Renal impairment in COVID-19. Review.

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In early December 2019, an outbreak of an acute respiratory infection occurred in Wuhan City, China, which rapidly spread to other regions of China and later to other countries, constituting a pandemic that has affected more than 1 million people, in more than 180 countries and territories of the world so far.

On January 7, 2020, the new virus was identified by the Chinese CDC and called SARS-CoV-2 and the disease caused by it was designated with the acronym COVID-19 by the WHO (coronavirus disease 2019).

On March 11, 2020 the WHO declared the pandemic 2020, affecting at the present time (April 6, 2020) 1,309,439 people in more than 180 countries and territories, with 72,638 deaths.

This virus is the third coronavirus that jumped from species (from wild animals to humans), after SARS-CoV-1, the agent of severe acute respiratory syndrome (SARS) that caused an epidemic in 2002-2003 (with whom it has a 79% genetic similarity), and MERS-CoV the cause of respiratory syndrome in the Middle East (MERS).

Although COVID-19 has a benign course in most patients, in about 20% of cases it requires hospitalization. In round numbers 80% of cases require isolation and basic home care. The remaining 20% must be hospitalized: 15% in conventional ward and 5% in intensive care unit. The fatality rate is low and mainly linked to advanced age

and comorbidities, but due to the high number of cases, this low percentage represents a considerable absolute number of deaths.

The most prominent feature of the present pandemic can be summarized in 3 main conditions: 1) the high transmissibility that explains the rapid and extensive spread; 2) the serious economic and social impact; 3) the potential saturation of the health system in its 3 levels with dramatic consequences.

Like SARS and other diseases caused by other members of the coronavirus family, kidney involvement may occur, either injury or dysfunction. So far, available literature is scarce and variable. Variability could be explained by the diversity in the cohorts studied (number of patients, unselected population, hospitalized patients, critically ill patients) but also to the quality of the studies, probably due to the urgency to communicate information for clinical decision-making.

The sources of information on COVID-19 and renal involvement can be grouped in 2 sort: epidemiological studies that just provide values of serum creatinine (Scr) and/or acute kidney injury (AKI) (yes/no); and studies aimed specifically to evaluate kidney disorders associated with the disease.

CDC website refers as of March 8, 2020, 36 publications on COVID-19 (1). Of these, 14 are clinical or epidemiological studies, 9 are comments or editorials, 6 are studies on transmission mechanisms, 2 on control and prevention measures, 2 on diagnostic techniques, 2 are case-reports and 1 on pathology.

The analysis of these clinical and epidemiological studies, shows a great variability in the number of patients, methodology, and characteristics of cohorts studied, that prevents comparison. The number of patients in these studies ranges from 13 to 1099.

As an example, the study by Guan W et al (2) on 1099 hospitalized patients shows a 1.6% of patients with Scr ≥ 133 μmol / L (4.3% and 1.0% in severe vs mild cases respectively) but AKI defined by KDIGO criteria was 0.5%. Yang X et al (3). in 52 critically ill patients found a frequency of AKI of 29%; only one of them received renal replacement therapy (RRT) (5%). Overall mortality rate was 25% being AKI associated with a higher mortality (37.5% vs. 15%). In Xu X et al cohort (4) only one of 62 cases required ICU admission and no deaths was observed. Five percent of the cases had Scr ≥ 133 μmol / L. In the series by Wang D et al. (5) AKI according to KDIGO criteria occurred in 3.6% out of 138 patients. Huang C et al (6) in a cohort of 41 cases observed AKI in 3 (7%), all of them were admitted in ICU and received CRRT. Finally, Chen N et al (7) in 99 cases found a 3% of AKI and a 9% of patients treated by RRT (9%). Neither the definition of AKI nor the reason for the difference in number of RRT and AKI is provided by the authors.

More recently, a study aimed to analyze clinical characteristics of surviving and non-surviving patients in two tertiary hospital in Wuhan (8) showed that non-surviving patients (n=109) were older, with more comorbidities, more severe symptoms at admission, and had more frequently in-hospital complications, among them AKI 18.3% vs =0% in survivors (n=116).

Other studies were aimed at describing renal involvement in patients with COVID-19, either injury (proteinuria, urinary sediment) or dysfunction. All of them are preprint and result from a search in Google Scholar.

The most comprehensive is that of Cheng Y et al. (9). The authors analyzed 710 hospitalized patients evaluating Scr and urinary sediment at hospital admission and

onset of AKI during hospital stay, defining AKI by KDIGO criteria. Scr at admission (baseline) was increased in 15.5% of patients. 44% had proteinuria and 26.9% had hematuria on admission. Hospital-acquired AKI developed in 3.2% of the patients. The frequency was higher in patients with increased baseline Scr (9.1% vs. 2.0%) as expected. In most cases, AKI occurred in the first 7 days. In patients with normal baseline Scr, onset of AKI was late and recovered promptly. Hospital mortality was 12.5%, significantly higher in patients with increased baseline Scr (30.9% vs. 9.2%). The risk of death was associated with increased baseline Scr (HR 3.61), increased BUN (HR 2.51), Scr peak (HR 2.59), proteinuria (HR 1.46), hematuria (HR 3.15), and AKI (HR 2.21). Authors speculate that AKI could be explained by several factors: direct renal cytopathic effect; vulnerability of the kidneys to the action of SARS-CoV-2 linked to the increased expression of angiotensin converting enzyme II, which is used by the virus as a receptor for cellular entry; cytokine storm induction affecting kidneys secondary to shock, hypoxemia, rhabdomyolysis; deposit of immune complex although there is no conclusive evidence for the latter. Hong X et al. (10) in a study with a small number of patients (n=12), detected signs of early injury through various urinary proteins: microalbuminuria, alpha microalbuminuria, urinary IgG and urinary transferrin, despite not changes in the level of Scr. They propose the use of this combination of biomarkers to detect kidney injury early and thus implement kidney protection measures.

A group led by Li Z is conducting an ongoing study from which they report preliminary data from 59 patients (11). In this cohort, there were 28 serious cases and 3 deaths. 63% had proteinuria especially early and 19% increased Scr. They performed CT scans in 27 patients and in all of them they found an imaging profile suggestive of kidney

inflammation and edema. Li Q et al. describe 2 cases of kidney transplant patients with COVID-19 and AKI, one of whom died (12).

Finally, a study published on line on March 31 (13) was carried out in a cohort of 116 patients (9.5% in ICU) in one of the tertiary hospitals in Wuhan city. The aim of the study was to analyze the effects of SARS-CoV-2 infection on renal function and AKI was defined according KDIGO definition. Proteinuria was found in 7.2% of patient but surprisingly no cases of AKI was detected.

Of note, five studies reported data on urine protein that was positive in 41.7% to 63% of patients. Proteinuria was detected early which offer a window of opportunity to implement a strategy for kidney protection.

Mortality rate shows a substantial rise in patients with AKI with regard to non-AKI cases (8,9,11).

In conclusion: renal involvement could be observed in patients with SARS-CoV-2 disease but to date only preliminary information is available. AKI and early proteinuria and hematuria were demonstrated but data on frequency and severity of these disorders are scarce and divers. Testing urine protein at admission could detect kidney injury early. Available studies concur that renal impairment is associated with high mortality rate. Surely, more accurate information will emerge in the course of this dire pandemic.

References

1. https://www.cdc.gov/coronavirus/2019-ncov/publications.html. Accessed March 19, 2020.
2. Guan W, Ni Z, Hu Y, et al for the China Medical Treatment Expert Group for Covid-19*. Clinical characteristics of coronavirus disease 2109 in China. . N Engl J Med. Published ahead-online February 28, 2020, and last updated on March 6, 2020.DOI: 10.1056/NEJMoa2002032
3. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. Published online February 21, 2020 https://doi.org/10.1016/S2213-2600(20)30079-5
4. Xu X,Wu X, Jiang X, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606, http://dx.doi.org/10.1136/bmj.m606.
5. Wang D, Hu B, Hu Ch et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585.
6. Huang Ch, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
7. Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, Published online January 29, 2020, https://doi.org/10.1016/S0140-6736(20)30211-7 1

8. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chinese Med J, Publish Ahead of Print. DOI: 10.1097/CM9.0000000000000824
9. Cheng Y, Luo R, Wang K, et al. (Kidney impairment is associated with in-hospital death of COVID-19 patients. medRxiv preprint doi: https://doi.org/10.1101/2020.02.18.20023242).
10. Hong X, Chi Z, Liu G, et al. Analysis of early renal injury in COVID-19 and diagnostic value of multi-index combined detection. medRxiv preprint doi: https://doi.org/10.1101/2020.03.07.20032599).
11. Li Z, Wu M, Guo J, et al. Caution on kidney dysfunction of 2019-nCoV patients. medRxiv preprint doi: https://doi.org/10.1101/2020.02.08.20021212)
12. Li Q Cheng Q, Zaho Z, et al. Novel coronavirus infection and AKI in two transplant recipients: case report. www.preprints.org. Posted: 12 March 2020.
13. Wang L, Li X, Chen H et al. Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China. Am J Nephrol. DOI: 10.1159/000507471

Table 1. Comparative table of data on renal impairment across studies

Author	Number of patients	Population	Scr≥133 µmol/L (%)	AKI * (%)	Definition of AKI	Proteinuria (%)	RRT** (%)	Mortality (%)
Guan W ¥	1099	Hospital/ICU	1.6	0.5	KDIGO	n/a	0.8	1.4
Yang X ¥	52	ICU	n/a	29	KDIGO	n/a	17	61.5
Xu X ¥	62	Hospital/ICU	5%	n/a	n/a	n/a	n/a	0
Wang D ¥	138	Hospital/ICU	n/a	3.6	KDIGO	n/a	n/a	4.3
Huang C ¥	41	Hospital/ICU	0	7.0	n/a	n/a	7	15.2
Chen T ¥	274	Hospital/ICU	n/a	11	KDIGO	60.0	1.0	41.0
Chen N ¥	99	Hospital/ICU	n/a	3.0	n/a	n/a	9.0	11.0
Deng Y ¥	225	Hospital/ICU	n/a	18.3	n/a	n/a	n/a	48.0
Wang L §	116	Hospital/ICU	0.0	0	KDIGO	7.2	0	6.0
Cheng Y §	710	Hospital	n/a	3.2	KDIGO	44.1	n/a	12.5
Hong X §	12	Hospital/ICU	n/a	0	n/a	41.7	n/a	n/a
Li Z §	59	Hospital/ICU	n/a	19	n/a	63.0	n/a	5
Xie Z §	60	Hospital	n/a	n/a	n/a	n/a	51.7	n/a

*Acute kidney injury

**Renal replacement therapy

¥ Epidemiologic studies

§ Studies focused on renal impairment