

Outcomes in Patients with Alcoholic Hepatitis May be Affected by When an Infection is Presented

by

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Alcohol-associated hepatitis is a severe condition in patients with heavy alcohol use. It is characterized by acute onset of jaundice, and complications such as ascites and hepatic encephalopathy (1). These patients often develop bacterial infections which can negatively impact their outcomes (2). When the infection was acquired relative to being admitted to the hospital can possibly predict negative outcomes including intubation, development of septic shock, and multiorgan failure. We hypothesize that patients with alcohol-associated hepatitis who present with an infection at admission versus those that develop infection during hospitalization have different clinical outcomes. Overall, there is no difference between the two groups among the different clinical outcomes. Furthermore, there are more infections presented at admission than developed during hospitalization. These findings may indicate that the University of Pittsburgh Medical Center may place great importance on infection control and preventing hospital acquired infections. While this is the case, this study suggests that outside hospitals should focus on preventing infections in their facilities to prevent poor outcomes in patients when transferred to other hospital systems.

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Preface

The author would like to thank Dr. Ramon Bataller for his mentorship and providing the database and clinical expertise in alcohol-associated hepatitis. She would also like to thank Dr. Jenna Carlson for providing the R code and insight that was used to perform the statistical analysis, and Dr. Jeremy Martinson and Dr. Robbie Mailliard for their support, advice, and encouragement.

1.0 Introduction

Alcohol-associated hepatitis is a condition that is associated with patients who heavily consume alcohol. Heavy drinking is defined by consuming at least 60 grams per day of alcohol in men, and at least 40 grams per day in women, with less than 60 days of abstinence in both sexes (3). Clinical features include an acute onset of jaundice (defined by a serum bilirubin greater than or equal to 3 milligrams per deciliter) and a ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) greater than 1.5, with both enzymes having levels less than 400 international units per liter and the AST being greater than 50 international units per liter (3). Other complications of alcohol-associated hepatitis include hepatic encephalopathy and ascites.

In this patient population, infections can affect the prognosis of the disease. Generally, patients with liver diseases may develop infections such as spontaneous bacterial peritonitis which occurs as a result of bacterial translocation from intestine to the abdominal cavity, infecting the ascitic fluid (ascites) which builds up in the abdomen due to impaired liver function (4). Other infections may include bacteremia (developed in the blood), pneumonia, and soft tissue infections. In addition to bacterial infections, there are some cases where patients may develop viral infections such as in the upper respiratory tract.

Some studies have demonstrated that there are differences between patient outcomes based on influences such as location of the patient and when the infection was presented or acquired. For instance, in a study comparing non-academic and academic hospitals, admissions to an academic center were more likely to develop hospital acquired infections (5). Furthermore, another study suggests that infections developed during hospitalization are more likely to be a predictor of multi-organ failure (and death) rather than infections that are already in existence at admission (6).

Studies have mainly discussed the impact of outcomes on mortality (6) (7). For this project, data from the University of Pittsburgh Medical Center, an academic hospital, was analyzed. In this study, the point of when an infection was diagnosed was analyzed to understand three clinical outcomes of patients with alcohol-associated hepatitis in an academic hospital setting. In addition to death, septic shock and intubation were also analyzed. This study hypothesizes that there will be differences between clinical outcomes depending on whether the infection was presented at admission or developed during hospitalization.

2.0 Methods

The patients analyzed for this study were admitted to the University of Pittsburgh Medical Center (UPMC) between 2017 and 2021 in a database with deidentified information collected from medical health records. Patients were admitted to UPMC facilities in Southwest Pennsylvania. These hospitals included UPMC Montefiore, UPMC Presbyterian, UPMC East, UPMC Shadyside, UPMC Passavant, UPMC St. Margaret's, UPMC McKeesport, UPMC Magee-Women's Hospital, and UPMC Mercy. The patients had a first-time diagnosis of alcohol-associated hepatitis. They were divided into two groups depending on whether they presented with infection at admission or developed an infection during their hospitalization. Overall, the sample characterized 100 patients with alcohol-associated hepatitis who were diagnosed with an infection.

An infection was defined to be hospital acquired if the event was 48 hours after admission (considered as Day 3) as according to the guidelines established by the National Healthcare Safety Network (Figure 1). Variables collected in the database included prevalence of infection, whether an infection was presented at admission or developed during hospitalization, type of infection, and the impact of key parameters which included septic shock, intubation, and death.

Hospital Day	Date of Event Assignment for RIT	Classification
2 days before admit	Hospital Day 1	POA
1 day before admit	Hospital Day 1	
1	Hospital Day 1	
2	Hospital Day 2	
3	Hospital Day 3	HAI
4	Hospital Day 4	
5	Hospital Day 5	

Figure 1 Infection window defined by the National Healthcare Safety Network.¹

Statistical analysis was done via R, using Chi-square tests and Fisher’s exact tests (12). The Fisher’s exact test was used to analyze the differences among clinical outcomes between the two groups for patients transferred from the emergency department. Chi-square tests were used to analyze the difference between if an infection was presented at admission versus developed during hospitalization, the differences among clinical outcomes between the two groups for all patients (regardless of being transferred from the emergency department or outside hospitals), and for the differences among clinical outcomes between groups for patients who were transferred from outside hospitals. The alpha used for statistical significance was 0.05. UPMC was considered the index case since data from hospitals outside the UPMC system was not available.

¹ 11.NHSN. 2023. Identifying Healthcare-associated Infections (HAI) for NHSN Surveillance, National Healthcare Safety Network (NHSN) Patient Safety Component Manual.

3.0 Results

3.1 Description of Sample

The sample consisted of 100 patients who were diagnosed with alcoholic hepatitis for the first time. Gender, age, and race were characterized (Table 1). Among the patients, 53 were male and 45 were female (2 did not report their gender). Furthermore, 60 of the patients were between the ages of 30 and 49. In addition, among the patients that reported their race, 74 identified as white.

Table 1 Demographics of sample.

Variables	n = 100
<i>Gender</i>	
Male	53
Female	45
Not Reported	2
<i>Age</i>	
18-29	6
30-49	60
50-64	32
65+	2
<i>Race</i>	
White	74
Black	3
Asian	1
American Indian	2
Unknown/Not Reported	20

3.2 Prevalence of Infection at Admission and During Hospitalization

The diagnosis of infection was analyzed in the cohort of 100 patients. Two groups were compared; patients either presenting with infection at admission or developing infection during hospitalization. More patients presented with infection at admission compared to acquiring an infection during hospitalization (Figure 2). This was a statistically significant finding, with the p-value equaling 0.002.

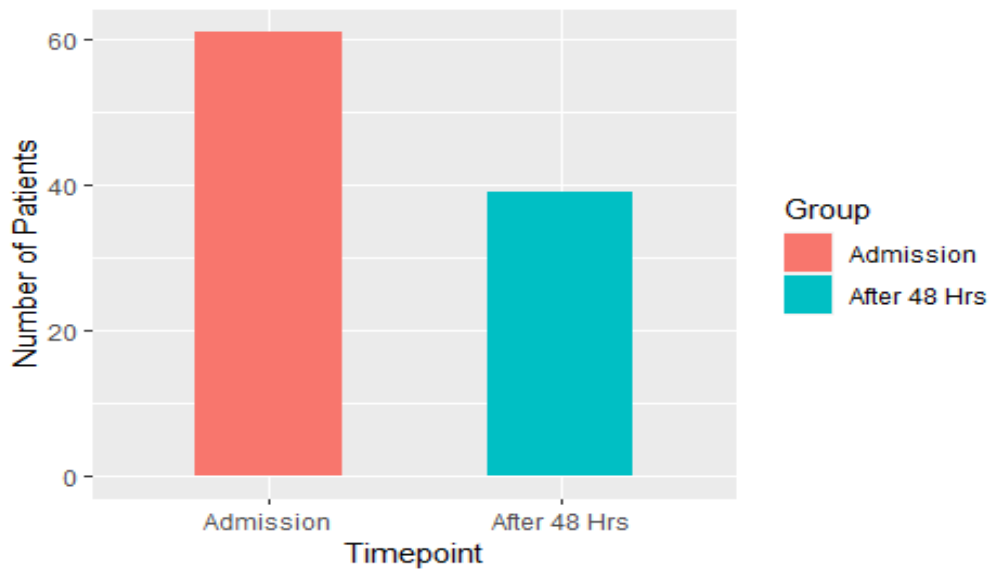


Figure 2 More patients develop infection at admission.²

² *p = 0.002

3.3 Types of Infection at Admission and During Hospitalization

Types of infections were observed between the two groups. These infections included bacteremia (specifically in blood cultures), *Clostridioides difficile* (*C. diff*), pneumonia, spontaneous bacterial peritonitis, soft tissue infections, urinary tract infections, and viral upper respiratory infections (Figure 3). There was also a number of patients in both groups who presented with or developed multiple infections. Out of all of the patients who had multiple infections, either presenting at admission or developing an infection during hospitalization, most patients developed a co-infection with pneumonia (Figure 4-6). The second most common co-infection that appeared in both groups was bacteremia. Interestingly, more patients at admission presented with *C. diff* as a co-infection, which may be related to treating other infections with antibiotics, perhaps giving *C. diff* an environment which is ideal for replication (8). Among the different infection types in individuals who had a single infection, most patients presented with pneumonia in the admission group and in the hospitalization group.

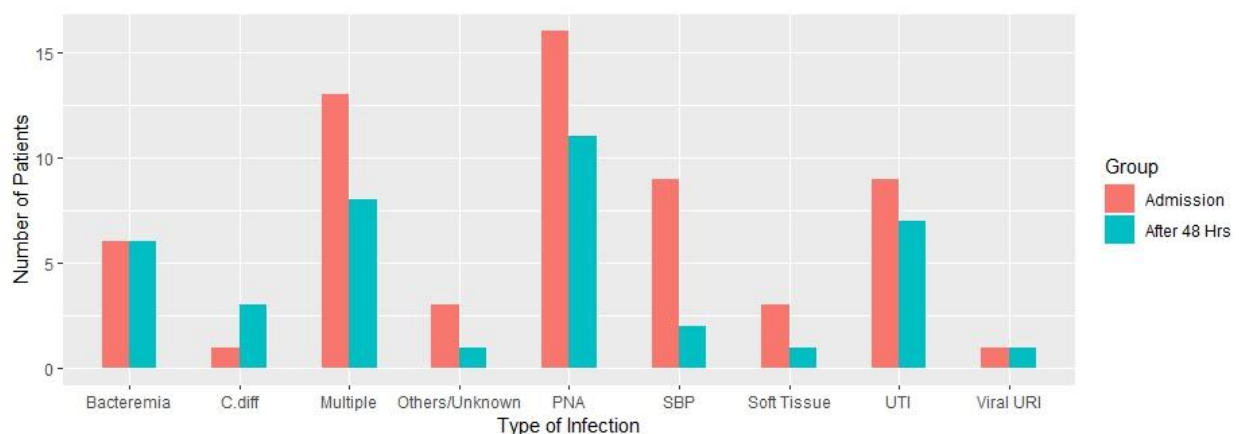


Figure 3 Patients are diagnosed with different types of infections at admission and during hospitalization. Some of these infections include *Clostridioides difficile* (*C.diff*), pneumonia (PNA), spontaneous bacterial peritonitis (SBP), urinary tract infections (UTI), and viral upper respiratory infections (Viral URI).

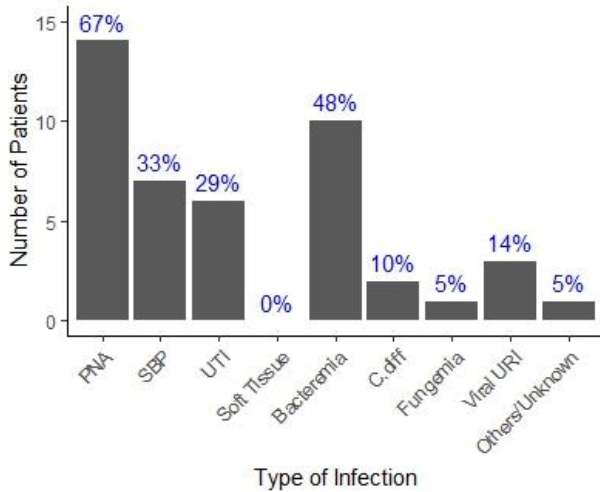


Figure 4 There were several infections identified among the multiple types group for all patients. Some of these infections included pneumonia (PNA), spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), *Clostridioides difficile* (C.diff), and viral upper respiratory infections (Viral URI).

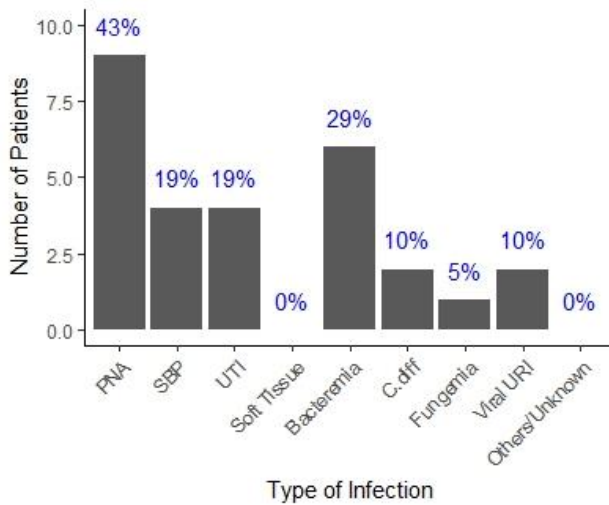


Figure 5 There were infections identified among the multiple types group for patients who were presenting with infection at admission. Some of these infections included pneumonia (PNA), spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), *Clostridioides difficile* (C.diff), and viral upper respiratory infections (Viral URI).

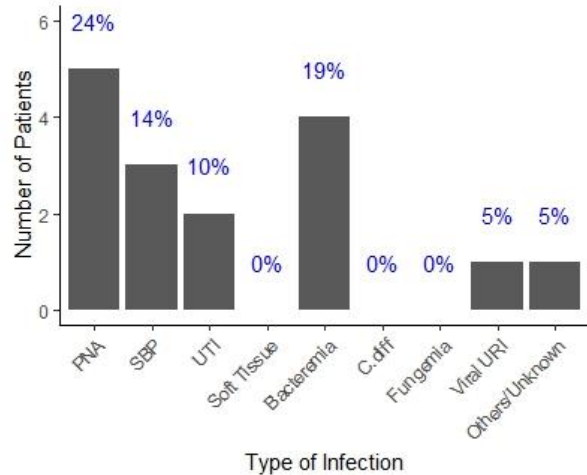


Figure 6 There were infections identified among the multiple types group for patients who developed during hospitalization. These infections included pneumonia (PNA), spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), *Clostridiodes difficile* (C.diff), and viral upper respiratory infections (Viral URI).

3.4 Impact of When an Infection was Presented on Different Outcomes

Three common outcomes of patients with alcohol-associated hepatitis were analyzed in relation to whether infections were presented at admission versus developed during hospitalization. These outcomes include death, septic shock, and intubation.

3.4.1 Death

Some patients with alcohol-associated hepatitis develop complications leading to death, including multi-organ failure and infections which may interfere with the immune response. This clinical outcome was observed in both groups (Figure 7). Conclusively, there was no significant difference between the two groups for this outcome ($p = 0.41$).

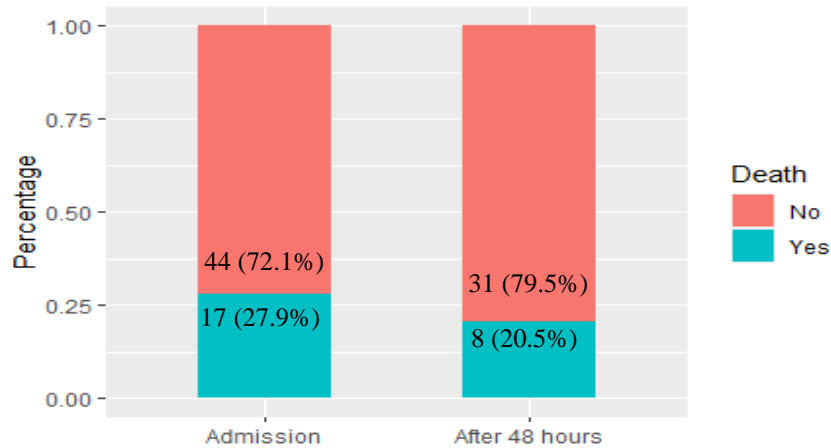


Figure 7 There is no significant difference between the two groups for the outcome of death.³

3.4.2 Septic Shock

Septic shock is organ dysfunction caused by an impaired host response to infection by association with circulatory, cellular, and metabolic abnormalities and a higher risk of mortality (9). The condition is common in patients who develop SIRS criteria (systemic inflammatory response syndrome) in parallel to an infection. In comparing admission vs hospitalization, there is no significant difference in developing septic shock between the two groups; this is suggested by the p-value being 0.11 (Figure 8).

³ p = 0.41

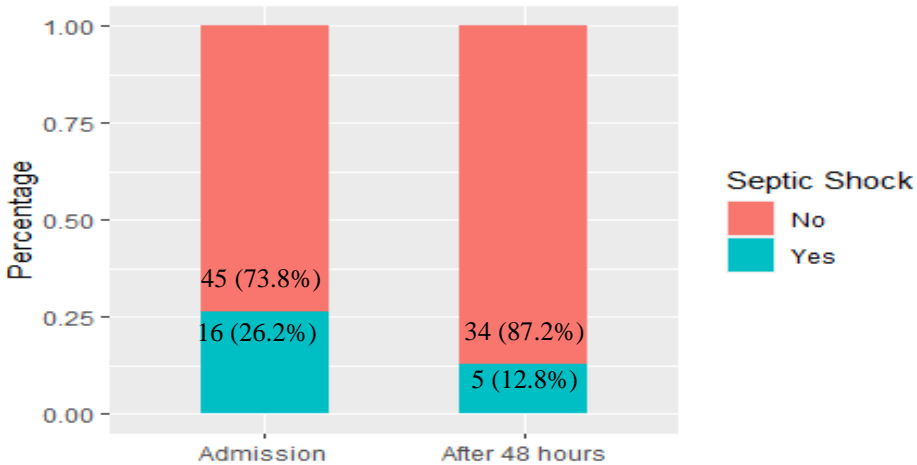


Figure 8 There is no significant difference between the two groups for the outcome of septic shock.⁴

3.4.3 Intubation

Intubation occurs when a patient’s airway is obstructed or develops a risk in relation to lung function and needs assistance to breathe (10). This procedure is commonly used in severe diagnoses of alcoholic hepatitis where the patient is admitted to the ICU and could be experiencing multi-organ failure, especially in regards to respiratory function. Between the two groups, there is no significant difference for in developing this outcome, with the p-value equaling 0.16 (Figure 9).

⁴ p = 0.11

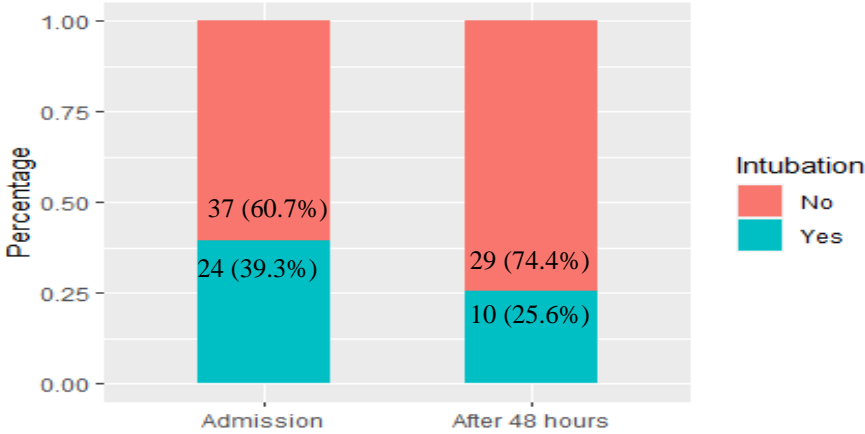


Figure 9 There is no significant difference between the two groups for the outcome of intubation.⁵

3.5 Impact of When an Infection was Presented on Different Outcomes in Transferred Patients

The University of Pittsburgh Medical Center (UPMC) is an academic hospital center in Western Pennsylvania. In general, UPMC admits patients who are transferred from outside hospitals for a higher level of care, such as in an ICU or for potential liver transplant evaluation. To see if transfers had an influence on the overall data analysis, the database was filtered to specifically analyze the outcomes of death, septic shock, and intubation in transferred patients (n = 65). For the two groups, there was no significant difference among death, septic shock, and intubation, with the p-values equaling 0.46, 0.50, and 0.17 respectively (Figure 10-12).

⁵ p = 0.16

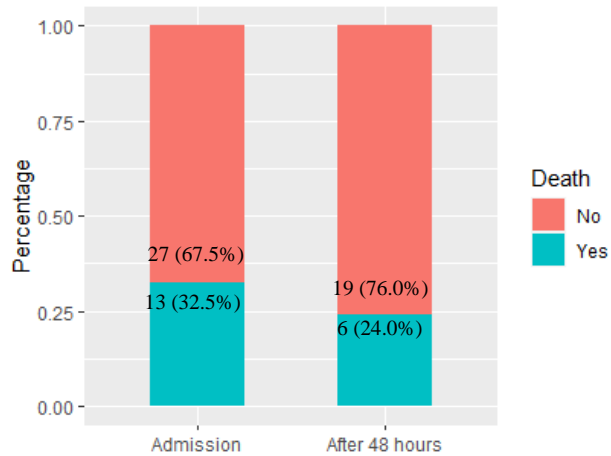


Figure 10 There is no significant difference between the two groups for the outcome of death in transferred patients.⁶

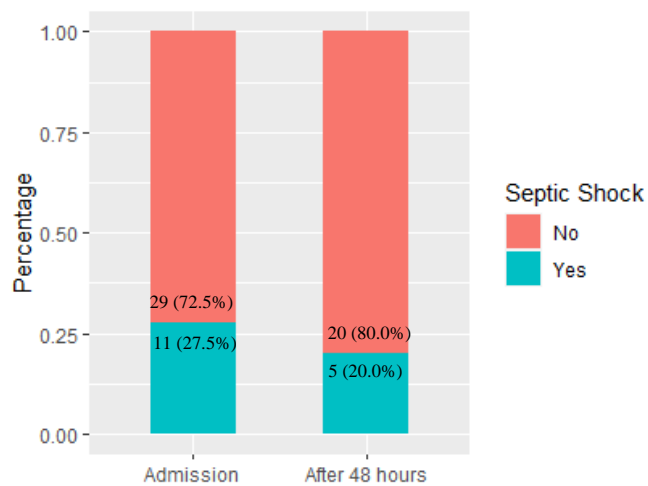


Figure 11 There is no significant difference between the two groups for the outcome of septic shock in transferred patients.⁷

⁶ p = 0.46

⁷ p = 0.50

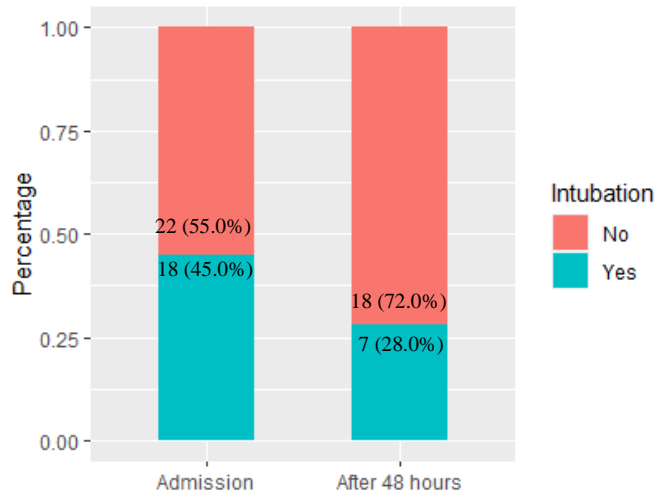


Figure 12 There is no significant difference between the two groups for the outcome of intubation in transferred patients.⁸

3.6 Impact of When an Infection was Presented on Different Outcomes in Patients Admitted through the Emergency Department

Patients with alcohol-associated hepatitis may sometimes be self-referred and enter the hospital through the emergency department, whether it be that their symptoms are observed by themselves or significant others. To assess if admission from the emergency department may affect development of the clinical outcomes in the two groups, the data was analyzed for only those who were self-referred and admitted through the emergency department (n = 32). Among the two groups, there was no difference between each of the outcomes (Figure 13-15). The p values for death, septic shock, and intubation were 1, 0.13, and 1, respectively.

⁸ p = 0.17

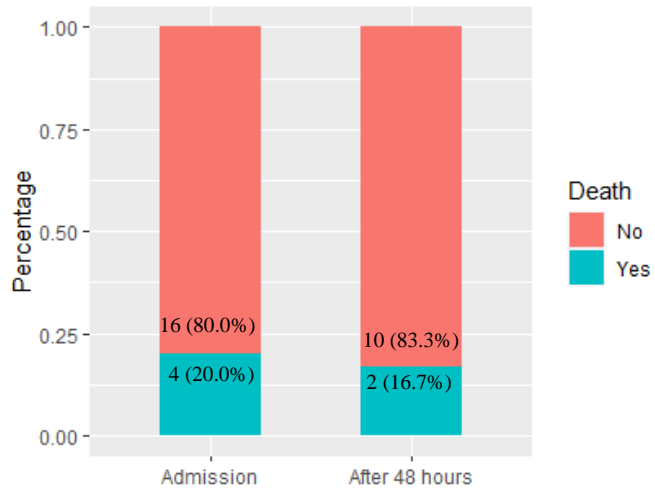


Figure 13 There is no difference between the two groups for the outcome of death in self-referred patients, admitted through the emergency department.⁹

⁹ p = 1.0

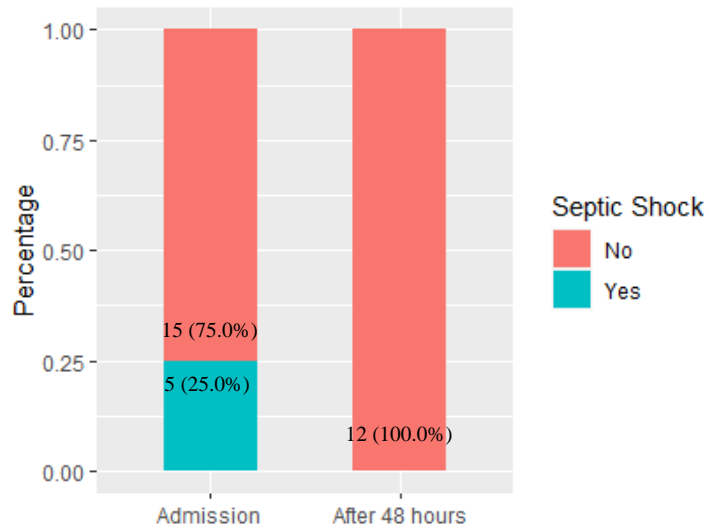


Figure 14 There is no significant difference between the two groups for the outcome of septic shock in self-referred patients, admitted through the emergency department.¹⁰

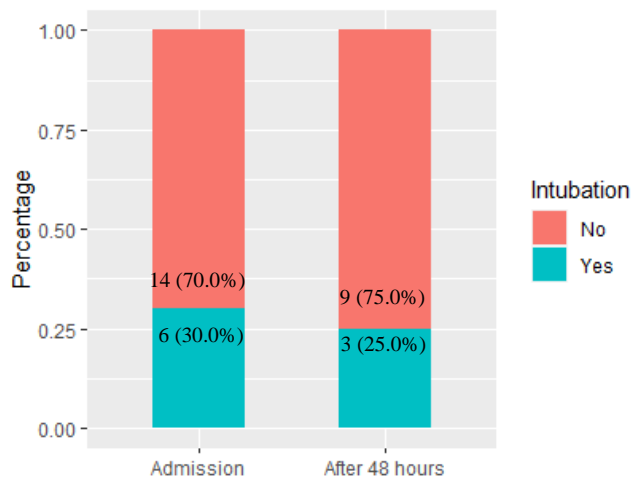


Figure 15 There is no significant difference between the two groups for the outcome of intubation in self-referred patients, admitted through the emergency department.¹¹

¹⁰ p = 0.13

¹¹ p = 1.0

4.0 Discussion and Conclusions

Patients with alcohol-associated hepatitis may have complications associated with infections that may be presented during admission or developed during hospitalization. Some complications that may occur include death, septic shock, and intubation. In this study, UPMC was considered the index case. The two groups compared for this study included those who presented infection at admission and those who developed infection during hospitalization (which was defined as presenting with infection in the hospital after 48 hours). In this cohort, 61% were found to have infection at admission (61/100) while 39% were found to develop infection during hospitalization (39/100). Interestingly, in a cohort of 102 patients from Penrice et. al (2021) observed that 33% of the patients presented with infection at admission and 30% of the patients were diagnosed with infection during hospitalization (7). The cohort of patients in this study was from academic institutions, Mayo Clinic and Virginia Commonwealth University, which differed from what was seen at UPMC.

Overall, more infections were presented at admission, compared to infections developed during hospitalization. Among the two groups, a variety of infections were observed with the most common infections being pneumonia and urinary tract infections, as well as having multiple infections in the hospitalization group. Pneumonia, multiple infections, urinary tract infections, and spontaneous bacterial peritonitis were more common in the admissions group.

The outcomes of death, septic shock, and intubation were compared between the two groups. For each group, there was no significant difference between the number of patients who developed each of the outcomes. Furthermore, the overall cohort of patients was filtered by transferred patients from outside hospitals and those who were self-referred and admitted through

the emergency department. 65% of the patients in the cohort were transferred from an outside hospital and 32% of the patients in the cohort were admitted directly from the emergency department. The analysis of these two groups were used to see if the admission of these patients either through transfer or self-referral may have an impact on the data. In comparing each of these types of admission to the overall cohort, there was still no difference in the development of the three outcomes depending on when they acquired an infection.

The analysis from this cohort suggests certain notions in relation to public health significance. While there is a limitation in that UPMC was the index case for this study, the data analysis performed at this institution suggests public health consciousness. The lower number of infections during hospitalization compared to admission may indicate the effectiveness of infection control programs for this disease population in an academic institution, specifically in the UPMC hospital system. It may emphasize the importance that UPMC places on preventing hospital acquired infections. Although this is the case, there is still a number of patients that are admitted to UPMC with infections. Conclusively, discussions should center on the effectiveness of infection control in the community and in hospitals from which patients were transferred to focus on preventing infections before admission to other healthcare facilities.

Bibliography

1. Clemente-Sanchez A, Oliveira-Mello A, Bataller R. 2021. Moderate Alcoholic Hepatitis. *Clin Liver Dis* 25:537-555.
2. Vergis N, Atkinson SR, Thursz MR. 2020. Assessment and Management of Infection in Alcoholic Hepatitis. *Semin Liver Dis* 40:11-19.
3. Bataller R, Arab JP, Shah VH. 2022. Alcohol-Associated Hepatitis. *N Engl J Med* 387:2436-2448.
4. Zhang G, Jazwinski Faust A. 2021. Spontaneous Bacterial Peritonitis. *JAMA* 325:1118.
5. Waleed M, Abdallah MA, Kuo YF, Arab JP, Wong R, Singal AK. 2020. Higher Frequency of Hospital-Acquired Infections but Similar In-Hospital Mortality Among Admissions With Alcoholic Hepatitis at Academic vs. Non-academic Centers. *Front Physiol* 11:594138.
6. Michelena J, Altamirano J, Abraldes JG, Affo S, Morales-Ibanez O, Sancho-Bru P, Dominguez M, Garcia-Pagan JC, Fernandez J, Arroyo V, Gines P, Louvet A, Mathurin P, Mehal WZ, Caballeria J, Bataller R. 2015. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology* 62:762-72.
7. Penrice DD, Shah S, Kezer CA, Peeraphatdit TB, Sanyal AJ, Davis B, Mara KC, Shah VH, Kamath PS, Simonetto DA. 2021. Risk Prediction of Nosocomial and Posthospital Discharge Infections in Alcohol-Associated Hepatitis. *Hepatol Commun* 5:2096-2103.
8. Perez R, Khanna S, Tillotson GS, Lett JE, 2nd, Prince MA, Lattimer C. 2022. Reducing Recurrence and Complications Related to *Clostridioides difficile* Infection: A Panel Discussion Summary. *Prof Case Manag* 27:277-287.
9. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315:801-10.
10. Miller AG, Gentile MA, Coyle JP. 2020. Respiratory Therapist Endotracheal Intubation Practices. *Respir Care* 65:954-960.

11. NHSN. 2023. Identifying Healthcare-associated Infections (HAI) for NHSN Surveillance, National Healthcare Safety Network (NHSN) Patient Safety Component Manual.
12. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.