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ORIGINAL ARTICLE

Retrospective Cohort Study

Echocardiographic predictors and associated outcomes of multiple vegetations in infective endocarditis: A pilot study

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Abstract

BACKGROUND

Infective endocarditis (IE) is a life-threatening infection with an annual mortality of 40%. Embolic events reported in up to 80% of patients. Vegetations of > 10 mm size are associated with increased embolic events and poor prognosis. There is a paucity of literature on the association of multiple vegetations with outcome.

AIM

To study the echocardiographic (ECHO) features and outcomes associated with the presence of multiple vegetations.

METHODS

In this retrospective, single-center, cohort study patients diagnosed with IE were recruited from June 2017 to June 2019. A total of 84 patients were diagnosed to have IE, of whom 67 with vegetation were identified. Baseline demographic, clinical, laboratory, and ECHO parameters were reviewed. Outcomes that were studied included recurrent admission, embolic phenomenon, and mortality.

RESULTS

Twenty-three (34%) patients were noted to have multiple vegetations, 13 (56.5%) were male and 10 (43.5%) were female. The mean age of these patients was 50.

Eight (35%) had a prior episode of IE. ECHO features of moderate to severe valvular regurgitation [odds ratio (OR) = 4], presence of pacemaker lead (OR = 4.8), impaired left ventricle (LV) relaxation (OR = 4), and elevated pulmonary artery systolic pressure (PASP) (OR = 2.2) are associated with higher odds of multiple vegetations. Of these moderate to severe valvular regurgitation (P = 0.028), pacemaker lead (P = 0.039) and impaired relaxation (P = 0.028) were statistically significant. These patients were noted to have an increased association of recurrent admissions (OR = 3.6), recurrent bacteremia (OR = 2.4), embolic phenomenon (OR = 2.5), intensive care unit stay (OR = 2.8), hypotension (OR = 2.1), surgical intervention (OR = 2.8) and device removal (OR = 4.8). Of this device removal (P = 0.039) and recurrent admissions (P = 0.017) were statistically significant.

CONCLUSION

This study highlights the associations of ECHO predictors and outcomes in patients with IE having multiple vegetations. ECHO features of moderate to severe regurgitation, presence of pacemaker lead, impaired LV relaxation, and elevated PASP and outcomes including recurrent admissions and device removal were found to be associated with multiple vegetations.

Key Words: Endocarditis; Echocardiography; Vegetations; Predictors; Outcome

Core Tip: Embolic events occur in up to 80% of patients with infective endocarditis (IE). Vegetations of > 10 mm in size are associated with increased embolic events and poor prognosis. In this retrospective cohort study, patients diagnosed with IE were recruited over 2 years. 34% of these had multiple vegetations. Echocardiographic features of moderate to severe regurgitation, presence of pacemaker lead, impaired left ventricle relaxation, and elevated pulmonary artery systolic pressure were associated with higher odds of multiple vegetation and outcomes including recurrent admissions and device removal were found to be associated with multiple vegetations.

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INTRODUCTION

Infective endocarditis (IE) is a life-threatening infection with an annual mortality of 40%. The complications of this disease are protean, with embolic events reported in up to 80% of patients[1]. There are several epidemiological, clinical, microbiological risk factors that contribute to adverse outcomes in patients with IE. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are the most effective diagnostic tools for IE. Even though used for diagnosis, the role of echocardiography in predicting outcome in these patients is still limited. Large vegetation size especially vegetations of > 10 mm size has been shown to be associated with increased embolic events and poor prognosis [2]. In patients with *Staphylococcus aureus* IE, ejection fraction of less than 40%, and intra-cardiac abscess has been shown to predict in-hospital mortality and perforation of valve[3-5]. Intra-cardiac abscess has been shown to independently predict 1-year mortality. There is a paucity of literature on the association of multiple vegetations with the outcome. The main objective of our study was to study the echocardiographic (ECHO) features associated with the presence of multiple vegetations and the implications of the presence of multiple vegetations on the outcome.

MATERIALS AND METHODS

In this retrospective, single center, cohort study patients diagnosed with IE were recruited from June 2017 to June 2019 from a community based tertiary care center in Massachusetts. All patients with microbiological and ECHO evidence of IE were eligible to be admitted to the study. Patients had to fulfill modified Duke's criteria to be diagnosed have IE. Once diagnosis of IE was established, patients were further subdivided as cases and controls based on presence or absence of multiple vegetations (defined as presence of 2 or more vegetations as identified in ECHO).

Instruments and protocols

For echocardiography GE (Vivid E95 model), Philips (Epic CVx3D model) machines were used. TTE for these patients were performed by skilled, American Society of Echocardiography (ASE) certified echocardiographers. During echocardiography qualitative and quantitative images of all 4 cardiac chambers, valves, vegetations, intra-cardiac complications

were obtained. Subsequently, echocardiography was analyzed by 2 independent skilled cardiologists. Initial diagnostic modality was TTE, subsequently TEE was done based on further clinical requirements.

Definitions

The following definition was used to define ECHO variables. The key papers of the ASE were used to define chamber quantifications, severity of valvular dysfunction, vegetation and diastolic dysfunction as discussed below: (1) Vegetation: 2019 American College of Cardiology/American Heart Association/ASE report defined vegetation as a mass present on a valve or its adjacent structure related to infective or collagen vascular (inflammatory) endocarditis[6]. Multiple vegetations: Defined as more than one vegetation visualized in multiple echocardiography views; (2) Valvular abnormalities: ECHO evidence of leaflet perforation, leaflet destruction, leaflet prolapse, leaflet mal coaptation, flail leaflet, valvular stenosis, and regurgitation in the presence of vegetations were defined as valvular abnormalities; (3) Valvular regurgitation: The overall interpretation of the severity of valvular regurgitation was based on the integration of all information obtained during the imaging study[6]. Acceptable degrees to describe severity of valvular regurgitation are outlined below: None - regurgitant flow is not present. Trace - minimal leakage valve is present. Mild - mild leakage of the valve is present. Mild to moderate - mild-to-moderate leakage of the valve is present. Moderate - moderate leakage of the valve is present. Moderate to severe - moderate-to-severe leakage of the valve is present. Severe - severe leakage of the valve is present; (4) Low ejection fraction: Male < 52%, female < 54% as per ASE chamber quantifications guidelines [7]; (5) Impaired left ventricle (LV) relaxation: Left ventricular diastolic function is defined by ASE as relaxation and filling during the period after aortic valve closure and before aortic valve opening. Assessment of left ventricular diastolic function includes evaluation of relaxation and compliance, using mitral inflow patterns, annular tissue Doppler velocities, tricuspid regurgitation velocity, left atrial size and pulmonary vein flow velocities[6,7]; and (6) Elevated pulmonary artery systolic pressure (PASP): As per ASE definitions, mean pressure in the pulmonary arteries ≥ 25 mmHg at rest or 30 mmHg during physical activity based on assessment of the tricuspid regurgitation jet velocity suggests probable presence of pulmonary hypertension[7].

Outcome measures

During this period a total of 84 patients were diagnosed to have IE. Sixty-seven patients with ECHO evidence of vegetation were identified. Baseline demographic, clinical, laboratory and ECHO parameters were obtained. ECHO images of these patients were reviewed for findings such as valvular abnormalities including leaflet perforation, leaflet aneurysm, flail leaflet, valvular obstruction, regurgitation, paravalvular abscess, intracardiac abscess, pseudoaneurysm, fistula, prosthetic valve dehiscence, low ejection fraction, pacemaker wire vegetation, and pericardial effusion. Outcomes that were studied included recurrent admission, recurrent bacteremia, requirement of prolonged antibiotics, embolic phenomenon, hypotension, requirement of intensive care unit (ICU) stay, mechanical ventilation, removal of device, requirement of surgical intervention and mortality. Subsequent admission for the same clinical diagnosis or its complications was defined as recurrent admissions. Repeat isolation of the prior organism with presence of bacteremia was defined as recurrent bacteremia. Requirement of longer duration of antibiotics for persistence of bacteremia was defined as prolonged antibiotics use. Definitions of outcome variables: Recurrent admission: Defined as readmission for clinical diagnosis or complications related to the prior episode of IE. Recurrent bacteremia: Subsequent isolation of the initial organism with evidence of bacteremia. Prolonged antibiotics: Longer duration of antibiotics because of persistence of bacteremia (> 8 wk) or prior discontinuation. Embolic phenomenon: Occurrence of any new embolic event or occurrence of an embolic event at a different site during the hospital stay. Hypotension: Defined as persistent low systolic blood pressure of < 90 mmHg requiring fluid or pressors. ICU stay: Is defined as upgrading of care, in a specialized unit, for the need of cardiac or respiratory support with mechanical ventilation or pressors. Mechanical ventilation: Requirement of invasive and noninvasive mechanical ventilatory support. Removal of device: Requirement of removal of temporary intravenous cannula, and cardiac implantable electronic devices.

Data analysis

TTE imaging was obtained by skilled and ASE certified echocardiographers. TTE images were reviewed and reported by two trained cardiologist blinded towards the outcome. TEE was obtained and interpreted by a trained cardiologist. Clinical data was entered in a preformed proforma by 2 independent physicians. Data obtained were entered into Microsoft Excel version 22 (Microsoft Corp.Redmond, Washington) and were analyzed using IBM SPSS version 28 (IBM Corp., Armonk, New York). Continuous data were measured as mean, median, range, and percentage. The odds ratio (OR) was used to measure the association. We used the χ^2 test to calculate the OR for categorical variables and unadjusted binary logistic regression to calculate the OR of continuous variables. A P value less than 0.05 was considered significant. Institutional review board approval was obtained before the initiation of the study.

RESULTS

Among the 67 patients 23 (34%) patients were noted to have multiple vegetations as shown in Figure 1. Among these 13 (56.5%) were male and 10 (43.5%) were female. The distribution of gender in both the subgroups were identical. Patients with multiple vegetations were older with the mean age of the patients with multiple vegetations being 50 as compared to 45 for the patients with single vegetation. Eight (35%) had a prior episode of IE. This was similar to the patients with single vegetation. Single vegetation occurred in higher percentage (84%) of patients with native valve IE. The tricuspid valve was involved in 9 (50%) patients with multiple vegetations and 21 (50%) patients in single vegetation. The mitral

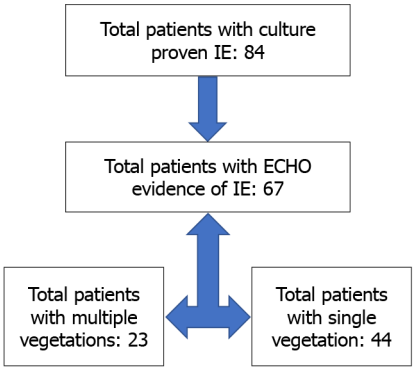

Figure 1 Strobe diagram showing the flow of the patients. IE: Infective endocarditis; ECHO: Echocardiographic.

valve was involved in 4 (22%) patients with multiple vegetations and 12 (27%) patients with single vegetation. Multiple valvular involvement was noted in 4 (22%) patients with multiple vegetation. A higher percentage of patients with multiple vegetations had transesophageal echocardiogram (78%). Heart rate and left arterial volume were almost similar in both the groups. Higher PASP was noted in patients with multiple vegetations. However, none of the differences in the baseline demographic details were statistically significant as shown in Table 1. Valvular abnormalities including leaflet perforation, leaflet destruction, flail leaflet, and regurgitation were noted in around 10% of patients. The presence of prosthetic valve (26%), pacemaker lead (26%), impaired left ventricular relaxation (83%), and elevated PASP (48%) and moderate to severe valvular regurgitation (83%) were higher in patients with multiple vegetations. The presence of an indwelling catheter, low ejection fraction (< 50%), right and left atrial enlargement were equal in both the groups. ECHO features of moderate to severe valvular regurgitation (OR = 4), presence of pacemaker lead (OR = 4.8), impaired LV relaxation (OR = 4), and elevated PASP (OR = 2.2) were associated with higher odds of multiple vegetations. Of these, moderate to severe valvular regurgitation (P = 0.028), the presence of pacemaker lead (P = 0.039) and impaired relaxation (P = 0.028) were statistically significant (Table 2).

Patients with multiple vegetation had increased percentages of requirement of prolonged antibiotics (30%), recurrent bacteremia (48%), recurrent admission (65%), embolic events (39%), requirement of ICU care (48%), hypotension (35%), requirement of mechanical ventilation (22%), removal of device (26%), and surgical intervention (35%) as shown in Table 3. Among these variables, higher odds of association (OR > 2) was present in recurrent admissions (OR = 3.6), recurrent bacteremia (OR = 2.4), embolic phenomenon (OR = 2.5), ICU stay (OR = 2.8), hypotension (OR = 2.1), surgical intervention (OR = 2.8), and device removal (OR = 4.8). However, only requirement of device removal (P = 0.039) and recurrent admissions (P = 0.017) were statistically significant. No significant difference in mortality was seen between the groups.

DISCUSSION

IE is an infectious condition that affects the cardiac endocardial surface, most commonly cardiac valves. Annual incidence of 3-7 per 100000 years have been documented in previous population surveys[1,8]. A 20-year trend analysis showed a significant decrease in annual mortality percentage change between 2004 and 2010, but age- adjusted mortality has stabilized since 2010 till 2019 at 51 deaths per 100000 person-year[9]. Demographic factors including male sex, black population, older age (> 65 years old), and rural location were associated with a higher crude and adjusted mortality rates [9,10]. Mortality ranges from 3% to 14% during index hospital admission, which increases substantially to 36%-37% at 1-year follow-up[11].

Similarly, our study had a mortality of 3% to 7%. This systematic review also showed *Staphylococcus aureus* as the most common microbe encountered in IE like in our study. Other common pathogens include *Enterococcus spp.*, *Viridians Streptococcus* and Coagulase- negative *Staphylococci*[5,11,12]. With recent developments in diagnostic investigations, including cultures and TEE, multiple organisms have been implicated in causing IE[12-14]. Based on an International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) of more than 2700 definite IE, native valve IE (72%) was most frequent followed by prosthetic valve IE (21%). Native valve endocarditis was noted in > 70% of patients in our study and > 30% patients had a remote history of IE. Vegetations were more common on the mitral valve (41%), followed by aortic (38%), and tricuspid (12%) valves[15,16].

Many risk factors including recent increase in bioprosthetic valves, use of cardiac prosthesis and grafts in adult patients with congenital heart diseases, and intravenous drug use (IVDU) with opioid epidemic are associated with increased incidence of IE. In our study 30% of patients had IVDU related IE. IVDU related increase has been seen more prominently in younger and uninsured population and associated with high health care expenditure burden[11]. A significant proportion, 6%-16%, require valvular surgery for IE thereby necessitating multidisciplinary care for this vulnerable patient population[11].

Table 1 Baseline demographic parameters of the patients with multiple vegetation as compared to single vegetation

Variable	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Gender, *n* (%)			1	0.98
Female	10 (43.5)	19 (43)		
Male	13 (56.5)	25 (57)		
Mean age (SD)	50 (20.6)	45 (18.6)	1.01	0.33
Prior IE, *n* (%)	8 (35)	14 (32)	1.1	0.8
Native valve IE, *n* (%)	18 (78)	37 (84)	0.68	0.55
TTE (*N* = 49), *n* (%)	11 (48)	20 (45)	0.91	0.8
TEE (*N* = 49), *n* (%)	18 (78)	30 (68)	1.6	0.54
HR (SD)	105 (18.5)	106 (21.8)	0.99	0.83
LAVI (SD)	32 (11.7)	30 (10.5)	1.01	0.50
PASP (SD)	38 (14.2)	32.5 (10.9)	1.03	0.10

SD: Standard deviation; IE: Infective endocarditis; TTE: Trans thoracic echocardiogram; TEE: Transesophageal echocardiogram; HR: Heart rate; LAVI: Left atrial volume index; PASP: Pulmonary artery systolic pressure; OR: Odds ratio.

Table 2 Baseline echocardiographic parameters of the patients with multiple vegetation as compared to single vegetation, *n* (%)

ECHO variable	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Valvular abnormality	2 (9)	6 (14)	0.603	0.5
Moderate to severe regurgitation	19 (83)	24 (55)	4	0.028[a]
Prosthetic valve	6 (26)	7 (16)	1.9	0.32
Pacemaker lead	6 (26)	3 (7)	4.8	0.039[a]
Indwelling catheter	3 (13)	10 (23)	0.5	0.34
Low EF (EF < 50)	2 (9)	6 (14)	0.6	0.55
RAE	8 (35)	13 (29.5)	1.3	0.66
LAE	8 (35)	15 (34)	1	0.95
Impaired LV relaxation	19 (83)	24 (55)	4	0.028[a]
Elevated PASP	11 (48)	13 (29.5)	2.2	0.1

[a]$P < 0.05$.

ECHO: Echocardiographic; OR: Odds ratio; EF: Ejection fraction; RAE: Right atrial enlargement; LAE: Left atrial enlargement; LV: Left ventricle; PASP: Pulmonary artery systolic pressure.

Predictors of poor outcomes in IE

Multiple epidemiological, clinical, microbiological, risk factors contribute to adverse outcomes in patients with IE. Embolization of vegetation is one of the feared complications of IE associated with poor prognosis, increased mortality, and increased health care utilization. Brain, spleen, lungs, coronaries, bowel, and extremities are some of the sites with highest predilection of getting affected by septic emboli. A vegetation size of 10 mm or more was associated with higher odds of systemic embolic events and all-cause mortality based on systematic review of 21 studies[3,17,18]. In our study embolic events occurred in 29% of study population, and was even higher in among patients with multiple vegetations (39%). Embolic events can complicate up to 80% of presentations. Pulmonary septic emboli are seen more commonly with right sided IE, whereas left sided IE embolizes frequently to brain and spleen. Embolic events are more prevalent with mitral vegetation of any size compared to aortic vegetation of similar size[19-21]. Anterior leaflet vegetations of mitral valve have increased propensity to detach and embolize in contrast to posterior leaflet vegetations[20]. Causative pathogens also affect embolic events incidence- more virulent microbes including *Staphylococcus aureus* and Candida are associated with higher rates[22,23]. Embolic phenomena are more common during the initial course of the disease, and decrease dramatically within 2-3 wk of appropriate antimicrobial therapy[22,24].

Table 3 Outcome of the patients with multiple vegetation as compared to single vegetation, *n* (%)

Outcomes	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Prolonged antibiotics	7 (30)	9 (20.5)	1.7	0.36
Recurrent bacteremia	11 (48)	12 (27)	2.4	0.09
Recurrent admission	15 (65)	15 (34)	3.6	0.017[a]
Embolic phenomenon	9 (39)	9 (20.5)	2.5	0.1
Hypotension	8 (35)	9 (20.5)	2.1	0.2
ICU stay	11 (48)	11	2.8	0.06
MV	5 (22)	7 (16)	1.5	0.55
Removal of device	6 (26)	3 (7)	4.8	0.039[a]
Surgical intervention	8 (35)	7 (16)	2.8	0.08
Mortality	1 (4)	3 (7)	0.6	0.68

[a]$P < 0.05$.

OR: Odds ratio; ICU: Intensive care unit; MV: Mechanical ventilation.

Metastatic sources of infection can develop from septic emboli [*e.g.*, splenic abscess, mycotic aneurysms (MA)] which may require additional interventions. Extracranial and intracranial MA are life-threatening especially when they become symptomatic after rupture. They can often go undetected which underestimates their incidence. Overall mortality with intracranial MA approximates 60% based on few reports, with mortality approaching 80% when these aneurysms rupture [25-27].

In addition to embolization, local extension of infection beyond annulus of valve is dangerous. Perivalvular abscess and later fistulization or shunting between various cardiac chambers often require surgical intervention. These complications have been demonstrated to predict higher mortality, requirement of valvular surgery, pacemakers, and longer course of antibiotics[4,13,27,28]. Aortic valve vegetations are more likely to develop perivalvular abscess[5,13,29]. Among patients who survived, changes in acute physiology causing a change in APACHE-II score was seen, as compared to patients who did not. Similarly, the presence of heart failure at presentation, any stroke during disease course, diabetes mellitus, were independently associated with poor outcomes in a retrospective cohort study at a tertiary center[4]. Interestingly, cardiac surgery during admission did not affect mortality on multivariable analysis[4].

ECHO manifestations of vegetations in IE

Echocardiography remains cornerstone for diagnosis of IE. The evolution of imaging techniques in recent times that lead to an improvement of spatial image resolution have improved the sensitivity of this modality to detect vegetations. TTE is the preferred initial investigation unless device infection or prosthetic valve endocarditis is suspected[30]. TEE is the gold standard investigation. Vegetation visualization in real time for location, mobility, size, and associated local complications - valvular dehiscence, fistula, abscess makes echocardiogram a primary modality of imaging[30,31]. Multiple vegetations can be identified in TEE as it is able to differentiate smaller vegetations. In our study TEE was able to identify multiple vegetations in 78% of patients (Figure 2). Aortic valve vegetations are located on ventricular side of valve and have diastolic outflow tract prolapse. Similarly, mitral, and tricuspid valve vegetations are located on atrial side of leaflets and have tendency to prolapse into their respective atria in systolic phase. Endocardial involvement on echocardiogram is one of the major criteria in original and modified Duke's criteria[32,33]. The presence of oscillating intracardiac mass, intracardiac abscess, new dehiscence of prosthetic valve, and new valvular regurgitation are the criteria to diagnose IE on echocardiogram. Duke's criteria was modified to exclude patients with worsening or changing of pre-existing murmur as a criterion for diagnosis[32,33].

Sensitivity and specificity of TTE for native valve endocarditis ranges from 50%-90% and 90% respectively[34]. The sensitivity is poor for prosthetic valve involvement at 29% while specificity was noted to be 100% in a systematic review [35]. In contrast, TEE has higher sensitivity and specificity reaching > 90% for native valve endocarditis[34]. However, sensitivity to detect prosthetic valve endocarditis is around 80% by TEE, with no difference in specificity compared to TTE[35]. Erbel *et al*[20] elucidated improved diagnostic accuracy of TEE over TTE as smaller vegetations were hard to discern on TTE. The presence of vegetations correlated with embolic events. Embolic events appear to occur more often with larger vegetations (> 10 mm) and location on mitral valve[17,20,36]. In our study, we also identified that higher proportions of patients noted to have multiple vegetations had undergone TEE. Echocardiography is crucial in identifying vegetations on pacemakers and defibrillators. TEE is instrumental in identifying the site, number, and extent of vegetations on cardiovascular implantable device (CIED). Vegetations on CIED can become large. Echocardiography is also used to detect complications associated with vegetations. The sensitivity to diagnose paravalvular abscess with TTE and TEE is 28% and 87%, respectively, while specificity is comparable at > 95% for both TTE and TEE[22]. Valve perforation is also better detected with TEE *vs* TEE (sensitivity 95% *vs* 45%) with specificity of > 95% for both modalities [37]. Valvular and paravalvular complications in our study subgroups were similar. This is in keeping with the prior

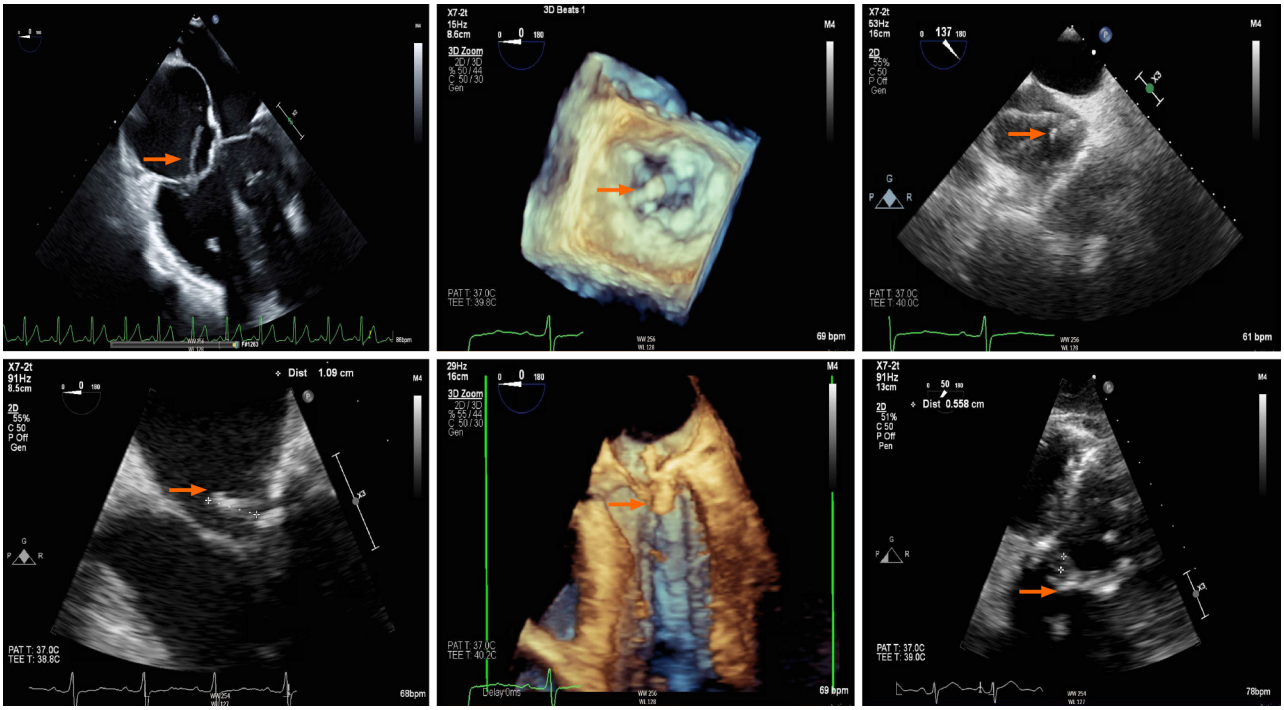

Figure 2 Echocardiographic images of vegetations.

literature showing lack of association between vegetation size and paravalvular complications[38].

ECHO features associated with outcomes of IE

Features visualized on echocardiogram can help to predict outcomes associated with IE and guide further management. As shown in Table 4 multiple ECHO parameters can predict outcome in patients with IE. A larger vegetation size (10 mm), mitral valve vegetation and anterior mitral leaflet involvement is associated with a higher odd of embolization, as described earlier. Vegetation size has been used as an independent ECHO predictor in Embolic Risk French Calculator [39]. However, caution should be maintained on discrepancy in cutoff size based on 3D *vs* 2D imaging as 3D imaging is more sensitive[40].

Vegetation mobility was noted to be an independent predictor of embolic events in an early study published in 2001 [41]. Many studies have been published since then, and cumulative evidence suggests presence of mobile vegetation was associated with double odds of embolic events in a comprehensive systematic review. Vegetation mobility with displacement angle of > 60° is further associated with higher embolic events[42]. In addition, presence of multiple vegetations was independently associated with more embolic events, however, presence of bivalvular vegetations didn't have statistical significance[43]. This was similar to our study where patients with multiple vegetations had higher odds of having embolic events.

The presence of large vegetation on CIED is known to increase hospital mortality. Similarly, CIED endocarditis is known to increase health care utilization, cost, need of intervention, surgical procedure and worsen quality of life similar to this study[44,45]. Valvular complications including leaflet perforation, flail leaflet, leaflet obstruction and acute valvular regurgitation can increase embolic events and morbidity and mortality in patients with IE. Demonstration of paravalvular complications including abscess, aneurysm, fistula and paravalvular regurgitation is associated with worst patient outcome. Presence of valvular and paravalvular complications is associated with increased odds of mortality and necessitating cardiac surgery and prolonged antibiotics[16]. In our study patients with multiple vegetations had higher odds of having severe valvular regurgitation and needing surgical intervention. There has been limited literature of implications of diastolic dysfunction in patients with endocarditis. While we found that impaired LV relaxation and elevated PASP was more among patients we are unable to conclude that elevated filling pressure and impaired LV relaxation was solely responsible for multiple vegetations.

ECHO features of IE, using modified Duke's criteria, were present in 87% of patients in ICE-PCS study[16]. Approximately 60% of these subjects had undergone TTE and TEE, and 99.2% of the study population had undergone either TTE or TEE. The most common paravalvular complication was abscess formation, noted in 14% of patients. In one-third of the patients with prosthetic valve endocarditis, their courses were complicated by dehiscence or new regurgitation lesion. Presence of mitral valve vegetations, paravalvular complications and prosthetic valve endocarditis were associated with higher odds of mortality. Interestingly in our study, patients with multiple vegetations had higher requirement of prolonged antibiotics, recurrent bacteremia, recurrent admission, embolic events, requirement of ICU care, hypotension, requirement of mechanical ventilation, removal of device, and surgical intervention. Among these variables, the requirement of device removal and recurrent admissions were statistically significant. However, there was no difference in mortality.

Table 4 Echocardiographic predictors of outcome in infective endocarditis

Finding	Embolism	Morbidity	Mortality
Vegetation size[1]	+	+	+
Mitral valve location	+	+	+
Anterior leaflet of MV	+	-	-
Vegetation mobility[2]	+	-	-
Multiple vegetation	+	+	-
Cardiac device vegetations	+	+	+
Valvular complications[3]	+	+	+
Perivalvular complications[4]	+	+	+
Prosthetic valve vegetation	+	+	+
Prosthetic valve dehiscence	+	+	+

[1]Size of 10 mm.
[2]> 60° of displacement angle.
[3]Flail leaflet, leaflet perforation, acute valvular regurgitation, valvular obstruction.
[4]Abscess, aneurysm, fistula, paravalvular regurgitation.
MV: Mechanical ventilation.

The limitations of this study are the retrospective nature, small sample size and lack of matching. While septic embolism to the lungs occurs with tricuspid valve endocarditis, systemic embolization is predominant with left sided IE. Embolic events are higher with mitral valve IE in comparison to aortic valve IE for any vegetation size. We were not able to compare the relationship between multiple vegetations on the individual valve with embolic outcomes due to identical and higher percentages of tricuspid valve involvement in both groups and a smaller number of patient involvement in the other valvular groups. We also did not have details of cost of care, patients' insurance details, lack of details on functional status at admission and at follow up which could independently affect outcome[21,44,46]. However, the strength of this study was inclusion of patients with definite IE and imaging evidence of vegetation in both the subgroups and identifying the predictors of multiple vegetations and their associated outcomes in patients with IE[47-49].

CONCLUSION

In conclusion, this study highlights the associations of ECHO features and its outcomes in patients with IE having multiple vegetations. TEE is better at identifying and characterizing multiple vegetations. ECHO evidence of moderate to severe regurgitation, presence of pacemaker lead, impaired LV relaxation, and elevated PASP were implicated with presence of multiple vegetations. IE patients with multiple vegetations can contribute to multiple comorbidities among which recurrent admissions and requirement of device removal are found to be statistically significant.

FOOTNOTES

Author contributions: Mishra AK and Jha A planned and formulated the study; Al-Seykal I, Bhattad PB, and George AA collected and analyzed the data; Mishra AK, Bansal K, George AA, and Jha A completed the manuscript; Mishra AK, Sharma N, Sargent J, and Kranis MJ reviewed the manuscript; Kranis MJ approved the manuscript.

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Informed consent statement: The ethical requirement for individual informed consent was appropriately waived by the institutional review board due to the retrospective nature of this study.

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