ON LINE SUPPLEMENT

CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE Registry

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METHODS

ASPIRE Registry [1] is a large single centre registry of patients referred to a high volume pulmonary hypertension referral centre. All patients in this registry underwent systematic evaluation including echocardiography, detailed blood tests, exercise tolerance test, lung function test, and depending on clinical features oximetry, isotope perfusion scintigraphy, high resolution CT, CT pulmonary angiography(CTPA) and right heart catheterization(RHC). Institutional review board approval from the North Sheffield Ethics Committee was obtained for retrospective review of routinely collected patient data and written patient consent was not required.

Right Heart Catheterization: RHC was performed using a 7 French Swan-Ganz catheter. The form of PAH was classified according to standard criteria (3) and required at right heart catheter a mPAP≥25 mmHg and a PCWP≤15 mmHg.

CT Pulmonary Angiography: CTPA was performed on a 64 slice MDCT scanner (Light-Speed General Electric Medical Systems, Milwaukee, WI). Standard acquisition parameters were used: 100mA with automated dose reduction, 120kV, pitch 1, rotation time 0.5s and 0.625mm collimation. The field of view was 400x400mm with an acquisition matrix of 512x512. 100ml of intravenous contrast

agent (Ultravist 300; Bayer Schering, Berlin, Germany) was administered at a rate of 5ml/sec. HRCT were reconstructed using the contrast enhanced acquisitions with 1.25 mm collimation from the apex of the lung to the diaphragm.

Image analysis and interpretation: Scans were analyzed by a chest radiologist blinded to haemodynamic parameters, clinical findings and outcome. The mutlislice CTPA images were reviewed on dedicated PACS workstations. A second radiologist independently analysed 50 random images.

Vascular changes: Pulmonary artery: aorta ratio (PA/Ao ratio) and the maximum depth of pericardial effusion were measured as previously described (9, 10) (Figure 1). Reflux of contrast into the hepatic veins was assessed using five grades of regurgitation[2] (Figure 2). Inferior vena cava (IVC) size was measured by calculating the cross sectional area of the IVC above the level of the diaphragm, below the right atrium.

Cardiac changes: The maximum mid-transverse diameters of the right and left ventricular cavities were measured in the axial plane at their widest points between the inner surfaces of the free wall and the interventricular septum (IV septum) (Figure 3A). This may lie at different levels. Using these measurements ratio of right to left ventricle (RV/LV ratio) was obtained [3]. From the axial mid-chamber view, right atrial length was measured from the centre of tricuspid annulus to the superior right atrial wall (figure 3B). The size of the right atrium was also qualitatively evaluated using a simple 3 point visual scale: mild, moderate and severe. Displacement of the IV septum was evaluated on a three-point scale as normal septum(i.e. convex toward the right ventricle), flattened septum(straight) and deviated septum(i.e. convex toward the left ventricle) [4]. Thickness of the right ventricular free wall was recorded from the axial images[5].

Parenchymal and mediastinal changes: Ground glass opacification (GGO) was defined as increased opacity of the lung parenchyma without obscuring the pulmonary vessels or bronchi. When GGO was present the pattern was noted as centrilobular, panlobular homogenous, panlobular heterogenous according to Engeler et al[6] (Figure 4). The distribution and extent of GGO was recorded using a system described by Resten et al[7] as upper, lower or random and whether the distribution was random, subpleural or central.

CT scans were also assessed for the presence of fibrosis[8], pleural effusions, mediastinal lymphadenopathy(defined as the transverse lymnphode diameter was greater than 10 mm), dilated bronchial collaterals (defined as transverse vessel diameter greater than 2 mm)[9], septal lines[7] and oesophageal dilatation.

Statistics:

Statistical analysis was performed using PASW Statistics v16(SPSS, Chicago, IL). Continuous variables were presented as mean and standard deviation. Comparisons of continuous variables were performed with analysis of variance (ANOVA) with Bonferroni correction. Categorical variables are presented as number and percentage and compared using Chi-square test. Pearson coefficients were used to examine the correlation of continuous quantitative findings. Prognostic value of CT signs and of baseline characteristics was assessed by means of both univariate and multivariate Cox proportional hazards using forward stepwise model. Collinearity was assessed using linear regression model. Multivariable analysis was performed using all variables with a $P<0.2$ in the univariate model. The agreement between the two readers for the presence or absence of categorical CT findings was evaluated using the κ statistic, as described by Landis and Koch [10]. A κ value of 0–0.20 indicates slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate

agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.

RESULTS

Table 2 summarizes baseline hemodynamic and demographic characteristics for the 5 main subgroups of PAH. The data for the patients who had CT scanning available for review or performed within 3 months of right heart catheterisation (292) was compared to the 442 patients for demographic, functional and hemodynamic characteristics and there was no significant difference between the two data sets.

Survival results:

The maximal duration of follow up was 6 years with a mean follow-up of 3 years. During this period there were 112 deaths.

For PAH as a group, univariate Cox regression analysis demonstrated that cardiac parameters of RV/LV ratio, right atrial size, deviation of interventricular septum and presence and depth of pericardial effusion to predict outcome. Reflux of contrast into the distal hepatic veins and size of IVC and lung changes of septal lines, presence of pleural effusion and mediastinal lymphadenopathy also predicted poor outcome in patients with PAH. Multivariable Cox proportional hazard analysis incorporating clinical, hemodynamic and CT parameters showed that of CT parameters that inferior vena area and the presence of pleural effusion/septal lines were all significant ($p<0.05$) predictors of death and there was a trend for RV:LV ratio ($p=0.06$).

TABLES:

Table 2: Characteristics of Study population

Characteristics	PAH	IPAH	PAH-SSc	PAH-CHD	PAH-CTD nonSSc	PAH-Portal
No. of patients	292	74	95	63	39	14
Age (yrs)	62 (16)	62 (16) †‡	69 (9) *†#	51 (18) *#‡	60 (16) †‡	59 (12)
Female (%)	73	59‡#	85*	71	84*	64
WHO III/IV (%)	62:11	69: 12	69: 13	59: 10	74: 10	64:-
FVC (%)	89 (19)	95 (11) †	95 (14) †	72 (23) *‡§#	85 (18) †	94 (20) †
FEV1 (%)	74 (20)	83 (15) #†	80 (17) †	64 (20) *‡§	73 (17) *	77 (18) †
TLCO (%)	55 (23)	50 (19)†‡	37 (16) †§*	71 (23) *‡#	48 (8) †§	66 (7) #‡
mRAP (mmHg)	9 (5)	10 (6) #‡	6 (5) *	-	7 (4) *	9 (7)
mPAP (mmHg)	46 (14)	51 (11) #‡	42 (14) *	-	43 (11) *	47(10)
PCWP (mmHg)	10 (4)	10 (3)	10 (4)	-	9 (4)	11 (2)
CI (L.min.m2)	2.8 (0.9)	2.4 (0.7) #‡§	3 (0.83)*	-	3.2 (1.03)*	3.4 (0.8)*
PVR (woods unit)	8.7 (5.3)	11.1 (5.2)	7.1 (4.7)	-	7.3(5.0)	6.0 (2.5)
mVO2 (%)	65 (9)	62 (7)	66 (9)	-	65 (8)	70 (8)
ISWD (m)	185 (160)	176 (179) †‡	166 (137) *†#	213 (123) *‡	130 (95) ‡	236 (126)

Data shown is expressed as mean (standard deviation) * p<0.05 in comparison to IPAH, † p<0.05 in comparison to PAH-CHD, # p<0.05 in comparison to PAH-CTD-non-SSc, ‡ p<0.05 in comparison to PAH-SSc, § p<0.05 in comparison to PAH-Portal. PAH: pulmonary arterial hypertension, IPAH: idiopathic pulmonary arterial hypertension, PAH-SSc PAH in association with systemic sclerosis, PAH-CHD: PAH in association with congenital heart disease, PAH-CTD-nonSSC: PAH associated with connective tissue diseae excluding SSc, PAH-portal: PAH in association with portal hypertension, WHO: World Health Organisation Functional Class, FVC: forced vital capacity, FEV1: Forced expired volume in one second, TLco: gas transfer for carbon monoxide, mRAP: mean right atrial pressure, mPAP mean pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, PVR: pulmonary vascular resistance, mVO2: oxygen saturation in the pulmonary artery, ISWD: incremental shuttle walking test distance.

Table 3: Demographic, Haemodynamic and CT predictors of outcome in PAH

Parameters	Univariate HR(CI)	P -value	Multivariate HR(CI)	P -value
Age (years)	1.04(1.02-1.05)	<0.001	1.06(1.02-1.07)	0.001
Gender	0.9(0.60-1.37)	0.65		
WHO classification	1.68(1.35-2.08)	<0.001	1.11(1.70-1.08)	0.01
mRAP (mmHg)	1.01(0.98-1.05)	0.39		
mPAP (mmHg)	0.99(0.98-1.01)	0.91		
CI (L.min.m2)	0.72(0.73-0.94)	<0.019	2.1(1.45-3.03)	<0.001
PVR (dyn.s.cm-5)	1.10(1.00-1.21)	<0.002	1.0(1.00-1.02)	0.17
mVO2 (%)	0.95(0.95-0.98)	<0.001	0.90(0.94-1.01)	0.31
TLCO	0.70(0.60-0.82)	<0.001	0.31(0.12-0.66)	0.003
Cardiac signs				
PA/Ao ratio	0.49(0.24-1.10)	0.09	0.41(0.70-2.3)	0.32
RV/LV ratio	2.59(1.89-3.57)	0.05	1.87(0.95-3.70)	0.06
RA size	1.35(1.17-1.56)	0.011	1.03(0.89-1.37)	0.36
RV hypertrophy	1.00(0.94-1.06)	0.96		
IV septal position				
Normal	Reference		Reference	
straightening	1.49(0.91-2.42)	0.020	1.28(0.89-2.41)	0.13
Deviated	3.10(1.98-4.86)	0.016	2.12(1.91-3.86)	0.11
Pericardial effusion				
presence	1.65(1.17-2.47)	0.010	0.78(0.30-2.03)	0.61
Depth	1.71(1.28-2.11)	<0.05	1.37(0.91-2.69)	0.09
Vascular signs				
IVC size	1.0(1.00-1.002)	0.003	1.10(1.00-1.20)	0.033
Hepatic vein reflux				
None	Reference			
trace into IVC	1.40(0.73-2.50)	0.25		
proximal hepatic vein	1.45(0.83-2.52)	0.19		
mid hepatic vein	1.27(0.63-2.53)	0.49		
distal hepatic vein	1.79(1.05-3.06)	0.03	1.54(0.83-3.70)	0.45
Collaterals	0.55(0.28-1.10)	0.09	0.47(0.10-2.30)	0.35
Lung signs				
GG nodules				
Present	1.00(0.69-1.47)	0.96		
extent <1/3rd	Reference			
1/3rd-2/3rd	0.88(0.39-1.98)	0.75		
>2/3rd	0.95(0.45-2.01)	0.89		
centrilobular	1.04(0.57-1.86)	0.91		
central	1.71(0.72-4.04)	0.22		
Pleural effusion	3.21(2.05-5.08)	<0.001	2.09(1.02-4.31)	0.04
Septal lines	2.64(1.78-3.95)	0.001	1.34(1.10-2.15)	0.02
Lymphadenopathy	1.71(1.13-2.60)	0.016	0.71(0.38-1.32)	0.28

Table 4: CT predictors of outcome by PAH subgroup (on-line supplement)

Parameters	IPAH		PAH-SSc		PAH-CTD-nonSSc		PAH-CHD	
	P value	HR(CI)	P value	HR(CI)	P value	HR(CI)	P value	HR(CI)
Cardiac signs								
PA/Ao ratio	0.23	0.29 (0.41-2.13)	0.68	1.45(0.23-9.13)	0.62	0.48(0.03-7.72)	0.63	1.31(0.43-3.97)
RV/LV ratio	<0.05	2.31(1.33-4.01)	<0.05	2.57(1.59-4.17)	<0.05	4.79(1.30-17.60)	0.08	3.04(0.85-10.88)
RA size	<0.05	2.07(1.47-2.93)	<0.05	1.38(1.08-1.77)	<0.05	1.51(1.03-2.23)	<0.05	1.46 (0.98-2.17)
RV hypertrophy	0.23	1.09(0.94-1.27)	<0.05	1.22(1.04-1.43)	0.23	1.08(0.95-1.24)	0.82	1.01(0.89-1.16)
IV septal position								
normal		Reference		Reference		Reference		Reference
straightening	0.29	1.75(0.61-4.99)	<0.05	2.58(1.23-5.41)	0.09	1.07(0.31-3.65)		1.13(0.41-3.75)
deviated	<0.05	4.11(1.49-11.29)	<0.05	3.63(1.66-7.93)	<0.05	3.69(1.26-10.71)		4.04(1.09 -14.97)
Pericardial effusion								
presence	0.11	1.76(0.88-3.51)	<0.05	2.75(1.44-5.26)	0.09	1.50(0.59-3.83)	0.29	0.49(0.14-1.81)
depth	<0.05	1.67(1.02-1.71)	<0.05	1.08(1.04-1.13)	0.14	1.12(0.96-1.09)	0.71	0.98(0.90-1.07)
Vascular signs								
IVC size	<0.05	1.26(1.09-1.45)	<0.05	1.14(1.01-1.92)	<0.05	1.23(1.02-1.49)	0.80	1.00(0.99- 1.00)
Hepatic vein reflux								
None		Reference		Reference		Reference		Reference
trace into IVC	0.39	1.71(0.49-5.94)	0.67	1.17(0.27-2.33)	0.65	1.28(0.42-3.94)	0.92	1.23(0.51-3.91)
proximal hepatic vein	0.39	1.79(0.59-5.36)	<0.05	1.31(0.41-4.25)	0.67	0.71(0.15-3.37)	0.93	0.63(0.17-2.27)
mid hepatic vein	0.17	2.28(0.69-7.53)	0.64	2.29(0.98-5.35)	0.31	0.34(0.04-2.75)	0.93	0.45(0.14-1.85)
distal hepatic vein	0.38	1.69(0.55-5.17)	<0.05	6.13(2.59-15.07)	0.80	1.21(0.25-5.78)	0.92	1.54(0.53-4.68)
Collaterals	0.95	1.03(0.32-3.40)	0.56	1.21(1.01-5.61)	0.45	0.56(0.13-2.47)	0.62	0.74(0.22-2.43)
Lung signs								
GG nodules								
presence	0.86	0.94(0.47-1.89)	0.31	1.37(0.74-2.57)	0.33	1.63(0.61-4.36)	0.94	1.04(0.34-3.18)
Centrilobular	0.03	3.45(1.19-10.67)	0.41	1.55(0.55-4.43)	0.08	6.9(0.78-62.38)	0.06	4.13(0.94-19.15)
Central	0.42	0.04(0.01-73.35)	0.08	0.33(0.11-0.94)	0.94	0.92(0.10-8.36)	0.65	0.05(0.00-33.06)
Pleural effusion	<0.05	3.68(1.73-8.62)	<0.05	3.06(1.49-6.31)	<0.05	2.87(0.55-3.94)	<0.05	4.55(1.0-20.16)
septal lines	<0.05	2.57(1.29-5.15)	0.18	1.55(0.81-2.97)	0.91	1.12(0.15-8.47)	0.14	2.44(0.74-8.01)
Lymphadenopathy	<0.05	3.42(1.66-7.07)	0.36	1.41(0.67-2.99)	0.60	1.29(0.49-3.46)	0.24	4.69(1.22- 17.97)

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FIGURE LEGENDS:

Figure 1: The pulmonary artery (PA) aorta ratio was obtained by measuring the widest transverse diameter of the PA (blue) and the corresponding transverse diameter of aorta (red).

Figure 2: Grading of tricuspid regurgitation (A) 0 = there is no reflux into IVC, (B) 2 = reflux into IVC but not hepatic veins, (C) 3 = reflux into IVC and proximal hepatic veins (D) 4 = reflux into IVC and distal hepatic veins

Figure 3: (A) The maximum mid-transverse diameters of the RV (blue arrow) and LV (left arrow) cavities were measured in the axial plane at their widest points between the inner surfaces of the free wall and the interventricular septum. (B) For assessing the right atrial size on CT, right atrial length was measured from the centre of tricuspid annulus to the superior right atrial margin

Figure 4: Centrilobular ground glass pattern (A) and central ground glass pattern (B)

Figure 5: Flow chart demonstrating patient inclusion

Figure 6: Kaplan-Myer curve demonstrating survival based on the presence/absence of pleural effusion