The humoral immune response to SARS-CoV-2 mounts and is durable in symptomatic hemodialysis patients

Vincenzo La Milia[1], Silvia Tonolo[2], Francesco Luzzaro[2], Claudio Bonato[3], Andrea Cavalli[1], Barbara Foglieni[4], Consuelo Debiase[1], Monica Limardo[1], Selena Longhi[1], Chiara Ravasi[1], Sara Viganò[1]

[1]Nephrology and Dialysis Unit, A. Manzoni Hospital, Lecco, Italy

[2]Microbiology Unit, A. Manzoni Hospital, Lecco, Italy

[3]Department of Clinical Services, A. Manzoni Hospital, Lecco, Italy

[4]Transfusion Medicine and Hematology Unit, A. Manzoni Hospital, Lecco, Italy

Correspondence to: Vincenzo La Milia; E-mail: v.lamilia@asst-lecco.it

Hemodialysis (HD) patients are at high risk of SARS-CoV-2 infection (1) and often develop COVID-19 with high mortality rate (2–4). Moreover, HD patients have a reduced humoral immune response (HIR) to infectious disease and might be less likely to mount a detectable antibodies (Abs) response (5).

Several tests are available for IgM and IgG against SARS-CoV-2 (6–8) detection.

No works highlighted long time persistence of SARS-CoV-2 Abs in HD population neither the difference in HIR between symptomatic (CoV-sympt) and asymptomatic (CoV-asympt) HD patients (9). This information may be of fundamental importance to assess the usefulness of a vaccination campaign in these patients.

From March 9th to April 6th 2020, all adult patients on chronic HD were included in the study. The follow-up length was 6 months. Every patient underwent nasopharyngeal swabbing (NPS) for SARS-CoV-2 and anti-SARS-CoV-2 spikes IgG measurement.

Real-Time Polymerase-Chain-Reaction assay was used to confirm the presence of SARS-CoV-2 in NPS specimens. The assay used to detect anti-SARS-CoV-2 spikes IgG was a chemiluminescent immunoassay (Liaison®, DiaSorin, Saluggia, Italy) using two spike glycoproteins (S1 and S2) antigens and detecting IgG against them [cutoff value 15 AU/ml, sensitivity 97.4% (95% CI: 86.8%-99.5%), specificity 98.5% (95% CI: 97.6%-99.1%)].

In NPS positive patients Abs titer was dosed at 2 months and then monthly from symptoms onset/NPS positivity. In NPS negative patients, Abs titer was dosed about 2 months and 6 months from the first NPS for SARS-CoV-2.

In health care staff members, who had a positive NPS and were symptomatic for SARS-CoV-2 infection, Abs titer was dosed only once, approximately 6 months after the onset of symptoms.

After March 2020, in our HD center, NPS swabbing and blood sampling for serology were part of the normal clinical assessment of all HD patients. All patients and health care staff members signed informed consent.

The data were expressed as mean values ± s.d. or as median values and interquartile ranges. The HSD test of Tukey-Kramer, repeated measures analysis of variance and paired t-test and Wilcoxon's signed-rank test were used.

Between March 9th to April 6th 2020, 210 HD patients were studied. Fifty-six (27%) of them were positive to SARS-CoV-2 NPS while 154 (73%) did not (3).

Among those with positive NPS, 29 patients (52%) were CoV-sympt and 27 (48%) remained CoV-asympt. Twenty-six CoV-sympt patients were treated as inpatients because of severe symptoms (fever and interstitial pneumonia), while 3 with mild symptoms were treated as outpatients.

Within the inpatients CoV-sympt group, 13 (50%) died and 13 (50%) recovered (one of them refused to continue HD and was lost to follow-up) while all 3 CoV-sympt outpatients recovered. Eleven members (26%) of the HD health care staff had positive NPS and symptomatic for SARS-CoV-2 infection in the same period; they were all treated as outpatients (Figure S1 in Supplementary Material).

All 15 CoV-sympt survivors patients developed anti-SARS-CoV-2 spikes IgG (one patient was transplanted at 5th month).

Mean CoV-sympt survivors patients anti-SARS-CoV-2 spikes IgG titers were 98 ± 46 AU/mL, 150 ± 111 AU/mL, 107 ± 65 AU/mL, 110 ± 67 AU/ml, 80 ± 48 AU/mL, respectively at 2, 3, 4, 5 and 6 months (Figure 1). The anti-SARS-CoV-2 spikes IgG titers had a peak at the 3rd month of follow-up and then a

slow reduction until 6th month, reaching almost the threshold of statistical significance (p=0.05), but always well above the cut-off threshold of positivity (>15 AU/mL). One CoV-sympt survivors patient lost anti-SARS-CoV-2 spikes IgG at 3rd month of follow-up.

Only two CoV-asympt patients (7%) were seropositive 2 months from the first NPS: at 3 months follow-up one of them became seronegative and the other died with persistent seropositivity (21.4 AU/mL). All other CoV-asympt patients had anti-SARS-CoV-2 spikes IgG titer below the limit of positivity in all assays performed (at 2nd month after NPS positivity for SARS-CoV-2 and then every month until the 6th month).

Only two negative NPS patients (1%) developed anti-SARS-CoV-2 spikes IgG which remained positive until the 6th month.

Mean anti-SARS-CoV-2 spikes IgG of the 11 HD health care staff members who suffered from SARS-CoV-2 infection was 68±51 AU/mL at six months. Only two (18%) nurses resulted seronegative.

Anti-SARS-Cov2 spikes IgG titer of Cov-sympt survivors patients were not lower than Cov-sympt health care staff members (80 ± 48 AU/mL vs 68±51 AU/mL, respectively, p=0.5).

To date it is not known whether HD patients infected with SARS-CoV-2 develop a long lasting HIR and if the Abs response is different between Cov-sympt, CoV-asympt patients and general population (7,10).

Data from studies published until now showed that HD patients are able to mount an Abs response against SARS-CoV-2 (9) and is more frequent in symptomatic patients. Our data confirmed these results, in fact 100% of our Cov-sympt survivors patients developed an Abs response and a subsequent titer decline with persistent seropositivity at 6 months.

Of course, a protective role of anti-SARS-CoV-2 spikes IgG, must be still demonstrated especially against reinfection. Studies regarding general population showed that asymptomatic SARS-CoV-2 infected patients tend to lose their HIR against the virus over time (10-11). In our case, CoV-asympt patients tended to not produce a HIR. However, in individuals with asymptomatic or mild COVID-19, the SARS-CoV-2 seems to induce a stronger memory T cell than HIR, therefore seroprevalence might be a bad indicator of protection against the virus (12).

Our study is monocentric and involves a small HD population. However, the main advantage of our study is that the whole HD population of patient was tested by NPS and serology. In addition, we were able to assess, not only the HIR of HD patients but also the persistence over time of this Abs response. To the best of our knowledge, this is the first study to assess Abs response persistence in a (relative) long period of time (6 months).

The results of a recent study are comparable to our results, but in a smaller HD patient population and with a short follow-up of about 3 months (13).

The epidemiological trend of the SARS-CoV-2 pandemic will provide us with important information on the ability of anti-SARS-CoV-2 spikes IgG to protect against a virus re-infection. This information would be of high value, seen that it would allow HD patient to access to a vaccination campaign as, as we demonstrated, they seem responsive to viral immune stimulation.

In conclusion, in survivor HD patients, symptomatic Covid-19 disease confers higher and durable anti-SARS-CoV-2 spikes IgG titers then asymptomatic one in chronic HD patients and these Abs titers were not lower than Cov-sympt health care staff members.

CONFLICT OF INTEREST STATEMENT

All Authors have no conflicts of interest and have not received any funding for this study.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

REFERENCES

1. Clarke C, Prendecki M, Dhutia A, Ali MA, Sajjad H, Shivakumar O, et al. High Prevalence of Asymptomatic COVID-19 Infection in Hemodialysis Patients Detected Using Serologic Screening. J Am Soc Nephrol. 2020;31(9):1969–75.

2. Corbett RW, Blakey S, Nitsch D, Loucaidou M, McLean A, Duncan N, et al. Epidemiology of COVID-19 in an Urban Dialysis Center. J Am Soc Nephrol. 2020 Aug;31(8):1815–23.

3. La Milia V, Bacchini G, Bigi MC, Casartelli D, Cavalli A, Corti M, et al. COVID-19 Outbreak in a Large Hemodialysis Center in Lombardy, Italy. Kidney Int reports. 2020 Jul;5(7):1095–9.

4. Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int. 2020 Oct 15;

5. Baragetti I, El Essawy B, Fiorina P. Targeting Immunity in End-Stage Renal Disease. Am J Nephrol. 2017;45(4):310–9.

6. Krammer F, Simon V. Serology assays to manage COVID-19. Science. 2020;368(6495):1060–1.

7. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020;26(8):1200–4.

8. Du Z, Zhu F, Guo F, Yang B, Wang T. Detection of antibodies against SARS-CoV-2 in patients with COVID-19. J Med Virol. 2020 Apr 3;

9. De Vriese AS, Reynders M. IgG Antibody Response to SARS-CoV-2 Infection and Viral RNA Persistence in Patients on Maintenance Hemodialysis. Am J Kidney Dis. 2020;76(3):440–1.

10. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. N Engl J Med. 2020;383(18):1724–34.

11. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, Elliott J, Hofmann C, Hausner MA, et al. Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N Engl J Med. 2020;383(11):1085–7.

12. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin J-B, Olsson A, et al. Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. Cell. 2020;183(1):158-168.e14.

13. Labriola L, Scohy A, Seghers F, Perlot Q, De Greef J, Desmet C, Romain C, Morelle J, Yombi JC, Kabamba B, Rodriguez-Villalobos H, Jadoul M. A Longitudinal, 3-Month Serologic Assessment of SARS-CoV-2 Infections in a Belgian Hemodialysis Facility. Clin J Am Soc Nephrol. 2020 Nov 18:CJN.12490720. doi: 10.2215/CJN.12490720. Epub ahead of print. PMID: 33208402.

Figure Caption

FIGURE 1: Anti-SARS-CoV-2 spikes IgG titer in CoV-asympt, CoV-sympt survivors, NPS swab-negative and CoV-sympt health staff members group during 6 months follow-up.

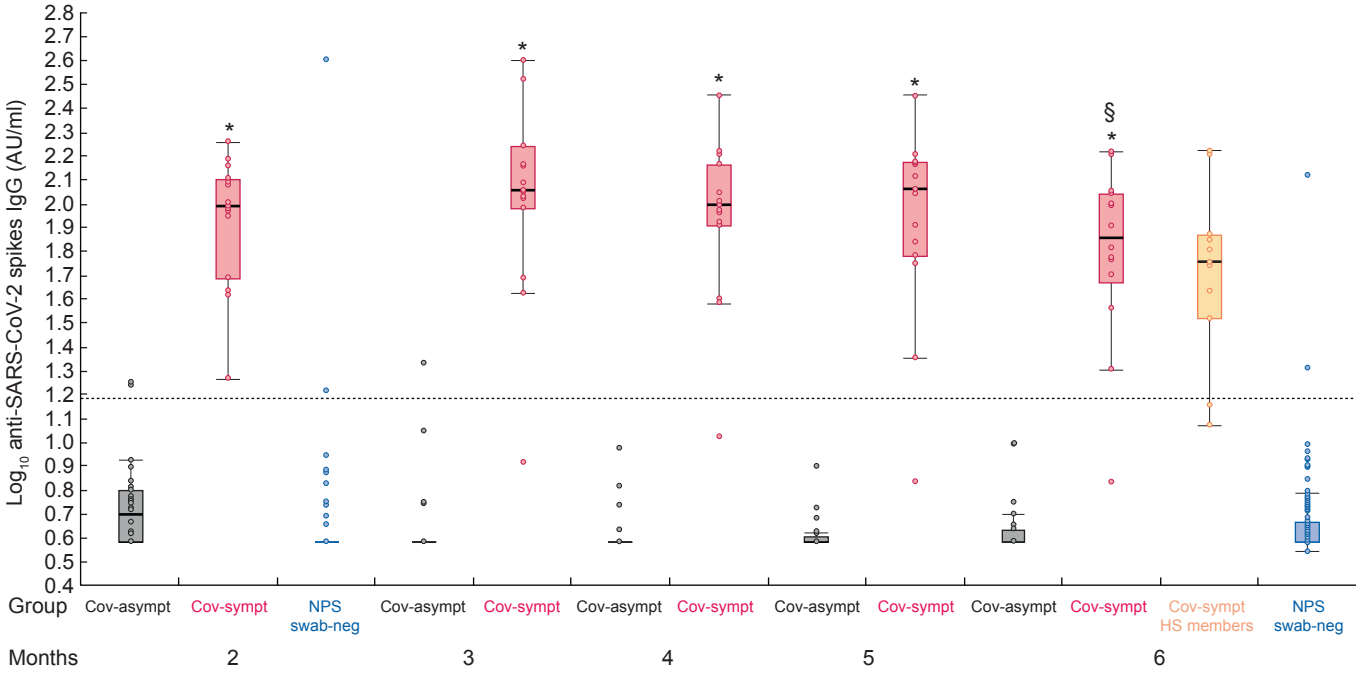
In CoV-asympt and CoV-sympt survivors, anti-SARS-CoV-2 spikes IgG titer was dosed at 2 months and then monthly from symptoms onset/NPS positivity. In NPS swab negative patients, anti-SARS-CoV-2 spikes IgG titer was dosed about 2 months and 6 months from the first NPS for SARS-CoV-2.

In CoV-sympt health care staff members, anti-SARS-CoV-2 spikes IgG titer was dosed only once, approximately 6 months after the onset of symptoms.

In the Figure are showed the outlier box plot; the horizontal line within the box represents the median sample value; the ends of the box represent the 75^{th} and 25^{th} quantiles, respectively; the distance or the difference between the 75^{th} and 25^{th}, also expressed as 3^{rd} and 1^{st} quartile, is the interquartile range; each box has lines, called whiskers, that extend from each end; the whiskers extend from ends of the box to outermost data point that falls within the distances computed as follows: 3^{rd} quartile + 1.5*(interquartile range), 1^{st} quartile - 1.5*(interquartile range), if the data points do not reach the computed ranges, then the whiskers are determined by the upper and lower data point values (not including outliers).

The the dashed black line represents the sensitivity threshold of the anti-SARS-CoV-2 spikes IgG dosing method.

*P<0.0001 vs CoV-asympt and NPS swab negative group; §p=0.5 vs CoV-sympt health care staff members



NDT-02169-2020.R2-fig1