Hulshof, HG, Eijsvogels, TMH, Kleinnibbelink, G, van Dijk, AP, George, KP, Oxborough, D and Thijssen, DHJ

Prognostic value of right ventricular longitudinal strain in patients with pulmonary hypertension: a systematic review and meta-analysis.

PROGNOSTIC VALUE OF RIGHT VENTRICULAR LONGITUDINAL STRAIN IN PATIENTS WITH PULMONARY HYPERTENSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

HUGO G. HULSHOF[1] (hugo.g.hulshof@radboudumc.nl)
THIJS M.H. EIJSVOGELS[1,2] (Thijs.Eijsvogels@radboudumc.nl)
GEERT KLEINNIBBELINK[1,2] (G.Kleinnibbelink@radboudumc.nl)
ARIE P. VAN DIJK[1] (Arie.vanDijk@radboudumc.nl)
KEITH P. GEORGE[2] (K.George@ljmu.ac.uk)
DAVID L. OXBOROUGH[2] (D.L.Oxborough@ljmu.ac.uk)
DICK H.J. THIJSSEN[1,2] (Dick.Thijssen@radboudumc.nl)

[1]Research Institute for Health Sciences, Departments of Physiology and Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands
[2] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom'

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Author for correspondence: Prof. Dick H.J. Thijssen, Department of Physiology Radboud University Medical Center, Philips van Leijdenlaan 15, 6525 EX, Nijmegen, The Netherlands, Email: dick.thijssen@radboudumc.nl, Tel: (+31)24 36 14222, Fax: (+31)24 366 8340

ABSTRACT

Aims. Pulmonary hypertension (PH) is associated with high morbidity and mortality and the predictive capacity of traditional functional echocardiographic measures is poor. Recent studies assessed the predictive capacity of right ventricular longitudinal strain (RVLS). Diversity in methods between these studies resulted in conflicting outcomes. The purpose of this systematic review and meta-analysis was to determine the independent prognostic value of RVLS for PH-related events and all-cause mortality.

Methods and results. A systematic search in Pubmed (MEDLINE), Embase, the Cochrane Library and Web of Science was performed to identify studies that examined the prognostic value of RVLS in patients with PH. Studies reporting Cox regression based Hazard Ratios (HR) for a combined endpoint of mortality and PH-related events or all-cause mortality for echocardiographic derived RVLS were included. A weighted mean of the multivariate HR was used to determine the independent predictive value of RVLS.

Eleven studies met our criteria, including 1,169 patients with PH (67% female, 0.6-3.8 years follow-up). PH patients with a relative reduction of RVLS of 19% had a significantly higher risk for the combined endpoint (HR: 1.22, 95%CI: 1.07-1.40), while patients with a relative reduction of RVLS of 22% had a significantly higher risk for all-cause mortality (HR: 2.96, 95%CI: 2.00-4.38).

Conclusion. This systematic review and meta-analysis showed that RVLS has independent prognostic value for a combined endpoint and all-cause mortality in patients with PH. Collectively, these findings emphasize that RVLS may have value for optimizing current predictive models for clinical events or mortality in patients with PH.

KEYWORDS: Right ventricular longitudinal strain, pulmonary hypertension, prognostic value, echocardiography

INTRODUCTION

Pulmonary hypertension (PH) is a progressive disease with a 5-year survival rate of approximately 50%, depending on aetiology and disease severity.(1) Although the aetiology of PH relates to an increased pulmonary artery resistance, the primary cause of death relates to right ventricular (RV) failure since the RV has to overcome the increased pulmonary resistance in order to maintain cardiac output.(2) Consequently, echocardiographic measurements of RV structure and function are routinely performed during follow-up of patients with PH.(3, 4) Due to complex RV geometry and load dependency of the RV functional parameters, traditional echocardiographic indices such as RV fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE), have limited prognostic power in patients with PH.(3)

The introduction of speckle tracking echocardiography has allowed for the measurement of ventricular longitudinal strain, a measure of ventricular deformation to assess specific local and global function.(5) In heart failure, valvular heart disease, cardiomyopathy and ischaemic heart disease, left ventricular longitudinal strain independently predicts future events.(6) Patients with PH demonstrate a reduced RV longitudinal strain (RVLS) compared to healthy controls, whilst several studies have examined the prognostic value of RVLS in patients with PH.(7-30) These studies report a broad range of outcomes, ranging from no significant predictive capacity to a high predictive capacity. These differences in outcome may relate to differences in methodology between studies, such as variation in aetiology (PH *vs* pulmonary arterial hypertension (PAH)), included population for HR calculation (inclusion of healthy controls or non PH patient *vs* just PH patients), patient management at time of inclusion (treatment naive vs. single or combined therapy), follow-up duration (0.6-5.0 years), outcome parameters (morbidity *vs* all-cause mortality), group size (n=17 up to n=406) and methods in

which the HRs were determined (percentile change (continuous parameter) *vs* a predefined cut-off point (dichotomous parameter)).(7-11, 14-17, 21, 23, 24, 28, 29) The heterogeneity in study designs and outcomes provide a challenge when attempting to establish the potential prognostic value of RVLS in patients with PH. Combining these studies in a systematic review and meta-analysis will provide clarity on the prognostic value of RVLS in patients with PH.

The purpose of this systematic review and meta-analysis was to determine the independent prognostic value of RVLS in patients with PH on PH-related events and all-cause mortality. We hypothesize that RVLS will have independent prognostic value in PH patients for PH-related events and all-cause mortality.

METHODS

Search strategy

A systematic search was performed with the use of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement 2015 (PRISMA).(31) Pubmed (MEDLINE), Embase, the Cochrane Library and Web of Science were systematically searched for articles published before February 1th, 2018. The following search strategy was used, with adaptation for each database: ((((("Hypertension, Pulmonary"[Mesh]) OR ((Pulmonary hypertension[tiab] OR Pulmonary artery hypertension[tiab] OR Pulmonary arterial hypertension[tiab] OR PAH[tiab] OR lung arterial hypertension[tiab] OR lung artery hypertension[tiab] OR lung hypertension[tiab])))) AND ((strain[tiab] OR deformation[tiab]))) AND ((("Prognosis"[Mesh] OR "Survival Analysis"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Hospitalization"[Mesh])) OR (Prognos*[tiab] OR Predict*[tiab] OR Surviv*[tiab] OR Mortalit*[tiab] OR Hazard ratio*[tiab] OR Hospitalization[tiab] OR

Hospitalisation[tiab])). References of included articles were manually checked for possible eligible studies that were missed during the literature search.

Study selection

After the initial search, duplicates were eliminated from the database. Two authors (H.H., G.K.) independently screened the remaining study titles and abstracts for eligibility using the predefined inclusion and exclusion criteria (Table 1), resulting in 42 articles from which full text was assessed (Fig. 1). We included studies in which either RV free wall longitudinal strain (RVFWS) or RV global longitudinal strain (RVGLS) was evaluated as a predictor for a combined endpoint of mortality and PH-related events or (all-cause) mortality. We excluded those studies, which did not perform Cox proportional hazard ratio analysis, or if the (independent) prognostic value of RVLS in PH patients was not reported. Additionally in order to ensure we determine the independent prognostic value of RVLS in patients with PH only, we excluded studies which performed Cox proportional hazard ratio analysis in a population which included non PH patients (i.e. healthy controls or suspected patients).

Data extraction

Data was independently extracted by two authors (H.H. and G.K.) using a predetermined data extraction file. Differences in data extraction were resolved by consensus and if necessary a third author was consulted (T.E.). Since all selected studies included strain, but only one study stain and strain rate, we focused on the prognostic value of strain only. Univariate and multivariate HR (95%-CI), the mean RVLS for the study population and the RVLS cutoff value for calculation of the HR were extracted from the individual studies (Table 2). The included studies reported HRs on either a continuous scale (i.e. change in risk per % RVLS) and/or a dichotomous scale (i.e. below/above a cut-off point). In case of a dichotomous scale

the HR should increase with a higher absolute value (due to the negative nature of RVLS), but as some studies investigated the beneficial effect of a RVLS value below a certain cut-off point, we calculated the inverse HR (1/HR – [1/95%-CI]) to ensure homogeneous presentation of the data. Additional information gathered consisted of: sample size, age, sex, World Health Organisation (WHO) class, New York Heart Association (NYHA) class, the follow-up period and the clinical endpoint of the individual studies (Table 3). For assessment of study quality, data regarding the echocardiographic assessment was gathered consisting of manufacturer, assessment software, echocardiographic window / image, included segments, methods of optimization and usage of the guidelines. When viable data was missing, an attempt was made to request missing data from the authors by email (n=4 studies). Three out of four studies with missing data provided the requested information and were included in our meta-analysis (Figure 1).

Study quality

All studies included in our meta-analysis were assessed for quality using the Quality In Prognosis Studies (QUIPS) checklist for measuring study quality by two authors (H.H. and G.K.).(32) The QUIPS checklist exists of 31 items divided over six domains; study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. For each domain, several items were evaluated after which the domain was scored for the presence of low, moderate or high risk of bias. As recommended, a predefined overall rating was applied.(32) Studies with a high risk of bias score in a single domain or ≥3 scores of moderate risk of bias in different domains were rated as high risk of bias and excluded from this review (Supplementary Table 1).

Echocardiographic assessment

To ensure high quality and consistency of the RVLS measurement we only included studies which reported adherence to the ASE guidelines for echocardiographic assessment of the right heart(33) and/or chamber quantification(34), used a (focused) RV apical 4 chamber view and traced the endocardial border for RVLS determination.

Statistical analysis

Review Manager 5.3 (Cochrane Community) was used to perform a meta-analysis of the reported multivariate HRs. The reported HRs [95%-CI] were converted to a log (HR) and the complementing standard error (SE) using the formula:

$$SE = \frac{\ln\big(upper\ boundary\ (95\% - CI)\big) - \ln\big(lower\ boundary\ (95\% - CI)\big)}{(2 * 1.96)}$$

The resulting values were inserted in the inverse variance method for calculation of HRs using a random effects analysis to calculate the mean weighted HR [95% CI] for all studies. Separate analysis were performed for 1) a combined endpoint of mortality and PH-related events and 2) all-cause mortality. To provide further insight in the relation between RVLS and the risk for the combined endpoint or all-cause mortality, we calculated the relative reduction of RVLS (in %) for which the HR was determined. For this purpose, we defined the relative reduction of RVLS as: the difference between the mean RVLS of the PH patients above the cut-off point and the cut-off point (for dichotomous scales) or between the mean RVLS of the PH patients and the chosen amount of change in % strain (for continuous scales). The weighted mean relative reduction in RVLS and follow-up time was calculated by multiplying the relative % reduction of RVLS or months of follow-up with the number of included patients per study, after which the cumulative value was divided by the total number of patients included in each analysis.

RESULTS

Study selection

During our search we identified 1,558 potential articles for inclusion. After removal of duplicates, 1,155 articles remained, from which title and abstract were screened for potential inclusion. Finally, a total of 42 studies were considered to be eligible for inclusion (Figure 1). After carefully reading through the full-texts, we identified 12 studies that met our inclusion criteria.(7-11, 14, 15, 21, 23, 26, 28, 29) From these 12 studies, six provided data on all-cause mortality(9, 10, 14, 15, 23, 28), from which one study did not report nor provide the results of multivariate analysis.(14) This study was therefore excluded from our meta-analysis. Seven studies reported data for the combined endpoint.(7, 8, 10, 11, 21, 26, 29) One study reported separate data for all-cause mortality and combined endpoint and was included for both analysis.(10) The remaining 11 studies included a total number of 1,169 patients with PH. Studies included predominantly female patients (range: 56-83%), with a mean age varying from 39 to 66 years. Details about the patient population, WHO class, NYHA class and study design of studies that were included are summarized in Table 3.

Study endpoints

Studies that examined the combined endpoint included 821 patients with PH, with a follow-up time ranging from 0.6-3.8 years. PH-related events varied from hospitalizations for worsening of PH(7, 8, 10, 21), lung transplantation(8, 10, 26), atrial septostomy(8), pulmonary endarterectomy(21), balloon pulmonary angioplasty(21) and intensified PH medical therapy.(8, 11) Studies that explored all-cause mortality as the primary endpoint included a total of 399 patients with PH, with a follow-up time ranging from 2.0-3.8 years.

Echocardiographic assessment

All studies reported that strain was calculated from 2D or 3D grey scale apical 4-chamber orientation, whilst one study performed both 2D and 3D-strain imaging.(28). Strain was calculated with a variety of software packages (EchoPAC, GE Medical Systems, n=8; Syngo vector velocity imaging, Siemens, n=2; 2D cardiac performance analysis, TomTec, n=1). 10 out of 11 studies determined a multivariate HR for RVFWS, while 4 out of 11 studies determined the multivariate HR for RVGLS. Half of the studies (6 out of 11) reported the methods applied for image optimization (i.e. adjustment of image sector width, gain and greyscale), while 9 out of 11 studies reported a frame-rate of >40 frames/s for strain analysis.

Combined endpoint

Seven studies adopted a combined endpoint of mortality and PH-related events and had a mean follow-up time of 26±17 months.(7, 8, 10, 11, 21, 26, 29) All but one (26) study revealed a significant HR after univariate analysis. After multivariate analysis, four studies revealed a significant HR for mortality and PH-related events(7, 8, 10, 26), while HR did not achieve statistical significance in three studies.(11, 21, 29) Combining all multivariate HRs in our meta-analysis revealed that a relative reduction of 19% (range -5 to -31%) of RVLS significantly increased the risk (HR: 1.22, 95%CI: 1.07-1.40) for the combined endpoint of mortality and PH-related events (Figure 2). Studies with a relative reduction below 10% of RVLS tended to be insignificant after multivariate analysis while studies with a relative reduction larger than 10% of RVLS did present significantly higher HR's after multivariate analysis (Figure 2).

All-cause mortality

Using data from univariate analysis, all five studies revealed a significant increased HR for RVLS in the prediction for future all-cause mortality after a mean follow-up time of 30±9

months. Multivariate analysis revealed that a lower RVLS was associated with a significantly higher HR for all-cause mortality in all studies.(9, 10, 15, 23, 28) Combining all multivariate HRs, our meta-analysis revealed that a relative reduction of 22% (range -10 to -33%) of RVLS was associated with an increased risk (HR: 2.96, 95%CI: 2.00-4.38) for all-cause mortality (Figure 3). No clear relation between a larger relative reduction in % of RVLS and HR was present (Figure 3).

DISCUSSION

The purpose of this systematic review and meta-analysis was to examine whether RVLS has prognostic value for future events in patients with PH. The key finding was that RVLS has independent prognostic value for all-cause mortality (Figure 3). To a lesser extent, RVLS also demonstrated independent predictive capacity for the combined endpoint of mortality and PH-related events (Figure 2). Collectively, these findings emphasize that RVLS is a valuable tool with independent prognostic value for all-cause mortality in PH patients.

Impact of PH on RVLS

The thin RV walls consist of longitudinal, circumferential and oblique oriented muscle fibers.(35) The free wall predominantly consists of transverse fibers with scanty subendocardial longitudinal oriented fibers, while in the septal wall the oblique fibers are in a helical shape.(35) Coiling and shortening of the helical-shaped oblique fibers determine the shortening of the RV, producing 80% of RV systolic function. In contrast, contraction of the transverse fibers accounts for just 20% of RV systolic function.(35) In a healthy RV, contraction is therefore predominantly driven by shortening of the RV in the longitudinal direction (35, 36), highlighting the importance of examining RVLS(35) in clinical and

research scenarios. In PH, an increase in afterload influences the mechanical function of the RV, which subsequently leads to a decrease in longitudinal shortening (37), indicating insufficient contraction and leading to a reduction of RV stroke volume. The increased afterload forces the RV to adapt, causing either hypertrophy and/or increased contractility to preserve function and stroke volume.(38) Ultimately, however, these processes may lead to maladaptive remodelling, which causes dilation of the chamber and altering of the helical orientation of the oblique fibers, leading to (progressive) attenuation of function.(35) This maladaptive process ultimately contributes to clinical progression and/or mortality. The strong relation between an increase in afterload and/or ventricular maladaptation alongside a decrease in RVLS likely explains the strong and independent prognostic value for RVLS for all-cause mortality in PH patients.

All-cause mortality vs. combined endpoint

Our meta-analysis revealed a lower predictive capacity for combined endpoints *versus* all-cause mortality. This difference may be explained by the fact that clinical events included in the analysis for the combined endpoint are heterogeneous and, therefore, not all events may directly relate to strain (hence, the lower predictive capacity). Other factors than cardiac strain (e.g. gas transfer in the lungs(39)) may contribute to the occurrence of these clinical events. In addition, several studies included intensified PH medical therapy as a combined endpoint, whilst this unlikely relates to cardiac strain. Therefore, the diversity in clinical events included in the combined endpoint, but also the weak link between some of these factors and cardiac strain, lowers the discriminating capacity of RVLS to predict a combined endpoint *versus* all-cause mortality.

Predictive capacity vs. a relative reduction in % of RVLS

As shown in Figure 3 there is no clear relation between the relative reduction in % of RVLS and the HR for all-cause mortality. This may be explained by the differences across study designs. In contrast to our expectations, the three studies with the lowest relative reduction in RVLS presented the highest HRs in the analysis for all-cause mortality. These three studies all used a dichotomous cut-off value (between -17% and -20%) for RVLS(9, 15, 28), which was higher than the mean RVLS value for the PH patients in the two remaining studies (i.e. -16.1% and -15%).(10, 23) The latter two studies calculated the HR per SD-unit change in RVLS, which resulted in a lower absolute cut-off (approximately -11.1 and -10%) value and in a higher incidence of mortality in the group above the cut-off value. In contrast to the cut-off values in the latter two studies, additional analysis to identify the ideal cut-off value in 4 out of these 5 studies showed that an absolute cut-off between -12.5% and -19.1% had the highest sensitivity and specificity to detect all-cause mortality in PH patients.(9, 10, 23, 28) This indicates that the calculated HR per SD-unit change underestimates the predictive value of RVLS in the latter two studies.

Future direction and clinical implications. Outcomes of the present meta-analysis supports the use of RVLS in patients with PH. Although RVLS has independent predictive value, recent strategies for predicting mortality and events in PH patients consists of constructing multi-parameter predictive models(40) including TAPSE and/or RFVAC to increase the predictive value in PH patients.(3, 41) Several studies included in our meta-analysis revealed RVLS to has superior predictive value over RVFAC and TAPSE, indicating that RVLS may be a more sensitive predictor for RV dysfunction.(8, 10, 15) Implementing RVLS in these multi-parameter predictive models therefore may increase their predictive value for future events. In addition to predicting future events, a relative reduction in RVLS might be indicative for (adjustment of) pharmacological therapy and/or surgery. Improvement of RVLS

after pharmacological therapy and/or surgery has shown to be related to lower risks for mortality and PH-related events.(16, 24) These data further support the use of RVLS in clinical practice, as RVLS changes across time are associated to clinically relevant outcomes in PH patients. Future studies determining reference values and confirming clinically-relevant cut-off values are warranted to improve clinical decision-making and implementation of RVLS in practice.

Limitations. The studies within this meta-analysis were non-uniform in design and varied in the inclusion criteria, methods to measure RVLS (intervendor and technique variabilities), follow-up periods and endpoints. We corrected for these between-study variation using a random effects model in our meta-analysis. Additionally to minimize the impact of intervendor and technique variability we reported the relative reduction of % of RVLS rather than absolute values. We also included studies which used RVFWS (n=7) and RVGLS (n=1) or both (n=3) to determine the predictive value of RVLS in PH patients. Unfortunately, the small amount of studies investigating RVGLS did not allow for a comparison between the predictive value of RVGLS and RVFWS. Similarly, we were not able to compare data obtained with 2D vs. 3D echocardiography and/or machines from different vendors. Due to differences in methodology and statistical approach, not all relevant studies could be included in our analysis. Studies using ROC-analysis(18, 20, 22, 25, 30), Kaplan Meier survival curves(18, 19, 22, 25), odds ratios (20) or predictive models (12, 13, 19) reported outcomes that align with the findings of the present meta-analysis.

Conclusion. This systematic review and meta-analysis showed that RVLS possess independent prognostic value for a combined endpoint (HR: 1.22, 95%CI: 1.07-1.40) and all-cause mortality (HR: 2.96, 95%CI: 2.00-4.38) in patients with PH. Collectively, these

findings emphasize that RVLS might be useful for optimizing current predictive models for morality or clinical events in PH patients.

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Disclosures

None

REFERENCES

1. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343-9.
2. Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013;188(3):365-9.
3. Haddad F, Spruijt OA, Denault AY, Mercier O, Brunner N, Furman D, et al. Right Heart Score for Predicting Outcome in Idiopathic, Familial, or Drug- and Toxin-Associated Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2015;8(6):627-38.
4. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
5. Artis NJ, Oxborough DL, Williams G, Pepper CB, Tan LB. Two-dimensional strain imaging: a new echocardiographic advance with research and clinical applications. Int J Cardiol. 2008;123(3):240-8.
6. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart. 2014;100(21):1673-80.
7. da Costa Junior AA, Ota-Arakaki JS, Ramos RP, Uellendahl M, Mancuso FJ, Gil MA, et al. Diagnostic and prognostic value of right ventricular strain in patients with pulmonary arterial hypertension and relatively preserved functional capacity studied with echocardiography and magnetic resonance. Int J Cardiovasc Imaging. 2017;33(1):39-46.
8. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(5):711-21.
9. van Kessel M, Seaton D, Chan J, Yamada A, Kermeen F, Butler T, et al. Prognostic value of right ventricular free wall strain in pulmonary hypertension patients with pseudo-normalized tricuspid annular plane systolic excursion values. Int J Cardiovasc Imaging. 2016;32(6):905-12.
10. Park JH, Park MM, Farha S, Sharp J, Lundgrin E, Comhair S, et al. Impaired Global Right Ventricular Longitudinal Strain Predicts Long-Term Adverse Outcomes in Patients with Pulmonary Arterial Hypertension. J Cardiovasc Ultrasound. 2015;23(2):91-9.
11. Giusca S, Jurcut R, Coman IM, Ghiorghiu I, Catrina D, Popescu BA, et al. Right ventricular function predicts clinical response to specific vasodilator therapy in patients with pulmonary hypertension. Echocardiography. 2013;30(1):17-26.
12. Fukuda Y, Tanaka H, Motoji Y, Ryo K, Sawa T, Imanishi J, et al. Utility of combining assessment of right ventricular function and right atrial remodeling as a prognostic factor for patients with pulmonary hypertension. Int J Cardiovasc Imaging. 2014;30(7):1269-77.
13. Fukuda Y, Tanaka H, Ryo-Koriyama K, Motoji Y, Sano H, Shimoura H, et al. Comprehensive Functional Assessment of Right-Sided Heart Using Speckle Tracking Strain for Patients with Pulmonary Hypertension. Echocardiography. 2016;33(7):1001-8.
14. Goda A, Ryo K, Delgado-Montero A, Tayal B, Handa R, Simon MA, et al. The Prognostic Utility of a Simplified Biventricular Echocardiographic Index of Cardiac Remodeling in Patients with Pulmonary Hypertension. Journal of the American Society of

Echocardiography : official publication of the American Society of Echocardiography. 2016;29(6):554-60.
15. Haeck ML, Scherptong RW, Marsan NA, Holman ER, Schalij MJ, Bax JJ, et al. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging. 2012;5(5):628-36.
16. Hardegree EL, Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Kushwaha SS, et al. Role of serial quantitative assessment of right ventricular function by strain in pulmonary arterial hypertension. Am J Cardiol. 2013;111(1):143-8.
17. Henein MY, Gronlund C, Tossavainen E, Soderberg S, Gonzalez M, Lindqvist P. Right and left heart dysfunction predict mortality in pulmonary hypertension. Clinical physiology and functional imaging. 2017;37(1):45-51.
18. Motoji Y, Tanaka H, Fukuda Y, Ryo K, Emoto N, Kawai H, et al. Efficacy of right ventricular free-wall longitudinal speckle-tracking strain for predicting long-term outcome in patients with pulmonary hypertension. Circ J. 2013;77(3):756-63.
19. Motoji Y, Tanaka H, Fukuda Y, Sano H, Ryo K, Imanishi J, et al. Interdependence of right ventricular systolic function and left ventricular filling and its association with outcome for patients with pulmonary hypertension. Int J Cardiovasc Imaging. 2015;31(4):691-8.
20. Muntean I, Benedek T, Melinte M, Suteu C, Toganel R. Deformation pattern and predictive value of right ventricular longitudinal strain in children with pulmonary arterial hypertension. Cardiovasc Ultrasound. 2016;14(1):27.
21. Murata M, Tsugu T, Kawakami T, Kataoka M, Minakata Y, Endo J, et al. Right ventricular dyssynchrony predicts clinical outcomes in patients with pulmonary hypertension. Int J Cardiol. 2017;228:912-8.
22. Okumura K, Humpl T, Dragulescu A, Mertens L, Friedberg MK. Longitudinal assessment of right ventricular myocardial strain in relation to transplant-free survival in children with idiopathic pulmonary hypertension. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2014;27(12):1344-51.
23. Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Hsiao JF, Maalouf JF, et al. Right ventricular strain for prediction of survival in patients with pulmonary arterial hypertension. Chest. 2011;139(6):1299-309.
24. Sano H, Tanaka H, Motoji Y, Fukuda Y, Sawa T, Mochizuki Y, et al. Right ventricular function and right-heart echocardiographic response to therapy predict long-term outcome in patients with pulmonary hypertension. Can J Cardiol. 2015;31(4):529-36.
25. Smith BC, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P. Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol. 2014;64(1):41-51.
26. Unlu S, Farsalinos K, Ameloot K, Daraban AM, Ciarka A, Delcroix M, et al. Apical traction: a novel visual echocardiographic parameter to predict survival in patients with pulmonary hypertension. Eur Heart J Cardiovasc Imaging. 2016;17(2):177-83.
27. de Siqueira ME, Pozo E, Fernandes VR, Sengupta PP, Modesto K, Gupta SS, et al. Characterization and clinical significance of right ventricular mechanics in pulmonary hypertension evaluated with cardiovascular magnetic resonance feature tracking. J Cardiovasc Magn Reson. 2016;18(1):39.
28. Vitarelli A, Mangieri E, Terzano C, Gaudio C, Salsano F, Rosato E, et al. Three-dimensional echocardiography and 2D-3D speckle-tracking imaging in chronic pulmonary hypertension: diagnostic accuracy in detecting hemodynamic signs of right ventricular (RV) failure. J Am Heart Assoc. 2015;4(3):e001584.

29. Moceri P, Duchateau N, Baudouy D, Schouver ED, Leroy S, Squara F, et al. Three-dimensional right-ventricular regional deformation and survival in pulmonary hypertension. Eur Heart J Cardiovasc Imaging. 2017.
30. Li Y, Wang Y, Meng X, Zhu W, Lu X. Assessment of right ventricular longitudinal strain by 2D speckle tracking imaging compared with RV function and hemodynamics in pulmonary hypertension. Int J Cardiovasc Imaging. 2017.
31. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
32. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
33. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2010;23(7):685-713; quiz 86-8.
34. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
35. Buckberg G, Hoffman JI. Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. J Thorac Cardiovasc Surg. 2014;148(6):3166-71 e1-4.
36. Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. Circ Res. 1953;1(2):162-70.
37. Brown SB, Raina A, Katz D, Szerlip M, Wiegers SE, Forfia PR. Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. Chest. 2011;140(1):27-33.
38. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol. 2013;62(25 Suppl):D22-33.
39. Farha S, Laskowski D, George D, Park MM, Tang WH, Dweik RA, et al. Loss of alveolar membrane diffusing capacity and pulmonary capillary blood volume in pulmonary arterial hypertension. Respir Res. 2013;14:6.
40. Oxborough D, Lord R. Predicting Mortality in Pulmonary Arterial Hypertension: Can It Really Be That Simple? JACC Cardiovasc Imaging. 2015;8(6):639-41.
41. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164-72.

Figure 1-Flow chart of study selection

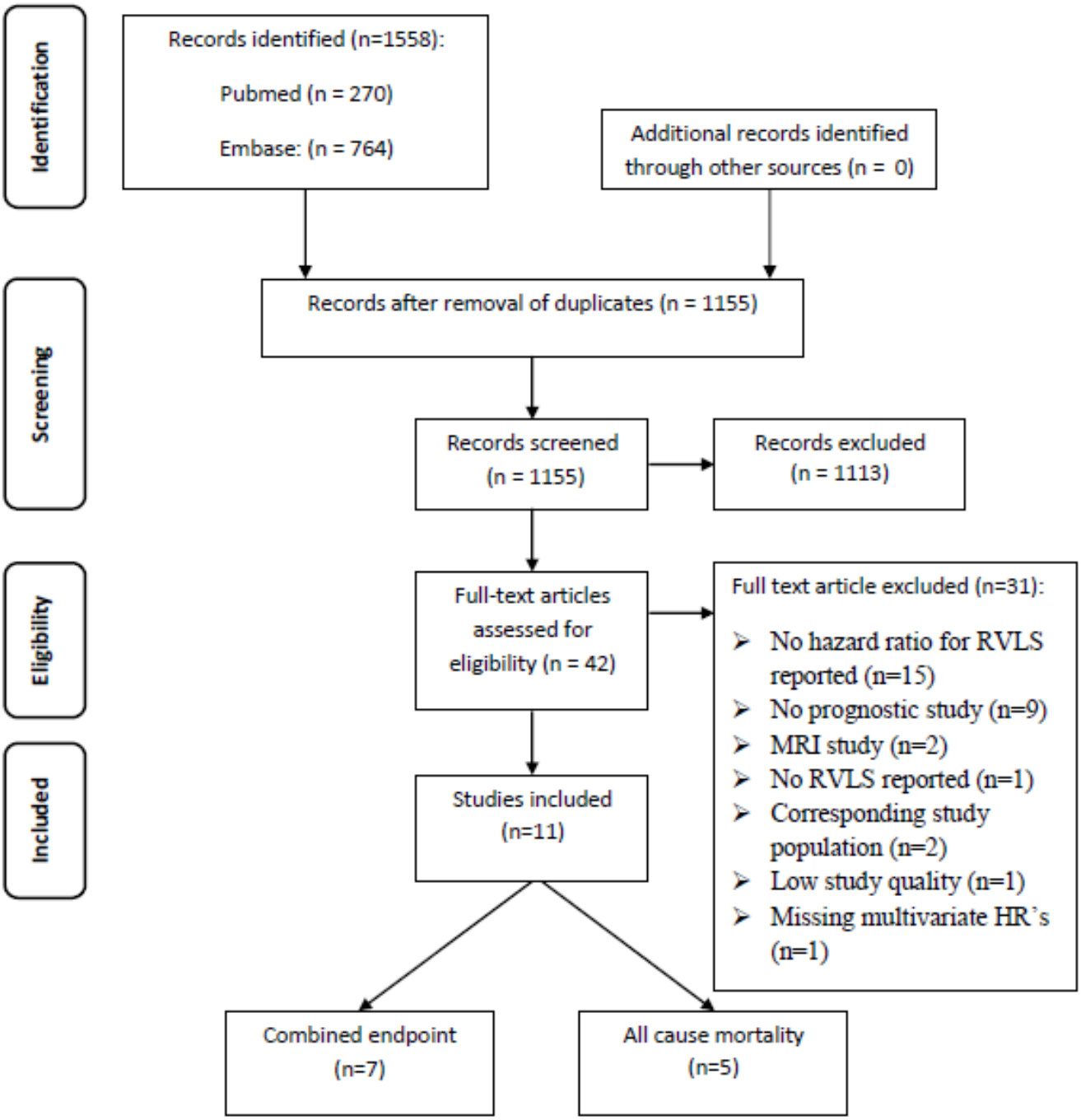


Figure 2-Forrest plot summarising the effect of a (relative) reduction of RVLS on a combined endpoint of mortality and PH-related events in PH patients. The red squares present the weighted effect size and the black lines the 95%-CIs. The size of the red squares indicate the weight of the study. The black diamond presents the mean weighted HR.

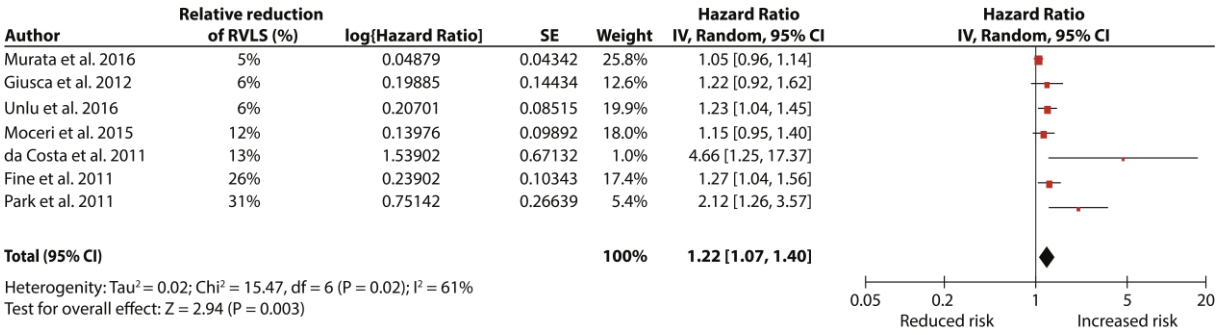
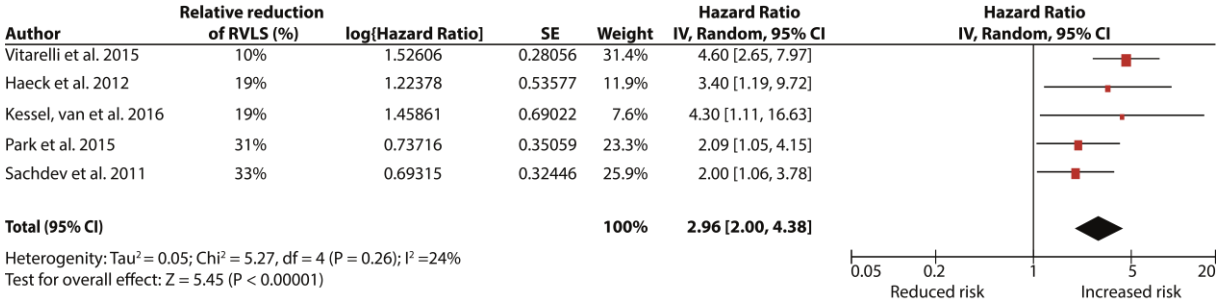


Figure 3-Forrest plot summarising the effect of a (relative) reduction of RVLS on all-cause mortality in PH patients. The red squares present the weighted effect size and the black lines the 95%-CIs. The size of the red squares indicate the weight of the study. The black diamond presents the mean weighted HR.



503 **Table 1. Inclusion and exclusion criteria**

Inclusion	Exclusion
Population	
- Pulmonary hypertension	- Animal studies
	- Paediatric studies
Outcome Echocardiography	
- Right ventricular strain	
Outcome measures	
- Hazard ratio's based on multivariate cox-regression analysis	- Receiver operating curves
	- Model based prediction
Other	
- English language	- Language other than English
- Full papers	- Abstract only
	- Conference proceedings

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Table 2: Values of right ventricular longitudinal strain and hazard ratio's extracted from the included studies

First author	Absolute values of RVLS (mean±SD)				Cut-off		Relative reduction of RVLS (%)	HR ratio [95% CI]	Log (HR)	SE
	Healthy controls	PH-patients	PH-patients above cut-off value	PH-patients below cut-off value	Dichotomous	Continuous				
Combined endpoint										
da Costa et al. (7)	-27.5±2.4%	-16.1±6.8%			< -14%		13%	4.66 (1.25-7.37)	1.53902	0.67132
Fine et al. (8)	-25.0±5.2%	-19.6±6.6%				-6.7%	26%	1.27 (1.04-1.56)	0.23902	0.10343
Giusca et al. (11)		-17.3±7.2%				-1%	6%	1.22 (0.92-1.62)	0.19885	0.14434
Moceri et al. (29) †	-14.1±3.6	-8.4±3.6%				-1%	12%	1.15 (0.95-1.40)	0.13976	0.09892
Murata et al. (21)		-19.9±6.4%				-1%	5%	1.05 (0.97-1.15)	0.04879	0.04342
Park et al. (10)		-16.1±5.0%				-5%	31%	2.09 (1.05-4.15)	0.75142	0.26639
Unlu et al. (26)*		-16.6%#				-1%	5%	1.23 (1.04-1.45)	0.20701	0.08515
All-cause mortality										
Haeck et al. (15)			-23.5±3.7%	-14.0±3.5	< -19%		19%	3.40 (1.19-9.72)	1.22378	0.53577
van Kessel et al. (9)			-24.8±4.0%	-15.9±2.9	< -20%		19%	4.30 (1.11-16.61)	1.45861	0.69022
Park et al. (10)		-16.1±5.0%				-5%	31%	2.08 (1.13-3.80)	0.73716	0.35059
Sachdev et al. (23)		-15±5.0%				-5%	33%	2.00 (1.11-3.96)	0.69315	0.32446
Vitarelli et al. (28) †	-23.8±5.8	-18.8%#			< -17%		10%	4.60 (2.79-8.38)	1.52606	0.28056

Symbols denote *=Inverse HR with respect to original article, †=3D strain analysis and #=mean value calculated from multiple groups. (RVLS=Right Ventricular Longitudinal Strain; HR=Hazard Ratio; SE=Standard Error)

Table 3: Population data extracted from the included studies

First author	Study design	Study population	WHO group	NYHA class	PH specific therapy at inclusion	Follow-up (y)	Endpoint
Combined endpoint							
da Costa et al. (7)	NR	N: 66 Age: 45±15 Female sex: 83%	1 (n=66)	I-II (67%) III (33%)	Bosentan and ambrisentan (n=16) Sildenafil (n=31) Calcium channel blockers (n=2) Combined therapy (n=17)	3.3y	Cardiovascular mortality and hospitalization for worsening of PH
Fine et al. (8)	Prospective	N: 406 Age: 59±16 Female sex: 65%	1 (n=300) 3 (n=58) 4 (n=48)	I (20%) II (34%) III (38%) IV (8%)	Prostacyclin (n=50) Endothelin receptor antagonist (n=82) Phosphodiesterase-5 inhibitor (n=89)	1.5y	Cardiopulmonary death and cardiopulmonary events
Giusca et al. (11)	NR	N: 32 Age: 39±15 Female sex: 69%	1 (n=29) 4 (n=3)	II (40.6%) III (56.2%) IV (3.2%)	Bosentan (n=11) Sildenafil (n=16) Combined (n=5)	1.2y	All-cause mortality and treatment failure
Moceri et al. (29) †	Prospective	N: 104 Age: 66±4 Female sex: 56%	1 (n=65) 3 (n=26) 4 (n=11) 5 (n=2)	II (36.5%) III (44.2%) IV (19.3%)	Advanced targeted PAH therapy (n=87)	0.6y	PH related mortality
Murata et al. (21)	Retrospective	N: 100 Age: 51±17 Female Sex:74%	1 (n=72) 4 (n=28)	I (22%) II (46%) III (32%)	Phosphodiesterase-5 inhibitor (n=69) Endothelin receptor antagonist (n=56) Prostacyclins (n=26) Calcium channel blockers (n=11) Vitamin K antagonist (n=28)	1.2y	All-cause mortality, hospitalization and intervention for deterioration right-sided heart-failure

Park et al. (10)	Retrospective	N: 51 Age: 48±14 Female sex: 78%	1 (n=51)	I (4%) II (61%) III (35%)	Phosphodiesterase-5 inhibitor (n=29) Endothelin receptor antagonist (n=26) Prostacyclins (n=32) Calcium channel blockers (n=9)	3.8y	Clinical events
Unlu et al. (26)*	Retrospective	N: 62 Age: 61±15 Female sex: 68%	1 (n=33) 4 (n=29)	I (6.5%) II (25.8%) III (58%) IV (9.7%)	Treatment naïve	3.8y	All-cause mortality and heart or lung transplantation
All-cause mortality							
Haeck et al. (15)	Retrospective	N: 142 Age: 59±15 Female sex: 63%	1 (n=53) 2 (n=46) 3 (n=32) 4 (n=7) 5 (n=4)	NR	Endothelin receptor antagonist (n=37) Phosphodiesterase-5 inhibitor (n=19) B-blocker (n=44) Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor antagonist (n=58) Diuretics (n=91) Anticoagulation (n=64)	2.6y	All-cause mortality
van Kessel et al. (9)	Retrospective	N: 53 Age: 56±9 (n=25); 54±17 (n=28) Female sex: 66%	Mixed (n=53)	II (41.5%) III (41.5%) IV (9.4%) NR (7.%)	Mono therapy (n=27) Double therapy (n=16) Triple therapy (n=8)	2.3y	All-cause mortality
Park et al. (10)	Retrospective	N: 51 Age: 48±14 Female sex: 78%	1 (n=51)	I (4%) II (61%) III (35%)	Phosphodiesterase-5 inhibitor (n=29 Endothelin receptor antagonist (n=26) Prostacyclins (n=32) Calcium channel blockers (n=9)	3.8y	All-cause mortality
Sachdev et al. (23)	NR	N: 80 Age: 56±14 Female sex: 76%	1 (n=80)	I-II (28%) III (63%) IV (9%)	Treatment naïve	2.0y	All-cause mortality
Vitarelli et al. (28) †	NR	N: 73 Age: 53±13 Female sex: 56%	1 (n=25) 2 (n=25) 4 (n=23)	I-II (71%) III-IV (29%)	NR	2.0y	All-cause mortality

Symbols denote †=3D strain analysis. (WHO=World Health Organisation; NYHA=New York Heart Association; PH=Pulmonary Hypertension;

NR=Not Reported)