

AN EPIDEMIOLOGICAL STUDY OF PULMONARY HYPERTENSION IN TURKISH ADULT POPULATION

Erişkin Türk Toplumunda Pulmoner Hipertansiyon; Epidemiyolojik Çalışma

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ÖZ

Amaç: Bu çalışma beş yıllık periyodu kapsayacak şekilde, Türk popülasyonunda erişkin pulmoner hipertansiyonun epidemiyolojik karakteristiklerinin incelenmesini amaçlamaktadır. Ülkesel boyutta ulusal sağlık sigorta sistemi kayıtları baz alınmıştır.

Yöntemler: Çalışmadaki tüm bireyler 18 yaş üstü, Türk hastanelerine 2009-2013 yılları arasında ilk kez başvuru yapanlar ve taburculuk tanıları primer pulmoner hipertansiyon (ICD-10 kod I27.0) ve sekonder pulmoner hipertansiyon (ICD-10 kod I27.2) olanlar olarak tanımlanmıştır.

Bulgular: Erişkin primer pulmoner hipertansiyonun toplam ortalama yıllık prevalansı bir milyonda 9,6 vaka olarak saptandı. Çalışma periyodu içerisinde diğer yaş grupları ile karşılaştırıldığında primer pulmoner hipertansiyonlu 45 yaş üstü birey sayısı anlamlı şekilde yüksekti ($p=0,001$ tüm yıllar için). Yine çalışma periyodu içerisinde erişkin primer pulmoner hipertansiyon prevalansı kadın erkek oranı 2,2:1 idi. Primer pulmoner hipertansiyon grubunda Kuzeybatı Anadolu yerleşik bireylerin sayısı anlamlı derecede yüksek idi ($p<0,05$ tüm yıllar için). Sekonder pulmoner hipertansiyon toplam ortalama yıllık prevalansı bir milyonda 6 vaka olarak saptandı. Çalışma periyodu içerisinde diğer yaş grupları ile karşılaştırıldığında sekonder pulmoner hipertansiyonlu 45 yaş üstü birey sayısı anlamlı şekilde yüksekti ($p=0,001$ tüm yıllar için).

Sonuç: Türkiye'de erişkin pulmoner hipertansiyon prevalansı batı ülkelerindekinden daha yüksektir ve erişkin pulmoner hipertansiyon Türk bireylerde daha fazla 45 yaş üstü olanları etkilemektedir.

Anahtar kelimeler: Erişkin; epidemiyoloji; pulmoner hipertansiyon

ABSTRACT

Objective: The present study aims to evaluate the nationwide epidemiological characteristics of adulthood pulmonary hypertension (PH) within whole Turkish population over a period of five years using the registry of the National Health Insurance System.

Methods: All individuals aged more than 18 years who were admitted to a Turkish hospital for the first time between 2009 and 2013 with a discharge diagnosis of primary PH (ICD-10 code I27.0) and secondary PH (ICD-10 code I27.2) were identified.

Results: The overall annual prevalence of primary PH during adulthood was 9.6 cases per million. When compared with other age groups, the number of individuals aged more than 45 years was significantly higher in adults affected by primary PH during the study period ($p=0.001$ for all years). The female to male ratio was 2.2:1 for adulthood primary PH throughout the study period. The number of patients settled in the Northwestern Anatolia was significantly higher in the primary PH group ($p<0.05$ for all years). The overall annual prevalence of secondary PH in adults was 6.0 cases per million. When compared with other age groups, the number of individuals aged more than 45 years was significantly higher in adults affected by secondary PH during the study period ($p=0.001$ for all years).

Conclusion: The prevalence of adulthood PH in Turkey may be higher than that of adulthood PH in Western countries and adulthood PH usually affects Turkish individuals aged over 45 years.

Keywords: Adult; epidemiology; pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is clinically defined as a mean pulmonary arterial pressure of more than 25 mm Hg at rest or 30 mm Hg during exercise. This disease can be idiopathic, familial or associated with a number of medical conditions including connective tissue diseases, congenital heart diseases, portal hypertension, human immunodeficiency virus (HIV) infection, and exposure to toxins and drugs such as appetite suppressants (1-3).

Estimates of the incidence of primary PH range from 1 to 2 cases per million people in the general population. The incidence of pulmonary vascular disease in patients with other illnesses is not known, but it appears that pulmonary vascular disease affects 0.5 to 2 percent of patients with portal hypertension or HIV infection. In a recent case-control study, any use of appetite suppressants was associated with an increased risk of primary PH (odds ratio: 6.3), and the odds ratio increased to more than 20 if drugs were used for more than three months. Serotonin uptake inhibitors that are widely used to treat obesity are regarded as the drugs most commonly associated with PH, but amphetamines were also implicated (4-7).

In the last decade, significant medical advances have occurred so that affected patients can be assessed systematically with objective parameters (e.g., 6-minute walk test and acute vasodilator challenge) and treated with more efficient agents (e.g., prostacyclin, endothelin receptor antagonists, and type 5 phosphodiesterase inhibitors) (8, 9). Rapid accumulation of knowledge in this field has prompted the need for the establishment of registries that would provide the foundation of knowledge upon which epidemiological studies and other clinical research might be constructed (10). However, there is still a lack of knowledge regarding the epidemiology of adulthood PH due to the lack of properly kept registries (11).

The present study aims to evaluate the nationwide epidemiological characteristics of adulthood PH within whole Turkish population over a period of five years using the registry of the National Health Insurance System.

MATERIALS AND METHODS

The present study is approved by the Ethical Committee and Institutional Review Board of Afyon Kocatepe University (grant no: 2014/05-128). This study specifically examines the data obtained from the National Health Insurance System of Turkey. This validated data set captures and records all hospital admissions and discharges in Turkey on an individual basis. The National Health Insurance System of Turkey also collects and collates data regarding all hospital discharges. The term discharge includes both live and fatal discharges. These data are linked to information held by the Turkish Ministry of Health relating to all deaths, and records are maintained using a unique identifier for each patient. Any readmission or death (and its cause) can be identified for each individual who is admitted to a Turkish hospital. Each hospital record provides information concerning the age of patient, sex of patient, residential address, date of admission, duration of hospital stay and type of hospital unit date (12). After 1996, the tenth revision of the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD-10) has been used to code hospital admissions and discharges in Turkey (13).

The National Health Insurance System financially covers the health care expenses of all adult individuals (aged more than 18 years) who are able to pay their health insurance premium or who declare that they are unable to pay their health insurance premium (12, 14). All adults with PH are investigated using a standard diagnostic protocol that includes right heart catheterization. Adulthood

PH is diagnosed only if mean pulmonary arterial pressure exceeds 25 mmHg at rest, with a pulmonary artery wedge pressure of less than 15 mmHg (1, 2). All individuals aged more than 18 years who were admitted to a Turkish hospital for the first time during the five-year period (2009–2013) with a discharge diagnosis of primary PH (ICD-10 code I27.0) and secondary PH (ICD-10 code I27.2) were identified.

In order to delineate the primary and secondary forms of PH captured by these data, the coding data from any prior admissions and combination of concurrently recorded diagnoses was used. Using these data, a series of filters, with a hierarchical order of priority, were applied to categorize each patient according to the latest classification system published in 2013 (3). In order to further increase the probability that a diagnosis of PH was based on a series of clinical investigations with determination of concurrent disease states, the present analyses were confined to adults aged more than 18 years.

All patients in whom an isolated coding of PH was recorded in the absence of any explanatory concurrent diagnoses from prior hospitalizations were designated as having primary or idiopathic PH. All individuals with a past or concurrent diagnosis of congenital systemic-to-pulmonary shunts (ICD-10 code Q25.79), systemic connective tissue disorders (ICD-10 codes M30–M36), left-sided heart failure or valvular disease (ICD-9 code I50.9), chronic respiratory disease (ICD-10 codes J00–J99) and thromboembolic disease (ICD-10 code I26) were denoted as having secondary PH.

A total of 35701 individuals aged more than 18 years were discharged from Turkish hospitals with a first-ever diagnosis of primary PH during the five-year period (2009–2013). A total of 22300 individuals aged more than 18 years were discharged from Turkish hospitals with a first-ever diagnosis of secondary PH during the same period. Subgroup analysis was done based on the year of

admission, clinical classification of PH as well as the age, sex and geographical settlement of the patient.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., IL, Chicago, USA). Graphs were drawn by Graphpad Prism 6.01 (GraphPad Software Inc., CA, USA). Mann-Whitney U and chi-square tests were used for comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

RESULTS

Figure 1 shows that annual prevalence of primary PH in adults was 6.3 cases per million in 2009, 9.4 cases per million in 2010, 11.1 cases per million in 2011, 11.3 cases per million in 2012 and 9.9 cases per million in 2013 respectively. The overall annual prevalence of primary PH during adulthood was 9.6 cases per million. The annual prevalence of primary PH increased significantly during the first three years of the study period ($p=0.001$).

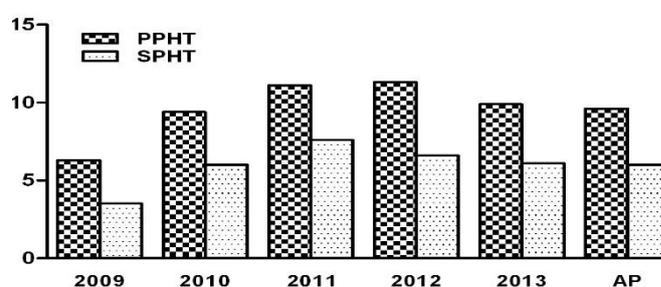


Figure 1. Total prevalence of primary and secondary pulmonary hypertension in Turkey. PPHT; primary pulmonary hypertension, SPHT; secondary pulmonary hypertension and AP; annual prevalence.

When compared with other age groups, the number of individuals aged more than 45 years was significantly higher in adults affected by primary PH ($p=0.001$). This significance was noted for all admission years (Table 1).

The adults diagnosed with primary PH included 11283 males (31.6%) and 24418 females (68.4%). The female to male ratio was 2.2:1 for primary PH at adulthood (Table 2). The number of patients

settled in the Northwestern Anatolia was significantly higher in the primary PH group. This significance existed for all admission years ($p < 0.05$ for all years) (Table 3).

Table 1. Distribution of adult pulmonary hypertension cases according to diagnostic classification, admission year and age

Admission year	Primary pulmonary hypertension					Secondary pulmonary hypertension					Total
	19-25 years	26-35 years	36-45 years	> 46 years	Total	19-25 years	26-35 years	36-45 years	> 46 years	Total	
2009	164 (3.6%)	229 (5.0%)	384 (8.4%)	3805† (83.0%)	4582	93 (3.6%)	153 (6.0%)	242 (9.4%)	2082† (81.0%)	2570	7152
2010	165 (2.4%)	368 (5.2%)	635 (9.2%)	5769† (83.2%)	6937	104 (2.3%)	204 (4.6%)	338 (7.6%)	3796† (85.5%)	4442	11379
2011	271 (3.4%)	466 (5.8%)	775 (9.6%)	6780† (84.2%)	8048	150 (2.7%)	218 (3.9%)	335 (5.8%)	4948† (87.6%)	5651	13699
2012	191 (2.2%)	555 (6.5%)	736 (8.6%)	7066† (82.7%)	8548	139 (2.8%)	283 (5.7%)	335 (6.7%)	4232† (84.8%)	4989	13537
2013	305 (4.0%)	607 (8.0%)	732 (9.7%)	5942† (78.3%)	7586	214 (4.6%)	443 (9.5%)	404 (8.7%)	3587† (77.2%)	4648	12234

† The number of individuals aged over 45 years was significantly higher in adult populations affected by primary and secondary pulmonary hypertension ($p = 0.001$ for all).

Table 2. Distribution of adult pulmonary hypertension cases according to diagnostic classification, admission year and sex

Year of admission	Primary pulmonary hypertension			Secondary pulmonary hypertension			Total
	Male	Female	Total	Male	Female	Total	
2009	1458 (31.8%)	3124 (68.2%)	4582	916 (35.6%)	1654 (64.4%)	2570	7152
2010	2228 (32.1%)	4709 (67.9%)	6937	1615 (36.4%)	2827 (63.6%)	4442	11379
2011	2675 (33.2%)	5373 (66.8%)	8048	1845 (32.6%)	3806 (67.4%)	5651	13699
2012	2685 (31.4%)	5863 (68.6%)	8548	1701 (34.1%)	3288 (65.9%)	4989	13537
2013	2237 (29.5%)	5349 (70.5%)	7586	1479 (31.8%)	3169 (68.2%)	4648	12234

Table 3. Distribution of adult pulmonary hypertension cases according to diagnostic classification, admission year and geographic settlement

Admission year	Primary Pulmonary Hypertension							Total
	Southern Anatolia	Eastern Anatolia	Southeastern Anatolia	Western Anatolia	Central Anatolia	Northern Anatolia	Northwestern Anatolia	
2009	694 (15.1%)	296 (6.5%)	294 (6.4%)	182 (4.0%)	892 (19.5%)	648 (14.1%)	1576† (34.4%)	4582
2010	1396 (20.1%)	302 (4.4%)	255 (3.7%)	208 (3.0%)	1208 (17.4%)	708 (10.2%)	2860† (41.2%)	6937
2011	977 (12.1%)	368 (4.6%)	313 (3.9%)	388 (4.8%)	1476 (18.3%)	1506 (18.8%)	3020† (37.5%)	8048
2012	980 (11.5%)	398 (4.7%)	374 (4.4%)	396 (4.6%)	1686 (19.7%)	1582 (18.5%)	3132† (36.6%)	8548
2013	982 (12.9%)	366 (4.8%)	328 (4.3%)	358 (4.7%)	1438 (19.0%)	1100 (14.5%)	3014† (39.7%)	7586
Admission year	Secondary Pulmonary Hypertension							Total
	Southern Anatolia	Eastern Anatolia	Southeastern Anatolia	Western Anatolia	Central Anatolia	Northern Anatolia	Northwestern Anatolia	
2009	306 (11.9%)	259 (10.1%)	258 (10.0%)	271 (10.5%)	338 (13.2%)	330 (12.8%)	808† (31.5%)	2570
2010	569 (12.8%)	570 (12.8%)	452 (10.2%)	530 (11.9%)	540 (12.2%)	624 (14.0%)	1157† (26.1%)	4442
2011	739 (13.1%)	745 (13.2%)	624 (11.0%)	703 (12.4%)	713 (12.6%)	696 (12.3%)	1431† (25.4%)	5651
2012	617 (12.4%)	621 (12.4%)	601 (12.0%)	579 (11.6%)	592 (11.9%)	674 (13.5%)	1305† (26.2%)	4989
2013	570 (12.3%)	571 (12.3%)	553 (11.9%)	531 (11.4%)	540 (11.6%)	625 (13.4%)	1258† (27.1%)	4648

† The number of individuals settled in the Northwestern Anatolia was significantly higher in adult populations affected by primary and secondary pulmonary hypertension ($p < 0.05$ for all).

DISCUSSION

It is well known that PH is a rarely encountered but almost deadly disease for adults. However, no studies have examined its epidemiology beyond the experiences and records of specialist centers and national registries. By their very nature, these are more likely to describe a younger and more relevant group of patients. Therefore, the annual incidence of idiopathic PH has been reported to be 1–2 cases per million populations previously. There was also a preponderance of relatively young females (4, 15-17).

The National Institutes of Health (NIH) registry was started in 1981, and results were published in 1987 in the United States of America. There were 187 patients with primary PH, with a mean age of 36 years and a female/male ratio of 1.7:1. Thus, it was concluded that the annual incidence of primary PH was 1–2 cases per million populations (15).

In 1996, a study was published that examined the patients diagnosed with primary PH at 220 centers in the United Kingdom, France, Belgium and the Netherlands during a two-year-long period. A total of 135 patients were recruited, although, in addition, 26 were dead or too sick to be interviewed. Of the 135, 23 were thought not to have primary PH and 17 could not be examined, leaving 95 cases with definite (n=80) or probable (n=15) primary PH. This study allowed the calculation of the annual incidence for primary PH in Belgium, where it was found to be 1.7 cases per million populations (95% confidence interval 1.0–2.4) (16).

The French national registry collected the records of patients from 17 centers in France during the period October 2002 to October 2003. Adulthood PH was only diagnosed if strict

cardiac catheter criteria were followed and significant lung disease was excluded. A total of 674 patients were entered into the database and annual incidence of PH was calculated to be 2.4 cases per million populations. Additionally, 25% of their cases were aged over 60 years, which was quite different from the NIH Registry but similar to the data held on the Scottish national database (17).

Using whole-population morbidity data from Scotland, 400 incident cases of PH were identified in the Scottish population of males and females aged 16–65 years during the period 1986–2001. Both the male and female patients in this Scottish study were older than their counterparts in previous reports. Moreover, the underlying annual incidence of idiopathic pulmonary arterial hypertension in the Scottish study, even taking into account the fact that the focus was on patients aged over 65 years, was higher than that in previous reports, being 2.5 and 4.0 cases per million population in males and females, respectively. Although the annual incidences of connective tissue-related PH and congenital heart disease-PH in males were approximately 1 case per million population), but these values were two- or three-fold higher (2.2 and 3.4 cases per million population) in females. During the prolonged follow-up period, these incidences were essentially stable over time. The Scottish Pulmonary Vascular Unit, founded in 1997, is the national referral centre for PH in Scotland. The database of this unit suggests an annual PH incidence of 7.6 cases per million populations. Moreover, nearly 30% of the recruited patients were aged over 65 years (4).

As for the present study, the overall annual prevalence of primary PH and secondary PH during adulthood were 9.6 cases per million and 6.0 cases per million, respectively. These numbers seem to be higher than those reported for the Western populations. Another contradiction was also detected about the age of the individuals diagnosed with PH. When compared with other age groups, the number of adults aged more than 45 years was found to be significantly higher in adults affected by either primary PH or secondary PH during the study period. Such discrepancies may be attributed to the differences in the study design, study cohort, timing of the study and the definitions adopted for PH classification. On the other hand, the female dominance in adulthood PH was also verified by this study. The female to male ratio was 2.2:1 for primary PH and 1.9:1 for secondary PH in adults throughout the five-year-long study period.

The significantly higher number of adults with primary and secondary PH in the Northwestern Anatolia may be related with the intense localization of tertiary hospitals and specialized treatment centers in Istanbul which is the largest city in both Northwestern Anatolia and Turkey. The adults living in other parts of Anatolia are usually referred to the experienced centers in Istanbul whenever there is a high index of suspicion.

The power of the present study is limited by several factors. First of all, this is not a prospective review of specific registry systems in which only adults diagnosed with PH would be registered. Rather, it is a retrospective evaluation of a nationwide registry. Since the nationwide registry which is used to identify the adults with PH was not specifically designed

to characterize the type of PH according to the current clinical classification, and no uniform criteria for assigning PH codes were defined previously. Second, represented data belong to the years between 2019 and 2013. Such an interval corresponds to a more recent period during which the awareness about adulthood PH has become prominent and the understanding of PH has been improved. It is possible that the expansion in both medical and surgical options may have directed the specialized treatment centers and tertiary hospitals to take an initiative for the management of a greater number of adults with this condition (18, 19). Third, only ICD-10 codes were used to define the PH cases in this study while both ICD-9 and ICD-10 codes were utilized to identify the affected adults in previously published studies. Another issue is the overestimation of PH due to non-expert registries which label the adults with PH even if they did not indeed meet the hemodynamic criteria for such a diagnosis (10). Moreover, the latter two factors may be the underlying reasons for an interesting finding of this study. In contrast with the literature, the prevalence of secondary PH is lower than that of primary PH in adults. Such discrepancy may be attributed to the inconsistencies and irrelevances in the adoption of diagnostic methods and ICD codes.

In conclusion, this nationwide epidemiological study suggests that the prevalence of adulthood PH in Turkey may be higher than that of adulthood PH in Western countries and adulthood PH usually affects individuals aged over 45 years. It is a possibility that the true prevalence of PH in adults may have been overestimated in this population study. Further research is warranted to clarify the epidemiology of adulthood PH in Turkey.

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