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Research Paper

# Economic Burden of Paroxysmal Nocturnal Hemoglobinuria (PNH) and Secondary Problems Caused by PNH

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## ABSTRACT

**Background:** Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare, acquired disorder of hematopoietic stem cells, in which red blood cells become susceptible to complement-mediated hemolysis. PNH is associated with a wide range of medical consequences and costs. This study was done to estimate the economic burden of PNH and the secondary consequences caused by PNH in Iran.

**Methods:** This study is a cross-sectional and non-interventional study conducted using the cost-of-illness framework. The top-down prevalence method was used to quantify the annual PNH-related costs. This study was conducted from the societal perspective, including all direct medical, non-medical, and indirect costs associated with PNH. Productivity losses were calculated using the human capital method. Costs were collected using the relative value unit of health services in Iran, related literature, and from one of the referral hospitals in Iran, as well.

**Results:** The average annual costs of blood transfusion and anemia, thromboembolic events, and renal problems are estimated to be around $5400, $5382, and $6422, respectively. The total average costs of the three mentioned consequences caused by PNH are estimated to be $17,204 US dollars per PNH patient per year in Iran.

**Conclusion:** This study suggests that the average cost of managing anemia, blood transfusion, thromboembolic events, and renal problems in PNH equals $17,204 annually. Dependent on the severity of the disease and other factors, this amount could increase significantly. Additional cost-effectiveness studies should be carried out to identify the most cost-efficient disease management protocol.

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## Introduction

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare acquired disorder of hematopoietic stem cells, in which red blood cells become susceptible to complement-mediated hemolysis. Patients may experience anemia, fatigue, life-threatening thrombosis, erectile dysfunction, and recurrent abdominal pain during the illness. More severely affected PNH patients may develop a kidney-related disease or pulmonary hypertension, resulting in more medically severe consequences [1, 2].

PNH is genetically acquired by somatic mutation of the X-linked PIG-A gene in a bone marrow stem cell. A resultant deficiency in Glycosylphosphatidylinositol (GPI)–anchored proteins from the surface of PNH blood cells cause sensitivity to complement-mediated hemolysis, bone marrow failure, susceptibility to thrombosis, and a variety of additional medical consequences [3]. PNH can be developed in the absence of other Bone Marrow Disorders (BMD) as a condition secondary to BMDs, such as Aplastic Anemia (AA) or Myelodysplastic Syndrome (MDS) or as subclinical PNH [4].

PNH is a rare disorder. The reported incidence of the clinically significant disease is in the range of 1 to 10 cases per million population [5]. However, this might be an underestimate since a substantial number of patients are likely to remain undiagnosed. There is no known ethnic or geographic distribution; almost every country globally has reports of PNH patients [6]. According to Hill et al. [7], the incidence and 15-year prevalence of the PNH were given 0.13/100,000/year and 1.59/100,000 patients, respectively. Considering that Iran's population is approximately 80.3 million, we expect a prevalence of about 1277 PNH patients in the country, and 105 newly diagnosed patients would annually supplement this number.

Many patients present with unexplained hemolytic anemia and anemia-related symptoms, including fatigue, jaundice, and red or black urine. Decreased bone marrow function in some patients may further exacerbate the anemia and cause other cytopenias. The only potentially curative therapy for PNH is allogeneic Bone Marrow Transplantation (BMT); however, this procedure increases morbidity and mortality rates. Furthermore, many patients may not be eligible for this treatment due to underlying medical conditions. Historically, the management of PNH was just limited to the use of the best supportive measures, including folic acid, iron, immunosuppressive medication, blood transfusions, and warfarin to prevent thrombotic events. It should be mentioned that thrombosis may still occur in patients with PNH on warfarin or other anticoagulants.

In 2007, eculizumab (Soliris®, Alexion Pharmaceuticals, Inc., Cheshire, CT, USA) as a recombinant humanized monoclonal IgG antibody that inhibits the complement protein C5, was approved for the treatment of patients with PNH. PILOT [8], TRIUMPH [9], and SHEPHERD [10] studies demonstrated that eculizumab was well tolerated and provided a sustained and significant reduction in fatigue, hemolysis, and blood transfusion requirements, it also improved the quality of life in patients with PNH. Median survival with PNH diagnosis is about 14.6 years, while thrombosis and renal failure account for 60% of deaths [6].

Cost-of-illness studies measure the economic burden of diseases and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated or managed initially [11]. Since cost-of-illness studies can declare the economic effect of diseases on public programs, these studies are usually considered by the governments and health authorities to support decision making. There is a paucity of literature describing the actual costs associated with PNH and its consequences in Iran. Our study investigated the economic burden of PNH and standard care on the PNH population in Iran. The objective of this study was to estimate the financial burden of PNH and the secondary medical consequences caused by PNH.

## Materials and Methods

This study is a cross-sectional and non-interventional study conducted using the cost-of-illness framework. The top-down prevalence method was utilized to quantify the annual PNH costs. This study was performed from the societal perspective, including all direct medical, non-medical, and indirect costs related to the PNH. Productivity loss was calculated using the human capital method.

The following three consequences were identified by analyzing the literature and the expert's opinions: 1) Anemia and need for blood transfusion, 2) Thromboembolic events, and 3) Renal Consequences. We ignored the intangible costs of pain and suffering as this category of costs is often omitted in cost-of-illness studies due to difficulties quantifying it in monetary terms [12-14]. For two reasons, this study did not include the cost of Acute Myeloid Leukemia (AML), Myelodysplastic Syndromes (MDS), or other bone marrow-related prob-

lems. The first reason was due to the very low incidence of these illnesses in PNH patients. The second reason is that eculizumab does not have any proven positive effects on them. Details about the search strategy are described below:

A comprehensive search was undertaken to identify systematic reviews and primary studies about the clinical manifestations, diagnosis, and economic burden of paroxysmal nocturnal hemoglobinuria. Prospective and retrospective studies were sought that analyzed the prognosis, natural history, and costs related to paroxysmal nocturnal hemoglobinuria. Relevant publications were those detailing incidences, prevalence, the progress of clinical features, survival information, costs in populations with PNH, and clinical management of PNH patients across the globe.

Data were collected by thoroughly searching the online database, including MEDLINE/PubMed, Scopus, Google Scholar, HEED (Wiley Inter-science) for economic evaluation studies, and National Research Register. We utilized the opinion of the hematologists, nephrologists, and interventional cardiologists in every step of the study. The expert's contribution was primarily on the current medical practice in Iran, medications, and the average length of treatment and follow-ups in patients. Due to various restrictions in Iran, the medical practice that physicians apply might be slightly different from other parts of the world.

Patient care plans and major direct and indirect costs were identified for each of the previously mentioned problems of PNH through experts' opinions and clinical guidelines. The amount of costs was collected using the relative value unit of health services in Iran, relevant literature, and from one of the PNH referral hospitals in Iran (Rajaei Cardiovascular Medical and Research Center of Tehran, Iran). We analyzed the reimbursement by the insurance companies as well as out-of-pocket payments made by patients. A fundamental assumption in our calculations was that 80% of the patients receive their treatments in public service hospitals, and 20% were referred to more expensive private services. All data were collected in one year during 2019, and for each problem, more than 150 patient records were investigated. Follow-up time was between three to six months, depending on the time and severity of the patient's condition. The reference year for the value of the Iranian Rial is 2019. All costs were reported in US dollars, of which one US dollar equals 42,000 Iranian Rials (IRR), local currency, December 2019.

Our method to calculate productivity loss is explained in detail in the section below. The scope of this study extends to one year only. In the case of mortality, we will calculate the workdays remaining in the year and multiply it by Iran's Gross Domestic Product (GDP) per capita per workday in 2019. This method will calculate the productivity loss caused by mortality in the remaining fraction of the year for one lost patient.

### Anemia and need for blood transfusion

The patient management protocols and significant direct and indirect costs for patients and caregivers were evaluated for anemic PNH patients through the aforementioned strategy. We also gained insights directly from patients and caregivers, when feasible and relevant. Productivity losses were measured by the average time away from work in the past 12 months because of anemia management and blood transfusion consequences for both patients and their informal caregivers. Please note that PNH patients need extensive support for their treatments; hence, work absences for the informal caregivers should also be calculated. Our research shows that informal caregivers miss a considerable number of workdays. Iranian GDP per capita in 2019 was retrieved from the World Bank website. The productivity loss due to work absences was calculated by multiplying work absences by GDP per capita per workday.

### Thromboembolic events

Regarding the direct costs, a database was collected using datasheets, and discharge bills from the thrombotic patients admitted and discharged from the Rajaei Cardiovascular, Medical, and Research Center of Tehran, Iran. Productivity loss for both patients and informal caregivers was calculated by multiplying the average length of absence from work multiplied by Iranian GDP per capita per workday.

### Renal consequences

Renal care and management of patients with PNH who also suffer from Chronic Kidney Disease (CKD) involve multiple clinicians. Concurrent medical care for multiple chronic conditions adds to the complexities in attributing costs to CKD. Assessment of the actual financial burden of PNH patients with renal insufficiency is further restricted due to the lack of health care records and restricted access to information in Iran. Due to the restrictions, we supplement our data with inputs from Key opinion leaders in the nephrology therapeutic area to ensure accuracy and relevance. Productivity

loss for patients and informal caregivers is calculated through the rationale described above.

## Results

### Anemia and need for blood transfusion

PNH patients need care all over their lives at high costs, including blood transfusion, iron chelation therapy, laboratory analysis and tests, nursing, frequent physician visits, hospitalization, and transportation costs. The average annual costs of care for anemia and blood transfusion management in PNH patients are highlighted in Table 1.

Regarding the costs of the medication, iron chelation drugs accounted for most of the drug costs. Among the iron chelation drugs, deferoxamine and deferasirox were used most frequently. Iron chelation drugs were the most commonly used medications, followed by erythropoietin, vitamins, folic acid, supplemental iron, zinc sulfate, calcium, and Vitamin C. The miscellaneous costs in Table 1 include nutrition costs, hoteling costs for patient and caregiver(s), complementary or alternative therapies, and additional minor costs. The highest and the lowest of the costs related to anemia and blood transfusion management belong to medication costs and transportation costs, respectively. The average annual amount was $5,400.

### Thromboembolic events

Direct costs related to thromboembolic complications include hospitalizations, physician visits, prescription, over-the-counter medications, medical equipment, laboratory test, paraclinical tests, imaging, and transportation costs. The average length of hospital stay for patients with thromboembolic events was 8.2 days. The summary and the costs of each item related to the thromboembolic events are presented in Table 2.

The costs mentioned in Table 2 are the average costs for one thromboembolic event. In patients with more than one event per year, approximately 70% of total expenses calculated in Table 2 will be added to the overall costs.

Medication costs mentioned in Table 2 are all the medicines a patient receives in and outside the hospital, including anticoagulation therapy to prevent thromboembolic events. The highest and the lowest costs associated with managing thromboembolic events are medication costs and transportation costs, respectively. The average annual cost per thromboembolic event in PNH patients was about $5,382.

### Renal problems

Direct costs related to renal complications include physician fees, medication, medical equipment, hospitalizations, nursing, laboratory tests, paraclinical tests, imaging, and transportation costs. Indirect costs consisted

**Table 1.** The average annual cost per patient for the management of anemia and blood transfusion

| | Costs | Amount (US $) | % |
|---|---|---|---|
| Direct costs | Blood transfusion | 948.1 | 17.56 |
| | Iron chelating therapy and medication | 1,835.8 | 34.00 |
| | Medical equipment | 211.5 | 3.92 |
| | Laboratory and para clinical test | 425.2 | 7.87 |
| | Physician fees | 533.5 | 9.88 |
| | Hospitalization | 298.8 | 5.53 |
| | Transportation | 146.4 | 2.71 |
| | Nursing | 219.2 | 4.06 |
| | Miscellaneous costs | 333.6 | 6.18 |
| Indirect costs | Productivity loss | 448.1 | 8.30 |
| Total costs | - | 5,400.3 | 100.00 |

**Table 2.** The average annual cost per thromboembolic event per patient

| Costs | | Amount (US $) | % |
|---|---|---|---|
| Direct costs | Physician fees | 844.6 | 15.69 |
| | Medication | 917.7 | 17.05 |
| | Medical equipment | 760.7 | 14.13 |
| | Imaging, laboratory, and paraclinical test | 865.5 | 16.08 |
| | Nursing | 235.1 | 4.37 |
| | Transportation | 71.2 | 1.32 |
| | Hospitalization | 541.9 | 10.07 |
| | Miscellaneous costs | 441.3 | 8.20 |
| Indirect costs | Productivity loss | 704.0 | 13.08 |
| Total costs | - | 5,382.0 | 100.00 |

of lost productivity caused by absence from work. The summary of direct and indirect costs related to renal problems is outlined in Table 3.

Medication costs in Table 3 are all the medicines for co-morbidities of PNH patients with renal problems. Many PNH patients with CKD receive concurrent cardiovascular or diabetic drugs. All drugs and medical equipment for undergoing dialysis are also included in the costs of the study. Miscellaneous costs mentioned in Table 3 are nutrition, hoteling for patients and caregivers, complementary or alternative therapies, and additional minor costs. As shown in Table 3, the highest and lowest costs related to managing renal problems are medication and blood transfusion, respectively. The average annual cost was equal to $6,422.

**Table 3.** The average annual cost of kidney disease management per Paroxysmal Nocturnal Hemoglobinuria (PNH) patient

| Costs | | Amount (US $) | % |
|---|---|---|---|
| Direct costs | Physician fees | 772.1 | 12.02 |
| | Medication costs | 1,386.4 | 21.59 |
| | Medical equipment | 1,379.8 | 21.49 |
| | Imaging, laboratory, and paraclinical test | 888.8 | 13.84 |
| | Nursing | 465.7 | 7.25 |
| | Hospitalization | 441.9 | 6.88 |
| | Transportation | 111.9 | 1.74 |
| | Blood transfusion | 90.6 | 1.41 |
| | Miscellaneous costs | 421.1 | 6.56 |
| Indirect costs | Productivity loss | 463.0 | 7.21 |
| Total costs | - | 6,421.6 | 100 |

## Discussion

To our knowledge, this study is the first study describing the actual costs associated with the management of secondary problems caused by PNH in Iran. In this study, we analyzed the economic burden of PNH and the secondary consequences caused by PNH. Other consequences, like AML and MDS, were ignored since eculizumab does not have a curative effect.

The de Latour [15] trial suggests that BMT is probably not a suitable treatment option for life-threatening thromboembolism in paroxysmal nocturnal hemoglobinuria. In a study by Saso et al. [16], which involved 57 patients, it was suggested that bone marrow transplantation could restore normal bone marrow function in about 50% of PNH patients. Historically, the management of PNH was just limited to the use of best supportive care, including folic acid, iron, blood transfusion, and warfarin to prevent thrombotic events. In Iran, most of the PNH patients are managed by supportive care.

Chronic intravascular hemolysis in PNH, as mentioned previously, appears to be responsible for a series of clinical complications. The inability to maintain endogenous hemoglobin levels leads to anemia, weakness, and fatigue. Patients may require frequent blood cell transfusions to sustain tolerable hemoglobin levels. Generally, when the underlying cause of anemia is not amenable to a specific treatment or where specific treatment would require a while to take effect, the blood transfusion is considered as the need to reverse anemia is urgent [17].

Frequent blood transfusion appears to be essential in anemic patients with PNH. In many cases, however, transfusion reactions, such as excessive iron deposited in the body may cause heart failure, chronic liver diseases, endocrine problems, growth disorders, and osteoporosis. According to our results, blood transfusion and iron-chelating therapy costs correlate to more than half of the expenses related to anemia management and the need for blood transfusion.

According to the study by Hillmen et al. [8], 12 months before starting eculizumab, the mean number of units of blood transfused to the patients was 19.9 (range 2-52 units), while 81% of patients required blood transfusions before eculizumab. In our study, we calculated the blood transfusion cost. In Iran, blood is given free of charge by volunteer donors. Patients do not pay out-of-pocket for blood. The cost of preparing a unit of blood for transfusion in Iran equals $44 at the time of the study, including the costs of laboratory and cross-match tests, transportation, and storage. In 2011, the number of transfusions in the United States was about 21 million units, at the cost of $210 per unit of blood [18]. According to National Institute for Clinical Excellence (NICE), the cost of the first and subsequent blood transfusions in the United Kingdom is £170 and £162, respectively.

The most frequent and life-threatening complication of PNH is thrombosis. Thromboembolism is the most common cause of mortality in PNH patients and accounts for approximately 40% to 67% of deaths. Moreover, 29% to 44% of patients with PNH have at least one thromboembolic event during their disease, although the reason(s) for thrombotic events remains unknown [4, 19-21]. Poor survival of PNH patients is associated with the occurrence of thromboembolic complications [22, 23]. Patients with thrombosis have only a 40% survival rate at four years [6], and the relative risk of death is increased 5 to 15 times [24]. Emergency intervention is essential whenever thrombosis occurs in a PNH patient because of the high risk of mortality and morbidity.

The numbers mentioned in Table 2 are the average costs for one thromboembolic event, which according to the international PNH registry with 1610 patients [25], 15.5% of patients experienced thrombotic events. In the aforementioned study, 10.5% of the population had one event, 2.8% had two events, 1.2% had three events, 0.6% had four or more events, and 0.4% were unknown. For patients with more than one event per year, 70% of total costs calculated in Table 2 will be added to the overall costs. According to a study by Socie et al. [6], the median mortality rate for PNH patients with and without thrombosis is 0.55 and 0.22, respectively.

Intravascular chronic hemolysis in PNH patients could lead to acute and chronic renal disease. Severe acute hemolytic episodes can cause acute renal failure from direct toxicity of free heme in the kidneys. Chronic hemolysis may lead to renal iron deposition (renal hemosiderosis), which can interfere with proximal tubule function and lead to interstitial scarring and cortical infarcts [26-29]. Kidney failure contributes to 8%-18% of PNH-related deaths [24]. Virtually all patients with PNH have evidence of kidney damage by biopsy or imaging techniques or at postmortem examination [26, 27, 30-35]. Previous reports have shown that repetitive exposure to cell-free hemoglobin causes renal hemosiderin accumulation, tubulointerstitial inflammation, and kidney damage [36].

In a study by Hillmen et al. [37], renal dysfunction or damage was a common finding in patients with PNH as

65% of the study population exhibited stages 1-5 CKD. Approximately 21% of patients had renal insufficiency comprising CKD stages 3 and 4 or kidney failure (stage 5). The population presented in the study above indicates that the overall prevalence of renal dysfunction or disease in PNH, as measured by CKD staging, is increased by 6.6 fold over that observed in the general population in the United States [37, 38]. Clark et al. [27] previously reported that 32% of patients with PNH had a creatinine clearance of under 60 ml/min/ 1.73 $m^2$ (CKD stages 3-5), indicating kidney damage.

Our study was performed from the societal perspective and has comprehensively considered all aspects of costs and included direct and indirect costs related to the consequences of PNH. This study could be used as a guiding light for the Food and Drug Administration of Iran and decision-makers regarding the policies pertaining to the treatment of PNH in Iran.

This study had several limitations related to measuring costs. First, we could not estimate intangible costs related to pain and fatigue because of limited data and difficulties in objective quantification. Second, there is a limitation regarding the lack of comprehensive medical data and records in Iran. Compared to the United States and European countries, Iran's current health care medical records databases are still largely underdeveloped. Third, due to a lack of registered PNH patients in Iran, we collected data about the length of hospital stay, work absenteeism, and income loss from non-PNH patients who had similar circumstances. Given the limitations in the availability of data in this study and the challenges mentioned above, the present study has taken a considerable step towards analyzing the economic burden of the three mentioned consequences caused by PNH. A more accurate and comparable estimation of costs associated with PNH could be achieved by addressing such limitations in future studies. Although PNH is rare, it has wide-ranging effects on patients' and their families' lives. The symptoms associated with the disease have severe consequences and diminish the quality of life of patients.

## Conclusion

Our analysis suggests that PNH is associated with a substantial financial burden in direct and indirect costs. This study found that the average costs of managing anemia, blood transfusion, thromboembolic events, and renal problems in PNH patients equal $17,204 annually. Contingent on the age, the severity of symptoms, other comorbidities, and referring patients to private care services, this number could increase significantly. About 1300 patients are suffering from PNH in Iran, yet the medical care plan for these patients faces plenty of challenges for the government with high costs associated with managing PNH. The Iranian government needs to apply the best management protocols to ensure that PNH patients receive the best care possible while keeping the costs manageable. To achieve optimal utilization of the health care budget, it is necessary to evaluate the cost-effectiveness of different treatment protocols. Additional cost-effectiveness studies should be carried out (e.g., comparing the cost of Eculizumab with standard care in Iran) to identify the most cost-efficient disease management protocol.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

### Funding

The study was extracted from the first author.

### Authors' contributions

Conceptualization: Sina Dadfar, Fatemeh Soleymani, Meysam Seyedifar; Methodology: Sina Dadfar, Fatemeh Soleymani, Meysam Seyedifar; Investigation: All Authors; Writing-original draft: Sina Dadfar, Sahar Roozbahani; Writing – review & editing: All Authors; Resources: Sina Dadfar; Supervision: Fatemeh Soleymani and Meysam Seyedifar.

### Conflict of interest

The authors declared no conflict of interest.

## References

[1] Hill A, Rother RP, Wang X, Morris SM Jr, Quinn-Senger K, Kelly R, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2010; 149(3):414-25. [DOI:10.1111/j.1365-2141.2010.08096.x] [PMID]

[2] Luzzatto L, Gianfaldoni G. Recent advances in biological and clinical aspects of paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2006; 84(2):104-12. [DOI:10.1532/IJH97.06117] [PMID]

[3] Hu R, Mukhina GL, Piantadosi S, Barber JP, Jones RJ, Brodsky RA. PIG-A mutations in normal hematopoiesis. Blood. 2005; 105(10):3848-54. [DOI:10.1182/blood-2004-04-1472] [PMID] [PMCID]

[4] Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106(12):3699-709. [DOI:10.1182/blood-2005-04-1717] [PMID] [PMCID]

[5] Gulbis B, Eleftheriou A, Angastiniotis M, Ball S, Surrallés J, Castella M, et al. Epidemiology of rare anaemias in Europe. Adv Exp Med Biol. 2010; 686:375-96. [PMID]

[6] Socié G, Mary JY, de Gramont A, Rio B, Leporrier M, Rose C, et al. Paroxysmal nocturnal haemoglobinuria: Long-term follow-up and prognostic factors. Lancet. 1996; 348(9027):573-7. [DOI:10.1016/S0140-6736(95)12360-1]

[7] Hill A, Platts PJ, Smith A, Richards SJ, Cullen MJ, Hill QA, et al. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire. Blood. 2006; 108(11):985. [DOI:10.1182/blood.V108.11.985.985]

[8] Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. New Engl J Med. 2004; 350(6):552-9. [DOI:10.1056/NEJMoa031688] [PMID]

[9] Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. New Engl J Med. 2006; 355(12):1233-43. [DOI:10.1056/NEJMoa061648] [PMID]

[10] Brodsky RA, Young NS, Antonioli E, Risitano AM, Schrezenmeier H, Schubert J, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008; 111(4):1840-7. [DOI:10.1182/blood-2007-06-094136] [PMID]

[11] Emamgholipour S, Akbari Sari A, Geravandi S, Mazrae H. [Estimation of out-of-pocket and catastrophic expenditures among patients with cardiovascular diseases in Khuzestan (Persian)]. J Payavard Salamat. 2017; 11(3):297-307. http://payavard.tums.ac.ir/article-1-6289-en.html

[12] Max W, Rice DP, Sung HY, Michel M, Breuer W, Zhang X. The economic burden of prostate cancer, California, 1998. Cancer. 2002; 94(11):2906-13. [DOI:10.1002/cncr.10532] [PMID]

[13] Javadi M, Asgari H, Yaghoobbi M, Tavazohi H. [Self-assessment of the non-communicable disease surveillance system in Medical University of Isfahan based on the model suggested by the World Health Organization (Persian)]. J Sch Public Health Inst Public Health Res. 2010; 8(3):47-60. http://sjsph.tums.ac.ir/article-1-77-en.html

[14] World Health Organization (WHO). National cancer control programmes: Policies and managerial guidelines. Geneva: World Health Organization; 2002. https://apps.who.int/iris/handle/10665/42494

[15] de Latour RP, Schrezenmeier H, Bacigalupo A, et al. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. Haematologica. 2012; 97(11):1666-73. [DOI:10.3324/haematol.2012.062828] [PMID] [PMCID]

[16] Sašo R, Marsh J, Cevreska L, Szer J, Gale RP, Rowlings PA, et al. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1999; 104(2):392-6. [DOI:10.1046/j.1365-2141.1999.01195.x] [PMID]

[17] Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 2007; 11(13):1-202. [DOI:10.3310/hta11130] [PMID]

[18] Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: A survey of hospital-based blood banks and transfusion services. Appl Health Econ Health Policy. 2011; 9(1):29-37. [DOI:10.2165/11530740-000000000-00000] [PMID]

[19] Moyo VM, Mukhina GL, Garrett ES, Brodsky RA. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. Br J Haematol. 2004; 126(1):133-8. [DOI:10.1111/j.1365-2141.2004.04992.x] [PMID]

[20] Araten DJ, Thaler HT, Luzzatto L. High incidence of thrombosis in African-American and Latin-American patients with paroxysmal nocturnal haemoglobinuria. Thromb Haemost. 2005; 93(1):88-91. [DOI:10.1160/TH04-06-0391] [PMID]

[21] de Latour RP, Mary JY, Salanoubat C, Terriou L, Etienne G, Mohty M, et al. Paroxysmal nocturnal hemoglobinuria: Natural history of disease subcategories. Blood. 2008; 112(8):3099-3106. [DOI:10.1182/blood-2008-01-133918] [PMID]

[22] Gralnick HR, Vail M, McKeown LP, Merryman P, Wilson O, Chu I, et al. Activated platelets in paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1995; 91(3):697-702. [DOI:10.1111/j.1365-2141.1995.tb05371.x] [PMID]

[23] Ray JG, Burows RF, Ginsberg JS, Burrows EA. Paroxysmal nocturnal hemoglobinuria and the risk of venous thrombosis: Review and recommendations for management of the pregnant and nonpregnant patient. Haemostasis. 2000; 30(3):103-17. [DOI:10.1159/000022532] [PMID]

[24] Nishimura JI, Kanakura Y, Ware RE, Shichishima T, Nakakuma H, Ninomiya H, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine. 2004; 83(3):193-207. [DOI:10.1097/01.md.0000126763.68170.46] [PMID]

[25] Schrezenmeier H, Muus P, Socié G, Szer J, Urbano-Ispizua A, Maciejewski JP, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014; 99(5):922-9. [PMID]

[26] Zachée P, Henckens M, Van Damme B, Boogaerts MA, Rigauts H, Verberckmoes RK. Chronic renal failure due to renal hemosiderosis in a patient with paroxysmal nocturnal hemoglobinuria. Clin Nephrol. 1993; 39(1):28-31. [PMID]

[27] Clark DA, Butler SA, Braren V, Hartmann RC, Jenkins DE Jr. The kidneys in paroxysmal nocturnal hemoglobinuria. Blood. 1981; 57(1):83-9. [PMID]

[28] Riley AL, Ryan LM, Roth DA. Renal proximal tubular dysfunction and paroxysmal nocturnal hemoglobinuria. Am J Med. 1977; 62(1):125-9. [DOI:10.1016/0002-9343(77)90357-6]

[29] Hsiao PJ, Wang SC, Wen MC, Diang LK, Lin SH. Fanconi syndrome and CKD in a patient with paroxysmal nocturnal hemoglobinuria and hemosiderosis. Am J Kidney Dis. 2010; 55(1):e1-5. [DOI:10.1053/j.ajkd.2009.07.022] [PMID]

[30] Mathieu D, Rahmouni A, Villeneuve P, Anglade MC, Rochant H, Vasile N. Impact of magnetic resonance imaging on the diagnosis of abdominal complications of paroxysmal nocturnal hemoglobinu-

ria. Blood. 1995; 85(11):3283-8. [DOI:10.1182/blood.V85.11.3283.bloodjournal85113283] [PMID]

[31] Mulopulos GP, Turner DA, Schwartz MM, Murakami ME, Clark JW. MRI of the kidneys in paroxysmal nocturnal hemoglobinuria. AJR Am J Roentgenol. 1986; 146(1):51-2. [DOI:10.2214/ajr.146.1.51] [PMID]

[32] Nguyen JS, Marinopoulos SS, Ashar BH, Flynn JA. Clinical problem-solving. More than meets the eye. N Engl J Med. 2006; 355(10):1048-52. [DOI:10.1056/NEJMcps044359] [PMID]

[33] Rimola J, Martín J, Puig J, Darnell A, Massuet A. The kidney in paroxysmal nocturnal haemoglobinuria: MRI findings. Br J Radiol. 2004; 77(923):953-6. [DOI:10.1259/bjr/51760601] [PMID]

[34] Suzukawa K, Ninomiya H, Mitsuhashi S, Anno I, Nagasawa T, Abe T. Demonstration of the deposition of hemosiderin in the kidneys of patients with paroxysmal nocturnal hemoglobinuria by magnetic resonance imaging. Intern Med. 1993; 32(9):686-90. [DOI:10.2169/internalmedicine.32.686] [PMID]

[35] Tanaka YO, Anno I, Itai Y, Abe T. Paroxysmal nocturnal hemoglobinuria: MR findings. J Comput Assisted Tomogr. 1993; 17(5):749-53. [DOI:10.1097/00004728-199309000-00016] [PMID]

[36] Nath KA, Vercellotti GM, Grande JP, Miyoshi H, Paya CV, Manivel JC, et al. Heme protein-induced chronic renal inflammation: Suppressive effect of induced heme oxygenase-1. Kidney Int. 2001; 59(1):106-17. [DOI:10.1046/j.1523-1755.2001.00471.x] [PMID]

[37] Hillmen P, Elebute M, Kelly R, Urbano-Ispizua A, Hill A, Rother RP, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2010; 85(8):553-9. [DOI:10.1002/ajh.21757] [PMID]

[38] Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354(23):2473-83. [DOI:10.1056/NEJMra054415] [PMID]