Hospital incidence and medical costs of polycythemia vera in Spain: a retrospective database analysis

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Author contributions

JD contributed to the investigation by analyzing and interpreting the burden associated to polycythemia vera in Spain and was a major contribution in the intellectual content revision. AM analyzed the current situation of polycythemia vera in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Abstract

Background: Polycythemia vera (PV) is one of the most common chronic myeloproliferative neoplasms, yet, little data is available on the epidemiology of PV in Spain and the costs of its management. This study aimed to evaluate the hospital incidence and mortality rate of PV in Spain, and to estimate hospital medical costs.

Methods: Hospital admission records of patients with PV registered between 2005 and 2019 were obtained from a Spanish hospital discharge database and analyzed in a retrospective multicenter study.

Results: Admission files of 490 patients were reviewed. Median age was 74 years; patients presented numerous conditions associated to age, namely hypertension, diabetes or anemia. Hospital mortality rate was associated to pulmonary heart disease, respiratory conditions and kidney disease. Most of the files analyzed corresponded to inpatient admissions; hospital incidence decreased over the study period in patients over 60 years. Median admission cost was €5580, increasing in patients deceased during the hospitalization. Admission cost increased significantly between 2006 and 2011.

Conclusions: This study provides an evaluation of hospital management and costs of PV in Spain. Future studies should focus on the revision of disease management in the country and measuring total medical costs, which could be higher than global estimations.

Keywords: polycythemia vera; blood cancer; hospital incidence; hospital mortality; medical costs; Spain.

1. Introduction

Chronic myeloproliferative neoplasms (MPN) are a heterogeneous group of diseases defined by the clonal expansion of an abnormal hematopoietic progenitor cell [1]. Polycythemia vera (PV) is one of the most common MPN, its incidence is estimated to range between 2.3 and 2.8 per 100,000 persons/year [2,3]. One of the main concerns in patients with PV is the presence of complications related to thrombosis, progression to myelofibrosis or leukemia [4]. In addition, thrombotic events and cardiovascular disease are the principal cause of mortality in these patients, and are often used to stratify patients based on prognosis [5].

The treatment of PV is varies depending on the patient's age and history of thrombosis, classifying patients into those with low-risk or high-risk disease, with an estimated survival in patients younger than 60 years of age of 24 years [6]. Phlebotomy is the first treatment option to control hematocrit level, contributing in reducing thrombotic events, additionally, low-dose aspirin therapy is recommended [7]. Other treatments include hydroxyurea and interferon-α, although the latter has not been widely approved [8,9]. In addition, targeted treatments are being developed in the recent years, focused on inhibiting JAK2 or class I/II histone deacetylases (HDAC) [10,11].

Despite the emerging treatments for PV, these patients still present numerous unmet clinical needs. In many cases, the response to available therapies is suboptimal, and patients' present thrombotic events, thrombocytosis, leukocytosis or splenomegaly, furthermore, the lack of curative treatments is a major limitation [12,13].

Overall, the frequent complications of the disease are associated to significant medical costs; specifically, thrombotic events have been associated with increased medical costs in patients with PV [14]. Nevertheless, few studies are available measuring the medical costs of PV, and epidemiologic and economic data in Spain are scarce, with no formal data available.

In this context, the objectives of this study were to analyze hospital incidence and hospital mortality rate of polycythemia vera in Spain, and to estimate medical costs at the hospital level.

2. Methods

2.1. Study setting

This study analyzed hospital admission records of patients with polycythemia vera registered between 1 Jan 2005 and 31 Dec 2019 in a Spanish National discharge database, which covers 90% of hospitals in Spain with data from all Spanish regions.

This database gathers admission data codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) the year 2016 [15,16]. Centers are responsible for data codification, evaluation and confidentiality. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated.

2.2. Data extraction

Only hospital admission files in which polycythemia vera was registered as the reason for admission were included in the study, identified using the ICD-9 and ICD-10 codes for the disease: 238.4 and D45, respectively. Admission records did not contain any parameters identifying healthcare centers or medical history that were previously re-

coded to maintain records anonymized, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [17].

2.3. Study variables

The variables obtained from the database were: patients' age, date of admission, type of admission, date of discharge, type of discharge (including death), readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), primary diagnosis, up to 20 secondary diagnoses registered during the admission, medical procedures and total admission cost.

2.4. Data analysis

The patients with polycythemia vera identified in the database were initially stratified in two age groups, ≤60 years and > 60 years of age, considering that age is one of the main risk factors for thromboembolic events which have a great effect in patients' prognosis [3,4]. In addition, the group of patients deceased during the hospitalization event was analyzed and compared to the group of patients non deceased during the admission.

Hospital incidence was measured as the annual number of patients admitted with polycythemia vera within the total number of admission files in the database. Hospital mortality was defined as the number of patients deceased during the hospital stay within the total patients admitted with the disease. Direct medical costs of specialized healthcare were extracted from the database, where they are assigned according to the standardized average expenses of admissions and medical procedures determined

by the Spanish Ministry of Health (include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources).

Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean or median with 95% confidence interval (CI) were calculated for continuous variables. Two-tailed non-parametric independent t-test (Mann-Whitney U test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate and two-sample Z tests were used to test for differences in sample proportions. Nonparametric Spearman correlation test was used to assess trends in incidence, mortality rate, length of hospital stay and cost. A $p<0.05$ was considered statistically significant in all tests.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2016 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

The ICD codes for polycythemia vera identified 555 admissions in the database, corresponding to 490 individual patients diagnosed with the disease between 2005 and 2019 (Table 1). The most frequent secondary diagnoses registered during the admission were essential hypertension, registered in 34.8% of admissions, and anemia, found in 18.2% of admissions. Chronic obstructive pulmonary disease and other respiratory system diseases were found in 10.3% and 15.7% of all admissions, respectively, and liver disorders were registered in 11.9% of admissions. In addition, respiratory conditions including pleural effusion, acute respiratory failure and other

specified respiratory conditions, acute kidney failure and chronic kidney disease were associated to death during the hospital admission (Table 1).

In total, 73 patients died during the hospital admission over the study period, leading to a total hospital mortality rate of 13.2%. Only 1 death was registered in patients under 60 years of age. No significant trends were identified in the mortality rate over time. Interestingly, thromboses were registered in only 2.7% of deaths.

The hospital incidence of polycythemia vera was 0.7 per 100,000 persons the year 2019, decreasing over the study period ($p=0.0001$) (Figure 1). The same trend was observed in patients over 60 years of age ($p<0.0001$), but not in those aged 60 and younger ($p=0.3066$).

The majority of files analyzed in the study corresponded to hospital inpatient admissions (98.7%), and 75.0% were urgent or non-scheduled admissions (Table 2). The portion of urgent admissions was significantly higher in patients over 60 years of age ($p<0.0001$), and represented 83.6% of the admissions in patients deceased during the admission. Median length of hospital stay was 7 days, with no significant differences between patient groups or over time. Hospital admissions were primarily registered in hematology departments and internal medicine.

The medical procedures registered during the admission were analyzed per age groups and in deceased patients (Table 3). Numerours diagnostic medical procedures were registered, primarily diagnostic ultrasounds of the abdomen and vascular system (37.7%). The transfusion of packed cells was registered in 26.3% of admissions, biopsies of the bone marrow were found in 15.0% of admissions, and phlebotomies in 9.7% of admissions. Several differences were found between age groups, and the

group of patients that died during the hospitalization required antibiotic injections and mechanical ventilation more frequently.

Admission files were associated to a cost per admission. The median admission cost over the study period was €5580 (Table 4). No significant differences were found in the admission cost per age group, whereas the admission cost in patients that died during the hospitalization was significantly higher to that in non-deceased patients ($p<0.0001$), despite the small sample size. Length of hospital stay affected admission cost significantly for all patients, except for deceased patients. Finally, admission cost increased significantly between 2006 and 2011 ($p<0.0001$) (Figure 2A), both in the total population and in patients over 60 years of age ($p=0.0028$) (Figure 2B). In patients aged 60 and younger, admission cost displayed a decreasing trend over the study period ($p=0.0010$) (Figure 2B).

4. Discussion

Few studies are available evaluating the medical costs of PV, and its incidence in Spain has not been formally evaluated. This study aimed to provide novel data on the incidence, mortality and costs of this disease at the hospital level in Spain, providing a basis for further evaluations at the population level.

The ICD codes corresponding to PV identified 490 individual patients, registered in the database between 2005 and 2019. The hospital incidence estimated in this context was 0.7 per 100,000 persons in 2019, decreasing over the study period. It must be considered that incidence within the hospital population cannot be extrapolated to the general population, in which unofficial sources cite an incidence of 0.4-0.6 per 100,000 persons [18]. These data would indicate that the incidence of PV in Spain could be lower to that estimated globally [2,3]. Interestingly, the gradual decrease observed in

the hospital incidence in this study corresponded to a decline in the number of hospital cases of patients over 60 years of age.

The patients evaluated herein had a median age of 74 years and presented a variety of comorbid conditions, identified as secondary diagnoses. Diabetes, hypercholesterolemia and coronary heart disease, among other conditions, were associated with patients' age. Frequent and major complications in patients with PV were also registered, including thrombosis, leukemic transformation and fibrotic progression [4,6].

Median survival was 14.1 years in a population with extensive follow-up in the United States, while in a poster publication focused on a Spanish population, survival reached the 20.2 years [19,20]. Hospital mortality rate estimated in this study was 13.2%, with the majority of deaths registered in patients over 60 years. Hospital death was associated to respiratory conditions, acute kidney failure and chronic kidney disease, while thromboses were found in only 2.7% of deaths. Thrombotic events are considered one of the most prevalent complications in PV, with patients over 60 years in a higher risk of suffering such complications [5]. However, the present study does not reflect this situation, with thromboses registered more frequently in younger patients and no association found with in-hospital death.

Treatment of PV is mainly focused on reducing the risk of thromboses and other complications and symptom management, and ambulatory treatment could be sufficient in some cases [7]. The data gathered in this study corresponds primarily to inpatient hospital admission data, however, the shift towards an ambulatory-based treatment could explain the observed decrease in hospital incidence. Previous disease burden studies have linked PV with a more intense use of healthcare resources,

including both inpatient and outpatient care [21]. Hospital admissions in this study registered numerous diagnostic procedures, and therapeutic procedures that included the transfusion of packed cells, whole blood or platelets, and phlebotomies, while the use of emerging treatment options cannot be evaluated. The elevated percentage of blood transfusions could be associated to PV complications that were otherwise not registered in the database. Hospital admissions were urgent or not scheduled in 75.0% of the cases, a percentage that increased with age.

The medical costs measured in this study correspond to the costs of hospital inpatient care of PV. Previous evaluations measured a mean medical cost in patients with PV of €10,034 ($11,927) to €12,538 ($14,903) per patient; of these, between €2878 ($3407) and €3944 ($4670) were inpatient care costs, representing about 30% of all costs [22-24]. In this study, median admission cost was €5580. Further studies will be required to evaluate the total medical cost of PV in Spain. Finally, admission cost increased between 2006 and 2011 in patients over 60 years of age, however, it decreased over the whole study period in patients aged 60 years and younger.

The results of this study may be influence by a series of limitations. Patients were identified via ICD-9 and ICD-10 codes registered in the database, and medical conditions and procedures were limited to those registered therein. It must be considered that the population described corresponds to hospitalized patients, presumably presenting more frequent complications than the patients with PV in the general population. Similarly, mortality rate is limited to deaths registered during a hospital admission, and the medical cost was evaluated at the hospital level; further research will be required to estimate the total medical cost of PV. Regarding medical costs, it must be noted that even though all admissions included in the study had PV

registered as the reason for admission, patients were treated for comorbidities and other conditions, which may have an impact in the overall cost of the admission. Finally, despite periodic audits and internal validation processes, coding errors may still exist in the database, and should be taken into account as a possible source of bias.

5. Conclusions

This study provides novel data describing the characteristics of patients with PV treated in Spanish hospitals over 15 years, and the associated medical costs. The trends observed in both the hospital incidence and the hospital mortality rate must be further explored, to identify disease management changes over time. Medical costs measured at the hospital level suggest that the total medical cost associated to this disorder could be increased versus global estimations.

6. Statements

6.1. Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

6.2. Data availability statement

Data sharing is restricted due to legal stipulations, yet the data that support the findings of this study is fully available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at: https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm.

6.3. Declaration of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.4. Declaration interest

The authors declare that they have no competing interests.

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8. Figures

Figure 1 Hospital incidence of polycythemia vera per age groups (2005-2019) with total trend p values.

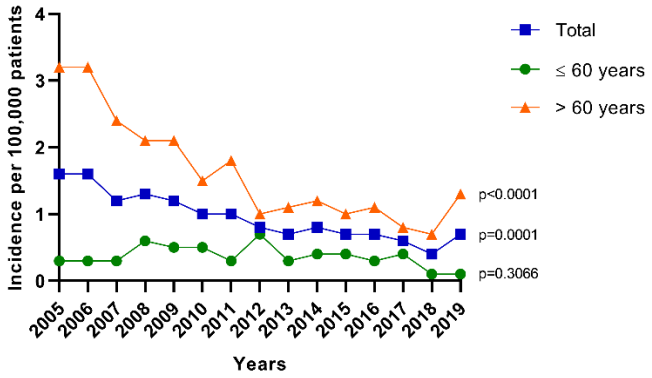
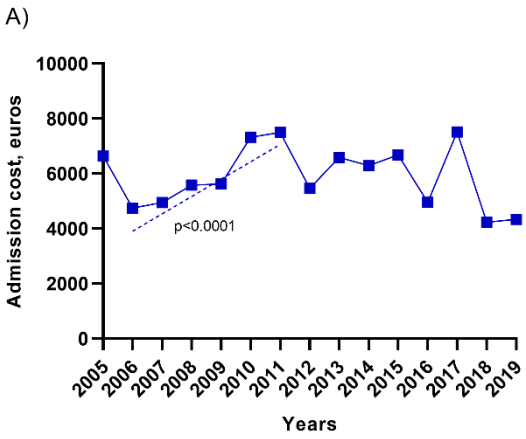
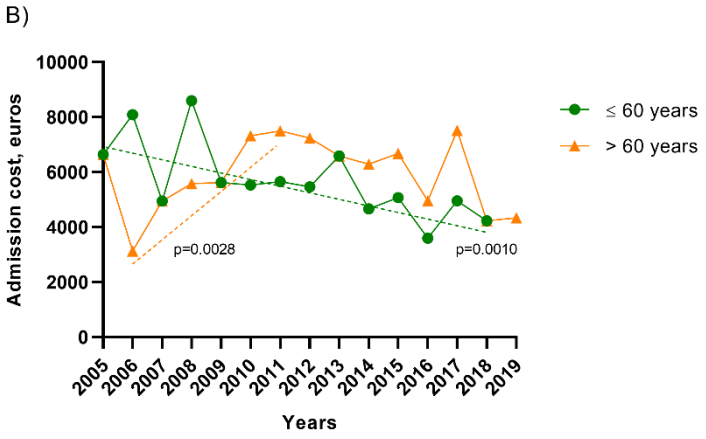


Figure 2 Median admission cost of polycythemia vera in all patients (A) and per age groups (B) (2005-2019) with significant trend p values.





9. Tables

Table 1 Characteristics of patients diagnosed with polycythemia vera per age groups and in deceased patients.

	Total	**≤ 60 years of age**	**> 60 years of age [p value age]**	**Deceased patients [p value vs. non deceased]**
Admissions, N	555	103	452	73
Males, %	51.0	46.6	52.0 [p=0.3235]	45.2 [p=0.2887]
Median age, years (95% CI)	74 (73-75)	49 (45-50)	77 (76-78) [p<0.0001]	80 (77-82) [p>0.9999]
Hospital mortality rate, %	13.2	1.0	15.9 [p<0.0001]	-
Secondary diagnoses, %	-	-	-	-
Thyroid disease	5.6	1.9	6.4 [p=0.0744]	8.2 [p=0.2931]
Diabetes mellitus	10.3	1.0	12.4 [p=0.0006]	15.1 [p=0.1473]
Hypercholesterolemia, hyperlipidemia	8.5	3.9	9.5 [p=0.0640]	5.5 [p=0.3250]
Disorders of fluid electrolyte and acid-base balance	5.4	2.9	6.0 [p=0.2151]	8.2 [p=0.2539]

Anemia	18.2	7.8	20.6 [p=0.0024]	16.4 [p=0.6758]
Secondary thrombocytopenia	3.2	3.9	3.1 [p=0.6844]	4.1 [p=0.6539]
Neutropenia	2.3	2.9	2.2 [p=0.6715]	2.7 [p=0.8096]
Essential hypertension	34.8	22.3	37.6 [p=0.0033]	34.2 [p=0.9190]
Atrial fibrillation	9.2	0.0	11.3 [p=0.0047]	9.6 [p=0.8990]
Heart failure	6.8	1.9	8.0 [p=0.0850]	8.2 [p=0.6183]
Coronary atherosclerosis	5.9	0.0	7.3 [p=0.0003]	8.2 [p=0.3781]
Venous embolism and thrombosis	5.9	11.7	4.6 [p=0.0067]	2.7 [p=0.2139]
Chronic pulmonary heart disease	5.4	1.9	6.2 [p=0.0850]	11.0 [p=0.0243]
Cerebrovascular disease	5.4	3.9	5.8 [p=0.4491]	6.8 [p=0.5583]
Chronic obstructive pulmonary disease	10.3	4.9	11.5 [p=0.0448]	5.5 [p=0.1479]
Other diseases of the respiratory system	15.7	6.8	17.7 [p=0.0060]	39.7 [p<0.0001]
Disorders of the liver	11.9	14.6	11.3 [p=0.3534]	6.8 [p=0.1532]
Chronic kidney disease (ckd)	9.2	1.0	11.1 [p=0.0014]	16.4 [p=0.0214]
Acute kidney failure	7.6	4.9	8.2 [p=0.2486]	23.3 [p<0.0001]
Splenomegaly	6.7	6.8	6.6 [p=0.9535]	8.2 [p=0.5683]

Table 2 Characteristics of the admissions registered in patients with polycythemia vera.

	Total	**≤ 60 years of age**	**> 60 years of age [p value age]**	**Deceased patients [p value vs. non deceased]**
Admissions, N	555	103	452	73
Urgent admissions, %	75.0	66.0	77.0 [p<0.0001]	83.6 [p=0.0686]
Readmission rate, %	10.6	5.7	9.7 [p=0.2547]	11.7 [p=0.2320]
Median LOHS, days (95% CI)	7 (6-7)	5 (4-7)	7 (7-8) [p>0.9999]	6 (4-12) [p>0.9999]
Hematology department, %	42.7	31.1	45.4 [p=0.0082]	43.8 [p=0.8337]
Internal medicine, %	33.3	32.0	33.6 [p=0.7575]	32.9 [p=0.9292]

Table 3 Medical procedures registered during the hospital admission per age groups and in deceased patients.

Medical procedures, %	Total	≤ 60 years of age	> 60 years of age [p value age]	Deceased patients [p value vs. non deceased]
Diagnostic ultrasound of abdomen, heart and peripheral vascular system	37.7	51.5	34.5 [p=0.0014]	24.7 [p=0.0139]
Computerized axial tomography or x-ray of thorax	19.5	17.5	19.9 [p=0.5731]	21.9 [p=0.5691]
Computerized axial tomography or x-ray of abdomen	16.8	27.2	14.4 [p=0.0017]	8.2 [p=0.0361]
Computerized axial tomography of head	8.3	12.6	7.3 [p=0.0772]	5.5 [p=0.3503]
Magnetic resonance imaging of abdomen, heart and peripheral vascular system	4.1	6.8	3.5 [p=0.1346]	2.7 [p=0.5183]
Transfusion of packed cells, whole blood or platelets	26.3	9.7	30.1 [p<0.0001]	31.5 [p=0.2789]
Other venous punction; i.e. phlebotomy	9.7	16.5	8.2 [p=0.0101]	5.5 [p=0.1886]
Injection of antibiotic	9.0	4.9	10.0 [p=0.1027]	21.9 [p<0.0001]
Injection or infusion of other therapeutic or prophylactic	6.1	1.9	7.1 [p=0.0497]	12.3 [p=0.0177]

substance				
Injection or infusion of cancer chemotherapeutic substance	2.0	5.8	1.1 [p=0.0019]	0.0 [p=0.1923]
Biopsy of bone marrow	15.0	21.4	13.5 [p=0.0434]	5.5 [p=0.1886]
Electrocardiogram	9.4	7.8	9.7 [p=0.5363]	6.8 [p=0.4279]
Non-invasive mechanical ventilation or oxygen enrichment	7.2	1.0	8.6 [p=0.0067]	19.2 [p<0.0001]

Table 4 Median admission cost per patient group and admission type.

Admissions	**Total**	**≤ 60 years of age**	**> 60 years of age [p value age]**	**Deceased patients [p value vs. non deceased]**
Median cost, € (95%CI)	5580 (5463-5657)	5525 (5328-5657)	5580 (5265-6209) [p>0.9999]	7865 (7494-10597) [p<0.0001]
LOHS < 7 days, € (95%CI)	5265 (4949-5525)	5265 (4666-5580)	5265 (4820-5624) [p>0.9999]	7865 (7494-10597) [p<0.0001]
LOHS > 7 days, € (95%CI)	6286 (5624-6634) [a]	7661 (5624-11241) [a]	6209 (5580-6615) [p>0.9999][a]	7679 (5463-11139) [p=0.1438]

[a] p<0.05 vs. LOHS < 7 days. LOHS: length of hospital stay.