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Increased dialysis symptom index burden in maintenance hemodialysis patients during the COVID-19 lockdown period

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Abstract

The high prevalence of dialysis-related symptoms in maintenance hemodialysis (MHD) patients severely affect quality of life. Therefore, in this study, we assessed the dialysis symptom index (DSI) of MHD patients during the second wave of COVID-19, which triggered a health crisis, resulting in many cities in China opting for social isolation. A total of 106 MHD patients from our center were screened. DSI, sleep quality, and fatigue scales were investigated separately before and during lockdown. Demographic and laboratory data of MHD patients were collected. A nomogram was used to predict high DSI by combining multiple indicators. Additionally, internal validation was performed to reduce overfitting bias. The mean age of patients was 56.0 years (SD 13.1). The prevalence and severity of DSI were significantly higher during lockdown than pre-lockdown. Notably, itching, trouble staying asleep, bone or joint pain, muscle cramps, feeling irritability, difficulty concentrating, headache, constipation, and feeling nervous were observed ($P<0.05$). Multivariate logistic regression analysis identified longer dialysis vintage, lower albumin level, and lower Kt/V as predictors of high DSI. Additionally, the nomogram showed good accuracy in estimating high DSI with a C-index and bootstrap-corrected index of 0.875 and 0.863, respectively. Moreover, calibration plots showed optimal consistency with the actual presence of high DSI. We found a higher prevalence of DSI in MHD patients during the COVID-19 lockdown. Furthermore, patients with longer dialysis vintage, lower albumin levels and Kt/V had a risk of developing high DSI. Further studies should identify targeted therapies for improving the symptom burden of MHD patients.

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Running title : Increased DSI burden in MHD patients during the COVID-19 lockdown.

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Abstract

The high prevalence of dialysis-related symptoms in maintenance hemodialysis (MHD) patients severely affect quality of life. Therefore, in this study, we assessed the dialysis symptom index (DSI) of MHD patients during the second wave of COVID-19, which triggered a health crisis, resulting in many cities in China opting for social isolation. A total of 106 MHD patients from our center were screened. DSI, sleep quality, and fatigue scales were investigated separately before and during lockdown. Demographic and laboratory data of MHD patients were collected. A nomogram was used to predict high DSI by combining multiple indicators. Additionally, internal validation was performed to reduce overfitting bias. The mean age of patients was 56.0 years (SD 13.1). The prevalence and severity of DSI were significantly higher during lockdown than pre-lockdown. Notably, itching, trouble staying asleep, bone or joint pain, muscle cramps, feeling irritability, difficulty concentrating, headache, constipation, and feeling nervous were observed (P <0.05). Multivariate logistic regression analysis identified longer dialysis vintage, lower albumin level, and lower Kt/V as predictors of high DSI. Additionally, the nomogram showed good accuracy in estimating high DSI with a C-index and bootstrap-corrected index of 0.875 and 0.863, respectively. Moreover, calibration plots showed optimal consistency with the actual presence of high DSI. We found a higher prevalence of DSI in MHD patients during the COVID-19 lockdown. Furthermore, patients with longer dialysis vintage, lower albumin levels and Kt/V had a risk of developing high DSI. Further studies should identify targeted therapies for improving the symptom burden of MHD patients.

KEYWORDS :

COVID-19, dialysis system index, lockdown, nomogram, predictive model

INTRODUCTION

Maintenance hemodialysis (MHD) patients have a high prevalence of physical and emotional illness-related symptoms[1-3]. A high symptom burden is associated with a high mortality risk in MHD patients[4]. In a Thai study, 98.7% of MHD patients reported one or more symptom burdens, with the most common ones being itchy skin, dryness, muscle ache, dry mouth, muscle cramps, and insomnia[5]. A Korean study revealed that 97.4% of all MHD patients reported one or more symptoms, with fatigue and dry skin being the most common physical symptoms and worry, tension, and anxiety as the most common emotional symptoms[6]. These symptoms cause distress and affect the overall well-being of patients, leading to a reduced quality of life, and may increase patient mortality[1,7]. Therefore, a symptom study of end-stage renal disease (ESRD) patients on hemodialysis would contribute to effective symptom management and maximize patient benefits.

Studies have shown that the isolation and containment of patients with COVID-19 have far-reaching effects on different groups, including insomnia, depression, anxiety, and post-traumatic stress disorder (PTSD)[8-11]. A study conducted among isolated college students confirmed the dramatic impact of the COVID-19 pandemic on their mental health[12]. Psychiatric symptoms were strikingly prevalent: 67.05% reported traumatic stress, 46.55% reported depressive symptoms, and 34.73% reported anxiety symptoms. In a study conducted in a Chinese isolation ward with infected patients[13], the prevalence of generalized anxiety symptoms was 51.3%; depressive symptoms, 41.2%; and post-traumatic stress symptoms (PTSS)/PTSD symptoms, 33.6%. A longitudinal study conducted in France revealed the impact of the pandemic on the mental health status of the French population[14]. The study included participants who had undergone a mental health study in 2014–2019. The results showed that isolation led to higher psychological stress and that those with poorer physical health showed more severe anxiety symptoms.

From the beginning of October till the end of November 2022, the COVID-19 epidemic in Hefei became increasingly severe. An epidemic is characterized by multi-point distribution, localized aggregation, and gradual spillover. Therefore, multiple regions of our city were under lockdown and static management during

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this period. With static management, residents cannot leave their houses and engage in outdoor activities. Concerns about daily life and disease treatment caused great psychological and physical distress to MHD patients. However, the dialysis symptom index (DSI) of MHD patients during the lockdown remains unclear. Therefore, to fully evaluate the psychological and mental status of MHD patients, we investigated the DSI of MHD patients during the COVID-19 lockdown period, so as to provide a reference for the development of comprehensive management programs for MHD patients.

METHODS

2.1 Study population

The study population included a cohort of adult MHD patients at the Second Hospital of Anhui Medical University who had completed their first DSI assessment 6 months earlier (March 2022). Exclusion criteria were 1) inability to comprehend with the questionnaire content, 2) presence of comorbid malignancies and infections (including COVID-19) based on clinical/laboratory findings, and 3) inability to provide consent without a proxy. A second DSI assessment was performed for screened patients during lockdown(between October and November 2022). This study was approved by the Ethics Review Committee of the Second Affiliated Hospital of the Anhui Medical University (No. pj - yx2020 - 006). Before participation, all patients were required to read and sign an informed consent form.

2.2 Baseline information

At the beginning of the study (March 2022), demographic and laboratory data were collected for all patients. General information included sex, age, and dialysis vintage. Laboratory parameters included creatinine, blood urea nitrogen, hemoglobin, albumin, blood calcium, blood phosphorus, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), and total Kt/V(dialysis effectiveness index).

2.3 Assessment of dialysis symptom index

The DSI is a validated instrument consisting of 30 questions to assess the severity of discomfort and unpleasant emotions in patients on MHD, with each question addressing a specific physical or emotional symptom[7,15]. The 30 questions can be summarized into eight groups of symptoms: 1) gastrointestinal, 2) musculoskeletal and fluid volume, 3) neurological symptoms, 4) irritation of the mucous membranes and skin, 5) depression, 6) sleep disturbance, 7) sexual symptoms, and 8) anemia. Patients were asked to report symptoms that occurred in the last week, answering “yes” or “no” to each symptom. Severity was assessed on a five-point Likert scale, with scores ranging from 0 to 4 for each answer (i.e., a response of ”0” means ”no,” whereas a response of ”4” means ”yes: very much”). The total DSI score represents the sum of individual scores (ranging from 0 to 120), with higher total scores indicating higher overall symptom severity.

2.4 Assessment of fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was used to assess fatigue in MHD patients. The 13-item questionnaire examined self-reported fatigue and its impact on daily activities and function. The scale consists of five points (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much). All items contributed equally to the total score. The scale ranged from 0 to 52, with 0 representing the worst possible score and 52 representing no fatigue. Previously, a FACIT-F score [?] 34 was considered indicative of fatigue[16].

2.5 Assessment of sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is an effective indicator of sleep quality and patterns. Subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruptions, use of sleep medications, and daytime dysfunction were evaluated. Each factor was weighted from 0 to 3, resulting in a global score between 0 and 21. Poor sleep quality was defined as a global PSQI score of >5[17].

2.6 Statistical analyses

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Categorical variables are expressed as percentages, and continuous variables are expressed as mean (SD) or median (IQR). Differences in baseline characteristics, and laboratory measures between groups were assessed using Chi square test, or Mann-Whitney U test, as appropriate. In the univariate logistic regression analysis, variables associated with a high risk of high DSI (P <0.05) were introduced into the multivariate model. The collinearity between the final model variables was evaluated using the variance inflation factor (VIF). VIF [?] 5 signified the absence of collinearity between the final model variables. Nomogram were generated based on the results of multivariate logistic regression on the dependent variable using the 'rms' package in R software (version 4.2.1). In addition, we used the bootstrapping method with 1000 resamples to conduct internal validation. The discriminative power of the model was assessed using the consistency index (C-index), and the goodness of fit is shown in the calibration plot. Statistical analyses were performed using R software (version 4.2.1). P value of <0.05 was considered statistically significant.

RESULTS

3.1 Effect of COVID-19 lockdown on DSI in MHD patients

A total of 130 patients had their first assessment before the lockdown. During the lockdown period, only 106 of the 130 cases participated in the second evaluation. Finally, 106 patients who were assessed twice were included in the trial. 60.4% of the patients were male (n = 64). The mean age of patients was 56.0 (SD = 13.1) years. We observed that DSI severity in MHD patients during lockdown was higher than that before lockdown (Table 1). In particular, itching, trouble staying asleep, bone or joint pain, muscle cramps, feeling irritable, difficulty concentrating, headache, constipation, and feeling nervous were observed (P <0.05, Table 1). Moreover, the prevalence of fatigue (PSQI>5) and poor sleep (FACIT-F[?]34) was higher during lockdown than before lockdown (P <0.05).

3.2 Overall severity of DSI in the MHD cohort

We compared differences in the distribution of DSI in MHD patients before and during lockdown (Figure 1, Figure 2.). The overall pattern of patients was similar in both groups. The most common symptoms reported by patients in Figure 1 included feeling tired or lacking energy (81.1%), dry skin (76.5%), trouble falling asleep (74.5%), feeling sad (66.0%), and dry mouth (63.2%). In contrast, most of the symptoms reported by patients in Figure 2 included itching (84.9%), trouble falling asleep (84.9%), dry skin (84.0%), feeling tired or lacking energy (80.2%), and dry mouth (73.6%).

3.3 Relationship between baseline data and DSI in MHD patients during lockdown

Based on the mean of the median DSI (40) from both surveys, patients were divided into a low DSI (DSI<40) and a high DSI (DSI[?]40) group in the second evaluation. We found that patients in the high DSI group had a longer dialysis vintage and lower albumin and Kt/V levels than those in the low DSI group (Table 2). There were no significant differences between the two groups in the percentage of women, age, Kt/V, and hemoglobin, blood urea nitrogen, alkaline phosphatase, serum Ca, serum P, iPTH, ferroprotein, and transferrin levels.

3.4 Univariate and multivariate logistic regression analysis

The univariate logistic regression analysis showed that dialysis vintage, albumin and Kt/V were associated with the development of high DSI in MHD patients during lockdown period. The multivariate logistic model's mean VIF of 1.22 indicates the direct absence of multicollinearity among variables. Multivariate logistic regression revealed that dialysis vintage (OR 1.031, 95%CI 1.013-1.050;P =0.001), albumin (OR 0.782, 95%CI 0.627-0.975; P =0.029) and Kt/V (OR 0.028, 95%CI 0.001-0.556; P =0.019) were significant risk variables for hige DSI (Table 3).

3.5 Nomogram construction and validation

The results of multivariate logistic regression were applied to construct a nomogram of hige DSI in MHD patients, and scores were assigned to the screened variables based on their regression coefficients (Figure 3). As shown in nomogram, patients with longer dialysis vintage, lower albumin levels and Kt/V had a

higher risk of developing high DSI. By summing the scores and locating them on the total score scale, it was possible to predict the occurrence of high DSI in individuals during lockdown period.

Internal validation was conducted to evaluate the model's discrimination and reduce overfitting bias. The results demonstrated a C-Index of 0.875 for the primary cohort and 0.863 for the internal validation cohort. The calibration plots showed excellent agreement between the nomogram predictions and the actual observation of high DSI (Figure 4).

DISCUSSION

Patients on MHD have a heavy burden of DSI symptoms, but they are often underestimated or even ignored, and thus undertreated[18]. COVID-19 has been a challenge to all humanity, both on physical and psychological level. Its impact is diverse and it has caused varying degrees of distress to everyone. Lockdowns increase MHD patients' anxiety and worry about the treatment of their disease. In this study, we used validated tools to assess the presence and severity of patient complaints[19]. The DSI is the most common tool used to assess the prevalence and severity of dialysis-related discomfort in patients with ESRD. A growing number of epidemiological studies have attempted to use DSI to reveal the prevalence of physical and emotional symptoms in MHD patients[4,20,21].

In this single-center cohort study, we investigated DSI in patients on MHD before and during lockdown. We found a significant increase in the prevalence of individual symptoms and overall symptom severity scores during the lockdown. Notably, the prevalence of itching, trouble staying asleep, bone or joint pain, muscle cramps, feeling irritability, difficulty concentrating, headache, constipation, and feeling nervous increased compared with pre-lockdown. Examination of symptoms across the cohort revealed that the most commonly reported symptoms were those related to fatigue, skin disorders (i.e., dry skin, pruritus), and sleep disturbances.

These symptoms can be mainly summarized in terms of physical and psychological aspects. We speculate that there may be the following reasons for the above changes. First, the lockdown caused inconvenience to the daily treatment of MHD patients, which may have led to insufficient treatment of some patients. Second, the concern of exposure to the virus may directly increase the psychological burden on MHD patients. Third, patients may not have received timely and adequate attention from physicians because physicians were overburdened with the care of the influx of COVID-19 patients. Given the high prevalence of these unpleasant symptoms and their dominance in the cluster, future studies to identify therapies that effectively target these symptoms may substantially improve the health and well-being of a large proportion of dialysis patients.

According to the nomogram, longer dialysis vintage is a risk factor of high DSI. However, patients with high albumin levels and Kt/V had a lower risk of developing high DSI. The Kt/V value, which represents the adequacy of dialysis, may decrease as dialysis vintage increases. Studies have shown that MHD patients are more prone to urinary toxin-related discomfort and vital organ dysfunction when dialysis is inadequate[19,22]. Therefore, it is important to reduce DSI severity by improving dialysis adequacy in patients on MHD. In addition, we found that low albumin level was a risk factor of high DSI. Albumin level is an important index for evaluating the nutritional status of the body. Studies have found that low albumin level is one of the main causes of serious complications in dialysis patients[23,24]. However, we also observed that nutritional parameters defined by albumin level were associated with a wider range of symptoms, including decreased energy (feeling tired or lacking energy), restless legs, muscle discomfort (muscle cramps, muscle aches), impaired cognition (difficulty concentrating), and overall symptom burden. Improving the nutritional status of patients on MHD may be beneficial for reducing discomfort symptoms.

The strengths of our study include the first-time assessment of DSI in MHD patients during COVID-19 lockdown, rigorous use of a symptom assessment tool (DSI) that has been validated in the dialysis population for symptom assessment in MHD patients, and the comprehensive availability of detailed patient data collected. However, our study has several limitations. First, the research subjects in this study is not representative of all HD population; patients who agreed to participate in the study may have been healthier

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than those who were not recruited and, therefore, may have had lower symptom scores than the broader hemodialysis population. Second, the limited sample size may not have allowed the detection of significant subgroup analysis-based interactions. Third, uncomfortable symptoms during dialysis can be exacerbated by comorbidities, medications, lifestyle and dietary regimens, renal replacement therapy, and aging. Due to data limitations, we were unable to examine the relationship between certain dialysis treatment features (i.e., hemodialysis membranes and medications on dialysis) and symptom burden.

CONCLUSION

DSI prevalence and severity were higher in MHD patients during lockdown period than before. The novel predictive nomogram achieved a good prediction of high DSI in patients on MHD. Using this model, the risk of high DSI in patients with MHD can be determined earlier.

AUTHOR CONTRIBUTIONS

The authors who conceived the study: Wen-Man Zhao and Liang Yuan. Authors who designed the study: Wen-Man Zhao and Li Zhu. Authors who performed the experiments: Wen-Man Zhao, Rui Shi and Yvyv Zhu. Authors who performed statistical analyses: Xun-Liang Li and Zhi-Juan Wang. Authors who wrote and edited the manuscript: Wen-Man Zhao, Hai-Feng Pan, De-Guang Wang. All authors read and approved the final version.

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Joint Research on Prevention and Control of Chronic Diseases in the Second Hospital of Anhui Medical University (MBLHJJ202008).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding open accessed websites.

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Tables

TABLE 1 Comparison of DSI scores of MHD cohort in different periods (n = 106).

Individual Symptoms	**Pre-lockdown**	**Lockdown**	***P*-value**
DSI, M (Q1, Q3)	36 (28, 42)	54 (32, 65)	**<0.001**
Itching, n (%)	61 (57.5)	90 (84.9)	**<0.001**
Dry skin, n (%)	81 (76.4)	89 (84.0)	0.168
Trouble falling asleep, n (%)	79 (74.5)	90 (84.9)	0.060
Trouble staying asleep, n (%)	56 (52.8)	72 (67.9)	**0.025**
Numbness or tingling in feet, n (%)	45 (42.5)	52 (49.1)	0.335
Muscle cramps, n (%)	66 (62.3)	60 (56.6)	0.401
Swelling in legs, n (%)	51 (48.1)	53 (50.0)	0.783
Restless legs or difficulty keeping legs still, n (%)	42 (39.6)	50 (47.2)	0.268
Bone or joint pain, n (%)	32 (30.2)	60 (56.6)	**<0.001**
Shortness of breath, n (%)	54 (50.9)	63 (59.4)	0.214
Cough, n (%)	41 (38.7)	44 (41.5)	0.674
Muscle soreness, n (%)	49 (46.2)	76 (71.7)	**<0.001**
Feeling tired or lacking energy, n (%)	86 (81.1)	85 (80.2)	0.862
Feeling anxious, n (%)	59 (55.7)	71 (67.0)	0.091
Feeling irritable, n (%)	47 (44.3)	67 (63.2)	**0.006**
Feeling sad, n (%)	70 (66.0)	69 (65.1)	0.885
Difficulty concentrating, n (%)	46 (43.4)	65 (61.3)	**0.009**
Headache, n (%)	39 (36.8)	63 (59.4)	**0.001**
Decreased appetite, n (%)	49 (46.2)	57 (53.8)	0.272
Diarrhea, n (%)	44 (41.5)	40 (37.7)	0.574
Nausea, n (%)	56 (52.8)	55 (51.9)	0.891
Vomiting, n (%)	37 (34.9)	47 (44.3)	0.160
Dry mouth, n (%)	67 (63.2)	78 (73.6)	0.104
Constipation, n (%)	42 (39.6)	61 (57.5)	**0.009**
Chest pain, n (%)	39 (36.8)	43 (40.6)	0.573
Lightheadedness or dizziness, n (%)	42 (39.6)	55 (51.9)	0.073
Worrying, n (%)	62 (58.5)	73 (68.9)	0.116
Feeling nervous, n (%)	52 (49.1)	73 (68.9)	**0.003**
Decreased interest in sex, n (%)	56 (52.8)	57 (53.8)	0.891
Difficulty becoming sexually aroused, n (%)	60 (56.6)	57 (53.8)	0.679
PSQI>5, n (%)	75(70.8)	88(83.0)	**0.034**
FACIT-F[?]34, n (%)	48(45.3)	65(61.3)	**0.019**

DSI, dialysis symptom index; MHD, maintenance hemodialysis; PSQI, Pittsburgh Sleep Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale.

TABLE 2 Baseline characteristics of MHD patients with high DSI scores during lockdown.

Variables	**Overall** (n = 106)	**DSI**<40 (n = 39)	**DSI**[?]40 (n = 67)	***P*-value**
Female, n (%)	42(39.6)	12(30.8)	30(44.8)	0.155
Age (years), mean (SD)	56.0(13.1)	53.9(13.0)	57.2(13.1)	0.216
Dialysis vintage (months), mean (SD)	64.8(36.2)	41.1(27.2)	78.6(33.7)	**<0.001**

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Hemoglobin (g/L), mean (SD)	114.8(13.0)	117.6(12.1)	113.1(13.4)	0.079
Albumin (g/L), mean (SD)	38.5(3.4)	40.1(2.5)	37.8(3.5)	**<0.001**
BUN (mmol/L), mean (SD)	22.2(8.1)	23.2(8.4)	22.2(7.4)	0.275
ALP (U/L), mean (SD)	100.3(37.0)	95.1(33.1)	103.4(39.0)	0.245
Serum Ca (mmol/L), mean (SD)	2.2(0.2)	2.2(0.3)	2.2(0.2)	0.605
Serum P (mmol/L), mean (SD)	1.8(0.5)	1.8(0.5)	1.9(0.6)	0.169
iPTH (pg/mL), median (IQR)	330.5(352.8)	331.0(335)	330.0(432)	0.171
Ferroprotein (ug/L), median (IQR)	100.1(150.7)	125.0(147)	99.0(151.8)	0.987
Transferrin (g/L), median (IQR)	2.0(0.7)	1.9(0.6)	2.0(0.6)	0.816
Kt/V, median (IQR)	1.8(0.2)	1.9(0.3)	1.7(0.3)	**<0.001**

BUN, blood urea nitrogen; ALP, Alkaline phosphatase; Kt/V, dialysis effectiveness index, DSI, dialysis effectiveness index; iPTH, intact parathyroid hormone; MHD, maintenance hemodialysis.

TABLE 3 Logistic regression analysis of predictors for high DSI of MHD patients during lockdown.

Variables	**Univariate OR**	**Univariate 95%CI**	**Univariate** P	**Multivariate OR**	**Multivariate 95%CI**	**Multivariate** P
Female, n (%)	0.548	0.238-1.261	0.157			
Age (years)	1.020	0.989-1.051	0.215			
dialysis vintage (months)	1.038	1.022-1.055	<0.001	1.031	1.013-1.050	0.001
Hemoglobin (g/L)	0.972	0.941-1.004	0.090			
Albumin (g/L)	0.718	0.604-0.854	<0.001	0.782	0.627-0.975	0.029
BUN (mmol/L)	0.996	0.968-1.024	0.759			
ALP (U/L)	1.006	0.995-1.018	0.265			
Serum Ca (mmol/L)	1.628	0.301-8.798	0.572			
Serum P (mmol/L)	1.676	0.790-3.556	0.179			
iPTH (pg/mL)	1.001	1.000-1.003	0.102			
Ferroprotein (ug/L)	1.000	0.997-1.002	0.835			
Transferrin (g/L)	0.874	0.336-2.271	0.782			
Kt/V	0.004	0.000-0.069	<0.001	0.028	0.001-0.556	0.019

BUN, blood urea nitrogen; ALP, Alkaline phosphatase; Kt/V, dialysis effectiveness index, DSI, dialysis effectiveness index; iPTH, intact parathyroid hormone; MHD, maintenance hemodialysis.

Figures

FIGURE 1

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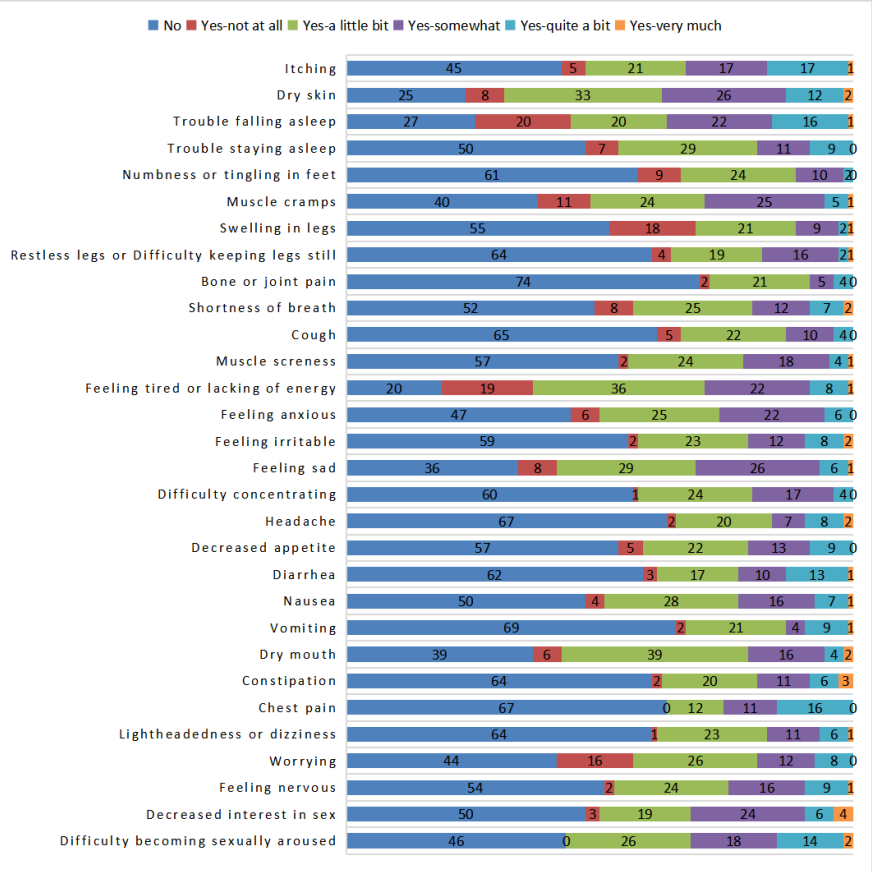

FIGURE 2

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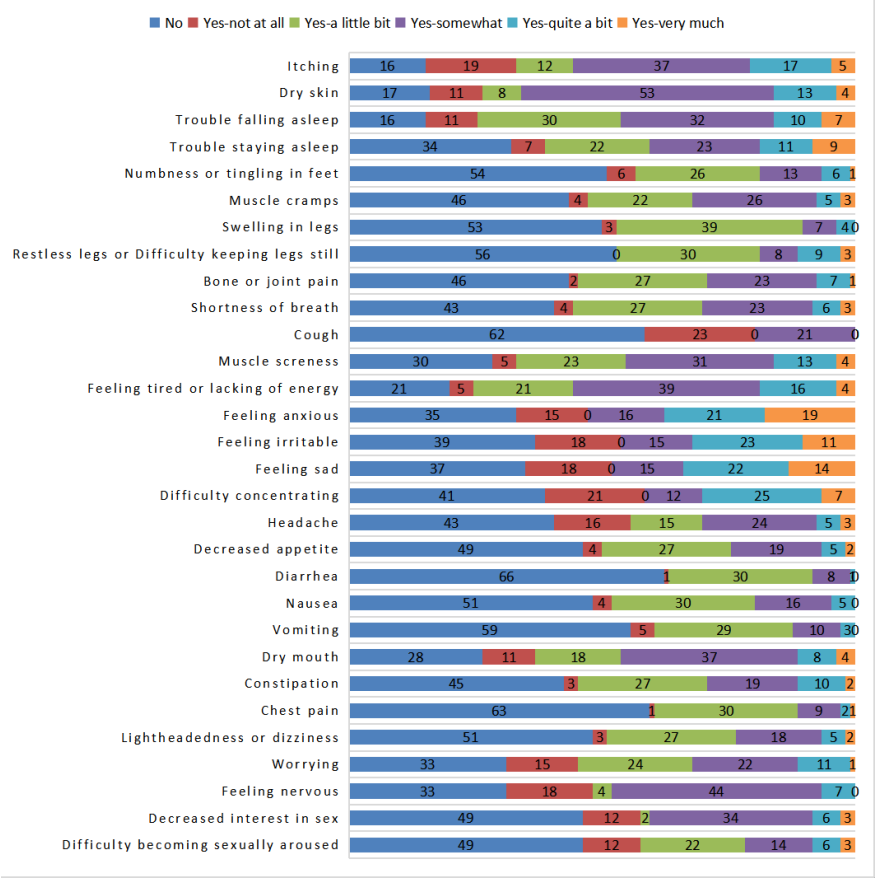

FIGURE 3

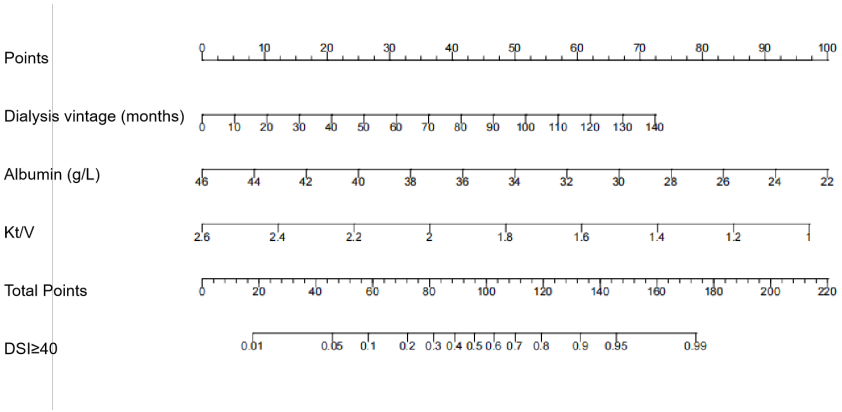

FIGURE 4

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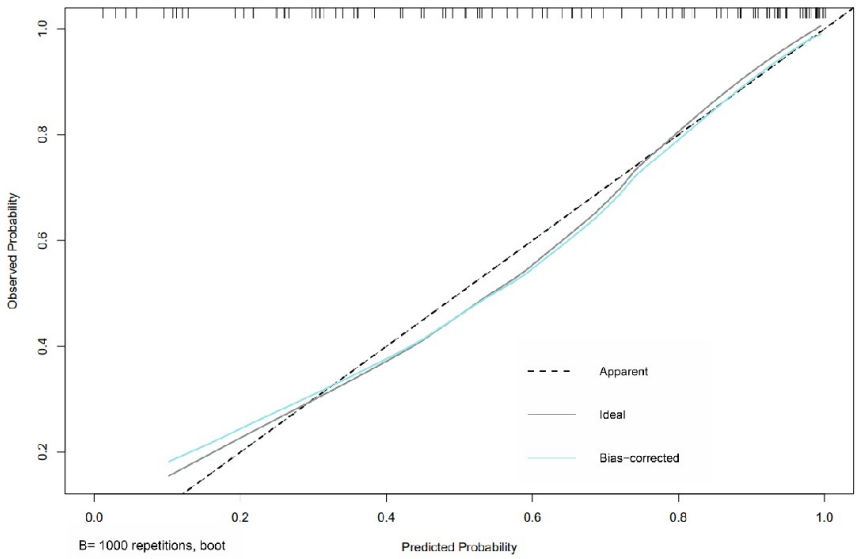

Figure legends

FIGURE 1 Prevalence of individual symptoms in the maintenance hemodialysis patient cohort before lockdown.

FIGURE 2 Prevalence of individual symptoms in the maintenance hemodialysis patient cohort during lockdown.

FIGURE 3 Nomogram of predictors based on multivariate regression analysis for predicting DSI>40.

FIGURE 4 Calibration plots of internal validation.

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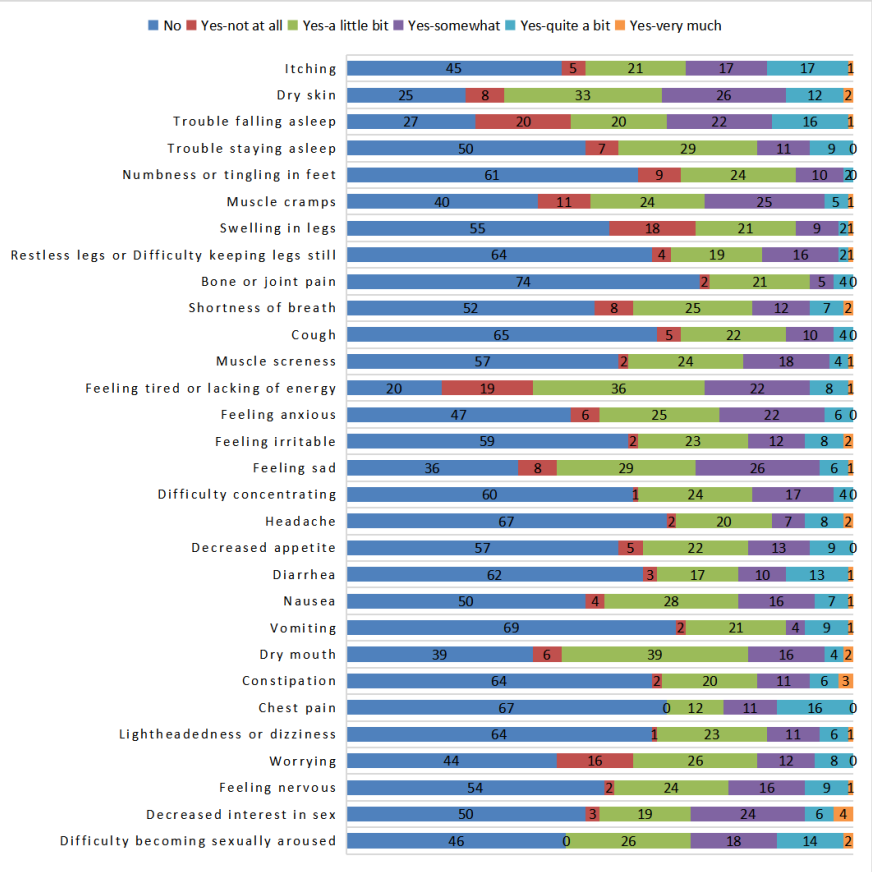

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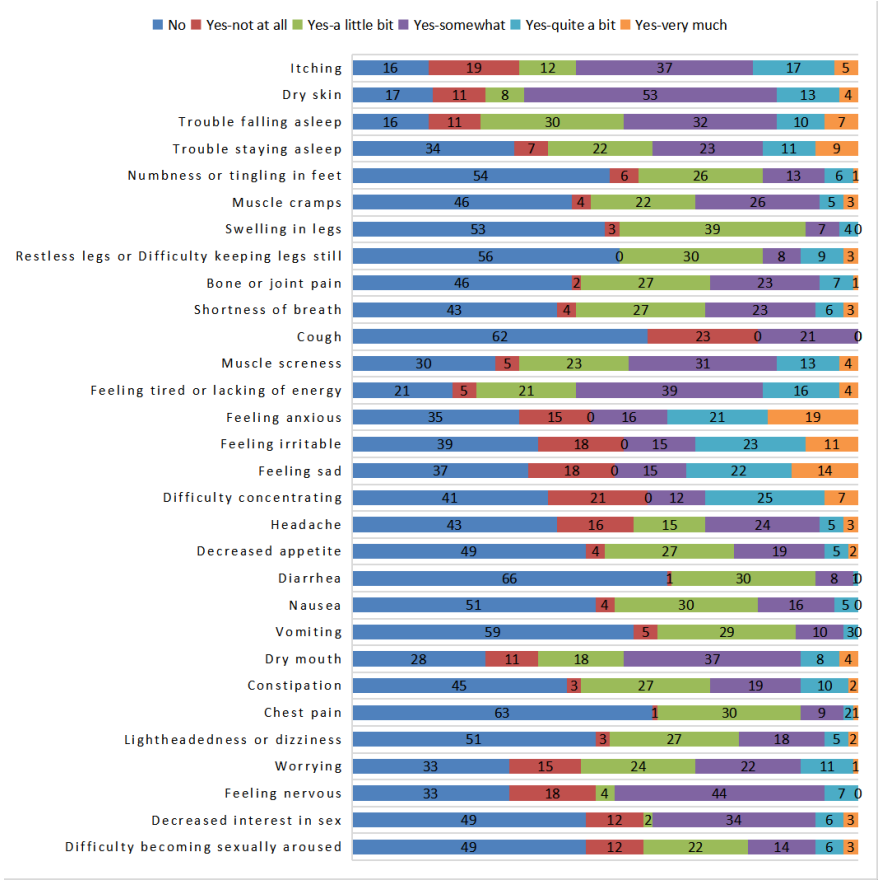

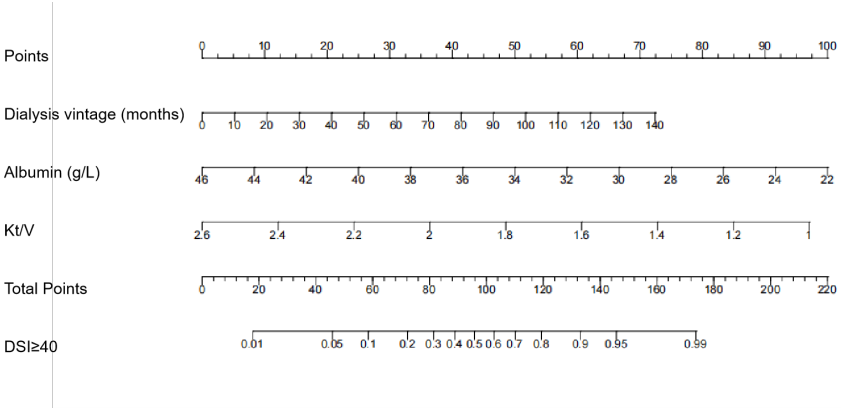

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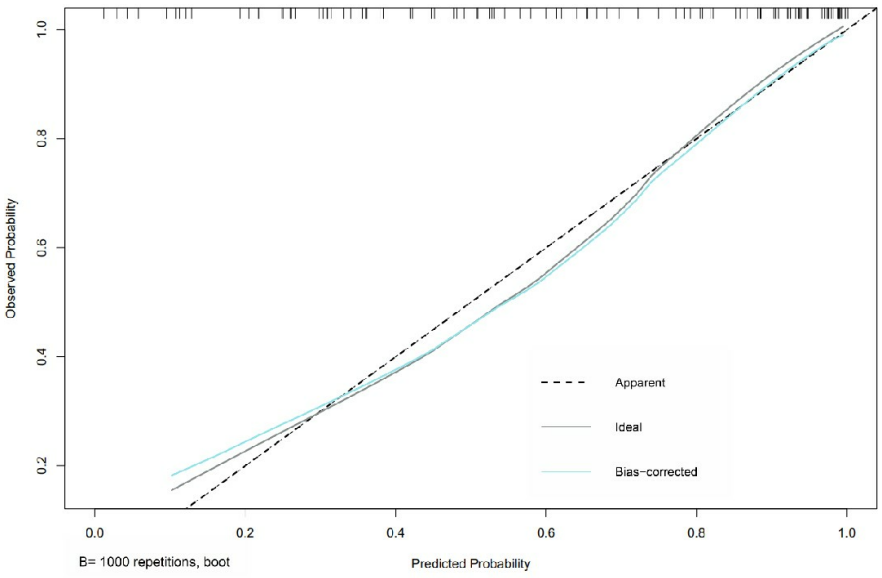

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TABLES.docx available at https://authorea.com/users/589197/articles/626138-increased-dialysis-symptom-index-burden-in-maintenance-hemodialysis-patients-during-the-covid-19-lockdown-period