

Big data analysis of Pulmonary Embolism in Greece

Ioannis Ch Lampropoulos

University of Thessaly Faculty of Medicine

Dimitrios G Raptis

University of Thessaly Faculty of Medicine

Zoe Daniil

University of Thessaly Faculty of Medicine

Sotirios K Tasoulis

University of Thessaly School of Science

Vassilis P Plagianakos

University of Thessaly School of Science

Foteini Malli (✉ mallifoteini@yahoo.gr)

University of Thessaly Faculty of Medicine <https://orcid.org/0000-0002-7595-6715>

Konstantinos I Gourgoulianis

University of Thessaly Faculty of Medicine

Research article

Keywords: pulmonary embolism, prevalence, prescribing patterns, epidemiology

Posted Date: November 4th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-25443/v2>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published on March 21st, 2021. See the published version at <https://doi.org/10.1186/s12889-021-10621-2>.

Abstract

Background: 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 medical 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 medical 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 prevalence in females is higher than males and displays 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 (USA) indicate that VTE incidence increased by 82% (from 73 to 133 per 100,000 population) in the period 1985-2009 [4]. This increase in PE 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 the sample studied (age and nationality), the retrieval of data from the patients medical records, and the insufficient assessment of primary and recurrent episodes [7] may be contributing factors for the differentiation among the studies.

It is remarkable that there is a small number of studies during the last two decades examining the trends in the incidence of PE although PE research data at national level can help significantly to evaluate the disease trends. There is a remarkable variation between countries around the world about the rates of 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 are increased in recent years [8,9] while in China, the incidence of PE has remained stable during the past decade while the mortality rate has 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 physician of 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 the years 2013-2017. For the purpose of the study, we analyzed electronic prescriptions that were issued with a diagnosis of PE. The term "prescription" corresponds to the term "medical prescription" that is defined as a health care provider's written authorization that is given to a patient in order to purchase a prescription drug from a pharmacy. The electronic prescription is entered into an electronic medical record system and then printed before being handed-out to a pharmacist.

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 KMES data provided to us relate to the period between January 2012 and December 2017. The year 2012 was a milestone year for EOPYY and the electronic prescriptions did not actually correspond to the reality, so the data were discarded 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 with a disease description (ICD_10 code of I26.0 for PE with Acute Cor Pulmonale and I26.9 for PE without Acute Cor Pulmonale), the date the prescriptions were issued and the date that they were carried-out by the pharmacist, pharmacy prefix, specialty of the prescribing physician (e.g. pulmonologist, cardiologist, hematologist), the prescription unit (e.g. Private Sector, Public Sector, Tertiary Sector, Primary care facility), and the number of prescriptions by Social Security Number (AMKA). The total number of electronic prescriptions provided to us was 101,426. The data correspond to individual Social Security Number so that we would not have patient replicates. We have assessed the prevalence of PE with and without Acute Cor pulmonale by using the different ICD10 codes in order to describe PE prevalence in more detail and to provide data on the prevalence of PE according to its severity.

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 (prevalence) 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 using a ICD10 code 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 (Figure 1).

The greater number of prescriptions was observed in the group of patients aged 70-80 years followed by the age group of 80-90 years and of 60-70 years (Figure 2). The number of prescriptions in each age group was expressed per 100,000 age-matched population (Figure 2).

We estimated the prevalence of PE and of PE with Acute Cor Pulmonale. The estimation of prevalence was 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 without Acute Cor Pulmonale 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 PE 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 cases per 100,000 population in 2013 to 11.03 cases in 2017 (Figure 3). Additionally, we estimated prevalence per age group (Table S1). Prevalence is consistently higher in all years studied in the age group of 70-80 years 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 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 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 grows faster for males. We may visually investigate the regression lines for males and females in Figure 5 where observations with different color correspond to different groups.

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

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

Pulmonary Embolism				Pulmonary Embolism with reference to acute cor pulmonale			
Specialty	Electronic Prescriptions	Doctors per Specialty	Ratio of Prescriptions Doctors	Specialty	Electronic Prescriptions	Doctors per Specialty	Ratio of Prescriptions
Pulmonologists	21187	6708	3,16	Pulmonologists	264	6708	0,04
Hematologists	4528	2277	1,99	Cardiologists	240	15852	0,02
General Medicine	18766	12990	1,44	Pathologists	284	19704	0,01
Pathologists	25792	19404	1,33	General Medicine	181	12990	0,01
Cardiologists	17567	14852	1,18	Hematologists	31	2277	0,01
Onologists - Pathologists	918	1368	0,67	Otherspecialties	1000	57531	0,02
Vascularsurgeons	771	1274	0,61				
Otherspecialties	11897	202704	0,06				

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 29.47 cases 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. *Age and gender distributions* is in agreement with other researchers.

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 Chronic Obstructive Pulmonary Disease [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 the same context, 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 with increased 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 of 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.

Conclusion

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 campaigns towards the diagnosis, treatment and prevention of PE.

List Of Abbreviations

VTE: Venous Thromboembolism

PE: Pulmonary Embolism

CTPA: Computed Tomography Pulmonary Angiography

USA: United State of America

EOPYY: National Organization for Healthcare Services Provision

PEDY: National Primary Care Network

KMES: Center of e-prescription data processing

SSF: Social Security Fund

AMKA: Social Security Number

SPSS: Statistical Package for Social Sciences

CT: Computed Tomography

Declarations

Ethics approval and consent to participate

The data were provided following a contract with EOPYY (Agreement on data availability and access to data for research purposes). The contract was signed by the researchers and the president of the organization at 09/01/2019. Further information can be obtained from Research Appraisal Working Team, info_research@eopyy.gov.gr.

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 ICL 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.

Acknowledgements

The Authors would like to thank National Organization for Healthcare Services Provision (EOPYY) for its determinant contribution to prosecution of the present research/article which consisted of data providing, as well as the general encouragement of this research effort.

References

1. Goldhaber SZ. Pulmonary embolism. *Lancet* 2004;363:1295–305.
2. Kyrle PA, Eichinger S. Deep vein thrombosis. *Lancet* 2005;365:1163-1174.
3. Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis*. 2009;28:401-9.
4. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med*.2014;127:829-39.
5. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*.2011;171:831-7.
6. Wändell P, Forslund T, Mankowitz HD, et al. Venous thromboembolism 2011–2018 in Stockholm: a demographic study. *J Thromb Thrombolysis*. 2019;48:668-673.
7. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol*. 2007;44:62-9.
8. Aylin P, Bottle A, Kirkwood G, Bell D. Trends in hospital admissions for pulmonary embolism in England: 1996/7 to 2005/6. *Clin Med*. 2008;8:388-392.
9. Shiraev TP, Omari A, Rushworth RL. Trends in pulmonary embolism morbidity and mortality in Australia. *Thromb Res*. 2013;132:19-25.
10. Yang Y, Liang L, Zhai Z et al. Pulmonary embolism incidence and fatality trends in Chinese hospitals from 1997 to 2008: a multicenter registration study. *PLoS One*. 2011;6:e26861.
11. Horlander, KT, Mannino, DM, Leeper, KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. *Arch Intern Med*. 2003;163:1711-1717.
12. Bakebe A, Kashongwe I, Mulenga C, et al. Pulmonary embolism: epidemiological data and diagnosis in Kinshasa hospitals. *IJTLD*. 2017;21:875-879.
13. Thiruganasambandamoorthy V, Sivilotti ML, Rowe BH et al. Prevalence of pulmonary embolism among emergency department patients with syncope: a multicenter prospective cohort study. *Ann Emerg Med*. 2019;73:500-510.
14. Aleva FE, Voets LW, Simons SO, de Mast Q, van der Ven AJ, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: a systematic review and meta-analysis. *Chest*. 2017;151:544-554.
15. Raptis DG, Gourgoulis KI, Daniil Z, Malli F. Time trends for pulmonary embolism incidence in Greece. *Thromb J*. 2020;18:1.
16. Dentali F, Ageno W, Pomero F, Fenoglio L, Squizzato A, Bonzini M. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. *Thromb Haemost*. 2016;116:399-405.
17. Park B, Messina L, Dargon P, Huang W, Ciocca R, Anderson FA. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: findings from the nationwide inpatient sample. *Chest*. 2009;136:983–990.
18. de Miguel-Díez J, Jiménez-García R, Jiménez D et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. *Eur Respir J*. 2014;44:942-950.
19. Mellekjær L, Sørensen HT, Dreyer L, Olsen J, Olsen JH. Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977–95. *BMJ*. 1999;319:820–821.
20. Udelson JE, Stevenson LW. The future of heart failure diagnosis, therapy, and management. *Circulation*. 2018;133:2671-2686.
21. Flegal KM, Kruszon-Moran D, Carrol MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005- 2014. *JAMA*. 2016;315:2284-2291.
22. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. 2004;117:19-25.
23. Countryeconomy.com. <https://countryeconomy.com/demography/lifeexpectancy/Greece>. Accessed 18 Mar 2020.
24. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2019;39:4208.

Figures

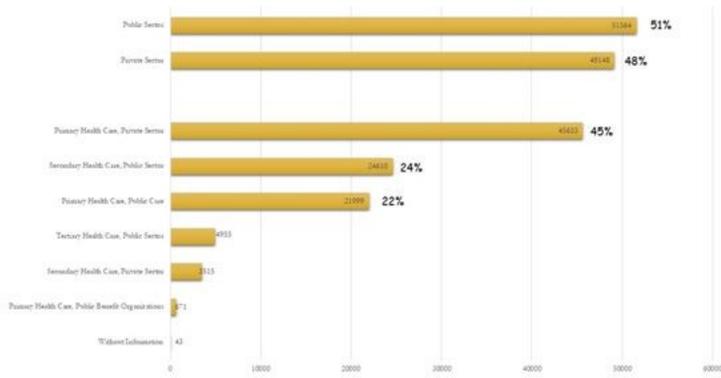


Figure 1

The issuance of e-prescriptions in Greece.

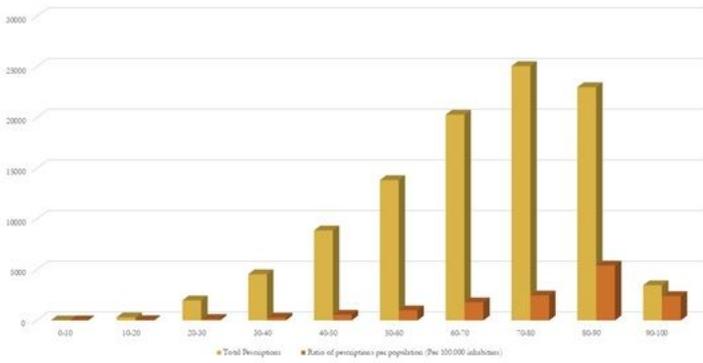


Figure 2

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

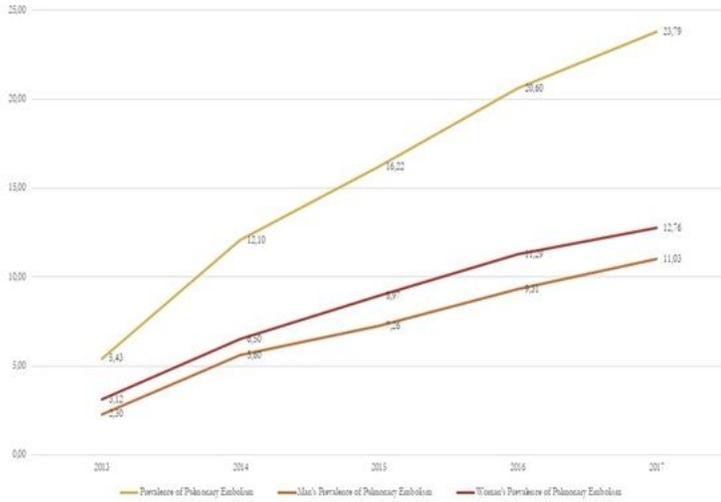


Figure 3

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

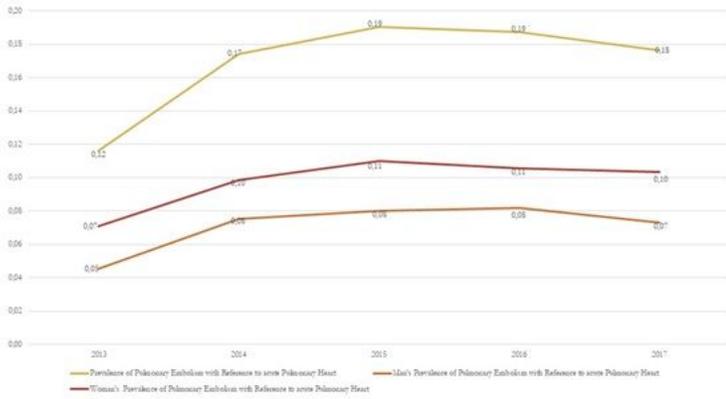


Figure 4

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

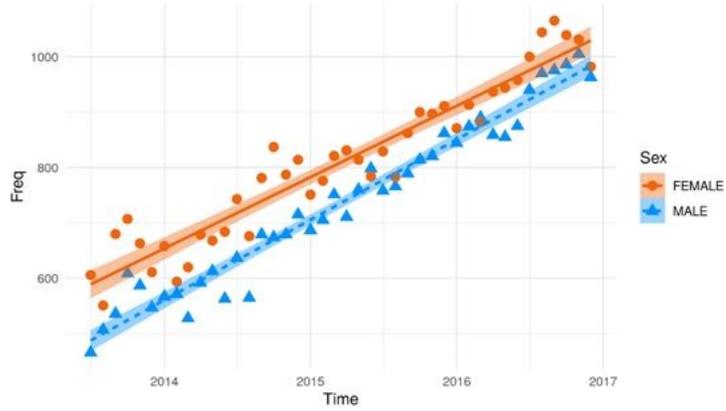


Figure 5

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

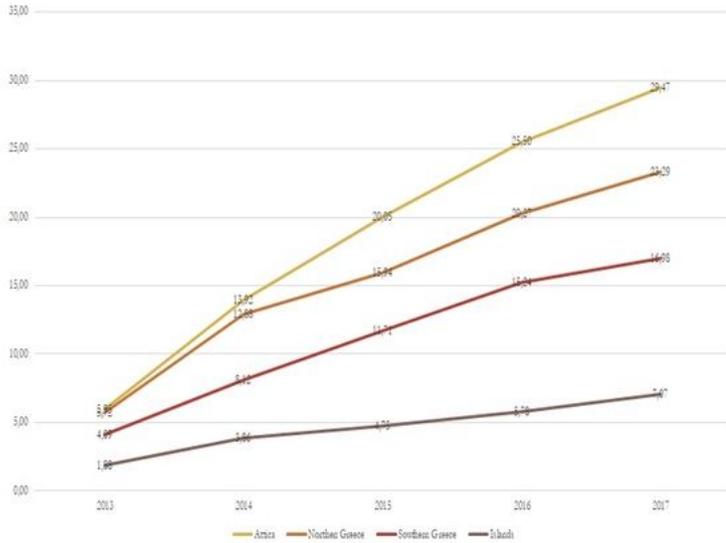


Figure 6

Prevalence of PE in Greece per geographical region.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterial.docx](#)