Research Square

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Utility of Systemic Inflammatory Syndrome Score in Predicting Healthcare-Associated Infections in Critically Ill Patients: A Matched Case-Control Study

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Abstract

Background

Effective prevention of healthcare-associated infections (HAIs) requires early identification of at-risk patients. There is no score designed to predict HAIs. The present study was aimed to explore an available score, Systemic inflammatory syndrome (SIRS) score, on admission in predicting HAIs among critically ill patients.

Methods

This study was based on the Medical Information Mart for Intensive Care III (MIMIC III) version 1.4. Patients with HAIs were matched with control patients who had no HAIs in a 1:1 ratio based on age, gender, mechanical ventilation, deep venous catheterization, urethral catheterization, and surgical operation. Subgroup analyses were conducted according to various variables including infection likelihood on admission. The prognostic values of SIRS and infectious SIRS on admission in predicting HAIs were analyzed using logistic regression.

Results

A total of 2437 patients with HAIs and 2437 matched controls were enrolled in the final analysis. Adjusted odds ratio (ORs) (95% confidence interval [CI]) for HAIs of SIRS scores (1 to 4) on admission was 1.48 (0.77-2.83), 1.86 (0.99-3.47), 2.14 (1.15-3.98), and 2.58 (1.39-4.80). Adjusted ORs (95%CI) for HAIs of SIRS (score≥2) and infectious SIRS were 1.57 (1.27-1.94) and 1.78 (1.52-2.09), respectively. Subgroup analyses showed that SIRS on admission was an independent risk factor for HAIs in patients admitted without definite and probable infection likelihood (OR=1.54, 95%CI 1.28-1.93). However, it was not a risk factor for HAIs inpatients admitted with infection, in non-white patients, and in patients with liver disease or obesity, and in patients who received total parenteral nutrition (TPN) (all P>0.05). In addition, it was showed that infectious SIRS on admission was not a risk factor for HAIs in black patients and in patients with obesity, and those received TPN (all P>0.05).

Conclusions

Infectious SIRS on admission significantly predicts HAIs among critical illness patients. SIRS on admission was a predictor of HAIs in ICU patients admitted without infection but not in patients admitted with infection.

Introduction

Healthcare-associated infections (HAIs) are common complications in hospitalized patients, especially in those admitted to the intensive care units (ICUs) [1]. HAIs contribute to increased morbidity, extra length of hospital stay and costs, and may be associated with increased mortality [2]. Although clear preventive guidelines exist, the incidence of HAIs remains high with an estimate of 3-10 per 100 ICU admissions as reported by the International Nosocomial Infection Control Consortium (INICC) [3, 4].

Effective prevention of HAIs requires early identification of at-risk patients. Based on National Nosocomial Infection Surveillance (NNIS) System, various investigators have developed methods to stratify populations of patients into categories of risk for HAIs [3–6]. Those methods stratified the patient population mainly on basis of medical device exposure, surgery types, and ICU types [5–6]. However, even exposed to the same medical condition, some of the patients did not acquire a HAI [5–6]. Moreover, a recent meta-analysis found that only preventive strategy has demonstrated effectiveness at reducing mortality of patients with hospital-acquired infections in ICUs [7]. Therefore, it would be valuable to identify patients at high risk for HAIs before they were exposed to medical interventions.

To date, clinical scores, such as Acute Physiology and Chronic Health Evaluation (APACHE) score and Therapeutic Intervention Scoring System (TISS), have been associated with the occurrence of HAIs [8]. Nevertheless, it has been proven that the severity-of-illness scores on admission are not useful predictors of HAIs in ICUs [9]. Recently, people come to realize that the immune status of the patients may play a central role in developing HAIs [10]. Systemic inflammatory response syndrome (SIRS), which induced the alterations of both innate and adaptive immunity, is a common reason for immune dysfunction in critically ill patients [11]. SIRS can be caused by infectious diseases, trauma, major surgery and burn [12]. High incidence of HAIs has been observed in some single diseases mentioned above [6, 13]. However, patients admitted with SIRS, as a special population of critically ill patients, have a higher susceptibility to HAIs or not remained to be investigated.

The present study was designed to explore the relationship between SIRS score on admission and the development of HAIs in critically ill patients. Then, SIRS was categorized according to the infection likelihood on admission, and the value of infectious SIRS in predicting HAIs was analyzed. In addition, the predictive value of SIRS for HAIs in patients admitted with and without infection was further evaluated.

Methods

Database

This study was conducted using the Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC III) version 1.4. MIMIC III is a publicly and freely available database which comprising more than 40,000 patients treated in various ICUs of Beth Israel Deaconess Medical Center from 2001 to 2012 [14]. MIMIC III database used in the present study was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology and does not contain protected health information.

Study population

For the purpose of the present analysis, 4 main types of HAIs were extracted from the database using the International Classification of Diseases, Ninth Revision (ICD-9) codes: (1) central line-associated bloodstream infections (CABSIs); (2) catheter-associated urinary tract infections (CAUTIs); (3) ventilator-associated pneumonia (VAPs); (4) surgical site infections (SSIs). Subjects were included if HAIs were listed as secondary diagnosis at discharge. Overall, 3482 subjects with HAIs and 59348 subjects without HAIs were extracted from the MIMIC-III database, respectively. After removing the repeated subjects, 2815 patients with HAIs and 56186 patients without HAIs were initially enrolled. The further exclusion criteria were: (1) age<18 years or >100 years; (2) HAIs were listed as a diagnosis at admission; (3) patients who were either discharged or died within 3 days after ICU admission. (4) patients with missing medical data. The eligible patients were then matched to patients without HAIs in a 1:1 ratio using age, gender, mechanical ventilation, deep venous catheterization, urethral catheterization and surgical operation. Patients were further excluded if a successful match could not be obtained (Figure. S1).

Data collection and definitions

The data including demographics (age and gender), diagnosis at admission, comorbidities, interventions and other potential confounding variables for HAIs were collected from MIMIC III using Structured Query Language (SQL) with Naviact Premium (version 12.0.28). The data of SIRS score at admission were extracted. SIRS was defined as the presence of two or more of the following criteria according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) [15]. The diagnosis on admission was evaluating by three assessors, and the plausibility of infection was categorized as definite, probable, and possible or none [16]. The top 15 most frequent admission diagnoses in four groups were shown in supplementary figure 1. Infectious SIRS was defined as a SIRS with definite and probable infection likelihood [10].

Statistical analysis

Data were expressed as percentages or mean±SD or interquartile ranges (25th and 75th percentiles). Continuous variables such as age and length of stay (LOS) were compared using a Students' T-test or Mann–Whitney U, while categorical variables analyzed by Pearson's chi-square and Fisher's exact test. Univariate analysis was applied to compare the risk factors for patients with and without HAIs. Binary logistic regression was used to identify the independent impact of SIRS and infectious SIRS on HAIs. Variables which were found to be significantly different between cases and controls in the univariate analysis were entered into the logistic model. Stratification analyses was conducted to explore whether the effect of the SIRS differed across various subgroups classified by admission variables including infection likelihood, ethnicity, renal failure, liver disease and obesity. All statistical analyses were performed using the IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA) and R 3.5.3 software for windows. Statistical significance was expressed as both P values and 95% confidence intervals (CI_{95}). A two-sided P-value <0.05 was considered statistically significant.

Results

Characteristics of the subjects

2437 patients with HAIs and 38555 patients without HAIs were enrolled in the present study (Figure. S2). The prevalence of HAIs among the patients was 5.9%. 2363 patients had HAIs at one site, 74 patients had two or more sites. Among 2512 HAIs, the most common HAIs were SSI (n=1511), followed by VAP (n=520), CRBSI (n=319), and CATUIS (n=162), respectively. Patients with HAIs were matched with patients without HAIs at a 1:1 ratio and 2437 patients without HAIs were selected. Baseline characteristics of patients were presented in Table 1 according to the development of HAIs or not. No significant differences were observed in age, gender, and invasive interventions between cases and controls. Other variables were also compared between the two groups. Significant differences were found in ethnicity, renal failure, liver disease, obesity, blood transfusion, and TPN between patients with HAIs and without HAIs (Table. 1).

Outcomes of patients with or without HAIs

As shown in Table 1, when compared with patients without HAIs, those who developed an infection had a longer ICU length of stay (4.24 days [IQR 1.99-11.75] vs 2.66 days [IQR 1.47-5.09], *P*<0.001) and hospital length of stay (16.06 days [IQR 9.22-26.84] vs 7.97 days [IQR 5.29-13.73], *P*<0.001). Additionally, although there was no significant difference in 30-day crude mortality between patients with and without HAIs (309 deaths [12.7%] vs 287 deaths [11.5%], *P*=0.219), and the crude mortality of patients with HAIs were higher than those without HAIs at 60-day (432deaths [17.7%] vs 353 deaths [14.5%], P=0.002), 90-day (509 deaths [20.9%] vs 394 deaths [16.2%], P<0.001) and 1-year (756 deaths [31.0%] vs 573 deaths [23.5%], *P*<0.001) (Table. 1).

As shown in Table 2, after adjusting for ethnicity, chronic comorbidity (renal failure, liver diseases and obesity) and interventions (blood transfusion and TPN), there was no significant difference in 30-day mortality (OR 1.14, CI_{95} 0.96-1.35, *P*=0.15) between patients with HAIs and those without HAIs (Table. 2). Significant differences in 60-day, 90-day, and 1-year mortality were noted between the two groups, and the adjusted ORs were 1.29 (CI_{95} 1.11-1.51, *P*=0.001), 1.39 (CI_{95} 1.20-1.61, *P*<0.001), and 1.46(CI_{95} 1.29-1.66, *P*<0.001), respectively (Table. 2).

Relationship between admission SIRS score and HAIs

Table 3 shows that the incidences of HAIs in SIRS score 0 to 4 groups were 31.9%, 40.9%, 46.6%, 50.1%, and 54.7%, respectively. The incidence of HAIs in patients with SIRS (score≥2) was higher than that in patients without SIRS (50.9% *vs*. 39.8%, *P*<0.001). The crude ORs for HAIs of SIRS score 1 to 4 on admission were 1.46 (CI_{95} 0.77-2.83, *P*=0.241), 1.86 (CI_{95} 0.99-3.47, *P*=0.052), 2.14 (CI_{95} 1.15-3.98, *P*=0.016), and 2.60 (CI_{95} 1.39-4.80, *P*=0.003), respectively. The crude OR for HAIs of SIRS was 1.57 (CI_{95} 1.27-1.94, *P*<0.001) (Table. 3). After adjusting for ethnicity, chronic comorbidity (renal failure, liver diseases and obesity) and interventions (blood transfusion and TPN), ORs for HAIs of SIRS score 1 to 4 on admission were 1.48 (CI_{95}0.77-2.83, *P*=0.232), 1.858 (CI_{95} 0.99-3.47, *P*=0.051), 2.142 (CI_{95} 1.15-3.98,

P<0.001), and 2.58 (CI_{95}1.39-4.80, *P*<0.001), respectively (Table. 3 and Figure. 1). Adjusted OR for HAIs of SIRS on admission was 1.57 (CI_{95}1.27-1.94, *P*<0.001) (Table. 3 and Figure. 1).

Association between infectious SIRS on admission and HAIs

The number of patients with definite, probable, possible, and none infection likelihoods on admission were 628 (12.9%), 189 (3.9%), 1103 (22.6%), and 2954 (60.6%) respectively (Table. S1). There were 778 SIRS with definite and probable infectious diseases. The incidence of HAIs in patients with infectious SIRS was 62.2%. The crude OR for HAIs of infectious SIRS was 1.81 (CI_{95}1.54-2.11, *P*<0.001) (Table. 3 and Figure. 3). Additionally, after adjusting for ethnicity, chronic comorbidity (renal failure, liver diseases and obesity) and interventions (blood transfusion and TPN), OR for HAIs of infectious SIRS was 1.78 (CI_{95}1.52-2.09, *P*<0.001) (Table. 3 and Figure. 1).

Subgroup analyses

As shown in Table S1 and Figure 2, when only patients with definite infection likelihood on admission were included in the analysis, the OR for HAIs of SIRS was 1.04 (CI_{95} 0.50-2.15, *P*=0.914). When the analysis was restricted to only patients with definite and probable infection likelihood on admission, the OR for HAIs of SIRS was 1.32 (CI_{95} 0.68-2.56, *P*=0.417). When only patients without definite infection likelihood on admission were included, the OR for HAIs of SIRS was 1.61 (CI_{95} 1.28-2.01, *P*<0.001). When only patients without definite and probable infection on admission were included, the OR for HAIs of SIRS was 1.54 (CI_{95} 1.28-1.93, *P*<0.001).

Subgroup analyses were also conducted according to admission variables including ethnicity and chronic comorbidity. It was shown that SIRS on admission was not the risk factor for HAIs in non-white patients, and in patients with liver disease or obesity (all *P*>0.05) (Table. S1 and Figure. 3). In addition, the results revealed that infectious SIRS on admission was not the risk factor for HAIs in black patients and in patients with obesity (all *P*>0.05) (Table. S1 and Figure. 3).

Discussion

SIRS is a nonspecific clinical state that can complicate a wide range of insults, including surgery, trauma, burns or any types of infection. In the past decades, SIRS score has been used to predict the outcomes of ICU patients and various diseases [17–18]. Recently, because of SIRS is always accompanied by immunoparalysis, experts suggest that SIRS may be a risk factor for the development of nosocomial infections [11, 19]. However, only few clinical studies were designed to explore this issue and most of them were confined in single disease. In trauma patients, studies showed that SIRS was predictive of nosocomial infection [20–21]. In this matched case-control study, we found that critical illness patients who admitted with SIRS was more susceptible to HAIs, and susceptibility to HAIs increased with the increase of SIRS score.

SIRS can be caused by both infections and non-infectious diseases. Previous studies illustrated that SIRS induced by infectious diseases and non-infectious diseases share many features. Additionally, immune dysfunction and increased susceptibility to opportunistic infections were observed in the two types of SIRS [6, 13, 20–21]. In the present study, we noticed that infectious SIRS was more effective than SIRS in predicting HAIs. A study of 21 patients with SIRS showed, a significant shift of Th2 response in T-cells, a prolonged reduction of proinflammatory cytokine production and a reduced human leukocyte antigen (HLA) -DR expression on monocyte (mHLA-DR) in septic SIRS, when compared with those in non-septic SIRS [22]. Similarly, using mHLA-DR to detect immune response, Lukaszewicz et al. [23] found that septic patients had lower mHLA-DR when compared with non-septic ICU patients, and a weak trend of mHLA-DR recovery was associated with an increased risk of secondary infection in septic patients. The results indicate that patients with infectious SIRS may cause more severe of immune dysfunction when compared with non-infectious SIRS, which contributes to the increased susceptibility to HAIs.

In subgroup analyses, we found that SIRS on admission was effective in predicting HAIs in patients who did not admit with infectious diseases while it was not working in infected patients. Little is known about the mechanism underlying this phenomenon. Nevertheless, the association between SIRS and infection has been documented by many studies [24–25]. In the current study, the incidence of SIRS in infectious patients' group and non-infectious patients' group was 95.2% and 91.4%, respectively. Additionally, patients admitted with infections usually received antibiotics which has been considered as a risk factor for nosocomial infections and may influence the predictive value of SIRS for HAIs [26–27].

The results of this study showed that SIRS was not a predictor of HAIs in non-white patients, and in patients with liver disease or obesity. We also found that there were interactions between infectious SIRS and ethnicity, and obesity in predicting HAIs. A recent research found that African Americans had fewer occurrences of SIRS and lower white blood cell count on admission to the ICUs after trauma, when compared with whites [28]. Moreover, the relationship between obesity and liver disease and systemic inflammation has been illustrated by some clinical studies [29–30]. Therefore, those factors should be taken into consideration when evaluating SIRS in predicting HAIs among critically ill patients.

The results of present study must be interpreted in the light of some limitations. Firstly, it was a retrospective design and conducted in a single center. Secondly, the present study included four main types of HAIs. the potential role of SIRS on admission in predicting other types of nosocomial infections including hospital acquired non-ventilator-associated pneumonia, gastrointestinal system infection, and eye, ear, nose or mouth infection, need to be further investigated. Thirdly, the categorization of infection likelihood on admission was based on the diagnosis. The evidence that infectious SIRS remains a significant predictor of HAIs would suggest that the diagnosis of infection on admission in MIMIC III database is accurate. Finally, persistent SIRS may cause more severe immune dysfunction, and maybe more effective in predicting HAIs [21]. Since the time of HAIs occurrence was not recorded in MIMIC III database, the duration of SIRS before HAIs could not be calculated and its relationship to HAIs was not analyzed in the present study.

Conclusions

In unselected critical illness patients, SIRS and infectious SIRS on admission significantly predict HAIs. In such patients admitted with infections, SIRS may be not an independent predictor of HAIs. Our findings should be validated by future large-scale prospective studies.

Declarations

Ethics approval and consent to participate

MIMIC III database used in the present study was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology and does not contain protected health information.

Consent for publication

Not applicable.

Availability of data and material

The datasets used in the present study are available from the corresponding author.

Conflicts of interest.

The authors declare that they have no completing interests

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Authors' contributions

GJZ designed the study; collected and analyzed data; and contributed to writing this manuscript. CX collected and analyzed data; LWC, GLH, MFL and BW helped with data analyzation. ZQL designed and supervised the study and drafted the manuscript. All authors have read and approved the final manuscript.

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Tables

Table1. Baseline characteristics and outcomes of critically ill patients stratified according to development of healthcare-associated infections or not.

Variables	Healthcare-associated infections No. (%) (n=2437)	No Healthcare-associated infections No. (%) (n=2437)	*P* Value
Age, mean(SD), years	63.9 (52.2, 75.0)	64.3 (52.5, 74.6)	0.940
Male	1343 (49.3)	1094 (50.9)	0.286
Ethnicity			
White	1805 (74.1)	1731 (71.0)	
Black	191 (7.8)	234 (9.6)	<0.001
other	515 (21.1)	398 (8.2%)	
Chronic comorbidity			
Hypertension	1295 (53.1)	1312 (53.8)	0.625
Heart failure	625 (25.6)	658 (27.0)	0.283
Chronic pulmonary	517 (21.2)	483 (19.8)	0.228
Diabetes	712 (29.2)	728 (29.9)	0.615
Renal failure	441 (18.1)	352 (14.4)	0.001
Liver disease	275 (11.3)	206 (8.5)	0.001
AIDS	16 (0.7)	24 (1.0)	0.204
Obesity	229 (9.4)	138 (5.7)	<0.001
Alcohol abuse	198 (8.1)	184 (7.6)	0.456
SAPSII score			
Overall, median (IQR)	35 (27-45)	35 (27-45)	0.329
Quartile			
1(0-27)	628 (28)	667 (27.4)	
2(28-35)	585 (24)	556 (22.8)	0.597
3(36-45)	580 (23.8)	612 (25.1)	
4(46-95)	590 (24.2)	602 (24.7)	
Invasive interventions			
Surgery	1426 (58.5)	1549 (56.1)	0.088

Urinary catheter	2235 (91.7)	2242 (92.0)	0.714
Mechanical ventilation	1561 (63.6)	1549 (64.1)	0.721
Central venous catheter	1943 (79.7)	1994 (81.8)	0.064
Non-invasive interventions			
Blood transfusion	1418 (58.2)	1128 (46.3)	<0.001
TPN	456 (18.7)	131 (5.4)	<0.001
Steroid use	452 (18.5)	405 (16.6)	0.077
Outcomes			
LOS			
ICU	4.2 (2.0, 11.8)	2.66 (1.5, 5.1)	<0.001
hospital	16.1 (9.2, 26.8)	8.0 (5.3, 13.7)	<0.001
Mortality			
30 d	309 (12.7)	287 (11.5)	0.219
60 d	432 (17.7)	353 (14.5)	0.002
90 d	509 (20.9)	394 (16.2)	<0.001
1 year	756 (31.0)	573 (23.5)	<0.001

Abbreviations: SIRS, systemic inflammatory response syndrome; AIDS, acquired immune deficiency syndrome; SAPS, simplified acute physiology score; IQR, interquartile range; TPN, total parenteral nutrition; length of stay.

Table 2. ORs (95% CIs) for all-cause mortality associated with HAIs

	Unadjusted		Adjusted	
Mortality	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value
30-day	1.11 (0.94-1.32)	0.219	1.14 (0.96-1.35)	0.147
60-day	1.27 (1.09-1.48)	0.002	1.29 (1.11-1.51)	0.001
90-day	1.37 (1.18-1.58)	0.000	1.39 (1.12-1.61)	0.000
1-year	1.46 (1.29-1.66)	0.000	1.46 (1.29-1.66)	0.000

Abbreviations: OR: Odds ratios, 95% CIs: 95% confidence intervals; HAIs: healthcare-associated infections.

Table 3. ORs (95% CIs) for HAIs associated with SIRS on admission

	No. of HAIs/	Unadjusted		Adjusted	
On admission	No. of patients	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value
SIRS score (per 1)		1.12(1.13-1.27)	<0.001	1.20 1.13-1.28)	<0.001
SIRS score					
0	15/47	1.00		1.00	
1	139/340	1.46 (0.77-2.83)	0.241	1.49 (0.78-2.86)	0.232
2	486/1044	1.86 (0.99-3.47)	0.052	1.87 (1.00-3.50)	0.051
3	946/1888	2.14 (1.15-3.98)	0.016	2.17 (1.12-4.04)	0.015
4	851/1555	2.60 (1.39-4.80)	0.003	2.61 (1.40-4.87)	0.003
SIRS (score≥2)					
No	154/387				
Yes	2283/4487	1.57 (1.27-1.94)	<0.001	1.57 (1.27-1.94	<0.001
Infectious SIRS					
No	1953/4096				
Yes	484/778	1.81(1.54-2.11)	<0.001	1.78 (1.52-2.09)	<0.001

Abbreviations: OR: Odds ratios, 95% CIs: 95% confidence intervals; SIRS, systemic inflammatory response syndrome; HAIs: healthcare-associated infections.

Figures

Vaiables	No. of HAIs/ No. of patients	OR (95% CI)	P Value
SIRS score (per 1)	—	1.20 (1.13-1.28)	<0.001
SIRS score			
0	15/47	1.00	
1	139/340	1.49 (0.78-2.86)	0.232
2	486/1044	1.87 (1.00-3.50)	0.051
3	946/1888	2.17 (1.12-4.04)	0.015
4	851/1555	2.61 (1.40-4.87)	0.003
SIRS (score≥2)			
No	154/387		
Yes	2283/4487	1.57 (1.27-1.94)	<0.001
Infectious SIRS			
No	1953/4096		
Yes	484/778	1.78 (1.52-2.09)	<0.001

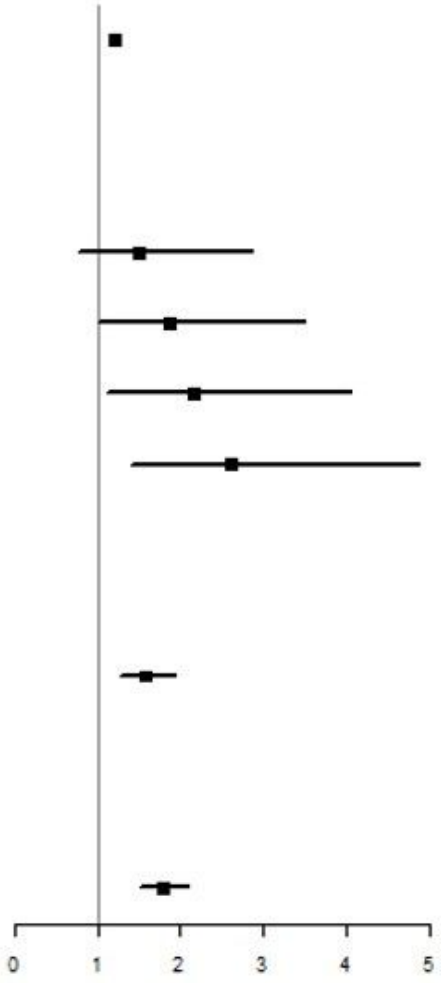

Figure 1

ORs (95% CIs) for HAIs associated with SIRS on admission

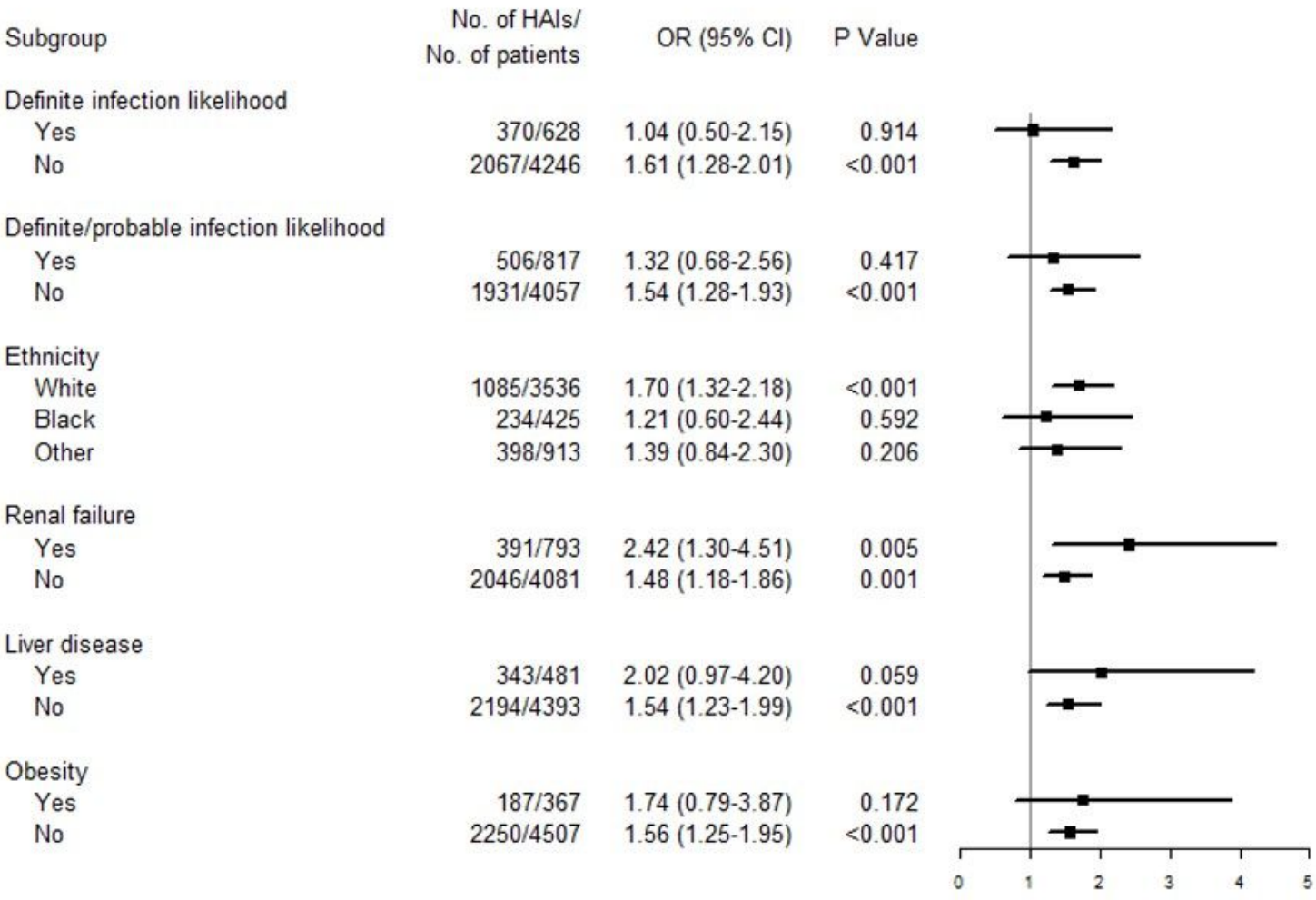

Figure 2

ORs (95% CIs) for HAIs associated with SIRS on admission in subgroups

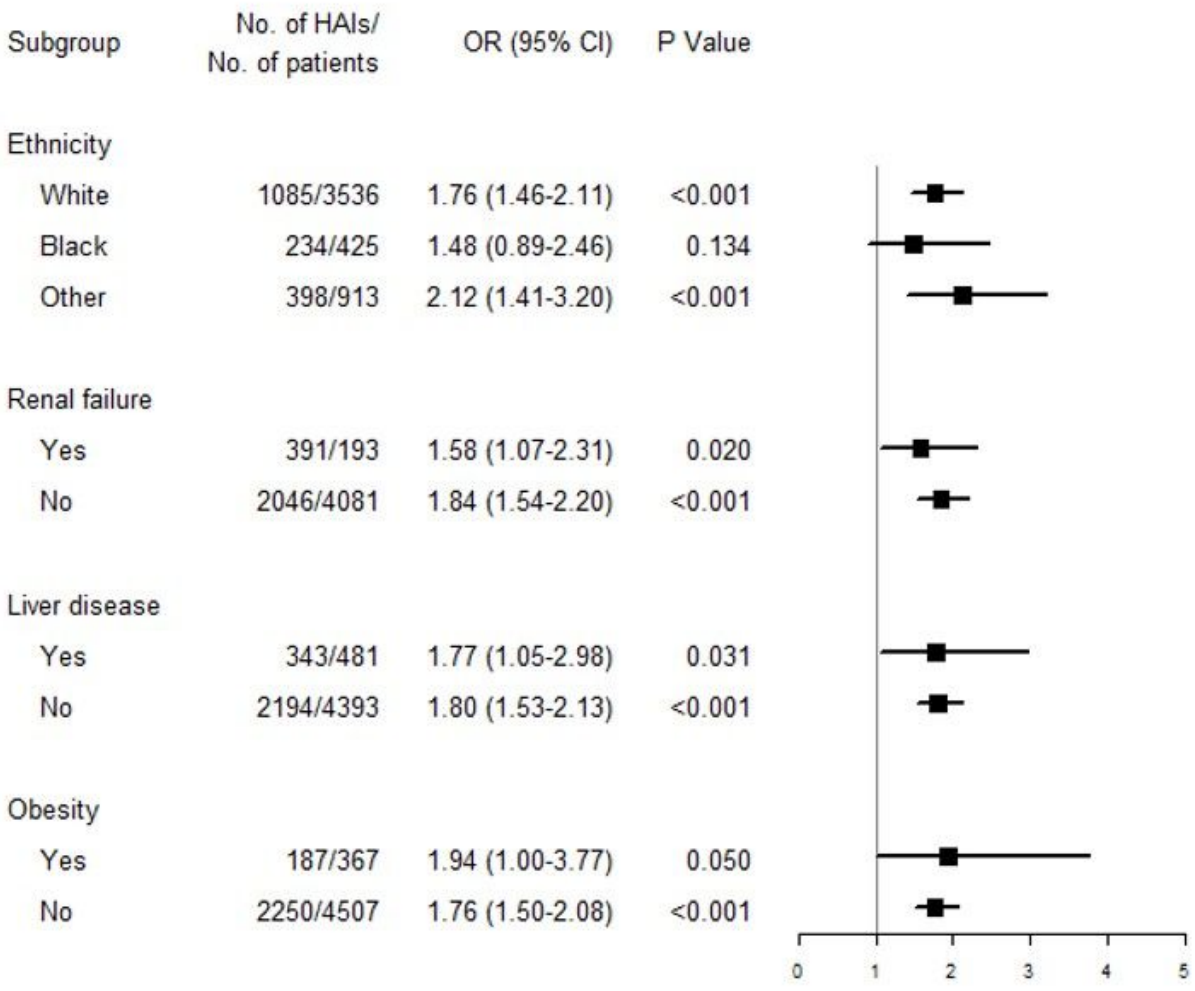

Figure 3

ORs (95% CIs) for HAIs associated with infectious SIRS on admission in subgroups

Supplementary Files

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- SupplementaryMaterial.docx