Journal of Cardiovascular Computed Tomography xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Research paper

A four-tier classification system of pulmonary artery metrics on computed tomography for the diagnosis and prognosis of pulmonary hypertension

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ARTICLE INFO

Keywords:
Pulmonary hypertension
Computed tomography
Main pulmonary artery
Ratio pulmonary artery

ABSTRACT

Background: We aimed to develop a severity classification system of the main pulmonary artery diameter (mPA) and its ratio to the ascending aorta diameter (ratio PA) for the diagnosis and prognosis of pulmonary hypertension (PH) on computed tomography (CT) scans.

Methods: In 228 patients (136 with PH) undergoing right heart catheterization (RHC) and CT for dyspnea, we measured mPA and ratio PA. In a derivation cohort (n = 114), we determined cutpoints for a four-tier severity grading system that would maximize sensitivity and specificity, and validated it in a separate cohort (n = 114). Cutpoints for mPA were defined with ≤27 mm(F) and ≤29 mm(M) as the normal reference range; mild as >27 to <31 mm(F) and >29 to <31 mm(M); moderate ≥31–34 mm; and severe >34 mm. Cutpoints for ratio PA were defined as normal ≤0.9; mild >0.9 to 1.0; moderate >1.0 to 1.1; and severe >1.1.

Results: Sensitivities for normal tier were 99% for mPA and 93% for ratio PA; while specificities for severe tier were 98% for mPA >34 mm and 100% for ratio PA >1.1. C-statistics for four-tier mPA and ratio PA were both 0.90 (derivation) and both 0.85 (validation). Severity of mPA and ratio PA corresponded to hemodynamics by RHC and echocardiography (both $p < 0.001$). Moderate-severe mPA values of ≥31 mm and ratio PA >1.1 had worse survival than normal values (all $p \leq 0.01$).

Conclusion: A CT-based four-tier severity classification system of PA diameter and its ratio to the aortic diameter has high accuracy for PH diagnosis with increased mortality in patients with moderate-severe severity grades. These results may support clinical utilization on chest and cardiac CT reports.

1. Introduction

Pulmonary hypertension (PH) is a heterogeneous disease with a poor prognosis and an estimated mortality of 15% within 1 year [1]. Worse prognosis is associated with more advanced disease and worsened functional class, which emphasizes the importance of early diagnosis and treatment [2]. PH is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg, irrespective of pulmonary capillary wedge pressure (PCWP) or pulmonary vascular resistance (PVR). Pulmonary *arterial* hypertension is further defined by elevated PVR >3 Wood units and normal PCWP, pulmonary *venous* hypertension by elevated PCWP ≥15 mm Hg and normal PVR, and mixed pulmonary hypertension as elevation of both PCWP and PVR [1]. The current gold standard for diagnosis, right heart catheterization (RHC) [1], is invasive and resource-intensive. Imaging may play a role in the early diagnosis of PH in a lower cost and non-invasive manner.

Computed tomography (CT) metrics have been studied as a method for the screening for and diagnosis of PH. Enlarged main pulmonary artery (mPA) diameters on CT [3–14] and increased ratios (ratio PA) of mPA to ascending aorta (Ao) diameter [3, 6, 7, 9, 12, 15–17] have been associated with the presence of PH. The Framingham Heart Study (FHS) established sex-specific normative values by CT for mPA diameters in men of ≤29 mm and in women of ≤27 mm as well as a normative value for ratio PA of ≤0.9 [18]. However, no severity classification for

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https://doi.org/10.1016/j.jcct.2017.12.001
Received 16 October 2017; Accepted 3 December 2017

Abbreviations list

CT	Computed Tomography
Echo	Echocardiogram
FHS	Framingham Heart Study
mPA	Main pulmonary artery
mPAP	Mean Pulmonary Artery Pressure
PAH	Pulmonary Arterial Hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PH	Pulmonary Hypertension
PVR	Pulmonary Vascular Resistance
Ratio PA	Ratio of main pulmonary artery to ascending aorta diameter
RHC	Right heart catheterization
WHO	World Health Organization

mPA and ratio PA has been established for in context with PH. Thus, we aimed to derive and validate a classification system for mPA and ratio PA (stratified as normal, mild, moderate and severe) that would allow the diagnosis of PH. Additionally, we assessed the prognostic implication of this severity classification and compared it to RHC and echocardiography (Echo).

2. Methods

2.1. Study population

We screened 278 consecutive adult (age ≥ 18 years) patients with suspected PH who underwent RHC and at least one chest or cardiac CT for the evaluation of dyspnea at a single tertiary medical center between March 2000 and February 2013. We excluded patients who did not have a CT during the peri-catheterization period, defined as 6 months prior to RHC through 6 weeks after RHC (n = 10), and those whose CT was deemed uninterpretable (n = 22) (i.e. due to incomplete visualization or motion of the mPA on chest or cardiac CT). In addition, 13 patients were excluded due to history of lung transplantation, and 5 were excluded due to missing mPAP values. Our final cohort included 228 patients who had both RHC and at least one chest or cardiac CT, of which 195 (86%) had a transthoracic Echo within 2 years of RHC. Median follow-up was 6.4 years [5.0 years, 8.2 years]. The primary endpoint was all-cause mortality.

We used the World Health Organization (WHO) classification of PH [19] by RHC as our gold standard, and defined patients with PH as those with mPAP ≥ 25 mmHg or PVR > 3 Wood units. We measured the diameters of the mPA and Ao at the level of the bifurcation of the right pulmonary artery in 489 transaxial CT scans and calculated ratio PA, which has previously been described as the mPA diameter divided by the Ao diameter [18].

2.2. Statistical analysis

Descriptive statistics are presented as mean ± standard deviation (SD) or median with interquartile range [IQR] for continuous variables and as frequency and percentages for categorical variables. We used Student *t*-test or Wilcoxon rank-sum tests for continuous variables and Fisher's exact test for categorical variables to compare differences between groups, as appropriate. We evaluated the effect of continuous mPA and ratio PA on long-term survival by using Cox proportional hazards models and adjusted for risk factors that were different ($p < 0.05$) between PH and non-PH patients, including (log-transformed) age, coronary artery disease (CAD), diabetes mellitus (DM), New York Heart Association (NYHA) Functional Class and (log-transformed) serum creatinine. To determine the mPA and ratio PA cutpoints for predicting PH, we used a derivation cohort of 114 patients and examined various cutpoints to (1) maximize the sensitivity for "ruling out" PH, (2) maximize the specificity for "ruling in" PH, and (3) define an intermediate gray-zone. We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and c-statistic of each cutpoint. We performed similar analyses using the remaining 114 patients as the validation cohort.

We further subdivided the intermediate range in order to obtain a four-tier severity classification (Fig. 1) of mPA size using sex-specific thresholds of: (1) normal from the FHS normative values [18] as ≤ 27 mm for women and ≤ 29 mm for men; (2) mild as > 27 to < 31 mm for women and > 29 to < 31 mm for men; (3) moderate as ≥ 31–34 mm for both sexes; (4) severe as > 34 mm for both sexes. Similarly, for ratio PA, we defined thresholds of: (1) normal as ≤ 0.9; (2) mild as > 0.9 to 1.0; (3) moderate as > 1.0 to 1.1; and (4) severe as > 1.1. Logistic regression was used to determine the c-statistic, or area under the receiver operating characteristic curve (AUC), for the four-tier severity classification of the pulmonary artery metrics in the derivation and validation cohorts for diagnosing PH. Survival probabilities stratified by four-tier severity classification were estimated

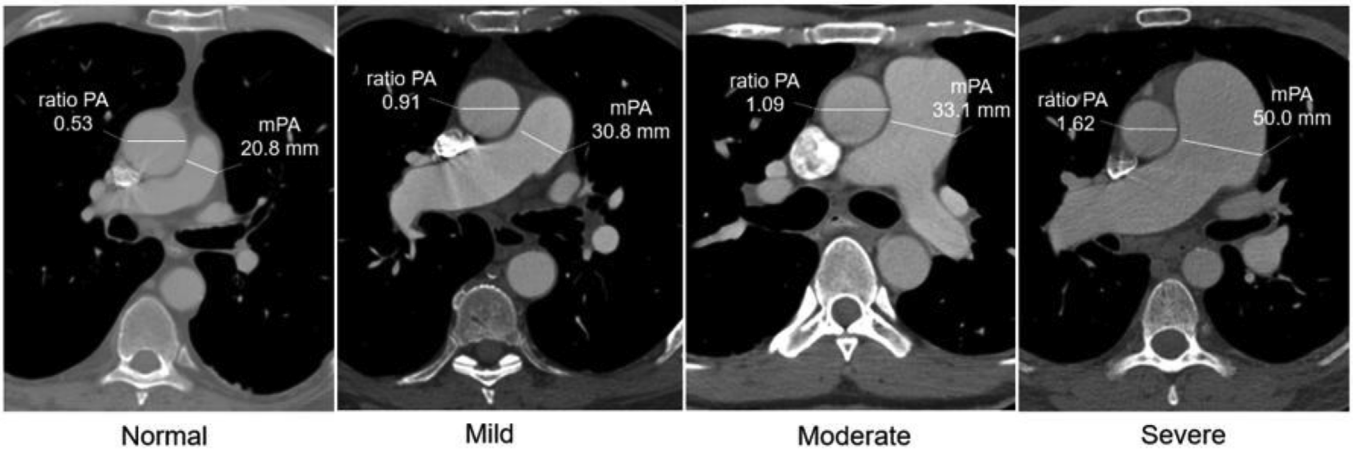

Fig. 1. Examples of mPA and ratio PA CT Measurements in Each of the Groups in the Four-Tier Severity Classification. Measures of mPA and ratio PA at the bifurcation of the right pulmonary artery on transaxial CTs are depicted in representative individuals classified as Normal, Mild, Moderate, and Severe.