Original Article

Type 2 diabetes mellitus and hypertension as predictors of community-acquired pneumonia in Peruvian older adults with cancer

Diabetes mellitus tipo 2 e hipertensión arterial como predictores de neumonía adquirida en la comunidad en adultos mayores peruanos con cáncer

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ABSTRACT

Objetive: To evaluate DM2 and hypertension as predictors of CAP in older adults with cancer. **Material and Methods:** We conducted a secondary data analysis of a prospective cohort study in older adults with cancer from the Geriatrics Service of the Centro Médico Naval (CEMENA) of Peru during 2013-2015. T2DM and hypertension diagnosis were obtained from medical records. CAP was defined according to clinical and radiological diagnostic criteria and it was collected from the medical records of the patients up to one year after their inclusion in the study. We used the statistical software STATA v14.0 to develop the analysis. We performed multivariate analysis using crude and adjusted Cox regression models. The reported measure was the hazard ratio (HR) with their respective 95% confidence intervals (95%CI). **Results:** A total of 231 older adults with cancer were analyzed. The mean age of the participants was 78.6 ± 4.2 (range: 74-92 years) and all of them were men. 33 (14.29%) patients developed CAP during the follow-up, 53 (21.65%) had hypertension, and 56 (22.65%) T2DM. CAP was more frequent in patients with lung cancer and lymphomas. In the adjusted Cox regression models, we found T2DM (aHR=1.49; 95%CI: 1.21-1.79) and hypertension (aHR=1.32; 95%CI: 1.24-1.50) were predictors of CAP incidence. **Conclusion:** T2DM and hypertension were associated with CAP incidence in oncogeriatric patients. Future intervention studies are needed to improve the functionality and prevent CAP in this vulnerable population.

Keywords: cancer; aged; diabetes mellitus; hypertension; pneumonia (Source: DeCS-BIREME).

RESUMEN

Objetivo: Evaluar la DM2 y la hipertensión como predictores de NAC en adultos mayores con cáncer. **Materiales y métodos:** Se realizó un análisis de base secundaria de una cohorte prospectiva en adultos mayores con diagnóstico de cáncer del Servicio de Geriatría del Centro Médico Naval (CEMENA) del Perú durante 2013-2015. Los diagnósticos de DM2 e hipertensión se obtuvieron de las historias clínicas. La NAC se definió según criterios diagnósticos clínicos y radiológicos y se recogió de las historias clínicas de los pacientes hasta un año después de su inclusión en el estudio. Utilizamos el software estadístico STATA v14.0 para desarrollar el análisis. Realizamos un análisis multivariante utilizando modelos de regresión de Cox crudos y ajustados. La medida reportada fue la razón de hazards (HR) con sus respectivos intervalos de confianza del 95% (IC95%). **Resultados:** Se analizaron un total de 231 adultos mayores con cáncer. La edad media de los participantes fue de 78,6 ± 4,2 (rango: 74-92 años) y todos ellos eran hombres. 33 (14,29%) pacientes desarrollaron NAC durante el seguimiento, 53 (21,65%) tenían hipertensión y 56 (22,65%) DM2. La NAC fue más frecuente en pacientes con cáncer de pulmón y linfomas. En los modelos de regresión de Cox ajustados se encontró que tener DM2 (HRa=1,49; IC95%: 1,21-1,79) o hipertensión arterial (HRa=1,32; IC95%: 1,24-1,50) fueron predictores

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para la incidencia de NAC. **Conclusiones:** La DM2 y la hipertensión se asociaron con la incidencia de NAC en pacientes oncogeriátricos. Son necesarios futuros estudios de intervención para mejorar la funcionalidad y prevenir la NAC en esta población vulnerable.

Palabras Clave: cáncer; adulto mayor; diabetes mellitus; hipertensión; neumonía. (Fuente: DeCS-BIREME).

INTRODUCTION

Neoplastic diseases in older adults are associated with disability and mortality[1]. A study carried out in France reported that about a third of oncogeriatric patients present disabilities[2]. Frequently, the usual forms of neoplastic complication are infections, being community-acquired pneumonia (CAP), one of the most common[3]. Cancer causes immunological changes such as neutropenia, cellular immunity deficit, and dysfunction of humoral immunity[4]. Therefore, about 80 % of oncologic patients develop any kind of infection during treatment[3,5,6]. However, the risk of getting infections is not only increased by the presence of cancer; there are other predisposing factors for the appearance of infectious diseases[5,7].

A systematic review described advanced age, immunosuppression, cardiovascular diseases, and type 2 diabetes mellitus (T2DM) as predictors of CAP[8]. Besides, a meta-analysis concluded that diabetic patients had an increased risk of suffering from cancer; however, important variables such as glycated hemoglobin (HbA1c) and duration of T2DM were not available in a considerable number of studies. Thus, it was difficult to determine whether the increased risk of cancer was attributable to T2DM[9]. Additionally, a previous study described T2DM as the only comorbid risk factor for death causes by CAP in non-oncologic geriatric patients[10] due to the association between insulin resistance and physical inactivity, which could lead to an autoimmune dysfunction[11]. Besides, a Spanish cohort study reported that 9% of older adults developed CAP at least once, being age, immunosuppression, T2DM, and heart failure the main risk factors[12]. Although CAP can develop in any age group, the risk in older adults was four times higher[8].

CAP can also coexist with other comorbidities. Previous studies described the association between hypertension and CAP in older adults with cerebrovascular diseases[13]; however, there is not yet a physiopathological connection to explain the relationship between CAP and hypertension in oncologic patients[10]. A study carried out by Shen Y. et al. mentioned that hypertension can coexist with lung cancer, resulting in an increased risk of suffering from venous thromboembolism; therefore, the impact of hypertension and cancer should be evaluated[14].

Previous studies have evaluated the association between T2DM and CAP, as well as its possible association with hypertension; however, there is no consensus. Likewise, this association could be more relevant in older adults with cancer due to their immunological status. For this reason, we aimed to assess the role of hypertension and T2DM as risk factors for CAP in oncogeriatric patients.

MATERIAL AND METHODS

Design and population
We conducted a secondary data analysis from a prospective cohort study in older adults from the Geriatrics Service of the Centro Médico Naval (CEMENA, by its initials in Spanish) during 2013-2015. The Geriatrics Service of CEMENA provides medical care to active or retired naval veterans and their family members. This study included male adults over 60 years with the pathological diagnosis of cancer and was diagnosed at CEMENA between September 2012 to November 2013; and have not begun treatment yet. All the participants received oncologic therapy with curative intent.

We included 317 patients in the study and 86 were excluded: 16 patients due to the presence of dementia and 33 because they obtained a score ≤23 in the Mini-Mental State Examination (MMSE), a tool used to evaluate cognitive impairment. Besides, 18 patients did not decide to participate in the study: 4 patients did not count with the variables of interest; 12 still did not have indications for oncologic treatment sessions, and 3 requested early retirement during the development of the study. Finally, data from 231 participants could be analyzed.

Procedure
The patients included in the study were asked to sign an informed consent. A month after signing for inclusion, a form indicating the report of the case was developed. This form included medical history, sociodemographic data, anthropometric measurements, continuous measurements of blood pressure, laboratory tests related to pathological findings of T2DM and CAP, questionnaires for mental assessments, and data associated with the oncologic disease for which they were recruited.

Variables
Outcome: community-acquired pneumonia (CAP)
CAP was defined by the clinical and radiological diagnostic criteria made by internists, pneumologists, and geriatricians of CEMENA. This information was collected from the medical records of the patients up to one year after their inclusion in the study. We considered the outcome if the patient presented at least one pneumonic episode during a year of follow-up. The patients with hospital-acquired pneumonia or aspiration pneumonia were excluded.

Exposure: hypertension and type 2 diabetes mellitus (T2DM)
The presence of hypertension or T2DM as comorbidities were extracted from the medical records of the patients and corroborated by the companion of the older adult during the medical evaluation.

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Other variables
Sociodemographic characteristics
We included the following sociodemographic variables: age (years) and marital status (single, married, divorced, widowed). The sociodemographic information was obtained from the medical record of the participant.

Medical background
The following variables were included: chronic obstructive pulmonary disease (yes or no) and body mass index (BMI) expressed in kg/m2. The measurements of size and weight to evaluate the nutritional status were obtained at the beginning of the follow-up. Polypharmacy was also considered, defined as the use of 5 or more drugs, under medical prescription[15].

Functional assessment
The Short Physical Performance Battery (SPPB) was used to evaluate the physical performance of the participants. SPPB is an instrument that includes three timed tasks: standing balance, walking or gait speed, and five repetitive chair stands. The timed results of each subtest are rescaled according to predefined cut points for obtaining a score ranging from 0 (worst performance) to 12 (best performance)[16].

We used the Lawton Index, a questionnaire about instrumental activities of daily living (IADL): use of the telephone, shopping, food preparation, housekeeping, laundry, transportation method, use of medications, and handling finances. The Lawton index scores range from 0 to 8[17].

Mental assessment
We used the Montreal Cognitive Assessment (MoCA), a questionnaire to evaluate cognitive impairment in older adults. It was considered the education level to obtain the score (maximum of 30 points)[18].

The five-item Yesavage questionnaire was used to measure depressive symptoms in the participants[19]. This questionnaire scores vary from 0 to 5.

Statistical analysis
We used the statistical software STATA v14.0 for our analysis. The descriptive results were described using measures of central tendency, dispersion measures, absolute and relative frequencies. The bivariate analysis comparing the results of patients with or without CAP was performed using the Chi-square test, Fisher´s exact test, and the Student t-test, as appropriate.

Multivariate analysis to evaluate the association between exposure variables and CAP was performed using Cox regression models. Three models were elaborated (1 crude and 2 adjusted models) to assess our association of interest. The adjusted models were carried out with an epidemiologist criterion including age, chronic obstructive pulmonary disease, the number of drugs, functional and cognitive tests, body mass index, and type of cancer. The reported measure was the hazard ratio (HR) with their respective 95% confidence interval (95%CI).

Ethical aspects
The study was developed, preserving the functional, cognitive, psychological, and social integrity of the patients included in the study. We obtained the informed consent of the participant's prior data collection. Also, the research project was evaluated and approved by CEMENA's Ethics Institutional Review Board.

RESULTS

General description of the study sample
A total of 231 older adults with the diagnosis of cancer were analyzed. The mean age of the participants was 78.6 ± 4.2 (range: 74-92 years) and all of them were men. 33 (14.29%) patients developed CAP during the follow-up, 53 (21.65%) had hypertension, and 56 (22.65%) T2DM. We found that the participants who developed CAP had a higher mean age (78.2 vs. 75.2; p=0.001), a lower SPPB mean (5.05 vs. 8.92; p=0.0001), a lower MoCA mean (15.48 vs. 23.26; p=0.0001), a higher mean of drugs used (7.02 vs. 4.62; p=0.02), as well as a higher prevalence of lung cancer (33.33% vs. 16.16%; p=0.0001) and lymphoma (24.24% vs. 11.62%; p=0.001), compared to those who did not develop CAP during follow-up (Table1).

Table 1. General description of the study population (N=231).

Variables	n	%	Mean ± SD	CAP during follow-up Yes n=33 (14.29%)	No n=198 (85.71%)	p-value
Age (year-specific)			78,6 ± 4,2	78,2 ± 3,3	75,2 ± 3,6	0,001
Marital status						-
Single	19	8,23		1 (3,03)	18 (89,09)	
Married/Partner	127	54,98		17 (51,52)	110 (55,56)	
Divorced	35	15,15		7 (21,21)	28 (14,14)	
Widowed	50	21,65		8 (24,24)	42 (2,12)	
Comorbidities						
Hypertension	53	21,65		14 (42,42)	39 (19,70)	0,001
COPD	39	16,02		11 (33,33)	28 (14,14)	0,0001
T2DM	56	22,65		16 (48,48)	40 (20,20)	0,0001
Body mass index			24,31 ± 3,01	23,31 ± 2,31	25,28 ± 2,23	0,05
Functional assessment						
SPPB			7,91 ± 1,04	5,05 ± 1,07	8,92 ± 1,13	0,0001
Lawton index			3,27 ± 0,49	1,62 ± 0,24	3,88 ± 0,76	0,05
Cognitive assessment						
Yesavage questionnaire			2,07 ± 0,45	2,81 ± 0,43	2,01 ± 0,23	0,04
MoCA			22,08 ± 1,98	15,48 ± 4,23	23,26 ± 3,64	0,0001
Number of drugs used			5,87 ± 1,13	7,02 ± 0,51	4,62 ± 1,33	0,02
Location of cancer						
Prostate	57	24,68		4 (12,12)	53 (26,77)	0,08
Stomach	38	16,45		2 (6,06)	36 (18,18)	0,1
Colon/rectum	39	16,88		4 (12,12)	35 (17,68)	0,1
Lung	43	18,61		11 (33,33)	32 (16,16)	0,0001
Pancreas	22	9,52		3 (9,09)	19 (9,60)	0,2
Lymphoma	31	13,42		8 (24,24)	23 (11,62)	0,0001
Kidney	1	0,43		1 (3,03)	0 (0)	-

SD: standard deviation; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes mellitus; SPPB: Short Performance Battery; MoCA: Montreal Cognitive Assessment.

In the oncogeriatric population included, the most common types of cancer in T2DM patients were: prostate cancer (26.79%), stomach (21.43%), pancreas (17.86%), colon/rectum (16.07%) and lung (14.29%). In contrast, the most common types of cancer in hypertensive patients were: prostate cancer (24.53%), colon/rectum (20.75%), stomach

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Table 2. Frequency of cancer location according to hypertension or type 2 diabetes mellitus.

Location of cancer	Hypertension n=53 (21.65%)		T2DM n=56 (22.65%)	
	Yes	No	Yes	No
Prostate	13 (24,53)	44 (83,01)	15 (26,79)	42 (75,00)
Stomach	10 (18,87)	28 (52,83)	12 (21,43)	26 (46,43)
Colon/rectum	11 (20,75)	28 (52,83)	9 (16,07)	30 (53,57)
Lung	8 (15,09)	35 (66,04)	8 (14,29)	35 (62,50)
Pancreas	6 (11,32)	16 (30,19)	10 (17,86)	11 (19,64)
Lymphoma	4 (7,58)	27 (50,94)	2 (3,57)	29 (51,79)
Kidney	1 (1,89)	0 (0)	0 (0)	1 (1,79)

T2DM: type 2 diabetes mellitus

Hypertension or type 2 diabetes mellitus as risk factors of community-acquired pneumonia in older adults with cancer
The development of CAP was more frequent in patients with hypertension (42.42% vs. 19.70%; p=0.0001) and T2DM (48.48% vs. 20.20%; p=0.0001), compared to those without these conditions (Table 1).

In the Cox regression models, adjusted for potential confounders, a statistically significant association was found between T2DM (HR=1.49; 95%CI: 1.21-1.79), hypertension (HR=1.32; 95%CI: 1.24-1.50), and the development of CAP (Table 3).

Table 3. Cox regression models to evaluate hypertension and type 2 diabetes mellitus as predictors of community-acquired pneumonia in oncogeriatric patients.

Variables	Crude model HR (95%CI)	Model 1: HR (95%CI)	Model 2: HR (95%CI)
Hypertension			
No	Reference	-	Reference
Yes	1.42 (1.31-1.56)	-	1.32 (1.24-1.50)
T2DM			
No	Reference	Reference	-
Yes	1.57 (1.25-1.88)	1.49 (1.21-1.79)	-

T2DM: type 2 diabetes mellitus; HR: hazard ratio; CI: confidence intervals.
Models 1 and 2 were adjusted for age, chronic obstructive pulmonary disease, number of drugs used, functional tests, cognitive tests. body mass index and type of cancer.

DISCUSSION

A total of 231 patients were evaluated, of which 14.29% developed CAP. The presence of CAP was higher in patients with lung cancer and lymphomas; furthermore, we found T2DM and hypertension were predictors of CAP incidence.

Previous studies have described the role of T2DM as a risk factor of suffering from a respiratory infection and increasing mortality[20,21], which could be higher in oncogeriatric patients[6]. Besides, this association was also described in patients with cardiovascular disease; however, they did not mention hypertension as a predictor of CAP incidence or mortality[22,23] or they did not find a significant association with this comorbidity and CAP[23]. In addition, other studies pointed out a significant association between T2DM and respiratory infections; nevertheless, these studies were not conducted in oncogeriatric patients who have suffered immunological and functional alterations due to cancer and therapy[6,20,21].

A previous study reported that patients with hyperinsulinemia had a higher probability of suffering cancer because insulin and insulin-like growth factor 1 (IGF-1) are the principal systemic hormones that activate the signaling routes involved in mitosis and the inhibition of apoptosis in the different human tissues[24]. Besides, it is necessary to consider aggravating factors for the development of cancer, such as body weight and physical inactivity that are also related to T2DM pathogenesis[25,26]. Prostate cancer was the most common cancer type in T2DM participants; this was also described in previous studies due to its association with increased levels of IGF; however, higher levels of IGF were also found in some types of cancer in women[27].

Studies have only investigated whether cardiovascular diseases are predisposing factors for CAP; however, they did not consider hypertension[22], or they did not find an association with it[23]. Nevertheless, the association between hypertension and CAP in older adults could be due to antihypertensive therapy. Previous studies have evaluated the role of angiotensin-converting enzyme (ACE) inhibitors in CAP incidence because they can cause cough in a substantial proportion of users[28,29]. Evidence suggests the use of beta-blockers, calcium channel blockers, and lipophilic ACE inhibitors increased the risk of CAP. However, this finding could differ according to genetic susceptibility rather than the ACE inhibitor by itself[28]. Recent findings support this hypothesis due to the association between ACE receptors and a higher risk of COVID-19 susceptibility and severity[30].

In this study, we found a statistically significant association between both chronic diseases and the development of CAP. Hypertension and T2DM pathogenesis occur with endothelial damage; however, the immunological alterations due to T2DM lead to a higher risk of CAP in older adults with cancer[31]. This could explain the greater association between T2DM and CAP. In addition, we found association between hypertension and the occurrence of CAP and despite we did not found several previous studies with this finding in older adults with cancer, they have described high systolic pressure as a risk factor for mortality and cancer incidence[23,32].

This is to our knowledge the first study that evaluated the association between hypertension and T2DM as predictors of CAP in oncogeriatric patients, who are more vulnerable to adverse outcomes. We found an association between T2DM, hypertension and the development of CAP. This finding could be due to the immunological and physiological changes occurring in oncogeriatric patients; however, functional reserve has an important role[33,34].

It has been described that older adults with T2DM and frailty have a higher risk of disability or death[29]. Also, sarcopenia and poor physical performance, which are one of the main physiopathological components of frailty, are risk factors for CAP in older adults[34]. In our study, the association between T2DM and CAP persisted after adjusting for physical performance. Then, it is necessary to conduct research studies to improve the functionality of older adults with comorbidities and cancer to reduce their mortality.

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This study has some limitations: 1) Due the follow-up of patients was only for 2 years, it exists the probability that later CAP events have not been recorded; 2) We did not collected antihypertensive therapy data and time of the disease from patients evaluated; however, this findings should be used to test pathophysiological hypothesis in future cohorts studies; 3) Main variables related to T2DM as antidiabetic treatment or complications as HbA1c and time of the disease were not collected; 4) We could not include relevant variables such as the severity of the CAP or the cancer severity; 5) The patients evaluated was formed exclusively by ex-marine men, whose physical performance and functionality could be different due to their military training; therefore, these results could not be representative to other oncogeriatric population; 6) We did not record the chemotherapy dose applied; then, this could lead to immunological changes and a higher risk of CAP; 7) During the follow-up we did not record information about previous influenza or pneumococcal vaccine, development of hematological complications such as neutropenia and mucositis that can increase the risk of CAP in oncologic patients [35].

In conclusion, T2DM and hypertension at the time of cancer diagnosis were associated with the development of CAP in oncogeriatric patients. It is necessary to carry out future studies evaluating the role of hypertension in the pathogenesis of CAP. Future intervention studies are needed to improve the functionality and prevent CAP in this vulnerable population.

BIBLIOGRAPHIC REFERENCES

1. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. Journal of Clinical Oncology 25 (14):1824-1831
2. Farcet A, De Decker L, Pauly V, Rousseau F, Bergman H, Molines C, Retornaz F (2016) Frailty markers and treatment decisions in patients seen in oncogeriatric clinics: results from the ASRO pilot study. PLoS One 11 (2):e0149732
3. Schmedt N, Heuer OD, Häckl D, Sato R, Theilacker C (2019) Burden of community-acquired pneumonia, predisposing factors and health-care related costs in patients with cancer. BMC health services research 19 (1):30
4. Cupp J, Culakova E, Poniewierski MS, Dale DC, Lyman GH, Crawford J (2018) Analysis of factors associated with in-hospital mortality in lung cancer chemotherapy patients with neutropenia. Clinical Lung Cancer 19 (2):e163-e169
5. Zoppini G, Fedeli U, Schievano E, Dauriz M, Targher G, Bonora E, Corti M (2018) Mortality from infectious diseases in diabetes. Nutrition, Metabolism and Cardiovascular Diseases 28 (5):444-450
6. Collaboration ERF (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. New England Journal of Medicine 364 (9):829-841
7. Nesher L, Rolston KV (2014) The current spectrum of infection in cancer patients with chemotherapy related neutropenia. Infection 42 (1):5-13
8. Torres A, Peetermans WE, Viegi G, Blasi F (2013) Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax 68 (11):1057-1065
9. Starup-Linde J, Karlstad O, Aistrup Eriksen S, Vestergaard P, K Bronsveld H, de Vries F, Andersen M, Auvinen A, Haukka J, Hjellvik V (2013) CARING (CAncer Risk and INsulin analoGues): the association of diabetes mellitus and cancer risk with focus on possible determinants-a systematic review and a meta-analysis. Current drug safety 8 (5):296-332
10. Manabe T, Mizukami K, Akatsu H, Hashizume Y, Ohkubo T, Kudo K, Hizawa N (2017) Factors associated with pneumonia-caused death in older adults with autopsy-confirmed dementia. Internal Medicine 56 (8):907-914
11. Chentli F, Azzoug S, Mahgoun S (2015) Diabetes mellitus in elderly. Indian journal of endocrinology and metabolism 19 (6):744
12. Dang T, Eurich D, Weir D, Marrie T, Majumdar S (2014) Rates and risk factors for recurrent pneumonia in patients hospitalized with community-acquired pneumonia: population-based prospective cohort study with 5 years of follow-up. Clinical infectious diseases 59 (1):74-80
13. Ishigami K, Okuro M, Koizumi Y, Satoh K, Iritani O, Yano H, Higashikawa T, Iwai K, Morimoto S (2012) Association of severe hypertension with pneumonia in elderly patients with acute ischemic stroke. Hypertension Research 35 (6):648-653
14. Shen Y, Tian Z, Lu D, Huang J, Zhang Z, Li X, Li J (2016) Impact of pneumonia and lung cancer on mortality of women with hypertension. Scientific reports 6 (1):1-9
15. Wastesson JW, Morin L, Tan EC, Johnell K (2018) An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert opinion on drug safety 17 (12):1185-1196
16. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. Journal of gerontology 49 (2):M85-M94
17. Graf C (2009) The Lawton instrumental activities of daily living (IADL) scale. The gerontologist 9 (3):179-186
18. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 53 (4):695-699
19. Del Valle RDD, Sánchez AH, Cano LR, Jentoft AC (2001) Validación de una versión de cinco ítems de la Escala de Depresión Geriátrica de Yesavage en población española. Revista Española de Geriatría y Gerontología 36 (5):276-280
20. López-de-Andrés A, de Miguel-Díez J, Jiménez-Trujillo I, Hernández-Barrera V, de Miguel-Yanes JM, Méndez-Bailón M, Pérez-Farinós N, ngel Salinero-Fort MÁ, Jiménez-García R (2017) Hospitalisation with community-acquired pneumonia among patients with type 2 diabetes: an observational population-based study in Spain from 2004 to 2013. BMJ open 7 (1)
21. Morros R, Vedia C, Giner-Soriano M, Casellas A, Amado E, Baena JM (2019) Neumonías adquiridas en la comunidad en pacientes con enfermedad pulmonar obstructiva crónica tratados con corticoides inhalados u otros broncodilatadores. Estudio PNEUMOCORT. Atención Primaria 51 (6):333-340
22. O'Meara ES, White M, Siscovick DS, Lyles MF, Kuller LH (2005) Hospitalization for pneumonia in the Cardiovascular Health Study: incidence, mortality, and influence on longer-term survival. Journal of the American Geriatrics Society 53 (7):1108-1116
23. Yeh J-J, Lin C-L, Kao C-H (2019) Relationship between pneumonia and cardiovascular diseases: A retrospective cohort study of the general population. European journal of internal medicine 59:39-45
24. Klement R, Fink M (2016) Dietary and pharmacological modification of the insulin/IGF-1 system: exploiting the full repertoire against cancer. Oncogenesis 5 (2):e193-e193
25. Giovannucci E (2018) A framework to understand diet, physical activity, body weight, and cancer risk. Cancer Causes & Control 29 (1):1-6
26. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, Ferlay J, Miranda JJ, Romieu I, Dikshit R (2015) Global burden of cancer attributable to high body-mass index in 2012: a population-based study. The Lancet Oncology 16 (1):36-46
27. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR (2015) Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis. European journal of cancer 51 (18):2747-2758
28. Mukamal KJ, Ghimire S, Pandey R, O'Meara ES, Gautam S (2010) Antihypertensive medications and risk of community-acquired pneumonia. Journal of hypertension 28 (2):401-405
29. Shah S, McArthur E, Farag A, Nartey M, Fleet JL, Knoll GA, Kim SJ, Garg AX, Jain AK (2014) Risk of hospitalization for community acquired pneumonia with renin-angiotensin blockade in elderly patients: a population-based study. PloS one 9 (10):e110165
30. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. New England Journal of Medicine 382 (17):1653-1659
31. Zhou T, Hu Z, Yang S, Sun L, Yu Z, Wang G (2018) Role of adaptive and innate immunity in type 2 diabetes mellitus. Journal of diabetes research 2018
32. Grossman E, Messerli FH, Boyko V, Goldbourt U (2002) Is there an association between hypertension and cancer mortality? The American journal of medicine 112 (6):479-486
33. Castro-Rodríguez M, Carnicero JA, Garcia-Garcia FJ, Walter S, Morley JE, Rodríguez-Artalejo F, Sinclair AJ, Rodríguez-Mañas L (2016) Frailty as a major factor in the increased risk of death and disability in older people with diabetes. Journal of the American Medical Directors Association 17 (10):949-955
34. Altuna-Venegas S, Aliaga-Vega R, Maguiña JL, Parodi JF, Runzer-Colmenares FM (2019) Risk of community-acquired pneumonia in older adults with sarcopenia of a hospital from Callao, Peru 2010-2015. Archives of gerontology and geriatrics 82:100-105
35. Wong JL, Evans SE (2017) Bacterial pneumonia in patients with cancer: novel risk factors and management. Clinics in chest medicine 38 (2):263-277.