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Relation between iron deficiency anemia and Rheumatoid Arthritis

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Abstract

Background: Anemia of inflammation (AI), also known as anemia of chronic disease (ACD), is regarded as the most frequent anemia in hospitalized and chronically ill patients. It is prevalent in patients with diseases that cause prolonged immune activation, including infection, autoimmune diseases, and cancer.

Given its frequency, it is second only to iron deficiency anemia. Rheumatoid arthritis is one of the most common types of chronic inflammatory arthritis. It is characterized by inflammation (pain, heat, swelling, redness) of the joints, especially of the hands and feet.

Objective: This paper aims to study the relation between iron deficiency anemia and rheumatoid arthritis.

Patients and Methods: This study has focused on the study of the relation between iron deficiency anemia and rheumatoid arthritis where data were collected from health outcomes for rheumatoid arthritis patients in different hospitals in Iraq between 12th March 2021 to 9th April 2022 for rheumatoid arthritis patients with ages from 45 to 65 years. These data were divided into two kinds of groups. Where the first one was considered patients who have rheumatoid arthritis, with a number of 75 cases, while the second one was represented the control group which have 62 cases. A statistical study was conducted for health outcomes for rheumatoid arthritis patients using the SPSS program.

Discussion: In RA patients, links between lower hemoglobin levels were found in the multi-factor model summarizing the interactions among hemoglobin levels and laboratory and clinical data. In RA patients with significant disease activity, an iron deficit is typical. The greatest associations were identified among both iron-deficiency anemia and participant becoming younger and/or female, or significantly reducing hemoglobin levels, increased platelet counts, greater GFR, lower disease activity, and less frequent use of sulfasalazine in both single- and multi-factor model types in RA patients both with and without iron deficiency. This study found that weight loss and Joint sensitivity to touch got the highest in complications of patients were, got 6 (8.33%) and 8 (11.11%).

Conclusion: Hemoglobin and RBC are dropped in the rheumatoid arthritis patients group more than to the controls group. In addition, this study found a disorder in MCV between the two groups. In conclusion, this study found that the control group is much better than the rheumatoid arthritis patients' group. As well as this study concludes that there is a positive relationship between patients' outcomes and iron deficiency, which indicates that rheumatoid arthritis causes iron deficiency.

Keywords: Rheumatoid Arthritis (RA); Anemia; Triglycerides; GFR; CRP; and Haemoglobin.

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Introduction

Inflammatory anemia is classically encountered during chronic inflammatory processes of infectious, rheumatic, or neoplastic origin. Given its frequency, it is second only to iron deficiency anemia [1,2]. The anemia is rarely severe (generally hemoglobin >90 g/L). Its severity correlates with the intensity of the inflammatory process (persistent fever, generalized malignancy of cancer). Most patients are asymptomatic in relation to anemia. [3,4,5]

Symptoms such as fatigue and a feeling of weakness may be related to the underlying condition or secondary depressive syndrome [6]. Cytolytic inflammatory anemia is usually normal but tends to be a microcytic deficiency. Serum iron and transferrin are low, while serum ferritin is normal or elevated [7]. It is essential to be aware that inflammatory anemia can be associated with iron deficiency anemia (e.g., in rheumatoid arthritis treated with NSAIDs causing gastrointestinal bleeding). Examination of the bone marrow does not help diagnose inflammatory anemia. It is relevant in the case of diagnostic indecision with iron deficiency anemia. In cases of inflammatory anemia, iron stores in the bone marrow are normal or increased. [8,9]

Anemia of chronic disease is the second most common type of anemia. Chronic diseases often cause anemia, especially in the elderly. Conditions such as infections, autoimmune disorders (particularly rheumatoid arthritis), kidney disorders, and cancers often cause anemia due to chronic disease. [10]

Rheumatoid arthritis is one of the most common types of chronic inflammatory arthritis. It is characterized by inflammation (pain, heat, swelling, redness) of the joints, especially of the hands and feet [11]. It is more common in women and most often occurs between the ages of 40-50. The exact cause of rheumatoid arthritis is unknown. A combination of factors appears to be involved in triggering the pathology [12,13]. A predisposing genetic background can favor the disease. Among the environmental factors blamed, smoking is a risk factor. Infectious causes were suspected, but no germ has been proven to date. Psychological factors such as stress can help the disease. Hormonal factors also seem to play a role. [14,15]

For its part, rheumatoid arthritis (RA) refers to rheumatoid arthritis, which is a disease but affects several joints [16]. It is an autoimmune disease that also belongs to the large family of arthritis. This type of arthritis causes the immune system to malfunction, which in turn attacks its own tissues to trigger an inflammatory reaction [17]. It is not uncommon for this autoimmune disease to affect multiple joints. Researchers are always looking for genes that change to cause disease in the presence of certain factors. These factors, although not known, could be related to a viral infection, disease, or certain elements present in our environment. This paper aims to study the relation between iron deficiency anemia and rheumatoid arthritis [18].

Patients and Methods

This study has focused on the study of the relation between iron deficiency anemia and rheumatoid arthritis, where data were collected from health outcomes for rheumatoid arthritis patients in different hospitals in Iraq between 12th March 2021 to 9th April 2022 for rheumatoid arthritis patients with ages from 45 to 65 years. These data were divided into two kinds of groups. Where the first one was considered patients who have rheumatoid arthritis, with a number of 75 cases, while the second one was represented the control group which have 62 cases. A statistical study was conducted for health outcomes for rheumatoid arthritis patients using the SPSS program. This study was presented the characteristics of demographic rheumatoid arthritis patients and controls which these parameters found age in between 45-65, BMI divided into (24-27) - (28-31) - (32-34), sex within male and female, comorbidities which got heart disease, hypertension, diabetes mellitus, and other diseases where all these characteristics found in Table 1. To follow that, this data examined complications of rheumatoid arthritis patients where it distributed into a swelling in the joints, joint sensitivity to touch, exhaustion, fever, and weight loss which can be seen in Table 2.

Furthermore, this study was evaluated laboratory findings of rheumatoid arthritis patients with a control group where these parameters designed to triglycerides [mg/dL], GFR, CRP, platelet count [G/L], and hemoglobin [g/dL], which findings can be shown in Table 3. To show the anemia pattern, this study was distributed of anemia outcomes for rheumatoid arthritis patients, which in divided within frequency and percentage of rheumatoid arthritis patients, which can be shown in Figure 1. Also, it can be defining the associated results OF these RBC, Hematocrit, MCV [FL], RDW, and Vitamin B12 in, where all these values

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were distributed between the rheumatoid arthritis patients group and control group, then can see in Table 4. According to Ferritin testing, this study focused on the distribution of rheumatoid arthritis patients according to Ferritin < 30 µg/L and see that in Figure 2. To the Iron deficiency side, this study analyzed the distribution of rheumatoid arthritis patients according to Iron deficiency, then and be found in Figure 3. In this study, it extended to determine of these evaluated data based on the length of stay and total cost of operation that present to two parameters into, length of stay and total cost of operation where it was shown in Table 5. In the last evaluation, this study was determined the results of the laboratory items for rheumatoid arthritis patients in comparison with control where the outcomes parameters presented Period from diagnosis of RA, Sulfasalazine, Sulfasalazine, daily dose [mg], Methotrexate, n (%) and Methotrexate, weekly dose [mg] then can be shown in Table 6.

Results

Table 1. The characteristics of demographic rheumatoid arthritis patients and controls.

Items	mothers' patients (N=75)	Controls (N=62)	P-value
Age			
45-49	12 (16%)	8 (12.90%)	0.0446
50-54	18 (24%)	11 (17.74%)	0.03665
55-59	24 (32%)	22 (35.48%)	0.0478
60-65	21 (28%)	21 (33.87%)	0.0447
BMI			
24-27	27 (36.0%)	20 (32.26%)	0.0470
28-31	14 (18.67%)	15 (24.19%)	0.0462
32-34	34 (45.33%)	27 (43.55%)	0.0477
Sex			
Female	45 (60.0%)	41 (66.13%)	0.0445
Male	30 (40.00%)	21 (33.87%)	0.0421
Comorbidities			
Heart disease	16 (21.33%)	13 (20.97%)	0.0492
Hypertension	22 (29.33%)	23 (37.10%)	0.0338
Diabetes mellitus	20 (26.67%)	17 (27.42%)	0.0496
Other diseases	17 (22.67%)	9 (14.52%)	0.04331

Table 2. Complications of rheumatoid arthritis patients.

Items	mothers' patients (N=75)	Percentage (%)
Swelling in the joints	4	5.56%
Joint sensitivity to touch	8	11.11%
Exhaustion	2	2.78%
Fever	5	6.94%
Weight loss	6	8.33%

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Table 3. Laboratory findings of rheumatoid arthritis patients with a control group.

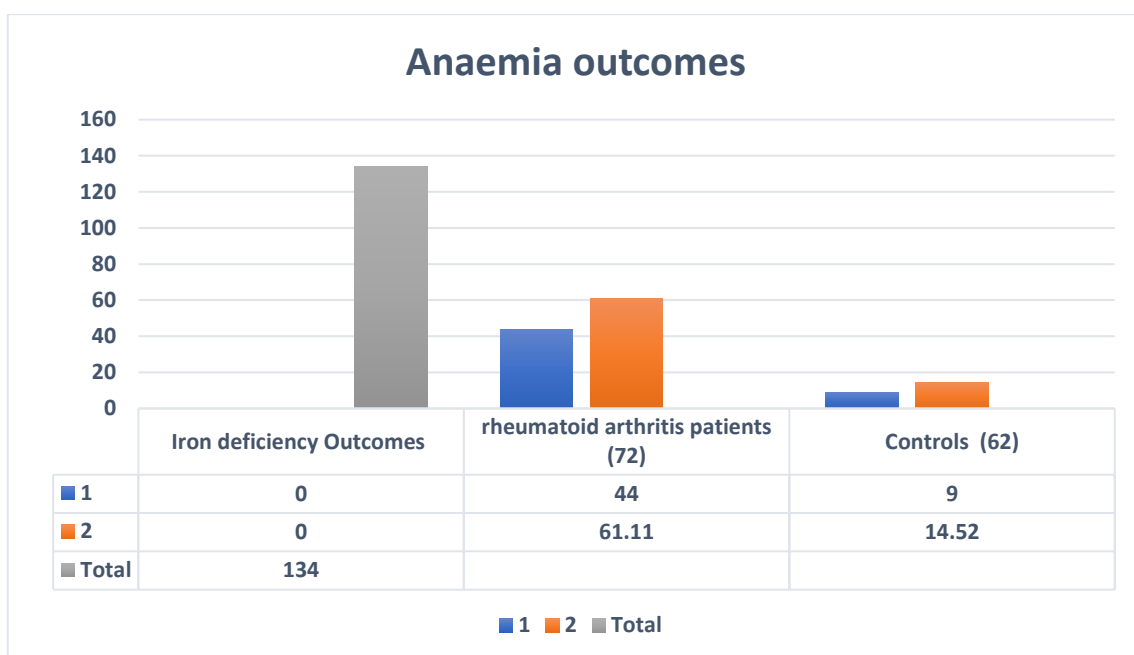| Items	mothers' patients (N=75)	Controls (N=62)	P-value
Triglycerides [mg/dL]	95.77 ± 76	182 ± 86	0.0455
GFR	92.11 ± 17.66	85.12 ± 22	0.0436
CRP	3.2 (1.22-14.5)	0.65 (0.55-1.7)	0.0432
Platelet count [G/L]	292.44 ±88.75	244.63 ± 64	0.0436
Haemoglobin [g/dL]	13.7 ± 1.4	14.6 ± 1.6	0.04936

Figure 1. Distribution of Anaemia outcomes for rheumatoid arthritis patients.

Table 4. Define associated results OF these RBC, Haematocrit, MCV [FL], RDW, and Vitamin B12.

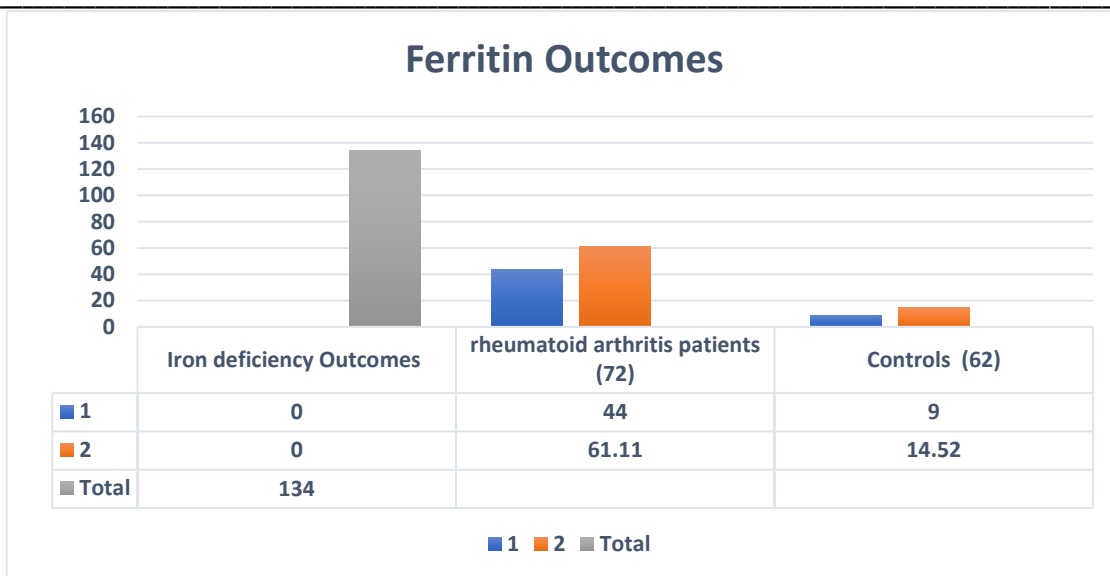| Variables	mothers' patients (N=75)	Controls (N=62)	P-value
RBC [T/L]	4.43 ± 0.38	4.72 ± 0.7	0.0472
Haematocrit [%]	39.4 ± 5.2	41.5 ± 3.4	0.0485
MCV [FL]	91 ± 4.4	86.43 ± 3.7	0.04332
RDW [%]	13.2 ± 1.4	12.3 ± 0.7	0.0491
Vitamin B12 < 200 pg./mL	6 (8.33%)	2 (3.23%)	0.0447

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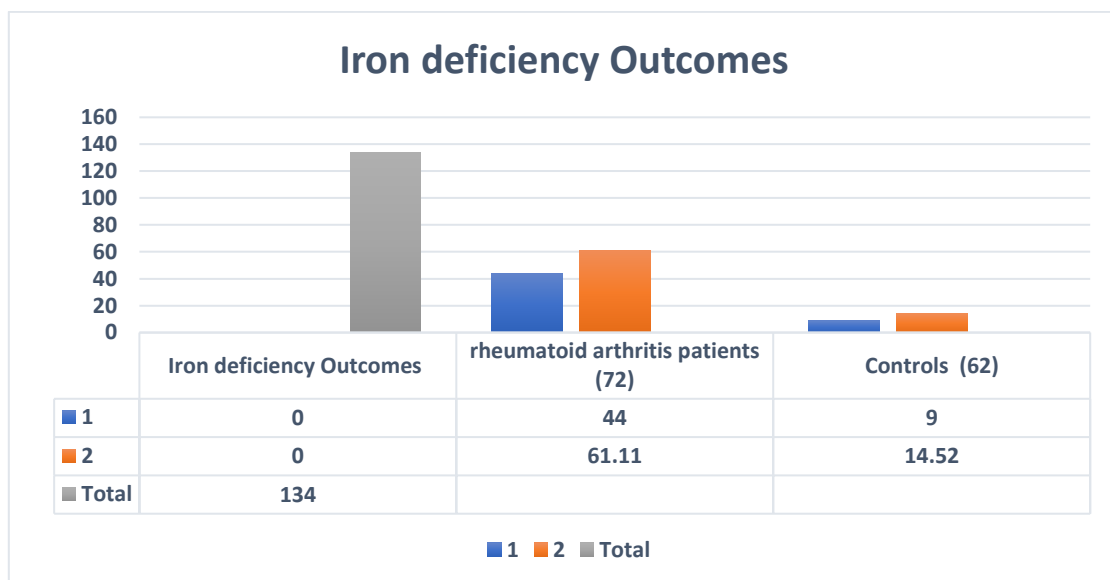**Figure 2.** Distribution of rheumatoid arthritis patients according to Ferritin < 30 µg/L.

Figure 3. Distribution of rheumatoid arthritis patients according to Iron deficiency.

Table 5. Determine of these evaluated data based on the length of stay and total cost of operation.

Variables	mothers' patients (N=75)	Controls (N=62)	P-value
length of stay (Days)	12.4	8.3	0.0473
Total cost of operation ($)	500 $-900 $	500 $- 600$	0.0488

Table 6. The results of the laboratory items for rheumatoid arthritis patients in comparison with the control

Variables	mothers' patients (N=75)
Period from diagnosis of RA [years]	6.2 (3.0 - 10.0)
Sulfasalazine, n (%)	8 (11.11%)

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Sulfasalazine, daily dose [mg]	2440 (2000-3000)
Methotrexate, n (%)	53 (73.61%)
Methotrexate, weekly dose [mg]	22.4 (20-25)

Discussion

Surprisingly, the study on iron efficiency in RA patients is extremely affectively on rheumatoid arthritis, considering the pathophysiological link between anemia, inflammation, and iron shortage. The present studies don't consider new, more precise biomarkers and only look at anemia in the setting of iron shortage in RA patients. [19]

All subjects were free of diabetes, hypertension, and triglycerides, had higher GFRs (glomerular filtration rates), and had higher platelet counts. Also, Reduced hemoglobin levels, lower red blood cell parameters (MCV, RBC, Hematocrit), and measures characterizing iron metabolism have all been linked to RA patients (drop serum ferritin and Sulfasalazine and reduced Methotrexate).

In RA patients, links between lower hemoglobin levels were found in the multi-factor model summarizing the interactions among hemoglobin levels and laboratory and clinical data. In RA patients with significant disease activity, an iron deficit is typical [20]. The greatest associations were identified among both iron-deficiency anemia and participant becoming younger and/or female, or significantly reducing hemoglobin levels, increased platelet counts, greater GFR, lower disease activity, and less frequent use of sulfasalazine in both single- and multi-factor model types in RA patients both with and without iron deficiency. This study found that weight loss and Joint sensitivity to touch got the highest in complications of patients were, got 6 (8.33%) and 8 (11.11%).

An English study shown that the prevalence of rheumatoid arthritis is often two to three times higher in women than in males, and it typically first manifests between the ages of 40 and 60. Nevertheless, it can also affect young children and the elderly [21]. It has been established that RA patients, both those with anemia and those in control, frequently have iron deficiency, which is determined by blood ferritin ratios and Sulfasalazine saturation. [22], as well as higher levels of the drug sulfasalazine. This suggests that these patients primarily had ultimate rather than usable (relative) iron deficiency, as one might anticipate. Methotrexate has often only been discussed in the literature in relation to anemia when it comes to RA patients. According to a number of articles as well as French research, anemia is frequently documented in RA patients and has a prevalence of 33-60%. [23]

The Germany study found that just 18% of anemic RA patients had anemia, although iron deficiency was more common in these individuals (64%) than anemia [24]. Anemia in RA patients has a complicated and multifaceted pathophysiology that is influenced by chronic inflammation, the lack of certain erythropoiesis-related components, including iron, and other factors.

Conclusion

Our study Emphasizes that women are more likely than men to develop rheumatoid arthritis. Women are more likely than men to develop rheumatoid arthritis. Also, this study found rheumatoid arthritis occurs at any age, but it is common starting in middle age. Moreover, about 40% of people with rheumatoid arthritis also experience signs and symptoms in areas other than the joints. Besides that, Hemoglobin and RBC are dropped in the rheumatoid arthritis patients group more than to the controls group. In addition, this study found a disorder in MCV between the two groups. In conclusion, this study found that the control group is much better than the rheumatoid arthritis patients' group. As well as this study concludes that there is a positive relationship between patients' outcomes and iron deficiency, which indicates that rheumatoid arthritis causes iron deficiency.

References

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH: National Arthritis Data Workgroup.

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Part I. Arthritis Rheum. 2008, 58 (1): 15-25. 10.1002/art.23177. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States.

2. Brooks PM: Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. Curr Opin Rheumatol. 2002, 14 (5): 573-577. 10.1097/00002281-200209000-00017.

3. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC: The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. Rheumatology (Oxford). 2005, 44 (12): 1531-1537. 10.1093/rheumatology/kei049.

4. World Health Organization and the Bone and Joint Decade 2000-2010: The Burden of Musculoskeletal Conditions at the Start of the New Millennium. Report of a WHO Scientific Group. 2003, WHO Technical Report Series No.919. Geneva, Switzerland, Accessed 2 Feb 2009, [http://whqlibdoc.who.int/trs/WHO_TRS_919.pdf]

5. Kvien TK: Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics. 2004, 22 (2 Suppl): 1-12.

6. Cooper NJ: Economic burden of rheumatoid arthritis: a systematic review. Rheumatology (Oxford). 2000, 39 (1): 28-33. 10.1093/rheumatology/39.1.28.

7. Guillemin F, Durieux S, Daures JP, Lafuma A, Saraux A, Sibilia J, Bourgeois P, Sany J: Costs of rheumatoid arthritis in France: a multicenter study of 1109 patients managed by hospital-based rheumatologists. J Rheumatol. 2004, 31 (7): 1297-1304.

8. World Health Organization: Nutritional Anaemias. Report of a WHO Scientific Group. 1968, WHO Technical Report Series No.405, Geneva Switzerland, Accessed 10 Dec 2008,

9. Spence RK: Medical and economic impact of anaemia in hospitalized patients. Am J Health Syst Pharm. 2007, 64 (16 Suppl 11): S3-10. 10.2146/ajhp070244.

10. Sharma JB: Nutritional anaemia during pregnancy in non-industrialized countries. Progress in Obstetrics and Gynaecology. Edited by: Studd J. 2003, Edinburgh Churchill Livingstone, 103-122.

11. Murphy EA, Bell AL, Wojtulewski J, Brzeski M, Madhok R, Capell HA: Study of erythropoietin in the treatment of anaemia in patients with rheumatoid arthritis. BMJ. 1994, 309 (6965): 1337-1338.

12. Penninx BW, Pahor M, Woodman RC, Guralnik JM: Anemia in old age is associated with increased mortality and hospitalization. J Gerontol a Biol Sci Med Sci. 2006, 61 (5): 474-479.

13. Penninx BW, Guralnik JM, Onder G, Ferrucci L, Wallace RB, Pahor M: Anemia and decline in physical performance among older persons. Am J Med. 2003, 115 (2): 104-110. 10.1016/S0002-9343 (03)00263-8.

14. Penninx BW, Pahor M, Cesari M, Corsi AM, Woodman RC, Bandinelli S, Guralnik JM, Ferrucci L: Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. J Am Geriatr Soc. 2004, 52 (5): 719-724. 10.1111/j.1532-5415.2004.52208. x.

15. Chaves PH, Semba RD, Leng SX, Woodman RC, Ferrucci L, Guralnik JM, Fried LP: Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. J Gerontol a Biol Sci Med Sci. 2005, 60 (6): 729-735.

16. Ershler WB, Chen K, Reyes EB, DuBois R: Economic burden of patients with anemia in selected diseases. Value Health. 2005, 8 (6): 629-638.

17. Nissenson AR, Wade S, Goodnough T, Knight K, Dubois RW: Economic burden of anemia in an insured population. J Manag Care Pharm. 2005, 11 (7): 565-574.

18. College des Economistes de la Sante (CES): Guide Methodologique pour l'evaluation economique des Strategies de Sante. Accessed 18 Aug 2010, [http://www.rees-france.com/article.php3?id_article=126]

19. World Health Organization: International Classification of Diseases (ICD). Accessed 18 Aug 2010, [http://www.who.int/classifications/icd/en/]

20. Assaf AR, Lapane KL, McKenney JL, Carleton RA: Possible influence of the prospective payment system on the assignment of discharge diagnoses for coronary heart disease. N Engl J Med. 1993, 329 (13): 931-935. 10.1056/NEJM199309233291307.

21. Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, Hui AJ, To KF, Leung WK, Wong VW, Chung SC, Sung JJ: Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent

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ulcer bleeding in patients with arthritis. N Engl J Med. 2002, 347 (26): 2104-2110. 10.1056/NEJMoa021907.

22. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, Yu Q, Bombardier C: Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology. 2003, 124 (2): 288-292. 10.1053/gast.2003.50054.

23. Hawkey CJ: NSAIDs, coxibs, and the intestine. J Cardiovasc Pharmacol. 2006, 47 (Suppl 1): S72-S75. 10.1097/00005344-200605001-00013.

24. Weiss G, Goodnough LT: Anemia of chronic disease. N Engl J Med. 2005, 352 (10): 1011-1023. 10.1056/NEJMra041809.

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