Original Article

Sepsis and acute kidney failure outcomes investigated in a rural, Midwestern population

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Background: The American healthcare system spends a large amount of economic and human resources on fighting acute sepsis. Even with years of research, mortality rates remain high. Reducing mortality outcomes from sepsis by elucidating biomarkers and the role secondary comorbidities play could assist in sepsis triage and improve outcomes in septic patients. The purpose of this study is to assess to what degree one secondary comorbidity, acute kidney failure, contributes to mortality rates among acutely septic patients in a rural Midwestern hospital located in southwest Missouri.

Methods: Cohort study assessing septic patients with and without acute kidney injuries (AKIs). ICD10 codes were submitted by physicians into Freeman Health System's Electronic Medical Records and gathered from January 2019 to June of 2020. Those cases were filtered by secondary diagnosis resulting in two comparison groups, one sepsis only group and one sepsis with acute kidney failure not otherwise specified (NOS) group, as defined by ICD10 codes. The data was analyzed for mortality outcomes looking at secondary diagnosis, age, and sex as variables.

Results: There were 1,122 septic patients in our study, with over 58% having a secondary diagnosis of acute kidney failure. There was a difference in the average mortality rates between patients with sepsis (16.59%) *vs.* those with sepsis and acute kidney failure (25.68%). We found the probable difference in mortality rate to be significant with a P value =0.003. We are 95% confident that the mortality is between 4.3% and 13.8% higher in acute kidney NOS patients. There was no significant mortality difference found when sex and aged 65 years and older were included as variables.

Conclusions: Specific to our sample, septic patients with a diagnosis of acute kidney NOS are at a higher risk of mortality than those without acute kidney NOS, irrespective of age or sex. Our study provides insights into variables affecting sepsis outcomes in a rural Midwestern population. Further studies are warranted into individual comorbidities affecting sepsis patient outcomes. Conclusions made here are specific to our sample; the role of acute kidney failure in the outcomes of septic patients should be further investigated in rural areas throughout the country.

Keywords: Sepsis; renal failure; acute kidney injury (AKI); rural; Midwest

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Introduction

Sepsis is the number one cost of hospitalization in the United States (U.S.) accounting for more than $38 billion annually (1). A recent study found the average hospital wide cost of each sepsis case to be $32,421 (2). It places a large financial burden on Medicare, Medicaid and private health insurance. According to the Sepsis Alliance, a charitable organization whose commitment is to battle sepsis, sepsis is the most expensive diagnosis and the primary cause for hospital readmission within 30 days of visit (3). Increasing our understanding of sepsis prevention, as well as decreasing secondary sepsis-associated conditions, will help to decrease patient mortality and cut national healthcare expenses.

In recent years, a large amount of research has focused on sepsis pathophysiology, early detection, and common drug therapies. The approach in this study was to further understand the most common comorbidity of sepsis, acute kidney failure, and how it affects septic patient outcomes. The goal of this study is to guide the focus of physicians for triaging sepsis patients treated in rural, Midwestern hospitals.

A plethora of comorbidities associated with sepsis can negatively affect both short-term and long-term patient outcomes. Perhaps the most common secondary diagnosis confronting sepsis patients is acute kidney injury (AKI) leading to kidney failure. Up to half of all cases of acute renal failure are associated with sepsis, and up to 60% of patients with sepsis have AKIs (4). It would be reasonable to assume that as comorbidities multiply, mortality rates would increase, especially with complications as severe as organ failure. Because AKI and renal failure are the most common comorbidities associated with sepsis, it is essential to understand to what extent they contribute to increases in patient mortality. The pathophysiology of the association between sepsis and AKI has been of recent interest; thus, it is important to understand the big-picture and how that relationship could be affecting communities.

Sepsis-associated AKI (SA-AKI) is associated with such a high mortality rate that it is sometimes used as a "biomarker" in predicting poor prognosis (5). Even when mortality is not the outcome, AKI from sepsis can result in long-lasting decrease in quality of life and high economic costs. Sepsis is the dominant cause of AKI in intensive care unit (ICU) patients, and frequently requires patients to utilize continuous renal replacement therapy (CRRT), which improves outcomes but at a large economic and quality of life burden (6,7). If the damage is severe enough to both kidneys, sepsis may cause permanent hypoxic damage requiring donor transplantation. The cost for patient treatment is high, and quality of life is greatly diminished. Prevention of permanent kidney damage via early sepsis detection and bundle therapy is the current standard treatment of care (8). Whether or not this approach is sufficient in prevention of kidney dysfunction has yet to be looked at and is currently unknown.

The Midwest has historically suffered from a higher-than-national-average mortality burden from sepsis (9). In 2016, half of those diagnosed with sepsis were expected to succumb to their illness (9). While rates of diagnoses follow national trends, the rate of mortality in Kansas and Missouri is slightly higher. In some Midwestern areas, the sepsis mortality rate is suggested to approach 50% (9). The increased risk of mortality faced by these patients could be due to a multitude of factors including healthcare accessibility, education, lifestyle or secondary comorbidities. In this study, we attempt to quantify to what degree one common secondary comorbidity, acute kidney failure, contributes to the local sepsis mortality rate.

While previous studies have investigated kidney injuries in association with sepsis, it has not been looked at in rural community hospitals. A large portion of the American population lives in what is arguably considered rural communities. It is well established that mortality rates associated with septic shock are higher in these communities, and thus merit deeper examination (10). Rural America faces unique challenges, such as increased transport time to hospitals and fewer public resources. For seriously ill patients, this could foreseeably cause postponed care. Upon arrival to rural hospitals, patients may encounter fewer resources and in-house specialists. Efficiency in triaging using biomarkers or secondary comorbidities has the potential to reduce the mortality rate in septic patients. AKI could be a critical piece to treating sepsis efficiently due to required fluid bolus intake. The ability for physicians to monitor biomarkers associated with worse sepsis outcomes will facilitate the formation of better triage protocols to help these severely ill patients. We present the following article in accordance with the STROBE reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-117/rc).

Methods

Data collection

This is a retrospective observational cohort study in which electronic medical records from Freeman Health System

Table 1 ICD10 codes used to isolate initial sample group of 1,122 patients

ICD 10 code	Corresponding diagnosis
A400	Sepsis due to *Streptococcus*, group A
A401	Sepsis due to *Streptococcus*, group B
A403	Sepsis due to *Streptococcus pneumonia*
A408	Other *Streptococcal* sepsis
A409	*Streptococcal* sepsis, unspecified
A4101	Sepsis due to Methicillin susceptible *Staphylococcus aureus*
A4102	Sepsis due to Methicillin resistant *Staphylococcus aureus*
A411	Sepsis due to other specified *Staphylococcus*
A412	Sepsis due to unspecified *Staphylococcus*
A413	Sepsis due to *Haemophilus influenza*
A414	Sepsis due to anaerobes
A4150	Gram-negative sepsis, unspecified
A4151	Sepsis due to *Escherichia coli*
A4152	Sepsis due to *Pseudomonas*
A4153	Sepsis due to *Serratia*
A4159	Other Gram-negative sepsis
A4181	Sepsis due to *Enterococcus*
A4189	Other specified sepsis
A419	Sepsis, unspecified organism
R6520	Severe sepsis without septic shock
R6521	Severe sepsis with septic shock

were analyzed. The data used in the study was gathered from January 1, 2019 to June 30, 2020. The data was derived from 1,122 patients admitted to Freeman Health System in Joplin, Missouri. Patients were selected for using the ICD10 codes listed in *Table 1*. Diagnostic requirements for sepsis generally follow CMS guidelines which include: two or more criteria of systemic inflammatory response syndrome (SIRS) and a known or suspected infection (11). The data represents patients from the surrounding areas and city of Joplin, Missouri; including the states of Arkansas, Kansas and Oklahoma, arguably considered the rural Midwest. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patient identifiers were removed in order to maintain patient anonymity and confidentiality. The Institutional Review Board at Freeman Health System approved this study under the IRB protocol: The Surviving Sepsis Campaign (SSC) and Its Effect on Patient Populations with Sepsis and Preexisting Comorbidities (ethics approval ID: 2021002). Due to its retrospective nature, consent was not needed.

Statistical analysis

Those cases that fulfilled the diagnostic requirements of having one of the ICD10 codes listed in *Table 1* were kept as our initial sample group and contained 1,122 patients. The data was separated further into patients categorized with ICD10 code N17.9, or having acute kidney failure NOS. Patients with both sepsis and acute kidney failure NOS ICD10 codes were one subgroup titled acute kidney NOS, and those with only sepsis ICD10 codes were the control subgroup titled non-acute kidney NOS. All provided data was accounted for. The goal of the analysis was to determine whether the mortality rate in the acute kidney NOS sample group is higher than the mortality rate in the non-acute kidney NOS sample group, or rather those that solely have sepsis. Mortality rate was defined as the proportion of the group that expire. The data was statistically analyzed using two sample proportion summary hypothesis tests. There was a baseline assumption that both samples were less than 10% of the general population and the dependent variable of mortality had to have ten or more patients. That data was considered significant when $P<0.05$, a 95% confidence interval (CI) for the proportion difference was also used. Confounding variables investigated were age and sex.

Results

Our sample included 1,122 patients with sepsis, 658 (58%) of which also had a diagnosis of acute kidney NOS. The sample was fairly evenly divided by sex with 574 males and 548 females. A slight majority 595 (53%) of the patients were above the age of 65.

The mortality rate of sepsis patients with acute kidney NOS is higher than the mortality rate of the patients without a diagnosis of acute kidney NOS in our sample. The probable difference in mortality rate is significant with a P value =0.003. We are 95% confident that the mortality is between 4.3% and 13.8% higher in acute kidney NOS patients (*Table 2*). It is notable that the difference is spread relatively evenly between the two sexes, so neither men nor women are driving the results of the overall sample group in *Table 2*. The probable difference in mortality rate for

Table 2 Comparison of patients with acute kidney NOS to non-acute kidney NOS patients

Difference	Count 1	Total 1	Count 2	Total 2	Sample difference	Std. err.	Z-stat	P value	L. limit	U. limit
Acute kidney NOS patients to non-acute kidney NOS patients										
p1 – p2	169	658	77	464	0.09089063	0.025081369	3.6238305	0.0003*	0.043348825	0.13843244
Males p1 – p2	84	336	39	238	0.086134454	0.033670807	2.4777081	0.0132*	0.020140885	0.15212802
Females p1 – p2	85	322	38	226	0.095833562	0.036205503	2.6469336	0.0081*	0.027310857	0.16435627
Acute kidney NOS patients to non-acute kidney NOS patients including variables: age and age + sex										
p1 – p2	117	426	59	268	0.054498634	0.03392105	1.6066317	0.1081	–	–
Age 65 + male p1 – p2	57	216	31	138	0.039251208	0.047099262	0.83337203	0.4046	–	–
Age 65 + females p1 – p2	62	210	28	120	0.07985348	0.049234607	1.6218974	0.1048	–	–

Comparison within male sample groups and female sample groups of patients with acute kidney NOS *vs.* non-acute kidney NOS. (*, indicates significant P value). Comparisons of patients with acute kidney NOS *vs.* non-acute kidney NOS with confounding variables age and age + sex. Two sample proportion summary hypothesis test with 95% confidence interval results: p1: proportion of successes for acute kidney NOS sample group; p2: proportion of successes for non-acute kidney NOS sample group; p1 – p2: difference in proportions; H0: p1 – p2 =0; HA: p1 – p2 ≠0. NOS, not otherwise specified; std. err., standard error; Z-stat, Z-statistic; P value, probability value; L. limit, lower limit; U. limit, upper limit; H0, null hypothesis; HA, alternative hypothesis.

both males and females with acute kidney NOS was also significant with P values = males 0.0132 and females 0.0081 (CI: males =2–3.3% and females =2.7–3.4%) (*Table 2*). Mortality does not appear to be impacted by the defined age categories. There were no significant differences detected in the 65+ age groups (*Table 2*). Thus, sepsis patients with acute kidney NOS, specifically in our population, are at a higher risk of mortality than those without acute kidney NOS irrespective of age or sex.

Discussion

The mortality rate of sepsis patients with acute kidney NOS is higher than the mortality rate of the non-acute kidney NOS patients. We expected this finding because logically any form of progression to organ failure can indicate a poor prognosis. Additionally, damage to the delicate vasculature of the kidney can be irreversible. Historically it was thought that renal hypoperfusion was responsible for kidney ischemia and injury (11,12). Blood flow to the kidney is moderated by a group of cells called the macula densa which line the distal tubule. When these cells sense an increase or decrease of chloride ion concentration, they activate tubuloglomerular feedback to correct renal blood flow by changing the diameter of the afferent arteriole (13). It is intuitive that sepsis-induced hypotension can throw this system out of balance and cause kidney injury. However, it is now understood that there are many factors influencing sepsis-related kidney injury, including microvascular endothelial dysfunction via inflammation, coagulation, and oxidative stress (14). Although the causes for SA-AKI are not fully understood, it is intuitive that damage to a delicate organ with an important function is associated with increased mortality.

Monitoring kidney function in septic patients from rural areas, which are known to have worse outcomes, signifies a greater emphasis is needed on research in this area. The data points to the kidney being an especially impactful organ in the pathophysiology of septic shock as indicated by the AKI ICD10 diagnostic code listed on the patient's electronic medical record (EMR) along with the sepsis diagnosis. Whether via decreased perfusion or alternative mechanism, sepsis appears to be inducing AKI in our sample group which is leading to poorer patient outcomes.

Perhaps less intuitively, there was not a significant difference in mortality detected in the 65+ age groups (*Table 2*). We would expect older patients concurrently battling sepsis and renal failure to have increased mortality, but we did not find this to be the case in our sample. One possibility is that once sepsis has progressed to organ failure, the condition is so severe that the prognosis is poor regardless of the age of the patient. We cannot be sure why mortality in patients age 65+ was not significantly higher than those under 65, and these results are specific to our

sample at this point in time.

It is important to note that our study is specific to our region in Southwestern Missouri. Rural Midwestern populations have different challenges than more urban regions of the U.S. Along with Southern states, Midwestern states have higher rates of obesity than other regions of the U.S. (15,16). Obesity is thought to be a risk factor for AKI, with increasing body mass index (BMI) corresponding to an increased risk of severe disease (17). Diet and exercise habits contribute to obesity in rural settings. Traditional weight management programs require further travel for rural patients, decreasing the accessibility of nutrition support groups and exercise facilities (18). These challenges may contribute to generalized poor health, which in turn contributes to the higher rates of mortality from sepsis in the Midwest.

Medical interventions that help combat both sepsis and kidney failure are still under development, and septic patients who develop kidney failure are at high risk. In 2002, the SSC was established to increase awareness surrounding sepsis and decrease associated mortality. In 2004, the SSC published guidelines for two clinical approaches in combating sepsis: "resuscitation" and "management" bundles (19). The bundles are sets of standardized intervention protocols to be completed during certain timeframes throughout the progression of sepsis. Although there is still plenty of room for improvement in bundle development and compliance protocols, studies show encouraging results regarding their effectiveness (20,21). A promising intervention for septic patients with severe renal failure, CRRT, has also shown beneficial results. Studies show that patients utilizing CRRT do not show higher mortality rates than the non-acute kidney NOS group (7,22). Thus, CRRT is likely a protective therapy for patients with sepsis-associated kidney injury.

Limitations of the study include a small sample size that was primarily Caucasian. Samples were also not randomly selected from the population; consequently, it is unclear whether or not the samples are representative of their respective populations as a whole. Although we cannot generalize our results across the population, we did show that renal failure is a significant factor in predicting mortality outcomes specific to our septic patient sample group. We chose to focus on the most common sepsis comorbidity that affected the kidney and filter out the rest such as ICD10 code N17, AKI. This was done to encompass the largest number of acute kidney + sepsis patients possible within our sample population, but other more specific kidney and ureter pathologies that could affect septic patients may have been missed. Socio-economic status, access to healthcare, education and pre-existing conditions all impact patient outcomes.

It is important to note that additional comorbidities were not considered in the study but are likely affecting patient health and mortality outcomes in our sample. The focus of the study was mortality which is a categorical variable. Therefore, a quantitative analysis such as multivariable regression could not be performed. Sample groups were insufficient in size to isolate the patients with multiple comorbidities. To address this in future studies, multicenter analysis, larger hospitals or combined health care systems that treat a greater number of patients could be used. Finally, EMRs collected via sepsis ICD10 codes that also had ICD10 codes for AKI diagnosis are assumed to have occurred on that visit. Our data set did not allow us to define personal history of AKI since records obtained was from one visit to Freeman Health System, and not their entire electronic health record (EHR). Thus, we assumed all patients isolated using ICD10 codes for AKI received their diagnosis at the time of sepsis diagnosis. The only way to definitively know would be to refer to the patient charts or EHRs which at the time of this research was restricted due to limited access on Hospital Campuses following the onset of COVID-19.

Conclusions

As one of the most expensive and deadly conditions plaguing the American healthcare system, sepsis has been a topic of interest for many years, yet a lack of understanding of how to reduce septic patient mortalities persists. In this study, we found that septic patients from Freeman Health System, located in Joplin, Missouri, with a diagnosis of acute kidney NOS are at a higher risk of mortality than those without acute kidney NOS, irrespective of age or sex. Their risk is between 4.3% and 13.8% higher.

Our study provides insights from a rural Midwestern population in a time where we, as a medical community, are searching for variables affecting outcomes in septic patients across the U.S. Further research investigating secondary comorbidities and biomarkers in severely ill sepsis patients is needed. These studies should address which key comorbidities warrant physician focus in order to save patient's lives. Additional knowledge in this area could lead to improved patient care in all geographical regions, with focus on reducing rural hospital mortality outcomes closer

to those found in urban centers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-117/rc

Data Sharing Statement: Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-117/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-117/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patient identifiers were removed in order to maintain patient anonymity and confidentiality. The Institutional Review Board at Freeman Health System approved this study under the IRB protocol: The Surviving Sepsis Campaign and Its Effect on Patient Populations with Sepsis and Preexisting Comorbidities (ethics approval ID: 2021002). Due to its retrospective nature, consent was not needed.

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