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A M E R I C A N C O L L E G E O F
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Primary Pulmonary Hypertension In Israel*

A National Survey

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Objectives: To characterize the incidence of patients with primary pulmonary hypertension (PPH) in Israel and their outcomes.

Methods: We have evaluated retrospectively all the patients in Israel in whom PPH was diagnosed between the years 1988 and 1997. We looked at medical history, hemodynamic data, pulmonary function and gas exchange, and demographic variables. Patients were followed up for survival until November 1997. Life table analysis and Kaplan-Meier statistics were used to estimate the overall survival distribution. Regression analysis was used to examine the relations between survival and selected variables.

Results: Overall, we found 44 patients with PPH. The estimated incidence of PPH in Israel is 1.4 new cases per year per million population. The mean (\pm SD) age at diagnosis was 43 ± 13 years. In the Jewish population, PPH was more frequent among immigrants from Europe and the United States. The mean interval from the onset of symptoms to diagnosis was 3 years (median, 2 years). The median survival time was 4 years. The 1-year, 3-year, and 5-year survival rates were 82%, 57%, and 43%, respectively. The major variables influencing the survival rate were the following: interval from symptom onset to diagnosis; and hemodynamic measurements (*ie*, mean pulmonary artery pressure, mean right atrial pressure, and cardiac index). In comparison to rates discerned from the National Institutes of Health registry data, the survival rate in Israel is somewhat better and prognosis is influenced by similar hemodynamic variables.

Conclusion: PPH is a rare and fatal disease in Israel. New therapeutic modalities such as prostacyclin therapy and lung transplantation may improve survival among patients with this malignant disease. (CHEST 2001; 119:1801-1806)

Key words: lung transplantation; primary pulmonary hypertension; prostacyclin

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; NIH = National Institutes of Health; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; RAP = right atrial pressure

Pprimary pulmonary hypertension (PPH) is a rare disease that is characterized by a progressive

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elevation of pulmonary artery pressure (PAP) and vascular resistance without a demonstrable cause. It is considered to be a progressive, incurable, and fatal disease.¹⁻⁹ PPH can start at any age, but it strikes mostly during the third and fourth decades of life. The ratio of women to men with PPH is 1.7:1. Estimates of the incidence of PPH range from one to two cases per million people in the general population,² and the number seems to be rising.⁹ Diagnosis is difficult to achieve and often is established only late in the course of the disease.^{2,3} Data from the US National Institutes of Health (NIH) registry on PPH^{2,3} show that PPH is a fatal disease in which most of the patients die within 2 to 3 years from the diagnosis and the 1-year survival rate is 68%, the 2-year survival rate is 48%, and the 5-year survival rate is 34%.

In Israel, characterization of the disease has not been performed. The goal of this study was to characterize PPH in Israel by estimating its incidence, discerning the survival rate of patients with the disease, characterizing the demographic, clinical, and hemodynamic variables of patients with the disease, clarifying the factors influencing survival rates, and estimating the length of time between the onset of symptoms and the time of diagnosis.

MATERIALS AND METHODS

Patients

The study series included all patients who received diagnoses of PPH in Israel between the years 1988 and 1997 (*ie*, 10 years). Follow-up for survival continued until the end of November 1997. The criteria used to establish the diagnosis of PPH included the following: the presence of an elevated mean PAP of > 25 mm Hg at rest or > 30 mm Hg during exercise; and the absence of other diseases known to cause or to be associated with secondary pulmonary hypertension.^{2,4} The data were obtained from the medical records of all of the main hospitals in Israel and from the registration of inhabitants or through the primary-care physician. The participating medical centers were the following: Hadassah and Shaarey-zedek (Jerusalem); Rabin Medical Center, Ichilov, Tel Hashomer, Meir and, Wolfson (Tel-Aviv area); Rambam and Afula (northern Israel); and Soroka (Beer-Sheba, southern Israel).

Variables

For each patient, a uniform protocol was completed that included the following: demographic data; clinical history; physical examination; laboratory tests; chest radiographs; ECG; pulmonary function tests; echocardiography; radionuclide perfusion lung scan and/or angiography; and cardiac catheterization.²

Length of survival was measured from the time of diagnosis and from the date of symptom onset. The clinical, hemodynamic, and laboratory variables also were measured at the time of diagnosis and were related to the subsequent mortality.

Information about the Israeli population was obtained from the main statistical bureau.

Analysis

Analysis of the demographic, clinical, and hemodynamic variables of the patients was performed as a whole group and separately as a comparison between two groups (*ie*, men and women). For survival analysis, we used life table analysis and the Kaplan-Meier method.^{2,10} We estimated the median survival time and the 1-year, 3-year, and 5-year survival rates. Univariate analysis based on the proportional hazards model^{2,10} was used to examine the relationship between survival and selected demographic, medical history, pulmonary function, laboratory, and hemodynamic variables measured during the initial catheterization. At the completion of the univariate analysis, any variable for which the univariate test had a value of $p < 0.05$ was considered to be a candidate for the multivariate model. A stepwise technique was used for choosing the best combination of variables. Multivariate analysis based on the Cox proportional-hazards regression analysis was used to examine the adjusted independent effect on survival of each variable, controlling for the possible

confounders. After analyzing the data, we compared the results with the existing data on PPH from the NIH registry.^{2,3}

Finally, we analyzed the applicability in our population of the equation for predicting a prognosis of PPH that was proposed by the NIH registry of PPH patients. According to this registry, the prognosis for patients with PPH could be established by use of the following equation, which takes into consideration the main factors affecting survival^{3,11}:

$$A(x,y,z) = e^{(0.007325x)+(0.0526y)-(0.3275z)}$$

where x is the mean PAP, y is the mean right atrial pressure (RAP), and z is the cardiac index. These values were obtained at the initial diagnostic catheterization. The probability to survive 1 year, 2 years, and 3 years then would be given by:

$$p(1) = 0.75^A$$

$$p(2) = 0.65^A$$

$$p(3) = 0.55^A$$

By using this formula, we calculated and compared the projected survival times with the real survival time of our patients.

For the rest of the statistical analysis, we used t tests and χ^2 tests. Values were expressed as mean \pm SD. A value of $p < 0.05$ was accepted for significance.

RESULTS

This study included 44 patients in Israel in whom PPH was diagnosed between 1988 and 1997, an average of 4 patients per year (range, 1 to 7 patients per year). The estimated prevalence of PPH in Israel is eight patients per million people, with an incidence of 1.4 new cases per million population per year.

Demographic Characteristics

The mean age of the patients at diagnosis was 42.8 ± 13 years (age range, 16 to 63 years), which was similar for male and female patients. The age distribution of the patients is shown in Figure 1, with the highest frequency for female patients in the fifth decade and the highest frequency for male patients

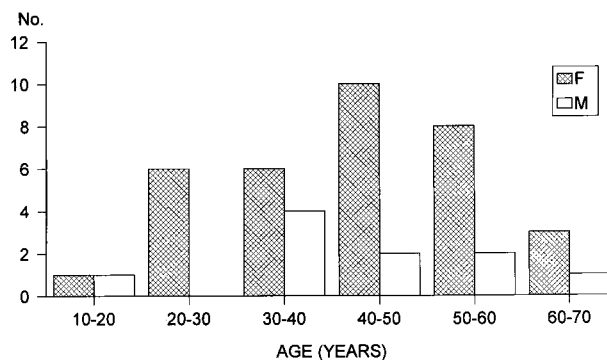


FIGURE 1. Distribution of PPH patients in Israel according to age and sex (No. of patients is on the y axis).

in the fourth decade. The ratio of women to men with the disease was 3.4:1. The patient distribution according to nationality (*ie*, Jews, Muslims, Christians, and Druze) was the same as the distribution in the population.

Among Jewish patients, the Ashkenazi population (immigrants from Europe or North America) had a higher incidence than their percentage in the general population (43% vs 26%). Immigrants from Romania had the highest incidence of PPH among those from Europe and the United States.

Medical and Family History

The percentage of smokers among the patients was similar to the percentage in the population (25%). Three patients (7%) had histories of using appetite-suppressant drugs. Two patients (5%) also had Gaucher's disease and were treated with the enzyme *alglucerase* (Ceredase; Genzyme; Cambridge, MA). None of the patients had a history of familial pulmonary hypertension.

Symptoms

Dyspnea was the most common presenting symptom and was present in 90% of the patients. Other, less common, presenting symptoms were fatigue (20%), chest pain (19%), syncope (16%), leg edema (11%), palpitations (10%), and presyncope (4%). Four patients (10%) reported symptoms of Raynaud's phenomenon. The functional status of the patients at diagnosis according to the New York Heart Association (NYHA) classification was as follows: class 1, 1 patient; class 2, 20 patients (45%); class 3, 18 patients (41%); and class 4, 4 patients (10%).

The mean time from the onset of symptoms to diagnosis was 2.9 years (median, 2 years) and was similar in men and women. A diagnosis of PPH was

made in 93% of patients within 3 years after symptom onset and in 80% of patients within 2 years after symptom onset.

Laboratory Findings

The ECG showed sinus rhythm in all the patients. Right-axis deviation with right ventricular hypertrophy and strain were reported in all except one patient. About half of the patients showed right bundle-branch block. The echocardiogram showed enlargement of the right atrium and ventricle with a normal left ventricle in all the patients. Tricuspid insufficiency was described in 90% of the patients, and paradoxical septal motion was described in 40% of patients.

The results of an antinuclear antibody test were positive in five patients (11%; four women and one man). The hemoglobin level was relatively high (men, 16.8 g/dL; women, 14.5 g/dL). The lung perfusion scan was interpreted as normal or with low probability for pulmonary embolism in 60% of patients. In 40% of the patients, the result of the lung perfusion scan was intermediate probability for pulmonary embolism, and the result of a pulmonary angiogram was negative.

Pulmonary Function

Selected variables of pulmonary function are presented in Table 1. Three patients showed a mild restrictive disturbance, and the diffusing capacity of the lung for carbon monoxide (DLCO) measured significantly less than that predicted (mean DLCO, 56.7% of predicted). Mild-to-moderate hypoxemia was present in 89% of the patients, and hypocapnia was present in 95%.

Table 1—Lung Function and Hemodynamics of Patients With PPH in Israel*

Variables	All	Men	Women
TLC, % predicted	94.2 ± 16.3	90.2 ± 19.8	95.4 ± 15.2
FVC, % predicted	86.9 ± 15.1	83.0 ± 19.5	88.1 ± 13.6
FEV ₁ , % predicted	82.1 ± 16.8	73.6 ± 24.6	84.8 ± 13.0
DLCO, % predicted	56.7 ± 20.5	44.1 ± 25.2	61.0 ± 17.2
SaO ₂ , %	92.3 ± 5.0	90.5 ± 5.7	92.9 ± 4.7
PcO ₂ , mm Hg	29.9 ± 4.2	30.1 ± 4.1	29.8 ± 4.3
PAP, mm Hg	60.6 ± 16.1	57.6 ± 19.2	61.5 ± 15.3
RAP, mm Hg	10.7 ± 6.4	9.6 ± 7.8	11.1 ± 6.0
Cardiac index, L/min/m ²	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8
PVR, dyne · s · cm ⁻⁵	1,486.6 ± 726.9	2,115.2 ± 402.8	1,346.9 ± 720.8
SVR, dyne · s · cm ⁻⁵	2,030.8 ± 814.3	1,548.0 ± 800	2,084.4 ± 844.8

*Values given as mean ± SD. None of the parameters were significantly different. TLC = total lung capacity; SaO₂ = arterial O₂ saturation; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

Table 2—Survival Data for 44 Patients in Whom PPH Was Diagnosed Who Were Observed Between 1988 and 1997

Data	Women (n = 34)	Men (n = 10)	All (n = 44)
Death, No. (%)	21 (62)	7 (70)	28 (64)
Median (\pm SD) survival time, mo	60 \pm 11.3	24 \pm 16.4*	48 \pm 8.5
Survival rates, %			
1 yr	82	80	82
3 yr	60	41*	57
5 yr	47	29*	43

* $p < 0.05$ for women vs men.

Hemodynamic Findings

Values for selected hemodynamic variables that were measured at the time the patients underwent diagnostic catheterization are summarized in Table 1. As a group, the patients had severe pulmonary hypertension, with a threefold increase in mean PAP (60.6 ± 16.4 mm Hg; range, 37 to 95 mm Hg), a mild-to-moderate elevation in RAP (10.7 mm Hg; range 0 to 26 mm Hg), a normal pulmonary capillary wedge pressure, and a reduced cardiac index (2.48 L/min/m²; range, 0.9 to 4.6 L/min/m²). In correlating the hemodynamic variables and the severity of symptoms (as measured by NYHA classification), no significant difference was found in mean PAP and mean RAP when comparing patients in NYHA functional classes III and IV to those in classes I and II. The patients with more severe symptoms (classes III and IV) had significantly lower cardiac index scores than patients in the classes I and II (2.1 ± 0.7 vs 2.8 ± 0.8 , respectively; $p < 0.007$).

Treatment

Anticoagulant therapy was administered to 95% of the patients. Most of the patients also were treated with vasodilator therapy, especially using nifedipine. Only six patients (13%) were treated with prostacyclin; three patients received transplants, and the other three died.

Three of the 44 patients received transplants, two women and one man. Two of the three patients underwent double lung transplantation, and one patient underwent heart-lung transplantation. Twelve patients died while waiting for transplants, both in Israel and abroad.

Survival

By the end of November 1997, 28 of 44 patients had died. Right-sided heart failure (16 patients) was the leading cause of death, and sudden death (12

patients) was the other main cause of death. After 1 year, no difference was found between the percentages of men and women who had survived, but after 3 years and 5 years a significant difference was found ($p < 0.05$), with women surviving longer.

The 1-year, 3-year, and 5-year survival rates were 82%, 57%, and 43%, respectively. Figure 2 shows a Kaplan-Meier survival curve from the time of diagnosis. The median survival time was 48 months.

Factors Affecting Survival

The time from symptom onset until diagnosis was found to affect survival. The later the diagnosis was made, the greater was the risk of death. The risk of death also was higher among patients classified in NYHA functional class IV than among those classified in classes I, II, or III ($p < 0.01$). The following three hemodynamic variables measured at the time the patients underwent diagnostic catheterization were found to affect survival: mean PAP; mean RAP; and cardiac index.

In the multivariate analysis, the most positive predictive values were the time until diagnosis and the mean RAP. When excluding the length of time until diagnosis, other variables (*ie*, FEV₁, PCO₂, and cardiac index) became positive, except for the RAP. Survival was not associated with patient gender, age at diagnosis, the presence of Raynaud's phenomenon, the results of pulmonary function tests and blood gas analyses, pulmonary vascular resistance, or systemic vascular resistance. Finally, by calculating and comparing the projected survival times with the real survival times of our patients, using the equation for prediction of prognosis for patients with PPH that was proposed by the NIH registry, we found a very poor correlation between the projected and real survival times (approximately 30% error).

DISCUSSION

The estimated prevalence of PPH in Israel of eight patients per million population and the incidence of

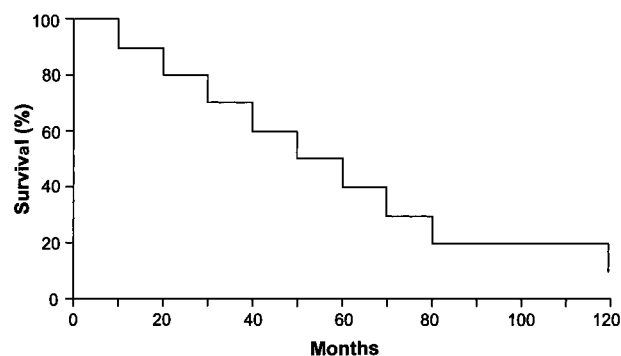


FIGURE 2. Kaplan-Meier survival curve in patients with PPH in Israel.

1.4 new cases per million cases a year are similar to those in the United States (*ie*, one to two new cases per million a year), Europe, or Mexico.^{2,11} Since our study is retrospective in nature and symptoms of this disease are not specific, it is conceivable that the true incidence is higher. In our Israeli cohort, the ratio of women to men was higher than that ratio in the US registry (3.4:1 vs 2:1, respectively) and was similar to that of the black population in the United States. As for age distribution, Israeli patients were older, with a mean age at diagnosis of 43 years compared to a mean age of 36 years in the US registry.

About 7% of the patients had a history of anorexiant usage. The higher incidence of PPH in anorexiant users is well-known.¹²⁻¹⁴ Two of our patients were treated for Gaucher's disease with the enzyme α -glucosidase. It is thought that there is a connection between PPH and Gaucher's disease, either through the diseases or through the treatment with α -glucosidase.¹⁵

Of our 44 patients, no positive familial history of PPH was reported, compared to 6% in the American survey.^{3,16} A long symptomatic period preceded the diagnosis in most of the patients. This could be explained by the low specificity of the symptoms. The most common presenting symptoms, dyspnea and fatigue, were present > 2 years before the diagnosis was made in most cases. The mean time from symptom onset to diagnosis was 3 years, which was longer than the mean time in the United States (2 years).

The median length of survival was 4 years, which was longer than that in the results of the American survey (2.8 years). The 1-year survival rate was 82%, the 3-year survival rate was 57%, and the 5-year survival rate was 43%. Every one of these values also was higher when compared with the NIH results. The median survival rate and the 3-year and 5-year survival rates were significantly higher for women than for men, but sex was not found to be a predictive value for survival in the regression analysis. This discrepancy could be explained by the difference between comparing the median survival rate in two groups and by analyzing the influence of different variables on survival by a regression analysis, which is nonparametric and takes into account the conditioned character of the survival distribution. We have found that the most important factors for predicting survival were the time from symptom onset until diagnosis and the mean pressure in the right atrium. The time between symptom onset and diagnosis was found to be an important parameter in predicting survival in our patients. The chance for the survival of the patient become better as the disease is diagnosed earlier. Although the data

were collected before the era of prostacyclin therapy,¹⁷⁻²² it is possible that earlier interventions, such as prostacyclin and anticoagulation therapy, will improve survival time. On the other hand, when a high RAP or a low cardiac index is observed, death is impending and therapy should be promptly instituted.

The nature of our study is retrospective, and, therefore, patients might have been missed, possibly those who died early on, which may explain the discrepancy between the results of our study and those based on the American registry.

While analyzing the usefulness of the equation for predicting survival that was proposed by the NIH,³ we found a poor correlation between the predicted survival time and the real survival time in our population. A possible explanation for this is the relatively small population and the rigidity of the equation. The equation takes into account only the hemodynamic measurements (*ie*, mean RAP, mean PAP, and cardiac index), and not other factors, such as the time until diagnosis, that had strong predictive values in our population.

We conclude that PPH is a rare and fatal disease in Israel with similar incidence and outcome to those in other areas of the world. Early diagnosis may lead to better prognosis if therapy with prostacyclin is instituted promptly.

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