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Exploring the effects of coronary artery disease as a preexisting comorbidity on mortality in hospitalized septic patients: a retrospective observation study

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Abstract

Background: Sepsis has high prevalence and mortality rate, and it is imperative to identify populations at risk of poor sepsis outcomes. Septic patients with preexisting chronic comorbidities are shown to have worse sepsis outcomes. By identifying comorbidities with greater influence on sepsis progression, we can direct limited resources to septic patients with comorbidities and reduce health care costs. Chronic comorbidities can impact the risk of developing sepsis and having worse outcomes. Coronary artery disease (CAD) is a common comorbidity, especially in the elderly, and a leading cause of death globally. We wished to investigate the influence of CAD as a comorbidity on sepsis and hypothesized that preexisting CAD would increase mortality in hospitalized septic patients.

Methods: We conducted retrospective observational study using patient data from Freeman Health System in Joplin, MO. We analyzed patient records from Freeman Health System database from January 1, 2019, to June 30, 2020. Septic patients were identified using the *International Classification of Diseases, Tenth Revision* sepsis codes. To identify septic patients with preexisting CAD, we used *International Classification of Diseases, Tenth Revision* codes for CAD. We compared mortality rates for septic patients with and without CAD.

Results: Two-sample proportion test was conducted to test the difference in mortality between septic patients with and without preexisting CAD. The difference in mortality for the total population was –0.016 ($P = 0.553$). In the male and female subgroups, the differences in mortality were 0.0122 ($P = 0.739$) and –0.0511 ($P = 0.208$), respectively. The differences in mortality in patients aged 40 to 64 years and 65 years and older were –0.0077 ($P = 0.870$) and 0.0007 ($P = 0.983$), respectively. The statistical tests failed to find significant differences when comparing septic patients with and without preexisting CAD. There was no significant difference in the age and sex subgroups.

Conclusion: Our study showed that CAD alone was not associated with higher mortality due to sepsis in our population.

Keywords: Comorbidity, Coronary artery disease, Inflammation, Mortality rate in sepsis prognosis, Sepsis

Introduction

The Third International Consensus Definitions for sepsis and septic shock defined sepsis as a critical condition arising from the body's immune system mounting a dysregulated response to infections triggered by microorganisms, ultimately leading to organ dysfunction.[1,2] Sepsis results in considerable mortality, morbidity, and health care costs. An astonishing number of 48.9 million cases of sepsis occur worldwide,[3] with 1.7 million adults affected in the United States every year.[4] Sepsis is responsible for causing 11 million deaths globally[3] and 250,000 deaths annually in the United States.[4] Sepsis also ranks number 1 in hospitalization costs as related cases account for $41.5 billion annually.[5] The average cost of a hospital stay for sepsis is double the cost of a stay for all other conditions.[6]

Given the high prevalence and mortality rate of sepsis, it is important for hospitals and other institutions to develop a risk stratification strategy. Identifying populations at greater risk of developing worse outcomes from sepsis would allow for the development of risk prevention strategies. Several studies have indicated that individuals with chronic comorbidities are at a higher risk of developing sepsis and having worse outcomes of sepsis.[4,7–10] One of the studies found that patients with a higher Charlson Comorbidity Index, a formula used to measure the risk of death due to the number and severity of comorbidities, had higher sepsis progression[11] and mortality.[12,13] This indicates that the presence of comorbidities affects outcomes in septic patients. Some studies have focused on precisely characterizing the specific preexisting chronic conditions responsible for enhancing the mortality risk of sepsis.[4,8,14] One study found that the second most common cause of mortality in patients with sepsis is due to chronic heart disease (15.3%), but the exact type of chronic heart disease was not specified.[4]

Coronary artery disease (CAD), an atherosclerotic disease that involves the buildup of plaque in the vessel walls and narrowing of the coronary arteries that supply the heart muscle, is the most common form of chronic heart disease.[15] Coronary artery disease is the leading cause of cardiac-related death globally, and it increases the risk of myocardial infarction and ischemic heart failure.[16] It afflicts 10.9% of adults 45 years or older and 17% of adults 65 years or older and is responsible for causing myocardial infarctions in 800,000 Americans every year.[17] Although studies have previously investigated and found that sepsis patients have an increased risk of developing CAD,[18,19] the goal of this article is to investigate the influence of CAD as a chronic comorbidity on outcomes of

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1

***ICD-10* Inclusion Criteria for Sepsis Patients**

ICD-10 Code	Diagnosis
A400	Sepsis due to *Streptococcus*, group A
A401	Sepsis due to *Streptococcus*, group B
A403	Sepsis due to *Streptococcus pneumoniae*
A408	Other streptococcal sepsis
A409	Streptococcal sepsis, unspecified
A4101	Sepsis due to methicillin-susceptible *Staphylococcus aureus*
A4102	Sepsis due to methicillin-resistant *S. aureus*
A411	Sepsis due to other specified *Staphylococcus*
A412	Sepsis due to unspecified *Staphylococcus*
A413	Sepsis due to *Haemophilus influenzae*
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

ICD-10, International Classification of Diseases, Tenth Revision.

patients admitted with sepsis. We focused on patients who have been previously diagnosed with CAD. This included asymptomatic and symptomatic patients who were found to have stable ischemic heart disease or acute coronary syndrome due to obstructive coronary arteries on coronary angiography, echocardiogram, or stress test or were previously treated with percutaneous interventions or coronary artery bypass grafting. While selecting patients for sepsis group, we included septic patients diagnosed with the systemic inflammatory response syndrome criteria and having active organ-specific bacterial, fungal, or viral infection of the gastrointestinal tract, lungs, urinary tract, or heart or disseminated bacteremia. It was hypothesized that there would be higher mortality outcomes in sepsis patients diagnosed with CAD as comorbidity. We also investigated if there is a difference in sepsis mortality of patients with and without CAD belonging to different sexes or age groups. We also focused on patients 40 years and older who were specifically chosen for the study because CAD and sepsis most widely affect older adults. The mean age of patients affected with CAD is 68 years,[20] and patients older than age 65 years comprise most (65%) of the sepsis cases.[21]

Materials and methods

Data source

Patient data were collected from patients of all age groups, who were admitted to Freeman Health System (FHS) in Joplin, MO, USA, from January 1, 2019, to June 30, 2020. The protocol was approved by the institutional review board (IRB) of the FHS (IRB approval no. 2021002) on August 24, 2020. This was a retrospective observational study, and informed consent was waived as the anonymity of the collected data was maintained. Collected information included demographic information, such as age and sex, and mortality. Patients were not stratified based on the type of sepsis or other comorbidities present.

Data selection and defined groups

Patients with sepsis were identified using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes listed in Table 1. From this initial sample of sepsis patients, we further selected patients who had CAD as a secondary diagnosis using *ICD-10* code 125.10 for atherosclerotic heart disease native (ASHD) coronary artery without angina pectoris. As shown in Fig. 1, we chose to include only patients 40 years or older, and we excluded 1 patient from our 350 ASHD patient population who belonged to the 18- to 39-year age group because CAD and sepsis are most prevalent in middle- to older-aged adults. Our baseline group included only patients who had sepsis but no ASHD CAD. From the baseline group, we excluded patients younger than 40 years.

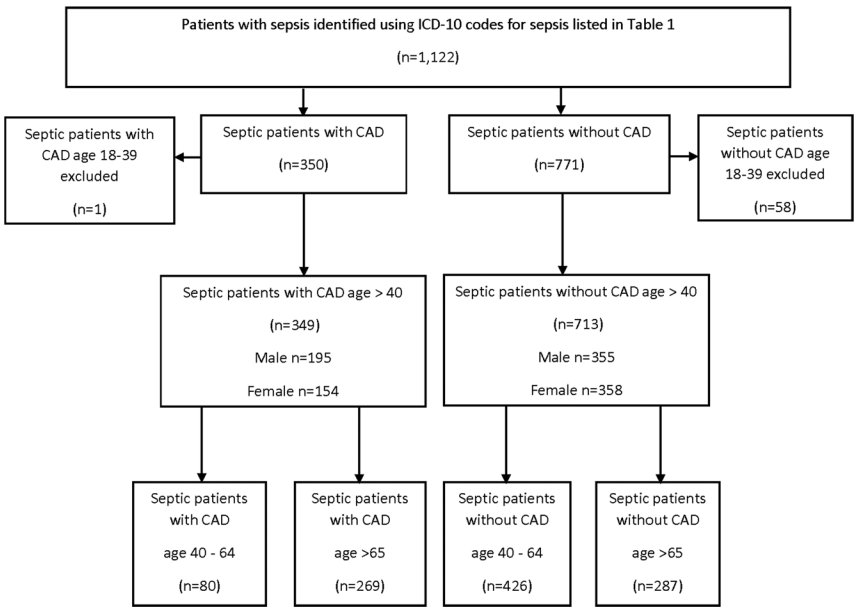

Figure 1. Flowchart showing selection of patients from hospital database into defined groups of sepsis. CAD, coronary artery disease; *ICD, International Classification of Diseases*.

Table 2

Patient Sample Groups

	Patient Group	No. Patients
Sepsis with no ASHD (control group)	Male	355
	Female	358
	Total	713
	Age group 40–64 y	287
	Age group 65+ y	426
Sepsis with ASHD CAD	Male	195
	Female	154
	Total	349
	Age group 40–64 y	80
	Age group 65+ y	269

ASHD, atherosclerotic heart disease; CAD, coronary artery disease.

Statistical analysis

We used StatCrunch software by Pearson Education Inc, Hoboken, NJ, USA, to conduct 2-sample proportion test to compare mortality rates, as a primary outcome, between the ASHD CAD group and the non-ASHD group. In the 2-sample proportion test, raw data points were expressed as "Y" or "N," indicating whether the patient died. $P < 0.05$ was considered significant. We also looked for differences in mortality between the 2 groups using sex and age as variables as we wished to analyze whether sex and age made a difference in sepsis outcomes of ASHD CAD and non-ASHD groups.

Results

As shown in Fig. 1, a total of 1122 patients with sepsis were identified. From the 1122 cases of sepsis, we found 350 patients who had ASHD CAD. After exclusion of 1 patient younger than 40 years, a total of 349 septic patients with ASHD CAD as a secondary diagnosis and comorbidity were identified and analyzed. In the ASHD CAD group, there were 195 male and 154 female patients (Table 2). In this group, 80 patients were in the 40- to 64-year age group and 269 in the age group 65 years and older.

The baseline group included patients with sepsis but no ASHD CAD, and there were 771 patients in this group. Fifty-eight patients younger than 40 years were excluded from the non-ASHD control group. As a result, the control group population had 713 patients.

The 2-sample proportion tests failed to find any differences in mortality when comparing the ASHD groups with the non-ASHD group (Table 3, $P < 0.05$ used), suggesting that the presence of CAD does not affect mortality rates in sepsis patients. The results were also insignificant when comparing mortality rates for age and sex subgroups in the ASHD and non-ASHD groups (Table 3). Patients were not stratified based on the type of sepsis or other comorbidities present.

There may or may not actually be differences, but we did not detect any with the evidence we collected and the statistical tests that we performed. Our results suggest that the presence of CAD does not affect mortality rates in sepsis patients.

Discussion

We initially hypothesized that CAD as preexisting comorbidity would negatively influence the prognosis of sepsis and cause increased mortality in patients with sepsis. Our results were unexpected and did not match our hypothesis regarding the relationship between CAD and sepsis mortality. We found no statistically significant difference in the mortality rates for sepsis patients with CAD compared with those without CAD. Past studies have suggested that the prognosis of CAD and sepsis individually differs between male and female patients,[22–25] which led us to investigate sex as a variable for comparing mortality rates between ASHD CAD and non-ASHD groups. However, there was no disparity found in the mortality rates for male or female patients from either group. Sex does not seem to influence sepsis outcomes in patients with or without CAD based on statistical tests conducted on our sample. Because mortality and morbidity have also been previously shown to increase with age for patients suffering from CAD or sepsis individually,[26,27] we wished to analyze if having both sepsis and CAD changed the mortality rate for patients in a specific age group. Our results suggested that the mortality rates were similar for patients belonging to the same age groups, and the presence of CAD did not influence the mortality rates of sepsis patients in different age groups. Our statistical analysis was not able to detect any significant differences in the mortality rates for ASHD CAD and non-ASHD groups, and differences may or may not exist for the general population.

Limitations

Our findings, in comparison to findings from previous studies, could be explained by the limitations of our study. We did not account the presence or absence of comorbidities other than CAD. The presence of other coexisting comorbidities could act as confounding variables and affect sepsis progression and outcomes. It is possible that patients in the baseline group and the CAD group had similar comorbidities with similar severity of illness, which can affect their vulnerability to sepsis-related damage. This study suggests that CAD alone was not associated with worse outcomes in patients hospitalized at our institution for sepsis. Future studies can analyze how CAD interacts with other common comorbidities including diabetes, human immunodeficiency virus, or chronic liver disease to possibly have an impact on sepsis outcomes.

Another potential limitation of our study was the fact that the patient samples came from a single rural Midwestern hospital that serves the 4-state area of Arkansas, Kansas, Missouri, and Oklahoma. Consequently, it is unclear whether our results could be generalized to the US population outside of the Midwest, including urban and suburban populations. This limitation could be easily overcome by increasing the sample size and including data from multiple different regions and hospitals located in both rural and urban settings.

Next, we did not examine or count for other confounding variables that could impact sepsis prognosis, including income, health insurance status,

Table 3

Comparison of Mortality in ASHD Versus Non-ASHD Population for Different Sex and Age Subgroups

Populations	Difference	Count 1	Total 1	Count 2	Total 2	Sample Difference	SE	*Z* Statistics	*P*
Male	p1 – p2	79	355	41	195	0.012278801	0.036813917	0.33353694	0.739
Female	p1 – p2	77	358	41	154	–0.051149967	0.040583758	–1.2603556	0.2075
Age group 40–64 y	p1 – p2	48	287	14	80	–0.0077526132	0.047372553	–0.163652	0.87
Age group 65+ y	p1 – p2	108	426	68	269	0.00073302267	0.033866216	0.021644658	0.9827
Total	p1 – p2	156	713	82	349	–0.016163191	0.027241583	–0.59332789	0.553

p1, proportion of mortality for ASHD population; p2, proportion of mortality for non-ASHD population; p1 – p2, difference in proportions; *Z* Stat, standard score.

geographical location of the patients, previous episodes of sepsis, education, and socioeconomic status. Additional research is required with study designs that control potential confounding variables and better assess the contributory relationship between CAD as a comorbidity and sepsis.

While defining ASHD and non-ASHD groups, we used the *ICD-10* codes to include only ASHD patients without angina pectoris because the hospitalized patients included in the database did not have symptoms consistent with angina pectoris. It would also be interesting to compare sepsis outcomes for ASHD patients with and without stable or unstable angina in future studies. Angina severity could be assessed to analyze whether the outcomes of septic patients change with increasing angina severity in ASHD patients.

Hospital patient records used in this study were collected for purposes of administration, instead of clinical research and analysis. As a result, there may be errors in the coding for diagnoses under which patients are classified, which could also affect the counts of mortality for patients in different groups. In addition, the records provided information on all-cause mortality instead of mortality due to sepsis only. It is possible that the mortality counts included patients who died due to causes unrelated to sepsis, such as previous chronic medical conditions.

Conclusion

There were no significant differences detected between the baseline group and the ASHD CAD group. This does not imply that there are no differences in the general population; instead, no significance was found within this population using the statistical tests that we performed. Other factors may be at play, including other comorbidities and socioeconomic status.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

All authors contributed to study design and conception, provision of study materials and patients, collection and assembly of data, data analysis, and interpretation and manuscript writing. Arnce RD, Goade S, Stahl G, and Johnson K provided administrative support. All authors approved the final manuscript.

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Ethical approval and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. Institutional Review Board Steering Committee of FHS in Joplin, MO, issued approval to the study (approval no. 2021002) on August 24, 2020. Written informed consent was waived by the IRB of FHS owing to the retrospective observational study design and the anonymized data retrieved from the hospital database.

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Presentation

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