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Impact of SARS-CoV-2 infection in the population on peritoneal dialysis. The Spanish experience : preliminary results

Impact de l'infection à SARS-CoV-2 chez les patients en dialyse péritonéale. Expérience Espagnole : résultats préliminaires.

Sánchez-Alvarez JE[1], Bajo Rubio MA[2], Paraíso Cuevas V[3], López de la Manzanara V[4], Llópez Carratala R[5], Rodríguez Puyol D[6], Trujillo Cuéllar H[7], Grande Villoria J[8], Cuiña Barja ML[9]

[1]Hospital Universitario de Cabueñes (Gijón), [2]Hospital Universitario La Paz (Madrid), [3]Hospital Universitario del Henares (Coslada),

[4]Hospital Clínico San Carlos (Madrid), [5]Hospital Universitario Puerta de Hierro (Madrid), [6]Hospital Universitario Príncipe de Asturias (Alcalá de Henares),

[7]Hospital Universitario 12 de octubre (Madrid), [8]Complejo Hospitalario de Zamora, [9]Complejo Hospitalario de de Pontevedra

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Résumé

L'apparition récente de la pandémie à coronavirus SRAS-CoV-2 a eu un retentissement significatif sur la population générale. Les patients sous traitement substitutif de la fonction rénale n'ont pas été épargnés et, en raison de leurs caractéristiques, sont particulièrement vulnérables. Nous présentons les résultats de l'analyse du registre COVID-19 de la Société espagnole de néphrologie. Le registre a débuté le 18 mars 2020. Il recueille des variables concernant l'épidémiologie, les contaminations et diagnostic, les signes et symptômes, les traitements et les résultats. C'est un registre « en ligne ». Les patients ont été diagnostiqués avec une infection par le SRAS-CoV-2 sur la base des résultats de la PCR du virus, réalisée à la fois chez les patients qui avaient manifesté des symptômes compatibles ou présentaient des signes suspects, ainsi que chez ceux qui avaient subi un dépistage à la suite d'un contact avec un autre patient.

Au 18 juillet, le registre disposait des données de 1748 patients, de toutes les communautés espagnoles autonomes. La forme la plus représentée de traitement substitutif est l'hémodialyse en centre (HDC) suivie par les patients transplantés. Seulement 55 (4%) étaient sous dialyse péritonéale (DP). Concernant les patients en DP, les symptômes étaient similaires à ceux de la population générale. Un pourcentage très élevé (93%) a nécessité une hospitalisation, mais aucune en unité de soins intensifs. Les traitements les plus utilisés étaient l'hydroxychloroquine, le lopinavir – ritonavir et les stéroïdes. La mortalité est élevée et atteint 18%. L'âge et la pneumonie étaient indépendamment associés au risque de décès. Nous avons trouvé un effet bénéfique de la DP par rapport à l'hémodialyse en centre.

En conclusion, l'infection par le SRAS-CoV-2 affecte déjà un nombre important de patients espagnols sous traitement substitutif, principalement ceux en HDC. La proportion de patients en DP infectés est significativement plus faible. Les taux d'hospitalisation sont très élevés et la mortalité est élevée ; l'âge et la survenue d'une pneumonie sont des facteurs associés à la mortalité, tandis que les sujets en DP avaient une mortalité plus faible.

Mots clés : Covid-19, SARS-Cov2,Dialyse, épidémiologie, Espagne

Summary

The recent appearance of the SARS-CoV-2 pandemic has had a significant impact on the general population. Patients on renal replacement therapy (RRT) have not been unaware of this situation, and due to their characteristics, they are especially vulnerable. We present the results of the analysis of the COVID-19 Registry of the Spanish Society of Nephrology. This online registry began operating on March 18, 2020. It collects epidemiological variables, contagion and diagnosis data, signs and symptoms, treatments, and outcomes. Patients were diagnosed with SARS-CoV-2 infection based on the results of the PCR of the virus, carried out both in patients who had manifested compatible symptoms or had suspicious signs and in those who had undergone screening after contact with another patient.

As of July 18, the registry had data on 1748 patients, from all the autonomous communities. The most represented form of RRT is in-center hemodialysis (HDC), followed by transplant patients. Only 55 (4%) were on peritoneal dialysis (PD). PD patients' symptoms are similar to those of the general population. A very high percentage (93%) required hospital admission, but none in intensive care units. The most used treatments were hydroxychloroquine, lopinavir–ritonavir, and steroids. Mortality is high and reaches 18%. Age and pneumonia were independently associated with the risk of death. We also found a beneficial effect of PD over HDC.

As conclusions, SARS-CoV-2 infection already affects a significant number of Spanish patients on RRT, mainly those on HDC. The proportion of infected patients on PD is significantly lower. Hospitalization rates are very high, and mortality is high; age and the development of pneumonia are factors associated with mortality, while those on PD had lower mortality.

Key words : Covid-19, SARS-Cov2,Dialysis, epidémiology, Spain

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INTRODUCTION

In late 2019, authorities in the People's Republic of China reported to the World Health Organization several cases of pneumonia of unknown etiology in Wuhan, a city located in the Chinese province of Hubei. Later, it was found that it was an infection caused by a new coronavirus called SARS-CoV-2. This virus causes various clinical manifestations encompassed under the term COVID-19, including respiratory symptoms that vary from the common cold to severe pneumonia with respiratory distress syndrome, septic shock, and multi-organ failure. Since then, the virus has been spreading throughout the world, reaching, to date, almost 17 million people [1].

As of July 28, the United States is the country with the most confirmed cases, followed by Brazil, India, and Russia. Spain has been one of the European countries hardest hit by this pandemic [1]. The appearance of a disease such as this has forced special attention to be given to particularly vulnerable population groups, including those with chronic kidney disease (CKD), especially those who undergo some type of renal replacement therapy (RRT).

Since the start of the pandemic, the Spanish Society of Nephrology (SEN) has begun to work jointly with the Ministry of Health, nephrology services throughout the country, patient associations, and other scientific societies in order to prepare contingency plans and specific protocols that provide knowledge of a very serious and new pathology in our environment [2].

One of the projects that took shape in the first weeks of the SARS-CoV-2 epidemic was the creation of a specific registry for patients in some form of RRT in Spain. This collective effort resulted in the SEN Registry of COVID-19.

Little has been said regarding the impact that SARS-CoV-2 infection is having on the peritoneal dialysis (PD) population. Undoubtedly, in a pandemic situation such as the current one, one of the advantages of home RRT modalities lies in better compliance with confinement and social distancing measures. The objective of this work is to present the results of the analysis of the registry data 4 months after its creation, making special reference to PD patients.

METHODS

The COVID-19 Registry began operating on March 18, 2020. Previously, an expert committee decided which variables should be included in it. Epidemiological variables, modalities of RRT, data on infection and diagnosis, clinical manifestations, treatments, and outcome were included in the registry. It is an anonymous registry that meets the requirements imposed by legislation. Authorization for its operation was requested from the Ethical Committee of the Principality of Asturias.

The SEN COVID-19 Registry has an online format, with access through the society's website (www.senefro.org); prior identification of the people who access it is necessary. Each user of the registry has access to the patient data that they have entered, but not to the rest of the information. The complete database can only be managed by the coordinator of the registry or by any other member of the society who requests it with the prior authorization of the committee of experts. The patients were diagnosed with SARS-CoV-2 infection based on the results of the virus PCR, performed when the patient had manifested compatible symptoms, had suspicious signs, or had

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been screened after some known contact with another patient.

The registry will remain operational as long as the current coronavirus pandemic situation is maintained. Periodic analyses of the registered information will be carried out to obtain conclusions about the impact of this infection on patients on TRS in Spain and the different ways of addressing this situation. The results that will be presented below correspond to the analysis with the data registered until July 18, 2020.

Statistical analysis

Continuous variables were expressed as means and standard deviations, and categorical variables as percentages. Baseline values were compared using the T test and Chi-square as appropriate. The Kolmogorov–Smirnov test was used to determine if the data were normally distributed. Linear or logistic regression models were used to know the factors associated with mortality. A p-value of less than 0.05 was considered significant. The statistical package SPSS 20® for Windows (SPSS Inc, Chicago, IL) was used to analyze the results.

RESULTS

As of July 18, data from 1748 patients on RRT with documented SARS-CoV-2 infection had been entered into the registry. All the regions, the so-called autonomous communities, have reported cases. Taking into account the number of patients on RRT in Spain, according to data from the Spanish Registry of Renal Patients (REER) for the end of the year 2018 [3], almost 2.5% of the total have been infected; this percentage ranges between 6.8% in Madrid and 0.1% in Murcia.

According to the RRT modality of the patients infected by SARS-Cov-2, only 55 (4%) were on PD. Most of the infected patients were on in-center hemodialysis (HDC) (1113 patients, 63%), and 574 (33%) were kidney transplant recipients. There have been six reported cases on home hemodialysis.

Three out of ten infected patients had had known prior contact with someone else infected. This percentage slightly rose to 32% in the case of patients on HDC, and 27% on PD. These differences were not significant. The average incubation period in those patients with known prior contact was 8 ± 4 days.

The average age of PD infected patients was 68 ± 14 years, and three out of four were male. Twenty-eight percent were diabetics. Dialysis vintage was 27 ± 28 months. Finally, nearly two-thirds were prescribed renin angiotensin aldosterone system (RAAS) inhibitors. Regarding clinical features (Table 1), 80% presented with fever, two-thirds had symptoms of upper respiratory infection, and nearly half had dyspnea. Half of the patients had gastrointestinal symptoms. Only 10% were asymptomatic. The most frequent complication developed was pneumonia, in 87% of patients, and 83% also had lymphopenia.

A very high percentage of registered PD patients (93%) required hospital admission, but none of the patients had to be admitted to the intensive care unit (ICU). The average length of hospital admission (considering only cured patients) was 12 ± 9 days.

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The most commonly used treatments (Table 2) were hydroxychloroquine (89%) and the combination of lopinavir–ritonavir (45%). A third of the patients received the three drugs together. Steroids, interferon, and tocilizumab were used less frequently.

Table 1. Clinical features

Symptoms/signs	Percentage (%)
Fever	80
Cough, expectoration, pharyngeal discomfort	70
Disnea	52
Digestive clinic	50
Pneumonia	87
Lymphopenia	83
Asymptomatic	10

Table 2. Treatments

Drug	Percentage (%)
Hydroxychloroquine	89
Lopinavir-ritonavir	45
Steroids	20
Tocilizumab	6
Interferon	11
Nothing	1

As of July 18, the mortality rate among PD patients was 18% (10 cases), while 39 (71%) had already recovered. Six patients still remained in a situation of active infection and were excluded from subsequent analyses. When comparing the deceased patients with the recovered, we found that the former were older, with no differences in terms of the presence of diabetes, sex, time on dialysis, or the different treatments they received.

The differences between HDC patients and those on PD were also analyzed (Table 3). The former had a longer dialysis vintage, were admitted less, but more often in the ICUs; they were treated less frequently with hydroxychloroquine and interferon and had previously been prescribed fewer RAAS inhibitors. It is especially important that patients on PD recovered more frequently and in less time than those on HDC; finally, fewer died.

We analyzed the factors associated with mortality, considering all dialysis patients. We found that age and development of pneumonia were associated with a worse prognosis, while those on PD had lower mortality. The analysis was adjusted to the condition of diabetes, but we do not have other factors such as comorbidity to include in the model. Diabetes was not independently associated with the risk of dying (although we only have registered the patients in whom diabetes was the underlying kidney disease and not the total number of diabetic patients, which can also lead to bias) (Table 4).

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Table 3. Hemodialysis vs. peritoneal dialysis in infected populations

Variable	Hemodialysis N: 1113	Peritoneal dialysis N: 55	p
Infected patients (%)*	4.5	1.8	<0.001
Age (years)	71 ± 15	68 ± 14	NS
Gender (% males)	64.3	72.7	NS
Dialysis vintage (months)	46 ± 44	30 ± 31	NS
Developed pneumonia (%)	63.4	87	<0.001
Admitted (%)	79.7	92.6	0.001
Admitted to ICU (%)	5.7	0	<0.001
Treatments (%)			
- Lopinavir/ritonavir	35.4	45.1	NS
- Hydroxychloroquine	77.7	89.1	0.027
- Steroids	27.2	20	NS
- Interferon	3.4	10.6	0.088
- Tocilizumab	5.9	12.8	NS
Previous treatment (%)			
- ACEI	11.1	20.4	0.038
- ARB	16.5	42.6	<0.001
- Any RAASi	26.8	61.1	<0.001
Days of admission	14 ± 11	12 ± 9	NS
Recovered (%)	55.1	65.5	0.015
Time to cure (days)	21 ± 10	16 ± 10	0.011
Death (%)	27.4	18.1	0.047

ICU: intensive care unit; ACEIs: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blockers, RAASi: renin angiotensin aldosterone system inhibitors.

Table 4. Factors associated with mortality

	Exp(B)	p	95% C.I.	
			lower	upper
Age	1.037	<0.001	1.024	1.051
Pneumonia	6.513	<0.001	4.319	9.822
HD (vs. PD)	2.225	0.036	1.025	4.706

DISCUSSION

The analysis of data collected during the first four months of the SEN Covid-19 Registry shows that SARS-CoV-2 infection affects a significant number of Spanish patients on RRT, mainly those that are in HDC, with significantly better results in patients on PD. In any case, the rate of hospital admissions is very high, and mortality is elevated; age and the development of pneumonia are risk factors for mortality, while the use of PD (versus HDC) could have a protective effect.

Despite the fact that more than half of the Spanish patients on RRT are transplanted [3], the spread of SARS-CoV-2 is more frequent in patients on HDC. This fact may not be surprising because HD patients failed to fulfill the regulatory confinement, since they have to move to the dialysis centers, use public transportation, or live in nursing homes, all places of frequent infection. Despite immunosuppression, transplant recipients represent only one-third of the registered infected patients. It should be noted that patients on PD represent a very low rate of infected pa-

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tients, although their representation in the total of RRT patients in Spain is relatively low. In any case, we appreciate that 4.5% of the total HD population in Spain was infected, 2.1% of kidney transplant recipients, and 1.8% of PD patients.

The mean age of infected PD patients matches the mean age of the patients on RRT in Spain. In the general population, it appears that the coronavirus affects more males than females. In the case of patients on RRT, there are also more men infected, but this could reflect the greater number of men in the RRT programs.

Regarding clinical features, there are no differences from what has been reported in the general population [4] or in patients on HDC [5]. The most frequent manifestations were fever and the symptoms of upper respiratory tract infection. Half of our PD patients also reported gastrointestinal symptoms, which is more frequent than in the general population and in patients on HDC. Moreover, the first case of SARS-CoV-2 infection in a hemodialysis patient in the United States presented with diarrhea as the first symptom of the infection [6]. The different forms of screening or diagnosis in the population may be the cause of nonuniform results.

Hospitalization rates in our patients are very high. Published studies in the general population reveal considerably lower rates of hospitalization [7]; however it should be taken into consideration that patients on RRT are older and have more comorbidities, which undoubtedly results in a worse clinical situation. The results of a recent meta-analysis concluded that CKD was a risk factor for developing a more severe SARS-CoV-2 infection [8]. One of the possible explanations lies in the role in the role of lymphocytes, whose function is impaired in uremia [9]. In our registry, admission rates of PD patients were higher than those of patients on HDC, although none were admitted to the ICU; some of them died in their homes or health centers, and some were rejected by ICUs for not meeting criteria for admission (age, comorbidity, dependency, etc.). Unfortunately, comorbidity was a variable not recorded.

The mortality rate is high. Dialysis patients have a higher risk of dying than transplanted ones, probably related to older age and comorbidity. The analysis of factors independently associated with the risk of death shows that age and the development of pneumonia determine a worse prognosis. Furthermore, in dialysis patients, we also found a beneficial effect of PD over HDC; analysis was adjusted by age and diabetic condition but not by comorbidity; this circumstance may bias the results.

The benefit of RAAS inhibitors is also controversial. Some publications warned about the possibility that the use of these drugs may increase the risk of infection by SARS-CoV-2. A recent meta-analysis suggests a beneficial effect of angiotensin II receptor blockers on the severity of SARS-CoV-2 pneumonia in elderly patients [10]. For all these reasons, the health authorities recommend maintaining the indication of these drugs [11]. In our registry, RAAS inhibitors are more frequently prescribed to PD patients than HDC ones, but their use did not have any impact on mortality.

It is amazing that the Spanish data are very similar to those coming from France [12]. In the latter country, of the 3,104 patients treated with PD, 59 (exactly 1.8%) contracted COVID-19, also a percentage significantly lower than that observed in HDC. The main difference is the mortality rate. In France it was 40%, but it was only 18% in the Spanish PD patients. In our case, the hi-

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ghest mortality rate was in HDC patients (27.1%).

In the work of the RDPLF, in PD patients, in France [12] only symptomatic patients were analysed. During the first weeks of the pandemic, in Spain, only the PCR of symptomatic patients was analyzed; but later on, the tests were generalized to patients who had had previous contact with infected persons and, on occasion, as a method of screening in dialysis units. This may be the explanation for the differences with France, as some asymptomatic patients have been included ; but in any case the rate seems to have remained significantly lower in Spain at that time. Further analysis will have to be conducted in both registries.

At the time of the present report, 71% of cases are cured, and 11% are shown as active infections. In the coming weeks, we will know the final outcomes of all these patients. This information will provide more knowledge on the effects of SARS-CoV-2 in RRT patients.

CONCLUSION

The SARS-CoV-2 pandemic is having a strong impact in today's globalized world, with special incidence among older and comorbid populations. RRT patients are one of the most affected groups, with very high hospitalization and mortality rates. Among them, those patients on PD, who can comply with the measures of confinement and social distance in a more effective way than those on HDC, turn out to be the least affected and those with the lowest mortality. This argument should join the rest of the strengths of the technique and promote its use.

DISCLOSURE

The authors have no conflict of interest to declare.

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