


ORIGINAL ARTICLE

Infection

Trajectories of clinical and laboratory characteristics associated with COVID-19 in hemodialysis patients by survival

Sheetal Chaudhuri^{1,2}  | Rachel Lasky¹ | Yue Jiao¹ | John Larkin¹ | Caitlin Monaghan¹ | Anke Winter³ | Luca Neri³ | Peter Kotanko^{4,5} | Jeffrey Hymes⁶ | Sangho Lee⁷ | Yuedong Wang⁸ | Jeroen P. Kooman² | Franklin Maddux⁹ | Len Usvyat¹

¹Global Medical Office, Fresenius Medical Care, Waltham, Massachusetts, USA

²Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

³Global Medical Office, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany

⁴Renal Research Institute, New York, New York, USA

⁵Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁶Fresenius Kidney Care, Fresenius Medical Care North America, Waltham, Massachusetts, USA

⁷Nephrology, Kyung Hee University Hospital at Gangdong, Seoul, Korea

⁸Statistics and Applied Probability, University of California, Santa Barbara, California, USA

⁹Global Medical Office, Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany

Correspondence

Len Usvyat, Fresenius Medical Care, Global Medical Office, 920 Winter Street, Waltham, MA 02451 USA.
Email: len.usvyat@fmc-na.com

Funding information

Fresenius Medical Care

Abstract

Introduction: The clinical impact of COVID-19 has not been established in the dialysis population. We evaluated the trajectories of clinical and laboratory parameters in hemodialysis (HD) patients.

Methods: We used data from adult HD patients treated at an integrated kidney disease company who received a reverse transcription polymerase chain reaction (RT-PCR) test to investigate suspicion of a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection between May 1 and September 1, 2020. Nonparametric smoothing splines were used to fit data for individual trajectories and estimate the mean change over time in patients testing positive or negative for SARS-CoV-2 and those who survived or died within 30 days of first suspicion or positive test date. For each clinical parameter of interest, the difference in average daily changes between COVID-19 positive versus negative group and COVID-19 survivor versus nonsurvivor group was estimated by fitting a linear mixed effects model based on measurements in the 14 days before (i.e., Day -14 to Day 0) Day 0.

Results: There were 12,836 HD patients with a suspicion of COVID-19 who received RT-PCR testing (8895 SARS-CoV-2 positive). We observed significantly different trends ($p < 0.05$) in pre-HD systolic blood pressure (SBP), pre-HD pulse rate, body temperature, ferritin, neutrophils, lymphocytes, albumin, and interdialytic weight gain (IDWG) between COVID-19 positive and negative patients. For COVID-19 positive group, we observed significantly different clinical trends ($p < 0.05$) in pre-HD pulse rate, lymphocytes, neutrophils, and albumin between survivors and nonsurvivors. We also observed that, in the group of survivors, most clinical parameters returned to pre-COVID-19 levels within 60–90 days.

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Conclusion: We observed unique temporal trends in various clinical and laboratory parameters among HD patients who tested positive versus negative for SARS-CoV-2 infection and those who survived the infection versus those who died. These trends can help to define the physiological disturbances that characterize the onset and course of COVID-19 in HD patients.

KEYWORDS

albumin, body temperature, clinical trajectories, COVID-19, creatinine, ferritin, interdialytic weight gain, lymphocytes, neutrophils, pulse rate, systolic blood pressure

INTRODUCTION

The coronavirus disease (COVID-19) pandemic has greatly affected the dialysis community. Dialysis patients appear to be at increased risk for viral transmission with relatively high mortality rates ranging from 11% to 30%.¹⁻⁶ During the first half of 2020, there were over 11,200 COVID-19 hospitalizations among Medicare beneficiaries undergoing dialysis in the United States.⁷ Various parameters such as pulse, body temperature, C-reactive protein (CRP), and lymphocyte counts at presentation were found to be associated with COVID-19 mortality in kidney failure.⁴ However, the incubation time has not been clearly defined and patients may be infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and potentially infectious weeks before presentation with symptoms. Early detection of changes in physiological parameters has been suggested to aid the identification/prediction of patients at risk for COVID-19.⁸ Apart from early detection, trends in clinical and laboratory parameters may also have prognostic significance. For example, distinct differences in trajectories of clinical and laboratory parameters before the start of kidney replacement therapy have been shown for patients who survived versus died during the first year on hemodialysis (HD).⁹

Albeit the clinical presentations in COVID-19 have been somewhat established,⁴ the changes in clinical parameters before presentation that characterize disease onset in humans are unknown secondary to a scarcity of longitudinal data available in the general population or collected in registries in the kidney failure population. HD patients have robust routine data collected in electronic health records (EHRs) affording the opportunity to define the pathophysiological disturbances characterizing the onset and course of COVID-19 in kidney failure patients. The goal of this analysis was to compare trends in clinical and laboratory parameters between HD patients who tested positive or negative for SARS CoV-2. The second goal of this study was to compare clinical trends between survivors and nonsurvivors who were diagnosed with COVID-19.

METHODS

General design

We used data from HD patients treated at a dialysis network in the United States of an integrated kidney disease company (Fresenius Medical Care, Waltham, MA, USA) between May and November 2020. HD patients who were suspected to have a SARS-CoV-2 infection at the outpatient dialysis clinics universally received reverse transcription polymerase chain reaction (RT-PCR) testing to diagnosis COVID-19. For this analysis, we retrospectively evaluated the trends in clinical and laboratory parameters 90 days before the date of suspicion for SARS-CoV-2 infection among HD patients who were diagnosed RT-PCR COVID-19 positive versus those that were negative. Among HD patients with RT-PCR confirmed COVID-19, we also assessed at the trajectories for those who survived versus died within 30 days after suspicion of SARS-CoV-2 infection.

This analysis was performed under a protocol reviewed by New England Institutional Review Board (Needham Heights, MA, USA; Version 1.0 NEIRB# 17-1376378-1) who determined this analysis of existing patient data that were de-identified by the investigator was exempt and did not require informed consent. This analysis was conducted in adherence with the Declaration of Helsinki.

Patient population

We included data from adult (age ≥ 18 years) HD patients who received RT-PCR testing to investigate suspicion of a SARS-CoV-2 infection between May 01 and September 01, 2020. We required patients to have a minimum follow-up period of 90 days; follow-up data were captured through November 30, 2020 as applicable. Suspicion of SARS-CoV-2 infection was determined at presentation by active signs and symptoms of a flu-like illness. We excluded data from patients under investigation for SARS-CoV-2 that did not have a documented

RT-PCR result, which included asymptomatic patients who were exposed to someone with known COVID-19 and were monitored for symptoms, as well as patients who were diagnosed with COVID-19 outside the outpatient clinic.

We used the first reported suspicion date to define the Day 0 among COVID-19 positive patients. In limited cases without a documented suspicion date, we used the RT-PCR positive test date to define the Day 0. For a control group, we identified patients who had one or more negative COVID-19 test result without any positive result during the analysis period. We used the first COVID-19 negative test date to define the Day 0 since the date of suspicion for negative patients was not recorded in the provider's EHR. Patients with invalid/inconclusive test results were excluded from the analysis.

Statistical methods

We computed mean daily values for an array of clinical variables across the 90 days before Day 0 for COVID-19 positive and COVID-19 negative groups. We reported findings from a priori selection of variables that appeared to have notable changes before COVID-19; these included pre-HD systolic blood pressure (SBP), pre-HD pulse, pre-HD body temperature, lymphocytes, neutrophils, ferritin, albumin, interdialytic weight gain (IDWG), and creatinine.

All data were collected during provision of standard medical care for HD patients. Data on SBP, pulse, body temperature, IDWG was collected on a per HD treatment basis. Laboratories were collected monthly with exception of ferritin that was collected on a quarterly basis.

Nonparametric smoothing splines¹⁰ were constructed to fit data for individual trajectories and estimate the mean change over time since first suspicion/COVID-19 positive or negative date. Among COVID-19 positive patients, we stratified data for those who survived or died within 30 days of first Day 0; trajectories were plotted 90 days after Day 0 in survivors and up to 30 days after Day 0 in COVID-19 in patients who died.

For each clinical parameter of interest, the difference in average daily changes between COVID-19 positive versus negative group and COVID-19 survivor versus non-survivor group was estimated by fitting a linear mixed effects model based on measurements in the 14 days before (i.e., day -14 to Day 0) Day 0. The analysis used all available data without any imputation.

Average value of clinical and laboratory parameters on Day 0 was compared using unpaired t-test. Average value of clinical and laboratory parameters on Day 0 between survivors and nonsurvivors was also compared using unpaired t-test.

TABLE 1 Demographics and comorbidities of patients who tested COVID-19 positive and negative

| Parameters | COVID-19 positive | COVID-19 negative |
|--|-------------------|-------------------|
| Total number of patients | 8895 | 3941 |
| Male | 54% | 55% |
| White | 37% | 43% |
| Mean age as of first symptom date (SD) | 61.8 (14.2) | 60.3 (14.7) |
| Mean vintage as of first symptom date (SD) | 4.0 (4.1) | 3.8 (3.8) |
| Diabetes | 69% | 66% |
| Congestive heart failure | 21% | 22% |
| Ischemic heart disease | 24% | 24% |

Analyses were performed using SAS version 9.4 (SAS, Cary, NC, USA). Smoothing splines and visualizations were conducted using R version 3.5.2 (R Foundation, Vienna, Austria).

RESULTS

Characteristics of HD patients who received COVID-19 testing

There were 12,836 HD patients with a suspicion of COVID-19 who received RT-PCR testing (8895 COVID-19 positive and 3941 COVID-19 negative patients) between 01 May 01 and September 01, 2020. The demographics and comorbidities for the two groups of patients are shown in Table 1. There was a slightly lower proportion of patients with a white race and higher proportion of patients with diabetes in the COVID-19 positive group compared with the negative group. The mean number of days between the suspicion date and the positive test date in COVID-19 positive group was 5.6 days.

Trajectories of vital signs before COVID-19 testing

We observed the COVID-19 positive group had decreases in pre-HD SBP weeks before Day 0; the SBP was around 5 mmHg lower at the suspicion date versus 14 days prior (Figure 1). Contrary to this, the COVID-19 negative group had trends for increases in pre-HD SBP in the weeks before testing. The linear mixed effects model estimated the daily change in pre-HD SBP during the 14 days before Day 0 and identified the COVID-19 positive group had an average decrease of -0.3 mmHg/day; this

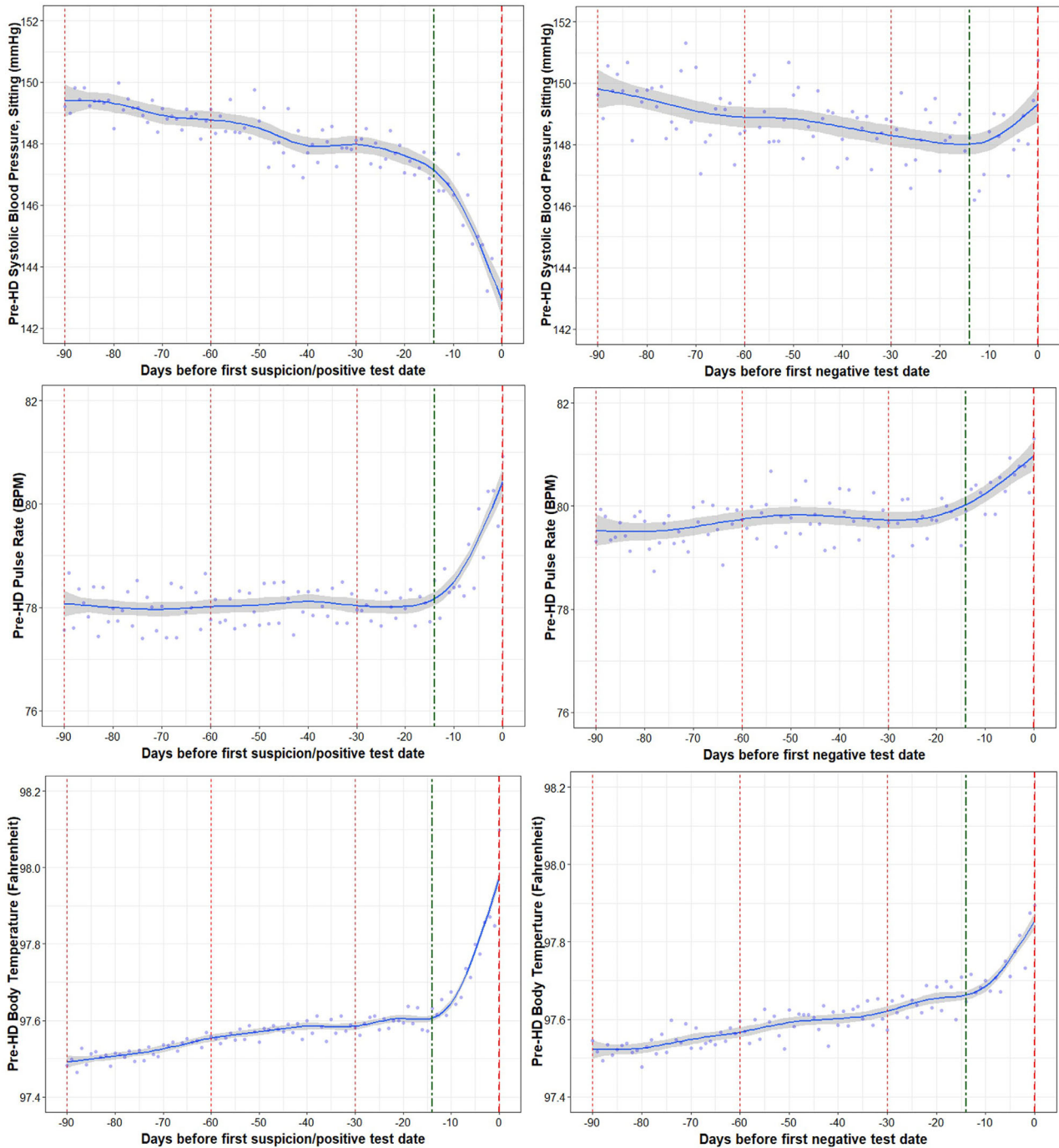


FIGURE 1 Trajectories of pre-HD vital signs (SBP, pulse rate, body temperature) in COVID-19 positive and negative patients [Color figure can be viewed at wileyonlinelibrary.com]

was distinct compared to the average increase of 0.2 mmHg/day found in the COVID-19 negative group ($p < 0.0001$) (Table 2).

The COVID-19 positive group was also found to have subtle increases in the pre-HD pulse and body temperature in the week before Day 0. These trends were consistent with the COVID-19 negative group but less pronounced. The

average daily change in pulse rate and body temperature was found to be significantly larger in the COVID-19 positive versus COVID-19 negative group ($p < 0.0001$).

The average values for the pre-HD SBP, pulse, and body temperature on Day 0 is shown in Table 3. There were significant differences between groups for pre-HD SBP and body temperature ($p < 0.0001$).

TABLE 2 Average daily change in clinical and laboratory parameters 14 days prior to Day 0

| Parameters | Mean daily change | Mean daily change | p value* |
|-----------------------------|-------------------|-------------------|----------|
| | COVID-19 positive | COVID-19 negative | |
| Pre-HD SBP (mmHg) | -0.2873 | 0.2293 | <0.0001 |
| Pre-HD pulse rate (BPM) | 0.1728 | 0.0880 | <0.0001 |
| Pre-HD body temperature (F) | 0.0259 | 0.0140 | <0.0001 |
| Ferritin (ng/ml) | 26.1162 | 3.6907 | <0.0001 |
| Lymphocytes (%) | -0.1772 | -0.1208 | 0.0063 |
| Neutrophils (%) | 0.2445 | 0.1438 | 0.0002 |
| Albumin (g/dl) | -0.0123 | -0.0035 | 0.0004 |
| IDWG (kg) | -0.0441 | 0.0068 | <0.0001 |
| Creatinine (mg/dl) | 0.0127 | 0.0222 | 0.5561 |

Note: Average daily changes are compared using linear mixed effects model in 14 days prior day 0.

*p value compares slopes in COVID-19 positive versus COVID-19 negative patients.

Trajectories of inflammatory markers before COVID-19 testing

Serum ferritin levels were found to have increased by around 400 ng/ml in the COVID-19 positive group in the 14 days prior to Day 0 (Figure 2). There was a daily change in ferritin of 26.12 ng/ml/day during the 14 days before Day 0 in the COVID-19 positive group, which was distinct compared to the COVID-19 negative group that exhibited no remarkable changes ($p < 0.0001$).

The percentage of lymphocytes were found to decrease below 20% in both COVID-19 positive and negative groups with a significant difference in trends of daily change ($p = 0.0063$). Neutrophils showed an increasing trend in the COVID-19 positive and negative group 14 days prior to Day 0 and the difference between the groups was significant ($p = 0.0002$).

On Day 0, ferritin and neutrophils were significantly higher in the COVID-19 positive group compared to the negative group ($p < 0.05$).

Trajectories of nutritional markers before COVID-19 testing

Among both groups, there was a decline in serum albumin in the 14 days prior to Day 0, yet the decline was more pronounced in the COVID-19 positive group compared to COVID-19 negative group. The decline in albumin was an average of 0.012 g/dl per day in the COVID-19 positive group compared to the decline of an average of 0.004 g/dl in the COVID-19 negative group ($p = 0.0004$) (Figure 3). Notably, IDWG decreased by of 0.6 kg per day in the COVID-19 positive group in the 14 days prior to Day 0 compared to

TABLE 3 Average value of clinical and laboratory parameters on Day 0

| Parameters | COVID-19 positive | COVID-19 negative | p value |
|-----------------------------|-------------------|-------------------|---------|
| Pre-HD SBP (mmHg) | 143.28 | 150.74 | <0.0001 |
| Pre-HD pulse rate (BPM) | 80.93 | 81.32 | 0.3266 |
| Pre-HD body temperature (F) | 98.10 | 97.89 | <0.0001 |
| Ferritin (ng/ml) | 1500.78 | 1038.42 | 0.0004 |
| Lymphocytes (%) | 17.42 | 18.01 | 0.1794 |
| Neutrophils (%) | 70.19 | 68.67 | 0.0064 |
| Albumin (g/dl) | 3.52 | 3.63 | 0.0074 |
| IDWG (kg) | 1.53 | 2.30 | <0.0001 |
| Creatinine (mg/dl) | 9.04 | 8.76 | 0.3725 |

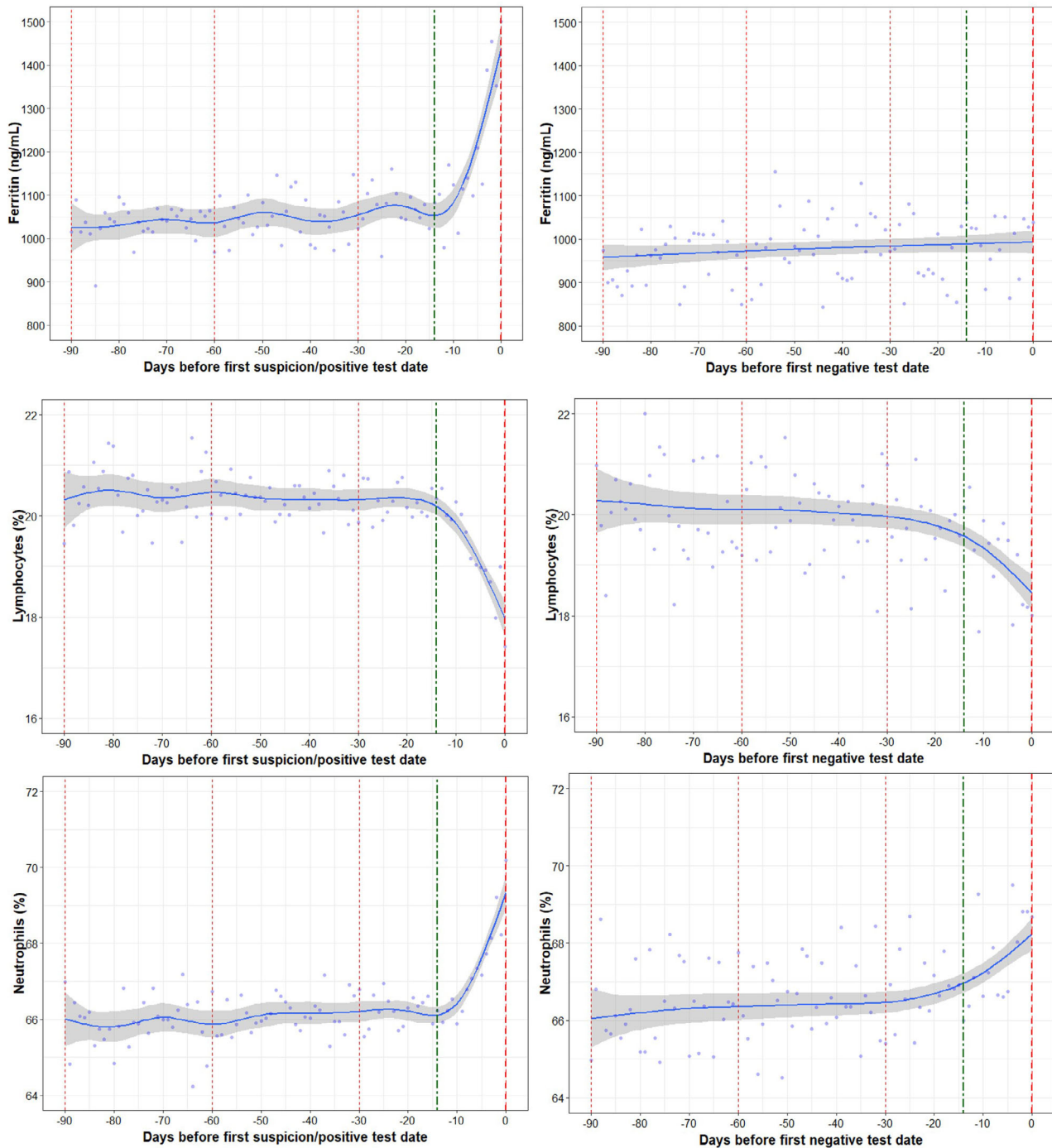


FIGURE 2 Trajectories in inflammatory markers (ferritin, lymphocytes, and neutrophils) in COVID-19 positive and negative patients [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

almost no change in COVID-19 negative group ($p < 0.0001$). There were no differences in the trends of creatinine between the COVID-19 positive and negative group.

Albumin and IDWG were significantly lower in the COVID-19 positive group on Day 0 compared to COVID-19 negative group on the negative test date.

Characteristics of HD patients with COVID-19 by survival

Table 4 shows the demographics and comorbidities for patients diagnosed with COVID-19 who died within 30 days of COVID-19 positive date (nonsurvivors) versus those who survived (survivors). There were 7897 survivors

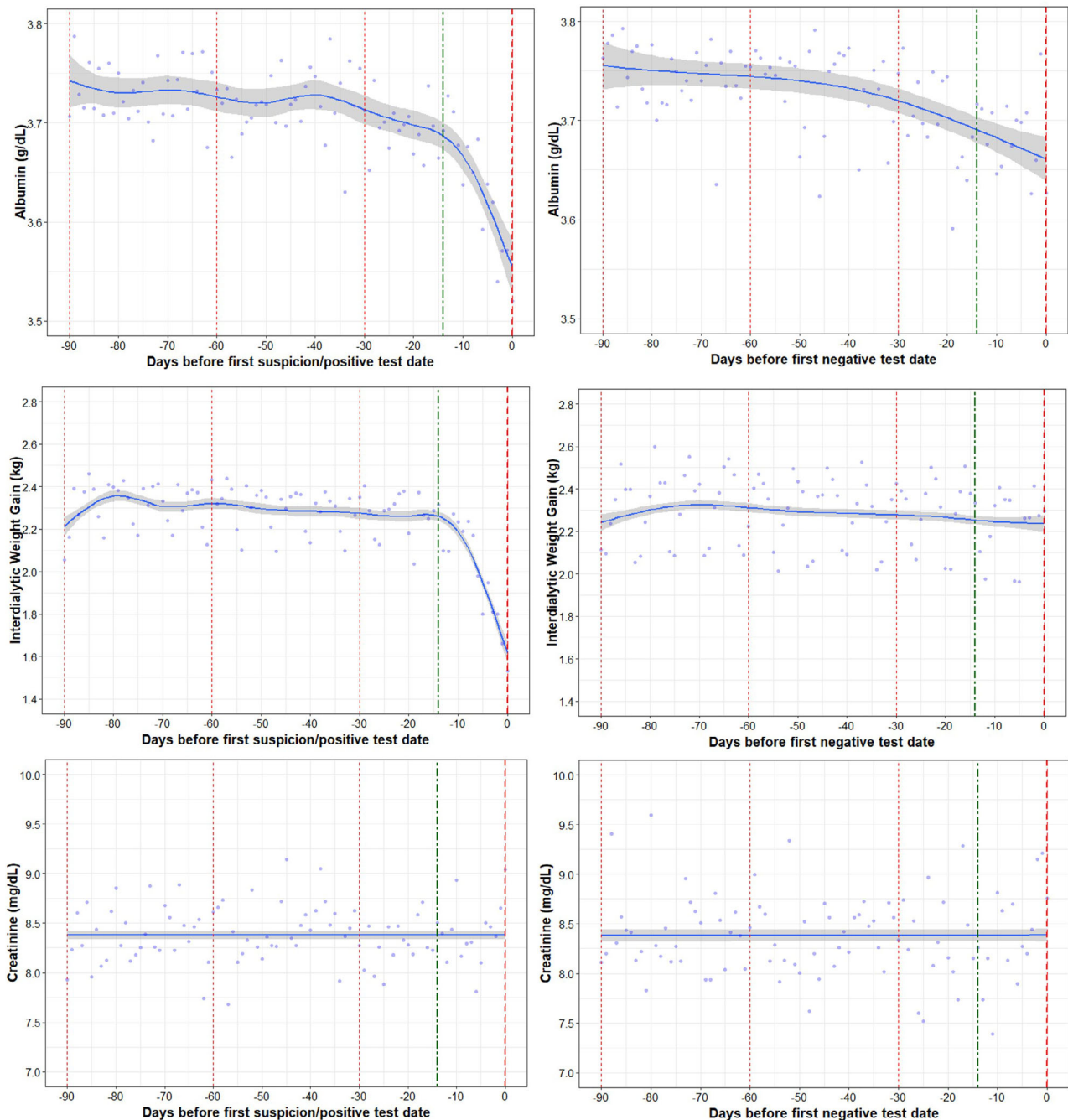


FIGURE 3 Trajectories in nutritional markers (albumin, IDWG, creatinine) in COVID-19 positive and negative patients [Color figure can be viewed at wileyonlinelibrary.com]

out of the 8895 COVID-19 positive patients. The 998 non-survivors were more often older, male, white race and had a higher comorbidity burden and longer dialysis vintage.

Trajectories of vital signs before and after COVID-19 by survival

We observed a significant increase in the pre-HD pulse rate in the nonsurvivors versus the survivors

with COVID-19. The linear mixed effects model showed an average increase of 0.29 BPM per day in the 14 days prior day 0 in the nonsurvivors compared to an average increase of 0.16 BPM per day in survivors ($p < 0.0001$) (Table 5). There was a difference in the pre-HD pulse rate between the survivors and nonsurvivors on Day 0 ($p = 0.0528$) (Table 6). Among survivors, it took 60 or more days after Day 0 for pre-HD pulse to return to levels observed in the months before COVID-19.

TABLE 4 Demographics and comorbidities of COVID-19 survivors and nonsurvivors

| Parameters | Survivors | Nonsurvivors |
|--|-------------|--------------|
| Total number of patients | 7897 | 998 |
| Male | 53% | 60% |
| White | 37% | 42% |
| Mean age as of first symptom date (SD) | 60.8 (14.1) | 69.1 (12.5) |
| Mean vintage as of first symptom date (SD) | 3.9 (4.1) | 4.7 (4.0) |
| Diabetes | 68% | 80% |
| Congestive heart failure | 21% | 28% |
| Ischemic heart disease | 23% | 29% |

There difference in the daily change of pre-HD DBP and body temperature in survivors versus nonsurvivors during the 14 days prior to Day 0 was not significant. On Day 0, there were distinctions in pre-HD SBP between the survivors and nonsurvivors ($p = 0.0002$). Among survivors, pre-HD SBP began to increase back up again around 10 days following Day 0 and it took 30 days or more to return to levels observed before the infection; trends in nonsurvivors showed further and more pronounced decreases in pre-HD SBP during the 30 days after Day 0 (Figure 4). There were no differences in pre-HD body temperature between the survivors and nonsurvivors on Day 0 ($p = 0.7363$). Pre-HD body temperature returned to levels seen in the months before COVID-19 around 60 days after Day 0.

TABLE 5 Average daily changes in clinical and laboratory parameters 14 days prior to Day 0

| Parameters | Survivors slope | Nonsurvivors slope | p value* |
|-----------------------------|-----------------|--------------------|------------|
| Pre-HD SBP (mmHg) | -0.2786 | -0.3575 | 0.2222 |
| Pre-HD pulse rate (BPM) | 0.1582 | 0.2862 | <0.0001 |
| Pre-HD body temperature (F) | 0.0261 | 0.0245 | 0.5362 |
| Ferritin (ng/ml) | 24.4168 | 41.1784 | 0.1998 |
| Lymphocytes (%) | -0.1569 | -0.3420 | <0.0001 |
| Neutrophils (%) | 0.2207 | 0.4345 | <0.0001 |
| Albumin (g/dl) | -0.0125 | -0.0126 | 0.9854 |
| IDWG (kg) | -0.0443 | -0.0438 | 0.9365 |
| Creatinine (mg/dl) | 0.0129 | 0.0067 | 0.8301 |

Note: Average daily changes are compared using linear mixed effects model in 14 days prior to Day 0 in COVID-19 positive patients.

* p value compares slopes in survivors versus nonsurvivors.

TABLE 6 Average value of clinical and laboratory parameters on Day 0

| Parameters | Survivors | Nonsurvivors | P value |
|-----------------------------|-----------|--------------|-----------|
| Pre-HD SBP (mmHg) | 143.98 | 136.5 | 0.0002 |
| Pre-HD pulse rate (BPM) | 80.73 | 82.77 | 0.0528 |
| Pre-HD body temperature (F) | 98.1 | 98.07 | 0.7363 |
| Ferritin (ng/ml) | 1497.37 | 1567.57 | 0.7386 |
| Lymphocytes (%) | 17.75 | 14.45 | 0.0038 |
| Neutrophils (%) | 69.67 | 74.77 | 0.0003 |
| Albumin (g/dl) | 3.54 | 3.21 | 0.0204 |
| IDWG (kg) | 1.56 | 1.26 | 0.0432 |
| Creatinine (mg/dl) | 9.06 | 8.68 | 0.7392 |

Trajectories of inflammatory markers before and after COVID-19 by survival

There were significant differences in inflammatory markers like lymphocytes and neutrophils in both COVID-19 positive survivors and nonsurvivors. The average decrease in the percentage of lymphocyte was about 0.34% in the 14 days prior to Day 0 in nonsurvivors compared to 0.16% in survivors ($p < 0.0001$). Similarly, there was a difference in the 14-day trend for neutrophils between the survivors and nonsurvivors ($p < 0.0001$). There were also significant differences in the percentage of lymphocytes and neutrophils between the survivors and nonsurvivors on Day 0.

As shown in Figure 5, the disturbances in inflammatory markers returned to the levels seen in the months before the infection within about 30 days after Day 0 in patients who survived. Patients who died experienced more robust decreasing trends in lymphocyte levels as well as more robust increasing trends in neutrophil levels during the 30 days following Day 0, as compared to those who survived.

Difference in Ferritin between survivors and nonsurvivors was not significant during 14 days prior to Day 0 and on Day 0.

Trajectories of nutritional markers before and after COVID-19 by survival

Albumin levels among patients who died decreased steadily during the 30 days following Day 0, whereas albumin levels began to rise after approximately 15 days following Day 0 for patients who survived.

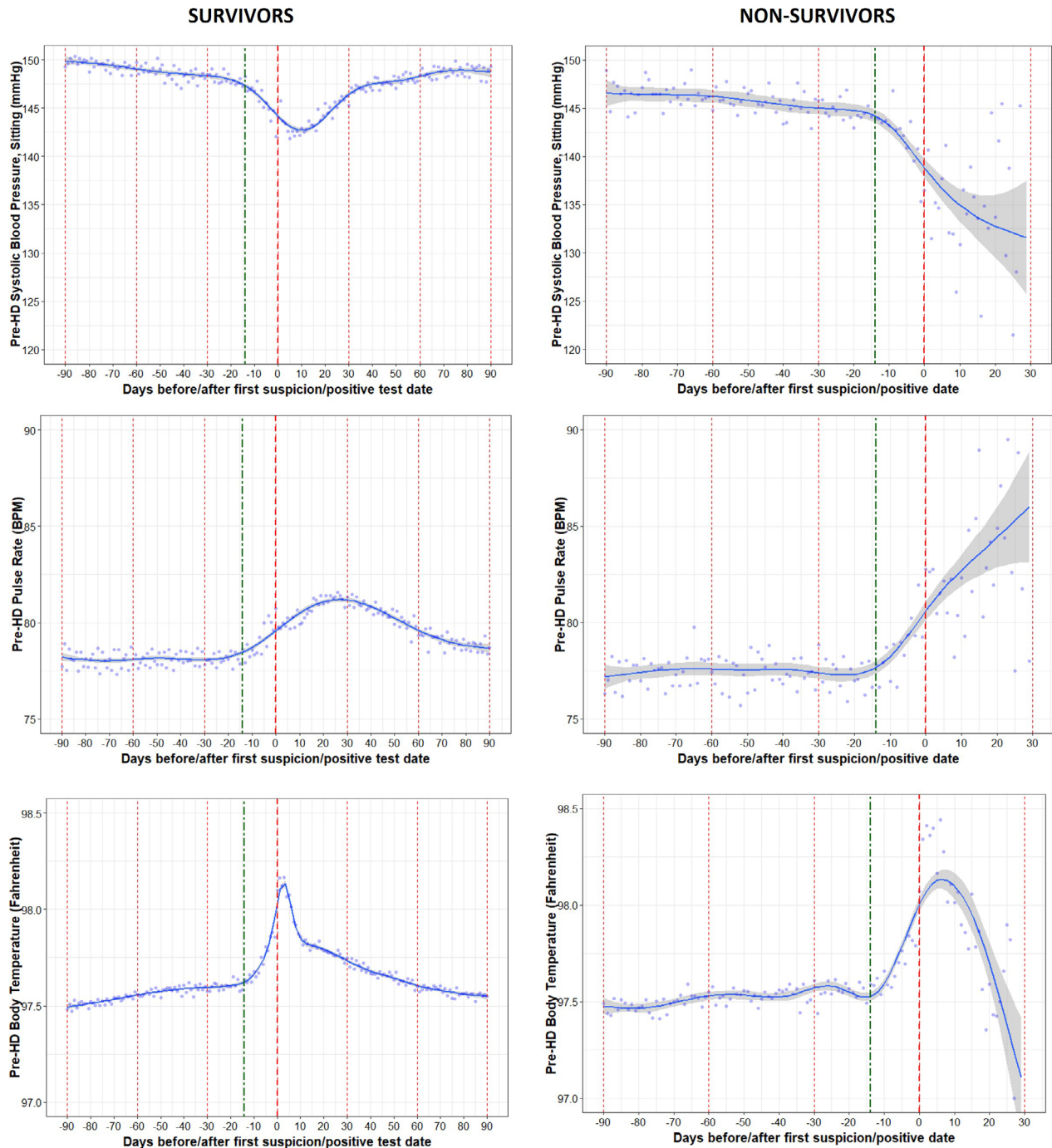


FIGURE 4 Trajectories in pre-HD vital signs (SBP, pulse rate, body temperature) in COVID-19 positive survivors and nonsurvivors [Color figure can be viewed at wileyonlinelibrary.com]

Patients who died also experienced a larger decline in IDWG than the group who survived. Survivors experienced a decline in creatinine shortly after Day 0, which remained lower than in the months before COVID-19 throughout the following 90 days. The average daily change was significantly different between groups for all nutritional markers (albumin and IDWG) in the 14 days prior to Day 0 test date between the survivors

and nonsurvivors ($p < 0.05$). The difference in the slope of creatinine between the survivors and nonsurvivors was not significant ($p = 0.7392$).

There were also significant differences in albumin and IDWG between the survivors and nonsurvivors on Day 0. Among survivors, the nutritional parameters took around 60–90 days to return to the same levels as in the months before the infection (Figure 6).

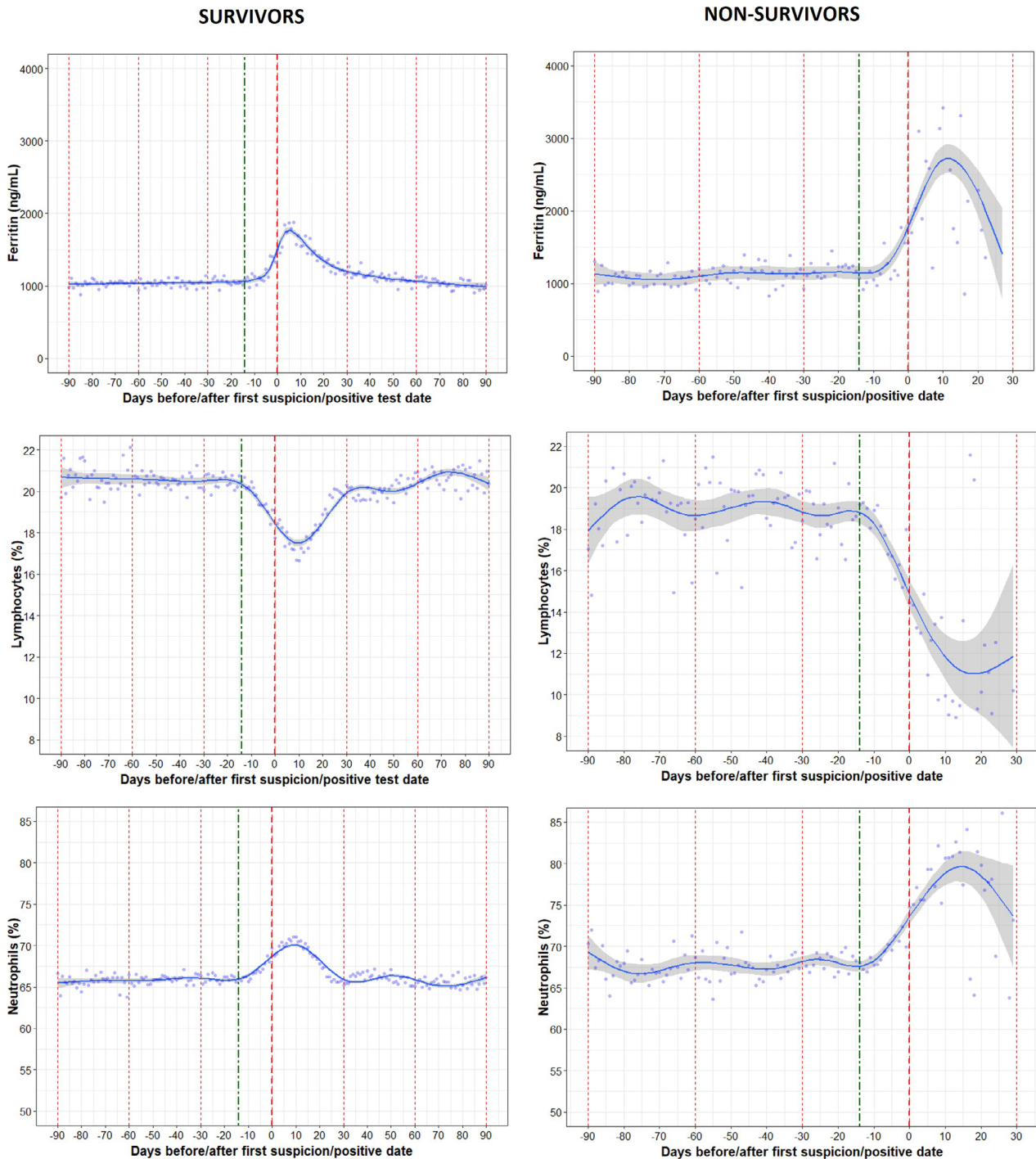


FIGURE 5 Trajectories in inflammatory markers (ferritin, lymphocytes, and neutrophils) in COVID-19 positive survivors and nonsurvivors [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

DISCUSSION

We observed unique temporal trends in various clinical and laboratory parameters among HD patients who tested positive versus negative for SARS-CoV-2 infection. Ultimately, these trends help to define the physiological disturbances that characterize the onset and course of

COVID-19 in HD patients. The disturbances in various parameters commonly started around 14 days before presentation and were more pronounced in patients who tested positive for COVID-19. We identified statistically distinct daily changes in vital signs, inflammatory, and nutritional markers across the weeks before presentation among patients who tested COVID-19 positive versus

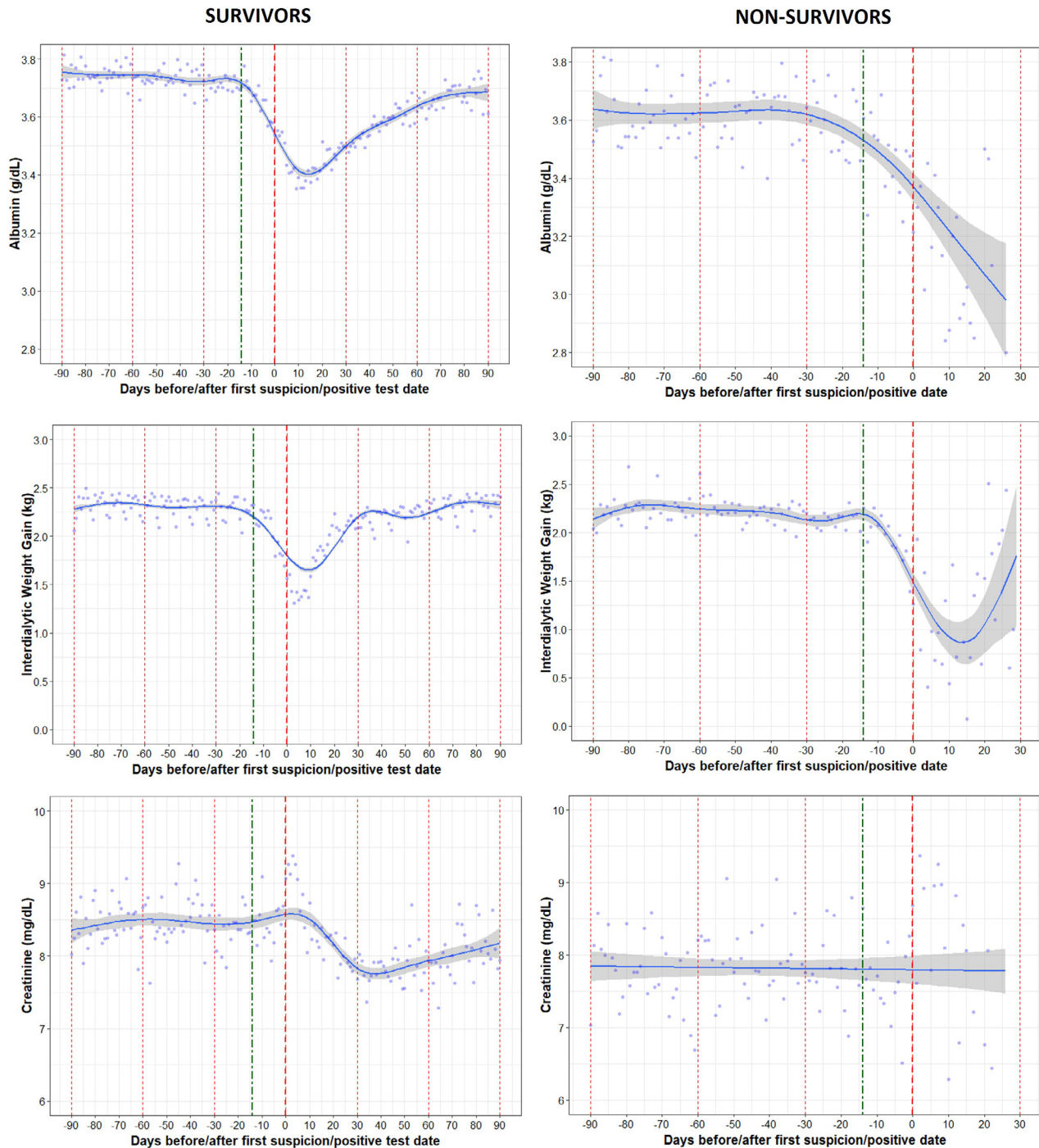


FIGURE 6 Trajectories in nutritional markers (albumin, IDWG, and creatinine) in COVID-19 positive survivors and nonsurvivors [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

negative, as well as unique differences between groups on the date of suspicion/testing. Albeit statistically significant, the differences were often clinically subtle for many parameters. Nonetheless, these findings are anticipated to be of use in development of diagnostic support risk scores and prediction models. Among patients in the COVID-19 negative group, there were observed in various parameters, which were anticipated since these

patients likely underwent testing due to presentation with symptoms of a flu-like illness; however, we cannot exclude that some were tested secondary to exposure to someone with known COVID-19. Among the COVID-19 positive group, we identified clinically remarkable disturbances in vital signs, inflammatory, and nutritional markers after being diagnosed with COVID-19 that commonly took more than 1 month to return to normal

among those who survived. The trajectories in parameters were statistically distinct between survivors and non-survivors bringing insights that will be of importance to consider in the development of prognostic support risk scores and prediction models.

Published studies showing clinical trends before and at onset in COVID-19 HD patients are scarce. We recently showed how a machine learning predictive model that uses changes in clinical parameters before diagnosis had reasonable performance in classification of patients with a SARS-CoV-2 infection 3 days before symptoms onset (area under the curve is the testing dataset was 0.68). The model developed showed changes in IDWG had the highest variable feature importance (reflecting the impact of the value to the prediction).¹¹ Our present analysis adds to previous findings by showing quantitative trends in key parameters during the period before and after presentation with COVID-19. One of the novel findings, we identified was the inverse trends in pre-HD SBP before presentation between COVID-19 positive versus negative patients. The decreases in SBP specifically associated with the onset of COVID-19 may be representative of some potential direct or indirect influences of the disease on the heart that caused a decompensation in cardiovascular system. The specificity of trends in physiological parameters for COVID-19 diagnosis should be assessed in future studies.

When comparing survivors and nonsurvivors, we found that mean age, dialysis vintage, and the proportion of males was higher in nonsurvivors, as was the presence of comorbidities such as diabetes and congestive heart failure and this consistent with previous findings.^{3,4,12} Previous studies also have showed that higher body temperature, lower lymphocyte counts, higher levels of C-reactive protein and white blood cell counts were related to mortality in HD patients.^{3,4,12-15} However, we observed that average change in temperature 14 days prior to Day 0 was not significantly different in survivors compared to nonsurvivors. The body temperature on Day 0 for nonsurvivors was also slightly higher than survivors, although the difference was not significant.

In patients testing positive for COVID-19, the laboratory parameters anticipated to be directly related to the infection, such as neutrophils, lymphocytes, and ferritin, returned to their baseline values within 30 days after suspicion/testing. The relatively long time for infection-related parameters to persist may be because SARS-CoV-2 infection may persist for longer period in HD patients. In a study of 19 HD patients with COVID-19 with repeat RT-PCR testing, SARS-CoV-2 tests remained positive in 68% patients after 20 days and in 32% after 40 days.¹⁶

We found a modest decline in IDWG in the weeks before presentation that was specific to the COVID-19

positive group. Among patients who contracted COVID-19, the decline in IDWG was more pronounced in non-survivors versus survivors, which may be a prognostic signal for malnutrition when accompanied by a deterioration in other nutritional parameters.¹⁷ Parameters related to nutrition appear to take longer to return to the baseline in patients who survived suggesting the systemic effects of COVID-19 may be prolonged. Serum creatinine, which can also be considered a marker of lean tissue mass,¹⁸ even had not return to baseline 90 days after diagnosis. This suggests profound catabolic effects of COVID-19, which are due to multiple mechanisms such as anorexia, hypoxia, immobilization and increased levels of pro-inflammatory cytokines.¹⁹ In our analysis, it also took 2–3 months for serum albumin to return to the baseline values seen in the months before infection.

This analysis assessed a large group of COVID-19 positive HD patients and provides novel information. However, it is important to note that patients could have been tested for presentation with symptoms or exposure to someone with known COVID-19, which cannot be fully deduced in cases where there is missing/unavailable data on the date of suspicion. Although most patients were likely tested for clinical reasons, which is known for most of the COVID-19 positive patients, this is a limitation of the analysis. In general, absolute differences in trends, although significant, were small and we therefore suggest using multiple markers in combination for risk prediction, as shown in our previous paper regarding a machine learning prediction model developed for early detection of patients with COVID-19.¹¹ Moreover, it is important to realize that the trends do not show the mean of individual trajectories, but an aggregate of the cohort groups. We cannot rule out that there might be some minimal temporal bias secondary to the definition of the reference date/Day 0 for suspicion/testing that may have an impact on the trajectories. Also, there is a possibility that the incubation period of the virus was prolonged due to low immunity in dialysis patients. Nonetheless, the comparisons in trends in daily changes during the weeks prior suspicion/testing are anticipated to have reasonably captured signals. Further investigations should consider inclusion of these insights to improve the precision of COVID-19 risk scores and prediction models being developed and used in care paradigms.

CONCLUSION

We found the trajectories of several clinical/laboratory parameters distinctly changed in patients during the weeks before presentation with COVID-19, as compared to patients who were tested for a SARS-CoV-2 infection

and found negative. Many parameters changed in similar directions for both groups, yet significantly more for patients found to be COVID-19 positive versus negative. These included increasing pulse, body temperature, and neutrophils, along with decreasing lymphocytes and albumin. However, several factors uniquely changed in patients who were found to be COVID-19 positive, which included decreasing SBP and IDWG, as well as increasing ferritin. Among patients who were diagnosed with COVID-19, the survivors appeared to have statistically distinct trajectories showing less robust increases in pulse and neutrophils, and decreases in lymphocytes, compared to patients who died within 30 days after COVID-19 suspicion/testing. In patients with COVID-19 who survived, inflammatory and cardiovascular parameters returned to baseline levels in 1 month; however, the effect of COVID-19 on nutritional status appeared to be more prolonged and disturbances were seen up to 90 days. These findings appear to reveal some of the pathophysiologic trends defining the onset and course of the disease in the HD population, however, many changes were small. These insights are anticipated to be of high importance for development of prediction models for early identification and prognosis of COVID-19.

CONFLICT OF INTEREST

Sheetal Chaudhuri is a student at Maastricht University Medical Center. Sheetal Chaudhuri, Rachel Lasky, Yue Jiao, John Larkin, Caitlin Monaghan, Anke Winter, Luca Neri, Jeffrey Hymes, Len Usvyat, and Franklin Maddux are employees of Fresenius Medical Care. Peter Kotanko is an employee of Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care. Sheetal Chaudhuri, Peter Kotanko, Jeffrey Hymes, Len Usvyat, Franklin Maddux have share options/ownership in Fresenius Medical Care. Peter Kotanko is an inventor on multiple patents in the field of dialysis and is on the Editorial Board of Blood Purification and Kidney and Blood Pressure Research. Franklin Maddux has directorships in the Fresenius Medical Care Management Board, Goldfinch Bio, and Vifor Fresenius Medical Care Renal Pharma. Sangho Lee, Yuedong Wang, and Jeroen P. Kooman have no relevant conflicts of interest to disclose.

FUNDING INFORMATION

Analysis and manuscript composition were supported by Fresenius Medical Care.

ORCID

Sheetal Chaudhuri  <https://orcid.org/0000-0002-8217-9520>

REFERENCES

1. 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;31(8):1815–23.
2. 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;98(6):1540–8.
3. Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. *Kidney Int*. 2020;98(6):1530–9.
4. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant*. 2020;35(11):1973–83.
5. Neumann ME. Latest data show 305 dialysis patient deaths due to COVID-19 in the US. *Nephrol News Issues*. 2020. (Accessed 22 Apr 2020) Available from: <https://www.healio.com/nephrology/infection-control/news/online/%7B3a263aa9-ad59-4c3f-aab7-07b8395508e5%7D/latest-data-show-305-dialysis-patient-deaths-due-to-covid-19-in-the-us>
6. Medicine JHUSo. Mortality analyses. Johns Hopkins Coronavirus Resource Center. 2020. Accessed December 2020, Available from: <https://coronavirus.jhu.edu/data/mortality>.
7. USRDS. COVID-19 Supplement. 2020. Accessed November 2020. Available from: <https://adr.usrds.org/2020/covid-19-supplement/1-covid-19-supplement>.
8. Seshadri DR, Davies EV, Harlow ER, Hsu JJ, Knighton SC, Walker TA, et al. Wearable sensors for COVID-19: A call to action to harness our digital infrastructure for remote patient monitoring and virtual assessments. *Front Digit Health*. 2020; 2. <https://doi.org/10.3389/fdgth.2020.00008>.
9. Maddux DW, Usvyat LA, Ketchersid T, Jiao Y, Blanchard TC, Kotanko P, et al. Clinical parameters before and after the transition to dialysis. *Hemodial Int*. 2018;22(2):235–44.
10. Wang Y. Smoothing splines: methods and applications. New York, NY: Chapman and Hall; 2011.
11. Monaghan CK, Larkin JW, Chaudhuri S, Han H, Jiao Y, Bermudez KM, et al. Machine learning for prediction of hemodialysis patients with an undetected SARS-CoV-2 infection. *Kidney360*. 2021;2(3):456–68. <https://doi.org/10.34067/KID.0003802020>
12. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A report from the Brescia renal COVID task force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. *Kidney Int*. 2020;98(1):20–6.
13. Goicoechea M, Sánchez Cámara LA, Macías N, Muñoz de Morales A, Rojas ÁG, Bascuñana A, et al. COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. *Kidney Int*. 2020;98(1):27–34.
14. Keller N, Chantrel F, Krummel T, Bazin-Kara D, Faller AL, Muller C, et al. Impact of first-wave COVID-19 infection in patients on haemodialysis in Alsace: the observational COVIDIAL study. *Nephrol Dial Transplant*. 2020;35(8):1338–411.

15. Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J, et al. Presentation and outcomes of patients with ESKD and COVID-19. *J Am Soc Nephrol*. 2020;31(7):1409–15.
16. Shaikh A, Zeldis E, Campbell KN, Chan L. Prolonged SARS-CoV-2 viral RNA shedding and IgG antibody response to SARS-CoV-2 in patients on hemodialysis. *Clin J Am Soc Nephrol*. 2021;16:290–2. <https://doi.org/10.2215/cjn.11120720>.
17. Ye X, Dekker MJE, Maddux FW, Kotanko P, Konings CJAM, Raimann JG, et al. Dynamics of nutritional competence in the last year before death in a large cohort of US hemodialysis patients. *J Ren Nutr*. 2017;27:412–20.
18. Canaud B, Ye X, Usvyat L, Kooman J, van der Sande F, Raimann J, et al. Clinical and predictive value of simplified creatinine index used as muscle mass surrogate in end-stage kidney disease haemodialysis patients—results from the international MONitoring dialysis outcome initiative. *Nephrol Dial Transplant*. 2020;35(12):2161–71.
19. Morley JE, Kalantar-Zadeh K, Anker SD. COVID-19: a major cause of cachexia and sarcopenia? *J Cachexia Sarcopenia Muscle*. 2020;11:863–5.

How to cite this article: Chaudhuri S, Lasky R, Jiao Y, Larkin J, Monaghan C, Winter A, et al. Trajectories of clinical and laboratory characteristics associated with COVID-19 in hemodialysis patients by survival. *Hemodialysis International*. 2022;26:94–107. <https://doi.org/10.1111/hdi.12977>