

Research Paper

Risk and clinical outcomes of acute myocardial infarction and acute ischemic stroke following gram-negative bloodstream infection



Vinh-An D. Vo^a, Mazen K. Khalil^{a,b}, Majdi N. Al-Hasan^{a,c,*}

^a University of South Carolina School of Medicine, Columbia, SC, USA

^b Department of Internal Medicine, Division of Cardiology, Prisma Health Midlands, Columbia, SC, USA

^c Department of Internal Medicine, Division of Infectious Diseases, Prisma Health Midlands, Columbia, SC, USA

ARTICLE INFO

Keywords:

Coronary artery disease
Acute coronary syndrome
Cardiovascular disease
Cerebrovascular disease
Bacteremia
Sepsis

ABSTRACT

Objectives: This retrospective cohort study examines incidence, risk factors, and clinical outcomes of acute myocardial infarction (AMI) and acute ischemic stroke (AIS) within one year of gram-negative bloodstream infection (GN-BSI) based on predefined clinical criteria.

Methods: Hospitalized adults with GN-BSI at Prisma Health-Midlands hospitals in South Carolina, USA from 2010 through 2015 were identified. Kaplan-Meier analysis was used to determine incidence of AMI and AIS within one year after GN-BSI. Multivariate Cox proportional hazards regression models were used to examine risk factors for AMI or AIS and impact on 1-year mortality.

Results: Among 1292 patients with GN-BSI, 263 and 17 developed AMI and AIS within 1-year with incidences of 23.4% and 1.9%, respectively. Majority of AMI were type 2 (164; 62%); 99 patients had type 1 AMI with incidence of 8.9%. Age >65 years (hazard ratio [HR] 1.52, 95% CI: 1.17–1.99), prior coronary artery disease or stroke (HR 1.74, 95% CI: 1.34–2.25), hypertension (HR 1.55, 95% CI: 1.13–2.15), end-stage renal disease (HR 1.52, 95% CI: 1.09–2.08), and quick Pitt bacteremia score (HR 1.55 per point, 95% CI: 1.40–1.72) were predictors of AMI/AIS. Development of type 1 AMI or AIS after GN-BSI was independently associated with increased 1-year mortality (HR 1.47, 95% CI: 1.03–2.07).

Conclusions: AMI and AIS occur frequently within one year of GN-BSI and have negative impact on 1-year survival. Future randomized clinical trials are needed to determine the most effective clinical interventions for prevention of AMI/AIS following BSI in high risk patients and improve survival after these events.

1. Introduction

Over half a million individuals develop bloodstream infection (BSI) every year in the United States [1]. An increased risk of acute myocardial infarction (AMI) and acute ischemic stroke (AIS) has been reported after various acute infections, including pneumonia, sepsis, and BSI [2–8]. A large population-based cohort study in Denmark estimated a combined 5% risk of AMI or AIS within one year of BSI, using administrative data based on International Classification of Diseases (ICD) codes [9]. Patients with BSI had significantly higher risk of AMI and AIS than both population and hospitalized controls [9]. To our knowledge, the incidence of AMI and AIS after BSI has not been established based on clinical data in the U.S. population. This retrospective observational cohort study aims to determine the incidence and risk factors of AMI and AIS within one-year of gram-negative BSI based on predefined criteria. The study also

examines the impact of the cardiovascular and cerebrovascular events on 1-year mortality.

2. Methods

2.1. Settings

The study was conducted at Prisma Health-Midlands hospitals in Columbia, South Carolina, USA. The healthcare system includes three hospitals in Columbia, Richland, Baptist and Parkridge hospitals. The three community hospitals combine for >1100 licensed beds and provide primary and specialty care for the local population. The Institutional Review Board at Prisma Health approved the study and waived informed consent.

* Corresponding author. Department of Internal Medicine, University of South Carolina School of Medicine, 2 Medical Park, Suite 502, Columbia, SC 29203, USA.
E-mail address: majdi.alhasan@uscmed.sc.edu (M.N. Al-Hasan).

<https://doi.org/10.1016/j.ijchy.2021.100079>

Received 8 October 2020; Received in revised form 15 January 2021; Accepted 18 January 2021

Available online 23 January 2021

2590-0862/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2.2. Definitions

Gram-negative BSI was defined as monomicrobial growth of aerobic or facultative anaerobic gram-negative bacilli in blood cultures. Blood cultures were processed using standard microbiology techniques according to the Clinical and Laboratory Standards Institute. The primary source of BSI was defined according to the Centers for Disease Control and Prevention criteria [10]. The quick Pitt bacteremia score was used to measure the acute severity of illness in patients with BSI [11,12]. The fourth universal definition of myocardial infarction was used to classify AMI based on clinical, electrocardiographic (ECG), and laboratory criteria [13]. Type 1 AMI involved myocardial injury and related ECG abnormalities and were further divided into ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). Type 2 AMI was related to the myocardial oxygen supply-demand mismatch. AIS was defined based on clinical and radiographic criteria [14].

2.3. Case ascertainment

In this retrospective cohort study, all patients ≥ 18 years old with first episodes of monomicrobial BSI due to gram-negative bacilli from January 1, 2010 to December 31, 2015 at Prisma Health-Midlands hospitals were identified through microbiology laboratory databases as described previously [15].

2.4. Statistical analysis

Kaplan-Meier analysis was used to estimate the incidence of AMI or AIS following BSI. Patients were followed from time of collection of index blood culture up to one year or until development of AMI, AIS or death. Patients who died or were lost to follow-up within one year of BSI were censored on the date of death or last health care visit, respectively. Kaplan-Meier analysis was also used to calculate the 30-day and 1-year incidence of type 1 AMI, type 2 AMI, and AIS separately.

Cox proportional hazards regression was used to determine risk factors for AMI or AIS within one-year of BSI. Variables were included in the multivariate Cox model based on clinical relevance or statistical significance (p -value < 0.05 in the univariable analysis) using backward selection.

The secondary aim of this study was to examine the impact of type 1 AMI and AIS on one-year mortality following BSI. In this analysis, patients with BSI were categorized in three groups: those who developed type 1 AMI or AIS, those with type 2 AMI, and those without cardiovascular or cerebrovascular events within one year of BSI. Multivariate Cox proportional hazards regression was used to examine predictors of one-year mortality following BSI. Patients were followed for up to one year from onset of BSI or until death; patients lost to follow up were censored.

Since not all patients with BSI had serum troponins measured, a subgroup analysis of patients who had at least one measurement of serum troponin I was performed to minimize the potential impact of selection bias on the results. Multivariate Cox proportional hazards regression was used to examine the association between highest serum troponin I value as a continuous variable and one-year mortality following BSI.

JMP Pro (version 13.0, SAS Institute Inc, Cary, North Carolina, USA) was used for statistical analysis. The level of significance for statistical testing was defined as $p < 0.05$ (2-sided) unless otherwise specified.

3. Results

3.1. Incidence of AMI and AIS after BSI

Among 1292 unique patients with gram-negative BSI, the median age was 65 years and 622 (48%) were men. Cardiovascular risk factors, namely, hypertension (68%), diabetes mellitus (38%), and

hyperlipidemia (32%) were prevalent in this cohort. The urinary tract was the most common source of BSI; *Escherichia coli* was the most common bloodstream isolate (Table 1).

Within one year of gram-negative BSI, 274 patients developed either AMI or AIS with an overall incidence of 24.5%. Most patients developed an AMI (263; 96.0%) with type 2 AMI being the most common (164; 62%). Of the 99 patients who developed type 1 AMI, 8 had STEMI and 91 had NSTEMI with combined incidence of 8.9%. Only 35/263 (13%) patients with AMI had corresponding ICD codes for AMI during the index hospitalization(s), including 33/99 (33%) with type 1 and only 2/164 (1.2%) with type 2 AMI. The majority of AMI/AIS occurred within 30 days of gram-negative BSI (Table 2).

3.2. Clinical course of AMI

The median time from collection of index blood culture to diagnosis of AMI was 0.67 days (range 0.02–357.5; interquartile range 0.22–11.78 days). Chest pain and dyspnea were the most common symptoms of AMI. ECG findings in patients with type 1 and type 2 AMI are summarized in Supplemental Table 1. The median serum troponin I was 1.45 ng/mL in type 1 AMI (range 0.40–112.5) and 0.12 ng/mL in type 2 AMI (range

Table 1
Demographics and clinical characteristics of patients with gram-negative bloodstream infection by presence of acute cardiovascular or cerebrovascular events.

Variable	Total N = 1292	With AMI/ AIS N = 274	Without AMI/AIS N = 1018	p-value
Age (years), median (IQR)	65 (54–77)	70 (61–81)	63 (52–76)	<0.001
Male sex, n (%)	622 (48)	135 (49)	487 (48)	0.54
Ethnicity, n (%)				0.34
White	595 (46)	136 (50)	459 (45)	
African American	654 (51)	131 (48)	523 (51)	
Other	43 (3)	7 (3)	36 (4)	
Weight (kg), median (IQR)	78 (66–93)	79 (67–94)	78 (65–93)	0.89
Body mass index (kg/m ²), median (IQR)	27 (22–32)	27 (22–32)	27 (22–32)	0.68
Cancer, n (%)	235 (18)	50 (18)	185 (18)	0.98
End-stage renal disease, n (%)	129 (10)	47 (17)	82 (8)	<0.001
Atrial fibrillation, n (%)	129 (10)	44 (16)	85 (8)	<0.001
Cardiovascular risk factors, n (%)				
Prior CAD or stroke	384 (30)	134 (49)	250 (25)	<0.001
Diabetes mellitus	491 (38)	126 (46)	365 (36)	0.002
Hypertension	873 (68)	222 (82)	651 (64)	<0.001
Hyperlipidemia	414 (32)	104 (38)	310 (30)	0.02
Family history of CAD	135 (10)	35 (13)	100 (10)	0.16
Current smoking	164 (13)	29 (11)	135 (13)	0.23
Cardiovascular medications, n (%)				
Statins	421 (33)	115 (42)	306 (30)	<0.001
Aspirin	287 (22)	86 (31)	201 (20)	<0.001
Other antiplatelet agents	49 (4)	19 (7)	30 (3)	0.004
Source of bloodstream infection, n (%)				0.26
Urinary tract	647 (50)	138 (50)	509 (50)	
Intraabdominal	168 (13)	27 (10)	141 (14)	
Central venous catheter	107 (8)	22 (8)	85 (8)	
Respiratory tract	73 (6)	21 (8)	52 (5)	
Skin and soft tissue	56 (4)	10 (4)	46 (5)	
Other	21 (2)	2 (1)	19 (2)	
Unknown	220 (17)	54 (20)	166 (16)	
Microbiology, n (%)				0.83
<i>Escherichia coli</i>	650 (50)	140 (51)	510 (50)	
<i>Klebsiella</i> species	257 (20)	51 (19)	206 (20)	
<i>Proteus mirabilis</i>	90 (7)	25 (9)	65 (6)	
<i>Enterobacter</i> species	87 (7)	14 (5)	73 (7)	
<i>Pseudomonas aeruginosa</i>	76 (6)	18 (7)	58 (6)	
Other	75 (6)	15 (5)	60 (6)	

AMI: acute myocardial infarction; AIS: acute ischemic stroke; IQR: interquartile range; CAD: coronary artery disease.

Table 2

Incidence of acute myocardial infarction and acute ischemic stroke within 30 days and 1 year following bloodstream infection.

Event	30-day incidence			1-year incidence		
	N	Incidence	(95% confidence intervals)	N	Incidence	(95% confidence intervals)
Acute myocardial infarction	215	17.1%	(15.0%–19.2%)	263	23.4%	(20.8%–26.0%)
Type 1	83	6.6%	(5.2%–8.0%)	99	8.9%	(7.2%–10.6%)
Type 2	132	10.9%	(9.1%–12.7%)	164	15.4%	(13.2%–17.7%)
Acute ischemic stroke	8	0.7%	(0.2%–1.2%)	17	1.9%	(1.0%–2.8%)
Total	223	17.6%	(15.5–19.7%)	274 ^a	24.5%	(21.9%–27.1%)

^a Six patients had both acute myocardial infarction and acute ischemic stroke.

0.04–1.0). Most patients with AMI received medical therapy; 17 patients (6.5%) underwent left heart catheterization. Of these 17 patients, 6 (35%) had no critical obstructive vascular disease, 7 (41%) had critical occlusion in one coronary artery, 3 (18%) had obstruction in 2 arteries, and the remaining 1 (6%) had 3-vessel disease. The right coronary and circumflex arteries were the most commonly involved blood vessels (Supplemental Table 2). Three patients underwent stent placement for critical coronary stenoses.

3.3. Risk factors for AMI and AIS

Univariate Cox model results for risk factors of AMI or AIS are demonstrated in Supplemental Table 3. Multivariate model identified five independent risk factors for AMI or AIS following BSI. Age >65 years (hazard ratio [HR] 1.52, 95% confidence intervals [CI]: 1.17–1.99), prior coronary artery disease (CAD) or stroke (HR 1.74, 95% CI: 1.34–2.25), hypertension (HR 1.55, 95% CI: 1.13–2.15), end-stage renal disease (HR 1.52, 95% CI: 1.09–2.08), and high acute severity of illness as measured by the quick Pitt bacteremia score (HR 1.55 per point, 95% CI: 1.40–1.72) were predictors for AMI/AIS. The incidence of AMI or AIS increased from 3.8% in patients without any risk factors to >50% in those with ≥ 4 risk factors (Fig. 1).

3.4. Impact of type 1 AMI and AIS on survival

A total of 314 patients died within 1-year of BSI with an overall 1-year mortality of 28.1%. One-year mortality was 49.5% in those who developed type 1 AMI or AIS following BSI, 37.4% in patients with type 2 AMI, and 24.3% in the absence of these events (log-rank $p < 0.001$; Fig. 2). Univariate Cox model results for risk factors of 1-year mortality following

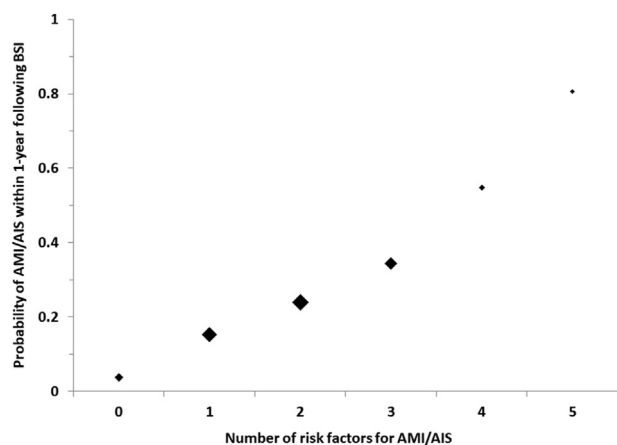


Fig. 1. Incidence of acute myocardial infarction and acute ischemic stroke following bloodstream infection by number of risk factors. AMI: acute myocardial infarction; AIS: acute ischemic stroke, BSI: bloodstream infection. The size of the point estimate proportionally corresponds to the number of patients in that category. Risk factors for AMI/AIS include age >65 years, prior history of coronary artery disease or stroke, hypertension, end-stage renal disease, and quick Pitt bacteremia score ≥ 2 .

BSI are shown in Supplemental Table 4. After adjustments in multivariate model, development of type 1 AMI or AIS following BSI was independently associated with an increase in 1-year mortality (HR 1.47, 95% CI: 1.03–2.07; $p = 0.03$) as demonstrated in Table 3.

In a subgroup analysis of 492 patients who underwent at least one measurement of serum troponin I, 263 (53.5%) had elevated troponin I (≥ 0.04 ng/mL) and the remaining 229 had serum troponin I < 0.04 ng/mL. After adjustment for other variables in the multivariate Cox model, there was a 3% relative increase in 1-year mortality with each increase in troponin I of 1 ng/mL (Supplemental Table 5).

4. Discussion

4.1. Variable risk of AMI and AIS after BSI based on methodology

In this large cohort, up to one-fourth of patients developed AMI or AIS within one-year of gram-negative BSI. Although most events represented myocardial oxygen supply-demand mismatch (type 2 AMI), type 1 AMI and AIS occurred in 8.9% and 1.9% of patients, respectively. The study identified risk factors for AMI and AIS after BSI and determined the prognostic impact of these events on long-term survival.

To our knowledge, this is the first study to determine the incidence of AMI and AIS following BSI in the U.S. using predefined objective criteria. The incidence of AMI following BSI in this study was relatively high. It was about 5 times higher than previously estimated in the Danish population using administrative data [9]. Although this may be due to dissimilarities between the two study populations, it is more likely due to differences in methodology. Using ICD codes in the Danish study likely underestimated the incidence of AMI [9]. In the current study, only 1 in 7 patients with objective criteria for AMI had corresponding ICD codes during the index hospitalization(s), including one-third of those with type 1 AMI. This is conceivable since most type 1 and type 2 AMI in the current study occurred in the absence of typical cardiac symptoms such as chest pain or dyspnea. In addition, the number of patients who underwent coronary angiography (which usually adds an AMI ICD code) was low likely due to the high acute severity of illness. High clinical suspicion for cardiovascular and cerebrovascular events in patients who have nonspecific symptoms or who are feeling unwell despite appropriate management of BSI prompted cardiac or stroke work up in this

Table 3

Predictors of 1-year mortality following bloodstream infection.

Variable	HR	(95% CI)	p-value
Age >65 years	1.48	(1.16–1.90)	0.002
Cancer	3.46	(2.66–4.48)	<0.001
Liver cirrhosis	2.92	(1.90–4.31)	<0.001
Non-urinary source of BSI	1.86	(1.44–2.42)	<0.001
Inappropriate empirical antibiotic therapy	1.74	(1.19–2.47)	0.005
qPitt (per point)	2.25	(2.02–2.51)	<0.001
Cardiovascular and cerebrovascular events			
No events	1.0	(referent)	
Type 1 AMI or AIS	1.47	(1.03–2.07)	0.03
Type 2 AMI	1.12	(0.80–1.59)	0.51

HR: hazards ratio; CI: confidence intervals; qPitt: quick Pitt bacteremia score; AMI: acute myocardial infarction; AIS: acute ischemic stroke.

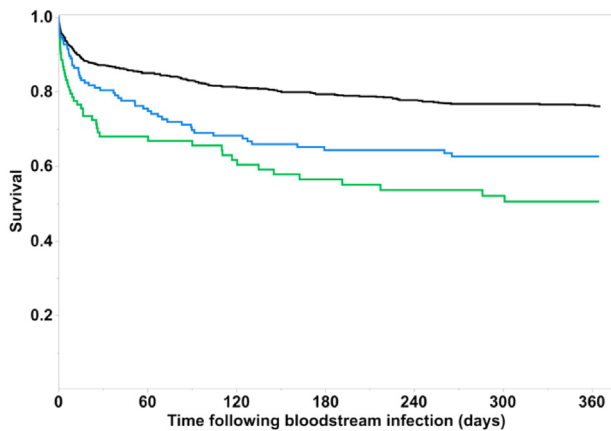


Fig. 2. One-year mortality following bloodstream infection by presence of cardiovascular and cerebrovascular events. AMI: acute myocardial infarction; AIS: acute ischemic stroke. Key: black line: no events; blue line: type 2 AMI; green line: type 1 AMI or AIS. Log-rank $p < 0.001$.

population. Similar to the results of the study in Denmark, the first 30 days after Gram-negative BSI represented the highest risk of AMI.

4.2. Prevention of AMI and AIS after BSI in high-risk patients

Risk factors for AMI or AIS following BSI in this cohort included well-established cardiovascular and cerebrovascular risk factors in the general population (older age, prior CAD or stroke, and hypertension) [16]. The current study identified end-stage renal disease and high acute severity of illness as two additional risk factors in patients with BSI. The absence of diabetes mellitus as an independent risk factor was notable in the current study. This was likely due to sample size and considerable overlap between diabetes mellitus, hypertension, and end-stage renal disease that might have limited the power of the multivariate model to identify all risk factors for AMI/AIS. High acute severity of illness is a surrogate for the stress imposed on the heart in the setting of acute infections. Most cardiovascular events occurred within 30 days of BSI. Acute inflammation in the setting of BSI is likely another contributing factor to AMI and AIS, particularly in late thrombotic events [17]. It would be useful to examine the association between these events and an objective inflammatory marker such as C-reactive protein in future studies.

The high incidence of AMI or AIS following BSI prompts future randomized clinical trials for prevention of these events. The use of statins, aspirin, and other antiplatelet agents has been suggested for prevention of AMI and AIS after serious infections [18]. The ability to estimate the incidence of AMI or AIS based on the number of risk factors in the current study assists in designing future randomized clinical trials for prevention of these events in high risk patients with BSI. Enrollment of patients with ≥ 2 risk factors seems reasonable since the incidence of AMI or AIS exceeds 20% in that setting. In addition, three-quarters of AMI and AIS in the current study occurred within 12 days of gram-negative BSI. This was consistent with the results of a previous study in Denmark that demonstrated the highest risk of cardiovascular and cerebrovascular events within 30 days of BSI [9]. This relatively short time frame implies that any future interventions for prevention of AMI and AIS should start soon after hospitalization for BSI.

4.3. Modification of long-term outcomes after type 1 AMI and AIS

Development of type 1 AMI or AIS after BSI had a negative impact on one-year survival. This was consistent with the results of a recent population-based cohort study in Queensland, Australia that demonstrated an increase in 1-year mortality in patients who developed AMI after *Staphylococcus aureus* BSI than those without AMI [19]. This highlights the importance of high suspicion for AMI and AIS following BSI

that allows early recognition, prompt diagnosis, and appropriate management. Identification of serum troponin I level as a prognostic marker in patients with BSI is a novel finding of the current study. These results improve our understanding of the impact of cardiovascular events on long-term survival of patients with BSI, sepsis, and other serious infections. This also opens the horizon for future investigations to identify the most appropriate short- and long-term management plans to improve the outcomes of these patients. Optimal medical management with beta-blockers, statins, antiplatelet agents, and anticoagulants is recommended in patients with AMI [20]. However, the dose and timing of initiation of these agents remain challenging in this setting. Many patients with BSI, particularly early in the course of illness, may not tolerate beta-blockers due to relative hemodynamic instability. Similarly, administration of antiplatelet agents and anticoagulation therapy may not be possible in critically-ill patients with suspicion of disseminated intravascular coagulation or in those requiring surgical procedures to control the source of BSI. The role of anti-inflammatory agents such as low-dose colchicine remains to be determined in these patients [21]. Optimization of medical management and modification of cardiovascular risk factors after discharge from the hospital are also crucial to reduce the long-term impacts of these events. This presents opportunities for improvement of the transitions of care from the hospital to primary care or subspecialty clinics.

The role of invasive management of AMI after BSI remains unclear. The patients included in the study had severe infections; some patients died within days of admission. In addition, some patients developed multi-organ failure which makes them less than ideal candidates for invasive management. This in part explains the fact that only few patients in the current study underwent left heart catheterization after AMI. One-third of those who underwent invasive management did not have hemodynamically significant coronary lesions. Since the majority of AMI were likely due to myocardial oxygen supply-demand mismatch in the setting of an acute infection, it remains possible that many patients may have undiagnosed severe CAD given high prevalence of cardiovascular risk factors in this population.

4.4. Strengths and limitations

Definition of AMI and AIS based on objective criteria rather than ICD codes represents a unique approach and adds strength to the current study. Estimation of the incidence of cardiovascular and cerebrovascular events by the number of risk factors provides a practical tool for designing future randomized clinical trials. The study has some limitations. The observational design may contribute to missing some events, particularly in patients with nonspecific symptoms who may not have complete cardiac or neurologic work up for diagnosis of AMI or AIS. In addition, retrospective chart review may underestimate the prevalence of poorly documented risk factors in existing medical records such as smoking status and family history of CAD. The study included only gram-negative BSI rather than all BSI. However, a previous large population-based study demonstrated a comparable incidence of cardiovascular and cerebrovascular events after gram-negative and gram-positive BSI [9]. Finally, the study lacked a control group of patients without gram-negative BSI to compare the risk of AMI or AIS between the two populations. However, the one-year risk of AMI/AIS following gram-negative BSI in the current study was substantially higher than hospital and population-based controls with relatively comparable age in a previous study in Denmark (4.1% and 1.8%, respectively) [9].

5. Conclusions

AMI and AIS occurred in up to one-quarter of patients in the first year following gram-negative BSI. Most cardiovascular and cerebrovascular events occurred early in the course of acute illness with three-quarters diagnosed within 12 days of BSI. The majority of these events represented myocardial oxygen supply-demand mismatch. However, more

than 10% of patients had either type 1 AMI or AIS within one year of BSI. The study results improve the understanding of the intricate relationship between acute infection, inflammation, and vascular disease. Identification of risk factors for AMI and AIS after BSI and estimation of the incidence by the number of risk factors assist in designing future randomized clinical trials to determine the most effective clinical interventions for prevention of cardiovascular and cerebrovascular ischemic complications. The significant increase in 1-year mortality in patients who develop type 1 AMI or AIS after BSI encourage prompt recognition, appropriate work up, and optimal inpatient and ambulatory management of these events to improve long-term survival.

Author contributions

Vinh-An D. Vo: Data curation; Funding acquisition; Investigation; Methodology; Visualization; Writing – original draft.

Mazen K. Khalil: Data curation; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing.

Majdi N. Al-Hasan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft.

Funding information

VDV received funding from the Student Opportunities for Academic Research program at the University of South Carolina School of Medicine Research Center for Transforming Health and the American Heart Association. The study had no other sources of funding.

Transparency declarations and potential conflicts of interest

VDV, MKK, and MNA: no conflicts.

VDV, MKK and MNA have full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the analysis.

Acknowledgements

The authors thank Prisma Health-Midlands Antimicrobial Stewardship and Support Team in South Carolina, USA for their help in facilitating the conduct of this study.

The preliminary results of this study were presented in part virtually at the American College of Cardiology annual meeting in March 28–30, 2020.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijchy.2021.100079>.

References

- [1] M. Goto, M.N. Al-Hasan, Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe, *Clin. Microbiol. Infect.* 19 (2013) 501–509.
- [2] R.L. Levine, J.R. LeClerc, J.E. Bailey, M.J. Monberg, S. Sarwat, Venous and arterial thromboembolism in severe sepsis, *Thromb. Haemost.* 99 (2008) 892–898.
- [3] V.F. Corrales-Medina, D.M. Musher, G.A. Wells, J.A. Chirinos, L. Chen, M.J. Fine, Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and associations with short term mortality, *Circulation* 125 (2012) 773–781.
- [4] V.F. Corrales-Medina, J. Serpa, A.M. Rueda, et al., Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes, *Medicine (Baltim.)* 88 (2009) 154–159.
- [5] D.M. Musher, A.M. Rueda, A.S. Kaka, S.M. Mapara, The association between pneumococcal pneumonia and acute cardiac events, *Clin. Infect. Dis.* 45 (2007) 158–165.
- [6] T.W. Perry, M.J. Pugh, G.W. Waterer, et al., Incidence of cardiovascular events after hospital admission for pneumonia, *Am. J. Med.* 124 (2011) 244–251.
- [7] A.J. Walkey, R.S. Wiener, J.M. Ghobrial, L.H. Curtis, E.J. Benjamin, Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis, *J. Am. Med. Assoc.* 306 (2011) 2248–2254.
- [8] E.S. Schut, M.J. Lucas, M.C. Brouwer, M.D. Vergouwen, A. van der Ende, D. van de Beek, Cerebral infarction in adults with bacterial meningitis, *Neurocrit. Care* 16 (2012) 421–427.
- [9] M. Dalager-Pedersen, M. Søgaard, H.C. Schönheyder, H. Nielsen, R.W. Thomsen, Risk for myocardial infarction and stroke after community-acquired bacteremia: a 20-year population-based cohort study, *Circulation* 129 (2014) 1387–1396.
- [10] T.C. Horan, M. Andrus, M.A. Dudeck, CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting, *Am. J. Infect. Contr.* 36 (2008) 309–332.
- [11] S.E. Battle, M.R. Augustine, C.M. Watson, P.B. Bookstaver, J. Kohn, W. Owens, L.M. Baddour, M.N. Al-Hasan, Derivation of a quick Pitt bacteremia score to predict mortality in patients with gram-negative bloodstream infection, *Infection* 47 (2019) 571–578.
- [12] M.N. Al-Hasan, L.M. Baddour, Resilience of the Pitt bacteremia score: three decades and counting, *Clin. Infect. Dis.* 70 (2019) 1834–1836.
- [13] K. Thygesen, J.S. Alpert, A.S. Jaffe, et al., Fourth universal definition of myocardial infarction (2018), *Circulation* 138 (2018) e618–e651.
- [14] R.L. Sacco, S.E. Kasner, J.P. Broderick, et al., An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 44 (2013) 2064–2089.
- [15] P.B. Bookstaver, E.B. Nimmich, T.J. Smith 3rd, J.A. Justo, J. Kohn, K.L. Hammer, et al., Cumulative effect of an antimicrobial stewardship and rapid diagnostic testing bundle on early streamlining of antimicrobial therapy in gram-negative bloodstream infections, *Antimicrob. Agents Chemother.* 61 (2017) e00189-17.
- [16] D.K. Arnett, R.S. Blumenthal, M.A. Albert, et al., ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines, *J. Am. Coll. Cardiol.* 74 (2019) 1376–1414, 2019.
- [17] S. Yende, J.A. Kellum, V.B. Talisa, et al., Long-term host immune response trajectories among hospitalized patients with sepsis, *JAMA Netw Open* 2 (2019), e198686.
- [18] A.J. Walkey, Preventing cardiovascular complications of acute infection: a missed opportunity? *Circulation* 129 (2014) 1375–1377.
- [19] J.F. McNamara, P.N.A. Harris, M.D. Chatfield, D.L. Paterson, Acute myocardial infarction and community-acquired *Staphylococcus aureus* bloodstream infection: an observational cohort study, *Clin. Infect. Dis.* (2020), <https://doi.org/10.1093/cid/ciaa1197> [Published online ahead of print].
- [20] E.A. Amsterdam, N.K. Wenger, R.G. Brindis, et al., AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, *J. Am. Coll. Cardiol.* 64 (2014) e139–e228, 2014.
- [21] J.C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, *N. Engl. J. Med.* 381 (2019) 2497–2505.