

**Increasing Incidence and Prevalence of WHO Groups 1-4 Pulmonary Hypertension: A
*Population-Based Cohort Study in Ontario, Canada.***

Thiwanka D Wijeratne MD, assistant professor^{1,2}, Katherine Lajkosz MSc, research analyst², Susan B. Brogly PhD, assistant professor^{2,3}, M. Diane Lougheed MD, professor^{1,2,4}, Li Jiang MSc, epidemiologist², Ahmad Housin MD Medical resident¹, David Barber MSc, research analyst¹, Ana Johnson PhD, associate professor^{2,4}, Katharine M Doliszny PhD, research assistant¹, Stephen L Archer MD, professor¹

¹Department of Medicine, Queen's University, Kingston, Ontario, Canada

²Institute for Clinical Evaluative Sciences Queen's, Queen's University, Kingston, Ontario

³Department of Surgery, Queen's University, Kingston, Ontario, Canada

⁴Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada

SUPPLEMENTAL MATERIAL

Table of Contents

Definitions	3
Standardized Mortality Ratio (SMR)	
Calculation of Usage of PH Medication	
Table S1: Among patients with PH, codes used to describe their comorbidities	4
Figure S1: Multiple etiologies of Pulmonary Hypertension	5
Table S2: Comorbidities of Pulmonary Hypertension Patients by WHO Group Classification	6
Table S3: Prevalence of PH in Adults with Comorbid Conditions	7
Table S4: Trend Analysis of Incidence Rates (2003-2012)	8
Figure S2: Incidence rates of Pulmonary Hypertension per 100,000 persons by year (by gender)	9
Table S5: Crude Mortality Rate (per 100) by Group of PH and by Age group	10
Figure S3: Crude 1 year mortality rate by calendar year for patients with Pediatric Pulmonary Hypertension	12
Table S6: Description of Group 2/3 adult PH Patients with/without Combination Diagnoses (Group 2+3)	13
Table S7: Standardized Mortality Ratios (2003/2011) for Group 2/3 adult PH patients	14
Figure S4: Survival of Group 2/3 adult PH patients with/without combination diagnoses	15

Standardized Mortality Ratio (SMR)

To determine the impact of PH on mortality we calculated a gender and age-adjusted Standardized Mortality Ratios (SMRs) for two years of our study, 2003 and 2011 using the 2007 Canadian population as the standard population, as described below and in. For PH patients diagnosed in 2003, the observed number of deaths occurring in the 12 months following diagnosis was determined by gender and age. The expected number of deaths in each gender-age category was estimated by multiplying the number of PH patients in each gender-age category in 2003 by the death rate for the respective gender-age category, The observed number of deaths for 2003 was then summed across gender-age categories and then divided by the sum of the expected number of deaths to determine the SMR. The 95% confidence interval for the SMR was calculated using the gamma distribution. This same approach was used for PH cases diagnosed in 2011 and for WHO PH groups.

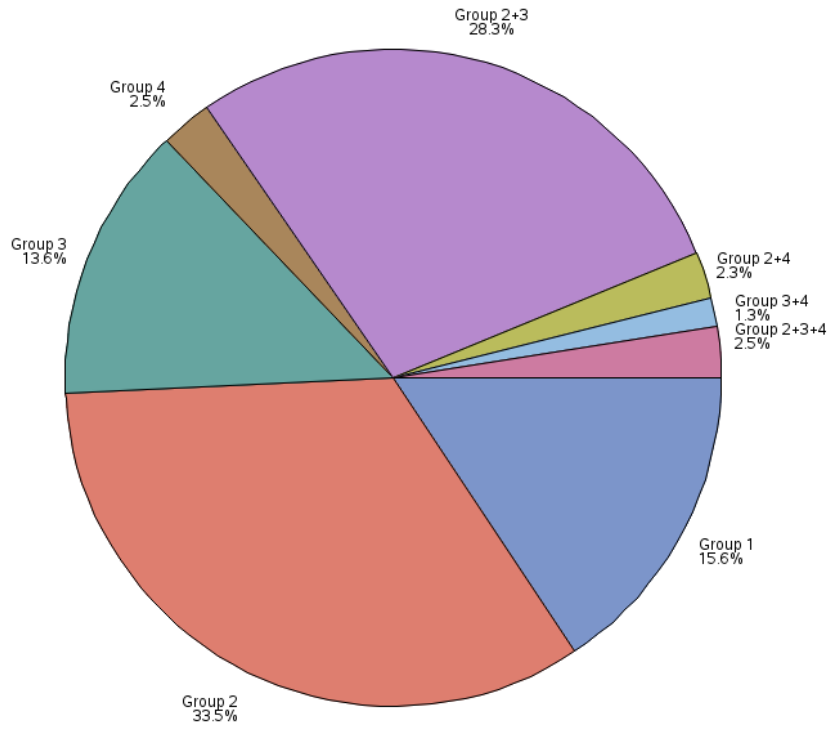
Calculation of Usage of PH Medication:

Medications were considered to be taken in combination if their prescription start and end dates (calculated by adding the number of days supplied to the start date) overlapped by ≥ 7 days. For medication combinations the number of total days supplied was calculated by adding the number of overlapping days in the prescriptions of the two combined medications. The total number of days supplied by calendar year was also determined.

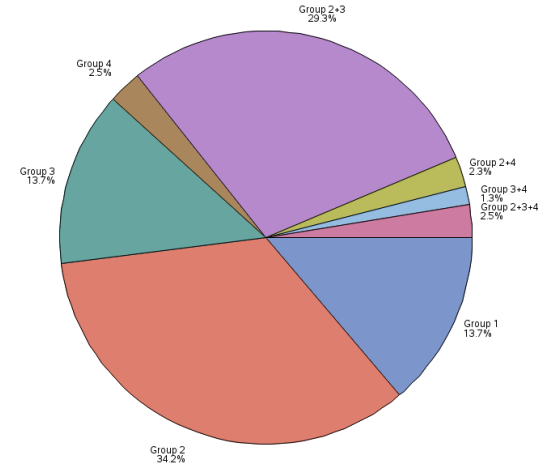
Table S1: Among patients with PH, codes used to describe their comorbidities

Group	ICD-9	ICD-10	OHIP
Group 1	4160, 695.4, 710.0, 710.1, 710.2, 710.3, 710.4, 710.8, 710.9, 714.0, 042, 043, 044, 572.3, 571.2, 571.5, 571.6, 746.84, 746.89, 746.9, V136, 745.4, 745.5, 745.9, 74710, 74711, 74720, 74721, 74722, 74729	I27.0, M32, M33, M34, M35, M05, J99.0, J99.1, B24, K70-K77, Q21, Q25.0, B65	710, 714, 042, 043, 044, 571, 745, 746, 747
Group 2	428.0, 428.1, 428.9, 394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.2, 396.3, 396.8, 396.9, 424.0, 746.5, 746.6, 395.0, 395.1, 395.2, 395.9, 424.1, 746.3, 746.4, 425	I50, Q23, I05, I06, I08.0, I34, I35, I39.0, I39.1, I25.5, I25.6, I25.8, I25.9, O99.4, O90.3, I42.0, I42.1, I42.2, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8	-
Group 3	492.0, 492.8, 518.1, 277.00, 277.01, 518.2, 490, 491.0, 491.1, 491.2, 491.8, 491.9, 496, 5163, 18.1, 500, 502, 503, 505, 515, 748.5, 551.3, 552.3, 553.3, 780.51, 780.53	J40-J44, E84, J60-J70, J82, J84, P27.1, Q79.0, G47.30, G47.31, G47.38, I26, I80.2, 180.3, 182.2	-
Group 4	415.1, 673.80, 673.81, 673.82, 673.83, 673.84, 453.2, 453.8, 453.9	I26, I80.2, I80.3, I82.2	-

All PH patients



Patients ≥ 16 years



Patients <16 years

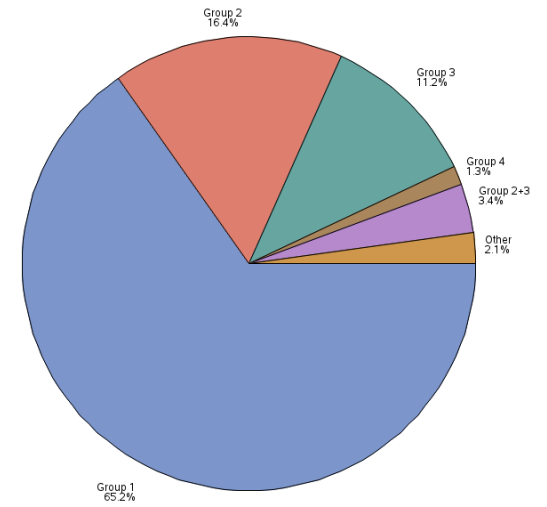


Figure S1: Multiple etiologies of Pulmonary Hypertension

Table S2: Comorbidities of Pulmonary Hypertension Patients by WHO Group Classification

	<16 years	>= 16 years	Total
All Group 1*	N = 1,198	N = 6,705	N = 7,903
Idiopathic PH (%)	78.6	50.4	54.7
Connective Tissue Diseases (%)	0.0	6.4	5.4
Congenital Heart Diseases (%)	41.8	6.1	11.5
All Group 2 (Left Heart Disease) *	N = 394	N = 33,374	N = 33,768
Diastolic/Systolic Dysfunction (%)	67.5	86.8	86.5
Mitral/Aortic Valve Disease (%)	43.9	37.1	37.2
Cardiomyopathy (%)	9.6	16.5	16.4
All Group 3 (Lung Disease/Hypoxia)*	N = 295	N = 22,894	N = 23,189
COPD (%)	12.9	83.0	82.1
Interstitial Lung Disease (%)	81.4	24.2	24.9
Sleep-Disordered Breathing (%)	12.5	10.1	10.1
Group 4: CTEPH	N = 65	N = 4,360	N = 4,425

* = denominator within each group

Abbreviations: PH- pulmonary hypertension; COPD – Chronic Obstructive Pulmonary Disease CTEPH- Chronic Thromboembolic Pulmonary Hypertension

Table S3: Prevalence of PH in Adults with Comorbid Conditions

Comorbid Conditions	2002		2012	
	Prevalence in General Population	Prevalence of PH	Prevalence in General Population	Prevalence of PH
	Number (%)*	Number (%)*	Number (%)*	Number (%)*
Left Heart Disease	212,675 (1.9%)	12,763 (6.0%)	246,852 (2.2%)	8,805 (3.6%)
Diastolic/Systolic Dysfunction	167,068 (1.5%)	10,839 (6.5%)	152,906 (1.4%)	6,760 (4.4%)
Mitral/Aortic Valve Disease	69,739 (0.6%)	5,354 (7.7%)	78,760 (0.7%)	4,008 (5.1%)
Cardiomyopathy	51,659 (0.5%)	2,347 (4.5%)	74,892 (0.7%)	1,669 (2.2%)
Lung disease/Hypoxia	367,866 (3.3%)	8,693 (2.4%)	663,855 (6.0%)	4,691 (0.7%)
COPD	248,046 (2.2%)	7,496 (3.0%)	513,503 (4.6%)	3,613 (0.7%)
Interstitial Lung Disease	157,663 (1.4%)	1,945 (1.2%)	131,360 (1.2%)	0,874 (0.7%)
Thromboembolic disease	56,343 (0.5%)	1,576 (2.8%)	112,880 (1.0%)	1,557 (1.4%)

* The % under the column “Prevalence in General Population” refers to the % of patients with the diagnosis of interest among the population in Ontario ≥16 years of age. The % under column “Prevalence of PH” refers to the % of patients with PH among those who have the diagnosis of interest.

Abbreviations: PH- pulmonary hypertension; COPD – Chronic Obstructive Pulmonary Disease

Note - For each group, % PH cohorts were compared between 2002 and 2012. All comparisons showed a statistically significant change in the percentage of PH cohorts between years (p <0.001)

Table S4: Trend Analysis of Incidence Rates (2003-2012)

	PH Group									
	All		1		2		3		4	
Group	Mean Estimate	P-Value	Mean Estimate	P-Value	Mean Estimate	P-Value	Mean Estimate	P-Value	Mean Estimate	P-Value
All Patients	1.029	<.0001	1.037	0.0014	1.030	<.0001	1.021	0.0011	1.086	<.0001
Adults	1.025	<.0001	1.035	0.0022	1.027	0.0001	1.017	0.0025	1.083	<.0001
Pediatrics	1.041	0.0329	1.031	0.1996	1.051	0.0896	1.054	0.0904	1.078	0.2154
Females	1.030	0.0001	1.038	0.0036	1.031	0.0003	1.024	0.0023	1.086	0.0002
Males	1.027	0.0004	1.035	0.0141	1.029	0.0005	1.017	0.0118	1.087	0.0004

Mean Estimate = average change in incidence between 2003-2012 (e.g. a mean estimate of 1.026 means the average increase in incidence between 2003-2012 was 2.6%)

Trend analysis was done using general additive model

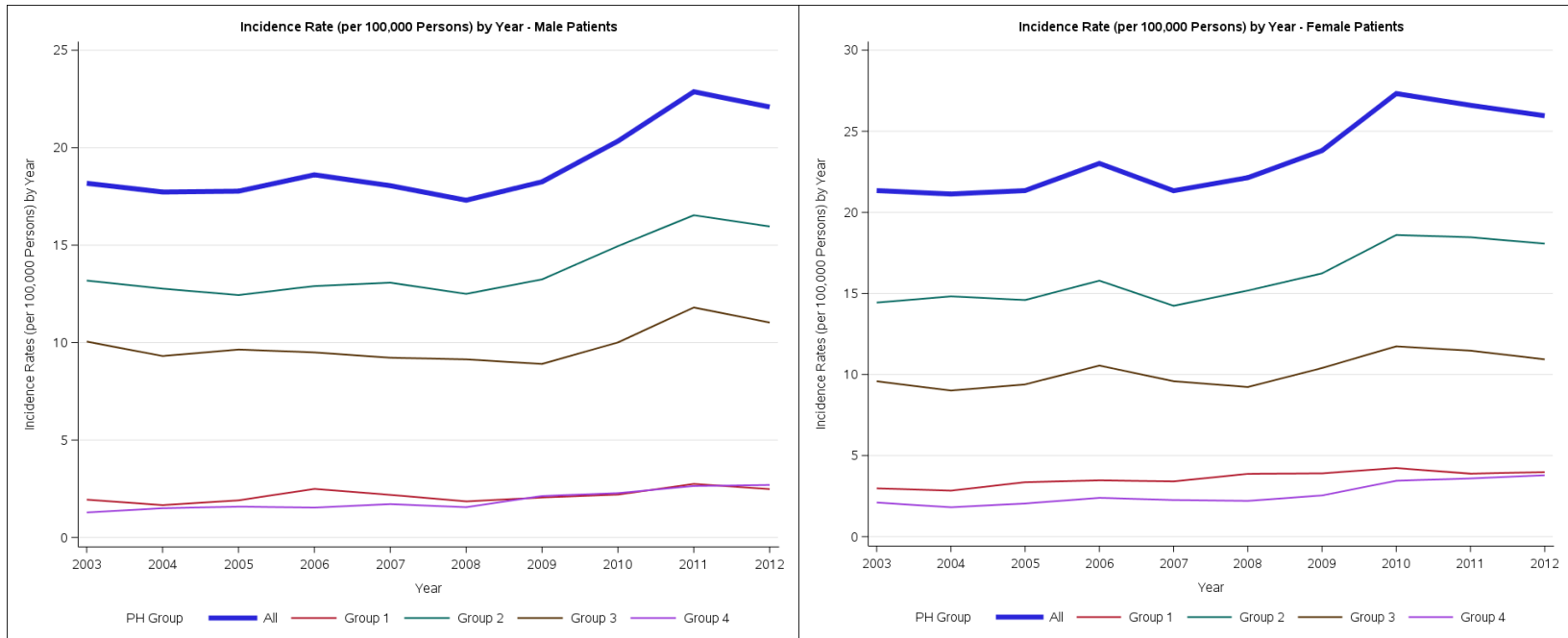


Figure S2: Incident rates of Pulmonary Hypertension per 100,000 persons by year (by gender)

Table S5: Crude Mortality Rate (per 100) by Group of PH and by Age group

All PH patients															
Year	30 Day					1 Year					5 Year				
	All	1	2	3	4	All	1	2	3	4	All	1	2	3	4
2003	14.0	13.4	13.7	15.5	11.9	35.9	23.0	38.0	41.9	36.2	64.2	44.9	67.7	74.9	59.5
2004	11.4	8.2	11.4	13.4	10.6	33.5	21.3	35.2	39.8	30.0	63.1	48.2	65.2	74.3	57
2005	13.7	10.8	14.2	15.2	11.8	35.1	24.0	36.9	40.1	31.9	65.1	42.6	68.9	75.9	61.6
2006	12.4	7.1	12.8	14.8	20.7	35.5	21.0	37.9	42.0	44.2	64.4	42.0	68.7	73.5	69.7
2007	13.7	9.4	14.0	17.3	16.4	36.9	26.6	39.1	42.9	34.4	64.0	47.6	67.7	74.6	62.5
2008	13.5	8.6	14.5	16.4	16.3	38.2	25.1	41.4	46.1	41.2	65.7	49.2	69.4	75.8	62.9
2009	12.7	7.6	13.5	16.2	14.3	35.0	21.4	38.6	41.3	36.5	64.0	41.7	68.9	74.4	63.2
2010	12.8	6.5	13.9	15.8	12.6	37.2	22.8	40.8	44.1	36.7	63.5	44.5	68.1	72.6	61.2
2011	11.7	6.3	12.8	13.6	14.1	34.2	17.3	37.8	40.2	36.4	55.2	32.8	59.7	64.4	56.9
2012	12.8	7.3	13.7	16.3	14.8	37.4	22.8	40.9	46.0	40.8	50.1	30.6	54.8	59.6	50.8
Overall	12.8	8.3	13.4	15.4	14.4	35.9	22.4	38.8	42.5	37.2	61.5	41.9	65.5	71.5	59.8
Patients ≥ 16 years															
Year	30 Day					1 Year					5 Year				
	All	1	2	3	4	All	1	2	3	4	All	1	2	3	4
2003	14.1	14.1	13.7	15.6	12.3	36.7	24.5	38.3	42.2	37.3	65.6	48.7	68.3	75.7	61.3
2004	11.5	8.2	11.5	13.6	10.7	33.9	21.9	35.5	40.2	30.1	63.9	49.4	65.7	75.0	57.3
2005	13.7	11.0	14.2	15.3	11.9	35.4	24.4	37.0	40.4	32.2	65.9	43.8	69.2	76.5	62.1
2006	12.4	7.0	12.8	14.8	21.0	35.7	20.9	37.9	42.1	44.8	65.1	42.9	68.9	74.2	70.2
2007	13.9	9.7	14.2	17.5	16.5	37.4	27.4	39.5	43.4	34.6	65.0	49.9	68.3	75.4	63.0
2008	13.7	8.7	14.6	16.5	16.6	38.6	25.8	41.6	46.2	41.5	66.5	50.8	69.9	76.1	63.5
2009	13.0	8.1	13.6	16.3	14.7	35.6	22.9	38.8	41.7	37.1	65.3	45.0	69.5	75.2	64.5
2010	12.9	6.7	13.9	15.9	12.5	37.6	22.9	41.0	44.5	37.0	64.4	46.1	68.6	73.3	61.4
2011	11.8	6.1	12.9	13.7	14.3	34.4	16.8	37.9	40.4	36.7	55.9	33.4	60.0	64.9	57.5
2012	12.9	7.1	13.9	16.5	14.7	37.9	22.9	41.3	46.7	40.6	50.8	31.0	55.2	60.4	50.7
Overall	13.0	8.4	13.5	15.6	14.5	36.4	22.9	39.0	42.8	37.5	62.4	43.5	66.0	72.2	60.4
Patients < 16 years															
Year	30 Day					1 Year					5 Year				
	All	1	2	3	4	All	1	2	3	4	All	1	2	3	4
2003	8.6	8.3	10.5	11.1	0	11.4	11.1	10.5	16.7	0	15.7	16.7	10.5	22.2	0
2004	4.4	7.7	4.5	0	0	11.1	7.7	18.2	7.1	0	22.2	23.1	22.7	21.4	0

2005	9.1	8.0	10.0	7.7	0	18.2	20.0	20.0	7.7	0	25.0	28.0	20.0	15.4	0
2006	10.9	9.1	16.7	14.3	0	27.3	22.7	38.9	33.3	0	30.9	27.3	44.4	33.3	33.3
2007	3.2	4.5	0	4.5	0	15.9	13.6	16	18.2	0	22.2	13.6	28.0	31.8	0
2008	4.8	5.6	5.3	0	0	11.9	11.1	15.8	14.3	25	19.0	16.7	21.1	28.6	25.0
2009	4.1	2.9	4.5	5.6	0	13.5	5.7	22.7	16.7	12.5	16.2	8.6	22.7	22.2	12.5
2010	6.2	3.6	8.3	10.5	20.0	16.9	21.4	16.7	10.5	20.0	20.0	21.4	20.8	15.8	40.0
2011	6.7	8.6	4.3	4.5	0	24	22.9	26.1	27.3	16.7	25.3	25.7	26.1	27.3	16.7
2012	6.8	10.7	3.6	7.4	20.0	16.2	21.4	14.3	11.1	60.0	20.3	25.0	21.4	14.8	60.0
Overall	6.4	6.9	6.2	7.2	4.8	16.8	16.0	19.5	17.1	16.7	21.4	20.2	23.8	23.2	21.4

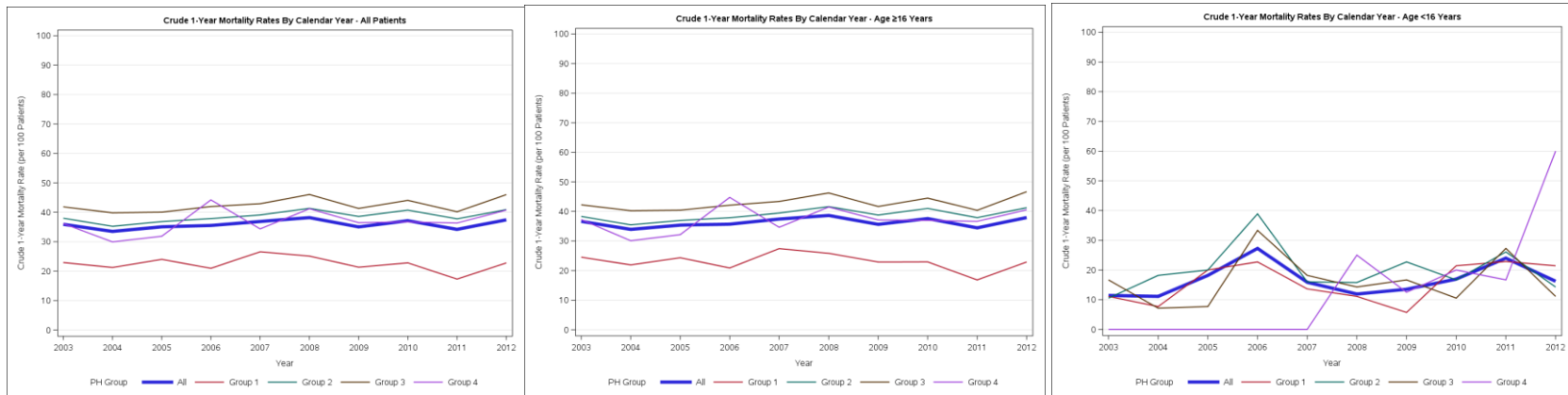


Figure S3: Crude 1 year mortality rate by calendar year for patients with Pulmonary Hypertension

Table S6: Description of Group 2/3 adult PH Patients with/without Combination Diagnoses (Group 2+3)

	Group 2	Group 3	Group 2+3	p value
	N = 9,956	N = 3,641	N = 9,155	
Female Gender (%)	58.2%	53.4%	51.1%	<0.001
Mean age at index date* (SD)	73.7 (14.0)	69.3 (13.2)	74.4 (11.6)	<0.001
Mean total ADG Score (SD)	14.6 (4.0)	15.0 (3.9)	16.1 (3.8)	<0.001
Mean major ADG Score (SD)	3.8 (1.5)	3.8 (1.5)	4.2 (1.5)	<0.001

Abbreviations: PH- pulmonary hypertension; SD- standard deviation; ADG- the Johns Hopkins Aggregated Diagnosis Groups
Statistical comparisons conducted using one way ANOVA test

Table S7: Standardized Mortality Ratios (2003/2011) for Group 2/3 adult PH patients with/without combination diagnoses (Group 2+3)

Year	Group	SMR	95% Confidence Interval
2003	Group 2	8.4	(7.4, 9.4)
	Group 3	13.3	(11.2, 15.5)
	Group 2+3	10.4	(9.3, 11.5)
2011	Group 2	5.9	(5.3, 6.5)
	Group 3	10.5	(8.8, 12.1)
	Group 2+3	8.5	(7.8, 9.3)

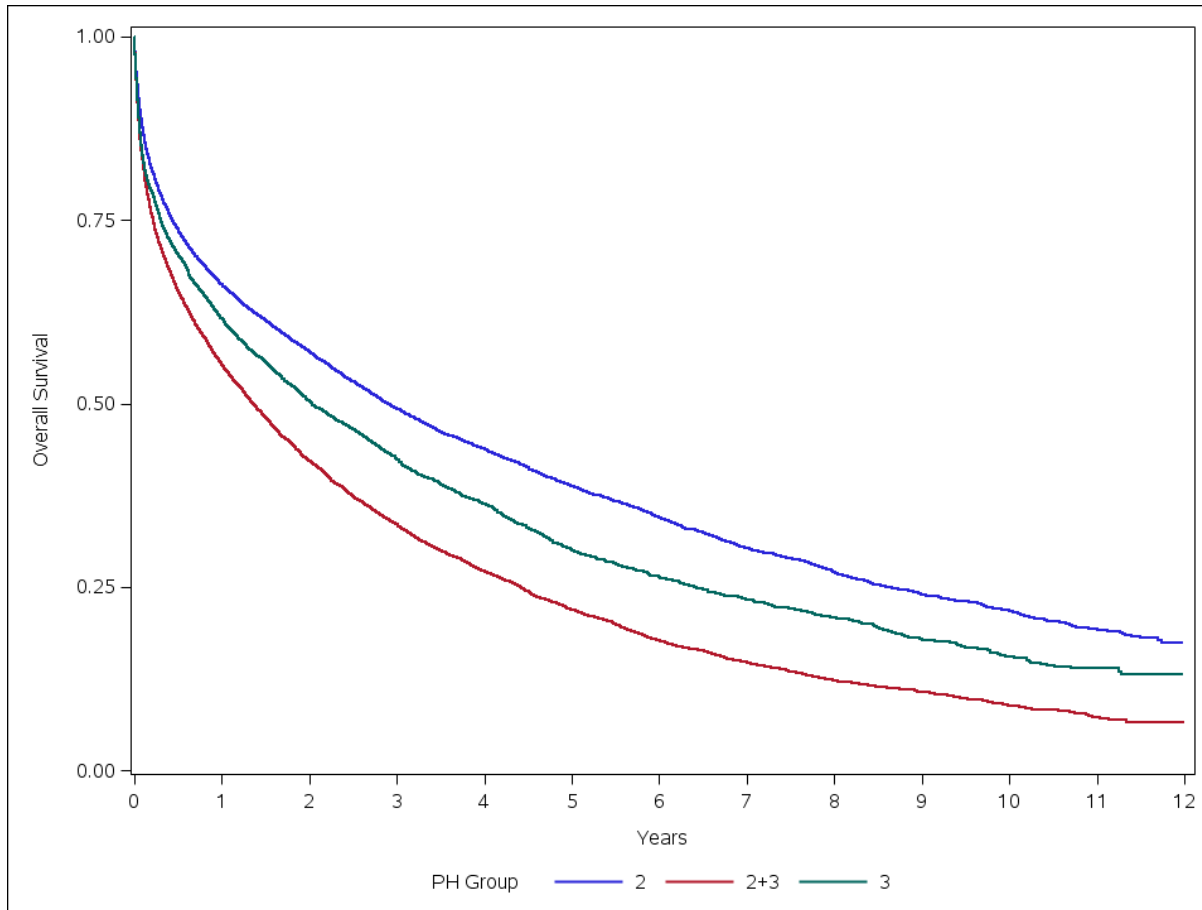


Figure S4: Survival of Group 2/3 adult PH patients with/without combination diagnoses