Big data analysis of Pulmonary Embolism in Greece

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Abstract

Introduction Pulmonary embolism (PE) epidemiological data are unclear considering the disease prevalence in the general population. The present study aims to investigate the prevalence of PE at the Greek population and the associated trends for the years 2013-2017. Methods Data on prescriptions for PE in the years 2013-2017 were provided by the Greek National Health Service Organization (EOPYY). Data on age, gender, specialty of the prescribing physician and prescription unit were provided as well. Results The total number of prescriptions for PE for the study period was 101.426. Of the total prescriptions, 51% were issued by the Public Sector, while 48% by the Private Sector. In 2013 the prevalence of PE was 5.43 cases per 100.000 citizens and increased constantly until 2017 with 23.79 cases per 100.000 population. Prevalence is higher in all years studied in the age group 70-80 with 69.35 cases per 100.000 population for the year 2017 followed by the ages 80-90 (60.58/100.000) and 60-70 (56.47/100.000) for the same year. Females display higher PE prevalence than males and higher increasing trend. Conclusion PE prevalence displays an increasing trend throughout the years while female prevalence is higher than males with a higher increasing trend. Our results may be used to appropriately organize nationwide health care systems aiming at the diagnosis, treatment and prevention of PE.

Background

Venous thromboembolism (VTE) (including pulmonary embolism (PE) and deep vein thrombosis) diagnosis and management remains difficult mainly due to its multifactorial causes such as aging, cancer and/or hormone replacement therapy [1, 2]. The variation of annual incidence rates of VTE among countries is significant and ranges from 62 to 143 per 100,000 persons in Canada [3] while data from United States of America indicate that VTE incidence increased by 82% from 73 to 133 per 100,000 population in the period 1985–2009. This increase in PE [4] corresponded to the high use of Computed Tomography Pulmonary Angiography (CTPA) among other diagnostic tests in the USA [5], while in a new Swedish study PE diagnosis increased from 0.69/1000 to 0.76/1000 during 2011–2018 [6]. The characteristics of sample studied (age and nationality), the data from the patients medical records only, and on insufficient assessment of primary and recurrent episodes [7] may be constituted factors for the differentiation of the studies results.

It is remarkable that there is a small number of studies during the last two decades for the trends in the incidence of PE although PE research data at national level can help significantly to evaluate trends PE. There is a remarkable variation between countries around the world about the rates of the PE incidence, due to both the differences in risk factors for PE and the inconsistencies in PE diagnosis among countries: In Australia and United Kingdom, rates of admission for PE have been increased in recent years [8, 9] while in China, the incidence of PE has remained stable during the past decade and the mortality rate has been decreased [10]. In USA studies have shown an increase in incidence and a significant fall in mortality [5, 11].

PE diagnosis usually takes place in the hospital setting and more rarely a doctor in the private sector diagnoses the disease and then usually refers the patient to a hospital facility for further evaluation. Outpatient physicians offer primary care services either at a private clinic that has signed a contract with the organization for social security fund, i.e. the National Organization for Healthcare Services Provision (EOPYY), or at the health centers of the National Primary Care Network (PEDY).

The aim of the present study was to describe PE prescribing patterns in Greece by using existing health administrative data for a large number of outpatients. These data were used to elucidate changes in the prevalence of PE in Greece during 2013–2017.

Methods

The present study is a retrospective observational epidemiological study undertaken in a large cohort of Greek patients with a diagnosis of PE. Health administrative data were collected from the Center of e-prescription data processing (KMES) of

the Greek National Health Service Organization (EOPYY). KMES is a platform and business intelligence system which incorporates data from electronically prescribed and hand written prescriptions. It should be noted that e-prescribing penetration is above 95% in the Hellenic system for outpatients. EOPYY is the largest social security fund (SSF) covering more than 90% of the insured population, and was created in 2012 from the merger of individual SSFs. EOPYY provides health insurance under a single benefits package for the Greek population, either through a network of contracted physicians, or through the health centers of PEDY (Primary National Health Network).

KMES is a structure that ensures recording, filing, processing and analyzing of all prescriptions submitted in the system and dispensed by all the private pharmacies contracted with EOPYY. In the present study, the CMSS data provided to us relate to the period between January 2012 and December 2017. 2012 was a milestone year for EOPYY and the electronic prescriptions did not actually correspond to the reality so the data were removed and the period under consideration sets out from January 2013 up to December 2017. The data that were provided to us by the KMES database have the following features: diagnosis of PE, disease description (ICD_10 code, ie, with or without cor pulmonale),date of prescriptions being dispensed, date, pharmacy prefix, specialty of the prescribing physician, prescription unit, and the number of prescriptions by Social Security Number (AMKA).

The authorization to use the anonymized data was obtained by EOPYY (9/1/2019 Data Acquisition and Data Access Agreement for Research Purposes, President's Approval Decision), in accordance with the applicable legislation on the protection and processing of personal data. Data on all patients identifiers were not provided to the authors in order to assure patient confidentiality. The study protocol was approved by the ethics committee of our institution.

Statistical analysis

Demographic characteristics are reported as mean ± standard deviation unless otherwise indicated. Datasets were tested for normality using the Shapiro-Wilk normality test. Incidence rates comparison was performed using a parametric t-test. All the statistical analysis was performed at the statistical significance level of 5% corresponding to p value of 0.05.

The time period investigated concerns monthly observations for approximately four years (2014 to 2017). We expected a positive correlation however we were not sure how strong it was and whether it behaved differently with respect to the categorical variable that separates samples in males and females. For this reason we inspected differences in intercept and slope for the corresponding regression lines. To achieve this we employed the analysis of covariance (ANCOVA) which is usually used to compare two or more regression lines by testing the effect of the categorical factor on the dependent variable (”Frequency”) while controlling the effect of a continuous co-variable (”Time”). As we are interested in comparing two regression lines, the categorical factor (Sex) splits the relationship between the two variables into two linear equations. We compared them by testing differences in slopes and intercepts. Differences in intercepts are interpreted as differences in magnitude while difference in slopes is interpreted as differences in the rate of change. Slopes were tested first, by testing for the interaction between the covariate and the factor. If the interaction between the covariate and the factor is not significantly different from zero, then we can assume the slopes are similar between equations. In this case, we proceeded to test for differences in intercept values among regression lines.

Data were analyzed using SPSS software, version 22 (Statistical Package for Social Sciences Inc., 2003, Chicago, USA).

Results

The total number of e-prescriptions for PE, according to the EOPYY records, for the study period was 101.426. Figure 1 presents the issuance of e-prescriptions in Greece. Of the total prescriptions, 51% (n = 51.654) were issued by the Public Sector, while 49.148 (48%) by the Private Sector. Further analysis revealed that the Primary Health Care Private Sector covered 45% (n = 45.633) of prescriptions, followed by the Secondary Health Care Public Sector with 24% (n = 24.610), the

Primary Health Care Public Sector at 22% (n = 21.999) followed by the Tertiary Health Care Public Sector and the Secondary Health Care Private Sector (Fig. 1).

The greater number of prescriptions was observed in the age group 70–80 followed by the age group 80–90 and 60–70 years (Fig. 2). The number of prescriptions in each age group was expressed per 100.000 age-matched population (Fig. 2).

We estimated the prevalence of PE and of PE with Acute Cor Pulmonale. The estimation of prevalence was made based on the monthly e-prescriptions. Since e-prescriptions that are issued per patient are monthly, the average can equal the prevalence of PE for the study period. In 2013 the prevalence of PE was estimated at 5.43 cases per 100.000 citizens and shows constant increase until 2017 with 23.79 cases per 100.000 population. In more detail, for women in 2013 prevalence was estimated at 3.12 cases per 100.000 population and in 2017 at 12.76 cases per 100.000 while for the men prevalence increased from 2.30 in 2013 to 11.03 cases per 100.000 in 2017 (Fig. 3). Additionally, we estimated prevalence per age group (Table S1).Prevalence is consistently higher in all years studied in the age group 70–80 with 69.35 cases per 100.000 population for the year 2017 followed by the ages 80–90 (60.58/100.000) and 60–70 (56.47/100.000) for the same year.

As for PE with mention of Acute Cor Pulmonale, its prevalence presents an increase between 2013 and 2017, starting at 0.12 and reaching 0.18 per 100.000 population, respectively. Figure 4 presents the prevalence of PE and of PE with mention of Acute Cor Pulmonale for both sexes.

We used regression to determine the causal relationship between the years studied, gender and PE prevalence. There is a significant effect of time and sex and also a significant interaction with PE prevalence. The slope of the regression between prevalence and time is not similar for males and females. Since slopes are significantly different between groups, then testing for different intercepts is not necessary. To this end, having tested the differences in regression lines we can fit linear regressions separately for males and females to investigate them further. Table S2 summarizes the results for both models (model 1 for males and model 2 for females respectively). The regression lines indicate that females have a higher intercept and while regression slope is positive for both groups the prevalence (“Frequency”) grows faster for males. We may visually investigate the regression lines for males and females in Fig. 5 where observations with different color correspond to different groups.

The bulk of prescriptions are issued by pulmonologists with 3.16 prescriptions per doctor, followed by hematologists with 1.99 prescriptions per doctor. Table 1 presents analytically prescriptions issued by specialization, the number of registered doctors in every specialization and the proportion of prescriptions both for PE and for PE with mention of Acute Cor Pulmonale. We noticed that Pulmonologists issue most of the prescriptions both for patients with PE and PE with Acute Cor Pulmonale. For PE with mention of Acute Cor Pulmonale, cardiologists follow, while in the case of PE without cor pulmonale Hematologists come second.

Finally, we performed prevalence estimation by geographical region. Greece was divided into 4 geographical regions (that is, Attica – Northern Greece – Southern Greece – Islands. Figure 6 presents prevalence by geographical region. The higher increase of prevalence is noticed in Attica with 5.95 cases per 100.000 population in 2013 while in 2017 the prevalence reached 29.47cases per 100.000. Next comes Northern Greece, then Southern Greece and last the Islands. For Attica and Northern Greece the level of statistical significance is 99%.

Discussion

The present study included data from 101.426 prescriptions for PE cases from Greece during 2013–2017. According to our results. PE prevalence is 23.79 cases per 100,000 population for 2017 that seems to be lower than previously published reports from other countries [3, 4]. Moreover, we revealed that there is an ascending tendency in PE prevalence from 2013 to

2017 that may reflect the progress in diagnostic tests in this field. Ageand gender distributionsis in agreement with other researches.

The PE annual prevalence for 2017 was estimated to 23.79 per 100,000 population in Greece. The reported trends in PE are lower than previously reported by others studies. To our knowledge this is the first study to describe the prevalence of PE in the general population of a country. Most studies report data on PE prevalence for in-hospital population. The prevalence of PE has been reported as high as 37% among selected hospitalized patients [12] while others reported a prevalence of 0.6% for subjects reporting syncope in the emergency department [13] and 16.1% in patients suffering from acute exacerbation of pulmonary embolism [14]. We have estimated PE prevalence by assessing the number of prescriptions by Social Security Number so that we would not have patient replicates counted more than one time so our study gives a rather fair estimate of the disease prevalence on the general population of Greece.

We observed annual increases in PE prevalence in the 4 years studied. PE prevalence raised from 5.43 cases per 100.000 population in 2013 to 23.79 in 2017. In addition, a slight increase was observed in the prevalence of PE with acute right heart dysfunction. Our data revealed a female predominance of PE prevalence throughout the study period consistent with the higher frequency of the disease in females [15]. Our results are in accordance with earlier published data [5, 8, 15–19], indicating a rising trend in PE case rates all over the years. We have previously reported an increase in PE incidence in Greece and a rather small mortality rate for the years preceding our study [15]. The increase in PE prevalence may be attributed to the wide availability and use of CT imaging among clinicians [5]. The correlation of the increase in PE prevalence may be additionally associated within creased prevalence of venous thromboembolism associated risk factors such as aging, heart failure and obesity [20, 21].

Our results provide further support to the age-dependent increase in VTE risk. We have observed increased PE prevalence in older subjects with a peak at the age groups 80–90 years for both genders. Our findings are consistent with previously published data. Other studies showed that incidence rates of PE in elderly patients are three times as high when compared to younger patients [22].

Additionally, in our research we found that the increase in PE prevalence was evident in both genders although females have a higher rate of prevalence increase throughout the study period The reasons underlying the gender differences cannot be addressed on the present study, however we hypothesize that discrepancies in life expectancy amongst sexes may at least in part provide an explanation. During the study period, the life expectancy of females ranged from 84.00 to 83.90 years (from 2013 to 2017, respectively) while life expectancy in males varied from 78.70 to 78.80 (from 2013 to 2017, respectively) and constantly remained lower than those for women [23].

In our study, we observed that patients with PE choose 51% of public health services versus 48% of the private sector. Also, we demonstrated that patients with PE are followed-up usually by a Pulmonologist than other specialties. This probably reflects the distribution of PE hospitalizations in Greece where there is anecdotal evidence that patients suffering from PE (occurring in the outpatient setting) are hospitalized mainly in Respiratory Medicine Departments. Venous thromboembolism is a multifactorial disease and may require multidisciplinary approach involving almost any medical specialty but more commonly Pulmonologists, Cardiologists and Hematologists. Our results reflect the national distribution of PE follow-up trends and highlight the need for national training programs for PE that aim in these specialties (both in the Public and Private sector).

Our study has several strengths and limitations. This is the first report of PE prevalence in Greece, with recent data from the entire Greek population. However, our study is of retrospective nature while we did not have available data on demographics of the cases (besides age, gender and health provider) or VTE related risk factors like cancer or hormone-replacement therapy. Additionally, data on PE with acute cor pulmonale were based on physician reporting and not on a standard definition of acute cor pulmonale. Therefore, we suppose that most of the cases reported as PE with acute cor Pulmonale

may reflect patients with High risk PE (according to international guidelines [24]), however we cannot exclude that some patients would be classified as Intermediate-high risk PE.

In conclusion, this is the first report of PE prevalence in a nationwide general population of a country (Greece) where we report an increasing trend for PE prevalence throughout the years. Female prevalence is higher than males with a higher increasing trend. The present results may be used to effectively organize nationwide health care systems organization towards the diagnosis, treatment and prevention of PE.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The data analyzed during the current study were available from the National Organization for Healthcare Services Provision (EOPYY) and are presented within the paper. The detailed clinical data are not publicly available in order to ensure study subjects anonymity and protect confidentiality.

Competing interests

The authors declare that they have no competing interests

Funding

The authors declare that they received no funding for the study

Authors' contributions

KIG was involved in the study conception and performed the design of the study. FM was involved in the literature search and in data interpretation. DGR and IChL performed the literature search, the data collection, the statistical analysis and prepared and wrote the manuscript. SKT and VPP were involved in statistical analysis, preparation of the manuscript. KIG, ZD and FM were involved in revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1: Prescriptions issued by specialist for patients diagnosed with PE and PE with cor pulmonale

PulmonaryEmbolism			
Specialty	ElectronicPrescriptions	Doctors per Specialty	Ratio of PrescriptionsDoctors
Pulmonologistics	21187	6708	3,16
Hematologists	4528	2277	1,99
General Medicine	18766	12990	1,44
Pathologists	25792	19404	1,33
Cardiologists	17567	14852	1,18
Onologists - Pathologists	918	1368	0,67
Vascularsurgeons	771	1274	0,61
Otherspecialties	11897	202704	0,06

Pulmonary Embolism with reference to acute cor pulmonale			
Specialty	ElectronicPrescriptions	Doctors per Specialty	Ratio of PrescriptionsDoctors
Pulmonologists	264	6708	0,04
Cardiologists	240	15852	0,02
Pathologists	284	19704	0,01
General Medicine	181	12990	0,01
Hematologists	31	2277	0,01
Otherspecialties	1000	57531	0,02

Figures

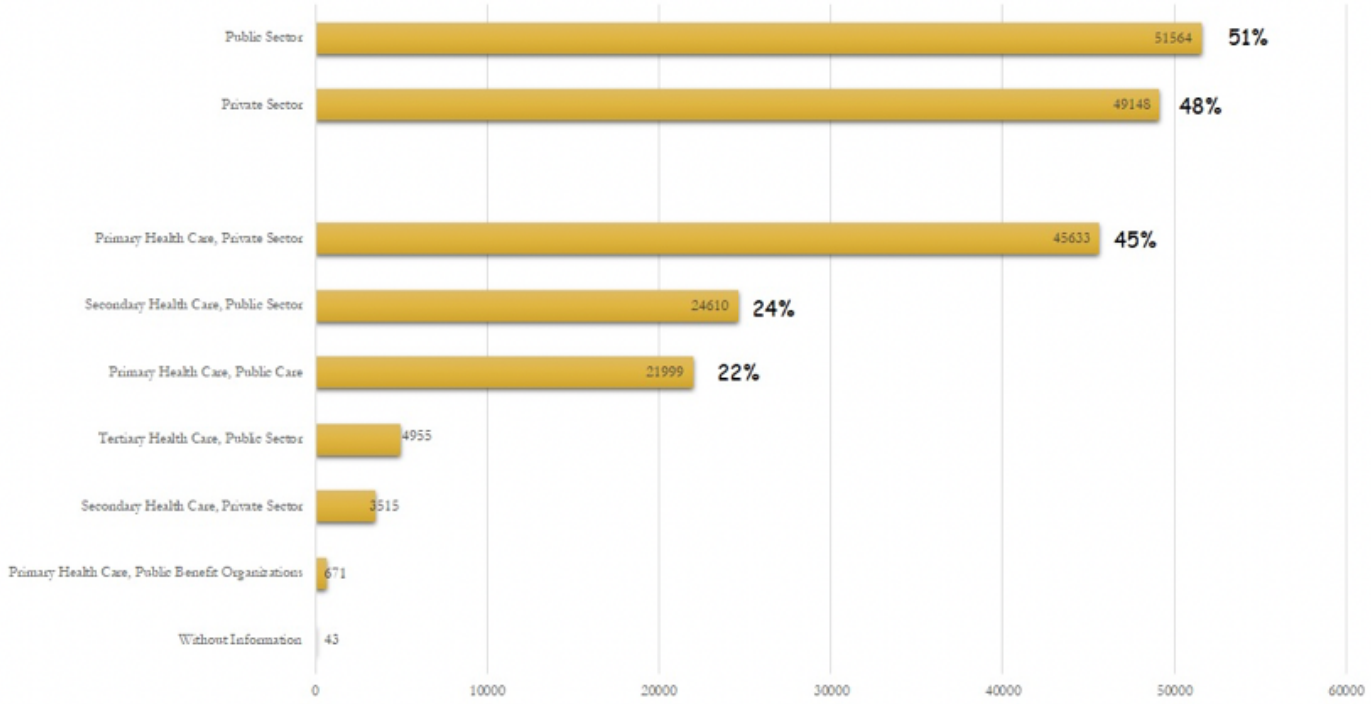

Figure 1

The issuance of e-prescriptions in Greece.

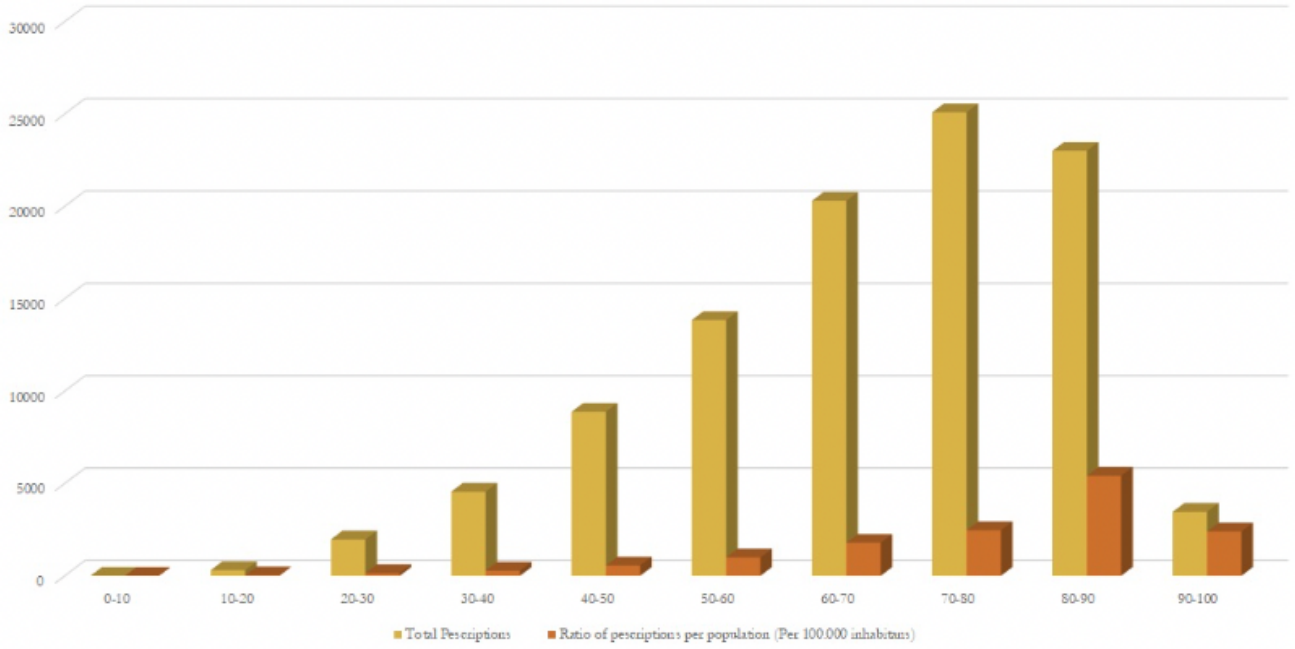

Figure 2

Absolute number of prescriptions sorted by age and number of prescriptions per 100.000 populations in each age group (prescriptions in age group/100.000 population of the same age group) for all study period

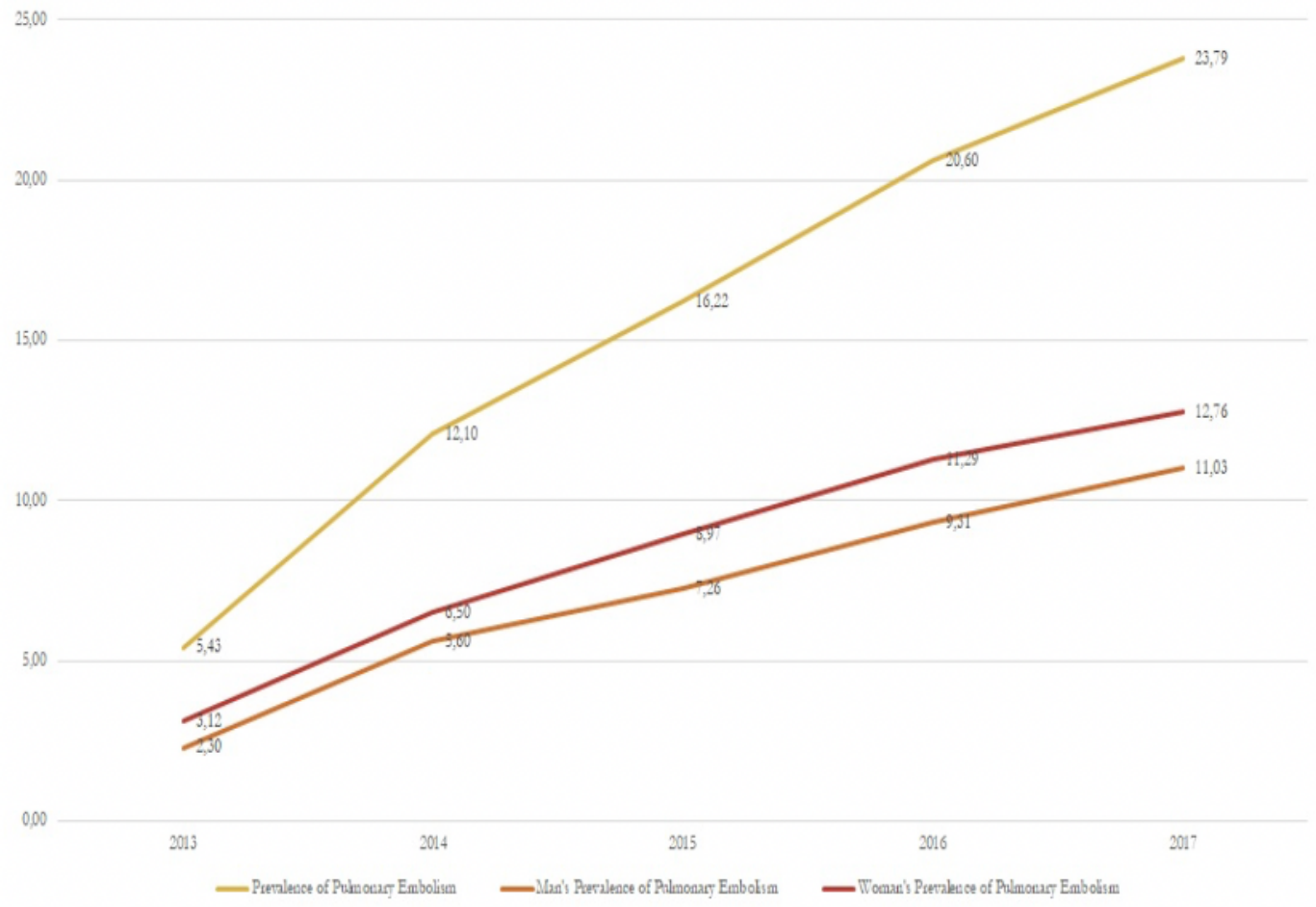

Figure 3

Prevalence of PE in Greece for the study period for both genders. The numbers correspond to cases per 100.000 population

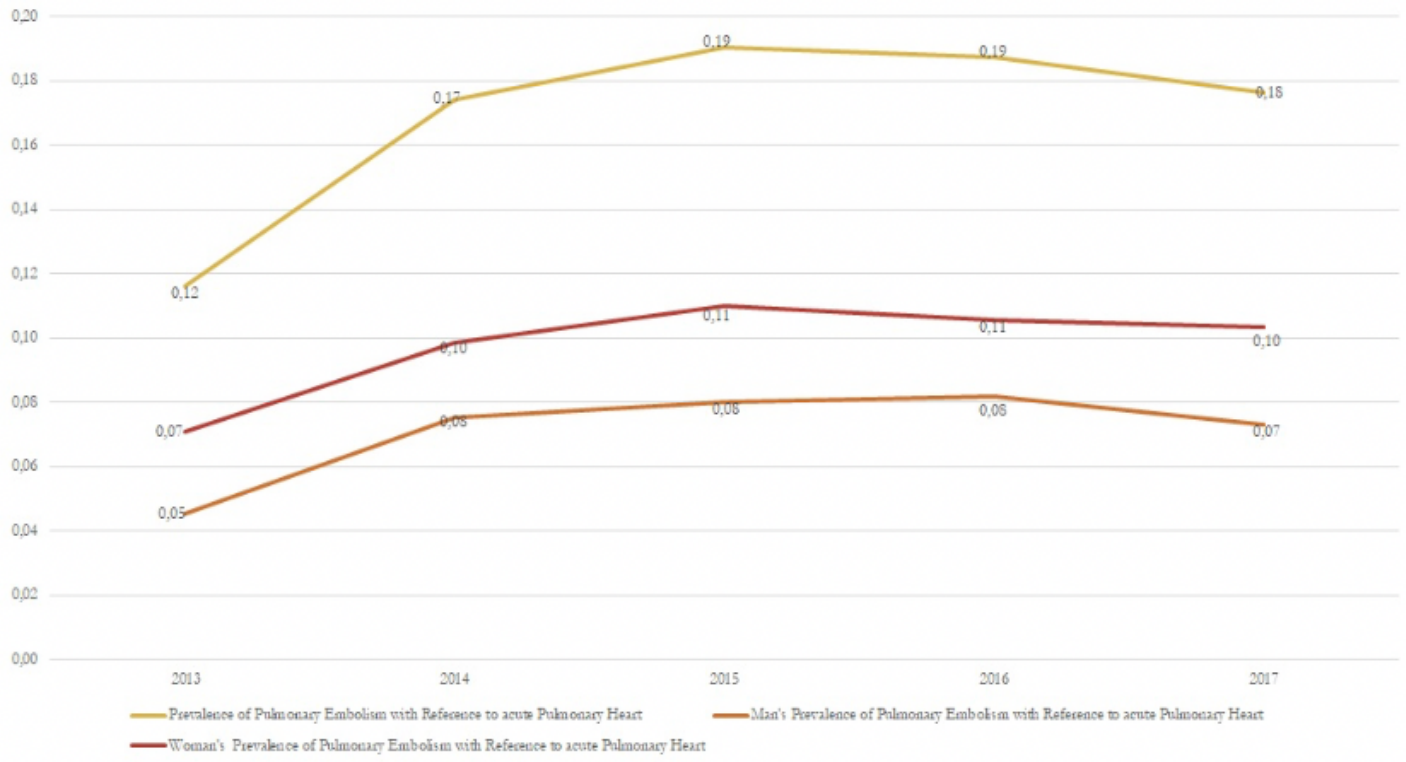

Figure 4

Prevalence of PE with Acute Cor Pulmonale in both sexes. The numbers correspond to cases per 100.000 population.

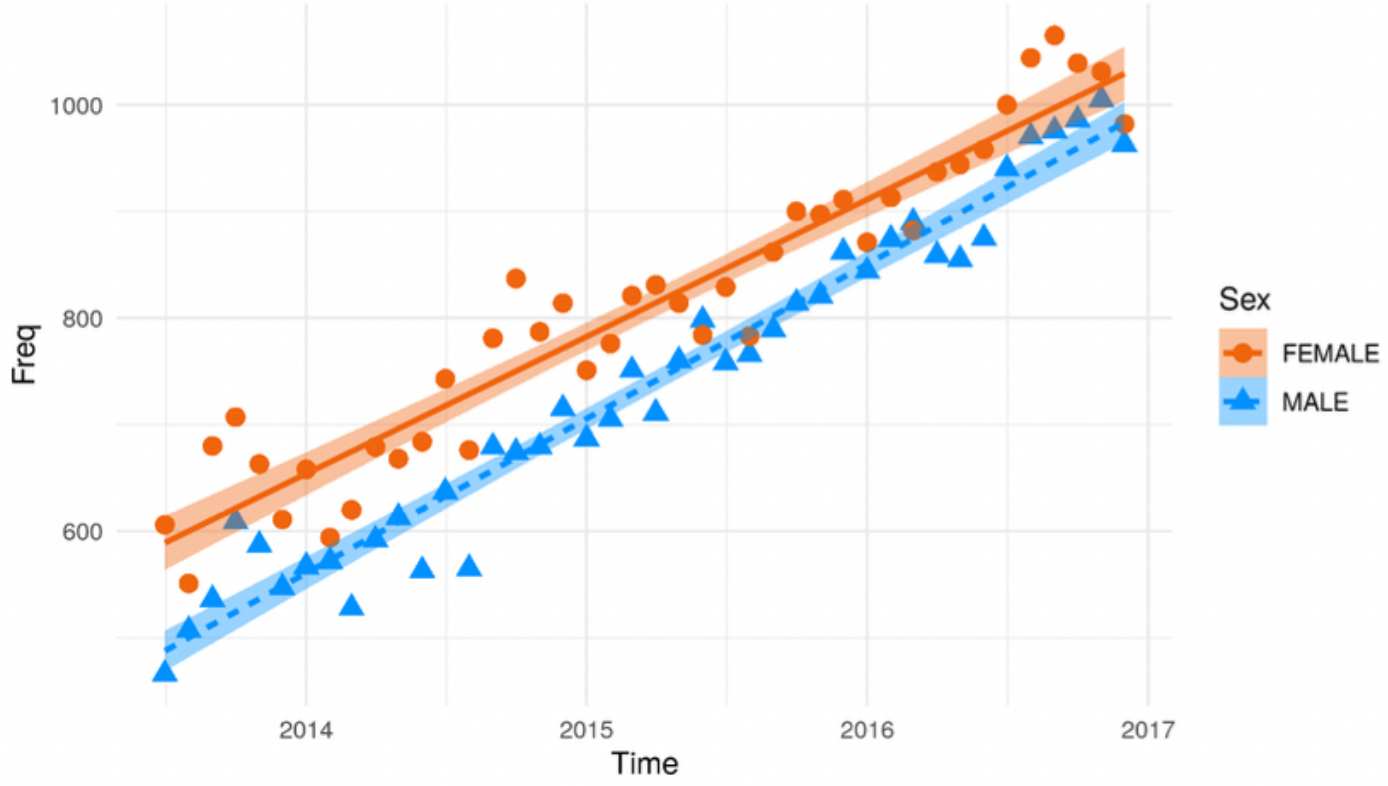

Figure 5

The two regression lines that correspond to male and female population respectively.

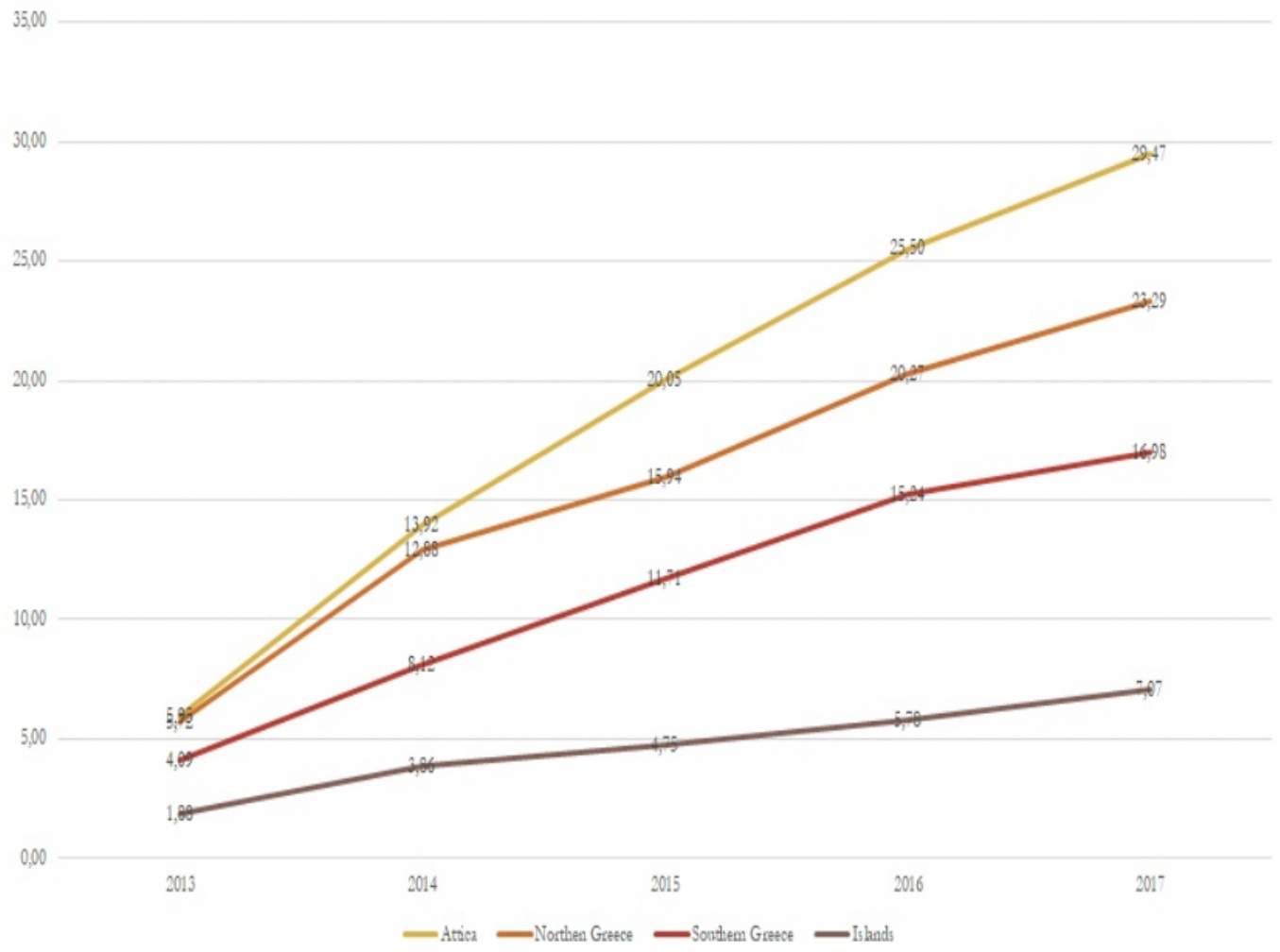

Figure 6

Prevalence of PE in Greece per geographical region.

Supplementary Files

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- Supplementarymaterial.docx