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APPROACH TO THE ASSOCIATION OF GOUT AND DIABETES AND ITS REPERCUSSIONS ON MORBIDITY USING A NATIONWIDE DATASET OF HOSPITALIZATIONS

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ABSTRACT

Introduction: Gout and diabetes mellitus (DM) are two highly prevalent diseases worldwide, closely related by pathophysiology. The implications of people with gout co-presenting DM have received little attention in the literature, especially in terms of morbidity development. **Objective**: To analyze the impact of presenting DM in a Spanish nation-wide hospitalized population with gout.

Methods: The Minimal Basic Data Set from 192,062 Spanish hospitalizations with gout (ICD-9 coding) from 2005 to 2015 was analyzed. The comorbidities of interest were cerebrovascular diseases, venous thromboembolism, sepsis, chronic kidney disease, arrhythmia, dementia, liver disease, obstructive pulmonary disease, and other rheumatic diseases, among others. Firstly, the prevalence of DM in the entire population was estimated, later stratified by type of DM ("Type 1 DM", "Type 2 DM", and "Other DM"), as well as "Complicated" or "Uncomplicated," according to suitable ICD-9 codes, estimating their 95% confidence intervals (CI). A logistic regression analysis was built to discern the characteristics of patients with gout and DM. Secondly, patients with repeated admissions in the dataset were identified and matched by age, sex, chronic kidney disease, cardiovascular disease and infections at the first tercile (2005-2008); later, the frequencies of comorbidities of interest were compared in second (2009-2012) and third terciles (2012-2015) by chi-2 test.

Results: In the gout dataset, the prevalence of DM was 27.72% (95%CI 27.52-27.92). By subtypes, type 2 DM (27.43% 95%CI 27.23-27.63) was far more prevalent than type 1 DM (0.13% 95%CI 0.12 -0.15) or other forms of DM (0.35% 95%CI 0.32-0.37). The presence of complicated DM was 19.76% (95%CI 19.43-20.10).

In the multiple logistic regression model, variables linked to DM were older age, female sex, dyslipidemia, obesity, coronary heart disease, congestive heart failure, chronic kidney disease,

liver disease, cerebrovascular diseases, obstructive pulmonary disease, peripheral vascular disease, urinary tract infection, and dementia. On the other hand, venous thromboembolism and other concurrent rheumatic diseases were associated with not having DM. Regarding the most prevalent comorbidities in those with recurrent admission, patients with DM presented a higher number of cardiovascular events (driven by coronary heart disease and heart failure) and renal disease, similar for infections, and lower presence of venous thromboembolism.

Conclusions: An analysis of 11 years of hospitalizations for gout confirms a different comorbidity profile between DM and non-DM, with a close relationship to metabolic syndrome. Assessing readmission, the co-presence of DM had a significant impact on the cardiovascular and renal profile of the patient with gout, identifying no impact on infections and less risk of thromboembolism. Our findings may be of interest when attending to a patient with gout and DM.

Keywords: GOUT, DIABETES MELLITUS, COMORBIDITIES, RECURRENT ADMISSION, CARDIOVASCULAR DISEASE, INFECTIONS

RESUMEN

Introducción: La gota y la diabetes mellitus (DM) son dos enfermedades muy prevalentes en todo el mundo, estrechamente relacionadas por su fisiopatología. Las implicaciones de que las personas con gota presenten conjuntamente DM han recibido poca atención en la literatura, especialmente en términos de desarrollo de morbilidad.

Objetivo: Analizar el impacto de la asociación de DM en una población española hospitalizada a nivel nacional con gota.

Métodos: Se analizó el Conjunto Mínimo Básico de Datos de 192.062 hospitalizaciones españolas con gota (codificación CIE-9) entre 2005 y 2015. Las comorbilidades de interés fueron enfermedades cerebrovasculares, tromboembolismo venoso, sepsis, enfermedad renal

crónica, arritmia, demencia, enfermedad hepática, enfermedad pulmonar obstructiva y otras enfermedades reumáticas, entre otras. En primer lugar, se estimó la prevalencia de DM en toda la población, estratificándola posteriormente por tipo de DM ("DM tipo 1", "DM tipo 2" y "Otros tipos de DM"), así como, "Complicada" o "No complicada", según los códigos CIE-9 adecuados, estimando sus intervalos de confianza (IC) al 95%. Se construyó un análisis de regresión logística para discernir las características de los pacientes gotosos con y sin DM. En segundo lugar, se identificaron los pacientes con ingresos repetidos en el conjunto de datos, y se emparejaron por edad, sexo, enfermedad renal crónica, enfermedad cardiovascular (variable combinada de enfermedad cardíaca, cerebral y periférica) e infecciones (variable combinada de neumonía, infecciones urinarias y sepsis) en el primer tercil (2005-2008); posteriormente, se compararon las frecuencias de comorbilidades de interés en segundo (2009-2012) y tercer terciles (2012-2015) mediante la prueba de chi-2.

Resultados: En el conjunto de datos sobre gota, la prevalencia de DM fue del 27,72% (95%CI 27,52-27,92). Por subtipos, la DM tipo 2 (27,43% 95%CI 27,23-27,63) era mucho más prevalente que la DM tipo 1 (0,13% 95%CI 0,12 -0,15) u otras formas de DM (0,35% 95%CI 0,32-0,37). La presencia de DM complicada fue del 19,76% (95%CI 19,43-20,10).

En el modelo de regresión logística múltiple, se demostró que los pacientes con DM eran de más edad, con mayor frecuencia mujeres y con dislipemia, obesidad, cardiopatía coronaria, insuficiencia cardíaca congestiva, enfermedad renal crónica, hepatopatía, enfermedades cerebrovasculares, enfermedad pulmonar obstructiva, enfermedad vascular periférica, infección urinaria y demencia. Por otra parte, el tromboembolismo venoso y otras enfermedades reumáticas concurrentes eran más frecuentes en los pacientes sin DM.

En cuanto a las comorbilidades más prevalentes en aquellos con ingreso recurrente, los pacientes con DM presentaron un mayor número de eventos cardiovasculares (impulsados por

enfermedad coronaria e insuficiencia cardiaca) y enfermedad renal, similar para infecciones y menor presencia de tromboembolismo venoso.

Conclusiones: Un análisis de 11 años de hospitalizaciones por gota confirma un perfil de comorbilidad diferente entre DM y no DM, con estrecha relación con el síndrome metabólico. Evaluando los reingresos, la co-presencia de DM tuvo un impacto significativo en el perfil cardiovascular y renal del paciente con gota, no identificando impacto en infecciones y menor riesgo de tromboembolismo. Nuestros hallazgos pueden ser de interés a la hora de atender a un paciente con gota y DM.

Palabras clave: GOTA, DIABETES MELLITUS, COMORBILIDADES, REINGRESOS, EVENTOS CARDIOVASCULARES, INFECCIONES

1 INTRODUCTION

1.1 GOUT

Gout is the arthritis caused by the crystallization of monosodium urate (MSU) in joints and tissues, associated with persistent hyperuricemia and the inflammatory response to the crystals (1). Its prevalence ranges from 0.5 to 5% worldwide, being the most frequent form of acute arthritis (2). Under normal conditions, 75% of urate production is eliminated via the kidneys and the rest via the intestine (3). However, when serum uric acid concentrations exceed 6.8 mg/dL (408 µmol/L) under normal pH and temperature conditions, urate crystallizes as MSU and deposits in tissues (1).

We distinguish three clinical phases in gout (acute flares, intercrisis period, and tophaceous gout), but some authors include a fourth phase, prior to the previous ones, of silent deposit of MSU crystals in subjects with asymptomatic hyperuricemia. Flares affect mainly the first metatarsophalangeal joint, although the knee, ankle, midfoot or wrists are also frequently affected. They usually present abruptly, with intense pain and marked swelling and erythema,

are self-limiting and, although the clinical presentation strongly suggests the diagnosis of gout, the definitive diagnosis is confirmed by the presence of MSU crystals in the synovial fluid (4).

Hyperuricemia and gout are not usually isolated processes but are accompanied by comorbidities (13). Classical cardiovascular risk factors such as obesity, diabetes mellitus (DM) and hypertension have been shown to be more prevalent among people with gout. However, an association between gout and cardiovascular disease persists after adjustment for these factors, illustrating that gout carries its own independent risk, potentially as a result of chronic, systemic subclinical inflammation with intermittent clinical acute episodes.

1.2 DIABETES MELLITUS (DM)

DM is a group of diseases characterized by elevated serum glucose. Various pathological processes are involved in developing this pathology, although most cases can be included in two categories. In the first (type 1 DM), the cause is an absolute deficiency in insulin secretion, often with evidence of autoimmune destruction of insulin-producing pancreatic cells. In the second, much more prevalent category, type 2 DM, the cause is a combination of resistance to insulin action and an inadequate compensatory secretory response (5).

DM has a significant social and health impact, not only because of its high prevalence but also because of its chronic complications and derived mortality rate, ranking third in women and seventh in men. In Spain, the estimated prevalence is 6.2% for age groups 30-65 years and 10% for 30-89 years (6).

The association of DM with metabolic syndrome (MS) is noteworthy. MS constitutes a set of metabolic disturbances and risk factors derived from centrally distributed obesity and insulin resistance, associated with an increased risk of type 2 DM and cardiovascular disease (7). It is closely related to visceral obesity, the consequence of which is the massive influx of fatty acids or lipotoxicity. First, these are directed towards the liver, inducing the deposition of triglycerides that infiltrate the parenchyma, favoring hepatic steatosis or fatty liver. The

increased oxidation of fatty acids by the liver is associated with decreased glucose oxidation and increased gluconeogenesis, resulting in insulin resistance. At the muscle level, fatty acids, together with cytokines and adipokines from visceral adipose tissue, alter intracellular insulin signaling by disrupting the mechanisms that translocate the glucose transporter GLUT-4 to the cell surface, thus preventing insulin from promoting glucose uptake by muscles (7).

In response to the reduced insulin action, compensated hyperinsulinemia occurs by the pancreatic beta cell, which leads to hypertension and an increase in visceral adipose tissue, perpetuating obesity (7). The continuous lipotoxicity ends up with beta cell apoptosis, losing their ability to compensate insulin resistance, which in turn progressively increases serum glucose levels and leads to type 2 DM (7).

The association of DM with MS is not only a cause-consequence relationship, but the pathogenesis of MS is also implicated in the comorbidities associated with DM since the microangiopathic complications of DM (retinopathy, nephropathy, and neuropathy) develop due to hyperglycemia (glucotoxicity phenomenon) (7). On the other hand, DM2 is a significant risk factor for coronary heart disease and early atherosclerosis. Cardiovascular morbidity in these patients is 2-4 times higher than in the non-diabetic population, with a risk of myocardial infarction similar to that of non-diabetics with a previous infarction (8). Taking into account that, according to the literature, MS is associated with a 50% increase in the risk of coronary heart disease and stroke in men and a nearly 100% increase in women, the coexistence of MS and DM2 multiplies the cardiovascular and coronary risk fivefold, increasing the probability of developing macrovascular complications of DM (7).

1.3 GOUT AND DM

Prior studies from outpatient settings indicated that DM occurs in approximately 25% of people with gout (9), and hyperuricemia can be both cause and consequence of insulin resistance and, therefore, of DM. The first mechanism linking both pathologies is the action of

proinflammatory cytokines in gout, which causes an increase in inflammation and insulin resistance (10). Hyperinsulinemia, derived from peripheral insulin resistance, increases urate reabsorption in the renal proximal convoluted tubule, decreasing urate excretion (10).

The endogenous production of uric acid from fructose consumption deserves special mention since the consumption of this sugar has increased considerably in recent decades and is closely related to the increase in obesity (11), a fundamental risk factor for the development of type 2 DM. Furthermore, hyperuricemia increases oxidative stress, hepatic fat (fatty liver) accumulation, and insulin resistance, all associated with DM (10).

Given that, as we have mentioned, gout and DM are closely related by etiopathogenesis and pathophysiology, few studies in the literature have analyzed this association in terms of the clinical impact on the patient and the development of comorbidities. An example would be a retrospective study that collected data from multiple US health plans from 2007 to 2010, which concluded that having gout and DM confers an incremental risk compared to DM or gout alone for both myocardial infarction and stroke incidence (12).

Another example to mention would be a cohort study that included almost 6 million gout patients from the USA that showed that the risk of lower extremity amputation (LEA) in patients with gout was higher if associated with DM (adjusted hazard ratio of 3.36), with this finding also having severe prognostic implications, since the 5-year mortality after LEA of these patients with gout and DM was close to 70% (13); however, the association of gout with AEI was increased even in those without DM, which may mean that it is possible that recommended surveillance and standardized foot care applied in the context of DM (but not routinely implemented in gout alone) may lead to reductions in gout-attributable AEI among those with both conditions (13).

Therefore, because DM and gout are very prevalent metabolic diseases worldwide, and their onset and development are closely related, our study will focus on the impact of this

combination on the profile, evolution, and mortality of patients with both pathologies. Very few studies have examined so far the impact of the relationship between gout and DM on the patient. However, given the importance of recognizing the impact of this association on the pattern of targeted treatment, there is a need to expand the literature on this subject.

2 HYPOTHESES AND OBJECTIVES

2.1 HYPOTHESES

Main hypothesis:

The coexistence of gout and DM will be associated with a higher number of complications and increased hospital readmissions.

Secondary hypothesis:

- The prevalence of patients with Type 2 Diabetes Mellitus in a hospitalized population with gout will be higher compared to the general population.

- Patients with gout and Diabetes Mellitus will show a comorbidity profile largely different from patients without Diabetes Mellitus.

- Patients with Diabetes Mellitus in a hospitalized population with gout will present more vascular complications with respect to those without Diabetes Mellitus.

- Diabetic patients in a hospitalized population with gout will manifest a higher risk of infectious complications with compared to those without Diabetes Mellitus.

- Patients with Diabetes Mellitus in a population with hospitalized gout will have a higher rate of hospital readmissions than those without Diabetes Mellitus.

2.2 OBJETIVES

General objective:

- To analyze the impact of the association of diabetes mellitus with gout in hospitalized patients in Spain from 2005 to 2015.

Specific objectives:

- To estimate the prevalence of each type of Diabetes Mellitus and its complications in a hospitalized population with gout.

- To discriminate the comorbidity profile of hospitalized patients with gout according to the presence of Diabetes Mellitus.

- To know the risk of developing vascular complications in a population with hospitalized gout if Diabetes Mellitus is also associated.

- To find out the impact of Diabetes Mellitus on the development of infectious complications in a hospitalized gout population.

- To know the impact of Diabetes Mellitus on readmission rates in a population with hospitalized gout.

3 MATERIALS AND METHODS

3.1 STUDY DESIGN, POPULATION, AND STUDY VARIABLES

This was an observational, multicenter, and longitudinal study.

We used the Minimum Basic Data Set (MBDS), an administrative registry of the National Institute of Statistics that contains information on each patient's episodes of care (patient identification and personal data such as date of birth or sex, diagnoses, and medical-surgical procedures, among others), both in public and private hospitals in the country, extracted from the discharge reports.

The study period was from 1/01/2005 to 31/12/2015.

From the complete sample, the study sample was drawn applying the following inclusion criteria: diagnosis of gout (either as primary or secondary) and adult age (≥ 18 years). Gout was coded using the ninth version of the International Classification of Diseases -ICD-9- as 274.0, 274.00, 274.01, 274.02, 274.03, 274.1, 274.10, 274.11, 274.19, 274.8, 274.81, 274.82, 274.89 or 274.9. No exclusion criteria were applied.

Later years were not included in the analysis due to the introduction of the new ICD-10.

Our study focused on the presence of Diabetes Mellitus (DM) and its macroangiopathic and microangiopathic complications in the hospitalized population with gout.

The primary study variable was DM and its types, using the ninth version of the International Classification of Diseases - ICD-9 - to code each of them: DM type 1 (250.01, 250.03, 250. 11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91 or 250.93), DM type 2 (250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250. 32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90 or 250.92) and other types of diabetes (secondary diabetes mellitus 249.0 - 249. 9, post-surgical hypoinsulinemia-hypoinsulinemia following total or partial pancreatectomy-postpancreatectomy hyperglycemia 251.3, steroid-induced diabetes 962.0, diabetes when complicating pregnancy, childbirth, or puerperium 648.0).

At the same time, we reclassified into complicated DM (250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9, 249.1, 249.2, 249.3, 249.4, 249.5, 249.6, 249.7, 249.8 and 249.9) and uncomplicated DM (250.0, 249.0).

Secondary study variables were age at admission, sex, and comorbidities (according to ICD-9, see appendix): obesity, dyslipidemia, cerebrovascular disease, coronary artery disease, arrhythmia, congestive heart failure, peripheral vascular disease, venous thromboembolism, chronic kidney disease, obstructive pulmonary disease, pneumonia, sepsis, dementia, liver disease, urinary tract infection, and other rheumatic diseases.

To evaluate the possible impact of the association between gout and DM at follow-up, two composite variables were built as outcome variables: Infections (including pneumonia, sepsis and urinary tract infection) and Cardiovascular Disease (cerebrovascular disease, coronary artery disease, congestive heart failure and peripheral vascular disease). Chronic kidney disease and venous thromboembolic disease were also analyzed in the follow-up.

3.2 STATISTICAL ANALYSIS

We used the complete sample size of 192,062 hospitalizations with gout.

As for the variables, qualitative variables such as sex, DM, and the different comorbidities were expressed as frequencies and percentages, while the only quantitative variable presented, age, was expressed as arithmetic mean with standard deviation. But, for comparative analysis, it was recoded to categorical as age quintiles (<=70 years, 71-80 years, 81-85 years, 86-90 years, 91-95 years and >95 years).

Firstly, the prevalence of DM in the entire population was estimated and then stratified by type of DM ("Type 1 DM", "Type 2 DM" and "Other DM"), as well as "Complicated" or "Uncomplicated", according to the corresponding ICD-9 codes, estimating their 95% confidence intervals (CI).

The chi-2 test was used to compare between patients with and without DM, and subsequently within DM subtypes (type 1 DM, type 2 DM and Other DM) for qualitative variables.

For a better differentiation of the characteristics of patients with and without DM in the population of hospitalized patients with gout and to control the effect of possible confounding variables, a multiple logistic regression analysis was constructed for all types of DM and each of them.

Secondly, patients with repeat admissions were identified in the data-set and matched for age, sex, chronic kidney disease, and composite cardiovascular disease and infections in the first

tertile (2005-2008). In addition, the sample sizes were balanced to avoid the possible over-effect of the non-DM group, the majority group in the sample. Subsequently, the frequencies of comorbidities of interest in the second (2009-2012) and third (2012-2015) tertiles were compared using the chi-2 test.

Google Colab (Alphabet, Mountain View, California), which allows Python to be run, was used to analyze the data, using the packages matplotlib V.3.2.2, pandas V.1.3.5, scikit-learn V.1.0.2 and statsmodels V.0.12.2. The level of significance was set at $p<0.05$.

3.3 ETHICAL ASPECTS

This work is part of a project approved by the research ethics committee of the Hospital General Universitario Dr. Balmis de Alicante (PI2022-113) and by the UMH research office responsible (COIR TFG.GME.MAC.PMV.231214.). Because we review pseudonymized data, an exemption was given from obtaining informed consent from the participants.

4 RESULTS

We studied 192,062 hospitalizations with gout, 53,242 with DM (prevalence 27.72%; 95%CI: 27.52-27.92%); of this group, 41,175 were male (77.34%). **Table 1** compares diabetics and non-diabetics regarding sex, age quintiles, and comorbidities. The comorbidities more prevalent in the population with DM were dyslipidemia, chronic kidney disease, coronary heart disease, congestive heart failure, and obesity. On the other hand, in the population without DM were dyslipidemia, chronic kidney disease, coronary heart disease, congestive heart failure, and obesity. Arrhythmia, pneumonia, and sepsis were not different in the crude comparison between diabetics and non-diabetics.

Table 1. Prevalences of <=70 years, 71-80 years, 81-85 years, 86-90 years, 91-95 years, >95 years, women, obesity, dyslipidemia, cerebrovascular disease, coronary heart disease, arrhythmia, congestive heart failure, peripheral vascular disease,venous thromboembolism, chronic kidney disease, obstructive pulmonary disease, pneumonia, sepsis, urinary tract infection, dementia, liver disease and other rheumatic diseases in diabetics (DM) and non-diabetics (non-DM).

	DM, n (%)	Non DM, n (%)	p-value
Age			<0.001
<=70 years	5199 (9.8)	24927 (18.0)	
71-80 years	10492 (19.7)	26500 (19.1)	
81-85 years	7707 (14.5)	16243 (11.7)	
86-90 years	10932 (20.5)	22728 (16.4)	
91-95 years	10045 (18.9)	22361 (16.1)	
>95 years	8867 (16.7)	26061 (18.8)	
Women	12067 (22.7)	21327 (15.4)	<0.001
Obesity	9090 (17.1)	13438 (9.7)	<0.001
Dyslipidemia	21750 (40.9)	37508 (27.0)	<0.001
Cerebrovascular diseases	2169 (4.1)	4621 (3.3)	<0.001
Coronary heart disease	14341 (26.9)	25799 (18.6)	<0.001
Arrhythmia	660 (1.2)	1686 (1.2)	0.671
Congestive heart failure	13034 (24.5)	24003 (17.3)	<0.001
Peripheral vascular disease	1998 (3.8)	4367 (3.1)	<0.001
Venous thromboembolism	1000 (1.9)	3949 (2.8)	<0.001
Chronic kidney disease	16959 (31.9)	34148 (24.6)	<0.001
Obstructive pulmonary disease	4426 (8.3)	10415 (7.5)	<0.001
Pneumonía	2375 (4.5)	5966 (4.3)	0.119
Sepsis	786 (1.5)	2094 (1.5)	0.619
Urinary tract infection	3752 (7.0)	8745 (6.3)	<0.001
Dementia	846 (1.6)	1766 (1.3)	<0.001
Liver Disease	1290 (2.4)	2684 (1.9)	<0.001
Other rheumatic diseases	792 (1.5)	2365 (1.7)	<0.001

After stratification by type of DM and presence of associated complications (**Table 2**), type 2 DM (27.43% 95%CI 27.23-27.63%) was found much more prevalent than type 1 DM (0.13% 95%CI 0.12 -0.15%) or other forms of DM (0.35% 95%CI 0.32-0.37%); and the presence of complicated DM was 19.76% (95%CI 19.43-20.10). Regarding the comparison of comorbidities between subtypes of DM and complicated versus uncomplicated DM, it was observed that, besides vascular and renal disorders, infections and obstructive pulmonary disease were more prevalent in complicated type 2 DM.

Figure 1 and **Table 3** show the multiple logistic regression model results between the gout population with and without DM. The comorbidities significantly related to DM were advanced age, female sex, dyslipidemia, obesity, coronary heart disease, congestive heart failure, chronic kidney disease, liver disease, cerebrovascular disease, obstructive pulmonary disease, peripheral vascular disease, urinary tract infection, and dementia. On the other hand, the comorbidities significantly related to the non-diabetic population were other concurrent rheumatic diseases and venous thromboembolism. **Figure 2** shows the results of the logistic regression stratified for each type of DM, in which we noticed a very different profile of comorbidities between them.

Table 2. Prevalences of <=70 years, 71-80 years, 81-85 years, 86-90 years, 91-95 years, >95 years, women, obesity, dyslipidemia, cerebrovascular disease, coronary heart disease, arrhythmia, congestive heart failure, peripheral vascular disease, venous thromboembolism, chronic kidney disease, obstructive pulmonary disease,pneumonia, sepsis, urinary tract infection, dementia, liver disease and other rheumatic diseases in complicated and uncomplicated subtypes of the different forms of DM.

	Type 1 DM			**Type 2 DM**			**Other types of DM**		
	Complicated	Not complicated	p-value	Complicated	Not complicated	p-value	Complicated	Not complicated	p-value
Age			0.277			0.270			0.015
<=70 years	28 (29.5)	35 (22.2)		1006 (9.8)	4087 (9.6)		35 (25.0)	91 (17.4)	
71-80 years	17 (17.9)	22 (13.9)		1998 (19.4)	8377 (19.8)		31 (22.1)	139 (26.6)	
81-85 years	10 (10.5)	23 (14.6)		1468 (14.3)	6155 (14.5)		11 (7.9)	74 (14.1)	
86-90 years	9 (9.5)	30 (19.0)		2199 (21.4)	8637 (20.4)		18 (12.9)	65 (12.4)	
91-95 years	15 (15.8)	25 (15.8)		1942 (18.9)	8022 (18.9)		18 (12.9)	93 (17.8)	
>95 years	16 (16.8)	23 (14.6)		1675 (16.3)	7123 (16.8)		27 (19.3)	61 (11.7)	
Women	27 (28.4)	38 (24.1)	0.534	2497 (24.3)	9426 (22.2)	0.024	36 (25.7)	93 (17.8)	0.047
Obesity	21 (22.1)	32 (20.3)	0.849	1848 (18.0)	7135 (16.8)	0.006	19 (13.6)	64 (12.2)	0.779
Dyslipidemia	26 (27.4)	63 (39.9)	0.060	3801 (36.9)	17735 (41.8)	<0.001	44 (31.4)	171 (32.7)	0.855
Cerebrovascular diseases	6 (6.3)	11 (7.0)	1.0	460 (4.5)	1688 (4.0)	0.026	2 (1.4)	12 (2.3)	0.763
Coronary heart disease	22 (23.2)	40 (25.3)	0.814	2706 (26.3)	11487 (27.1)	0.108	28 (20.0)	81 (15.5)	0.250
Arrhythmia	3 (3.2)	0 (0.0)	0.099	104 (1.0)	549 (1.3)	0.022	0 (0.0)	6 (1.1)	0.441
Congestive heart failure	19 (20.0)	31 (19.6)	1.0	2788 (27.1)	10128 (23.9)	<0.001	26 (18.6)	114 (21.8)	0.475
Peripheral vascular disease	7 (7.4)	4 (2.5)	0.131	463 (4.5)	1510 (3.6)	0.019	4 (2.9)	14 (2.7)	1.0
Venous thromboembolism	1 (1.1)	1 (0.6)	1.0	181 (1.8)	817 (1.9)	0.281	1 (0.7)	17 (3.3)	0.178
Chronic	32 (33.7)	46 (29.1)	0.534	4825 (46.9)	11907 (28.1)	<0.001	58 (41.4)	195 (37.3)	0.425

kidney disease									
Obstructive pulmonary disease	5 (5.3)	12 (7.6)	0.647	756 (7.3)	3637 (8.6)	0.038	13 (9.3)	32 (6.1)	0.257
Pneumonía	2 (2.1)	6 (3.8)	0.708	546 (5.3)	1807 (4.3)	0.012	12 (8.6)	41 (7.8)	0.914
Sepsis	0 (0)	3 (1.9)	0.452	191 (1.9)	586 (1.4)	<0.001	1 (0.7)	19 (3.6)	0.130
Urinary tract infection	7 (7.4)	13 (8.2)	0.996	964 (9.4)	2747 (6.5)	<0.001	11 (7.9)	47 (9.0)	0.801
Dementia	2 (2.1)	4 (2.5)	1.0	149 (1.4)	687 (1.6)	0.227	4 (2.9)	4 (0.8)	0.115
Liver Disease	0 (0.0)	4 (2.5)	0.297	191 (1.9)	1089 (2.6)	0.020	1 (0.7)	15 (2.9)	0.244
Other rheumatic diseases	3 (3.2)	1 (0.6)	0.299	163 (1.6)	621 (1.5)	0.393	2 (1.4)	23 (4.4)	0.165

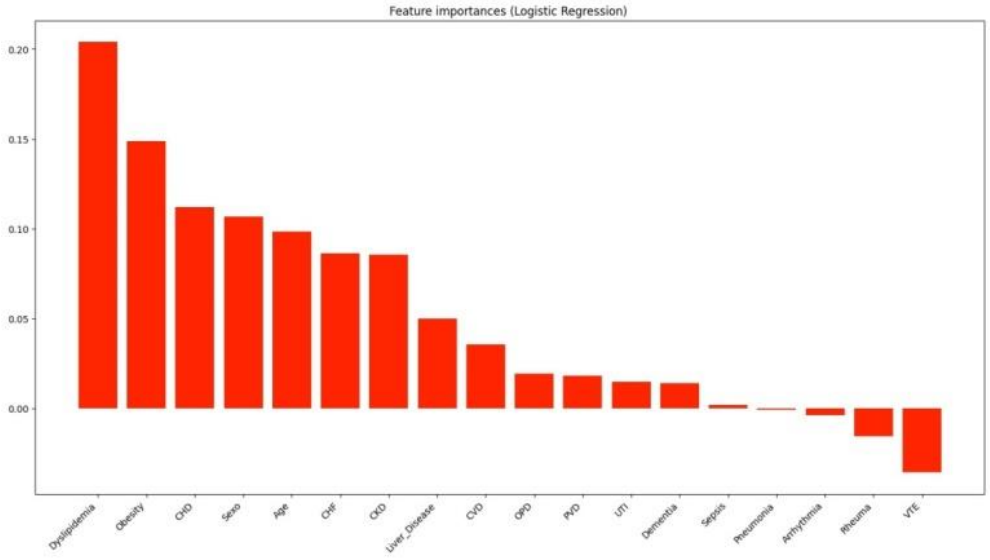

Figure 1. ***Coefficients of each comorbidity from the baseline logistic regression model.*** *Positive coefficients are associated with DM, negative coefficients otherwise. Legend: CHD, coronary heart disease; CHF, chronic heart failure; CKD, chronic kidney disease; CVD, cerebrovascular disease; OPD, obstructive pulmonary disease; PVD, peripheral vascular disease; UTI, urinary tract infection; VTE, venous thromboembolism.*

Table 3. Coefficient, Odds ratio, 95% confidence interval (95% CI) and p-value for the association analysis between gout and DM.

	Coefficient	Odds ratio	95% CI	p-value
Age (per year)	±0.01	1.01	1.10-1.11	< 0.001
Women	±0.35	1.42	1.11-1.12	< 0.001
Obesity	±0.61	1.84	1.16-1.17	< 0.001
Dyslipemia	±0.60	1.82	1.23-1.24	< 0.001
Cerebrovascular diseases	±0.27	1.31	1.03-1.04	< 0.001
Coronary heart disease	±0.34	1.40	1.12-1.12	< 0.001
Arrhythmia	-0.07	0.93	1.00-1.00	0.235
Congestive heart failure	±0.26	1.30	1.10-1.10	< 0.001
Peripheral vascular disease	±0.12	1.13	1.01-1.02	< 0.001
Venous thromboembolism	-0.32	0.73	0.96-0.96	< 0.001
Chronic kidney disease	±0.24	1.27	1.09-1.10	< 0.001
Obstructive pulmonary disease	±0.10	1.11	1.01-1.02	< 0.001
Pneumonia	-0.01	0.99	1.00-1.01	0.859
Sepsis	±0.04	1.04	1.00-1.01	0.417
Urinary tract infection	±0.07	1.07	1.01-1.02	0.005
Dementia	±0.15	1.16	1.01-1.02	0.005
Liver Disease	±0.56	1.75	1.04-1.05	< 0.001
Other rheumatic diseases	-0.18	0.84	0.98-0.99	< 0.001

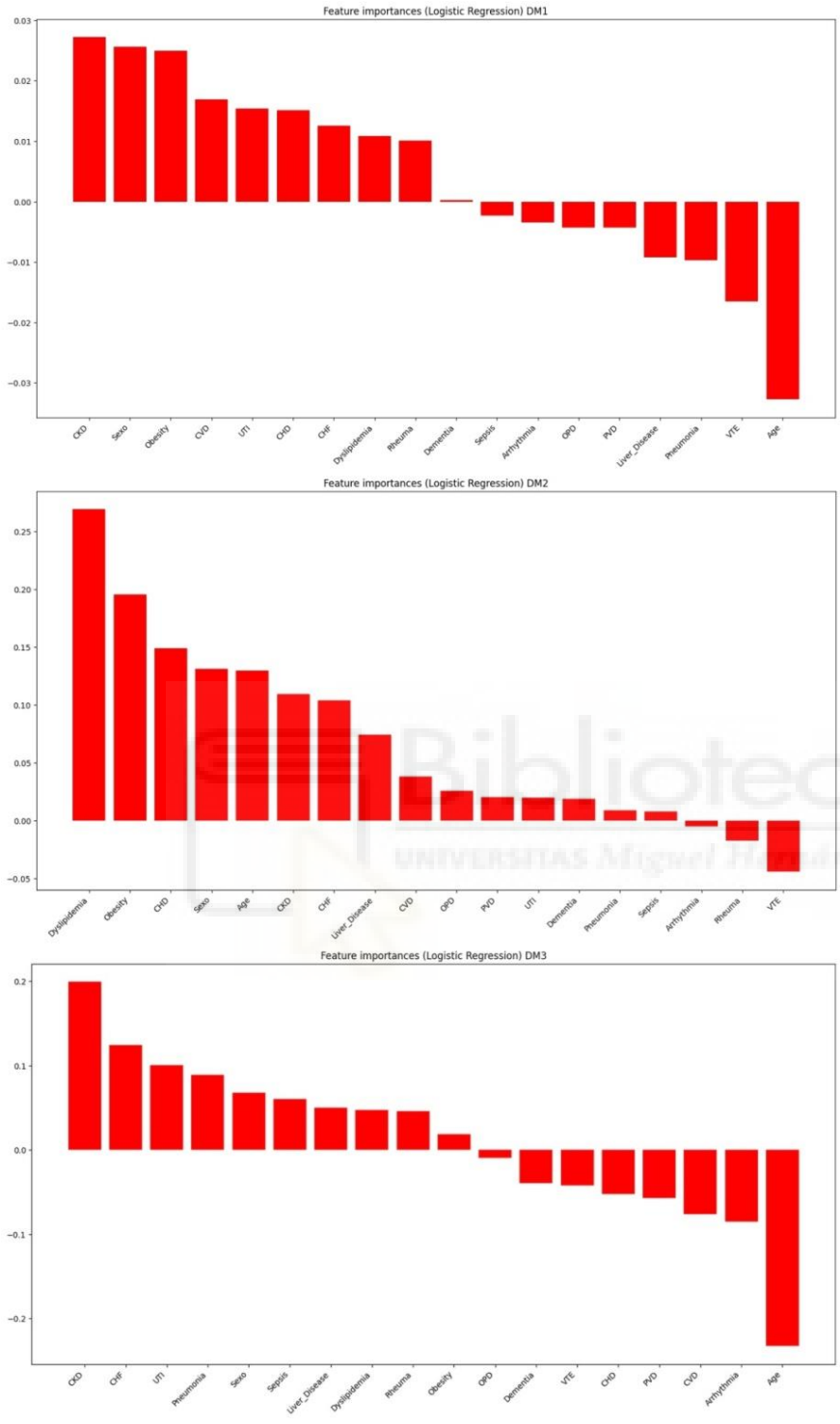

Figure 2. Coefficients for each comorbidity in the logistic regression model for each type of diabetes mellitus (DM): type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM 2) and other types of diabetes (DM3). Positive coefficients are associated with DM, negative coefficients otherwise. Legend: see Figure 1.

4.1 FOLLOW-UP ASSESSMENT

We identified 65,376 patients with readmission during the study period, of whom 16,623 were diabetic (25.43%) and 48,753 were non-diabetic (74.57%). Patients with readmission in the first tercile were 55,214 (13,513 DM and 41,701 non-DM); in the second tercile were 7,106 (2,129 DM and 4,977 non-DM); and in the third tercile were 3056 patients (981 DM 2,075 non-DM).

Table 4 shows that the group with DM presented a higher number of cardiovascular events over time (T3: 53.9%) than the non-diabetic population (T3: 41.2%), driven by coronary heart disease (T3 DM: 30.1%; T3 Non-DM: 19.5%) and congestive heart failure (T3 DM: 28.5%; T3 Non-DM: 21.0%). They also had a higher prevalence of renal disease (T3 DM: 44.2%; T3 Non-DM: 36.2%). The presence of infections in both groups was similar (T3 DM: 12.8%; T3 Non-DM: 13.9%), and diabetics presented fewer venous thromboembolism events (T3=1.8%) compared to non-diabetics (T3=3.1%).

Table 4. Follow-up of the development of comorbidities by tertiles of years in the diabetic and non-diabetic population, matched at tercil 1 by age, sex, chronic kidney disease, cardiovascular disease (combined variable of cardiac, cerebral and peripheral disease) and infections (combined variable of pneumonia, urinary tract infections and sepsis).

	Tercil 1 (2005-2008)		**Tercil 2 (2009-2012)**		**Tercil 3 (2012-2015)**		
	Non DM	DM	Non DM	DM	Non DM	DM	p-value
Cardiovascular disease	6169 (47.2)	6593 (48.8)	1033 (45.3)	934 (55.4)	388 (43.6)	354 (57.9)	<0.001
Cerebrovascular diseases	545 (4.2)	544 (4.0)	103 (4.5)	70 (4.1)	46 (5.2)	29 (4.7)	0.530
Coronary heart disease	3473 (26.6)	4029 (29.8)	565 (24.8)	505 (29.9)	193 (21.7)	200 (32.7)	<0.001
Congestive heart failure	2850 (21.8)	3077 (22.8)	534 (23.4)	522 (31.0)	187 (21.0)	200 (32.7)	<0.001
Peripheral vascular disease	500 (3.8)	522 (3.9)	86 (3.8)	68 (4.0)	43 (4.8)	27 (4.4)	0.709
Infections	1381 (10.6)	1415 (10.5)	283 (12.4)	199 (11.8)	123 (13.8)	81 (13.3)	<0.001
Pneumonia	515 (3.9)	524 (3.9)	94 (4.1)	83 (4.9)	45 (5.1)	31 (5.1)	0.119
Sepsis	94 (0.7)	89 (0.7)	40 (1.8)	22 (1.3)	19 (2.1)	12 (2.0)	<0.001
Urinary Tract Infection	832 (6.4)	855 (6.3)	170 (7.5)	107 (6.3)	68 (7.6)	43 (7.0)	0.238
Venous thromboembolism	347 (2.7)	262 (1.9)	46 (2.0)	27 (1.6)	31 (3.5)	14 (2.3)	<0.001
Chronic Kidney Disease	2427 (18.6)	2621 (19.4)	912 (40.0)	717 (42.5)	339 (38.1)	289 (47.3)	<0.001

5 DISCUSSION

In a large, nation-based adult hospitalized population with gout, we observed that the presence of DM in this population is high, affecting one in four patients. The vast majority were type 2 DM, with less than 2% being type 1 DM or other DM. The prevalence of complicated DM in the sample was 19.76%. Using multiple logistic regression, we identified distinct comorbidity profiles for the gout population with and without DM, with dyslipidemia, obesity, advanced age, coronary artery disease, and heart and kidney failure being those that best classified DM. In contrast, venous thromboembolic disease and concurrent rheumatic disease were more associated with those without DM. The model stratified by each DM subtype revealed very different results. Evaluating the subpopulation with readmissions during the study period, the co-presence of DM at baseline translated into a nearly 10% difference in cardiovascular disease (led by coronary heart disease followed by congestive heart failure) and renal disease in later tertiles, compared to non-DM. However, we did not identify differences in infections, and strikingly, diabetics presented a lower risk of thromboembolism compared to non-diabetics.

Other studies have evaluated the prevalence of DM in the gout population, but used outpatient data. In the case-control study by Kuo et al., which analyzed data from 39,111 UK patients with gout, the prevalence of uncomplicated DM was 7.08% at diagnosis of gout. In the control group (no gout), there was a prevalence of 6.46%. Differences were also identified in the prevalences of complicated DM, being 1.30% and 13.92% in the case group, and 1.43% and 8.41% in the control group (14). The French multicenter CACTUS study analyzed data from 2763 patients with gout and showed that 25% had type 2 DM (15). In this study, the mean time of gout evolution was ~6 years on average. In another cross-sectional study carried out in the United Kingdom by Bevis et al., including 1,079 patients with gout mainly from primary care, a prevalence of DM of 16% was obtained (16). Comparing our results, based on hospitalizations,

we observe that they are similar to those previously presented, both in the prevalence of DM and complicated DM in patients with gout of a certain evolution. Gout characteristics are not available in our sample, but due to the population's mean age we assume long duration, as we already saw in a previous local study (17). Despite being from populations in different settings, similar prevalence figures reinforce the strength of the association between gout and DM.

Regarding the association study, we found similarities in the literature. In the CACTUS study, the authors observed that in the cluster where 75% of the patients had DM, the prevalence of other comorbidities increased, led by dyslipidemia, hypertension and obesity, followed by liver disease and coronary heart disease (15). Likewise, Singh et al. showed a higher prevalence of female sex and complications in the diabetic population, driven by hypertension, hyperlipidemia, and chronic kidney disease (12). In our population, we did not analyse arterial hypertension because it was considered underreported in the discharge reports, but the other comorbidities followed the same path. Nevertheless, the inverse association of venous thromboembolism with DM is noteworthy. This fact has not been previously published and stands out because both entities have a demonstrated intrinsic thrombotic risk (18,19), although it has recently been questioned for DM whether there is direct causality (20). We can speculate that our result may be due to the control of certain comorbidities by the diabetic population in their follow-up compared to those without DM; however, this may be controversial since it is common for patients with DM of many years of evolution to present a decline in the control of their disease, which is reflected in the literature, as is the case of the longitudinal study conducted by Domínguez et al. that showed the negative influence of the time of evolution for treatment adherence (21). Therefore, other specific studies aimed at addressing this issue are needed.

Some projects have previously addressed the follow-up of patients with gout and diabetes in terms of comorbidity profile. A cohort study by Mikuls et al. that analyzed data from nearly 6

million US patients with gout from 2000 to 2015 resulted in a marked increase in the risk of AEI in patients with gout associated with DM (13). Similarly, the previously mentioned study by Singh et al. concluded that the association of gout and DM markedly increases the risk of both myocardial infarction and stroke (12).

A Taiwanese cohort study evaluated the comorbidities associated over time in patients with gout, remarking DM as the most notable and, in that setting, leading women to develop stroke. The authors claimed that systemic inflammation caused by gout could contribute to insulin resistance and the development of type 2 DM in these patients, and on the other hand, hyperglycemia could affect endothelial cells, leading to blood vessel dysfunction and, potentially, the development of atherosclerosis and other cardiovascular comorbidities over time, especially in older women with gout (22). Our results are in agreement with previous studies, but the increased development of cardiovascular disease was led by heart diseases, with no differences in cerebrovascular and peripheral artery complications (we did not specifically assessed rates of LEA). We confirm, therefore, that in patients with gout and DM, the increase in potential cardiovascular complications over time is more than evident, especially in the elderly female population. For this reason, it is necessary to diagnose DM as early as possible in patients with gout since this would effectively reduce the future risk of presenting these comorbidities or slow their progression and, therefore, considerably improve the prognosis of these patients.

5.1 STRENGTHS AND LIMITATIONS

Our study has several strengths. First, the large sample size (n=192,062) allows the development of robust multivariate models to rule out the effect of confounding factors. In addition, this sample size allowed longitudinal analysis in over 65,000 subjects with readmissions, supporting the causal associations. Likewise, it is representative of the Spanish

population and uses the CMBD (in this case, ICD-9), which has proven useful in other population-based field studies.

Some limitations should be noted. On the one hand, given the high prevalence of type 2 DM compared to the other subtypes, most results obtained will correspond to patients with this condition. Specific studies with type 1 diabetics or other types of DM are necessary, especially about the impact of the association between DM and gout, which is expected to be significant, as we have observed in the stratified multiple logistic regression models. The data corresponding to gout cases are obtained from discharge reports, and there could be some variability in the diagnosis of gout in our population due to possible discrepancies in the diagnostic methods used by each clinician, especially considering the low implementation of crystal-based diagnosis in rheumatology clinics in Spain (23). The same happens with DM, causing some patients (although a minority) to be registered with diagnoses of different types of DM.

In addition, mention should be made of the possible impact of the usual lack of recording of gout in discharge reports, although the available data seem sufficient to carry out conclusive analyses. The study period was selected until 2015 because in 2016, the diagnostic coding in the CMBD was replaced by ICD-10, and there could be mismatches, which should be corroborated in a future study.

6 CONCLUSION

A national analysis of 11 years of hospitalizations for gout confirms a different comorbidity profile between DM and non-DM, with a close relationship with MS. DM is prevalent in patients with gout; type 2 was the most frequent subtype of DM, presenting a profile of comorbidities different from the other subtypes and headed by cardiovascular comorbidities. Evaluating readmissions, the co-presence of DM translated into an increase in the

development of vascular and renal comorbidities, except venous thromboembolism, which was more frequent in the population without DM. No impact on infections was identified. These results confirm the importance of early diagnosis of DM in patients with gout, to prescribe more targeted treatment and preventing or, failing that, treating as early as possible the associated comorbidities whose incidence increases notably due to this association.

6.1 WHAT I HAVE LEARNED FROM THIS PROJECT

Thanks to the elaboration of this project I have learned how to carry out research work and I have practised some skills which will be very useful in my professional future: working as a team with my tutors and collaborator and using databases unknown to me until now, among others. In addition, I have been able to expand my knowledge about two diseases that, not only are of high prevalence and therefore of great current importance, but they are also of great personal interest to me due to the fact that I have close relatives who suffer from them. I hope that I have been able to obtain results which may be useful to other researchers. Finally, I do not rule out continuing this project in a future thesis because Rheumatology and Endocrinology are two specialties that I am considering for the future.

7 REFERENCES

1. Ludeña Suárez MC, Marín Ferrín RE, Anchundia Cunalata EF, Villacrés Mosquera LF, Torres Ramírez MI. Diagnóstico, tratamiento y prevención de la gota. Correo científico médico. 2020;24(1):222–52.
2. Sicras-Mainar A, Navarro-Artieda R, Ibáñez-Nolla J. Uso de recursos e impacto económico de los pacientes con gota: estudio multicéntrico de ámbito poblacional. Reumatología Clínica. 2013;9(2):94–100.
3. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet. 2021;397(10287):1843-1855.
4. Metola Gómez M, Dones Carvajal JJ, Camacho MA, Moncloa C. Gota tofácea: ¿indisciplina o desconocimiento? Medifam. 2002; 12(4): 81-84.

5. Lozano JA. Diabetes mellitus. Offarm. 2006;25(10):66–78.

6. Goday A, Delgado E, Díaz Cadórniga F, De Pablos P, Vázquez JA, Soto E. Epidemiología de la diabetes tipo 2 en España. Endocrinología y Nutrición. 2002;49(4):113–26.

7. Rodolfo Lahsen M. Sindrome metabólico y diabetes. Revista médica Clínica Las Condes. 2014;25(1):47–52.

8. González Sarmiento E, Pascual Calleja I, Laclaustra Gimeno M, Casasnovas Lenguas J. Síndrome metabólico y diabetes mellitus. Síndrome metabólico. Retos y esperanzas. 2005;5(1): 30-37.

9. Álvarez-Lario B, Alonso-Valdivielso JL. Hiperuricemia y gota: el papel de la dieta. Nutrición Hospitalaria. 2014;29(4):760–70.

10. Carvajal Carvajal C. El ácido úrico y otros males. Medicina Legal de Costa Rica. 2016;33(1): 182-189.

11. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol. 2006 Mar;290(3):F625-31.

12. Singh JA, Ramachandaran R, Yu S, Yang S, Xie F, Yun H, et al. Is gout a risk equivalent to diabetes for stroke and myocardial infarction? A retrospective claims database study. Arthritis Res Ther. 2017; 19(1):228.

13. Mikuls TR, Soto Q, Petro A, Helget L, Roul P, Sayles H, et al. Comparison of rates of lower extremity amputation in patients with and without gout in the US department of veterans affairs health system. JAMA Netw Open. 2022;5(1):e2142347.

14. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis. 2016;75(1):210–7.

15. Richette P, Clerson P, Périssin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis. 2015;74(1):142–7.

16. Bevis M, Blagojevic-Bucknall M, Mallen C, Hider S, Roddy E. Comorbidity clusters in people with gout: an observational cohort study with linked medical record review. Rheumatology (Oxford). 2018;57(8):1358–63.

17. Calabuig I, Gómez-Garberí M, Andrés M. Gout Is Prevalent but Under-Registered Among Patients With Cardiovascular Events: A Field Study. Front Med (Lausanne). 2020;7:560.

18. Cipolletta E, Tata LJ, Nakafero G, Avery AJ, Mamas MA, Abhishek A. Risk of Venous Thromboembolism With Gout Flares. Arthritis Rheumatol. 2023;75(9):1638-1647.

19. Bai J, Ding X, Du X, Zhao X, Wang Z, Ma Z. Diabetes is associated with increased risk of venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2015;135(1):90-95.

20. Hu S, Tan JS, Hu MJ, Guo TT, Chen L, Hua Lu, et al. The Causality between Diabetes and Venous Thromboembolism: A Bidirectional Two-Sample Mendelian Randomization Study. Thromb Haemost. 2023;123(9):913-919.

21. Domínguez Gallardo LA, Ortega Filártiga E. Factors associated with lack of adherence to treatment in patients with type 2 diabetes mellitus. Rev Virtual Soc Paraguaya Med Interna. 2019;6(1):63–74.

22. Huang HC, Chiang HP, Hsu NW, Huang CF, Chang SH, Lin KC. Differential risk group of developing stroke among older women with gouty arthritis: A latent transition analysis. Eur J Clin Invest. 2019;49(5): 1-8.

23. Perez Ruiz F, Sanchez-Piedra CA, Sanchez-Costa JT, et al. Improvement in Diagnosis and Treat-to-Target Management of Hyperuricemia in Gout: Results from the GEMA-2 Transversal Study on Practice. Rheumatol Ther. 2018;5(1): 243-253.

8 SUPPLEMENTARY MATERIAL

8.1 APPROVAL FROM THE ETHICS COMMITTEE OF DR. BALMIS GENERAL UNIVERSITY HOSPITAL OF ALICANTE

COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE - HOSPITAL GENERAL

C/. Pintor Baeza, 12 – 03010 Alicante
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Ref. CEIm: PI2022-113 - Ref. ISABIAL: 2022-0388

INFORME DEL COMITE DE ETICA PARA LA INVESTIGACION CON MEDICAMENTOS

Reunidos los miembros del Comité de Ética para la Investigación con medicamentos del Departamento de Salud de Alicante – Hospital General, en su sesión del día 28 de septiembre de 2022 (Acta 2022-08), y una vez estudiada la documentación presentada por **D. Mariano Andrés Collado** del Servicio de Reumatología del Hospital General Universitario Dr. Balmis, tiene bien a informar que el proyecto de investigación titulado **"Conociendo mejor la gota en la mujer: análisis de comorbilidades a través de las altas hospitalarias españolas (2005-2015)"**, se ajusta a las normas deontológicas establecidas para tales casos. Se informa a su vez de que este estudio ha solicitado la exención del Consentimiento Informado.

Y para que conste a los efectos oportunos, firmo la presente en Alicante con fecha 29 de septiembre de 2022.

Firmado por Luis Manuel Hernandez Blasco - 21424371D el 05/10/2022 09:20:04

Fdo. Dr. Luis Manuel Hernández Blasco
Secretario Técnico CEIm Departamento de Salud de Alicante – Hospital General

CSV:FIFISEAK:SRIIQZ7L:UY99HU7Q URL de validación:https://www.tramita.gva.es/csv-front/index.faces?cadena=FIFISEAK:SRIIQZ7L:UY99HU7Q

8.2 APPROVAL FROM UMH RESPONSIBLE INVESTIGATION OFFICE

INFORME DE EVALUACIÓN DE INVESTIGACIÓN RESPONSABLE DE 1. TFG (Trabajo Fin de Grado)

Elche, a 21/12/2023

Nombre del tutor/a	MARIANO ANDRÉS COLLADO
Nombre del alumno/a	PATRICIA MORA VÁZQUEZ
Tipo de actividad	Adherido a un proyecto autorizado
Título del 1. TFG (Trabajo Fin de Grado)	Evaluación del impacto de la asociación de gota y diabetes en una población hospitalizada
Evaluación de riesgos laborales	No solicitado/No procede
Evaluación ética humanos	No solicitado/No procede
Código provisional	231214103723
Código de autorización COIR	**TFG.GME.MAC.PMV.231214**
Caducidad	2 años

Se considera que la presente actividad no supone riesgos laborales adicionales a los ya evaluados en el proyecto de investigación al que se adhiere. No obstante, es responsabilidad del tutor/a informar y/o formar al estudiante de los posibles riesgos laborales de la presente actividad.

La necesidad de evaluación ética del trabajo titulado: **Evaluación del impacto de la asociación de gota y diabetes en una población hospitalizada** ha sido realizada en base a la información aportada en el formulario online: "TFG/TFM: Solicitud Código de Investigación Responsable (COIR)", habiéndose determinado que no requiere ninguna evaluación adicional. Es importante destacar que si la información aportada en dicho formulario no es correcta este informe no tiene validez.

Por todo lo anterior, **se autoriza** la realización de la presente actividad.

Atentamente,

Alberto Pastor Campos
Jefe de la Oficina de Investigación Responsable
Vicerrectorado de Investigación y Transferencia

Información adicional:

- En caso de que la presente actividad se desarrolle total o parcialmente en otras instituciones es responsabilidad del investigador principal solicitar cuantas autorizaciones sean pertinentes, de manera que se garantice, al menos, que los responsables de las mismas están informados.
- Le recordamos que durante la realización de este trabajo debe cumplir con las exigencias en materia de prevención de riesgos laborales. En concreto: las recogidas en el plan de prevención de la UMH y en las planificaciones preventivas de las unidades en las que se integra la investigación. Igualmente, debe promover la realización de reconocimientos médicos periódicos entre su personal; cumplir con los procedimientos sobre coordinación de actividades empresariales en el caso de que trabaje en el centro de trabajo de otra empresa o que personal de otra empresa se desplace a las instalaciones de la UMH; y atender a las obligaciones formativas del personal en materia de prevención de riesgos laborales. Le indicamos que tiene a su disposición al Servicio de Prevención de la UMH para asesorarle en esta materia.

La información descriptiva básica del presente trabajo será incorporada al repositorio público de Trabajos fin de Grado y Trabajos Fin de Máster autorizados por la Oficina de Investigación Responsable de la Universidad Miguel Hernández. También se puede acceder a través de https://oir.umh.es/solicitud-de-evaluacion/tfg-tfm/

8.3 ICD-9 CODES OF COMORBIDITIES INCLUDED

- 274 Gout:
    - 274.0 Gouty arthropathy
        - 274.00 Gouty arthropathy, unspecified
        - 274.01 Acute gouty arthropathy
        - 274.02 Chronic gouty arthropathy without mention of tophus (tophi)
        - 274.03 Chronic gouty arthropathy with tophus (tophi)
    - 274.1 Gouty nephropathy
        - 274.10 Gouty nephropathy, unspecified
        - 274.11 Uric acid nephrolithiasis
        - 274.19 Other
    - 274.8 Gout with other specified manifestations
        - 274.81 Gouty tophi of ear
        - 274.82 Gouty tophi of other sites
        - 274.89 Other
    - 274.9 Gout, unspecified
- 250 Diabetes mellitus
    - 250.0 Diabetes mellitus without mention of complication
        - 250.00 Type II or unspecified type, not stated as uncontrolled
        - 250.01 Type I [juvenile type], not stated as uncontrolled
        - 250.02 Type II or unspecified type, uncontrolled
        - 250.03 Type I [juvenile type], uncontrolled
    - 250.1 Diabetes with ketoacidosis
        - 250.10 Type II or unspecified type, not stated as uncontrolled
        - 250.11 Type I [juvenile type], not stated as uncontrolled
        - 250.12 Type II or unspecified type, uncontrolled
        - 250.13 Type I [juvenile type], uncontrolled
    - 250.2 Diabetes with hyperosmolarity

- 250.20 Type II or unspecified type, not stated as uncontrolled
- 250.21 Type I [juvenile type], not stated as uncontrolled
- 250.22 Type II or unspecified type, uncontrolled
- 250.23 Type I [juvenile type], uncontrolled

- 250.3 Diabetes with other coma
  - 250.30 Type II or unspecified type, not stated as uncontrolled
  - 250.31 Type I [juvenile type], not stated as uncontrolled
  - 250.32 Type II or unspecified type, uncontrolled
  - 250.33 Type I [juvenile type], uncontrolled
- 250.4 Diabetes with renal manifestations
  - 250.40 Type II or unspecified type, not stated as uncontrolled
  - 250.41 Type I [juvenile type], not stated as uncontrolled
  - 250.42 Type II or unspecified type, uncontrolled
  - 250.43 Type I [juvenile type], uncontrolled
- 250.5 Diabetes with ophthalmic manifestations
  - 250.50 Type II or unspecified type, not stated as uncontrolled
  - 250.51 Type I [juvenile type], not stated as uncontrolled
  - 250.52 Type II or unspecified type, uncontrolled
  - 250.53 Type I [juvenile type], uncontrolled
- 250.6 Diabetes with neurological manifestations
  - 250.60 Type II or unspecified type, not stated as uncontrolled
  - 250.61 Type I [juvenile type], not stated as uncontrolled
  - 250.62 Type II or unspecified type, uncontrolled
  - 250.63 Type I [juvenile type], uncontrolled
- 250.7 Diabetes with peripheral circulatory disorders
  - 250.70 Type II or unspecified type, not stated as uncontrolled
  - 250.71 Type I [juvenile type], not stated as uncontrolled
  - 250.72 Type II or unspecified type, uncontrolled
  - 250.73 Type I [juvenile type], uncontrolled
- 250.8 Diabetes with other specified manifestations

        - 250.80 Type II or unspecified type, not stated as uncontrolled
        - 250.81 Type I [juvenile type], not stated as uncontrolled
        - 250.82 Type II or unspecified type, uncontrolled
        - 250.83 Type I [juvenile type], uncontrolled
    - 250.9 Diabetes with unspecified complication
        - 250.90 Type II or unspecified type, not stated as uncontrolled
        - 250.91 Type I [juvenile type], not stated as uncontrolled
        - 250.92 Type II or unspecified type, uncontrolled
        - 250.93 Type I [juvenile type], uncontrolled
- 272 Dyslipidemia:
    - 272.0 Pure hypercholesterolemia
    - 272.1 Pure hyperglyceridemia
    - 272.2 Mixed hyperlipidemia
    - 272.3 Hyperchylomicronemia
    - 272.4 Other and unspecified hyperlipidemia
    - 272.9 Unspecified disorder of lipoid metabolism
- 278 Obesity:
    - 278.0 Overweight and obesity
        - 278.00 Obesity, unspecified
        - 278.01 Morbid obesity
        - 278.02 Overweight
        - 278.03 Obesity hypoventilation syndrome
    - 278.1 Localized adiposity
    - 278.8 Other hyperalimentation
- Dementia
    - 290 Dementias
        - 290.0 Senile dementia, uncomplicated
        - 290.1 Presenile dementia
            - 290.10 Presenile dementia, uncomplicated

        - 290.11 Presenile dementia with delirium
        - 290.12 Presenile dementia with delusional features
        - 290.13 Presenile dementia with depressive features
    - 290.2 Senile dementia with delusional or depressive features
        - 290.20 Senile dementia with delusional features
        - 290.21 Senile dementia with depressive features
    - 290.3 Senile dementia with delirium
    - 290.4 Vascular dementia
        - 290.40 Vascular dementia, uncomplicated
        - 290.41 Vascular dementia with delirium
        - 290.42 Vascular dementia with delusions
        - 290.43 Vascular dementia with depressed mood
    - 290.8 Other specified senile psychotic conditions
    - 290.9 Unspecified senile psychotic condition
  - 294 Persistent mental disorders due to conditions classified elsewhere
    - 294.0 Amnestic disorder in conditions classified elsewhere
    - 294.1 Dementia in conditions classified elsewhere
        - 294.10 Dementia in conditions classified elsewhere without behavioral disturbance
        - 294.11 Dementia in conditions classified elsewhere with behavioral disturbance
    - 294.2 Dementia, unspecified
        - 294.20 Dementia, unspecified, without behavioral disturbance
        - 294.21 Dementia, unspecified, with behavioral disturbance
    - 294.8 Other persistent mental disorders due to conditions classified elsewhere
    - 294.9 Unspecified persistent mental disorders due to conditions classified elsewhere
- Hypertension:
  - 401 Essential hypertension
    - 401.0 Malignant
    - 401.1 Benign

- 401.9 Unspecified

- 402 Hypertensive heart disease
  - 402.0 Malignant
    - 402.00 Without heart failure
    - 402.01 With heart failure
  - 402.1 Benign
    - 402.10 Without heart failure
    - 402.11 With heart failure
  - 402.9 Unspecified
    - 402.90 Without heart failure
    - 402.91 With heart failure
- 403 Hypertensive chronic kidney disease
  - 403.0 Malignant
    - 403.00 With chronic kidney disease stage I through stage IV, or unspecified
    - 403.01 With chronic kidney disease stage V or end stage renal disease
  - 403.1 Benign
    - 403.10 With chronic kidney disease stage I through stage IV, or unspecified
    - 403.11 With chronic kidney disease stage V or end stage renal disease
  - 403.9 Unspecified
    - 403.90 With chronic kidney disease stage I through stage IV, or unspecified
    - 403.91 With chronic kidney disease stage V or end stage renal disease
- 404 Hypertensive heart and chronic kidney disease
  - 404.0 Malignant
    - 404.00 Without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
    - 404.01 With heart failure and with chronic kidney disease stage I through stage IV, or unspecified
    - 404.02 Without heart failure and with chronic kidney disease stage V or end stage renal disease
    - 404.03 With heart failure and chronic kidney disease stage V or end stage renal disease

        - 404.1 Benign
            - 404.10 Without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
            - 404.11 With heart failure and with chronic kidney disease stage I through stage IV, or unspecified
            - 404.12 Without heart failure and with chronic kidney disease stage V or end stage renal disease
            - 404.13 With heart failure and chronic kidney disease stage V or end stage renal disease
        - 404.9 Unspecified
            - 404.90 Without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
            - 404.91 With heart failure and with chronic kidney disease stage I through stage IV, or unspecified
            - 404.92 Without heart failure and with chronic kidney disease stage V or end stage renal disease
            - 404.93 With heart failure and chronic kidney disease stage V or end stage renal disease
    - 405 Secondary hypertension
        - 405.0 Malignant
            - 405.01 Renovascular
            - 405.09 Other
        - 405.1 Benign
            - 405.11 Renovascular
            - 405.19 Other
        - 405.9 Unspecified
            - 405.91 Renovascular
            - 405.99 Other
- Coronary heart disease
    - 410 Acute myocardial infarction
        - 410.0 Of anterolateral wall
            - 410.00 Episode of care unspecified
            - 410.01 Initial episode of care

- 410.02 Subsequent episode of care

- 410.1 Of other anterior wall
  - 410.10 Episode of care unspecified
  - 410.11 Initial episode of care
  - 410.12 Subsequent episode of care
- 410.2 Of inferolateral wall
  - 410.20 Episode of care unspecified
  - 410.21 Initial episode of care
  - 410.22 Subsequent episode of care
- 410.3 Of inferoposterior wall
  - 410.30 Episode of care unspecified
  - 410.31 Initial episode of care
  - 410.32 Subsequent episode of care
- 410.4 Of other inferior wall
  - 410.40 Episode of care unspecified
  - 410.41 Initial episode of care
  - 410.42 Subsequent episode of care
- 410.5 Of other lateral wall
  - 410.50 Episode of care unspecified
  - 410.51 Initial episode of care
  - 410.52 Subsequent episode of care
- 410.6 True posterior wall infarction
  - 410.60 Episode of care unspecified
  - 410.61 Initial episode of care
  - 410.62 Subsequent episode of care
- 410.7 Subendocardial infarction
  - 410.70 Episode of care unspecified
  - 410.71 Initial episode of care
  - 410.72 Subsequent episode of care

- 410.8 Of other specified sites
    - 410.80 Episode of care unspecified
    - 410.81 Initial episode of care
    - 410.82 Subsequent episode of care
- 410.9 Unspecified site
    - 410.90 Episode of care unspecified
    - 410.91 Initial episode of care
    - 410.92 Subsequent episode of care

- 411 Other acute and subacute forms of ischemic heart disease
    - 411.0 Postmyocardial infarction syndrome
    - 411.1 Intermediate coronary syndrome
    - 411.8 Other
        - 411.81 Acute coronary occlusion without myocardial infarction
        - 411.89 Other
- 412 Old myocardial infarction
- 413 Angina pectoris
    - 413.0 Angina decubitus
    - 413.1 Prinzmetal angina
    - 413.9 Other and unspecified angina pectoris
- 414 Other forms of chronic ischemic heart disease
    - 414.0 Coronary atherosclerosis
        - 414.00 Of unspecified type of vessel, native or graft
        - 414.01 Of native coronary artery
        - 414.02 Of autologous biological bypass graft
        - 414.03 Of nonautologous biological bypass graft
        - 414.04 Of artery bypass graft
        - 414.05 Of unspecified type of bypass graft
        - 414.06 Of native coronary artery of transplanted heart
        - 414.07 Of bypass graft (artery) (vein) of transplanted heart

        - 414.1 Aneurysm and dissection of heart
            - 414.10 Aneurysm of heart (wall)
            - 414.11 Aneurysm of coronary vessels
            - 414.12 Dissection of coronary artery
            - 414.19 Other aneurysm of heart
        - 414.2 Chronic total occlusion of coronary artery
        - 414.3 Coronary atherosclerosis due to lipid rich plaque
        - 414.4 Coronary atherosclerosis due to calcified coronary lesion
        - 414.8 Other specified forms of chronic ischemic heart disease
        - 414.9 Chronic ischemic heart disease, unspecified
- 427 Arrhythmia:
    - 427.0 Paroxysmal supraventricular tachycardia
    - 427.1 Paroxysmal ventricular tachycardia
    - 427.2 Paroxysmal tachycardia, unspecified
    - 427.3 Atrial fibrillation and flutter
        - 427.31 Atrial fibrillation
        - 427.32 Atrial flutter
    - 427.4 Ventricular fibrillation and flutter
        - 427.41 Ventricular fibrillation
        - 427.42 Ventricular flutter
    - 427.5 Cardiac arrest
    - 427.6 Premature beats
        - 427.60 Premature beats, unspecified
        - 427.61 Supraventricular premature beats
        - 427.69 Other
    - 427.8 Other specified cardiac dysrhythmias
        - 427.81 Sinoatrial node dysfunction
        - 427.89 Other
    - 427.9 Cardiac dysrhythmia, unspecified
- 428 Heart failure

- 428.0 Congestive heart failure, unspecified
- 428.1 Left heart failure
- 428.2 Systolic heart failure
  - 428.20 Unspecified
  - 428.21 Acute
  - 428.22 Chronic
  - 428.23 Acute on chronic
- 428.3 Diastolic heart failure
  - 428.30 Unspecified
  - 428.31 Acute
  - 428.32 Chronic
  - 428.33 Acute on chronic
- 428.4 Combined systolic and diastolic heart failure
  - 428.40 Unspecified
  - 428.41 Acute
  - 428.42 Chronic
  - 428.43 Acute on chronic
- 428.9 Heart failure, unspecified

- Cerebrovascular disease:
  - 430 Subarachnoid hemorrhage
  - 431 Intracerebral hemorrhage
  - 432 Other and unspecified intracranial hemorrhage
    - 432.0 Nontraumatic extradural hemorrhage
    - 432.1 Subdural hemorrhage
    - 432.9 Unspecified intracranial hemorrhage
  - 433 Occlusion and stenosis of precerebral arteries
    - 433.0 Basilar artery
      - 433.00 Without mention of cerebral infarction
      - 433.01 With cerebral infarction
    - 433.1 Carotid artery

        - 433.10 Without mention of cerebral infarction
        - 433.11 With cerebral infarction
    - 433.2 Vertebral artery
        - 433.20 Without mention of cerebral infarction
        - 433.21 With cerebral infarction
    - 433.3 Multiple and bilateral
        - 433.30 Without mention of cerebral infarction
        - 433.31 With cerebral infarction
    - 433.8 Other specified precerebral artery
        - 433.80 Without mention of cerebral infarction
        - 433.81 With cerebral infarction
    - 433.9 Unspecified precerebral artery
        - 433.90 Without mention of cerebral infarction
        - 433.91 With cerebral infarction
- 434 Occlusion of cerebral arteries
    - 434.0 Cerebral thrombosis
        - 434.00 Without mention of cerebral infarction
        - 434.01 With cerebral infarction
    - 434.1 Cerebral embolism
        - 434.10 Without mention of cerebral infarction
        - 434.11 With cerebral infarction
    - 434.9 Cerebral artery occlusion, unspecified
        - 434.90 Without mention of cerebral infarction
        - 434.91 With cerebral infarction
- 435 Transient cerebral ischemia
    - 435.0 Basilar artery syndrome
    - 435.1 Vertebral artery syndrome
    - 435.2 Subclavian steal syndrome
    - 435.3 Vertebrobasilar artery syndrome

- 435.8 Other specified transient cerebral ischemias
- 435.9 Unspecified transient cerebral ischemia

- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other and ill-defined cerebrovascular disease
  - 437.0 Cerebral atherosclerosis
  - 437.1 Other generalized ischemic cerebrovascular disease
  - 437.2 Hypertensive encephalopathy
  - 437.3 Cerebral aneurysm, nonruptured
  - 437.4 Cerebral arteritis
  - 437.5 Moyamoya disease
  - 437.6 Nonpyogenic thrombosis of intracranial venous sinus
  - 437.7 Transient global amnesia
  - 437.8 Other
  - 437.9 Unspecified
- 438 Late effects of cerebrovascular disease
  - 438.0 Cognitive deficits
  - 438.1 Speech and language deficits
    - 438.10 Speech and language deficit, unspecified
    - 438.11 Aphasia
    - 438.12 Dysphasia
    - 438.13 Dysarthria
    - 438.14 Fluency disorder
    - 438.19 Other speech and language deficits
  - 438.2 Hemiplegia/hemiparesis
    - 438.20 Hemiplegia affecting unspecified side
    - 438.21 Hemiplegia affecting dominant side
    - 438.22 Hemiplegia affecting nondominant side
  - 438.3 Monoplegia of upper limb
    - 438.30 Monoplegia of upper limb affecting unspecified side

- 438.31 Monoplegia of upper limb affecting dominant side
- 438.32 Monoplegia of upper limb affecting nondominant side

- 438.4 Monoplegia of lower limb
  - 438.40 Monoplegia of lower limb affecting unspecified side
  - 438.41 Monoplegia of lower limb affecting dominant side
  - 438.42 Monoplegia of lower limb affecting nondominant side
- 438.5 Other paralytic syndrome
  - 438.50 Other paralytic syndrome affecting unspecified side
  - 438.51 Other paralytic syndrome affecting dominant side
  - 438.52 Other paralytic syndrome affecting nondominant side
  - 438.53 Other paralytic syndrome, bilateral
- 438.6 Alterations of sensations
- 438.7 Disturbances of vision
- 438.8 Other late effects of cerebrovascular disease
  - 438.81 Apraxia
  - 438.82 Dysphagia
  - 438.83 Facial weakness
  - 438.84 Ataxia
  - 438.85 Vertigo
  - 438.89 Other late effects of cerebrovascular disease
- 438.9 Unspecified late effects of cerebrovascular disease

- 443 Peripheral vascular disease
  - 443.0 Raynaud's syndrome
  - 443.1 Thromboangiitis obliterans [Buerger's disease]
  - 443.2 Other arterial dissection
    - 443.21 Dissection of carotid artery
    - 443.22 Dissection of iliac artery
    - 443.23 Dissection of renal artery
    - 443.24 Dissection of vertebral artery

        - 443.29 Dissection of other artery
    - 443.8 Other specified peripheral vascular diseases
        - 443.81 Peripheral angiopathy in diseases classified elsewhere
        - 443.82 Erythromelalgia
        - 443.89 Other
    - 443.9 Peripheral vascular disease, unspecified
- Venous thromboembolism:
    - 415 Acute pulmonary heart disease
        - 415.1 Pulmonary embolism and infarction
            - 415.11 Iatrogenic pulmonary embolism and infarction
            - 415.13 Saddle embolus of pulmonary artery
            - 415.19 Other
    - 416 Chronic pulmonary heart disease
        - 416.2 Chronic pulmonary embolism
    - 451 Phlebitis and thrombophlebitis
        - 451.0 Of superficial vessels of lower extremities
        - 451.1 Of deep vessels of lower extremities
            - 451.11 Femoral vein (deep) (superficial)
            - 451.19 Other
        - 451.2 Of lower extremities, unspecified
        - 451.8 Of other sites
            - 451.81 Iliac vein
            - 451.82 Of superficial veins of upper extremities
            - 451.83 Of deep veins of upper extremities
            - 451.84 Of upper extremities, unspecified
            - 451.89 Other
        - 451.9 Of unspecified site
    - 452 Portal vein thrombosis
    - 453 Other venous embolism and thrombosis

- 453.0 Budd-Chiari syndrome
- 453.1 Thrombophlebitis migrans
- 453.2 Of inferior vena cava
- 453.3 Of renal vein
- 453.4 Acute venous embolism and thrombosis of deep vessels of lower extremity
    - 453.40 Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
    - 453.41 Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
    - 453.42 Acute venous embolism and thrombosis of deep vessels of distal lower extremity
- 453.5 Chronic venous embolism and thrombosis of deep vessels of lower extremity
    - 453.50 Chronic venous embolism and thrombosis of unspecified deep vessels of lower extremity
    - 453.51 Chronic venous embolism and thrombosis of deep vessels of proximal lower extremity
    - 453.52 Chronic venous embolism and thrombosis of deep vessels of distal lower extremity
- 453.6 Venous embolism and thrombosis of superficial vessels of lower extremity
- 453.7 Chronic venous embolism and thrombosis of other specified vessels
    - 453.71 Chronic venous embolism and thrombosis of superficial veins of upper extremity
    - 453.72 Chronic venous embolism and thrombosis of deep veins of upper extremity
    - 453.73 Chronic venous embolism and thrombosis of upper extremity, unspecified
    - 453.74 Chronic venous embolism and thrombosis of axillary veins
    - 453.75 Chronic venous embolism and thrombosis of subclavian veins
    - 453.76 Chronic venous embolism and thrombosis of internal jugular veins
    - 453.77 Chronic venous embolism and thrombosis of other thoracic veins
    - 453.79 Chronic venous embolism and thrombosis of other specified veins
- 453.8 Acute venous embolism and thrombosis of other specified veins

- 453.81 Acute venous embolism and thrombosis of superficial veins of upper extremity
- 453.82 Acute venous embolism and thrombosis of deep veins of upper extremity
- 453.83 Acute venous embolism and thrombosis of upper extremity, unspecified
- 453.84 Acute venous embolism and thrombosis of axillary veins
- 453.85 Acute venous embolism and thrombosis of subclavian veins
- 453.86 Acute venous embolism and thrombosis of internal jugular veins
- 453.87 Acute venous embolism and thrombosis of other thoracic veins
- 453.89 Acute venous embolism and thrombosis of other specified veins

        - 453.9 Of unspecified site

    - 459 Other disorders of circulatory system
        - 459.1 Postphlebitic syndrome
            - 459.10 Postphlebitic syndrome without complications
            - 459.11 Postphlebitic syndrome with ulcer
            - 459.12 Postphlebitic syndrome with inflammation
            - 459.13 Postphlebitic syndrome with ulcer and inflammation
            - 459.19 Postphlebitic syndrome with other complication

- Pneumonia:
    - 480 Viral pneumonia
        - 480.0 Pneumonia due to adenovirus
        - 480.1 Pneumonia due to respiratory syncytial virus
        - 480.2 Pneumonia due to parainfluenza virus
        - 480.3 Pneumonia due to SARS-associated coronavirus
        - 480.8 Pneumonia due to other virus not elsewhere classified
        - 480.9 Viral pneumonia, unspecified
    - 481 Pneumococcal pneumonia
    - 482 Other bacterial pneumonia
        - 482.0 Pneumonia due to Klebsiella pneumoniae
        - 482.1 Pneumonia due to Pseudomonas

- 482.2 Pneumonia due to Hemophilus influenzae [H. influenzae]
- 482.3 Pneumonia due to Streptococcus
    - 482.30 Streptococcus, unspecified
    - 482.31 Group A
    - 482.32 Group B
    - 482.39 Other Streptococcus
- 482.4 Pneumonia due to Staphylococcus
    - 482.40 Pneumonia due to Staphylococcus, unspecified
    - 482.41 Methicillin susceptible pneumonia due to Staphylococcus aureus
    - 482.42 Methicillin resistant pneumonia due to Staphylococcus aureus
    - 482.49 Other Staphylococcus pneumonia
- 482.8 Pneumonia due to other specified bacteria
    - 482.81 Anaerobes
    - 482.82 Escherichia coli [E. coli]
    - 482.83 Other gram-negative bacteria
    - 482.84 Legionnaires' disease
    - 482.89 Other specified bacteria
- 482.9 Bacterial pneumonia unspecified

○ 483 Pneumonia due to other specified organism

- 483.0 Mycoplasma pneumoniae
- 483.1 Chlamydia
- 483.8 Other specified organism

○ 484 Pneumonia in infectious diseases classified elsewhere

- 484.1 Pneumonia in cytomegalic inclusion disease
- 484.3 Pneumonia in whooping cough
- 484.5 Pneumonia in anthrax
- 484.6 Pneumonia in aspergillosis
- 484.7 Pneumonia in other systemic mycoses
- 484.8 Pneumonia in other infectious diseases classified elsewhere

- 485 Bronchopneumonia, organism unspecified
- 486 Pneumonia, organism unspecified

- Obstructive pulmonary disease:
  - 490 Bronchitis, not specified as acute or chronic
  - 491 Chronic bronchitis
    - 491.0 Simple chronic bronchitis
    - 491.1 Mucopurulent chronic bronchitis
    - 491.2 Obstructive chronic bronchitis
    - 491.20 Without exacerbation
      - 491.21 With (acute) exacerbation
      - 491.22 With acute bronchitis
    - 491.8 Other chronic bronchitis
    - 491.9 Unspecified chronic bronchitis
  - 492 Emphysema
    - 492.0 Emphysematous bleb
    - 492.8 Other emphysema
  - 493 Asthma
    - 493.0 Extrinsic asthma
      - 493.00 Unspecified
      - 493.01 With status asthmaticus
      - 493.02 With (acute) exacerbation
    - 493.1 Intrinsic asthma
      - 493.10 Unspecified
      - 493.11 With status asthmaticus
      - 493.12 With (acute) exacerbation
    - 493.2 Chronic obstructive asthma
      - 493.20 Unspecified
      - 493.21 With status asthmaticus
      - 493.22 With (acute) exacerbation

- 494 Bronchiectasis
    - 494.0 Bronchiectasis without acute exacerbation
    - 494.1 Bronchiectasis with acute exacerbation
- 495 Extrinsic allergic alveolitis
    - 495.0 Farmers' lung
    - 495.1 Bagassosis
    - 495.2 Bird-fanciers' lung
    - 495.3 Suberosis
    - 495.4 Malt workers' lung
    - 495.5 Mushroom workers' lung
    - 495.6 Maple bark-strippers' lung
    - 495.7 "Ventilation" pneumonitis
    - 495.8 Other specified allergic alveolitis and pneumonitis
    - 495.9 Unspecified allergic alveolitis and pneumonitis
- 496 Chronic airway obstruction, not elsewhere classified

- Liver disease:
    - 571 Chronic liver disease and cirrhosis
        - 571.0 Alcoholic fatty liver
        - 571.1 Acute alcoholic hepatitis
        - 571.2 Alcoholic cirrhosis of liver
        - 571.3 Alcoholic liver damage, unspecified
        - 571.4 Chronic hepatitis
            - 571.40 Chronic hepatitis, unspecified
            - 571.41 Chronic persistent hepatitis
            - 571.42 Autoimmune hepatitis
            - 571.49 Other
        - 571.5 Cirrhosis of liver without mention of alcohol
        - 571.6 Biliary cirrhosis
        - 571.8 Other chronic nonalcoholic liver disease
        - 571.9 Unspecified chronic liver disease without mention of alcohol

- 572 Liver abscess and sequelae of chronic liver disease
  - 572.2 Hepatic encephalopathy
  - 572.3 Portal hypertension
  - 572.4 Hepatorenal syndrome
  - 572.8 Other sequelae of chronic liver disease
- 573 Other disorders of liver
  - 573.0 Chronic passive congestion of liver
  - 573.5 Hepatopulmonary syndrome
  - 573.8 Other specified disorders of liver
  - 573.9 Unspecified disorder of liver

- 585 Chronic kidney disease
  - 585.1 Chronic kidney disease, Stage I
  - 585.2 Chronic kidney disease, Stage II (mild)
  - 585.3 Chronic kidney disease, Stage III (moderate)
  - 585.4 Chronic kidney disease, Stage IV (severe)
  - 585.5 Chronic kidney disease, Stage V
  - 585.6 End stage renal disease
  - 585.9 Chronic kidney disease, unspecified
- Urinary tract infection:
  - 590 Infections of kidney
    - 590.0 Chronic pyelonephritis
      - 590.00 Without lesion of renal medullary necrosis
      - 590.01 With lesion of renal medullary necrosis
    - 590.1 Acute pyelonephritis
      - 590.10 Without lesion of renal medullary necrosis
      - 590.11 With lesion of renal medullary necrosis
    - 590.2 Renal and perinephric abscess
    - 590.3 Pyeloureteritis cystica
    - 590.8 Other pyelonephritis or pyonephrosis, not specified as acute or chronic
      - 590.80 Pyelonephritis, unspecified

        - 590.81 Pyelitis or pyelonephritis in diseases classified elsewhere
    - 590.9 Infection of kidney, unspecified
  - 595 Cystitis
    - 595.0 Acute cystitis
    - 595.1 Chronic interstitial cystitis
    - 595.2 Other chronic cystitis
    - 595.3 Trigonitis
    - 595.4 Cystitis in diseases classified elsewhere
    - 595.8 Other specified types of cystitis
        - 595.81 Cystitis cystica
        - 595.89 Other
    - 595.9 Cystitis, unspecified
  - 597 Urethritis, not sexually transmitted, and urethral syndrome
    - 597.0 Urethral abscess
    - 597.8 Other urethritis
    - 597.80 Urethritis, unspecified
        - 597.81 Urethral syndrome NOS
        - 597.89 Other
  - 599 Other disorders of urethra and urinary tract
    - 599.0 Urinary tract infection, site not specified
- Urinary lithiasis
  - 591 Hydronephrosis
  - 592 Calculus of kidney and ureter
    - 592.0 Calculus of kidney
    - 592.1 Calculus of ureter
    - 592.9 Urinary calculus, unspecified
  - 594 Calculus of lower urinary tract
    - 594.0 Calculus in diverticulum of bladder
    - 594.1 Other calculus in bladder
    - 594.2 Calculus in urethra

        - 594.8 Other lower urinary tract calculus
        - 594.9 Calculus of lower urinary tract, unspecified
- Rheumatological disease
    - 710 Diffuse diseases of connective tissue
        - 710.0 Systemic lupus erythematosus
        - 710.1 Systemic sclerosis
        - 710.2 Sicca syndrome
        - 710.3 Dermatomyositis
        - 710.4 Polymyositis
        - 710.5 Eosinophilia myalgia syndrome
        - 710.8 Other specified diffuse diseases of connective tissue
        - 710.9 Unspecified diffuse connective tissue disease
    - 714 Rheumatoid arthritis and other inflammatory polyarthropathies
        - 714.0 Rheumatoid arthritis
        - 714.1 Felty's syndrome
        - 714.2 Other rheumatoid arthritis with visceral or systemic involvement
        - 714.3 Juvenile chronic polyarthritis
            - 714.30 Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
            - 714.31 Polyarticular juvenile rheumatoid arthritis, acute
            - 714.32 Pauciarticular juvenile rheumatoid arthritis
            - 714.33 Monoarticular juvenile rheumatoid arthritis
        - 714.4 Chronic postrheumatic arthropathy
        - 714.8 Other specified inflammatory polyarthropathies
            - 714.81 Rheumatoid lung
            - 714.89 Other
        - 714.9 Unspecified inflammatory polyarthropathy
- 995 Sepsis
    - 995.91 Sepsis
    - 995.92 Severe sepsis