



openheart Characteristics of infective endocarditis in a cancer population

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ABSTRACT

Background Infective endocarditis (IE) is more common in patients with cancer as compared with the general population. Due to an immunocompromised state, the need for invasive procedures, hypercoagulability and the presence of indwelling catheters, patients with cancer are particularly predisposed to the development of IE.

Objectives Limited information exists about IE in patients with cancer. We aimed to evaluate the characteristics of patients with cancer and IE at our tertiary care centre, including a comparison of the microorganisms implicated and their association with mortality.

Methods A retrospective chart review of patients with cancer who had echocardiography for suspicion of endocarditis was conducted. A total of 56 patients with a confirmed diagnosis of cancer and endocarditis, based on the modified Duke criteria, were included in the study. Baseline demographics, risk factors for developing IE, echocardiography findings, microbiology and mortality data were analysed.

Results Following the findings of vegetations by echocardiography, the median survival time was 8.5 months. *Staphylococcus aureus* was the most common organism identified as causing endocarditis. The mitral and aortic valves were the most commonly involved sites of endocarditis. Patients with *S. aureus* endocarditis (SAE) had a significantly poorer survival when compared with patients without SAE ($p=0.0217$) over the 12-month period from diagnosis of endocarditis.

Conclusions Overall survival of patients with cancer and endocarditis is poor, with a worse outcome in patients with SAE.

INTRODUCTION

Endocarditis is a relatively uncommon but potentially fatal disease affecting 3–10 per 100 000 people, with a 1-year mortality rate of almost 30%.^{1–4} The demographics of patients infected with endocarditis have been changing. Until the 1980s, infective endocarditis (IE) was most prevalent in patients between 40 and 50 years of age and was mainly due to streptococcal organisms.^{1,5,6} IE is now most common in patients older than 70 years.⁷ Advances in therapy across many areas of medicine have led to the increasing use of indwelling devices such as prosthetic heart valves and long-term intravenous

Key questions

What is already known about this subject?

- ▶ Infective endocarditis (IE) occurs more commonly in patients with cancer as compared with the general population due to a myriad of factors including an immunocompromised state, the need for invasive procedures, hypercoagulability and the presence of indwelling catheters.

What does this study add?

- ▶ There is limited information about the characteristics of IE in patients with cancer. Our study shows that overall survival of patients with cancer and endocarditis is poor (median survival of 8.5 months), IE occurs most commonly on the mitral and aortic valves, and that *Staphylococcus aureus* endocarditis has worse outcome.

How might this impact on clinical practice?

- ▶ Our study illustrates that there must be a high index of suspicion and a thorough investigation in patients with cancer with suspected IE. Given the poor prognosis of IE in patients with cancer, it is of the utmost importance that these patients are efficiently diagnosed and treated.

lines, which in turn have led to increased prevalence of staphylococcal bacteraemia, a precursor to endocarditis.^{8–10} This has also led to the emergence of *Staphylococcus aureus* as the most common organism in IE in some series, with >25% of cases being due to this organism.⁴

Due to an immunocompromised state, the need for invasive procedures, hypercoagulability, the presence of indwelling catheters and pre-existing valvular heart disease (VHD) (figure 1), patients with cancer are particularly predisposed to the development of IE.^{11–13} In addition, patients with cancer often develop recurrent local or systemic infections, which increases the possibility of IE. IE is common in patients with cancer, with a prevalence of about 18% in one study.¹⁴ In another prospective, multicentre study, 5.6% of patients with endocarditis had cancer.¹⁵ IE also has grave consequences in patients with

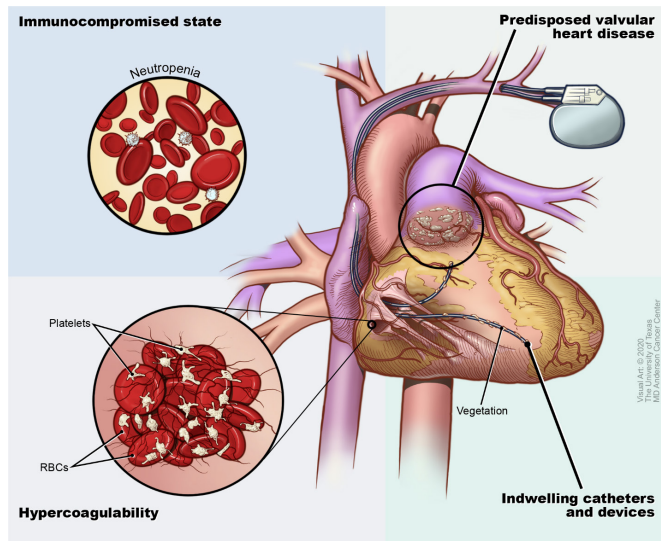


Figure 1 Conditions in patients with cancer that are conducive to infective endocarditis. RBC, red blood cells.

cancer, as it is associated not only with increased mortality as compared with non-cancer patients but also cessation of chemotherapy and denial of more aggressive interventions.^{2 14 15} Limited information exists about the associated risk of IE with different types of cancer and the microorganisms commonly involved in IE in patients with cancer. A better understanding of predisposing factors may lead to improved identification and management of IE in this at-risk population of patients. Herein, we aimed to evaluate the characteristics of patients with cancer and IE at our tertiary care centre, including a comparison of the microorganisms implicated and their association with 12-month survival following the diagnosis of endocarditis.

METHODS

Patient selection and data collection

We conducted a retrospective chart review of 1839 patients with cancer who had echocardiography for suspicion of endocarditis from May 2001 to December 2006 and from July 2015 to December 2018 at The University of Texas MD Anderson Cancer Center (figure 2). Records in between these dates were not accessible due to electronic health record transition made by our institution during the study period. Among these patients, we identified 56 with a confirmed diagnosis of cancer as well as endocarditis, based on the modified Duke criteria.¹⁶ Data were extracted from the patient charts and analysed to confirm the diagnosis of endocarditis as per the modified Duke criteria. Data collected included baseline demographics (including age at diagnosis of cancer and IE, sex and race/ethnicity), findings of echocardiography (including transthoracic and transoesophageal studies), type of cancer, use of chemotherapeutics, use of steroids and mortality data. We also analysed the traditional risk factors for IE, including VHD, a pacemaker, a central line, dental surgery, recent invasive procedures, recent

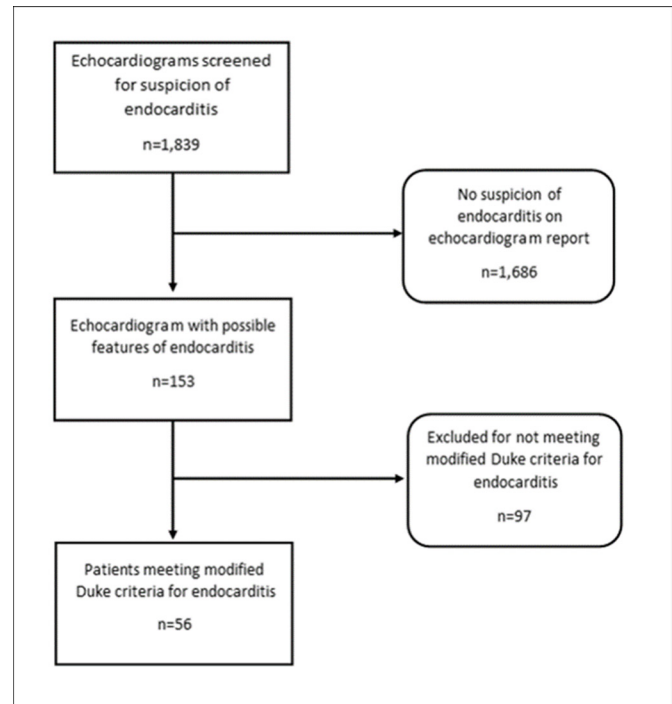


Figure 2 Flow diagram for patient inclusion.

surgery, diabetes mellitus, HIV, heart failure and chronic kidney disease. Lastly, we evaluated the presence of modified Duke major and minor criteria for endocarditis, baseline serum chemistry data, septic emboli based on imaging studies, as well as blood culture results.

Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of this study as it was done retrospectively.

Microbiology

The blood cultures were processed by the Microbiology Laboratory at MD Anderson Cancer Center at the time of IE diagnosis. After the samples were processed, standard techniques were employed to determine which pathogen was responsible, as well as antimicrobial sensitivities.^{17 18}

Definitions

The modified Duke criteria were used to identify patients with endocarditis.^{16 19} Blood cultures that grew *S. aureus* and other typical organisms associated with endocarditis were considered clinically significant as the likely causative organism for IE. Patients with platelet counts less than 50 000/ μ L were considered thrombocytopenic. Neutropenia was defined to be absolute neutrophil count (ANC) of less than 500 cells/ μ L. Active cancer was defined as any cancer that was diagnosed or being managed by cancer therapeutics at the time of diagnosis of IE. Culture-negative IE was defined as endocarditis without microbiological aetiology following inoculation of samples in a standard blood-culture system with negative cultures after 7 days of incubation and subculturing. Predisposing valvular heart disease (VHD) was defined

as patients at risk of VHD (stage A) or with progressive VHD (stage B) to severe asymptomatic (stage C) and symptomatic (stage D) VHD as per the American College of Cardiology/American Heart Association (AHA) societal guidelines, including patients with patients history of rheumatic heart disease, mitral valve stenosis, mitral regurgitation, bicuspid aortic valve, aortic stenosis, aortic regurgitation, prosthetic heart valve, history of IE, history of congenital heart disease or abnormal thickening of heart valves with greater than mild regurgitation.

Statistical analysis

Patient demographic and other characteristics were summarised by *S. aureus* status (presence or absence) using descriptive statistics. Survival time over 12 months (12-month survival) from diagnosis of endocarditis was calculated from first transthoracic or transoesophageal study to death or last follow-up occurred within 12 months. For those who survived longer than 12 months were censored at 12 months. Univariate and multivariate Cox proportional hazards regression models were used to identify factors associated with 12-month survival. Multivariate Cox models included factors with a significant p value based on univariate Cox models. The proportional hazards assumption was checked by the interaction between each covariate and the logarithm of survival time. When the proportional hazards assumption was violated, the time-covariate interaction was included in the multivariate model. A $p < 0.05$ indicated statistical significance. SAS V.9.4 software (SAS Institute) was used for statistical analysis.

RESULTS

Patient characteristics

We included 56 patients with a concurrent diagnosis of cancer and IE (table 1). The mean patient age was 54 years at diagnosis of cancer and 60 years at diagnosis of endocarditis. Most patients were white (45%) and male (55%). Thirty-six (64%) had active cancer. More than half of the patients had an underlying solid cancer (68%), while 18 patients (32%) had a haematological malignancy. The most common comorbidities among the cohort were diabetes (77%), chronic kidney disease (18%), and congestive heart failure (13%). Thirty-nine patients (70%) had culture-positive endocarditis and 17 (30%) had culture-negative endocarditis. *S. aureus* was the most common organism isolated in this cohort (20 patients), while 10 patients had *Enterococcus* species, 7 had *Streptococcus viridans*, 1 had a HACEK organism (*Klebsiella*) and 1 had *Streptococcus gallolyticus*. Among patients with *S. aureus* endocarditis (SAE), 11 patients were infected with methicillin-resistant *S. aureus* (MRSA). The most commonly involved site was the mitral valve, in 23 (41%) patients, followed by the aortic valve in 20 (36%) patients and the tricuspid valve in 9 (16%) patients. Two patients (4%) had pacemaker lead-associated endocarditis. Of the 23 patients with mitral valve endocarditis, seven (30%)

Table 1 Patient characteristics

Patient characteristics (n=56)	Mean±SD or No (%)
Age at cancer diagnosis (years)	53.74±16.18
Age at endocarditis diagnosis (years)	59.54±15.32
Sex	
Male	31 (55.4%)
Female	25 (44.6%)
Race/ethnicity	
Non-black (white/other)	36 (64.3%)
Black	20 (35.7%)
Diabetes mellitus	43 (76.8%)
Congestive heart failure	7 (12.5%)
Chronic kidney disease	10 (17.9%)
Type of cancer	
Haematologic cancer	18 (32.1%)
Solid cancer	38 (67.9%)
Cancer status	
Cancer in remission	20 (35.7%)
Active cancer	36 (64.3%)
Chemotherapy treatment	
Not active	22 (39.3%)
Active	34 (60.7%)
Pacemaker	4 (7.1%)
Catheter/line presence	20 (35.7%)
Endocarditis location	
Mitral valve	23 (41.1%)
Aortic valve	20 (35.7%)
Tricuspid valve	9 (16.1%)
Pacemaker lead	2 (3.6%)
Superior Vena Cava	2 (3.6%)
Vegetation >10 mm	5 (8.9%)
Systemic emboli	11 (19.6%)
Blood microorganism	
<i>Streptococcus viridans</i>	7 (12.5%)
<i>Streptococcus gallolyticus</i>	1 (1.8%)
<i>Klebsiella</i>	1 (1.8%)
<i>Staphylococcus aureus</i>	20 (35.7%)
<i>Enterococcus</i>	10 (17.9%)
Negative culture	17 (30.4%)

had evidence of systemic embolisation, and four patients had vegetations ≥ 10 mm (17%). Three of four patients with vegetations ≥ 10 mm had systemic emboli. Of the 20 patients with aortic valve endocarditis, four (20%) had systemic emboli, one had large vegetations ≥ 10 mm and one had an abscess. Of the nine patients with tricuspid valve endocarditis, two (22%) had evidence of pulmonary infarcts, suggesting small pulmonary emboli. Twenty of the 56 patients (36%) had a central venous catheter at the time of IE diagnosis. Twenty-one patients had an

indwelling foley catheter (38%), with five patients having a nephrostomy tube (9%) and one patient having a urostomy with an ileal conduit (2%).

Table 2 compares the characteristics of patients with SAE and those without *S. aureus*. Patients with SAE had a significantly higher white cell count (WCC) (14.68 K/ μ L vs 11.29 K/ μ L in those without SAE; $p=0.044$) and had a significantly lower percentage of predisposing VHD (0% vs 22% in those without SAE; $p=0.04$). Otherwise, there were no significant differences between the two groups in age, sex, race/ethnicity, cancer status, comorbidities, indwelling catheter or location of IE involvement.

IE outcomes

After diagnosis of IE by echocardiography, the median survival time for our cohort was 8.5 months. In univariate analysis, black race was associated with significantly poorer 12-month survival when compared with all other races/ethnicities (HR 2.320; 95% CI 1.114 to 4.833; $p=0.0246$). Over the 12 months after diagnosis of IE, patients with active cancer had significantly poorer survival when compared with patients in remission (HR 2.497; 95% CI 1.062 to 5.868; $p=0.0358$).

Furthermore, increasing WCC, blood urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), WCC <4000 cells/ μ L and $>11\ 000$ cells/ μ L, ALT ≥ 41 U/L, AST ≥ 40 U/L and bilirubin ≥ 1.2 mg/dL (above-normal institutional laboratory values) were significantly associated with increased risk of death within 12 months (table 3). A total of seven patients had cardiac valve surgery for endocarditis; six of them had SAE. Surgical treatment was not significantly associated with increased risk of death (HR 0.671; 95% CI 0.086 to 5.242; $p=0.7036$).

Although all patients were followed by an infectious diseases specialist and treated accordingly to AHA guidelines,²⁰ patients with SAE had significantly worse 12-month survival when compared with those without SAE (HR 2.305; 95% CI 1.107 to 4.802; $p=0.0257$). The use of steroids was also associated with an increased risk of death within 12 months (HR 8.151; 95% CI 3.059 to 21.719; $p<0.0001$).

Multivariate Cox regression analyses revealed that the presence of SAE (HR 2.52; 95% CI 1.193 to 5.323; $p=0.0015$) and active cancer status (HR 2.967; 95% CI 1.253 to 7.025; $p=0.013$) and black race (HR 2.209; 95% CI 1.038 to 4.701, $p=0.0396$) remained significant risk factors for 12-month survival (table 4, model 1). The proportional hazards assumption was violated for SAE. Therefore, HR for SAE was interpreted as the weighted average over follow-up in the model without time-covariate interaction (table 4, model 1). In a second model (table 4, model 2), we considered time and SAE interaction (allowing two different HRs for two-time intervals, ≤ 4 months and >4 months of follow-up). Presence of SAE was not significantly associated with overall survival during the first 4 months but was significantly associated with overall survival after 4 months (HR

17.316; 95% CI 1.993 to 150.44; $p=0.0097$). Active cancer status (HR 2.892; 95% CI 1.217 to 6.875; $p=0.0162$) and black race (HR 2.140; 95% CI 1.008 to 4.453; $p=0.0476$) was significantly associated with 12-month survival. The Kaplan-Meier survival curve comparing patients with SAE versus non-SAE also reflects significantly poorer survival with SAE ($p=0.0217$) over the 12-month period from diagnosis of endocarditis (figure 3).

DISCUSSION

Patients with cancer with IE have poor prognosis,¹⁵ and among such patients, those with SAE may in fact have the worst mortality after IE diagnosis. Our study showed a statistically significant association between mortality and SAE compared with non-SAE in patients with cancer. In fact, after 4 months patients with SAE were 20 times more likely to die compared with non-SAE patients.

Few studies have focused on IE in patients with cancer, and there is a relative paucity of data about the most prominent types of cancer associated with IE, which valves/sites are involved, and rates due to venous lines or cardiac devices. One study of 161 patients with cancer and IE showed that the majority of patients with solid tumours had intestinal cancers (42%) and the majority of those with haematological malignancies had lymphoma (42%).¹⁵ Studies have also showed that the vast majority of vegetations involve the mitral and aortic valves in patients with and without cancer.^{3 15} The source of the IE was documented to be associated with a central venous catheter in 23% of patients in a previous study of patients with cancer and IE, and up to 10% of the vegetations were associated with pacemaker leads.¹⁵ Our study showed that the mitral valve was most commonly involved, followed closely by the aortic valve, and 4% of patients had pacemaker-lead endocarditis.

The typical causative organism for non-cancer patients with IE has been found to be *S. aureus*.^{3 21 22} Some studies report *Streptococcus* spp most commonly, followed by *S. aureus*.^{15 23} One study of patients with cancer with IE showed equal prevalence of *S. aureus* and *Streptococcus* spp, with each comprising 23.6% of cases.¹⁵ Others have shown *S. aureus* to be the most common causative organism for IE in patients with cancer.²⁴ Our study found that 20 (51%) of the 39 patients with culture-positive endocarditis had presence of *S. aureus*; this was 36% of all the patients (20 of 56).

SAE has been associated with a significant increase in in-hospital death in non-cancer patients and significantly increased 30-day mortality in surgical patients.^{3 22 23} Fernández-Cruz *et al* showed SAE to be a risk factor for 30-day mortality in patients with cancer with IE.¹⁵ Our study builds on this association of SAE and poor outcomes by showing significantly worse 12-month survival when compared with culture-negative IE and presence of other organisms. *S. aureus* is more problematic due to multiple factors, including its ability to adhere to and multiply on

Table 2 Comparison of patient characteristics with and without *Staphylococcus aureus* endocarditis

Variable	No <i>S. aureus</i> (n=36)	<i>S. aureus</i> (n=20)	P value
Patient/diagnosis data			
Age at cancer diagnosis (years)	52.9±16.82	55.25±15.27	0.8844
Age at endocarditis diagnosis (years)	60.08±15.59	58.57±15.16	0.4069
Time from cancer diagnosis to endocarditis diagnosis (months)	86.6±146.12	40.31±51.54	0.5158
Sex			0.5478
Male	21 (58.3%)	10 (50%)	
Female	15 (41.7%)	10 (50%)	
Race/ethnicity			0.61
Non-black (white/other)	24 (66.7%)	12 (60%)	
Black	12 (33.3%)	8 (40%)	
Comorbidities			
Diabetes mellitus	10 (27.8%)	3 (15%)	0.3392
HIV	0 (0%)	1 (5)	0.3455
Congestive heart failure	5 (13.9%)	2 (10%)	1
Chronic kidney disease	6 (16.7%)	4 (20%)	0.7234
Oncologic data			
Type of cancer			0.798
Haematological cancer	12 (33.3%)	6 (30%)	
Solid cancer	24 (66.7%)	14 (70%)	
Cancer status			0.0963
Cancer in remission	10 (27.8%)	10 (50%)	
Active cancer	26 (72.2%)	10 (50%)	
Active chemotherapy treatment	22 (61.1%)	12 (60%)	0.935
Steroid treatment	3 (8.3%)	3 (15%)	0.4055
Invasive procedures/endocarditis risk factors			
Preexisting valvular heart disease	8 (22.2%)	0 (0%)	0.0405
Pacemaker presence	3 (8.3%)	1 (5%)	1
Bone marrow treatment/procedure	8 (22.2%)	2 (10%)	0.3036
Dental extraction	0 (0%)	2 (10%)	0.1234
Cystoscopy	0 (0%)	2 (10%)	0.1234
Upper GI endoscopy	1 (2.8%)	2 (10%)	0.2879
Lower GI endoscopy	1 (2.8%)	1 (5%)	1
Indwelling catheter/line	10 (27.8%)	10 (50%)	0.0742
Lab values			
Haemoglobin (g/dL)	9.96±2	10.24±2.04	0.6772
White blood cell count (K/μL)	11.29±13.68	14.68±11	0.0442
Platelets (K/μL)	163.12±120.13	205.70±141.10	0.2865
Blood urea nitrogen (mg/dL)	26.47±19.26	25.85±18.63	0.8019
Creatinine (mg/dL)	1.43±1.4	1.25±0.74	0.7506
Alanine aminotransferase (U/L)	59.72±111.25	47.3±45.82	0.5156
Aspartate aminotransferase (U/L)	60.63±85.59	44.05±31.28	0.8359
Total bilirubin (mg/dL)	0.97±1.15	1.48±3.09	0.374
Site of involvement			
Aortic valve	13 (36.1%)	7 (35%)	0.9337
Mitral valve	17 (47.2%)	6 (30%)	0.2094

Continued

Table 2 Continued

Variable	No <i>S. aureus</i> (n=36)	<i>S. aureus</i> (n=20)	P value
Tricuspid valve	6 (16.7%)	3 (15%)	1
Pacemaker lead	1 (2.8%)	1 (5%)	1

GI, gastrointestinal.

cardiac cells, form biofilms preventing eradication and rapidly develop resistance.^{22 25 26}

Compared with the general population, patients with cancer are more likely to die from IE, but the mechanism is not completely known.²⁷ Patients with cancer are more frequently neutropaenic, may be immunocompromised because of chemotherapy or the malignancy itself, and frequently have indwelling catheters that may serve as a source of infection.²⁸ Specifically, cancer may predispose to IE by facilitating not only bacterial translocation into the bloodstream but also localisation to the endocardium through existence of non-bacterial thrombotic vegetations that may be preexisting due to the hypercoagulable state associated with cancer.^{27 29} Among patients with solid malignancies, patients with intestinal tumours have been found to be most likely to develop IE with *Streptococcus gallolyticus* (formerly known as *S. bovis*).¹⁵ This may be due to the tumour facilitating intestinal bacterial

translocation to the bloodstream. In haematological malignancies, lymphoma has been found to be the most prevalent cancer associated with IE.¹⁵ Particularly, *S. aureus* IE has been associated with cutaneous portals of entry.³⁰ This, combined with the frequency of indwelling catheters, may be the reason for patients with cancer with IE most frequently grow *S. aureus*.

Thirty per cent of the patients in our study had blood culture-negative endocarditis. Our group previously reported a 42% frequency of culture-negative endocarditis in a retrospective series of patients with cancer.⁶ This culture-negative rate may be due to a variety of factors including early administration of antibiotics,³ non-infectious aetiologies of the vegetations, and lack of use of PCR techniques to identify organisms.^{31 32} This yield may be increased by using reverse transcription-PCR in addition to culture, valvular biopsies, serological analysis and evaluation for non-infectious causes, including autoimmune and thrombotic.^{31 32} Some of these patients may have had non-bacterial thrombotic endocarditis, which can be found in patients with cancer; previous studies have shown that this form of endocarditis can be associated with an embolic phenomenon in solid-tumour cancers such as lung, pancreatic and gastric cancer.^{33 34} Although culture negative patients in our study were classified as definitive IE by the modified Duke's Criteria, its diagnostic specificity is estimated to only be 74% based on the results of a recent cohort study.³⁵ This is further complicated by the fact that no single laboratory, imaging, nor clinical criteria can definitively diagnose marantic endocarditis. Therefore, distinguishing true culture negative IE from marantic endocarditis is challenging and often requires a high degree of clinical suspicion, with definitive distinction often made during autopsy.³⁶ The use of fluoro-18-fluorodeoxyglucose positron emission tomography/CT and radiolabeled WCC scintigraphy has been explored to identify underlying infectious valvular foci, although the diagnostic utility of these imaging techniques appears to be greatest with suspected prosthetic valve and cardiac implantable electronic device (CIED) endocarditis.³⁷

Endocarditis frequently is believed to originate from cutaneous portals of entry into the bloodstream.³⁰ The most common healthcare-associated causes of cutaneous portals are vascular access and implantable cardiac devices and prosthetic valves.^{3 30} For example, within the first year of valve replacement, infections with coagulase negative staphylococci, *S. aureus*, HACEK organisms and fungi are much more common, whereas *Streptococcus* spp

Table 3 Univariate Cox regression analysis: variables that were significantly associated with survival within 12 months

Variable	Level	HR (95% CI)	P value
WCC (K/ μ L)	In 1-unit increase	1.052 (1.026 to 1.080)	<0.0001
BUN (mg/dL)	In 1-unit increase	1.020 (1.002 to 1.039)	0.0284
ALT (U/L)	In 1-unit increase	1.004 (1.001 to 1.007)	0.0035
AST (U/L)	In 1-unit increase	1.006 (1.002 to 1.010)	0.0015
Race/ethnicity	Black vs non-black	2.320 (1.114 to 4.833)	0.0246
Cancer status	Active vs remission	2.497 (1.062 to 5.868)	0.0358
Organism	<i>S. aureus</i> vs no <i>S. aureus</i>	2.305 (1.107 to 4.802)	0.0257
Steroid usage	Yes vs No	8.151 (3.059 to 21.719)	<0.0001
WCC (K/ μ L)	<4 vs 4–11	3.845 (1.233 to 11.990)	0.0203
	>11 vs 4–11	6.723 (2.783 to 16.241)	<0.0001
ALT (U/L)	\geq 41 vs <41	4.032 (1.836 to 8.854)	0.0005
AST (U/L)	\geq 40 vs <40	2.276 (1.071 to 4.836)	0.0325
Total bilirubin (mg/dL)	\geq 1.2 vs <1.2	3.014 (1.285 to 7.070)	0.0112

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; WCC, white cell count.

Table 4 Multivariate Cox regression model

Model 1, without time-covariate interaction				
Model 1				
Covariate	Level	HR (95% CI)	P value	
Organism	No <i>Staphylococcus aureus</i>	1		
	<i>S. aureus</i>	2.520 (1.193 to 5.323)	0.0154	
Cancer status	Remission	1		
	Active	2.967 (1.253 to 7.025)	0.0134	
Race/ethnicity	Non-black	1		
	Black	2.209 (1.038 to 4.701)	0.0396	
Model 2, with time-covariate interaction				
Model 2				
Covariate	Time interval	Level	HR (95% CI)	P value
Cancer status		Remission	1	
		Active	2.892 (1.217 to 6.875)	0.0162
Race/ethnicity		Non-black	1	
		Black	2.140 (1.008 to 4.543)	0.0476
Organism	≤4 months	No <i>S. aureus</i>	1	
		<i>S. aureus</i>	1.648 (0.713 to 3.810)	0.2425
	>4 months	No <i>S. aureus</i>	1	
		<i>S. aureus</i>	17.316 (1.993 to 150.440)	0.0097

and *Enterococcus* infections occur less frequently.³⁸ This microbiology reflects the nosocomial nature of prosthetic valve endocarditis acquired perioperatively. Of note, however, prosthetic valve endocarditis after the first year of valve replacement tends to be community acquired, as reflected by increased incidence of *Streptococcus* spp and *Enterococcus* infections.³⁸ Antibiotic prophylaxis for staphylococci prior to implantation of a CIED is a class I recommendation by the AHA and was shown to be beneficial in a randomised clinical trial.^{39 40} However, antibiotic prophylaxis in minor invasive procedures

has been challenged and remains under debate.²⁶ It has been suggested that antibiotic prophylaxis be used in invasive procedures for those with congenital heart defects because of increased risk of infection.²³ Perhaps prophylaxis with antibiotics should be considered before procedures in patients with cancer due to the myriad factors discussed above. However, both the Society of Interventional Radiology and American Society of Clinical Oncology (ASCO) recommend against routine antibiotic prophylaxis in the general cancer population in the setting of placement of a totally implantable vascular access device (ie, a chemotherapy port).^{41 42} Instead, they recommend ensuring a clean procedure is done with the use of central venous catheter clinical care bundles. These guidelines were based on prior surgical literature and retrospective studies demonstrating lack of clinical benefit with routine antibiotic prophylaxis and low baseline rate of device-associated infections. Further supporting evidence came from two randomised controlled studies that demonstrated no difference in the rate of device-associated infections between antibiotic-prophylaxis and placebo groups. However, these studies were limited by their small sample sizes, low incidence of infectious complications, exclusion of liquid tumours in one study, and exclusion of patients with neutropaenia in both.^{43 44} A meta-analysis of these studies combined with two prior retrospective studies recapitulated the lack of benefit of antibiotic prophylaxis.⁴⁵⁻⁴⁷ Interestingly, a recent clinical trial found that universal MRSA decolonisation in intensive care unit patients resulted in a

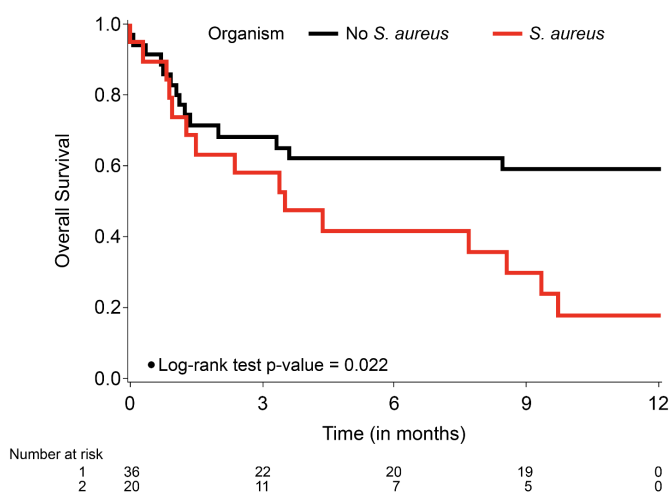


Figure 3 Kaplan-Meier survival curves by presence of *Staphylococcus aureus* endocarditis. The curves were censored at 12 months after endocarditis diagnosis.

greater reduction in all-cause bloodstream infections and MRSA clinical isolates compared with targeted decolonisation (MRSA screening followed by decolonisation) and isolation measures.⁴⁸ However, although targeted MRSA decolonisation has been studied extensively in surgical populations, concerns for cost-effectiveness and the development of multidrug-resistant MRSA remain with widespread adoption of this approach.⁴⁹

There is conflicting evidence regarding the risk of device-related infectious complications and neutropaenia at the time of device placement, but a 2019 retrospective single-centre cohort study addressed this question and found a significantly greater rate of infection-related port removal within 30 days of device placement in neutropaenic patients.⁵⁰ However, the study was limited by its retrospective nature, a higher rate of liquid tumours in the neutropaenic cohort and lack of documentation of pre-procedure antibiotic prophylaxis. There are currently no specific recommendations by the Infectious Diseases Society of America or ASCO on the use of antibiotic prophylaxis in the neutropaenic and liquid tumour patient populations. Future studies are needed to help further assess which patients, if any, may benefit from antibiotic prophylaxis prior to invasive procedures.

CONCLUSIONS

Among patients with cancer treated at our tertiary care centre, the development of endocarditis portended poor survival, and the presence of SAE or active cancer further increased mortality. This study further contributes to the limited knowledge about endocarditis, particularly SAE, in the cancer population. Given these findings, we emphasise the need for further research in prevention and treatment of this life-altering complication.

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Correction notice Since the publication of this article, initials have been added to the following author names: Saamir A Hassan and Syed W Yusuf.

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REFERENCES

- Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet* 2016;387:882–93.
- García-Albéniz X, Hsu J, Lipsitch M, *et al*. Infective endocarditis and cancer in the elderly. *Eur J Epidemiol* 2016;31:41–9.
- Murdoch DR, Corey GR, Hoen B, *et al*. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International collaboration on Endocarditis-Pro prospective cohort study. *Arch Intern Med* 2009;169:463–73.
- Selton-Suty C, Célard M, Le Moing V, *et al*. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis* 2012;54:1230–9.
- Finland M, Barnes MW. Changing etiology of bacterial endocarditis in the antibacterial era. experiences at Boston City Hospital 1933–1965. *Ann Intern Med* 1970;72:341–8.
- Yusuf SW, Ali SS, Swafford J, *et al*. Culture-Positive and culture-negative endocarditis in patients with cancer: a retrospective observational study, 1994–2004. *Medicine* 2006;85:86–94.
- Correa de Sa DD, Tleyjeh IM, Anavekar NS, *et al*. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota. *Mayo Clin Proc* 2010;85:422–6.
- Fowler VG, Miro JM, Hoen B, *et al*. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA* 2005;293:3012–21.
- Iung B, Baron G, Butchart EG, *et al*. A prospective survey of patients with valvular heart disease in Europe: the Euro heart survey on valvular heart disease. *Eur Heart J* 2003;24:1231–43.
- Pittet D, Wenzel RP. Nosocomial bloodstream infections. secular trends in rates, mortality, and contribution to total hospital deaths. *Arch Intern Med* 1995;155:1177–84.
- Fowler VG, Justice A, Moore C, *et al*. Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2005;40:695–703.
- Janszky I, Gémes K, Ahnve S, *et al*. Invasive procedures associated with the development of infective endocarditis. *J Am Coll Cardiol* 2018;71:2744–52.
- Wisplinghoff H, Bischoff T, Tallent SM, *et al*. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;39:309–17.
- Kim K, Kim D, Lee S-E, *et al*. Infective Endocarditis in Cancer Patients - Causative Organisms, Predisposing Procedures, and Prognosis Differ From Infective Endocarditis in Non-Cancer Patients. *Circ J* 2019;83:452–60.
- Fernández-Cruz A, Muñoz P, Sandoval C, *et al*. Infective endocarditis in patients with cancer: a consequence of invasive procedures or a harbinger of neoplasm?: a prospective, multicenter cohort. *Medicine* 2017;96:e7913.
- Li JS, Sexton DJ, Mick N, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–8.
- Safdar A, Chaturvedi V, Koll BS, *et al*. Prospective, multicenter surveillance study of *Candida glabrata*: fluconazole and itraconazole susceptibility profiles in bloodstream, invasive, and colonizing strains and differences between isolates from three urban teaching hospitals in New York City (*Candida* susceptibility trends study, 1998 to 1999). *Antimicrob Agents Chemother* 2002;46:3268–72.
- Tarrand JJ, Guillot C, Wenglar M, *et al*. Clinical comparison of the resin-containing BACTEC 26 plus and the isolator 10 blood culturing systems. *J Clin Microbiol* 1991;29:2245–9.
- Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke endocarditis service. *Am J Med* 1994;96:200–9.
- Baddour LM, Wilson WR, Bayer AS, *et al*. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. *Circulation* 2015;132:1435–86.
- Hoerr V, Franz M, Pletz MW, *et al*. *S. aureus* endocarditis: clinical aspects and experimental approaches. *Int J Med Microbiol* 2018;308:640–52.
- Williams JB, Shah AA, Zhang S, *et al*. Impact of microbiological organism type on surgically managed endocarditis. *Ann Thorac Surg* 2019;108:1325–9.

- 23 Cahill TJ, Jewell PD, Denne L, *et al.* Contemporary epidemiology of infective endocarditis in patients with congenital heart disease: a UK prospective study. *Am Heart J* 2019;215:70–7.
- 24 Mesa Del Castillo-Payá C, Rodríguez-Esteban M, Quijada-Fumero A, *et al.* Infective endocarditis in patients with oncological diseases. *Enferm Infecc Microbiol Clin* 2018;36:72–7.
- 25 Bhattacharya M, Wozniak DJ, Stoodley P, *et al.* Prevention and treatment of Staphylococcus aureus biofilms. *Expert Rev Anti Infect Ther* 2015;13:1499–516.
- 26 Saeed K, Bal AM, Gould IM, *et al.* An update on Staphylococcus aureus infective endocarditis from the International Society of antimicrobial chemotherapy (ISAC). *Int J Antimicrob Agents* 2019;53:9–15.
- 27 Sun L-M, Wu J-N, Lin C-L, *et al.* Infective endocarditis and cancer risk: a population-based cohort study. *Medicine* 2016;95:e3198.
- 28 Nørgaard M, Larsson H, Pedersen G, *et al.* Risk of bacteraemia and mortality in patients with haematological malignancies. *Clin Microbiol Infect* 2006;12:217–23.
- 29 Decousus H, Moulin N, Quenet S, *et al.* Thrombophilia and risk of venous thrombosis in patients with cancer. *Thromb Res* 2007;120 Suppl 2:S51–61.
- 30 Delahaye F, M'Hammedi A, Guerpillon B, *et al.* Systematic search for present and potential portals of entry for infective endocarditis. *J Am Coll Cardiol* 2016;67:151–8.
- 31 Fournier P-E, Gouriet F, Casalta J-P, *et al.* Blood culture-negative endocarditis: improving the diagnostic yield using new diagnostic tools. *Medicine* 2017;96:e8392.
- 32 Fournier P-E, Thuny F, Richet H, *et al.* Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clin Infect Dis* 2010;51:131–40.
- 33 Asopa S, Patel A, Khan OA, *et al.* Non-Bacterial thrombotic endocarditis. *Eur J Cardiothorac Surg* 2007;32:696–701.
- 34 el-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. *Oncologist* 2007;12:518–23.
- 35 Shrestha N, Shakya S, Hussain S, *et al.* Sensitivity and specificity of Duke criteria for diagnosis of definite infective endocarditis: a cohort study. *Open Forum Infect Dis* 2017;4:S550–1.
- 36 Bussani R, DE-Giorgio F, Pesel G, *et al.* Overview and comparison of infectious endocarditis and non-infectious endocarditis: a review of 814 autopsic cases. *In Vivo* 2019;33:1565–72.
- 37 Galea N, Bandera F, Lauri C, *et al.* Multimodality imaging in the diagnostic work-up of endocarditis and cardiac implantable electronic device (CIED) infection. *J Clin Med* 2020;9:2237.
- 38 Piper C, Körfer R, Horstkotte D. Prosthetic valve endocarditis. *Heart* 2001;85:590–3.
- 39 Baddour LM, Epstein AE, Erickson CC, *et al.* Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American heart association. *Circulation* 2010;121:458–77.
- 40 de Oliveira JC, Martinelli M, Nishioka Silvana Angelina D'Orio, *et al.* Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;2:29–34.
- 41 O'Grady NP, Alexander M, Burns LA, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39:S1–34.
- 42 Schiffer CA, Mangu PB, Wade JC, *et al.* Central venous catheter care for the patient with cancer: American Society of clinical oncology clinical practice guideline. *J Clin Oncol* 2013;31:1357–70.
- 43 Di Carlo I, Toro A, Pulvirenti E, *et al.* Could antibiotic prophylaxis be not necessary to implant totally implantable venous access devices? randomized prospective study. *Surg Oncol* 2011;20:20–5.
- 44 Karanlik H, Kurul S, Saip P, *et al.* The role of antibiotic prophylaxis in totally implantable venous access device placement: results of a single-center prospective randomized trial. *Am J Surg* 2011;202:10–15.
- 45 Covey AM, Toro-Pape FW, Thornton RH, *et al.* Totally implantable venous access device placement by interventional radiologists: are prophylactic antibiotics necessary? *J Vasc Interv Radiol* 2012;23:358–62.
- 46 Scaife CL, Gross ME, Mone MC, *et al.* Antibiotic prophylaxis in the placement of totally implanted central venous access ports. *Am J Surg* 2010;200:719–23.
- 47 Johnson E, Babb J, Sridhar D. Routine antibiotic prophylaxis for totally implantable venous access device placement: meta-analysis of 2,154 patients. *J Vasc Interv Radiol* 2016;27:339–43.
- 48 Huang SS, Septimus E, Kleinman K, *et al.* Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255–65.
- 49 Septimus EJ, Schweizer ML. Decolonization in prevention of health care-associated infections. *Clin Microbiol Rev* 2016;29:201–22.
- 50 Perez AW, Watchmaker JM, Brown DB, *et al.* Association between perioperative neutropenia and early infection-related chest Port removal. *Radiology* 2019;291:513–8.