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Cardiac magnetic resonance findings predicting mortality in patients with pulmonary arterial hypertension: a systematic review and meta-analysis

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Abstract

Objectives To provide a comprehensive overview of all reported cardiac magnetic resonance (CMR) findings that predict clinical deterioration in pulmonary arterial hypertension (PAH).

Methods MEDLINE and EMBASE electronic databases were systematically searched for longitudinal studies published by April 2015 that reported associations between CMR findings and adverse clinical outcome in PAH. Studies were appraised using previously developed criteria for prognostic studies. Meta-analysis using random effect models was performed for CMR findings investigated by three or more studies.

Results Eight papers (539 patients) investigating 21 different CMR findings were included. Meta-analysis showed that right ventricular (RV) ejection fraction was the strongest predictor of mortality in PAH (pooled HR 1.23 [95 % CI 1.07–1.41],

p = 0.003) per 5 % decrease. In addition, RV end-diastolic volume index (pooled HR 1.06 [95 % CI 1.00–1.12], p = 0.049), RV end-systolic volume index (pooled HR 1.05 [95 % CI 1.01–1.09], p = 0.013) and left ventricular end-diastolic volume index (pooled HR 1.16 [95 % CI 1.00–1.34], p = 0.045) were of prognostic importance. RV and LV mass did not provide prognostic information (p = 0.852 and p = 0.983, respectively).

Conclusion This meta-analysis substantiates the clinical yield of specific CMR findings in the prognostication of PAH patients. Decreased RV ejection is the strongest and most well established predictor of mortality.

Key Points

• *Cardiac magnetic resonance imaging is useful for prognostication in pulmonary arterial hypertension.*

• *Right ventricular ejection fraction is the strongest predictor of mortality.*

• *Serial CMR evaluation seems to be of additional prognostic importance.*

• *Accurate prognostication can aid in adequate and timely intensification of PAH-specific therapy.*

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Abbreviations

CMR	Cardiac magnetic resonance imaging
HR	Hazard ratio
LV	Left ventricle/left ventricular
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
RV	Right ventricle/right ventricular

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Introduction

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure ≥25 mmHg in the presence of a pulmonary capillary wedge pressure ≤15 mmHg as assessed by right heart catheterization, and is characterized by progressive remodelling of the distal pulmonary arteries [1]. PAH includes apparent heterogeneous conditions (idiopathic, heritable, induced by drugs or toxins, associated with connective tissue diseases, HIV infection, portal hypertension and congenital heart disease), but is characterized by similar clinical, haemodynamic and pathological pictures [1, 2]. Left untreated, the resultant increase in pulmonary vascular resistance leads to progressive deterioration of right ventricular (RV) function and eventually death in 45 % of incident cases within 3 years [2, 3]. Although recent advances in therapeutic modalities have significantly improved the outcomes of this devastating disease, the course of the disease widely varies between individuals [4–6]. In order to guide optimal clinical management of patients with PAH, accurate prognostication and monitoring of disease progression is therefore of great importance [5].

Previously reported predictors of mortality include aetiology of PAH, sex and several functional, biochemical and haemodynamic variables [3, 7–10]. Although it is inferred that cardiac magnetic resonance imaging (CMR) could be of important additional value, evidence for the prognostic merit of specific imaging findings is still far from robust. This study therefore aims to provide a comprehensive overview of commonly investigated CMR findings that are predictive of adverse clinical outcome in PAH.

Methods

This systematic review was conducted in accordance with the PRISMA statement [11]. A pre-defined review protocol as adopted by this study can be accessed through PROSPERO (registration number: CRD42014009231).

Literature search strategy

CMR studies as described in this review were identified through a general search syntax that was designed to aggregate all studies concerning the prognostic value of non-invasive imaging in PAH. A comprehensive systematic search was performed on 29 April 2015 in MEDLINE (via PubMed interface) and EMBASE electronic databases using combinations of all synonyms for: population (PAH), non-invasive imaging and relevant clinical outcomes (components of the Dana Point Time To Clinical Worsening composite endpoint) [2, 12]. A validated prognostic search filter with the highest sensitivity (98 %) was added to the search syntax [13, 14]. No language or publication period restrictions were applied. The full original search syntax is supplied in Supplemental File 1.

Selection of papers

A flow diagram of the selection process is shown in Fig. 1 [11]. After deduplication, one author (VB) performed screening and selection of articles based on title and abstract, using the following exclusion criteria: cross-sectional study design, study population without PH (e.g. acute pulmonary embolism, exercise-induced PH), >30 % study population with other than WHO group I PAH, inclusion of children <12 years of age, CMR findings not investigated as a potential predictor for clinical outcome, lack of Cox regression analysis. Full-text screening was performed by two authors (VB, JH); exclusion criteria are described in Fig. 1. All references of the excluded reviews and included articles were cross-checked to identify possible relevant articles missed in the original search syntax.
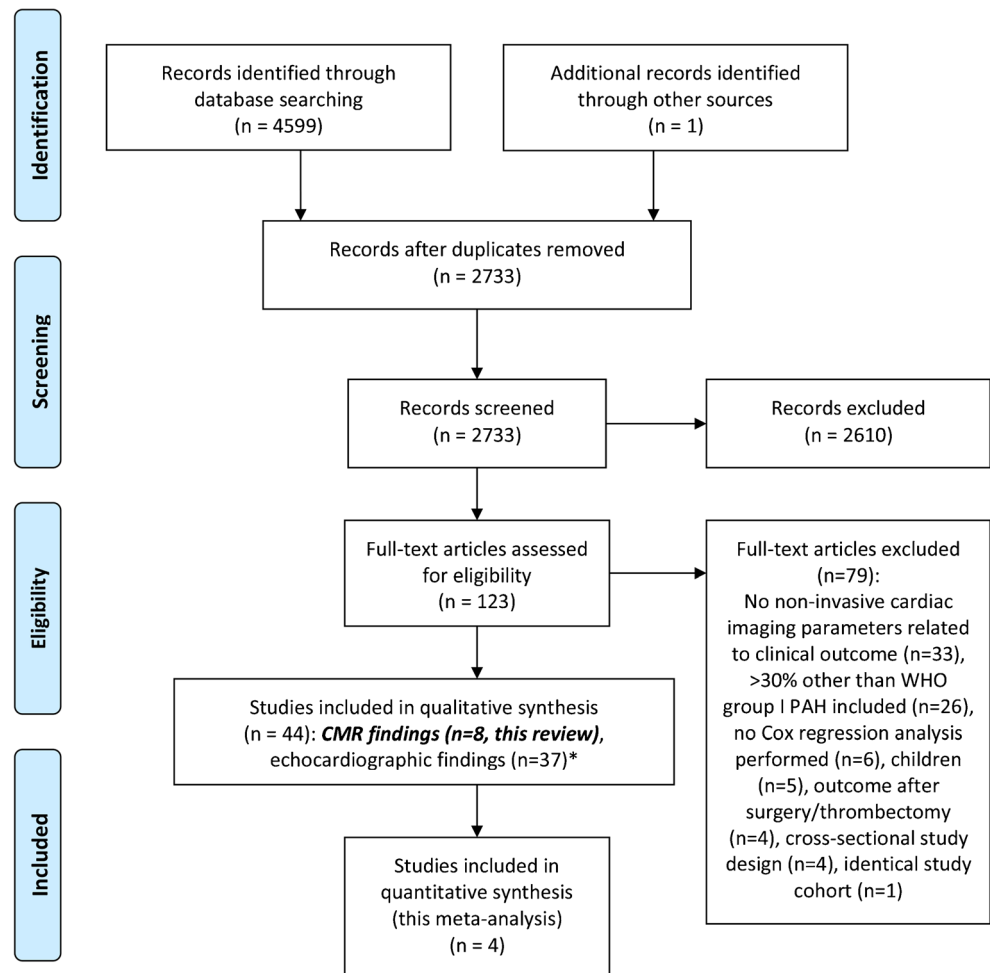
Assessment of methodological quality

Study quality was critically appraised using previously developed criteria for prognostic studies [15]. We assessed study design, missing data and loss to follow-up (selection bias), adequate description and measurement of imaging features and outcome (information bias), reported effect size, treatment of continuous risk predictors and multivariable adjustment for possible confounders.

Data extraction and analysis

Study characteristics and hazard ratios (HRs) for all investigated CMR findings with accompanying 95 % confidence intervals (CIs) were extracted using a standardized form. Meta-analysis was performed for all CMR findings investigated by three of more studies, using random effect models. HRs for specific findings were recalculated to one uniform clinically applicable number of units change. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic [16]. CMR findings investigated as dichotomous variables were additionally presented in the corresponding forest plots. To determine the effect of individual study data, sensitivity analyses were performed by recalculating pooled HRs after excluding the results of one study. If study data were used in multiple papers and the same CMR findings were evaluated, only the study with the largest sample size was selected, thus excluding the risk of using duplicate data in our meta-analysis. The risk of publication bias was assessed using visual inspection of funnel plots and Egger's test [17].

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 flow diagram. * One study investigated both echocardiographic and cardiac magnetic resonance imaging (CMR) findings. *PAH* pulmonary arterial hypertension

Results

Search results

Through a systematic literature search in MEDLINE and EMBASE and extensive reference cross-checking, 2,733 potentially relevant records were retrieved, of which 2,610 were excluded based on title and abstract. After full-text review of the remaining 123 articles, 44 papers were finally selected, of which eight studies in 539 patients described CMR findings (Fig. 1) [18–25].

Study and patient characteristics of the included studies are presented in Table 1. The studies were published between 2007 and 2014; study size ranged from 37 to 110 patients, mean age ranged from 39 to 62 years, and 60–79 % of the population was female. The majority of patients were diagnosed with idiopathic PAH (41–100 %), two studies included a subset of patients with congenital heart disease (9 % and 24 %, respectively) [23, 25] and one study included patients with PH group III, IV or V

(24 % of patients) [21]. Two studies did not report information on the use of PAH-specific mediation [24, 25]; in all other studies >60 % of patients were on PAH-specific therapy at baseline.

The majority of studies used death (or transplant) as the primary outcome; two studies used a composite outcome, additionally including hospitalization for heart failure [21, 23]. Mean follow-up duration varied between 10 and 45 months, and the primary outcome event occurred in 4–25 patients (10–33 % of the study population).

Methodological aspects

The individual bias assessment per study is detailed in Table 2. Five out of eight studies had a retrospective study design. Information on missing values and loss to follow-up was not reported in two studies. It is therefore important to recognize the possible impact of selection bias.

Right heart catheterization was used for the diagnosis of PAH in 100 % of the included patients. The majority

Table 1 Study characteristics

Author, year (ref)	Study population				WHO classification (%)												PAH medication (%)				Outcome		
	Size (n)	Age (mean±SD)	Sex (% female)	NYHA class III-IV (%)	Idiopathic PAH	Hereditary PAH	Drug/toxin	PAH-CTD	PAH-HIV	Po-PAH	PAH-CHD	WHO I PAH (other/not specified)	WHO II (left heart disease)	WHO III (lung disease)	WHO IV (CTEPH)	WHO V (unclear/multifactorial)	Calcium antagonist	PD5-inhibitor	Endothelin receptor antagonist	Prostacyclin analogue	Endpoint	Follow-up duration (months, mean±SD or median [IQR])	Events n (%)
Gan, 2007 [18]	70	50±15	79	nr	70	–	–	23	3	–	–	4	–	–	–	–	4	6	51	29	Death	nr	18 (26)
Van Wolferen, 2007 [19]	64	43±13	73	89	100	–	–	–	–	–	–	–	–	–	–	–	8	6	39	47	Death, transplant	32±16	19 (30)
Van de Veerdonk, 2011 [20]	110	53±15	76	52	66	6	3	18	2	5	–	–	–	–	–	–	3	15	35	14	Death	12 [10–16]	13 (12)
Freed, 2012 [21]	58	53±14	74	nr	41	–	–	–	–	–	–	34	14	2	3	5	–	31	1	31	Death, transplant, admission for HF	10±6	19 (33)
Yamada, 2012 [22]	41	39±14	71	51	100	–	–	–	–	–	–	–	–	–	–	–	22	88	54	34	Death	45±26	4 (10)
Cho, 2014 [23]	37	46±14	76	35	65	–	–	5	–	–	24	5	–	–	–	–	8	21	62	14	Death, admission for HF	16 [13–18]	7 (19)
Swift, 2014 [24]	80	59±17	60	66	100	–	–	–	–	–	–	–	–	–	–	–	nr	nr	nr	nr	Death	32±14	23 (29)
Swift, 2014 [25]	79	62±16	61	nr	44	–	–	47	–	–	9	–	–	–	–	–	nr	nr	nr	nr	Death	nr	25 (32)

CHD congenital heart disease, *CTD* connective tissue disease, *CTEPH* chronic thrombo-embolic pulmonary hypertension, *HF* heart failure, *HIV* human immunodeficiency virus, *IQR* interquartile range, *NYHA* New York Heart Association, *PAH* pulmonary arterial hypertension, *PD5* phosphodiesterase 5, *SD* standard deviation, *nr* not reported, *WHO* World Health Organization

Table 2 Methodological quality of the included studies

Author, year	Selection bias			Information bias: defined and measured appropriately?				Statistical calculation of effect size			
	Study design	Missing data	Loss to follow-up	Description of CMR protocol	Measurement of CMR findings	Definition and measurement of outcome	Description of statistical analysis	Effect size: hazard ratios	Treatment of continuous predictors	Multivariable adjustment	Multivariable analysis appropriate
Gan, 2007 [18]	−	nr	+	+	+	+	+	+	+	±	−
Van Wolferen, 2007 [19]	+	+	+	±	±	+	±	+	+	±	−
Van de Veerdonk, 2011 [20]	+	±	+	+	+	+	+	+	+	±	−
Freed, 2012 [21]	+	±	+	±	+	+	+	+	+	±	−
Yamada, 2012 [22]	−	+	+	+	±	+	±	+	+	−	NA
Cho, 2014 [23]	−	nr	nr	±	+	+	±	+	−	−	NA
Swift, 2014 [24]	−	+	+	±	+	±	+	+	+	−	NA
Swift, 2014 [25]	−	+	nr	+	+	±	+	+	+	+	+

nr not reported, *NA* not applicable

Study design: + prospective cohort, − retrospective cohort

Missing data: + <5 %, ± 5 − 10 % or <5 % selective

Loss to follow-up: + <5 %

CMR protocol and statistical analysis: + well defined, ± moderately defined

CMR findings and outcome: + well defined and measured appropriately, ± moderately defined or moderately measured

Effect size: + Cox regression model and outcomes presented as HR [95 % CI]

Treatment of continuous predictors: + all kept continuous, − all categorized/dichotomized *Multivariable adjustment:* + yes, at least for age and sex, ± multivariate adjustment for other factors, − no multivariate analysis performed or not described

Multivariable analysis appropriate: + ≥10 events per predictor used, − <10 events per predictor used

Table 3 Overview of investigated cardiac magnetic resonance imaging (CMR) findings per study

CMR finding	Total studies (n)	Gan, 2007 [18]	Van Wolferen, 2007 [19]	Van de Veerdonk, 2011 [20]	Freed, 2012 [21]	Yamada, 2012 [22]	Cho, 2014 [23]	Swift, 2014 [24]	Swift , 2014 [25]
RV ejection fraction	6		x[a]	x[a]	x	x	x	x	
RV end-diastolic volume	5		x[a]	x[a]	x	x		x	
RV end-systolic volume	4			x[a]	x	x		x	
RV stroke volume	3				x	x		x	
PA flow stroke volume index	2		x[a]					x	
PA flow cardiac index	2		x[a]					x	
RV mass	3		x[a]		x	x			
LV ejection fraction	5		x[a]	x[a]	x	x		x	
LV end-diastolic volume	5		x[a]	x[a]	x	x		x	
LV end-systolic volume	4			x[a]	x	x		x	
LV stroke volume	2			x[a]				x	
LV mass	3		x[a]		x	x			
RV wall thickness	1		x[a]						
LV wall thickness	1		x[a]						
Ventricular mass index (RV/LV mass)	1							x	
RA volume	1				x				
LA volume	1				x				
PA relative area change	1	x							
RV insertion points late gadolinium enhancement	1				x				
Full width at half maximum of the bolus passage	1								x
Pulmonary transit time	1								x

LV left ventricular, *PA* pulmonary artery, *RV* right ventricular

[a] Additional serial investigation of CMR finding (change between baseline and follow-up)

of studies used short-axis segmentation for the measurement of RV volumes [19–21, 23, 24]; one study used a transverse segmenting method [22] and none of the studies used axial slice segmentation. Slice thickness varied between 5 and 10 mm and temporal resolution between 20 and 25 frames/cycle or 35–45 ms. Two studies did not report spatial or temporal resolution [19, 21]. None of the studies explicitly described if the valvular planes were taken into account in the segmentation and how the tricuspid valve was delineated; however, most studies do mention that both ventricles were covered from base to apex. Most studies are not clear about the methodology used for the selection of the trabeculae. The technical details regarding the CMR acquisition and analysis are described in more detail in Supplemental File 2.

Although all studies reported HRs using Cox regression analysis, large differences were found regarding the type and number of predictors per event used in the multivariable analysis. Five studies performed some form of multivariable adjustment, of which only one study adjusted for age and sex. Only one study used ten or more

events per predictor. Because of this large variety between studies and overall suboptimal methodological quality of multivariable adjustment, it was decided to present only univariable HRs in the forest plots.

Prognostic value of baseline CMR findings

Eight studies evaluated 21 different CMR findings, as shown in Table 3. Meta-analysis was performed for nine CMR findings that were evaluated by three or more studies. Forest plots and pooled HRs are presented in Fig. 2. The strongest predictor of mortality was RV ejection fraction: pooled HR 1.23 (95 % CI 1.07–1.41, p = 0.003) per 5 % decrease. In addition, RV end-diastolic volume index (p = 0.049) and end-systolic volume index (p = 0.013) and left ventricular (LV) end-diastolic volume index (p = 0.045) were of prognostic importance. Notably, measurements of RV and LV mass did not provide prognostic information in PAH (p = 0.852 and p = 0.983, respectively).

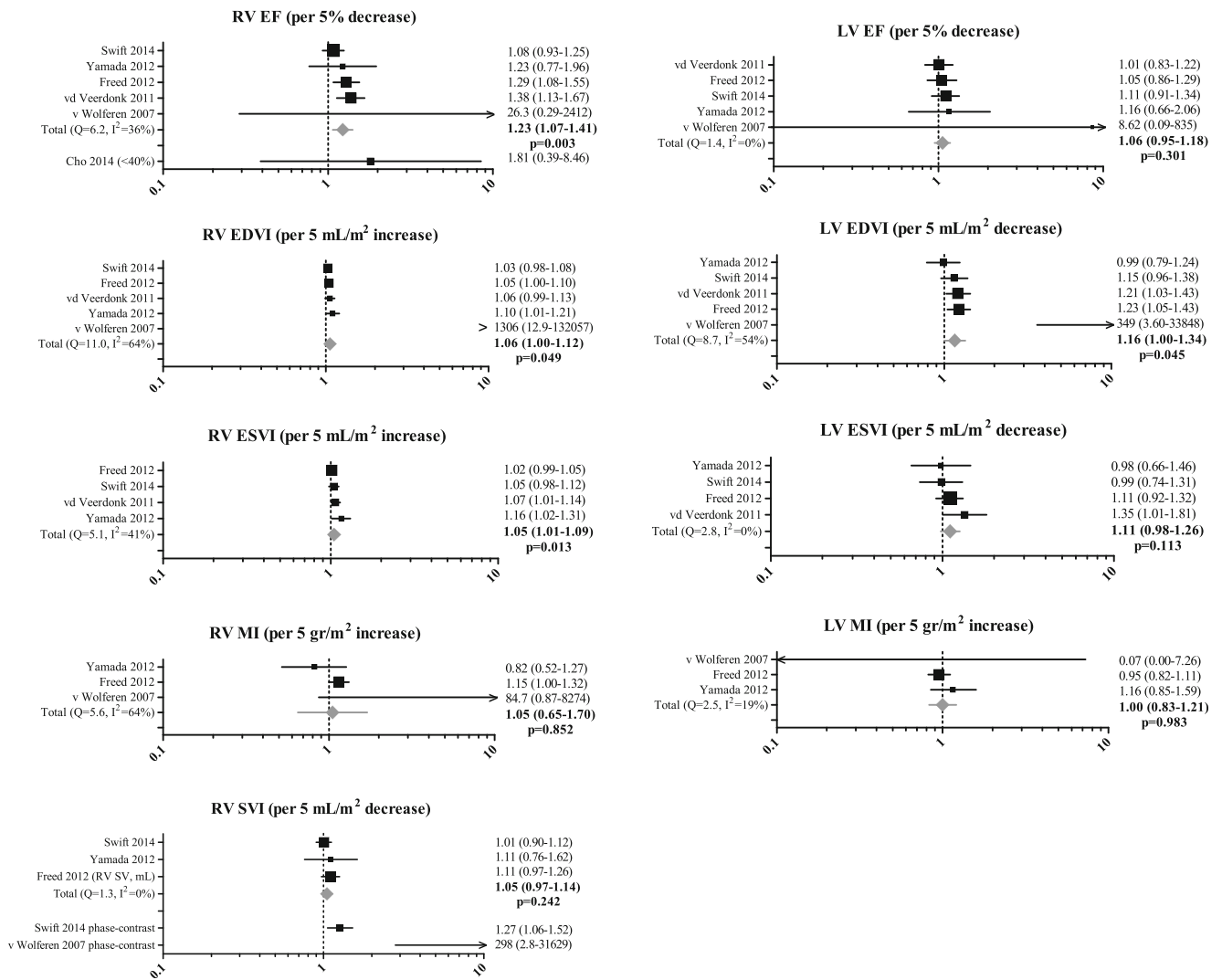Although RV stroke volume index as measured by the summation of disks method did not have a significant

Fig. 2 Prognostic value of cardiac magnetic resonance imaging (CMR) findings evaluated by three or more studies. Values are presented as mean [95 % confidence interval]. *EDVI* end-diastolic volume index, *EF* ejection fraction, *ESVI* end-systolic volume index, *LV* left ventricular, *MI* mass index, *RV* right ventricular, *SVI* stroke volume index

prognostic value (pooled HR 1.05, p = 0.242) [21, 22, 24], the pulmonary artery (PA) flow stroke volume index as measured by CMR phase-contrast imaging predicted mortality in two studies [19, 24]. Less investigated CMR measurements such as LV stroke volume [20, 24], pulmonary artery relative area change [18], left atrial volume, late gadolinium enhancement at RV insertion points [21] and two novel dynamic contrast-enhanced CMR measurements (full width at half maximum of the bolus passage and pulmonary transit time) [25] seem promising but require further evaluation.

Serial CMR evaluation

Two studies included in this review additionally quantified the individual change in specific CMR findings during a follow-up period and directly associated these with patient outcomes.

Van Wolferen et al. [19] showed that overall mortality was associated with a decrease in RV ejection fraction (p = 0.015) and PA flow stroke volume index (p = 0.006) at 1-year follow-up. Van de Veerdonk's group [20] reported a 1-year change in RV ejection fraction (p = 0.014), RV end-diastolic and end-systolic volume index (both p < 0.001) as significant predictors of long-term outcome.

Risk of bias assessment

A combination of visual assessment of funnel plots and Egger's [17] test did not provide statistical evidence for publication bias for any of the CMR findings included in the meta-analysis. Statistical heterogeneity among studies was generally low, as presented by Cochran's Q and I^2 statistics in Fig. 2 in the corresponding forest plots. We noted a discrepancy between the values that were reported in the study by van

Wolferen et al. [19] compared to the other studies, as effect sizes and standard errors were extremely large in this study. We therefore conducted sensitivity analyses by excluding the results of this study. This did not result in significantly different HRs and did thus not change our conclusions.

Discussion

To our knowledge, this is the first systematic review and meta-analysis that substantiates the clinical yield of CMR findings in the prognostication of PAH patients. Among eight studies (539 patients) that investigated 21 different CMR findings, RV ejection fraction was found to be the strongest and most well established predictor of mortality in PAH. In addition, increased RV volumes and decreased LV end-diastolic volume at baseline were found to be associated with a higher mortality risk in PAH patients.

Right heart failure

The primary cause of death in PAH is right heart decompensation [8]. This is congruent with the observation that a decrease in RV function is such an important prognostic factor, as it indicates that the RV is no longer able to cope with the high pulmonary pressures, leading to increased RV diastolic pressures and RV dilatation. RV cardiac output as invasively assessed during right heart catheterization has similarly shown to predict mortality in PAH [7, 8]. Studies that have investigated echocardiographic measurements of RV function, such as TAPSE or RV longitudinal strain, report similar findings [26, 27]. RV ejection fraction assessed with equilibrium radionuclide angiography also showed to be of prognostic importance [28]. Nevertheless, CMR is currently considered as the reference standard for the assessment of RV volumes and function [29]. RV function as measured with CMR may therefore be the most accurate and thus most reliable predictor. However, it has to be acknowledged that direct comparisons between the different imaging modalities are not reported yet.

Ventricular-ventricular interaction

Whereas CMR-derived RV volumes are increased in high-risk PAH patients, LV end-diastolic volume is decreased. Similar results have been reported in several echocardiographic studies [30–32]. These findings emphasize even more the inextricable connection between the two ventricles. Although often considered as separate entities, the two ventricles share common myofibers, a noncompliant pericardium and of course the interventricular septum [33]. The pressure-overloaded RV will alter LV geometry by a leftward septal shift, resulting in a D-shaped LV, which is generally considered as one of the hallmarks of pulmonary hypertension. This so-called systolic D-

sign is primarily an expression of RV pressure overload, in contrast to a diastolic D-sign which is considered a sign of a volume-overloaded RV [34]. Interestingly, previous studies have shown that the diastolic leftward septal shift is associated with mortality in PAH, in contrast to the systolic leftward septal shift [35]. Accordingly, we found decreased LV end-diastolic volume to be of prognostic value, in contrast to LV end-systolic volume.

The overall observation that systolic LV geometry is not associated with mortality may be explained by the fact that RV systolic pressures are generally high in a stable PAH state. However, once the RV starts to fail, LV preload will decrease due to lower transpulmonary flow, and RV diastolic pressures will rise. The accompanied altered diastolic LV geometry can therefore be seen as a direct expression of RV failure [35]. Subsequently, this altered shape could impair LV filling and function, further leading to increased pulmonary pressures, which may create a vicious circle tilting a stable PAH state towards clinical deterioration and, ultimately, death.

Serial measurements

Apart from baseline findings evaluated at the time of diagnosis, changes in several haemodynamic, functional, biochemical and imaging variables could carry incremental prognostic information, as they conceivably better reflect an individual's course of disease [19, 20, 36, 37]. Thus far, only two studies have directly related subject-specific changes in CMR measurements to clinical outcome using Cox regression [19, 20]. Both studies report the prognostic importance of a decrease in RV ejection fraction over time. In addition, van de Veerdonk et al. [38] recently published the results of repeated CMR measurements during a follow-up period of 10 years in patients with initially stable idiopathic PAH for 5 years. Although no HRs were presented, this study showed that late disease progression is also accompanied by increased RV volumes and decreased RV ejection fraction.

RV mass

Based on three studies, our results showed that RV mass does not provide prognostic information in PAH [19, 21, 22]. This is probably because concentric RV hypertrophy is an adaptive response to increased RV pressures that serves to maintain wall stress as low as possible, as is also seen in the LV [39, 40].

RV mass-to-volume ratio allows the distinction between RV concentric and eccentric hypertrophy, which might better reflect the RV's adaptive or maladaptive response. A recently published cross-sectional study in patients with idiopathic PAH showed that eccentric hypertrophy, reflected by a lower RV mass-to-volume ratio, was clearly related to worse RV systolic function, right ventricular to arterial coupling and

clinical impairment [40]. Moreover, in patients with tetralogy of Fallot, a lower RV mass-to-volume ratio was predictive of death [41]. Therefore, it may be more prudent to focus on RV mass-to-volume ratios rather than on RV mass alone.

Study limitations

Although we calculated pooled effect estimates in our review, the results of the random effect models should be interpreted with caution, as we included only univariable HRs in the meta-analysis, due to the large variability between studies in which multivariable adjustment was performed (regarding the type and number of predictors per event used). Second, although formal tests for publication bias yielded mainly non-significant results, the relative lack of power of Egger's test in detecting publication bias for imaging findings investigated in less than ten studies should be recognized. Theoretically, publication bias can cause under-reporting of non-significant HRs, leading to a relative overestimation of the pooled HRs. Finally, although differences within studies regarding the CMR acquisition and analysis probably reflect the normal variance in day-to-day practice, they may lead to less precise measurements (independent of the outcome). While the vast majority of the studies used short-axis segmentation, it has been suggested that axial segmentation results in higher reproducibility, as it may decrease the difficulty of valve delineation in the basal slices [42, 43]. Incomplete segmentation of the tricuspid plane, inaccurate delineation of the basal slice and the methodology used to deal with the trabeculae can substantially impact the measurements of RV volumes [44, 45]. The subsequent 'random noise' would dilute the effect and thus could cause a relative underestimation of the actual hazard ratios.

Clinical implications

This review substantiates the clinical yield of specific CMR findings in the identification of patients with PAH at higher risk of clinical deterioration. This is important, as timely intensification of PAH-specific therapy could prevent further clinical worsening and death. In addition, CMR-derived RV ejection fraction could be of additional value for the longitudinal assessment of PAH. More research is needed to investigate the prognostic value of other serial CMR measurements, and baseline measurements such as RV mass-to-volume ratio, LV stroke volume, pulmonary artery relative area change and left atrial volume. In addition, it would be worthwhile to directly compare the prognostic value of RV function measured using CMR with RV function measured using other non-invasive imaging modalities, such as echocardiography.

Conclusion

CMR is useful and accurate in the prognostication of PAH patients. RV ejection fraction at baseline and during follow-up is the strongest and most well investigated predictor of mortality in patients with PAH. In addition, increased RV volumes and decreased LV end-diastolic volume are of prognostic importance.

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