CYP3A4 (el paciente tenía niveles supraterapéuticos a pesar de haber suspendido tacrolimus) y su mayor capacidad de atravesar la barrera hematoencefálica[9]. Sin embargo, es cada vez más frecuente la resistencia del *Aspergillus fumigatus* a los azoles. Algunos autores recomiendan evitar monoterapia y usar tratamiento combinado con equinocandinas o anfotericina B liposomal si existe sospecha de resistencia o mala evolución, realizando una identificación molecular[10].

Desafortunadamente la susceptibilidad antifúngica para el *Aspergillus* spp. no está disponible en todos los laboratorios o puede demorar mucho tiempo, por lo que es posible que la tasa de resistencia a azoles en nuestro medio esté infraestimada.

En conclusión, la coinfección entre SARS-CoV-2 y micosis invasoras en pacientes inmunosuprimidos probablemente sea mayor de la descrita en la literatura. Por este motivo, y dadas las limitaciones del diagnóstico, la presencia de marcadores fúngicos debería aconsejar la instauración precoz de tratamiento.

BIBLIOGRAFÍA

1. REGISTRO S.E.N. COVID-19. INFORME 16 (18 marzo – 3 octubre). 2020. Disponible en la red: https://mailchi.mp/senefro/registro-epidemiolgico-vhc-vhb-vih-1314798.
2. Guillen E, Pineiro GJ, Revuelta I, Rodríguez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant. 2020;20:1875–8.
3. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;11:1446.
4. Pemán J, Ruiz-Gaitán A, García Vidal C, Salavert M, Ramírez P, Puchades F, et al. Fungal co-infection in COVID-19 patients: Should we be concerned? Rev Iberoam Micol. 2020;37:41–6.
5. López-Medrano F, Fernández-Ruiz M, Silva JT, Carver PL, van Delden C, Merino M, et al. Clinical Presentation and Determinants of Mortality of Invasive Pulmonary Aspergillosis in Kidney Transplant Recipients: A Multinational Cohort Study. Am J Transplant. 2016;16:3220–34.
6. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2019;71:1367–76.
7. Koehler P, Bassetti M, Kochanek M, Shimabukuro-Vornhagen A, Cornely OA. Intensive care management of influenza-associated pulmonary aspergillosis. Clin Microbiol Infect. 2019;25:1501–9.
8. Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Bot S, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med. 2020;46:1524–35.
9. Azanza Perea JR, Sádaba Díaz de Rada B. Pharmacological profile of isavuconazole. Rev Iberoam Micol. 2018;35:186–91.
10. Friedman DZP, Schwartz IS. Emerging fungal infections: new patients, new patterns, and new pathogens. J Fungi (Basel). 2019;5:67.

Leónidas Luis Cruzado Vega* y Alba Santos García

Sección de Nefrología, Hospital General Universitario de Elche, Elche, España

* Autor para correspondencia.
Correo electrónico: leocruzadov@gmail.com
(L.L. Cruzado Vega).

https://doi.org/10.1016/j.nefro.2020.11.005

Chronic kidney disease is associated with worse outcomes following SARS-CoV2 infection among 18647 patients: A population-based cohort study

La enfermedad renal crónica se asocia con peores resultados después de la infección por SARS CoV2 entre 18647 pacientes: estudio de cohorte basado en la población

Dear Editor:

The clinical spectrum of COVID-19 ranges from asymptomatic cases to those who develop acute-respiratory distress syndrome and require intensive care unit (ICU) admission.[1,2]

Previous studies have identified chronic kidney disease (CKD) as a risk factor for severe outcomes following SARS-CoV2 infection.[3] This observation derives from data from small cohorts of hospitalized patients mainly from China[4–7] and a UK cross-sectional survey describing 16,749 patients hospitalized with COVID-19.[8] Recently, the largest nationwide cohort study describing the impact of clinical risk factors on COVID-19 related deaths has been published and reports the negative impact of CKD on mortality among an unselected population of cases with COVID-19.[9] Whether the same association is observed among non-hospitalized patients from

Table 1 – Baseline characteristics stratified by the presence of chronic kidney disease.

Characteristic *n* (%) or median (IQR)	Overall (*n* = 18,647)	CKD (*n* = 383)	No CKD (*n* = 18,264)	P*
Age (years)	50 (36–66)	78 (70–86)	50 (35–65)	<0.001
Sex (male)	7701 (41.3%)	222 (58.0%)	7479 (40.9%)	<0.001
Number of comorbidities				<0.001
None	15,651 (83.9%)	0 (0.0%)	15,651 (85.7%)	
1	2213 (11.9%)	155 (40.5%)	2058 (11.3%)	
2	600 (3.2%)	138 (36.0%)	462 (2.5%)	
≥3	183 (1.0%)	90 (23.5%)	93 (0.5%)	
Types of comorbidities				
Diabetes mellitus	1056 (5.7%)	101 (26.4%)	955 (5.2%)	<0.001
Respiratory	841 (4.5%)	64 (16.7%)	777 (4.3%)	<0.001
Neurological/muscular	730 (3.9%)	75 (19.6%)	655 (3.6%)	<0.001
Malignancy	568 (3.0%)	44 (11.5%)	524 (2.9%)	<0.001
Cardiovascular	51 (0.3%)	24 (6.3%)	27 (0.1%)	<0.001
Haematological	201 (1.1%)	31 (8.1%)	170 (0.9%)	<0.001
Liver	102 (0.5%)	16 (4.2%)	86 (0.5%)	<0.001
HIV infection	99 (0.5%)	15 (3.9%)	84 (0.5%)	<0.001
Hospital admission	2952 (15.8%)	273 (71.3%)	2679 (14.7%)	<0.001
ICU admission	258 (1.4%)	34 (8.9%)	224 (1.2%)	<0.001
Mortality	456 (2.4%)	95 (24.8%)	361 (2.0%)	<0.001
Time from symptoms onset to hospital admission (days) (n = 1910)	4 (2–7)	4 (1–7)	4 (2–7)	0.856

IQR: interquartile range. HIV: human immunodeficiency virus. ICU: intensive care unit.

* Chi-square (categorical variables) or Mann–Whitney (continuous variables) tests ($\alpha = 0.05$).

different regions is yet to be confirmed. We aimed to determine the modifying impact of CKD among a Portuguese nationwide cohort of cases of SARS-CoV2 infection, including those with and without hospitalization.

This was a retrospective analysis from a nationwide prospective registry, including all confirmed (nasal/pharynx swab real-time polymerase chain reaction) cases of SARS-CoV2 infection notified to the Directorate-General of Health from March 02 until April 21, 2020, in Portugal. The country (population of 10.6 million inhabitants) has been using the National Epidemiological Surveillance System (SINAVE) to capture cases of SARS-CoV2 infection occurring nationally (25 administrative regions, 100 hospitals, and 357 primary care centres) since January 01, 2020. CKD was defined according to the physician who notified the case of SARS-CoV2 infection.

Overall, 18,647 cases were included in our analyses, following exclusion of 1623 (8.0%) cases without hospital admission status and 23 (0.1%) cases without outcome status. Among all cases, median (IQR) age was 50 (36–66) years (Table 1). Male sex accounted for 7701 (41.3%) of all cases. While 15,651 (83.9%) cases did not have any comorbidity, the remainder of cases had the following number of comorbidities: one in 2213 (11.9%) cases, 2 in 600 (3.2%) cases, and ≥3 in 183 (1.0%) cases. Median (IQR) follow-up was 27 (19–33) days. Peak ICU bed occupancy rate occurred on April 06 (58.1% of national standard official capacity). Median (IQR) time from symptoms onset to hospital admission was 4 (2–7) days. Overall, 2952 (15.8%) or 258 (1.4%) cases required hospital or ICU admission, respectively. All-cause mortality occurred in 456 (2.4%) cases. There were 687 (3.7%) cases admitted to the ICU or deceased.

Cases with CKD (*n* = 383; 2.1%) had higher median (IQR) age [78 (70–86) vs. 50 (35–65) years; $P < 0.001$), were more frequently men (58.0% vs. 40.9%; $P < 0.001$) and had higher burden of disease (any comorbidity 100% vs. 14.3%; $P < 0.001$) compared to those without CKD.

All types of comorbidities were more frequently reported in cases with CKD compared to those without CKD (Table 1).

Cases with CKD had higher odds of hospital admission [OR 14.4 95%CI (11.5–18.1)], ICU admission [OR 7.9 95%CI (5.4–11.4)], mortality [OR 16.4 95%CI (12.7–21.1)] and composite endpoint of mortality or ICU admission [OR 14.0 95%CI (11.1–17.7)] compared to cases without CKD. In multivariable analysis with logistic regression, only higher age [aOR (95%CI) 1.02 (1.01–1.04), $P = 0.01$] was associated with higher risk of death or ICU admission among the population with CKD, irrespective of gender [male gender aOR 1.07 (0.69–1.68), $P = 0.76$] or number of comorbidities [≥2 vs. 1 (ref) aOR 1.21 (0.76–1.92), $P = 0.42$]. Interestingly, median (IQR) age (years) of cases with CKD [78 (70–86)] was similar to cases that were admitted to the ICU or died [80 (69–87)] among the entire population.[10]

The interpretation of our findings should consider the following limitations. Firstly, the absence of a prespecified definition of CKD or serum creatinine measurements might have excluded from our analysis patients with earlier stages of the disease and interfered with the measurement of the strength of the association between CKD and clinical outcomes. However, the standardized national electronic reporting system through SINAVE has likely minimized such limitation. Secondly, we reported no laboratory data to characterize SARS-CoV2 infection among CKD cases because the majority of cases were not admitted to the hospital. While we recognize their importance to predict worse outcomes among hospitalized cases, the performance of the model previously published by our group[10] strongly suggests that demographics and chronic conditions greatly impact clinical outcomes, irre-

spective of acute disease severity and its specific management strategies.

Among cases with SARS-CoV2 infection at an early phase of the epidemic in Portugal CKD was associated with worse outcomes. Age seems to be the only demographic risk factor associated with worse outcomes. These findings may inform health policies designed to protect this specific subgroup of the population, especially while measures of containment are being eased in many countries.

BIBLIOGRAFÍA

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in cases with COVID-19 in Wuhan, China: a retrospective cohort studyJT Lancet. 2020;395:1038.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
3. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol. 2020;52:1193–4.
4. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364–74.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323: 1061–9.
6. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730–41.
7. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829–38.
8. Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv. 2020, http://dx.doi.org/10.1101/2 020.04.23.20076042.
9. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature. 2020.
10. Cardoso FS, Papoila AL, Machado RS, Fidalgo P. Age, sex, and comorbidities predict ICU admission or mortality in cases with SARS-CoV2 infection: a population-based cohort study. Crit Care. 2020;24:465.

Pedro Fidalgo[a,*], Rita Veríssimo[b], Filipe S. Cardoso[c]

[a] *Intensive Care Unit, São Francisco Xavier Hospital, Western Lisbon Hospital Centre, Lisbon, Portugal*
[b] *Nephrology Department, Santa Cruz Hospital, Western Lisbon Hospital Centre, Lisbon, Portugal*
[c] *Intensive Care Unit, Curry Cabral Hospital, Central Lisbon University Hospital Centre, Nova Medical School, Nova University, Lisbon, Portugal*

[*] *Corresponding author.*
E-mail address: pedrofidalgo.com@gmail.com (P. Fidalgo).

https://doi.org/10.1016/j.nefro.2020.11.004