Mortality, disease progression, and disease burden of acute kidney injury in alcohol use disorder subpopulation

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ABSTRACT

Background: The aim of the study was to quantify the relationship between acute kidney injury (AKI) and alcohol use disorder (AUD).

Methods: We used a large academic medical center and the MIMIC-III databases to quantify AKI disease and mortality burden as well as AKI disease progression in the AUD and non-AUD subpopulations. We used the MIMIC-III dataset to compare two different methods of encoding AKI: ICD-9 codes, and the Kidney Disease: Improving Global Outcomes scheme (KDIGO) definition. In addition to the AUD subpopulation, we also present analyses for the hepatorenal syndrome (HRS) and alcohol-related cirrhosis subpopulations identified via ICD-9/ICD-10 coding.

Results: In both the ICD-9 and KDIGO encodings of AKI, the AUD subpopulation had a higher incidence of AKI (ICD-9: 43.3% vs. 37.92% AKI in the non-AUD subpopulations; KDIGO: 48.65% vs. 40.53%) in the MIMIC-III dataset. In the academic dataset, the AUD subpopulation also had a higher incidence of AKI than the non-AUD subpopulation (ICD-9/ICD-10: 12.76% vs. 10.71%). The mortality rate of the subpopulation with both AKI and AUD, HRS, or alcohol-related cirrhosis was consistently higher than that of the subpopulation with only AKI in both datasets, including after adjusting for disease severity using two methods of severity estimation in the MIMIC-III dataset. Disease progression rates were similar for AUD and non-AUD subpopulations.

Conclusions: Our work shows that the AUD patient subpopulation had a higher number of AKI patients than the non-AUD subpopulation, and that patients with both AKI and AUD, HRS, or alcohol-related cirrhosis had higher rates of mortality than the non-AUD subpopulation with AKI.

Key Indexing Terms: Alcohol use disorder; Alcohol-related cirrhosis; Hepatorenal syndrome; Acute kidney disease; Mortality; Disease burden. **[Am J Med Sci 2022;364(1):46–52.]**

INTRODUCTION

Acute kidney injury (AKI; previously referred to as acute renal failure),[1] affects approximately 7% of all inpatients, up to one-in-five ICU patients, and incurs an annual cost of $5.4B in the United States.[2-5] AKI is correlated with an increased risk of death,[6] and occurs abruptly with a sudden loss of kidney function over the course of several days. AKI treatment involves determining and treating the cause of AKI[7-9] in addition to providing supportive treatment until the patient improves.

Alcohol use disorder (AUD) is a prevalent condition associated with multiple comorbidities.[10,11] Alcohol consumption is reported to be the third most important preventable cause of disease, after smoking and hypertension,[12,13] and accounts for 4.2% of the global burden of disease measured in disability-adjusted life years.[12,14] Although the mechanisms through which AUD might directly lead to AKI are not clearly defined,[15] AUD may result in alcohol-related cirrhosis [16] and alcoholic hepatitis,[17,18] conditions that leave patients particularly vulnerable to AKI.[1,19] Hepatorenal syndrome (HRS) is a common complication of cirrhosis and alcoholic hepatitis.[20,21] Approximately 75% of patients with cirrhosis develop renal dysfunction,[22,23] and approximately 20% of patients hospitalized with cirrhosis develop AKI.[1] Taken together, these data suggest that AUD may increase the risk of developing AKI.[24,25] However, it remains unclear if AUD patients are more likely to be diagnosed with AKI and if they are more likely to develop an advanced stage of AKI (vs. non-AUD patients).

Towards this end, this work aims to quantify the relationship between AKI and AUD, in terms of disease burden, mortality burden, and disease progression.

METHODS

Datasets

The analysis presented here utilizes data obtained from a large academic medical center containing general ward and ICU patients, as well as data obtained from the MIMIC-III[26] dataset. Data from the academic center were obtained from EHRs of individuals treated between 2011 and 2016. The MIMIC-III dataset contains adult patients admitted to the ICU between 2001 and 2012. Encounters with no raw data, encounters with no age data, and pediatric encounters (age < 18) were excluded. Data collection was passive and had no impact on patient safety. All data were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Studies performed on the de-identified data constitute non-human subject studies, and therefore, this study did not require Institutional Review Board approval.

Disease Definitions

We investigated two different methods of encoding AKI: 1) ICD-9/ICD-10 codes (**Table 1**; used in academic and MIMIC-III datasets) and 2) the 2012 Kidney Disease: Improving Global Outcomes scheme (KDIGO; used in MIMIC-III dataset)[27], where stage 2 and stage 3 are considered AKI positive. Stage 2 AKI is defined in the KDIGO staging system as an increase in serum creatinine (SCr) to more than 200% to 300% (>2- to 3-fold) from baseline or urine output <0.5 ml/kg per hour for more than 12 hours.[3] Stage 3 AKI is defined as an increase in SCr to more than 300% (>3-fold) from baseline, or ≥ 4.0 mg/dl (≥ 354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/L), or renal replacement therapy, or a decrease in estimated glomerular filtration rate (eGFR) to < 35 ml/min per 1.73m^2 (if <18 years of age), or urine output < 0.5 mL/kg/hr for ≥ 24 hours or anuria for ≥ 12 hours.[3] In addition to the AUD subpopulation, we also present analysis for HRS and alcohol-related cirrhosis subpopulations. The ICD-9/ICD-10 codes used for generating the AUD, HRS and alcohol-related cirrhosis subpopulations are listed in Table 1.

Alcohol Use Disorder and Acute Kidney Injury Correlations

To quantify the relationship between AKI and AUD in the MIMIC-III and academic datasets, we investigated the following three potential interactions:

Disease burden

We investigated the relative incidence of AKI inside of and outside of the AUD subpopulation, or HRS, or alcohol-related cirrhosis populations (designated Alcohol-Related Conditions (ARCs)) in the MIMIC-III and academic datasets. If AKI is linked to AUD in a substantive way, one would expect to see AKI as more likely to occur in the AUD (or the other ARCs) subpopulation than the non-AUD subpopulation. We examine this interaction between AKI and AUD using both ICD-9/ICD-10 and KDIGO encodings of AKI.

Mortality burden

We investigated the relative mortality rates associated with AKI inside of and outside of the AUD subpopulation (or HRS or alcohol-related cirrhosis) in the MIMIC-III and academic datasets. If AUD exacerbates AKI in a substantive way, one would expect to see mortality rates higher in the subpopulation which has both AKI and AUD than in the subpopulation which only has AKI.

We also performed the mortality burden experiment on analysis subpopulations controlled for patient severity. Patients who have ARCs may be predisposed to worsened mortality outcomes. To control for this potential confounding effect, we downsampled our analysis subpopulations such that the distributions of severity among the subpopulations are equivalent. Patient severity was defined in two ways; using modified early warning scores (MEWS) and using the number of unique ICD-9/ICD-10 diagnoses present. If AUD exacerbates AKI in a substantive way, one would expect to see mortality rates higher in the subpopulation which has both AKI and AUD than in the subpopulation which only has AKI.

Disease progression

We investigated the relative disease progression of AKI inside of and outside of the AUD subpopulation (or HRS or alcohol-related cirrhosis) in the MIMIC-III dataset. Disease progression is defined here as moving from KDIGO stage 1 to stage 2, or from stage 2 to stage 3. If AUD exacerbates AKI in a substantive way, one would expect to see AKI progress to a higher level of severity more often in patients with AUD.

Table 1. ICD-9 and ICD-10 codes used to identify diagnoses for alcohol-related conditions and acute kidney injury.

	ICD-9 codes	ICD-10 codes
Acute Kidney Injury	593.9, 584.5-584.9	N17.0, N17.1, N17.2, N17.8, N17.9
Alcohol Use Disorder	291, 305.0, 303.0, 303.9, 357.5, 425.5, 535.3, 571.0-571.3	F10.1, F10.2, F10.9, G62.1, I42.6, K29.2, K70
Hepatorenal Syndrome	572.4	K76.7
Alcohol-Related Cirrhosis	571.2	K70.30, K70.31

STATISTICS

In order to compare the incidence, mortality rates and disease progressions between subpopulations with and without alcohol related comorbidities, we performed tests for proportions using the normal (z) test. Using the *Statsmodels* library,[28] the p-values were calculated to test for significant increase of incidence, mortality rates and disease progression in ARC subpopulations in comparison to non-ARC subpopulations.

RESULTS

Disease Burden

Population-level baseline incidence rates for the ARCs and AKI differ between the MIMIC-III and academic datasets (as shown in Table 2). This likely reflects the differing compositions of the two datasets, as MIMIC-III is comprised of data from ICU patients and the academic dataset is mixed-ward. In the MIMIC-III dataset for both the ICD-9/ICD-10 and KDIGO encodings of AKI, there were notable differences in the incidence of AKI in the AUD (or the other ARCs) and non-AUD subpopulations. In the ICD-9 encoding of AKI, whereas the non-AUD subpopulation reported AKI incidence of 29.68%, the AUD subpopulation reported an incidence of 48.18%. We observed a similar difference for the KDIGO encoding: 27.99% to 39.84%, as shown in Table 3. In the academic dataset we also observed a difference in the incidence of AKI in the AUD (or the other ARCs) versus non-AUD subpopulations (as shown in Table 4).

We have included mean baseline serum creatinine values for all subpopulations from the MIMIC-III dataset (Table 5), as the KDIGO staging system can rely in part on an increase in SCr levels. Table 5 shows a significant difference in mean baseline SCr levels in AKI patients with and without an ARC.

Table 2. Population demographics for the MIMIC-III and academic datasets, filtered according to our exclusion criteria. Incidence rates of Alcohol-Related Conditions (ARCs) are determined using ICD-9 coding.

Demographics	MIMIC-III	Academic
Age, median (IQR)	65 (53, 78)	55 (38, 67)
Age (years)		
18-29	4.32%	11.65%
30-39	4.99%	15.21%
40-49	9.77%	12.99%
50-59	17.87%	18.56%
60-69	22.76%	21.17%
70+	40.28%	20.43%
Sex		
Female	43.78%	54.61%
Male	56.22%	45.39%
Length of stay, median (IQR)	1 (1, 3)	4 (2, 7)
Length of stay, duration (days)		
0-2	67.19%	32.57%
3-5	18.32%	18.32%
6-8	5.97%	19.93%
9-11	2.92%	5.85%
12+	5.60%	11.92%
In-hospital mortality rate	8.50%	3.40%
Alcohol use disorder (AUD) incidence	4.18%	5.75%
Hepatorenal syndrome (HRS) incidence	0.99%	0.63%
Alcohol-related cirrhosis incidence	2.81%	1.54%
AKI incidence	30.76%	21.40%

Mortality Burden

For each of the ARCs we chose for this experiment (AUD, HRS, alcohol-related cirrhosis), we observed that the mortality rate of the subpopulation with both AKI and the ARC was consistently higher than that of the subpopulation with AKI but not the ARC, as shown in Table 6 for the MIMIC-III dataset and Table 7 for the academic dataset. In the MIMIC-III dataset, as seen in the KDIGO-encoded AKI, there was more variance in the difference in mortality rate between the subpopulations that had AKI without the ARC and those that had the ARC without AKI. For example, as shown in Table 6, the mortality rate of the AUD/non-AKI subpopulation (14.99%) was significantly lower than that of the AKI/non-AUD subpopulation (40.53%), while the HRS/non-AKI subpopulation had a higher mortality rate (46.67%) than that of the AKI/non-HRS subpopulation (40.42%). This suggests that while AUD does seem to interact with AKI to produce increased mortality rates, the relationship between AKI, these ARCs, and mortality rate is complex. Given that alcohol abuse may cause conditions such as alcohol-related cirrhosis[16] or alcohol-related hepatitis,[17,18] which in turn causes patients to be more vulnerable to AKI,[19] these entangled relational links complicate the relationship between AKI, AUD, and mortality.

For AUD and alcohol-related cirrhosis, we observed that the mortality rate of the subpopulation with both AKI and the ARC was consistently higher than that of the subpopulation with AKI, but not the ARC, across two methods of severity control (MEWS score and comorbidity count), as shown in Table 8 for the MIMIC-III dataset. For HRS, the subpopulation which had HRS alone experienced the highest mortality rates, though the subpopulation with both HRS and AKI continued to experience higher mortality rates than the subpopulation which had AKI alone. Average severity scores are listed in Table 9.

Disease Progression

In addition to AKI incidence, we investigated AKI progression in AUD vs non-AUD subpopulations in order to explore the possibility that AUD may exacerbate AKI, such that AKI progresses to a higher level of severity more often in patients with AUD. The AKI progression rate for the subpopulation with AUD in the experiment was 19.95%, while the progression rate for the

Table 3. Incidence of AKI in subpopulations in the MIMIC-III dataset with and without alcohol use disorder (AUD), hepatorenal syndrome (HRS) and alcohol-related cirrhosis. Results are listed for the two AKI-encoding methods used in this study.

	Encoding Method					
	ICD-9		p-value	KDIGO		p-value
Alcohol-Related Condition (ARC)	ARC with AKI (%)	No ARC with AKI (%)	p-value	ARC with AKI (%)	No ARC with AKI (%)	p-value
AUD	48.18	29.68	<0.001	39.84	27.99	<0.0001
HRS	97.18	29.78	<0.001	91.53	27.85	<0.0001
Cirrhosis	58.20	29.63	<0.001	49.80	27.87	<0.0001

Table 4. Incidence of AKI (as encoded by ICD-9 codes) in subpopulations in the academic dataset with and without alcohol use disorder (AUD), hepatorenal syndrome (HRS) and alcohol-related cirrhosis.

Alcohol-Related Condition (ARC)	ARC with AKI (%)	No ARC with AKI (%)	p-value
AUD	39.12	20.29	<0.0001
HRS	98.72	20.88	<0.0001
Cirrhosis	62.11	20.70	<0.0001

Table 5. Mean baseline serum creatinine values for all subpopulations from the MIMIC-III dataset.

	Mean Baseline Serum Creatinine (std dev)						
Alcohol-Related C ondition (ARC)	ARC with AKI	ARC without AKI	p-value (ARC with and without AKI)	AKI with ARC	AKI without ARC	p-value (AKI with and without ARC)	Neither AKI nor ARC
AUD	0.838 (0.031)	0.842 (0.034)	0.12	0.838 (0.031)	0.812 (0.04)	< 0.0001	0.828 (0.052)
HRS	0.842 (0.031)	0.844 (0.030)	0.74	0.842 (0.031)	0.812 (0.04)	< 0.0001	0.828 (0.052)
Cirrhosis	0.835 (0.026)	0.838 (0.031)	0.17	0.835 (0.026)	0.812 (0.04)	< 0.0001	0.828 (0.052)

Table 6. Mortality rates and absolute (percentage point) increases in mortality for four subpopulations in the MIMIC-III dataset: 1) with both AKI and the indicated Alcohol-Related Condition (ARC), 2) with the ARC but not AKI, 3) with AKI but not the ARC, and 4) with neither AKI nor the ARC.

	ARC with AKI (%)	ARC without AKI (%)	AKI without ARC (%)	Neither AKI nor ARC (%)	p-value for AKI with and without ARC	AKI Mortality increase with ARC (%)
ICD-9 encoding of AKI						
AUD	43.30	14.55	37.92	16.84	<0.0001	5.38
HRS	58.72	20.00	37.61	16.77	<0.0001	21.11
Cirrhosis	48.64	23.79	37.69	16.65	<0.0001	10.95
KDIGO encoding of AKI						
AUD	48.65	14.99	40.53	16.32	<0.0001	8.12
HRS	58.64	46.67	40.42	16.24	<0.0001	18.22
Cirrhosis	54.22	22.71	40.32	16.14	<0.0001	13.90

Table 7. Mortality rates and absolute (percentage point) increases in mortality for four subpopulations in the academic dataset: 1) with both AKI and the indicated Alcohol-Related Condition (ARC), 2) with the ARC but not AKI, 3) with AKI but not the ARC, and 4) with neither AKI nor the ARC.

	ARC with AKI (%)	ARC without AKI (%)	AKI without ARC (%)	Neither AKI nor ARC (%)	p-value for AKI with and without ARC	AKI Mortality increase with ARC (%)
ICD-9 encoding of AKI						
AUD	12.76	1.56	10.71	1.41	0.01	2.05
HRS	26.87	20.00	10.45	1.41	<0.0001	16.42
Cirrhosis	19.66	2.48	10.52	1.41	<0.0001	9.14

Table 8. Mortality rates, across two methods of severity control, for four subpopulations in the MIMIC-III dataset: 1) with both AKI and the indicated Alcohol-Related Condition (ARC), 2) with the ARC but not AKI, 3) with AKI but not the ARC, and 4) with neither AKI nor the ARC.

	ARC with AKI (%)	ARC without AKI (%)	AKI without ARC (%)	Neither AKI nor ARC (%)	p-value for AKI with and without ARC
Severity Control Method: MEWS Score					
AUD	52.04	21.86	40.24	21.73	<0.0001
HRS	65.19	57.14	39.74	21.32	<0.0001
Cirrhosis	55.31	31.88	39.97	21.54	<0.0001
Severity Control Method: Comorbidity count					
	ARC with AKI (%)	**ARC without AKI (%)**	**AKI without ARC (%)**	**Neither AKI nor ARC (%)**	**p-value for AKI with and without ARC**
AUD	48.39	31.38	40.06	33.52	0.0009
HRS	66.67	64.71	43.29	37.29	<0.0001
Cirrhosis	51.85	47.11	39.86	34.52	<0.0001

Table 9. Average severity scores 1) with both AKI and the indicated Alcohol-Related Condition (ARC), 2) with the ARC but not AKI, 3) with AKI but not the ARC, and 4) with neither AKI nor the ARC. Std dev, standard deviation.

	ARC with AKI	ARC without AKI	p-value	AKI without ARC	Neither AKI nor ARC	p-value for AKI with and without ARC
Severity Control Method: MEWS Score (std dev)						
AUD	2.18 (2.18)	1.84(1.90)	0.042	1.91(2.11)	1.91(2.11)	0.128
HRS	2.12(2.15)	1.89(1.94)	0.372	1.92(2.12)	1.92(2.12)	0.349
Cirrhosis	2.10(2.16)	1.75(1.88)	0.055	1.92(2.11)	1.92(2.11)	0.332
Severity Control Method: Comorbidity count (std dev)						
AUD	25.07(7.71)	16.84(6.71)	< 0.0001	22.67(7.82)	22.67(7.82)	0.0002
HRS	29.36(7.22)	22.78(7.00)	< 0.0001	22.39(7.66)	22.39(7.66)	< 0.0001
Cirrhosis	25.62(7.59)	17.45(6.66)	< 0.0001	22.64(7.81)	22.64(7.81)	< 0.0001

subpopulation without AUD was 18.39%. Similar results were seen in progression rates of the other subpopulations (Table 9). The relatively small difference between the AKI progression rates between these two subpopulations suggests that there is little interaction between AUD and AKI in this domain. We note that the criteria for AUD in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) allow for a large degree of heterogeneity in presentation of AUD, and further refinement of the AUD criteria used may yield different results.[10,11]

DISCUSSION

Our preliminary work using MIMIC-III and academic datasets show that from a disease burden standpoint, AUD patients have a higher incidence of AKI than the non-AUD subpopulation, consistent with a previous single-center study that focused on critically ill patients.[24] In our study, the MIMIC-III and academic AUD subpopulations had 18.5% and 18.83% more AKI patients, respectively, than the non-AUD subpopulations (Tables 3 and 4). This higher incidence of AKI was even more pronounced for HRS and alcohol-related cirrhosis subpopulations in both datasets, consistent with a prior report on AKI in patients with cirrhosis.[1] Although we observed a significant difference in mean baseline SCr levels in AKI patients with and without an ARC (Table 5), the higher incidence of AKI was observed in all ARC subpopulations regardless of KDIGO or ICD-9/10 encodings or dataset. In terms of mortality burden, in both datasets we observed that patients with both AKI and AUD or alcohol-related cirrhosis were shown to have higher rates of mortality as compared to AKI patients without these conditions (Tables 6 and 7), and these results were maintained across two methods of disease severity control measurements performed on the MIMIC-III dataset (Table 8). Our mortality burden results are consistent with previously reported numbers on survival of advanced-cirrhosis patients who develop AKI.[16,25] A disease progression analysis performed on the MIMIC-III

Table 10. AKI progression rates for the subpopulations in the MIMIC-III dataset with and without alcohol use disorder (AUD), hepatorenal syndrome (HRS) and alcohol-related cirrhosis.

Alcohol-Related Condition (ARC)	ARC (%)	No ARC (%)	p-value
AUD	19.95	18.39	0.211
HRS	20.00	18.43	0.305
Cirrhosis	20.85	18.37	0.133

dataset indicated that AKI is not more likely to progress from a lower KDIGO stage to a higher KDIGO stage in AUD patients relative to the non-AUD patients (Table 9). Results in the experiments which used both ICD-9 coding and KDIGO encoding of AKI were of similar magnitude in the MIMIC III dataset, regardless of how AKI was defined.

Several studies have shown that alcohol consumption may provide protection against chronic kidney disease (CKD),[29,30] potentially via bioactivators in alcohols such as red wine, which contains polyphenols that have reactive oxygen species scavenging effects which may reduce oxidative stress.[31–35] The multiple mechanisms through which AUD may leave patients vulnerable to AKI include oxidative stress on the kidney, which metabolizes roughly 10% of consumed ethanol.[36] Alcohol induces production of free radicals[37–41] and also decreases antioxidant capabilities of enzymes in the kidney.[42–44] In a recent comprehensive review on clinical studies looking at links between CKD and alcohol consumption, Fan et al. (2019) concluded that light-to-moderate drinking may not have adverse effects on patients with CKD.[45] While the DSM-5 definition of AUD does not quantify alcohol consumption,[46] National Institute on Alcohol Abuse and Alcoholism defines moderate drinking as "up to 1 drink per day for women and up to 2 drinks per day for men" whereas "binge drinking and heavy alcohol use can increase an individual's risk of alcohol use disorder".[47] Indeed, a recent study by Pan et al. (2018) found that AUD patients were at an increased risk of developing CKD.[48]

While these initial proof-of-concept experiments are based on retrospective datasets, the results provide evidence for the negative influence of AUD on the clinical outcome of AKI. This is consistent with a significant impact of AUD on clinical AKI outcomes.[49] In particular, an effect of AUD on AKI-related mortality rates appears to be significant, and further research in this area may be effective and useful. A limitation of this study was the use of ICD codes from multiple stages of the diagnostic process, which may have included encounters in which the working diagnosis was not aligned with the discharge diagnosis. Given that the DSM-5 criteria for AUD allow for a large degree of heterogeneity in presentation,[6,8] future studies on the relationship between AKI and AUD could benefit from stratifying the AUD population by AUD severity. The DSM-5 AUD diagnosis requires that patients meet only two of 11 criteria during a 12-month period,[10,11,46] making it possible to tabulate severity based on number of criteria met and time since initial diagnosis of AUD. Lastly, as a retrospective study, it is not within the scope of this project to determine the clinical utility and impact on patient outcomes that arise from use of this type of analytical tool. Future research may include a prospective clinical study to examine physician response and the impact on patient outcomes.

CONCLUSIONS

The results presented in this study augment and quantify existing research suggesting direct links between AUD and AKI. While these results do not determine causation or the mechanisms driving these outcomes, we have observed pronounced relationships between AUD and AKI, which manifested themselves in each of the three ARCs we studied. In separate datasets with differing compositions and in different encodings of AKI, the presence of AUD and other ARCs was linked to increased AKI and worsened mortality outcomes. However, the severity of AKI, represented by progression of AKI along the KDIGO stages, did not present a significant correlation with ARCs. Taken together with existing research, it appears that AUD likely has a negative influence on patients in terms of the risks posed by AKI.

AUTHOR CONTRIBUTIONS

Sidney Le: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing; Abigail Green-Saxena: Conceptualization, Methodology, Writing - Original Draft, Visualization; Jenish Maharjan: Methodology, Formal analysis, Review & Editing; Manan Khattar: Methodology, Formal analysis; Jacob Calvert: Conceptualization, Methodology, Writing - Review & Editing; Emily Pellegrini: Conceptualization, Writing - Review & Editing; Jana Hoffman: Conceptualization, Methodology, Writing - Review & Editing, Supervision; Ritankar Das: Conceptualization, Supervision, Project administration, Funding acquisition (Table 10).

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DECLARATION OF COMPETING INTEREST

All authors who have affiliations listed with Dascena (Houston, Texas, USA) are employees or contractors of Dascena.

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