# QUALITY OF LIFE AND CLINICAL CHARACTERISTICS OF RENAL TRANSPLANT PATIENTS WITH AND WITHOUT CHRONIC RHINOSINUSITIS

CALIDAD DE VIDA Y CARACTERÍSTICAS CLÍNICAS DE PACIENTES CON TRASPLANTE RENAL CON Y SIN RINOSINUSITIS CRÓNICA

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# ABSTRACT

Introduction: Transplantation is the treatment of choice for patients with chronic kidney disease (CKD). It requires immunosuppression, which predisposes to the development of complications; chronic rhinosinusitis (CRS) is one of the most significant. Objective: To compare the characteristics of patients with CKD and without CRS in a renal transplant protocol at a specialized hospital in Puebla, Mexico. Methods: A comparative, cross-sectional, retrospective study in patients with CKD and in renal transplant protocol at a third-level care hospital. The SNOT-22 and Lund-Mackay scales were applied. Descriptive statistics, Mann-Whitney U tests, Fisher's exact test, and Phi coefficient were used; p<0.05 was considered significant. Results: 360 patients were recruited: 49 presented with CRS; prevalence: 13.61%; mean age: 39.22 ± 12.09 years and duration of progression: 17.73 ± 5.91 weeks. Naso-sinusal polyposis was present in 14.3%; nasal obstruction in 95.9%; facial pain in 67.3%; rhinorrhea in 49% and hyposmia/anosmia in 40.8%. Associated risk factors: allergy to acetylsalicylic acid (p=0.014) and atopy (p=0.000). Anatomical variants in patients with and without CRS, respectively: Agger nasi cell 95% and 15.4%; septal deviation, 50% and 6.4%; turbinate hypertrophy, 50% and 1.3%; concha bullosa, 30% and 4.2%; and paradoxical turbinate, 10% and 1.6%. The predominant quality of life impact in patients with and without CRS was moderate at 53.1% and mild at 97.1% (p=0.000). Conclusion: The prevalence of CRS was 13.61%; the associated risk factors were allergy to acetylsalicylic acid and atopy, and the predominant anatomical variant was Agger nasi. The tomographic severity was mild, and the impact on quality of life was moderate.

Keywords: Quality of life; Sinusitis; Chronic kidney disease; Kidney transplantation. (Source: MESH-NLM)

# RESUMEN

Introducción: El trasplante es el tratamiento de elección en pacientes con enfermedad renal crónica (ERC). Requiere inmunosupresión, que predispone al desarrollo de complicaciones; la rinosinusitis crónica (RSC) es una de las más importantes. Objetivo: Comparar las características de pacientes con ERC con y sin RSC en protocolo de trasplante en un hospital de concentración en Puebla, en México. Métodos: Estudio comparativo, transversal, retrospectivo, en pacientes de un hospital de tercer nivel de atención, con ERC y en protocolo de trasplante renal. Se aplicaron las escalas SNOT-22 y Lund-Mackay. Se utilizó estadística descriptiva y pruebas U de Mann-Whitney, exacta de Fisher y coeficiente de Phi; p<0.05, por lo que se consideró significativa. Resultados: Se reclutaron 360 pacientes: 49 presentaron RSC; prevalencia, 13.61 %; medias edad, 39.22 ± 12.09 años y tiempo de evolución, 17.73 ± 5.91 semanas. Presentaron poliposis nasosinusal 14.3 %; obstrucción nasal, 95.9 %; algia facial, 67.3%; rinorrea, 49 % e hiposmia/anosmia, 40.8 %. Factores de riesgo asociados: alergia a ácido acetilsalicílico (p=0.014) y atopia (p=0.000). Variantes anatómicas en pacientes con y sin RSC, respectivamente: Celdilla Agger-Nasi 95 % y 15.4 %; desviación septal, 50 % y 6.4 %; hipertrofia de cornetes, 50 % y 1.3 %; concha bullosa, 30 % y 4.2 % y cornete paradójico, 10 % y 1.6 %. La afectación de calidad de vida predominante en pacientes con y sin RSC fue moderada con un 53.1 % y leve, 97.1 % (p=0.000). Conclusión: La prevalencia de RSC fue 13.61 %; los factores de riesgo asociados, alergia al ácido acetilsalicílico y atopia y la variante anatómica predominante, Agger-nasal. La severidad tomográfica fue leve y la afectación de la calidad de vida, moderada.

Palabras clave: Calidad de vida; Sinusitis; Enfermedad crónica del riñón; Trasplante de riñón. (Fuente: DeCS- BIREME)

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# **INTRODUCTION**

Chronic rhinosinusitis (CRS) is defined as inflammation of the nose and paranasal sinuses lasting at least 12 weeks<sup>(1)</sup>. It is multifactorial in etiology, but its infectious origin underscores the importance of the patient's immune status<sup>(2)</sup>. Patients with chronic kidney disease (CKD) who are preparing for kidney transplantation receive immunosuppressive therapy to decrease the likelihood of graft rejection. The resulting exacerbated immunosuppression state favors infections <sup>(3,4,5)</sup>. CRS is one of the most significant infectious complications and a major factor of morbidity <sup>(3)</sup>.

The prevalence of rhinosinusitis in solid organ transplant recipients is 12% among adults <sup>(5)</sup>. The diagnosis of CRS is clinical, and the most commonly used criteria are those established by the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020), which retained the 2012 criteria. These include: purulent rhinorrhea, nasal obstruction, hyposmia/anosmia, and facial pain. At least two of these cardinal symptoms for 12 weeks and at least one of the first two must be present <sup>(6,7,8,9)</sup>.

There are two clinical spectra of CRS based on the presence or absence of nasal polyps. Patients with CRS plus nasal polyps predominantly present with nasal obstruction, hyposmia/anosmia, and rhinorrhea, while those without nasal polyps show predominant alterations in taste, fatigue, facial pain, and posterior nasal discharge (10,11). CRS is associated with comorbidities such as asthma and chronic obstructive pulmonary disease, allergic rhinitis, atopy, respiratory disease exacerbated by acetylsalicylic acid, gastroesophageal reflux disease, and Helicobacter pylori infection<sup>(12,13)</sup>. Timely detection of CRS in patients with CKD optimizes decisions and interventions in the preparation for renal transplantation, reduces morbidity and mortality, and avoids major complications such as graft rejection and/or death<sup>(3)</sup>.

The aim of this research was to identify the prevalence of CRS, associated risk factors, anatomical variants, different subtypes, and their clinical characteristics in patients with CKD on protocol for renal transplantation.

### **METHODS**

#### Study design and area

This was a comparative, cross-sectional, retrospective study at a third-level medical unit of the Instituto Mexicano del Seguro Social in Puebla, Mexico, from 2017 to 2021.

#### Population and sample

Patients diagnosed with stage 5 chronic kidney disease of any etiology, in study protocol and management for kidney transplantation, of any age and gender, were included.

#### **Variables and instruments**

The included variables were age, sex, presence of CRS (according to criteria established by EPOS in 2020), duration of CRS, associated comorbidities, clinical symptoms and signs, variants and anatomical alterations, and affected paranasal sinuses.

Using this information, the following scales were applied:

• SNOT-22 (Sino-Nasal Outcome Test–22): Measures the impact on quality of life and severity of symptoms in patients with CRS. Validated by EPOS 2012, it includes 4 domains: otic and facial symptoms, nasal symptoms, sleep function, and psychological issues. Scores range from 0 to 110, with better quality of life and less clinical severity achieved with lower scores <sup>(14)</sup>. Scores were stratified as: mild 1-36, moderate 37-73, and severe over 74.

• Lund-Mackay Scale: Identifies tomographic severity of chronic rhinosinusitis and the presence of disease in each paranasal sinus and ostiomeatal complex. The scale scores from 0 to 24, proportional to severity. Scores are stratified as: 1 to 8, 9 to 12, 13 to 16, and 17 to 24<sup>(15)</sup>.

#### Procedures

Once the research project was approved by the corresponding Local Health Research Committee, patient records with CKD in transplantation protocol were reviewed to gather information.

#### **Statistical Analysis**

Descriptive statistics were used. Mann-Whitney U was

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used for the comparison of qualitative variables and Fisher's exact test and Phi coefficient were used for dichotomous variables. Significant values were considered at p<0.05. Data were processed in the SPSS program for IBM version 25.

#### **Ethical Considerations**

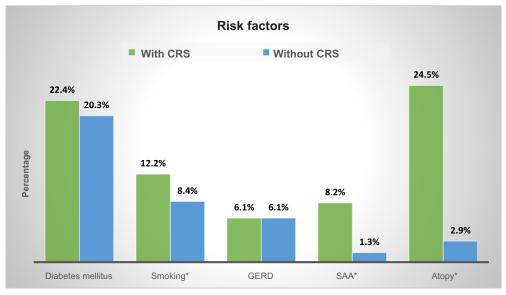
This study was approved by the Local Research Committee in Health 2101 of the Instituto Mexicano del Seguro Social. Personal data of the patients were handled with strict confidentiality and exclusively for the purposes of the research.

## RESULTS

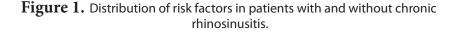
Out of 360 patients in the renal transplant protocol, 49 had CRS, yielding a prevalence of 13.61%. Those without CRS had a mean age of 37.3 years ( $\pm$ 11.67,

minimum 17, maximum 63); 54.7% were composed of 170 men. The mean age of patients with CRS was 39.22 years ( $\pm$ 12.09, minimum 21, maximum 61), with a predominance of females: 53.1% (26 women). The most frequent respiratory clinical manifestation in CRS patients, in decreasing order of percentage, was nasal obstruction at 95.9%; facial pain at 67.3%; nasal discharge at 49%, and hyposmia at 40.8%.

In patients without CRS, nasal obstruction was 7.7%; facial pain, 4.2%; nasal discharge, 0.6% and hyposmia, 0.3%. Risk factors present in both groups with similar frequencies were diabetes, smoking, and gastroesophageal reflux disease. Notable differences were in terms of allergy to acetylsalicylic acid (p=0.014) and atopy (p=0.000). See figure 1.



GERD: Gastroesophageal reflux disease. SAA: Salicylic Acid Allergy. \* Factors with significant association (p<0.05).



Regarding physical examination findings, in patients with CRS, edema/hyperemia is the most frequent at 95.9%, followed by mucopurulent meatal discharge at 46.9%. Meanwhile, the only finding in patients without CRS is mucosal edema at 5.5%. Those with CRS and nasal polyps: 14.3%. Risk factors significantly related to the presence of nasal polyps were: smoking (p=0.018), allergy to acetylsalicylic acid (p=0.000), and atopy

(p=0.000). Anatomical variation in CRS occurred in 40.8% of patients; while in patients without CRS it is 16.4% (p=0.000).

The distribution of the type of anatomical variant in patients with and without chronic rhinosinusitis, both their percentage and frequency, are represented in Figure 2.

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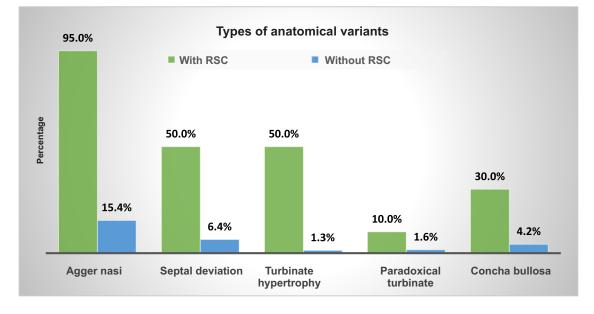


Figure 2. Types of anatomical variants in patients with and without chronic rhinosinusitis.

The average duration of illness before the diagnosis of chronic rhinosinusitis was 17.73±5.91 weeks. The group of paranasal sinuses affected in patients with CRS were, in order of frequency: maxillary 93.9%, ethmoidal 36.7%, sphenoidal 10.2%, and frontal 8.2%.

Regarding the distribution of the Lund-Mackay score in patients with chronic rhinosinusitis, the most frequent range was from 1 to 8 with 57.1%, followed by 9 to 12 with 30.6%, then 13 to 16 and 17 to 24 with 6.1%, respectively. (See figure 3).

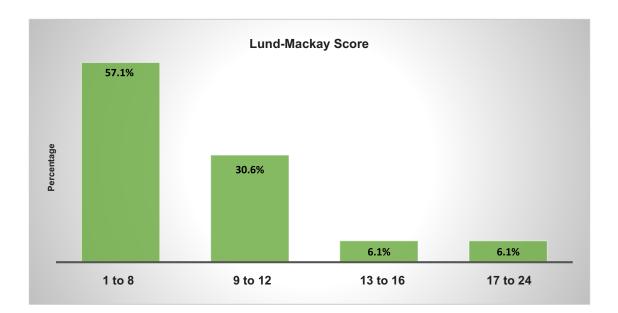


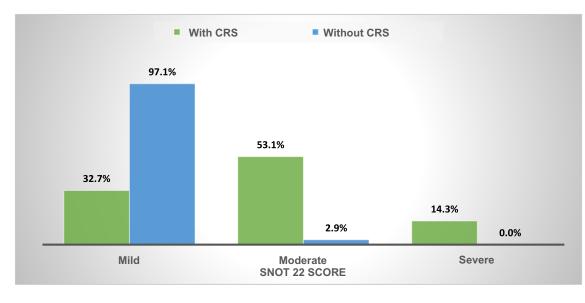
Figure 3. Distribution of the Lund-Mackay score in patients with chronic rhinosinusitis.

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The SNOT 22 score distribution found in patients with CRS was moderate in 53.1%, followed by mild in 32.7%, and finally severe in 14.3%. In patients without CRS, it

was mild in 97.1% and moderate in 2.9% (p=0.000) (See Figure 4).



**Figura 4.** Distribución del puntaje de SNOT 22 en pacientes con rinosinusitis crónica.

# DISCUSSION

CRS has a high incidence in immunocompetent patients. However, in those preparing for renal transplantation, it has been little explored and often underdiagnosed. These patients undergo immunosuppression, both due to the presence of CKD and pre-transplant therapy. Additionally, comorbidities such as diabetes contribute to immunosuppression<sup>(1,2,3)</sup>. This makes patients especially susceptible to acquiring CRS, which often goes unnoticed. These cases cause additional complications and increase the possibility of death <sup>(3,4)</sup>. This study shows the prevalence of CRS in patients preparing for renal transplantation treated at a specialized hospital of the Instituto Mexicano del Seguro Social in Puebla, Mexico.

The prevalence found in this study (13.6%) is higher than that reported in South Korea (4.2%), and very similar to that in the USA (12%) in transplant populations <sup>(5,16)</sup>. This reaffirms the importance of deliberate detection in transplant candidate patients.

The age and gender are similar to other reports in similar studies. The female-to-male ratio generally remains between 45-50 or the reverse, depending on the study<sup>(17,18)</sup>. The most frequent clinical manifestations

found in this study align with those described in other populations with CRS: Nasal congestion and discharge, facial pain, and olfactory alterations <sup>(19)</sup>. The same similarity occurs regarding comorbidities, with predominance of: Atopy/allergy, diabetes, smoking, sensitivity to acetylsalicylic acid, and gastroesophageal reflux<sup>(16)</sup>. The prevalence of atopy in different populations indicates its deliberate search in patients to be transplanted to detect hidden naso-sinusal disease.

The relatively low frequency of polyps in the CRS patients in this study (14.3%) contrasts with previous reports in populations without renal pathology (44.6% and 52.6%)<sup>(16,20)</sup>. This finding requires subsequent work to confirm this low prevalence of polyps in patients with CKD. In this study, a significant presence of atopy and allergy to acetylsalicylic acid in patients with nasal polyps stands out.

They make up the so-called Samter's triad, which explains the high prevalence of respiratory disease exacerbated by this substance in patients with chronic rhinosinusitis <sup>(21)</sup>. Also, the prevalence of anatomical variants in populations with and without CRS was similar to other reports, with predominance of Agger

nasi and septal deviation. The low frequency of frontal sinus involvement supports the pathophysiological theory of naso-sinusal mucosal inflammation over mechanical obstruction in CRS <sup>(22)</sup>. The severity of CRS, in this study, assessed by the Lund-Mackay scale (predominantly in stage 1-8), did not differ greatly from other studies of patients with CRS unrelated to transplants<sup>(23)</sup>.

The quality of life in patients with CRS, in various studies, varies widely from mild to moderate <sup>(20,24)</sup>. In our research, the most frequent assessment was moderate. As a reminder, the construct of quality of life refers to sociodemographic, cultural, and economic factors that differ according to the surveyed population <sup>(25)</sup>. This study is expected to provide necessary information for decision-making in these patients preparing for transplantation.

**Authorship contribution:** CMAB participated in the conception and design of the article, analysis and interpretation of data, drafting, critical revision, and approval of the final version. JHFF participated in the conception and design of the article, analysis and interpretation of data, drafting, and approval of the final version. MAGM contributed to data analysis and interpretation, critical review of the article, technical or administrative advice, and approval of the final version. AGG participated in the article design, data analysis and interpretation, drafting of the article, critical revision, and approval of the final version.

The deliberate search for these clinical manifestations in these patients and their timely study favors the early diagnosis of CRS, which can improve their outcome and prevent transplant failure.

## CONCLUSION

The prevalence of chronic rhinosinusitis in patients in the renal transplant protocol in the central-southern region of Mexico is 13.61%. It predominates in women in their third decade of life. The associated factors are atopy and allergy to acetylsalicylic acid. The most frequent anatomical variants are Agger nasi and septal deviation. The most affected paranasal sinuses were the maxillary sinuses, and the severity was mild by tomography. The quality of life was moderate.

This high prevalence can lead these patients to transplant failure and even death.

AJMJ collaborated in data analysis and interpretation, drafting of the article, critical revision, and approval of the final version. NRBR participated in data analysis and interpretation, drafting of the article, critical revision, and approval of the final version.

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#### REFERENCES

1. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015; 152(2):1-39.

2. Martínez Campos L., Albañil Ballesteros R., Flor Bru J. de la, Piñeiro Pérez R., Cervera J., Baquero Artigao F. et al. Documento de consenso sobre etiología, diagnóstico y tratamiento de la sinusitis. Rev Pediatr Aten Primaria. 2013; 15(59): 203-218.

 Patiño-López M, Echeverri-Toro L, Bonfante-Olivares L, Atehortúa-Muñoz S, Ospina-Ospina S. Infecciones tempranas en pacientes trasplantados en un hospital de alta complejidad.Infectio.2017;21(3):148-153.

4. Chung B, Yun J, Ha S, Kim JI, Moon IS, Choi BS, et al. Combined use of rituximab and plasmapheresis pre-transplant increases post-transplant infections in renal transplant recipients with basiliximab induction therapy. Transpl Infect Dis. 2013; 15(6):559–568.  $5.\,Patel\,Z.\,Practice\,patterns\,regarding\,noninvasive\,rhinosinusitis\,in\,the\,immunosuppressed\,patient\,population.\,Allergy\,Rhinol.\,2013; 4(3): 151-154.$ 

6. Tzelnick S, Soudry E. Rhinosinusitis in Solid Organ Transplant Recipients: Analysis of 4562 Transplanted Patients. Am J Rhinol Allergy. 2019; 33(1): 56–61.

7. Fokkens WJ, Lund VL, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020; 29: 1-464.

8. Orlandi RR, Kingdom TT, Hwan PH, Smith TL, Alt JA, Baroody FM, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Int Forum Allergy Rhinol 2016;6(1):22-209.

9. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600



10. Loose DD, Lourijsen ES, Wildeman MA, Freling NJ, Wolvers MD, Reitsma S, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J Allergy Clin Immunol. 2019; 143 (3):1207-1214.

11. Lam K, Schleimer R, Kern R. The Etiology and Pathogenesis of Chronic Rhinosinusitis: a review of current hypotheses. Curr Allergy Asthma Rep. 2015; 15(7): 1-17.

12. Cho SH, Bacher C, Lockey RF. Chronic Rhinosinusitis Phenotypes: An approach to better medical care for chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2016; 4(4): 639-642

13. Lam K, Hirsch H, BruceT. The association of premorbid diseases with chronic rhinosinusitis with and without polyps. Curr Opin Otolaryngol Head Neck Surg .2014 Jun; 22(3):231-41.

14. Marcus S, Roland LT, DelGaudio JM, Wise SK, DelGaudio JM. The relationship between allergy and chronic rhinosinusitis. Laryngoscope Investig Otolaryngol. 2019;4(1): 13-17.

15. Hopkins C, Rudmik L, Lund VJ. The predictive value of the preoperative Sinonasal outcome test-22 score in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2015; 125(8): 1779–1784

16. Brooks SG, Trope M, Blasetti M, Doghramji L, Parasher A, Glicksman JT, et al. Preoperative Lund-Mackay computed tomography score is associated with preoperative symptom severity and predicts quality-of-life outcome trajectories after sinus surgery. Int Forum Allergy Rhinol. 2018; 8(6):668–675

17. Ryu G, Seo MY, Lee KE, Kim HY, Dhong HJ, Chung SK, et al. Clinical course of rhinosinusitis and efficacy of sinonasal evaluation in kidney transplant recipients: review of 1589 patients. Eur Arch Otorhinolaryngol. 2018; 275(5): 1183-1188.

18. DeConde AS, Mace JC, Alt JA, Rudmik L, Soler ZM, Smith TL. Longitudinal improvement and stability of the SNOT-22 survey in the evaluation of surgical management for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2014; 5(3): 233–239. 19. Spillinger A, Low CM, Smith BM, Stokken JK, O'Brien EK, Choby G. Presentation and outcomes of chronic rhinosinusitis following liver and kidney transplant. World J Otorhinolaryngol Head Neck Surg. 2020; (2020): 1-15.

20. Gray ST, Phillips KM, Hoehle LP, Caradonna DS, Sedaghat AR. The 22-item Sino-Nasal Outcome Test accurately reflects patient-reported control of chronic rhinosinusitis symptomatology. Int Forum Allergy Rhinol. 2017; 7(10):945–951.

21. Hernández-Moreno Karen Estefanía, Cardona Ricardo. Enfermedad respiratoria exacerbada por aspirina. Revisión a partir de casos clínicos. Rev. Alerg. Méx. [revista en la Internet].2018;65(1):78-91.

22. Pereira DA, Guedes L, Leonardo A, Duarte D, Viana M. Paranasal Sinuses Anatomic Variants and its Association with Chronic Rhinosinusitis. Otolaryngol online [Internet]. 2019;9(2).

23. Hirsch AG, Nordberg C, Bandeen-Roche K, Tan BK, Schleimer RP, Kern RC, et al. Radiologic sinus inflammation and symptoms of chronic rhinosinusitis in a population-based sample. Allergy. 2020; 75(4):911-920.

24. Chowdhury NI, Mace JC, Bodner TE, Alt JA, Deconde AS, Levy JM, et al. Investigating the minimal clinically important difference for SNOT-22 symptom domains in surgically managed chronic rhinosinusitis. Int Forum Allergy Rhinol. 2017;7(12): 1149–1155.

25. Erskine S, Hopkins C, Kumar N, Wilson J, Clark K, Robertson A, et al. A cross sectional analysis of a case-control study about quality of life in CRS in the UK; a comparison between CRS subtypes. Rhinology 2016;54(4):311-315