were screened for inclusion and only the first admission of the calendar year for an individual patient was included. Patients with known end-stage kidney disease (ESKD) or suspected advanced CKD, with an abnormal baseline serum creatinine value were excluded (n = 9). Baseline serum creatinine was defined as either the lowest value in the 3-months preceding the admission, or, if no value existed, a validated expected value for age was assigned.[20–22]

Of these, 639 (98%) of patients had creatinine data available in the medical record, and 593 (92%) of patients had at least one creatinine value available within one week of their admission. Height data was available for 572/593 (96%) patients for calculation of estimated GFR (eGFR). All eligible creatinine values were then abstracted to determine those who met criteria for at least stage II (severe) KDIGO-based AKI during their index admission, and these were manually verified by review of the medical records.[16]

AKI Subphenotypes

AKI clinical subphenotypes were manually assigned to each AKI event. Subphenotype categories used included: sepsis-associated, nephrotoxic medication-associated, hemato-oncologic, cardiac, neonatal, primary kidney dysfunction, or other/unspecified, which are commonly discussed in the existing literature.[23] Patients were assigned to the most appropriate subphenotype based upon available data within the patient's medical record using pediatric nephrology consultation notes from the index hospitalization (if available) or subsequent review of the medical record by a pediatric nephrologist (AS) if nephrology consultation did not occur at the time of the AKI event. If applicable, AKI events were assigned to multiple subphenotypes, with a maximum of two.

Kidney Outcomes: Kidney Replacement Therapy, Kidney Recovery, Subsequent AKI Events, CKD, Proteinuria, and Hypertension

Kidney Replacement Therapy (KRT) was defined as documented use of intermittent hemodialysis, continuous kidney replacement therapy or peritoneal dialysis. Kidney recovery was defined consistent with previously utilized definitions, as return of serum creatinine to less than 1.5 times the baseline serum creatinine for more than 48 hours.[12] CKD was defined as an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m2 based on two serum creatinine values at least three months apart.[16,24] Patients were classified as having proteinuria if they had a protein to creatinine ratio greater than 0.2 mg/mg without interval normal values at any point during follow-up. Hypertension was defined as the presence of a billing code for hypertension or documentation of anti-hypertensive therapy for that indication within the medical record.

Healthcare Utilization Outcomes: Duration of Index Admission, Subsequent Inpatient Days

To examine the impact of severe AKI on healthcare utilization metrics, we collected length of stay of the index admission, subsequent inpatient hospitalization days over the entire ten years, time from discharge to most recent outpatient contact, and total number of serum creatinine values obtained over the subsequent ten years. Time to most recent outpatient contact was defined as either a documented patient encounter or laboratory value, whichever was most recent.

Statistical Analyses:

Categorical variables are reported as counts (percentages) and continuous variables are reported as medians (interquartile range). Statistical testing for differences in categorical variables was performed via Chi-square tests and Fisher's exact tests where applicable. For differences between continuous variables, t-tests were used. The significance level was 0.05. All analyses were performed using R v 4.5.0.

Results

Severe AKI and Subphenotypes

Criteria for severe AKI were met in 57/572 (10%) of the eligible patients during their index admission. Of these, 29/57 (51%) met criteria for stage III AKI (Table 1A). In-hospital mortality was 16% (9/57) in patients with severe AKI compared to 3% (17/515) in those without severe AKI ($p < 0.001$). All severe AKI events were stratified into the 7 AKI subphenotypes which totaled 78 different event classifications. The cardiac subphenotype (33/78; 42%) was the most assigned subphenotype (Table 1B). Kidney replacement therapy (KRT) was used for 16/57 (28%) of the patients with severe AKI during their index admission (Table 1A). KRT utilization was the highest (33%) in the sepsis, cardiac, and primary kidney dysfunction AKI subphenotypes. Hemato-oncologic associated AKI had the highest proportion of stage III AKI, with 6/7 (86%) meeting this criterion (Table 1B).

Kidney Outcomes: Kidney Recovery, CKD, Proteinuria, and Hypertension

The prevalence of CKD at latest follow-up in patients who experienced severe AKI during their index admission was (23/57; 40%), which was higher than those without severe AKI (67/515; 13%) ($p < 0.001$) (Table 2A). Neither the rate of kidney recovery nor CKD differed between stage II nor stage III AKI. (**Supplemental Table 1**). The presence of proteinuria at latest follow-up was significantly higher in those patients who experienced severe AKI (27/57; 47%) compared to those without (92/515; 18%) ($p = 0.02$). Similarly, hypertension at latest follow-up was more common in patients who experienced severe AKI (15/57; 26%) compared to patients without severe AKI (39/515; 7.6%) ($p < 0.001$) (Table 2A). By subphenotype, patients in the hemato-oncologic AKI cohort had the highest prevalence of CKD (3/7; 43%). Patients with cardiac AKI had the lowest prevalence of CKD (5/31; 16%). Proteinuria and hypertension were most frequent in the primary kidney dysfunction subphenotype (3/6; 50% for each) (Table 2B).

Healthcare Utilization Outcomes: Duration of Index Admission, Subsequent Inpatient Days

The duration of the index for patients with severe AKI was longer (18 days) than those without AKI (5 days) ($p < 0.001$). Following discharge from the index hospitalization, the subsequent number of inpatient days over the next 10 years was also greater for patients with severe AKI (89 days vs 10 days, $p < 0.03$). The overall median duration of outpatient follow-up did not differ between those with severe AKI and those without (304 days vs 325 days, $p = 0.60$) (Table 3A). Patients with hemato-oncologic AKI experienced the longest index hospitalization (66 days), the most subsequent inpatient days (384 days), and the highest number of serum creatinine values obtained following their index hospitalization (178) of the patients stratified by subphenotype. Patients with primary kidney dysfunction had the longest laboratory follow-up time and the longest kidney function monitoring time with a median of 2,877 days. For all sub-phenotypes creatinine was obtained with long term laboratory assessment, as evidenced by equal follow up times (Table 3B).

Discussion

Epidemiology of AKI and CKD & Associations of AKI with Healthcare Utilization and Mortality

While estimates of AKI incidence in pediatric ICU populations vary, the incidence of severe AKI in our cohort (9.9%) is consistent with the multi-center “Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults” (AWARE) Study (11.5%). [4] Accordingly, we defined severe AKI (stage II/III) as our primary exposure. Our findings align with the existing literature which demonstrates worse outcomes are associated with severe AKI both during and following hospitalization.[14,25] Compared with patients without severe AKI, we found that those with severe AKI experienced higher mortality, as well as a longer index hospitalization.

In contrast to AKI, the existing data on the epidemiology of CKD following AKI events is less clearly defined. In an analysis of all patients hospitalized with AKI, Askenazi et al reported a 3–5-year CKD rate

of 59%.[14] Using nationalized healthcare data Robinson et al reported that – over a median follow-up rate of 10 years – 18% of all patients with dialysis dependent AKI had a long-term major adverse kidney event and 13% had CKD[26] The prevalence of CKD (40%) observed in our cohort differed from both studies. This difference may reflect differences in sample size, patient populations, follow-up duration or methods used in the identification of CKD. Despite this variability, our findings reinforce that, when compared to PICU patients without severe AKI, PICU patients with severe AKI experience a higher prevalence of long-term kidney-related morbidities such as CKD, proteinuria and hypertension, and underscore the need for close post-discharge monitoring.

Outcomes by Subphenotype

Given emerging evidence that AKI subphenotypes may be associated with differential outcomes, we examined outcome differences within our cohort. In-hospital mortality among patients with sepsis-associated (11.1%), nephrotoxic medication-associated (16.7%), and hemato-oncologic-associated (14.2%) severe AKI was higher than the cohort without severe AKI (3.3%). These findings support the concept that AKI subphenotype may influence clinical outcomes, although the patients underlying disease also likely contributes to these differential outcomes. [27–34]

Notably, mortality among patients with cardiac-associated AKI in this study was lower than the general PICU population and lower than rates previously reported for this population.[27,29,35,36] This finding may reflect differences in baseline risk or underlying cardiac disease, rather than a protective effect of the subphenotype itself. Given study limitations, we are unable to adequately stratify patient level risk in this population.[27,29,35,36]

As AKI subphenoytpes may also predict the need for, or the likelihood of providers to utilize KRT, we examined utilization of KRT by subphenotype as well.[18,23,37–41] KRT utilization was highest among patients with sepsis-associated (33.3%), cardiac-associated (33.3%), and primary kidney dysfunction-associated severe AKI(33.3%). While causal relationships between KRT use and outcomes cannot be inferred from this study, these findings suggest meaningful variation in KRT utilization across AKI subphenotypes.

Collectively, these findings support the concept that patients with various AKI subphenotypes experience distinct clinical trajectories and may be influenced by differing pathophysiologic mechanisms, confounding factors, and therapeutic responses.[42] Future studies should prioritize standardized subphenotype definitions and direct comparisons between subgroups to better evaluate targeted therapies and outcome prediction.

Limitations:

This study has several limitations. The relatively small sample size and retrospective single-center design limit generalizability. AKI subphenotypes were defined subjectively primarily through chart review, introducing potential misclassification. Only patients from the pediatric intensive care unit were included, limiting the ability to consider AKI events which would have been considered “neonatal” or those which may have happened in a non-PICU setting. Additionally, the absence of severity-of-illness scores limited our ability to control for overall illness severity, restricting causal inference and raising the possibility that increased morbidity, mortality, and healthcare utilization reflect greater baseline illness rather than the independent effect of severe AKI.[43] Finally, given that the data used for this analysis was retrospective, ascertainment bias may be present due to more frequent follow up of those with a higher illness severity. Despite these limitations, our findings are consistent with existing pediatric AKI literature and add important insight into the long-term kidney burden and outcome heterogeneity associated with severe AKI in critically ill children.

Conclusion

In this single-center cohort of critically ill pediatric patients with severe AKI, we demonstrate higher mortality and longer hospital lengths of stay compared to those without severe AKI. Additionally, we provide novel insights into outcomes stratified by AKI subphenotype. Although limited by the retrospective design, this study extends prior work by evaluating outcomes across multiple AKI subphenotypes simultaneously, enabling direct comparison between groups.

These findings may help inform future efforts to more precisely define AKI subphenotypes enabling direct comparisons between groups and informing outcome predictions. Ultimately, this work serves as preliminary groundwork for studies aimed at linking AKI pathophysiology to targeted, mechanism-specific therapeutic strategies which may help improve outcomes for these patients.

Declarations

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Tables

Table 1A: Demographic Variables by Presence of Severe AKI

	n (%)	Severe AKI n=57 (10%)	No AKI or Stage I AKI n=515 (90%)	p-value[c]
Median Age (years) [IQR]	572	10.2 [4.7, 15.5]	12.5 [7.3, 17.8]	0.04
Sex	572			0.24
Male	318 (55.6)	27 (47.4)	291 (56.5)	
Female	254 (44.4)	30 (52.6)	224 (43.4)	
In-Hospital Mortality	572			< 0.001
Yes	26 (4.5)	9 (15.8)	17 (3.3)	
No	546 (95.5)	48 (84.2)	498 (96.7)	
AKI Stage[a]				-
Stage II		28 (49.1)	-	
Stage III		29 (50.9)		
In-Hospital Kidney Replacement Therapy Utilization				-
Yes		16 (28.1)	-	
No		41 (71.9)		
Other/Missing		0		

[a]: KDIGO AKI Stage (Stage I: SCr 1.5 – 1.9x baseline, Stage II: SCr 2 – 2.9x baseline and Stage III: SCr >3x baseline value)[16]

[b]: Kidney Replacement Therapy Utilization defined as receipt of continuous renal replacement therapy, intermittent Kidney Replacement Therapy and/or peritoneal Kidney Replacement Therapy

[c]: Categorical variables are reported as counts (percentages) and continuous variables are reported as medians (interquartile range).

Table 1B: **Demographic Variables by AKI Subphenotype**

	n	Sepsis n=9	Nephrotoxic Medication n=12	Hemato-Oncologic n=7	Cardiac n=33	Primary Kidney Dysfunction n=6	Other n=11
Median Age [IQR]	78	16.1 [13.4, 17.3)	14.8 [10.0, 21.3]	14.8 [12.8, 17.5]	5.5 [2.13, 10.2]	13.5 [11.0, 14.9]	12.4 [6.0, 16.8]
Sex	78						
Male		4 (44.4)	5 (41.7)	3 (42.9)	16 (48.4)	3 (50)	4 (36.3)
Female		5 (55.6)	7 (58.3)	4 (57.1)	17 (51.6)	3 (50)	7 (63.6)
AKI Stage[a]	78						
Stage II		4 (44.4)	7 (58.3)	1 (14.3)	19 (57.6)	1 (16.7)	4 (36.4)
Stage III		5 (55.6)	5 (41.7)	6 (85.7)	14 (42.4)	5 (58.3)	7 (63.6)
In-Hospital Mortality	78						
Yes		1 (11.1)	2 (16.7)	1 (14.2)	3 (0.9)	0 (0)	0 (0)
No		8 (88.9)	10 (83.3)	6 (85.8)	30 (99.1)	6 (100)	11 (100)
In-Hospital Kidney Replacement Therapy Utilization	78						
Yes		3 (33.3)	1 (0.08)	2 (28.6)	11 (33.3)	2 (33.3)	3 (27.3)
No		6 (66.7)	11 (91.7)	5 (71.4)	22 (66.7)	4 (66.7)	8 (72.7)

[a]: KDIGO AKI Stage (Stage I: SCr 1.5 – 1.9x baseline, Stage II: SCr 2 – 2.9x baseline and Stage III: SCr >3x baseline value)[16]

[b]: Kidney Replacement Therapy Utilization defined as receipt of continuous renal replacement therapy, intermittent Kidney Replacement Therapy and/or peritoneal Kidney Replacement Therapy

Table 2A: Long-Term Kidney Outcomes by Presence of Severe AKI During Index Admission

	n (%)	Severe AKI n=57 (%)	No AKI or Stage I AKI n=515 (%)	p-value[d]
CKD[a]				<0.001
Yes	90 (15.9)	23 (40.4)	67 (13)	
No	475(84.1)	33 (57.9)	442 (85.8)	
Missing	6	1	6	
CKD[a]	90	23	67	0.02
Stage II	71 (78.8)	14 (60.9)	57 (85.1)	
Stage III	13 (14.4)	6 (26.1)	7 (10.4)	
Stage IV	4 (4.4)	3 (13.0)	1 (1.7)	
Stage V	2 (2.2)	0	2 (3.5)	
Missing	0	0	0	
Proteinuria[b]				0.02
Yes	119 (21.0)	27 (47.4)	92 (17.9)	
No	453 (79.0)	30 (52.6)	423 (82.0)	
Missing	0	0	0	
Hypertension[c]				<0.001
Yes	54 (9.0)	15 (26.3)	39 (7.6)	
No	518 (91.0)	42 (73.7)	476 (92.4)	
Missing	0	0	0	

[a]: CKD as defined by KDIGO Stage II or Greater (Stage II: eGFR = 60-69, Stage III: eGFR 30-60, Stage IV eGFR 15-30, Stage V eGFR < 15) units mL/min/1.73m2[44]

[b]: Proteinuria defined as two urinary protein to creatinine ratios greater than 0.2 separated by more than 3 months

[c]: Hypertension as defined by billing code for hypertension or documentation of anti-hypertensive therapy for that indication within the medical record

[d]: Categorical variables are reported as counts (percentages) and continuous variables are reported as medians (interquartile range).

Table 2B: Long Term-Kidney Outcomes by AKI Subphenotype

	n	Sepsis n=9	Nephrotoxic Medication n=12	Hemato-Oncologic n=7	Cardiac n=33	Primary Kidney Dysfunction n=6	Other n=11
CKD	78						
Yes	18	2 (22%)	4 (33%)	3 (43%)	5 (16.1%)	2 (33%)	2 (18%)
No	58	7 (78%)	8 (67%)	4 (57%)	26 (83.9%)	4 (67%)	9 (82%)
Missing	2	0	0	0	2	0	0
CKD Stage	16						
Stage II	11	1 (50%)	2 (16%)	2 (29%)	4 (12%)	1 (16%)	1 (9%)
Stage III	5	1 (50%)	1 (8%)	0	1 (3%)	1 (16%)	1 (9%)
Stage IV	2	0	1 (8%)	1 (14%)	0	0	0
Stage V	0	0	0	0	0	0	0
Proteinuria	78						
Yes	9	1 (11%)	1 (8%)	1 (14%)	2 (6.3%)	3 (50%)	1 (9%)
No	68	8 (89%)	11 (92%)	6 (86%)	30 (93.7%)	3 (50%)	10 (91%)
Missing	1	0	0	0	1	0	0
Hypertension	78						
Yes	21	2 (78%)	2 (17%)	3 (43%)	6 (18.2%)	5 (83%)	3 (27%)
No	57	7 (22%)	10 (83%)	4 (57%)	27 (81.8%)	1 (17%)	8 (73%)

[a]: CKD as defined by KDIGO Stage II or Greater (Stage II: eGFR = 60-69, Stage III: eGFR 30-60, Stage IV eGFR 15-30, Stage V eGFR < 15) units mL/min/1.73m2[44]

[b]: Proteinuria defined as two urinary protein to creatinine ratios greater than 0.2 separated by more than 3 months

[c]: Hypertension as defined by billing code for hypertension or documentation of anti-hypertensive therapy for that indication within the medical record

Table 3A: Healthcare Utilization Outcomes by Presence of Severe AKI During Index Admission

	n		Severe AKI n=57 (10%)	No AKI or Stage I AKI n=515 (90%)	p-value[c]
Median Duration of Index Hospitalization	572	Days	18.2 [9.0, 46.8]	5 [0.4, 1.3]	<0.001
Median Subsequent Inpatient Time Following Discharge From Index Admission*	572	Days	89.0 [47.8, 325.0]	9.8 [4.7, 22.4]	<0.03
Median Time to Most Recent Outpatient Contact*	572	Days	304.0 [24.0, 513]	325.0 [90.4, 510]	0.60
Median Time to Most Recent (any) Lab[b]*	572	Days	1,085.0 [0.0, 3059.0]	125.3 [0.9, 2681.0]	0.24
Median Time to Most Recent Creatinine Value*	572	Days	980.0 [0.0, 2814.0]	53.2 [0.0, 2387.0]	0.19
Total Number of Serum Creatinine Values Obtained Following Discharge from Index Admission*	572	—	34 [20.0, 133.0]	7 [3.0, 17.5]	<0.001

[a]: Defined the time from index hospitalization discharge date to latest outpatient visit with any specialty in the healthcare system

[b]: Median time from hospital discharge to latest lab collection date in the healthcare system

[c]: Categorical variables are reported as counts (percentages) and continuous variables are reported as medians (interquartile range).

*All variables are defined by the latest available date in the EMR at time of data collection (10/2023)

Table 3B: Healthcare Utilization Outcomes by AKI Subphenotype

	n		Sepsis n=9	Nephrotoxic Medication n=12	Hemato-Oncologic n=7	Cardiac n=33	Primary Kidney Dysfunction n=6	Other n=11
Median Duration of Index Hospitalization [IQR]	78	Days	14.7 [9.1, 66.2]	66.0 [9.8, 130.2]	66.0 [32.9, 140.0]	18.5 [10.5, 41.3.0]	5.0 [4.9, 11.2]	14.0 [4.2, 20.3]
Median Subsequent Inpatient Time Following Discharge from Index Admission* [IQR]	78	Days	104.0 [-]	244.0 [174.0, 314.0]	384.0 [-]	74.0 [48.5, 283.0]	-	4.0 [-]
Median Time to Most Recent Outpatient Contact[a*] [IQR]	78	Days	1,792.0 [1.5, 3,640.0]	3,430.0 [3,045.0, 3,619.0]	2,681.0 [661.5, 3,507.0]	2,051.0 [60.9, 3,598.0]	2,989.0 [1,645.0, 3,619.0]	511.0 [0.7, 1827.0]
Median Time to Most Recent (any) Lab[a] [IQR]	78	Days	1,701.0 [0.07, 3,612.0]	1,722.0 [111.3, 3409.0]	2,814.0 [686.0, 3,703.0]	917.0 [0.2, 1,855.0]	2,877.0 [1,393.0, 3,458.0]	0.2 [0.07, 665.0]
Median Time to Most Recent Creatinine Value	78	Days	1,701.0 [0.07, 3,612]	1,722.0 [111.3, 3409.0]	2814.0 [686.0, 3703.0]	917.0 [0.2, 1,855.0]	2,877.0 [1,393.0, 3,458.0]	0.2 [0.07, 665.0]
Total Number of Serum Creatinine Values Obtained Following Discharge from Index Admission* [IQR]	78	Count	34.0 [25.0, 137.0]	75.0 [20.3, 177.0]	178.0 [130.0, 333.0]	30.0 [20.0, 74.5]	67.0 [26.5, 127.0]	22.0 [9.0, 69.0]

[a] Defined the time from index hospitalization discharge date to latest outpatient visit with any specialty in the healthcare system

[b] Median time from hospital discharge to latest lab collection date in the healthcare system

*All variables are defined by the latest available date in the EMR at time of data collection (10/2023)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- VisualAbstract.pptx
- SupplementalTable1.docx