ORIGINAL ARTICLE

Echocardiography detection rate of newly diagnosed valvular heart disease amongst patients 12 years old and beyond, referred for transthoracic echocardiography in tertiary care settings

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ABSTRACT

Introduction: Valvular heart disease (VHD) is a significant contributor to cardiovascular morbidity and mortality. Despite global awareness, data on the epidemiology and clinical profile of VHD in Malaysia remain limited. This study aimed to determine the echocardiographic detection rate of newly diagnosed VHD in tertiary care centres in Perak, Malaysia, as well as to examine its clinical characteristics, aetiologies, severity, associated comorbidities, and the rate of patient acceptance for valve intervention.

Materials and Methods: A retrospective, multi-center study was conducted involving patients who underwent echocardiography over a six-month period. The data were then analysed to address the study objectives. Statistical analysis was performed using SPSS version 25.0.

Results: Of the 12,610 patients who underwent echocardiography, 946 were newly diagnosed with VHD, yielding a detection rate of 7.5%. The median age of VHD patients was 67 years, with a slight female predominance. The median left ventricular ejection fraction (LVEF) was 57%. Approximately 66% of patients were symptomatic, with dyspnoea being the most common symptom (46.85%). Pulmonary hypertension was observed in 35.3% of patients. Atrial fibrillation (AF) was present in 12.2% of cases. Mitral regurgitation (MR) was the most common valve lesion (34.1%), followed by tricuspid regurgitation (TR, 32.3%) and aortic regurgitation (AR, 19.2%). Functional aetiology was the most frequent cause of VHD, accounting for 59%. Rheumatic heart disease (RHD) was responsible for 51.7% of mitral stenosis (MS) cases, while degenerative causes predominated in AR (74.9%), aortic stenosis (AS) (84.6%), and primary MR (71.4%). The majority of VHD cases were mild (65.6%), with 29.2% moderate and 5.1% severe. Among VHD patients, 34.7% had clinically significant moderate or severe disease. In this subgroup, the predominant aetiologies were functional for MR (52.1%), TR (96.7%), and pulmonary regurgitation (PR, 100%), while degenerative causes were prevalent in AR (63.6%) and AS (84.3%), and RHD was the leading cause of MS (57.1%). Multiple valve involvement was observed in 72.6% of cases. Two-valve involvement accounted for 52.5%, with MR and TR being the most common combination (68.7%), mainly due to functional causes. AS was significantly associated with hypertension and dyslipidaemia. MR showed strong associations with AF, chronic kidney disease (CKD), and ischemic heart disease (IHD), while TR was more common in females. Despite 6.7% of patients requiring valve intervention, only 24.2% consented. A total of 36.4% declined intervention, primarily due to concerns about advanced age (62.5%) and fear of surgery (29.2%), while 39.4% remained undecided.

Conclusion: The echocardiographic detection rate of newly diagnosed VHD was 7.5%, with functional MR being the most common lesion (20.7%). The majority of patients refused valve intervention, primarily due to old age. This study provides valuable insight into the burden and management challenges of VHD in Malaysia.

KEYWORDS:
Newly diagnosed, Valvular heart disease, echocardiography, detection rate, aetiology, severity, Malaysia,

INTRODUCTION

Valvular heart disease (VHD) is a major cause of cardiovascular mortality and morbidity worldwide, affecting more than 2% of the global population.[1] This could potentially be the 'new cardiac epidemic' and remains a crucial clinical burden.[2,3] Based on data from large population-based epidemiological studies in the USA, the estimated prevalence of significant VHD in developed countries is 2.5%.[2]

Although mild to moderate VHD mostly does not require intervention, severe VHD is associated with impaired quality of life and prolonged hospitalization and can progress to

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complication such as heart failure, arrhythmia and death. There is no effective medical therapy, but early detection of individuals with moderate to severe VHD who may benefit from valve intervention can reduce or eliminate symptoms, prevent further complications and improve outcome of morbidity and mortality.[4]

Following adequate clinical evaluation, echocardiography is the key technique used to confirm the diagnosis of VHD and to assess its severity. With advancement in catheter-based valvular interventions, outcomes of VHD patients have improved dramatically, particularly for those at high risk for surgical interventions. In fact, recent updates in both the American College of Cardiology (ACC) and European Society of Cardiology (ESC) clinical practice guidelines reflect the change in management of these novel techniques, with stronger recommendations for adopting such treatment options.[5,6] Large datasets provide real-world insights into the epidemiology of VHD, and better use of analytics may lead to improvements in care.[7]

Despite the clinical significance of VHD, there is a lack of epidemiological data describing its burden in Malaysia.[3] Thus, the primary objective of this study was to describe the echocardiography detection rate of VHD in four main tertiary centres in Perak over six-month period. Our secondary objectives were to explore the baseline characteristics, severity and aetiology of VHD, to test for association between comorbidities and types of VHD and finally, to explore the proportion of patients who are agreeable for cardiac intervention and reasons for refusing such intervention

MATERIALS AND METHODS

Study design and Study Population

This was a retrospective study conducted in Perak's four main tertiary healthcare centres: Hospital Raja Permaisuri Bainun, Hospital Taiping, Hospital Teluk Intan, and Hospital Slim River over a period of six months (July 2023 - December 2023). All patients who undergone outpatient and inpatient echocardiography examinations during the study period will be included. Health records will then be reviewed for those patients with newly diagnosed VHD and data will be collected.

Inclusion criteria

All patients aged 12 years and above at the time of diagnosis who undergone echocardiography from July 2023 until December 2023 at the healthcare centres mentioned in the study design were included in this study.

Exclusion criteria

The exclusion criteria included pre-existing VHD, non-valvular cardiac structural abnormalities, trivial regurgitations, prosthetic heart valves and repeated echocardiography.

Echocardiography procedures

Echocardiography is the first-line modality for assessing of valvular regurgitation and stenosis.[3] All transthoracic echocardiography were performed by experience cardiac sonographers who were trained to assess VHD. All study sites used the American Society of Echocardiography (ASE) guidelines and standards to define VHD and as the reference parameters to classify severity of VHD.[8-10] The aetiology of the VHD were then determined based on the ACC/AHA and ESC/EACTS Guidelines for the management of valvular heart disease.[5-6]

Data collection

Case Report Forms (CRFs) were filled out by designated personnel in the respective hospitals if patients met the inclusion and exclusion criteria. All information for the CRFs, particularly demographics, comorbidities, clinical symptoms, echocardiography findings, aetiology, treatment strategy, and medications, was extracted from the medical records and echocardiography reports and images. This study utilized a paper CRF to collect the required variables/data. The study investigator entered relevant data from patients into the study CRF.

Statistical Analysis

All statistical analyses were performed by using Statistical Package for Social Science (SPSS) software version 25.0. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented in frequency and percentage (%). Numerical variables were expressed in median with interquartile range (IQR) as our data showed a non - normal distribution.

The number of patients with echocardiographic evidence of VHD relative to the total number of patients who underwent echocardiography during the study period will be recorded to establish the echocardiography detection rate of VHD. Those with newly diagnosed VHD were classified according to demographic, clinical symptoms, echocardiographic findings and aetiology of VHD. Pearson chi-square and Fisher's exact test were used to look for any association between comorbidities and types of VHD among those patients with newly diagnosed VHD (Table IV).

RESULTS

Echocardiography detection rate of newly diagnosed VHD

Of all 12,610 patients who underwent echocardiography over a 6 month period, 946 were newly diagnosed with VHD, corresponding to a echocardiography detection rate of VHD of 7.5%

Baseline Demographics among patients with newly diagnosed valvular heart disease (Table I)

The median age was 67 year-old (IQR 57, 74). There was a slight female preponderance, with 51.7% female and 48.3% male patients. Division according to ethnicity shows that Malays were the majority (53.8%), followed by Chinese (31.5%), Indians (13.6%), and other ethnicities (1.1%). 27.2% of patients were current or ex-smokers, while 72.8% were non-smokers. 66% of patients were symptomatic. The most common symptom was dyspnoea (46.5%), with most patients classified as NYHA Class II (49.7%). Other symptoms included chest pain (17.4%), leg swelling (16.2%), orthopnoea (11.3%), and paroxysmal nocturnal dyspnoea (9.7%).The median left ventricular ejection fraction (LVEF) was 57% (IQR 42, 63). Pulmonary hypertension was present in 35.3% of patients with VHD. The median pulmonary arterial systolic pressure was 33 mmHg (IQR 25, 44).

Table I: Baseline demographics among patients who has newly diagnosed valvular heart disease

	n (%)
Age (Range) (years) [a]	67 (57, 74)
BMI (kg/m^2) [a]	25.4 (22.7, 28)
Ethnicity	
Malay	509(53.8)
Chinese	298(31.5)
Indian	129(13.6)
Others	10(1.1)
Gender	
Male	457(48.3)
Female	489(51.7)
Smoking status	
Current/Ex-smoker	257(27.2)
Non-smoker	689(72.8)
Alcohol consumption	
Current or Ex drinker	22
Non-alcohol consumer	924(97.7)
Family history of valve disease	
Yes	16(1.7)
No	930(98.3)
Comorbidities	
Yes	870 (92)
No	76 (8)
Types of Comorbidities	
Diabetes Mellitus	388(41.0)
Dyslipidaemia	144(15.2)
Hypertension	709(74.9)
IHD	204(21.6)
Kidney disease	156(16.5)
Stroke	44(4.7)
Peripheral vascular disease	3(0.3)
Clinical symptoms	
Symptomatic	624 (66)
Asymptomatic	322 (34)
Types of Symptoms	
Dyspnoea	440 (46.5)
Chest pain	165 (17.4)
Leg swelling	153 (16.2)
Orthopnea	107 (11.3)
Paroxysmal nocturnal dyspnoea	92 (9.7)
Palpitation	59 (6.2)
Syncope	11 (1.2)
NYHA Classification for Dyspnoea	
NYHA Class I	406 (42.9)
NYHA class II	470 (49.7)
NYHA class III	70 (7.4)
NYHA class IV	0 (0)
ECG Rhythms	
Sinus rhythm	808 (85.4)
Atrial Fibrillation	115 (12.2)
Atrial Flutter	4 (0.4)
Atrial tachycardia	1 (0.1)
Bradyarrhythmia	18 (1.9)
Medications	
Antiplatelet	443 (46.8)
Statins	676(71.5)
Angiotensin Converting Enzyme inhibitor (ACE-I)/ Angiotensin Receptor Blockers (ARB)/ Angiotensin Receptor Neprilysin Inhibitor (ARNI)	421 (44.5)
Beta blockers	465 (49.2)
Diuretics	265 (28)
Digoxin	1
Warfarin	26 (2.7)
Non Vitamin K Antagonist Oral anticoagulation	44 (4.7)
Mineralocorticoid Receptor Antagonist (MRA)	95(10)
Sodium Glucose Transport Protein 2 inhibitors (SGLT2-I)	56 (5.9)

[a] Median (IQR)

Table II: Aetiology of valvular heart disease among patients who has newly diagnosed valvular heart disease

Etiology	AR n =354	AS n =104	PR n = 132	PS n = 2	TR n = 595	MR n = 628	MS n = 29
Degenerative (%)	75.98	84.62	0	0	0	21.98	48.3
Rheumatic (%)	10.17	12.5	0	0	0.17	7.8	51.7
Infective Endocarditis (%)	0.85	0	0	0	0.51	0.32	0
Congenital (%)	1.13	0.96	0	100	0.17	0	0
Inflammatory (%)	0.28	0	0.76	0	0.84	0.64	0
Ischemic (%)	0	0	0	0	0	8.28	0
Functional (%)	0	0	99.24	0	98.15	60.67	0
Aortic root disease (%)	11.58	1.92	0	0	0	0	0
Hereditary (%)	0	0	0	0	0	0.32	0

Table III: Valve Lesion severity for overall or Division by Type of valve lesion among patients who has newly diagnosed valvular heart disease

	Overall	MR	MS	TR	AR	AS	PR	PS
Severity	n=1844	n= 628	n= 29	n=595	n=354	n=104	n=132	n=2
Mild (%)	65.7	66.4	56.6	59.5	72.3	51.0	87.0	50
Moderate (%)	29.2	29.9	36.7	33.5	26.0	30.8	13.0	0
Severe (%)	5.10	3.7	6.7	7.0	1.7	18.2	0	50

Table IV: Association between comorbidities and types of VHD

Comorbidities (May have multiple in each patients) Types of VHD		HTN	DM	Dyslipidemia	IHD	Kidney disease	Stroke	Peripheral vascular disease
MR	n(%)	526 (83.8)	290 (46.2)	97(15.5)	162(25.8)	130(20.7)	33(5.3)	1(0.2)
(n=628)	p-value	0.134[a]	0.298[a]	0.102[a]	0.019[a]	0.001[a]	0.753[a]	0.180[b]
MS	n (%)	22(75.9)	13(44.8)	9(31.0)	6(20.7)	4(13.8)	0	0
(n=29)	p-value	0.836[a]	0.793a	0.035[b]	0.832[a]	0.805b	0.393[b]	1.000[b]
TR	n(%)	517(86.9)	281(47.2)	98(16.5)	145(24.4)	120(20.2)	28(4.7)	2(0.3)
n=595	p-value	0.881a	0.719[a]	0.143a	0.475[a]	0.232[a]	0.150[a]	1.000[b]
AR	n (%)	270(76.3)	121(34.2)	59(16.7)	80(22.6)	60(17.0)	21(5.9)	1(0.3)
n=354	p-value	0.794a	0.000[a]	0.400[a]	0.648[a]	0.862[a]	0.166[a]	1.000[b]
AS	n(%)	89(85.6)	47(45.2)	26(25.0)	18(17.3)	10(9.6)	3(2.9)	0
n=104	p-value	0.014[a]	0.408[a]	0.004a	0.243[a]	0.041[a]	0.466[b]	1.000[b]
PR	n (%)	126(95.5)	72(54.5)	28(21.2)	42(31.8)	32(24.2)	3(2.3)	1(0.8)
n=132	p-value	0.478[a]	0.858a	0.696a	0.337[a]	0.431[a]	0.044[a]	0.455[b]
PS	n(%)	1(50.0)	1(50.0)	0	0	0	0	0
n=2	p-value	0.438[b]	1.000[b]	1.000[b]	1.000[b]	1.000[b]	1.000[b]	1.000[b]

[a]Pearson's Chi Square, [b]Fisher's exact

Table V: Decision for Valve Intervention among patients who has newly diagnosed valvular heart disease

Decision for Valve intervention	n (%)
Agreed	16 (24.2%)
Undecided	26 (39.4%)
Refused	24 (36.4%)
Reason for Refusal	**n (%)**
Old age	15 (62.5%)
Fear of surgical risk	7 (29.2%)
Severe comorbidities	1 (4.2%)
Symptoms tolerable	1 (4.2%)

Types, aetiology and severity of VHD (Table II & III)

Mitral regurgitation (MR) was the most frequent valve lesion (34.1%), followed by tricuspid regurgitation (TR) (32.3%), aortic regurgitation (AR) (19.2%), pulmonary regurgitation (PR) (7.2%), aortic stenosis (AS) (5.6%), mitral stenosis (MS) (1.6%), and pulmonary stenosis (PS) (0.05%). The most common aetiology for overall valvular heart disease (VHD) was functional, accounting for 59%. Rheumatic heart disease (RHD) accounted for 51.7% of MS, while degenerative causes represented 74.9% of AR and 84.6% of AS. Functional MR was the most common aetiology for all cases of MR, and degenerative aetiology was the predominant cause of primary MR (71.4%). In terms of severity, there were 65.6% mild, 29.2% moderate, and 5.1% severe valve lesions. MR was the most common valve lesion for both mild and severe severity, at 34.4% and 24.4%, respectively, whereas TR was the most common valve lesion for moderate severity at 34.9%.

Moderate to severe subgroup
Moderate or severe VHD comprises 34.7% of all VHD cases. Among those with moderate or severe VHD, the most common aetiology was functional for MR (52.6%), RHD for MS (61.5%), functional for TR (97.9%) and PR (100%); and degenerative for AR (63.6%) and AS (84.3%).

Rheumatic Heart Disease
RHD constitute 6.2% of all VHD, affecting the mitral valve in 56.1% (43% MR, 13.1% MS) and aortic valve in 43% (31.6% AR, 11.4% AS). 52.6% of RHD are of moderate or severe severity.

Multiple Valves
Multiple valves were involved in 72.6% of cases. Two-valve involvement accounted for 52.5%, with MR plus TR being the most common combination (68.7%). The most common aetiology for two-valve involvement were functional MR and functional TR. 33.8% of patients had three valves involved, with MR plus TR plus AR being the most common combination (46.6%). The most common aetiologies for three-valve involvement were degenerative AR, functional MR, and functional TR. Four valves were involved in 12.7% of cases, with MR plus TR plus AR plus PR being the most common combination at 66.7%. The most common aetiology for four-valve involvement were degenerative AR, functional MR, functional TR, and functional PR.

Comorbidities and associations (Table IV)
AF was strongly associated with MR ($p < 0.001$) and TR ($p < 0.001$). It was present in 12.2% of VHD cases, with MR and TR each comprising 34% ($p < 0.001$). AS was strongly associated with hypertension (p=0.014) and dyslipidaemia (p=0.004). Hypertension was present in 84.8% of AS cases, while dyslipidaemia was present in 24.8% of AS cases. MR had a strong association with AF (p=0.001), Chronic kidney Disease (CKD) (p=0.0001), and ischaemic heart disease (IHD) (p=0.019), with MR being the most common valve lesion in AF (34.3%), CKD (36.4%), and IHD (35.8%).

Classification by LVEF
23.7% of our population had a LVEF of ≤40%, 11.3% had a LVEF between 41% and 49%, and 64.6% had a LVEF of ≥50%. The highest proportion of LVEF ≤40% was in the MR group ($p < 0.001$). In our study, most patients with LVEF ≤40% were on beta blockers (70%) and ACE-I/ARB/ARNI (59%). However, only a small percentage of patients were on MRA (27.2%) and SGLT2-I (18%).

Valvular Intervention (Table V)
6.7% of patients required valve intervention, but only 24.2% consented. Meanwhile, 36.4% declined, and 39.4% were uncertain ($p < 0.001$). The primary reasons for refusal included old age (62.5%), fear of surgical risks (29.2%), and severe comorbidities (4.2%) ($p < 0.001$)

DISCUSSION

This is the first echocardiography-based multicenter study to determine the detection rate of VHD in Malaysia. The overall detection rate of 7.5% among patients referred for transthoracic echocardiography suggests a substantial burden of previously undiagnosed VHD in the tertiary care setting. Compared to Manjunath et al., who reported a detection rate of 9.7% in a similar echocardiography based study in India,[11] the slightly lower rate in our study may reflect differences in RHD prevalence as India has a higher prevalence of RHD. [12]

Globally, the most common valve pathology is RHD affecting the mitral valve. In developed countries, however, degenerative disease is more prevalent, paralleling the increasing proportion of the aging population.[5,13-15]

As regards to the distribution of VHD in our study, MR was the most frequent valve lesion (34.1%). The most common aetiology was functional MR (60.67% of all MR). The most common cause of primary MR was degenerative (22% of all MR). Rheumatic MR accounted for only 6.2% of all VHD. Valve degeneration was the predominant aetiology for AR and AS.

This contrasts with the study by Manjunath et al, whereby Rheumatic MR was the most common primary valve lesion. That study indicated that calcific degeneration was the main aetiology of AS whereas rheumatic aetiology dominated the AR cases.[11]

Our results show some similarity to the Euro Heart Survey, another hospital based multicentre study of VHD involving 5001 patients from 92 centres in 25 European countries. In that study, the most common lesions in were AS and MR, mainly attributed to degenerative causes. The mean age in that study was 65±14 years with 83.2% population are ≥50 years. [16]

Another large Swedish nationwide hospital-based register study showed the most common lesions were AS followed by MR, also mainly due to degenerative causes. The majority of VHD were diagnosed in the elderly (68.9% in subjects aged ≥65 years). [17]

Both the Euroheart study and the Swedish study above were conducted in European countries which were developed nations, which consist of more elderly population.[16,17] The similarity in the predominant aetiology of VHD in those studies to our study could be explained by the increase in elderly population in Malaysia. Based on findings of the department of statistics Malaysia, the old population (65 years and over) increased from 2.5 million (7.6%) to 2.6 million (7.7%) in the fourth quarter of 2024 as compared to the fourth quadrant of 2023.[18] The decrement in rheumatic heart disease cases in our study could be due to better accessibility to health care and antibiotic therapy.

There were no population based studies on the incidence or prevalence of RHD in adult patients in Malaysia.[19] The only relevant study focused on patients undergoing mitral valve repair at a tertiary heart centre, revealing that RHD accounted for 46.7% of all mitral valve repair.[20]
In contrast to our study which consist mainly of adult population, the worldwide age-standardized incidence rate (ASIR) was very much higher in children less than 15 years of age at 52.3 cases per 100,000 children in 2019.[21] In Sabah, Malaysia whereby RHD is endemic, the average incidence of pediatric RHD from 2015 until 2018 was 2.19 per 100000

population. [22] The most common VHD in this study was MR followed by AR.[22]

Although women represent a larger share of VHD cases globally, they have frequently been underrepresented in the key studies that inform treatment guidelines and have been shown to experience worse postoperative outcomes.[23] In our study, females make up a substantial portion, at 51.7%.

Our study identified several significant associations between VHD and baseline characteristics or comorbidities. The first association was found between AF and both MR and TR. Previous studies have established AF as a risk factor for developing MR and TR.[24-27] Our study also showed that AS was strongly associated with hypertension and dyslipidemia. The CANHEART Aortic Stenosis Study showed that both hypertension and dyslipidemia have independent and dose-response associations with incident AS.[28] Additionally, another study indicated that hypercholesterolemia and hypertension are significantly associated with severe symptomatic AS.[29] There was also a significant association between female gender and TR, similar to two earlier studies that reported a higher prevalence of TR in women.[30,31] Lastly, our study established a significant association between MR with CKD and IHD. CKD patients developed MR due to either degenerative mitral annular calcification or functional.[32-33] Ischemic MR occurs due to left ventricular dysfunction in IHD.[34-36]

Heart failure with reduced EF (HFrEF) is defined as heart failure with an LVEF of ≤40% while Heart failure with mildly reduced EF (HFmrEF) is defined as heart failure with an LVEF of 41% to 49%.[37] Recent studies revealed that VHD contributes to 5.0%–13.6% of HFrEF and HFmrEF cases.[38,39] The most recent heart failure guidelines strongly recommended for guideline directed medical therapy for HFrEF.[40] In our study, the use of ACE inhibitors, ARBs, ARNI, and beta blockers among patients was commendable and consistent with these guidelines. However, the adoption of SGLT2 inhibitors and MRAs remains low, highlighting the need for increased awareness regarding these treatments.

In our study, valve intervention was not performed in 75.8% patients despite having adequate indications for intervention. The main reasons were patient indecision and refusal due to old age. This contrasts with the EURO HEART study, where valve intervention was not performed in 31.8% of eligible patients. The primary reasons for not proceeding with valve interventions were symptoms regression under medical treatment and old age.[16] Our study allows us to identify the reasons behind patients refusal of valve intervention and provide insights on how to address this issue during future discussions with patients.

Therefore, the findings of our study suggests that there is a need for policy makers in Malaysia to formulate policies that focus on the management of VHD especially degenerative type valvular heart disease. This includes provision of specialist training to increase the number of cardiothoracic surgeons and cardiologist with expertise in the management of valvular heart disease in Malaysia.

LIMITATIONS

Since our study is not a population-based study, it is subjected to inherent biases. Symptomatic lesions may be overrepresented due to the nature of research conducted in hospital settings. Furthermore, patients with severe lesions may be more inclined to seek treatment at these facilities, which could skew the observed patterns of severity.

Despite the efforts of the investigators, accurately assigning etiologies to all VHD cases based on echocardiographic findings remains challenging and may not be as reliable as data obtained from surgical or autopsy studies.

CONFLICTS OF INTEREST

All authors of this study have no conflicts of interest to declare.

ETHICAL APPROVAL

The ethical approval was obtained from Medical Research & Ethics Committee's (MREC), Ministry of Health Malaysia (NMRR ID23-00579-NAR). Permission has also been obtained from the hospital authorities for accessing medical records.

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CONCLUSION

This is the first echocardiographic base multicenter study estimating the echocardiographic detection rate of VHD in multiple tertiary care settings in Perak. The echocardiographic detection rate of VHD was 7.5%, of which functional MR is the commonest valve lesion. Majority of patients refused valve intervention due to old age. Our results highlight the evolving landscape of valvular heart disease in Malaysia, marked by a predominance of degenerative and functional etiologies. Echocardiography remains a vital tool in early diagnosis, risk stratification, and treatment planning for patients with VHD.

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